Systematic Overview of Clinical Trials of Antiarrhythmic Drugs

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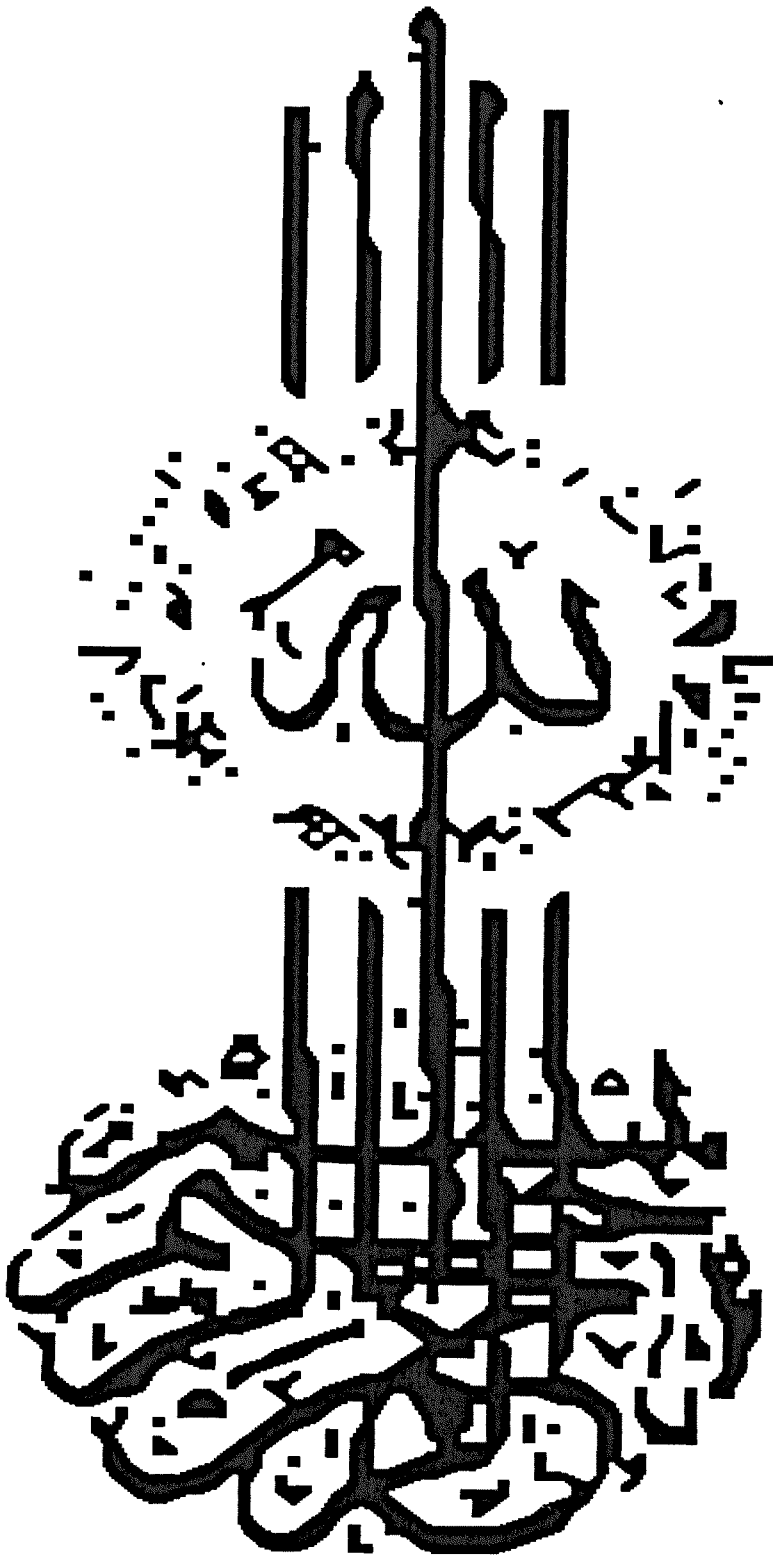

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SUMMARY

BACKGROUND

Arrhythmia is a cardiovascular disorder which can lead to several complications. Over the past decade the introduction of many new drugs has raised concerns about their questionable benefits and cost-effectiveness. Classification of antiarrhythmic drugs has not been fully resolved. Although numerous clinical trials have been conducted, the value of antiarrhythmic drugs in many indications remains controversial. Two meta-analyses of clinical trials addressing the indication of quinidine (Class I) for maintenance of sinus rhythm after cardioversion have suggested high efficacy rates but increased mortality relative to placebo. Several overviews which were conducted to evaluate the impact of antiarrhythmic therapy on improving survival post acute myocardial infarction, have defined a turning point in the management strategy from Class I to Class III drugs, particularly amiodarone and sotalol, due to the unfavourable mortality outcome with the former Class.

MAJOR AIMS

This thesis was conducted with three major aims:

1) To assess both qualitatively and quantitatively the benefits and risks associated with flecainide (Class Ic), amiodarone (Class III), and sotalol (Class III & II) in treatment of chronic atrial fibrillation, acute medical or surgical supraventricular arrhythmias, and life-threatening ventricular arrhythmias developing post acute myocardial infarction;

2) To produce an overall summary estimate of effectiveness and probabilities of incidence of adverse effects, which can be useful for subsequent incorporation in cost-effectiveness analysis;

3) To validate the usefulness of various therapeutic outcomes implemented by general treatment guidelines.

OVERVIEW OF THESIS

A meta-analysis was carried out to compare the efficacy and safety of three antiarrhythmic agents (flecainide, sotalol, and amiodarone) in maintaining sinus rhythm after cardioversion of chronic atrial fibrillation. 42 of 119 clinical trials retrieved satisfied the predefined inclusion criteria. Data from 17 amiodarone trials (5 randomised, and 12 uncontrolled), 8 sotalol trials (6 randomised, and 2 nonrandomised), and 19 flecainide trials (8 randomised, 4 nonrandomised controlled, and 6 uncontrolled) were pooled separately after testing for homogeneity of treatment effect across the trials. Although the pooled rate difference in proportion of patients remaining in sinus rhythm between amiodarone and placebo (2 trials) was statistically nonsignificant (RD_{3mon} = 16.1%, 95% CI = -29.7 to 61.7, P>0.05), the pooled effect compared to Class IA drugs (3 trials) demonstrated significant differences at all time intervals (RDs were 20.5%, 31%, and 28.8% at 3, 6, and 12 months respectively). Aggregating sotalol efficacy data in randomised or nonrandomised controlled trials has yielded highly significant effect in favour of sotalol as compared to placebo and equal effect as compared to Class IA and Class IC at all time points. Furthermore, comparison of flecainide to placebo or Class IA has revealed a highly superior effect in favour of flecainide. The calculated summary statistics (OR_{Peto}, OR_{MH}, RD, and RR) for the incidence of mortality and proarrhythmia in the full-exposure group in

amiodarone and sotalol trials were not significant, affirming the safety of those two drugs. In flecainide placebo-controlled trials, the OR_{MH} for mortality and proarrhythmia were 1.8 (95% CI, 1.2-2.7, P=0.002), and (95% CI, 4.23-10.6, P<0.001) respectively, thus indicating low benefit-risk ratio for flecainide as compared to amiodarone. The validity of this meta-analysis was examined by assessment of publication bias using funnel-plots. A funnel-plot of the amiodarone clinical trials displayed the shape of an 'inverted funnel', thus suggesting an evidence of low retrieval bias. However, due to the small sample size identified (18 trials only), a firm conclusion with regard to absence of publication bias could not be drawn.

Evolving strategies for management of newly occurring supraventricular arrhythmias were reviewed. A meta-analysis was undertaken to determine the most effective agent for prompt cardioversion to sinus rhythm. Flecainide efficacy relative to placebo was confirmed by pooling data from 5 placebo-controlled trials (OR_{3hrs}, 7.2; 95% CI, 4.7 to 11.1; Z=8.9; and OR_{8hrs}, 5.5; 95% CI, 3.6 to 8.4; Z=7.85). However, pooling the data from three amiodarone, placebo-controlled trials at 3 and 8 hour-intervals demonstrated a nonsignificant effect (OR_{3hrs}, 1.3; 95% CI, 0.7-2.4; Z=0.85; and OR_{8hrs}, 1.03; 95% CI, 0.6-1.8, Z=0.12). All individual odds ratios for intravenous sotalol compared to placebo were highly significant with pooled OR at 1 hour of 8.8 (95% CI, 4.7-16.5; Z=6.8). The effect sizes of the three agents on mean ventricular response rate was estimated for both converted and unconverted patients. Whilst the effect size of flecainide versus placebo was not statistically significant at any time point, those of sotalol and amiodarone were statistically and clinically meaningful for both converted and unconverted patients. It is suggested that for acute cardioversion, intravenous flecainide or sotalol should be initially implemented. Intravenous amiodarone can be subsequently introduced for controlling the ventricular rate in persistent unconverted patients.

Recent meta-analyses of randomised controlled trials of secondary prevention of myocardial infarction by antiarrhythmic agents have questioned the validity of using arrhythmia suppression as a substitutive end point for mortality. A meta-analysis examining the effect of sotalol and amiodarone for prevention of death post acute myocardial infarction was undertaken. In addition to single point estimates of pooled odds ratios of total mortality and sudden death, a meta-analysis of survival data which included censored end points was employed. An attempt was made to reconstruct the life tables in individual trials of amiodarone. The Kaplan-Meier percentages were recalculated and pooled at specific time points to reproduce the final meta-analytic survival curves of total mortality and sudden death. The meta-analysis confirmed the clinical efficacy of amiodarone for prolonging the survival in patients with congestive heart failure or myocardial infarction. The nonparametric log-rank odds ratio method was applied to raw actuarial data deduced from published Kaplan-Meier graphs as well as data generated by curve fitting. Pooling each set of data separately has yielded highly significant log-rank ORs for total mortality in the first set of four trials with censoring (log-rank OR at 102 months, 0.598; 95% CI, 0.43 to 0.83; Z = -3). However, log-rank ORs from data generated by curve fitting of data from a further three trials, were nonsignificant up to 48 months (log-rank OR, 0.87; 95% CI, 0.72 to 1.06, Z = -1.4). Merging of the two data sets has suggested strong evidence of efficacy for improving survival in terms of both total mortality and sudden death.

CHAPTER ONE

CARDIAC ARRHYTHMIAS

1.1 INTRODUCTION

Disturbances in cardiac rhythm are a common problem in clinical practice and a number of drugs are available to treat these disorders. To understand how these drugs work it is essential to understand the electrical properties of cardiac cells, and the genesis of the arrhythmia. This chapter presents a brief description of the electrophysiological characteristics of cardiac cells. Some universal definitions and classifications of arrhythmias are introduced. The main mechanisms by which arrhythmia develops are delineated and the various techniques for the assessment of arrhythmia are described as follows:

1.2 Electrophysiological Properties of Cardiac Cells

1.2.1 Action Potential

There is a voltage difference referred to as the resting membrane potential across the cell membrane of all types of cardiac cells. This membrane potential is caused by an uneven distribution of ions (principally sodium, potassium, and calcium) across the cell membrane (Neal, 1992; Scott, 1994). The membrane potential of specific cells in the myocardium gradually and spontaneously decreases (depolarises, or becomes less negative) over time. The exact mechanism for this alteration remains unclear, but it possibly involves small changes in the flux of sodium and potassium ions. Principally, the cell membrane is permeable to potassium ions, but is relatively impermeable to sodium and calcium. The potassium ions continue to diffuse out of the cell until the resting concentration gradient of the normal cardiac cells is reached (usually sodium/potassium = 0.01 to 0.07 mM/litre). The outward movement of potassium ions is impaired by fixed negative charges inside the cell presumably proteins and polypeptides which are two large to diffuse out of the cell, thus tend to attract potassium ions. The intracellular potential at which the net passive flux of potassium ions equals zero is called the equilibrium potential for potassium or intracellular potassium. The movement of other ions is subsequently modulated by this phenomenon. Eventually, if the cell is allowed to depolarize to a certain critical voltage (the threshold potential), a full blown action potential results. The action potential is composed of five phases (Bigger, 1994). The dominant ion movement in each phase is illustrated in Table 1.1 and Figure 1.1.

Table 1.1 Phases of Cardiac Action Potential

Phase	Dominant ion movement
0	Fast sodium inward / rapid depolarisation
1	Transient potassium outward / partial repolarisation
2	Slow calcium inward / slow repolarisation
3	Fast potassium outward / rapid repolarisation
4	Sodium inward and potassium outward / resting potential

The period between phase 0 and midway through phase 3 is called the effective refractory period during which the cell cannot be depolarised or conduct an impulse. The long refractory period of cardiac fibres normally protects them from re-excitation during a heart beat. Afterwards, the cell is repolarised to its baseline level due to fast outward flow of potassium at the end of phase 3.

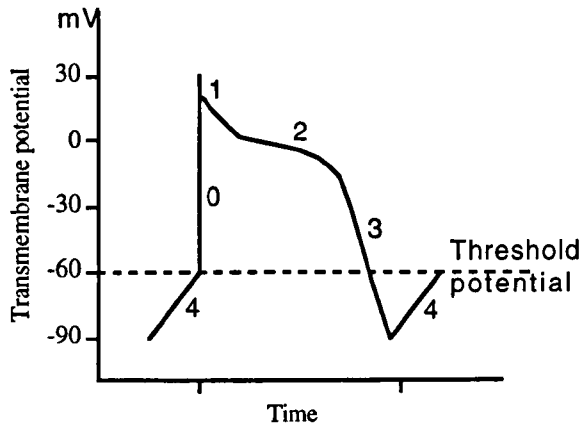

Figure 1.1 Schamtic representation of cardiac action potential

1.2.2 Automaticity and Sinus Rhythm

The process of spontaneous depolarization is referred to as automaticity (or pacemaker activity). This phenomenon normally occurs in tissues comprising the *Sinoatrial* node (SAN), *Atrioventricular* (AV) node, *bundle of His*, and the *Purkinje fibres*. Under

certain pathologic conditions, nonpacemaker tissues can assume the property of spontaneous depolarization leading to dysrhythmias. Different pacemaker cells possess different intrinsic rates of depolarization, and thus different levels of automaticities. The SA node is the normal pacemaker of the heart and possesses the fastest, intrinsic rate followed by the AV node and the ventricular Purkinje fibres (Singer *et al.*, 1967).

In a normal heart, the SA node depolarises rapidly and steadily until it reaches a threshould potential at which it generates an impulse. The impulses are conducted from the SA node across the atria to the AV node and then down the bundle of His to Purkinje fibres and ventricles (Bigger, 1994). This is referred to as *sinus rhythm.* However, under pathologic conditions, certain nonpacemaker cells are allowed to reach their thresholds earlier and initiate a wave of depolarization (Noble, 1979; DiFrancesco, 1981).

1.3 Relationship of the Electrocardiogram to the Anatomy of Cardiac Conduction System

The electrical activities induced by the conduction of impulse to myocardial tissue and its subsequent depolarisation and repolarisation can be recorded by the surface electrocardiogram (ECG) (Myerburg *et al.*, 1994). The ECG is practical in providing indications to the nature and cause of an arrhythmia (Figure 1.2) (Scott, 1994).

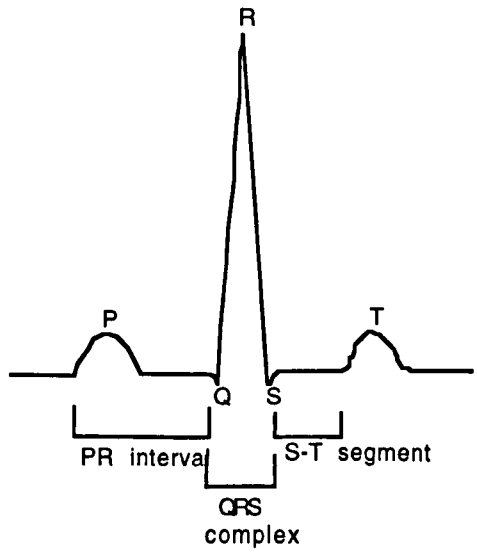

Figure 1.2 Electrocardiogram (ECG)

The P wave depicts atrial depolarization and the QRS complex represents ventricular depolarization. The interval between the two (PR interval) is the time required to conduct the beat through the AV node which is prolonged in AV block. The QRS complex is usually narrow when the impulses to the ventricles are initiated from above (SAN), and wide when they are originating from an ectopic site. The T wave designates ventricular repolarization, thus a QT interval is a measurement of the duration of depolarisation and repolarisation of the ventricular myocardium. QT interval may be modified by some drugs such as class III antiarrhythmics (Scott, 1994). A prolonged QT interval referred to as QTc (usually more than 0.38 seconds) predisposes to a pathological condition characterised by polymorphic QRS complex due to fast ventricular rhythm. This condition is termed torsades de pointes.

1.4 Definition of Arrhythmia

Arrhythmia is an abnormal cardiac rhythm which consists of cardiac depolarizations that deviate from normal sinus rhythm in one or more aspects: there is an abnormality in the site of origin of impulse, its rate or regularity, or its conduction (WHO/ISC Task Force, 1978).

1.5 Mechanisms of Arrhythmias

Many factors can precipitate or exacerbate arrhythmias: ischemia, hypoxia, acidosis or alkalosis, electrolyte abnormalities, excessive catecholamine exposure, autonomic influences, drug toxicity (e.g. digitalis intoxication) and the presence of scarred or otherwise diseased tissue (Hoffman *et al.*, 1964). However, all arrhythmias result from disturbances in impulse formation, impulse conduction, or both (Waldo and Wit, 1994).

Disturbances in Impulse Formation

Abnormal impulse formation can originate from a normal pacemaker site (sinus node) or at an abnormal pacemaker site (ectopic site). Examples of arrhythmia caused by abnormal impulse formation at the normal pacemaker site include *sinus tachycardia* and *sinus bradycardia*. Arrhythmias originating from a site other than the sinus node (ectopic site) occur under several conditions. If the rate of the sinus node discharge is

especially slowed, other cells possessing automaticity (cells of the electrical conducting system) and atrial or ventricular muscle cells, which do not possess the ability to depolarize simultaneously, may be allowed to reach a threshold and initiate a beat. In addition, automaticity of such tissues may be enhanced by reduced level of membrane potential which may lead to partial or complete inactivation of the fast inward sodium current, and thus, the upstroke of action potential will be primarily due to inward calcium current (Grant, 1992).

Disturbances in impulse conduction

Severely depressed conduction may result in several, easily recognised arrhythmias (for example, atrioventricular nodal block, bundle branch block. A more subtle, common abnormality of conduction is re-entry, in which one impulse re-enters and excites areas of the heart more than once. Three main conditions must coexist for initiation of re-entry (Myerburg *et al.*, 1994). Firstly, there must be an obstacle (anatomic or physiologic) to homogenous conduction, thus establishing a circuit around which the re-entrant wavefront can propagate. Secondly, there must be unidirectional block at some point in the circuit. Thirdly, conduction time around the circuit must be long enough so that the impulse does not enter refractory tissue as it travels around the obstacle. Thus, the conduction time must exceed the effective refractory period.

1.6 Classification of Arrhythmia

A simple and useful way to classify rhythm disorders is by anatomic location of the disorder. Arrhythmias, originating in the SA node, atrial muscle, AV node or His bundle, occur above the ventricles and may be classified as *Supraventricular* arrhythmias. This includes sinus bradycardia, paroxysmal atrial tachycardia, atrial flutter, and atrial fibrillation. Arrhythmias originating from ventricular tissue may be classified as ventricular arrhythmias.

1.6.1 Supraventricular Arrhythmias

1.6.1.1 Atrial Fibrillation

Atrial fibrillation is the most frequently sustained arrhythmia, and it was termed by cardiologists as "grandfather of the arrhythmia" due to its old recognition (Selzer,

1982). Later on, due to its high prevalence in the elderly population, it was regarded as the "arrhythmia of grandfathers" (Meijler and Wittkampf, 1991).

1.6.1.1.2 Definition

The definition of atrial fibrillation according to WHO-ISFC task force is "an irregular, disorganised, electrical activity of the atria. P waves are absent and the baseline consists of irregular wave forms which continuously change in shape, duration, amplitude and direction" (WHO/ISC Task Force, 1978).

1.6.1.1.3 Epidemiology and Risk Factors

A number of conditions were reported to be associated with atrial fibrillation (Kannel *et al.*, 1982; Kannel *et al.*, 1983). Some of these conditions are listed in Table 1.2. The presence of rheumatic heart disease was found to be the most powerful predictor of risk of atrial fibrillation followed by the presence of heart failure, hypertensive heart disease, and coronary heart disease (Kannel and Wolf, 1992).

Table 1.2 Cardiovascular and Noncardiovascular Precipitants of Atrial Fibrillation

Etiologic Category	Disease State or Drug
Cardiovascular	Mitral valve disease Congestive cardiomyopathy Coronary artery disease Myocardial infarction Hypertension Pericarditis Cardiac surgery
Pulmonary	Pulmonary embolus Pneumonia Chronic obstructive pulmonary disease (cor pulmonale)
Endocrine	Hyperthyroidism Pheochromocytoma
Drugs	Alcohol Methylxanthines Sympathomimetics Amphetamines

1.6.1.2 Atrial Flutter

Atrial flutter is another form of supraventricular arrhythmia with more rapid, regular rhythm than atrial fibrillation (Waldo, 1987). There are two types of atrial flutter: type I (classical) and type II (very rapid). Type I atrial flutter is characterised by a range of atrial rates from 240 to 340 beats/min, and type II atrial flutter by a range of 340 to 433 beats/min (Waldo and Maclean, 1980; Wells *et al.*, 1979). Both types are not usually persistent, and frequently revert to sinus rhythm or atrial fibrillation either spontaneously or as a result of therapy (Bellet, 1963). Its clinical significance is primarily due to its association with a rapid ventricular response rate, thus leading to severe symptoms.

1.6.2 Ventricular Arrhythmias

1.6.2.1 Prevalence

A number of studies have demonstrated that simple ventricular arrhythmias are common in the general population and may be observed in 35%-50% of healthy young adults during ambulatory ECG monitoring (Bigger, 1983; Messineo, 1989). However, the incidence of ventricular arrhythmia increases with age in subjects both with and without clinically evident heart disease (Hinkle *et al.*, 1974). Moreover, several studies have suggested significantly greater chance of severe ventricular arrhythmia with ventricular scarring due to infarction, hypertrophy, or infection. In addition, it may be triggered or aggravated by exercise due to increased sympathetic activity and heart rate (Bigger, 1983).

1.6.2.2 Clinical and Diagnostic Subclassification

Ventricular arrhythmias can be classified into four main clinical categories which are defined as follows (Anderson, 1994):

i. Ventricular fibrillation, characterised on the EGG by irregular undulations of various sizes and number.
ii. Non-sustained ventricular tachycardia (VT) which is defined as three or more consecutive ventricular premature beats at a rate of >120/min and lasting <30

seconds.

iii. Sustained VT which is defined as three or more consecutive ventricular premature beats at a rate of >120/min, continuing for >30 seconds or requiring termination before this time because of haemodynamic instability.

iv. Simple ventricular ectopic activity may be defined as ventricular premature beats (VPBs) that exhibit a simple QRS morphology (uniform or unifocal VPBs). This may occur in an isolated or nonrepetitive pattern rather than in pairs or salvos, and occur beyond the T-wave of the preceding QRS complex.

1.6.2.3 Prognostic Subclassifications

Ventricular arrhythmia has recently been divided into risk categories of benign, prognostically important (potentially malignant), and malignant for purposes of risk assessment and clinical management (Bigger, 1983; Anderson, 1990; Morganroth, 1993). This classification of ventricular arrhythmia was based primarily on the risk of sudden cardiac death associated with the ventricular arrhythmia, and depended less on the actual form of ventricular arrhythmia (Morganroth *et al.*, 1984).

Benign Ventricular Arrhythmias

The arrhythmia would be considered benign if the patient had ventricular tachycardia which did not produce hemodynamic consequences, and was associated with a normal left ventricle. This type of arrhythmias would be in the form of ventricularly premature complexes and episodic nonsustained ventricular tachycardia (NSVT). They are not often associated with any presenting symptoms, and there is no evidence of any major increase in the risk of mortality. Therefore, there would be no indication for drug therapy, since no benefit could be expected from suppressing the arrhythmia. Patients who fall in this group are usually without any underlying, structural heart disease.

Malignant Ventricular Arrhythmias

At the other end of the spectrum are patients with malignant or lethal ventricular arrhythmias, which are associated with the highest risk of sudden cardiac death due to severe hemodynamic consequences which include definite presyncope, angina, heart failure, syncope or cardiac collapse. This type of ventricular arrhythmia is usually in the form of sustained ventricular tachycardia and/or ventricular fibrillation. In contrast to benign arrhythmia, aggressive treatment of malignant arrhythmias has been

emphasised for immediate relief of hemodynamic symptoms and subsequent prevention of sudden cardiac death. The majority of these patients have serious left ventricular dysfunction (mean left ventricular ejection fraction (LVEF), approximately 30% or less) (Anderson *et al.*, 1990).

Potentially Malignant Ventricular Arrhythmias

The most complex part of the spectrum between benign and malignant ventricular arrhythmias embraces patients with potentially lethal ventricular arrhythmias, which are characterised by a grade increase in risk of mortality due to left ventricular dysfunction and the presence of VPCs and/or NSVT. Patients in this spectrum are different from those in the benign ventricular arrhythmia group, since they have some mild structural heart disease. They also differ from malignant ventricular arrhythmia because they do not have any significant hemodynamic symptoms. These patients may occasionally feel palpitations or dizziness, but the majority are unaware of even frequently occurring PVCs.

1.7.3 Arrhythmias following Cardiac Surgery

Cardiac arrhythmias are the most common, significant postoperative complications of cardiac surgery which requires cardiac consultations (Table 1.3). Atrial fibrillation is probably the most frequent type of significant arrhythmia following both valvular and coronary artery bypass grafting (CABG) (Ormerod *et al.*, 1984). Although ventricular arrhythmias are less frequent (Abedin *et al.*, 1977), postsurgically sustained ventricular tachycardia and ventricular fibrillation are still regarded life-threatening events which will demand long-term treatment.

Table 1.3 Incidence of Arrhythmias after Cardiac Surgery (Abedin *et al.*, 1977)

Type of Arrhythmia	Incidence (%)
Atrial fibrillation	5-40
Nonsustained ventricular ectopy	36
Sustained ventricular ectopy	0.5-1.5
Bundle branch block	17-45
Complete AV block	≤4

1.8 Techniques for Assessment of the Arrhythmia

1.8.1 Electrocardiogram (ECG)

ECG is the most commonly employed cardiovascular laboratory technique which is non-invasive, simple to record and highly reproducible (Fisch, 1995). However, despite its high sensitivity and specificity for diagnosis of arrhythmia, it has drawbacks. It only detects the activity voltage of atrial and ventricular myocardium, without recording the electrical activity of more specialised tissue on which the mechanism of arrhythmia is most commonly dependent. Thus, a single accurate arrhythmia mechanism, or diagnosis may not often be obtained.

1.8.2 Ambulatory (Holter) Electrocardiography

In contrast to previous standard ECG, continuous examination of the patients over an extended period of time under different physical and psychological conditions is significant (Kennedy, 1995). Moreover, due to its higher sensitivity, the detection of transient, widely variable cardiac arrhythmia is possible. In addition, it has been widely employed for assessment of management of arrhythmia in clinical trials.

1.8.3 Exercise Testing

Exercise testing is an established tool for assessment of patients with heart diseases (Podrid, 1995). Exercise causes several physiologic changes due to sympathetic stimulation leading to an increase in heart rate, systolic blood pressure, and myocardial contractility. These alterations cause an increase in myocardial oxygen demand, and myocardial ischemia in patients with impaired oxygen delivery. This ischemia can provoke clinical arrhythmia due to disturbance in impulse conduction. However, exercise testing is of significant value for detecting arrhythmia in patients with transient symptoms when other techniques fail to detect the cause. It is also useful for exposing harmful drugs effects such as proarrhythmia, which will be discussed later in Chapter Two.

1.8.4 Invasive Cardiac Electrophysiology Studies

The newer intracardiac electrophysiological studies provide more detailed analysis of the mechanism underlying the cardiac arrhythmia. As a result, it enables clinicians to: 1) produce a more accurate diagnosis, 2) assess the prognosis, 3) and initiate antiarrhythmic treatments on a more logical basis (Zaim *et al.*, 1995).

In these tests, a pacing catheter is placed in the patient's right atrium and ventricle. Single or repeated pulses of electrical current are given at various times within the cardiac cycle to induce premature ventricular depolarization (Podrid, 1985; Zaim *et al.*, 1995). The end point of stimulation may include induction of sustained ventricular tachycardia, non-sustained ventricular tachycardia or fibrillation. Once the arrhythmia has been reproducibly induced, an antiarrhythmic drug is administered and the procedure is repeated. Failure to induce the arrhythmia after drug administration is strongly predictive of long-term efficacy of the drug. Enhanced induction or induction in a patient who was previously uninducible indicates a proarrhythmic drug effect. After a washout period, another drug is evaluated.

In the next chapter we will examine the various treatment options.

CHAPTER TWO

PERSPECTIVES ON THE CURRENT TREATMENTS OF CARDIAC ARRHYTHMIAS

2.1 INTRODUCTION

Therapeutic modalities of cardiac arrhythmias have grown far more complex in recent years compared to simple approaches of the past (Vaughan Williams, 1984). Our understanding of the various factors predisposing to arrhythmia, and of electrophysiological mechanisms involved in receptor and channel function in the myocardium, has advanced substantially over recent years (Vaughan Williams, 1989; Task Force of the Working Group on Arrhythmias of the European Society of Cardiology, 1991; Vaughan Williams, 1992; Ahmed and Singh, 1993; Singh, 1996). Clinicians can now select from 80 agents licensed for a wide range of antiarrhythmic indications. Generally, antiarrhythmic drugs are initiated with two aims (Morganroth, 1993):

- reducing the frequency of recurrence of symptomatic arrhythmias, thus improving the quality of life of the patient.

- to prolong life in patients with potentially lethal arrhythmias.

However, these potential benefits are rarely devoid of serious risks (Roden, 1994). Thus, a general understanding of the pharmacology of these drugs and factors which modify their benefit:risk ratios is important.

In addition to pharmacological therapy, several nonpharmacological interventions have been introduced. These include electrical cardioversion, permanent pacemakers, surgery, and implantation of cardioverter-defibrillator (Anderson, 1994). Drug therapy, however, remains the most common approach but there has been increased concern about its efficacy, safety, and cost-effectiveness.

The aims of this chapter are firstly to clarify the various Classifications of antiarrhythmic drugs, related pharmacological and electrophysiological phenomena and secondly, to delineate major reported complications of those drugs.

2.2 Classifications Of Antiarrhythmic Drugs

The actions of antiarrhythmic drugs have been classified by several means. Each

approach has its strengths and limitations. Most commonly employed approaches were devised by Vaughan-Williams classification and Sicilian Gambit (Task Force of the Working Group on Arrhythmias of the European Society of Cardiology, 1991; Vaughan Williams, 1984; Vaughan Williams, 1989; Vaughan Williams, 1992).

2.2.1 Vaughan-Williams Classification

This system categorises antiarrhythmic drugs into five main classes, according to their cellular electrophysiologic effects on the action potential of various tissue models as shown in Table 2.1 (Vaughan Williams, 1992; Hondeghem, 1995; Siddoway, 1995). The primary sites of drug action in this classification are the ion channels (sodium, potassium and calcium channels) and the receptors (mainly ß receptors).

Table 2.1 Vaughan-Williams classification of antiarrhythmics (Siddoway, 1995)

Class	Membrane Effect	ECG Effect	Drugs
IA	Sodium channel block, intermediate kinetics, potassium channel block	↑ QRS, ↑ QT (intervals)	Quinidine Procainamide Disopyramide
IB	Sodium channel block, rapid kinetics	↓ QT interval	Lidocaine Tocainide Mexiletine
IC	Sodium channel block, slow kinetics	↑↑ QRS interval	Flecainide Propafenone Moricizine Cibenzoline
II	ß-Receptor inhibition	↓ HR, ↑ PR interval	Propranolol
III	Potassium channel block	↑ QT interval	Bretylium Amiodarone Sotalol
IV	Calcium channel block	↓ HR, ↑ PR interval	Verapamil Diltiazem
V	Time-dependent block of inward current activated by hyperpolarisation (I_h)	↓ HR	Alinidine
Digitalis	Sodium, potassium--ATPase inhibition	↑ PR, ↓ QT interval	Digoxin Digitoxin
Adenosine	A_1-Receptor agonist	↓ HR, ↑ PR interval	Adenosine

↑, increase; ↓, decrease; ECG, electrocardiogram; HR, heart rate

2.2.1.1 Class I Antiarrhythmic Agents

The subdivision of Class I drugs, which are all sodium channel blockers, into subclasses IA, IB, and IC was mainly based on three pharmacodynamic theories: electrical modulation of channel activity, use dependence, and onset / offset kinetics (Vaughan Williams, 1992; Hondeghem, 1995).

Sodium channels are usually modulated into three states according to membrane potential in a time-dependent mode. During each action potential, the channels are transiently open (activated) during phase 0, inactivated during the phases 1 and 2, and during the repolarisation in phases 3 and 4 they are rested. Class I drugs possess high affinity for the sodium channels in the activated and inactivated states, and low affinity in the resting stages (Hondeghem and Katzung, 1977). Two mechanisms have been proposed to show how drugs reduce the inward sodium current through the channels; modification of the voltage dependent behaviour of the channel (Class Ib) and/or blocking the channel (Class Ia and Class Ic).

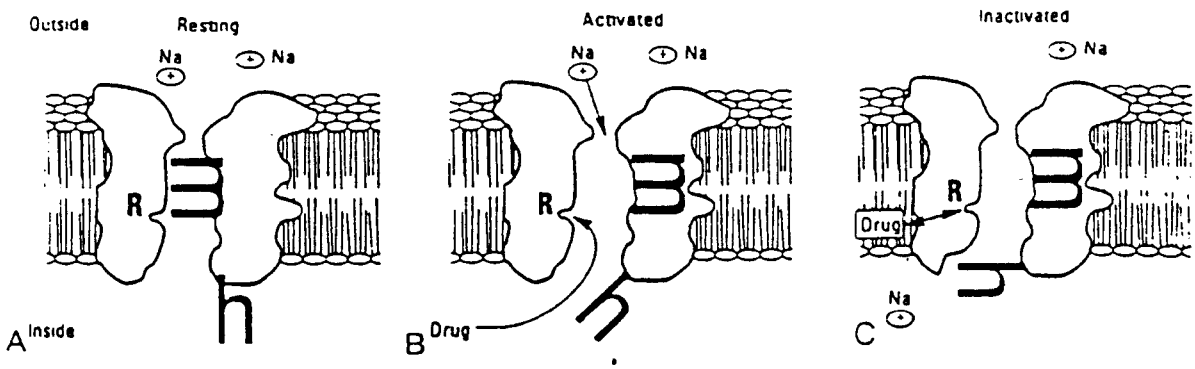

Figure 2.1 Schematic representation of the electrical modulation of cardiac sodium channel (adapted from Hondeghem, 1995).

2.2.1.1.1 Use Dependence and Onset / Offset Kinetics

Since blocking of the channels occurs only during the activated and/or inactivated states

with each action potential, and dissipates by the end of depolarisation when the channels are inactivated, the degree of blocking is thought to increase the higher the intensity of the channel usage per unit time. This phenomenon which is termed *use dependence* accord the drugs to affect abnormal premature diastole rather than normal sinus rhythm.

However, the level of use-dependent blocking by various Class I subdivisions is based on the speed of their attachment to, and detachment from the sodium channels (Vaughan-Williams, 1989). Until the *onset / offset kinetics* (receptor binding kinetics) of these agents were examined, a distinct explanation for the reported increase in arrhythmic mortality associated with Class Ic drugs in The Cardiac Arrhythmia Suppression Trial was not possible (Vaughan-Williams, 1992). Class Ic were found to have slow-in/slow-out (SISO) kinetics, thus resulting in excessive levels of block, while Class Ia and Ib drugs produced intermediate blocking with fast onset/offset kinetics respectively (Hondeghem, 1995).

2.2.1.1.2 Selectivity, Efficacy and Potency

Selectivity of an antiarrhythmic agent may be defined as the ability to interfere with a certain arrhythmia in more than 99% of cases, while with normal sinus rhythm in less than 1% of cases (Hondeghem, 1995). Efficacy indicates the maximum effect that the drug can produce, while potency refers to the concentration required to achieve 50% of the maximum effect. It was reported that Class I agents in general have poor selectivity, particularly against tachycardias. Thus, they would be frequently proarrhythmic. Furthermore, although Class Ic (flecainide and encainide) were extremely potent (producing significant blocking during normal sinus beat at a very low concentrations), they fail to suppress the tachycardia effectively. Consequently, effective concentrations of Class Ic would be expected to be highly toxic.

2.2.1.2 Class II Antiarrhythmic Agents

Several beta-adrenergic blockers are now approved as Class II antiarrhythmic agents (Frishman and Cavusoglu, 1995). Beta-blockers are commonly marketed as racemic mixtures, with the beta-blocking activity mainly found in the levorotatory isomer (*l*). The dextrorotatory (*d*) isomer possess no clinical effect except for *d*-sotalol, which has Class III antiarrhythmic activity, and *d*-propranolol, which has Class I (quinidine-like)

membrane stabilising activity (Frishman, 1981).

Three major mechanisms have been proposed for the antiarrhythmic effect of beta-blockers. The first and major effect results from a catecholamine inhibitory effects leading to inhibition of pacemaker potential and depression of excitability and conduction. The second, an electrophysiologic effect is due to a membrane stabilising 'local anesthetic' activity. The third effect which is a Class III antiarrhythmic activity is specific for sotalol. However, the antiarrhythmic effectiveness of beta-blockers is primarily due to beta-blockade, with the membrane stabilising activity being clinically nonsignificant. The later effect is only manifested at excessive propranolol doses, and many other beta-blockers devoid of this activity are clinically effective (Frishman and Cavusoglu, 1995).

Although beta-blockers have different selectivity for blocking $ß_1$ and $ß_2$ receptors, they show no differences in their antiarrhythmic potencies (Frishman, 1981).

2.2.1.3 Class III Antiarrhythmic Agents

Class III antiarrhythmic agents block outward flow through potassium channels, consequently slowing repolarisation of the cell and prolonging the duration of the action potential and the effective refractory period (Siddoway, 1995). In addition, some agents (amiodarone and sotalol) have Class II antiadrenergic actions. Two major drawbacks characteristic of these agents are reverse use-dependence and *torsades de pointes*.

2.2.1.3.1 Reverse Use-dependence

Unlike Class I agents which exhibit use-dependence (more intense blocking at higher heart rates), most new Class III agents, including sotalol, displayed a reverse use-dependence phenomenon (Lazzara, 1996). Reverse use-dependence implies that they tend to substantially prolong the action potential at slow heart rates (normal sinus beat), and their effect declines at fast heart rates (tachycardias) (Hondeghem, 1995). In addition, an excessive effect appeared following a long diastolic interval. This may be responsible for their proarrhythmic actions. The mechanism by which these agent prolong the action potential is not entirely resolved. Amiodarone is an exception in that it uniformly lengthens the action potential irrespective of heart rate (Naccarelli and

Dougherty, 1995).

2.2.1.3.2 Torsades de pointes

This type of proarrhythmia occurs as a result of excessive prolongation of the QT interval, which triggers premature ventricular contractions (PVCs) and ventricular tachycardia (Lazzara, 1996).

2.2.1.4 Class IV Antiarrhythmic Agents

Class IV antiarrhythmics primarily act by blocking the slow calcium channels, thus causing a depressant effect on the SA and AV nodes which are depolarised predominantly due to the inward calcium currents (Singh, 1995). This depressant effect involves an increase in refractoriness. However, not all calcium channel blockers are antiarrhythmics. For example, nifedipine and other calcium antagonists with a selective action on blood vessels, despite blocking calcium current in nodal cells, can cause a reflex sympathetic stimulation due to their negative inotropic effect on other myocardial and vascular smooth muscle cells. These lead to an increase in heart rate and shortening of duration of the action potential (Vaughan-Williams, 1992).

2.2.1.5 Other Antiarrhythmic Agents

Some drugs possessing antiarrhythmic effects are not described in the Vaughan-Williams Classification scheme. For example, adenosine and digoxin (Vaughan-Williams, 1992). Adenosine is a cardioselective cholinergic agonist which produces a depressant effect on nodal tissues (Siddoway, 1995). Digoxin induces blocking of sodium-potassium ATPase, thus causing an increase in intracellular sodium and calcium, leading to enhancement of myocardial contractility and reduction of AV conduction (Siddoway, 1995).

2.2.2 How Useful is the Vaughan-Williams Classification?

Although the previous classification is widely used by clinicians, the following criticisms have recently been raised (Task Force of the Working Group on Arrhythmias

of the European Society of Cardiology, 1991; Ahmed and Singh, 1993):

1. A drug in one class may produce multiple class effects. For example, it is not known which class action determines amiodarone's efficacy in prevention of mortality prior to myocardial infarction.

2. The classification does not take into account the effect of active metabolites which may have diverse actions from their 'parent' drugs. For instance, *N*-acetylprocainamide which is the major metabolite of procainamide (Class I drug) produces a Class III effect. As a result, the clinical effect manifested during procainamide therapy may be dependent on relative concentration of the two compounds. This is again determined by other factors such as genetically determined drug metabolism pathways (Siddoway, 1995).

3. The classification, with the exception of Class II drugs, is essentially based on electrophysiological studies using isolated, normal cardiac tissues. In diseased tissues, the channels and receptors are modified, and the actions of drugs on these tissues may not be firmly predicted.

However, the classification is still worthwhile. Drugs in one class share similar toxicity profiles (Siddoway, 1995). For example, drugs delaying conduction (Class I, III, or IV) would be contraindicated in diseases characterised by conduction disorder, while drugs prolonging the QT interval (Class IA or III) would exacerbate the proarrhythmia in patients with pre-existing QT prolongation.

2.2.3 Sicilian Gambit

To overcome the problems highlighted in Vaughan-Williams classification, the "Sicilian Gambit" framework was developed in an attempt to link the cellular electrophysiologic action of antiarrhythmic drugs to their observed clinical efficacy in humans (Task Force of the Working Group on Arrhythmias of the European Society of Cardiology, 1991; Ahmed and Singh, 1993). This approach uses three alternative levels for classification: classification at the molecular level, classification according to effect on different types of human arrhythmias, and classification on the basis of effect on measurable clinical parameters.

Although the "Sicilian Gambit" provides a useful theoretical framework to which new

knowledge can be added, and from which ideas regarding drug development can be gained, Vaughan-Williams (1992) has criticised its limited clinical utility due to the following (Vaughan-Williams, 1992):

1. The molecular basis used is deemed more practical for basic scientists rather than clinicians.

2. Classification based on type of human arrhythmias would lead to a large number of diagnostic classes. Secondly, drug efficacy differs for evenly morphologically similar arrhythmias. Moreover, only a limited number of studies have involved interindividual comparisons of drugs in the same setting, and different mechanisms might lead to the same "phenotype" of arrhythmia on the surface electrocardiogram.

3. The third level of classification depends on defining the mechanism of an arrhythmia and to predict the "vulnerable clinical parameters" that can be targeted by specific ion current. However, in clinical practice, a definite mechanism for most arrhythmias is difficult to define, and if known cannot be instantly correlated to cellular electrophysiology. In addition, this new classification system is very similar to the old Vaughan-Williams classification.

For the present, rejecting the conventional classification of antiarrhythmics seems unreasonable and consideration of the two systems as complementary is worthwhile (Singh, 1996).

2.3 Complications Induced by Antiarrhythmics

The risks of antiarrhythmic therapy involve not only noncardiac side-effects and the potential for organ toxicity, but also cardiac effects, such as aggravation of arrhythmia, namely proarrhythmia and sudden death (Podrid, 1985; Morganroth, 1993).

2.3.1 Proarrhythmia

The term "*proarrhythmia*" or "*arrhythmogenicity*" is defined as "the capacity of cardiac or noncardiac drugs to aggravate an existing arrhythmia or provoke a new arrhythmia at therapeutic or subtheraputic level" (Kerin *et al.*, 1994). In 1987, it was agreed by a

group of European and American physicians at the American College of Cardiology meeting to employ the term *arrhythmogenesis* if aggravation of arrhythmias is due to any cause, and the term *proarrhythmia* for specific drug therapy (Morganroth, 1992). Proarrhythmia is described as "early" if it occurs within 30 days of treatment. Later on, with the evolution of new concepts on proarrhythmia, more detailed clinical definitions were proposed (Velebit *et al.*, 1982; Morganroth and Horowitz, 1984). Morganroth (1992) classified early proarrhythmia into two types:

1. Provocation types which include the new onset of:

   Ventricular premature complexes > 100 per day
   Nonsustained ventricular tachycardia
   Sustained ventricular tachycardia
   Polymorphic ventricular tachycardia
   Ventricular fibrillation

2. Aggravation types which include:

   Increased frequency of ventricular premature contractions or couplets
   Increased duration, frequency (rate increase ≥10%), or rate of ventricular tachycardia

A number of predisposing factors to proarrhythmia have been suggested; organic heart disease particularly, if patients are treated with Class Ic drugs, rapid high dose titration, the presence of atrial arrhythmias, or electrolyte imbalance (Kerin *et al.*, 1994; Morganroth, 1993).

2.3.2 Sudden Cardiac Death

The potential increase in likelihood of sudden death with antiarrhythmic therapy is a serious shortcoming, particularly if the benefit of treatment is considered to be very minimal, and especially in asymptomatic ventricular arrhythmias (Roden, 1994). Sudden death, which is also referred to as "late" proarrhythmia or arrhythmic death, is defined as "death restricted to a narrow time span, such as instantaneous death, death within less than 24 hours, or simply prehospitalisation death" (Segal *et al.*, 1985).

Thus, the definition should include three essential elements: a natural process, an unexpected occurrence, and a rapid development. The risk of arrhythmic mortality is markedly increased in the setting of myocardial infarction complicated with premature ventricular contractions, which may degenerate into serious sudden lethal arrhythmia (The Cardiac Arrhythmia Suppression Trial Investigators, 1989).

2.4 Aims and Objectives of This Thesis

This thesis summarises the research based-evidence for the effectiveness of common antiarrhythmic drugs in the management of three major types of arrhythmia:

(A) Acute, recent-onset supraventricular arrhythmia in medical and postsurgical patients.

(B) Chronic atrial fibrillation.

(C) Ventricular arrhythmias prior to or after acute myocardial infarction.

The aims of the quantitative work described in this thesis are:

2.4.1 To define and comment on the various therapeutic end points and treatment strategies employed for the various arrhythmias.

2.4.2 To summarise quantitatively the evidence on the efficacy of drugs used for each of the types of arrhythmias described above.

2.4.3 To undertake a risk and benefit assessment of antiarrhythmic drug therapy.

CHAPTER THREE

METHODS OF ANALYSIS AND CROSS DESIGN SYNTHESIS

3.1 INTRODUCTION

It is now recognised that the relationship between research findings and their implementation into practice is complex (Delamothe, 1994; Sacket and Cook, 1994). The question of how research findings are used has in itself become an exciting field for research and development (Fowkes and Fulton, 1991; McCormack and Levine, 1993). There is an increasing awareness that critical appraisal of information from medical literature would have important implications for the clinical management of patients and resources within the health system (Mulrow, 1994). Three barriers have been identified by clinicians in obtaining clinically important information. These are the lack of adequate time necessary for keeping up to date information, the use of out of date text books, and disorganised journals (Oxman, 1995).

In this chapter, the rationale for meta-analysis, the steps involved and the various statistical techniques applied, are discussed. These techniques have been assembled into 3 groups; firstly those which could be employed for combining primary studies even in the absence of complete sets of outcome data, secondly, those generated to combine studies with discrete data as outcomes and thirdly those which are ideal for combining outcomes expressed as continuous data. The problems and limitations associated with meta-analysis, particularly publication bias and missing data, are highlighted.

3.2 Definition of Medical Effectiveness

"Medical effectiveness" refers to the extent to which treatments achieve specific outcomes (Silberman *et al.*, 1992; Tones, 1997).

Silberman *et al.* (1992) have identified three major dimensions or sources of complexity which comprise the "effectiveness domain". These include the following:

(1) Variety of patients and forms of the disease. A treatment may be more effective for certain types of patients than others.

(2) Varying implementations of the treatment under investigation. A treatment may be less effective if it is executed in a less than optimal method.

(3) Different outcome measures. A treatment may seem to be more or less effective depending upon the particular type of outcome measure that is employed as an end point.

Accordingly, they stated that:

"*..A study that captures only a very limited number of points may not, by itself, adequately capture the full story or "truth" about the effectiveness of the treatment in question. If a rigorous scientific study includes only certain kinds of patients, only selected (perhaps optimal) forms of implementing the treatment, and a single outcome measure, that study can tell a small part of the story. Certainly, an equally scientific study of the same treatment could yield very different results if it highlighted different kinds of patients, implementations, and outcomes.*" As a result, clinical researchers aspired to improve the evaluation strategy and to develop optimal study designs for achieving greater coverage of the effectiveness domain, while maximising scientific rigor (Silberman *et al.*, 1992).

3.3 Efficacy versus Effectiveness

The term efficacy refers to the extent of benefit derived from a particular treatment under ideal circumstances of formal randomised clinical trials. On the other hand, effectiveness describes the degree to which a given intervention has achieved its goals under the prime conditions of the real word of clinical practice (Sinclair and Bracken, 1992; Tones, 1997).

In fact, two types of trial design were defined according to the objective undertaken. The first kind of study is termed the 'explanatory' trial, in which the principal question to be answered is '*Can* this treatment work?'. In the second type of study, the 'pragmatic trial', the main question addressed is '*Does* this treatment work?'. Thus, the explanatory trials aim to evaluate the 'efficacy' of a particular intervention when it is provided in ideal circumstances, while pragmatic trials tend to appraise the 'effectiveness' of the same form of intervention as it is manipulated in conditions that are similar to everyday practice (Chalmers, 1992).

The ultimate applicability of the results of a randomised trial is limited by the degree of modification of the patients inclusion criteria and intervention procedures as delineated

in the registered trial. Extrapolation of the results to broader limits is not always valid. Applicability depends on the type of outcome measures and efficacy end points which is targeted in a particular trial (Charlson and Horwitz, 1984). Many interventions can be evaluated using different outcomes. A reviewer should concentrate on the major outcomes of clinical significance and watch out for 'substitution game' or what has been called the 'surrogate markers', when a transitional outcome such as blood cholesterol level is substituted for a more relevant clinical outcome of heart attack, stroke or death (Sinclair and Bracken, 1992; Li Wan Po, 1996).

3.4 Study Designs

Over the past few years, a variety of studies with different designs have been employed to evaluate treatment effects. Each design, however, has characteristic strengths and weaknesses.

3.4.1 Early Approaches

In the past 150 to 200 years, the practice of medicine with regard to treatment effectiveness was primarily based on personal observations by individual clinicians, which reflects their expertise and sagacity to interpret the observed merits of treating a specific patient with a particular therapy (Sechrest and Figueredo, 1991). The advantage of this approach is that conclusions obtained are strengthened with clinically relevant experiences. However, this approach is associated with a number of weaknesses which may include the possibility that the observed outcomes are coincidental to the treatment, rather than induced by it (Silberman *et al.*, 1992).

Consequently, a more objective approach, which was termed the "numerical method", was developed (Louis, 1834; 1835). This method highlighted the significance of accurate recordings of treatments and numerical presentations of patient outcomes. Other controlled designs have been generated since. For example, historical control trials compare outcomes for patients currently receiving new treatment with historically recorded outcomes for patients who had previously received different treatments (Mike, 1982). The weakness of these studies derives primarily from the inadequacy to confirm that the observed effect is solely attributed to treatment.

3.4.2 Randomised Clinical Trials

In early 1920s, a significant controlled tool for comparing interventions was introduced in the form of randomised controlled trial (Fisher, 1935). Randomised clinical trial (RCT) depends on a chance process (randomisation) for assigning all individuals to two alternative treatments, therefore confirming that the only source of differences between the two groups, at baseline, will be chance (Chalmers, 1989; Armitage and Berry, 1994).

The employment of strict randomisation procedures prevents the possibility of investigators assigning healthier patients to the new treatment, and insures a statistical expectation of equivalence in the two groups (Peto *et al.*, 1993). Therefore, it would be appropriate to interprete any difference in outcome, which is larger than that which would be expected on the basis of chance alone, as a statistically significant indicator of a treatment effect (Peto *et al.*, 1993).

However, studies that claim to have assigned individuals to alternative forms of treatment may have become subject to selection biases if precautions have not been taken to secure true randomisation. Such biases can be introduced by selectively entering a candidate, depending on prior knowledge of the group to which they have been allocated, or selectively withdrawing him before complete formal registration. As a result, to ensure true randomisation, it is important that assignment is carried out by a central co-ordinating office and only after registration of all eligible candidates in the trial (Chalmers, 1989). Furthermore, the power of randomisation is greatly maximised by reducing the investigator bias when interpreting outcomes. A common suggestion to alleviate this bias is the use of the double-blind method, in which neither the investigator nor the recipient has any knowledge of which particular intervention is to be received. This method is essentially recommended when the outcome in question is of a subjective "soft" nature such as self-reported symptoms, rather than unambiguous "hard" outcomes such as death (Chalmers, 1989).

In spite of properly designing randomised controlled trials to reduce the potential of selection and observer bias, the results may still be misleading due to *random errors* resulting from the play of chance. This can occur as a result of falsely interpreting an important clinical difference between two interventions when it does not exist or interpreting no clinical difference when it does exists (Peto *et al.*, 1976). Random error

can be reduced by increasing the sample size.

Non-randomised clinical trials using historical or concurrent controls are more prone to bias. It has been shown that such designs were much more likely to find a treatment benefit than studies utilising randomised controls (Bracken, 1992). This was explained by the fact that the control groups in the historical control studies had worse outcomes than the controls in the randomised controlled studies, since they are usually constituted of patients with poor prognosis, non-compliant patients, or patients who have other adverse characteristics that might preclude them from enrolment in prospective randomised trials (Sinclair and Bracken, 1992).

Clinical trials are designed to answer a specific question or questions. Generally, these questions can be answered with two different approaches. The first approach has been given such names as *fastidious*, *explanatory*, and *intention-to-treat.* The second approach has been termed as *pragmatic* and *management* (Feinstein, 1983). The conflicts in the two approaches involve the choice of patients to be included in the trial, the comparative agent to be tested against the principal agent under investigation, the dosage regimen, the type of data used to show responses to treatment and the method of analysing the data after the trial has been completed. Explanatory trials address whether or not an intervention has any effects and how it produces its effects. This is usually tested by including a relatively homogeneous group of patients obtained with strict inclusion criteria (with similar gender and race, without any other associated diseases and concomitant medications). Fastidious (explanatory) investigators standardise the comparison by choosing placebo controls, double blind procedures and fixed regimens. Moreover, they tend to express the treatment outcomes as "hard" clinical endpoints and prefer to reduce the bias due to any personal or clinical decisions that are made after randomisation by using intention-to-treat analysis (Sackett and Gent, 1979). On the other hand, pragmatic trials are conducted not only to test if the intervention has any effects, but also to explain the consequences of its employment in similar aspects to ordinary clinical practice. As a result, a pragmatic designer will include heterogeneous populations of patients and favour to choose active controls with flexible regimens. In addition, intervention is evaluated using "soft" outcomes such as comfort and quality of life, which are more meaningful to the patients and their families. Despite all the conflicts that could arise, it may always be possible to justify both approaches when a trial is designed to satisfy questions to be answered.

The weaknesses of randomised studies are mainly due to their typically high cost.

Consequently, randomised studies have been conducted to formally evaluate relatively few medical interventions. Moreover, many trials were designed to enroll a limited subset of patients, and to answer only a specific question. However, it is uncertain that the results of such trials may be generalised to all patients.

3.4.3 Traditional Reviewing Techniques

A summary of the findings of a collection of individual research studies is called a review. A literature review is a fundamental scientific tool which is not new and plausibly employed in many research fields (Glass, 1976; Sackett *et al.*, 1991). Its rationale is based on four major concepts. Firstly, individual primary studies may contribute incomplete evidence of treatment effectiveness due to poor design and small sample size. Secondly, a particular study may include a narrow spectrum of patients which will make the generalisability of findings to other type of patients uncertain. Thirdly, large quantities of information are published annually in the literature which need refinement, evaluation, and synthesis. Mulrow (1994) stated *"systematic review separates the insignificant, unsound, or redundant deadwood in the medical literature from the salient and critical studies that are worthy of reflection"*. Finally, overviews facilitate integration of the serious portions of available medical information to make decisions about cost-effectiveness of certain treatment protocols and diagnostic tests (Sackett *et al.*, 1991; Haynes, 1992; Mulrow, 1994).

However, traditional reviewing techniques are qualitative in nature which means that formal statistical techniques are usually not applied. A survey of 50 review articles published in four major medical journals, conducted in 1987 by Mulrow, has shown that at that time the majority of medical reviews did not use scientific methods to identify, assess, and synthesise information. As a result, subjective narrative conclusions can be drawn. Further, with a traditional review, the process of identifying and including relevant studies is often performed selectively and unsystematically. Consequently, several reviewers often draw very different conclusions from the same set of studies. Chalmers (1982) has stated that 'in some instances, there is evidence that the conclusions reached by reviewers are based more on factors such as their training and how they make their living than on the available evidence'.

In recent years, many authors have recognised the imperfections associated with

traditional and informal reviews (Light and Smith, 1971; Cooper and Arkin, 1981; Peto, 1987; Fowkes and Fulton, 1991). Consequently, the technique of overview has evolved. This technique systematically retrieves all the primary studies. Sackett *et al.* (1991) elucidated that "*when a review strives to comprehensively identify and track down all the literature on a topic, we call it an overview.*"

The systematic review process attempts to make reviewing practices distinct and it is based on objective procedures rather than personal judgment rules. The reviewer describes how primary studies were identified, and defines the objectives and criteria for inclusion or exclusion of the primary studies to increase the reliability and representativeness of the review (Oxman and Guyatt, 1988; Sackett *et al.*, 1991). Different reviewers using the same research and analytic strategy should arrive at the same conclusion.

The *magnitude* of the findings is not conventionally confronted in a review (Light and Smith, 1971). A formal quantitative approach for the synthesis of evidence derived from a set of similar but independent experiments is called meta-analysis.

3.4.4 Data-base Analyses

With the novel advances in computer storage and retrieval, data base-analysis has been proposed. Computerised data-bases routinely preserve records for thousands of patients. In several data-bases, details regarding diagnosis, treatment, and outcome are recorded for each patient (McDonald, 1991). Recently, analysts concerned with medical effectiveness have begun to use these data-bases (McDonald, 1991; Ellwood, 1988; Roper *et al.*, 1988).

Data-base analyses have a number of advantageous characteristics. A clear advantage is that many data-bases cover the full range of patients receiving the treatment in medical practice. This is considered important, particularly since randomised studies and even meta-analyses of randomised studies, have limited coverage. Furthermore, other advantages of data-base analyses include (1) their timeliness (2) their low cost, because the data have already been collected and (3) their independence from the ethical affections identified with manipulation of interventions in randomised clinical trials (Silberman *et al.*, 1992).

Nevertheless, the outcome of this approach suffers from several potential deficiencies.

These include limited patient descriptors, possible recording and transcription errors, and missing data. Focusing on treatment effect estimation, the outstanding defect of data base analyses is "comparison bias", which means that the patient groups being compared were not comparable at baseline (Byar, 1980).

3.4.5 Meta-Analyses

3.4.5.1 Definition and Nomenclature

"Meta-analyses" or "quantitative overviews", as many medical researchers call them (Yusuf *et al.*, 1987; Peto, 1987), expand knowledge by statistically combining the results of multiple studies, and randomised studies, that all address essentially the same research question (Teagarden, 1989). Other definitions are similar: "a quantitative methodology for integrating empirical research literature" (Diamond and Forrester, 1983); "an attempt to improve traditional methods of narrative review by systematically aggregating information and quantifying its impact" (Wittes, 1987).

The word Meta is derived from the Greek word *meta* which means "after". Other terms used to describe this type of research include integrative research review, research consolidation, data synthesis, pooled analysis and combining studies (Jenicek, 1989). Most of these terms are used interchangeably. In this thesis, the term meta-analysis will be used to designate the process of synthesising the results of similar but separate randomised clinical trials.

Meta-analysis includes a collection of techniques which were first employed in social sciences, particularly in psychological and educational research. Some examples were also to be found in agricultural research (Pearson, 1904; Tippet, 1931; Fisher, 1932; Cochran, 1937; Glass, 1976). Clinical and medical researchers adopted the method in the 1980s (Sacks *et al.*, 1987).

Social scientists who first practised meta-analysis, used a standardised "effect size" to combine results from studies with different outcome measures (for example, different measures of self-esteem) (Hedges, 1982). Later, many medical researchers combined only studies which had the same "endpoint" (for example, 5-year survival), only randomised, placebo-controlled clinical trials, or those that met both criteria (Peto, 1987).

3.4.5.2 Potentials of Meta-Analysis

1. To approximate the results of a single large study at a small fraction of the cost of conducting a new large study.
2. To increase statistical power as a result of 'pooled estimate'.
3. To resolve uncertainty of complex medical problems when a number of primary studies disagree.
4. To draw conclusions on how to plan new studies or clinical trials.
5. To answer questions not posed at the start of individual trials.
6. To identify beneficial or harmful interventions many years before this is discovered by subjective, narrative and qualitative review.
7. To provide a greater stability for the estimate of a treatment's effect in a particular subgroup. When the numbers of patients in that subgroup are not large enough, within individual small studies, drawing a stable conclusion about a treatment effect is not feasible. However, using meta-analysis to combine the outcomes for that subgroup in multiple studies enables more stable evaluation (Light, 1984).
8. To investigate potential sources of clinical and statistical heterogeneity, in particular the clinical differences between the studies included, and to attempt to quantify a better overall estimate of the influence of these sources (Thompson, 1994).
9. To provide more useful summary measures for incorporation in pharmacoeconomic analysis (for example, cost effectiveness, cost benefit or cost utility analysis).
10. To ensure the validity of original research studies, particularly when there are difficulties in interpretation which may render research results invalid (Cooper, 1984). For example, some methods of problem formulation (e.g. post hoc hypothesis formulation), data collection (e.g. nonrandom sampling), data evaluation (e.g. eliminating subjects whose behaviour contradicts the research hypothesis), data analysis (e.g. failure to apply a statistical methods to evaluate a certain outcome measure) and reporting (e.g. failure to describe procedures conclusively).

3.4.5.3 Why Meta-analysis of Randomised Clinical Trials?

Randomised clinical trials have increasingly become the principal method by which the efficacy of drug therapy is evaluated (Chalmers, 1989; Feinstein, 1983). Statistically significant results reported in these trials may significantly affect medical practice and the physicians' opinions in prescribing drug treatment.

The appropriate application of the results of clinical trials to practice of medicine requires that both the scientific validity of the experiments and the generalisability of their results to large patient populations are properly documented.

In cardiovascular fields, many clinical trials have been designed to investigate the efficacy of various interventions, preventing clinical events such as myocardial infarction, sudden death, and stroke. Some of these controlled trials compare treatments and may produce moderate differences in outcome, but these differences can be clinically important. Such differences are sometimes hardly detected if the sample size of the trial is small and requires the recruitment of several thousands of patients (Peto, 1987). For example, if a treatment which produces 10% reduction in the risk of death is tested in a trial involving one thousand patients equally randomised, 450 deaths would be expected in the treatment group and 500 deaths in the control group. The significance of such a result is minimal and nonessential from a statistical point of view and it may be dispersed or even ejected as irrelevant. However, Glass (1987), the creator of the term 'meta-analysis', has declared, "by what logic would one want to overlook small effects that are actually present but are obscured by uncontrolled error? One may not be satisfied with small effects, but rejecting them as inadequate is different from not seeing them at all. If effects are small, one tries to increase them if one can, or one lives with them if one must." (Gottman and Glass, 1978). Due to this reason, Peto (1987) has highlighted the value of meta-analysis for capturing a credible conclusion by basing evidence primarily on an overview of all patients studied in all related unbiased trials.

In addition to a sufficiently large sample size, randomisation is an important element to avoid bias particularly if the treatment does not produce a large effect. Therefore, meta-analyses have to be confined to RCTs (Sinclair and Bracken, 1992).

Chalmers *et al.* (1987) measured the degree by which meta-analyses of smaller

controlled trials agreed with large multicentre studies. They found that the results produced by one meta-analysis which included 12 trials of intravenous beta-blocker for acute myocardial infarction in a total of 4408 patients, were similar to the results of two separate, large trials, one of which included 5778 patients and the other 16,027. Another meta-analysis of intravenous streptokinase for acute myocardial infarction involving 11 randomised, controlled trials and a total of 5268 patients resulted in an estimate of effect of similar magnitude to that of a large cooperative study involving 11,712 patients.

3.4.5.4 Meta-analysis Methodology

Most of the fundamental, methodological issues associated with primary research studies are applicable to meta-analysis. This requires an explicit statement of the objective and precise description of research design; data definition including determination of the sample size and verifying independent and dependent variables; data retrieval procedures; considerations of data quality and use of appropriate statistical techniques. However, meta-analysis differs from primary research in certain aspects. In meta-analysis, a single study forms the unit of analysis and its findings and features contribute to the data set for a meta-analysis (McCain, 1986).

Regardless of the analytical and statistical methods employed, all meta-analyses involves a series of steps. Some of which are associated with preparation, performance, or presentation stage. The sequence of these stages is the same as for any other type of research. Since the method of research of this thesis is mainly meta-analysis the practical steps are discussed in detail in this chapter.

3.4.5.4.1 Statement of Objective and Research Question

This is the initial step of the planning phase and the foundation on which any meta-analysis is built. During this phase, the research question and protocol should be explicitly defined (L'Abbe *et al.*, 1987). For example, does the intervention prevent a specific clinical event? Formulation of research question and objectives should take place before collecting any data.

The statement of the objective must capture the essence of the project but does not need to include all the details (Teagarden, 1989). Investigators can also suggest additional

secondary questions such as what is the subgroup for which the intervention may be most effective or how the intervention may affect other efficacy outcomes.

In considering the research questions and objectives, it is important to be satisfied that the trials retrieved are addressing the same questions, enrolling comparable patients, inspecting the same interventions, and evaluating the same outcome.

3.4.5.4.2 Data Definition

As mentioned above, data definition should be performed before data collection. It is vital to provide a clear definitions for the variables of interest which include the independent and dependent variables, design and sample of trials to be included, and methods used for identifying and analysing studies. Independent variables include the patient characteristics, diagnoses and drug dosage. Dependent variables are outcome measures such as quality of life, decrease in blood pressure, success rates, pain scores or sudden death.

3.4.5.4.3 Definition of Inclusion Criteria

A meta-analyst should set a list of inclusion criteria for entry into the analysis. Generally, there is no standardised criteria for inclusion into a meta-analysis and they are usually adjusted according to the distinctive objectives of the analysis (Sacks *et al.*, 1987; L'Abbe *et al.*, 1987). A clear explanation for the adoption of such criteria should be provided.

3.4.5.4.3.1 Defining acceptable studies

Inclusion criteria with respect to study design is the subject of debate. Most studies on treatment or prevention utilise designs which can be categorised into one of five classes. These classes can be listed in the following ascending order of methodological quality (Li Wan Po, 1996):

1. Case reports
2. Surveillance data
3. Cross sectional study
4. Case control study

5. Cohort study
6. Non-randomised trials with historical controls (i.e. observational studies comparing current patients who receive the intervention of interest with earlier patients of similar criteria, either from a similar institution or from the literature, but they did not receive the intervention).
7. Non-randomised trials with concurrent controls (i.e. observational studies comparing a contemporaneous treatment group with a control group).
8. Randomised controlled trials (RCTs).

The majority of meta-analyses in health care have tested the effectiveness of interventions using RCTs only, since they are the least prone to bias.

Some meta-analysts have used data from non-randomised studies (Schneider, 1986), while others restrict their analyses to RCTs (Thompson and Pocock, 1991). In situations when RCTs are unethical or not appropriate in certain clinical settings, an overview of available studies still seems to offer the advantage of systematic search.

Some authors (Wortman and Yeaton, 1983; L'Abbe *et al.*, 1987) have suggested that changing inclusion criteria to include various types of studies can reinforce the analysis and lead to more reliable and valid conclusions. For instance, a primary analysis for data from RCTs can be undertaken first. Then, a secondary analysis can be repeated in the same manner, but this time by adding data from studies which were primarily excluded, such as nonrandomised trials. Such a sensitivity analysis can be used to test the validity of inclusion and exclusion criteria which constitute basic subjective components of meta-analysis.

In addition to combining study results within the separate design categories, some analysts have created a new technique for combining results across categories called cross-design synthesis which is a topic of current methodologic interest (Colditz, 1988; Eddy *et al.*, 1989; Rubin, 1990). These techniques were developed to account for the weaknesses associated with the generalisability problems in existing randomised studies and comparison bias in data-base analyses. These challenges consider the elucidation of recognised bias in individual studies and bias due to cross-study differences, which include major differences in study designs and in the patient population included. A number of methodological options can be followed by the investigator to satisfy these demands which can be summarised in the following tasks:

1. Adjusting each randomised study's treatment effect. For example, standardise results to correct for over or under representation (Fleiss, 1973; Deming, 1964).

2. Stratifying studies by type of design (Light and Pillemer, 1984) and by coverage of patient subgroups (Himel *et al.*, 1986).

3. Matching data base patients to those covered in randomised studies (Hlatky, 1991) and identifying those remaining data-base patients not covered in randomised studies.

4. Combing estimates of the treatment's effect within each stratum with adjustment for differences in quality, in studies' population coverage, and in reliability. This is by using models that account for differences (Eddy *et al.*, 1989) or by taking a weighted average with weights defined by the inverse of variances (Hedges and Olkin, 1985).

5. Synthesising estimates across design categories (i.e. across strata).

6. Providing an estimate for the empty stratum by using results from other strata. This process is called "projection" (Rubin, 1990; Colditz *et al.*, 1988).

However, many refinements need to be generated. Regardless of the employed study criteria, their rationale should be explained and a list of included and excluded studies should be provided.

3.4.5.4.3.2 Defining acceptable patients

Any patient characteristic or factor that could precipitate a systematic variation in results needs to be determined. Methods for treating systematic differences, such as blocking or blinding must be considered.

3.4.5.4.3.3 Defining acceptable treatments

The analyst must define the drug or intervention used and designate equivalent forms (for example, tablets, capsules, injectables, suppositories) or products (for example,

brands, generics) that would be permissible as equivalents. The dose and route of administration should be specified as well as acceptable regimens. Different dose regimens can lead to different response rates and stratification may be required at the analysis. Exposure to the drug and patient compliance must be confirmed, particularly in epidemiologic studies or uncontrolled trials (Einarson *et al.*, 1988).

3.4.5.4.3.4 Defining acceptable comparison groups

Many clinical trials employ a control group which may receive placebo, standard therapy, or another comparable drug. Other studies may use historical controls or each subject may serve as his own control. A satisfactory meta-analysis requires that the comparison groups be either identical or very similar. Otherwise, differences in effect could be attributed to the differences in comparison groups and not to the drug under investigation. The analyst must determine what comprises acceptable comparisons. If different comparison types are used, sub-analyses for subgroups could be performed.

3.4.5.4.3.5 Defining outcomes

For each analysis, the acceptable outcomes must be defined. The outcome of interest may be measured by a continuous variable, such as a pain relief, or a quality of life score. Also it can be measured by categorical variables, such as sudden death, cured, not cured, or adverse events, by an ordered categorical variable, such as tumor stage. Categorical variables which change with time can be represented using life tables or survival curves.

3.4.5.4.4 Definition of Exclusion Criteria

Exclusion criteria should describe the reasons for rejecting some studies which met the inclusion criteria. The most common reason is inadequacy to provide sufficient substantial data.

Exclusion criteria may explain variables more precisely than the inclusion criteria. For example, if the inclusion criteria accepted RCTs of amiodarone in patients with atrial fibrillation, the exclusion criteria could exclude patients with atrial fibrillation due to surgery (postoperative atrial fibrillation).

Exclusion criteria also specify confounding variables and how they must be controlled. It may exclude studies that did not match or control for confounding factors, including age, diet, smoking, alcohol consumption, or concurrent drug use.

3.4.5.4.5 Data Collection

For the results to be satisfactory, as for any literature review in a particular research field, one of the prerequisites is that they have been established on thorough inspection of the opinions of as big a fraction as possible of all the pertinent investigations. Consequently, an exhaustive literature of published and unpublished sources is required to retrieve as many of the relevant articles as possible (Glass, 1976).

Data collection in meta-analysis includes all the procedures related to data identification including definition of data-base to be used, Key words employed, research strategy, and methods of data extraction.

3.4.5.4.5.1 Identification of literature sources

A very important aspect of meta-analysis is that it constrains a careful systematic search of all available sources of literature for complete verification of pertinent studies. As a result, a researcher should approach all accessible computerised and printed sources. Manual search of relevant journals, text books, dissertation theses, and reports from conferences and meetings is compulsory with regard to the financial and time limitations for performing a meta-analysis. Theses are high quality research materials, even if they may not have been published because they addressed an unpopular subject. Hence, "Dissertation Abstracts" may be a good source for location of such studies. Other forms of unpublished literature may be obtained by either formal or informal contact with experts in the field. Manual scrutinising of printed abstracting agencies and indices such as *Index Medicus, Current Contents,* and *International Pharmaceutical Abstracts* is recommended.

A computerised search is performed through electronic data-bases, available in ON-Line or CD-ROM versions. The On-line versions are universally applied and more widespread than CD-ROM versions, since they accommodate a larger bulk of literature than do the CD-ROM versions.

MEDLINE is the on-line version of 3 print indexes: Index Medicus, Index to Dental Literature and the International Nursing Index. It is provided by the U.S. National Library of Medicine, Bethesda, MD. It has strong English language and American literature preference. It covers more than 3,600 international journals published in over 70 countries. In MEDLINE, an article is indexed using index terms (called MeSH headings) describing the content of the article and characteristics of research.

The Excerpta Medica Data-bases (EMBASE) and the Institute for Scientific Information Inc Databases are available on-line. The Bath Information & Data Services (BIDS) of these databases are provided by Bath University.

The BIDS EMBASE provides access to a major pharmacological and biomedical literature data-base covering about 3,500 journals from 110 countries. EMBASE comprises mainly journal literature (plus some book reviews and conference proceedings) with strong coverage of European journals. It goes back to 1980 and is updated weekly. The basic unit of information is an article.

3.4.5.4.5.2 What are the potential biases in identification of relevant studies?

Despite the efficiency of electronic databases for providing easier and faster access to a large body of published literature, identification of all relevant studies is still difficult. It has been reported that electronic searches may identify only 20 and 50% of acceptable studies (Bernstein, 1988; Chalmers *et al.*, 1992). However, applying various search strategies will improve the generation of eligible reports. Gotzsche (1991) has shown that a search strategy for recalling double-blind trials in MEDLINE using the Medical Subject Heading (MeSH) "Comparative study" gave a yield of 122 reports with recall equal to 93.1% and precision of 19%. When a combined search strategy with additional Key words such as "Double-blind method" was applied, the recall increased to 97.9% with a reduced precision of 17.3%.

Ideally, a manual search of the pertinent journals as well as the references of all retrieved articles should be performed for further information. However, to depend entirely on the reference lists of published reports may lead to citation bias. A recent study of double-blind trials of non-steroidal anti-inflammatory drugs showed a high frequency of multiple publication and reference bias (Gotzsche, 1987). This was ascribed to citation of previously published reports which were biased towards positive

trials of the drug.

In addition to citation bias, there are difficulties arising from indexing biases due to studies submitted only to minor or unimportant journals which are not indexed in any of the available databases, or indexed under wrong Key words.

Furthermore, in many areas of research, two types of studies are most unlikely to be published. They are those which do not report significant differences between a certain treatment and control, and studies which show results not consistent with contemporary experiences (Jenicek, 1989). Consequently, such studies may be rejected from publication in major journals, submitted to minor journals, or have their publication post-poned for several years with an increased chance of being lost forever. When these studies are not published, they would remain in "file drawers" which would result in publication bias (Rosenthal, 1979). This can affect the conclusion derived from a meta-analysis based entirely on published studies (Simes, 1987; Chalmers, 1989).

An attempt to minimise publication bias by obtaining data unreported in published reports, or by seeking information about any completed but unpublished studies from authors, was suggested (L'Abbe and Detsky, 1987; Chalmers, 1989). Nevertheless, there remains a debate about the significance of obtaining such information and the influence of their inclusion on the results of a meta-analysis (Peto, 1987; Yusuf, 1987; Sacks *et al.*, 1987; Begg and Berlin, 1988). Chalmers *et al.* (1987) have conducted comparisons of overviews which included unpublished data and those which utilised only published results. Although the conclusions sometimes differed, in most cases they were similar.

In general, publication bias tends to favour positive treatment effects (Christensen and Gluud, 1995; Reid *et al.*, 1996).

3.4.5.4.6 Evaluating the Quality of Relevant Studies

The assessment of the quality of research is a subject of continuing debate (Chalmers *et al.*, 1981; L'Abbe, 1987; Liberati *et al.*, 1986; Colditz *et al.*, 1988; Jenicek *et al.*, 1989; Miller *et al.*, 1989; Fowkes and Fulton, 1991). The importance of qualitative assessment of individual studies before combining them in meta-analysis has been stressed by several authors (Sacks *et al.*, 1987; Jenicek, 1989; Vandekerckhove *et al.*,

1993).

Assessment of quality is not an easy task. For a study to be included in a meta-analysis, it should be of sufficiently high quality of design and execution to confirm the scientific validity and generalisability of the results to larger populations.

For assessing the quality of a study, at least two authors should review and score the articles independently (L'Abbe *et al.*, 1987). In order to minimise bias, the journal in which the report appeared, the institution, the authors, the sponsoring agencies and the results should be masked. The articles should be judged on the methods used rather than on their results. Blinding and photocopying of the articles must be performed by a person not involved in data analysis.

3.4.5.4.6.1 Quality assessment tools

Several quality assessment tools have been developed for the evaluation of clinical trials (Chalmers, 1981; Liberati *et al.*, 1986; Detsky *et al.*, 1992; Simon and Wittes, 1985).

Feinstein (1985) designed a qualitative tool for assessing case-control studies. He proposed the availability of 20 conditions for conforming the autonomy from random errors and significant types of biases. Although this tool would produce a quantitative quality scores, it was considered of no value if a major bias existed.

A collection of criteria was introduced by Simon and Wittes (1985) and Grant (1989) to be employed by the editorial committee. The set included nine components for qualitative assessment of medical reports such as sufficient explanation of patient characteristics and reporting of loss to follow-up. Since it was formulated to be used by editorials, numerical scores were not given.

Lichtenstein *et al.* (1987) generated 34 guidelines to be used for rating distinctions of case-control studies. The most essential items were procedures of data collection, sources of cases and controls, blinding of investigators, delineation of sampling and analytic techniques, and details of exposure. However, a quality score was not provided.

Fowkes and Fulton (1991) highlighted important features which they thought should be cosidered when appraising medical research papers. They provided a set of six

guidelines each with its individual criteria, which were not essentially applicable to all categories of study design. The guidelines were in the form of the following questions: Study design appropriate to objectives?, study sample representative?, control group acceptable?, quality of measurements and outcomes?, completeness?, distorting influences?. In judging the quality of measurements and outcomes, it was essential to consider the validity of measurements made, as well as its reproducibility, which is the evidence of consistency of measurement, by repeating the evaluation at different intervals and on different subjects. Thus, criteria of guidelines facilitated the conduction of detailed assessment of the methods and results to check its adequacy and completeness for achieving the objectives. When examining the criteria for each guideline, they recommended accrediting the deficiency of each criteria as 'major' or 'minor' in terms of their anticipated influence on outcomes, and hence, on drawing conclusions. Unfortunately, the detailed assessments would not be converted to an overall score on the virtue of a paper.

The previous quality assessment tools suffer from inherent subjectivity, since the criteria within these tools are usually not weighted, and the pros and cons of a particular research are not adjusted properly. For instance, depending on the objectives of the research, certain features of study design have a greater influences on the results and conclusion, such as in clinical trials blind allocation and randomisation of patients to different treatment may, apparently, be more serious than the influence of confounding factors or reproducibility of measurements. Furthermore, these tools were not developed specifically for the evaluation of the quality of RCTs or to distinguish their suitablity to be combined in meta-analysis. The major tools manipulated in meta-analysis are discussed following.

Chalmers *et al.* (1981) created a quality scoring system with the objective of producing a quantitative score, reflecting the overall quality of each RCT to be used in meta-analysis. This system was based on their personal experiences in analysing clinical trials. The assessment scheme consisted of four divisions: basic descriptive material, the study protocol, the analysis of data, and data useful for potential combining of several RCT results. The first part was concerned with fundamentally identifying information, such as the name of the author(s), journal, sources of financial support, and whether or not the journal was peer reviewed. This part was not given any score. The second part dealt with the specific elements of good protocol design and was considered the most essential. The overall index is divided into three parts: a) the design and protocol of the trial with 60% of the weights; b) the statistical analysis of the

trial with 30% of the weights; and c) the presentation of the trial results with 10% of the weights. Within each division, a score is assigned for each applicable item. The score is then divided by the total possible score, giving an overall quality index by adding up the three forms' itemised scores and dividing by the total possible score. Although the flexibility of the method allows its application for the assessment of trials with different objectives and endpoints, it has some defects, due to its subjective interpretations, even after the evaluators discussion which may add to subjectivity of the evaluation. Further, its meticulous grading for incomplete reporting in published study report, which may improperly reduce the quality score for a study, particularly when such items were omitted from reports due to restricted publication policy rather than because they were not considered in the study design.

Liberati *et al.* (1986) modified Chalmers' instrument to satisfy specific requirements of long-term trials in oncology, since there are usually high dropout rates, treatment groups are commonly small, and predicted outcomes require long-term follow-up. Consequently, some new points were introduced, and adjusted weights were assigned to others. The overall score was split into two divisions to assess the internal validity of a study. These divisions were concerned with the merit of its design and adminstration, and the external validity which assess the information that reflects the generalisability of the results. Nevertheless, assigned scores were not based on any discerned absolute measures of quality, and a clear justification for its use was not provided.

Koes *et al.* (1991) introduced a list of criteria which they had modified after it was first developed by Ter Riet *et al.* (1990). Although they claimed that the criteria were based on generally accepted principles of intervention research, a detailed explanation was not presented. Furthermore, the weight assigned for each criterion was arbitrarily selected (for example, five points were added to the study if it was stated that the intervention was handled by qualified therapist, and the five points were subtracted from the 17 points given for the sample size). In addition, marking a study as positive or negative was based on the results without taking into account that negative results might be produced due to the inadequacy of small study populations for observing the treatment differences between the intervention and reference treatments.

An illustrated bibliography of 25 scales and checklists for assessment of RCT quality was introduced by Moher *et al.* (1995) who have carried a MEDLINE search between January 1966 and December 1992. These tools were published between 1961 and

1993. Three of the scales were developed to assess the quality of trial reports which reflect the extent of "providing information about the design, conduct, and analysis of the trial". 8 were developed to assess "methodological quality" which was defined as "the confidence that the trial design, conduct, and analysis has minimised or avoided biases in its treatment comparisons". The remaining 14 were to judge both methodological quality and the quality of the report. Most of the scales were designed to be used in the context of assessing the quality of trials combined in meta-analysis. Since some of the scales were restricted for use in specific trials, they recommended caution in employing for other types of trials, and they suggested the utilisation of more than scales to verify whether different scales would produce comparable results. Consequently, this would assist the evaluators in choosing the appropriate scale, or performing some modification to former scales, in order to develop a fitting scale for distinctive new issues that need to be addressed.

3.4.5.4.6.2 What is the impact of study quality on the results of a meta-analysis?

The extent to which quality index of RCTs influence the estimation of effectiveness is unknown and discrepancies of authors' opinions continues. Some researchers have affirmed that they have not observed any association between effect size and overall quality index (Emerson *et al.*, 1990). On the other hand, others have highlighted the impact of variations in the quality of the individual studies on meta-analysis, its threats to validity, and its consideration as an identified source of heterogeneity in the results (Peto, 1987; Chalmers *et al.*, 1989; Jenicek, 1989; Detsky *et al.*, 1992).

Detsky *et al.* (1992) highlighted the possibility of reducing precision and adding variability to estimates of effect, when poor studies are combined with high quality studies. They stated that the conclusion of a meta-analysis, combining studies with diverse quality, may suffer from Type 1 error (by concluding that treatment has effect when in fact it has not), or Type 2 error (by concluding that treatment does not work when it does).

3.4.5.4.6.3 How the quality score can be incorporated into meta-analysis?

Individual quality scores can be used in the process of generating pooled estimates of

treatment effects by one of the following five methods (L'Abbe *et al.*, 1987; Einarson, 1988; Detsky *et al.*, 1992):

1. Setting a quality score as a cut off point for inclusion or exclusion of studies in a meta-analysis.

2. Incorporating the quality scores as a weight in the statistical pooling of the data.

3. Sensitivity analysis to identify whether design flaws may affect the overall results.

4. Examination of the relationship between study quality and effect size. A visual plot of the effect size against quality score can be performed (Detsky *et al.*, 1992).

5. Sequential combination of trial results based on quality scores. This technique can be used to investigate the impact of individual trials on the accumulated effect size estimates.

3.4.5.4.6.4 Inter-rater reliability

If several evaluators assess the quality of the trials, inter-rater agreement should be assessed to resolve the contradictions and to minimise the potential for error and bias due to the subjectivity element (Fleiss, 1981; Rosenthal, 1984).

3.4.5.4.7 Data Extraction

A number of authors have emphasised the significance of controlling for observer bias during the process of data extraction (Sacks *et al.*, 1987; Chalmers *et al.*, 1981) and have suggested separation of Materials and Methods sections from the Results section. Data describing details of patients characteristics in included studies, such as age, sex, ranges of diagnostic criteria, or other associated diseases, should be collected since these details are essential for determining the validity and generalisability of a meta-analysis.

3.4.5.4.8 Statistical Analysis and Pooling Techniques

Various statistical methods for pooling results from individual studies have been presented (Light & Pillemer, 1984; Hedges & Olkin, 1985; Dersimonian & Laird, 1986; Cooper, 1989; Berlin *et al.*, 1989; Laird & Mosteller, 1990; Rosenthal,1991). The application of two or more methods and comparison of results are recommended by some authors (Fleiss, 1993).

Some of the techniques are only used to test the statistical significance of the overall effect and to determine its direction without giving an estimation for the magnitude of the treatment effect (Light & Pillemer, 1984; Thompson & Pocock, 1991).

Combining summary statistics in meta-analysis can be approached using two models. The first of these, which is referred to as a fixed-effects model, assumes a common underlying true treatment effect in the individual trials and any difference among the trials is ascribed only to chance. This model reflects the random variation within each trial but not potential heterogeneity between trials. Conversely, a random effects model assumes that the true treatment effects in the different trials are randomly positioned about some central value and takes into account both random variation within trials and heterogeneity between them (Dersimonian & Laird, 1986; Laird & Mosteller, 1991; Thompson & Pocock, 1991).

The two groups of statistical techniques are now discussed in detail.

3.4.5.4.8.1 Methods for pooling primary studies which are not based on outcome measurements

3.4.5.4.8.1.1 "Vote Counting" method

The simplest quantitative method available for combination of the results of several studies is "vote counting". A sign test is carried out to establish whether the pooled, statistically significant, studies suggest that "positive" studies occur more frequently than "negative" studies as follows:

$$Z=[(N_p) - (0.5 \times N_t)] \div [0.5 \times (\sqrt{N_t})]$$

Where, Z is the standard normal deviate;

Np = the number of significant positive findings; and

N_t = the total number of significant findings: "positive" or "negative".

The p-value is obtained by referring the Z-statistic to the Standard Normal distribution. A statistically significant Z value would suggest that the treatment is effective (Cooper, 1989).

3.4.5.4.8.1.2 Combining of studies using significance tests

One of the best known methods is Fisher's method based on the U statistic (Rosenthal, 1991; Jones, 1995):

$$U = -2\sum_{i=1}^{k} \log_e P_i$$

which has a χ^2 distribution with 2k degrees of freedom. *Pi* is the one-sided p-value from the *i*th of k studies. Another method proposed by Mosteller and Bush (1954) involves adding the Z values corresponding to each of the p levels in the studies included. For example, to combine the results of two studies, the two Z values obtained can be summed and divided by $\sqrt{2}$ to get a new Z value:

$$\frac{Z_1 + Z_2}{\sqrt{2}}$$, which is again standard normal.

However, the advantages of such methods are excessively confined to hypothesis testing and are of limited application, particularly where the estimation methods of the magnitude of effects and the confidence intervals are favoured.

3.4.5.4.8.2 Statistical techniques for conversion and pooling of outcome data

A variety of statistical methods are used for pooling reported trial outcomes. An important common feature is the conversion of individual study outcomes to a common

metrics, such as standardised mean difference (effect size), relative risk (RR), or odds ratio (OR). The choice of metric depends on the type of outcome data. Discrete or proportional data are usually combined using odds ratio (OR) or rate difference (RD), while continuous data can be expressed by the effect size (ES).

3.4.5.4.8.2.1 Combining categorical variables (discrete data)

3.4.5.4.8.2.1.1 Combining raw data

Combining raw data from the different studies does not account for the random variation within each study or across studies and hence it may present deceptive consequences. Furthermore, the estimations may be contradictory.

3.4.5.4.8.2.1.2 Conversion to summary measures

The most commonly used summary measures for categorical outcomes are: odds ratio (OR), relative risk (RR), and rate difference (RD).

A. The Odds Ratio

An individual odds ratio is calculated from a single contingency table ("2 × 2" table). Mantel and Haenszel method (1959) pools the odds ratios from a series of contingency tables ("2 × 2" tables). This method has been subsequently represented by Yusuf and Peto (1985) to calculate individual OR and pooled OR in meta-analysis, and since then it is commonly referred to as Mantel-Haenszel-Peto method or simply, as Peto method. This method allows the calculation of individual OR for each study with the associated 95% confidence interval and the pooled OR with its 95% confidence interval by designating a weight for each study based on their sample sizes. The Mantel-Haenzel method weights unlogged ORs inversely to the variance. As a result, these methods can be used to test the "null hypothesis" (for the direction of the effect) as well as to determine the range of the effect and the significance of any differential effects (Berlin *et al.*, 1989).

Careful interpretation of the results is recommended when Peto's method is used. It has been shown that this method may produce biased summary odds ratios (Greenland

and Salvan, 1990) when there is a serious imbalance in the number of patients or frequencies of events between the treatment groups and the control groups, which is very common in observational studies (Thompson and Pocock, 1991; Fleiss, 1993). Also there is a potential bias when the overall OR is far from unity (Fleiss, 1993). However, this is infrequent in RCTs.

The fixed-effects model assumes no differences in the underlying true treatment effect, and the authors have presented a formal test for the homogeneity of the odds ratios, that is, a test that the observed treatment effects vary only randomly around some common value. The test statistic has an approximate chi-square distribution with a degrees of freedom equal to K-1 (where K is usually exactly equal to the number of studies) (Yusuf *et al.*, 1985; Berlin *et al.*, 1989).

The procedures for estimation of pooled OR by Peto's method can be summarised as follows:

In the i^{th} trial, (i=1,....,K), with Ni the total number of patients in the trial, let n_i be the number of patients in the treatment group, let the total number of events from both treatment and control groups be d_i , and let the number of events in the treatment group be Oi. Expected number of events in the treatment group can be calculated by $E_i = (n_i/N_i)d_i$. Under the null hypothesis of no treatment effect, the quantity O_i-E_i should vary randomly around zero, with variance $V_i = Ei \times [(1- n_i/N_i) (N_i-d_i)/(N_i-1)]$. The individual odds ratios for each trial can be calculated as follows:

$$OR_i = \exp\left[\frac{(O_i - E_i)}{Var_i}\right]$$

The approximate standard error of the natural logarithm of OR_i is estimated by

$$SE\,(LnOR_i) = (Var_i)^{-1/2}$$

and its 95% confidence interval by

$$\exp\,[\ln OR_i \pm 1.96\ SE\ (\ln OR_i)]$$

A test statistic for the hypothesis of no effect of treatment which has an approximate χ^2 distribution with one degree of freedom is

$$\chi_i^2 = \frac{(O_i - E_i)^2}{Var_i}$$

An approximate χ^2 test of homogeneity uses the test statistic

$$\chi_{k-1}^2 = \sum_{i=1}^{k} \left[\frac{(O_i - E_i)^2}{Var_i}\right] - \frac{\left[\sum_{i=1}^{k} (O_i - E_i)\right]^2}{\sum_{i=1}^{k} Var_i}$$

The pooled odds ratio ($\hat{OR}$) from k studies is estimated by:

$$\hat{OR} = \exp\left[\frac{\sum_{i=1}^{k} (O_i - E_i)}{\sum_{i=1}^{k} Var_i}\right]$$

and an estimate of the approximate standard error of the natural logarithm of $\hat{OR}$ is presented by:

$$SE\,(LnOR) = \left(\sum Var_i\right)^{-1/2}$$

with 95% confidence interval

$$\exp[LnOR \pm 1.96\ SE\ (LnOR)], \text{ with } df=1.$$

Other fixed-effect methods used for calculating the pooled odds ratio include the Woolf's method, which uses a weighted average of log OR's (Thompson and Pocock, 1991; Fleiss, 1993).

B. The Relative Risk

For calculation of categorical response variables in clinical trials (such as improved/unimproved), or in cross-sectional or longitudinal epidemiological studies, the following procedures can be followed (Rothman, 1986; Fleiss, 1993):

Within a study with sample sizes of n_1 and n_2, let a_i and b_i be the observed rates of occurrence of an event in the treatment and control groups respectively, and let P_1 and P_2 be the expected values of a_i and b_i. The relative risk in the i^{th} trial is given by:

$$RR_i = \frac{P_{1i}}{P_{2i}} = \frac{a_i / n_{1i}}{b_i / n_{2i}}$$

Consider the values for the two possible outcomes as presented for the i^{th} study in the following 2×2 table:

Table X: Contingency Table

	Group (Number of patients)		
Outcome	**Treatment**	**Control**	**Total**
Good	a_i	b_i	N_1
Poor	c_i	d_i	N_2
Total	n_1	n_2	N_t

If $a_i = 0$ or $b_i = 0$, RR_i is usually adjusted to

$$RR_i = \frac{(a_i + 0.5)/[(a_i + 0.5) + (c_i + 0.5)]}{(b_i + 0.5)/[(b_i + 0.5) + (d_i + 0.5)]}$$

RR_i is approximately normally distributed about a mean of $R\hat{R}$. The logarithm of RR_i ($lnRR_i$) has a sampling variance estimated by

$$\text{Var}(\ln RR_i) = \frac{c_i}{a_i n_{1i}} + \frac{d_i}{b_i n_{2i}}$$

The standard error of $lnRR_i$ is

$$\text{SE}(\ln RR_i) = \sqrt{\text{Var}(\ln RR_i)}$$

and the 95% confidence interval of RR_i is produced by

$$\exp[\ln RR_i \pm 1.96\ \text{SE}(\ln RR_i)]$$

A significance test for RR_i is based on the Z statistic

$$Z = \frac{\ln RR_i}{\text{SE}(\ln RR_i)}$$

To test the null hypothesis of homogeneity of RR_i's, the Q statistic (DerSimonian and Laird, 1986) is calculated:

$$Q = \sum \frac{(\ln RR_i - \ln R\hat{R})^2}{\text{Var}(\ln RR_i)}$$

where $\ln R\hat{R}$ is a weighted average logarithm value of $lnRR_i$'s, that is

$$\ln RR = \frac{\sum w_i \ln RR_i}{\sum w_i}$$

where w_i, the individual study weight is estimated asw_i= 1/Var ($\ln RR_i$), with standard error of natural logarithm of RR

$$SE(\ln RR) = (\sum W_i)^{-1/2}$$

The pooled $R\hat{R}$, therefore, is obtained by

$$R\hat{R} = \exp\left(\frac{\sum w_i \ln RR_i}{\sum w_i}\right)$$

C. The Rate Difference

The RR describes the relative, rather than the absolute, magnitude of reduction in the event rate. For example, an RR of 0.8 indicates a 20% reduction in the rate of events in the treatment group relative to the rate of events in the controls. The rate difference, on the other hand, is an absolute difference scale worthwhile for the assessment of the potential public health consequences of treatment (Berlin *et al.*, 1989). Hence, an RD of -0.4 indicates an absolute 40 percentage point reduction of events in the treated group (Hamilton, 1979; Rothman, 1986). The inverse of rate difference ($1/R\hat{D}$) allows the estimation of the numbers needed to treat (NNT) in order to prevent one patient having an event (Sackett *et al.*, 1991).

The pooled difference between event rates in the treatment and control groups can be estimated by using the DerSimonian and Laird-modified Cochran method (D&L method). Assuming d_{ti} and d_{ci} to be the number of events in the treated and control groups, respectively, and the corresponding sample size to be n_{ti} and n_{ci}, the proportions of events in the treated and control groups are $\hat{P} = d_{ti}/n_{ti}$ and $\hat{P} = d_{ci}/n_{ci}$. The rate difference in the i^{th} study is estimated by:

$$\hat{\theta} = RD_i = p_{ti} - p_{ci}$$

with a binomial variance estimated by

$$S_i = [\hat{p}_{ti}(1-\hat{p}_{ti})/n_{ti}] + [\hat{p}_{ci}(1-\hat{p}_{ci})/n_{ci}]$$

with $w_i = 1/S_i$. The standard error of $\ln RD_i$ is $SE(\ln RD_i) = \sqrt{S_i}$, giving an approximate for RD_i of

$$\exp[\ln RD_i \pm 1.96\ SE\ (\ln RD_i)]$$

A test of homogeneity (Cochran, 1954) is given by

$$Q = \sum_{i=1}^{k} w_i(\hat{\theta}_i - \bar{\theta}_w)^2$$

where $w_i = S_i^{-1}$. $\bar{\theta}_w$, the pooled RD is approximated by

$$\bar{\theta}_w = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}$$

3.4.5.4.8.2.2 Combining continuous variables

The most commonly applied methods for combining continuous data are the standardised mean difference (SMD) and the weighted mean difference (MDw).

A. Standardised mean difference

The SMD, which is also called effect size, is useful for combining results of studies' expressed as continuous outcomes (Laird and Mosteller, 1990). The main objective is to convert the effect to a unitless measure to allow the combination of different outcomes (Glass, 1976; Rosenthal & Rubin, 1978; Hedges & Olkin, 1985). However, it is essential to differentiate between "effect size" and the more general expression "size

of the effect", since the latter can be used interchangeably with any logical measure, while the former has specific technical assumption in meta-analysis (Laird and Mosteller, 1990).

Many effect sizes have been employed in meta-analysis including Cohen's d, Glass's Δ, and Hedges's g. Glass (1976) suggested that the difference between two means of the treatment and control group, $\overline{X}_{ti}$ and $\overline{X}_{ci}$, in the i^{th} trial, (i = 1, 2,....., k) be divided by the standard deviation of the control group, S_{ci}, and hence Glass's delta or Δ can be represent as:

$$SMD_i = \frac{\overline{X}_{ti} - \overline{X}_{ci}}{S_{ci}}$$

Hedges (1982) showed that the Glass's estimator is biased and the replacement of S_{ci} by S_i, the pooled within-groups standard deviation produced less bias

$$g_i = \frac{\overline{X}_{ti} - \overline{X}_{ci}}{S_i},\ i = 1,\ 2,...,\ k,\ \text{where}\ S_i = \sqrt{\frac{(n_{ci}-1)(S_{ci})^2 + (n_{ti}-1)(S_{ti})^2}{n_{ti}+n_{ci}-2}},$$

However, when the S is based on two different conditions which vary greatly from each other, or if the comparison is undertaken among different treatment levels, it is suggested that the standard deviation of control is more appropriate, since pooling two variances could result in two different standardized values of the identical mean difference within a trial, where several treatments are compared to a control. In this case, the assumption of equal population standard deviations is not valid and the use of Glass's delta is recommended (Hedges & Olkin, 1985).

In addition, Hedges (1982) has also reported on the following simple estimator that is more accurate:

$$ES_i = C(m)\frac{\overline{X}_{ti} - \overline{X}_{ci}}{S_c},\quad i = 1,...., k$$

where $m = n_{ti} + n_{ci} - 2$. C(m) is given approximately by:

$$C(m) = 1 - \frac{3}{4m - 1}$$

Hedges showed that if the assumption for the t test between means are met in each study, then the sampling variance of ES_i is approximately

$$v_i = \frac{n_{ti} + n_{ci}}{n_{ti} n_{ci}} + \frac{ES_i}{2(n_{ti} + n_{ci})}$$

Consequently, the standard error of ES_i is

$$SE_i = \sqrt{v_i}$$

If the components for effect sizes are not reported precisely in articles, estimation of effect size can be obtained from sample sizes, t tests and correlation coefficients reported as shown by Laird and Mosteller (1990):

$$ES_i = t \sqrt{\frac{n_t + n_c}{n_t n_c}}$$

Furthermore, Hedges pointed out the possibility of computing pooled S_{cp} from the standard error data by applying the following equation:

$$S_{cp} = \overline{SE_C} \times \sqrt{n_{ci}}$$

where SE_c is the standard error of the control group. Then, effect size is estimated by

$$ES_i = C(m) \frac{\overline{X_{ti}} - \overline{X_{ci}}}{S_{cp}}$$

Before pooling the individual effect sizes it is essential to test for the homogeneity

across them by the calculation of Q statistics as:

$$Q = \sum_i w_i (SMD_i - \overline{SMD_W})^2$$

where $\overline{SMD_W}$ is the weighted average value of ES_i given by the formula:

$$\overline{SMD}_W = \frac{\sum_i w_i SMD_i}{\sum_i w_i}, \text{ with weight calculated as } w_i = 1/v_i.$$

B. Weighted mean difference

The weighted mean difference is the opposite of SMD and it is calculated as

$$MDw = \frac{\sum_{i=1}^{k} w_i MD_i}{\sum_{i=1}^{k} w_i}$$

where MD_i represents the absolute difference in mean values between the treatment and control groups, $\overline{X}_{ti} - \overline{X}_{ci}$ without standardisation and $w_i = \frac{1}{(\frac{S_{ti}^2}{n_{ti}} + \frac{S_{ci}^2}{n_{ci}})}$, where S_{ti} and S_{ci} represent the standard deviations for the treatment and control groups, and n_{ti} and n_{ci}, the sample sizes.

The 95% CI for MD_i is $MD_i \pm 1.96SE(MD_i)$, where $SE(MD_i) = \sqrt{\frac{S_{ti}^2}{n_{ti}} + \frac{S_{ci}^2}{n_{ci}}}$. The

95% CI of MDw calculated as MDw±1.96SE (MDw) and its standard error as SE (MDw) = $\frac{1}{\sqrt{\sum_{i=1}^{k} w_i}}$ (Sinclair and Bracken, 1992).

The overall effect is expressed in the same units as the individual mean values in the primary studies and thus it can be easily interpreted. If the interval of the 95% CI does not include 0, the difference can be considered as significant at least for the nominal p value of 0.05 (Bracken, 1992).

3.4.5.4.9 Evaluation of Bias and Confounding

An important concern in meta-analysis is to achieve a greater objectivity, generalisability, and precision by including all the available evidence from relevant studies. However, the aims of meta-analysis are usually broader than those of smaller individual studies which differ substantially in their patient selection, baseline disease severity, treatment regimens, and various other forms of confounding, interactions, and bias which account for differences in results among studies other than that due to chance (Thompson, 1994). Hence, a failure to investigate potential sources of heterogeneity may lead to misleading conclusions (L'Abbe *et al.*, 1987; Thompson & Pocock, 1991).

Although a test for heterogeneity of treatment effects between trials can be performed, such a test is of limited value in clinical practice, not only because it has low power to detect any real difference that may exist, but mainly because some heterogeneity will definitely exist even if the test was statistically non-significant (Thompson & Pocock, 1991; Morris *et al.*, 1992; Gansevoort *et al.*; 1995). A meta-analysis that merely displays the pooled result of a group of studies using the random-effects method without appraising the impact of differences in study design, is a misuse of this method (Morris, 1994).

Several statistical approaches and formal tools can be employed in meta-analysis for detecting and quantifying the influence of certain biases and confounders that contribute to heterogeneity in study results (Morris *et al.*, 1992). These tools are comparable to conventional statistical techniques used for evaluation of bias in a single experimental

study and they include stratification, meta-regression, sensitivity analysis, and quality scoring (Licciardone *et al.*, 1990; Teo *et al.*, 1991; Morris, 1994; Berkey *et al.*, 1995; Tweedie & Mengersen, 1995). Stratified analysis is the most commonly utilised tool, particularly for grouping studies according to differences in study design to inspect the impact of such differences on final outcome.

In addition, meta-regression was proposed for estimating the effect of treatment versus control as a function of continuous or categorical clinical variables that influence efficacy (for example, age, weight, gender) and other design factors (for example, sample size, randomisation, blindness) (Greenland, 1987). A random-effects regression model was developed in that context to augment the random-effects model of DerSimonian and Laird for the synthesis of 2×2 tables (Berkey *et al.*, 1995). This model is based on the general relationship operated in weighted least squares regression techniques:

$$\ln (R) = B_0 + B_1 M_1 + e$$

where R is the relative risk, B_0 is the baseline risk, M_1 is the effect modifier with coefficient B_1, and e is an error term. The effect and effect modifier are weighted by the reciprocal of the variance for each study. The random-effect regression model can be represented by:

$$y_i = X_i a + \delta_i + e_i$$

where X_i is a row vector representing the values of covariates for study i, a is a column vector of regression coefficients. The δ_i symbolise the ith trial's true deviation from the true mean of all trials having the same covariate values (specified in X_i). The δ_i and e_i are independent, therefore var $(y_i) = D + \sigma_i^2$, where σ_i^2 is the within-study variance estimated from individual studies and D is across-study variance. When studies are homogenous, the D approaches 0 and the random-effects regression model reduces to a fixed effect analysis.

Although the meta-regression is a more powerful tool than simple stratification, its implementation is not always obtainable if most fitting data is missing from published

reports of clinical trials and a meta-analyst must employ stratification.

Sensitivity analysis is another tool which can be applied in meta-analysis to study the quantal dose-response relationships (Berlin, 1993; Tweedie & Mengersen, 1995). The merit of such an approach derives from its importance for investigating causal relationships.

Furthermore, quality scoring techniques represent a constructive tool for evaluating the sources of bias which are difficult to quantify, precisely those related to study design and methodology. Therefore, developed quality scores may provide possible, credible explanation for heterogeneity in results among studies of various designs (Yusuf *et al.*, 1985; Morris *et al.*, 1992).

3.4.5.4.10 Assessing the Risk of Publication Bias

Publication bias originates in several ways (Chann, 1982; Parmley, 1994). Dickersin *et al.* (1987) contacted 318 authors of published trials asking whether they had taken part in any unpublished randomised clinical trials. 156 responded that they had participated in 271 unpublished and 1,041 published trials. They claimed that the dominant rationality for nonpublication was negative results and a lack of interest. As a result, they advised the registration of all studies before data collection, so that they could be traced regardless of their publication status. Morris (1994) stated that "in the absence of a registry of epidemiologic studies, it is difficult, if not impossible, to quantify publication bias.

Glass *et al.* (1981) reported that published sources tended to contain studies that agreed with existing scientific consensus, and that any study not substantiating validated practice might not be submitted by the investigator for publication or accepted for publication.

Due to former information, publication bias is considered to has a serious implications for the validity and reliability of meta-analyses conclusions (Begg and Berlin, 1989). Cooper (1987) confirmed that all published and unpublished conducted studies should be identified and included in meta-analysis to minimise the publication bias in a meta-analysis. Several methods aiming to detect the existence of publication bias and estimating its impact on certain meta-analysis have been presented. These methods are either graphical or numerical.

A technique for detecting the presence of publication bias was first introduced by Light and Pillemer (1984). Termed a funnel-graph, the technique involves plotting the sample sizes of the component published studies versus the summary outcome measures, or effect sizes. The individual study measures should be distributed symetrically around the unidentified true effect to yield a funnel-shaped graph in the absence of publication bias. Truncation of the lower half of the funnel will indicate that small negative studies have probably not been published.

In addition to the informal examination of publication bias by visual inspection of the funnel-plot, formal test for publication bias was proposed by Begg and Mazumdar (1994) using an adjusted rank correlation as a statistical analog of the funnel plot. The concept of this test is to examine the correlation between effect estimates and their variances after standardising for the effect sizes to stabilise the variances (Begg, 1994) as follows:

$$t_i^* = (t_i - \bar{t}) / (u_i^*)^{1/2}$$

where t_i and υ_i are the estimated effect sizes and sampling variances from the k studies in the meta-analysis, i = 1,....., k. The $\bar{t}$ is estimated by:

$$\bar{t} = (\sum \upsilon_j^{-1} t_j) / \sum \upsilon_j^{-1}$$

where $\upsilon_i^* = \upsilon_i - (\sum \upsilon_j^{-1})^{-1}$ is the variance of $t_i - \bar{t}$.

The variances are usually inversely proportional to the sample sizes. Thus the test is similar to correlating effect size with sample size. Nevertheless, the two approaches may yield different results if an odds ratio or relative risk is employed, and if a significant imbalance in sample sizes exists (Begg and Mazumdar, 1994).

Rosenthal (1979) termed publication bias as a "file drawer problem" due to the

accumulation of a number of unpublished studies in researchers' file drawers. He introduced a formula for estimating the number of studies that would have to accumulate in the file drawers before the overall probability of a Type I error is brought to any level of significance (p = 0.05). This number is termed by Cooper (1979) as the fail safe N (N_{fs}):

$$N_{fs.05} = \left(\frac{\sum Z}{1.645}\right)^2 - N$$

where N is the number of included studies in a meta-analysis. Z scores corresponding to the P values for individual effect sizes can be obtained from tables of normal distribution.

Rosenthal's "Fail-Safe N" does not assess the impact of publication bias on the actual effect size. It is only appropriate when the number of studies themselves are the variable of concern (Einarson *et al.*, 1988). An alternative approach which considers the influence of the file drawer problem on the effect size was proposed by Orwin (1983). The statistic is calculated as follows:

$$N_{fs} = \frac{N(\overline{ES} - \overline{ES_c})}{\overline{ES_c} - \overline{ES_{fs}}}$$

where N is the number of included studies, $\overline{ES}$ is the weighted average effect size obtained from meta-analysis, N_{fs} is the number of studies of a given effect size $\overline{ES_{fs}}$ required to be added to N, to produce an overall effect size of $\overline{ES_c}$. The $\overline{ES_c}$ is the criterion effect size selected according to Cohen's (1969) specification for an effect size of 0.2 as small, 0.5 as medium, and 0.8 as large. The $\overline{ES_{fs}}$ of the studies to be added is usually considered to be "0" or any Cohen's criterion value required to be tested by an investigator (Einarson *et al.*, 1988). Although this method was developed for effect size, other estimation of the size of effect, such as OR, RR, or RD, can be tested by substituting $\overline{ES}$ with pooled OR, RR, or RD.

CHAPTER FOUR

ANTIARRHYTHMIC DRUGS FOR MAINTENANCE OF SINUS RHYTHM AFTER CARDIOVERSION
A META-ANALYSIS

4.1 INTRODUCTION

Chronic atrial fibrillation (AF) is one of the most frequently encountered arrhythmias, occurring in 0.4% of the general population and 2% to 5% of patients over 60 years of age (Cairns and Connolly, 1991). A number of predisposing factors described earlier in Chapter One may result in atrial fibrillation including cardiovascular, pulmonary, or endocrine problems. Usually chronic atrial fibrillation is associated with symptoms due to haemodynamic insufficiency as a result of inadequate ventricular filling. Such symptoms, include palpitations, shortness of breath, headache, or even syncope, may occur at rest or during exercise, thus affecting the quality of life of the patients. In addition, chronic atrial fibrillation has a deleterious effect on cardiac function and consequently increases the risk of premature death (Levy, 1994). The risk of embolic complication was estimated to range from 5.6 fold in chronic atrial fibrillation not associated with heart disease, to 17-fold when it is secondary to rheumatic heart disease (Kannel *et al.*, 1982). The primary end points of therapy were thought to be the rapid restoration of sinus rhythm, prevention of embolism, and maintenance of sinus rhythm prior to cardioversion. However, although the conversion to sinus rhythm, either by electrical or pharmacological means, is reported to be highly successful in this group of patients. The probability of recurrence of the attacks is also very high regardless of maintenance with further theraputic interventions (Clark and Cotter, 1993). As a result, secondary end points are often of interest when conversion to sinus rhythm or complete abolishing of atrial arrhythmia is not possible, and they include the following: i) control of ventricular rate both at rest and during exercise, ii) shortening the duration of the recurrent episodes, iii) and lengthening of the time to first recurrence and the interval between attacks (Pritchett and Lee, 1988). These end points are considered important for improving the quality of life of the patients.

Cardioversion to sinus rhythm can be safely repeated by electrical or pharmacological methods. Electrical cardioversion successfully restores sinus rhythm in more than 90% of patients. However, only 25% remain in sinus rhythm for one year without chronic antiarrhythmic therapy (Sodermark *et al.*, 1975; Hillestad *et al.*, 1971). In addition, electrical transthoracic countershock needs general anesthesia and prolonged anticoagulation before it can be performed. Therefore, several medical protocols using various drugs, administered either intravenously or orally, have been proposed in the past 10 years for rapid cardioversion (Middlekauff *et al.*, 1992). Afterwards, prophylactic antiarrhythmic therapy can be initiated, sometimes even prior to

cardioversion, since the relapse risk is reported to be high in the first few days after cardioversion (Sopher and Camm, 1996). Although prophylactic therapy is crucial for many patients, it is frequently associated with intolerance and increased risk of more malignant ventricular arrhythmia developing. As a result, rigorous investigations are deemed to be essential prior to making a decision to institute antiarrhythmic therapy (Clark and Cotter, 1993).

Class IA drugs (Chapter Two), particularly quinidine, have been commonly employed for conversion and maintenance of sinus rhythm after cardioversion. Two recent meta-analyses evaluated the efficacy of quinidine for maintenance of sinus rhythm and the associated risk of proarrhythmia and mortality (Coplen *et al.*, 1990; Reimold *et al.*, 1992). The first meta-analysis pooled data only from randomised controlled trials, while the second meta-analysis pooled data separately from randomised controlled, non-randomised controlled, and uncontrolled clinical trials. Both meta-analyses reported higher efficacy rates for maintenance of sinus rhythm for quinidine treatment compared to placebo. The pooled results of randomised clinical trials showed a consistent positive difference in terms of proportion of patients maintaining sinus rhythm relative to placebo (rate differences were 23.6%, 23.4%, 24.4% at 3, 6, and 12 months respectively), although the absolute percentage of patients maintaining sinus rhythm decreased with time. However, quinidine treatment was associated with a threefold excess in total mortality at one year (the summary odds ratio of Mantel and Haenszel was 3.5; 95% CI, 1-12.4; $P < 0.05$). Furthermore, several studies have reported major problems with quinidine, such as proarrhythmia in the form of torsade de pointes, and serious noncardiac and organ toxicity (for example, syncope), during its use in the long-term treatment of atrial fibrillation (Selzer and Wray, 1964; Anderson, 1990; Feld, 1990). All of these previous studies have raised several questions about the safety of this agent and its appropriate indication for treatment of atrial fibrillation. Furthermore, in some countries the results from the two quinidine meta-analyses have led to major changes in choice of treatment for atrial fibrillation. For instance, in Sweden, use of quinidine in patients with atrial fibrillation has been abandoned (Edvardsson, 1993).

Subsequently, other Class IA drugs such as disopyramide and Class IC antiarrhythmic agents, including flecainide, encainide, and propafenone, have been evaluated for terminating episodes of acute or paroxysmal atrial fibrillation and for maintenance of sinus rhythm after successful DC conversion in patients refractory to Class IA agents. Several small clinical trials have been conducted with various designs and involving a

wide range of patient populations. These trials involved either placebo-control and/or direct comparisons with other active antiarrhythmic drugs. Efficacy in those trials ranged from 39% to 64% at 6 months. Most have reported that noncardiovascular side-effects are rare, but cardiovascular toxicity, such as heart failure exacerbation, bradyarrhythmias, and atrial and ventricular proarrhythmia, occured in 7% to 27% of patients receiving those drugs (Bauernfeind and Welch, 1990; Edvardsson, 1993). In addition, although Class IC agents appear to be effective in preventing the recurrence of atrial fibrillation, even in patients who have been refractory to quinidine, they tend to depress myocardial function and thus increase the risk of serious proarrhythmia, particularly late proarrhythmia (Falk, 1989). The Cardiac Arrhythmia Suppression Trial (CAST) has highlighted this postulation since 1989 (The Cardiac Arrhythmia Suppression Trial Investigators, 1989). Although this study was designed to test whether suppression of premature ventricular contraction would improve survival prior to myocardial infarction, some physicians have suggested that such agents should also not be used for treating atrial fibrillation or for maintaining sinus rhythm (Anderson, 1990). In the USA and Sweden, these drugs are only approved for treatment of supraventricular arrhythmia in patients devoid of any complicated heart disease (Edvardsson, 1993).

Recently, newer Class III agents, mainly amiodarone and sotalol, have been introduced to the market as alternatives to quinidine and Class IC agents (Anonymous, 1989; Follath *et al.*, 1993; Levy, 1994). These agents act by prolonging the duration of action potential with corresponding prolongation of refractoriness of the myocardial tissue (Vaughan Williams, 1992). Amiodarone is being unique by possessing all other four Classes' actions (Edvardsson, 1993). Several studies have reported high efficacy rates with this agent ranging from 50% to almost 80% (Zarembski *et al.*, 1995). Studies have shown that amiodarone may produce lower mortality compared with Class I drugs in patients with previous myocardial infarction or advanced heart disease (Middlekauff, 1991). However, it was associated with long-term toxicity, particularly pulmonary fibrosis, alopecia, hyperthyroidism or hypothyroidism, and visual disturbances (Wilson and Podrid, 1991). Nevertheless, most of these adverse effects were dose-related, and were not reported in patients receiving less than 300 mg/day (Dusman, 1990). Furthermore, amiodarone has a long half-life, with considerable interindividual variation (13 to 17 days), and the elimination period can reach 12 months, particularly in elderly subjects (Puech, 1991). This would limit its use to second-line therapy where other agents fail (Bauernfeind and Welch, 1990). On the other hand, sotalol, which possesses a non-selective beta-blocker activity in addition to

Class III action, has been shown to be highly effective for maintenance of sinus rhythm in up to 50% of patients at 6 months with little serious toxicity (Juul-Moller *et al.*, 1990). The antiarrhythmic efficacy of sotalol in maintenance of sinus rhythm is mainly ascribed to its beta-blocking activity, which rendered sufficient rate-control, either during chronic atrial fibrillation or during relapse of paroxysmal atrial fibrillation (Edvardsson, 1993). However, sotalol is contraindicated in the patient with impaired cardiac function, due to its significant negative inotropic effects.

A recent meta-analysis was conducted to assess the efficacy of flecainide and amiodarone for maintenance of sinus rhythm (Zarembski *et al.*, 1995). The studies included in that meta-analysis have no placebo-controlled population. Furthermore, direct comparisons of the data obtained from the amiodarone and flecainide population were not possible. In this meta-analysis patients with paroxysmal atrial fibrillation and those who develop atrial arrhythmias prior to surgery were excluded.

A systematic search for published meta-analyses of antiarrhythmic drugs clinical trials did not identify any meta-analysis designed to estimate the magnitude of effect of sotalol for the treatment of atrial fibrillation.

Due to the previously reported difficulties associated with the treatment of atrial fibrillation, and as a result of the growing interest in this broad area of use of antiarrhythmic drugs (Singh, 1995), this chapter describes a meta-analysis which was conducted with the following objectives:

- To confirm the results of the previously conducted meta-analyses of quinidine for maintenance of sinus rhythm (Coplen *et al.*, 1990; Reimold *et al.*, 1992).

- To estimate the relative efficacy of sotalol, amiodarone, and flecainide for maintenance of sinus rhythm in patients with paroxysmal or chronic atrial fibrillation in studies with long term follow-up ($\geq$ 3 months).

- To undertake a subgroup analysis to identify patients, who are more likely to benefit from a particular treatment.

- To examine the impact of various study designs on outcome in trials of antiarrhythmic agents.

- To assess quantitatively the incidence rate of proarrhythmic events, mortality due to various causes, new congestive heart failure, and other serious side effects upon treatment with any of the agents considered.

- Assessment of possible publication bias using contemporary approved graphical and numerical techniques.

4.2 METHODS

4.2.1 Definition of Inclusion Criteria

4.2.1.1 Design of Primary Studies

Studies using the following designs were included: randomised controlled trial with parallel control group(s), randomised controlled trial with sequential controls (cross-over study), non-randomised controlled trial with parallel control group(s), non-randomised controlled trial with sequential controls (non-random cross-over), and uncontrolled trials which involved one treatment group without application of randomisation for allocation of treatment group. For the randomised controlled and non-randomised controlled, the simultaneous control group may either receive placebo, no active treatment, or any other active antiarrhythmic agents for the purpose of direct comparison.

In the clinical trials evaluating the effectiveness of treatment for maintenance of sinus rhythm, it was crucial for a study to be included to have carried a longitudinal follow-up of the patients after cardioversion for a period of not less than three months.

4.2.1.2 Diagnostic Criteria and Types of Patients Included

Patients of any age, and of either sex, with an established diagnosis of chronic or paroxysmal AF undergoing cardioversion to sinus rhythm, were included. Chronic AF was defined as continuous AF, in which sinus rhythm had been present briefly after prior pharmacological or electrical cardioversion. Paroxysmal AF was defined as recurrent self-terminating episodes lasting 48 hours, alternating with periods of sinus rhythm (Reimold *et al.*, 1993). Patients with chronic atrial flutter (AFL) or with other

forms of atrial tachycardia, such as supraventricular tachycardia (SVT), paroxysmal supraventricular tachycardia (PSVT), or paroxysmal atrial tachycardia (PAT), were also included. These patterns of arrhythmias usually occur simultaneously and generally degenerate into atrial fibrillation, which sometimes makes it difficult to distinguish from each other (Roark *et al.*, 1986; Henthorn *et al.*, 1991).

Trials that enrolled only patients with acute AF (<1 months), and/or AF that developed prior to cardiac or thoracic surgery, were excluded.

4.2.1.3 Types of Interventions

Interventions involved comparisons of orally or intravenously administered doses of quinidine, flecainide, amiodarone, or sotalol versus placebo and/or any other antiarrhythmic agents given initially for cardioversion to restore sinus rhythm. The trials were included if the dose was titrated sequently to the maximum tolerated doses or until the sinus rhythm was restored, to avoid misinterpretation of inefficacy at low doses. If the atrial fibrillation persisted, direct-current cardioversion could be performed. After restoration of sinus rhythm by either electrical or pharmacologic cardioversion prior to the dose titration phase, maintenance doses could be adjusted downward to avoid or reduce side-effects if necessary.

4.2.1.4 Study Parameters and Outcomes

Trials were included if they reported the maintenance of sinus rhythm as the primary end point, and if they provided information from which the number of patients remaining in sinus rhythm at different follow-up time points could be obtained. Maintenance of sinus rhythm was documented by the absence of AF attack as recorded in a telemetry ward, and later by 12-lead electrocardiogram, Holter monitoring as reported by general practitioners, and/or electrocardiogrphic telephone transmitteror as reported by patients (Reimold *et al.*, 1993; Zarembski *et al.*, 1995).

The secondary end points reported in the clinical trials were the incidence of deaths, proarrhythmic events, or other severe adverse effects. Proarrhythmia was defined according to the criteria proposed by Morganroth *et al.* (Chapter Two).

Trials were excluded if they did not satisfy any of the above inclusion criteria, if they

provide unclear explanation of study design, or if follow-up data at different time points were not reported.

4.2.2 Data Identification and Selection of Primary Trials

To identify all clinical trials of flecainide, sotalol, and amiodarone in maintaining sinus rhythm after cardioversion, the English and non-English language literature was scrutinised from 1966 to July 1997, using MEDLINE database and the Bath Institute of Scientific Information Data Service (BIDS). Both the BIDS EMBASE and BIDS ISI were searched respectively. The subject heading employed were 'atrial fibrillation', 'clinical trials', 'comparative study', 'random allocation', 'randomised controlled trials', 'placebo', 'double-blind method', 'single-blind method'.

Table 4.1 MEDLINE search strategy

Step No.	Method of search
1	ANTIARRHYTHMIC AGENTS explode
2	ATRIAL FIBRILLATION*
3	explode ATRIAL FIBRILLATION/all subheadings in MeSH
4	ATRIAL ARRHYTHMIA*
5	explode ATRIAL ARRHYTHMIA / all subheadings in MeSH
6	CARDIOVERSION explode
7	HUMAN
8	(1 or 2 or 3 or 5 or 6) and (HUMAN in MeSH)
9	Name of the drug explode
10	8 and 9
11	CLINICAL
12	TRIALS
13	CLINICAL TRIALS
14	EXPLODE CLINICAL-TRIALS / all subheadings in MeSH
15	RANDOM*
16	RANDOM-ALLOCATION (Term allows no subheadings) in MeSH
17	RANDOMISED-CONTROLLED-TRIALS / all subheadings in MEeSH
18	DOUBLE-BLIND-METHOD explode
19	SINGLE-BLIND-METHOD explode
20	PLACEBO (Term allows no subheadings) in MeSH
21	PLACEBO (text word)
22	META-ANALYSIS explode
23	OVERVIEW explode
24	HUMAN
25	(11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23) and
26	25 and 8
27	25 and 9
28	26 and 9

All of these terms were combined with each drug in MEDLINE database by applying a strategy which allows the identification of the maximum number of clinical trials reports using the combination of text words, "wild cards" and MeSH (Medical Subject Headings) terms as shown in Table 4.1.

A similar strategy was used in BIDS EMBASE and BIDS ISI by combining the previous terms with drug names cited in the title, abstract, and/or keywords as shown in the Table 4.2. Although the period covered by MEDLINE extended back to 1966, BIDS search covered the period from 1981 to July 1997.

Table 4.2 BIDS search strategy

Step No.	Method of search
1	ANTIARRHYTHMIC AGENTS in title, keyword, and abstract
2	ATRIAL FIBRILLATION* in title, keyword, and abstract
3	ATRIAL ARRHYTHMIA* in title, keyword, and abstract
4	CARDIOVERSION in title, keyword, and abstract
5	HUMAN in title, keyword, and abstract
6	Name of the drug
7	1+5+6
8	2+5+6
9	3+5+6
10	4+5+6
11	CLINICAL TRIALS in title, keyword, and abstract
12	11+6
13	RANDOM in title, keyword, and abstract
14	13+6
15	DOUBLE-BLIND in title, keyword, and abstract
16	15+6
17	SINGLE-BLIND in title, keyword, and abstract
18	17+6
19	PLACEBO
20	19+6
21	1+12, 1+14, 1+16, 1+18, then 1+20
22	2+12, 2+14, 2+16, 2+18, then 2+20
23	3+12, 3+14, 3+16, 3+18, then 3+20
24	4+12, 4+14, 4+16, 4+18, then 4+20

Trade names of the drugs such as Tambocor and R-818 for flecainide; Cordarone and Amiodarone Hydrochloride for amiodarone; and Beta-Cardone, Sotacor, Sotazide, and Tolerzide for sotalol, were also combined.

Relevant reports of clinical trials and meta-analyses were identified, recorded and

photocopied. The references cited in reports of clinical trials, meta-analyses, and reviews were scanned to identify other pertinent studies missed by the computerised search. Articles not available in the local university's libraries were requested through inter-library loans. Manual search of germane textbooks and INDEX MEDICUS (1996-1997) complemented the search. Letters were sent to the information officers of the pharmaceutical companies which are known to manufacture or market each drug to supply any information on unpublished trials. An attempt was made to identify obvious duplications in the studies retrieved. When there was duplication, the most recent report was used in the analysis, supplemented with information in earlier reports where necessary. Letters to the editors, case reports, foreign language reports without English abstracts, trials of the drugs for other potential indications, pharmacokinetic trials, and reviews were obtained and cited, but were not included in the analysis. Clinical trials of flecainide, amiodarone, and sotalol, were assessed for inclusion using the predefined inclusion and exclusion criteria (section 4.2.1).

4.2.3 Data Extraction

Data concerned with any of the following subheadings were extracted from the text, tables, and figures in the published clinical trials.

4.2.3.1 Study Design Characteristics

Clinical trials identified for each drug (flecainide, amiodarone, sotalol) were Classified according to the scheme proposed by Bailar *et al.* (1984): randomised controlled trials with parallel or sequential control groups, non-randomised controlled trials with parallel or sequential control; uncontrolled studies. For each trial the following information with regard to execution and protocol was extracted:

- Name of the first author
- Publication status (full report/ abstract/ unpublished data)
- Publication date
- Design of the study
- Number of patients enrolled
- Number of patients in the full-exposure group defined as patients who were randomised, and received study medication even if the patient did not achieve sinus rhythm after cardioversion, or had no long-term follow-up

• Number of patients in the long-term treatment group, which includes patients who received one of the maintenance drugs under investigation or placebo, and were followed up longitudinally after they were successfully converted to sinus rhythm, either pharmacologically or electrically. This group excludes patients who failed to achieve sinus rhythm after cardioversion, patients who experienced intolerable side effects, patients lost to follow-up due to death, or patients excluded from longitudinal follow-up for various reasons
• Number of patients allocated to each treatment group
• Control used (active (name of drug) or placebo)
• Dosage regimen during the initial titration phase and then maintenance dose during follow-up (mg/day)
• Time of randomisation to study medication or control (before or after cardioversion)
• The use of direct current cardioversion (DCC)
• Previous agents used
• Concomitant drugs administered which are most commonly ventricular rate regulating agents (digoxin, beta-blockers, and calcium-channel blockers) and anticoagulants
• Duration of follow-up (months).

4.2.3.2 Population Characteristics of the Included Studies

The following details of patient population (in all treatment groups) were extracted from each trial when available:

• Overall reported mean age (range) for all study groups, and for each study group if available
• Number of males/ number of females
• Left atrial diameter, mm (range), as measured by echocardiographic examination
• Duration of atrial fibrillation (AF) defined as the number of months since the first documented occurrence of AF
• Pattern of AF (chronic, paroxysmal), and number of patients with each pattern
• Number of patients with other forms of supraventricular arrhythmias (AFL, PAT, and PSVT)
• Cardiac diagnosis and likely etiologies of AF in patients enrolled. The number of patients with a given cardiac diagnosis in both the treatment and control group was tabulated separately.

4.2.3.3 Outcome Measures

The following data essential for analysis of efficacy and adverse effects was extracted:

- The number of patients converted to sinus rhythm by means of drug alone in each of the study groups
- The number of patients converted to sinus rhythm by means of drug and direct current cardioversion in each of the study groups
- The number of patients remaining in sinus rhythm at 3, 6, and 12 months after successful cardioversion in each of the study groups, where available.
- Censored observations in each study according to Kaplan-Meier analysis from the text (Coldman and Elwood, 1979; Reimold *et al.*, 1992).
- The number of patients remaining at risk was deduced from the Kaplan-Meier survival graph. However, if the numbers of patients remaining in sinus rhythm at 3, 6, and 12 months tabulated in the paper matched the ones on the graph, it was assumed that there was no censoring.
- The cumulative incidence of death, proarrhythmia, or any adverse effect in each study arm was collected, on an intention-to-treat basis.

4.2.4 Statistical Analysis and Data Synthesis

4.2.4.1 Efficacy Outcome

The pooled proportion (P) of patients remaining in sinus rhythm at 3, 6, and 12 months, in either the treatment or control group, was calculated separately for each trial design (Coplen *et al.*, 1990; Reimold *et al.*, 1992) as follows:

$$P = \frac{\sum(S.W)}{\sum W}$$

where S is the Kaplan-Meier estimate (proportion) of patients remaining in sinus rhythm at certain time point t for each individual study, and W = 1/(variance of S). The variance of S is calculated according to Greenwood's formula (Hunter and Schmidt, 1990) as follows:

$$(S)^2 . \frac{d}{n\ (n-d)}$$

where d is the number of patients reverting to sinus rhythm in the interval (t-1) to t, and n_t is the total number of patients at risk during, or at the beginning of, the same interval.

For comparing treatments the rate difference (RD) in the proportions of patients maintaining sinus rhythm with the two drugs being compared, was calculated for each individual study. The RD values were pooled using the fixed-effects assumption, unless a test of homogeneity was statistically significant. In such a case, the DerSimonian and Laird random-effects model was employed (Chapter 3).

In addition, reference standard values for P with quinidine at 3, 6 and 12 months (that were obtained from the meta-analysis by Coplen *et al.* (1990)), were employed to calculate the individual and pooled RDs of each trial design, particularly, uncontrolled studies, which lack a formal comparison to placebo or active control. These values were equal to 69.4%, 57.7% and 50.2% at 3, 6 and 12 months respectively.

To compare the P of different treatment groups in different trial designs (for example, P_T of randomised controlled trials versus P_T of non-randomised controlled), the Z value was calculated as follows:

$$z = \frac{P1_T - P2_T}{\sqrt{SIV}}$$

where $P1_T$ and $P2_T$ are pooled estimates of the percentage of patients in sinus rhythm at time t for groups 1 and 2 respectively, and SIV is the sum of the variances of $P1_T$ and $P2_T$. The statistical significance of z can be obtained from tables of standard normal distribution, where $z > 1.96$ gives a two-sided significance p value of < 0.05.

4.2.4.2 Subgroup Stratified Analyses

Stratified analysis according to the trial design, type of control (placebo or active drug), and type of patients (chronic or paroxysmal AF), was undertaken to identify sources of clinical and statistical heterogeneity of effect. Details of this analysis are shown in Table 6 of Appendix 4.2.

4.2.4.3 Mortality and Adverse Effects

The incidence of mortality, proarrhythmia, and other side effects were estimated by employment of various statistical parameters that are well defined for dichotomous data. These parameters included the odds ratio (OR), relative risk (RR), and rate difference (RD) and their 95% CI. The employment of these different parameters would verify the robustness of the results, since each one has its own value, and none of them was judged to be better than the others (Berlin *et al.*, 1989). However, RD is typically preferred due to its absolute clinical representation.

The individual and pooled OR were calculated by both the Mantel and Haenszel technique for combining data from a series of 2×2 tables, as well as by Peto's method as described in Chapter 2. The 95% confidence interval for the Mantel-Haenszel odds ratio were calculated by the method of Woolf (1955). The individual and pooled RR and RD were calculated under the assumption of fixed-effects model (Rothman, 1986). To avoid bias in OR estimation when small numbers are analysed, or when zero values are reported, 0.5 was added to each cell in the 2×2 table before calculation. The test of homogeneity was performed in each case to examine the consistency of trend across studies. The random-effects model would be utilised if heterogeneity existed.

The previous parameters were computed separately for each trial design and for each drug.

4.2.4.4 Patients' Cardiac Diagnoses

The chi-square test was used to estimate the differences in distribution of cardiac diagnoses across trials' populations of different drugs (amiodarone, sotalol, and flecainide clinical trials), and across various treatment groups.

4.3 RESULTS

4.3.1 Description of Trials Identified

Literature search between 1966 and July 1997 identified a total of 119 published studies of amiodarone (45), sotalol (28), and flecainide (47), examining their efficacy for

maintenance of sinus rhythm prior to cardioversion of chronic or paroxysmal atrial fibrillation. Only 42 (Appendix 4.1) of these studies were trials that satisfied the inclusion criteria (17 for amiodarone, 8 for sotalol, and 19 for flecainide). The remaining 77 studies (28 for amiodarone, 20 for sotalol, and 29 for flecainide) were omitted from analysis due to the following reasons: the trial was designed to test the efficacy for acute conversion of recent-onset AF of ≤72 hours (Appendix 5.1: 12 for amiodarone, 5 for sotalol, 15 for flecainide), or AF developed after a cardiac or thoracic surgery (Appendix 5.1: 3 for amiodarone, 5 for sotalol, 4 for flecainide) to normal sinus rhythm, with short study observation period; the study was designed to evaluate other secondary efficacy endpoints such as control of ventricular rate both at rest and during exercise (1 for sotalol, Appendix 4.1: 1); published report did not contain longitudinal follow-up data for the patients at different time points prior to cardioversion (9 for amiodarone, Appendix 4.1: 1, 3, 4, 5, 6, 7, 8, 9, 10; 5 for sotalol, Appendix 4.1: 3, 4, 7, 8, 9; 3 for flecainide, Appendix 4.1: 3, 4, 9); the design of the trial permitted the addition of other concomitant antiarrhythmic drugs to the amiodarone sotalol, or flecainide treatment arms at any stage of the trial (1 for amiodarone, Appendix 4.1: 3; 1 for sotalol, Appendix 4.1: 2); the trial was a duplicate publication (1 for sotalol, Appendix 4.1: 6; 5 for flecainide, Appendix 4.1: 1, 2, 5, 6, 7); and data were reported in the form of review (2 for the flecainide, Appendix 4.1: 8, 11), or case report (1 for sotalol, Appendix 4.1: 5).

The characteristics of the trials of amiodarone, sotalol, and flecainide included in the analysis are summarised in Tables 4.3, 4.4, and 4.5 respectively. As shown for amiodarone, 5 studies were RCTs, and 12 trials were uncontrolled. For sotalol, 6 studies were RCTs, and 2 trials were nonrandomised controlled. For flecainide, 9 studies were RCTs, 4 trials were nonrandomised controlled, and 6 trials were uncontrolled. 11 of the total 20 RCTs employed placebo comparisons (2 for amiodarone, 2 for sotalol, and 7 for flecainide). 11 were head to head comparisons of various antiarrhythmic drugs. 10 RCTs adopted an open-label, parallel design (5 for amiodarone, 3 for sotalol, and 2 for flecainide). 2 RCTs were double-blind, parallel design (1 for sotalol, and 1 for flecainide), and 5 RCTs were double-blind, crossover design (all for flecainide). All the nonrandomised trials utilised an open-label, crossover design.

The included trials enrolled a total of 3937 patients, however; the full exposure group involved 3712 patients. Data regarding the maintenance of sinus rhythm during the long-term follow-up were provided for 3534 patients: 876 patients received

Table 4.3 Characteristics of randomised controlled, and uncontrolled trials of amiodarone included in analysis

Randomised

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Amiodarone/Control)*	*Type of control*	*Full exposure group*	*Dosage; LD and maintenance dose (mg/day)*	*Time amiodarone started*	*DCC*	*Concomitant drugs*	*Duration of follow-up months (range)*
Vitolo *et al.* 1981	54 chronic AF	54	28/26	Quinidine	23	400 mg/day for the first 15 days; then for 5 days each week (oral)	After CV	NA	Quinidine was added to amiodarone for the first 7 days	12.6 (6-36)
Martin *et al.* 1986	70 PAF	65	43/22	Disopyramide	70	600 mg/day for 2 weeks; then 400 mg for a further 2 weeks; then 200 mg daily (oral)	NA	NA	Possibly digoxin	16.2
Bosi *et al.* 1990	97 chronic AF	97	48/49	Placebo	97	600 mg/day for 10 days; then 1 gm/week for 30 days; then maintenance dose (NS) for 12 to 48 months (oral)	After CV	NA	Not used	(12-48)
Zehender *et al.* 1992	40 chronic AF	23	12/11	Quinidine + Verapamil	40	200 mg/3 h (IV); then 50 mg/h for 3 days; then 200 mg 4 times/day for 11 days; then maintenance dose of 200 mg/day	Before CV	Nonresponders to amiodarone were treated with electrical cardioversion	Heparin 15,000 I.U./day subcutaneously	24
Jong *et al.* 1995	87 chronic AF	83	40/43	Placebo	87	200 mg three times a day for 4 weeks; then 200 mg/day for 1 month; then 200 mg every other day for 1 month (oral)	Before CV	After 4 weeks if patient not in NSR	Possibly low dose propranolol or verapamil to control the ventricular rate of AF below 100 beats per minute	6 (2-15)

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; IV, intravenous; NSR, normal sinus rhythm

Table 4.3 Characteristics of randomised controlled, and uncontrolled trials of amiodarone included in analysis (continued)

Uncontrolled

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Amiodarone /Control)*	*Full exposure group*	*Dosage*	*Time amiodarone started*	*DCC*	*Previous agent used*	*Concomitant drug*	*Duration of follow-up months (range)*
Leak *et al.* 1979	9 PSVT 2 PAF 3 PSVT+WPW	14	14	14	600-800 mg/day for 3 weeks; then 200-600 mg/day	Before CV	Only when required due to attacks	Quinidine, procainamide, disopyramide, antazoline, lidocaine, bretylium, propranolol, phenytoin	NS	16.8
Blomtrom *et al.* 1984	13 chronic AF 8 PAF	21	21	21	600 mg/day for 1 week; then 200 mg daily	Before CV	After 2-4 weeks	NS	Conceivably digoxin	19 (3-48)
Podrid *et al.* 1981	20 PAF 9 PSVT	29	29	29	600 mg/day for 1 week; then reduced to 200 mg/day; then it may be increased to 400 mg/day	NA	NA	Quinidine, procainamide, aprinidine, mexiletine, bretylium, propranolol, phenytoin, disopyramide, lorcainide, encainide	NS	13.4 (4-40)
Grasboys *et al.* 1983	121 chronic AF	121	121; 95 AF, 21 SVT, 5 AF+SVT	121	600-1200 mg/day for 5-7 days; then 200-600 mg/day	Before CV	After loading dose if required	Quinidine, procainamide, aprinidine, mexiletine	Digoxin, verapamil, ß-blockers	27.3
Horowitz *et al.* 1985	11 chronic AF 27 PAF	38; 10 chronic AF 27 PAF	11 chronic AF 27 PAF	11 chronic AF 27 PAF	1 g/day for 5 day; then 600 mg/day for 1 month; then 400 mg/day for 3 months; then 200 mg/day	Before CV	After 1 month if patient not in NSR	Quinidine, procainamide, disopyramide	Digoxin, ß-blockers, calcium channel blockers	15
Gold *et al.* 1986	68 chronic AF or PAF	68	68	68	800 mg/day for 1 week; then 400 mg/day	Before CV	After 4-6 weeks if patient not reverted to NSR	Quinidine, procainamide, disopyramide	Digoxin, ß-blockers, calcium channel blockers	21 (3-56)

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; WPW, Wolf-Parkinson syndrome; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; NSR, normal sinus rhythm

Table 4.3 Characteristics of randomised controlled, and uncontrolled trials of amiodarone included in analysis (continued)

Uncontrolled (continued)

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Amiodarone/Control)*	*Full exposure group*	*Dosage*	*Time amiodarone started*	*DCC*	*Previous agent used*	*Concomitant drug*	*Duration of follow-up months (range)*
Blevins *et al.* 1987	38; 25 chronic AF 13 PAF	32; 19 chronic AF, 13 PAF	32	38	5 mg/kg IV over 30 min; then 600-800 mg/day for 5-7 days; then 200-400 mg/day	Before CV	after 4-5 weeks if no conversion, or earlier if hemodynamically unstable	Quinidine, procainamide, disopyramide	Digoxin, ß-blockers, calcium channel blockers	16 (3-27)
Brodsky *et al.* 1987	28 chronic AF	28	28	28	600 mg/day for 30 days; then 400 mg/day for 30 days; then 200-400 mg/day	Before CV	After 1 month of amiodarone therapy if patient not in NSR	Quinidine, procainamide, flecainide	Digoxin, ß-blockers, calcium channel blockers	22 (12-38)
Mostow *et al.* 1990	19; 9 AF, 1 AFL, 6 PAF, 3 atrial tachycardia	19	19	19	1600 mg/day for 4 days; then 400-800 mg/day	Before CV	After 48-96 hours if the patient not in NSR	Quinidine, procainamide, disopyramide	discontinued before amiodarone dosing	16.1
Levy *et al.* 1991 (abstract)	112 chronic AF	102	102	112	200 mg/day	Before CV	After 4 weeks for all patients	Class IA antiarrhythmic drugs	NS	12
Gosselink *et al.* 1992	89 chronic AF	89	89	89	600 mg/day for 4 weeks; then 200 mg/day	Before CV	After 1 month if patient not in NSR	Flecainide, sotalol, quinidine, disopyramide, propafenone	Discontinued before starting amiodarone dosage	20.7
Chun *et al.* 1995	110; 53 chronic AF or AFL 57 PAF	110	110	110	800 mg to 1,600 mg/day for 7 to 14 days; then 200 to 300 mg/day (mean 268±100)	Before CV	After 30 days if sinus rhythm was not restored	NS	NS	36 (1-137)

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; NSR, normal sinus rhythm

Table 4.4 Characteristics of sotalol clinical trials included in analysis

Randomised controlled

Study name	*Year of publication*	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Sotalol/Control)*	*Type of control*	*Full exposure group*	*Dosage; LD and maintenance dose (mg/day)*	*Time sotalol started*	*DCC*	*Previous agent used*	*Concomitant drug*	*Duration of follow-up months*
Juul-Moller *et al.*	1990	183 AF	174	95/79	Quinidine	174	160 mg/day for 1 week; then 320 mg/day	After CV	Started before randomisation for all patients	NS	Digoxin	6
Singh *et al.*	1991	34 AF	18	12/6	Placebo	34	80-320 mg/day	Before CV	If sinus rhythm could not be established during treatment	NS	Digoxin	6
Reimold *et al.*	1993	53 AF 47 PAF	98	49/49	Propafenone	100	160-320 mg/day; then a maintenance dose of 160-960 mg/day	Before CV	If sinus rhythm was not restored at the highest tolerated dose	Quinidine, procainamide, disopyramide	Possibly ß-blockers, calcium channel blockers	12
Kalusche *et al.*	1994	82 AF	78	41/37	Quinidine/verapamil combination	82	NS	Before CV	If sinus rhythm could not be established during treatment	NS	NS	12
Carunchio *et al.*	1995	66 PAF	66	20/26/20	26 Placebo 20 Flecainide	66	NS	NA	NA	NS	NS	12
Hohnloser *et al.*	1995	50 AF	38	17/21	Quinidine	50	160 mg/day at day 1; then 320 mg/day for the next 6 days; then 160-320 mg/day	Before CV	On day 8 in patients with persistent AF	NA	Digoxin, warfarin sodium, heparin	6

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; NSR, normal sinus rhythm

Table 4.4 Characteristics of sotalol clinical trials included in analysis (continued)

Non-randomised controlled (sequential or serial treatment)

Study name	*Year of publication*	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Sotalol/Control)*	*Type of control*	*Full exposure group*	*Dosage; LD and maintenance dose (mg/day)*	*Time sotalol started*	*DCC*	*Previous agent used*	*Duration of follow-up*
Crijns *et al.*	1991	186 AF	127	53/ 127/ 34	127 Flecainide 34 Amiodarone	127	320 mg/day	After CV	Before initiation of treatment with flecainide in stage I and electrical recardioversion for a recurrence before entering stage II (sotalol) and stage III (amiodarone)	NA	5.6
Antman *et al.*	1990	109 AF 53 PAF 56	109	48/109	Propafenone	109	160-960 mg/day	Before CV	Cardioversion was performed when sinus rhythm had not been restored pharmacologically at the maximum tolerated dose. One or more additional cardioversion procedures were performed if recurrent atrial fibrillation occurred after an initial successful cardioversion	Conventional. type IA antiarrhythmic drugs: Quinidine, procainamide or disopyramide	5.6

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; NSR, normal sinus rhythm

Table 4.5 Characteristics of randomised controlled, nonrandomised control, and uncontrolled trials of flecainide included in analysis

Randomised controlled

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Flecainide/Control)*	*Type of control*	*Full exposure group*	*Dosage; LD and maintenance dose (mg/day)*	*Time Flecainide started*	*DCC*	*Previous agent used*	*Concomitant drugs*	*Duration of follow-up months (range)*
Rasmussen *et al.* 1988 (abstract)	60 chronic AF	56	28/28	Disopyramide	60	300 mg/day	Before CV	NA	NS	NS	6
Van-Gelder *et al.* 1989	180 chronic AF	73	36/37	No treatment	81	180±32 mg/day	After CV	Before initiation of treatment for all patients and recardioversion for no-treatment group if arrhythmia recurred	NS	Anticoagulants, verapamil	12
Anderson *et al.* 1989‡	64 PAF	48	48/48	Placebo	64	200-400 mg/day	Before CV	NA	Digitalis, class I agents, amiodarone, Beta-blocker, Calcium channel antagonist	Digitalis glycosides	5
Pritchett *et al.* 1991‡	73; 28 PSVT, 45 PAF or PAFL	42; 14 PSVT, 28 PAF or PAFL	42/42	Placebo	50	50, 100, 200, and 300 mg/day (patients entered all dosage period)	Before CV	NA	NS	Digitalis glycosides	4
Henthorn *et al.* 1991‡	51 PSVT	34	34/34	Placebo	48	300 mg/day	Before CV	NA	Digoxin, Beta-blocker, Calcium channel antagonist	All agents discontinued before initiation of treatment	4
Pietersen *et al.* 1991‡	48 PAF or PAFL	43	43/43	Placebo	48	300 mg/day	Before CV	NA	NS	Digitalis glycosides	3
Lau *et al.* 1992‡	19 PAF	19	19/15/18	15 Placebo 18 Quinidine	19	200 mg/day	Before CV	NA	Digoxin, Beta-blocker	All agents discontinued before initiation of treatment	32
Chimienti *et al.* 1994	335; 200 PAF, 135 PSVT	265; 159 PAF, 106 PSVT	129/136	Propafenone	335	100 or 200 mg/day	Before CV	NA	NS	NS	12

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; NSR, normal sinus rhythm; ‡, randomised placebo-controlled crossover study

Table 4.5 Characteristics of randomised controlled, nonrandomised control, and uncontrolled trials of flecainide included in analysis (continued)

Non-randomised controlled

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Flecainide/Control)*	*Type of control*	*Full exposure group*	*Dosage; LD and maintenance dose (mg/day)*	*Time Flecainide started*	*DCC*	*Previous agent used*	*Concomitant drugs*	*Duration of follow-up months (range)*
Crijns *et al.* 1991	186 AF	127	127/ 34/ 53	53 Sotalol 34 Amiodarone	127	420±98 mg/day	After CV	Before initiation of treatment with flecainide in stage I and electrical recardioversion for a recurrence before entering stage II (sotalol) and stage III (amiodarone)	NA	Diuretics, angiotensin-converting enzyme inhibitor, verapamil	25
Anderson *et al.*† 1994	49; 21 PSVT, 28 PAF	42	42/42	Placebo-baseline	49	200 or 300 mg/day	Open label follow up after CV	NA	Flecainide	NS	17
Mary-Rabine *et al.* 1988	55; 39 PAF, 16 PSVT	55	55/13	Amiodarone + flecainide	55	100-300 mg/day	Before CV	NA	Digoxin, disopyramide, quinidine, Beta-blockers, amiodarone	NS	3-32
Leclercq *et al.* 1992	52 PAF	52	19/33	Amiodarone + flecainide	53	200 mg±22 mg/day without a loading dose	Before CV	NA	Amiodarone, quinidine	NS	12-69.6

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated; †, multicentre, open-label, outpatient, placebo-baseline controlled

Table 4.5 Characteristics of randomised controlled, nonrandomised control, and uncontrolled trials of flecainide included in analysis (continued)

Uncontrolled

Study name	*No. of patients enrolled*	*Long-term follow-up group*	*Treatment allocation (Flecainide /Control)*	*Full exposure group*	*Dosage*	*Time flecainide started*	*DCC*	*Previous agent used*	*Concomitant drug*	*Duration of follow-up months (range)*
Berns *et al.* 1987	39; 5 AF, 25 PAF, 9 PAT	39	39	39	200 mg/day; then dose adjustments (total dose 100-400 mg/day)	Before CV	For patients who did not convert to sinus rhythm within 10 days of initiation of therapy	Digoxin, Beta-blockers, Calcium channel antagonist, at least one class IA agent	Digoxin, Beta-blockers, Calcium channel antagonist	5.4
Zeigler *et al.* 1988	16 SVT	16	16	16	2.8-5.6 mg/Kg/day	Before CV	NA	NS	NS	9 (4-16)
Sonnhag *et al.* 1988	20 PAF	20	20	20	300 mg/day	Before CV	Had been attempted in 5 patients, totally, 14 times	Verapamil, digoxin, atenolol, disopyramide, quinidine, diltiazem, Beta-blockers, sotalol	Digoxin	11-38
Zee-Cheng *et al.* 1988	19 PSVT	15	15	19	200-400 mg/day	After CV	NA	NS	Beta-blockers	19 (2-48)
Anderson JL 1992	66; 41 PAF, 25 PSVT	66	66	66	300 mg/day	Open label follow up after CV	Only in 3 patients to terminate attacks of AF	Verapamil, digoxin, atenolol, disopyramide, quinidine, diltiazem	NS	15
Clementy *et al.* 1992	944 PAF	944	944	944	200-400 mg/day (mean; 190±33)	After CV	NS	Digoxin, Beta-blockers, Calcium channel antagonist	Attempted for conversion to sinus rhythm before initiation of treatment	9

AF, atrial fibrillation; AFL, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; PSVT, paroxysmal supraventricular tachycardia; LD, loading dose; CV, cardioversion; DCC, direct current cardioversion; NA, not applicable; NS, not stated

amiodarone, 335 received sotalol, 1746 received flecainide, 385 received placebo, and 636 received other antiarrhythmic drugs as active control (of which 144 patients received quinidine, 50 received disopyramide, 48 received quinidine/verapamil combination, 294 received propafenone, and 46 received amiodarone plus flecainide). The sample size of each study ranged from 14 to 944, with a mean of 94 patients over all the studies.

Initiation of treatment was started before cardioversion in 31 trials, after cardioversion in 9 trials, and it was not stated in 3 trials. The direct current cardioversion (DCC) was applicable in 24 trials (13 for amiodarone, 7 for sotalol, 5 for flecainide). An attempt for electrical recardioversion was made after a mean of 3.42 weeks (range 0.28 to 6) if sinus rhythm was not restored at the highest tolerated dose during treatment. However, DCC was not applicable in 18 trials (4 for sotalol, 1 for sotalol, 14 for flecainide).

The average follow-up time for all patients was 16.34±13.2 months (range 3 to 69.6), for amiodarone trials 19.23±10.3 months (range 4 to 48), for sotalol trials 9.83±6.5 months (range 3.9 to 25), and for flecainide trials 16.68±16.9 months (range 3 to 69.6).

The amiodarone dosage schedule varied across studies with an average loading dose of 766±371 mg/day (range 200 to 1600) for an average of 15 days (range 3 to 40), then an average maintenance dose of 333.41±184 mg/day (range 200 to 800). The sotalol dosage was started with an average loading dose of 296±250.3 mg/day for an average of 5 days (range 1 to 7), then a maintenance dose of 330±272 mg/day (range 80 to 960). Flecainide dose was initially titrated for individual patient from 200 to 400 mg/day, and the largest dose that was well tolerated was selected. The mean dose of flecainide received over all the studies was 232±101.1 mg/day (range 50 to 420).

4.3.2 Population Characteristics of the Included Studies

The mean age of the patients, across all studies which reported the age (38 studies) was 57.51±11.33 years (range 13 to 77). In the 36 studies reporting gender, there was a total of 1208 women and 1894 men with a mean of 55 men and 36 women in the sample. Only 29 studies stated the duration of atrial fibrillation disorders with a mean of 61.04±98.8 months (range 0.033 to 444). The left atrial diameter was mentioned in

18 studies, with a mean of 46.16±3.8 mm (range 42 to 57). Tables 1, 2, and 3 of Appendix 4.2 describe the details for characteristics of populations included in amiodarone, sotalol, and flecainide individual trials respectively.

Most trials enrolled only patients with chronic atrial fibrillation (7 for amiodarone, 5 for sotalol, and 3 for flecainide). Eight trials enrolled only patients with paroxysmal atrial fibrillation (1 for amiodarone, 1 for sotalol, and 6 for flecainide). Four trials (for flecainide) were performed in patients with paroxysmal supraventricular tachycardia or paroxysmal atrial tachycardia only. Sixteen trials dealt with a mixed patient population (9 for amiodarone, 1 for sotalol, and 6 for flecainide). From the total 4001 patients enrolled, 1743 patients had chronic atrial fibrillation (901 in amiodarone clinical trials, 638 in sotalol clinical trials, and 260 in flecainide clinical trials), 81 had atrial flutter (in amiodarone trials), 1942 had paroxysmal atrial fibrillation (271 in amiodarone clinical trials, 149 in sotalol clinical trials, and 1522 in flecainide clinical trials), 350 had paroxysmal supraventricular tachycardia (63 in amiodarone clinical trials, and 303 in flecainide clinical trials), and 12 had paroxysmal atrial tachycardia (3 in amiodarone clinical trials, and 9 in flecainide clinical trials).

The mean heart volume was only stated in two trials of amiodarone (Vitolo *et al.*, 1981; and Blomstrom *et al.*, 1984), and it was within radiologically normal limits. The cardiothoracic ratio was used for manifestation of cardiac severity in only one trial of amiodarone (Vitolo *et al.*, 1981), and it was <0.5.

Table 4.6 summarises the mean characteristics of patients treated with amiodarone, sotalol, flecainide, placebo, and other comparative antiarrhythmic drugs employed including quinidine, quinidine/verapamil combination, disopyramide, and propafenone. Patients' characteristics for each type of treatment group were tabulated separately. Continuous data were compared using unpaired t-test, and one way analysis of the variance. Discrete variables were compared using the chi-square test. The comparison in age, duration of atrial fibrillation, and left atrial diameter did not show any statistical differences among the treatment groups (P>0.05).

Cardiac diagnoses were reported for a total of 4073 patients. Tables 4, 5, and 6 of Appendix 4.2 show the different cardiac diagnoses of patients enrolled in amiodarone, sotalol, and flecainide clinical trials respectively. The distribution of the diagnoses was tabulated, and examined with respect to various treatment groups (Table 4.6), as well as different drugs' trial populations (Table 4.7). Valvular heart disease was the primary

Table 4.6 Mean characteristics of all treatment groups included in the analysis

Variables	*All treatment groups*	*Amiodarone*	*Sotalol*	*Flecainide*	*Placebo*	*Other comparative drugs (all)*	*Test of significance*	*P-value*
Study groups (N)	64	17	8	18	9	12	-	-
Patients (n)	3937	888	335	1746	385	645	-	-
Age	57.5±11.33	58.53±14.7	60.75±1.67	53.98±12.55	54.9±14.32	60.53±6.84	ANOVA F=0.7408	P=0.566
Chronic AF (n)	1743	803	269	198	139	252	χ^2=1019.24	P<0.0001
AFL (n)	81	81	0	0	0	0	χ^2=283.8	P<0.0001
PAF (n)	1942	244	42	1386	223	206	χ^2=501.9	P<0.0001
PSVT (n)	350	47	0	240	96	63	χ^2=141.9	P<0.0001
PAT (n)	12	3	0	9	0	0	χ^2=6.82	P=0.2511
Duration (months)	61.04±98.8	80.71±124	21.47±20.83	42.19±42.56	18.05±19.97	11.26±22.24	ANOVA F=1.3969	P=0.2511
Left atrial diameter (mm)	46.16±3.8	47.22±4.46	45.4±2.97	44.33±1.15	45.5±3.79	46.4±3.2	ANOVA F=0.3724	P=0.864
Cardiac diagnosis (n)	4073	887	608	1952	366	260	-	-
Valvular (n)	730	192	131	320	41	46	23.1	0.00012
Hypertension (n)	595	54	76	363	55	47	69.37	P<0.0001
Ischemic heart disease (n)	453	171	68	147	20	47	97.5	P<0.0001
Thyroid (n)	75	0	6	69	0	0	60.7	P<0.0001
Lone fibrillator (n)	1064	195	103	578	101	87	40.2	P<0.0001
Congenital heart disease (n)	43	15	9	16	3	0	8.4	P=0.078
Pericarditis (n)	0	0	0	0	0	0	-	-
Cardiac surgery (n)	117	31	36	38	6	6	28.92	P<0.0001
CHF (n)	554	110	130	217	95	2	109.41	P<0.0001
Cardiomyopathy (n)	172	84	15	46	5	22	96.51	P<0.0001
Miscellaneous (n)	270	35	34	158	40	3	38.9	P<0.0001

AF, atrial fibrillation; AFL, atrial flutter; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; ANOVA, One-way Analysis of the variance; χ^2, Chi-square test; †, total number of patients for whom cardiac diagnosis was reported; CHF, congestive heart failure

diagnosis in 20.7% of the population enrolled in the amiodarone clinical trials, 24.9% of the patients in the sotalol trials, and 15.7% of the patients in flecainide trials (P<0.0001). Hypertension was found in 5.8% of the amiodarone trials' populations, 18.7% of sotalol trials' populations, and 17.4% of flecainide populations (P<0.0001). The proportion of patients with ischemic heart diseases and cardiomyopathy was significantly higher in amiodarone and sotalol clinical trials than flecainide trials (P<0.0001). There were more patients with congestive heart failure or cardiac surgery in the sotalol clinical trials than in the amiodarone and flecainide trials. However, patients with thyroid dysfunction and lone fibrillator were more common in the flecainide trials (P<0.0001). In addition, examination of distribution of the same diagnoses across individual treatment groups as shown in Table 4.6 (patients receiving amiodarone, sotalol, flecainide, placebo, and active control separately), has confirmed significant statistical differences in all diagnoses categories (P<0.0001).

Table 4.7 Distribution of cardiac diagnoses in amiodarone, sotalol, and flecainide clinical trials

Diagnosis	*Amiodarone clinical trials n (%)*	*Sotalol clinical trials n (%)*	*Flecainide clinical trials n (%)*	*Chi-square test*	*P-value*
Valvular heart disease	225 (20.7%)	160 (24.9%)	332 (15.7%)	25.496	P<0.0001
Hypertension	63 (5.8%)	120 (18.7%)	367 (17.4%)	77.886	P<0.0001
Ischemic heart disease	193 (17.7%)	97 (15.1%)	157 (7.4%)	73.232	P<0.0001
Thyroid	0 (0%)	6 (0.9%)	69 (3.3%)	43.43	P<0.0001
Lone fibrillator (no heart disease)	258 (23.7%)	170 (26.5%)	605 (28.7%)	6.677	P=0.035
Congenital heart disease	16 (1.47%)	9 (1.4%)	18 (0.85%)	2.985	P=0.225
Pericarditis	0 (0%)	0 (0%)	0 (0%)	-	-
Alcohol associated	43 (3.9%)	36 (5.6%)	38 (1.8%)	27.48	P<0.0001
CHF	110 (10.1%)	132 (20.6%)	296 (14%)	31.544	P<0.0001
Cardiomyopathy	88 (8.1%)	33 (5.1%)	46 (2.2%)	58.635	P<0.0001
Miscellaneous	38 (3.5%)	34 (5.3%)	158 (7.5%)	19.797	P<0.0001
Total	1089	642	2110		

$\chi 2$, Chi-square test; CHF, congestive heart failure

4.3.3 Efficacy

4.3.3.1 Conversion to Sinus Rhythm

The efficacy for conversion to sinus rhythm via drug alone, or via drug and direct current cardioversion (DCC) was reported in only 22 papers: 10 for amiodarone (Zehender *et al.*, 1992; Jong *et al.*, 1995; Horowitz *et al.*, 1985; Gold *et al.*, 1986; Brodsky *et al.*, 1987; Levy *et al.*, 1991; Mostow *et al.*, 1990; Gosselink *et al.*, 1992; Blevins *et al.*, 1987; Leak *et al.*, 1979), 6 for sotalol (Juul-Moller *et al.*, 1990; Singh *et al.*, 1991; Reimold *et al.*, 1993; Kalusche *et al.*, 1994; Hohnloser *et al.*, 1995; Antman *et al.*, 1990) and 6 for flecainide: Gelder *et al.*, 1988; Rasmussen *et al.*, 1988; Anderson *et al.*, 1989; Pietersen *et al.*, 1991; Pritchett *et al.*, 1991; Henthorn *et al.*, 1991; Lau *et al.*, 1992; Sonnhag *et al.*, 1988; Anderson, 1992; Clementy *et al.*, 1992; Anderson *et al.*, 1994; Leclercq *et al.*, 1992; Crijns *et al.*, 1991; Mary-Rabine *et al.*, 1988; Chimienti *et al.*, 1994; Zeigler *et al.*, 1988; Berns *et al.*, 1987; Chouty *et al.*, 1988; Zee-Cheng *et al.*, 1988) as illustrated in Table 4.8.

Table 4.8 Conversion to NSR

Drug RCTs	*Converted to NSR via drug alone (no.of patients)*		*Converted to NSR via drug and DCC (no.of patients)*	
	Tx.group	*Cont.group*	*Tx.group*	*Cont.group*
Amiodarone RCTs	130/430 (30.2%)	11/63 (17.5%)	260/430 (60.5%)	25/63 (39.7%)
Sotalol RCTs	32/242 (13.2%)	54/239 (22.6%)	189/242 (78%)	177/239 (74%)
Flecainide RCTs	242/1068 (22.7%)	30/86 (34.9%)	215/1115 (19.3%)	37/86 (43%)

NSR, normal sinus rhythm; DCC, direct current cardioversion; Tx, treatment; Cont, control

The incomplete reporting of cardioversion efficacy data in many individual trials, as well as the variation in control groups, prevented the systematic pooling by meta-analysis techniques.

4.3.3.2 Maintenance of Sinus Rhythm

Prior to cardioversion, a total of 3937 patients were followed up for maintenance of sinus rhythm (993 in amiodarone clinical trials, 708 in sotalol clinical trials, and 1956 in flecainide clinical trials). Of the total 4088 patients enrolled initially (1006 in

amiodarone clinical trials, 810 in sotalol clinical trials, and 2276 in flecainide clinical trials) 284 patients were excluded from analysis for various reasons as shown in Table 4.9. A further 234 patients were lost to follow up (33 in amiodarone group, 2 in sotalol group, 199 in flecainide group, 2 in quinidine group, and 2 in placebo group), and a total of 456 patients were withdrawn due to intolerable side effects (77 receiving amiodarone, 23 receiving sotalol, 263 receiving flecainide, 38 receiving quinidine, 8 receiving quinidine plus verapamil, 10 receiving disopyramide, 13 receiving propafenone, and 24 receiving placebo).

The Kaplan-Meier percentages of patients remaining in sinus rhythm in the different treatment groups, the rate differences (RDs) obtained from individual trials, as well as the weight assigned to each trial, are listed in Tables 4.10, 4.11, and 4.12. Table 4.10 .a and Table 4.10.b give the results for amiodarone in the randomised controlled and uncontrolled trials respectively. Table 4.10.c and Table 4.10.d provide the results for sotalol from the randomised and nonrandomised controlled trials respectively. Similarly Tables 4.10.e, 4.10.f, and 4.10.g give the results for flecainide from randomised, nonrandomised controlled, and uncontrolled trials respectively. Tables 4.11, and 4.12 present similar results for the three drugs at 6, and 12 months respectively.

4.3.3.2.1 Amiodarone Clinical Trials

Figure 4.1 shows a conventional meta-analysis plot (Walker *et al.*, 1988) for the individual RDs, fixed-effects weighted mean RDs, and the random-effects corrected weighted mean RDs at 3, 6, and 12 months intervals. The solid vertical line on the plot indicates a zero-effect. The dark points represent the individual study effects. A negative RD value indicates lower efficacy for the treatment than control group. The horizontal lines around these point estimates represent the 95% confidence intervals for each trial's mean effect. A point estimate of the RD to the right of the solid line suggests higher efficacy level in the treatment group. However, it is only significantly higher (at $P<0.05$) if the entire confidence interval for that trial is also to the right of the solid line. This was only noticed for three trials (Vitolo *et al.*, 1981; Martin *et al.*, 1986; Jong *et al.*, 1995).

The absolute efficacy of amiodarone was tested in two trials only (Figure 4.1: Analysis group 1). One trial provided data at 3 months only (Jong *et al.*, 1995) and the other at

Table 4.9 Details of follow-up

Treatment group	*Amiodarone*	*Sotalol*	*Flecainide*	*Placebo*	*Others*
No. of patients excluded from analysis	47	24	142	37	34
Reasons for exclusion					
Failure to achieve sinus rhythm	22	20	6	28	13
Death	20	0	2	0	0
Intolerable side effects	5	0	24	8	12
Protocol violation	3	4	20	5	8
Others	15	0	21	14	1
No. lost to follow-up	33	2	199	2	2
No. of withdrawals due to intolerable side effects (%)	77 (8.7%)	23 (7%)	263 (15.1%)	24 (6.2%)	69 (10.8%)

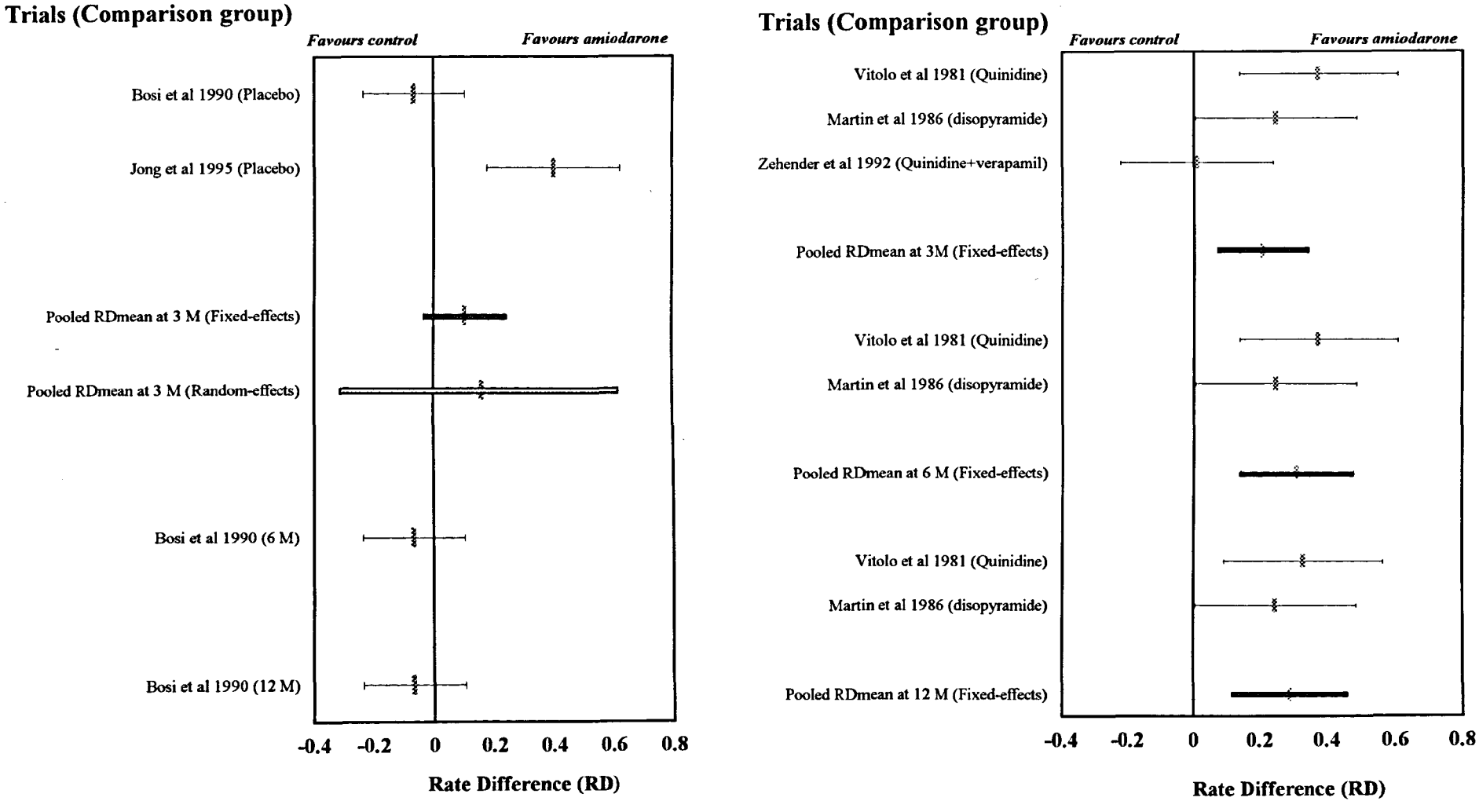

Figure 4.1 Amiodarone randomised clinical trials for maintenance of sinus rhythm (N=5); Analysis group 1: amiodarone vs placebo **(left panel)** and Analysis group 2: amiodarone vs class I **(right panel)**. The figure illustrates the individual study RDs with their associated 95%CI (error bars, thin lines). The weighted pooled mean RD in fixed or random-effects models are displayed at the bottom for each time interval (at 3, 6, and 12 months) in thick lines. The trials are in ascending order of the year of publication. The comparison groups are shown in brackets.

all time intervals (Bosi *et al.*, 1990). The pooled mean RD at 3 months was 10.2% (95% CI -3.34 to 23.7), which is statistically not significant (Z=1.48, P=0.139). The test of homogeneity was significant (Q=10.61, df=1, P=0.001). As a result, the data were pooled using a random effect model. The weight assigned for each trial in fixed and random-effects model are shown in Table 4.10.a. The corrected mean RD was 16.1 (95% CI -29.7 to 61.9). Although the point estimates of the pooled fixed and random-effects RDs versus placebo at three months intervals are to the right of the solid line, their wide confidence interval crosses it, indicating nonstatistical significance. The individual RD of the second trial at 6 and 12 months was statistically not significant (RD% = -6.7, 95% CI -23.6 to 10.2; Z= -0.77, P>0.05). However, the result of this trial may suffer from type two error reflected by the small sample size. A possible explanation for the heterogeneity in treatment effect between the two trials is the employment of low dose propranolol or verapamil to control the ventricular rate in the second trial (Jong *et al.*, 1995).

The direct comparisons of amiodarone (head to head comparison) to other antiarrhythmic drugs in Class I, have shown a significant treatment advantage in favour of amiodarone, which was maintained at all time intervals (Figure 4.1). The pooled mean RDs were 20.5%, 31.01%, 28.8% at 3, 6, and 12 months respectively. In contrast to analysis group 1, there was no evidence of heterogeneity (P>0.1).

Pooling the data from all the amiodarone RCTs, regardless of control group type, have shown statistically significant results at 3 and 6 month intervals as the pooled RDs were 15.3% (SE, 4.8; Z=3.3, P<0.01) and 12.24% (SE, 6; Z=2.01, P<0.05) respectively. However, the pooled RD did not reach statistical significance at 12 months (RD=11.1; SE, 6.1; Z=1.8, P=0.0718). To test the homogeneity of effect across the studies, the Q statistic was calculated for each time point. This calculation has revealed statistical heterogeneity for the effect at all time intervals (at 3 months, Q=16.58, df=4, P=0.01; at 6 months, Q=10.15, df=2, P=0.006; and at 12 months, Q=8.7, df=2, P=0.013). This would primarily be due to variation in control group type (placebo or active), or due to differences in population type (chronic or paroxysmal AF). As a result, a stratified analysis was carried out. Table 7.a of Appendix 4.2 illustrates the recalculated pooled mean RDs, and Q statistic for the analysis subgroups predefined in section 4.2.4.2.

An indirect comparison of amiodarone to quinidine was performed by pooling individual RDs which were obtained by substraction of quinidine reference standard

(Reimold *et al.*, 1992) from the rate observed in the amiodarone treatment arms of RCTs (Table 7.a of Appendix 4.2). The pooled mean RDs obtained from this comparison were highly statistically significant (P<0.01) at 3, 6, and 12 months.

Figure 4.5 displays the weighted pooled percentages of patients in sinus rhythm in the amiodarone-treated group (P_t) compared to weighted pooled percentages of patients in sinus rhythm in comparator drug group, placebo group, as well as quinidine reference standard pooled percentages at 3, 6, and 12 months intervals. This figure has the advantage that it shows the effect of treatments under investigation separately.

The data regarding the maintenance of sinus rhythm in chronic and paroxysmal AF patients were also provided in 11 uncontrolled trials of amiodarone at 3 and 6 months, and in 8 uncontrolled trials at 12 months. The P_t obtained from pooling these trials compared to P_t of RCTs was not statistically different at 3, and 6 months (P>0.05). However, it was statistically significant at 12 months, showing more efficacy of amiodarone in RCTs (P<0.05). The pooled RDs between P_t in uncontrolled trials and quinidine reference standard were also highly statistically different at 3, 6, and 12 months (P<0.01). However, the homogeneity test demonstrated heterogeneity across the individual studies RDs at 3, and 6 month intervals (at 3 months; Q=53.8, df=10, P<0.01; and at 6 months; Q=63.3, df=10, P<0.01). Applying the random-effects model has yielded non-significant RDs at all times intervals. This may be due to the fact that the uncontrolled trials of amiodarone enrolled populations with different types of patients including both chronic (79.8%) and paroxysmal AF (20%), while the RCTs of quinidine (from which the standard quinidine meta-analytic P_t was calculated), included only chronic AF patients. To test for this possibility, stratified analysis was performed by calculating the P_t values for chronic and paroxysmal AF patients separately in uncontrolled trials, as well as RCTs of amiodarone.

Recomparison of the new amiodarone uncontrolled trials' P_t values for chronic AF patients only to standard quinidine meta-analytic P_t values, shows highly significant differences at 3, and 6 months (P<0.01), but not at 12 months (P=0.45). In addition, evidence of heterogeneity disappeared (P>0.05) when RDs of chronic AF patients for uncontrolled trials and RCTs were pooled separately (Table 7.a of Appendix 4.2). The pooled RDs between P_t of RCTs and standard quinidine reference were highly statistically significant at all time intervals, and the test of homogeneity was not significant (Table 7.a of Appendix 4.2: Analysis group 5A).

Pooling the efficacy of amiodarone for paroxysmal AF (PAF) patients in uncontrolled trials have shown important effect, with absolute percentages of patients remaining free of any attacks equal to 86.6% (95% CI 81.3 to 91.9), 67.5% (95% CI 58.8 to 76.1), 61.9% (95% CI 54.1 to 69.6) at 3, 6, and 12 months respectively. The weighted RDs comparing these percentages to standard quinidine reference, except at 6 months, were statistically significant. The efficacy of amiodarone for (PAF) was evaluated in only one RCT (Martin *et al.*, 1986).

4.3.3.2.2 Sotalol Clinical Trials

A total of 8 trials of sotalol were identified (Table 4.4). 6 were RCTs involving direct comparison to other antiarrhythmic drugs (2 to quinidine; 1 to quinidine plus verapamil; 1 to propafenone; and 1 to flecainide) or to placebo (2 trials). 2 were nonrandomised controlled (NonRCTs); involving sequential or serial treatments with flecainide, sotalol, and then amiodarone in one trial, or propafenone, then sotalol in another trial. Actuarial survival curves were presented in five trials. Kaplan-Meier percentages of patients in sinus rhythm were either extracted from the text or estimated from the survival curves (Table 4.10.c and Table 4.10.d at 3 months; Table 4.11.c and 4.11.d at 6 months; then, Table 4.12.c and Table 4.12.d at 12 months for RCTs and NonRCTs respectively).

Figure 4.3 gives a confidence interval plot for results from individual RCTs and NonRCTs with associated 95% CI intervals. The trials are ordered by year of initiation of the trial. In RCT, pooling the effect of sotalol versus Class IA drugs (3 trials), and versus Class IC (2 trials) did not show any superiority of sotalol over other treatments at any time point. In NonRCTs, the pooled effect versus Class IC (2 trials) has also indicated equal efficacy. Another trial which employed sequental design has demonstrated a nonsignificant difference in the rate of relapse between sotalol-treated patients and amiodarone-treated patients at all time points. Comparing the pooled size of effect versus all other drugs in RCTs and NonRCTs has confirmed the conclusions of the previous stratified analysis without any evidence of heterogeneity (Table 7.b of Appendix 4.2: Analysis group 4 and group 5).

Comparing the efficacy of sotalol to placebo in two RCTs has demonstrated highly significant efficacy at 6 and 12 months, with RDs equal to 36 (95% CI 16.32 to 55.7), and 33.1 (95% CI 5.7 to 60.5) respectively (Figures 4.2, and 4.6).

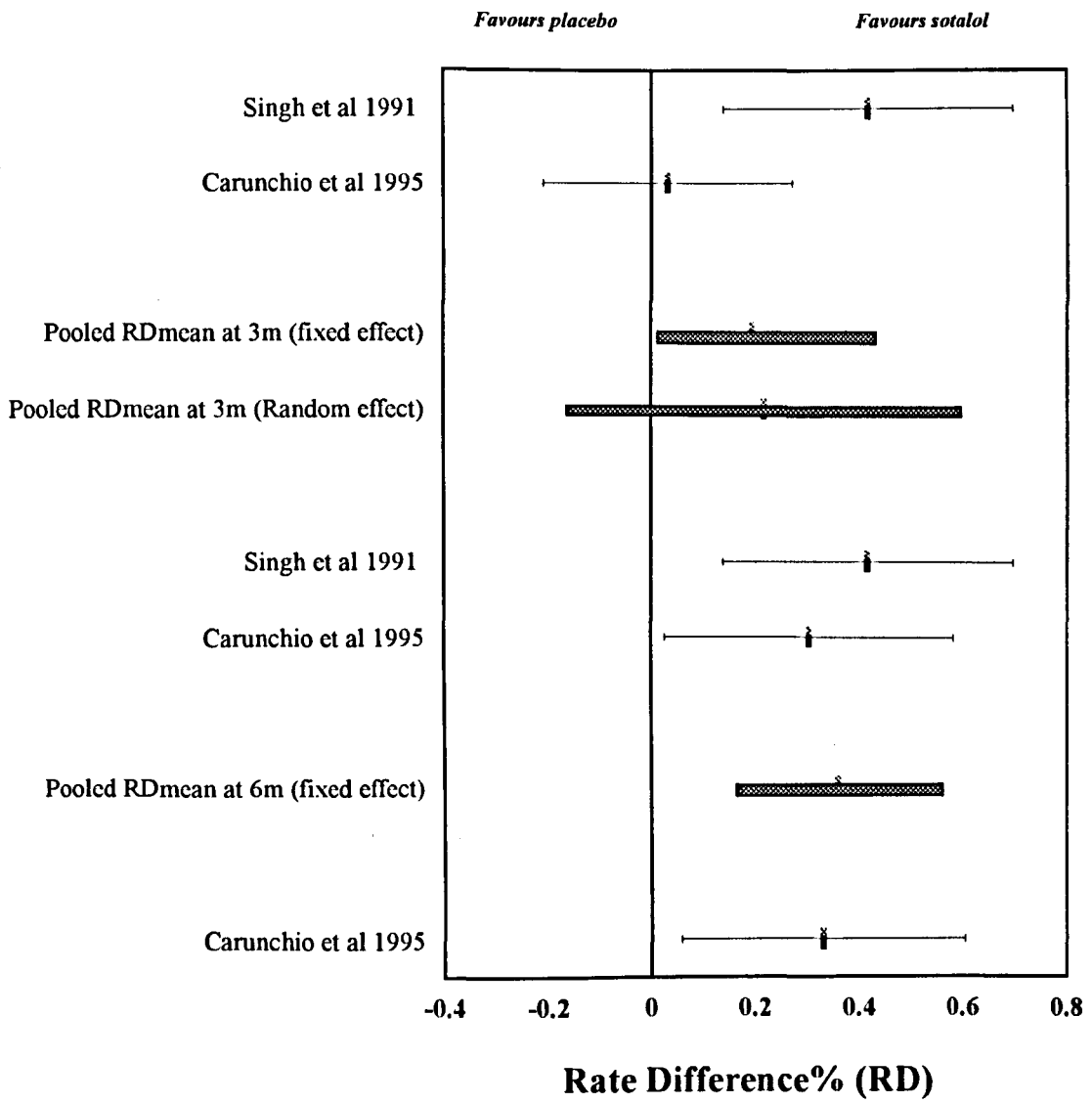

Figure 4.2 Efficacy of sotalol versus placebo in RCTs for maintenance of sinus rhythm. The figure illustrates the individual study RDs with their associated 95% CI (error bars, thin lines). The weighted pooled mean RD using the fixed and random-effects models are displayed at the bottom for each time interval (at 3, 6, and 12 months) in thick lines.

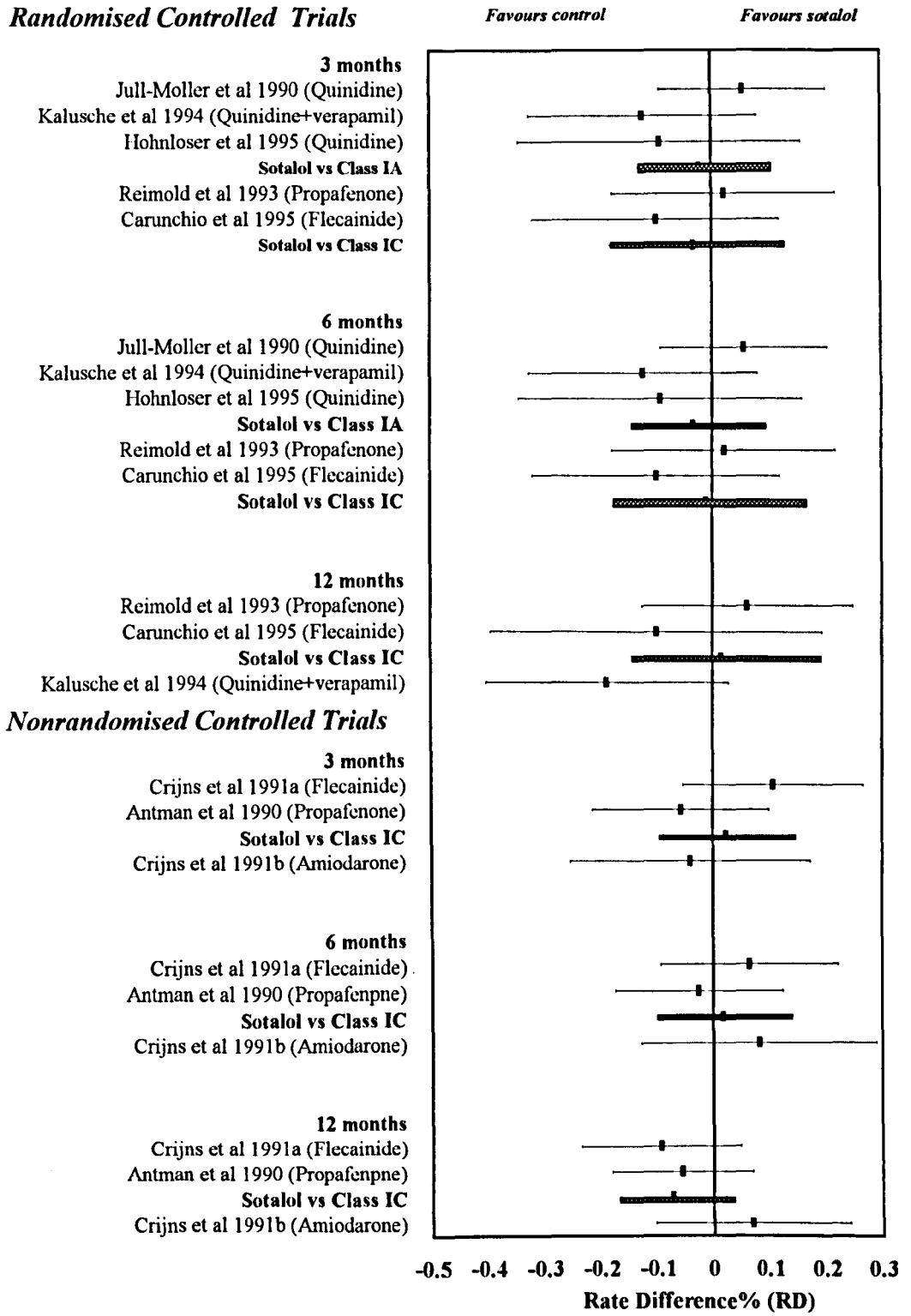

Figure 4.3 Sotalol randomised (N=5) and nonrandomised (N=3) clinical trials for maintenance of sinus rhythm (Analysis group 4 & 5: sotalol vs other antiarrhythmic drugs in RCTs and NonRCTs). The figure illustrates the individual study RDs with their associated 95% CI (error bars, thin lines). The weighted pooled mean RD versus Class IA & IC under fixed-effects model are displayed at the bottom for each time interval (at 3, 6, and 12 months) in thick lines. The comparison groups are shown in brackets.

When the results of sotalol treatment arms in RCTs were indirectly compared to standard quinidine reference, the pooled RD was statistically significant only at three months in favour of quinidine (RD, -7.7; z=-2.34, P<0.05). However, when PAF patients were excluded from pooling, the RDs were not significant at all times, indicating that sotalol and quinidine are equally effective. Furthermore, sotalol treatment arms in NonRCTs (Crijns *et al.*, 1991; and Antman *et al.*, 1990), in which sotalol was initiated as a second choice prior to failure of the first drug, were compared to quinidine standard, and in contrast to RCTs, the pooled RDs were highly significant at all time points in favour of quinidine. Comparison of the absolute percentages (P_t) in RCTs and NonRCTs was statistically significant at all time points (P<0.05). These results have showed that sotalol fared better in RCTs than in NonRCTs. Furthermore, this meta-analytic pooling have negated the theory which suggested that sequentially changing the type of drug after a recurrence may improve arrhythmia prognosis, as each drug exert its beneficial effect in suppressing atrial fibrillation by different mechanism of action (Crijns *et al.*, 1991; and Antman *et al.*, 1990). On the contrary, it has been concluded that continuation of treatment with the same drug would yield a better outcome.

4.3.3.2.3 Flecainide Clinical Trials

A total of 18 trials of flecainide were identified. 8 were RCTs with parallel (N=3) or crossover design (N=5). In the crossover design trials, flecainide was compared to placebo in 4 trials, and to placebo and quinidine in 1 trial. The parallel design trials involved comparison to placebo in one trial, and to active treatment with disopyramide or propafenone in two trials. In addition, 4 nonrandomised controlled trials, and 6 uncontrolled studies met the inclusion criteria. All the nonrandomised trials adapted open-label crossover design, and the comparison group received amiodarone plus flecainide in two trials (Mary-Rabine *et al.*, 1988; Leclercq *et al.*, 1992), placebo in one (Anderson *et al.*, 1994), and sotalol then amiodarone in one trial (Crijns *et al.*, 1991).

Figure 4.4 illustrates individual and mean RDs for each trial design separately. As shown in the previous figure, pooling data from randomised, placebo-controlled, crossover design trials (N=5), and placebo-controlled, parallel design trial (N=1) was only possible at 3 months (RDmean, 33.35; Z=9.3, P<0.01; Q, 24.8; P<0.001). Excluding the placebo-controlled parallel design trial (Van-Gelder *et al.*, 1989) from the previous group did not affect the significance of the results (Analysis group 6).

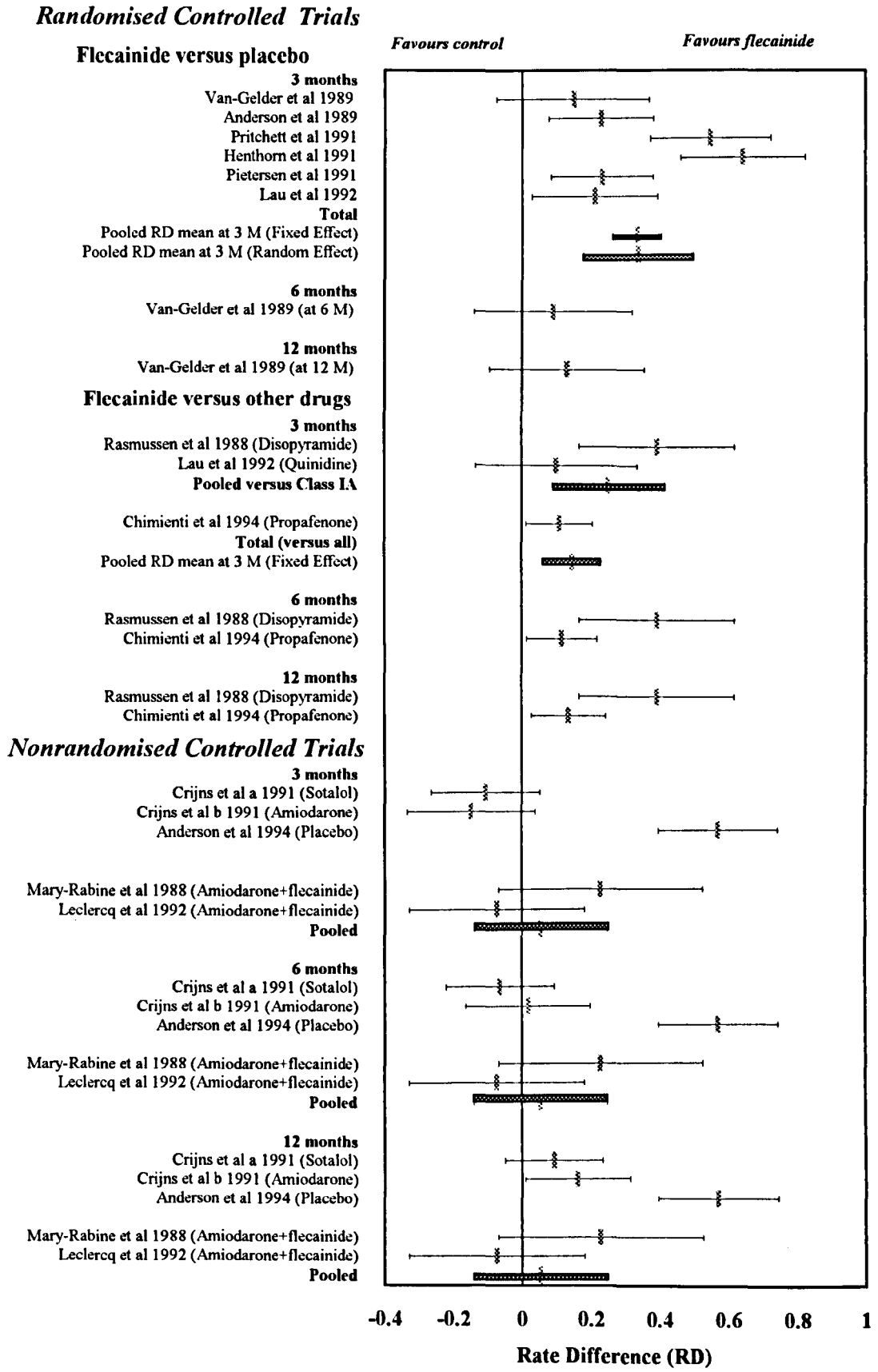

Figure 4.4 Flecainide randomised, placebo-controlled trials (N=6), randomised comparative trials (N=3), and nonrandomised trials (N=4). The figure illustrates the individual study RDs with their associated 95% CI (error bars, thin lines). The weighted pooled mean RD in fixed and random-effects model are displayed at the bottom , only when pooling is justified (thick lines). The comparison groups are shown in brackets.

The pooled effect from two RCTs compared to Class IA (quinidine and disopyramide) was highly statistically significant in favour of flecainide. However, pooling data from the two non-randomised trials involving the comparison of flecainide against flecainide with amiodarone did not suggest any statistically significant difference (RD mean, 5.5 Z=0.56, P>0.05), despite the significance of the point estimate in one of the trials as shown in Figure 4.4.

The indirect comparison of flecainide treatment arms in RCTs, NonRCTs, and uncontrolled trials against quinidine standard suggest efficacy in favour of quinidine at 3 months. However, at 6 and 12 months, the pooled estimates were in favour of flecainide in RCTs, but no statistically significant difference was seen in the NonRCTs and uncontrolled trials (Table 7.c of Appendix 4.2).

4.3.3.2.4 Indirect comparisons

The meta-analytic pooled percentages of patients remaining in sinus rhythm in flecainide, sotalol, amiodarone treatment arms in RCTs, as well as quinidine standard are depicted in Figure 4.7.A for comparison. As shown, amiodarone showed the highest efficacy at 3 months only, with statistically significant difference compared to all other drugs. However, flecainide showed the highest efficacy at 6 and 12 months with statistically significant difference compared to quinidine and sotalol. These results suggested equal efficacy of amiodarone and flecainide at 6 and 12 months.

Figure 4.7.B depicted the pooled percentages in NonRCTs. As shown, flecainide displayed higher efficacy compared to quinidine and sotalol (P<0.05). Figure 4.7.C depicted the pooled percentages in uncontrolled trials with highly significant difference in favour of amiodarone compared to quinidine and flecainide at 3 and 6 months, yet flecainide and amiodarone were equally effective for prevention of relapse at 12 months.

To confirm the previous conclusions, the drugs were compared with respect to their effects on chronic AF only as shown in Figure 4.8 for RCTs and NonRCTs. In this comparison, flecainide and amiodarone have demonstrated equal efficacy at the three time intervals, and sotalol exhibited the least efficacy.

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months

a. Amiodarone randomised clinical trial

Study name	*Amiodarone (no. of patients and type of arrhythmias)*	*Control (no. of patients, type of control or drug)*	S_T %(SE)	$W.S_T$	S_P %(SE)	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Vitolo *et al.* 1981	28 chronic AF	29 Quinidine	78.6 (7.8)	0.0166	41.4 (9)	0.01196	37.2 (13.6-60.7)	3.1** P<0.001	69.553	18.9
Martin *et al.* 1986	43 PAF	22 Disopyramide	79.1 (6.2)	0.02598	54.5 (10.6)	0.00887	24.5 (0.4-48.6)	1.99* (P=0.047)	66.144	18.64
Bosi *et al.* 1990	48 chronic AF	49 Placebo	72.9 (6.4)	0.024	79.6 (5.8)	0.03	-6.7 (-23.6-10.2)	-0.77 NS (P=1.56)	134.61	21.7625
Zehender *et al.* 1992	12 chronic AF	11 Quinidine /Verapamil	91.7 (7.97)	0.0157	90.9 (8.7)	0.01331	0.75 (-22.3-23.9)	0.064 NS (P=0.95)	72.052	19.0838
Jong *et al.* 1995	39 chronic AF	25 Placebo	64.1 (7.7)	0.0169	24 (8.5)	0.0137	40.1 (17.6-62.6)	3.49** P<0.01	75.779	19.3357
Pooled rates (SE)	170	136	76.9 (3.2)	0.099	63.1 (3.6)	0.078			418.138	97.722
95% CI			(70.7-83.1)		(56-70.1)					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

b. Amiodarone uncontrolled clinical trials

Study name	*Amiodarone (no. of patients, and type of arrhythmias)*	*Control (no. of patients, type of control or drug)*	*ST (SE)*	*W.S$_T$*	*S$_P$(SE)*	*W.S$_P$*	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Leak *et al.* 1979	14; 9 PSVT, 2 PAF, 3 PSVT+WPW	-	50 (13.4)	0.0056	69.4 (2.4)	0.1756	-19.4 (-46-7.3)	-1.4 NS (P=0.162)	54.3	15.69
Podrid *et al.* 1981	26; 18 PAF, 8 PSVT	-	80.8 (7.7)	0.01674	69.4 (2.4)	0.1756	11.4 (-4.5-27.2)	1.4 NS (P=0.162)	152.83	19.3
Grasboys *et al.* 1983	121; 95 chronic AF , 21 SVT and 5 SVT+AF	-	80.99 (3.6)	0.078596	69.4 (2.4)	0.1756	11.6 (3.2-20)	2.7**	542.99	21.2024
Blomstrom *et al.* 1984	21; 13 chronic AF, 8 PAF	-	71.4 (9.9)	0.01029	69.4 (2.4)	0.1756	2.1 (-17.9-21.9)	0.2 NS (P=0.842)	97.205	17.98
Horowitz *et al.* 1985	38; 11 chronic AF 27 PAF	-	52.6 (8.1)	0.015242	69.4 (2.4)	0.1756	-16.8 (-33.3_-0.22)	-1.99* (P=0.047)	140.25	19.0648
Gold *et al.* 1986	68; 54 chronic or paroxysmal AF, 14 chronic AF	-	86.8 (4.1)	0.059215	69.4 (2.4)	0.1756	17.4 (-6.3-25.5)	3.3**	414.26	20.95
Blevins *et al.* 1987	32; 19 chronic AF 13 PAF	-	53.1 (8.8)	0.01285	69.4 (2.4)	0.1756	-16.3 (-34.2_1.6)	-1.7 NS (0.09)	119.742	20.3261
Brodsky *et al.* 1987	28 chronic AF	-	75 (8.2)	0.014933	69.4 (2.4)	0.1756	5.6 (-11.1_22.3)	0.66 NS (P=0.51)	137.6	19.0156
Levy *et al.* 1991	102 chronic AF	-	32.4 (4.6)	0.046606	69.4 (2.4)	0.1756	-37 (-47.3_-26.8)	-7.1**	368.323	22.9561
Gossenlink *et al.* 1992	80 AF or AFL	-	63.8 (5.4)	0.034618	69.4 (2.4)	0.1756	-5.7 (-17.2-5.9)	-0.96 NS (P=0.34)	289.2	20.5
Chun *et al.* 1995§	110; 53 chronic AF or AFL and 57 PAF	-	92.7 (2.5)	0.163	69.4 (2.4)	0.1756	23.4 (16.6-30.1)	6.8**	845.7	21.5
Mostow *et al.* 1990	19; 9 AF, 1 AFL, 6 PAF, 3 atrial arrhythmia	-	52.6 (11.5)	0.0076	69.4 (2.4)	0.1756	-16.8 (-39.7-6.2)	-1.4 NS (P=0.16)	73.042	16.95
Pooled rates (SE)	675; 470 AF, 205 PAF	-	76.7 (1.5)	0.4685	69.4 (0.69)	2.12	4.5 (1.8)		3290.75	232.129
95% CI			73.9-79.6		68.1-70.8		-1.03-7.8			
Z (P)							2.6** (P=0.009)			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S$_T$% (SE) and S$_P$% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; W.S$_T$, weight of S$_T$; W.S$_P$, weight of S$_P$; RD, risk difference; 95% CI; 95% confidence interval; §, retrospective uncontrolled study, which was grouped with uncontrolled studies; ‡, NSR sustained, but it there may be a relapse during the NSR period and number of patients with AF or PAF was not stated; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

c. Sotalol randomised clinical trials

Study name	*Sotalol (no. of patients and type of arrhythmia)*	*Control (no. of patients and type of control or drug)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Juul-Moller *et al.* 1990	95 chronic AF	79 Quinidine	60 (5.03)	0.03958	54.4 (5.6)	0.03185	5.6 (-9.2-20.3)	0.74 NS (P=0.459)	176.491	59.3183
Singh *et al.* 1991	12 chronic AF	6 Placebo	41.7 (14.2)	0.00494	0	-	41.7 (13.8-69.6)	2.93**	49.371	31.7997
Reimold *et al.* 1993	49; 27 AF, 22 PAF	49 Propafenone; 24 AF, 25 PAF	48.98 (7.14)	0.01961	46.9 (7.13)	0.019674	2.04 (-17-21.8)	0.2 NS (P=0.84)	98.205	46.784
Kalusche *et al.* 1994	41 chronic AF	37 Quinidine/Verapamil	63.4 (7.5)	0.01767	75.7 (7.1)	0.0201	-12.3 (-32.5-7.95)	-1.19 NS (P=0.234)	94.041	45.82
Carunchio *et al.* 1995	20 PAF	26 Placebo	80 (8.9)	0.0125	76.9 (8.3)	0.014646	3.1 (-20.8-26.9)	0.253 NS (P=0.8)	67.442	38.4
Carunchio *et al.* 1995	20 PAF	20 Flecainide	80 (8.9)	0.0125	90 (6.7)	0.022	-10 (-31.9-11.9)	-0.89 NS (P=0.37)	80	42.21
Hohnloser *et al.* 1995	17 chronic AF	21 Quinidine	76.5 (10.3)	0.009448	85.7 (7.64)	0.01715	-9.24 (-34.6-15.9)	-0.72 NS (P=0.47)	60.92	36.22
Pooled rates (SE)	234	238	63.5 (2.9)	0.1163	69.8 (2.8)	0.1254			626.47	300.6
95% CI			57.8-69.3		64.3-75.4					
Z (P)										

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

d. Sotalol nonrandomised clinical trials

Study name	*Sotalol (no. of patients and type of arrhythmias)*	*Control (no. of patients, type of control or active drug)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991**	53 chronic AF	127 Flecainide	54.72 (6.8)	0.021391	44.1 (4.4)	0.05152	10.6 (-5.3-26.6)	1.31 NS (P=0.19)	151.148	126.788
Crijns *et al.* 1991**	53 chronic AF	34 Amiodarone	54.72 (6.8)	0.021391	58.8 (8.4)	0.01404	-4.12 (-25.4-17.2)	-0.38 NS (P=0.7)	84.753	76.51
Antman *et al.* 1990**	48 chronic AF or PAF	109 Propafenone	29.2 (6.6)	0.023234	34.86 (4.6)	0.04799	-5.7 (-21.4-9.97)	-0.71 NS (P=0.48)	156.557	130.572
Pooled rates (SE)	101	270	45.7 (3.9)	0.066	42.01 (2.97)	0.11356	0.9 (5)		392.458	333.87
95% CI			38.1-53.4		36.2-47.83		-8.96-10.8			
Z (P)							0.185 NS (P=0.85)			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI, 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

e. Flecainide randomised clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmias)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Rasmussen *et al.* (abstract) 1988	28 chronic AF	28 Disopyramide	85.7 (6.6)	0.02267	46.43 (9.4)	0.01126	39.3 (16.72-61.9)	3.4**	75.436	23.1
Van-Gelder *et al.* 1989	36 chronic AF	37 Placebo	64 (8)	0.015625	49 (8.22)	0.01481	15 (-7.5-37.5)	1.3 (P=0.19)	76.022	23.12
Anderson *et al.* 1989	48 PAF	48 Placebo	31.3 (6.7)	0.022342	8.33 (4)	0.06284	22.9 (7.6-38.2)	2.9**	164.817	27.6
Pritchett *et al.* 1991	42; 28 PAF, 14 PSVT	42; 28 PAF, 14 PSVT, Placebo	69.1 (7.1)	0.019652	14.3 (5.4)	0.0343	54.8 (37.23-72.3)	6.12**	124.938	26.3
Henthorn *et al.* 1991	34 PSVT	34 Placebo	79 (7)	0.020494	14.7 (6.1)	0.0271	64.3 (46.2-82.4)	6.95**	116.71	25.86
Pietersen *et al.* 1991	43 PAF	43 Placebo	27.91 (6.8)	0.021373	4.7 (3.2)	0.09696	23.3 (8.44-38.1)	3.1**	175.13	27.92
Lau *et al.* 1992	19 PAF	15 Placebo	21.1 (9.4)	0.011432	0 (0)	-	21.1 (2.7-39.4)	2.25*	114.32	25.74
Lau *et al.* 1992	19 PAF	18 Quinidine	21.1 (9.4)	0.011432	11.11 (7.4)	0.01822	9.94 (-13.4-33.33)	0.83 (P=0.4) NS	70.3	22.6
Chimienti *et al.* 1994	129; 77 PAF, 52 PSVT	136; 82 PAF, 54 PSVT, Propafenone	84.5 (3.2)	0.0983	73.7 (3.8)	0.0701	10.8 (1.1-20.5)	2.184*	409.1	30.7
Pooled rates (SE)	379; 64 chronic AF, 215 PAF, 100 PSVT	401; 65 chronic AF, 234 PAF, 102 PSVT	65.8 (2.03)	0.2435	25.3 (1.7)	0.33557			1326.67	232.86
95% CI			61.8-69.73		21.87-28.6					
Z (P)										

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

f. Flecainide nonrandomised clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients and type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991	127 chronic AF	53 Sotalol	44.1 (4.4)	0.05152	46.8 (6.8)	0.0214	-10.6 (-26.6-5.3)	-1.31 (NS)	151.148	8.9
Crijns *et al.* 1991	127 chronic AF	34 Amiodarone	44.1 (4.4)	0.05152	71.24 (8.4)	0.01404	-14.73 (-33.4-3.9)	-1.55 (NS)	110.314	8.7
Anderson *et al.*† 1994	42; 25 PAF, 17 PSVT	42 Placebo; 25 PAF, 17 PSVT	73.8 (6.8)	0.02173	33.1 (5.8)	0.0303	57 (39.7-74.6)	6.43**	126.43	8.8
Mary-Rabine *et al.* 1988	55; 39 PAF, 16 PSVT	13 Amiodarone+flecainide; 12 PAF, 1 PSVT	69.1 (6.2)	0.0258	191.2 (13.8)	0.00523	22.9 (-6.8-52.7)	1.5 (NS)	43.479	7.7597
Leclercq *et al.* 1992	19 PAF	33 Amiodarone+flecainide	68.4 (10.7)	0.00879	55.7 (7.5)	0.01797	-7.34 (-32.8-18.2)	-0.5 (NS)	59.042	8.1427
Pooled rates (SE)	243; 83 PAF, 127 chronic AF, 33 PSVT	175; 56 PAF, 87 chronic AF, 18 PSVT	53.5 (2.5)	0.15938	46.2 (3.4)	0.0889			490.413	42.28
95% CI			48.6-58.4		39.6-52.7					
Z (P)										

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant ($P<0.05$); ** highly statistically significant ($P<0.01$)

Table 4.10 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 3 months (continued)

g. Flecainide uncontrolled clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Berns *et al.* 1987	39; 5 chronic AF, 25 PAF, 9 AT	-	56.5 (7.9)	0.015861	69.4 (2.4)	0.17564	-13 (-29.2-3.3)	-1.6 (NS)	145.47	295.2
Zeigler *et al.* 1988	16 PSVT	-	50 (12.5)	0.0064	69.4 (2.4)	0.17564	-19.4 (-44.3-5.5)	-1.5 (NS)	61.75	78.69
Sonnhag *et al.* 1988	20 PAF	-	60 (11)	0.008333	69.4 (2.4)	0.17564	-9.4 (-31.4-12.6)	-0.84 (NS)	79.56	110.1
Zee-Cheng *et al.* 1988	15 PSVT	-	60 (12.6)	0.00625	69.4 (2.4)	0.17564	-9.4 (-34.6-15.83)	-0.73 (NS)	60.35	76.44
Anderson JL 1992	66; 25 PSVT, 41 PAF	-	65.2 (5.9)	0.029069	69.4 (2.4)	0.17564	-4.3 (-16.7-8.2)	-0.671 (NS)	249.41	1913.16
Clementy *et al.* 1992	944 PAF	-	62.7 (1.6)	0.403693	69.4 (2.4)	0.17564	-6.7 (-12.3_-1.1)	-2.34* (P=0.02)	1223.91	-374.58
Pooled rates (SE)	1100; 1030 PAF; 65 PSVT; 5 chronic AF	-	62.4 (1.5)	0.469606	69.4 (0.97)	1.054	-7.5 (2.3)		1820.45	2099.01
95% CI			59.5-65.3		67.5-71.31		-12.1_-2.9			
Z (P)							-3.2** (P=0.0014)			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 6 months

a. Amiodarone randomised clinical trials

Study name	*Amiodarone (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Vitolo *et al.* 1981	28 chronic AF	29 Quinidine	78.6 (7.8)	0.01663	41.4 (9.1)	0.01196	37.2 (13.7-60.7)	3.11**	69.553	15.99
Martin *et al.* 1986	43 PAF	22 Disopyramide	79.1 (6.2)	0.025983	54.5 (10.6)	0.00887	24.5 (0.4-48.6)	1.99**	66.144	15.81
Bosi *et al.* 1990	48 chronic AF	49 Placebo	72.9 (6.4)	0.024306	79.6 (5.8)	0.03017	-6.7 (-23.5-10.2)	-0.77 NS (P=0.44)	134.605	17.9961
Zehender *et al.* 1992	12 chronic AF	11 Quinidine /Verapamil	-	-	-	-	-	-	-	-
Jong *et al.* 1995	39 chronic AF	25 Placebo	-	-	-	-	-	-	-	-
Pooled rates (SE)	170	136	76.7 (3.9)	0.06692	66.3 (4.4)	0.05			270.3	49.796
95% CI			69.1-84.3		57.6-74.95					
Z (P)										

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 6 months (continued)

b. Amiodarone uncontrolled clinical trials

Study name	*Amiodarone (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Leak *et al.* 1979	14; 9 PSVT, 2 PAF, 3 PSVT+WPW	-	50 (13.4)	0.0056	57.7 (2.6)	0.152824	-7.7 (-34.4-18.9)	-0.57 NS (P=0.57)	54.02	14.13
Podrid *et al.* 1981	26; 18 PAF, 8 PSVT	-	-	-	-	-	-	-	-	-
Grasboys *et al.* 1983	121; 95 chronic AF , 21 SVT and 5 SVT+AF	-	80.99 (3.6)	0.078596	57.7 (2.6)	0.152824	23.3 (14.7-31.8)	5.31**	519.03	18.5
Blomstrom *et al.* 1984	21; 13 chronic AF, 8 PAF	-	61.9 (10.6)	0.008911	57.7 (2.6)	0.152824	4.2 (-17.2-25.6)	0.39 NS (P=0.7)	84.145	15.6
Horowitz *et al.* 1985	38; 11 chronic AF 27 PAF	-	52.6 (8.1)	0.01524	57.7 (2.6)	0.152824	-5.1 (-21.7-11.6)	-0.59 NS (P=0.56)	138.6	16.8
Gold *et al.* 1986	68; 54 chronic or paroxysmal AF, 14 chronic AF	-	73.5 (5.4)	0.034937	57.7 (2.6)	0.152824	15.8 (4.2-27.5)	2.7**	284.362	19.9914
Blevins *et al.* 1987	38; 25 chronic AF 13 PAF	-	53.1 (8.8)	0.01285	57.7 (2.6)	0.152824	-4.6 (-22.6-13.4)	-0.5 NS (P=0.62)	118.54	18.2
Brodsky *et al.* 1987	28 chronic AF	-	75 (8.2)	0.014933	57.7 (2.6)	0.152824	17.3 (0.49-34.1)	2.01* (P=0.04)	136.04	16.8
Levy *et al.* 1991	112 chronic AF	-	32.4 (4.6)	0.046606	57.7 (2.6)	0.152824	-25 (-35.7_-15)	-4.8**	357.141	20.3
Gossenlink *et al.* 1992	80 AF or AFL	-	63.8 (5.4)	0.034618	57.7 (2.6)	0.152824	6.1 (-5.6-17.7)	1.02 NS (P=0.154)	282.3	17.92
Chun *et al.* 1995§	110; 53 chronic AF or AFL and 57 PAF	-	92.7 (2.5)	0.163113	57.7 (2.6)	0.152824	35.11 (28.1-42)	9.8**	789.005	18.7
Mostow *et al.* 1990	19; 9 AF, 1 AFL, 6 PAF, 3 atrial arrhythmia	-	31.6 (10.7)	0.008794	57.7 (2.6)	0.152824	-26.1 (-47.6_-4.6)	-2.4*	83.151	15.6
Pooled rates (SE)	675; 470 AF, 205 PAF	-	74.2 (1.5)	0.451514	57.7 (0.77)	1.68	12.6 (1.9)		3014.775	187.2
95% CI			71.2-77.24		56.2-59.2		8.9-16.2			
Z (P)							6.7** (P<0.01)			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 6 months (continued)

c. Sotalol randomised clinical trials

Study name	*Sotalol (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Juul-Moller *et al.* 1990*	95	79 Quinidine	51.6 (5.13)	0.038	48.1 (5.6)	0.032	3.5 (-11.4-18.4)	0.46 NS (P=0.65)	172.7	37.4
Singh *et al.* 1991*	12	6 Placebo	41.7 (14.2)	0.0049	0	-	41.7 (13.8-69.6)	2.93**	49.371	24.3
Reimold *et al.* 1993*	49	49 Propafenone	46.94 (7.1)	0.0197	40.8 (7.02)	0.0202	6.12 (-13.5-25.7)	0.613 NS	99.872	32.3
Kalusche *et al.* 1994*	41	37 Quinidine/Verapamil	63.42 (7.5)	0.0177	75.7 (7.1)	0.0201	-12.3 (-32.5-7.95)	-1.189 NS (P=0.234)	94.041	31.7
Carunchio *et al.* 1995*	20	20 Flecainide	65 (10.7)	0.00879	80 (8.9)	0.0125	-15 (-42.3-12.3)	-1.078 NS (P=0.28)	51.613	24.8
Carunchio *et al.* 1995*	20	26 Placebo	65 (10.7)	0.00879	34.6 (9.3)	0.01149	30.4 (2.6-58.2)	2.144 NS (P=0.016)	49.8	24.4
Hohnloser *et al.* 1995	17	21 Quinidine	76.5 (10.3)	0.009448	85.7 (7.6)	0.0172	-9.24 (-34.4-15.9)	-0.72 NS (P=0.472)	60.92	26.8
Pooled rates (SE)	234	238	56.6 (3.1)	0.107357	59.5 (2.97)	0.1132			578.361	201.629
95% CI			50.6-62.6		53.7-65.4					
Z (P)										

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 6 months (continued)

d. Sotalol nonrandomised clinical trials

Study name	*Sotalol (no. of patients)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991	53	127 Flecainide	43.4 (6.81)	0.02158	37 (4.3)	0.05448	6.4 (-9.4-22.2)	0.79 NS (P=0.43)	154.553	398.044
Crijns *et al.* 1991	53	34 Amiodarone	43.4 (6.81)	0.02158	35.3 (8.2)	0.01489	8.1 (-12.8-28.98)	0.76 NS (P=0.45)	88.094	135.253
Antman *et al.* 1990	48	109 Propafenone	25 (6.3)	0.0256	27.5 (4.3)	0.05464	-2.5 (-17.4-12.3)	-0.33 NS (P=0.72)	147.328	562.33
Pooled rates (SE)	101	270	36.6 (3.8)	0.06876	32.6 (2.84)	0.124			416.98	1095.627
95% CI			29.1-44.02		27.1-38.2					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 6 months (continued)

e. Flecainide randomised clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Rasmussen *et al.* (abstract) 1988	28 chronic AF	28 Disopyramide	85.71 (6.6)	0.022867	46.43 (9.4)	0.01126	39.3 (16.72-61.9)	3.4**	75.44	37.58
Van-Gelder *et al.* 1989	36 chronic AF	37 Placebo	58 (8.23)	0.014778	49 (8.2)	0.01481	9 (-13.8-31.8)	0.77**	73.96	37.21
Anderson *et al.* 1989‡	48 PAF	48 Placebo	-	-	-	-	-	-	-	-
Pritchett *et al.* 1991‡	42; 28 PAF, 14 PSVT	42; 28 PAF, 14 PSVT, Placebo	-	-	-	-	-	-	-	-
Henthorn *et al.* 1991†	34 PSVT	34 Placebo	-	-	-	-	-	-	-	-
Pietersen *et al.* 1991‡	43 PAF	43 Placebo	-	-	-	-	-	-	-	-
Lau *et al.* 1992‡	19 PAF	15 Placebo	-	-	-	-	-	-	-	-
Lau *et al.* 1992‡	19 PAF	18 Quinidine	-	-	-	-	-	-	-	-
Chimienti *et al.* 1994	129; 77 PAF, 52 PSVT	136; 82 PAF, 54 PSVT, Propafenone	81.6 (3.4)	0.08591	69.96 (3.9)	0.06471		2.2* (P=0.025)	369.1	62.25
Pooled rates (SE)	379; 64 chronic AF, 215 PAF, 100 PSVT	401; 65 chronic AF, 234 PAF, 102 PSVT	79.54 (2.8)	0.12356	63.6 (3.3)	0.0908			518.484	137
95% CI			73.96-85.1		57-70.13					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; *statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 6 months (continued)

f. Flecainide nonrandomised clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991	127 chronic AF	53 Sotalol	37 (4.3)	0.054478	43.4 (6.8)	0.02158	-6.4 (-22.2-9.4)	-0.79 (NS)	154.56	11.5153
Crijns *et al.* 1991	127 chronic AF	34 Amiodarone	37 (4.3)	0.05448	35.3 (8.2)	0.01489	1.7 (-16.4-19.84)	0.185 (NS)	116.93	11.2457
Anderson *et al.* 1994†	42; 25 PAF, 17 PSVT	42 Placebo; 25 PAF, 17 PSVT	73.8 (6.8)	0.02173	16.7 (5.8)	0.0303	57.1 (39.7-74.6)	6.43**	126.43	11.3276
Mary-Rabine *et al.* 1988	55; 39 PAF, 16 PSVT	13 Amiodarone+flecainide; 12 PAF, 1 PSVT	69.1 (6.2)	0.0257	46.2 (13.8)	0.00523	22.94 (-6.8-52.7)	1.5 (NS)	43.479	9.6739
Leclercq *et al.* 1992	19 PAF	33 Amiodarone+flecainide	68.42 (10.7)	0.008794	75.8 (7.5)	0.01797	-7.34 (-32.8-18.2)	-0.56 (NS)	59.042	10.2767
Pooled rates (SE)	243; 83 PAF, 127 chronic AF, 33 PSVT	175; 56 PAF, 87 chronic AF, 18 PSVT	48.5 (2.5)	0.165232	39.7 (3.3)	0.0899			500.429	54.04
95% CI			43.7-53.3		33.2-46.2					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant ($P<0.05$); ** highly statistically significant ($P<0.01$)

Table 4.11 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 6 months (continued)

g. Flecainide uncontrolled clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Berns *et al.* 1987	39; 5 chronic AF, 25 PAF, 9 AT	-	56.4 (7.9)	0.015861	57.7 (2.6)	0.15282	-1.3 (-17.6-15.1)	-0.155 (NS)	143.69	198.247
Zeigler *et al.* 1988	16 PSVT	-	50 (12.5)	0.0064	57.7 (2.6)	0.15282	-7.7 (-32.7-17.3)	-0.6 (NS)	61.43	69.617
Sonnhag *et al.* 1988	20 PAF	-	55 (11.12)	0.008081	57.7 (2.6)	0.15282	-2.7 (-25.1-19.7)	-0.24 (NS)	76.75	89.974
Zee-Cheng *et al.* 1988	15 PSVT	-	46.7 (12.9)	0.006027	57.7 (2.6)	0.15282	-11 (-36.8-14.7)	-0.84 (NS)	57.98	65.223
Anderson JL 1992	66; 55 PSVT, 41 PAF	-	65.2 (5.9)	0.029069	57.7 (2.6)	0.15282	7.5 (-5.1-20)	1.16 (NS)	244.24	458.846
Clementy *et al.* 1992	944 PAF	-	62.7 (1.6)	0.403693	57.7 (2.6)	0.15282	5.01 (-0.87-10.9)	1.67 (NS)	1108.58	-987.209
Pooled rates (SE)	1100; 1030 PAF; 65 PSVT; 5 chronic AF	-	62.14 (1.5)	0.46913	57.7 (1.04)	0.92	3.5 (2.4)		1692.67	-105.302
95% CI			59.3-65		55.7-59.8		-1.3-8.2			
							1.43 (P=0.15) NS			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 12 months

a. Amiodarone randomised clinical trials

Study name	*Amiodarone (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Vitolo *et al.* 1981*	28 chronic AF	29 Quinidine	53.6 (9.4)	0.01126	20.7 (7.5)	0.01767	32.9 (9.3-56.5)	2.7**	68.77	18.4
Martin *et al.* 1986*	43 PAF	22 Disopyramide	79.1 (6.2)	0.02598	54.5 (10.6)	0.00887	24.5 (0.4-48.6)	1.99* (P=0.047)	66.144	18.2
Bosi *et al.* 1990*	48 chronic AF	49 Placebo	72.9 (6.4)	0.02431	79.6 (5.8)	0.0302	-6.7 (-23.6-10.2)	-0.77 NS	134.6	21.17
Zehender *et al.* 1992*	12 chronic AF	11 Quinidine /Verapamil	-	-	-	-	-	-	-	-
Jong *et al.* 1995*	39 chronic AF	25 Placebo	-	-	-	-	-	-	-	-
Pooled rates (SE)	170	136	71.97 (4.1)	0.061546	57.3 (4.2)	0.05672			269.514	57.77
95% CI			64.1-79.9		49.1-65.6					
Z (P)			17.9**		13.6**					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant ($P<0.05$); ** highly statistically significant ($P<0.01$)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 12 months (continued)

b. Amiodarone uncontrolled clinical trials

Study name	*Amiodarone (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Leak *et al.* 1979	14; 9 PSVT, 2 PAF, 3 PSVT+WPW	-	50 (13.4)	0.0056	50.2 (2.6)	0.149202	-0.2 (-26.87-26.5)	-0.015 NS (P=0.99)	53.97	23.8
Podrid *et al.* 1981	26; 18 PAF, 8 PSVT	-	-	-	-	-	-	-	-	-
Grasboys *et al.* 1983	121; 95 chronic AF , 21 SVT and 5 SVT+AF	-	-	-	-	-	-	-	-	-
Blomstrom *et al.* 1984	21; 13 chronic AF, 8 PAF	-	47.6 (10.9)	0.00842	50.2 (2.6)	0.149202	-2.6 (-24.5-19.4)	-0.23 NS	79.7	27.7
Horowitz *et al.* 1985	38; 11 chronic AF 27 PAF	-	52.6 (8.1)	0.015242	50.2 (2.6)	0.149202	2.4 (-14.2-19.1)	0.29 NS	138.3	42.3
Gold *et al.* 1986	68; 54 chronic or paroxysmal AF, 14 chronic AF	-	64.7 (5.8)	0.029776	50.2 (2.6)	0.149202	14.5 (2.1-26.9)	2.3*	248.221	48.98
Blevins *et al.* 1987	38; 17 chronic AF 13 PAF	-	53.1 (8.8)	0.01285	50.2 (2.6)	0.149202	2.9 (-15.1-20.9)	3.2**	118.312	40.26
Brodsky *et al.* 1987	28 chronic AF	-	35.7 (9.1)	0.012196	50.2 (2.6)	0.149202	-14.5 (-32.9-4)	-1.54 NS (P=0.124)	112.7	30.88
Levy *et al.* 1991	102 chronic AF	-	27.45 (4.4)	0.051216	50.2 (2.6)	0.149202	-22.7 (-32.8_-12.7)	-4.4**	381.283	52.6
Gossenlink *et al.* 1992	80 AF or AFL	-	61 (5.4)	0.033627	50.2 (2.6)	0.149202	10.8 (-0.01-22.6)	1.8 NS	274.425	49.9
Chun *et al.* 1995§	110; 53 chronic AF or AFL and 57 PAF	-	57.3 (4.7)	0.04495	50.2 (2.6)	0.149202	7.1 (-3.5-17.6)	1.32 NS (P=0.187)	345.44	37.88
Mostow *et al.* 1990	19; 9 AF, 1 AFL, 6 PAF, 3 atrial arrhythmia	-	-	-	-	-	-	-	-	-
Pooled rates (SE)	675; 470 AF, 205 PAF	-	49.4 (2.2)	0.22857	50.2 (0.86)	1.34282	-0.5		1855.822	299.2
95% CI			45.1-53.6		48.5-51.9		-5.2-4.2			
Z (P)							-0.19 NS (P=0.85)			

S_T (SE) and S_P (SE), Kaplan-Meier estimates for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; §, retrospective uncontrolled study, which was grouped with uncontrolled studies; ‡, NSR sustained, but it there may be a relapse during the NSR period and number of patients with AF or PAF was not stated; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 12 months (continued)

c. Sotalol randomised clinical trials

Study name	*Sotalol (no. of patients)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Juul-Moller *et al.* 1990*	95	79 Quinidine	-	-	-	-	-	-	-	-
Singh *et al.* 1991*	12	6 Placebo	-	-	-	-	-	-	-	-
Reimold *et al.* 1993*	49	49 Propafenone	36.7 (6.9)	0.0231	30.6 (6.6)	0.0231	6.12 (-12.5-24.8)	0.643 NS (P=0.52)	110.158	25.187
Kalusche *et al.* 1994*	41	37 Quinidine/Verapamil	48.8 (7.8)	0.01688	67.6 (7.7)	0.01688	-18.8 (-40.3-2.7)	-1.7 NS (P=0.089)	83.218	23.4512
Carunchio *et al.* 1995*	20	20 Flecainide	60 (10.95)	0.009524	70 (10.3)	0.00953	-10 (-39.4-19.4)	-0.67 NS (P=0.5)	44.444	18.8235
Carunchio *et al.* 1995*	20	26 Placebo	60 (10.95)	0.0132	26.9 (8.7)	0.01322	33.1 (5.7-60.5)	2.37 NS (P=0.018)	51.106	19.9234
Hohnloser *et al.* 1995	17	21 Quinidine	-	-	-	-	-	-	-	-
Pooled rates (SE)	110	132	47.5 (4.3)	0.062692	45.8 (4)	0.06269			288.768	87.3851
95% CI			39.1-55.97		37.9-53.6					

S_T (SE) and S_P (SE), Kaplan-Meier estimates for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; §, retrospective uncontrolled study, which was grouped with uncontrolled studies; ‡, NSR sustained, but it there may be a relapse during the NSR period and number of patients with AF or PAF was not stated; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RD at 12 months (continued)

d. Sotalol nonrandomised clinical trials

Study name	*Sotalol (no. of patients)*	*Control (no. of patients), type of control*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991	53	127 Flecainide	24.5 (5.9)	0.02863	33.89 (4.2)	0.0567	-9.3 (-23.5-4.9)	-1.29 NS (P=0.197)	190.253	178.355
Crijns *et al.* 1991	53	34 Amiodarone	24.5 (5.9)	0.02863	17.65 (6.5)	0.0233	6.9 (-10.4-24.2)	0.78 NS (P=0.435)	128.747	123.186
Antman *et al.* 1990	48	109 Propafenone	14.6 (5.1)	0.038534	20.18 (3.8)	0.067661	-5.6 (-18-6.91)	-0.88 NS (P=0.37)	245.514	226.055
Pooled rates (SE)	101	270	20.53 (3.2)	0.09579	25.03 (2.6)	0.14777	-4 (4.21)		564.514	527.6
95% CI			14.2-26.9		19.9-30.13		-12.3-4.2			
Z (P)			6.36**		9.6**		-0.95 NS (P=0.34)			

S_T (SE) and S_P (SE), Kaplan-Meier estimates for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 12 months (continued)

e. Flecainide randomised clinical trials

Study name	*Flecainide (no. of patients and type of patients)*	*Control (no. of patients), type of control*	S_T *(SE)*	$W.S_T$	S_P *(SE)*	$W.S_P$	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Rasmussen *et al.* (abstract) 1988	28 chronic AF	28 Disopyramide	85.7 (6.6)	0.022867	46.4 (9.4)	0.01126	39.3 (16.7-61.9)	3.4**	75.436	43.62
Van-Gelder *et al.* 1989	36 chronic AF	37 Placebo	49 (8.3)	0.04405	36 (7.9)	0.0161	13 (-9.5-35.5)	1.13 (NS)	75.94	43.8
Anderson *et al.*‡ 1989	48 PAF	48 Placebo	-	-	-	-	-	-	-	-
Pritchett *et al.*‡ 1991	42; 28 PAF, 14 PSVT	42; 28 PAF, 14 PSVT, Placebo	-	-	-	-	-	-	-	-
Henthorn *et al.*† 1991	34 PSVT	34 Placebo	-	-	-	-	-	-	-	-
Pietersen *et al.*‡ 1991	43 PAF	43 Placebo	-	-	-	-	-	-	-	-
Lau *et al.*‡ 1992	19 PAF	15 Placebo	-	-	-	-	-	-	-	-
Lau *et al.*‡ 1992	19 PAF	18 Quinidine	-	-	-	-	-	-	-	-
Chimienti *et al.* 1994	129; 77 PAF, 52 PSVT	136; 82 PAF, 54 PSVT, Propafenone	77.4 (3.7)	0.073717	63.8 (4.1)	0.05888	13.6 (2.8-24.4)	2.5* (P=0.012)	327.348	78.58
Pooled rates (SE)	379; 64 chronic AF, 215 PAF, 100 PSVT	401; 65 chronic AF, 234 PAF, 102 PSVT	75.42 (3)	0.112	56.4 (3.4)	0.0862			478.72	165.98
95% CI			69.5-81.3		49.7-63					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; $W.S_T$, weight of S_T; $W.S_P$, weight of S_P; RD, risk difference; 95% CI; 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 12 months (continued)

f. Flecainide nonrandomised clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmia)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Crijns *et al.* 1991	127 chronic AF	53 Sotalol	33.86 (4.2)	0.056711	24.5 (5.9)	0.02863	9.3 (-4.9-23.5)	1.29 (NS)	190.3	19.5
Crijns *et al.* 1991	127 chronic AF	34 Amiodarone	33.86 (4.2)	0.056711	17.7 (6.5)	0.0234	16.2 (0.98-31.4)	2.1*	165.6	19.2
Anderson *et al.* 1994†	42; 25 PAF, 17 PSVT	42 Placebo; 25 PAF, 17 PSVT	73.81 (6.8)	0.021727	16.7 (5.7)	0.03024	57.14 (39.7-74.6)	6.43**	126.43	18.53
Mary-Rabine *et al.* 1988	55; 39 PAF, 16 PSVT	13 Amiodarone+flecainide; 12 PAF, 1 PSVT	69.1 (6.23)	0.025755	46.2 (13.8)	0.00523	22.9 (-6.8-52.7)	1.5 (NS)	43.48	14.5
Leclercq *et al.* 1992	19 PAF	33 Amiodarone+flecainide	68.42 (10.7)	0.008794	75.8 (7.4)	0.01797		-0.56 (NS)	59.1	15.9
Pooled rates (SE)	243; 83 PAF, 127 chronic AF, 33 PSVT	175; 56 PAF, 87 chronic AF, 18 PSVT	46.1 (2.4)	0.169696	30.6 (3.1)	0.11			584.577	87.57
95% CI			41.4-50.9		24.5-36.6					

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE), Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Table 4.12 Kaplan-Meier estimates for patients remaining in sinus rhythm, and individual RDs at 12 months (continued)

g. Flecainide uncontrolled clinical trials

Study name	*Flecainide (no. of patients and type of arrhythmias)*	*Control (no. of patients, type of control)*	S_T *(SE)*	*W.*S_T	S_P *(SE)*	*W.*S_P	*RD (%) (95% CI)*	*Statistic for effect*	*% Weight Assigned in*	
									Fixed Effects	*Random Effects*
Berns *et al.* 1987	39; 5 chronic AF, 25 PAF, 9 AT	-	56.4 (7.9)	0.015861	50.2 (2.6)	0.14920	6.2 (-10.2-22.6)	0.74 (NS)	143.367	94.3
Zeigler *et al.* 1988	16 PSVT		50 (12.5)	0.0064	50.2 (2.6)	0.14920	-0.2 (-25.2-24.8)	-0.016 (NS)	61.368	50.189
Sonnhag *et al.* 1988	20 PAF	-	55 (11.1)	0.008081	50.2 (2.6)	0.14920	4.8 (-17.6-27.2)	0.42 (NS)	76.656	59.972
Zee-Cheng *et al.* 1988	15 PSVT	-	33.33 (12.2)	0.00675	50.2 (2.6)	0.14920	-16.9 (-41.3-7.5)	-1.36 (NS)	64.578	52.317
Anderson JL 1992	66; 55 PSVT, 41 PAF	-	65.2 (5.9)	0.02907	50.2 (2.6)	0.14920	15 (2.4-27.5)	2.33*	243.293	129.205
Clementy *et al.* 1992	944 PAF	-	-	-	-	-	-		-	-
Pooled rates (SE)	1100; 1030 PAF; 65 PSVT; 5 chronic AF	-	57.1 (3.9)	0.066	50.2 (1.16)	0.746	6.4 (4.12)		589.262	385.983
95% CI			49.5-64.7		49.5-64.7		-1.64-14.5			
Z (P)							1.56 (P=0.119) NS			

AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; S_T% (SE) and S_P% (SE),Kaplan-Meier estimates (% of patients remaining in sinus rhythm) for treatment group and controls, respectively with their standard errors; W.S_T, weight of S_T; W.S_P, weight of S_P; RD, risk difference; 95% CI 95% confidence interval; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

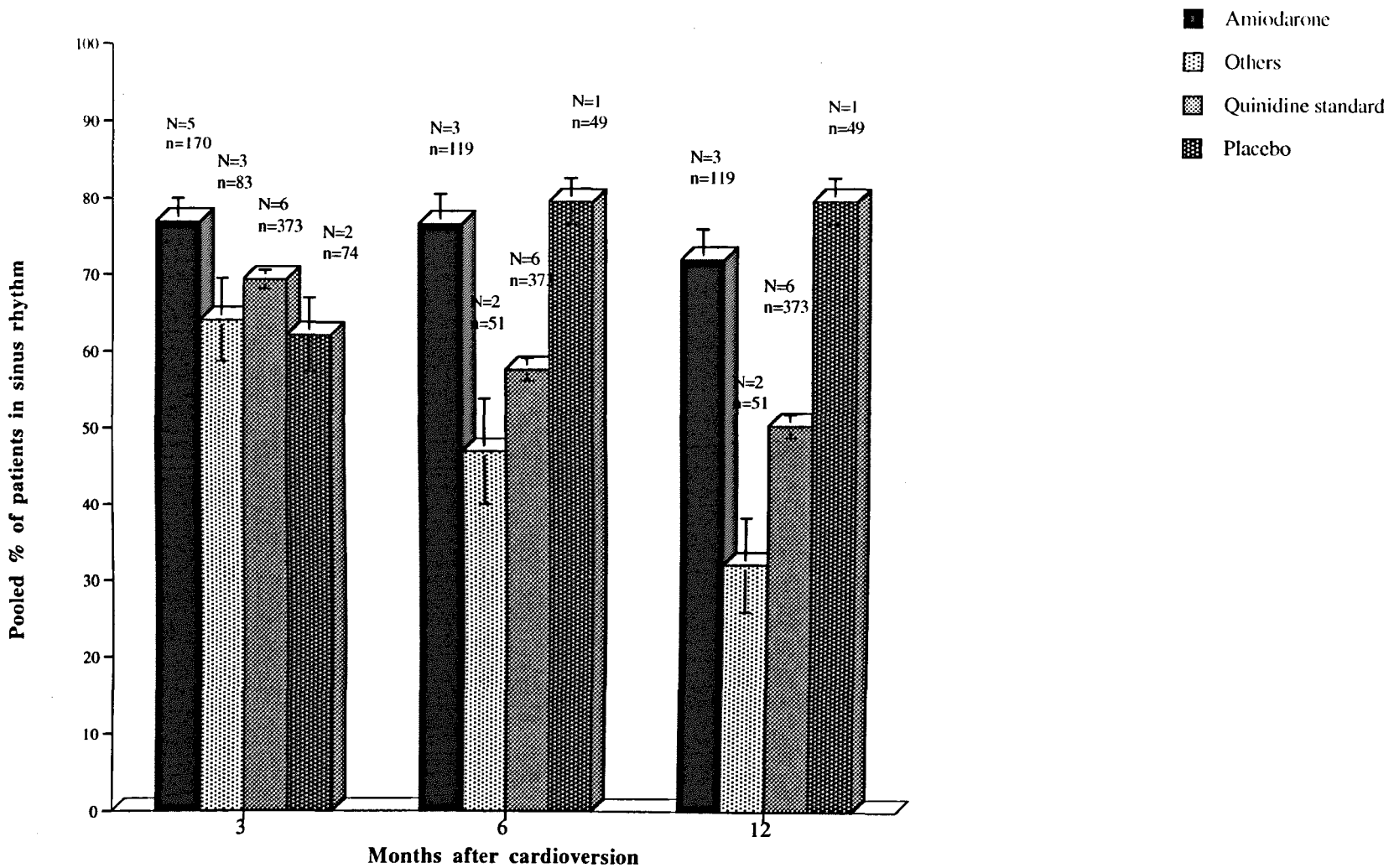

Figure 4.5 Pooled percentages of patients (and 95%CI, bars) in amiodarone group, other comparator antiarrhythmic drugs' group, and placebo group remaining in sinus rhythm at 3, 6, and 12 months after cardioversion are depicted for randomised controlled trials (RCTs). Standard reference quinidine values (obtained from recent meta-analysis) are represented for comparison at each time interval. The number of trials (N) included in analysis, and total number of patients at risk at the begining of the follow-up (n) are shown. The number of patients remaining in sinus rhythm at 6 and 12 months in the placebo group was only reported in one trial (n=49), as a result meta-analytic pooled percentages could not be obtained. However, since quinidine was compared to placebo, and amiodarone have showed better efficacy than quinidine, the results of this trial may be due to chance.

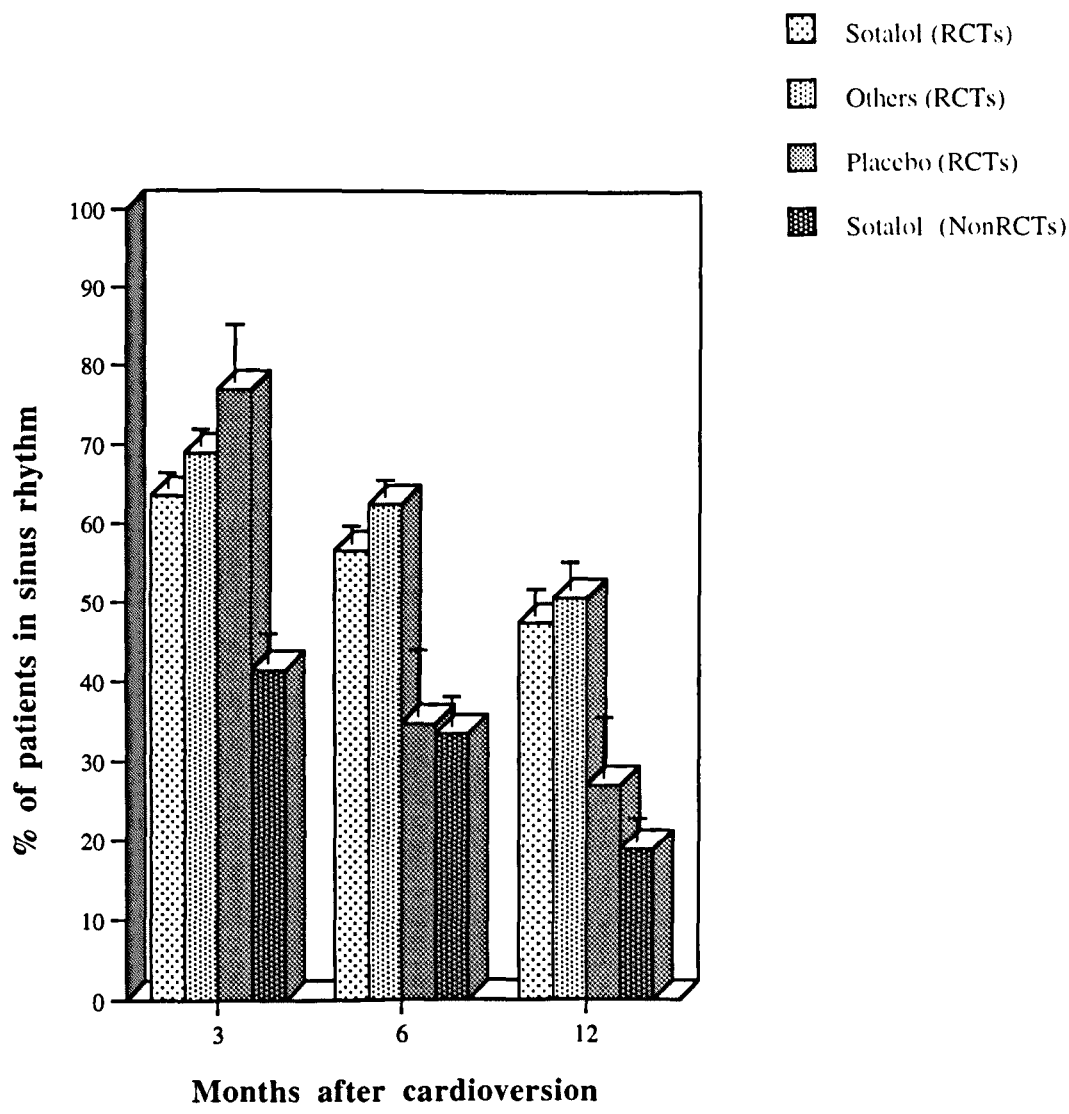

Figure 4.6 Direct comparison of sotalol, other antiarrhythmic drugs (quinidine, quinidine+verapamil, propafenone, and flecainide), and placebo for maintenance of sinus rhythm. Pooled percentages of patients remaining in sinus rhythm (Pt) at 3, 6, and 12 months are represented for each treatment group in RCTs (N=6). In addition, the pooled percentages of patients free of attack obtained from sequential NonRCTs are depicted for comparison at the three time intervals. The sotalol Pt was significantly higher in RCTs than NonRCTs ($P<0.05$).

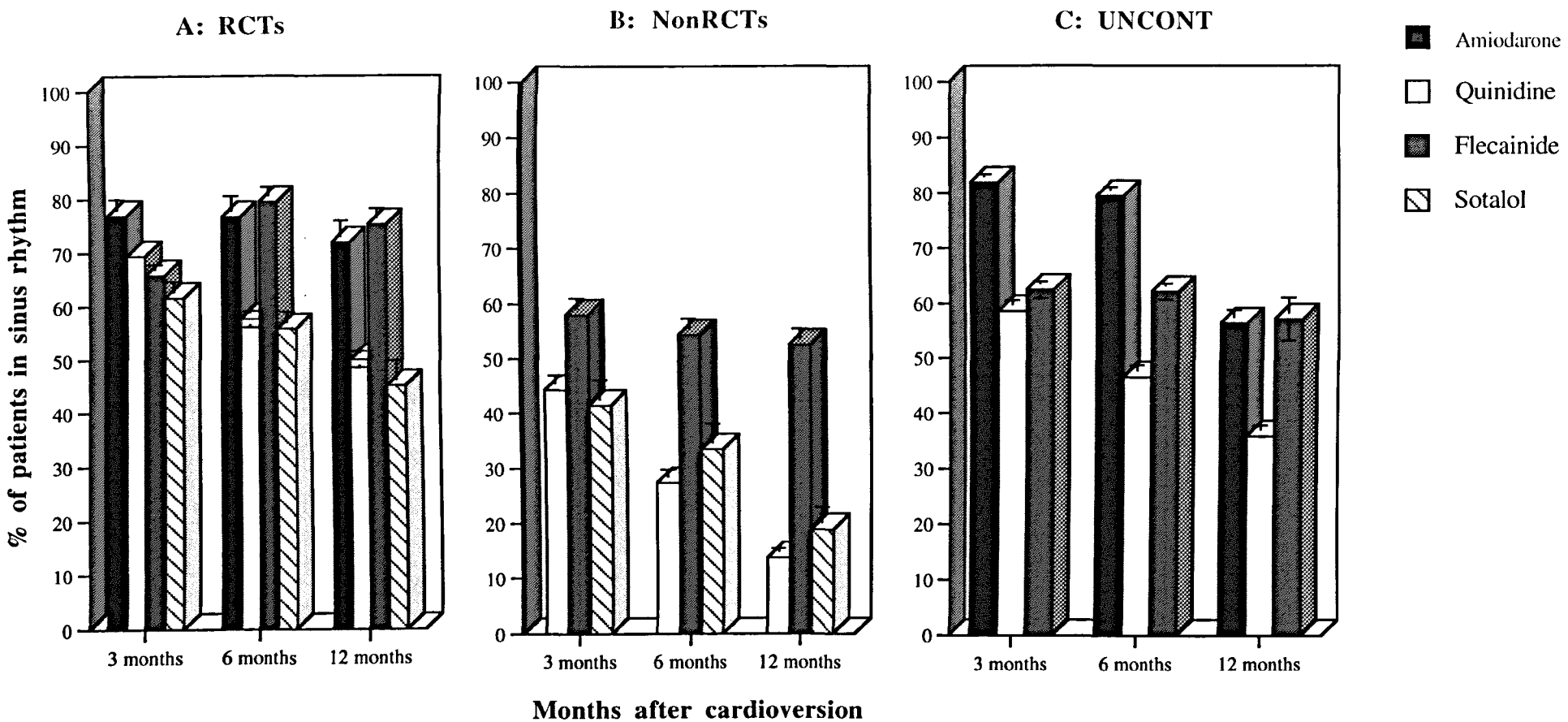

Figure 4.7 Pooled percentages of patients of (and 95% CI, bars) in amiodarone, flecainide, sotalol groups remaining in sinus rhythm at 3, 6, 12 months prior to cardioversion are represented for (A) randomised control trials (RCTs) and for (B) nonrandomised control trials (NonRCTs). The results obtained from our meta-analysis are compared to standard quinidine pooled percentages in RCTs and nonrandomised trials (Reimold *et al,* 1992).

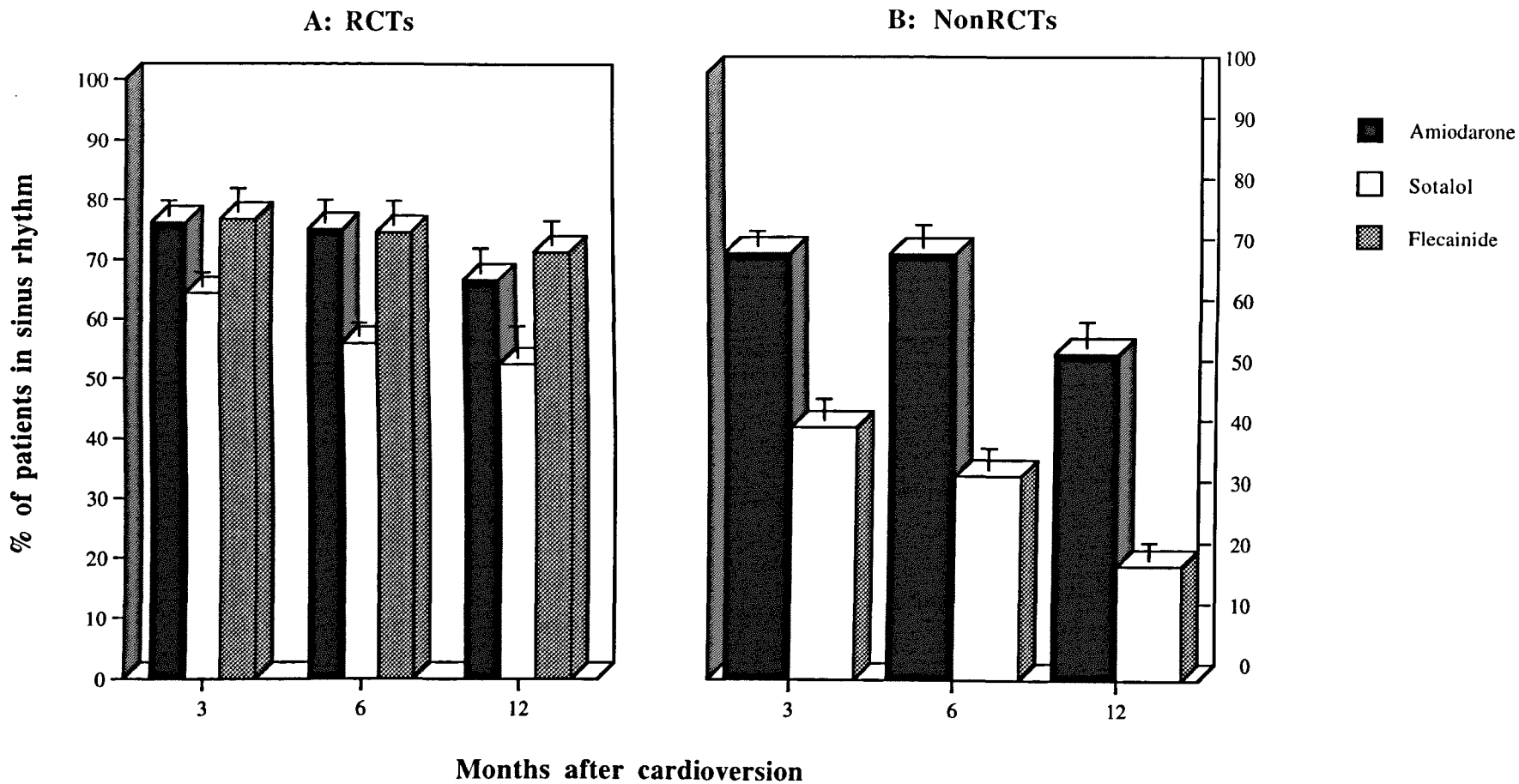

Figure 4.8 Indirect comparison of amiodarone, sotalol, and flecainide for treatment of chronic atrial fibrillation (CAF). The pooled percentages of patients remaining in sinus rhythm at 3, 6, and 12 months prior to cardioversion are depicted for (A) randomised clinical trials (RCTs) and (B) nonrandomised clinical trials (NonRCTs).

4.3.4 Mortality and Proarrhythmia

During the follow-up, a total of 456 patients (out of 3937 patients) discontinued use of medication due to intolerable adverse effects which included conduction disturbances, severe bradycardia, skin photosensitivity, sleeping disturbances, gastrointestinal irritation during amiodarone (77 patients, 8.7%), neurologic disturbances, proarrhythmia during sotalol (23 patients, 7%), visual disturbances, and palpitation during flecainide (263, 15.1%). Furthermore, 24 (6.2%) during placebo, and 69 (10.8%) during other comparative drugs were withdrawn due to other complications.

In the amiodarone trials (all trial designs, N = 18), the unadjusted crude mortality rate for all amiodarone-treated patients and all control groups was 2.6% (23/877) and 3.9% (7/179) respectively. The causes of death in the amiodarone-treated group included myocardial infarction (n = 3), sudden death (n = 1), ventricular fibrillation (n = 1), cerebrovascular accident (n = 3), pneumonia (n = 2), carcinomatosis (n = 1), renal failure (n = 1), leukaemia (n = 2), hepatic disorders (n = 2), congestive heart failure (n = 2), vascular disease (n = 1), and intolerable skin photoallergy (n = 1). In the comparative drug group, the cause of mortality was myocardial infarction (n = 1), carcinoma (n = 1), cancer (n = 1), pulmonary embolus (n = 1), torsades de pointes (n = 1), and unknown cause (n = 1).

In sotalol clinical trials (RCTs and NonRCTs, N = 8), the unadjusted crude mortality rate for all sotalol-treated patients and all control groups was 0.84% (3/358) and 0.79% (4/504) respectively. The causes of death in the sotalol-treated group included myocardial infarction (n = 3), and cardiac arrest (n = 2). The cause of death in the comparative drug group was myocardial infarction (n = 3), and cerebral embolism (n = 1).

In flecainide clinical trials (all trial design, N = 16), the unadjusted crude mortality rate for all flecainide-treated patients and all control groups was 0.34% (6/1791) and 0.2% (1/587) respectively. The causes of death in the flecainide-treated group included myocardial infarction (n = 2), cardiac arrest (n = 1), sudden death (n = 2), and pulmonary carcinoma (n = 1). The one event in the comparison group was acute myocardial infarction.

Since patients allocated to active treatment in one trial should only be compared directly

with patients allocated to the control group in the same trial and not with patients in any other trial, and due to the unavailability of placebo control group in most included trials, calculating pooled summary estimates of death risk versus active control group in the same trial was considered appropriate.

The summary statistics for mortality in the full-exposure groups in the RCTs and NonRCTs are given in Table 4.13 for amiodarone, Table 4.14 for sotalol, and Table 4.15 for flecainide.

As shown in Table 4.13, the difference between observed and expected value (O-E) was less than zero in three of the four amiodarone studies, and equal to 1.01 in one trial, and thus manifesting lower trend toward mortality in the amiodarone group. However, these differences were not significant in any of the trials (P>0.05). Overall, the typical pooled OR (Peto's method) was 0.91 (95% CI, 0.31 to 2.69; Z = -0.18; P=0.88). A test for heterogeneity between the various trial results was not significant (Q, 2.87; df=3, P=0.239). The summary OR calculated by Mantel-Haenszel method was 0.92 (95% CI, 0.5 to 1.7; Z= -0.27, P=0.8), the RD calculated by DerSimonian and Laird method was -4.628% (95% CI -12.3 to 3.04, P=0.238), and RR (Fleiss *et al.* method, 1993) was 1.02 (95% CI 0.42 to 2.48; P=0.97). All the previous summary estimates, although not statistically significant, implied lower incidence of mortality on amiodarone compared to other drugs.

For the sotalol clinical trials, the study specific values of OR, RD, RR, as well as the overall meta-analytical estimates of these statistics, are shown in Table 4.14. The typical OR was 0.85 (95% CI 0.815 to 3.945; Z= -0.2, P=0.84; Q, 4.385, df = 6, P=0.223). The Mantel-Haenszel OR, RD, RR were 0.99 (0.97), -0.79 (0.34), and 0.954 (0.94) respectively (P>0.05).

Table 4.15 illustrates mortality data in the flecainide clinical trials. The deaths were stated in seven placebo-controlled trials and four comparative studies. The O-E value was equal to zero in seven studies (5 placebo-controlled, and 2 comparative studies). In one nonrandomised trial, comparing flecainide to amiodarone, the O-E value was-0.3665 indicating lower incidence in flecainide. The overall pooled OR (Peto's method) versus other drugs was 1.9 (95% CI 0.3 to 2.5; Z=0.7, P=0.5), and versus placebo was 7.5 (95% CI 0.8 to 72.6; Z=1.7, P=0.08). All the other statistics for the difference between flecainide and the active drugs were not significant. However, the Mantel Haenszel OR versus placebo was highly statistically significant (OR_{MH}, 1.8;

95% CI, 1.2 to 2.7; Z=3.1, P=0.002), strongly suggesting increased mortality in the flecainide-treated group. However, the RD and RR versus placebo were 2.1 (95% CI, -0.5 to 4.8; Z=1.6, P=0.12), and 1.7 (95% CI, 0.4 to 6.5; Z=0.7, P=0.5) respectively.

The insufficient reporting of data regarding the age, sex, left atrial diameter, duration of AF, or cardiac diagnosis, hindered the estimation of adjusted mortality rates. Furthermore, the time of death was not consistently reported. Hence, a survival meta-analysis could not be performed.

The proarrhythmic events reported in the amiodarone, sotalol, and flecainide clinical trials are given in Table 4.16. All forms of proarrhythmic reactions considered by the principal authors to be drug-induced proarrhythmic effects, were included in the analysis.

The incidence rate of proarrhythmia in amiodarone-treated group in all study designs, ranged from 0% to 15% in the individual studies. The crude total incidence rate from all studies was 0.7% (6/857) in amiodarone treated patients as compared with 5.1% in the active control group. The nature of the presenting arrhythmia induced by amiodarone was severe symptomatic sinus bradycardia (n = 6). In the comparative drug group, proarrhythmia was in the form of prolongation of QT interval (n =1, receiving quinidine plus verapamil), ventricular arrhythmia (n = 6, receiving bepridil), and torsade de pointes (n = 2, receiving bepridil). Table 4.16 shows pooled estimates of proarrhythmia incidence in RCTs of amiodarone. As shown, the results of OR_{peto}, OR_{MH}, and RR suggest a trend towards decreased incidence of proarrhythmia with amiodarone when compared to other drug Classes.

The incidence rate of proarrhythmia in the sotalol-treated group in the RCTs and NonRCTs, ranged from 1.03 % to 6% in the individual studies. The crude total incidence rate from all studies was 1.96% (7/358) in the sotalol-treated group versus 1.5% (8/528) in the active control group. Sotalol-induced proarrhythmia was in the form of ventricular arrhythmia (n = 2), nonsustained ventricular tachycardia (n = 1), and supraventricular proarrhythmia (n = 1). In the control group, the proarrhythmic events were ventricular fibrillation (n = 2; 1 receiving quinidine, and 1 receiving propafenone), torsade de pointes (n = 3, receiving quinidine), sustained ventricular tachycardia (n = 1, receiving quinidine), and nonsustained ventricular tachycardia (n = 1, receiving propafenone). The pooled estimates for the incidence of proarrhythmia on

sotalol as compared to other drugs suggested nonsignificant difference (Table 4.16).

The incidence rate of proarrhythmia in the flecainide-treated group in the individual studies ranged from 1.5% to 20.5%. The crude total incidence rate from all studies was 1.7% (32/1884) in flecainide treated patients as compared with 0.3% in the active control group. The nature of flecainide-induced proarrhythmia was primarily supraventricular proarrhythmia (53.13% of the total events). In the control group, the two proarrhythmic events which occurred were symptomatic sustained ventricular tachycardia (receiving propafenone), and supraventricular proarrhythmia (receiving sotalol). On the contrary to amiodarone and sotalol, the overall pooled OR_{peto}, OR_{MH}, RR were highly significant as compared to the combined estimates of other drugs and placebo (Q = 0.6, 0.1, 0.6 respectively). Recalculating the same statistics against other drugs did not show significant difference. However, against placebo, the difference was highly significant ($P<0.01$).

Table 4.13 Mortality data and statistical analysis of full-exposure group in randomised clinical trials of amiodarone

Study name	*Basic data (No dead/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Amiodarone group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Vitolo *et al.* 1981	0/28	0/26 Q	0	0	-	0.8 (NS)	0.93	-0.04 (NS)	0	0.8 (NS)	0.931 (0.019-45.3)	-0.036 (NS)
Martin *et al.* 1986	9/43	4/27 D	1.01429	2.545	1.489 (0.44-5.1)	0.64 (NS)	1.42	0.58 (NS)	6.12 (-11.98-24.21)	0.662 (NS)	1.3434 (0.486-3.713)	0.5692 (NS)
Zehender *et al.* 1992	0/20	1/20 Q+V	-0.5	0.25	0.135 (0.002-6.82)	-1 (NS)	0.32	-0.69 (NS)	-5 (-14.55-4.55)	-1.025 (NS)	0.333 (0.014-7.724)	-0.6851 (NS)
Perelman *et al.* 1987	0/10	2/14 B	-0.833	0.465	0.1666 (0.09-2.95)	-1.22 (NS)	0.24	-0.89 (NS)	-14.29 (-32.62-4.05)	-1.53 (NS)	0.2727 (0.0145-5.13)	-0.8676 (NS)
Pooled rates vs other drugs	9/101	7/87	-0.319	3.26	0.91 (0.31-2.69)	-0.18 (NS) (P=0.88)	0.92 (0.5-1.7)	-0.27 (NS) (P=0.8)	-4.628 (-12.3-3.04)	-1.18 (NS) (P=0.238)	1.01522 (0.415-2.482)	0.033 (NS) (P=0.97)
Q statistic (P)					2.87 (P=0.239) NS	-	-		2.45 (P=0.4887) NS		1.546 (P=0.67) NS	
Pooled random-effects					1.01 (-0.938-0.95)	0.013 (NS) (P=0.98)	-		-0.0731 (-0.131_ -0.015)	-2.4* (P=0.02)	-	-
Pooled rates vs placebo (SE)					NA	-	-		NA	-	NA	-

O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), odds ratio and its 95% confidence interval; M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; * statistically significant (P<0.05); ** highly statistically significant

Table 4.14 Mortality data and statistical analysis of full-exposure group in randomised clinical trials of sotalol

Study name	*Basic data (No dead/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Sotalol group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Juul-Moller *et al.* 1990	1/97	1/86 Q	-0.06011	0.4954	0.88575	-0.0854 (NS)	0.886	0.76 (NS)	-0.131 (-3.2-2.9)	-0.085 (NS)	0.8878 (0.09-8.38)	-0.1 (NS)
Reimold *et al.* 1993	2/50	0/50 Pr	1	0.4949	7.5414	1.42141 (NS)	5.2	2.02*	4 (-1.4-9.4)	1.44 (NS)	5 (0.25-101.4)	1.05 (NS)
Kalusche *et al.* 1994	0/41	0/37 Q+V	0	0	-	-	0.9	-0.05 (NS)	0	-	0.91 (0.018-44.5)	-0.05 (NS)
Crijns *et al.* 1991	0/53	2/127 F	-0.5889	0.41317	0.24044	-0.916 (NS)	0.47	-0.486 (NS)	-1.57 (-3.7-0.6)	-1.426 (NS)	0.474 (0.023-9.7)	-0.48 (NS)
Crijns *et al.* 1991	0/53	1/34 A	-0.61	0.238076	0.0774	-1.248 (NS)	0.21	-0.95 (NS)	-2.94 (-8.6-2.7)	-1.015 (NS)	0.216 (0.009-5.1)	-0.95 (NS)
Antman *et al.* 1990	0/48	0/109 Pr	0	0	-	-	2.3	0.41 (NS)	0	-	2.245 (0.05-109.9)	0.41 (NS)
Hohnloser *et al* 1995	0/25	0/25 Q	0	0	-	-	1	0 (NS)	0	-	1 (0.68-48.5)	0 (NS)
Pooled rates vs other drugs	3/314	4/468	-0.2582	1.6416	0.855 (0.185-3.945)	-0.2015 (NS) (P=0.84)	0.99 (0.65-1.52)	-0.036 (NS) (P=0.97)	-0.79 (-2.4-0.8)	-0.96 (NS) (P=0.337)	0.954 (0.29-3.11)	-0.078 (NS) (P=0.94)
Q statistic (P)					4.385 P=0.223 (NS)		-		4.224 P=0.646 (NS)		2.4 (P=0.879)	
Pooled random-effects					-	-	-		-	-	1.5 (0.2-11.1)	0.4 (NS) (P=0.7)
Pooled rates vs placebo (SE)					NA	-	-		NA	-	NA	-

O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), odds ratio and its 95% confidence interval; M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; P, placebo; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; F, flecainide; A, amiodarone; * statistically significant (P<0.05); ** highly statistically significant

Table 4.15 Mortality data and statistical analysis of full-exposure group in randomised clinical trials of flecainide

Study name	*Basic data (No dead/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Flecainide group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Van-Gelder *et al.* 1989*	0/36	0/37 P	0	0	-	-	1.03	0.013 (NS)	0	-	1.03 (0.02-50)	0.013 (NS)
Rasmussen *et al.* 1988*	1/30	0/30 D	0.5	0.25	7.4 (0.14-365)	1 (NS)	3.1	0.7 (NS)	3.3 (-3.1-9.8)	1.02 (NS)	3 (0.13-71)	0.7 (NS)
Anderson *et al.* 1989*	1/64	0/64 P	0.5	0.25	7.4 (0.14-365)	1 (NS)	3.1	0.7 (NS)	1.6 (-1.5-4.6)	1.01 (NS)	3 (0.13-72)	0.7 (NS)
Pritchett *et al.* 1991*	0/73	0/73 P	0	0	-	-	1	0	0	-	1 (0.02-49)	0
Henthorn *et al.* 1991*	0/48	0/48 P	0	0	-	-	1	0	0	-	1 (0.02-49)	0
Pietersen *et al.* 1991*	2/48	0/48 P	1	0.494737	7.548 (0.46-121.5)	1.42 (NS)	5.2	1.07 (NS)	4.2 (-1.5-9.8)	1.44 (NS)	5 (0.24-99)	1.05 (NS)
Lau *et al.* 1992*	0/19	0/18 Q	0	0	-	-	0.95	-0.03 (NS)	0	-	0.95 (0.02-45)	-0.03 (NS)
Lau *et al.* 1992*	0/19	0/15 P	0	0	-	-	0.8	-0.11 (NS)	0	-	0.8 (0.02-36.6)	-0.11 (NS)
Chimienti *et al.* 1994*	0/169	0/166 Pr	0	0	-	-	0.98	-0.009 (NS)	0	-	0.98 (0.02-49)	-0.008 (NS)
Anderson *et al.*** 1994	0/49	0/49 P	0	0	-	-	1	0	0	-	1 (0.02-49)	0
Crijns *et al.* 1991**	2/127	0/53 S	0.58889	0.413173	4.15904 (0.2-90)	0.92 (NS)	2.13	0.5 (NS)	1.6 (-0.5-3.7)	1.43 (NS)	2.11 (0.1-43)	0.5 (NS)
Crijns *et al.* 1991**	2/127	1/34 A	-0.36646	0.493502	0.47589 (0.03-8.2)	-0.52 (NS)	0.45	-0.8 (NS)	-1.4 (-7.4-4.7)	-0.44 (NS)	0.46 (0.1-3.3)	-0.8 (NS)
Pooled rates vs others†	6/663	1/635	2.22243	1.9014	3.2 (0.78-13.3)	1.6 (NS) (P=0.11)	1.4 (1.04-1.9)	2.2* (P=0.03)	1.7 (0.1-3.3)	2.1* (P=0.04)	1.3 (0.5-3.2)	0.5 (NS) (P=0.6)
Pooled rates vs placebo (SE)					7.5 (0.8-72.6)	1.7 (NS) (P=0.08)	1.8 (1.2-2.7)	3.1** (P=0.002)	2.1 (-0.5-4.8)	1.6 (NS) (P=0.12)	1.7 (0.4-6.5)	0.7 (NS) (P=0.5)

O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), odds ratio and its 95% confidence interval; M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; P, placebo; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; F, flecainide; A, amiodarone; S, sotalol; * statistically significant (P<0.05); ** highly statistically significant; †, including placebo and other antiarrhythmics

4.16 Pooled estimates of proarrhythmic incidence in randomised clinical trials

Amiodarone clinical Trials

Study name	*Basic data (No events/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Amiodarone group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Vitolo *et al.* 1981	0/28	0/26 Q	-0.01786	0.24968	0.9311 (0.0184-47)	-0.0357 (NS)	0.93	-0.036 (NS)	-0.1 (-7-6.8)	-0.036 (NS)	0.93 (0.02-45.3)	-0.036 (NS)
Martin *et al.* 1986	0/43	0/27 D	-0.1111	0.23765	0.62655 (0.01-0.029)	-0.2279 (NS)	0.63	-0.228 (NS)	-0.6 (-6-5)	-0.218 (NS)	0.64 (0.013-31)	-0.228 (NS)
Bosi *et al.* 1990	0/48	0/49 P	0.00505	0.24997	1.0204 (0.02-51.4)	0.01 (NS)	1.02	0.01 (NS)	0.02 (-4-4)	0.01 (NS)	1.02 (0.02-50.4)	0.01 (NS)
Zehender *et al.* 1992	3/20	1/20 Q+V	1.25	1.02896	3.36967 (0.488-23.3)	1.232 (NS)	4	1.175 (NS)	11.9 (-6-30)	1.27 (NS)	3.5 (0.4-29.7)	1.148 (NS)
Jong *et al.* 1995	0/44	0/43 P	-0.00562	0.24997	0.97778 (0.019-49.3)	-0.01124 (NS)	0.98	-0.01 (NS)	-0.025 (-4.4-4)	-0.011 (NS)	0.98 (0.019-48)	-0.0113 (NS)
Perelman *et al.* 1987	0/10	8/14 B	-3.31	1.49	0.12 (0.022-0.54)	-2.7**	0.036	-2.15*	-52 (-80_-24)	-0.25 (NS)	0.08 (0.005-1.25)	-1.8 (NS)
Pooled rates vs other drugs	3/193	9/179	- 2.19	3.49	0.53626 (0.19-1.5)	-1.2 (NS) (P=0.23)	0.554 (0.357-0.86)	-2.6** (P=0.009)	-0.3 (-3-2)	-0.25 (NS) (P=0.8)	0.8557 (0.24-3.1)	-0.2396 (NS) (P=0.8)
Q statistic (P)					7.5 (P=0.184) NS				14.97** (P=0.01)		4.6 (P=0.5) NS	
Pooled random-effects					-	-			-0.9 (-0.059-0.04)	-0.38 (NS) (P=0.7)	-	-
Pooled rates vs placebo					NA	-			NA	-	NA	-

* Statistically significant; O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), odds ratio and its 95% confidence interval; M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; P, placebo; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; F, flecainide; A, amiodarone; * statistically significant (P<0.05); ** highly statistically significant

4.16 Pooled estimates of proarrhythmic incidence in randomised clinical trials (continued)

Sotalol clinical trials

Study name	*Basic data (No events/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Amiodarone group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Juul-Moller *et al.* 1990	1/97	1/86 Q	-0.08919	0.739	0.89 (0.1-8.7)	-0.1 (NS)	0.886	-0.1 (NS)	-0.2 (-4-3.5)	-0.1 (NS)	0.89 (0.09-8.4)	-0.1 (NS)
Singh *et al.* 1991	0/24	0/10 P	-0.19444	0.2122	0.39 (0.005-28)	-0.42 (NS)	0.43	-0.42 (NS)	-3 (-16-12)	-0.37 (NS)	0.44 (0.01-20.7)	-0.42 (NS)
Reimold *et al.* 1993	3/50	2/50 Pr	0.5	1.426	1.42 (0.28-7.3)	0.42 (NS)	1.43	0.42 (NS)	2 (-7-11)	0.42 (NS)	1.4 (0.29-6.7)	0.42 (NS)
Kalusche *et al.* 1994	0/41	0/41 Q+V	0	0.25	1 (0.02-50)	0 (NS)	1.07	0.035 (NS)	0 (-5-5)	0 (NS)	1 (0.02-49)	0
Carunchio *et al.* 1995	0/20	0/26 P	0.0625	0.2461	1.289 (0.03-66)	0.13 (NS)	1.293	0.13 (NS)	0.5 (-7.7-8.8)	0.125 (NS)	1.29 (0.027-62)	0.127 (NS)
Crijns *et al.* 1991	1/53	0/127 F	0.91	0.415	8.885 (2.4-186)	1.4 (NS)	7.2	0.98 (NS)	2.4 (-2-6.9)	1.04 (NS)	7.1 (0.29-171)	1.21 (NS)
Antman *et al.* 1990	2/48	1/109 Pr	1.2673	0.8366	4.548 (0.53-38)	1.385 (NS)	3.9	0.83 (NS)	3.7 (-2.8-10)	1.123 (NS)	3.74 (0.51-27.5)	1.295 (NS)
Hohnloser *et al.* 1995	0/25	4/25 Q	-2	1.152	0.176 (0.03-1.1)	-1.86 (NS)	0.094	-2.3*	-15 (-31-0.08)	-1.93 (NS)	0.11 (0.006-1.96)	-1.5 (NS)
Carunchio *et al.* 1995	0/20	0/20 F	0.0122	0.249	1.05 (0.021-52.1)	0.024 (NS)	1	0 (NS)	0.12 (-9-9.6)	0.025 (NS)	1.1 (0.02-50.4)	0.025 (NS)
Crijns *et al.* 1991	1/53	0/34 A	0.28652	0.472	1.835 (0.11-32)	0.4 (NS)	1.97	0.412 (NS)	1.4 (-5-7)	0.449 (NS)	1.94 (0.08-46.4)	0.41 (NS)
Pooled rates vs other drugs	7/358	8/528	0.752	6	1.133 (0.51-2.5)	0.3 (NS) (P=0.8)	1.13 (0.8-1.64)	0.613 (NS) (P=0.5)	0.7 (-1.2-2.6)	0.69 (NS) (P=0.49)	1.32 (0.57-3.04)	0.65 (NS) (P=0.52)
Q statistic (P)					7.83 (P=0.551) (NS)				6.19 (P=0.72) (NS)		5.5 (P=0.79) (NS)	
Pooled rates vs placebo					NA	-			NA	-	NA	-

O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; P, placebo; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; F, flecainide; A, amiodarone; * statistically significant (P<0.05); ** highly statistically significant

4.16 Pooled estimates of proarrhythmic incidence in randomised clinical trials (continued)

Flecainide clinical trials

Study name	*Basic data (No events/No followed up)*		*Peto method*				*M-H method*		*D-L method*		*Fleiss et al (1993)*	
	Flecainide group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*	*OR*	*statistic for effect*	*RD(%) (95% CI)*	*statistic for effect*	*RR (95% CI)*	*statistic for effect*
Van-Gelder *et al.* 1989*	4/36	0/37 P	2.033	1.182	5.6 (0.9-33.9)	1.9 (NS)	10.4	1.5 (NS)	10.8 (-0.2-21.9)	1.9 (NS)	9.2 (0.5-165.5)	1.5 (NS)
Rasmussen *et al.* 1988*	0/30	0/30 D	0	0.25	1 (0.02-50.4)	0	1	0	0 (-6.2-6.2)	0	1 (0.02-48)	0
Anderson *et al.* 1989*	3/64	0/64 P	1.5	0.9767	4.7 (0.6-33.8)	1.5 (NS)	7.34	1.3 (NS)	4.6 (-1.3-10.5)	1.54 (NS)	7 (0.4-132.8)	1.3 (NS)
Pritchett *et al.* 1991*	3/73	0/73 P	1.5	0.9796	4.6 (0.6-33.5)	1.5 (NS)	7.3	1.31 (NS)	4.1 (-1.1-9.2)	1.5 (NS)	7 (0.4-133)	1.3 (NS)
Henthorn *et al.* 1991*	2/51	0/51 P	1	0.7354	3.9 (0.4-38.3)	1.17 (NS)	5.2	1.1 (NS)	3.8 (-2.5-10)	1.2 (NS)	5 (0.3-101.6)	1.1 (NS)
Pietersen *et al.* 1991*	4/48	0/48 P	2	1.1984	5.3 (0.9-31.8)	1.83 (NS)	9.8	1.5 (NS)	8.2 (-0.4-16.7)	1.9 (NS)	9 (0.5-162.4)	1.5 (NS)
Lau *et al.* 1992*	3/19	0/18 P	1.449	0.9205	4.8 (0.6-37.2)	1.5 (NS)	7.9	1.3 (NS)	14.9 (-3.3-33)	1.6 (NS)	6.7 (0.4-120)	1.3 (NS)
Lau *et al.* 1992*	3/19	0/15 P	1.278	0.903	4.12 (0.5-32.4)	1.345 (NS)	6.6	1.22 (NS)	14.4 (-4.3-33.1)	1.5 (NS)	5.6 (0.3-99)	1.2 (NS)
Anderson *et al.* 1994**	0/49	0/49 P	0	0.25	1 (0.02-50.4)	0	1	0	0 (-3.9-3.9)	0	1 (0.02-49)	0
Leclercq *et al.* 1992**	2/19	0/33 F+A	1.89	0.67319	7.9 (0.75-90)	1.7 (NS)	9.6	1.43 (NS)	11 (-4-26)	1.4 (NS)	8.5 (0.43-168.2)	1.4 (NS)
Mary-Rabine *et al.* 1988**	0/55	0/13 F+A	-0.3	0.16	0.2 (0.001-20.7)	-0.75 (NS)	0.2432	-0.7 (NS)	-2.6 (-12.7-7.3)	-0.5 (NS)	0.25 (0.006-12)	-0.7 (NS)
Chimienti *et al.* 1994*	0/169	1/166 Pr	-0.51	0.49847	0.4 (0.02-5.8)	-0.72 (NS)	0.33	-0.6 (NS)	-0.6 (-2.3-1)	-0.72 (NS)	0.33 (0.01-7.9)	-0.7 (NS)
Crijns *et al.* 1991*	0/127	1/53 S	-0.91	0.415	0.113 (0.005-2.4)	-1.41 (NS)	0.14	-1.2 (NS)	-2.4 (-6.9-2)	-1.04 (NS)	0.14 (0.005-3.4)	-1.2 (NS)
Crijns *et al.* 1991*	0/127	0/34 A	0.107	0.08457	3.6 (0.004-2980)	0.37 (NS)	1	0	0.4 (-0.7-1.5)	0.71 (NS)	1	0
Pooled rates vs others†	21/740	2/684	10.54	9.2272	3.1 (1.6-5.98)	3.5** (P=0.0004)	3.37 (2.4-4.7)	7.3** (P<0.01)	0.5 (-0.4-1.3)	1.08 (NS) (P=0.3)	2.9 (1.24-7)	2.44* (P=0.014)
Pooled rates vs placebo (SE)					4.5 (2-9.8)	3.7** (P=0.0002)	6.7 (4.23-10.6)	8.1** (P<0.01)	3.42 (1.1-5.8)	2.9** (P=0.004)	5.9 (1.9-18.6)	3.1** (P=0.002)

O-E, observed minus expected deaths; Var (O-E), variance of (O-E); OR (95% CI), odds ratio and its 95% confidence interval; M-H method, Mantel and Haenszel method; D-L method, DerSimonian and Laird method; RD (95% CI), rate difference and its 95% confidence interval; RR (95% CI), relative risk and its 95% confidence interval; Q, quinidine; P, placebo; Pr, propafenone; D, disopyramide; Q+V, quinidine+verapamil; B, bepridil; F, flecainide; A, amiodarone; S, sotalol; * statistically significant (P<0.05); ** highly statistically significant; †, including placebo and other antiarrhythmics

4.3.5 Assessment of Publication Bias

To assess whether the highly significant effects seen in the present meta-analysis, regarding the superiority of amiodarone and flecainide over other drugs, were merely due to publication bias in favour of positive results, the graphical techniques explained in Chapter 3 were applied to our data. The results are presented below.

A funnel plot of the amiodarone clinical trials was plotted (Figure 4.9). This overall funnel plot follows the shape of an "inverted funnel" indicating no obvious publication bias. Furthermore, Figure 4.10 shows a similar funnel graph, but with the effect estimates (RDs) plotted as a function of the weight assigned for each individual trial. Again, this plot yielded a funnel-shaped scatter with a decrease in the scatter of results as precision increases. This supported the previous evidence of low retrieval bias. In addition, for demonstrating the absence of publication bias, a strong positive correlation between sample size and the weight of individual effects should exist (Mullen, 1989). This was presented in Figure 4.11.

All the preceding graphical techniques were also performed for flecainide clinical trials. Figure 4.12, and Figure 4.13 illustrate two scatterplots of RDs versus the sample size and versus the weights respectively. Although Figure 4.12 follows a funnel-shape plot, its peak is entirely dependent on only one large study (Clementy *et al.*, 1992). This figure indicate a deficiency of large studies in this meta-analysis which may not be ascribed to publication bias, since the results of small negative as well as small positive were incorporated in this meta-analysis. Figure 4.14 presents the relationship between the sample sizes and the weights assigned for various individual clinical trials of flecainide. This graph does not imply a strong positive correlation (as that shown previously in Figure 4.11), due to the high degree of scatter between the results of the small sample size studies with different design characteristics. However, these studies were subgrouped in our analysis into various strata depending on their design categories.

In addition to the graphical techniques for detecting the presence or absence of publication bias, numerical methods were developed for estimating the number of additional unpublished studies with null results (zero treatment difference), which would be needed to reverse the results of the significant meta-analysis to nonsignificant level. This was addressed by application of Rosenthal (1979) formula (fail-safe N) to

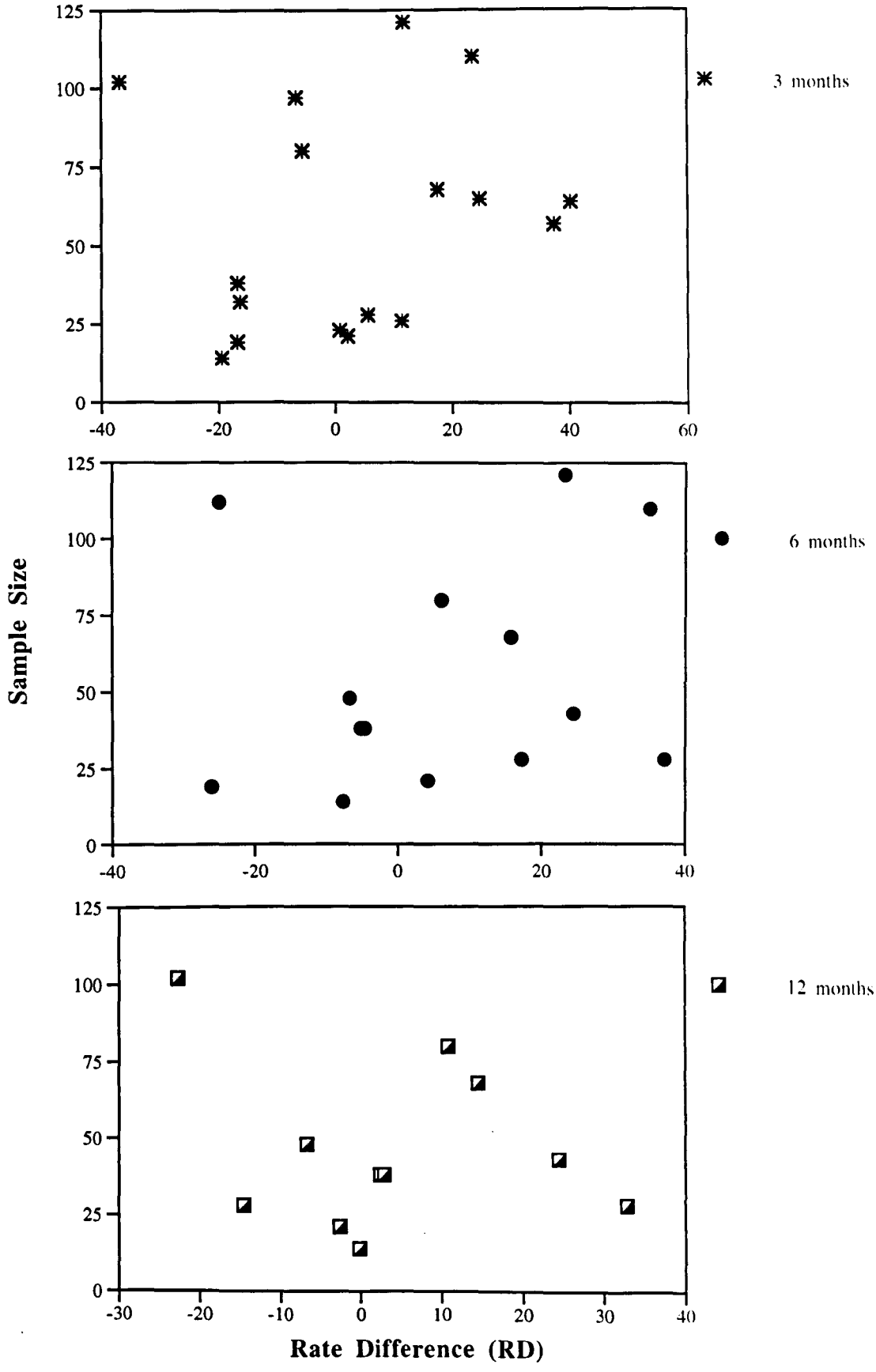

Figure 4.9 Funnel plot of amiodarone clinical trials (N=17). The figure illustrates the relationship between the study sample size and its effect estimate (RD) at 3 (N=17), 6 (N=14), and 12 (N=12) months for the 17 individual studies included in the analysis. This scatter plot has yielded approximately a funnel-shaped graph, where both the results of small negative as well as large positive trials were included. Therefore, indicating a slight evidence of publication bias.

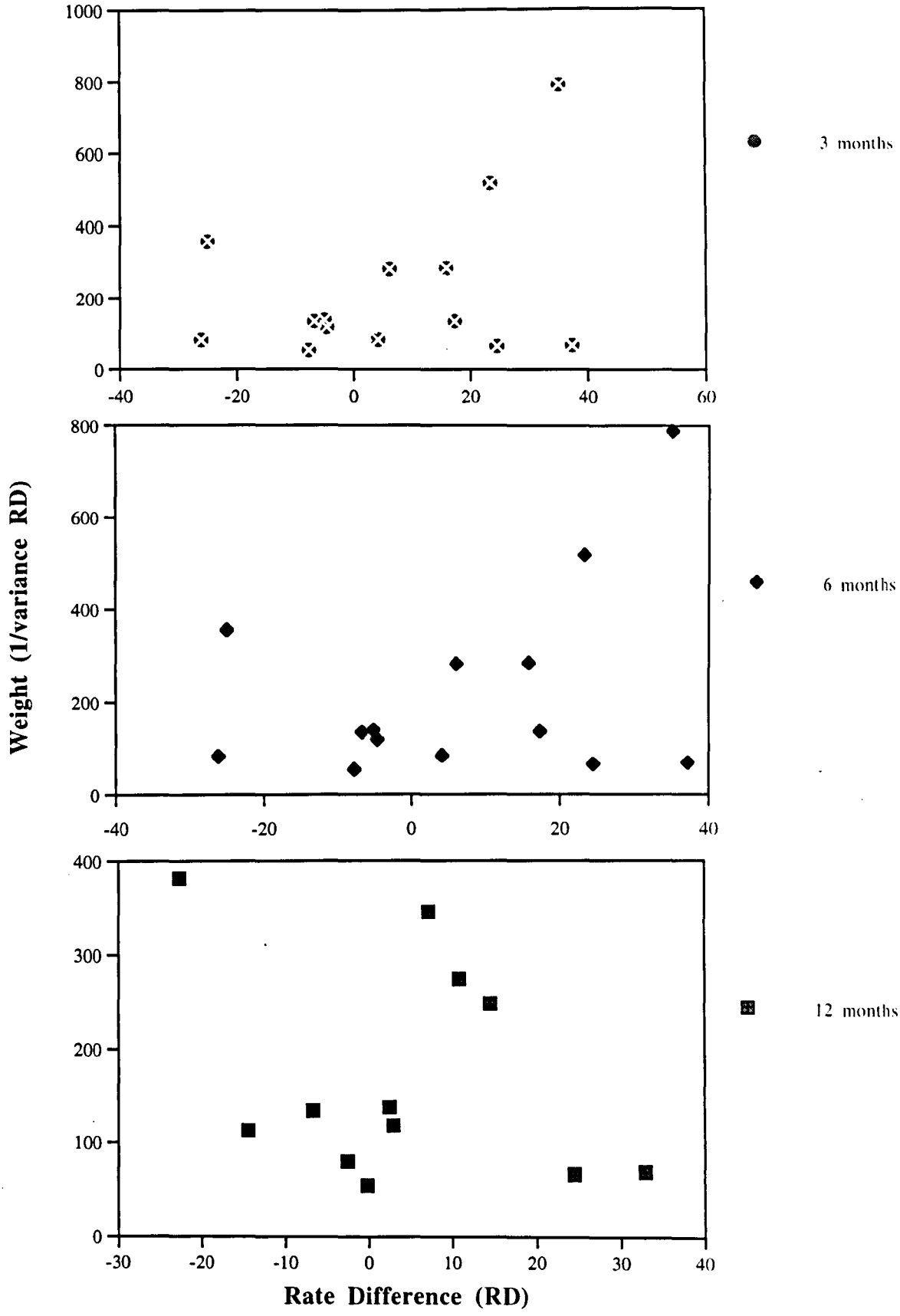

Figure 4.10 Rate difference vs. weight for amiodarone clinical trials (N=17). This figure illustrates the relationship between a trial's weight (a measure of the precision of the results) and its effect estimates at 3, 6, and 12 months for the 18 individual studies. This figure shows that large sample size studies where more precise estimates (less variance), and small sample size studies with less precise estimates were incorporated in this analysis. Thus eliminating probability of publication bias.

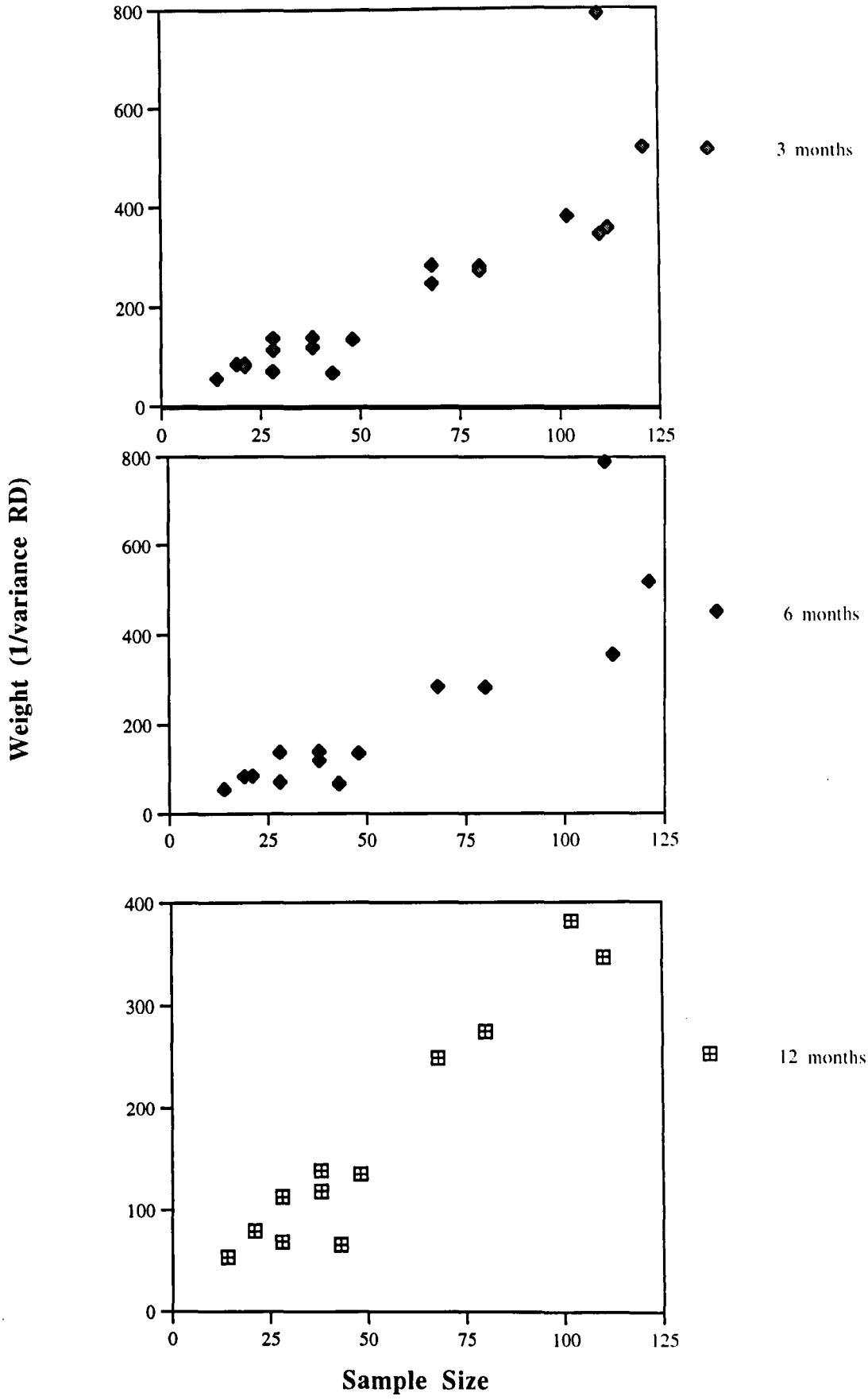

Figure 4.11 Sample size vs. weight (Amiodarone trials). This figure illustrates the relationship between a trial's weight and its sample size for the 17 trials of amiodarone: a positive curvilinear correlation exist. The pattern shown in this figure implies low evidence of publication bias existence.

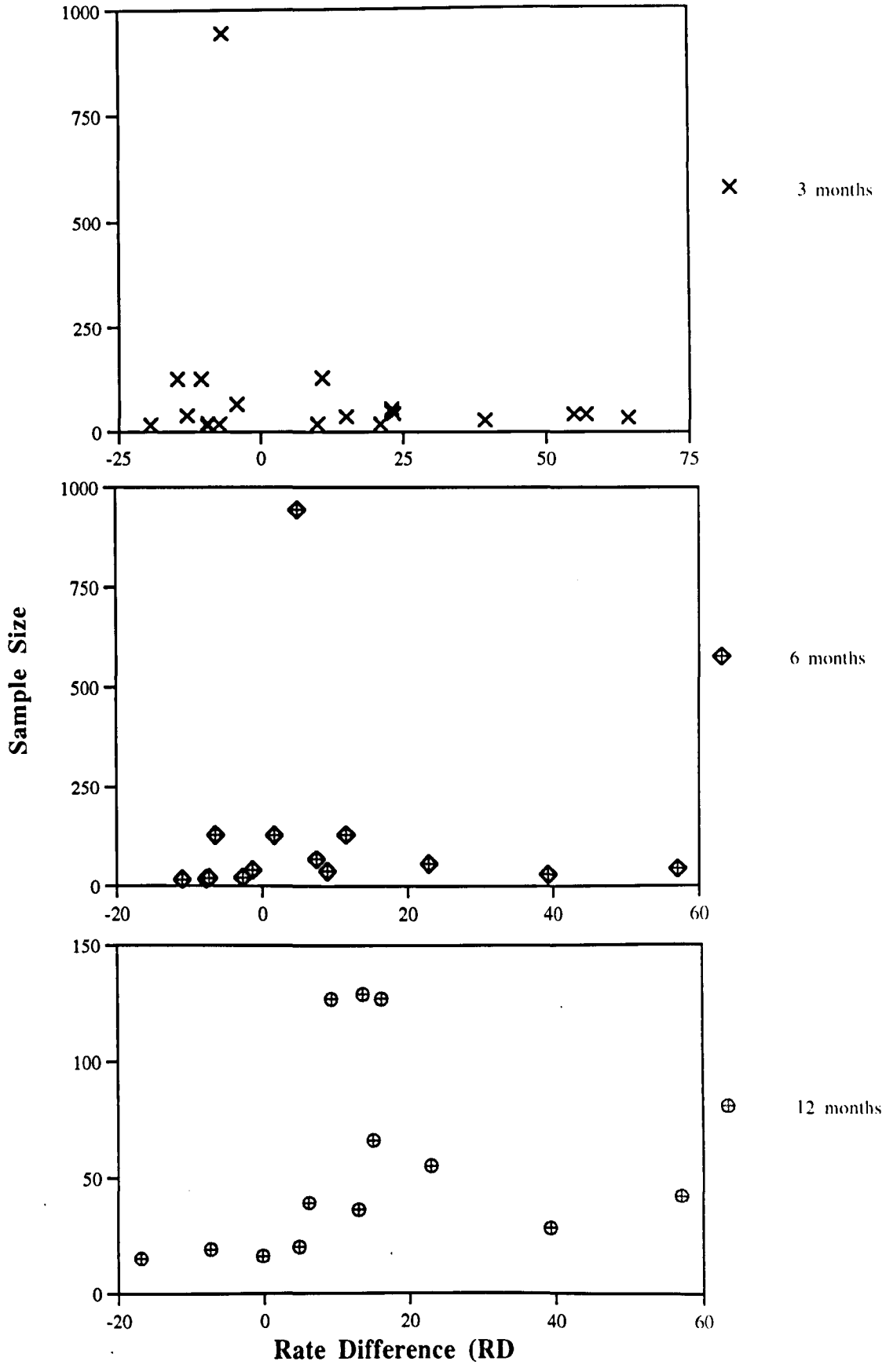

Figure 4.12 Funnel plot of flecainide clinical trials (N=19). The figure illustrates the relationship between the study sample size and its effect estimate (RD) at 3 (N=19), 6 (N=14), and 12 (N=13) months for the 19 individual studies included in the analysis. This scatter plot has yielded approximately a funnel-shaped graph, where both the results of small negative as well as large positive trials were included. Therefore, indicating a slight evidence of publication bias.

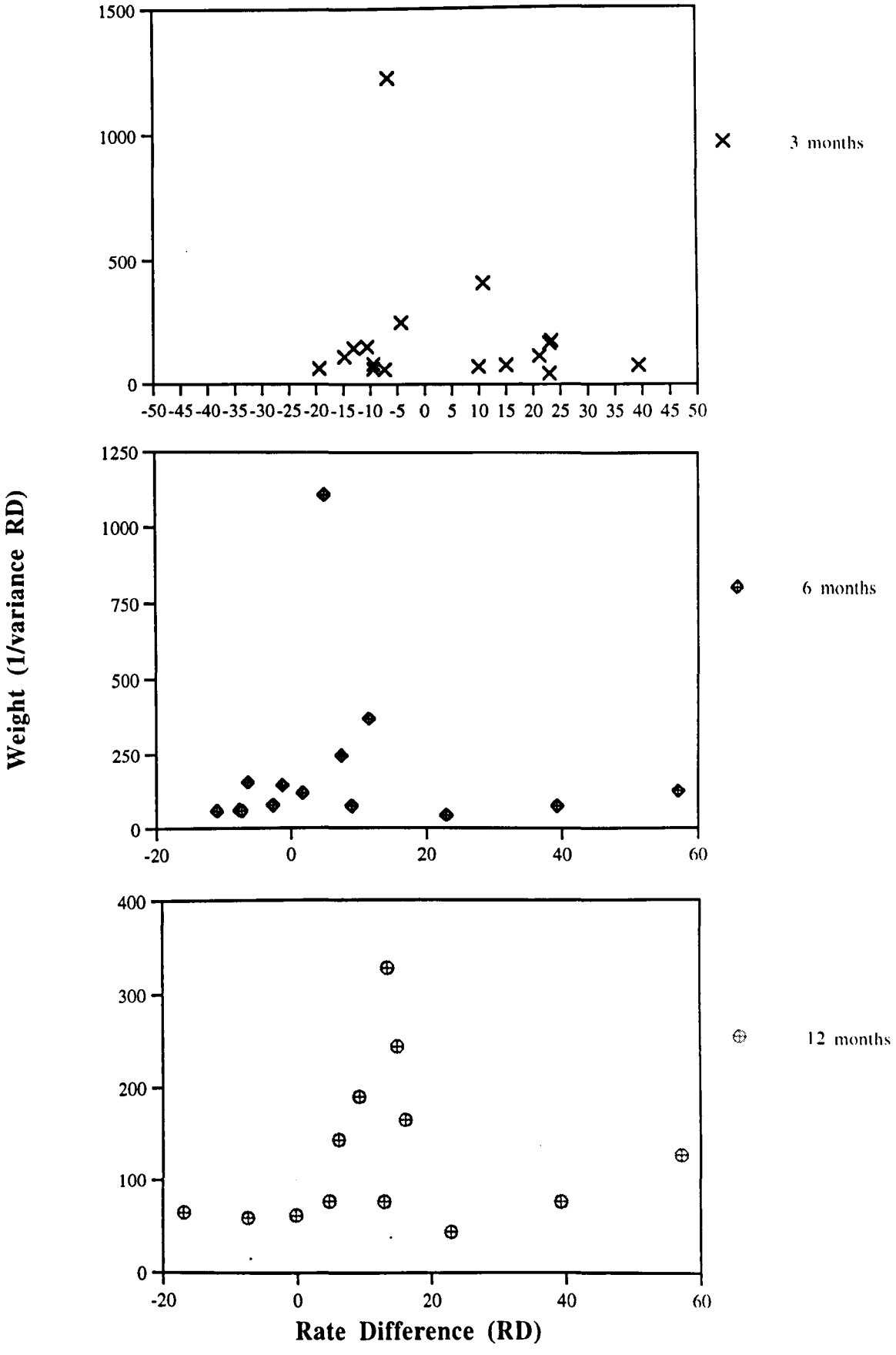

Figure 4.13 Rate difference vs. weight for flecainide clinical trials (N=19). This figure illustrates the relationship between a trial's weight (a measure of the precision of the results) and its effect estimates at 3, 6, and 12 months for the 19 individual studies. This figure shows that large sample size studies with more precise estimates (less variance), and small sample size studies with less precise estimates were incorporated in this analysis. Thus eliminating probability of publication bias.

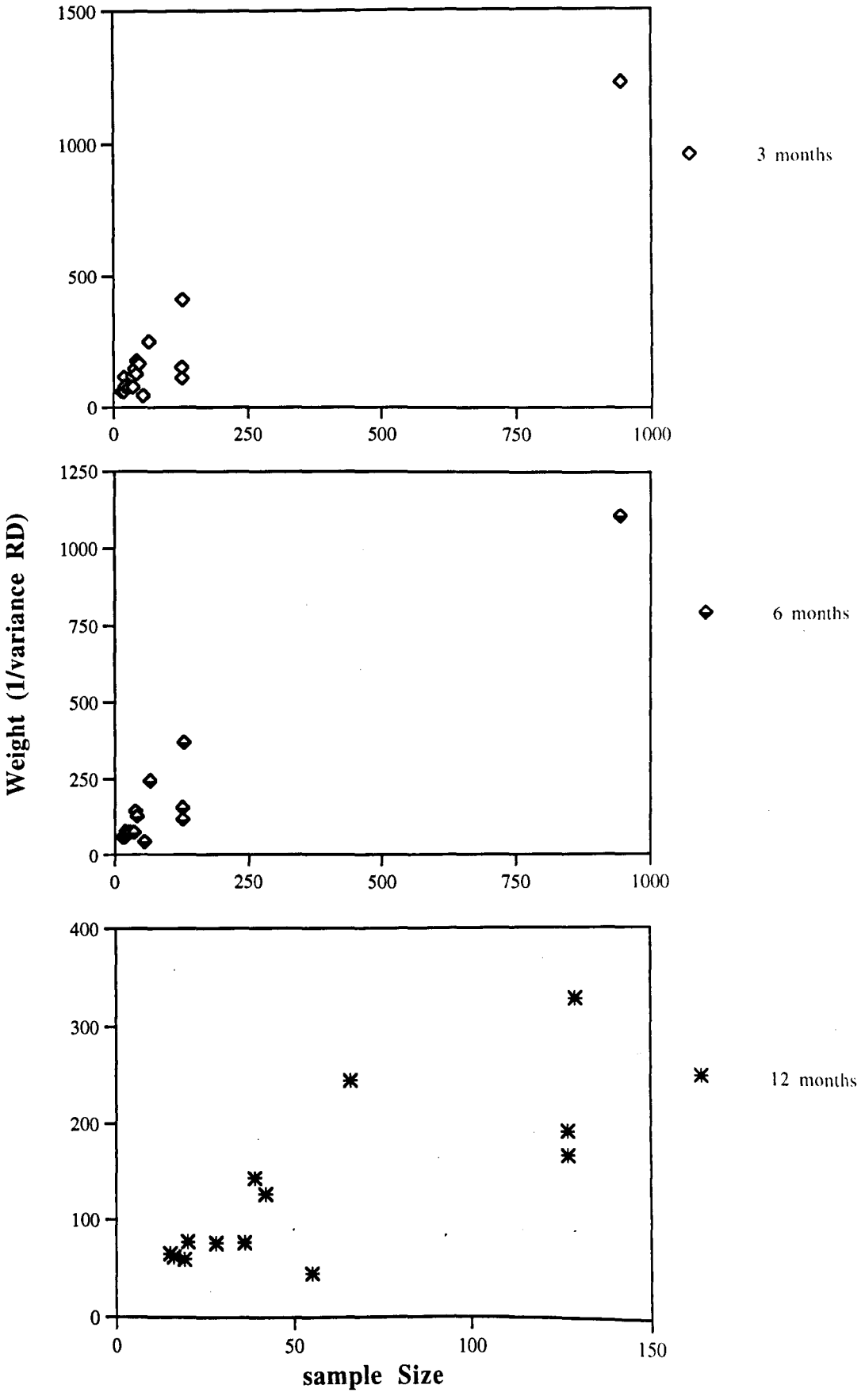

Figure 4.14 Sample size vs. weight (Flecainide trials). This figure illustrates the relationship between a trial's weight and its sample size for the 19 trials of flecainide: a positive curvilinear correlation does not exist. The pattern shown in this figure implies possible evidence of publication bias.

assess the robustness of the statistically significant results obtained from the meta-analyses of mortality and proarrhythmia data. It was found that a total of six studies with null results are required to reverse the significant pooled RD, favouring lower mortality rate in amiodarone-treated group to nonsignificant (Table 4.11). Similarly, fifteen trials were needed to negate the positively significant OR of death on flecainide as compared to placebo (Table 4.13). Overall, these findings suggest the statistically significant results obtained from meta-analysis of mortality data have a high level of robustness, since it can only be reversed to nonsignificance by a large number of hypothetical null trials (nearly double the number of included studies). Furthermore, for proarrhythmia, 10 studies were required to reverse the negatively significant OR of proarrhythmia on amiodarone as compared to other drugs. Similarly, 17 null trials were required to reverse the significance of OR_{peto} of proarrhythmia on flecainide as compared to placebo (Table 4.14). These large numbers of studies again definitely imply that the observed significant difference is not due to publication bias.

4.4 DISCUSSION

Patients with chronic atrial fibrillation are heterogenous with respect to underlying cardiac or other disease, functional status, age, and subjective symptoms. Electrocardioversion to sinus rhythm is frequently successful, but the choice of the subsequent treatment is difficult. The strategy for treatment of atrial fibrillation differs greatly between countries, since no antiarrhythmic agent was thought to be ideal in this context. Moreover, evidence that one agent is more effective than another for a certain category of patient was not established due to differences between published studies.

Recently published studies and meta-analyses suggest that a re-evaluation of the standard approach to the pharmacological suppression of atrial fibrillation is warranted from the standpoints of both drug efficacy and safety, since these studies have shown a significant increase in mortality, particularly due to sudden death (Coplen *et al.*, 1990; Reimold *et al.*, 1992; Zarembski *et al.*, 1995). However, the risks of these agents must be carefully weighed against their essential benefits for the treatment of atrial fibrillation. These benefits include alleviation of symptoms, such as palpitation and angina. In addition, they may eliminate the need for warfarin and avoidance of the latter's haemorrhagic complication.

As apparent from this review, many studies are more than 10 years old. Some studies

are not controlled, while others have small number of patients or short term of follow-up. Some of the individual placebo-controlled trials failed to show significant treatment benefit over placebo (Bosi *et al.*, 1990, for amiodarone; Carunchio *et al.*, 1995, for sotalol; Van-Gelder *et al.*, 1989, for flecainide). Therefore, the value of prophylactic therapy for the maintenance of sinus rhythm following cardioversion is uncertain.

The present meta-analysis shows clearly that amiodarone is significantly more effective than sotalol and quinidine for maintenance of sinus rhythm prior to cardioversion. However, it suggests that amiodarone and flecainide had similar efficacy for chronic AF patients at all time intervals, and for paroxysmal AF at 6 and 12 months. Amiodarone was superior to all drugs at 3 months, during which time the rate of relapse to AF is considered the highest. Two previous meta-analyses have been conducted to evaluate the efficacy and safety of quinidine for maintenance of sinus rhythm (Coplen *et al.*, 1990; Reimold *et al.*, 1992). A comparison of weighted pooled estimates produced by the present meta-analysis to those of previous meta-analyses suggests a statistically significant difference in favour of amiodarone and flecainide over quinidine, but not in favour of sotalol.

Unfortunately, in the present meta-analysis, only four placebo-controlled trials for amiodarone and sotalol were retrieved (2 for amiodarone, and 2 for sotalol). Nevertheless, the pooled estimates for treatment arms were further compared to quinidine data, which were previously compared to placebo controls.

Pooling the available mortality data showed significant difference in favour of flecainide compared to other Class I (quinidine, disopyramide), Class II (sotalol, amiodarone) antiarrhythmic agents, and placebo (OR_{MH}= 1.4, P<0.05).

Comparison of the pooled estimates of mortality rates in patients treated with flecainide versus placebo and estimates obtained for quinidine versus placebo in a published meta-analysis; (OR_{peto} of flecainide = 7.5, P=0.08) versus (OR_{peto} of quinidine = 2.98, P<0.05), and (OR_{MH} of flecainide = 1.8, P=3.1) versus (OR_{MH} of quinidine = 3.51, P=0.05), suggests more significant effect of quinidine treatment as compared to flecainide. One explanation of this result could be due to employment of cross-over design with placebo control as a second or first part in the flecainide clinical trials, which would increase the observed benefit on placebo as compared to the placebo group in the quinidine parallel design trials. As a result, this may negatively bias the estimates (OR, RD) calculated from the crossover design trials of flecainide compared

to placebo.

Furthermore, examining the mortality data on amiodarone compared to other drugs (direct comparison) have shown a trend towards decreased mortality on amiodarone, which was statistically significant using the Dersimonian Laird method (RD = -7%, Z= -2.4, P=0.02).

In general, this meta-analysis involved trials that included heterogenous patient groups with regard to, for example, different pattern of AF (chronic AF, PAF, PSVT), and underlying cardiac diagnoses (Table 4.6). However, as shown in Table 4.6 no significant difference was found with regard to some clinical variables which were identified as significant predictive factors of response to therapy (Levy, 1994; Crijns *et al.*, 1991), such as age (P=0.566), total duration of AF (P=0.2511), and left atrial diameter (P=0.864).

Despite the application of stratified analysis in this study, evidence of heterogeneity still existed in some subgroups. This may have occurred exclusively due to one or more of the following confounders:

(1) As shown in Table 4.6, the distribution of cardiac diagnoses were significantly different among the separate treatment groups compared in our meta-analysis procedures. All categories of diagnosis were significantly different (P<0.0001) except patients with congenital heart diseases (P=0.078). Moreover, the different drugs' trials enrolled patients with significantly different distributions as confirmed in Table 4.7.

(2) Some trial protocols permitted the use of concomitant medications, such as digoxin, verapamil, B-blockers, heparin, anticoagulants, or other ventricular rate regulating agents. Others have instructed discontinuation of all active treatment 4 to 5 weeks before randomisation. This would falsely cause more observed benefit in the treatment groups receiving such medications as compared to others, who were only taking the investigated drug in the trial.

(3) In the present meta-analysis, patients with chronic AF refractory to other antiarrhythmic drugs were included, as well as patients who had never received treatment, while the previous amiodarone meta-analysis (Zarembski *et al.*, 1995) enrolled only patients resistant to Class I antiarrhythmic drugs or sotalol hydrochloride.

On the basis of available data, a meta-analysis estimating the effect of the previous confounding variables on the response, and explaining the potential sources of heterogeneity was not feasible.

The results of this meta-analysis were further strengthened by the assessment of publication bias using graphical and numerical methods which showed low evidence of its existence.

4.5 CONCLUSIONS

In conclusion, the present meta-analysis has yielded a statistically significant results in terms of effectiveness of amiodarone and flecainide in maintenance of sinus rhythm prior to cardioversion. However, efficacy is not the only issue. Other factors should be taken into consideration to decide the strategy of treatment after CV, such as drug safety profile, local therapy tradition that guide the doctors in individual patient cases, as well as theoretical aspects concerning the mechanism of actions and pharmacokinetic properties of a drug. For instance, amiodarone has an unusual property of long half life taking from weeks to months. In addition, it has some other characteristic severe adverse effects such as sleeping disturbances, tremor, ataxia, corneal deposits, cutaneous changes, and impaired thyroid and liver functions. Also it increases the concentration of digitalis in serum, with a consequent risk of digitalis intoxication (Wheeler *et al.*, 1979).

All the previously mentioned factors may hinder amiodarone from being the first drug choice for treatment of AF. However, as shown in this study, it has very low arrhythmogenic tendency as compared to other drugs, which may be due to its negative inotropic effect. Consequently, this may increase its benefit-risk ratio for treatment of selected types of patients with severe structural ventricular myocardial damage. Also, it was noted in this review, that the number of withdrawals during the follow-up due to intolerable side effects, was not significantly different in the amiodarone-treated group (8.7%), as compared to other groups (sotalol, 7%; flecainide, 15.1%; placebo, 6.2%; and other comparatives, 10.8%). In addition, amiodarone has an antianginal effect, and this may be of value in patients with coronary artery disease (Heger *et al.*, 1984).

Furthermore, this study has shown that sotalol has an equal prophylactic effect to quinidine. However, due to the unavailability of sufficient proarrhythmia and mortality

data regarding sotalol compared to placebo, its value for maintenance of sinus rhythm remains undetermined. Secondly, it was shown in our meta-analysis of its RCTs and NonRCTs (sequential treatment) that sotalol fared better in RCTs than in serial treatment trials. This has negated the theory which advised that sequentially changing the type of drug after a recurrence may improve arrhythmia prognosis, as each drug exerts its beneficial effect in suppressing atrial fibrillation by a different mechanism of action (Crijns *et al.*, 1991; Antman *et al.*, 1990; Bauernfeind *et al.*, 1990).

Some questions are, however, left unanswered by this study. For example, whether the various pattern of AF, or the different dosage regimes employed (fixed single dose versus titrated) can influence the likelihood of relapse. In fact, the percentages of patients remaining in sinus rhythm reported in the published trials were not stratified on the basis of these factors. In addition, other secondary efficacy endpoints such as the control of ventricular rate during the chronic AF or PAF attacks, time to the first attack, and intervals between attacks, were not consistantly reported in the trials. This obstructed the application of meta-analysis. The former end point was thought to be attained through the use of digoxin, beta-blocking agents, and calcium antagonists as an alternative to Class I or Class III agents. However, this strategy was not tested in any of the trials. A further issue that has not been solved in the meta-analysis of this chapter is which agent is a good choice for rapid conversion of acute AF to sinus rhythm. Nevertheless, this issue will be addressed in the next chapter.

Appendix 4.1

I. Clinical Trials Included in The Meta-analysis

1) Amiodarone Clinical Trials

Blevins RD, Kerin NZ, Benaderet D, Frumin H, Faitel K, Jarandilla R, Rubenfire M. Amiodarone in the management of refractory atrial fibrillation. *Arch Intern Med* 1987; **147**: 1401.

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Vitolo E, Tronci M, Larover MT, Rumolo R, Morabito A. Amiodarone versus Quinidine in the prophylaxis of atrial fibrillation. *Acta Cardiol* 1981; **36** (6): 431-444.

Zehender M, Hohnloser S, Muller B, Meinertz T, Just H. Effects of amiodarone versus quinidine and verapamil in patients with chronic atrial fibrillation: Results of a comparative study and a 2-year follow up. *J Am Coll Cardiol* 1992; **19**: 1054-1059.

Zehender M, Meinertz T, Just H. Amiodarone and verapamil quinidine in treatment of patients with chronic atrial fibrillation. *Z kardiol* 1994; **83** (5): 101-108.

2) Sotalol Clinical Trials

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3) Flecainide Clinical Trials

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Chimienti M, Casadei G. Flecainide versus propafenone in the prevention of supraventricular arrhythmias. A long-term randomized multicentre study. *New Trends in Arrhythmias* 1993; **9** (3): 489-494.

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Lau CP, Leung WH, Wong CK. Randomized double-blind crossover study comparing the efficacy and tolerability of flecainide and quinidine in the control of patients with symptomatic paroxysmal atrial fibrillation. *Am Heart J* 1992; **124**: 645.

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II. Clinical Trials Excluded from The Meta-analysis

1) Amiodarone Clinical Trials

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2) Sotalol Clinical Trials

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3) Flecainide Clinical Trials

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CHAPTER FIVE

ANTIARRHYTHMIC DRUGS FOR RECENT-ONSET ATRIAL FIBRILLATION. WHICH IS THE BEST DRUG FOR RAPID AND SAFE CONVERSION TO SINUS RHYTHM ? A META-ANALYSIS

5.1 INTRODUCTION

Acute atrial fibrillation (AF) is usually defined as of recent onset within 24-48 hours (Sopher *et al.*, 1996). It may be associated with both cardiovascular or noncardiovascular medical conditions (Kannel and Wolf, 1992). In addition, it is a common disorder after open heart surgery, particularly coronary bypass surgery, with an incidence ranging between 11% and 100% (Groves *et al.*, 1991). This type of acute AF was thought to develop due to surgically-induced atrial enlargement, and local surgical trauma associated with increase in sympathetic activity (Boyden and Hoffman, 1981). It usually occurs 24 to 60 hours after surgery, causing a lengthening in hospital stay from 9.9 to 11.4 days, thus increasing resource utilisation (Rubin *et al.*, 1987). Although, this type of arrhythmia frequently reverts spontaneously, it may cause subsequent serious complications including sustained atrial fibrillation, embolic cerebrovascular accidents, and postoperative stroke (Waldo *et al.*, 1978). Furthermore, atrial fibrillation is frequently associated with atrial flutter, and they may alternate with each other in the same patient (Tunick *et al.*, 1992). Atrial flutter, however, is found to be more challenging after surgery, since it is nonresponsive to medical therapy and it may require electrical pacing (Podrid and Kowey, 1995).

Both atrial flutter and atrial fibrillation are associated with a rapid ventricular response rate which is difficult to control, and is primarily responsible for the associated symptoms, such as palpitation, lightheadedness, faintness and even syncope in some cases (Switzer *et al.*, 1990). Most of these symptoms arise from the decline in cardiac output and the sustained decrease in blood pressure. Within the normal physiologic range, the heart rate ranges between 40-50 and 160-170 beats/min (Podrid and Kowey, 1995). Although this variation in heart rate in normal individuals has little impact, in supraventricular arrhythmia this frequently leads to hemodynamic compromise with ischemia due to increase in oxygen demands. Furthermore, if the duration of the rapid ventricular response rate is prolonged, it may lead to ventricular dilation and congestive heart failure (Clark and Cotter, 1993; Sopher and Camm, 1996). Eventually, it may precipitate disabling stroke or even death (McAlister *et al.*, 1990).

5.2 EVOLVING STRATEGIES FOR MANAGEMENT OF ACUTE AF

Strategies for acute AF treatment vary widely across institutions (Faniel *et al.*, 1983;

Campbell, 1985; McAlister *et al.*, 1990; Sopher and Camm, 1996; Talajic *et al.*, 1996). Recently, a strong debate was introduced over whether to strive to convert patients to sinus rhythm or only to provide treatment for controlling the ventricular response "rhythm versus rate" (Sopher and Camm, 1996). In spite of considering the control of the ventricular rate as a chief target of therapy for acute AF (specifically in patients who initially fail to convert to sinus rhythm, nonconverters), due to improvement of ventricular function and alleviation of associated symptoms, drugs directed only towards control of the ventricular rate (such as digoxin, ß-blockers, and Ca blockers) are considered imperfect, since further risk of thromboembolism due to continuous fibrillation can possibly arise (Sopher and Camm, 1996). Consequently, a number of authors have recommended that ventricular rate regulating agents should not be the first-line treatment for acute AF. Furthermore, they suggested that more aggressive, invasive therapy should be initiated for rapid cardioversion to sinus rhythm (Biasi *et al.*, 1995).

Whether cardioversion to sinus rhythm, control of ventricular rate, or both are chosen as the desired therapeutic goal, rapidity of action of a particular drug will nevertheless still remain the key indicator of clinical effectiveness. Textbooks reflect no consensus on optimum ventricular rate control criteria (Zipes, 1992). Sopher and Camm (1996) have claimed that comparing ventricular rates during AF to rates during sinus rhythm may not be essential. However, since most trials have defined a supraventricular arrhythmia of > 100 beats per minute as clinically significant and requiring treatment (Butler *et al.*, 1993; Hou *et al.*, 1995), a treatment reducing the ventricular rate below this limit may be considered effective. Other authors of clinical trials have reported a reduction of > 20 beats/min in heart rate as a significant cut off point (Chapman *et al.*, 1993).

The ideal treatment of recent-onset atrial fibrillation is still questionable (Groves and Hall, 1991; Gentili *et al.*, 1992; Clark *et al.*, 1993; Madrid *et al.*, 1993; Dhala *et al.*, 1994; Ollitrault *et al.*, 1994). Although numerous clinical trials have been performed, the high spontaneous conversion rate of recent-onset AF (39% to 48% of patients within 8 hours) makes controlled trials essential (Capucci *et al.*, 1992; Capucci *et al.*, 1994). For many years, digoxin was used classically to decrease the ventricular rate, and to improve the hemodynamics, but usually this takes a long time and it may be only achieved by combination with a Ca antagonist or a ß-blocker (Zoble *et al.*, 1987; Vecht *et al.*, 1986). In addition, these agents are infrequently effective for instant cardioversion to sinus rhythm (Lown *et al.*, 1987; Gentili *et al.*, 1992).

Electrical cardioversion is highly efficient for all patients, but this requires general anaesthesia and anticoagulation before and after application to avoid thromboembolic complications (Clark and Cotter, 1993). In addition, after unsuccessful cardioversion, a new lethal ventricular arrhythmia may develop, particularly if the plasma level of digoxin is above the therapeutic range. It has even been shown that normal mechanical function of the atria takes a long time to be restored. As a result, little improvement in either exercise tolerance or cardiac output is shown prior to electrical cardioversion (Lewis, 1990).

Class 1A antiarrhythmic drugs (particularly quinidine) have been widely used for pharmacological cardioversion to sinus rhythm. Nevertheless, they possess no effect on the ventricular response rate. On the other hand, they may sometimes increase it due to facilitation of AV node conduction (Halpren *et al.*, 1980; Ollitrault *et al.*, 1994). As a result, many cardiologists tend to prescribe digoxin in conjunction with quinidine or disopyramide to reduce the ventricular rate (Campbell *et al.*, 1985; Gavaghan *et al.*, 1988; Halinen *et al.*, 1995). However, the results of trials conducted in this area were not always promising and have added uncertainty. Moreover, the utility of quinidine for cardioversion has been questioned, due to the latest meta-analysis showing increased mortality relative to placebo in patients randomised to quinidine for maintenance of sinus rhythm (Coplen *et al.*, 1990). Furthermore, intravenous quinidine requires in-hospital drug titration which is time consuming making the therapy more expensive than other antiarrhythmic drugs. Although oral quinidine would provide a cheaper alternative, it is less effective and is associated with serious gastrointestinal complications (Crijns *et al.*, 1988).

Class 1C antiarrhythmic drugs, including flecainide and cibenzoline, have shown theoretical ability to control the ventricular rate as well as to suppress the atrial arrhythmia by prolonging the effective refractory period in the atria and slowing the atrioventricular node (AV) conduction (Connolly *et al.*, 1987; Ollitrault *et al.*, 1994; Ravi-Kishore and Camm, 1995). However, these agents are contraindicated in critical heart diseases, since they possess a negative inotropic effect which may be arrhythmogenic or may even diminish the beneficial hemodynamic effect obtained by heart rate reduction (Gentili *et al.*, 1992).

A number of clinical trials have been undertaken to test the effect of new intravenous and oral antiarrhythmic treatment with Class I and Class III activity on rapid ventricular

control as well as rapid cardioversion, in an attempt to define "best protocol" for management of acute AF associated with organic heart disease or cardiac surgery (McAlister *et al.*, 1990; Groves and Hall, 1991). However, the results remain controversial (Talajic *et al.*, 1996).

A recent meta-analysis was conducted to test the value of prophylactic ß-blocker, verapamil, and digoxin prior to bypass surgery to prevent the development of AF (Andrews *et al.*, 1991). However, this meta-analysis did not address the efficacy for prompt cardioversion of postoperative atrial arrhythmias, and although the efficacy for controlling the ventricular rate was tested, the data were pooled at a single particular time point.

In addition to choice of treatment, the probability of successful conversion to sinus rhythm may be influenced by a number of parameters, such as concomitant use of other antiarrhythmic drugs, left atrial size, underlying aetiology of arrhythmia (for example, rheumatic mitral valve disease), duration of the atrial fibrillation, and age of the patients (Sopher *et al.*, 1996). However, no consensus view among the studies which tested the significance of these variables on successful conversion to sinus rhythm have been reached. Dalzell *et al.* (1990) and Dittrich *et al.* (1989) reported that left atrial size was not a significant predictor for successful cardioversion, while it was usually regarded to be important in older studies (Goy *et al.*, 1988; Goldman *et al.*, 1975).

It was clear from the above review that data on antiarrhythmic therapy for this indication were mixed. Therefore, reanalysis of the data was undertaken;

- To estimate the relative efficacy of flecainide, amiodarone and sotalol for conversion of acute medical atrial fibrillation and atrial fibrillation following cardiac surgery (using oral or intravenous dosage schedules).

- To evaluate the differences between the three drugs in the time delay necessary to convert acute atrial fibrillation (AF) to sinus rhythm (estimate rapidity of action).

- To evaluate their effect in controlling the ventricular rate when reversion to sinus rhythm has failed.

- To evaluate the probability of incidence of major and minor side effects due to their use in this particular indication.

5.3 METHODS

5.3.1 Definition of Inclusion Criteria

5.3.1.1 Design of Primary Studies

Prospective, published clinical trials of all design categories (detailed earlier in section 4.2.1.1) were eligible for inclusion if they provided adequate delineation of treatments, dose, route of administration, number of patients included, and outcome measures of concerns to this chapter. In addition, the protocol of a trial had to include continuous electrocardiographic monitoring of cardiac rhythm. Unlike the previous meta-analysis (Chapter 4), the long-term follow-up postcardioversion (> 3 months) was not a crucial element for inclusion of a trial in the primary analysis, since outcomes of interest were mostly measured within 1 to 24 hours after administration of a trial intervention.

5.3.1.2 Diagnostic Criteria and Type of Patients Included

Patients of any age, of either sex, and with established diagnosis of acute supraventricular arrhythmia of any pattern (including atrial fibrillation, atrial flutter, or paroxysmal supraventricular tachycardia) were included. The arrhythmia was considered to be acute if it was stated by the author of the trial to be of recent-onset (mostly between 30 minutes and 72 hours), and/or presenting with a rapid ventricular response rate of ≥ 100 beats/min. The time of onset of supraventricular attacks is to be ascertained by documented electrocardiograms in hospitalised patients or by an abrupt, clear onset of relevant symptoms (such as palpitation, chest discomfort, or dyspnea) either in the emergency room or outpatient clinic.

Patients who developed supraventricular arrhythmia after they underwent cardiac surgery were also included. However, all patients with previously documented dysrhythmia of ≥ 6 months duration were excluded from the analysis.

5.3.1.3 Types of Intervention

Interventions involved comparisons of single or multiple doses of oral, intravenous, and intravenous plus oral treatment with flecainide, sotalol, or amiodarone versus

placebo and/or any other antiarrhythmic agents for rapid conversion to sinus rhythm.

5.3.1.4 Study Parameters and Outcomes

Trials were included if they reported data concerning the following primary therapeutic end points:

1. Rapid conversion to sinus rhythm, which has to be defined as documented conversion to sinus rhythm within a maximum of 8 hours after initiation of treatment, and sustained for the subsequent trial duration period. This cut-off point was thought to be mandatory to avoid misinterpretation of efficacy due to spontaneous conversion to sinus rhythm. A trial was still included if other time point measurements were reported for the purpose of comparison of relative efficacy of different drugs.
2. An acceptable control of the ventricular rate is another therapeutic goal of interest, particularly in nonconverted patients. It is usually defined as slowing of the ventricular rate of > 20 beats/min, or achievement of a rate of < 100 beats/min maintained throughout the subsequent 24 hour period.

Other secondary end points include the following:

1. Incidence of adverse effects that required initiation of other active treatments (such as atropine if hypotension develops due to antiarrhythmic effects).
2. Persistence of arrhythmia that required application of direct current cardioversion (DCC).
3. Incidence of withdrawals due to major side effects.
4. Incidence of other serious cardiovascular side effects of concern such as proarrhythmia and death.

Exclusion was considered appropriate if there was any uncertainty regarding the trial design and number of patients included, or if the definition of the outcome measure deviates from the above delineated criteria.

5.3.2 Data Identification and Selection of Primary Trials

A literature search was conducted through all available database sources (as detailed in Chapter 4) to identify all published trials addressing the use of flecainide, sotalol, and amiodarone in acute conversion to sinus rhythm. The following pertinent keywords to this chapter were combined with each drug under investigation cited in title and/or abstract: acute atrial fibrillation, atrial flutter, supraventricular arrhythmia, antiarrhythmic agents, cardiac surgery, coronary surgery, CABG, postoperative complications, cardioversion, and sinus rhythm.

5.3.3 Data Extraction

Data concerned with any of the following subheadings were extracted from text, tables, and figures (after scanning and magnifying them) in the clinical trial reports.

5.3.3.1 Study Design Characteristics

Clinical trials identified for each drug (flecainide, amiodarone, sotalol) were classified into the six study design categories described in section 4.2.3.1. For each trial the following information regarding execution and protocol was extracted:

- Name of the first author
- Publication status (full report/ abstract/ unpublished data)
- Publication date
- Design features (parallel or crossover; double-blind, single-blind, or open)
- Number of patients enrolled
- Number of patients randomised and received study medication
- Number of patients included in the analysis
- Number of patients allocated in each treatment group
- Type of control (active [name of drug] or placebo)
- Dosage regimens: for intravenous intervention it was reported as mg/Kg, mg/min, or mg/day, and for oral intervention as mg/day
- Previous medications
- Concomitant drugs administered such as ventricular rate regulating agents (digoxin, beta-blockers, and calcium-channel blockers) and anticoagulants

• Type of monitoring techniques
• Duration of monitoring period (study duration)
• Duration of follow-up (months)

5.3.3.2 Population Characteristics of the Included Studies

In addition to details of patients' demographic criteria which was mentioned in Chapter 4, other relevant diagnostic criteria for this chapter were extracted as follows:

• Definition of supraventricular arrhythmia in the trial
• Onset of acute AF (hours)
• Cause of supraventricular arrhythmias categorised into medical or surgical
• Baseline mean ventricular rate together with its standard error, or standard deviation for each treatment group
• Baseline mean blood pressure together with its standard error, or standard deviation for each treatment group

5.3.3.3 Outcome Measures

The following data essential for analysis of efficacy and adverse effects were extracted

• Definition of conversion to sinus rhythm
• The number of patients converted to sinus rhythm at all available time points in each of the study groups
• The cumulative number of patients converted and nonconverted to sinus rhythm in each of the study groups at the end of the monitoring period. Each study at least reported the number of patients converted at one time point
• Mean ventricular rate together with its standard error, or standard deviation for each treatment group at all available time points during the trial monitoring period, for both converted and nonconverted patients in each of the study groups. When data were reported for individual patients, the mean ventricular rate and its standard deviation for both category of response were calculated
• In addition some studies reported the mean/median time of conversion to sinus rhythm with its standard error, or standard deviation for each treatment group, as a result its extraction was deemed appropriate for further analysis
• The cumulative incidence of adverse effects and events described earlier in section 5.3.1.4, on an intension-to-treat basis

All the previous efficacy end points were stratified whenever possible according to the route of administration (oral, IV, or oral plus IV), pattern of the arrhythmia (AF, AFL, or PSVT), medical or surgical etiology, and duration of the arrhythmia (< 24 hours, or > 24 hours).

5.3.4 Statistical Analysis and Data Synthesis

5.3.4.1 Conversion to Sinus Rhythm

Two different techniques of meta-analysis were employed for estimation of efficacy for conversion to sinus rhythm:

1. *Calculation of pooled odds ratio (OR) according to Peto's method for each of the following time intervals: 0-3 hours, 3-8 hours, and 8-24 hours.*

In the present meta-analysis, this allows testing (for each time interval) of the hypothesis zero that the probability of conversion to sinus rhythm not due to treatment effect by comparing the observed number of converted patients (O) in a treatment group with the number of patients that would have been expected to be converted (E) in the same group if the number of converted were equally distributed among the treatment and control group.

2. *Calculation of meta-analytic weighted pooled percentages of patients converted to sinus rhythm at any time point reported in the trial.*

Due to the unsatisfactory reporting of all time measurements in some trial reports, an adjustment assumption was made. If the initial observation was not reported at time zero, it was assumed that there was no conversion until the first time point reported. The individual trials' percentages (P_t) were pooled separately at each time, using a weight proportional to the inverse of the variance of the percentage as follows (Gardner and Altman, 1986; Andrews *et al.*, 1991):

$$\text{Variance of } P_t = \frac{P_t\,(1-P_t)}{N_t}$$

and hence the weight for each individual trial is:

$$W_i = 1 / (\text{variance of } P_t)$$

$$\text{The pooled percentage} = \frac{\sum (P_t . W_i)}{\sum W_i}$$

The formulas given for the variance of the percentage is not applicable for proportions outside the range 0.1 to 0.9. As a result, percentages of 0% or 100% were substituted by 0.5 and 99.5 respectively. A random-effects model was employed if heterogeneity existed.

Indirect comparisons of pooled percentages from different treatment arms were performed as described in Chapter 4 (section 4.2.5.1). This test was also used for comparisons of subgroups of each treatment arm according to arrhythmia duration, type, pattern, and etiology.

5.3.4.2 Effect on the Ventricular Response Rate

To test the effect of antiarrhythmic treatment on the ventricular rate the following parameters estimates were calculated to allow direct and indirect comparisons between treatment groups:

5.3.4.2.1 Absolute Mean Ventricular Rate

For pooling the absolute ventricular rate in each treatment arm (VR_i) in the identified clinical trials, two meta-analytic methods were employed:

a. Pooled mean ventricular rate weighted by the inverse of the variance if the SEM (standard error of the mean), or SD (standard deviation of the mean) was reported in the original trials.

Where $SEM = SD / \sqrt{n}$; n = number of patients in a particular treatment group.

The variance of $VR_i = (SEM)^2$, and $W_i = 1 /$ (variance of VR_i). Hence, the pooled

mean ventricular rate is calculated according to the formula adopted by Andrews *et al.* (1991):

$$\text{Mean VR} = \frac{\sum (VR_i * W_i)}{\sum W_i}$$

$$\text{and its SEM} = \frac{1}{\sqrt{\sum W_i}}, \text{ with approximate 95\% CI of the mean given by:}$$

$$\text{Mean VR} \pm 1.96 \,.\, \text{SE}$$

The pooled VR was estimated at all time points starting from baseline. However, if a trial did not provide VR at a particular time point, the value of the previous time point was pooled. The Q statistic (Chi-square test) was calculated at each time point to estimate the degree of variability among the trials, and if heterogeneity existed, the pooled VR was recalculated using the random-effects model.

B. Pooled mean ventricular rate weighted by number of patients in each individual trial.

Some trials did not report the SD or SE of the mean VR, though they provided the values at all the time points. As a result, to pool the data from these trials as well, another macro containing the following equation was executed:

$$\text{Mean VR} = \frac{\sum VR_i . N_i}{\sum N_i},$$

where the Ni is the number of patients in a particular treatment group in each individual trial.

5.3.4.2.2 Weighted Mean Effect on Ventricular Rate

The weighted mean effect on ventricular rate was defined as mean change from the

baseline (Gansevoort *et al.*, 1995). For each treatment arm (for example, flecainide) in each individual study, the mean change from baseline was calculated by subtraction of mean VR baseline from mean VR at a certain time point as follows:

Δ treatment = $VR_T - VR_{Baseline}$, where VR_T is the ventricular rate at time point T.

However, since many studies did not provide SE or SD of VR_T or $VR_{Baseline}$, the standard deviation of the change (S Δ treatment) in each study was estimated according to an upper boundary assumption for paired data (Gardner and Altman, 1986; MacMahon *et al.*, 1987; Cappuccio *et al.*, 1989) as follows:

$$S_{\Delta Treatment} = \sqrt{\frac{n\ d^2}{K}}$$

where n= number of patients in each treatment group, d= Δ treatment, and K is a constant equal to the square of the sum of the standardised normal deviates for α and ß, with $\alpha = 0.05$ (two-tailed) and ß = 0.10 (one-tailed). Then the SE of the change in this paired case is given by:

$$SE_{\Delta treatment} = \frac{S_{\Delta\ treatment}}{N}$$

Thus the pooled mean treatment effect is calculated as:

$$\text{Pooled mean effect} = \frac{\sum d.W_i}{\sum W_i}$$

where d= Δ treatment, and Wi is proportional to the inverse of the variance of the change. Q statistic (Chi-square test) was performed at each time point to estimate the degree of variability among the trials, and if heterogeneity existed, the pooled weighted mean effect on ventricular rate was recalculated using the random-effects model.

5.3.4.2.3 Effect Size on Ventricular Rate Compared to Placebo

To calculate the individual effect size at each time point, the mean treatment effect was calculated using the equations in section (4.3.4.3), as well as the placebo mean effect (estimated using the same procedures) were employed. The pooled SD of the individual effect size was calculated using the two S Δ treatment (as was shown in the previous section 4.3.4.3) of active treatment and placebo groups as follows:

$$\text{pooled SDi} = SD_i = \sqrt{\frac{(N_T - 1).(S_T)^2 + (N_C - 1).(S_C)^2}{N_T + N_C - 2}}$$

Effect size was calculated according to Hedges (1982):

$$ESi = C(m)\frac{\Delta_T - \Delta_C}{S_{Pooled}}, \quad i = 1,\ldots., k$$

where m = nti + nci - 2, C(m) is given approximately by:

$$C(m) = 1 - \frac{3}{4m - 1}$$

Hedges showed that if the assumption for t test between means are met in each study, then the sampling variance of ESi is approximately

$$v_i = \frac{n_{ti} + n_{ci}}{n_{ti} n_{ci}} + \frac{ES_i}{2(n_{ti} + n_{ci})}$$

Consequently, the standard error of ESi is

$$SEi = \sqrt{vi}$$

Pooled ES is estimated as follows:

$$\frac{\sum ES_i . W_i}{\sum W_i}$$, with weight calculated as $w_i = 1/v_i$.

5.3.4.3 Mean Conversion Time

The individual trials' estimates of mean conversion time (T_i) were pooled for each treatment and control group separately, if the standard deviation or standard error was reported, using the following equation:

$$\text{Pooled mean conversion time} = \frac{\sum T_i W_i}{\sum W_i}, \text{ where, } W_i = 1 / (\text{variance of } T_i)$$

Furthermore, a weighted average difference between a two treatment group was calculated using the method of Dersimonian and Laird, which was also explained by Andrews *et al.* (1991).

5.3.4.4 Incidence of Adverse Effects and Mortality

The incidence of all types of adverse effects, described earlier in section 5.3.1.4 in this chapter, was estimated for flecainide, amiodarone, and sotalol treatment arms by calculation of weighted percentages (probabilities) detailed in section 5.3.4.4. This allowed the indirect comparison between the three drugs after adjusting for each drug trials separately the interstudy heterogeneity and variations due to design and patient populations. The incidence was further stratified according to the route of administration for each drug, and again an indirect comparison between similar groups for the three drugs was performed.

Furthermore, direct comparisons were carried out by calculation of the pooled relative risk (RR) according to methods described in Chapter 3.

5.4 RESULTS

5.4.1 Description of Trials Identified

Literature search between 1966 and July 1996 identified a total of 70 published studies of amiodarone (25), sotalol (20), and flecainide (26) examining their efficacy for rapid conversion of acute SVAs to sinus rhythm. Only 42 (Appendix 5.1) of these studies were trials that satisfied the inclusion criteria (19 for amiodarone, 9 for sotalol, and 14 for flecainide). The remaining 28 studies (6 for amiodarone, 9 for sotalol, and 13 for flecainide) were omitted from analysis (Appendix 5.1) due to the following reasons: the trial was designed to test the efficacy for conversion of established chronic AF patients only (4 for amiodarone [3, 4, 5, 6], 2 for sotalol [1, 7]); the study was designed to evaluate the prophylactic use for prevention of SVAs development postoperatively and the treatment was initiated few hours prior to surgery (2 for amiodarone [1, 2], 3 for sotalol [3, 5, 8], 1 for flecainide [2]); invasive electrophysiologic studies (3 for flecainide [10, 12, 13], 2 for sotalol [2, 9]); the study was published in abstract format which did not contain sufficient information to allow the use of meta-analytic techniques (3 for flecainide [1, 4, 11]); the trial was a duplicate publication (3 for flecainide [7, 8, 9]); and data were reported in the form of retrospective review (2 for the flecainide [3, 5]), or case report (1 for sotalol [6]); phase II efficacy study (1 for sotalol [4]); and study involved different patient population (1 for flecainide [6]).

Characteristics of the randomised controlled and uncontrolled trials of flecainide, amiodarone, and sotalol included in the analysis, are summarised in Tables 5.1.1, 5.1.2, and 5.1.3 respectively. As shown for flecainide, 12 studies were RCTs, and 4 trials were uncontrolled. For amiodarone, 17 studies were RCTs, and 2 trials were uncontrolled. For sotalol 7 studies were RCTs, and 2 trials were uncontrolled. 8 RCTs employed placebo comparisons (2 for amiodarone, 3 for sotalol, and 4 for flecainide), and 25 employed head to head comparisons to various antiarrhythmic drugs. 17 RCTs adopted an open-label, parallel design (6 for flecainide, 11 for amiodarone, and 2 for sotalol) and two employed open-label crossover (1 for amiodarone, and 1 for sotalol). 6 RCTs were double-blind, parallel design (3 for flecainide, 2 for amiodarone, and 3 for sotalol), and one RCT (for sotalol) was a double-blind, crossover design. 4 RCTs had single-blind, parallel design (3 for flecainide, and 2 for amiodarone), and one another trial for flecainide had additional single-blind, crossover period for patients who did not convert to sinus rhythm during the first drug (Madrid *et al.*, 1993).

Table 5.1.1 Characteristics of randomised controlled and uncontrolled trials of flecainide included in analysis

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Flecainide/ Control)*	*Type of control*	*Dose of flecainide - (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Borgeat *et al.* 1986	60; 60	P, C	30/30	Quinidine	50 mg infusion over 10 mins; followed by a bolus up to a maximum of 2 mg/Kg; then 200 or 300 mg/day	IV+O	M	-	0/0	Digoxin; 18/24	NS
Gavaghan *et al.* 1988	58; 56	P, C	29/27	Digoxin+Disopyramide	2 mg/Kg over 20 mins; followed by continuous infusion of 0.2 mg/Kg/hr for 12 hrs; then 200 mg/day for the rest of the study	IV+O	M	Digoxin	0/27	ß-blockers preoperatively; 20/21	1 month
Suttorp *et al.* 1989	40; 40	P, C	20/20	Verapamil	2 mg/Kg over 10 mins	IV	S	-	0	Digoxin ß-blockers	1 month
Wafa *et al.* 1989	84; 29	P, C	15/14	Digoxin or Digoxin +Verapamil	1 mg/Kg over 10 mins; followed by infusion of 1.5 mg/Kg/hr for 1 hour and then by 0.25 mg/Kg/hr for the rest of the 24 hour study period	IV	M	Verapamil Digoxin	6/14 0/14	NS	24 hours
Suttorp *et al.* 1990	50; 50	P, C	25/25	Propafenone	2 mg/Kg over 10 mins	IV	S	Digoxin ß-blockers Calcium antagonist Anticoagulants	3/4 6/3 4/1 9/6	Class IA agents	11.4±5.2 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.1 Characteristics of randomised controlled and uncontrolled trials of flecainide included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Flecainide/ Control)*	*Type of control*	*Dose of flecainide (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Villani *et al.* 1990	37; 37	P, PI	19/18	Placebo	200 mg followed by 100 mg if AF persists	O	S	NS	0/0	NS	NS
Donovan *et al.* 1991	104; 102	DB, P, C, PL	51/51	Placebo+Digoxin	2 mg/Kg over 30 mins; maximum 150 mg	IV	S	Digoxin Patients receiving ß-blockers or calcium channel blockers were not excluded	51/51	NS	6 hours
Capucci *et al.* 1992	62; 62	SB, P, C, PL	22/19/21	19 Amiodarone 21 Placebo	300 mg/day	O	S	-	0/0	NS	24 hours
Madrid *et al.* 1993	80; 80	SB, P, C, CO	40/40	Procainamide	1.5 mg/Kg over 15 mins; followed by 1.5 mg/kg over 1 h	IV	M	-	-	-	NS
Capucci *et al.* 1994	181; 181	SB, P, C, PL	58/61/62	61 Propafenone 62 Placebo	300 mg/day	O	S	-	-	-	8 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.1 Characteristics of randomised controlled and uncontrolled trials of flecainide included in analysis (continued)

Uncontrolled

Study name	*No. of patients enrolled*	*Treatment allocation (Flecainide/ Control)*	*Dose of flecainide (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomitant drugs*	*Previous medications*	*Duration of study*
Goy *et al.* 1985	50	50	50 mg infusion over 10 mins; followed by a bolus up to a maximum of 2 mg/Kg; then 200 or 300 mg/day	O+IV	M	Digoxin	34	ß-blocker; 1	48 hours
Crozier *et al.* 1987	50	50	2 mg/Kg or 150 mg	IV	S	Digoxin	7	-	45 mins
Nathan *et al.* 1987	21	21	2 mg/Kg infused over 5-10 mins	IV	S	-	-	-	NS
Crijns *et al.* 1988 (a)	20	20	200 mg, if sinus rhythm was not restored within 1 hr; another 100 mg given if necessary; then a final dose of 100 mg administered 3h from the start of treatment	O	M	Digoxin Verapamil	3 7	-	24 hours
Crijns *et al.* 1988 (b)	20	20	2 mg/Kg infused over 10 mins	IV	S	Digoxin Verapamil	4 5	-	24 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.2 Characteristics of randomised controlled and uncontrolled trials of amiodarone included in analysis

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Amiodarone / Control)*	*Type of Amiodarone control*	*Dose of (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Posada *et al.* 1988	76; 36	P, C	14/22	Quinidine+Amiodarone vs Quinidine	2 boluses of 150 mg followed by an infusion of 600 mg over 6 hours	IV	M	Quinidine	14/22	NS	10 hours
Bertini *et al.* 1990	39; 39	P, C	15/24	Propafenone	5 mg/Kg over 30 sec; if the arrhythmia persists the dose was repeated at an infusion rate of 10 to 15 mg/min; followed by oral therapy of 200 mg/day for 2 days and 400 mg for the next 5 days	IV; O	M	NS	-	NS	5 days
McAlister *et al.* 1990	83; 80	CO, C	41/39	Quinidine	5 mg/Kg over 20 min	IV	S	Digoxin Propranolol	41/39 16/6	NS	16 hours
Andrivet *et al.* 1990	46; 46	P, C	21/25	Cibenzoline	Either orally, with a single dose of 30 mg/Kg/24 h; or IV loading dose of 5 to 7.5 mg/Kg over 30 mins; followed by continuous IV of 10 to 15 mg/Kg/24 h	O or IV	S M	Digoxin	21/25	Digoxin; 3/0 Amiodarone; 2/1 Class I; 7/2 ß-blocker; 3/6	24 hours
Bellandi *et al.* 1993	196; 196	P, C	98/98	Propafenone	A bolus of 5 mg/Kg (3 min); followed by 15 mg/Kg/24 hr	IV	M	NS	-	NS	1 year

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.2 Characteristics of randomised controlled and uncontrolled trials of amiodarone included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Amiodarone / Control)*	*Type of Amiodarone control*	*Dose of (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomitant drugs*	*Previous medications*	*Duration of study*
Chapman *et al.* 1993	26; 24	P, C	10/14	Procainamide	3 mg/kg infused over 15-20 min followed by 10 mg/Kg/24 h, and if no response was documented by 1 h, 3 mg/kg	IV	M	Digoxin	8/12	Digoxin ß-blockers	72 hours
Cesar *et al.* 1994	60; 60	P, C	16/23/21	Quinidine+Digoxin; 2 Procainamide +Digoxin; 23	5 mg/Kg infused over 10 min	IV	S	Digoxin	0/21Q/Prc23	NS	4 hours
Cochrane *et al.* 1994	30; 30	P, C	15/15	Digoxin	A loading dose of 5 mg/Kg (max 400 mg), infused IV over 30 min, followed by 25 mg/h, and if VR uncontrolled, the infusion increased to 40 mg/h	IV	M	-	0	ß-blocker; 8/7	24 hours
Treglia *et al.* 1994	71; 54	P; C	27/27	Propafenone	5 mg/Kg over 15 min followed by, for non-converting, infusion of 15 mg/Kg over the 24 hours	IV	M	NS	-	NS	48 hours
Biasi *et al.* 1995	85; 84	DB, P, C	46/38	Propafenone	5 mg/Kg over 15 min followed by, for non-converting, infusion of 15 mg/Kg over the 24 hours	IV	M	-	-	-	24 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.2 Characteristics of randomised controlled and uncontrolled trials of amiodarone included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Amiodarone/ Control)*	*Type of Amiodarone control*	*Dose of (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomitant drugs*	*Previous medications*	*Duration of study*
Chapman *et al.* 1993	26; 24	P, C	10/14	Procainamide	3 mg/kg infused over 15-20 min followed by 10 mg/Kg/24 h, and if no response was documented by 1 h, 3 mg/kg	IV	M	Digoxin	8/12	Digoxin ß-blockers	72 hours
Cesar *et al.* 1994	60; 60	P, C	16/23/21	Quinidine+Digoxin; 2 Procainamide +Digoxin; 23	5 mg/Kg infused over 10 min	IV	S	Digoxin	0/21Q/Prc23	NS	4 hours
Cochrane *et al.* 1994	30; 30	P, C	15/15	Digoxin	A loading dose of 5 mg/Kg (max 400 mg), infused IV over 30 min; followed by 25mg/h, and if VR uncontrolled, the infusion increased to 40 mg/h	IV	M	-	0	ß-blocker; 8/7	24 hours
Treglia *et al.* 1994	71; 54	P; C	27/27	Propafenone	5 mg/Kg over 15 min; followed by for non-converting, infusion of 15 mg/Kg over the 24 hours	IV	M	NS	-	NS	48 hours
Biasi *et al.* 1995	85; 84	DB, P, C	46/38	Propafenone	5 mg/Kg over 15 min; followed by for non-converting, infusion of 15 mg/Kg over the 24 hours	IV	M	-	-	-	24 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.2 Characteristics of randomised controlled and uncontrolled trials of amiodarone included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Amiodarone / Control)*	*Type of Amiodarone control*	*Dose of (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Donovan *et al.* 1995	98; 98	DB, P, C, PL	32/34/32	Flecainide; 34 Placebo; 32	7 mg/Kg over 30 mins	IV	S	Digoxin ß-blockers Calcium antagonist	4/3/4 8/4/2 4/2/2	-	8 hours
Moran *et al.* 1995	42; 42	P, C	21/21	Magnesium sulfate	5 mg/Kg loading dose over 15 to 20 mins followed by an infusion of 10 mg/Kg/24 hrs	IV	M	Digoxin Aminophylline Sympathomimetics	11/9 6/4 11/6	NS	24 hours
Galve *et al.* 1996	100; 100	P, PL, SB	50/50	Amiodarone+ Digoxin vs Placebo+Digoxin	5 mg/Kg over 30 mins; followed by 1200 mg diluted in 500 ml of saline over 24 hours	IV	M	Digoxin	50/50	No previous antiarrhythmic therapy including digoxin	15 days
*Larbuisson *et al.* 1996	40; 40	P, C	22/18	Propafenone	2.5 to 5 mg/Kg infused over 10 mins; if reversion was not achieved in 20 min, additional doses were given up to 900 mg/24 hrs	IV	M	Digoxin ß-blockers Calcium antagonist Nitrates	0/1 6/6 11/10 6/3	NS	1 week
Capucci *et al.* 1992	62; 62	SB, P, C, PL	19/22/21	22 flecainide 21 Placebo	300 mg/day	O	S	-	0/0	NS	24 hours

DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study

Table 5.1.2 Characteristics of randomised controlled and uncontrolled trials of amiodarone included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Amiodarone / Control)*	*Type of Amiodarone control*	*Dose of (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Hou *et al.* 1995	50; 50	P, C	26/24	Digoxin	5 mg/min for the first hour, 3 mg/min for the next 3 hours, 1 mg/min for another 6 hours and 0.5 mg/min for the remaining 14 hours	IV	M	Digoxin Ca blockers ß-blockers	0/24 2/2 1/2	-	24 hours

DB, double-blind; SB, single-blind; P, parallel; æ, nonrandomised open-label trial; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study; VR, ventricular rate '

Table 5.1.2 Characteristics of randomised controlled, and uncontrolled trials of amiodarone included in analysis (continued)

Uncontrolled

Study name	*Year of publi-cation*	*No. of patients enrolled*	*Treatment allocation (Amiodarone / Control)*	*Dose of Amiodarone (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomitant drugs*	*Previous medications*	*Arrhythmia monitoring method*	*Duration of study*
Faniel *et al.*	1983	26	26	Repeated boluses of 3 mg/Kg in 3 min, or 30 min infusion of 5 to 7.5 mg/Kg; followed by continuous infusion to a maximum of 1500 mg/24 h	IV	M	-	0	Digitalis; 7 Verapamil; 4 Digitalis+ Verapamil; 2 Hydroquinine; 1	ECG	48 hours
Strasberg *et al.*	1985	26	26	A slow bolus of 5 mg/Kg over 3 to 5 mins	IV	S	-	0	Digoxin; 4 Quinidine; 1	ECG	12 hours
Contini *et al.*	1993	61	61	A bolus of 300 mg; followed by infusion of 900 mg/24 h; then either IV or oral 600 mg/24 h	IV+O	M	-	0	-	ECG	7 days

DB, double-blind; SB, single-blind; P, parallel; æ, nonrandomised open-label trial; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study; VR, ventricular rate

Table 5.1.3 Characteristics of randomised controlled and uncontrolled trials of Sotalol included in analysis

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Sotalol/ Control)*	*Type of control*	*Dose of Sotalol (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomi-tant drugs*	*Previous medications*	*Duration of study*
Campbell *et al.* 1985	42; 40	C, P	20; 20	Digoxin/ Disopyramide+Digoxin	A bolus of 1mg/Kg; and a further 0.2 mg/Kg infused over 12 hours	IV	O	-	0	ß-blockers; 15/15	24 hours
Levy *et al.* 1986	23; 23	CO, PL	23/23	Placebo	0.5 mg/Kg in 6 mins	IV	S	-	-	-	-
Janssen *et al.* 1986	151; 130	C, P, PL	41/39/50	Metoprolol; 39 No therapy; 50	0.3 mg/Kg IV for prevention of SVAs; and 240 mg orally for acute treatment of SVAs after CABG	IV+O	S	-	0	-	48 hours
Suttorp *et al.* 1990	450; 429	P, C	207/222	High dose Propranolol; 156 Low dose Propranolol; 66	High; 40 mg/8 h Low; 80 mg/8 h	O	M	-	0	ß-blocker; 147/179 Digoxin; 9/14	6 days
Jordaens *et al.* 1991	43, 43	DB, PL, CO	38/22	Placebo	A bolus of 1.5 mg/Kg over 10 mins	IV	S	-	0	0	1 hour
Suttorp *et al.* 1991	303; 300	DB, PL, P	150/150	Placebo	Low; 80 mg/6 h	O	M	-	0	ß-blocker; 118/108 Digoxin; 4/7	6 days

DB, double-blind; SB, single-blind; P, parallel; æ, nonrandomised open-label trial; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study; VR, ventricular rate; ¶, the antiarrhythmic drugs were introduced as crushed tablets mixed in 100 mL of orange juice

Table 5.1.3 Characteristics of randomised controlled and uncontrolled trials of Sotalol included in analysis (continued)

Randomised controlled

Study name	*No. of patients enrolled; randomised*	*Design features*	*Treatment allocation (Sotalol/ Control)*	*Type of control*	*Dose of Sotalol (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving Concomi-tant drugs*	*Previous medications*	*Duration of study*
Hamer *et al.* 1993	6; 6	DB, CO, C	6/6/6	6 Flecainide 6 Verapamil	Sotalol; 2-2.9 mg/Kg Flecainide; 2-3.3 mg/Kg	O¶	S	-	0	Verapamil;(6/6/6) Atenolol; (1/1/1)	4.5 hours
Nystrom *et al.* 1993	101; 101	C, P	50/51	Routine treatment with other ß-blockers	Preoperatively, the first dose was 160 mg in the morning of the day of the operation; and postoperative a dose of 320 mg/day	O	M	-	0	ß-blocker; 42/40 Digoxin; 3/1 Calcium-channel blocker; 36/28	6 days
Halinen *et al.* 1995	61; 61	DB, P, C	33/28	28 Quinidine	80 mg; then the same dose repeated after 2, 6, 10 hours if the arrhythmia persisted (up to a max of 320 mg)	O	M	Digoxin	0/28	Digoxin; (5/1) ß-blockers; (6/13) Verapamil /Diltiazem; (4/3) Diuretic; (1/8)	24 hours
Sung *et al.* 1995	93; 93	First part: DB, PL, P Second part: Open-label, uncontrolled	62/33/29	62 Sotalol 1.5 mg/Kg 33 Sotalol 1 mg/Kg 29 Placebo	1 mg/Kg or 1.5 mg/Kg infusion over 10 mins	IV	S or M	NS	0	-	1 hour

DB, double-blind; SB, single-blind; P, parallel; æ, nonrandomised open-label trial; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study; VR, ventricular rate

Table 5.1.3 Characteristics of randomised controlled and uncontrolled trials of Sotalol included in analysis

Uncontrolled

Study name	*No. of patients enrolled*	*Treatment allocation (Sotalol/ Control)*	*Dose of Sotalol (mg/Kg)*	*Route*	*No. of doses*	*Concomitant drugs*	*No. of patients receiving concomitant drugs*	*Previous medications*	*Duration of study*
Teo *et al.* 1985	29	29	A bolus of 30 mg at a rate of 2 mg/min, or infusion of 100 mg over 120 mins	IV	S	-	0	Digitalis; (8) Disopyramide; (4) Sotalol; (2) Propranolol; (1) Atenolol; (1)	48 hours
Denis *et al.* 1988	20	20	One to three injection of 0.5 mg/Kg	IV	M	NS	-	NS	NS

DB, double-blind; SB, single-blind; P, parallel; æ, nonrandomised open-label trial; CO, crossover; PL, placebo-controlled; S, single; M, multiple; IV, intravenous; O, oral; C, comparative study; VR, ventricular rate

The included trials enrolled a total of 2528 patients, however; 2383 patients were randomised and received trials' treatment: 533 patients received flecainide, 610 patients received amiodarone, 272 patients received sotalol, 368 patients received placebo, and 733 patients were receiving other antiarrhythmic drugs as active control (of which 140 patients received quinidine; 22 received quinidine plus amiodarone; 47 patients received disopyramide; 77 patients received procainamide; 273 patients received propafenone; 21 received cibenzoline; 39 patients received metoprolol; 21 patients received magnesium sulfate; and 93 patients received digoxin, verapamil or combination of the two). The sample size of each study ranged from 6 to 196 patients, with a mean of 58 patients over all the studies.

The arrhythmia monitoring technique throughout the trials' observation period was a continuous 24-hour Holter monitoring (11 trials); continuous 12-lead electrocardiogram every hour which was recorded as soon as the patient convert to sinus rhythm (24 trials), and/or recording of the symptoms. The average study duration was 86±43 hours (range 45 minutes to 1 month), for flecainide trials 196±306 hours (range 45 minutes to 1 month), for amiodarone trials 39.5±45 hours (range 4 hours to 7 days), and for sotalol trials 21±20.6 hours (range 1 hour to 48 hours).

30 trials tested intravenous interventions (9 for flecainide, 14 for amiodarone, and 6 for sotalol), 6 trials tested oral interventions (5 for flecainide, and 2 for sotalol), and 7 trials tested oral plus intravenous interventions (3 for flecainide, 3 for amiodarone, and 1 for sotalol). For intravenous interventions, the dosages and rates of infusion varied across the studies. Flecainide dosage employed varied between 1 to 2 mg/Kg infused over 10 to 30 minutes, and in some studies followed by a continuous infusion of 0.2 to 1.5 mg/Kg/hr for the rest of the study, or untill conversion to sinus rhythm was achieved. Amiodarone initial intravenous dose was mostly 5 mg/Kg over 3 to 30 mins, followed by 10 to 15 mg/Kg/hr. Sotalol dosage varied between 0.5 to 1.5 mg/Kg over 10 mins.

5.4.2 Population Characteristics of the Included Studies

The mean age of the patients across all studies, which reported the age (34 studies), was 58.57±7.85 years (range 23 to 71). In the 41 studies reporting gender, there was a total of 808 women and 1490 men, with a mean of 36 men and 20 women in the

sample. The mean onset of the arrhythmia was reported in 29 studies with an average overall mean of 160±538 hours (range 15 minutes to 4.6 months). The left atrial diameter was mentioned in 15 studies with a mean of 41.63±5.1 mm (range 32.9 to 55).

Tables 1, 2, and 3 of Appendix 5.2 show the characteristics of populations included in flecainide, amiodarone, and sotalol individual trials respectively. Table 5.2 summarises the mean characteristics of patients treated with amiodarone, sotalol, flecainide, and placebo groups. Patients characteristics for each type of treatment group were tabulated separately. Continuous data were compared using unpaired t-test, and one way analysis of the variance. Discrete variables were compared using chi-square test. The comparison of mean age have revealed that patients allocated to amiodarone were significantly older than other groups (ANOVA=5.48; P=0.0023). The time elapsed since the first onset of arrhythmia and left atrial diameter were not significantly different among the treatment groups (P=0.3911 and 0.524 respectively). Patients of medical or surgical etiology were not equally distributed among the groups (P=0). Furthermore, the comparisons of baseline mean heart rate and systolic blood pressure were not considered significant (P=0.35, and 0.449 respectively).

Cardiac diagnoses were reported for a total of 1971 patients. Table 4, 5, and 6 of Appendix 5.2 show the different cardiac diagnoses of patients enrolled in flecainide, amiodarone, and sotalol clinical trials respectively. The distribution of the assorted diagnoses was tabulated, and examined with respect to various treatment groups (Table 5.2), as well as different drugs' trials populations (Table 5.3). The valvular heart disease was the primary diagnosis in 16% of the population enrolled in amiodarone clinical trials, 4.8% of the patients in the sotalol trials, and 6.5% of the patients in flecainide trials (P<0.0001). Hypertension was found in 10.5% of the amiodarone trials' populations, 18% of sotalol trials' populations, and 18.43% of flecainide populations (P<0.0001). The proportion of patients with ischemic heart diseases and cardiomyopathy was more significant in amiodarone and sotalol clinical trials than flecainide trials (P<0.0001). Patients with ischemic heart diseases were equally distributed among the groups (P=0.06). Patients with congestive heart failure and cardiomyopathy existed more in amiodarone clinical trials than sotalol and flecainide trials. However, patients with lone fibrillator were more common in flecainide trials (P<0.0001). In addition, examination of distribution of the same diagnoses across individual treatment groups as shown in Table 5.2 (patients receiving amiodarone, sotalol, flecainide, placebo, and active control separately), has confirmed significant

statistical differences in all diagnoses categories ($P<0.0001$) except cardiomyopathy and pericarditis ($P=0.08$ and 0.27 respectively).

Table 5.2 Mean characteristics of all study groups included in the analysis

Variables	All groups	Amiodarone	Sotalol	Flecainide	Placebo	Test of significance	P-value
Study groups (N)	26	20	9	17	10	-	-
Patients (n)	1783	610	272	533	368	-	-
Age	58.57±7.85	62.7±5.3	50.3±12.5	55.74±9.6	53.99±7.97	ANOVA F=5.4745	P=0.0023**
Male	1131	410	163	337	221		
Female	635	200	98	193	144		
Arrhythmia pattern							
Acute AF (n)	1254	531	73	416	234	$\chi2$=104.3	P=0.00
AFL (n)	222	102	33	38	9	$\chi2$=53	P=0.00
PAF (n)	117	34	34	30	19	$\chi2$=17	P=0.00
PSVT (n)	159	18	96	21	24	$\chi2$=253.7	P=0.00
Onset of arrhythmia (hours)	160±538	49.38±53.02	120.7±274.75	283.62±671	19.24±11.83	ANOVA F=1.0296	P=0.3911
Left atrial diameter (mm)	41.63±5.09	43.6±6.24	-	40.84±4.23	42.62±22.93	ANOVA F=0.6694	P=0.5243
Baseline heart rate (Ventricular response rate, beats/min)	141.17±14.04	140.94±12.26	147.46±20.14	134.54±13.48	140.8±19.15	ANOVA F=1.1213	P=0.3513
Systolic blood pressure (mm Hg)	125.02±12.3	123.27±12.63	114.74±9.66	118	119.5±9.66	ANOVA F=0.8397	P=0.449
Surgical etiology (n)	1079	236	217	374	252	$\chi2$=352.8	P=0.00
Medical etiology (n)	699	482	36	106	75	$\chi2$=423.1	P=0.00
Cardiac diagnosis† (n)	1528	448	190	422	468	–	–
Valvular (n)	210	97	11	44	58	$\chi2$=33.132	P=0.000
Hypertension (n)	217	49	33	74	61	$\chi2$=8.455	P=0.0375
Ischemic heart disease (n)	320	137	23	99	61	$\chi2$=42.209	P=0.000
Thyroid (n)	11	0	4	5	2	$\chi2$=10.114	P=0.017621
Lone fibrillator (n)	532	132	73	168	159	$\chi2$=7.513	P=0.057221
Congenital heart disease (n)	6	1	3	0	2	$\chi2$=8.81	P=0.031952
Pericarditis (n)	15	5	1	7	2	$\chi2$=3.919	P=0.270296
Alcohol-associated (n)	28	7	8	3	10	$\chi2$=9.175	P=0.027051
CHF (n)	115	50	10	20	35	$\chi2$=13.512	P=0.00365
Cardiomyopathy (n)	37	17	2	11	7	$\chi2$=6.675	P=0.083015
Miscellaneous (n)	151	43	13	57	38	$\chi2$=8.896	P=0.031

AF, atrial fibrillation; AFL, atrial flutter; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia ANOVA, One-way Analysis of the variance; $\chi2$, Chi-square test; †, total number of patients for whom cardiac diagnosis was reported; CHF, congestive heart failure

Table 5.3 Distribution of cardiac diagnoses in amiodarone, sotalol, and flecainide clinical trials

Diagnosis	*Amiodarone clinical trials n (%)*	*Sotalol clinical trials n (%)*	*Flecainide clinical trials n (%)*	*Chi-square test*	*P-value*
Valvular heart disease	153 (16%)	12 (4.8%)	50 (6.5%)	44.717	P<0.000
Hypertension	100 (10.5%)	45 (18%)	141 (18.43%)	21.011	P<0.00027
Ischemic heart disease	196 (20.5%)	33 (13.2%)	140 (18.3%)	5.762	P=0.056065
Thyroid	0 (0%)	4 (1.6%)	5 (0.65%)	12.173	P=0.002274
Lone fibrillator (no heart disease)	263 (27.5%)	74 (29.6%)	315 (41.2%)	25.04	P<0.000
Congenital heart disease	1 (0.1%)	3 (1.2%)	1 (0.13%)	10.119	P<0.00643282
Pericarditis	6 (0.63%)	1 (0.4%)	7 (0.92%)	0.882	P=0.000
Alcohol associated	7 (0.73%)	12 (4.8%)	3 (0.39%)	35.25	P=0.000
CHF	121 (12.7%)	10 (4%)	57 (7.5%)	21.282	P=0.05
Cardiomyopathy	27 (2.8%)	2 (0.8%)	11 (1.44%)	6.157	P=0.3991
Miscellaneous	64 (6.7%)	13 (5.2%)	59 (7.7%)	6.837	P=1
Total	956	250	765	-	-

$\chi 2$, Chi-square test; CHF, congestive heart failure

5.4.3 Efficacy

5.4.3.1 Conversion to Sinus Rhythm

Different trials considered various time intervals as the end-point for successful conversion to sinus rhythm depending on the dose and route of administration employed. The definition of conversion success rate was stated in 30 studies (Table 5.4). A total of 11 clinical trials reported the percentage of patients converted to sinus rhythm, in the form of curves, for different treatment arms at various time points during the study observation period. This varied between 6 to 24 hours (listed in Table 5.5.1). 30 trials reported the incidence of successful conversion in the text at one or more time points (listed in Table 5.5.2).

5.4.3.1.1 Direct Comparisons

Flecainide Clinical Trials

Table 5.6.1 displays the results of flecainide estimated effects (individual odds ratios), compared to direct control groups in individual trials at the three time-intervals specified in section 5.3.4.1. In all the 5 placebo-controlled trials the differences between flecainide and placebo were statistically significant at the end of the three hour-interval. Furthermore, flecainide absolute efficacy relative to placebo was confirmed by pooling as shown in Figure 5.1. The typical pooled OR at 3 and 8 hours was highly statistically significant ($OR_{3\ hrs}$, 7.2; 95% CI, 4.7 to 11.12; Z=8.9; and $OR_{8\ hrs}$, 5.5; 95% CI, 3.6 to 8.4; Z=7.85). The test of heterogeneity among trials was not significant at 3 hrs, but was at 8 hrs. Despite application of random-effects model, flecainide was still superior to placebo at 8 hrs.

Head to head comparisons of flecainide to other drugs from different classes in 10 RCTs were not consistently significant (Figure 5.2). Pooling the data from two amiodarone controlled trials (of a total of 56 vs 51 patients) demonstrated superior conversion rate with flecainide at 3 hours, as well as at 8 hours ($OR_{3\ hrs}$, 3.44; 95% CI, 1.6 to 7.3; Z=7.8; and $OR_{8\ hrs}$, 3.02; 95% CI, 1.4 to 6.6; Z=2.7). In addition, the pooled effect estimate expressed as RD was highly statistically significant ($RD_{3\ hrs}$, 34%; 95% CI, 16.7% to 51.5%; Z=3.9, and $RD_{8\ hrs}$, 29.6%, 95% CI, 12.7% to 46.5%; Z=3.4). However, the results at 8 hours should be interpreted with caution as

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Goy *et al.* 1985	Flecainide	AF lasting at least 1 day but less than 3 months	Reversion to sinus rhythm not more than 48 hours after the treatment is begun
Borgeat *et al.* 1986	Flecainide vs Quinidine	NS	NS
Crozier *et al.* 1987	Flecainide	Acute SVT (within 24 h)	Reversion to sinus rhythm within 45 min after the start of the infusion
Nathan *et al.* 1987	Flecainide	NS	NS
Crijns *et al.* 1988	Flecainide	Recent-onset AF <24 h, and chronic AF>24 h	Reversion to sinus rhythm within 5h (oral) or within 30 min (intravenous regimen)
Gavaghan *et al.* 1988	Flecainide vs Digoxin+Disopyramide	Atrial tachyarrhythmia developing after bypass grafting surgery or valve replacement surgery	NS
Suttorp *et al.* 1989	Flecainide vs Verapamil	AF or AFL < 6 months and ventricular rate > 100 bpm and no signs of heart failure	Reversion to sinus rhythm within 1 hour after the start of the infusion
Wafa *et al.* 1989	Flecainide or Flecainide +Verapamil vs Digoxin or Digoxin +Verapamil	Atrial tachyarrhythmia developing in the first 96 hours after bypass grafting surgery and lasting for at least 15 mins	Reversion to sinus rhythm within 45 mins, or within 1 hour if verapamil was added at 45 mins (due to persistence of AF), and maintained for 24 hours The treatment was also considered successful if it control the ventricular response rate

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Suttorp *et al.* 1990	Flecainide vs Propafenone	AF or AFL < 6 months and ventricular rate > 100 bpm and no signs of heart failure	Reversion to sinus rhythm within 1 hour after the start of the infusion
Donovan *et al.* 1991	Flecainide+Digoxin vs Placebo +Digoxin	Recent-onset AF ≥30 mins and ≤72 hours	Early reversion: stable sinus rhythm within 1 hour of starting the medication and maintained until the end of the 6-hour monitoring period Late reversion: reversion between 1 and 6 hours
Capucci *et al.* 1992	Flecainide vs Placebo vs Amiodarone	Recent-onset AF ≤7 days	NS
Villani *et al.* 1990	Flecainide vs Placebo	Recent-onset PAF ≥8 hours and ≤ 24 hours	NS
Madrid *et al.* 1993	Flecainide vs Procainamide	Paroxysmal atrial fibrillation lasting <24 hours	Reversion to sinus rhythm within 1 hour after the start of the infusion

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Faniel *et al.* 1983	Amiodarone	AF or AFL with rapid ventricular response that had been unsuccessfully treated by drugs (other than amiodarone) and/or DC shock	Reversion to sinus rhythm within 24 h, maintained for more than 48 h
Strasberg *et al.* 1985	Amiodarone	Recent-onset AF or PAF	NS
Posada *et al.* 1988	Amiodarone+Quinidine vs Quinidine	Recent-onset AF (≤7 days)	Reversion to sinus rhythm over 10 hours
Bertini *et al.* 1990	Amiodarone vs Propafenone	AF or SVT	Acute reversion: Reversion to sinus rhythm within 2 hours via intravenous therapy at home Late reversion: Reversion to sinus rhythm within 1-2 days after hospitalisation via oral therapy
Noc *et al.* 1990	Amiodarone vs Verapamil	PAF	Reversion to sinus rhythm within 3 hours
McAlister *et al.* 1990	Amiodarone vs Quinidine	AF or AFL sustained for more than 2 hours after cardiac operation, and refractory to digoxin therapy or atrial pacing	Reversion to sinus rhythm within 8 hours, sustained for at least 4 hours
Andrivet *et al.* 1990	Amiodarone vs Cibenzoline	Sustained atrial tachyarrhythmia; lasting for at least 3 hours	Reversion to sinus rhythm over 24 hours

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Bellandi *et al.* 1993	Amiodarone vs Propafenone	Stable AF of recent onset	Reversion to sinus rhythm over 24 hours
Chapman *et al.* 1993	Amiodarone vs Procainamide	AT sustained for at least 1 h (including AF, AFL, and SVT), and which failed to respond to correction of possible precipitating factors	Conversion to sinus rhythm by 1 hr (or slowing of ventricular rate > 20 beats/min)
Contini *et al.* 1993	Amiodarone	AF developed after CABG	Reversion to sinus rhythm over 48 hours
Cesar *et al.* 1994	Amiodarone vs Quinidine+Digoxin vs Procainamide+Digoxin	Acute AF ≤ 7 days	NS
Cochrane *et al.* 1994	Amiodarone vs Digoxin	AF developed due to open heart surgery and persisted for more than 20 min with systolic blood pressure of 85 mmHg or above without inotropic support	Reversion to sinus rhythm over 24 hours with subsequent sustain throughout the study observation period
Treglia *et al.* 1994	Amiodarone vs Propafenone	Recent-onset AF (≤7 days)	Reversion to sinus rhythm over 48 hours
Biasi *et al.* 1995	Amiodarone vs Propafenone	AF or AFL lasting for at least 15 min prior to cardiac surgery and ventricular rate more than 100 beats/min	Reversion to sinus rhythm within the 24-hour study period and sustained at least 3 hours

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Hou *et al.* 1995	Amiodarone vs Digoxin	Persistent atrial fibrillation or flutter with ventricular rates above 130 beats/min for less than 10 days	Reversion to sinus rhythm over 24 hours
Moran *et al.* 1995	Amiodarone vs Magnesium sulfate	Sustained atrial tachyarrhythmia of ≥ 1 hr duration, with a ventricular rate of 120 beats/min	Reversion to sinus rhythm over 24 hours
Donovan *et al.* 1995	Amiodarone vs Flecainide vs Placebo	Recent-onset AF ≥30 mins and ≤72 hours	Early reversion: stable sinus rhythm within 1 hour of starting the medication and maintained until the end of the 6-hour monitoring period Late reversion: reversion between 1 and 6 hours
Larbuisson *et al.* 1996	Amiodarone vs Propafenone	Atrial fibrillation or flutter with a ventricular rate > 120 beats/min within 1 week after cardiac surgery	Efficacy was termed as: 'Success' (if sinus rhythm was achieved within 20 mins after first dose and hemodynamic parameters were improved by more than 20%) or as 'Improvement' (if sinus rhythm achieved within 24 hours and hemodynamic parameters were improved by more than 10%)

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Campbell *et al.* 1985	Sotalol vs Digoxin+Disopyramide	Atrial tachyarrhythmia developing after bypass grafting surgery or valve replacement surgery	NS
Teo *et al.* 1985	Sotalol	Acute or chronic, persistent or intermittent AF, AFL, or PSVT	Reversion to sinus rhythm within 1 hours
Levy *et al.* 1986	Sotalol vs Placebo	Recent-onset AF, AFL, or junctional tachycardia, with ventricular rate > 120 beats/min	NS
Janssen *et al.* 1986	Sotalol vs Metoprolol vs no treatment	AF developed after CABG	NS
Denis *et al.* 1988	Sotalol	Recent-onset AF, AFL, or junctional tachycardia	Reversion to sinus rhythm within 30 mins
Jordaens *et al.* 1991	Sotalol vs Placebo	Spontaneous or induced PSVT of ≥ 15 mins duration and a ventricular rate of > 120 beats/min	Reversion to sinus rhythm within 30 mins

Table 5.4 Definition of AF and successful conversion to sinus rhythm (CSR) employed in individual trials (continued)

Trial	*Drug treatment(s)*	*Definition of AF*	*Definition of CSR*
Hamer *et al.* 1993	Sotalol vs Verapamil vs Flecainide	PSVT normally controlled by antitachycardia atrial pacemaker	NS
Halinen *et al.* 1995	Sotalol vs Quinidine + Digoxin	PAF lasting than 48 hours with heart rate > 80 beats/mins, and systolic blood pressure ≥ 120 mm Hg	Reversion to sinus rhythm over 24 hours
Sung *et al.* 1995	Sotalol vs Placebo	SVT, AF, or AFL of > 5 mins and < 7 days duration with ventricular rate of ≥ 120 beats/min (spontaneous or induced in the electrophysiology laboratory)	Reversion to sinus rhythm within 30 mins

Table 5.5.1 Trials reporting curves with percentage of patients converted to sinus rhythm

Trial	*Treatment*	*Control*	*Time interval*
Cochrane *et al.* 1994	Amiodarone	Digoxin	0-24 hrs
Hou *et al.* 1995	Amiodarone	Digoxin	0-24 hrs*
Donovan *et al.* 1995	Amiodarone Flecainide	Placebo	0-8 hrs
Larbuisson *et al.* 1996	Amiodarone	Propafenone	0-24 hrs*
Galve *et al.* 1996	Amiodarone	Digoxin+Placebo	0-24 hrs
Posada *et al.* 1988	Amiodarone +Quinidine	Quinidine	0-10 hrs
Donovan *et al.* 1991	Flecainide+Digoxin	Placebo+Digoxin	1/2-6 hrs
Wafa *et al.* 1989	Flecainide	Digoxin alone or with Verapamil	0-24 hrs
Gavaghan *et al.* 1988	Flecainide	Digoxin+Disopyramide	1-12 hrs
Campbell *et al.* 1985	Sotalol	Digoxin+Disopyramide	1-12 hrs
Halinen *et al.* 1995	Sotalol	Quinidine+Digoxin	0-24 hrs

* Censored end points (the analysis was performed on an intention to treat basis)

Table 5.5.2 Trials reporting conversion success rates in the text

Trial	*Treatment*	*Control*	*Time interval*
Chapman *et al.* 1993	Amiodarone	Procainamide	1 h, and between 1 and 12 hrs
McAlister *et al.* 1990	Amiodarone	Quinidine	0-2, 2-4, 4-6, 6-8, 10-12, 12-4, and 14-16 hrs
Cesar *et al.* 1994	Amiodarone	Quinidine Procainamide	mean conversion time
Treglia *et al.* 1994	Amiodarone	Propafenone	5, 24, and 48 hrs
Biasi *et al.* 1995	Amiodarone	Propafenone	1, and 24 hrs
Bellandi *et al.* 1993	Amiodarone	Propafenone	mean conversion time
Bertini *et al.* 1990	Amiodarone	Propafenone	24 hrs
Noc *et al.* 1990	Amiodarone	Verapamil	20 mins, 40 mins, 1, 1.5, 2.3, and 3 hrs
Moran *et al.* 1995	Amiodarone	Magnesium Sulfate	1, 2, 4, 12, and 24 hrs
Andrivet *et al.* 1993	Amiodarone	Cibenzoline	24 hrs
Contini *et al.* 1993	Amiodarone	-	1, 12, and 24 hrs
Strasberg *et al.* 1985	Amiodarone	-	Individual pts data; 10 mins to 8 hrs
Faniel *et al.* 1983	Amiodarone	-	Individual pts data; 10 mins to 13 hrs
Crozier *et al.* 1987	Flecainide	-	0-45 mins
Nathan *et al.* 1987	Flecainide	-	2-15 mins
Goy *et al.* 1985	Flecainide	-	Individual pts data, 2mins to 26 hrs
Suttorp *et al.* 1990	Flecainide	Propafenone	1 hr
Capucci *et al.* 1992	Flecainide Amiodarone	Placebo	3, 8, 12, and 24 hrs
Villani *et al.* 1990	Flecainide	No treatment	mean conversion time
Capucci *et al.* 1994	Flecainide	Propafenone	3, and 8 hrs
Madrid *et al.* 1993	Flecainide	Procainamide	1 hr
Borgeat *et al.* 1986	Flecainide	Quinidine	1, 4, and 8.20 hrs
Crijns *et al.* 1988	Flecainide	-	1, 3, and 8 hrs
Suttorp *et al.* 1989	Flecainide	Verapamil	1 hr
Sung *et al.* 1995	Sotalol	Placebo	30 mins, and 1 hr
Jordaens *et al.* 1991	Sotalol	Placebo	30 mins
Hamer *et al.* 1993	Sotalol Flecainide	Verapamil	60, 65, 45, and 85 mins
Denis *et al.* 1988	Sotalol	-	Individual pts data, 2min to 26 hrs
Levy *et al.* 1986	Sotalol	Placebo	Individual pts data, 5 min to 40 mins
Teo *et al.* 1985	Sotalol	-	1, and 24 hrs

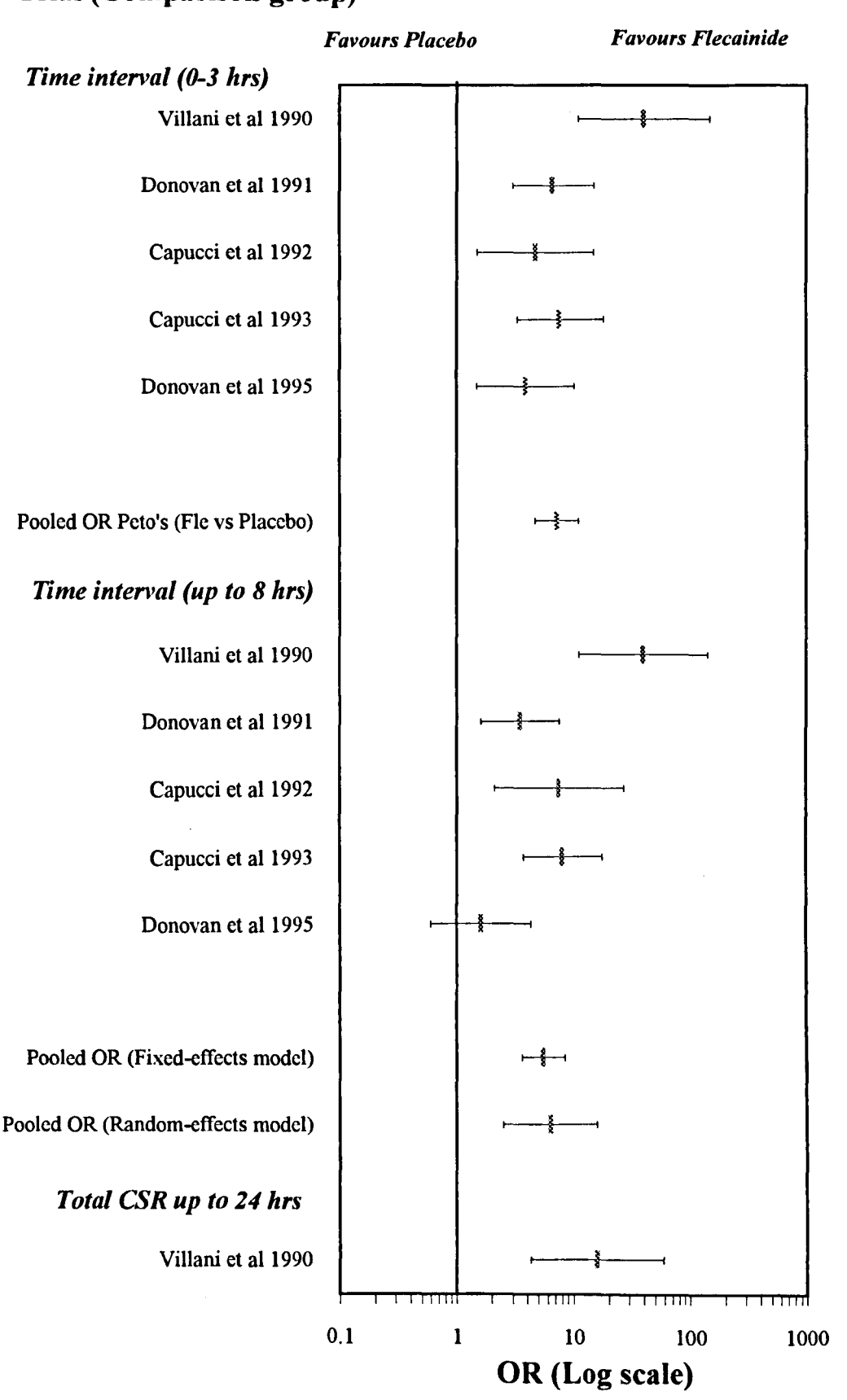

Figure 5.1 OR of conversion success rates (CSR) in the flecainide treatment groups as compared to direct placebo groups in RCTs. The results are represented stratified into 3, 8, and 24 hour-intervals.

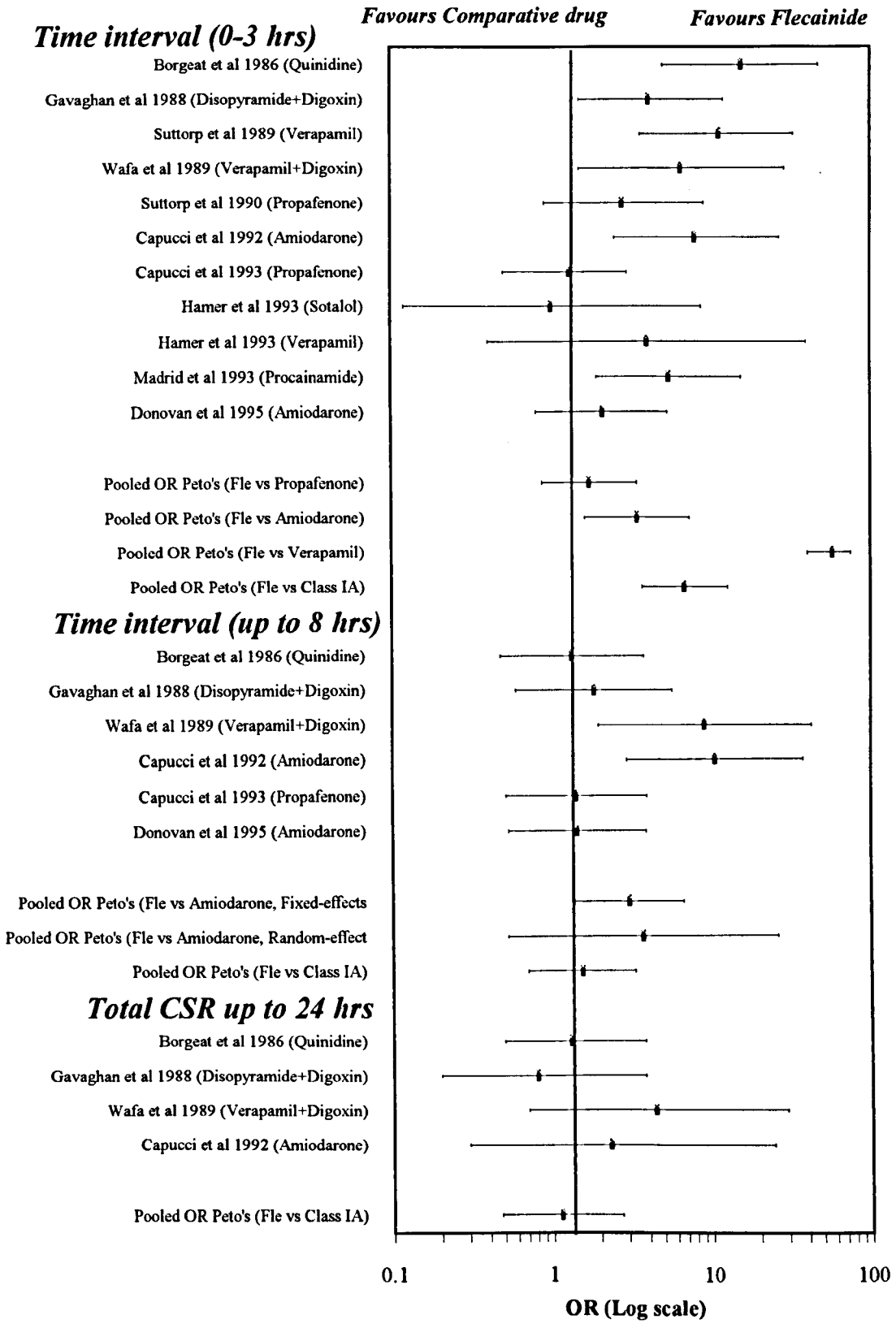

Figure 5.2 OR of conversion success rates (CSR) in flecainide treatment groups as compared to direct control groups in RCTs. The results are represented stratified into 3, 8, and 24 hour-intervals.

Q statistic was significant (P=0.02). A possible explanation for the heterogeneity in the treatment effect is the employment of different routes of administration in the two studies. Donovan *et al.* (1995) trial compared intravenous flecainide versus intravenous amiodarone, while Capucci *et al.* (1992) compared single oral loading dose with the intravenous amiodarone. Comparison of flecainide with another Class III agent sotalol was performed in one trial, and there was no significant difference in outcome (OR, 1; 95% CI; 0.12-8.7). Nevertheless, due to the crossover design, and the small sample size of the study, a definite conclusion regarding their relative efficacy could not be drawn.

Pooling the data was possible at 3 hours for only two propafenone controlled trials, and it showed no significant difference in the conversion rate between the two Class IC drugs, although a positive trend was evident in favour of flecainide (as shown in Figure 5.2; $OR_{3\ hrs}$, 1.73; 95% CI, 0.87 to 3.4; Z=1.6; and $RD_{3\ hrs}$, 14; 95% CI, -2.4 to 30.4; Z=1.7). Comparing the results at 8 hours in Capucci *et al.* (1994) trial only, the insignificant rate difference was still present ($OR_{8\ hrs}$, 1.4; 95% CI, 0.5-3.89, and $RD_{8\ hrs}$, 6; 95% CI, -11.7-23.9; Z=0.7).

Furthermore, the pooled estimate for flecainide in two verapamil controlled trials (of a total of 41 vs 26 patients) suggests highly significant efficacy for flecainide over oral or intravenous verapamil ($OR_{3\ hrs}$, 9.3; 95% CI, 3.5-25; Z=4.4; Q=0.7, P=NS). In fact, the very high significant difference between the two agents has confirmed that the use of verapamil is of no proven value for acute conversion of AF (Pt, 63.6% vs 6%). In another RCT (Wafa *et al.*, 1989), flecainide was even superior to the digoxin / verapamil combination in cardioversion efficacy up to 6 hrs (OR, 6.5; 95% CI, 1.5-29).

Three identified RCTs (Borgeat *et al.*, 1986; Gavaghan *et al.*, 1988; Madrid *et al.*, 1993) compared flecainide to three different Class IA antiarrhythmic agents (quinidine, disopyramide, and procainamide). The ORs of each individual trial were all highly statistically significant (P<0.01) at three hours ($OR_{3\ hrs}$ was 15.6, 4.1, and 5.5 respectively). Pooling the data at this time point has also yielded a highly significant difference in favour of flecainide without significant evidence of heterogeneity (pooled $OR_{3\ hrs}$, 6.7; 95% CI, 3.7 to 12.6; Z=6 (P<0.01); Q=3.2, df=2, P=0.2). However, by 8 as well as by 24 hours, there was no significant difference in individual and pooled estimates ($OR_{8\ hrs}$, 1.5; 95% CI, 0.7-3.3; and $OR_{24\ hrs}$, 1.1; 95% CI, 0.5-2.7).

Table 5.6.1 Results of conversion success rate (CSR) in individual clinical trials (randomised and uncontrolled) of flecainide

Trial	No. of patients randomised (Rx/Control)	CSR at ≤ 3 h; (N)		OR_{Peto} (95% CI)	CSR at ≤ 8 h (N)		OR_{Peto} (95% CI)	CSR up to 24 h (N)		OR_{Peto} (95% CI)
		Rx	Control		Rx	Control		Rx	Control	
Goy *et al.* 1985§	50	20/50	-	-	23/50	-	-	36/50	-	-
Borgeat *et al.* 1986	30/30 Q	17/30	0/30	15.6 (5-47.4)	20/30	18/30	1.33 (0.5-3.76)	20/30	18/30 Q	1.3 (0.5-3.8)
Crozier *et al.* 1987§	50	38/50	-	-	-	-	-	38/50	-	-
Nathan *et al.* 1987§	21	11/21	-	-	-	-	-	11/21	-	-
Crijns *et al.* (a) 1988§	20	10/20	-	-	11/20	-	-	11/20	-	-
Crijns *et al.* (b) 1988§	20	13/20	-	-	-	-	-	13/20	-	-
Gavaghan *et al.* 1988	29/27 Dig+D	19/29	8/27	4.1 (1.5-12)	22/29	17/27	1.8 (0.59-5.6)	25/29	24/27 Dig+D	0.8 (0.2-3.8)
Suttorp *et al.* 1989	20/20 V	23/35	1/20	11.3 (3.6-33)	-	-	-	-	-	-
Wafa *et al.* 1989	15/13 V+Dig	11/15	3/12	6.5 (1.5-29)	13/15	4/12	9.1 (1.9-42.3)	14/15	10/14 V+Dig	4.4 (0.7-29.3)
Suttorp *et al.* 1990	25/25 Pr	19/25	13/25	2.8 (0.9-9)	19/25	13/25	-	-	-	-
Villani *et al.* 1990	19/18 PL	18/19	0/18	40 (11-148)	18/19	0/18	40 (11-148)	18/19	5/18 PL	15.9 (4.3-59)
Donovan *et al.* 1991	51/51 PL+Dig	29/51	7/51	6.5 (3-14.8)	34/51	18/51	3.5 (1.6-7.5)	-	-	-
Capucci *et al.* 1992	22/19 A/21 PL	15/22	3/19 A 6/21 PL	7.97 (2.5-27) 4.7 (1.5-14.9)	20/22	7/19 A 10/21 PL	10.4 (2.9-37.5) 7.4 (2-26.9)	21/22	17/19 A 10/21 PL	2.3 (0.3-24.3) 10.2 (2.7-38)
Capucci *et al.* 1993	41/43 Pr/61 PL	23/41	21/43 Pr 8/61 PL	1.3 (0.5-3) 7.5 (3.3-18)	33/41	32/43 Pr 17/61 PL	1.4 (0.5-3.9) 8 (3.7-17.7)	-	-	-
Hamer *et al.* 1993	6/6 S/6 V	3/6	3/6 S 1/6 V	1 (0.12-8.7) 4 (0.4-39.4)	-	-	-	-	-	-
Madrid *et al.* 1993	40/40 Prc	37/40	25/40	5.47 (1.9-15.5)	-	-	-	-	-	-
Donovan *et al.* 1995	34/32 A/32 PL	20/34	13/32 A 8/32 PL	2.1 (0.8-5.34) 3.9 (1.5-10.3)	23/34	19/32 A 18/32 PL	1.4 (0.5-3.9) 1.6 (0.6-4)	-	-	-
Pooled rates (%) in RCTs; (95% CI)		69.3% (59-79.5)	Others#; 25% (19.4-30.6) PL; 16.3% (10.7-21.8)		79.3% (71.5-86.7)	Others#; 58.6% (51.4-65.9) PL; 37.3% (30-44.5)		85.5% (76-95)	Others#; 92.7% (78.5-95)	
Pooled rates (%) in Uncont; (95% CI)		58.9% (51.7-66.2)	-		61.3% (54.1-68.6)	-		68.7% (61.7-75.7)		
Pooled OR (Fle vs PL)				7.2			5.5			-
95% CI for the OR				4.7-11.12			3.6-8.4			-
Z (P)				8.9**			7.85**			-
Q statistic (P)				9.1 (0.06) NS			17.8* (0.0014)			-

CSR; conversion success rate = no. of patients converted to sinus rhythm / no. of patients at risk at the beginning of the interval; §, uncontrolled trials (Uncont); Fle, Flecainide; PL, Placebo; #, including other antiarrhythmic drugs; A, Amiodarone; Dig, Digoxin; D, Disopyramide; Pr, Propafenone; Prc, Procainamide; Q, Quinidine; S, Sotalol; V, Verapamil; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

From this analysis, it can be concluded that flecainide is more effective than a Class IA drug for prompt cardioversion, particularly in the first few hours.

The percentage of patients converted to sinus rhythm with flecainide in the individual RCTs varied between 65.4% to 75.1% at 3 hrs (with a weighted pooled percentage, P_t= 70.2%), and between 74.95% and 83.7% at 8 hrs (with P_t= 79.3%). These estimates were not significantly different from corresponding estimates in the uncontrolled trials (P_t=58.9%; 95% CI, 51.7-66.2, and P_t=61.3%; 95% CI, 54-68.6, at 3 and 8 hrs respectively).

Subgroup Analyses of Flecainide RCTs

Figure 5.7 and Table 7.a of Appendix 5.2 display the stratified analysis of flecainide direct comparisons in RCTs. The subanalysis according to cause, onset of the arrhythmia, and route of administration did not show any change in the previous conclusions. Noteworthy, flecainide demonstrated very limited value for conversion of AFL compared to AF; the RD compared to verapamil and propafenone was 0, and -20 (95% CI, -75 to 35) respectively.

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Figure 5.3 displays the individual and pooled ORs for conversion efficacy versus placebo. The analysis was performed first by pooling the data from the three placebo-controlled trials at 3 and 8 hour intervals, which has demonstrated nonsignificant difference from placebo ($OR_{3\ hrs}$, 1.3; 95% CI, 0.7-2.4; Q=2.4, df=2, P=0.3; and $OR_{8\ hrs}$, 1.034; 95% CI, 0.6-1.8; Q=0.7, df=2, P=0.7). A second sensitivity analysis was later undertaken by excluding Galve *et al.* (1996) trial, in which intravenous digoxin was given to both amiodarone and placebo arms. The later analysis did not alter the conclusion. Data at 24 hours was available only in one trial (Galve *et al.*, 1996), and again it was statistically nonsignificant (OR, 1.3; 95% CI, 0.6-2.8).

Direct head to head comparisons to other antiarrhythmic agents in different classes are displayed in Figure 5.4 and Table 5.6.2. At 3 hours amiodarone had displayed conversion efficacy which was only superior to digoxin (pooled $OR_{3\ hrs}$, 2.04; 95% CI, 1.1-3.9; Q=3.2, P=0.2), and to verapamil in one trial of a total of 24 patients ($OR_{3\ hrs}$, 12; 95% CI, 3.3-44). Nevertheless, no significant difference in the conversion rate

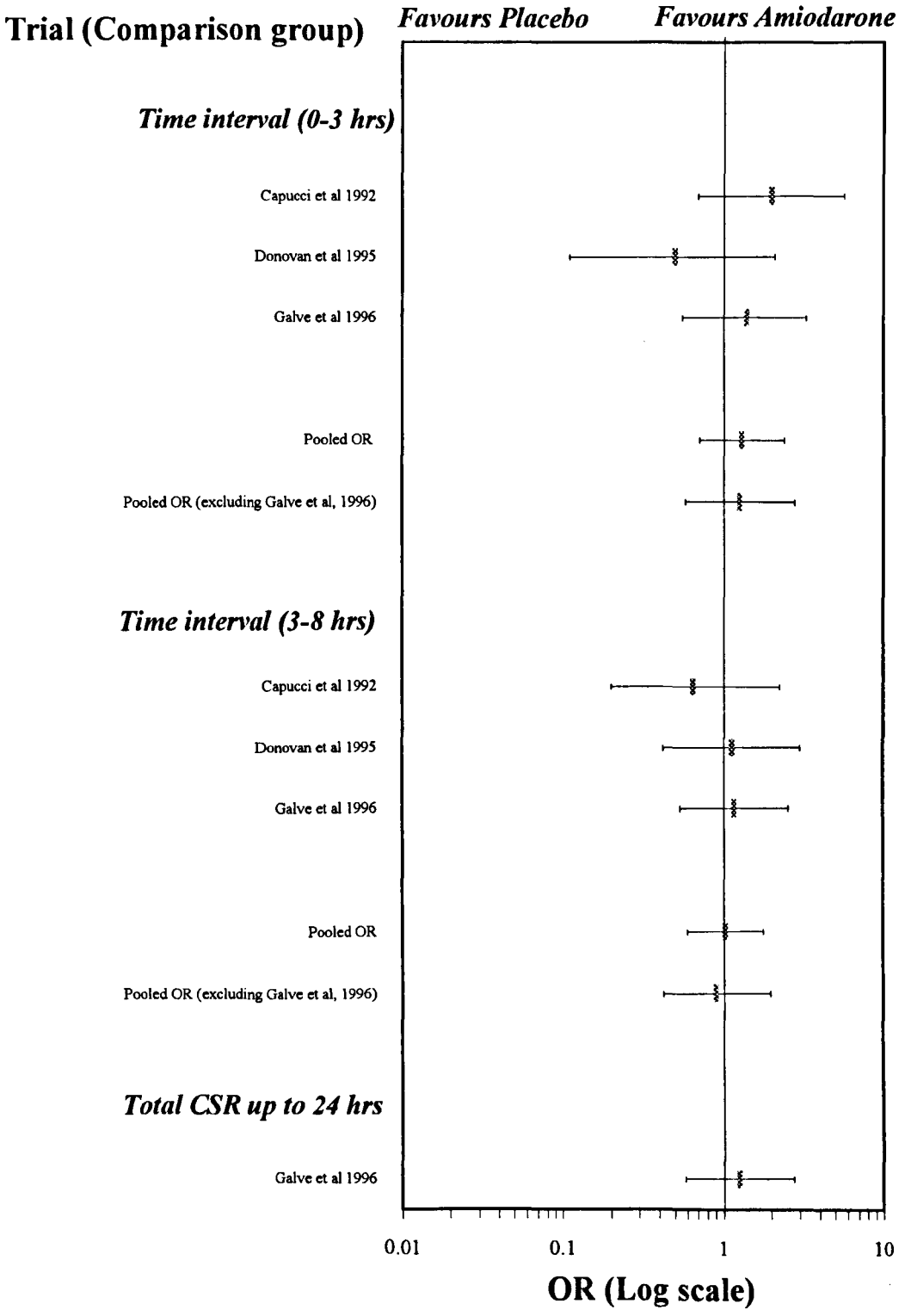

Figure 5.3 OR of conversion success rates (CSR) in the amiodarone treatment groups as compared to direct placebo groups in RCTs. The results are represented stratified into 3, 8, 24 hour-interval.

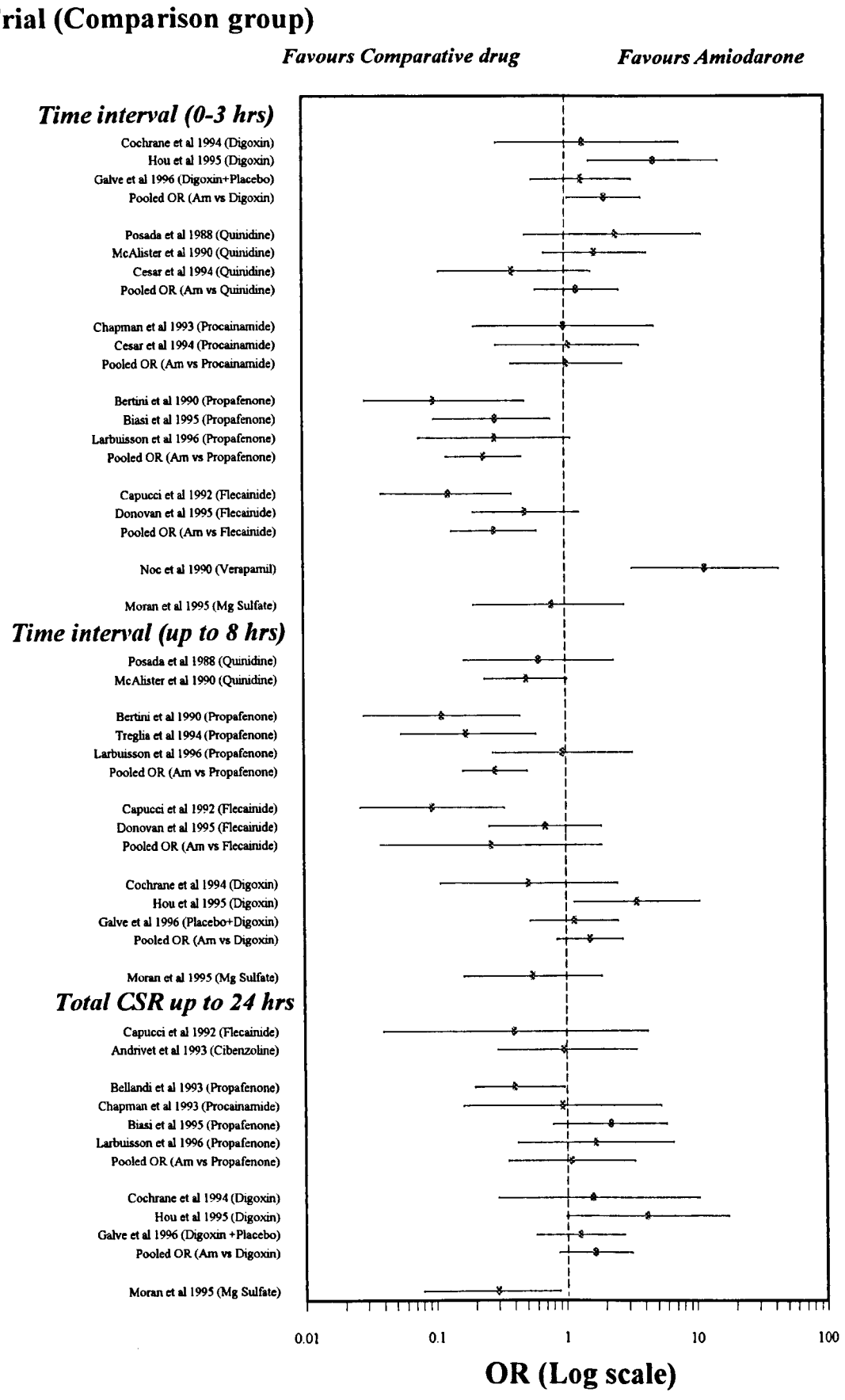

Figure 5.4 OR of conversion success rates (CSR) in amiodarone treatment groups as compared to direct control groups in RCTs. The results are represented stratified into 3, 8, and 24 hour-intervals.

Table 5.6.2 Results of conversion success rate in individual clinical trials (randomised and uncontrolled) of Amiodarone

Trial	No. of patients randomised (Rx/Control)	CSR at ≤ 3 h; (N)		OR_{Peto} (95% CI)	CSR at ≤ 8 h (N)		OR_{Peto} (95% CI)	CSR up to 24 h (N)		OR_{Peto} (95% CI)
		Rx	Control		Rx	Control		Rx	Control	
Faniel *et al.* 1983§	26	14/26	-	-	18/26	-	-	19/26	-	-
Strasberg *et al.* 1985§	26	16/26	-	-	-	-	-	-	-	-
Posada *et al.* 1988	14 Q+A/22 Q	5/14	4/22	2.5 (0.5-11.4)	6/14	12/22	0.64 (0.17-2.4)	-	-	-
Bertini *et al.* 1990	15/24 Pr	6/15	21/24	0.1 (0.03-0.5)	6/15	21/24	0.11 (0.03-0.5)	-	-	-
Andrivet *et al.* 1993	21/25 C	-	-	-	-	-	-	15/21	18/25 C	0.97 (0.3-3.5)
Noc *et al.* 1990	24/14 V	17/24	1/14	12 (3.3-44)	-	-	-	-	-	-
McAlister *et al.* 1990	53/63 Q	13/53	10/63	1.72 (0.7-4.3)	22/53	37/63	0.5 (0.24-1.05)	-	-	-
Capucci *et al.* 1992	19/22 F/21 PL	3/19	15/22 F 6/21 PL	0.13 (0.04-0.4) 2 (0.7-5.7)	7/19	20/22 F 10/21 PL	0.1 (0.03-0.34) 0.65 (0.19-2.3)	17/19	21/22 F 10/21 PL	0.4 (0.04-4.3) 6.4 (1.7-23.8)
Bellandi *et al.* 1993	98/98 Pr	-	-	-	-	-	-	79/98	89/98 Pr	0.4 (0.2-0.97)
Chapman *et al.* 1993	10/14 Prc	5/10	7/14	1 (0.2-4.9)	-	-	-	7/10	10/14	0.94 (0.2-5.4)
Contini *et al.* 1993§	61	33/61	-	-	-	-	-	47/61	-	-
Cesar *et al.* 1994	16/21 P/23 Q	8/16	11/23 P 15/21 Q	1.1 (0.3-3.8) 0.4 (0.11-1.6)	-	-	-	-	-	-
Cochrane *et al.* 1994	15/ 15 Dig	4/15	3/15	1.4 (0.3-7.6)	9/15	9/15	1 (0.24-4.22)	13/15	12/15 Dig	1.6 (0.3-10.5)
Treglia *et al.* 1994	27/27 Pr	0/27	0/27	-	3/27	13/27	-1.7 (0.05-0.6)	13/27	18/27	0.8 (0.3-2.7)
Biasi *et al.* 1995	46/38 Pr	9/46	17/38	0.3 (0.1-0.8)	-	-	-	38/46	26/38 Pr	2.2 (0.8-5.9)
Donovan *et al.* 1995	32/34 F/32 PL	13/32	8/32 PL 20/34 F	0.5 (0.11-2.1) 0.5 (0.2-1.3)	19/32	18/32 PL 23/34 F	1.1 (0.4-3.04) 0.7 (0.3-1.9)	-	-	-
Hou *et al.* 1995	26/24 Dig	14/26	4/24	4.9 (1.6-15.3)	19/26	10/24	3.5 (1.2-10.8)	24/26	17/24	4.2 (1-17.4)
Moran *et al.* 1995	21/21 M	6/21	7/21	0.8 (0.2-2.9)	7/21	10/21	0.6 (0.2-1.89)	7/21	14/21 M	0.3 (0.08-0.89)
Galve *et al.* 1996	50/50 PL+Dig	15/50	12/50	1.3 (0.56-3.3)	26/50	24/50	1.2 (0.54-2.6)	28/50	25/50	1.3 (0.58-2.8)
Larbuisson *et al.* 1996	22/18 Pr	4/22	8/18	0.3 (0.01-1.1)	12/22	10/18	0.96 (0.28-3.3)	17/22	12/18	1.7 (0.4-6.7)
Pooled rates (%) in RCTs; (95% CI)		32.5% (21.5-43.5)	PL; 26.3% (14.5-38.2)		45.5% (33.5-57.6)	PL; 52.9% (39.5-66.3)		75.3% (65.7-84.9)	PL; 16.3% (10.7-21.8)	
Pooled rates (%) in Uncont; (95% CI)		55.8% (46.7-64.9)	-		62.8% (54-71.6)	-		75.3% (67.4-83.3)		
Pooled OR (A vs PL)				1.3			1.034			-
95% CI for the OR				0.71-2.4			0.6-1.8			-
Z (P)				0.85 NS			0.12 NS			-
Q statistic (P)				2.4 (0.3)			0.7 (0.7)			-

CSR; conversion success rate = no. of patients converted to sinus rhythm / no. of patients at risk at the beginning of the interval; §, uncontrolled trials (Uncont); Fle, Flecainide; PL, Placebo; #, including other antiarrhythmic drugs; A, Amiodarone; Dig, Digoxin; D, Disopyramide; Pr, Propafenone; Q, Quinidine; S, Sotalol; V, Verapamil; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

between amiodarone and digoxin was noted after pooling the data at 8, and at the end of the 24 hour-interval (pooled $OR_{8\ hrs}$, 1.6; 95% CI, 0.9-2.8; Q=2.97, P=0.2; and pooled $OR_{24\ hrs}$, 1.7; 95% CI, 0.87-3.2; Q=2, P=0.4).

Pooling the data from two Class IA agents trials (4 RCTs; 2 vs quinidine, and 2 vs procainamide) did not reveal significant difference in the rapidity of action. The pooled $OR_{3\ hrs}$ versus quinidine was 1.3 (95% CI, 0.6-2.6) and versus procainamide was 1.1 (95% CI, 0.4-2.8). In addition, the results of another trial of 10 hour duration (Posada *et al.*, 1988), which compared oral quinidine plus intravenous amiodarone combination to oral quinidine only, did not show significant increase in the number of patients converted, or even a significant decrease in the time required for cardioversion ($OR_{3\ hrs}$, 2.5; 95% CI, 0.5-11.4; and $OR_{8\ hrs}$, 0.64; 95% CI, 0.17-2.4).

However, pooling data from two Class IC agents (4 RCTs; 2 vs flecainide, and 2 vs propafenone) has demonstrated a highly significant difference in favour of Class IC, particularly at 3 hours. The pooled $OR_{3\ hrs}$ versus flecainide was 0.3 (95% CI, 0.14-0.6) and versus propafenone was 0.24 (95% CI, 0.13-0.5).

It is clear from our present meta-analysis (particularly the three placebo-controlled trials), that although intravenous amiodarone is widely used in Europe for emergency conversion of SVAs to sinus rhythm, it is not effective for prompt effect, and thus it is of no value for this indication. Surprisingly, the results of uncontrolled trials (4 trials; Faniel *et al.*, 1983; Strasberg *et al.*, 1985; Contini *et al.*, 1993; Vietti-Ramus *et al.*, 1992) have concluded very high efficacy of intravenous amiodarone in all recently occurring SVAs (at 3 hrs: P_t=55.8%; 95% CI, 46.7-64.9; at 8 hrs: P_t=62.8%; 95% CI, 54-71.6; at 24 hrs: 75.3%; 95% CI, 67.4-83.3). These estimates were significantly different from corresponding estimates in amiodarone RCTs (Z=3.4, P<0.01), but not from those obtained in uncontrolled trials of flecainide (Z=0.4, P>0.05). However, results from uncontrolled trials should be interpreted with caution due to unavailability of any control group.

Subgroup Analyses of Amiodarone RCTs

Figure 5.8 and Table 7.b of Appendix 5.2 display the stratified analysis of RCTs in which amiodarone was directly compared to placebo or other antiarrhythmic drugs. This subanalysis did not alter the previous conclusions.

Sotalol Clinical Trials

Table 5.6.3, Figure 5.5, and Figure 5.6 display the individual and pooled ORs for conversion efficacy from sotalol RCTs. All individual ORs for intravenous sotalol versus placebo were highly significant and ranged between 6.04 and 14.3 (Figure 5.5). The pooled OR at 1 hour was 8.8 (95% CI, 4.7-16.5; Z=6.8; Q=1.53, P=0.5).

Direct head to head comparison of sotalol to other active drugs was only available in four trials (Figure 5.6). However, due to different control groups, pooling was initially not justified. Intravenous sotalol was superior to intravenous combination of digoxin plus disopyramide for up to 2 hours (Campbell *et al.*, 1985), displaying a more prompt effect. The individual ORs at 1 and 2 hours were 4 (95% CI, 1.2-13.9; Z, 2.2, P=0.03), and 4.8 (95% CI, 1.4-16.2; Z, 2.4, P=0.008) respectively. However, the individual OR of this trial did not reach the level of statistical significance at 3 hours ($OR_{3\ hrs}$, 2.8; 95% CI, 0.8-10). In another trial (Halinen *et al.*, 1995) of oral intervention, quinidine plus digoxin combination was superior to oral sotalol with regard to the time required for conversion ($OR_{3\ hrs}$, 0.3; 95% CI, 0.1-0.9), as well as the total efficacy rate ($OR_{24\ hrs}$, 0.47, 95% CI, 0.1-2.4). An attempt for pooling the data from the previous two Class IA controlled trials was made ($OR_{3\ hrs}$, 0.8; 95% CI, 0.34-1.9), nevertheless the results were heterogenous (Q=7.1, P<0.01). The most probable explanation is the employment of different routes of administration. Consequently, the results of this pooling was neglected.

Comparison of sotalol to another beta-blocker, metoprolol, has shown superior effect in favour of the former, particularly at 3 hours (Figure 5.6).

Subgroup Analyses of Sotalol RCTs

Figure 5.9 and Table 7.c of Appendix 5.2 display the stratified analysis of sotalol's direct comparisons in RCTs. This subanalysis, according to the type of SVAs, showed very high efficacy rate for the drug for termination of PSVT (pooled $RD_{3\ hrs}$, 58.5; 95% CI, 32.9-84) and AF (pooled $RD_{3\ hrs}$, 26.4; 95% CI, 5.9-46.9, Z=2.5), as compared to placebo. However, it was not effective for AFL (pooled RD_{3hrs}, 12.97; 95% CI, -22.2-48.1, Z=0.7).

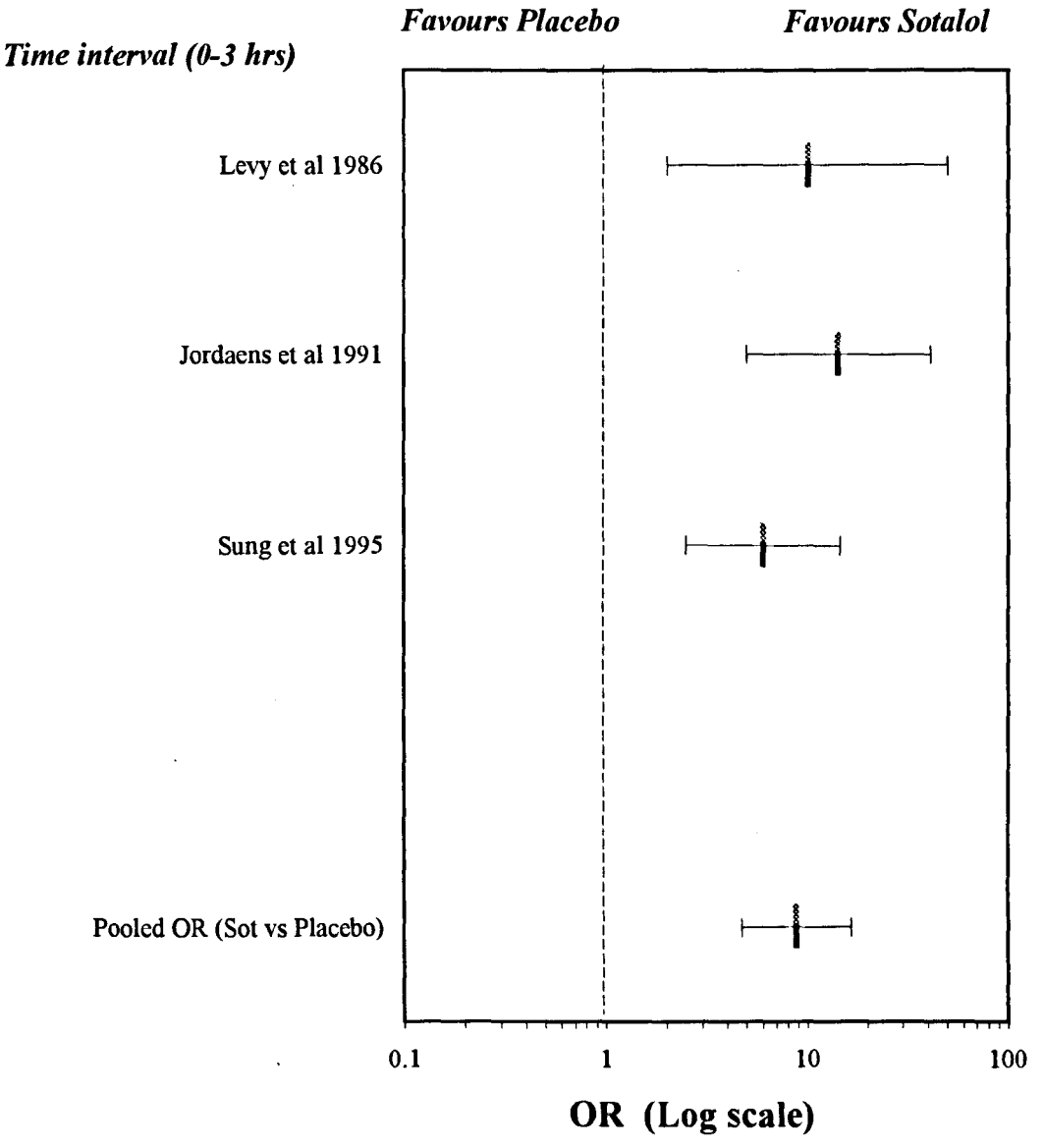

Figure 5.5 Pooled OR of conversion success rates (CSR) in the Sotalol treatment groups as compared to direct placebo groups in RCTs. The results are represented at 3 hours only.

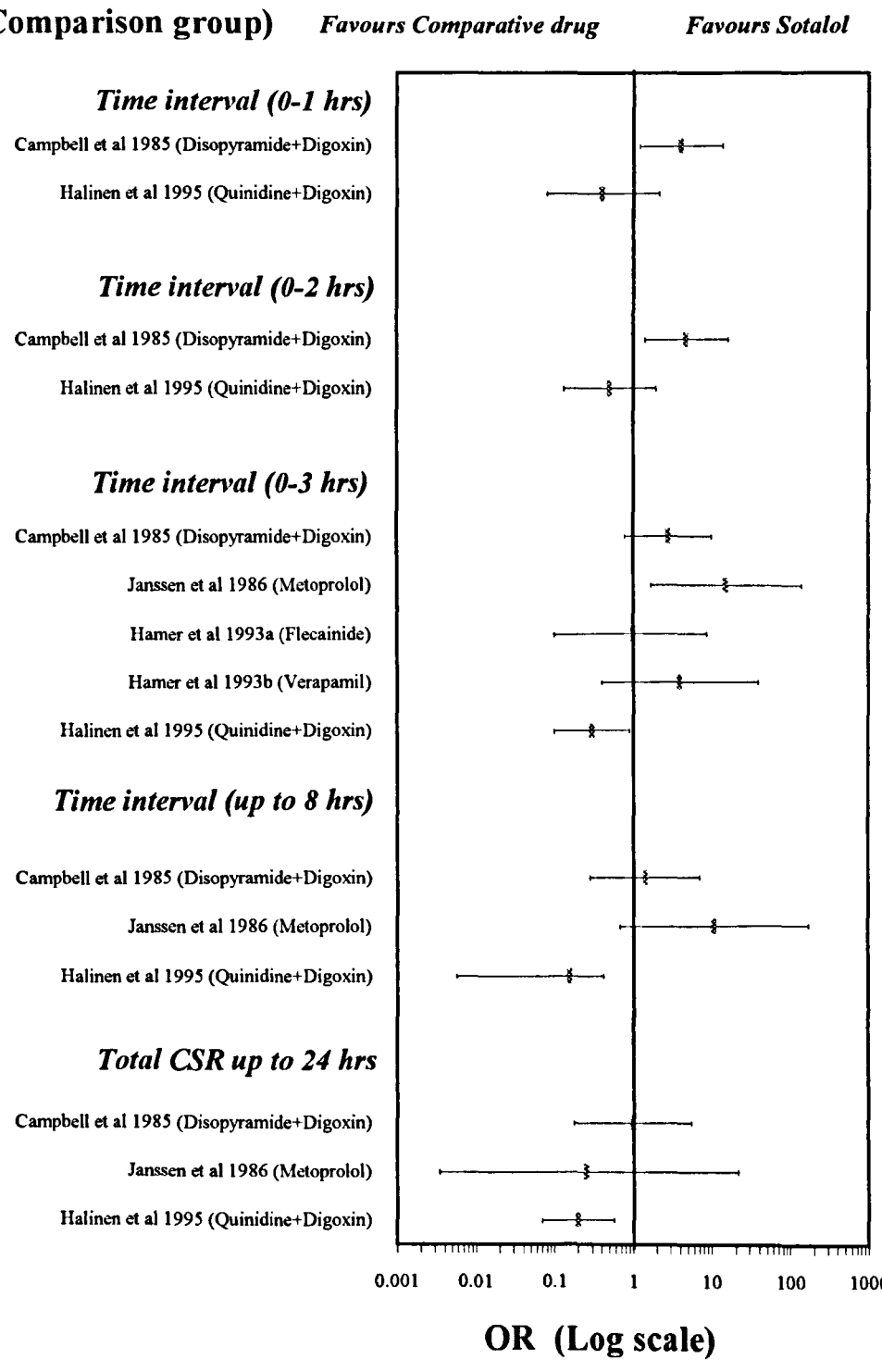

Figure 5.6 OR of conversion success rates (CSR) in sotalol treatment groups as compared to direct control groups in RCTs. The results are represented stratified into 3, 8, and 24 hour-intervals.

Table 5.6.3 Results of conversion success rate in individual clinical trials (randomised and uncontrolled) of Sotalol

Trial	No. of patients randomised (Rx/Control)	CSR at ≤ 3 h; (N)		OR_{Peto} (95% CI)	CSR at ≤ 8 h (N)		OR_{Peto} (95% CI)	CSR at ≤ 24 h (N)		OR_{Peto} (95% CI)
		Rx	Control		Rx	Control		Rx	Control	
Campbell *et al.* 1985	20/20 D+Dig	15/20	10/20	2.83 (0.8-10)	17/20	16/20	1.4 (0.28-7.02)	17/20	17/20 D+Dig	1 (0.2-5.6)
Teo *et al.* 1985§	29	16/29	-	-	-	-	-	19/29	-	-
Levy *et al.* 1986	23/23 PL	7/23	0/23	10.1 (2-49.4)	-	-	-	-	-	-
Janssen *et al.* 1986	11/4 MT	8/11	0/4	15.3 (1.7-140)	10/11	2/4	10.9 (0.7-172.5)	10/11	4/4 MT	0.26 (0.003-21.5)
Denis *et al.* 1988§	20	8/20	-	-	-	-	-	-	-	-
Jordaens *et al.* 1991	36/22 PL	29/36	3/22	14.3 (5-41)	-	-	-	-	-	-
Hamer *et al.* 1993	6/6 F/6 V	3/6	3/6 F 1/6 V	1 (0.1-8.7) 3.96 (0.4-39.4)	-	-	-	-	-	-
Halinen *et al.* 1995	33/28 Q+Dig	4/33	10/28	0.3 (0.1-0.9)	8/33	20/28	0.15 (0.01-0.4)	16/33	24/28 Q+Dig	0.2 (0.07-0.6)
Sung *et al.* 1995	64/28 PL	38/64	4/28	6.04 (2.5-14.6)	-	-	-	-	-	-
Pooled rates (%) in RCTs; (95% CI)		49.6% (43.7-55.5)	Others#; 38.2% (26-50) PL; 14% (4.4-23.6)		75.3% (65.7-84.9)	Others#; 65.2% (54.7-75.8)		67.6% (61.6-73.7)	Others#; 72.7% (61.3-84)	
Pooled rates (%) in Uncont; (95% CI)		48.9% (35-62.7)	-		48.9% (35-62.7)	-		55.5% (42-68.9)	-	
Pooled OR (S vs PL)				8.8			-			-
95% CI for the OR				4.7-16.5			-			-
Z (P)				6.8**			-			-
Q statistic (P)				1.53 (0.5) NS			-			-
Pooled OR (S vs others#)				1.32			0.77			0.62
95% CI for the OR				0.64-2.7			0.43-1.4			0.4-1.1
Z (P)				0.75 (0.05) NS			-0.9 (0.4) NS			-1.8 (0.072) NS
Q statistic (P)				13.9 (0.001)**			3.02 (0.22) NS			3.24 (0.2) NS

CSR; conversion success rate = no. of patients converted to sinus rhythm / no. of patients at risk at the beginning of the interval; §, uncontrolled trials (Uncont); Fle, Flecainide; PL, Placebo; #, including other antiarrhythmic drugs; A, Amiodarone; Dig, Digoxin; D, Disopyramide; Pr, Propafenone; Q, Quinidine; S, Sotalol; V, Verapamil; * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

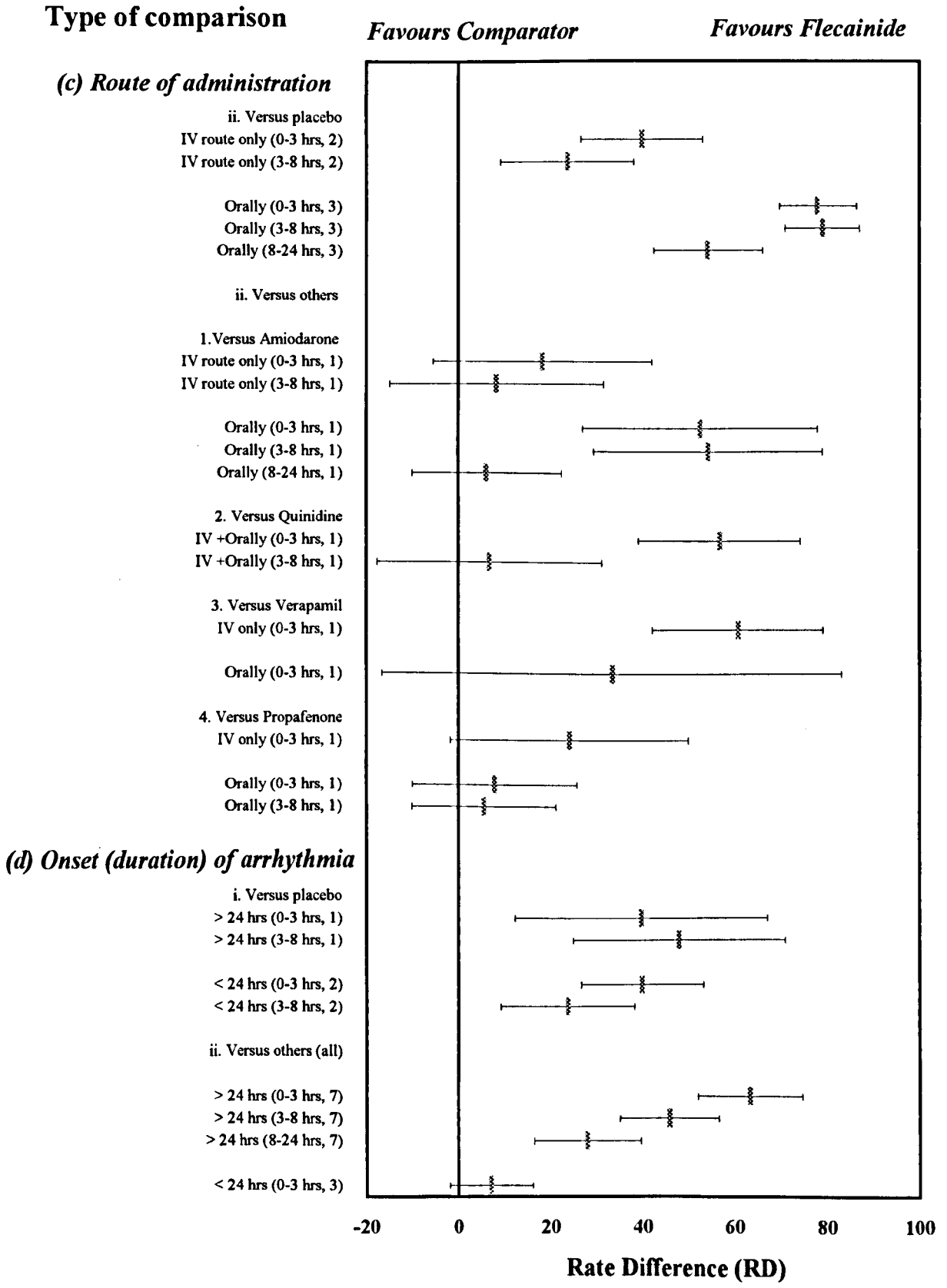

Figure 5.7 Summary of subgroup analyses of Flecainide RCTs (continued). The dark points represent the pooled estimates of subgroups' RDs and bars represent the 95% CI. Time intervals and number of trials in each subgroup are shown in brackets.

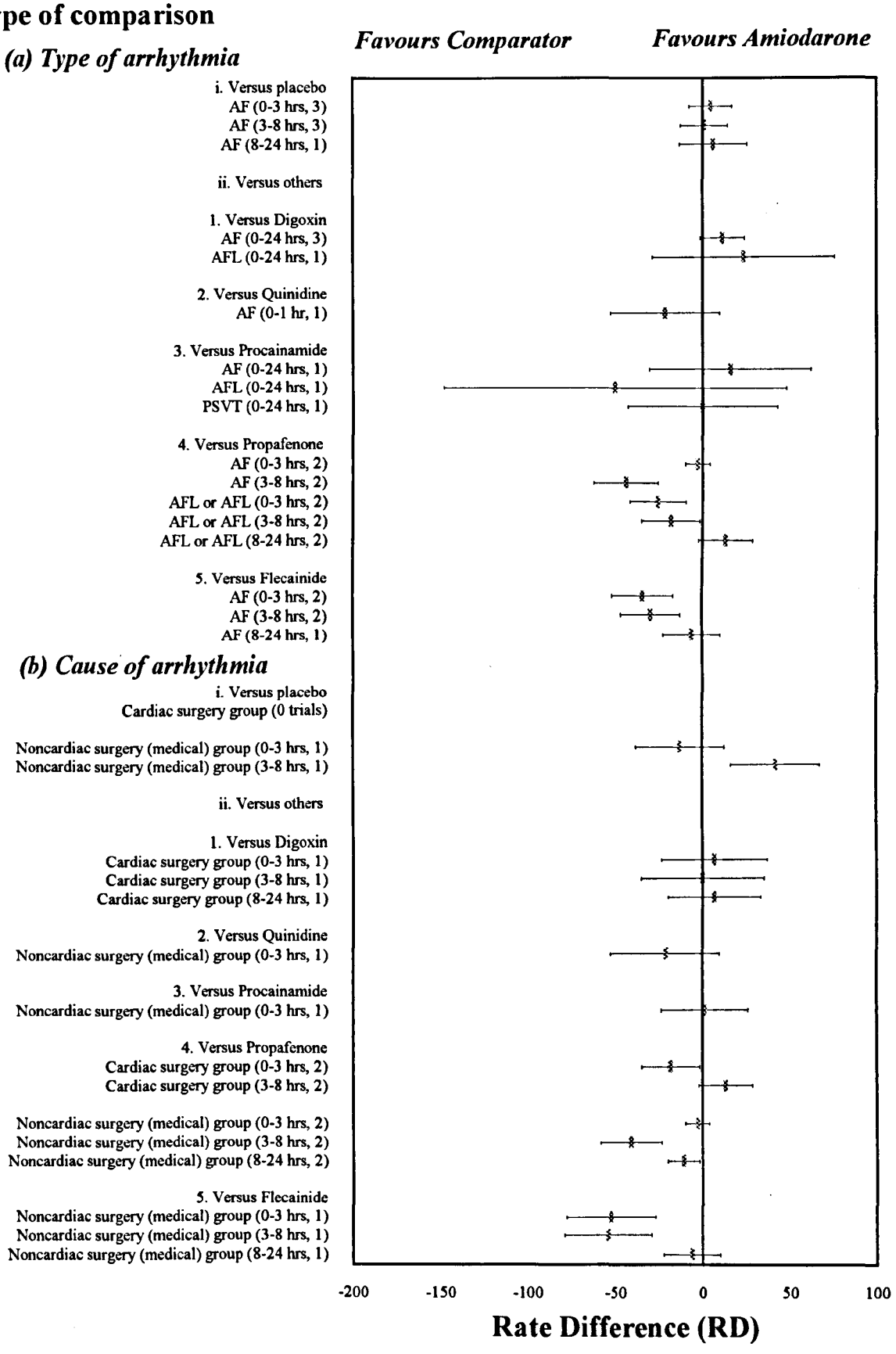

Figure 5.8 Summary of subgroup analyses of amiodarone RCTs. The dark points represent the pooled estimates of subgroups' RDs and bars represent the 95% CI. Time intervals and number of trials in each subgroup are shown in brackets.

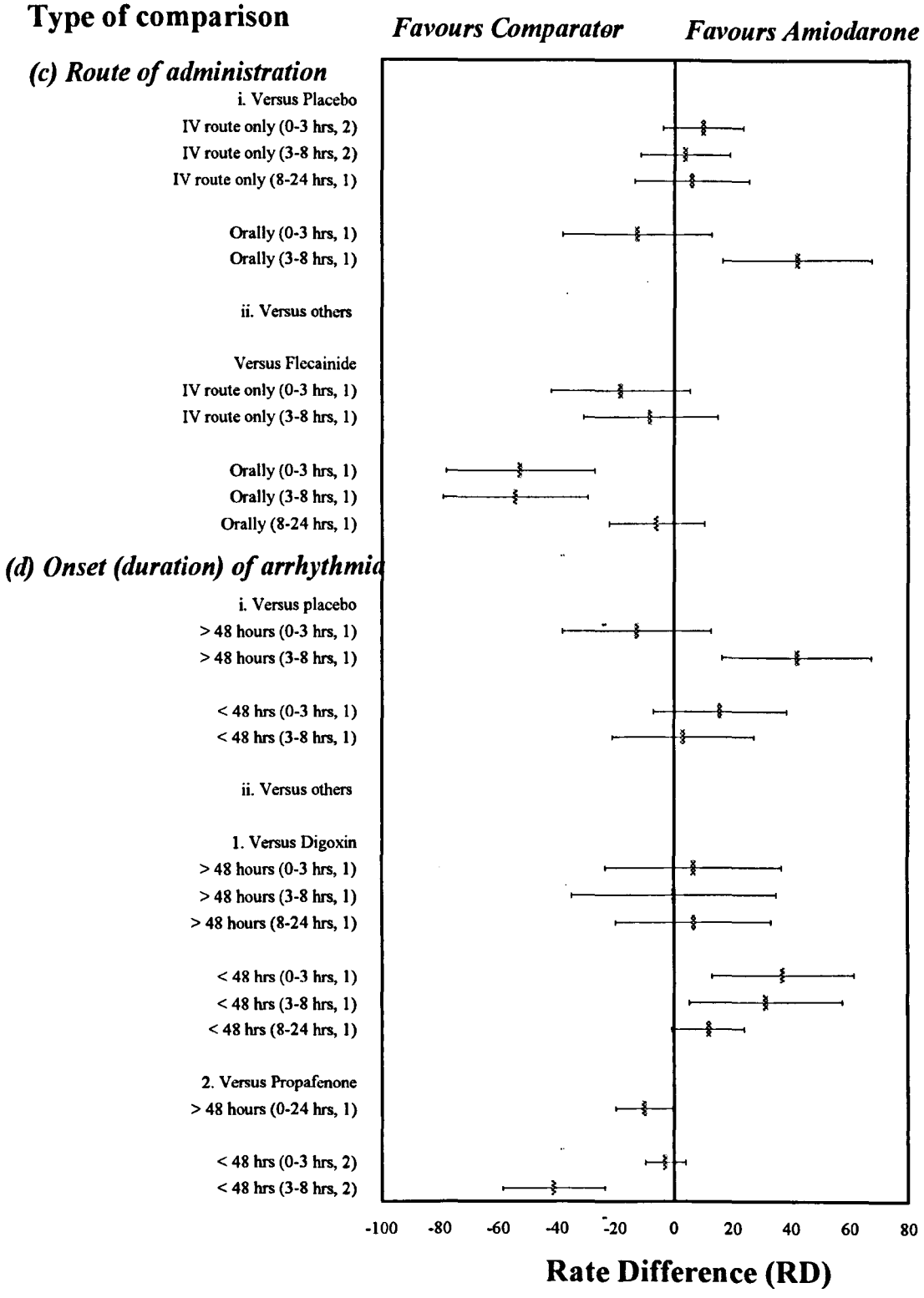

Figure 5.8 Summary of subgroup analyses of amiodarone RCTs (continued). The dark points represent the pooled estimates of subgroups' RDs and bars represent the 95% CI. Time intervals and number of trials in each subgroup are shown in brackets.

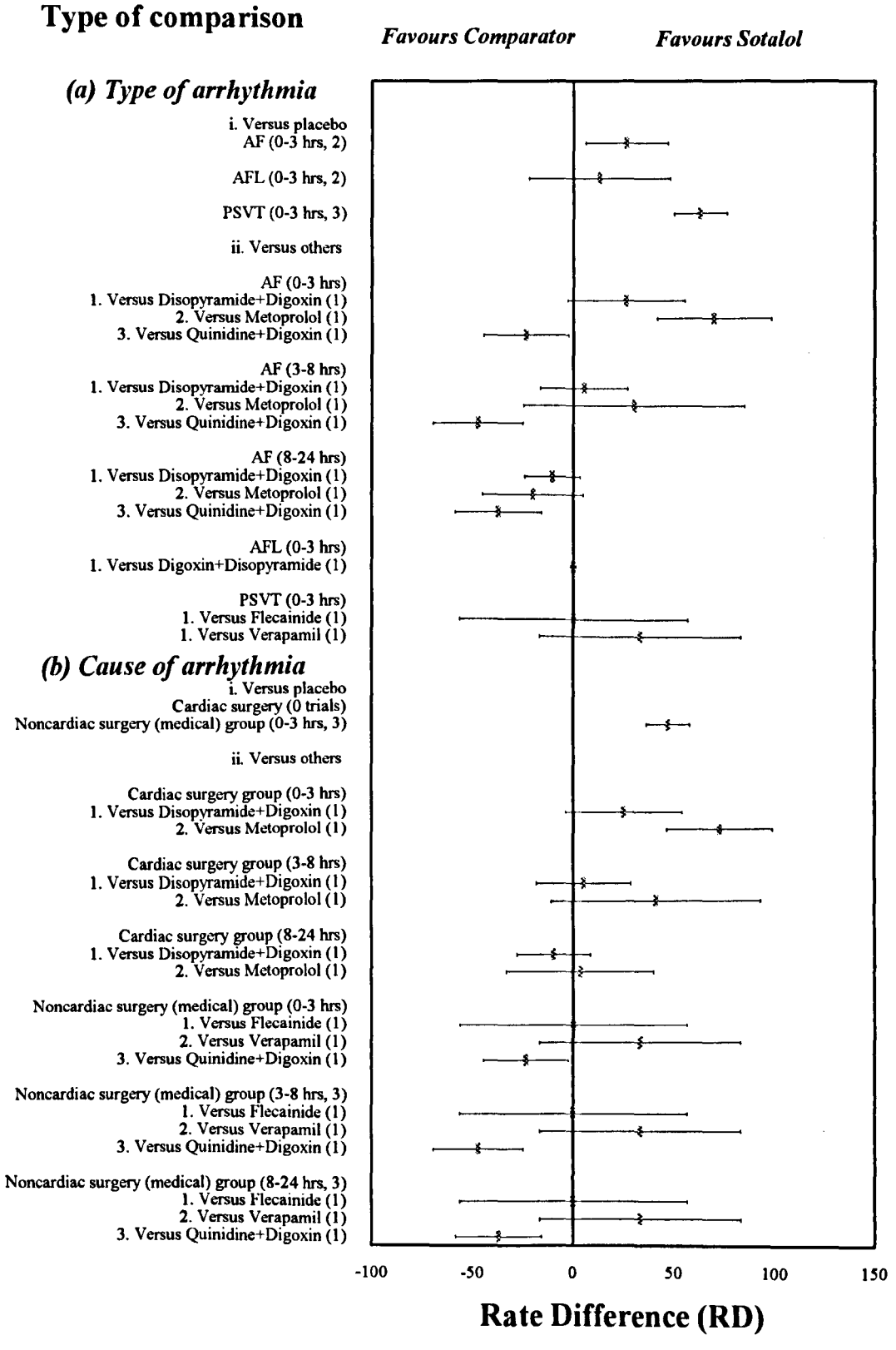

Figure 5.9 Summary of subgroup analyses of sotalol RCTs. The dark points represent the pooled estimates of subgroups' RDs and bars represent the 95% CI. Time intervals and number of trials in each subgroup are shown in brackets.

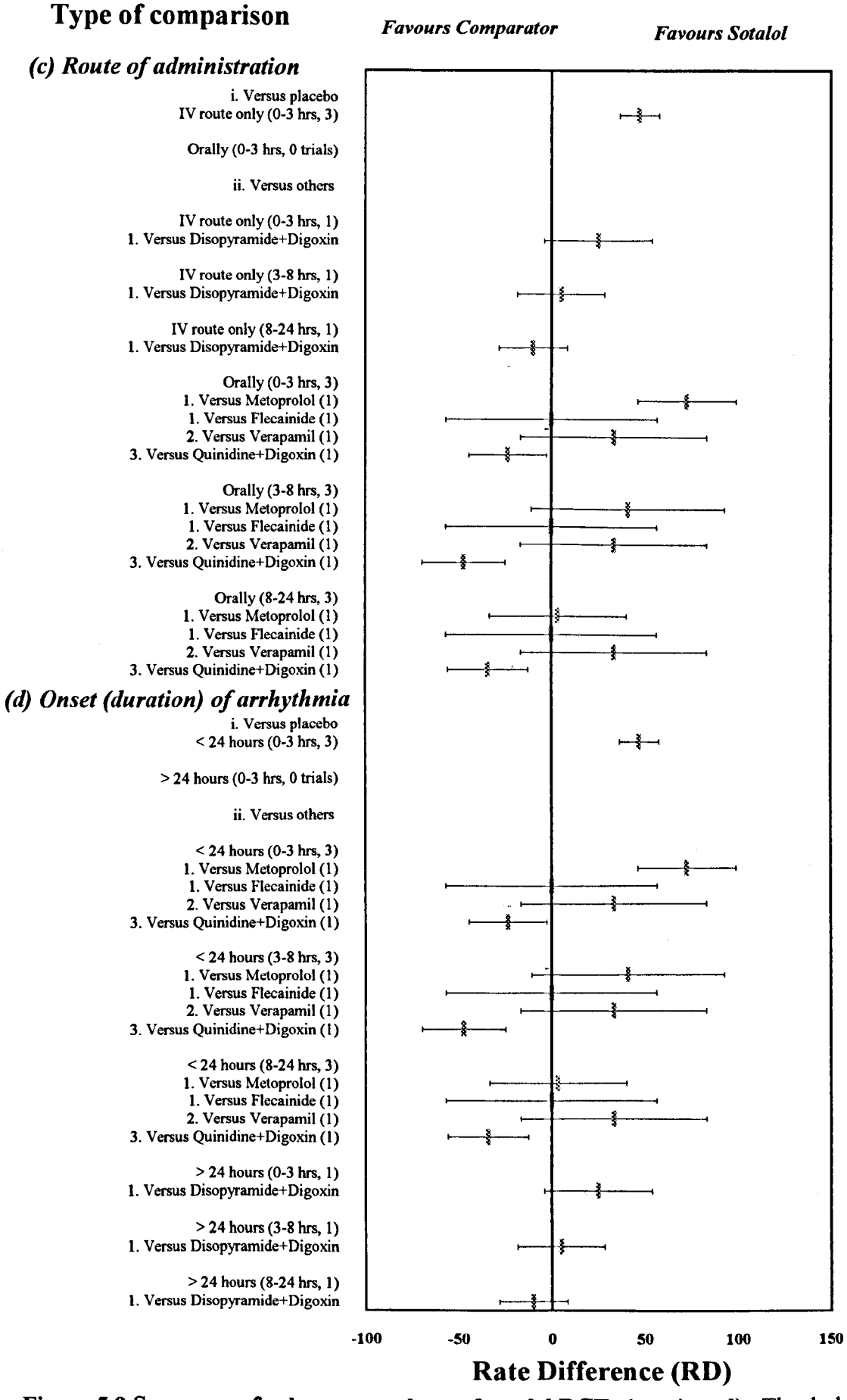

Figure 5.9 Summary of subgroup analyses of sotalol RCTs (continued). The dark points represent the pooled estimates of subgroups' RDs and bars represent the 95% CI. Time intervals and number of trials in each subgroup are shown in brackets.

5.4.3.1.2 Indirect Comparisons

Tables 5.7.1 and 5.7.2 show the weighted pooled percentages of patients converted to sinus rhythm in all treatment arms at any available time point using fixed and random-effects models respectively. Figure 5.10.1 displays the indirect comparison between the three drugs and placebo up to one hour, which has shown superior effect for flecainide over the other two drugs and placebo under the fixed-effects model. However, under the random-effects model (Figure 5.10.2) sotalol and flecainide were equally effective, and amiodarone was more effective than placebo. The same results were obtained at 10 hours after commencement of treatment (Figure 5.11). At 24 hours, all the drugs were equally effective and superior to placebo (Figure 5.12).

The indirect comparisons stratified by the route of administration has demonstrated equal efficacy of intravenous flecainide and sotalol at 3, 8, and 24 hours (Figure 5.13). In addition, they demonstrated the very low efficacy of intravenous amiodarone (Figure 5.13). However, oral flecainide was more effective than oral sotalol at all the time points (Figure 5.14).

5.4.3.2 Mean Conversion Time

The mean conversion time with its standard error or standard deviation was reported in 22 trials: 10 for flecainide (Goy *et al.*, 1985; Borgeat *et al.*, 1986; Crijns *et al.*, 1988; Suttorp *et al.*, 1989; Suttorp *et al.*, 1990; Villani *et al.*, 1990; Donovan *et al.*, 1991; Capucci *et al.*, 1992; Capucci *et al.*, 1993; Madrid *et al.*, 1993), 7 for amiodarone (Posada *et al.*, 1988; McAlister *et al.*, 1990; Bellandi *et al.*, 1993; Cesar *et al.*, 1994; Treglia *et al.*, 1994; Donovan *et al.*, 1995; Galve *et al.*, 1996), and 5 for sotalol (Campbell *et al.*, 1985; Levy *et al.*, 1986; Janssen *et al.*, 1986; Denis *et al.*, 1988; Halinen *et al.*, 1995). The pooled means of conversion time for flecainide, amiodarone, and sotalol were 120.6±11.3, 315.6±33.3, and 27.2±5.3 minutes respectively, thus, indicating more rapid effect for sotalol.

Table 5.7.1 Weighted pooled percentages in different treatment groups in RCTs included in meta-analysis calculated using fixed-effects model

Time interval	*P_T. Placebo (SE)*	*P_T. Flecainide (SE)*	*P_T. Quinidine (SE)*	*P_T. Sotalol (SE)*	*P_T. Amiodarone (SE)*	*P_T. Propafenone (SE)*	*P_T. Q+A (SE)*	*P_T. D+Dig (SE)*	*P_T. VRRA (SE)*
0-2 mins	0	1.6 (0.6)	0	0	0	0	0	0	0
2-5 mins	0	1.79 (0.6)	0	1.5 (0.8)	0	0	0	0	0
6 mins	0	1.79845 (0.6)	0	1.5 (0.8)	0	0	0	0	0
7 mins	0	1.81 (0.6014)	0	1.5 (0.8)	0	0	0	0	0
10 mins	0	1.89237 (0.61)	0	1.544 (0.78)	1.4484(5.95)	0	0	0	0
12 mins	0	1.89237 (0.61)	0	1.5598 (0.78)	1.44845 (5.95)	0	0	0	0
13 mins	0	1.89237 (0.61)	0	1.5598 (0.78)	1.46986 (0.598)	0	0	0	0
15 mins	0	1.983 (0.61)	0	1.59997 (0.79)	1.46986 (0.598)	0	0	0	0
16 mins	0	1.983 (0.61)	0	1.6 (0.79)	1.46986 (0.598)	0	0	0	0
18.2 mins	0	1.983 (0.61)	0	1.63 (0.79)	1.46986 (0.598)	0	0	0	0
22.2 mins	0	2.03 (0.61)	0	1.64 (0.79)	1.533 (0.61)	0	0	0	0
26 mins	0	2.03 (0.61)	0	1.66 (0.8)	1.533 (0.61)	0	0	0	0
27 mins	0	2.03 (0.61)	0	1.67 (0.8)	1.533 (0.61)	0	0	0	0
30 mins	1.9959 (0.96)	2.35 (0.64)	0	8.6 (1.33)	1.954 (0.65)	0	0	0	0
45 mins	1.9959 (0.96)	3.899 (0.72)	0	8.6 (1.33)	2.068 (0.656)	0	0	0	1.58931 (1.14)
50 mins	1.9959 (0.96)	3.92 (0.72)	0	8.6 (1.33)	2.068 (0.656)	0	0	0	1.58931 (1.14)
1 hr	2.045 (0.962)	15.32 (1.2)	1.54 (0.9)	37.3 (2.5)	5.18 (0.95)	1.213 (0.62)	7.1 (6.9)	3.403 (2.51)	1.58931 (1.14)
1.5 hr	2.045 (0.962)	15.32 (1.2)	1.54 (0.9)	38.2 (2.5)	5.23 (0.95)	1.213 (0.62)	7.1 (6.9)	3.403 (2.51)	1.58931 (1.14)
2 hrs	2.084 (0.96)	16.19 (1.207)	8.7 (1.9)	48.1 (2.8)	13.54 (1.5)	1.928 (0.63)	28.6 (12.1)	3.55 (2.52)	9.37 (2.6)
2.5 hrs	2.084 (0.96)	16.19 (1.207)	8.7 (1.9)	48.1 (2.8)	13.64 (1.45)	1.928 (0.63)	28.6 (12.1)	3.55 (2.52)	9.37 (2.6)
2.7 hrs	2.084 (0.96)	22.34 (1.24)	8.7 (1.9)	48.1 (2.8)	14.1 (1.45)	1.928 (0.63)	28.6 (12.1)	3.55 (2.52)	9.37 (2.6)
3 hrs	8.2 (1.8)	66.73 (2.1)	9.3 (1.93)	49.5 (2.8)	16.94 (1.56)	2.44 (0.683)	35.7 (12.8)	37.41 (6.91)	10.8 (2.8)
4 hrs	8.348 (1.84)	67.24 (2.05)	10.88 (2)	54.6 (2.8)	18.21 (1.57)	2.44 (0.683)	42.9 (13.2)	53.31 (7.23)	11 (2.8)
5 hrs	8.54 (1.84)	67.59 (2.042)	11.5 (2)	54.6 (2.8)	26.7 (1.87)	2.73 (0.71)	42.9 (13.2)	58.4 (7)	11.6 (2.8)
6 hrs	9.15 (1.85)	69.82 (2)	13.6 (2)	58.2 (2.7)	27.4 (1.88)	2.73 (0.71)	42.9 (13.2)	62.3 (7)	16.9 (3.1)
7 hrs	9.15 (1.85)	70.2 (2)	14 (2.03)	59.4 (2.8)	27.84 (1.87)	2.73 (0.71)	42.9 (13.2)	66.9 (6.8)	16.9 (3.1)
8 hrs	11.1 (1.9)	74.4 (1.9)	14 (2.03)	60.4 (2.8)	29.66 (1.89)	3.14 (0.71)	42.9 (13.2)	71.8 (6.4)	17.4 (3.1)
8.20 hrs	11.1 (1.9)	74.4 (1.9)	53.3 (3.72)	60.4 (2.8)	29.66 (1.89)	3.14 (0.71)	42.9 (13.2)	71.8 (6.4)	17.4 (3.1)
9 hrs	11.1 (1.9)	74.7 (1.89)	56.82 (3.7)	61.8 (2.8)	29.66 (1.89)	3.14 (0.71)	50 (13.4)	71.8 (6.4)	17.4 (3.1)
10 hrs	11.1 (1.9)	74.7 (1.89)	61 (3.52)	61.8 (2.8)	29.87 (1.888)	24.14 (0.62)	50 (13.4)	81.4 (5.7)	18.96 (3.1)
11 hrs	11.1 (1.9)	74.95 (1.9)	-	62.3 (2.8)	29.87 (1.888)	24.14 (0.62)	-	85.1 (5.2)	18.96 (3.1)

Table 5.7.1 Weighted pooled percentages in different treatment groups in RCTs included in meta-analysis calculated using fixed-effects model (continued)

Time interval	*P_C. Placebo (SE)*	*P_T. Flecainide (SE)*	*P_T.Quinidine (SE)*	*P_T.Sotalol (SE)*	*P_T. Amiodarone (SE)*	*P_T Propafenone (SE)*	*P_T. Q+A (SE)*	*P_T. D+Dig (SE)*	*P_T. VRRA (SE)*
12 hrs	11.1 (1.9)	78.27 (1.77)	-	62.3 (2.8)	32.1 (1.88)	24.14 (0.62)	-	87.5 (4.8)	20 (3.11)
13 hrs	11.1 (1.9)	78.27 (1.77)	-	62.8 (2.8)	32.41 (1.88)	24.14 (0.62)	-	87.5 (4.8)	20 (3.11)
14 hrs	11.1 (1.9)	78.52 (1.77)	-	62.8 (2.8)	32.41 (1.88)	24.14 (0.62)	-	87.5 (4.8)	20 (3.11)
16 hrs	11.1 (1.9)	78.86 (1.77)	-	63.2 (2.8)	32.41 (1.88)	24.14 (0.62)	-	87.5 (4.8)	24.2 (3.04)
17 hrs	11.1 (1.9)	78.86 (1.77)	-	63.9 (2.8)	32.41 (1.88)	24.14 (0.62)	-	87.5 (4.8)	24.2 (3.04)
18 hrs	11.1 (1.9)	79.34 (1.75)	-	64.63 (2.8)	32.41 (1.88)	24.14 (0.62)	-	87.5 (4.8)	24.2 (3.04)
19 hrs	14.5 (2.18)	79.45 (1.75)	-	64.63 (2.8)	32.41 (1.88)	24.14 (0.62)	-	89.4 (4.5)	24.2 (3.04)
20 hrs	-	79.45 (1.75)	-	64.63 (2.8)	33.2 (1.87)	24.14 (0.62)	-	92.6 (3.8)	21.5 (3.1)
24 hrs	-	79.9 (1.7)	-	66.4 (2.8)	68.6 (2.152)	24.423 (0.62)	-	93.8 (3.5)	25.9 (3)
25 hrs	-	80 (1.7)	-	-	68.6 (2.2)	24.423 (0.62)	-	93.8 (3.5)	-
26 hrs	-	80.13 (1.7)	-	-	68.6 (2.2)	24.423 (0.62)	-	93.8 (3.5)	-
29 hrs	-	-	-	-	68.6 (2.2)	24.423 (0.62)	-	99.4 (1.14)	-
48 hrs	-	-	-	-	69.7 (2.1)	24.494 (0.62)	-	99.4 (1.14)	-
32 hrs	-	-	-	-	85.5 (1.5)	-	-	99.4 (1.14)	-
72 hrs	-	-	-	-	-	-	-	99.6 (0.94)	-
Q statistic for P_T (P)	21.7 (<0.0013)**	59.6 (0)**	28 (0)**	43 (0)**	52.7 (0)**	3.9 (0.6)	-	0 (1)	90 (0)
Total No.of trials	7	16	5	9	13	6	1	2	6
Total No. of pts (events/total included)	57/205	342/468	93/164	150/242	256/402	115/255	7/14	46/47	44/120
RD vs Placebo (%) (95% CI)	-	51.3 (47.5-55)** RE; 47.5 (40.2-54.7)**	33.7 (26-41.2)** RE; 33.9 (15.6-52.4)**	38.6 (32.7-44.6)** 36 (22.7-49.5)**	40.2 (35.5-44.95)** RE; 37 (26.7-47.3)**	26.5 (22.7-30.4)** RE; 34 (-10.2-78.2) NS	22.5 (-4.4-49) NS	71.4 (66-76.8)**	0.42 (-6.2-7) NS RE; 9.2 (-17.9-36.4) NS

P_T, meta-analytic pooled percentage of patients converted to sinus rhythm; Fle, Flecainide; PL, Placebo; #, including other antiarrhythmic drugs; A, Amiodarone; Dig, Digoxin; D, Disopyramide; Pr, Propafenone; Q, Quinidine; S, Sotalol; V, Verapamil; * statistically significant (P<0.05); ** highly statistically significant (P<0.01); RE, random-effects model

Table 5.7.2 Weighted pooled percentages in different treatment groups in RCTs included in meta-analysis calculated using random-effects model

Time interval	P_C. *Placebo (SE)*	P_T. *Flecainide (SE)*	P_T *.Quinidine (SE)*	P_T *.Sotalol (SE)*	P_T. *Amiodarone (SE)*	P_T *Propafenone (SE)*	P_T. *Q+A (SE)*	P_T. *D+Dig (SE)*	P_T. *VRRA (SE)*
0-2 mins	0	1.6 (0.6)	0	0	0	0	0	0	0
2-5 mins	0	1.79 (0.6)	0	1.5 (0.8)	0	0	0	0	0
6 mins	0	1.79845 (0.6)	0	1.5 (0.8)	0	0	0	0	0
7 mins	0	1.81 (0.6014)	0	1.5 (0.8)	0	0	0	0	0
10 mins	0	2.77 (1.016)	0	1.544 (0.78)	1.4484(5.95)	0	0	0	0
12 mins	0	2.77 (1.016)	0	1.5598 (0.78)	1.44845 (5.95)	0	0	0	0
13 mins	0	2.77 (1.016)	0	1.5598 (0.78)	1.46986 (0.598)	0	0	0	0
15 mins	0	3.83 (1.34)	0	1.59997 (0.79)	1.46986 (0.598)	0	0	0	0
16 mins	0	3.83 (1.34)	0	1.6 (0.79)	1.46986 (0.598)	0	0	0	0
18.2 mins	0	3.83 (1.34)	0	1.63 (0.79)	1.46986 (0.598)	0	0	0	0
22.2 mins	0	4.465 (1.4845)	0	1.64 (0.79)	1.533 (0.61)	0	0	0	0
26 mins	0	4.465 (1.4845)	0	1.66 (0.8)	1.533 (0.61)	0	0	0	0
27 mins	0	4.465 (1.4845)	0	1.67 (0.8)	1.533 (0.61)	0	0	0	0
30 mins	1.9959 (0.96)	7.1 (1.887)	0	8.6 (1.33)	4.75 (1.545)	0	0	0	0
45 mins	1.9959 (0.96)	17.492 (3.38)	0	8.6 (1.33)	6.536 (1.885)	0	0	0	1.58931 (1.14)
50 mins	1.9959 (0.96)	17.759 (3.41)	0	8.6 (1.33)	6.536 (1.885)	0	0	0	1.58931 (1.14)
1 hr	2.045 (0.962)	42.09 (7.5)	1.54 (0.94)	37.3 (2.5)	18.16 (3.85)	9.17 (3.26)	7.1 (6.9)	11.546 (11.42)	1.58931 (1.14)
1.5 hr	2.045 (0.962)	42.09 (7.5)	1.54 (0.94)	38.2 (2.5)	18.5 (3.898)	9.17 (3.26)	7.1 (6.9)	11.546 (11.42)	1.58931 (1.14)
2 hrs	5.007 (2.3)	46.524 (7.85)	23.2 (8.95)	48.1 (2.8)	29.33 (5.49)	27.96 (6.55)	28.6 (12.1)	14.18 (13.97)	9.37 (2.6)
2.5 hrs	5.007 (2.3)	46.84 (7.889)	23.2 (8.95)	48.1 (2.8)	29.651 (5.55)	27.96 (6.55)	28.6 (12.1)	14.18 (13.97)	9.37 (2.6)
2.7 hrs	5.007 (2.3)	53.1 (9.74)	23.2 (8.95)	48.1 (2.8)	30.7 (5.83)	27.96 (6.55)	28.6 (12.1)	14.18 (13.97)	9.37 (2.6)
3 hrs	11.796 (3.489)	63.72 (4.25)	27.1 (9.92)	52.613 (9.398)	34.1 (6.4)	38.195 (10.64)	35.7 (12.8)	37.41 (6.91)	10.8 (2.8)
4 hrs	12.7 (3.8)	64.4 (4.187)	32.879 (12.12)	55.376 (9.3)	37.35 (6.87)	38.195 (10.64)	42.9 (13.2)	53.31 (7.23)	11 (2.8)
5 hrs	13.634 (4.14)	64.797 (4.156)	35.999 (13.07)	55.376 (9.3)	38.99 (6.9)	46.74 (17.84)	42.9 (13.2)	58.4 (7)	11.6 (2.8)
6 hrs	16.2 (5.144)	67 (3.959)	42.82 (15.77)	57 (9.15)	40.38 (7.1)	46.74 (17.84)	42.9 (13.2)	62.3 (7)	22.84 (7.67)
7 hrs	16.2 (5.144)	67.4058 (3.859)	43.575 (16.174)	57.48 (8.75)	40.97 (7.2)	46.74 (17.84)	42.9 (13.2)	66.9 (6.8)	22.84 (7.67)
8 hrs	21.77 (6.7)	71.17 (3.87)	43.575 (16.174)	57.92 (8.4)	43.82 (7.53)	51.07 (19.54)	42.9 (13.2)	71.8 (6.4)	24.04 (8.17)
8.20 hrs	21.77 (6.7)	71.17 (3.87)	55.46 (7.68)	57.92 (8.4)	43.82 (7.53)	51.07 (19.54)	42.9 (13.2)	71.8 (6.4)	24.04 (8.17)
9 hrs	21.77 (6.7)	71.41 (3.8665)	58.85 (8.24)	58.77 (7.88)	43.82 (7.53)	51.07 (19.54)	50 (13.4)	71.8 (6.4)	24.04 (8.17)
10 hrs	21.77 (6.7)	71.41 (3.8665)	61.43 (9.64)	58.77 (7.88)	29.87 (1.888)	53.24 (27.562)	50 (13.4)	81.4 (5.7)	26.81 (9.612)
11 hrs	21.77 (6.7)	71.654 (3.8786)	-	59.18 (7.67)	44.28 (7.59)	53.24 (27.562)	-	85.1 (5.2)	26.81 (9.612)

Table 5.7.2 Weighted pooled percentages in different treatment groups in RCTs included in meta-analysis calculated using random-effects model (continued)

Time interval	P_C. *Placebo (SE)*	P_T. *Flecainide (SE)*	P_T *.Quinidine (SE)*	P_T *.Sotalol (SE)*	P_T. *Amiodarone (SE)*	P_T *Propafenone (SE)*	P_T. *Q+A (SE)*	P_T. *D+Dig (SE)*	P_T. *VRRA (SE)*
12 hrs	21.77 (6.7)	73.03 (4.1)	-	59.18 (7.67)	46.5 (8.12)	53.24 (27.562)	-	87.5 (4.8)	30.1 (10.25)
13 hrs	21.77 (6.7)	73.03 (4.1)	-	59.59 (7.49)	46.8 (8.197)	53.24 (27.562)	-	87.5 (4.8)	30.1 (10.25)
14 hrs	21.77 (6.7)	73.391 (3.962)	-	59.59 (7.49)	46.8 (8.197)	53.24 (27.562)	-	87.5 (4.8)	30.1 (10.25)
16 hrs	21.77 (6.7)	73.92 (3.815)	-	59.99 (7.34)	46.8 (8.197)	53.24 (27.562)	-	87.5 (4.8)	33.18 (12.9)
17 hrs	21.77 (6.7)	73.92 (3.815)	-	60.776 (7.1)	46.8 (8.197)	53.24 (27.562)	-	87.5 (4.8)	33.18 (12.9)
18 hrs	21.77 (6.7)	74.2 (3.84)	-	61.535 (6.89)	46.8 (8.197)	53.24 (27.562)	-	87.5 (4.8)	33.18 (12.9)
19 hrs	25.9 (7.57)	74.35 (3.8)	-	61.535 (6.89)	46.8 (8.197)	53.24 (27.562)	-	89.4 (4.5)	33.18 (12.9)
20 hrs	-	74.35 (3.8)	-	61.535 (6.89)	47.83 (8.374)	53.24 (27.562)	-	92.6 (3.8)	31.62 (11.3)
24 hrs	-	74.92 (3.696)	-	63.566 (6.765)	65.13 (4.89)	60.24 (27.61)	-	93.8 (3.5)	36.694 (13.67)
25 hrs	-	75.1 (3.7)	-	-	65.13 (4.89)	60.24 (27.61)	-	93.8 (3.5)	-
26 hrs	-	75.26 (3.64)	-	-	65.13 (4.89)	60.24 (27.61)	-	93.8 (3.5)	-
29 hrs	-	-	-	-	65.13 (4.89)	60.24 (27.61)	-	99.4 (1.14)	-
48 hrs	-	-	-	-	66.75 (4.68)	61.47 (27.598)	-	99.4 (1.14)	-
32 hrs	-	-	-	-	85.45 (1.5)	-	-	99.4 (1.14)	-
72 hrs	-	-	-	-	-	-	-	99.6 (0.94)	-
Total No.of trials	7	16	5	9	13	6	1	2	6
Total No. of pts (events/total included)	57/205	342/468	93/164	150/242	256/402	115/255	7/14	46/47	44/120

P_T, meta-analytic pooled percentage of patients converted to sinus rhythm; Fle, Flecainide; PL, Placebo; #, including other antiarrhythmic drugs; A, Amiodarone; Dig, Digoxin; D, Disopyramide; Pr, Propafenone; Q, Quinidine; S, Sotalol; V, Verapamil; * statistically significant (P<0.05); ** highly statistically significant (P<0.01); RE, random-effects model

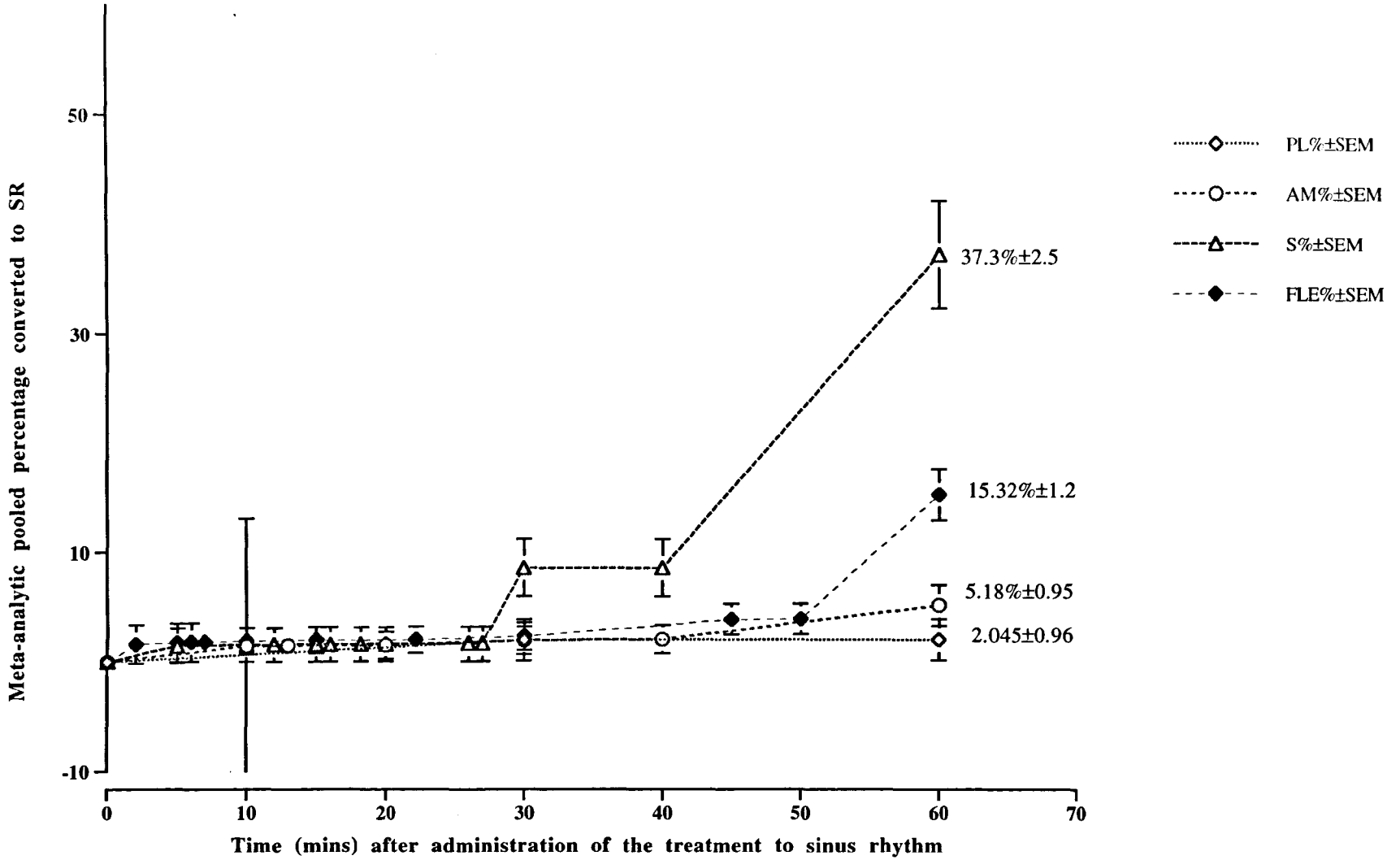

Figure 5.10.1 Indirect comparison of the efficacy of flecainide, amiodarone, sotalol, quinidine, and placebo treatment arms for acute conversion to sinus rhythm within 1 hour (Fixed-effects model): the figure depicts the weighted percentages (probabilities) of patients converted to sinus rhythm at each follow-up time point during the first hour after administration of treatment. The error bars show the 95% confidence intervals (=1.96.SEM).

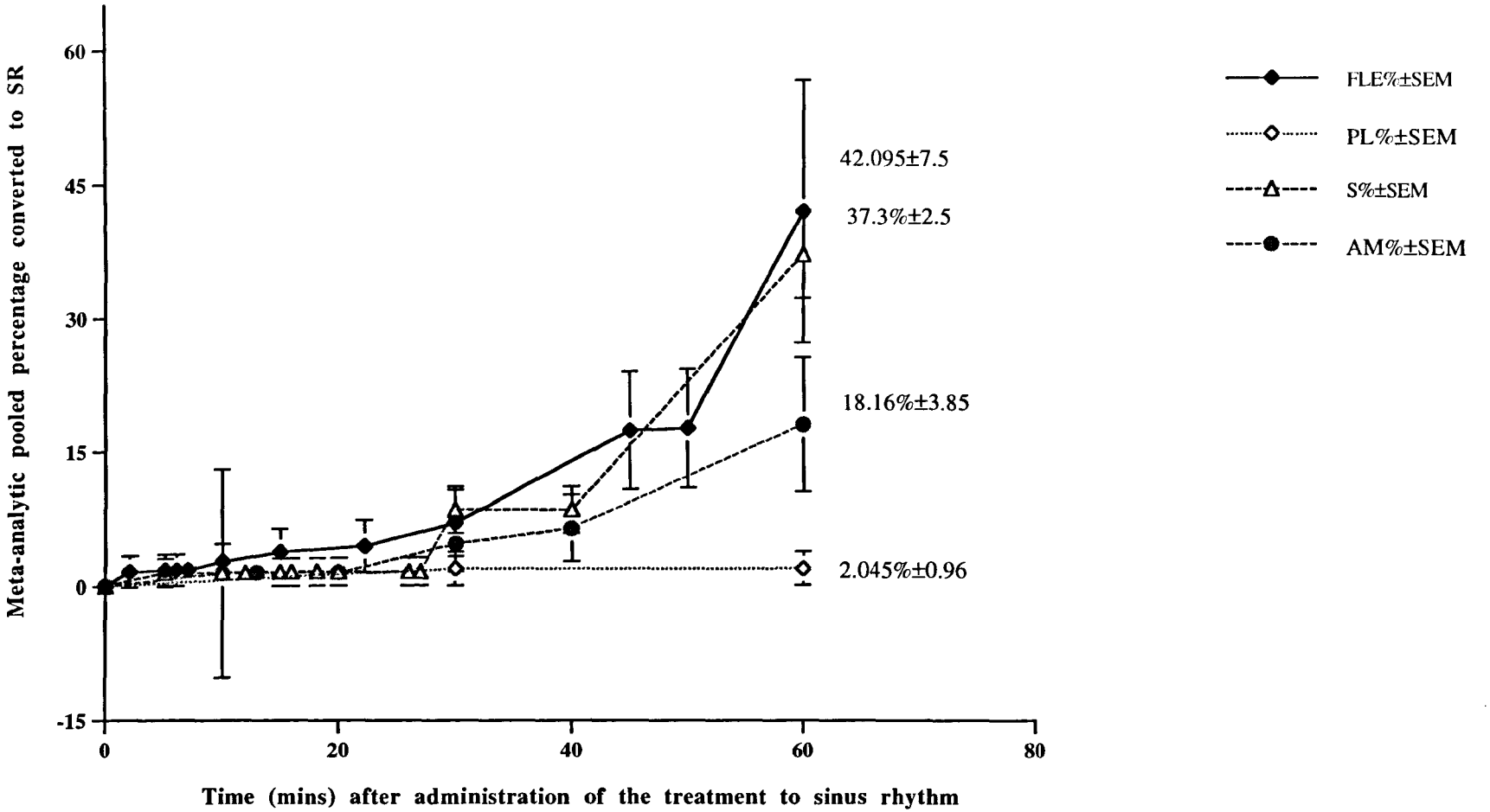

Figure 5.10.2 Indirect comparison of the efficacy of flecainide, amiodarone, sotalol, quinidine, and placebo treatment arms for acute conversion to sinus rhythm within 1 hour (Random-effects model): the figure depicts the weighted percentages (probabilities) of patients converted to sinus rhythm at each follow-up time point during the first hour after administration of treatment. The error bars show the 95% confidence intervals (=1.96.SEM).

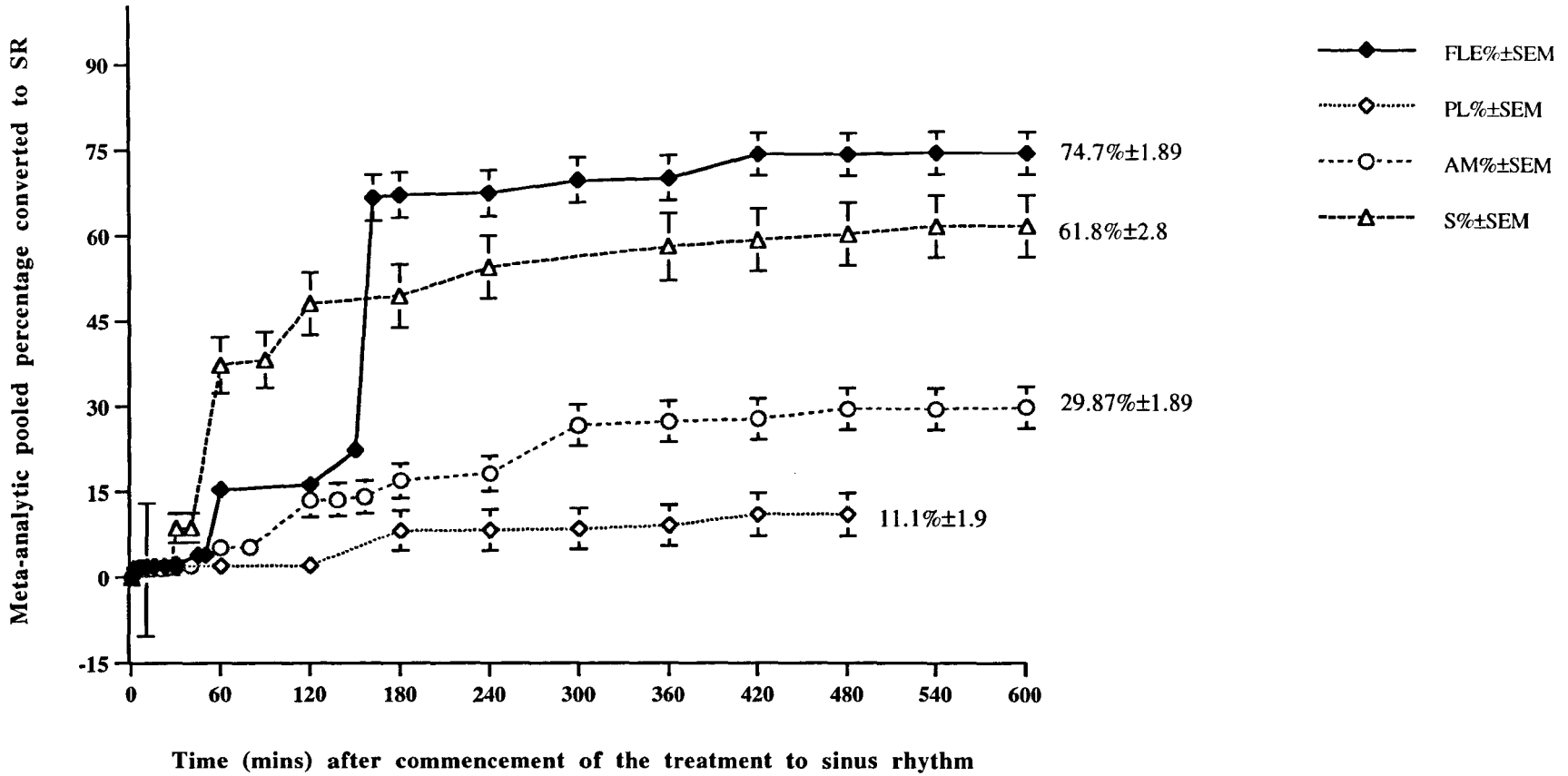

Figure 5.11 Indirect comparison of the efficacy of flecainide, amiodarone, sotalol, and placebo treatment arms for acute conversion to sinus rhythm during the 10 hours after commencement of treatment (Fixed-effects model): the figure depicts the weighted percentages (probabilities) of patients converted to sinus rhythm at each follow-up time point during the 10 hours after administration of treatment. The error bars show the 95% confidence intervals (=1.96.SEM). The P values shown next to legands express the significance of the absolute effect of each treatment arm as compared to placebo.

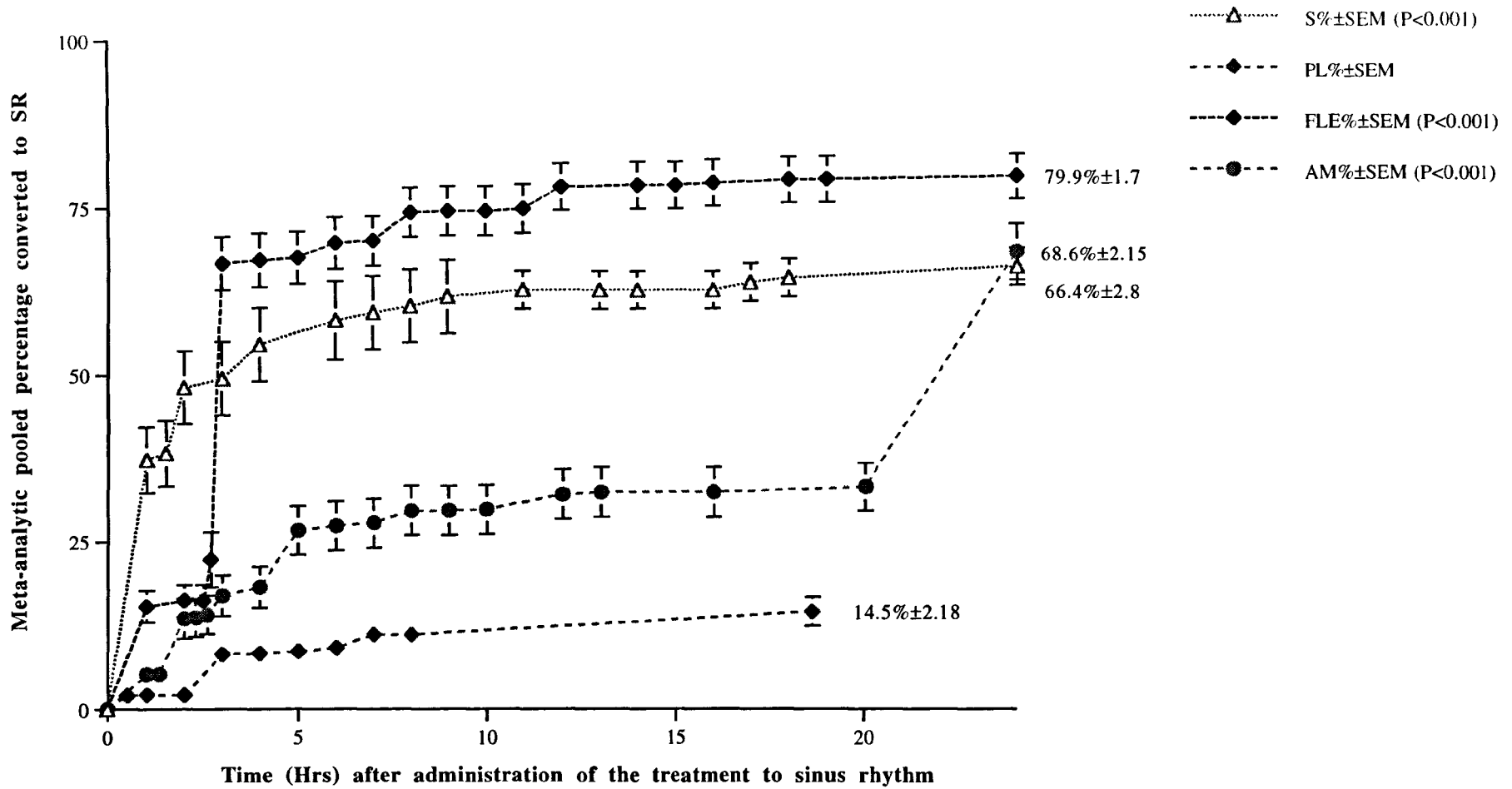

Figure 5.12 Indirect comparison of the efficacy of flecainide, amiodarone, sotalol, and placebo treatment arms for acute conversion to sinus rhythm during 24 hours (Fixed-effects model): the figure depicts the weighted percentages (probabilities) of patients converted to sinus rhythm at each follow-up time point during the 24 hours after administration of treatment. The error bars show the 95% confidence intervals (=1.96.SEM). The P values shown next to legands express the significance of the absolute effect of each treatment arm as compared to placebo.

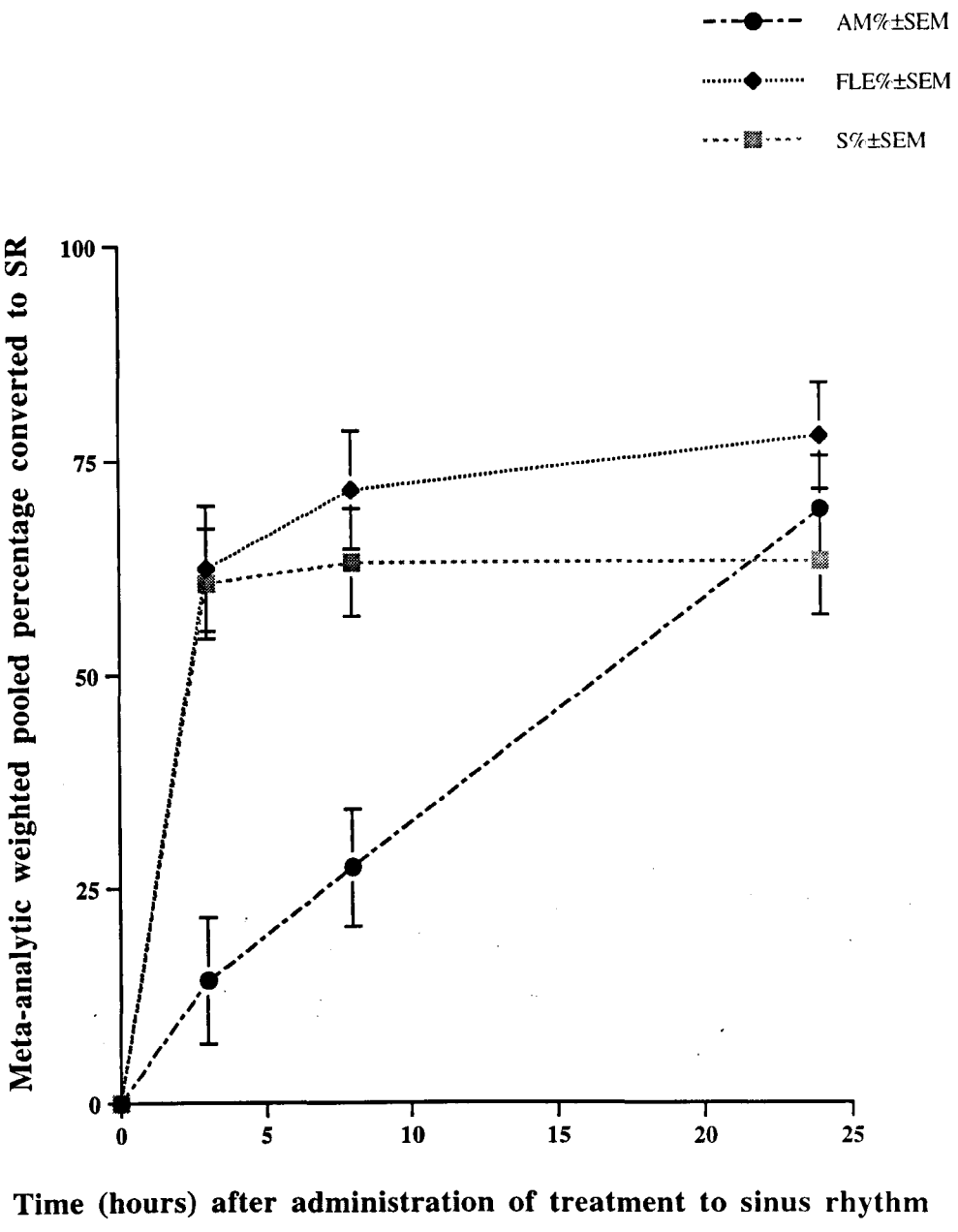

Figure 5.13 Indirect comparison of intravenous flecainide, sotalol, and amiodarone treatment arms in all trial designs for conversion to SR (Fixed-effects model). The figure depicts the weighted percentage (probabilities) of patients converted to sinus rhythm at 3, 8, and 24 hours. The error bars show the 95% CI (=1.96.SEM).

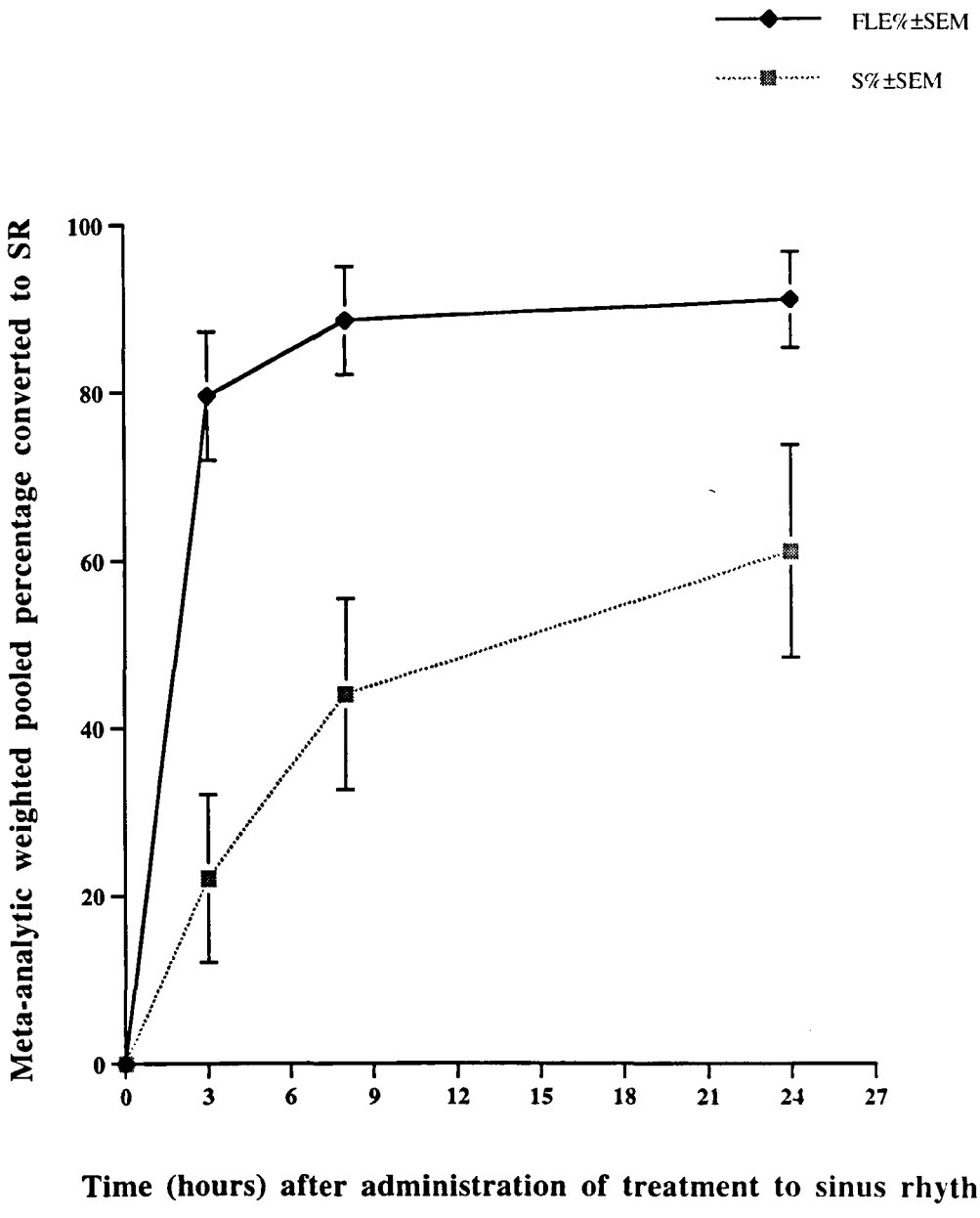

Figure 5.14 Indirect comparison of oral flecainide, and sotalol treatment arms in all trial designs for conversion to SR (Fixed-effects model). The figure depicts the weighted percentage (probabilities) of patients converted to sinus rhythm at 3, 8, and 24 hours. The error bars show the 95% CI (=1.96.SEM).

5.4.3.3 Effect on Ventricular Response

Figure 5.15.1 displays the pooled weighted mean effects of placebo, flecainide, sotalol and amiodarone on the ventricular rate, compared to the baseline. For the placebo treatment arm, data regarding the ventricular rate in converted and nonconverted patients was reported in 3 trials. Pooling the data did not show statistically significant change from baseline during the 8 hours in converted and unconverted patients.

For converted patients in the flecainide treatment group, the pooled mean decrease in the ventricular rate (from 5 trials) was statistically significant (dmean = -9.12; 95% CI, -2 to -16.2) at 1 and 2 hours, and reached clinically significant limits at 3 hours (dmean = -17.7; 95% CI, -4.8 to -26.6). This remained significant throughout the 24 hours (>20 beats/min decrease). Furthermore, for unconverted patients, the mean ventricular rate slowed significantly after 1 hour and remained significant up to the end of the 24 hours (dmean = -19; 95% CI, -32.2 to -5.8).

For sotalol, the data was only available from one trial for converted patients (Levy *et al.*, 1986) and one for unconverted (Sung *et al.*, 1995), and the change was not statistically significant at any time point.

For amiodarone, the mean treatment effect was statistically and clinically significant compared to the baseline after 1 hour in converted (dmean = -26.5; 95% CI, -46.5 to -6.5; Z = 2.6), as well as unconverted patients (dmean = -28.6; 95% CI, -50 to -7; Z = 2.6).

Pooling the data from two verapamil trials did not show any statistically significant effect compared to the baseline, either in converted (dmean = -13.2; 95% CI, 2.8 to-29; Z = 1.6) or in nonconverted (dmean = -53.5; 95% CI, 0.5 to -107; Z = 1.9) (Figure 5.15.2). The same results were obtained for propafenone.

A direct comparison with placebo was performed in six trials; two for flecainide (Capucci *et al.*, 1992; Donovan *et al.*, 1995), two for sotalol (Levy *et al.*, 1986; Sung *et al.*, 1995), and two for amiodarone (Capucci *et al.*, 1992; Donovan *et al.*, 1995). As shown in Figure 5.16, the effect size of flecainide versus placebo was not statistically significant at any time point for both converted and unconverted patients. For a sotalol trial with 23 patients (Levy *et al.*, 1986), the effect size in all patients was statistically

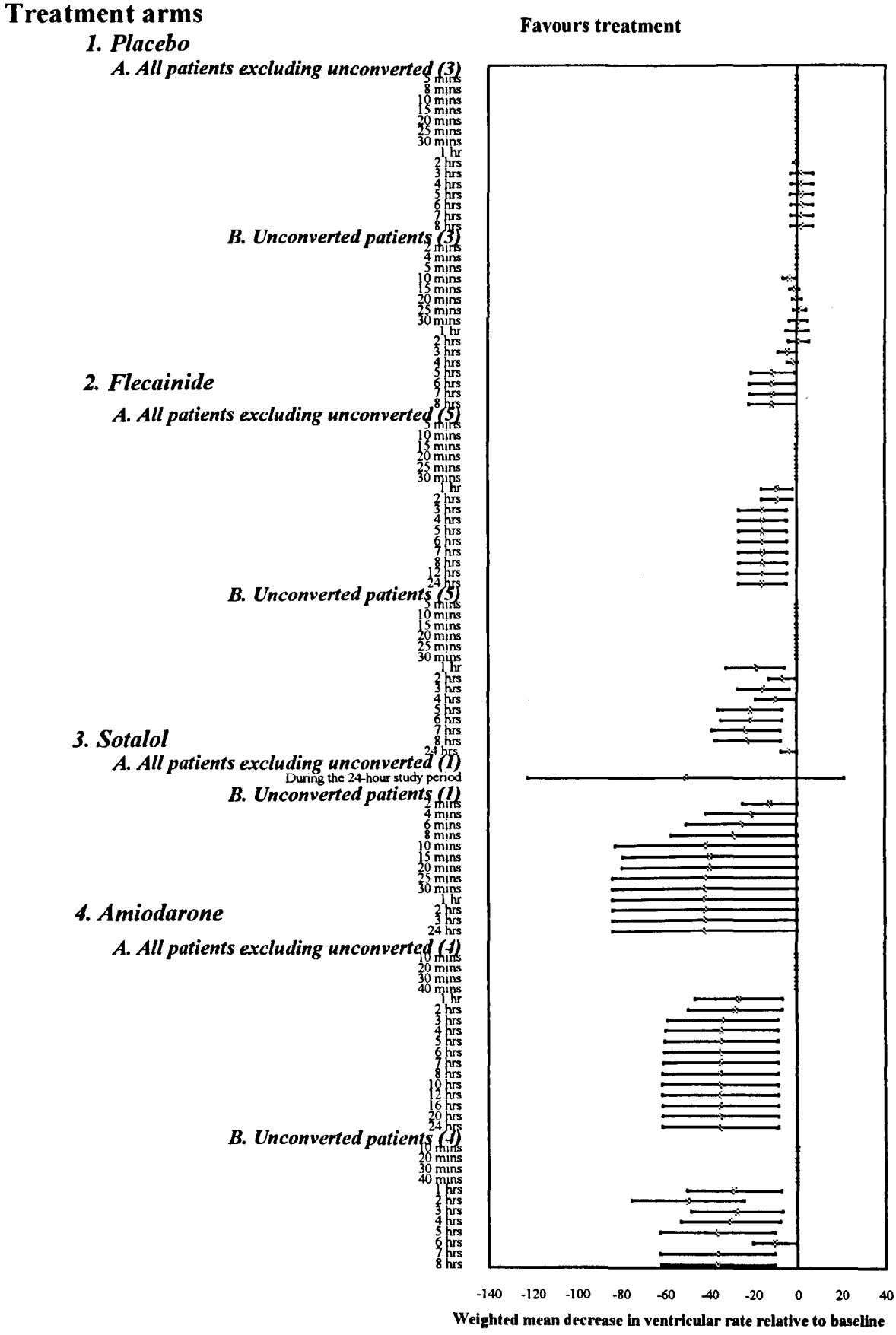

Figure 5.15.1 Effect of various treatment arms on the ventricular response as compared to the baseline. The figure depicts the weighted pooled treatment effect compared to baseline (expressed as weighted mean difference with 95% CI) at each follow-up time point. The results for each drug are stratified into three groups: 1. all patients after excluding unconverted if it was reported in the original trial; and 2. unconverted patients only. The number of trials included for each subgroup is shown in brackets. Random-effects model was employed if heterogeneity existed.

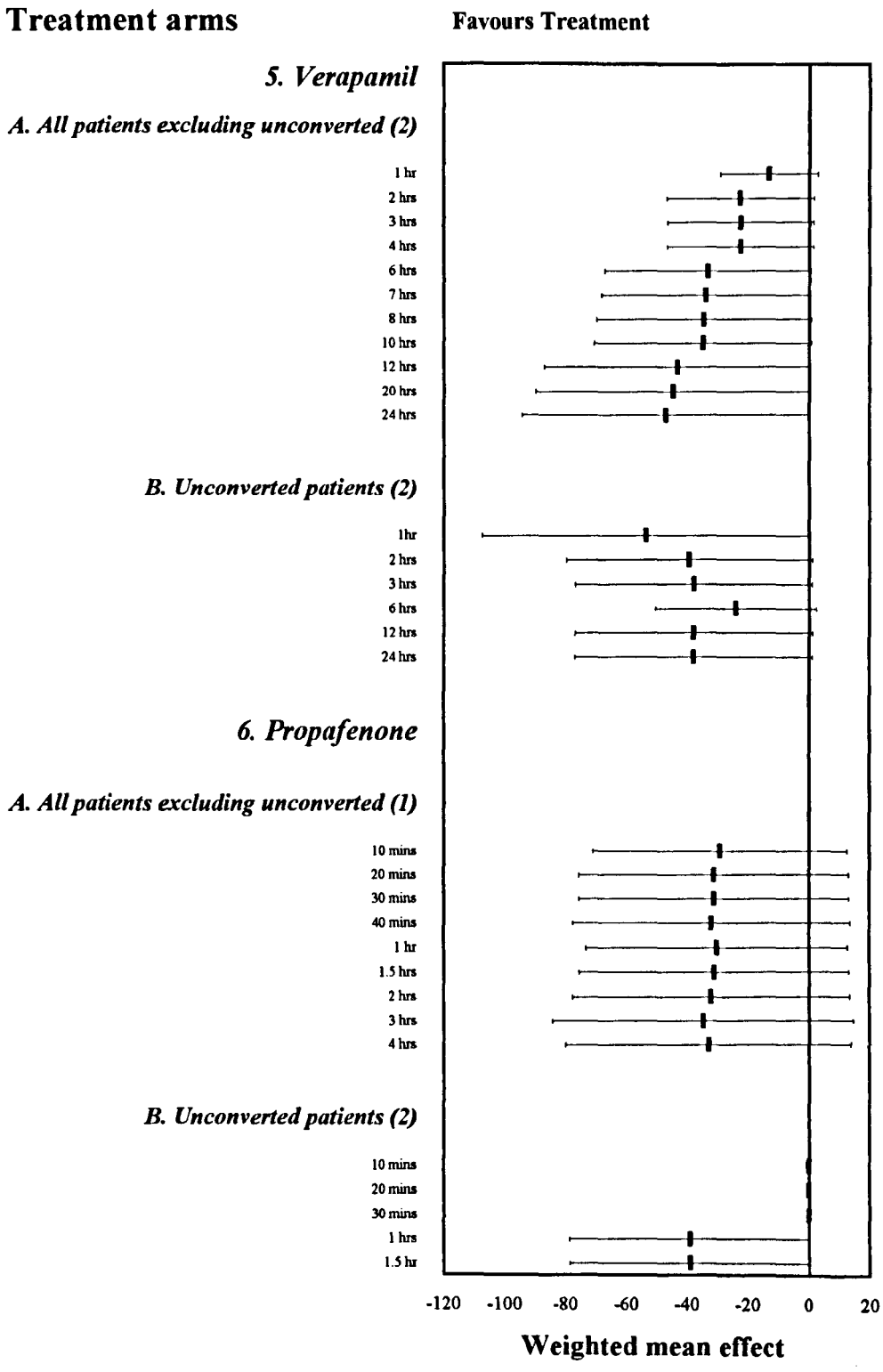

Figure 5.15.2 Effect of various treatment arms on the ventricular response in all patients included. The figure depicts the weighted pooled treatment effect compared to baseline (expressed as weighted mean difference with 95% CI) at each follow-up time point. The results for each drug are stratified into three groups: 1. all patients after excluding unconverted if it was reported in the original trial; and 2. unconverted patients only. The number of trials included for each subgroup is shown in brackets. Random-effects model was employed if heterogeneity existed.

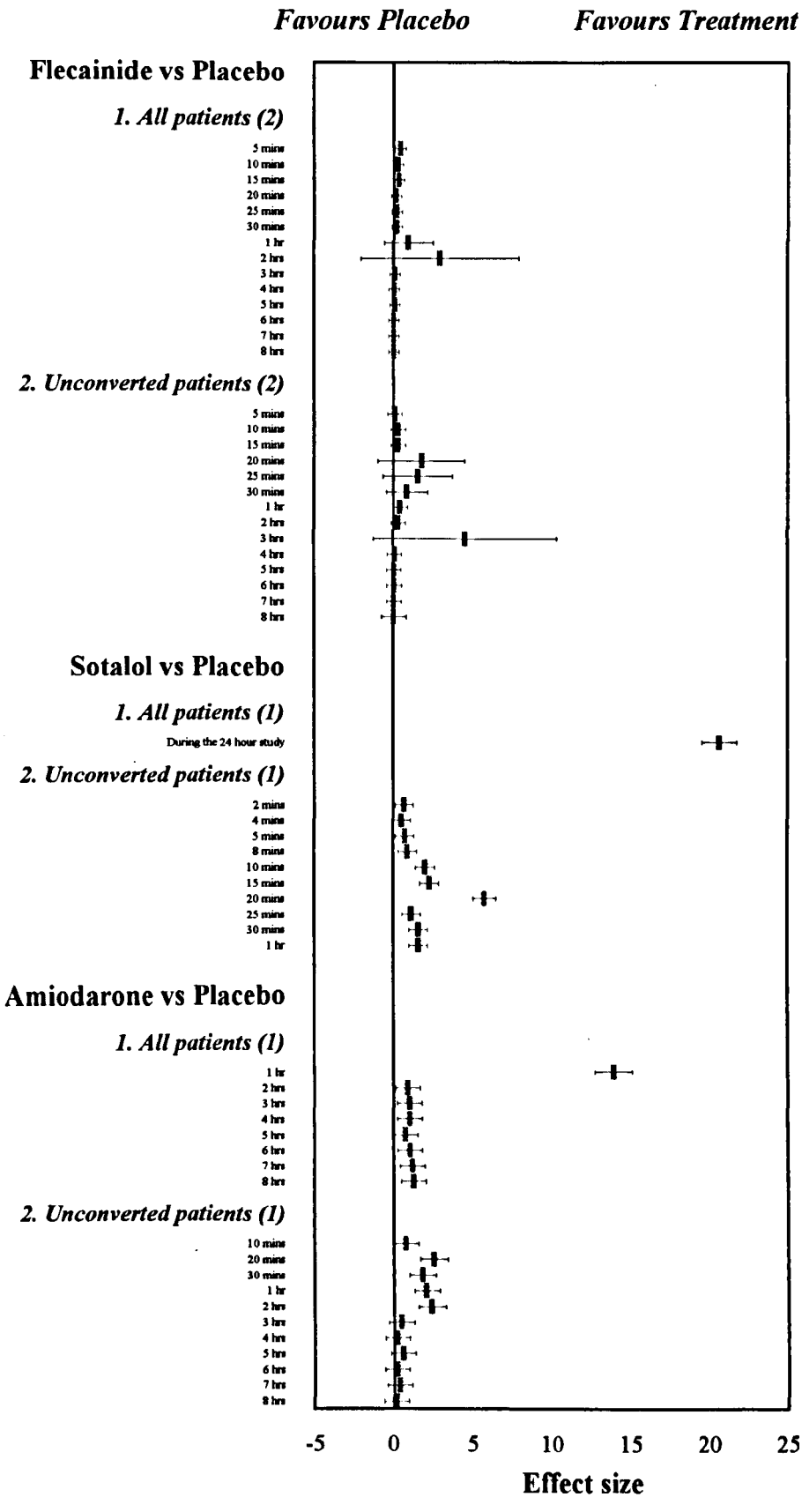

Figure 5.16 Effect of flecainide, sotalol, and amiodarone on ventricular response as compared directly to placebo (included 3 RCTs). The figure depicts pooled effect size estimates at different time points with their associated 95% CI (Fixed-effects model). The results for each drug are stratified into two patients groups: 1. all patients (after excluding unconverted if possible); 2. unconverted patients only. Also the number of trials included in each subgroup is shown in brackets. Random-effects model was employed if heterogeneity existed.

and clinically significant (ES, 20.7; 19.6-21.7). Another trial evaluated the effect in nonconverted patients (Sung *et al.*, 1995). The results were significant starting at 2 minutes with the maximum effect size reached at 20 minutes (ES, 5.8; 5.1-6.5). For amiodarone, the effect size was statistically significant at all time points from 1 to 8 hours, with a highly significant difference, from the clinical point of view, at 1 hour (ES, 13.96; 12.8-15.2). In nonconverted patients the effect was significant at 20 minutes to 1 hour. However, there was no significant difference after 3 hours.

Indirect comparison using the pooled mean ventricular rate weighted by the number of the patients is depicted in Figure 5.17. There was a significant difference between flecainide and placebo, while amiodarone and sotalol has displayed more prompt effect for controlling the ventricular response. However, the indirect comparison, using the pooled mean weighted by the inverse of the variance (Figure 5.18), did not show any significant difference between the three drugs.

5.4.4 Side Effects

Common side effects of antiarrhythmic drugs can be classified into cardiovascular and noncardiovascular toxicities. Cardiac side effects include bradycardia (heart rate consistently < than 50 beats/min), conduction disturbances (for example, second or third degree AV block), worsened or new congestive heart failure, severe hypotension (blood pressure < 90 mm Hg), drug-induced proarrhythmia (such as conversion of AF to AFL with more rapid ventricular response rate, also called 1:1 AV conduction), and sudden cardiac death. Noncardiac side effects may be minor or major. Minor noncardiac side effects include gastrointestinal disturbances (nausea, vomiting, and diarrhea), and those of the central nervous system (dizziness, light-headedness, and drowsiness). Major noncardiac side effects are those associated with amiodarone, such as thyroid dysfunction, and pulmonary fibrosis. Minor side effects can usually be eliminated by decreasing the dose. However, major side effects generally require discontinuations of the drug. The frequency of side effects is dose related and also duration related, thus increasing over time. Some of the previous side effects appear to be more common with one drug than the other. Flecainide, for example, is associated with visual disturbances which include blurred vision, difficulty in focusing, and spots before the eyes. Sotalol adverse effects are those related to ß-blocker activity such as dyspnea and those associated with QT prolongation (due to its Class III effect), especially torsade de pointes.

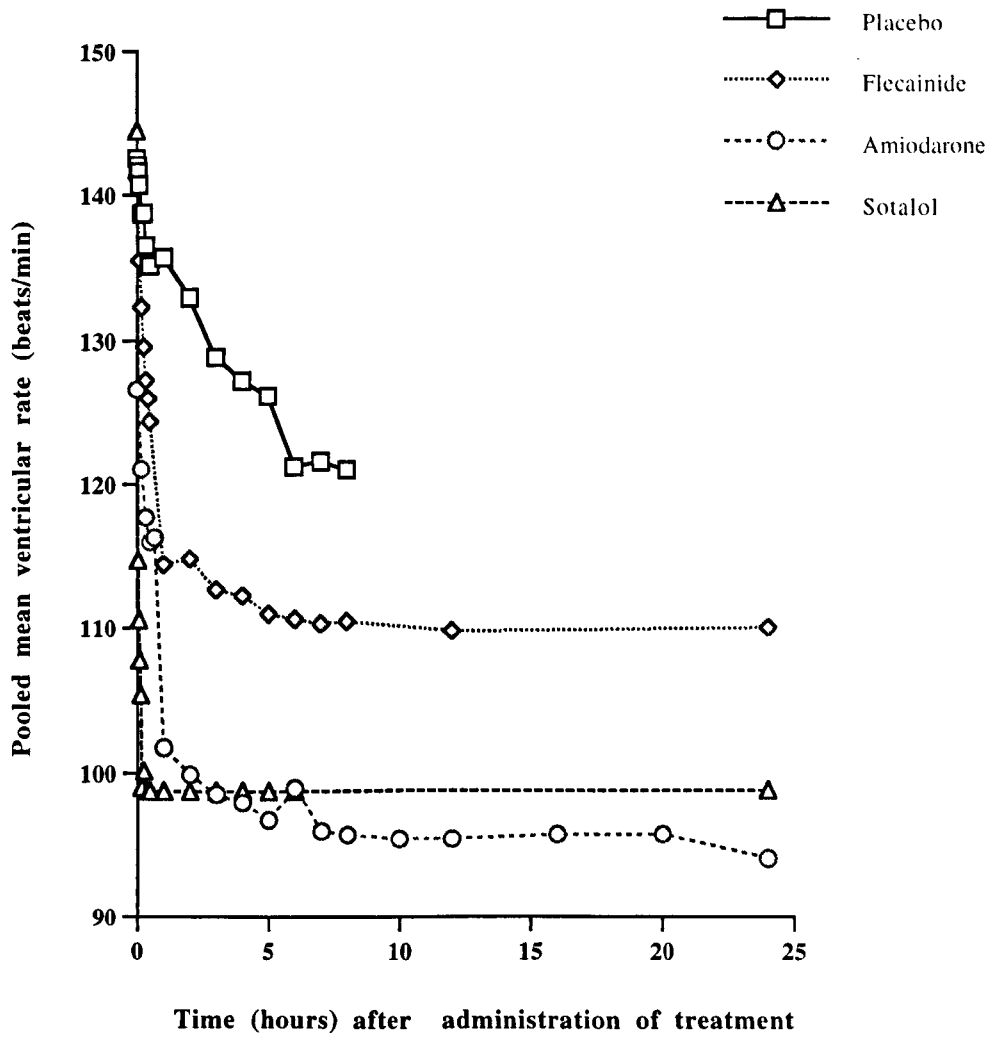

Figure 5.17 Indirect comparison of pooled mean ventricular rate in all patients (converted and unconverted to SR) in flecainide, amiodarone, sotalol, and placebo treatment arms during the 24-hour follow-up interval. The points represent the pooled mean weighted by the number of patients.

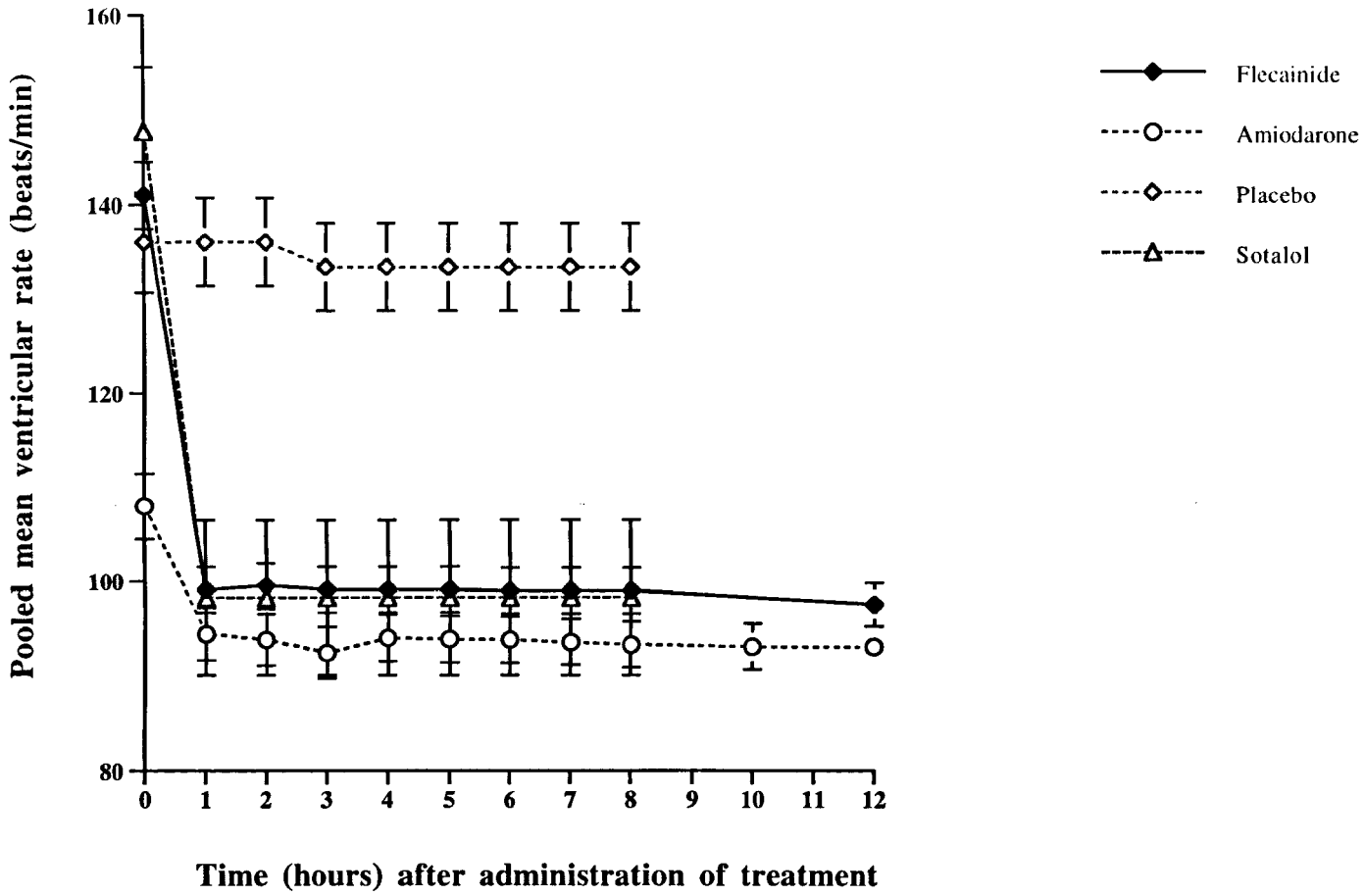

Figure 5.18 Indirect comparison of pooled mean ventricular rate in all patients (converted and unconverted to SR) in flecainide, amiodarone, sotalol, and placebo treatment arms during 12-hour follow-up period. The points represent the pooled mean weighted by the inverse of the variance and the error bars show the 95% CI (=1.96 SEM) under the fixed-effects model.

In this review, 14 flecainide clinical trials (4 uncontrolled and 10 RCTs) involving a total of 434 patients reported the incidence of side effects. Four of these trials (Villani *et al.*, 1990; Capucci *et al.*, 1992; Donovan *et al.*, 1991; Capucci *et al.*, 1994) were randomised placebo-controlled (3 also compared to active control), and 6 were comparative studies without placebo (Borgeat *et al.*, 1986; Gavaghan *et al.*, 1988; Suttorp *et al.*, 1989; Wafa *et al.*, 1989; Suttorp *et al.*, 1990; Madrid *et al.*, 1993).

For amiodarone, 13 trials (3 uncontrolled and 11 RCTs) involving a total of 347 patients provided data concerning adverse effects. Two trials were placebo-controlled (Capucci *et al.*, 1992; Donovan *et al.*, 1995) and 9 were randomised comparative studies (Bertini *et al.*, 1990; McAlister *et al.*, 1990; Adrivet *et al.*, 1990; Bellandi *et al.*, 1993; Chapman *et al.*, 1993; Cesar *et al.*, 1994; Cochrane *et al.*, 1994; Treglia *et al.*, 1994; Biasi *et al.*, 1995). One RCTs in which quinidine plus amiodarone was compared to quinidine (Posada *et al.*, 1988) was excluded from the analysis.

For sotalol, 8 trials (two uncontrolled and 6 RCTs) including a total of 373 patients described the incidence of adverse effects. Three of them were placebo-controlled (Levy *et al.*, 1986; Jordaens *et al.*, 1991; Sung *et al.*, 1995) and three were only comparative studies (Campbell *et al.*, 1985; Hamer *et al.*, 1993; Halinen *et al.*, 1995).

Table 5.8 shows the weighted pooled percentage incidence of adverse events in flecainide, amiodarone, and sotalol treatment groups separately. There was no significant difference in the incidence of cardiovascular side effects among the three treatment groups ($P < 0.05$). Although intravenous amiodarone is known to produce hypotension as a result of its peripheral systemic vasodilatory effects (Kopelman and Horowitz, 1989), this review of a limited number of patients (8 trials of 231 patients) shows that it was associated with a very low incidence of hypotension as compared to flecainide (2.7%±1.1 vs 10%±2). Extracardiac side effects occurred frequently at different rates with each drug but these were not serious. The commonest noncardiac problems in the flecainide group were nausea (2.42%), central nervous system side effects (dizziness/headache/drowsiness) with overall incidence rate of 1.9%, as well as paraesthesia and hyperthermia (1.85%). Amiodarone was frequently associated with rashes (1.45%) and sotalol with respiratory distress or dyspnea (1.89%). Nevertheless, the overall incidence of side effects requiring active therapy (such as infusion of intravenous fluids), direct current cardioversion (DCC), and withdrawals as a direct result of the drug toxicity, were not significantly different.

Table 5.8 Comparison of the overall incidence of adverse effects and dropouts among different treatment groups

Group	Flecainide	Amiodarone	Sotalol
1. All routes of administration			
Total number of trials	14	13	8
Total number of patients	434	373	234
Cardiac adverse effects			
Hypotension	2.6 (1.18-4.1)	1.95 (0.51-3.4)	5.5 (3.2-7.8)
Bradycardia	1.7 (0.48-2.9)	1.8 (0.4-3.24)	1.9 (0.3-3.5)
Proarrhythmia	2.28 (0.89-3.7)	1.4 (0.18-2.7)	1.52 (-0.04-3.1)
New/Worse CHF	1.36 (0.27-2.5)	1.4 (0.18-2.7)	0
Conduction disturbances	1.8 (0.57-3.1)	1.5 (0.2-2.7)	1.4 (-0.12-2.85)
Death	1.73 (0.52-2.9)	1.48 (0.2-2.7)	0
Noncardiac adverse effects			
Visual disturbances	1.49 (0.35-2.63)	1.5 (0.2-2.8)	0
Respiratory distress/Dyspnea	0	0	1.98 (0.2-3.8)
Nausea	2.42 (0.9-3.9)	1.84 (0.4-3.23)	1.3 (-0.1-2.8)
Dizziness /Headache/Drowsiness	1.9 (0.65-3.2)	1.5 (0.2-2.7)	0
Hyperthermia /Parasthesia/Fatigue	1.85 (0.6-3.1)	0	0
Superficial phlebitis	1.4 (0.3-2.5)	0	0
Cold extremities	0	0	1.38 (-0.1-2.9)
Rash	0	1.45 (0.2-2.7)	0
ANAT	1.93 (0.65-3.2)	1.6 (0.3-2.83)	3.1 (0.95-5.2)
DCC	2.1 (0.8-3.4)	2.64 (0.98-4.3)	2 (0.31-3.7)
Dropouts	1.65 (0.5-2.8)	1.9 (0.5-3.3)	3.3 (1.2-5.5)
2. Oral (single and multiple doses)			
Number of trials	4	2	2
Number of patients	89	40	39
Cardiac adverse effects			
Hypotension	1.7 (-0.97-4.4)	2.5 (-2-7.3)	33.5 (20-47)
Bradycardia	1.7 (-0.97-4.4)	2.5 (-2-7.3)	33.5 (20-47)
Proarrhythmia	3.34 (-0.4-7.1)	2.5 (-2-7.3)	11.4 (1.4-21.3)
New/Worse CHF	1.98 (-0.9-4.84)	0	0
Conduction disturbances	1.7 (-0.97-4.4)	4.34 (-1.9-10.6)	1.75 (-2.4-5.8)
Death	0	0	0
Noncardiac adverse effects			
Visual disturbances	0	0	0
Respiratory distress/Dyspnea	0	0	0
Nausea	1.7 (-0.96-4.45)	2.5 (-2-7.3)	1.75 (-2.4-5.8)
Dizziness /Headache/Drowsiness	1.9 (-0.9-4.7)	2.5 (-2-7.3)	0
Hyperthermia /Parasthesia/Fatigue	1.7 (-0.97-4.4)	0	0
Superficial phlebitis	2 (-0.9-4.9)	0	0
Cold extremities	0	0	0
Rash	0	0	0
ANAT	1.98 (-0.9-4.8)	2.5 (-2.34-7.33)	1.75 (-2.3-5.8)
DCC	2.2 (-0.7-5)	2.5 (-2.34-7.33)	28 (14.83-41.5)
Dropouts	1.4 (-0.97-4.4)	2.5 (-2.34-7.33)	35.4 (21.9-48.9)

The incidence rate is shown in terms of weighted pooled percentage (episodes per 100 patients) together with its 95% CI; ANAT, adverse effects needed active treatment; DCC; direct current cardioversion

Table 5.8 Comparison of the overall incidence of adverse effects and dropouts among different treatment groups (continued)

Group	Flecainide	Amiodarone	Sotalol
3. IV (single and multiple doses)			
Number of trials	8	8	6
Number Of patients	236	231	195
Cardiac adverse effects			
Hypotension	10 (6.2-14.1)	2.7 (0.7-4.82)	4.7 (2.4-7)
Bradycardia	1.7 (-0.04-3.4)	2.4 (0.47-4.4)	1.43 (-0.2-3.1)
Proarrhythmia	3.3 (0.96-5.7)	1.6 (-0.03-3.2)	1.3 (-0.3-2.8)
New/Worse CHF	1.5 (-0.1-3)	1.6 (-0.03-3.2)	0
Conduction disturbances	1.7 (-0.03-3.35)	1.6 (-0.03-3.2)	1.3 (-0.3-2.9)
Death	2 (0.23-3.8)	1.6 (0.01-3.3)	0
Noncardiac adverse effects			
Visual disturbances	0	1.7 (0.024-3.3)	0
Respiratory distress/Dyspnea	0	0	0
Nausea	3.5 (1.03-5.9)	1.99 (0.21-3.8)	1.3 (-0.3-2.8)
Dizziness /Headache/Drowsiness	2.8 (0.8-4.9)	1.6 (-0.04-3.2)	0
Hyperthermia /Paraesthesia/Fatigue	2.5 (0.6-4.4)	0	0
Superficial phlebitis	0	0	0
Cold extremities	0	0	1.32 (-0.3-2.9)
Rash	0	0	0
ANAT	2.1 (2.8-3.9)	1.8 (0.1-3.4)	3.5 (1.1-6)
DCC	2.3 (0.4-4.2)	2.5 (0.54-4.5)	1.6 (-0.14-3.3)
Dropouts	1.7 (0.04-3.3)	2.5 (0.54-4.5)	2.5 (0.3-4.7)
4. IV+Oral			
Number of trials	3	2	0
Number of patients	109	76	0
Cardiac adverse effects			
Hypotension	1.4 (-0.8-3.7)	1 (-1.23-3.2)	0
Bradycardia	2.15 (-0.6-4.9)	1 (-1.23-3.2)	0
Proarrhythmia	1.4 (-0.8-3.7)	1 (-1.23-3.2)	0
New/Worse CHF	0	0	0
Conduction disturbances	3.2 (-0.08-6.5)	1 (-1.23-3.2)	0
Death	1.4 (-0.8-3.7)	0	0
Noncardiac adverse effects			
Visual disturbances	1.8 (-0.7-4.3)	0	0
Respiratory distress/Dyspnea	0	0	0
Nausea	0	1 (-1.23-3.2)	0
Dizziness /Headache/Drowsiness	2.6 (-0.4-5.5)	1 (-1.2-3.3)	0
Hyperthermia /Paraesthesia/Fatigue	1.8 (-0.7-4.3)	0	0
Superficial phlebitis	0	0	0
Cold extremities	0	0	0
Rash	0	1 (-1.23-3.23)	0
ANAT	1.63 (-0.74-4)	1 (-1.23-3.2)	0
DCC	1.4 (-0.8-3.7)	3.3 (-0.7-7.3)	0
Dropouts	3.6 (0.13-7)	1 (-1.3-3.2)	

The incidence rate is shown in terms of weighted pooled percentage (episodes per 100 patients) together with its 95% CI; ANAT, adverse effects needed active treatment; DCC; direct current cardioversion

As shown in the Table 5.8, further analysis of the incidence of side effects according to the route of administration did not reveal any important variation between the three drugs in intravenous and intravenous plus oral treatment trials. On the other hand, oral sotalol was associated with a very high incidence rate of hypotension and bradycardia, requiring drug discontinuation (35.4%; 95% CI, 21.9-48.9). However, the authors of the trial stated that all events were symptomless (Halinen *et al.*, 1995).

In general, the use of the three drugs for this indication was relatively safe and the incidence rates of proarrhythmia and death were very low. The cause of death of five patients in the flecainide group were neither attributed to treatment nor to AF (Donovan *et al.*, 1991). However, one death in another flecainide trial occurred due to aggravation of the arrhythmia in a congestive heart failure patient who developed AF after repeated GABG surgery (Gavaghan *et al.*, 1988). As a result, cautious monitoring of flecainide plasma concentrations is required, particularly in patients with heart failure due to its negative inotropic effect. In amiodarone group, two deaths were reported but it was not deemed due to therapy (McAlister *et al.*, 1990).

In addition to the indirect comparison of incidence of side effects among different groups, the pooled relative risk for the incidence of each adverse effect was estimated for the three drugs as compared directly to the control group in the same trial. Figures 5.19, 5.20, and 5.21 depict the pooled log relative risk of cardiac, noncardiac side effects, adverse effects needed active therapy (ANAT) or direct current cardioversion (DCC), and those required withdrawals of treatment (dropouts) in flecainide, amiodarone, and sotalol respectively.

Four flecainide placebo-controlled trials (148 vs 165 patients) permitted the analysis (Figure 5.19). The meta-analysis has confirmed that none of the side effects reported occured at a significantly higher rate than placebo. Furthermore, pooling the data from two amiodarone controlled trials (56 vs 51), one compared to quinidine (30 vs 30), and one compared to disopyramide plus digoxin (29 vs 27), did not show any statistically significant difference for the incidence of side effects. On the contrary, the overall incidence of side effects was significantly higher with flecainide than propafenone (2 trials of 66 vs 68 patients) and digoxin/verapamil combination (2 trials of 35 vs 34 patients).

Two amiodarone placebo-controlled trials permitted the estimation of pooled relative risk of adverse effects (Figure 5.20). The pooling has shown that there was no

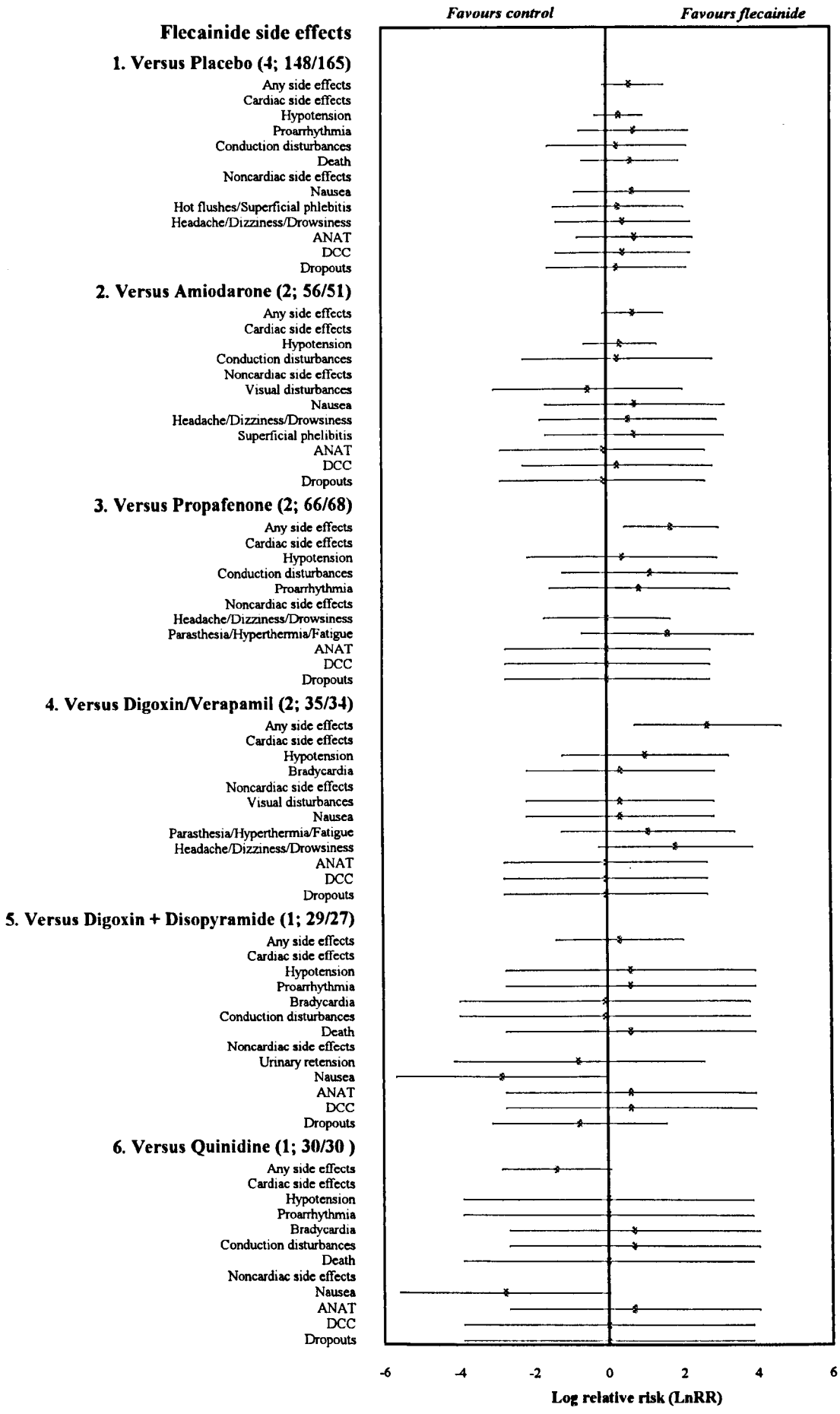

Figure 5.19 Flecainide cardiovascular and noncardiovascular side effects, as compared to direct control group (placebo or active control), in conversion to sinus rhythm. The figure depicts the relative risk of each side effect categorised into cardiac or noncardiac with the relatrive risk of ANAT, DCC, or dropouts displayed at the bottom for each comparison. The number of trial pooled and total number of patients included are shown in brackets.

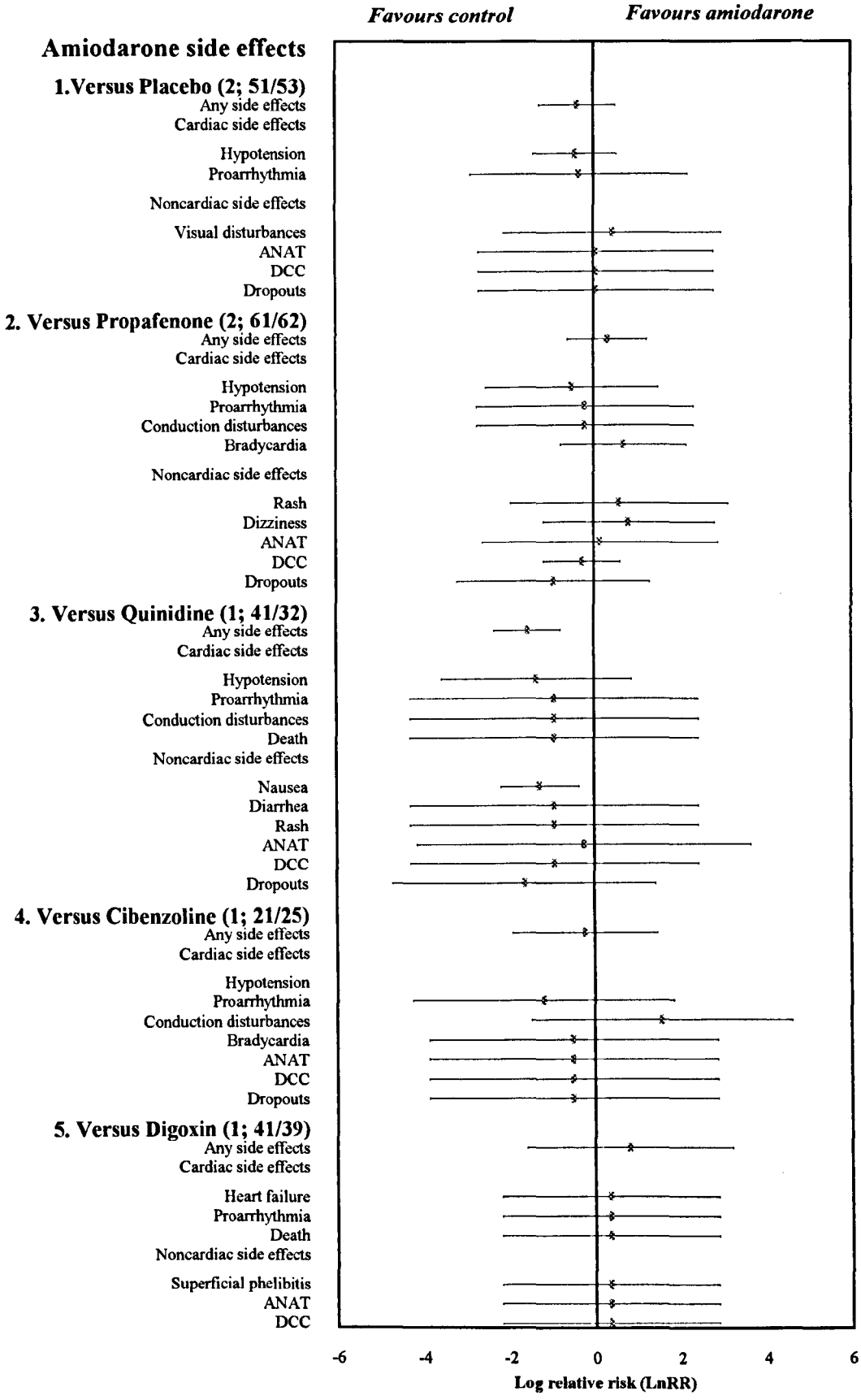

Figure 5.20 Amiodarone cardiovascular and noncardiovascular side effects, as compared to direct control group (placebo or active control), in conversion to sinus rhythm. The figure depicts the relative risk of each side effect categorised into cardiac or noncardiac with the relatrive risk of ANAT, DCC, or dropouts displayed at the bottom for each comparison. The number of trial pooled and total number of patients included are shown in brackets.

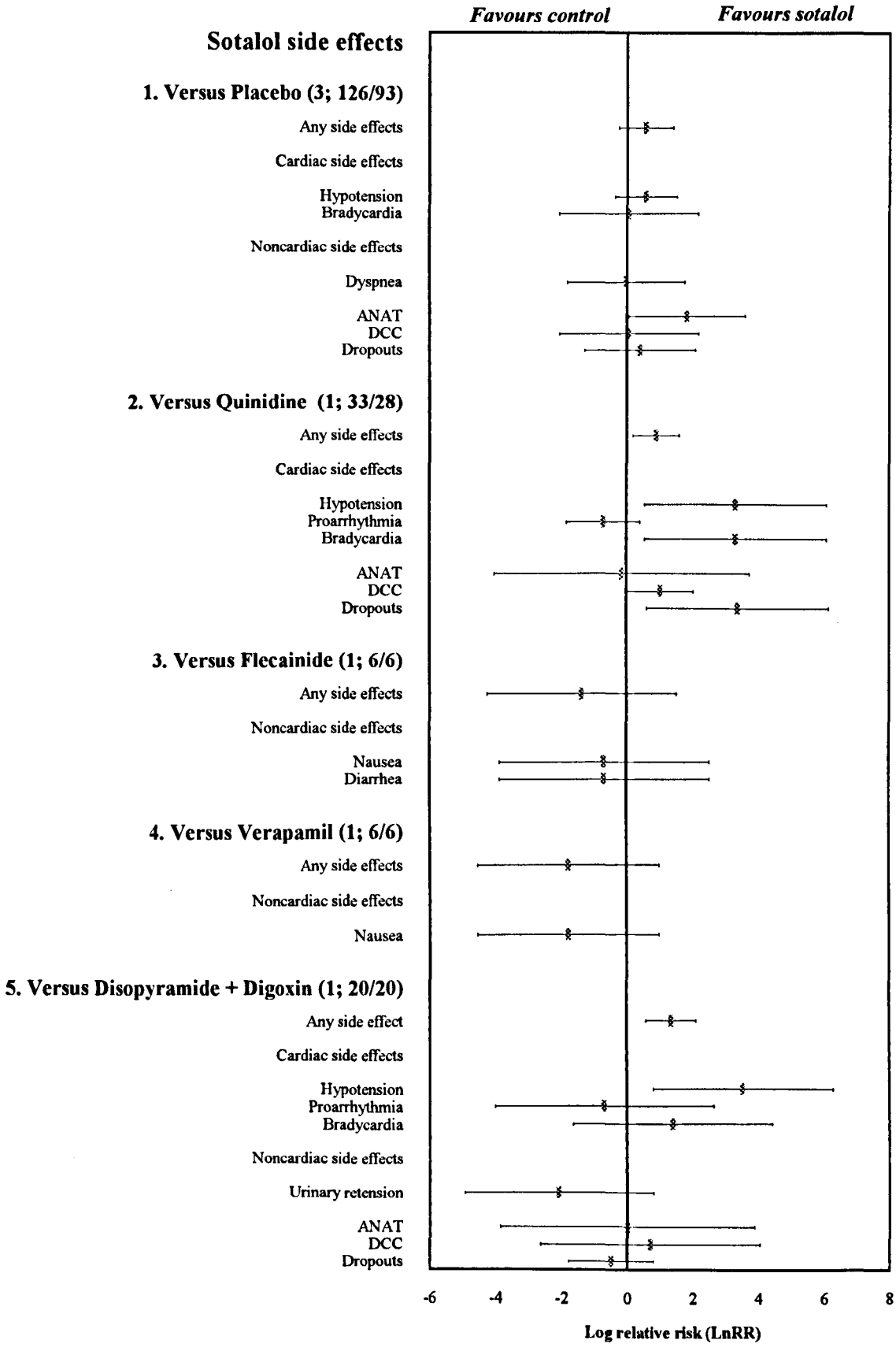

Figure 5.21 Sotalol cardiovascular and noncardiovascular side effects, as compared to direct control group (placebo or active control), in conversion to sinus rhythm. The figure depicts the relative risk of each side effect categorised into cardiac or noncardiac with the relatrive risk of ANAT, DCC, or dropouts displayed at the bottom for each comparison. The number of trial pooled and total number of patients included are shown in brackets.

significant difference. Furthermore, amiodarone was associated with lower relative risk for the total incidence of side effects as compared to quinidine in a head to head comparison trial of 41 vs 32 patients (McAlister *et al.*, 1990).

The comparison of incidence of adverse effects between sotalol and placebo was possible in three trials of 126 vs 93 patients. Neither cardiovascular nor noncardiovascular adverse events were significantly different from placebo (Figure 5.21). The direct comparison of sotalol to quinidine and to disopyramide plus digoxin in two head to head comparison, displayed highly statistically significant incidence of hypotension in favour of sotalol (LnRR, 3.3 with 95% CI of 0.5 to 6.07; and 3.53 with 95% CI of 0.78 to 6.3 respectively). However, the authors of these trials have claimed nonseverity of events in any patient and in 16 cases the blood pressure returned to pretreatment levels over one to two hours, although sotalol infusion was continued (Campbell *et al.*, 1985).

5.5 DISCUSSION

Rapid, reliable, and safe reestablishment of sinus rhythm is the major aim of pharmacologic treatment of acute atrial fibrillation. The previous analysis was performed in an attempt to answer the following questions: (1) which is the most effective agent ?, (2) which is the most quickly effective agent ?, and (3) which is the safest agent ?

Flecainide is available in the United Kingdom for oral and intravenous use with very favourable pharmacokinetic features, achieving therapeutic plasma levels within 2-3 hours. Thus it can be proposed for acute treatment of supraventricular arrhythmias. In both approaches employed in the present analysis (direct and indirect comparison), it was superior to placebo, amiodarone and Class IA agents (quinidine, disopyramide, and procainamide) in terms of rapidity of action, and total efficacy for conversion to sinus rhythm. Although it has displayed significant efficacy when the analysis was carried out separately for AF complicating coronary artery bypass surgery, it was thought that it would be unlikely to be widely adopted for this indication, due to the concern about its use in patients with ischemic heart disease (Camm and Bashir, 1990).

In addition, this analysis has revealed an interesting finding. Intravenous amiodarone was not significantly different in effect from placebo for conversion of acute AF,

particularly in the first few hours. This low efficacy of intravenous amiodarone might be explained in the light of its pharmacokinetic and electrophysiological properties. Although intravenous amiodarone was reported to have a faster onset of action after a small intravenous dose (1-30 minutes, with duration of effect of 1-3 hours) than oral amiodarone, which usually would take days to weeks to start working (Wellens *et al.*, 1984; Ikede *et al.*, 1984), it has been shown that the latter has more prominent effect on prolonging the effective refractory period in all cardiac tissues, particularly the atria (Vietti-Ramus *et al.*, 1992). Thus intravenous amiodarone possess little if any efficacy for rapid cardioversion.

However, the other Class III drug, sotalol, has shown very high efficacy compared to placebo in three trials. The indirect comparison between intravenous sotalol and intravenous flecainide suggest equal efficacy up to 24 hours. Nevertheless, further validation of this conclusion in large-scale direct comparison trials with flecainide and placebo is mandatory.

Considering other data such as mean time of conversion which was pooled for flecainide, amiodarone, and sotalol treatment arms separately, one can conclude that sotalol is the most effective agent for rapid cardioversion.

The other acceptable therapeutic end point was to achieve a sufficient decrease in the ventricular rate (less than 100 beats/min). Direct comparison of the three treatment effects (flecainide, amiodarone, and sotalol) on the ventricular rate to placebo was carried out in six trials. This comparison produced contradictory results relative to baseline, particularly for sotalol. This can be explained by the limited data available for sotalol effect on the ventricular rate (for only 23 converted, and 12 unconverted patients). The effect size of sotalol compared to placebo was statistically significant, indicating the existence of a sotalol effect on the ventricular rate which can be due to its beta-blocking effect on the atrioventricular node.

The evidence was much stronger for amiodarone effectiveness in both methods of comparison due to the availability of more data (effect compared to baseline, 4 trials; and effect compared to placebo, 1 trial for converted, and 1 trial for unconverted). The effect was even evident if AF persists in unconverted patients. As a result its indication as an intravenous injection can be retained for cases which failed the cardioversion by other antiarrhythmic agent, to provide rapid improvement for the hemodynamic deterioration.

Finally, comparison of the three drugs with respect to incidence of any side effect, or stratified according to cardiac and noncardiac side effects did not reveal any serious difference in favour of treatment. In addition, dropout rates due to any cause or due to toxicity were not statistically significant. An important finding was that calculated relative risk for the incidence of death and proarrhythmia, due to this particular indication of antiarrhythmic drugs, was very low. As a result, the weight of evidence still supports the recommendation for their use in an emergency room for acute medical and surgical AF.

5.6 CONCLUSION

The meta-analysis described in this chapter suggested that, for patients presenting with acute AF, intravenous sotalol or intravenous flecainide should be tried first. Intravenous amiodarone should be retained for resistant unconverted cases for controlling the ventricular response to atrial fibrillation due to its salutory effects on the atrioventricular node by prolonging refractoriness and slowing of intranodal conduction (Donovan *et al.*, 1995).

APPENDIX 5.2

Appendix 5.1

I. Clinical Trials Included In The Meta-Analysis

1) Flecainide Clinical Trials

Borgeat A, Goy JJ, Meandly R, Kaufmann URS, Grbic M, Sigwart UELI. Flecainide versus Quinidine for cardioversion of atrial fibrillation to sinus rhythm. *Am J Cardiol* 1986; **58**: 496-498.

Botto GL, Bonini W, Broffoni T, Gappelletti G, Falcone C, Lombardi R, Paulesu A, Pedraglio E, Ferrari G. Conversion of recent-onset atrial fibrillation to sinus rhythm using a single oral loading dose of propafenone: A single-blind controlled study (abstract). *Circulation* 1993; **88**: 341.

Capucci A, Coriani G, Botto GL, Falcone C, Rubino I, Lenzi T, Trisoline G. A controlled study on efficacy and safety of a single oral loading dose of propafenone or flecainide in converting recent onset atrial fibrillation to sinus rhythm. *JACC* 1993; **21**(2):171A : 743-744.

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Capucci A, Boriani G, Botto GI, Lenzi T, Rubino I, Falcone C, Trisolino G, Casa SD, Binetti N, Cavazza M, Sanguinetti M, Magnani B. Conversion of recent-onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. *Am J Cardiol* 1994; **74** (5): 503-505.

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Crozier IG, Ikrom H, Kenealy M, Levy L. Flecainide acetate for conversion of acute supraventricular tachycardia to sinus rhythm. *Am J Cardiol* 1987; **59**: 607-609.

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Goy JJ, Kaufmann U, Kappenberger L, Sigwart V. Restoration of sinus rhythm with flecainide in patients with atrial fibrillation. *Am J Cardiol* 1988; **62**: 38D-40D.

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flutter: the role of flecainide, propafenone and verapamil. *Am J Cardiol* 1992; **70**: 56A-61A.

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CHAPTER SIX

EFFECT OF ANTIARRHYTHMIC DRUGS ON EARLY AND LATE MORTALITY POST ACUTE MYOCARDIAL INFARCTION A META-ANALYSIS

6.1 INTRODUCTION

The prophylactic use of antiarrhythmic agents after acute myocardial infarction (AMI) was based on two major concepts. The first was the increased risk of developing potentially malignant ventricular fibrillation during the early acute phase of myocardial infarction, and the second was the increased risk of sudden death due to arrhythmia in patients who survived myocardial infarction (Toe *et al.*, 1993).

Many clinical and epidemiological studies have demonstrated that the two major risk factors of sudden cardiac death in patients who survived acute myocardial infarction, or who have advanced cardiac diseases (for example, congestive heart failure or cardiomyopathy) are the presence of left ventricular dysfunction and repetitive or complex forms of premature ventricular contractions (PVCs) (The Coronary Drug Project Research Group, 1973; Bigger, 1984; Lubsen, 1986). This observation has generated the hypothesis that suppression of PVCs with antiarrhythmic drugs, which does not possess a negative effect on left ventricular ejection fraction (LVEF), would potentially improve survival in patients with complicated cardiac diseases and prevent sudden cardiac death (Schaffer *et al.*, 1975).

As a result, numerous randomised clinical trials were conducted to determine whether antiarrhythmics reduced the incidence of sudden death and reinfarction in survivors of MI (Chamberlain *et al.*, 1980; Ryden *et al.*, 1980; Bell *et al.*, 1982; Lubsen *et al.*, 1984; Impact Research Group, 1984; Smyllie *et al.*, 1984). The Cardiac Arrhythmia Suppression Trials (CAST-I and CAST-II) showed increased mortality in patients treated with the Class IA (moricizine) and Class IC agents (encainide hydrochloride and flecainide) compared to placebo. This opened the possibility that antiarrhythmic drugs may actually have aggravated the arrhythmia which they were designed to treat (CAST Investigators, 1989; CAST Investigators II, 1992).

A number of overviews were performed to analyze systematically the data from all randomised controlled trials that evaluated Class IA, IB, IC, II, and III agents to test whether this effect could be extrapolated to all antiarrhythmics (Furberg, 1983; Yusuf *et al.*, 1988; Hine *et al.*, 1989; Burckhardt *et al.*, 1991; Lievre *et al.*, 1991; Nademanee *et al.*, 1993; Teo *et al.*, 1993; Zarembski *et al.*, 1993). Most of these reviews pooled together the results from all the available clinical trials of various classes, instead of performing a subgroup analysis for each class (particularly for all Class I

subdivisions). It was concluded that the routine use of Class I antiarrhythmic drugs after MI was associated with increased mortality, while beta-blockers showed a significant overall reduction in mortality. In fact, a meta-analysis of 6 trials of secondary prevention of MI by Class I antiarrhythmics, in which the antiarrhythmic effect was correlated with mortality, demonstrated that even before the evaluation of CAST, it was evident that suppression of arrhythmia criteria was a surrogate marker for a more relevant endpoint which is mortality (Lievre *et al.*, 1991). As a result, an alternative approach was suggested for explaining the cardioprotective effect of beta-blockers, which was to minimize the ischemia by reducing oxygen consumption (Singh, 1991; Kjekshus, 1986). In addition, a shift toward other antiarrhythmic classes which would not act via depression of cardiac conduction, particularly Class III, was considered (Advani and Singh, 1995).

Amiodarone, as a Class III agent with several mechanisms of actions (potassium channels blocking, as well as antianginal properties) demonstrated variable levels of efficacy for prevention of sudden death in several individual trials. Two recent meta-analyses of its long-term prophylaxis confirmed its beneficial effects for reduction of both sudden cardiac death and total mortality (Teo *et al.*, 1993; Zarembski *et al.*, 1993). However, the results were pooled at one time point without considering censored events in individual trials. New trials have been completed since publication of these studies necessitating an update.

Sotalol, as a Class III agent with additional beta-blockade activity, was also examined in recent trials for treatment of acute and chronic myocardial infarction. However, the results were inconclusive. The *d*-sotalol is the dextrorotary optical isomer of racemate *d,l*-sotalol, which has a pure Class III action of lengthening the action potential duration, and devoid of beta-blocking properties (Advani and Singh, 1995). It was developed on the presumption that its clinical efficacy would approach that of amiodarone and sotalol (racemic), but without the serious toxicity profile of amiodarone and the risk of torsades de pointes (TDP) associated with beta-blockade action of sotalol.

In this chapter it was intended to review systematically the effectiveness of *d,l*-sotalol, *d*-sotalol, and amiodarone for patients with myocardial infarction in short-term 'early intervention' and long-term 'late intervention' trials, with the former indicating that treatment allocation was assigned within 72 hours of onset of symptoms, or as soon as possible after hospital admission, and the latter patients were enrolled at least 4 days

after MI (Furberg, 1983; Toe *et al.*, 1993).

The primary objectives for analysis were as follows:

- To review the role of intravenous or oral sotalol following myocardial infarction and to obtain data on various therapeutic end points (surrogate markers) employed in both RCTs for treatment of suspected acute MI (primary prevention RCTs), and RCTs following documented acute MI (secondary prevention RCTs).

- To validate the beneficial impact of amiodarone on mortality of any cause in patients at high-risk by updating recent meta-analyses with further emphasis on pooling survival analysis from individual trials.

- To test whether this effect of amiodarone in the first year (all previous analysis) would continue to improve the mortality in subsequent years.

- To examine the toxicity of amiodarone treatment during its long-term use.

6.2 METHODS

6.2.1 Data Identification and Selection of Primary Trials

A literature search was conducted through all available database sources as detailed in Chapter 4, to identify all published trials addressing the use of *d*-sotalol, *d,l*-sotalol, and amiodarone for treatment of myocardial infarction. The following pertinent keyword to this chapter were combined with each drug under investigation cited in the title and / or abstract: myocardial infarction, congestive heart failure, sudden death, and mortality. The search was completed for the period 1966 to 1997. Hard copies for all the clinical trials were obtained. A manual search for the references obtained complemented the computerised search.

6.2.2 Study Selection and Inclusion Criteria

Trials were included provided they satisfied the following inclusion criteria:

i. Trials were randomised, prospective and published trials.
ii. Trials evaluated the use of sotalol for patients with suspected acute myocardial infarction (primary prevention of acute MI) or patients with documented acute myocardial infarction (secondary prevention of MI).
iii. Sudden cardiac death, cardiac death, noncardiac death, or total mortality were the primary end points or secondary end points of the trials. Total mortality, however, was the preferred outcome, since it depend on a count without any possible bias in determining the cause of death. Moreover, it would permit direct comparisons across trials.
iv. Abstracts and full length articles were included.
v. Time of enrollment following AMI was specified in the trials.
vi. Duration of treatment and follow up was continued for at least 6 months in the secondary prevention studies.

6.2.3 Data Extraction

6.2.3.1 Study Design Characteristics

Data regarding the number of patients allocated in each treatment group, design, time of enrollment with regard to the acute event, time treatment started, dose of sotalol, route of administration, duration of exposure and follow up during the long-term studies were extracted from text, tables and figures.

6.2.3.2 Population Demographic and Diagnostic Criteria

In addition to details of patients' demographic criteria which was mentioned in Chapter 4, other relevant diagnostic criteria for this chapter were extracted as follows:

- Left ventricular ejection fraction (LVEF).
- PVCs inclusion criteria, and/or baseline PVCs (mean or median ± SD/SE).
- Number of patients with prior history of MI.

• Number of patients with congestive heart failure (CHF), together with its severity measurement according to New York Heart Association (NYHA).
• Number of patients with coronary artery disease (CAD).
• Number of patients receiving other ß-blockers.
• The major arrhythmic type and pattern in the subpatient populations.

6.2.3.3 Outcome Measures

Data regarding the following end points were extracted as number of events for dichotomous type, and mean or median together with its standard error or standard deviation for continuous type:

- Conventional therapeutic end points employed in sotalol RCTs: heart rate, infarction size, arrhythmias, and non-fatal cardiovascular events
- Short-term mortality data in acute trials
- Long-term mortality data in chronic trials:
  i. For trials which utilised survival analysis techniques, particularly Kaplan-Meier product-limit method, to delineate life table curves, the actuarial percentages were deduced from the published curves which were scanned and read carefully at different time points by using Cricket Graph Computer Package.

  ii. For trials which did not report the published survival curves, the total number of deaths at the end of the follow-up interval, was extracted.

6.2.4 Statistical Analysis and Data Synthesis

6.2.4.1 Kaplan-Meier Product-Limit Method

A survival curve for a group of patients is a graph representing the estimate of the probability of a dichotomous outcome (for example, death or reversion to sinus rhythm) at various times (Coldman and Elwood, 1979). This curve has a step-pattern.

Kaplan-Meier Product-Limit Method is one of the methods employed for constructing such a curve, which requires knowledge of number of patients lost to follow-up at each

time point (censored observations).

The procedures for calculation of Kaplan-Meier percentage can be summarised as follows (Kaplan and Meier, 1958; Coldman and Elwood, 1979): for the i^{th} time interval, (i=0, ...K), with R_i being the number of patients actually remaining under follow-up in the trial at the beginning of the interval, let d_i be the number of events during this interval, and let c_i be the number of patients lost to follow-up (censored observations) up to the end of the interval. The number of patients remaining at risk at the beginning of the interval (N_i) can be calculated by:

$$N_i = R_i - c_i$$

Then, the probability of surviving that interval (P_i) is estimated by:

$$P_i = 1-(d_i/n_i)$$

Assuming the first cumulative survival curve estimate (S_0) as well as the probability of surviving at time zero (P_0) to be equal to 1, the subsequent survival curve value is given by:

$$S_i = S_{i-1} \times P_i$$

The approximate variance of the survival curve estimate is obtained by:

$$\text{Variance of } S_i = (S_i)^2 \sum_{j=1}^{i} \frac{1-P_j}{P_j n_j}$$

Where the summation sign implies summation over all intervals preceding the one (i) interval for which the calculation is being performed and including the latter.

To combine the Kaplan-Meier survival percentages across various trials the following equation was employed (Coplen *et al.*, 1990; Messori and Rampazzo, 1993):

$$P_T = \frac{\sum (S_i . W_i)}{\sum W_i}$$

Where W_T is equal to the inverse of the variance of S_i.

6.2.4.2 Calculation of 'Log-rank' Odds Ratios of Meta-analysis

This method is usually employed for pooling data from survival studies with censored end points to test the effect of time on the progress of outcome (Pignon *et al.*, 1992; EBCTCG, 1990). It has the advantage of enabling the comparison of the overall difference between two treatments while taking the whole survival curves into account (Messori and Rampazzo, 1993).

In the present meta-analysis this method allows testing (for each time interval) the hypothesis zero that the probability of death not due to treatment effect by comparing the observed number of converted patients (O) in a treatment group with the number of patients that would have been expected to be converted (E) in the same group if the number of converted were equally distributed among the treatment and control group. The value of (E) can be calculated as the product of the total number of deaths during the first interval (in both treatment and control groups) by the number of patients at risk (in the treatment group) at the beginning of the same interval which is equal to N_i (equation 1), divided by the total number of patients in the trial. The value of O-E would be expected to differ only randomly from zero if the death was not due to treatment. After calculations of the sum of (O-E) values, and pooled OR according to Peto's method as described in Chapter 3, the 'log-rank OR' of the second time interval is calculated from the overall grand total of the quantities (O-E) for the first plus the second time interval, and their corresponding variances to yield the overall 'log-rank OR' of death during the period from zero time to the end of the second interval (till 6 months). The same procedures were repeated for calculation of 'log-rank OR' for the subsequent third interval (till 102 months).

6.3 RESULTS

6.3.1 Description of Trials Identified

6.3.1.1 Sotalol Clinical Trials

A total of thirteen studies met the inclusion criteria. For the racemic sotalol, five trials were short-term 'early intervention' trials (Table 6.1), and seven were long-term 'late intervention' trials (Table 6.2). For *d*-sotalol, only one long-term trial was identified (SWORD Investigators, 1996).

Short-term trials

All five trials were randomised, placebo-controlled, parallel-design studies. The total number of patients included was 2165; 1088 received sotalol, 68 received placebo, and 1009 received sotalol+aspirin. Three of the five used a double-blind design (Astrom *et al.*, 1986; McGrath *et al.*, 1986; Juul-Moller *et al.*, 1992), except that in the Swedish Angina Pectoris Aspirin Trial (SAPAT), the employment of sotalol was open-label, since both, treatment (aspirin) group, and control (placebo) group were treated simultaneously with sotalol. Three trials evaluated intravenous intervention (Astrom *et al.*, 1986; Lloyd *et al.*, 1988; McGrath *et al.*, 1986), one oral intervention (Juul-Moller *et al.*, 1992), and one intravenous plus oral doses (Llewellyn *et al.*, 1986). The length of treatment in the acute phase varied from 24 hours to 7 days. The enrollment of patients in the acute studies varied from 6 to 12 hours after the onset of pain, with the exception of SAPAT trial again, in which the treatment was initiated prior to the development of acute MI phase.

All trials were designed to evaluate the therapeutic end points concerned with the beneficial effects of the early beta-blockade in acute MI phase, particularly heomodynamic effects on heart rate and blood pressure. In addition, one trial was designed to assess the effect on plasma and urinary catecholamine responses (McGrath *et al.*, 1986). Another study tested the induced adverse effect of sotalol on increasing the left ventricular end-diastolic volume (Lloyd *et al.*, 1988). Other therapeutic end points will be discussed later in detail in section (6.3.3.1.1).

d,l-sotalol trials enrolled a total of 1744 patients; 1027 received sotalol, and 621 received placebo, 18 received flecainide, 20 received timolol, 18 received encainide, 49 received atenolol, 30 received amiodarone, and 17 received lignocaine. Three of the seven studies were randomised placebo-controlled (Myburgh *et al.*, 1979; Julian *et al.*, 1982; Langbehn *et al.*, 1985), while the remainder were randomised, active-controlled studies (Spielman *et al.*, 1985; Cobbe *et al.*, 1988; Amiodarone vs Sotalol Study Group, 1989; Ho *et al.*, 1994). Five trials used double-blind with crossover (Myburgh *et al.*, 1979; Langbehn *et al.*, 1985, Cobbe *et al.*, 1988; and Ho *et al.*, 1994) or parallel design (Julian *et al.*, 1982) and two were open-label, parallel design (Spielman *et al.*, 1985; Amiodarone vs Sotalol Study Group, 1989).

Four trials evaluated fixed oral dosage of 320 mg/day, while titration up to maximum tolerated level was permitted in two studies (Cobbe *et al.*, 1988; Spielman *et al.*, 1985). Only one study evaluated the acute effect of intravenous intervention in patients with remote MI admitted in emergency room (Ho *et al.*, 1994).

Patient enrollment varied between 5 days to 96 months post acute phase of MI. The intervention phases lasted 21 days to 23 months. The major arrhythmic type reported was of ventricular origin in all studies, and the antiarrhythmic effect of the treatment was provided in all trials except one (Julian *et al.*, 1982).

The SWORD trial was multicenter, randomised, double-blind, placebo-controlled and parallel designed trial which evaluated oral dosage of 200 mg/day of *d*-sotalol, that was increased to 400 mg if required. It enrolled a total of 3121 patients (1549 sotalol-treated, and 1572 placebo-treated). While racemic sotalol trials enrolled only patients with chronic MI, the SWORD trial enrolled patients with either a recent (6-42 days) MI, or a remote (> 42 days) MI. The duration of the follow-up was continued for 300 days.

Table 6.1 Characteristics of randomised clinical trials of sotalol in treatment of recent or suspected acute myocardial infarction 'early intervention'

Trial	*Design*	*Dosage*	*Enrollment Sotalol/Control¶*	*No. of patients randomised*	*Treatment allocation (Flecainide/ Control)*	*Type of control*	*Primary end points*	*Duration of treatment*
Astrom *et al.* 1986	R, DB, PL, P	IV 254 mg/day (214-336)	Within 24 hours 16±1.5/15±1.5	20	10/10	Placebo	Infarction size, arrhythmias, heart rate	48 hours
Llewellyn *et al.* 1986	R, PL, P	IV (120 mg) and oral (320 mg) daily	Within 12 hour	50	22/28	Placebo	Heart rate, arrhythmias	24 hours
Lloyd *et al.* 1988	R, PL, P	40 mg IV over 10 mins, if no side effects occurred two further doses of 40 mg were similarly given to a maximum total dose of 120 mg	Less than 12 hours 5.3/5.9	30	15/15	Placebo	Heart rate, blood pressure, infarction size, arrhythmias	72 hours
Juul-Moller *et al.* 1992	DB, PL, R, P. The use of Sotalol was unblinded.	160 mg orally (40-480 mg) / day	Before the occurrence of MI	2035	Sotalol+Aspirin; 1009	Sotalol+Placebo; 1026	All cause mortality, fatal and non-fatal myocardial infarction, vascular events	50 (range 23-76) months
McGrath *et al.* 1986	R, DB, PL, P	1mg/kg IV at 10 mg/min followed by 160 mg/day for 7 days	< 6 hours 5.3±0.2/4.8±0.4	30	15/15	Placebo	Infarction size, arrhythmias, heart rate, catecholamine level	7 days

'Early intervention' indicates that treatment allocation was assigned within 72 hours of onset of symptoms or as soon as possible after hospital admission.
Enrollment; the time elapsed after the incidence of index acute myocardial infarction.
DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; IV, intravenous; O, oral; C, comparative study; ¶, mean time from onset of symptoms or pain to infusion start

Table 6.2 Randomised clinical trials of sotalol in treatment of myocardial infarction 'long-term interventions'

Study (Reference)	*Design*	*Dose*	*Route*	*N.randomised / N.Continued The Study*	*Treatment allocation (Sot/ Cont)*	*Type of control*	*Enrollment*	*Primary end points*	*Duration of treatment*
Myburgh *et al.* 1979	R, DB, PL, CO	320 mg/d for 28-day period then an open phase in which the dose titrated for optimal requirements	Oral	20/20	20/20	Placebo	6-96 months (mean 42 months)	Suppression of PVCs	6 months
Julian *et al.* 1982	Multicenter, R, DB, PL, P	320 mg/day	Oral	1456/NS	873/583	Placebo	5-14 days after MI	Mortality, reinfarction	12 months
Langbehn *et al.* 1985	R, DB, PL, CO	320 mg/day	Oral	18/18	18/18/18	Flecainide Placebo	NS	PVCs% suppression, blood pressure	21 days
Spielman *et al.* 1985	R, C, P	320 mg/day	Oral	55/55	17/20/18	Timolol; 20 Encainide; 18	7-28 days post MI	Arrhythmias, mortality	NS
Cobbe *et al.* 1988	R, DB, CO	320 mg/day, titration up to 480 mg/day was permitted	Oral	103/103	54/49	Atenolol	7-10 days after admission	Arrhythmia frequency, effect on QT-interval, deaths, reinfarction	12 months
Amiodarone vs Sotalol Study Group 1989	Multicenter, R, P	The initial dose was 256±77 (range 160-320) mg/day and that on which patients were stabilized was 491±163 (range 160-640) mg/day	Oral	59/32	29/30	Amiodarone	16 patients > 1 year after AMI 10 patients between 1-12 months prior AMI 9 patients between 1 week and 1 month	Termination of VT, deaths	23 months
Ho *et al.* 1994	R, DB, CO	IV sotalol; 100 mg over 5 min	IV	33/33	16/17	Lignocaine	NS	Termination of VT, deaths	30 min
Waldo and the SWORD investigators 1995	Multicenter, R, DB, PL, P	200 mg or 400 mg of d-Sotalol daily	Oral	3121/NS	1549/1572	Placebo	2208 pts had remote MI(>42 days) and 911 had AMI (6-42 days)	Mortality, reinfarction	300 days

Long-term 'late intervention' trials are those in which patients enrolled at least 4 days after MI.
Enrollment; the time elapsed after the incidence of index acute myocardial infarction.
DB, double-blind; SB, single-blind; P, parallel; CO, crossover; PL, placebo-controlled; IV, intravenous; Com, comparative study; PVCs, premature ventricular contractions; VA, ventricular arrhythmia; VT, ventricular tachycardia; Sot, sotalol; Cont, control.

6.3.1.2 Amiodarone Clinical Trials

Thirty three clinical trials were initially identified addressing the indication of amiodarone for prolonging the survival in patients at high risk for sudden death. 20 trials were excluded from the analysis: seven due to employment of open-label, uncontrolled design (Cleland *et al.*, 1987; Herre *et al.*, 1989; Strasberg *et al.*, 1990; Kerin *et al.*, 1991; Rodriguez *et al.*, 1992; Proclemer *et al.*, 1993; Scheinman *et al.*, 1995); five were designed to evaluate different efficacy end points and long-term mortality data were not reported (McKenna *et al.*, 1981; Schmidt *et al.*, 1985; Novo *et al.*, 1988; Fournier *et al.*, 1989; Greco *et al.*, 1989; Mahmarian *et al.*, 1994); 4 were in the form of preceding abstract (Hamer *et al.*, 1988; Luna *et al.*, 1990; Stewart *et al.*, 1989; Siebels *et al.*, 1992); and three were duplicate publications for the same trial (Singh *et al.*, 1992; Singh *et al.*, 1993; Massie *et al.*, 1996). Only 12 trials satisfied the inclusion criteria, two of which, the Canadian Acute Myocardial Infarction Amiodarone Trial (CAMIAT) and the European Myocardial Infarction Amiodarone Trial (EMIAT), were still ongoing trials, with incomplete mortality data and were also excluded from analysis.

The design characteristics of the remaining 11 trials are shown in Table 6.3. The trials collectively randomised 3229 patients: 1497 received amiodarone, 841 received placebo, 215 received Class I, 130 received metoprolol, and 542 acted as a control and did not receive any antiarrhythmic treatment. The sample size of each study varied between 34 to 674 patients, with a mean of 293 patients over all studies.

Six trials employed randomised, double-blind, placebo-controlled, parallel design (Hockings *et al.*, 1987; Hamer *et al.*, 1989; Cairns *et al.*, 1991; Nicklas *et al.*, 1991; Ceremuzynski *et al.*, 1992; Singh *et al.*, 1995). Four other randomised trials employed a control group, and allocation to treatment was single-blind (Garguichevich *et al.*, 1995), or on an open-label basis (Pfisterer *et al.*, 1993; Navarro-Lopez *et al.*, 1993; Doval *et al.*, 1994; and Garguichevich *et al.*, 1995). Another large trial compared amiodarone to conventional treatment with Class I agents (The CASCADE investigators, 1993).

All trials employed an initial oral loading dose which varied between 400 to 1000 mg/day for 5 to 28 days (mean 740±231 mg/day for a mean of 15 days), followed by a lower maintenance dose which varied between 200 to 600 mg (mean 330±11 mg/day).

Table 6.3 Randomised clinical trials of amiodarone in treatment of myocardial infarction 'long-term interventions'

Study (Reference)	*Design*	*Dose*	*Route*	*N.randomised / N.Continued The Study*	*Type of control*	*Enrollment*	*Primary end points*	*Duration of treatment*
Hockings *et al.* 1987	R, DB, P, PL	600 mg/day for 4 weeks, then 200 mg/day	Oral	100/100	Placebo	< 8-10 days after AMI	Suppression of arrhythmia, death	6-42 months
Hamer *et al.* 1989	R, DB, P, PL	600 mg/day for 2 weeks, then 200 mg/day	Oral	16/14	Placebo	-	Beneficial effect of amiodarone on LVEF, exercise tolerance, side effects, and mortality	22 (3-30) months
Cairns *et al.* 1991 (CAMIAT pilot study)	R, DB, P, PL	Loading dose of 10 mg/Kg/day for 3 weeks, then a maintenance dose of 300-400 mg/day, which was then tapered depending on the response	Oral	48/29	Placebo	Within 6-30 days after AMI	Arrhythmia suppression, arrhythmic death, resuscitated VF, cardiac death, noncardiac vascular death, and nonvascular death	2 years
Nicklas *et al.* 1991	R, DB, P, PL	400 mg for 4 weeks, then a maintenance dose of 200 mg/day	Oral	49/52	Placebo	-	Sudden death, noncardiac, suppression of arrhythmia	12 months
Ceremuzynski *et al.* 1992	R, DB, P, PL	Initial dose of 800 mg/day for the first 7 days, thereafter, 400 mg for 6 days a week for 12 months (decreased to 200 or 100 mg/day if heart rate is <55 beats/min)	Oral	305/308	Placebo	Between the 5th and 7th days after admission	Sudden cardiac death, mortality from any cause, and occurrence of serious VA	12 months

Long-term 'late intervention' trials are those in which patients enrolled at least 4 days after MI.
Enrollment; the time elapsed after the incidence of index acute myocardial infarction.
DB, double-blind; SB, single-blind; P, parallel; C, controlled study; CO, crossover; PL, placebo-controlled; IV, intravenous; Com, comparative study; PVCs, premature ventricular contractions; VA, ventricular arrhythmia; VT, ventricular tachycardia; Am, amiodarone; Cont, control; AMI, acute myocardial infarction.

Table 6.3 Randomised clinical trials of amiodarone in treatment of myocardial infarction 'long-term interventions' (continued)

Study (Reference)	*Design*	*Dose*	*Route*	*Treatment allocation (Am/ Cont)*	*Type of control*	*Enrollment*	*Primary end points*	*Duration of treatment*
The CASCADE investigators 1993	R, P, O, Com	Initial loading dose of 1200 mg/day for 10 days, then 200-800 mg/day (mean 600 mg) for 1-2 months, then the dose was tapered to a maintenance dose of 100-400 mg/day	Oral	113/115	Conventional therapy with other Class I drugs	Within 6 months of the index VF	Cardiac mortality, sudden arrhythmic death, resuscitated out-of-hospital VF, and nonarrhythmic cardiac death	8 years
Pfisterer *et al.* 1993 (BASIS)	R, O, C, P	A loading dose of 1000 mg for 5 days, followed by 200 mg/day	Oral	98/114/100	Control (No antiarrhythmic treatment); 114 Class I; 100	Within 16±9 days after the acute phase of infarction	Sudden cardiac death, nonsudden cardiac death, noncardiac death, arrhythmic events, and effect on ventricular arrhythmia	72 (55-125) months
Navarro-Lopez *et al.* 1993 (SSSD)	R, O, C, P	A loading dose of 600 mg/day, followed by 200 mg/day for the first week, then 400 mg/day the second week	Oral	115/130/123	Metoprolol; 130 Control (No antiarrhythmic treatment); 123	10-60 days after AMI Median time, (36/37/47)	Sudden or nonsudden cardiac death, cardiovascular or noncardiovascular, nonfatal cardiac events	3 years
Doval *et al.* 1994 (GESICA)	R, O, C, P	600 mg/day for 14 days, then 300 mg/day for 2 years	Oral	260/256	Control (undefined)	-	Total mortality, sudden death, death due to progressive heart failure	720 days

Long-term 'late intervention' trials are those in which patients enrolled at least 4 days after MI.
Enrollment; the time elapsed after the incidence of index acute myocardial infarction.
DB, double-blind; SB, single-blind; P, parallel; C, controlled study; CO, crossover; PL, placebo-controlled; IV, intravenous; Com, comparative study; PVCs, premature ventricular contractions; VA, ventricular arrhythmia; VT, ventricular tachycardia; Am, amiodarone; Cont, control; AMI, acute myocardial infarction.

Table 6.3 Randomised clinical trials of amiodarone in treatment of myocardial infarction 'long-term interventions' (continued)

Study (Reference)	*Design*	*Dose*	*Route*	*Treatment allocation (Am/ Cont)*	*Type of control*	*Enrollment*	*Primary end points*	*Duration of treatment*
Garguichevich *et al.* 1995 (EPAMSA)	R, SB, C, P	A loading dose of 800 mg/day for 14 days, then 400 mg/day for the rest of 12 months	Oral	57/49	Control (No antiarrhythmic treatment); 49	≥ 6 months after MI	Sudden death, congestive heart failure death, other cardiac death, noncardiac death	12 months
Singh *et al.* 1995 (STATCHF)	R, DB, PL, P	800 mg/day for 14 days, then 400 mg/day for 50 weeks, then 300 mg/day till the end of the study	Oral	336/338	Placebo	-	Sudden death, congestive heart failure death, other cardiac death, noncardiac death, suppression of arrhythmia, effect on left ventricular ejection fraction	4.5 years

Long-term 'late intervention' trials are those in which patients enrolled at least 4 days after MI.
Enrollment; the time elapsed after the incidence of index acute myocardial infarction.
DB, double-blind; SB, single-blind; P, parallel; C, controlled study; CO, crossover; PL, placebo-controlled; IV, intravenous; Com, comparative study; PVCs, premature ventricular contractions; VA, ventricular arrhythmia; VT, ventricular tachycardia; Am, amiodarone; Cont, control; AMI, acute myocardial infarction.

The patient enrollment varied between 5 days to 6 months post acute phase of MI. Four trials enrolled patients with congestive heart failure or serious coronary artery disease, with or without MI (Hamer *et al.*, 1989; Nicklas *et al.*, 1991; Doval *et al.*, 1994; Singh *et al.*, 1995). Inclusion of those trials was justified, since the overwhelming majority of those patients have the potential for development of MI with increased risk of sudden death (Teo *et al.*, 1993).

The duration of follow-up in the studies varied between 6 to 96 months, with a mean of 34.33 months.

6.3.2 Patient Demographic Criteria

6.3.2.1 Sotalol Clinical Trials

Table 6.4 shows details of patient characteristics in sotalol (racemic) trials. The mean age of the patients across all studies which reported the age (9 studies), was 58.66±5.22 years (range 52.5 to 68). In the 7 studies reporting gender, there was a total of 1057 women and 1433 men. The total number of patients who had a previous history of MI attack before the index MI was 5 (3 sotalol-treated; and 2 control-treated) in short-term studies, and 183 (89 sotalol-treated; and 114 control-treated) in long-term studies. Data regarding the mean left ventricular ejection fraction (LVEF) was mentioned in 3 studies, with a total mean of 37.52±7 mm (range 32.04 to 43). The mean PVCs/hr inclusion criteria varied significantly across the 6 studies reporting it from 1/hr to 406/hr.

In addition to MI, other associated cardiac complications were congestive heart failure in 44 patients (22 sotalol-treated, and 22-control-treated), angina in 2107 patients (1047 sotalol-treated, and 1060 control-treated), and hypertension in 124 patients (65 sotalol-treated, and 59-control-treated). Total number of patients receiving other beta-blockers was 61 patients (32 sotalol-treated, and 29-control-treated) in one trial (Cobbe *et al.*, 1988), zero in 8 trials, and not stated in two trials. Prognostic classification of the arrhythmia associated with patients included in this analysis was based primarily on the risk of sudden cardiac death according to the criteria discussed earlier in Chapter 2. Consequently, the ventricular arrhythmia was considered prognostically important or potentially lethal in eight studies (3410 patients), and malignant in two studies (1515

patients).

Comparison between the trials' subgroups data regarding the age and left ventricular ejection fraction by using unpaired t-test and one way analysis of the variance, did not reveal a significant difference in distribution.

6.3.2.2 Amiodarone Clinical Trials

Table 6.5 delineates the details of patient characteristics in amiodarone trials. The mean age of the patients across all studies, which reported the age (10 studies), was 61.44±3.5 years (range 56 to 70). In the 9 studies reporting gender, there was a total of 728 women and 2251 men. Data regarding the mean left ventricular ejection fraction (LVEF) was available in 9 studies, with a total mean of 30.63±9.3 mm (range 17 to 46). The mean PVCs/hr inclusion criteria ranged between 3.4 and 30 PVCs/min.

Comparison of mean age and mean LVEF among treatment subgroups in individual studies by one way analysis of the variance suggested nonsignificant difference.

In five trials (Cairns *et al.*, 1991; The CASCADE investigators, 1993; Pfisterer *et al.*, 1993; Navarro-Lopez *et al.*, 1993; and Singh *et al.*, 1995) the total number of patients concomitantly receiving beta-blocker therapy was 306 patients; 112 in amiodarone group, and 194 in control group (chi-square = 4.798, df=4, P=0.0285). Examination of the distribution of other dichotomous diagnostic variables, including the number of patients with a previous history of MI, coronary artery disease, and anterior or inferior MI, did not reveal significant difference (P>0.05). However, the male percentage was significantly higher in amiodarone-treated patients (chi-square = 16.8, P=0.000042).

Table 6.4 Population characteristics of included sotalol studies

Study	*Mean Age±SD*	*Gender, M/F*	*History of AMI*	*PVCs inclusion criteria*	*LVEF, mean%±SD%*	*No. CHF*	*NYHA Class*	*No. Coronary artery diseases*	*No. patients with other associated cardiac diseases*	*Patients Receiving B-Blocker*	*No. patient with Cardiomyopathy*
Myburgh *et al.*	53 (38-65)	-	20	15/hr	-	-	-	20 MI	-	0	-
Julian *et al.*	55.4±7.9, 55.2±7.9	160/40	15, 15	NS	-	21/22	-	873/583 MI 28/23 angina	12, 13 hypertension	0	0
Spielman *et al.*	-	-	17 sotalol, 18 encainide, 20 timolol	≥ 10/hr	≤ 40	-	-	17/18/20 MI	-	NS	-
Astrom *et al.*	57±2.9, 64±3	-	1, 0	300/hr	-	-	-	15/15 AMI	0	0	-
Llewellyn *et al.*	-	-	-	mean±SD; S; 206±284 P; 406±513	-	-	-	-	-	NS	-
Lloyd *et al.*	58.2 (37-70), 52.5 (34-69)	22/8	-	360/hr	48.7±16.5, 49.4±14.5	-	-	-	-	0	-
Cobbe *et al.*	56.7±7.3, 53.7±9.4	93/10	5, 5	> 1/hr in 88 pts and > 110/hr in 13 pts	-	1/0	-	5/5 MI	13, 3 hypertension	32, 28	-
Amiodarone vs Sotalol study group	59.8±14.6, 60.8±12.2	48/11	18, 20	NS	32.8±12, 36± 16.	-	-	10/11 angina	-	0	-
Juul-Moller *et al.*	67±8, 67±8	1058/977	-	NS	-	-	-	1009/1026 angina	40, 43 hypertension	0	-
McGrath *et al.*	53±3, 55±2	26/4	2, 2	NS	-	-	-	15/15 MI	-	0	-
Ho *et al.*	68±6 (56-80), 61±18 (21-90)	26/7	Old MI; 13, 15 Acute MI; 1, 1	NS	33±10 (18-45), 36±17(19-76)	-	-	14/16 MI	-	0, 1	0, 1
Waldo and SWORD investigators	60.4±10, 59.9±9.8	2684/437	527, 503	NS	31±6.8, 30.8±7	108/126 1115/1131 341/330	Class I Class II Class III	1549/1572 MI	573, 550 hypertension	511, 503	-

The first data set represents a sotalol-treated group; second data set represents a control-treated group; AMI, acute myocardial infarction; CHF, number of patients with congestive heart failure; LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association functional class; PVCs, premature ventricular contractions

Table 6.5 Population characteristics of included amiodarone studies

Study	*Mean Age±SD*	*Gender, M/F*	*History of AMI*	*PVCs inclusion criteria*	*LVEF, mean%±SD%*	*No. CHF*	*NYHA Class*	*No. Coronary artery diseases*	*No. patients with other associated cardiac diseases*	*Patients Receiving B-Blocker*	*Anterior/Inferior MI*
Hockings *et al.* 1987	-	-	-	-	-	-	-	-	-	-	57/34, 58/42
Hamer *et al.* 1989	70, 66	-	-	-	19, 17	4/3 11/10 1/1	II III IV	8/10	8, 4 cardiomyopathy	-	-
Cairns *et al.* 1991 (CAMIAT pilot study)	64, 66	35/13, 23/6	56/48	≥10 PVCs/min	-	13/9	-	27/14	-	17, 8	18/30, 12/17
Nicklas *et al.* 1991	56±1, 59±1	41/8, 45/7	-	204 PVCs/hr	19±1, 21±1	39/44 10/8	III IV	25/28	-	-	-
Ceremuzynski *et al.* 1992	59.4±12.3, 58.6±11.8	88/217, 98/210	50/45	NS	≥40 154, 155 ≤40 98, 105	-	-	-	132, 148 hypertension	-	156/138, 157/136
The CASCADE investigators 1993	63±10, 62±10	103/10, 99/16	80/72	≥10 PVCs/min	35±10, 35±14	54/48	I, II, IV	96/92	17, 23 noncoronary artery disease	7, 6	-
Pfisterer *et al.* 1993 (BASIS)	61±7, 61±6 C, 60±8 CI	79/19, 97/17, 91/9	37/56/36	≥10 PVCs/min	46±2, 42±2, 41±2	-	-	-	46, 50, 45 hypertension	35, 49, 46	31/67, 50/64, 44/56
Navarro-Lopez *et al.* 1993	58±10, 59±10 M, 57±9 C	100/15, 123/7, 108/15	32/26/25	≥3 PVCs/hour	35±7, 34±7, 35±7	22/17/20	I, II	-	37, 36, 32 hypertension	40, 22, 47	36/29, 42/32, 43/31
Doval *et al.* 1994 (GESICA)	58.5, 60.1	211/45, 198/62	98/103	≥10 PVCs/min	20, 19	52/56 123/126 81/78	II III IV	-	102, 105 hypertension	-	-
Garguichevich *et al.* 1995 (EPAMSA)	62±8, 60±10	82/18, 73/27	25/18	≥30 PVCs/min	27±7, 27±7	-	-	25/18, MI	20, 19 cardiomyopathy 12, 12 chagasic heart disease	-	-
Singh *et al.* 1995 (STATCHF)	65±8.5, 66.1±8.1	333/3, 334/4	-	≥10 PVCs/min	<30 226, 222 30-40 110, 116	4/4 179/179 135/144	I II III or IV	242/239	-	13, 16	-

The first data set represents amiodarone-treated group; second data set represents control-treated group; C, control group; CI, class I; M, metoprolol; AMI, acute myocardial infarction; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA class, New York Heart Association functional class; PVCs, premature ventricular contractions

6.3.3 Efficacy

6.3.3.1 Sotalol clinical trials

6.3.3.1.1 Conventional therapeutic end points employed in short-term acute trials

6.3.3.1.1.1 *Infarct size*

Recent studies have demonstrated a significant correlation between infarct size and total creatine phosphokinase (CPK) into the circulation (Willerson *et al.*, 1972; Norris *et al.*, 1980; International Collaborative Study Group, 1984). Hence, early therapeutic intervention, which can alter the enzyme release and consequently reduce the myocardial damage, were thought to be determinant for improving the prognosis of acute MI. Clinical trials frequently produce indirect measurement of infarct size as the percentage reduction in enzyme release or ECG changes (Yusuf *et al.*, 1985). In this review, three short-term, placebo-controlled trials evaluated the effect of early intravenous sotalol for limiting infarct size in the acute phase of MI (Astrom *et al.*, 1986; McGrath *et al.*, 1986; Lloyd *et al.*, 1988). The infarct size was determined by accumulated creatine kinase release and peak CK. Table 6.6 displays the results observed in these trials. Estimation of a pooled effect size was hindered by incomplete and inconsistent reporting of means together with their standard errors or standard deviations in individual trials. The treatment effect on the enzyme level was favourable in only one trial of 30 patients (Lloyd *et al.*, 1988). However, further validation is required in a larger trial.

Table 6.6 Summary of the effect of antiarrhythmic treatment with sotalol on serum enzyme release

Trial	Enzyme	Cumulated release and/or peak value of the enzyme		P
		Rx	Control	
Astrom *et al.* 1986	CK	-	-	NS
McGrath *et al.* 1986	CK	Peak CK (IU/l); 113±13 Cumulated release; 199±24	Peak CK (IU/l); 125±16 Cumulated release; 184±21	NS
Lloyd *et al.* 1988	CK	Peak CK (IU/l); 912	Peak CK (IU/l); 257	P< 0.03

CK, creatine kinase

6.3.3.1.1.2 *Effect on heart rate*

Heart rate was considered an important haemodynamic index which might predict, better than any other parameter the beneficial effect of beta-blockers in acute myocardial infarction with regard to mortality and nonfatal reinfarctions (Kjekshus *et al.*, 1986). This was explained by the possible decrease in oxygen requirement with a subsequent reduction in infarction size. This had supported the concept of the antiischemic rather than antiarrhythmic mechanism of action (Kjekshus *et al.*, 1982). A previous overview of early intervention trials of beta-blockers has shown a close relation between reduction in heart rate of at least 15 beats/min during infarct evolution, and reduction of infarct size between 25% and 30% (Kjekshus *et al.*, 1986). It has also suggested that a reduction of the heart rate of < 8 beats/min has no effect or may even increase infarct size.

In this overview, four sotalol placebo-controlled RCTs (of a total of 62 sotalol-treated; and 67 placebo-treated patients) examined the effect of sotalol on heart rate at different time points throughout the study period after intravenous infusions in the ICU unit. Mean heart rate at each time point together with its standard deviation, or standard error, were extracted from the published graphs (Astrom *et al.*, 1986; McGrath *et al.*, 1986), or tables (Llewellyn *et al.*, 1986; Lloyd *et al.*, 1988).

The weighted mean change compared to baseline for sotalol and placebo treated groups (dt and dp respectively), individual trial effect sizes, and pooled effect sizes under fixed and random effects models are listed in Table 6.7. As shown in Figure 6.1, the pooled effect size was statistically significant at all time points under the fixed-effects model. However, due to heterogeneity of effect, random-effects model was employed at 30 mins, 2, 4, and 6 hours. As a result, the pooled effect has not reached the level of significance at 2 and 4 hours. Correlation analysis between the effect on heart rate and the reduction in all cause mortality or morbidity (non-fatal reinfarctions) by reduction of infarct size was not feasible, since the later data were missing from most trial reports.

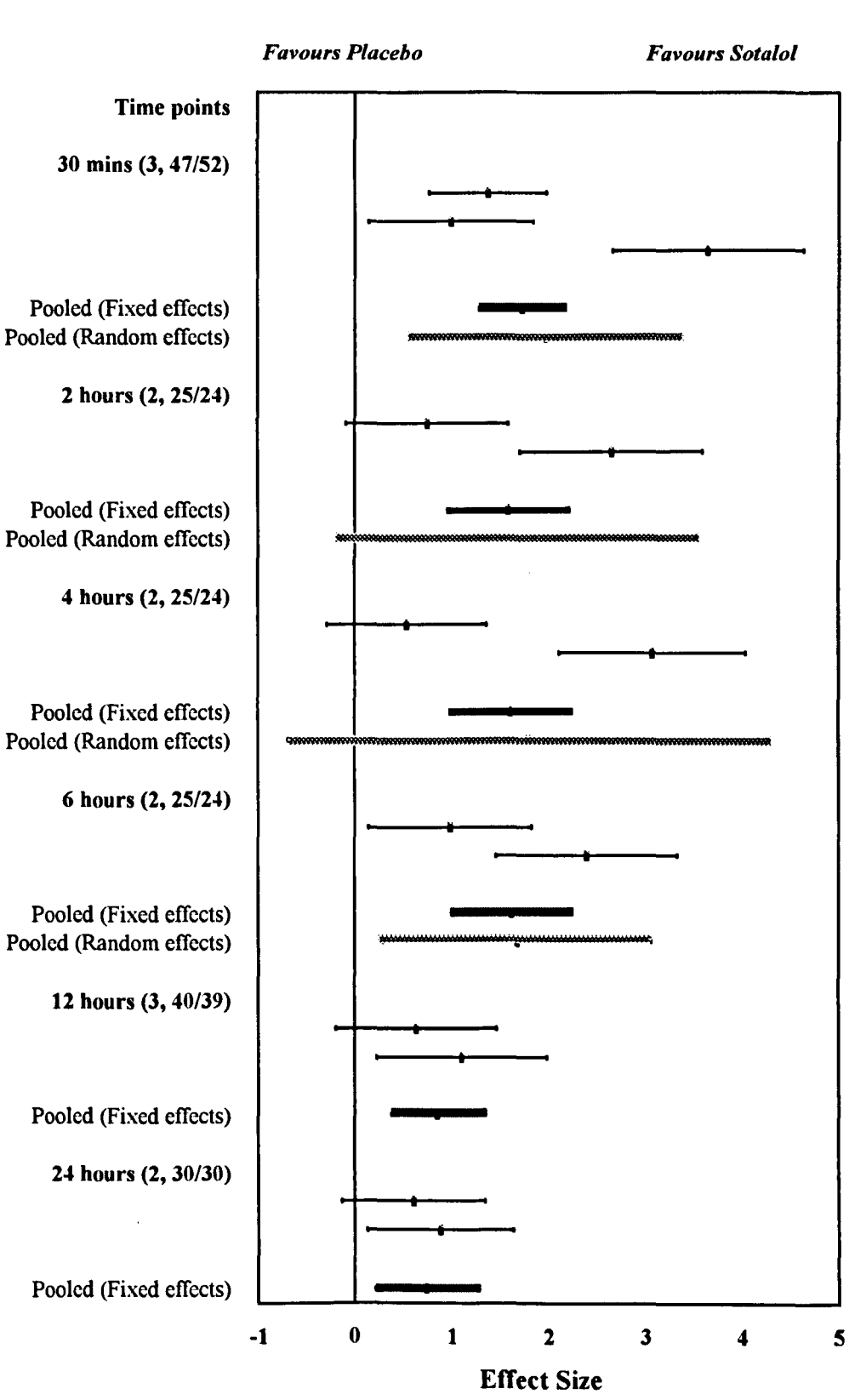

Figure 6.1 Effect of early administration of intravenous sotalol on heart rate in acute myocardial infarction as compared to placebo. The number of trials pooled and total number of patients are shown in brackets.

Table 6.7 Meta-analytic estimates for the effect of sotalol on heart rate

Trial	*Time point*	*No.pts (S/C)*	*Treatment effect (dt)§, (beats/mins)±SDP*	*Placebo effect (dp)§, (beats/mins)±SDP*	*Effect size (95% CI)*	*Z (P)*	*Infarct reduction (OR; P)*	*Mortality reduction*
Llewellyn *et al.* 1986*	30 mins	22/28	-17±9.4	2±13.2	1.378 (0.8-1.98)	4.5**	Not stated	Not stated
Astrom *et al.* 1986*	30 mins	10/9	-8±7.1318	-6±12	0.998 (0.15-1.9)	2.3**	NS	Not stated
McGrath *et al.* 1986*	30 mins	15/15	-20±19.02	1.6±5.2	3.65 (2.7-4.6)	7.2**	NS	OR; 0.5 (NS)
Pooled	30 mins	47/52	-	-	FEs; 1.73 (1.3-2.2) REs; 1.97 (0.56-3.39)	7.7** 2.7**	-	-
Astrom *et al.* 1986*	2 hrs	10/9	-6.2±6.93	1±28.6423	0.76 (-0.08-1.59)	1.8 (NS)	NS	Not stated
Lloyd *et al.* 1988*	2 hrs	15/15	-20.5±19.04	4±6	2.66 (1.7-3.6)	5.5**	Significant compared to placebo	Not stated
Pooled	2 hrs	25/24	-	-	FEs; 1.59 (0.96-2.214) REs; 1.692 (-0.17-3.6)	4.97** 1.78 (NS)	-	-
Astrom *et al.* 1986*	4 hrs	10/9	-6.2±5.513	-2.74±28.8	0.54 (-0.28-1.37)	1.3 (NS)	NS	Not stated
McGrath *et al.* 1986*	4 hrs	15/15	-20±19.02	5.2±5.8	3.1 (2-4.04)	6.3**	NS	OR; 0.5 (NS)
Pooled	4 hrs	25/24	-	-	FEs; 1.6 (0.99-2.2) REs; 1.8 (-0.69-4.3)	5** 1.42 (NS)	-	-
Astrom *et al.* 1986*	6 hrs	10/9	-5±5.5127	2.1±27.5	0.99 (0.14-1.834)	2.3**	NS	Not stated
Lloyd *et al.* 1988*	6 hrs	15/15	-21.9±18.7	4±6.4	2.4 (1.5-3.34)	5**	Significant compared to placebo	Not stated
Pooled	6 hrs	25/24	-	-	FEs; 1.6 (0.996-2.3) REs; 1.68 (0.29-3.1)	5** 2.4**	-	-
Astrom *et al.* 1986*	12 hrs	10/9	-6.4±7.3342	-3.67±14	0.64 (-0.19-1.5)	1.5 (NS)	NS	Not stated
McGrath *et al.* 1986*	12 hrs	15/15	-19.67±17.6872	-15.4±7.9644	1.11 (0.23-1.98)	2.5**	NS	OR; 0.5 (NS)
Lloyd *et al.* 1988*	12 hrs	15/15	-20.6±15.597	-3.1±26.964	0.85 (0.1-1.597)	2.2*	Significant compared to placebo	Not stated
Pooled	12 hrs	40/39	-	-	FEs; 0.85 (0.4-1.3)	3.6**	-	-
McGrath *et al.* 1986*	24 hrs	15/15	-15.495±17.695	4.7±14.8472	0.61 (-0.13-1.35)	1.6 (NS)	NS	OR; 0.5 (NS)
Lloyd *et al.* 1988*	24 hrs	15/15	-17.2±15.7519	0.7±26.9382	0.9 (0.13-1.64)	2.3*	Significant compared to placebo	Not stated
Pooled	24 hrs	30/30	-	-	FEs; 0.74 (0.22-1.3)	2.76**	-	-

S, sotalol; C, control; §, Mean change compared to baseline; SD_P, pooled standard deviation of the change; *, statistically significant; **, highly statistically significant; FEs, fixed-effects model; REs, random-effects model; NS, not significant.

6.3.3.1.1.3 *Prevention and termination of arrhythmias*

Two placebo-controlled, short-term trials evaluated the efficacy of sotalol in preventing the development of various types of arrhythmia episodes post acute MI (McGrath *et al.*, 1986; Lloyd *et al.*, 1988). Figure 6.2 and Table 6.8 display the meta-analytic ORs for prevention of PVCs, VT, and VF. The results were significant in favour of sotalol for prevention of PVCs only (OR, 0.229; 95% CI, 0.08-0.65; Z=-2.8, P<0.01). However, three other trials have estimated the difference in the PVCs frequency (Table 6.9) between sotalol and placebo (Llewellyn *et al.*, 1986; Astrom *et al.*, 1986) or another beta-blocker atenolol (Cobbe *et al.*, 1988), and the individual trial results were not significant. Due to the inconsistent reporting of mean PVCs/24 hours in the three trials, a meta-analytic rate difference could not be estimated.

Furthermore, the remedial action of sotalol for termination of various episodes of arrhythmia development during chronic MI was evaluated in long-term trials (Myburgh *et al.*, 1979; Langbehn *et al.*, 1985; Spielman *et al.*, 1985; Hou *et al.*, 1994). Although the data were reported in various forms (for example, number of patients with a specific percentage of PVCs suppression), only the number of patients with complete VT and ≥ 70% suppression were included in the analysis. Table 6.10 and Figure 6.2 give the individual odds ratios for suppression of arrhythmia with various treatments. Due to variation in duration of treatment, route of administration, as well as employment of different control groups, pooling was not possible. In the placebo-controlled trial (Myburgh *et al.*, 1979) sotalol displayed more efficacy than placebo in completely abolishing PVCs. However, this did not reach the conventional level of significance. It has also been shown to be more efficacious than timolol in suppressing PVCs and VT (Spielman *et al.*, 1985) with OR equal to 9.7 (95% CI, 1.6-59.7). Furthermore, intravenous sotalol was superior to intravenous lignocaine for acute termination of VT (Hou *et al.*, 1994) and of comparable efficacy to flecainide and encainide (a two Class IC agents), with OR equal to 0.42 (95% CI, 0.12-1.5) and 0.45 (95% CI, 0.08-2.5) respectively.

In spite of the previous estimations, a firm conclusion, with regard to sotalol's efficacy relative to other drugs for termination of arrhythmia in patients at high risk, can not be drawn without a larger trial. In addition, validation of this efficacy criterion in the light of its effect on mortality and morbidity in MI patients is also essential.

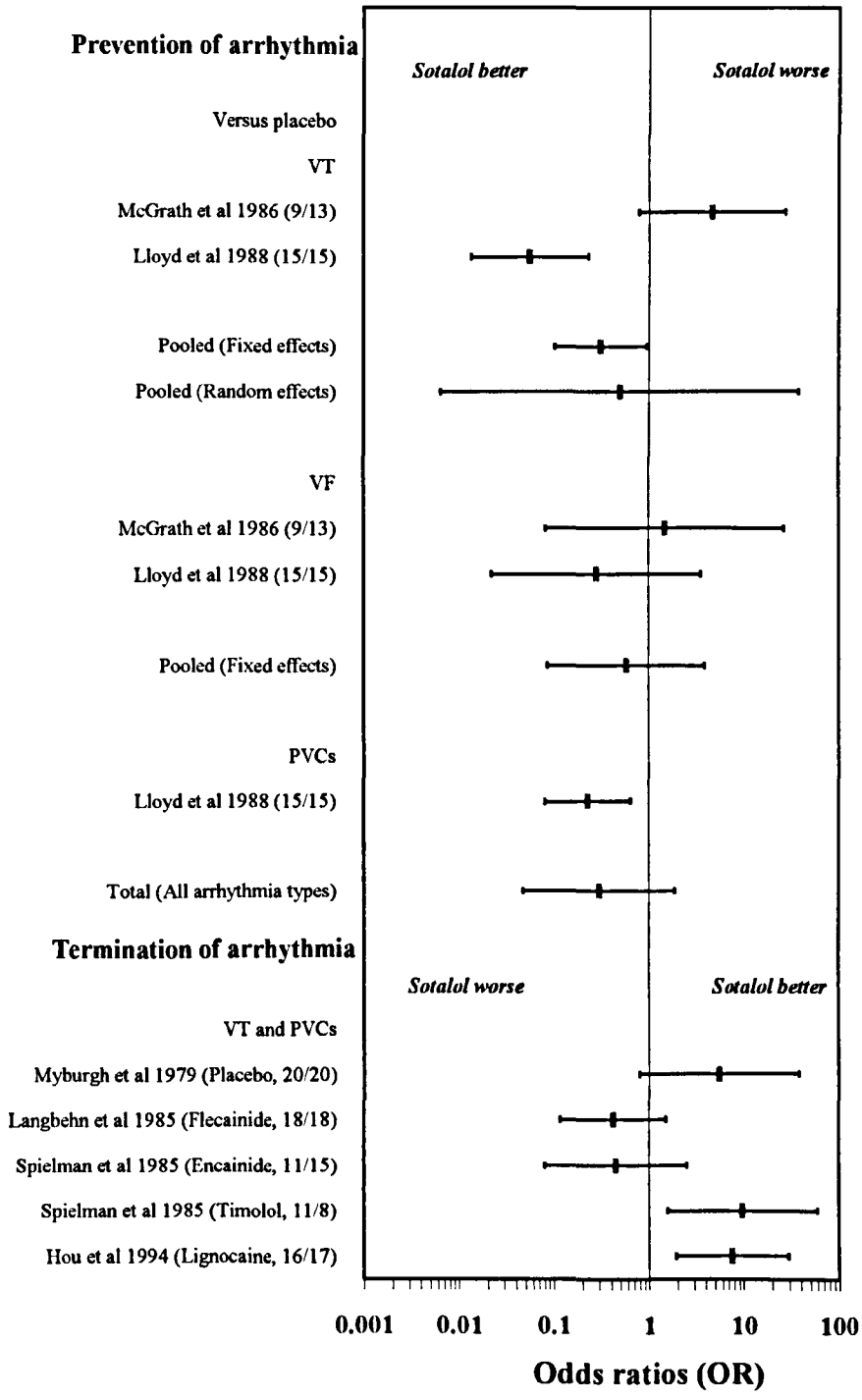

Figure 6.2 Efficacy of sotalol for prevention or termination of arrhythmias in patients with acute or chronic myocardial infarction respectively. The figure depicts odds ratios with their 95% CI as compared to a direct control group in acute and long-term studies.

Table 6.8 Prevention of arrhythmia incidence from sotalol short-term trials

Study name	*Basic data (no. arrhythmia event/no. randomised)*		*Peto's method*			
	Sotalol group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*Z statistic for effect (P)*
McGrath *et al.* 1986	VT; 8/9 VF; 1/9	7/13 1/13	1.864 0.18182	1.21 0.46	4.6 (0.79-27.8) 1.48 (0.08-26.7)	1.7 (NS) 0.27 (NS)
Lloyd *et al.* 1988	PVCs 6/min; 15/15 PVCs, coupled; 4/15 PVCs, multiform; 0/15 VT; 3/15 VF; 0/15	15/15 8/15 7/15 14/15 2/15	0 -2 -3.25 -5.5 -0.75	14.5 6 3.75 1.91 0.593	1 (0.019-50.4) 0.34 (0.08-1.44) 0.11 (0.02-0.54) 0.06 (0.014-0.23) 0.28 (0.02-3.6)	0 (NS) -1.5 (NS) -2.7 (NS) -3.99** -0.97 (NS)
Pooled for VT	11/24	21/28	-3.636	3.12	FEs, 0.3 (0.1-0.95) REs, 0.49 (0.01-37.8)	-2* -0.32 (NS)
Pooled for VF	1/24	3/28	-0.5682	1.05	FEs, 0.58 (0.086-3.9)	-0.6 (NS)
Pooled for PVCs	No. events; 19	30	-5.25	3.6	FEs, 0.23 (0.08-0.65)	-2.8**
Pooled for all types	No. events; 31	54	-10	6.4	FEs, 0.2 (0.097-0.5) REs, 0.299 (0.05-1.9)	-3.9** -1.3 (NS)

PVCs, premature ventricular contractions; VF, ventricular fibrillation; VT, ventricular tacchycard; *, statistically significant; **, highly statistically significant; FEs, fixed-effects model; REs, random-effects model; NS, not significant

Table 6.9 The sotalol effect on VPCs frequency in post MI trials

Trial	*VPCs/24 hrs*		*Type of control*	*Significance of the difference*
	Rx	*Control*		
Llewellyn *et al.* 1986	Mean±SD; 206±284	406±513	Placebo	NS (P=0.07)
Astrom *et al.* 1986	Not stated	Not stated	Placebo	NS
Cobbe *et al.* 1988	Median (range); Baseline, 11.5 (0-2226) 6 days, 16 (0-4202)	Baseline, 5 (0-10429) 6 days, 8 (0-672)	Atenolol	NS

PVCs, premature ventricular contractions

Table 6.10 Efficacy for termination of arrhythmias during chronic MI

Trial	*No. of pts with terminated arrhythmia/No.total*		*Peto's method*			
	Sotalol	*Control*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*Z statistic for effect (P)*
Myburgh *et al.* 1979	PVCs, 4/20	0/20 PL	1.75	1.02404	5.523 (0.796-38.3)	1.73 (NS)
Langbehn *et al.* 1985	PVCs, 7/18	11/18 Flecainide	-2	2.31429	0.42 (0.116-1.5)	-1.3 (NS)
Spielman *et al.* 1985	70% PVCs and VT, 7/11	12/15, Encainide 0/8, Timolol	-1.04 2.7	1.29852 1.2	0.4495 (0.08-2.5) 9.7 (1.6-59.7)	-0.9 (NS) 2.5*
Hou *et al.* 1994	VT, 11/16	3/17 Lignocaine	4.2	2.07622	7.61 (1.95-29.6)	2.9**

PL, placebo; PVCs, premature ventricular contractions; VF, ventricular fibrillation; VT, ventricular tacchycard; *, statistically significant; **, highly statistically significant; FEs, fixed-effects model; REs, random-effects model; NS, not significant

6.3.3.1.1.4 *Short-term Mortality*

Mortality data were classified into sudden cardiac (presumed arrhythmic), other cardiac, noncardiac, undefined, and total mortality (all cause) as shown in Table 6.11 for the acute short-term, and long-term trials (discussed in the subsequent section).

Table 6.12 and Figure 6.3 provide the calculated odds ratios for total mortality on sotalol in both types of trials. When mortality was not reported, an assumption that no deaths occurred in either treatment groups was made. Unfortunately, short-term trials of oral or intravenous sotalol reported very limited data on mortality. Only in one acute trial (McGrath *et al.*, 1986) of 30 patients (15 sotalol-treated and 15 placebo-treated), one death was reported in the placebo group. Another RCT (Juul-Moller *et al.*, 1992) involving 2035 patients had a comparison of the effect of sotalol+placebo versus sotalol+aspirin for the prevention of all cause mortality as primary objective, and sudden death in patients with chronic unstable angina. The study demonstrated a significant reduction in sudden cardiac death when aspirin was added to sotalol but no conclusions could be drawn with regard to sotalol's absolute efficacy in reducing mortality (Figure 6.3).

In general, the acute studies were very small in sample size and were not designed to examine short-term mortality.

6.3.3.1.2 Chronic long-term trials

6.3.3.1.2.1 *Long-term mortality*

A total of six *d,l*-sotalol (racemic sotalol) long-term trials have reported on mortality (Myburgh *et al.*, 1979; Julian *et al.*, 1982; Spielman *et al.*, 1985; Cobbe *et al.*, 1988; Amiodarone vs Sotalol Study Group, 1989; Hou *et al.*, 1994). Only three of these were designed primarily to assess the effect of the drug on mortality (Julian *et al.*, 1982; Spielman *et al.*, 1985; Amiodarone vs Sotalol Study Group, 1989), and only one was placebo-controlled (Julian *et al.*, 1982). Thus a meta-analytic pooled odds ratio was not calculated.

Table 6.12 and Figure 6.3 display the individual odds ratio for total mortality in the six studies. As shown, no additional benefit for racemic sotalol over placebo, other beta-

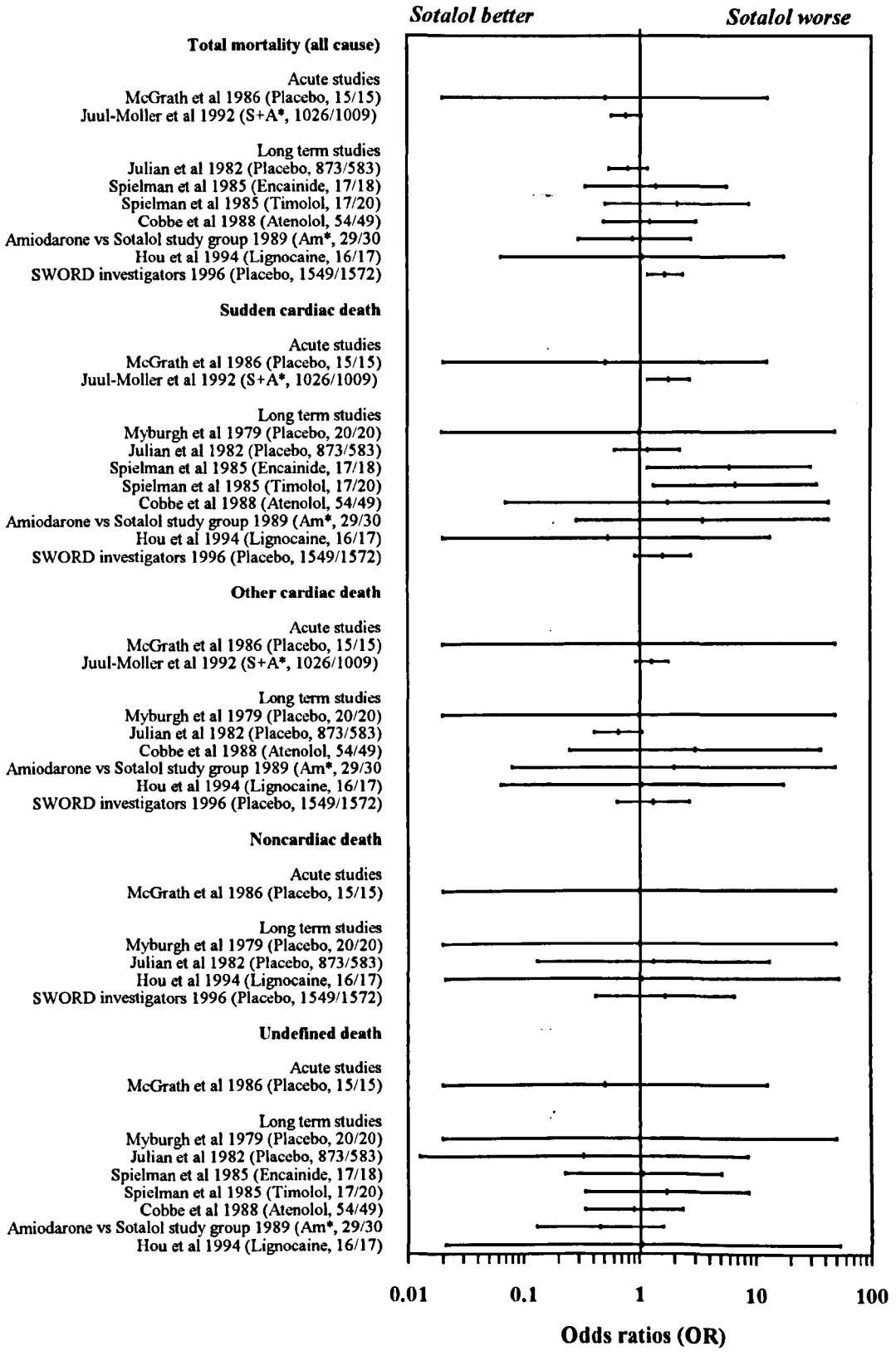

Figure 6.3 Odds ratios for total mortality, sudden cardiac death, other cardiac deaths, noncardiac death, and undefined death in sotalol short-term acute or long-term chronic interventions for treatment of myocardial infarction. Type of control and number of patients randomised in each group are shown in brackets. *S+A, sotalol+aspirin; Am, amiodarone.

Table 6.11 Mortality data reported in sotalol randomised clinical trials

Study	*Sudden Cardiac Deaths*	*Other cardiac Deaths*	*Noncardiac deaths*	*Undefined Deaths*	*Total Mortality*
Myburgh *et al.*	0/20 S, 0/20 PL	0/20 S, 0/20 PL	0/20 S, 0/20 PL	0/20 S, 0/20 PL	0/20, 0/20 PL
Julian *et al.*	25/873 S, 14/583 PL	37/873 S, 36/583 PL	2/873 S, 1/583 PL	1/583 PL	64/873 S, 52/583 PL
Spielman *et al.*	6/17 S, 1/18 E, 1/20 T	NS	NS	4/18 E, 3/20 T	6/17 S, 5/18 E, 4/20 T
Astrom *et al.**	0/10 S, 0/9 PL	0/10 S, 0/9 PL	0/10 S, 0/9 PL	0/10 S, 0/9 PL	0/10 S, 0/9 PL
Llewellyn *et al.**	0/28 S, 0/28 PL	0/28 S, 0/28 PL	0/28 S, 0/28 PL	0/28 S, 0/28 PL	0/28 S, 0/28 PL
Lloyd *et al.*	NS	NS	NS	NS	NS
Cobbe *et al.*	1/54 S, 0/49 A	2/54 S, 0/49 A	NS	10/54 S, 10/49 A	13/54 S, 10/49 A
Amiodarone vs sotalol study group.	2/29 S, 0/30 Am	1/29 S, 0/30 Am	NS	4/29 S, 8/30 Am	7/29 S, 8/30 Am
Hou *et al.*	0/16 S, 1/17 Lig	1/16 S, 1/17 Lig	0/16 S, 0/17 Lig	0/16 S, 0/17 Lig	1/16 S, 1/17 Lig
Juul-Moller *et al.*¶	19/1009 S+As, 31/1026 S+PL	66/1009 S+As, 85/1026 S+PL	-	-	82/1009 S+As, 106/1026 S+PL
McGrath *et al.**	0/15 S, 1/15 PL	0/15 S, 0/15 PL	0/15 S, 0/15 PL	0/15 S, 1/15 PL	0/15 S, 1/15 PL
Waldo and SWORD investigators	56/1549, 32/1572 PL	17/1549, 13/1572 PL	5/1549, 3/1572 PL	-	78/1549 S, 48/1572 PL

* Early intervention trial; A, Atenolol; Am, Amiodarone; As, Aspirin, E, Encainide; Fle, Flecainide; PL, Placebo; Lig, Lignocaine; S, Sotalol; T, Timolol; ¶, The patients included in this study had chronic stable angina pectoris which can predispose to fatal or non-fatal myocardial infarction

Table 6.12 Total mortality data and statistical analysis of full-exposure group in randomised clinical trials of sotalol

Study name	*Basic data (No dead/No followed up)*		*Peto's method*			
	Sotalol group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*
McGrath *et al.**1986	0/15	1/15 PL	-0.25	0.3685	0.5075 (0.02-12.8)	-0.4
Julian *et al.* 1982	64/873	52/583 PL	-5.5522	25.6484	0.81 (0.6-1.19)	-1.1
Spielman *et al.* 1985	6/17	5/18 E 4/20 T	0.6571 1.4054	1.9396 1.8627	1.4 (0.34-5.7) 2.13 (0.5-8.9)	0.472 1.03
Cobbe *et al.* 1988	13/54	10/49 A	0.9417	4.4992	1.23 (0.49-3)	0.44398
Amiodarone vs sotalol study group 1989	7/29	8/30 Am	-0.3729	2.844	0.88 (0.3-2.8)	-0.22
Juul-Moller *et al.* 1992	106/1026 PL+S	82/1009 As+S	-11.2147	42.676	0.77 (0.57-1.04)	-1.72
Hou *et al.* 1994	1/16	1/17 Lig	0.0303	0.4839	1.065 (0.064-17.8)	0.0436
Waldo and SWORD investigators 1996	78/1549	48/1572 PL	15.4643	30.2363	1.67 (1.17-2.4)	2.812

* Early intervention trial; A, Atenolol; Am, Amiodarone; As, Aspirin, E, Encainide; Fle, Flecainide; PL, Placebo; Lig, Lignocaine; S, Sotalol; T, Timolol; * statistically significant ($P<0.05$); ** highly statistically significant ($P<0.01$)

blockers (timolol and atenolol), Class IC agent (encainide), another Class III drug (amiodarone), or lignocaine was demonstrated.

Restricting the comparison to sotalol versus other beta-blockers, the pooled OR for total mortality and undefined deaths in two trials (of total 71 versus 69 patients) did not show any significant difference for the two treatments (OR_{total}, 1.44; 95% CI, 0.67-3.15; Q=0.39, P=0.53; and $OR_{undefined}$, 0.72; 95% CI; 0.296-1.8; Q=1.05, P=0.31). On the other hand, the pooled results for prevention of sudden arrhythmic death suggested a statistically significant effect for other beta-blockers over sotalol (OR, 5.19; 95% CI, 1.214-22.2; Q=0.54, P=0.46), indicating that beta-blocker activity may be the main protective mechanism against sudden arrhythmic death.

The survival with oral *d*-sotalol (SWORD) trial was a large (3121 patients), multinational, multicenter, placebo-controlled, randomised, and double-blind trial of d-sotalol designed to test the hypothesis that the preventive effect was mainly due to a Class III activity. However, this study was stopped abruptly as *d*-sotalol increased total mortality relative to placebo (OR, 1.7; 95% CI, 1.2-2.4; Z=2.8; P<0.01).

6.3.3.1.2.2 *Non-fatal cardiovascular events*

Reduction of reinfarction in patients who survived an acute MI is one of the major aims of further treatment (Singh, 1991). The prevention of non-fatal reinfarction was examined in four trials. Three were for racemic sotalol (Julian *et al.*, 1982; Cobbe *et al.*, 1988; Juul-Moller *et al.*, 1992), and one for *d*-sotalol (SWORD investigators, 1996). Due to employment of different control groups (placebo in Julian *et al.*, 1982; atenolol in Cobbe *et al.*, 1988; and sotalol+aspirin in SAPAT trial, 1992), pooling the data was not possible.

d,l-sotalol was significantly more effective than placebo in preventing reinfarction (Table 6.13.1). However, when compared to atenolol, there was no difference in the preventive effect. Addition of aspirin to sotalol increased the efficacy of sotalol in preventing non-fatal reinfarction in patients with chronic unstable angina (Juul-Moller *et al.*, 1992).

As shown in the Figure 6.4, no significant effect on other non-fatal events was observed. Moreover, *d*-sotalol has been shown not to have any superior efficacy when

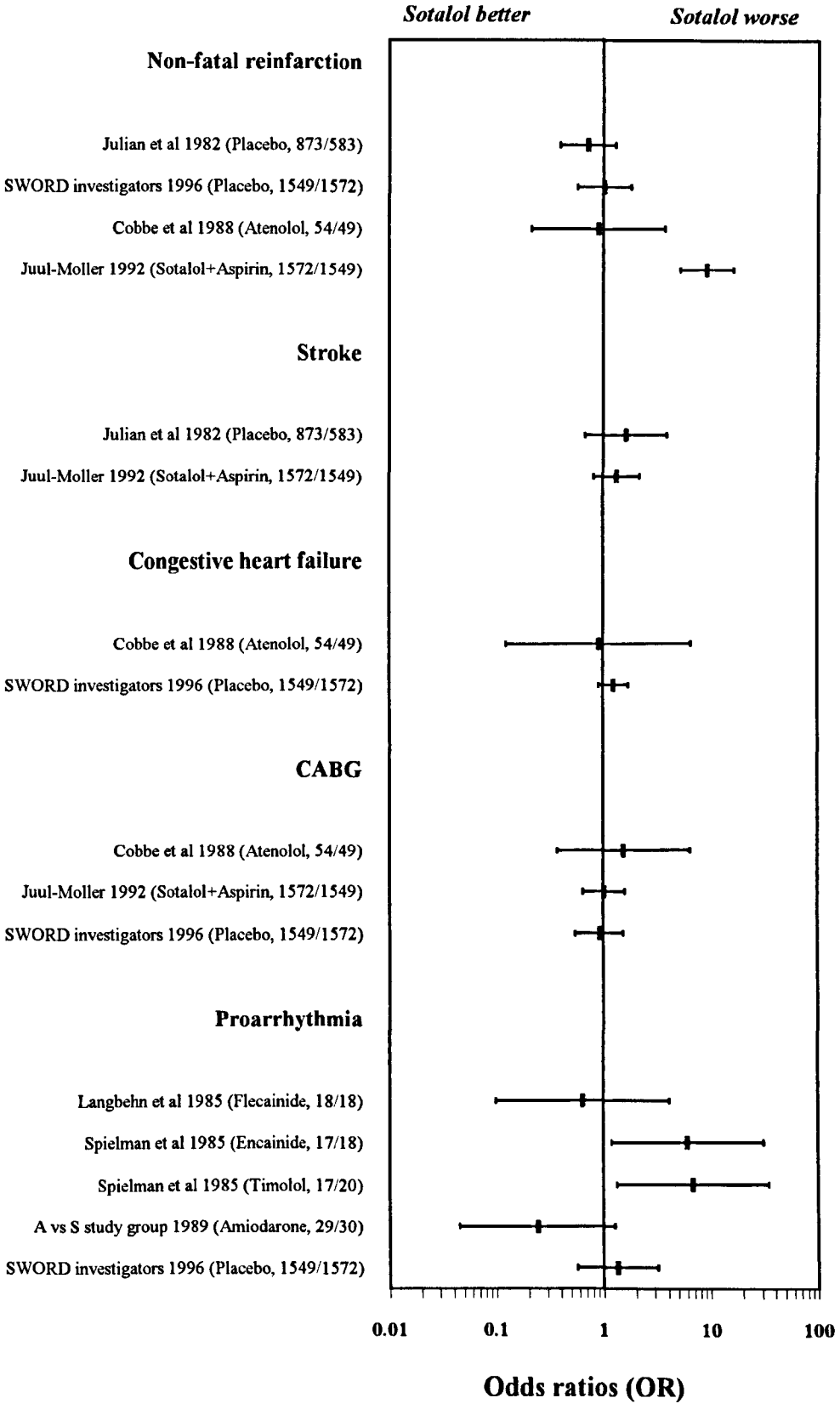

Figure 6.4 Odds ratios for non-fatal cardiac events in sotalol long-term chronic interventions for treatment of myocardial infarction. Type of control and number of patients randomised in each group are shown in brackets.

Table 6.13.1 Nonfatal reinfarction from long-term trials of sotalol

Study name	*Basic data (nonfatal reinfarctions/no.randomised)*		*Peto's method*			
	Sotalol group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect (P)*
Julian *et al.* 1982	24/873	PL, 22/583	-3.6	10.7	0.7 (0.39-1.3)	-1.1 (NS)
Cobbe *et al.* 1988	4/54	A, 4/49	-0.1942	1.86	0.9 (0.22-3.8)	-0.14 (NS)
Juul-Moller *et al.* 1992	S+PL, 78/124	As+S, 7/81	26.5854	11.95	9.3 (5.3-16.3)	7.7 (NS)
Waldo and SWORD investigators 1996	24/1549	PL, 24/1572	0.17687	11.82	1.02 (0.6-1.8)	0.05 (NS)

A, Atenolol; As, Aspirin; PL, placebo; S, Sotalol

Table 6.13.2 Nonfatal reinfarction from long-term trials of amiodarone

Study name	*Basic data (nonfatal reinfarctions/no.randomised)*		*Peto's method*			
	Amiodarone group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect (P)*
Ceremuzynski *et al.* 1992	14/305	PL, 10/308	2.05873	5.77	1.43 (0.63-3.23)	0.86 (NS)
Navarro-Lopez *et al.* 1993	7/115	C, 6/123 M, 5/130	0.71849 1.36735	3.083 2.854	1.26 (0.4-3.9) 1.61 (0.5-5.2)	0.41 (NS) 0.81 (NS)

Am, Amiodarone; M, Metoprolol; C, control (no antiarrhythmic drugs or undefined); PL, placebo

compared to placebo in preventing any non-fatal cardiac complications (SWORD Investigators, 1996).

6.3.3.2 Amiodarone Clinical Trials

6.3.3.2.1 *Suppression of Ventricular Arrhythmias*

The efficacy of amiodarone for suppressing ventricular ectopy was assessed in four trials, with respect to frequency of ventricular premature beats (Nicklas *et al.*, 1991; Navarro-Lopez *et al.*, 1993; Pfisterer *et al.*, 1993; Singh *et al.*, 1995). Frequency was defined by average number of ventricular premature beats per hour during the entire 20 to 24 hours of ECG recording.

Table 6.14 and Figure 6.5 display the results of treatment effect expressed as weighted mean change compared to baseline for amiodarone, placebo, comparative drug (Class I, and metoprolol), individual trial effect sizes, and pooled effect sizes at 1, 3, 6, and 12 months. Generally, amiodarone was more effective than placebo at 1, 3, 6, and 12 months. However, it appeared as effective as Class I drugs in one trial (Pfisterer *et al.*, 1993). Similar results were obtained from the comparison to metoprolol in another trial (Navarro-Lopez *et al.*, 1993). Regression analysis of the treatment effect and odds of sudden arrhythmic death (Table 6.14) suggest a positive linear trend.

6.3.3.2.2 *Analysis of Mortality Data*

6.3.3.2.2.1 *Single point estimates*

A total of eleven trials reported mortality data at the end of the observation period, according to the previously mentioned death classifications (section 6.3.3.1.1.4). Raw mortality data are shown in Table 6.15. In addition, eight trials presented actuarial survival curves for total mortality. Furthermore, in three trials separate survival curves were provided for sudden death.

The Peto method was applied to mortality data reported at the end of the follow-up intervals. Table 6.16 and Figure 6.6.1 display the individual odds ratios of total mortality in all eleven trials. As shown in the Figure 6.6.1, pooling the results from the six placebo-controlled trials has demonstrated a trend for beneficial effect of

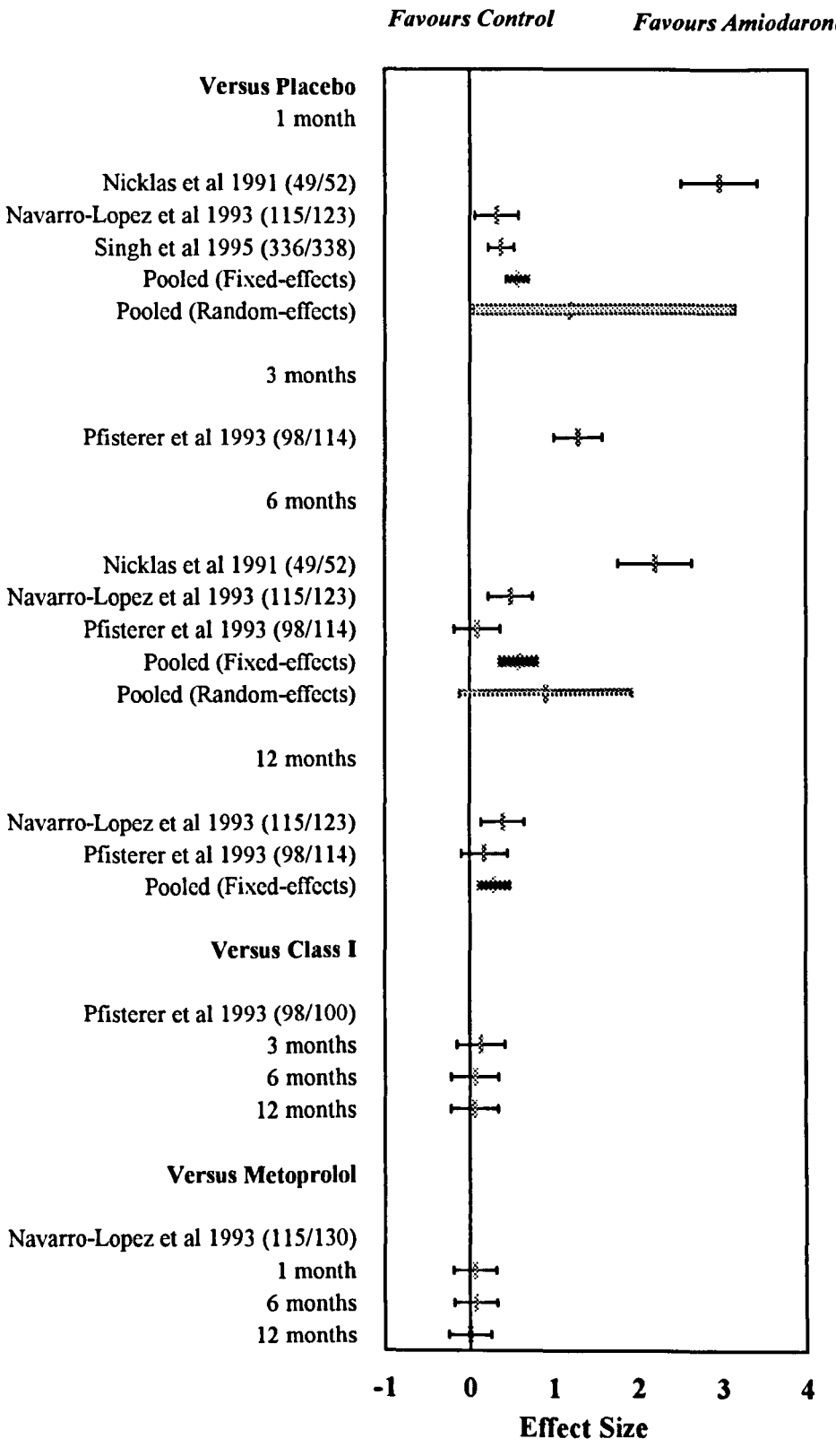

Figure 6.5 Efficacy of amiodarone for arrhythmia suppression (PVCs/hr) as compared to placebo, Class I, and metoprolol. The total number of patients included in each trial is shown in brackets.

Table 6.14 Efficacy of amiodarone for arrhythmia suppression following myocardial infarction

Trial	*Time point (months)*	*No.pts (A/C)*	*Treatment effect (dt)§, (PVCs/hr)±SDp*	*Control effect (dp)§, (PVCs/hr)±SDp*	*Effect size (95% CI)*	*Z (P)*	*Odds of sudden death*
Versus Placebo							
Nicklas *et al.* 1991	1	49/52	-160.7±57.5	-13.7±49.4	2.95 (2.497-3.4)	12.7**	2.4
Navarro-Lopez *et al.* 1993	1	115/123	-20±37.72	-8±37.8	0.32 (0.06-0.58)	2.39**	0.64
Singh *et al.* 1995	1	336/338	-188±415.95	-13±465.5	0.38 (0.22-0.53)	4.76**	0.83
Pooled	1	500/513			FEs; 0.6 (0.44-0.69) REs; 1.2 (0.043-2.3)	8.65** 2.033*	-
Pfisterer *et al.* 1993	3	98/114	-23±110	20±33.3	1.29 (0.997-1.58)	8.7**	0.4485
Nicklas *et al.* 1991	6	49/52	-137.75±59	-25.2±50.6	2.2 (1.77-2.65)	9.82**	2.4
Navarro-Lopez *et al.* 1993	6	115/123	-19±41.4	1±40.8	0.49 (0.23-0.75)	3.65**	0.64
Pfisterer *et al.* 1993	6	98/114	-7±105.6	-19±133.4	0.09 (-0.2-0.36)	0.65 (NS)	0.4485
Pooled	6	262/289			FEs; 0.59 (0.42-0.77) REs; 0.9 (-0.12-1.9)	6.7** 1.7 (NS)	-
Navarro-Lopez *et al.* 1993	12	115/123	-26±37	-11±37.4	0.4 (0.14-0.66)	3**	0.64
Pfisterer *et al.* 1993	12	98/114	-32±107.7	-7±139.4	0.18 (-0.09-0.45)	1.28 (NS)	0.4485
Pooled	12	213/237			FEs; 0.29 (0.1-0.483)	3.1**	-
Versus Class I							
Pfisterer *et al.* 1993	3	98/100	-23±110.5	-9±103.3	0.14 (-0.15-0.42)	0.94 (NS)	1.304
Pfisterer *et al.* 1993	6	98/100	-7±105.6	-13±93.85	0.064 (-0.22-0.34)	0.45 (NS)	1.304
Pfisterer *et al.* 1993	12	98/100	-32±107.7	-26±96.15	0.0622 (-0.22-0.34)	0.45 (NS)	1.304
Versus Metoprolol							
Navarro-Lopez *et al.* 1993	1	115/130	-20±37.72	-10±147.16	0.068 (-0.18-0.32)	0.53 (NS)	0.398
Navarro-Lopez *et al.* 1993	6	115/130	-19±41.4	-7±149.35	0.08 (-0.17-0.33)	0.62 (NS)	0.398
Navarro-Lopez *et al.* 1993	12	115/130	-26±37	-25±144.175	0.007 (-0.24-0.26)	0.054 (NS)	0.398

A, amiodarone; C, control; §, Mean change compared to baseline; SD_P, pooled standard deviation of the change; *, statistically significant; **, highly statistically significant; FEs, fixed-effects model; REs, random-effects model; NS, not significant.

Table 6.15 Mortality data reported in amiodarone randomised clinical trials

Study	*Sudden Cardiac Deaths*	*Other cardiac Deaths*	*Noncardiac deaths*	*Undefined Deaths*	*Total Mortality*
Hockings *et al.* 1987	4/100 Am, 3/100 PL	5/100 Am, 4/100 PL	3/100 PL	7/100 Am, 1/100 PL	16/100 Am, 11/100 PL
Hamer *et al.* 1989	0/19 Am, 4/15 PL	4/19 Am, 2/15 PL	2/19 Am, 0/15 PL	-	6/19 Am, 6/15 PL
Cairns *et al.* 1991 (CAMIAT)	1/48 Am, 4/29 PL	4/48 Am, 1/29 PL	0/48 Am, 1/29 PL	-	5/48 Am, 6/29 PL
Nicklas *et al.* 1991	12/49 Am, 6/52 PL	2/49 Am, 3/52 PL	-	-	14/49 Am, 9/52 PL
Ceremuzynski *et al.* 1992	10/305 Am, 20/308 PL	9/305 Am, 13/308 PL	2/305 Am, 0/308 PL	-	21/305 Am, 33/308 PL
The CASCADE investigators 1993	13/113 Am, 19/115 Class I	10/113 Am, 13/115 Class I	4/113 Am, 2/115 Class I	-	38/113 Am, 55/115 Class I
Pfisterer *et al.* 1993 (BASIS)	10/98 Am, 24/114 C, 8/100 Class I	9/98 Am, 12/114 C, 1/100 Class I	5/98 Am, 11/114 C, 1/100 Class I	7/98 Am, 6/114 C	31/98 Am, 53/114 C, 10/100 Class I
Navarro-Lopez *et al.* 1993	3/115 Am, 9/130 M, 5/123 C	1/115 Am, 6/130 M, 4/123 C	0/115 Am, 2/130 M, 0/123 C	-	4/115 Am, 17/130 M, 9/123 C
Doval *et al.* 1994 (GESICA)	32/260 Am, 39/256 C	44/260 Am, 52/256 C	4/260 Am, 4/256 C	7/260 Am, 11/256 C	87/260 Am, 106/256 C
Garguichevich *et al.* 1995 (EPAMSA)	4/57 Am, 10/49 C	2/57 Am, 4/49 C	0/0	0/0	6/57 Am, 14/49 C
Singh *et al.* 1995 (CHFSTAT)	64/336 Am, 75/338 PL	34/336 Am, 40/338 PL	22/336 Am, 23/338 PL	11/336 Am, 5/338 PL	131/336 Am, 143/338 PL

Am, Amiodarone; M, Metoprolol; C, control (no antiarrhythmic drugs or undefined)

Table 6.16 Total mortality data and statistical analysis of full-exposure group in randomised clinical trials of amiodarone

Study name	*Basic data (No dead/No followed up)*		*Peto's method*			
	Amiodarone group	*Control group*	*O-E*	*Var (O-E)*	*OR (95% CI)*	*statistic for effect*
Hockings *et al.* 1987	16/100	11/100 PL	2.5	5.868	1.5 (0.68-3.44)	1.03
Hamer *et al.* 1989	6/19	6/15 PL	-0.706	1.9723	0.7 (0.174-2.8)	-0.5
Cairns *et al.* 1991 (CAMIAT)	5/48	6/29 PL	-1.857	2.2427	0.44 (0.12-1.62)	-1.24
Nicklas *et al.* 1991	14/49	9/52 PL	2.8416	4.48	1.89 (0.75-4.76)	1.34
Ceremuzynski *et al.* 1992	21/305	33/308 PL	-5.8679	12.3306	0.62 (0.36-1.09)	-1.67
The CASCADE investigators 1993	38/113	55/115 Class I	-8.09	13.826	0.56 (0.33-0.94)	-2.2
Pfisterer *et al.* 1993 (BASIS)	31/98	53/114 C 10/100 Class I	-7.8302 10.71	12.67 8.2	0.54 (0.3-0.94) 3.7 (1.87-7.4)	-2.2 3.75
Navarro-Lopez *et al.* 1993 (SSSD)	4/115	17/130 M 9/123 C	-5.86 -2.2815	4.8 3.08	0.295 (0.12-0.7) 0.48 (0.16-1.5)	-2.7 -1.3
Doval *et al.* 1994 (GESICA)	87/260	106/256 C	-10.2481	30.3	0.71 (0.5-1.02)	-1.9
Garguichevich *et al.* 1995 (EPAMSA)	6/57	14/49 C	-4.7547	4.072	0.31 (0.118-0.82)	-2.4
Singh *et al.* 1995 (STATCHF)	131/336	143/338 PL	-5.5935	40.7129	0.87 (0.64-1.2)	-0.88

M, Metoprolol; C, control (no antiarrhythmic drugs or undefined); * statistically significant (P<0.05); ** highly statistically significant (P<0.01)

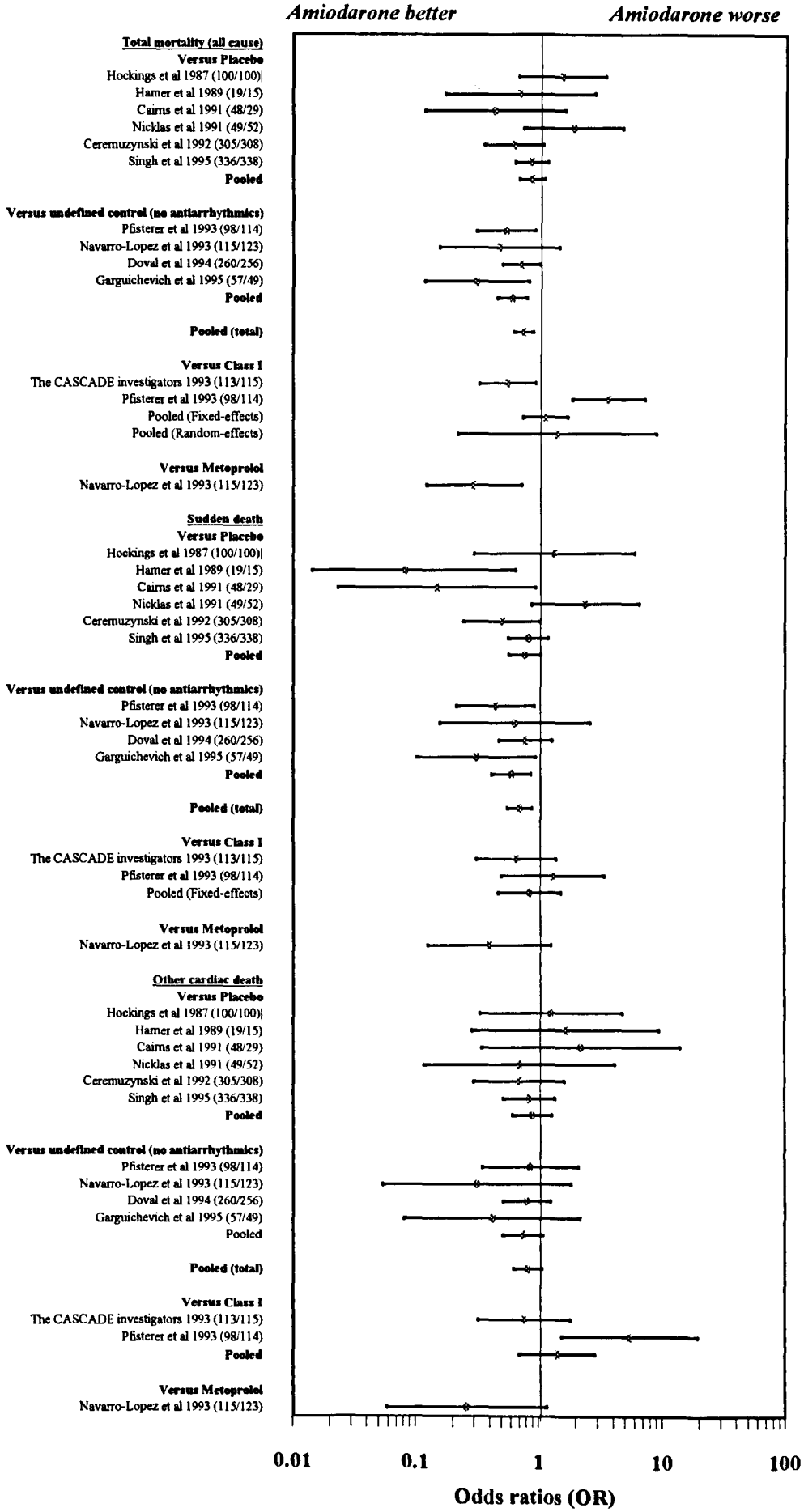

Figure 6.6.1 Odds ratios for total mortality, sudden cardiac death, and other cardiac deaths in amiodarone long-term chronic interventions for treatment of myocardial infarction. Number of patients randomised in each group are shown in brackets.

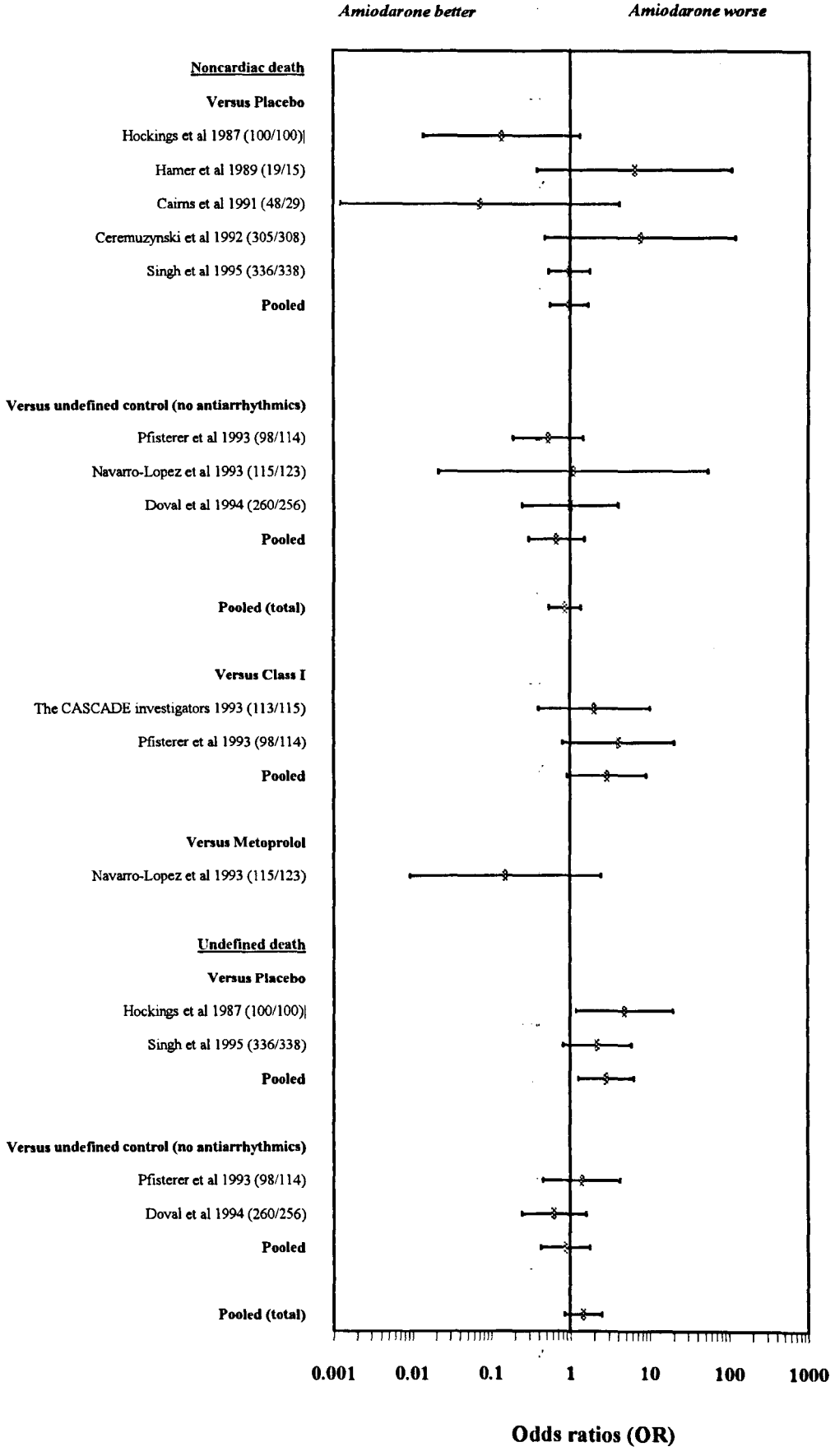

Figure 6.6.2 Odds ratios for noncardiac, and undefined deaths in amiodarone long-term chronic interventions for treatment of myocardial infarction. Number of patients randomised in each group are shown in brackets.

amiodarone over placebo, but, the difference was not statistically significant. Pooled odds ratios of total mortality, sudden death, and death due to other cardiac causes were: 0.77 (95% CI, 0.6-1.05; Z=-1.7), 0.88 (95% CI, 0.7-1.12; Z=-1.06), and 0.9 (95% CI, 0.6-1.3; Z=-0.62) respectively. However, combining the results of those trials with data from another three trials (The CASCADE Investigators, 1993; Pfisterer *et al.*, 1993; Navarro-Lopez *et al.*, 1993), which employed a control group not receiving any antiarrhythmic treatment, has shown a highly significant effect in favour of amiodarone for reducing total mortality and sudden death, with pooled OR equal to 0.75 (95% CI, 0.63-0.89; Z=-3), and 0.7 (95% CI, 0.6-0.89; Z=-2.96) respectively. The test of heterogeneity was nonsignificant (Q=14, df=9, P=0.12), confirming the validity of this pooling. Pooling cardiac mortality data only did not show any significant effect for amiodarone on prevention of death due to other cardiac causes (OR, 0.82; 95% CI, 0.63-1.07, Z=-1.5; heterogeneity Q=4, df=9, P=0.9).

Pooling the results from two trials comparing amiodarone to Class I drugs (211 versus 229 patients) did not show any significant difference for prevention of any type of deaths. Direct comparison of amiodarone with metoprolol in one trial (115 versus 123 patients) suggested that the former was associated with a more favourable 3-year effect on total mortality (OR_{total}, 0.3; 95% CI, 0.13-0.7, Z=-2.7). Nevertheless, no significant difference in efficacy for prevention of sudden or other cardiac deaths was observed (OR_{sudden}, 0.398, 95% CI, 0.13-1.3, Z=-1.6; and $OR_{other\ cardiac}$, 0.26; 95% CI, 0.06-1.2, Z=1.8).

Further investigation for effect on noncardiac and undefined death did not detect any favourable trends with amiodarone (Figure 6.6.2).

6.3.3.2.2.2 *Meta-analytic survival analysis*

Table 1 and Table 2 of Appendix 6.2 display the raw actuarial survival data generated by the life-table method from eight published survival graphs for total mortality. As shown in Table 1 (Appendix 6.2), the data in four trials were considered completely censored due to the availability of the number of patients remaining at risk at the beginning of each time interval during the follow-up (Ceremuzynski *et al.*, 1992; Navarro-Lopez *et al.*, 1993; Pfisterer *et al.*, 1993; Garguichevich *et al.*, 1995). For the other four trials (Nicklas *et al.*, 1991; The CASCADE Investigators, 1993; Doval *et al.*, 1994; Singh *et al.*, 1995), in which the number of patients at risk was not provided, total death events were approximated by calculations described earlier in section

6.2.4.1.

Later on, the distribution of death events, and termination of follow-up over time was estimated by curve fitting using equation 4b of Kaplan-Meier method (1958), as shown in Table 3 of Appendix 6.2.

For the three trials which contributed additional survival curves for sudden death only (Doval *et al.*, 1994; Garguichevich *et al.*, 1995; Singh *et al.*, 1995), the actuarial estimates were generated using the previous sequence (Table 4, Table 5, and Table 6 of Appendix 6.2).

The meta-analytic log-rank ORs for total mortality in trials with completely censored data yielded highly statistically significant results over the time interval from randomisation up to 102 months Table 7 (Appendix 6.2), indicating superior effect of amiodarone for prevention of total mortality as compared to placebo. With regard to the partially censored trials, the meta-analytic statistics conducted over the whole period, from randomisation to 36 months, produced nonsignificant ORs (Table 7: Appendix 6.2). However, with respect to the subsequent 12 months (at the end of 4 years), the meta-analytic log-rank OR of 0.53 (95% CI, 0.3 to 0.9; $Z = -2.28$, $P < 0.01$) was highly significant. Concerning the meta-analysis of data generated by curve fitting in the same three trials, the results were not promising over the whole observation period. One trial was excluded from the primary direct comparison analysis due to the employment of Class I as a control group rather than placebo (CASCADE Investigators, 1993).

A sensitivity analysis was performed by reconducting the pooling of the data from censored and partially censored trials (Analysis group 4, Table 7), then censored with those obtained by curve fitting (Analysis group 5, Table 7). The ORs of this repeated analysis were highly significant up to 102 months (8 years), which again suggested that amiodarone decreased the overall mortality rate compared to placebo.

The analysis of the three trials, which contributed actuarial survival data for sudden death, involved a total of 1296 patients. This pooling demonstrated a marked reduction in sudden death for amiodarone, particularly during the first two years ($P < 0.01$). Separate pooling of completely censored data, and data generated by curve fitting, (Analysis group 1 and 3; Table 8) revealed evident beneficial effects of amiodarone only during the first two years but not thereafter (log-rank ORs were 0.66 [$Z = -2.23$,

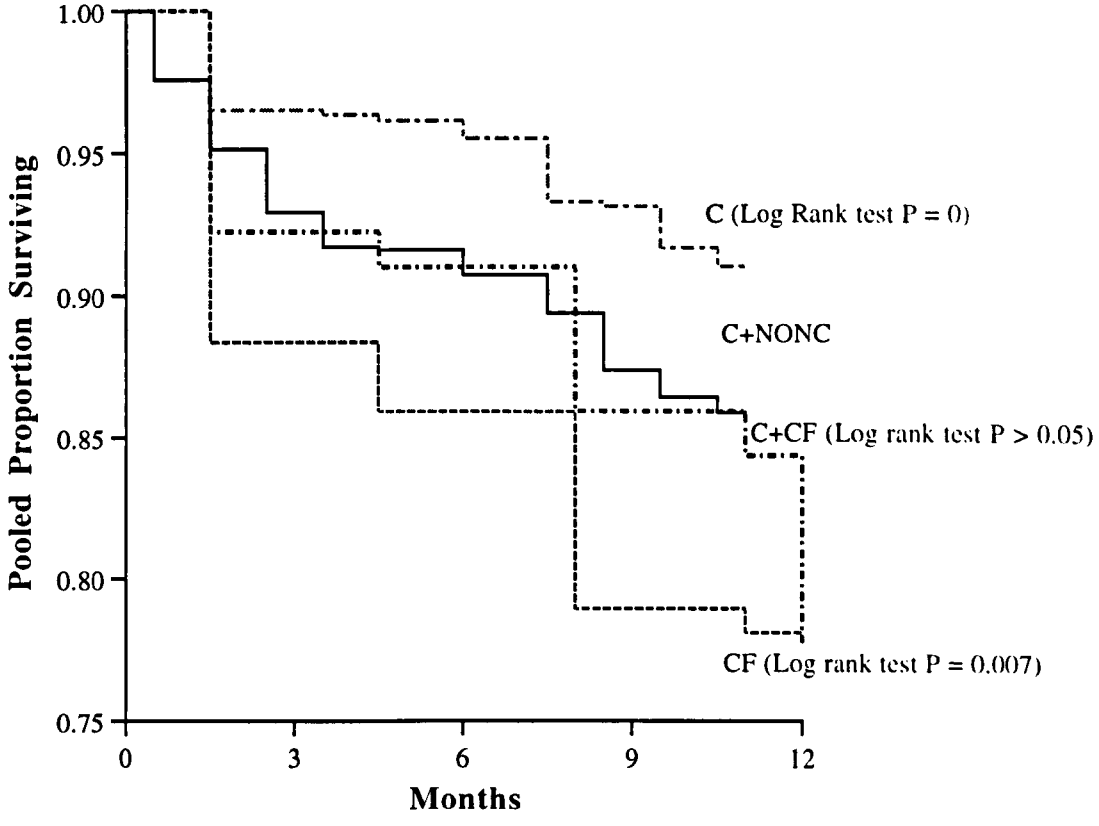

Figure 6.7 Meta-analytic survival curve of total mortality for amiodarone treatment arms reconstructed for censored trials (N=4), censored pooled with noncensored trials (N=8), censored pooled with curve fitting trials (N=8), and curve fitting trials separately (N=4).

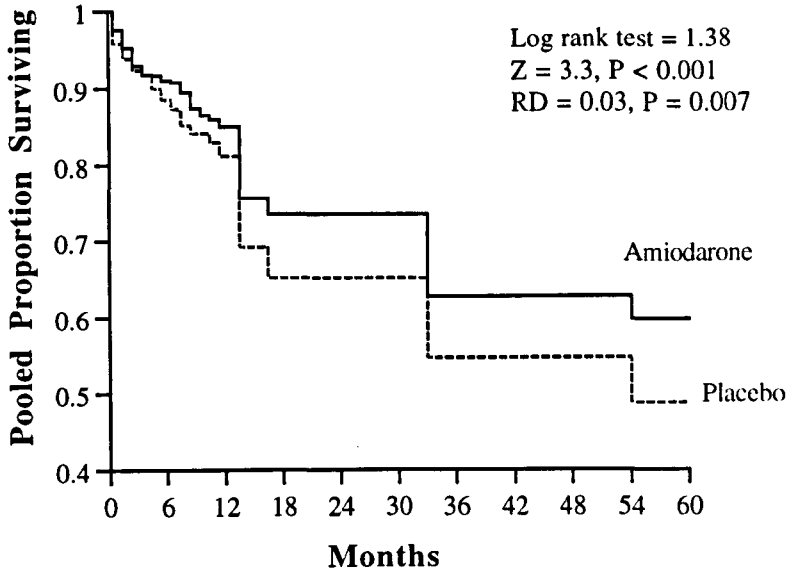

Figure 6.8.1 Meta-analytic survival curve of total mortality reconstructed from all trials with censored and noncensored observations. The amiodarone displayed a highly significant effect for reduction of overall deaths, as compared to placebo.

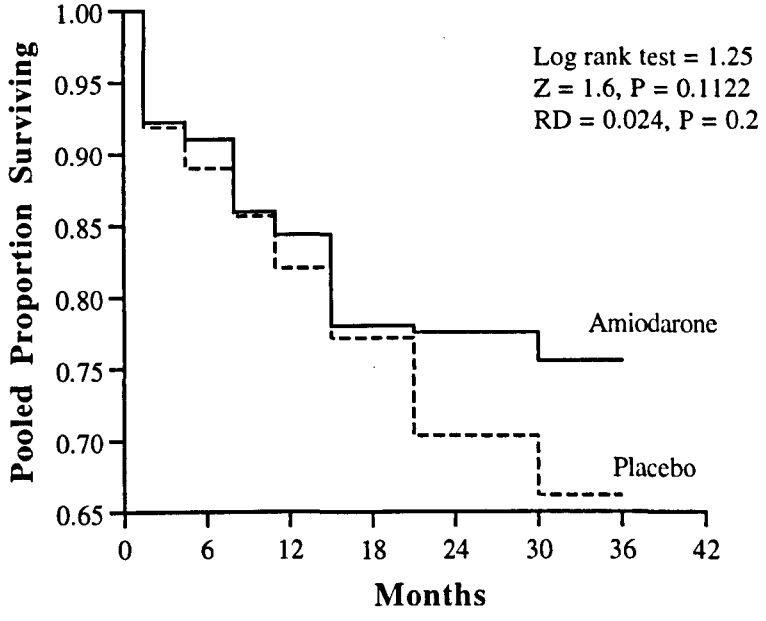

Figure 6.8.2 Meta-analytic survival curve of total mortality reconstructed from all trials with censored observations (both reported and generated by curve fitting). There was no significant difference in the overall mortality.

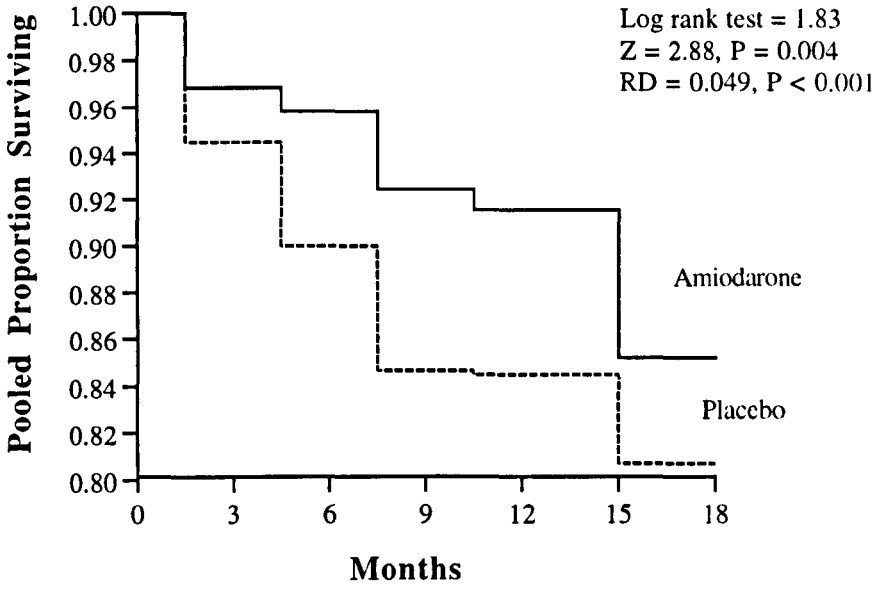

Figure 6.9.1 Meta-analytic survival curve of sudden death reconstructed from trials with censored and noncensored data. The amiodarone displayed a highly significant effect for reduction of sudden death, as compared to placebo.

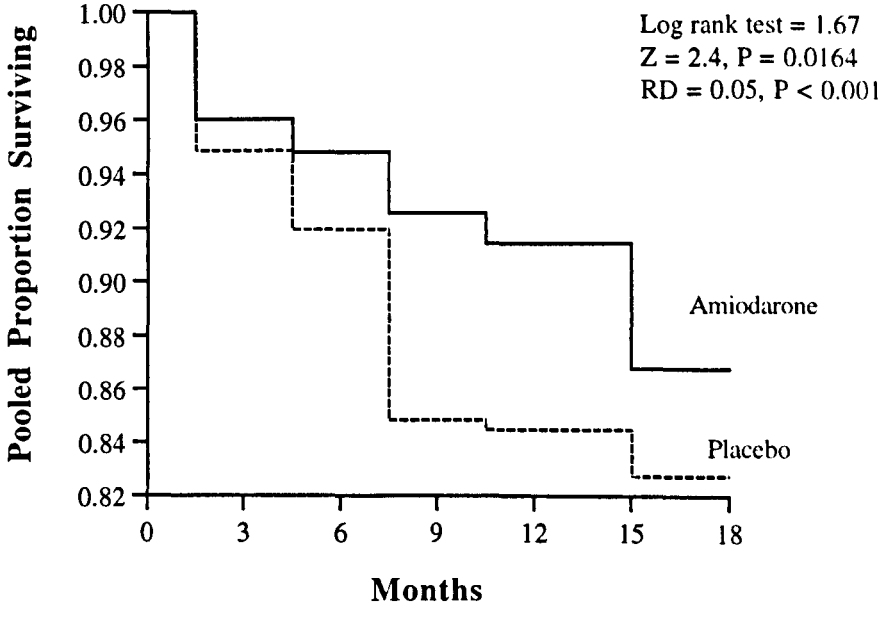

Figure 6.9.2 Meta-analytic survival curve of sudden death reconstructed from one trial with censored data and two trials with data generated by curve fit. The amiodarone displayed a highly significant effect for reduction of sudden death, as compared to placebo.

$P < 0.05$] and 0.72 [$Z = -2.1$, $P < 0.05$] respectively).

Table 9 and Table 10 of Appendix 6.2 displays the pooled survival rates together with their standard errors and the estimate of homogeneity which was consistently nonsignificant. Reconstructing the survival graph for the amiodarone treatment arm, by merging the life tables in the censored trials, censored pooled with noncensored trials, censored pooled with curve fitting trials, and curve fitting trials separately, demonstrated the significance of mixed meta-analytic pooling for providing more statistical power for detecting amiodarone effect (Figure 6.7). The indirect comparison of the whole profile of the four survival curves by log-rank test yielded a highly significant difference with respect to the curve obtained from censored and partially censored trials. Applications of the two techniques for reconstructing the survival curves for total mortality and sudden death in amiodarone and placebo treatment arms are presented in Figure 6.8 and Figure 6.9 respectively. The indirect comparison approach has confirmed that the conclusions of the previous direct comparison estimates favouring amiodarone efficacy. Notably, there was a greater difference between the whole curves of amiodarone and placebo for surviving sudden death, establishing a more marked effect of treatment on prevention of death due to arrhythmia.

6.3.3.2.3 *Non-fatal Cardiovascular Events*

The efficacy of amiodarone for prevention of non-fatal cardiovascular events was examined by combining the available data from trials which prospectively defined these events as primary or secondary end-points. Figure 6.10 displays the incidence calculated as individual and pooled odds ratios of non-fatal reinfarction, resuscitated sudden ventricular arrhythmia, proarrhythmia, congestive heart failure, stroke, syncope, angina, CABG, as well as any non-fatal cardiovascular events. Noticeably, although the results did not research the level of significance, amiodarone, like sotalol, did not show effectiveness for prevention of reinfarction, or development of new congestive heart failure. In fact, there were increased trends for reinfarction in amiodarone-treated patients in two trials (pooled OR, 1.37; 95% CI, 0.71-2.6; Z=0.9), and congestive heart failure in another two (pooled OR, 1.4; 95% CI, 0.88-2.4, Z=1.41). With the exception of resuscitated sudden VA, there was no significant difference in the occurrence of other types of events.

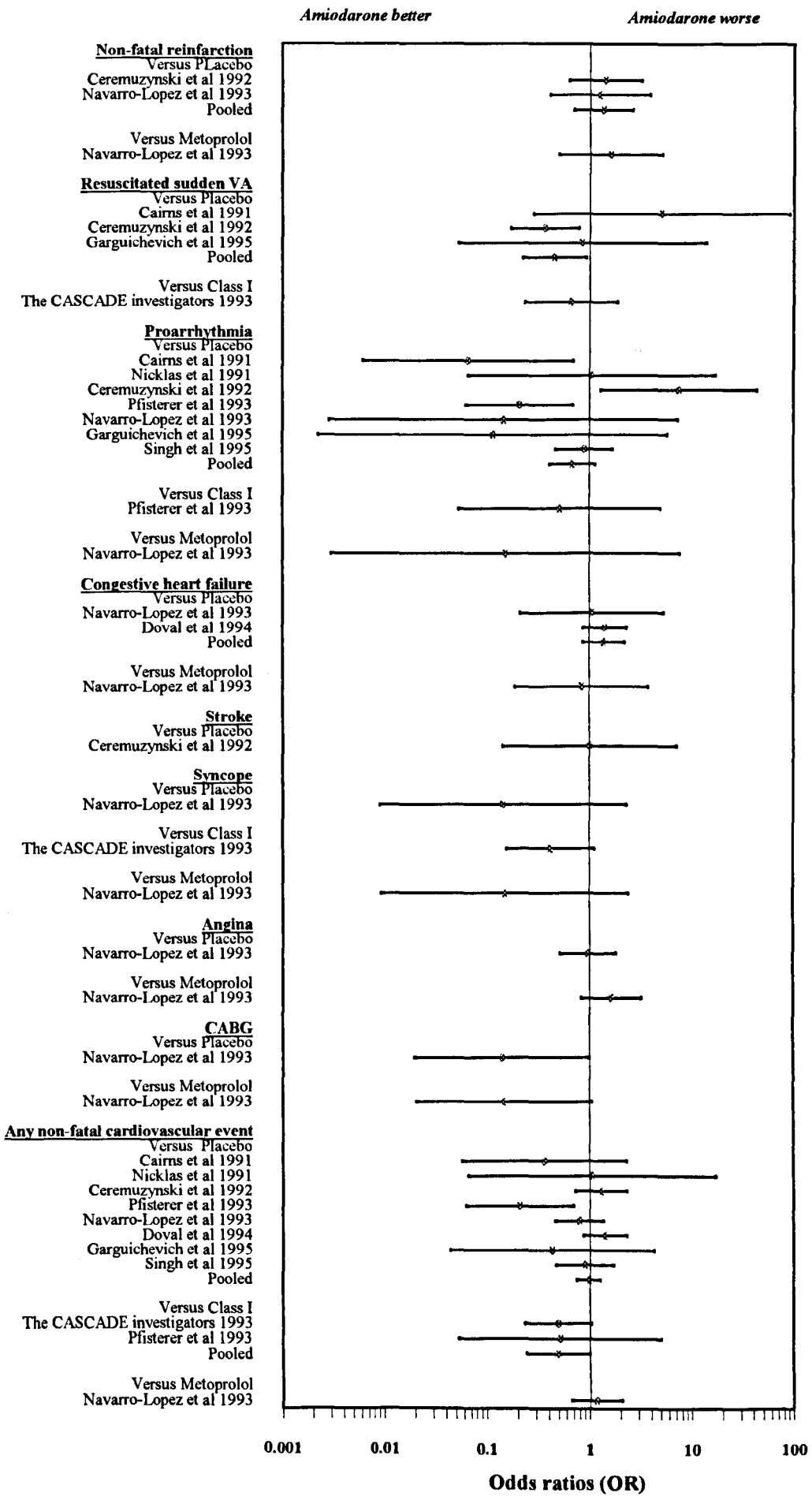

Figure 6.10 Odds ratios for non-fatal cardiac events in amiodarone long-term chronic interventions for treatment of myocardial infarction.

6.3.3.2.4 *Side Effects and Toxicity*

Table 6.17 and Figure 6.11 show the pooled relative risk of side effects, toxicity, and withdrawals in the long-term intervention trials of amiodarone. The reported adverse events were categorised into nine types: ocular, dermatological, gastrointestinal, neurological, hepatic, cardiovascular, pulmonary toxicity, thyroid toxicity, and withdrawals. As shown, the pooled relative risks of ocular, dermatological, gastrointestinal, neurological, hepatic, cardiovascular, and pulmonary toxicity events with amiodarone relative to placebo or class I antiarrhythmics, was not statistically significant.

6.4 DISCUSSION

The belief that suppression of premature ventricular contractions (PVCs) in survivors of acute myocardial infarction (AMI) can reduce the incidence of sudden death, has led the pharmaceutical industry to search for more effective antiarrhythmic agents for ventricular arrhythmia suppression in an attempt to improve the survival rate. Consequently, the number of antiarrhythmic drugs rose spectacularly throughout the 1980s (Morganroth and Goin, 1991). However, after the results of CAST (I & II) showing increased mortality with Class Ic agents, many physicians started in early 1990s to appraise the use of other classes for treating potentially life-threatening ventricular tachyarrhythmias in MI survivors. The fact that beta-blockers prevent mortality in a variety of subsets of patients has led to a shift to more complex Class III molecules, which also possess sympatholytic activity. Today, despite the extensive research with Class III compounds, their precise role in prevention of sudden death remains questionable (Lazzara, 1996; Singh, 1996).

The employment of intravenous beta-blockers, among many other interventions during the first few hours of AMI, is mainly considered for limitation of myocardial damage or mortality, or both (ACC / AHA Task Force, 1990). Beta-blockers act primarily by reducing the need for nutrients and oxygen by the ischemic myocardium (Yusuf *et al.*, 1985; Yusuf *et al.*, 1988). Intravenous sotalol, which is a non-selective beta-blocker, may confer more benefit since it is devoid of unfavourable intrinsic sympathomimetic activity (Frishman and Cavusoglu, 1995). Review of available trials which assessed beneficial effects of early administration of sotalol in AMI, has revealed significant

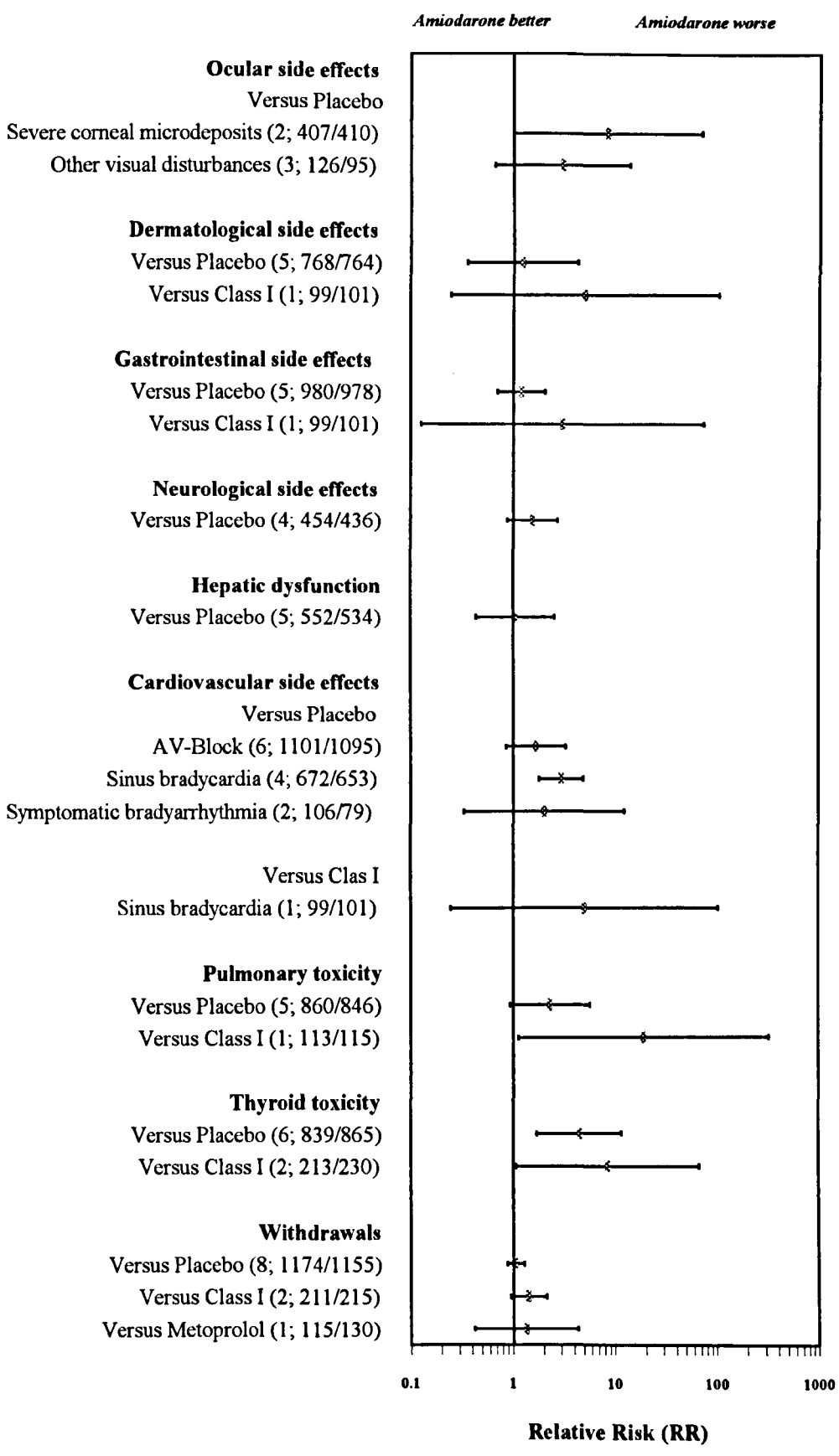

Figure 6.11 Relative risk of amiodarone toxicity and side effects as compared to placebo or active control in long-term intervention trials. The number of pooled trial and total number of patients included are shown in brackets.

Table 6.17 Relative risk of amiodarone toxicity and side effects in long-term intervention trials

Category	*Comparison*	*No. of trials*	*No. of patients*	*Pooled RR§ (95% CI)*	*Z*
Ocular side effects					
Severe corneal microdeposits	Versus placebo	2	407/410	8.4 (1.01-70.4)	1.97
Other visual disturbances	Versus placebo	3	126/95	3.08 (0.68-14)	1.5
Dermatological side effects	Versus placebo	5	768/764	1.24 (0.36-4.3)	0.34
	Versus Class I	1	99/101	5.1 (0.25-104.9)	1.06
Gastrointestinal side effects	Versus placebo	5	980/978	1.22 (0.7-2.1)	0.7
	Versus Class I	1	99/101	3.1 (0.13-74.24)	0.7
Neurological side effects	Versus placebo	4	454/436	1.6 (0.885-2.7)	1.54
Hepatic side effects	Versus placebo	5	552/534	1.06 (0.44-2.6)	0.14
Cardiovascular side effects					
AV-block	Versus placebo	6	1101/1095	1.696 (0.87-3.32)	1.54
Sinus bradycardia	Versus placebo	4	672/653	2.99 (1.8-4.9)	4.3**
	Versus Class I	2	106/79	5.1 (0.25-104.9)	1.06
Symptomatic bradyarrhythmia	Versus placebo	1	99/101	2.04 (0.33-12.54)	0.77
Pulmonary toxicity	Versus placebo	5	860/846	2.33 (0.94-5.75)	1.83
	Versus Class I	1	113/115	19.34 (1.4-328.3)	2.05
Thyroid toxicity	Versus placebo	6	839/865	4.5 (1.7-11.8)	3.1
	Versus Class I	2	213/230	8.5 (1.1-67.74)	2.03
Withdrawals	Versus placebo	8	1174/1155	1.08 (0.885-1.3)	0.74
	Versus Class I	2	211/215	1.43 (0.95-2.2)	1.73
	Versus Metoprolol	1	115/130	1.4 (0.43-4.33)	0.52

RR, relative risk

impacts on heart rate, infarction size, and suppression of PVCs (which are well-established effects by all beta-blockers). Nevertheless, its definite value requires further validation in direct comparison of 'early intervention' studies, due to the confined reporting of short-term mortality data. In this analysis, comparison of sotalol to placebo did not show greater survival. Furthermore, direct comparisons have yielded superior effect for other beta-blockers compared to sotalol, which suggested that the additional Class III action of sotalol may not be solely responsible for the protective effect of ischemic myocardium against arrhythmic sudden death. In addition, this can be explained by sotalol being a Class III agent has exhibited a reverse use dependence phenomenon in which excess delay in repolarisation was produced at slower heart rate. This effect predisposed to *torsades de pointes* and proarrhythmias leading to excessive sudden death in sotalol-treatment group compared to placebo-treatment group. Moreover, the results of SWORD trial evaluating the efficacy of pure Class III agent, *d*-sotalol has supported the findings of pharmacological studies which proved attenuated or nullified beneficial antifibrillatory effect of all pure Class III agents in the presence of high release of catecholamines as in acute ischemia due to myocardial infarction (Singh, 1995). However, these studies did not demonstrate pronounced attenuation of Class III action when a drug was associated with additional beta-blocking activity such as amiodarone and racemic sotalol.

Amiodarone is an extremely complex drug possessing the 4 electrophysiologic actions which are proposed by Vaughan Williams classification of antiarrhythmic mechanisms (Nademanee *et al.*, 1993). The drug was first introduced as an antianginal vasodilator in 1962 (Singh and Vaughan Williams, 1970), and only recently it was found to have antiarrhythmic effects by blocking potassium channels, and thus lengthening the duration of action potential, but unlike other Class III agents, in a use-dependent fashion. In addition it depresses the sodium channel with a fast onset and offset kinetics. Consequently, it delays the conduction, particularly at faster heart rates and more often in diseased tissues rather than healthy tissues at normal heart rates. It also blocks the calcium channels in SA and AV nodal tissues, thereby slowing the phase 4 depolarisation with subsequent decrease in the heart rate. More remarkablely, it is regarded as a potent antiadrenergic agent.

The meta-analysis described in this chapter has produced a highly significant single point estimates of pooled ORs confirming amiodarone clinical effectiveness for prolonging the survival in patients with congestive heart failure or myocardial infarction. Furthermore, specific techniques for extracting actuarial survival data from

all published graphs in RCTs were employed to examine its long-term effect in congestive heart failure or AMI. The results of this survival meta-analysis support the previous conclusions based on single point estimates. The nonparametric log-rank odds ratios method was applied to raw actuarial data deduced from published Kaplan-Meier graphs as well as data generated by curve fitting, using the original Kaplan-Meier equation to approximate the number of events and lost to follow-up (censored observations) in each study. Pooling each set of data separately has yielded highly significant log-rank ORs for total mortality in the first set of four censored trials (log-rank OR at 102 months, 0.598; 95% CI, 0.43 to 0.83; Z = -3). However, log-rank ORs from data generated by curve fitting in a further three trials, were nonsignificant up to 48 months (log-rank OR, 0.87; 95% CI, 0.72 to 1.06, Z = -1.4). Merging of the two data sets has provided strong evidence of efficacy for improving survival in terms of both total mortality and sudden death.

The precise link between the clinical evidence suggested by this overview of RCTs, regarding its superiority over other drug classes, and evidence contributed by the in vitro electrophysiological massive examinations remains uncertain. During ischemia, a rapid loss of intracellular potassium with over accumulation of extracellular potassium is reported to partially depolarise the membrane. Intracellular alteration of calcium ions concentrations will predispose to membrane depolarisation leading to abnormal automaticity and reentery (Nademanee *et al.*, 1993). Amiodarone possesses the ability to block the potassium channels and may help to prevent the arrhythmias, due to ischemia. In addition, the binding of amiodarone to sodium channels was found to increase in depolarised tissues with subsequent increase of its effect on excitability of these tissues. Although this effect can be achieved by other Class III agents, such as sotalol (potassium channel blocking) and Class I agents (sodium channel blocking), amiodarone can also block calcium channels with a further inhibition of calcium-mediated triggered activity inside the cells, such as accumulation of free fatty acids, causing arrhythmogenesis. Nevertheless, the effect of pure calcium channel blockers on mortality appeared to be neutral or even deleterious (Teo *et al.*, 1993), thus indicating that protective actions of amiodarone are essentially mediated by beta-blocking activity. Amiodarone, unlike other Class III agents, blocks the channels in a use-dependence manner without interfering with normal sinus rhythm. Therefore, it has a low proarrhythmic potential which is an advantage over other agents.

Prophylactic treatment with amiodarone should be initiated as early as possible post AMI, particularly within the first 6 months, during which time the risk of death was

highest (Zarembski *et al.*, 1993; Pfisterer *et al.*, 1992). In some individual trials (Pfisterer *et al.*, 1993; Garguichevich *et al.*, 1995) the two survival curves of amiodarone and control tended to diverge widely in the first 0-12 months period, then remained parallel thereafter without displaying any further significant difference. Yet, the pooled estimates of log-rank ORs yielded by the meta-analysis persisted significant throughout the follow-up period (mean of 34.33 months). This suggested the importance of continuation of amiodarone treatment for delaying of death. In fact, the beneficial effect of amiodarone was evident in some of the sensitivity subgroup analyses only after 6-12 months of treatment.

It was reported that for a drug to significantly reduce the rate of ischemia-related deaths, it had to reduce either the incidence of recurrent MI or the associated fatal ventricular arrhythmias (Singh, 1991; Kjekshus, 1986). Yet in RCTs of sotalol and amiodarone reviewed in this meta-analysis, the pooled estimates for incidence of reinfarction, congestive heart failure, or any other non-fatal cardiovascular event, were not significantly different from placebo (Figure 6.4 & Figure 6.10). These events were not consistently employed as secondary outcome measures in all post MI trials making statistical analysis difficult.

The ability of sotalol and amiodarone to suppress PVCs prior MI was also validated. However, a correlation of pooled effect size estimates at different time points to odds of mortality, did not display any dependent response or systematic relation. This confirmed that PVCs suppression criterion was merely a surrogate marker for mortality in this type of patients.

Amiodarone-induced toxicity, was generally not serious possibly due employment of low doses (mean 330 mg/day within the range 200 to 600 mg/day).

6.5 CONCLUSION

The present study supports the recommendations of the World Health Organisation and Medicines Control Agency in the United Kingdom to restrict indication of racémic sotalol and *d*-sotalol to the treatment of ventricular arrhythmias or prophylaxis of supraventricular tachyarrhythmias, and to stop its use for secondary prevention after MI and for life-threatening ventricular arrhythmias (Committee on Safety of Medicines / Medicines Control Agency, 1996; WHO Drug Information, 1997). However, the

results strongly suggest that continued prophylactic use of amiodarone to prolong the survival in patients at high risk of sudden death due to arrhythmia complicating congestive heart failure or AMI is justified.

Further validation of all the previous conclusions by updating this meta-analysis in the light of new data from trials which are still in progress is also recommended.

Appendix 6.1

Clinical Trials Included In The Meta-Analysis

1) Sotalol Clinical Trials

Amiodarone vs Sotalol Study Group. Multicentre randomized trial of sotalol vs amiodarone for chronic malignant ventricular tachyarrhythmias. *Eur Heart J* 1989; **10** (8): 685-694.

Astrom M, Edhag O, Nyquist O, Vallin H. Electrophysiological effects of intravenous sotalol in acute myocardial infarction: a double blind placebo-controlled study. *Eur Heart J* 1990; **11** (1): 35-42.

Astrom M, Edhag O, Nyquist O, Vallin H. Haemodynamic effects of intravenous sotalol in acute myocardial infarction. *Eur Heart J* 1986; **7** (11): 931-936.

Cobbe S, Alexopoulos D, Winner SJ, McCaie CP, Cobbe PC, Johnston J. A comparison of the long term effects of sotalol and atenolol on QT interval and arrhythmias after myocardial infarction. *Eur Heart J* 1988; **9** (1): 24-31.

Ho DS, Zecchin RP, Richards DAB, Uther JB, Ross DL. Double-blind trial of lignocaine versus sotalol for acute termination of spontaneous sustained ventricular tachycardia. *Lancet* 1994; **344** (8914): 18-23.

Julian DG, Jackson FS, Prescott RJ, Szekely P. Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982; **1** (8282): 1172-1147.

Juul-Möller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R, The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris: The Swedish Angina-M Pectoris Aspirin Trial. *Lancet* 1992; **340** (8833): 1421-1425.

Langbehn AF, Sheikhzadeh A, Stickle U, Weide A. Efficacy of sotalol in chronic ventricular arrhythmias compared with flecainide. *New Trends in Arrhythmias* 1985; **1** (3): 261-268.

Llewellyn M. Effects of early IV sotalol on ventricular arrhythmias in acute myocardial infarction. (Abstract 1711). 10th Word Congress of Cardiology, Washington DC, 1986.

Lloyd EA, Charles RG, Gordon GD, Adama CM, Mabin TA, Commerford PJ, Opie LH. Beta-blockade by sotalol in early myocardial infarction decreases ventricular arrhythmias without increasing left ventricular volume. *S Afr Med J* 1988; **74** (1): 5-10.

McGrath B, Arnolda L, Saltups A. The catecholamine response to acute myocardial infarction: effect of early administration of sotalol. *Aust N Z J Med* 1986; **16** (5): 658-664.

Myburgh DP, Goldman AP, Cartoon J, Schamroth JM. The efficacy of sotalol in suppressing ventricular ectopic beats. *S Afr Med J* 1979; **56** (8): 295-298.

Spielman S, Kay HR, Morganroth J, Horowitz LN, Greenspan AM, Hahnemann Cardiovascular Research Group. Drug therapy in high risk patients following acute myocardial infarction. The results of timolol, encainide, sotalol trial. *Circulation* 1985; **72** (57): 111-115.

Waldo AL, Camm AJ, de Ruyter H, Friedman PL, MacNeil DJ, Pauls JF, Pitt B, Pratt CM, Schwartz PJ, Beltri EP, for the SWORD investigators. *Lancet*, 1996; **348**: 7-12.

Waldo AL, Camm AJ, de Ruyter H, Friedman PL, MacNeil DJ, Pitt B, Pratt CM, Rodda BE, Schwartz PJ, The SWORD investigators. Survival with oral *d*-sotalol in patients with left ventricular dysfunction after myocardial infarction: rationale, design and methods (the SWORD Trial). *Am J Cardiol* 1995; **15**: 1023-1027.

Waldo AL, Camm AJ, The SWORD investigators. Preliminary mortality results from the survival with oral *d*-sotalol (SWORD) trial. *J Am Coll Cardiol* 1995; **25**: 15A.

2) Amiodarone Clinical Trials

Burkart F, Pfisterer M, Kiowski W, Follath F, Burckhardt D. Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias: Basel Antiarrhythmic Study of Infarct Survival (BASIS). *J Am Coll Cardiol* 1990; **16**: 1711-1718.

Cairns JA, Connolly SJ, Gent M, Roberts R. Post-myocardial infarction mortality in patients with ventricular premature depolarizations: Canadian amiodarone myocardial infarction arrhythmia trial pilot study. *Circulation* 1991; **84**: 550-557.

Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, Kuch J, Nartowicz E, Smitlak-Korombel J, Dyduszynski A, Maciejewicz J, Zaleska T, Lazarczyk-Kedzia E, Motyka J, Paczkowska B, Sczaniecka O, Ysuf S. Effect of amiodarone on mortality after myocardial infarction: a double-blind, placebo-controlled, pilot study. *J Am Coll Cardiol* 1992; **20**: 1056-1062.

Daval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low dose amiodarone in severe congestive heart failure. *Lancet* 1994; **344**: 493-498.

Garguichevich J, Ramos J, Cambarte E, Gentile A, Hauad S, Scapin O, Sirena J, Tibaldi M, Toplikar J, The Argentine Pilot Study of Sudden Death. Effect of amiodarone therapy on mortality in patients with left ventricular dysfunction and asymptomatic complex ventricular arrhythmias: Argentine pilot study of sudden death and amiodarone (EPAMSA). *Am Heart J* 1995; **130**: 494-500.

Hamer AWF, Arkles LB, Johns JA. Beneficial effects of low dose amiodarone in patients with congestive cardiac failure: a placebo-controlled trial. *J Am Coll Cardiol* 1989; **14**: 1768-1774.

Hockings BEF, George T, Mahrous F, Taylor RR, Hajar AH. Effectiveness of amiodarone on ventricular arrhythmias during and after acute myocardial infarction. *Am J Cardiol* 1987; **60**: 967-970.

Navarro-Lopez F, Cosin J, Marruagat J, Guindo J, Antonio Bayes L, SSD Investigators. Comparison of the effects of amiodarone versus metoprolol on the

frequency of ventricular arrhythmias and on the mortality after acute myocardial infarction. *Am J Cardiol* 1993; **72**: 1243-1248.

Nicklas JM, McKenna WJ, Stewart RA, Mickelson JK, Das SK, Schork A, Krikler SJ, Quain LA, Morady F, Pitt B. Prospective, double-blind, placebo-controlled trial of low dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy. *Am Heart J* 1991; **122**: 1016-1021.

Pfisterer ME, Kiowski W, Brunner H, Burckhardt D, Burkart F. Long-term benefit of 1-year amiodarone treatment for persistent complex ventricular arrhythmias after myocardial infarction. *Circulation* 1993; **87**: 309-311.

Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D, for The Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995; **333**: 77-82.

The CASCADE Investigators. Randomised antiarrhythmic drug therapy in survivors of cardiac arrest (the CASCADE study). *Am J Cardiol* 1993; **72**: 280-287.

CHAPTER SEVEN

GENERAL DISCUSSION, CONCLUSION, AND FUTURE DIRECTIONS

7.1 DISCUSSION

The general aim of this thesis was to undertake a systematic review of the use of antiarrhythmic agents in the management of cardiac arrhythmias.

Three strategies are usually considered for conversion of acute atrial fibrillation: treatments directed at controlling the ventricular response rate while awaiting spontaneous conversion, pharmacological conversion, and electrical cardioversion (Talajic *et al.*, 1996). Although several trials have suggested that class I or III agents are advantageous over others, it was not possible to identify the ideal drug class from the overall bulk of data. In addition, there was no published systematic overview covering the issue of pharmacological cardioversion by different antiarrhythmic drugs. Consequently, a systematic overview (Chapter 5) was undertaken including a total of 42 trials which examined the efficacy and safety of the most frequently employed class I (flecainide), and class III (amiodarone and sotalol) drugs. Although some individual trials have concluded that intravenous amiodarone is superior to placebo for acute cardioversion and despite its increasing use in current clinical practice (Olshansky, 1996), the present meta-analysis has failed to confirm its value for this indication.

Data on the mean ventricular rate together with the associated standard deviation or standard error are not reported in most trials. In those cases, an upper bound assumption for calculating the standard deviation of mean difference in individual trials was employed (Cappuccio *et al.*, 1989). The confidence interval of the individual effect sizes and the weighted mean change compared to baseline were therefore wider than would be the case with observed variances. Ventricular rate was considered a very important therapeutic end point. Yet, it was rarely provided for converted and unconverted patients separately. This made pooling and comparisons of response between these two subgroups impossible.

The results of this meta-analysis has supported the high efficacy of intravenous and oral flecainide for prompt cardioversion. Although there was only limited data on oral and intravenous sotalol (3 randomised controlled trials), the pooled estimates at one hour confirmed the drug's superiority over placebo. Insufficient direct head to head comparison data were available to compare sotalol with flecainide.

Patient diagnostic variables which are frequently identified in the literature as being important for successful conversion to sinus rhythm are: duration of arrhythmia, left

atrial diameter, age, and the presence and extent of structural heart diseases. Unfortunately, the relevant data are rarely reported and analysis of their impact on the efficacy of drug treatment could not be carried out.

Although flecainide and sotalol are commonly employed in the United Kingdom, a new pure class III drug, ibutilide, was recently approved by FDA in the United States as a first line agent for pharmacoconversion mainly due to its apparent safety, rapid onset of action, and availability for intravenous administration for acute conversion. It was classed as a primary choice in The Adult Advanced Cardiac Life Support (ACLS) guidelines (Anderson, 1996).

The issue of chronic treatment which should be initiated post-cardioversion for maintenance of sinus rhythm is still a controversial area in clinical practice due to the high relapse rate observed during long-term treatment following discharge. Unlike the use of amiodarone for acute cardioversion, the analysis in Chapter 4 has demonstrated improved benefit for amiodarone given orally on a chronic basis. The pooled percentage of patients maintaining sinus rhythm was consistently higher with amiodarone than with placebo and other traditional antiarrhythmic agents (quinidine, flecainide, or sotalol). This advantage was not associated with a higher incidence of proarrhythmic events.

It is important to emphasize that maintenance of sinus rhythm is not the only strategy for management of chronic atrial fibrillation and that Canadian Consensus Guidelines (Newman *et al.*, 1996) propose two alternative strategies to prevent or reduce the symptoms associated with chronic relapse (dyspnea, palpitations, fatigue, and syncope), and to prevent serious thromboembolic complications. These strategies are heart rate control, and/or anticoagulation. However, none of the 42 clinical trials included in the meta-analysis has prospectively compared these strategies or evaluated the efficacy of antiarrhythmic drugs for reduction of thromboembolic complications. Therefore, the benefit obtained from maintenance of sinus rhythm may still have been introduced as a surrogate outcome measure in some patient categories, particularly those at highest risk for proarrhythmia, stroke, and systemic thromboembolism. Thus, although the meta-analysis undertaken had involved follow-up data concerning a total of 3937 patients for a mean of 16 months, a clear conclusion about the value of initiating antiarrhythmic therapy post-cardioversion can only be made by further investigation in larger trials which are precisely designed to compare the previously defined alternative approaches to the management of chronic atrial fibrillation.

The final part of the thesis involved a meta-analysis (Chapter 6) to assimilate the strongest evidence on the impact of antiarrhythmic drugs on mortality in patients at high risk of sudden death (post myocardial infarction and congestive heart failure).

A meta-analysis based on pooling individual patient data from each study enables a more precise and less biased estimate of effect than can be achieved from a meta-analysis of summary data (Clarke and Stewart, 1994). With such a method, it would have been possible to overcome the problems experienced in pooling censored outcome measures such as total mortality and sudden death, particularly in randomised clinical trials which employed the product-limit method to analyse the survival data. Moreover, the analysis based on time to each event would contribute greater statistical power than that produced using a limited number of time points with aggregate data. Although the authors of the individual trials which did not report individual length of follow-up for each patient, or total number of censored observations at each time point were contacted, they were all reluctant to share their data.

An attempt was made to approximate the distribution of lost to follow-up and deaths by curve fitting. The pooled log-rank odds ratios as well as the single point pooled odds ratios confirmed the positive impact of amiodarone on prolonging the survival after acute myocardial infarction.

Although curve fitting has been implemented by many authors to generate the number of events during follow-up duration (Pignon *et al.*, 1992; Fine *et al.*, 1993; Gregory *et al.*, 1992; Messori *et al.*, 1994), its application to any Kaplan-Meier survival curve to produce the final meta-analytic survival graph requires further validation. Its sensitivity to detect the censored estimates that should approximate the true original values remains to be determined by assembling larger numbers of randomised clinical trials which provided the raw actuarial data and reconducting the meta-analysis on original and curve fitting data separately.

7.2 CONCLUSION

The present meta-analyses suggest that amiodarone is a useful agent for maintenance of sinus rhythm. Overall, it is well tolerated and safe for this indication compared with other available agents such as flecainide and sotalol.

However, for acute conversion to sinus rhythm, the overall pooling of existing data has demonstrated optimal benefit and minimal risk with oral and intravenous flecainide, or intravenous sotalol. The lack of evidence supporting the use of intravenous amiodarone in the early period after cardiac surgery is important and impressive. The value of recently promoted pure class III agents for prompt cardioversion needs to be elucidated.

The meta-analysis of survival curves supports the continuous indication of prophylactic antiarrhythmic therapy with oral amiodarone for improving survival in life threatening ventricular arrhythmias particularly in the setting of post myocardial infarction. The data from trials comparing *d, l*-sotalol or *d*-sotalol with placebo or other beta-blockers failed to show any prophylactic effect with respect to deaths.

7.3 FUTURE DIRECTIONS

1. To update the meta-analysis of amiodarone effect on survival (Chapter 6) by adding the results of two large-scale, multicentre, recently completed clinical trials (the Canadian Acute Myocardial Infarction Amiodarone Trial (CAMIAT) and the European Myocardial Infarction Amiodarone Trial (EMIAT).

2. To validate the results of this meta-analysis by conducting another meta-analytic approach based on individual patient data (in which the patient is the unit of analysis). This method would have several advantages as follows: (1) the ability to test the agreement between the two meta-analytic estimates, (2) the facility to examine the impact of confounding variables not investigated in the individual studies (such as patients diagnostic criteria, dose, and concomitant medications), and (3) the possibility to analyse the homogeneity of the patient populations.

3. To undertake a systematic overview of randomised clinical trials addressing the efficacy and safety of Ibutilide (pure class III agent) which was recently approved by FDA for acute cardioversion. The results ofthis systematic evaluation would be further compared to pooled estimates of the efficacy and safety of flecainide and sotalol which were obtained in

this thesis (Chapter 5).

4. To evaluate the impact of amiodarone on the quality of life of patients during long-term maintenance therapy by using a general health-status measure (the UK Sickness Impact Profile).

5. A decision analytic approach to compare the various strategies for treatment of chronic atrial fibrillation would be worthwhile. Variables to be incorporated should include the following:

- The meta-analytic estimates for the probability of maintenance of sinus rhythm or reversion to atrial fibrillation at 3, 6, and 12 months.

- The pooled relative risk for the incidence of proarrhythmia, stroke, any nonfatal toxicity, and sudden death during the three treatment strategies.

The overall cost should include the costs of drug acquisition for 1-year treatment, drug administration, routine medical care, adverse event management, and monitoring techniques for arrhythmia.

APPENDIX 4.2

Appendix 4.2

Table (1) Population Characteristics of the Included Studies (amiodarone clinical trials)

Study name	*Age;mean years (range/±SD) (Amiodarone/Control)*	*M:F*	*Duration of AF (months) (Amiodarone/Control)*	*Left atrial diameter, mm (range) (Amiodarone/Control)*	*No. pts. chronic AF or AFL (Amiodarone/Control)*	*No. pts. paroxysmal AF (Amiodarone/Control)*	*No. pts with other forms of supraventricular arrhythmias*
Vitolo *et al.* 1981*	52.6±10.7 (54.7±10.7, 50.4±10.5)	20:34	1.01±0.97, 1.03±0.92	NA	54 AF (28/26)	0	0
Martin *et al.* 1986*	75.6, 74.1	29:41	NA	NA	0	70 (43/27)	0
Bosi *et al.* 1990*	20-77	60:37	24 hours-30 days	≤45	97 AF (48/49)	0	0
Zehender *et al.* 1992*	59±5, 57±6	23:17	6.1±3.7 (11-22), 4.8±3.9 (1-19)	50±5.2 (42-66), 49±4.1 (43-64)	40 AF (20/20)	0	0
Jong *et al.* 1995*	63±12, 62±11	74:13	18±12, 19±10	50±12, 51±13	7 AF (4/3) 80 AFL (40/40)	0	0
Perelman *et al.* 1987**	63.7	7:7	Ranged from 3 months to several years	NS	14 AF	0	0
Leak *et al.* 1979***	22-77	6:7	2 months-37 years	NS	0	2	12 PSVT
Podrid *et al.* 1981***	56 (16-78)	NA	1 to 61 years (average 9.9)	NS	0	20	9 PSVT
Grasboys *et al.* 1983***	59 (14-80)	82:39	Average 8 years	NS	95 AF	0	21 SVT 5 SVT+AF
Blomstrom *et al.* 1984***	61 47-73)	12:9	chronic AF 18.8 (1-62) months PAF 74 (4-180) months	NS	13 AF	8	0
Horowitz *et al.* 1985***	60 (26-78)	29:9	At least 3 months (4-108)	48 (32-90)	11 AF	27	0

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; AF, atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; SVT, supraventricular tachycardia; §, retrospective uncontrolled study, which was grouped with uncontrolled studies

Appendix 4.2

Table (1) Population Characteristics of the Included Studies (amiodarone clinical trials), (continued)

Study name	*Age; mean years (range/±SD) (Amiodarone/Control)*	*M:F*	*Duration of AF (mo) (Amiodarone/Control)*	*Left atrial diameter, mm (range) (Amiodarone/Control)*	*No. pts. chronic AF or AFL (Amiodarone/Control)*	*No. pts. paroxysmal AF (Amiodarone/Control)*	*No. pts with other forms of supraventricular arrhythmias*
Brodsky *et al.* 1987***	61 (32-87)	18:10	4 days to 215.37 months	57 (46-78)	228 AF	0	0
Blevins *et al.* 1987***	chronic AF 62 (35-79) PAF 60 (46-76)	NS	chronic AF 75 (0.5-360) PAF 65 (18-120)	chronic AF 44 (18-80) PAF 39 (28-65)	25 AF	13 PAF	0
Gold *et al.* 1988***	59 (25-75)	37:31	At least 1 year in 14 patients with chronic AF 54 patients with PAF less than 1 year	42.2±8.9 (29-70)	68 AF	68 PAF	0
Mostow *et al.* 1990***	62.7	13:6	55 (0.1-324) months	45.7	9 AF, 1 AFL	6 PAF	3 atrial tachycardia
Levy *et al.* 1991***	NS	NS	At least 1 month	NS	112 AF	0	0
Gosselink *et al.* 1992***	63±10	53:36	At least 2-350 months	48	89 AF or AFL	0	0
Chun *et al.* 1995§	60±13	95:15	NS	44±9	53 AF or AFL	57 PAF	0

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; AF, atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; PAF, paroxysmal atrial fibrillation; SVT, supraventricular tachycardia; §, retrospective uncontrolled study, which was grouped with uncontrolled studies

Appendix 4.2

Table (2) Population Characteristics of the Included Studies (sotalol clinical trials)

Study name	*Age;mean years (range/±SD) (Sotalol/Control)*	*M:F*	*Duration of AF (Sotalol/Control)*	*Left atrial diameter, mm (range) (Sotalol/Control)*	*No.pts.chronic AF or AFL (Sotalol/Control)*	*No.pts. paroxysmal AF (Sotalol/Control)*	*No. pts with other forms of supraventricular arrhythmias (Sotalol/Control)*	*Mean heart volume (Sotalol/Control)*
Juul-Moller *et al.* 1990*	59±9, 59±9	149:34	5.1±3.7, 5.2±3.3 months (median 4/4.2 months)	42±7, 42±7	AF (98/85)	0/0	0/0	521±93, 522±82
Singh *et al.* 1991*	60±14, 61±9	24:10	3.4≠4.9, 4.1±5.7 years	44±4, 43±6	AF (24/10)	0/0	0/0	NA
Reimold *et al.* 1993*	62±12, 61±12	64:36	52±45, 66±96 (median 35.5, range 0.25 to 504) months	46±8, 46±8	AF (28/25)	22/25	0/0	NA
Kalusche *et al.* 1994*	63.5±5.4, 58.7±5.5	56:26	Mean 219 days	NS	AF (41/41)	0/0	0/0	NA
Hohnloser *et al.* 1995*	62±11; (60±10, 65±13)	18:32	44±56 (median 20 days); (49±63, 39±48)	50±7	AF (25/25)	0/0	0/0	NA
Carunchio *et al.* 1995*	NS	NS	NS	NS	0	20/26	0/0	NA
Crijns *et al.* 1991**	60±12	65:62	22 months (0.1-300)	45±7	AF (53/127/34)	0	0	NA
Antman *et al.* 1990**	63±13	70:39	24 (0.3-576)	44±9	53	56	0	NA

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; AF, atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; PAF, paroxysmal atrial fibrillation; SVT, supraventricular tachycardia; §, retrospective uncontrolled study, which was grouped with uncontrolled studies

Appendix 4.2

Table (3) Population Characteristics of the Included Studies (flecainide clinical trials)

Study name	*Age; mean years (range/±SD) (Flecainide/Control)*	*M:F*	*Duration of AF (mo) (Flecainide/Control)*	*Left atrial diameter, mm (range) (Flecainide/Control)*	*No. pts. chronic AF or AFL (Flecainide/Control)*	*No. pts. paroxysmal AF (Flecainide/Control)*	*No. pts with other forms of supraventricular arrhythmias (Flecainide/Control)*
Van-Gelder *et al.* 1989*	60±11/57±14	42:31	12±14 / 21±27 months	45±7, 43±8	AF (36/37)	0/0	0/0
Rasmussen *et al.* 1988*	-	-	> 2 weeks	-	AF (30/30)	0/0	0/0
Sonnhag *et al.* 1988***	62 (44-73)	9:11	1 month to 20 years (8±6 years)	-	0	20	0
Anderson *et al.* 1989*	56±13	30:18	-	-	0/0	64/64	0/0
Pritchett *et al.* 1991*	54.1± 5.2	44:29	-	-	0/0	45/45	28/28 PSVT
Henthorn *et al.* 1991*	50±15	11:23	-	-	0/0	0/0	51/51 PSVT
Pietersen *et al.* 1991*	53±13	23:20	-	-	0/0	48/48	0/0
Clementy *et al.* 1992***	65.3±11	555:389	-	-	-	944	0
Lau *et al.* 1992*	59±8	17:12	-	-	0/0/0	19 / 15 Placebo/ 18 Quinidine	0/0/0
Crijns *et al.* 1991**	60±12	65:62	22 months (0.1-300)	45±7	AF (127/34/53)	0	0
Berns *et al.* 1987***	64±13	24:15	34±36 months	43±6	5	25	9 Ectopic atrial tachycardia (PAT)
Zee-Cheng *et al.* 1988***	43	11:8	2-10 years	-	0	0	15 PSVT
Anderson JL 1992***	53.4±5.5	38:28	-	-	0	41	25 PSVT
Anderson *et al.* 1994**	55.64±5.2	26:23	-	-	0/0	25/25	17/17 PSVT
Leclercq *et al.* 1992**	56.3±9.1	38:14	-	-	0/0	19/33	0
Mary-Rabine *et al.* 1988**	55±1	34:21	6 months-36 years (mean, 5.6±1 years)	-	0/0	39	16 PSVT
Zeigler *et al.* 1988***	13 (1-32)	-	-	-	0	0	16 SVT
Chimienti *et al.* 1994*	-	-	> 4 months prior to study	-	0/0	97/103	72/63 PSVT

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; AF, atrial fibrillation; AFL, atrial flutter; PSVT, paroxysmal supraventricular tachycardia; PAF, paroxysmal atrial fibrillation; SVT, supraventricular tachycardia; §, retrospective uncontrolled study, which was grouped with uncontrolled studies

Appendix 4.2

Table (4) Cardiac diagnoses in patients enrolled in randomised control, nonrandomised control, and uncontrolled trials (amiodarone clinical trials)

Study name	*Patients (n)*	*Valvular (Amio/Cont)*	*Hypertension (Amio/Cont)*	*Ischemic heart disease (Amio/Cont)*	*Thyroid (Amio/Cont)*	*Lone fibrillator (Amio/Cont)*	*Congenital heart disease (Amio/Cont)*	*Pericarditis (Amio/Cont)*	*Cardiac surgery (Amio/Cont)*	*CHF (NYHA class) (Amio/Cont)*	*Cardiomyopathy (Amio/Cont)*	*Miscellaneous (Amio/Cont)*
Vitolo *et al* 1981*	54	12/12	0/0	16/14	0/0	0/0	0/0	0/0	5/6	0/0	0/0	0/0
Martin *et al* 1986*	70	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bosi *et al* 1990*	97	0/0	0/0	0/0	0/0	48/49	0/0	0/0	0/0	0/0	0/0	0/0
Zehender *et al* 1992*	40	5/5	2/3	4/4	0/0	2/1	0/0	0/0	0/0	0/0	4/4	3/3
Jong *et al* 1995*	87	20/16	7/6	3/4	0/0	8/13	3/1	0/0	9/6	0/0	0/0	0/0
Perelman *et al* 1987**	14	4/6	0/0	0/0	0/0	2/3	0/0	0/0	0/0	0/0	3/4	1/1
Leak *et al* 1979***	14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Blomstrom *et al* 1984***	21	8	0	2	0	3	1	0	0	0	3	4
Podrid *et al* 1981***	29	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Grasboys *et al* 1983***	121	16	0	17	0	74	5	0	0	0	0	9
Horowitz *et al* 1985***	78	11	0	13	0	9	0	0	NS	10	10	0
Gold *et al* 1986***	68	16	12	15	0	9	2	0	0	0	7	9
Blevin *et al* 1987***	38	3	0	16	0	7	0	0	0	0	12	0
Brodsky *et al* 1987***	28	13	0	5	0	0	1	0	0	0	11	3
Mostow *et al* 1990***	19	6	0	11	0	2	0	0	6	11	5	7
Levy *et al* 1991***	112	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Gosselink *et al* 1992***	89	69	18	33	0	9	2	0	11	89; class I 16, class II 44, class III 26, class IV 3	10	0
Chun *et al* 1995***	110	14	15	36	0	24	1	0	0	0	19	0
Sum (Amio)	887	192	54	171	0	195	15	0	31	110	84	35
Sum (Placebo)	95	16	6	4	0	62	1	0	6	0	0	0
Sum (Others)	52	17	3	18	0	1	0	0	6	0	4	3
Pooled (all), %	1089	225 (20.7%)	63 (5.8%)	193 (17.7%)	0	258 (23.7%)	16 (1.47%)	0	43 (3.9%)	110 (10.1%)	88 (8.1%)	38 (3.5%)

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Amio/Cont), the number of patients with a given cardiac diagnosis in amiodarone (Amio) and control (Cont) group; others, including patients in active control group.

Appendix 4.2

Table (5) Cardiac diagnoses in patients enrolled in randomised control, and nonrandomised control trials (sotalol clinical trials)

Study name	*Patients (n)*	*Valvular (Sota/Cont)*	*Hypertension (Sota/Cont)*	*Ischemic heart disease (Sota/Cont)*	*Thyroid (Sota/Cont)*	*Lone fibrillator (Sota/Cont)*	*Congenital heart disease (Sota/Cont)*	*Pericarditis (Sota/Cont)*	*Cardiac surgery (Sota/Cont)*	*CHF (NYHA class) (Sota/Cont)*	*Cardiomyopathy (Sota/Cont)*	*Miscellaneous (Sota/Cont)*
Juul-Moller *et al* 1990*	183	7/3	26/22	16/13	0/0	49/47	0/0	0/0	0/0	0/0	0/0	0/0
Singh *et al* 1991*	34	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Reimold *et al* 1993*	100	12/18	12/7	11/5	2/0	13/6	0/0	0/0	0/0	3/2	0/0	31
Kalusche *et al* 1994*	82	0/0	14/9	2/5	0/0	15/11	0/0	0/0	0/0	0/0	7/16	3/0
Carunchio *et al* 1995*	66	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hohnloser *et al* 1995*	50	6/8	4/6	9/6	0/0	4/3	0/0	0/0	0/0	0/0	2/2	0/0
Crijns *et al* 1991**	127	106	20	30	4	22	9	0	36	56 (class I) 58 (class II) 13 (class III)	6	0
Sum (Sota)	608	131	76	68	6	103	9	0	36	130	15	34
Sum (Placebo)	0	0	0	0	0	0	0	0	0	0	0	0
Sum (Others)	189	29	44	29	0	67	0	0	0	2	18	0
Pooled (all), %	642	160 (24.9%)	120 (18.7%)	97 (15.1%)	6 (0.9%)	170 (26.5%)	9 (1.4%)	0	36 (5.6%)	132 (20.6%)	33 (5.1%)	34 (5.3%)

*Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Sota/Cont), the number of patients with a given cardiac diagnosis in sotalol (Sota) and control (Cont) group, others, including patients in active control group.

Appendix 4.2

Table (6) Cardiac diagnoses in patients enrolled in randomised control, nonrandomised control, and uncontrolled trials (flecainide clinical trials)

Study name	*Patients (n)*	*Valvular (Fle/Cont)*	*Hypertension (Fle/Cont)*	*Ischemic heart disease (Fle/Cont)*	*Thyroid (Fle/Cont)*	*Lone fibrillator (Fle/Cont)*	*Congenital heart disease (Fle/Cont)*	*Pericarditis (Fle/Cont)*	*Cardiac surgery (Fle/Cont)*	*CHF (NYHA class) (Fle/Cont)*	*Cardiomyopathy (Fle/Cont)*	*Miscellaneous (Fle/Cont)*
Rasmussen*et al* 1988*	60	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
Gelder*et al* 1989*	73	15/12	3/4	10/10	0/0	5/8	2/2	0/0	0/0	Class I, 8/8 Class II 28/29	1/1	0/0
Anderson*et al* 1989*	64	4/4	18/18	0/0	0/0	12/12	-	-	0/0	Class I, 4 Class II, 4	-	32/32
Pietersen*et al* 1991*	48	1/1	2/2	3/3	0/0	0/0	0/0	0/0	0/0	Class I, 42/42	0/0	0/0
Henthorn*et al* 1991*	51	8/8	7/7	0/0	0/0	0/0	0/0	0/0	0/0	0/0	4/4	8/8
Pritchett*et al* 1991*	73	-	-	-	-	-	-	-	-	-	-	-
Lau*et al* 1992*	19	0/0	0/0	0/0	0/0	19/19/19	0/0	0/0	0/0	0/0	0/0	0/0
Anderson JL 1992***	66	-	25	13	-	16	-	-	-	-	-	-
Anderson*et al* 1994*	49	0/0	18/18	3/3	0/0	0/0	0/0	0/0	0/0	Class I, 2	0/0	10
Chimienti*et al* 1994*	335	-	-	-	-	-	-	-	-	-	-	-
Crijns*et al* 1991**	127	106	20	30	4	22	9	0	36	56 (class I) 58 (class II) 13 (class III)	6	0
Leclercq*et al* 1992**	52	3	0	3	0	-	0	0	0	0	2	35
Mary-Rabine*et al* 1988**	55	2	0	10	0	40	1	0	0	0	0	5
Clementy*et al* 1992***	944	171	262	55	65	435	-	-	-	0	23	54
Zeigler*et al* 1988***	16	0	-	-	-	12	4	0	2	0	0	0
Berns*et al* 1987***	39	6	0	16	0	7	0	0	0	0	10	0
Zee-Cheng*et al* 1988***	19	4	0	1	0	0	0	0	0	0	0	13
Sonnhag*et al* 1988***	20	-	8	3	-	10	-	-	-	0	-	1
Sum (Fle)	1952	320	363	147	69	578	16	0	38	217	46	158
Sum (Placebo)	271	25	49	16	0	39	2	0	0	95	5	40
Sum (Others)	19	0	0	0	19	0	0	0	0	0	0	0
Pooled (all), %	2110	332 (15.75%)	367 (17.4%)	157 (7.4%)	69 (3.3%)	605 (28.7%)	18 (0.85%)	0	38 (1.8%)	296 (14%)	46 (2.2%)	158 (7.5%)

Randomised controlled trials, **Nonrandomised controlled, ***Uncontrolled; NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Flec/Cont), the number of patients with a given cardiac diagnosis in flecainide (Fle) and control (Cont) group.

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model

a. Amiodarone clinical trials

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Amiodarone P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
1	All RCTs	3 months	5	5	170/136	76.9 (70.7-83.1)	63.1 (70.7-83.1)	15.3 (5.7-24.9)	3.13**	16.58** (P=0.01)	18.5 (-1.4-38.3)	1.83 NS
1	All RCTs	6 months	3	3	119/100	76.7 (69.13-84.3)	66.3 (57.6-74.95)	12.3 (0.33-24.2)	2.01* (P=0.04)	10.15** (P=0.006)	17.32 (-10.5-45.1)	1.22 NS (P=0.22)
1	All RCTs	12 months	3	3	119/100	71.97 (64.1-79.9)	57.32 (49.1-65.6)	11.1 (-0.9-23)	1.82 (P=0.069)	8.7* (P=0.013)	15.8 (-10-41.5)	1.2 NS (P=0.22)
2	Amiodarone vs placebo	3 months	2	2	87/74	69.3 (59.6-78.9)	62.2 (52.9-71.6)	10.2 (-3.34-23.7)	1.48 (P=0.139)	10.61** (P=0.001)	16.1 (-29.7-61.9)	0.69 NS (P=0.49)
2	Amiodarone vs placebo	6 months	1	1	48/49	72.9 (60.4-85.5)	79.6 (68.2-90.4)	-6.7 (-23.6-10.2)	-0.77 (P=1.56)	-	-	-
2	Amiodarone vs placebo	12 months	1	1	48/49	72.9 (60.4-85.5)	79.6 (68.2-90.4)	-6.7 (-23.6-10.2)	-0.77 (P=1.56)	-	-	-
3	Amiodarone vs class IA (quinidine and disopyramide)	3 months	3	3	83/62	82.3 (74.2-90.4)	64.11 (53.5-74.7)	20.5 (6.9-34.1)	2.96**	4.9 (P=0.088) NS	20.7 (-0.49-41.9)	1.92
3	Amiodarone vs class IA (quinidine and disopyramide)	6 months	2	2	71/51	78.9 (69.4-88.4)	46.99 (33.4-60.6)	31.01 (14.2-47.8)	3.6**	0.54 (P=0.46) NS	31.2 (18.8-43.6)	4.9
3	Amiodarone vs class IA (quinidine and disopyramide)	12 months	2	2	71/51	71.4 (61.2-81.5)	32 (19.97-44)	28.8 (11.9-45.7)	3.3**	0.24 (P=0.63) NS	29.1 (20.9-37.2)	6.98
4A	Amiodarone vs quinidine standard (RCTs)	3 months	5	5	170/373	76.9 (70.7-83.1)	69.4 (67.3-71.5)	7.6 (0.98-14.1)	2.3* (P=0.02)	6.2 (P=0.19) NS	7.6 (-0.6-15.8)	1.83
4A	Amiodarone vs quinidine standard (RCTs)	6 months	3	3	91/373	76.7 (69.1-84.3)	57.7 (54.8-60.6)	19.02 (10.9-27.2)	4.6**	0.48 (P=0.79) NS	19.11 (15.8-22.4)	11.4

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

a. Amiodarone clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Amiodarone P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
4A	Amiodarone vs quinidine standard (RCTs)	12 months	3	3	119/373	71.98 (64.1-79.88)	50.2 (47.3-53)	21.5 (13-29.95)	4.97**	4.7 (P=0.0967) NS	19.9 (6.6-33.2)	2.94
4B	Amiodarone vs quinidine standard (uncontrolled trials)	3 months	11	11	512/373	81.8 (78.7-84.7)	69.4 (68.1-70.8)	9.7 (6.1-13.4)	5.2**	53.8** (P=0)	17.7 (-7.5-11.03)	0.38 NS
4B	Amiodarone vs quinidine standard (uncontrolled trials)	6 months	11	11	512/373	79.4 (76.2-82.6)	57.7 (56.2-59.2)	18 (14.1-21.9)	8.98**	63.3** (P=0)	7.7 (-3.7-19)	1.03 NS
4B	Amiodarone vs quinidine standard (uncontrolled trials)	12 months	8	8	391/373	56.3 (51.4-61.1)	50.2 (48.5-51.9)	5.7 (0.4-11)	2.12**	8.3 (P=0.31)	5.3 (-0.6-11)	1.75 NS
5A	Amiodarone vs quinidine standard (RCTs with chronic AF only)	3 months	4	4	127/373	76.2 (68.9-83.4)	69.4 (67.1-71.7)	6.8 (-0.8-14.4)	1.8 NS (P=0.072)	6.027 (P=0.11) NS	7.13 (-3.7-17.97)	1.29 NS (P=0.2)
5A	Amiodarone vs quinidine standard (RCTs with chronic AF only)	6 months	2	2	76/373	75.2 (65.5-84.9)	57.7 (54.2-61.2)	17.6 (7.2-27.9)	3.3**	0.28 (P=0.597) NS	16.4 (11.9-20.8)	7.2**
5A	Amiodarone vs quinidine standard (RCTs with chronic AF only)	12 months	2	2	76/373	66.8 (56.4-77.2)	50.2 (46.6-53.8)	16.3 (5.2-27.3)	2.88**	2.6 (P=0.12) NS	14.3 (-4.5-33.1)	1.5 NS (P=0.134)
5B	Amiodarone vs quinidine standard (uncontrolled trials with chronic AF only)	3 months	8	8	273/373	70.3 (65-75.6)	69.4 (67.8-70.96)	0.4 (-5.4-6.1)	12.1**	13.2 (P=0.068) NS	-2.1 (-10.9-6.7)	-0.47 NS
5B	Amiodarone vs quinidine standard (uncontrolled trials with chronic AF only)	6 months	8	8	250/373	70.1 (64.6-75.7)	57.7 (55.8-59.5)	11.73 (5.6-17.9)	3.74**	9.4 (P=0.15) NS	9.4 (0.7-18.14)	2.11* (P=0.034)
5B	Amiodarone vs quinidine standard (uncontrolled trials with chronic AF only)	12 months	6	6	199/373	53.6 (46.8-60.3)	50.2 (48.13-52.3)	2.8 (-4.5-10)	0.75 NS (P=0.45)	8.41 (P=0.135) NS	0.25 (-9.9-10.4)	0.05 NS

RD, risk difference; 95% CI; 95% confidence interval; PT and PC, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant P< 0.05; ** highly statistically significant P < 0.01

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

a. Amiodarone clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Amiodarone P_T (95% CI)	*Controls P_C (95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
6	Amiodarone vs quinidine standard (uncontrolled trials with PAF only)	3 months	6	6	126/373	86.6 (81.3-91.9)	69.4 (67.5-71.3)	14.4 (8.1-20.8)	4.5**	26.8** (P=0.0001)	-2.8 (-22.5-16.9)	-0.28 NS
6	Amiodarone vs quinidine standard (uncontrolled trials with PAF only)	6 months	6	6	95/373	67.5 (58.8-76.1)	57.7 (55.2-60.2)	8.5 (-0.8-17.7)	1.799 NS (P=0.07)	17.2** (P=0.0006)	-4.8 (-31.1-21.5)	-0.4 NS
6	Amiodarone vs quinidine standard (uncontrolled trials with PAF only)	12 months	4	4	146/373	61.9 (54.1-69.6)	50.2 (47.7-52.7)	11.4 (3.1-19.7)	2.7** (P=0.007)	4.4 NS (P=0.22)	10.6 (-0.08-21.2)	1.94* (P=0.05)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

b. Sotalol clinical trials

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Sotalol P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
1	All trials (RCTs and non-RCTs)	3 months	8	10	335/508	57.1 (52.5-61.7)	56.63 (52.6-60.64)	1.3 (-4.87-7.4)	0.41 NS (P=0.68)	14.15 (P=0.1171) NS	1.31 (-6.6-9.2)	3.3**
1	All trials (RCTs and non-RCTs)	6 months	8	10	335/508	48.8 (44.12-53.5)	45.5 (41.5-49.5)	3.6 (-2.6-9.8)	1.13 NS (P=0.26)	16.9 (P=0.0503) NS	4.33 (-4.5-13.2)	9.6**
1	All trials (RCTs and non-RCTs)	12 months	5	7	211/402	30.3 (25.23-35.4)	31.21 (26.9-35.5)	-2.23 (-8.9-4.5)	-0.653 NS (P=0.5)	11.996 (P=0.062) NS	-1.1 (-11.1-8.95)	-0.21 NS (P=0.8)
2	All RCTs	3 months	6	7	234/238	63.5 (57.8-69.3)	69.84 (64.3-75.4)	1.5 (-6.34-9.32)	0.37 NS (P=0.7)	11.82 (P=0.066) NS	1.8 (-9.5-13)	0.318 NS (P=0.75)
2	All RCTs	6 months	6	7	234/238	56.6 (50.63-62.6)	59.6 (53.7-65.4)	3.96 (-4.2-12.1)	0.95 NS (P=0.34)	15.94** (P=0.014)	5.32 (-8.5-19.1)	0.76 NS (P=0.45)
2	All RCTs	12 months	3	4	110/132	47.5 (39.12-55.97)	45.8 (37.9-53.6)	1.24 (-10.3-12.8)	0.21 NS (P=0.8)	9.342* (P=0.0251)	2.11 (-18.9-23.1)	0.197 NS (P=0.8)
3	Sotalol vs placebo (RCTs)	3 months	2	2	32/32	69.15 (54.3-83.99)	76.9 (60.73-93.12)	19.4 (1.3-37.5)	2.1 NS (P=0.04)	4.25* (P=0.0394)	21.7 (-16.1-59.5)	1.124 NS (P=0.26)
3	Sotalol vs placebo (RCTs	6 months	2	2	32/32	56.61 (39.9-73.34)	34.62 (16.33-52.9)	36 (16.32-55.7)	3.6**	0.3156 (P=0.5) NS	35.95 (24.9-47)	6.4**
3	Sotalol vs placebo (RCTs)	12 months	1	1	20/26	60 (38.5-81.5)	26.9 (9.87-43.973)	1.96 (5.7-60.5)	2.36**	-	-	-
4	Sotalol vs other antiarrhythmic drugs (RCTs)	3 months	5	5	222/206	62.53 (56.3-68.8)	68.9 (63-74.8)	-2.6 (-11.3-6.1)	-0.95 NS (P=0.34)	2.97 (P=0.5) NS	-1.5 (-8.6-5.7)	-0.41 NS (P=0.7)
4	Sotalol vs other antiarrhythmic drugs (RCTs)	6 months	5	5	222/206	56.6 (50.2-63.02)	62.4 (56.22-68.5)	-2.7 (-11.6-6.3)	-0.58 NS (P=0.56)	3.34 (P=0.5) NS	-2.1 (-10-5.9)	-0.5 NS (P=0.62)
4	Sotalol vs other antiarrhythmic drugs (RCTs)	12 months	3	3	110/106	45.3 (36.1-54.4)	50.8 (45-59.6)	-5.6 (-18.32-7.1)	-0.9 NS (P=0.37)	3.1 (P=0.22) NS	-6.4 (-22.4-9.7)	-0.78 NS (P=0.44)
4 A	Sotalol vs Class IC (RCTs)	3 months	2	2	69/69	-	-	-3.4 (-18-11.3)	-0.5 NS	0.64 (P=0.4) NS	-	-
4 A	Sotalol vs Class IC (RCTs)	6 months	2	2	69/69	-	-	-1.2 (-17-14.9)	-0.13 NS	1.52 (P=0.22)	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

b. Sotalol clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Sotalol P_T (95% CI)	*Controls P_C (95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
4 A	Sotalol vs Class IC (RCTs)	12 months	2	2	69/69	-	-	1.5 (-14.3-17.3)	0.2 NS	0.8 (P=0.4)	-	-
4 A	Sotalol vs Class IA (RCTs)	3 months	3	3	153/137	-	-	-2.2 (-13-8.6)	-0.4	2.3 (0.3)	-	-
4 A	Sotalol vs Class IA (RCTs)	6 months	3	3	153/137	-	-	-3.4 (-14-7.4)	-0.62	1.8 (0.42)	-	-
5	Sotalol vs other antiarrhythmic drugs (non-RCTs)	3 months	2	3	101/270	45.7 (38.1-53.4)	42.013 (36.2-47.83)	0.9 (-8.96-10.83)	0.185 NS (P=0.85)	2.3 (P=0.313) NS	0.87 (-9.9-11.6)	0.16 NS (P=0.9)
5	Sotalol vs other antiarrhythmic drugs (non-RCTs)	6 months	2	3	101/270	36.6 (29.1-44.02)	32.6 (27.1-38.2)	3.02 (-6.6-12.6)	0.62 NS (P=0.5)	0.94 (P=0.626) NS	2.03 (-3.9-7.95)	0.671 NS (P=0.5)
5	Sotalol vs other antiarrhythmic drugs (non-RCTs)	12 months	2	3	101/270	20.6 (14.2-26.86)	25.03 (19.9-30.13)	-4.01 (-12.3-4.24)	-0.953 NS (P=1.66)	2.1277 (P=0.345) NS	-3.95 (-12.5-4.6)	-0.91 NS (P=0.4)
5A	Sotalol vs Class IC (non-RCTs)	3 months	2	2	101/236	-	-	2.3 (-8.9-13.5)	0.4 NS	2.05 (P=0.2)	-	-
5A	Sotalol vs Class IC (non-RCTs)	3 months	2	2	101/236	-	-	1.7 (-9-12.5)	0.3 NS	0.7 (P=0.4)	-	-
5A	Sotalol vs Class IC (non-RCTs)	3 months	2	2	101/236	-	-	-7 (-16.6-2.2)	-1.5 NS	0.15 (P=0.7)	-	-
6A	Sotalol vs quinidine standard (RCTs)	3 months	6	6	234/373	61.54 (55.5-67.6)	69.4 (67.5-71.4)	-7.7 (-14.2_-1.24)	-2.34*	10.8 (P=0.0557) NS	-7.13 (-17.2_2.96)	-1.38 NS (P=0.17)
6A	Sotalol vs quinidine standard (RCTs)	6 months	6	6	234/373	55.86 (49.62-62.1)	57.7 (55.7-59.7)	-1.6 (-8.2-5.2)	-0.5 NS (P=0.6)	8.3 (P=0.1412) NS	-0.592 (-9.7-8.5)	-0.13 NS (P=0.897)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

b. Sotalol clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Sotalol P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
6A	Sotalol vs quinidine standard (RCTs)	12 months	3	3	110/373	45.3 (36-54.4)	50.2 (47.3-53.13)	-4.7 (-14.3-5)	-0.95 NS (P=0.3)	3.238 (P=0.198) NS	-3.65 (-16.2-8.94)	-0.57 NS (P=0.6)
6B	Sotalol vs quinidine standard (non-RCTs)	3 months	2	2	101/373	41.4 (32.14-50.7)	69.4 (66.1-72.7)	-27.9 (-37.8_-18.1)	-5.56**	6.5** (P=0.01)	-27.5 (-52.6_-2.5)	-2.2 NS (P=0.028)
6B	Sotalol vs quinidine standard (non-RCTs)	6 months	2	2	101/373	33.4 (24.4-42.4)	57.7 (54.2-61.3)	-24.2 (-33.9_-14.5)	-4.9**	3.41 (P=0.0638) NS	-23.7 (-41.7_-5.7)	-2.58**
6B	Sotalol vs quinidine standard (non-RCTs)	12 months	2	2	101/373	18.8 (11.3-26.4)	50.2 (46.6-53.8)	-31.2 (-39.6_-22.9)	-7.3**	1.33 (P=0.2486) NS	-31.1 (-40.8_-21.4)	-6.3**
7	Sotalol vs quinidine standard (RCTs with chronic AF only)	3 months	5	5	185/373	64.5 (57.7-71.2)	69.4 (67.31-71.5)	-4.7 (-11.9-2.53)	-1.27 NS (P=0.2)	7.262 (P=0.1227) NS	-3.98 (-14.44-6.5)	-0.75 NS (P=0.45)
7	Sotalol vs quinidine standard (RCTs with chronic AF only)	6 months	6	6	213/373	56.2 (49.6-62.7)	57.7 (55.7-59.7)	-1.3 (-8.3-5.7)	-0.37 NS (P=0.7)	8.7 (P=0.1225) NS	-0.643 (-10.4-9.13)	-0.12886 NS (P=0.897)
7	Sotalol vs quinidine standard (RCTs with chronic	12 months	2	2	61/373	52.6 (40.1-65)	50.2 (46.6-53.8)	2.5 (-10.5-15.5)	0.37 NS (P=0.7)	0.648 (P=0.4209) NS	1.6 (-8.2-11.3)	0.315 NS (P=0.75)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

c. Flecainide clinical trials

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T (95% CI)	*Controls P_C (95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
1	All trials (RCTs and non-RCTs)	3 months	12	14	622/533	60.9 (57.8-64)	29.6 (26.6-32.6)	21 (16.5-25.7)	9**	94.6** (P=0)	22.2 (9.4-35.1)	3.4**
1	All trials (RCTs and non-RCTs)	6 months	7	8	436/376	61.8 (58-65.4)	51.7 (47.1-56.3)	14.7 (8.5-20.8)	4.7**	39.9** (P=0)	14.7 (8.5-20.8)	4.7**
1	All trials (RCTs and non-RCTs)	12 months	7	8	436/376	57.7 (54-61.4)	42.2 (37.7-46.6)	19.4 (13-25.4)	6.33**	28.8** (P=0.0002)	20.7 (7.7-33.7)	6.3**
2	All RCTs	3 months	8	9	379/401	65.8 (61.8-69.7)	25.3 (21.9-28.6)	25.5 (20-30.9)	9.3**	41.5** (P=0)	28.9 (16.1-41.8)	4.4**
2	All RCTs	6 months	3	3	193/201	79.5 (74-85)	63.6 (57-70)	15.3 (6.7-23.9)	3.5**	5.13 NS (P=0.08)	18.5 (1.8-35.2)	2.2* (P=0.03)
2	All RCTs	12 months	3	3	193/201	75.4 (69.5-81.3)	56.3 (49.7-63)	17.5 (8.6-26.5)	3.8**	4.23 NS (P=0.1204)	20.2 (5-35.4)	2.6** (P=0.009)
3	Flecainide vs placebo (RCTs)	3 months	6	6	222/219	49.7 (43.8-55.6)	10.97 (6.9-15)	33.35 (26-40)	9.3**	24.8** (P=0.0002)	33.7 (17.8-49.6)	4.2**
3	Flecainide vs placebo (RCTs)	6 months	1	1	36/37	58 (41.9-74.1)	49 (32.9-65.1)	9 (-13.9-31.9)	0.77 (P=0.4)	-	-	-
3	Flecainide vs placebo (RCTs)	12 months	1	1	36/37	49 (32.7-65)	36 (20.5-51.5)	13 (-9.5-35.5)	1.133 (P=0.3)	-	-	-
4	Flecainide vs other antiarrhythmic drugs (RCTs)	3 months	3	3	176/182	79 (73.8-84..6)	59 (52.9-65.34)	14.6 (6.2-22.9)	3.4**	5.34 NS (P=0.0693)	18.5 (1.4-35.6)	2.1* (P=0.0346)
4	Flecainide vs other antiarrhythmic drugs (RCTs)	6 months	2	2	157/164	82.5 (76.5-88.4)	66.5 (59.4-73.6)	16.3 (7-25.6)	3.4**	4.8* (P=0.03)	23.6 (-3.3-0.5)	1.72 NS (P=0.085)
4	Flecainide vs other antiarrhythmic drugs (RCTs)	12 months	2	2	157/164	79.4 (73.1-85.7)	61 (53.6-68.4)	18.4 (8.6-28.2)	3.7**	4.05* (P=0.04)	24.5 (-0.4-49)	1.93 NS (P=0.054)
5	Flecainide vs others† RCTs (parallel design)	3 months	3	3	193/201	82.3 (77-87.6)	66.7 (60.3-73)	15.2 (6.9-23.5)	3.6**	5.2 NS (P=0.08)	19.6 (3.1-36.2)	2.33* (P=0.019)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; †, including placebo and other antiarrhythmics; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

c. Flecainide clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
5	Flecainide vs others† RCTs (parallel design)	6 months	3	3	193/201	79.5 (74-85)	63.6 (57-70)	15.3 (6.7-23.9)	3.5**	5.13 NS (P=0.08)	18.5 (1.8-35.2)	2.2* (P=0.03)
5	Flecainide vs others† RCTs (parallel design)	12 months	3	3	193/201	75.4 (69.5-81.3)	56.3 (49.7-63)	17.5 (8.6-26.5)	3.8**	4.23 NS (P=0.1204)	20.2 (5-35.4)	2.6** (P=0.009)
6	Flecainide vs Placebo RCTs (crossover design)	3 months	5	5	186/182	47.3 (41-53.7)	8.4 (4.3-12.6)	35 (27.9-42.8)	9.3**	21.9** (P=0.0002)	36.9 (19.4-54.4)	4.14**
6	Flecainide vs Placebo RCTs (crossover design)	6 months	0	-	-	-	-	-	-	-	-	-
6	Flecainide vs Placebo RCTs (crossover design)	12 months	0	-	-	-	-	-	-	-	-	-
7	Flecainide vs Class IA	3 months	2	2	47/46	-	-	25 (8.9-41.4)	3.04**	3 (P=0.08)	-	-
8A	Flecainide vs others† (non-RCTs)	3 months	4	5	243/175	53.5 (48.6-58.4)	46.2 (39.6-52.7)	9.3 (0.4-18.2)	2.1* (P=0.03)	43.8** (P=0)	9.4 (-20.7-39.6)	0.6 NS
8A	Flecainide vs others† (non-RCTs)	6 months	4	5	243/175	48.5 (43.7-53.3)	39.7 (33.2-46.2)	14 (5.23-22.7)	3.13**	34.8** (P=0)	13.7 (-13-40)	1.01 NS
8A	Flecainide vs others† (non-RCTs)	12 months	4	5	243/175	46 (41.4-50.9)	30.5 (24.5-36.6)	20.9 (12.8-29)	5.1**	24.2** (P=0.0001)	20.2 (-0.7-41)	1.9 NS
8B	Flecainide vs Amiodarone+flecainide	3 months	2	2	74/46	68.9 (58.4-79.5)	69.1 (56.2-82)	5.5 (-13.9-25)	0.56 NS	2.3 NS (P=0.13)	6.8 (-22.8-36.4)	0.5 NS
8B	Flecainide vs Amiodarone+flecainide	6 months	2	2	74/46	68.9 (58.4-79.5)	69.1 (56.2-82)	5.5 (-13.9-25)	0.56 NS	2.3 NS (P=0.13)	6.8 (-22.8-36.4)	0.5 NS
8B	Flecainide vs Amiodarone+flecainide	12 months	2	2	74/46	68.9 (58.4-79.5)	69.1 (56.2-82)	5.5 (-13.9-25)	0.56 NS	2.3 NS (P=0.13)	6.8 (-22.8-36.4)	0.5 NS
9A	Flecainide vs quinidine standard (RCTs)	3 months	8	8	379/373	65.8 (61.8-69.7)	69.4 (67.8-71)	-6 (-10.7_-1.8)	-2.8* (P=0.005)	126** (P=0)	-15.2 (-33.5-3.2)	-1.6 NS
9A	Flecainide vs quinidine standard (RCTs)	6 months	3	3	193/373	79.5 (74-85)	57.7 (54.8-60.6)	21 (14.6-27.8)	6.3**	7.2** (P=0.03)	18.6 (4.6-32.7)	2.6** (P=0.009)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; †, including placebo and other antiarrhythmics; NS, nonsignificant

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects model (continued)

c. Flecainide clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
9A	Flecainide vs quinidine standard (RCTs)	12 months	3	3	193/373	75.4 (69.5-81.3)	50.2 (47.3-53)	24.7 (17.8-31.5)	7.1**	11.4** (P=0.003)	21.4 (3.5-39.4)	2.34* (P=0.019)
9B	Flecainide vs quinidine standard (non-RCTs)	3 months	4	4	243/373	58 (52.1-64)	69.4 (67.1-71.7)	-10.4 (-17_-3.9)	-3.13**	16** (P=0.001)	-6.31 (-22.4-9.7)	-0.8 NS
9B	Flecainide vs quinidine standard (non-RCTs)	6 months	4	4	243/373	54.2 (48.3-60.1)	57.7 (55.2-60.2)	-2.1 (-8.6-4.5)	-0.62 NS	25.6** (P=0)	3.7 (-16.5-24)	0.4 NS
9B	Flecainide vs quinidine standard (non-RCTs)	12 months	4	4	243/373	52.3 (46.4-58.1)	50.2 (47.7-52.7)	3.8 (-2.7-10.3)	1.13 NS	30.84** (P=0)	10.5 (-11.7_32.6)	0.93 NS
9C	Flecainide vs quinidine standard (uncontrolled trials)	3 months	6	6	1100/373	62.4 (59.5-65.3)	69.4 (67.5-71.3)	-7.5 (-12_-2.9)	-3.2**	1.71 NS (P=0.9)	-6.1 (-10.3_-17.9)	-2.8** (P=0.005)
9C	Flecainide vs quinidine standard (uncontrolled trials)	6 months	6	6	1100/373	62 (59.3-65)	57.7 (55.7-59.7)	3.5 (-1.3-8.2)	1.43 NS (P=0.15)	3.3 NS (P=0.7)	3.2	-
9C	Flecainide vs quinidine standard (uncontrolled trials)	12 months	5	5	156/373	57.1 (49.5-64.7)	50.2 (47.9-52.5)	6.44 (-1.6-14.5)	1.6 NS (P=0.12)	5.6 NS (P=0.2343)	5 (-5-15)	0.97 NS
10 A	Flecainide vs Placebo for PAF (RCTs)	3 months	4	4	138/134	33.6 (26-41.2)	6.3 (1.96-10.7)	27.8 (19.4-36.2)	6.5**	7.4 NS (P=0.061)	29.1 (15.7-42.4)	4.3**
10 A	Flecainide vs Placebo for PAF (RCTs)	6 months	0	-	-	-	-	-	-	-	-	-
10A	Flecainide vs Placebo for PAF (RCTs)	12 months	0	-	-	-	-	-	-	-	-	-
10B	Flecainide vs other antiarrhythmics for PAF (RCTs)	3 months	2	2	96/100	75 (67.95-82.5)	51.3 (43.1-59.5)	14.2 (2.9-25.2)	2.48** (P=0.01)	0.1558 NS (P=0.7)	22	-

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects models (continued)

c. Flecainide clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T (95% CI)	*Controls P_C (95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
10B	Flecainide vs Propafenone for PAF (RCTs)	6 months	1	1	77/82	84.5 (79.4-92.6)	69.6 (59.6-79.6)	14.9 (2.1-27.7)	2.3* P=0.02	-	-	-
10B	Flecainide vs Propafenone for PAF (RCTs)	12 months	1	1	77/82	79 (69.9-88.1)	63 (52.6-73.5)	16 (2.14-29.9)	2.3* P=0.02	-	-	-
10C	Flecainide vs Placebo for PSVT (RCTs)	3 months	2	2	48/48	81.4 (70.4-92.4)	17.5 (6.9-28.14)	62.4 (46.9-77.9)	7.9**	0.16 NS (P=0.69)	71.03	-
10C	Flecainide vs Placebo for PSVT (RCTs)	6 months	0	-	-	-	-	-	-	-	-	-
10D	Flecainide vs Propafenone for PSVT (RCTs)	3 months	1	1	52/54	83.2 (73-93.4)	79.2 (68.4-90)	4 (-10.8-18.9)	0.53 NS	-	-	-
10D	Flecainide vs Propafenone for PSVT (RCTs)	6 months	1	1	52/54	77.3 (65.9-88.7)	70.5 (58.3-82.7)	6.8 (-9.9-23.5)	0.8 NS	-	-	-
10D	Flecainide vs Propafenone for PSVT (RCTs)	12 months	1	1	52/54	75 (63.2-86.8)	65 (52.3-77.7)	10 (-7.3-27)	1.1 NS	-	-	-
11A	Flecainide vs Placebo for PAF (non-RCTs)	3 months	1	1	25/25	68 (49.7-86.3)	12 (0.74-24.7)	56 (33.7-78.3)	4.93**	-	-	-
11A	Flecainide vs Placebo for PAF (non-RCTs)	6 months	1	1	25/25	68 (49.7-86.3)	12 (0.74-24.7)	56 (33.7-78.3)	4.93**	-	-	-
11A	Flecainide vs Placebo for PAF (non-RCTs)	12 months	1	1	25/25	68 (49.7-86.3)	12 (0.74-24.7)	56 (33.7-78.3)	4.93**	-	-	-
11B	Flecainide vs Amiodarone+flecainide for PAF (non-RCTs)	3 months	2	2	58/45	62.3 (49.9-74.7)	70.3 (57.3-83.3)	-1.1 (-21.1-18.9)	-0.1 NS	0.61 NS (P=0.44)	-2.3 (-17.1-12.5)	-0.3

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; †, including placebo and other antiarrhythmics; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects models (continued)

c. Flecainide clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T (95% CI)	*Controls P_C (95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
11B	Flecainide vs Amiodarone+flecainide for PAF (non-RCTs)	6 months	2	2	58/45	62.3 (49.9-74.7)	70.3 (57.3-83.3)	-1.1 (-21.1-18.9)	-0.1 NS	0.61 NS (P=0.44)	-2.3 (-17.1-12.5)	-0.3 NS
11B	Flecainide vs Amiodarone+flecainide for PAF (non-RCTs)	12 months	2	2	58/45	62.3 (49.9-74.7)	70.3 (57.3-83.3)	-1.1 (-21.1-18.9)	-0.1 NS	0.61 NS (P=0.44)	-2.3 (-17.1-12.5)	-0.3 NS
11C	Flecainide vs others† for PSVT (non-RCTs)	3 months	2	2	33/18	90.3 (80.4-100.3)	23.5 (3.4-43.7)	88 (77.3-99)	15.9**	5.4* (P=0.021)	78.5 (44.6-1.12)	4.5**
11C	Flecainide vs others† for PSVT (non-RCTs)	6 months	2	2	33/18	90.3 (80.4-100.3)	23.5 (3.4-43.7)	88 (77.3-99)	15.9**	5.4* (P=0.021)	78.5 (44.6-1.12)	4.5**
11C	Flecainide vs others† for PSVT (non-RCTs)	12 months	2	2	33/18	90.3 (80.4-100.3)	23.5 (3.4-43.7)	88 (77.3-99)	15.9**	5.4* (P=0.021)	78.5 (44.6-1.12)	4.5**
12A	Flecainide vs standard quinidine (uncontrolled trials for PAF only)	3 months	4	4	1030/373	62.3 (59.3-65.2)	69.4 (67.1-71.7)	-7.9 (-12.9_-2.9)	-3.11**	1.93 NS (P=0.59)	-1.9	-
12A	Flecainide vs standard quinidine (uncontrolled trials for PAF only)	6 months	4	4	1030/373	62.2 (59.2-65.1)	57.7 (55.2-60.2)	3.45 (-1.7-8.6)	1.31 NS	2.2 NS (P=0.535)	7	-
12A	Flecainide vs standard quinidine (uncontrolled trials for PAF only)	12 months	4	4	1030/373	62.2 (59.2-65)	50.2 (47.7-52.7)	10.9 (5.7-16)	4.11**	2.2 NS (P=0.536)	14.5	-
12B	Flecainide vs standard quinidine (uncontrolled trials for PSVT only)	3 months	4	4	65/373	70.2 (59.5-80.8)	69.4 (67.1-71.7)	0.7 (-10.2-11.6)	0.12 NS	6.2 NS (P=0.1)	-0.5 (-16.4-15.4)	-0.06 NS

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; †, including placebo and other antiarrhythmics; NS, nonsignificant

Appendix 4.2

Table (7) Pooled RD of different analysis subgroups estimated under fixed-effects and random-effects models (continued)

c. Flecainide clinical trials (continued)

Analysis group	*Comparisons*	*Time interval*	*No. of studies*	*No. of comparisons*	*No. of patients*	*Pooled effect (%)*		*Fixed-effects*		*Q statistic (P)*	*Random-effects*	
						Flecainide P_T(95% CI)	*Controls P_C(95% CI)*	*RD(%) (95% CI)*	*Z*		*RD(%) (95% CI)*	*Z*
12B	Flecainide vs standard quinidine (uncontrolled trials for PSVT only)	6 months	4	4	65/373	67.9 (57.2-78.5)	57.7 (55.2-60.2)	10.03 (-0.9-21)	1.79 NS (P=0.0734)	8.6* (P=0.0357)	8 (-10.9-26.8)	0.83 NS
12B	Flecainide vs standard quinidine (uncontrolled trials for PSVT only)	12 months	4	4	65/373	64.8 (54.3-75.4)	50.2 (47.7-52.7)	14.5 (3.6-25.3)	2.6**	13.3** (P=0.004)	11.7 (-11.5-34.9)	0.99 NS
13	Flecainide vs standard quinidine for chronic AF (RCTs)	3 months	2	2	64/373	76.9 (66.9-86.9)	69.4 (66.1-72.7)	7.3 (-3.2-17.8)	1.4 NS	3.958* (P=0.047)	5.9 (-15.34-27.2)	0.55 NS
13	Flecainide vs standard quinidine for chronic AF (RCTs)	6 months	2	2	64/373	74.8 (64.7-84.9)	57.7 (54.2-61.3)	16.8 (6.1-27.6)	3.1**	6.2** (P=0.013)	14.6 (-12.6-41.7)	1.05 NS
13	Flecainide vs standard quinidine for chronic AF (RCTs)	12 months	2	2	64/373	71.5 (61.4-81.7)	50.2 (46.6-53.8)	20.9 (10-31.7)	3.8**	10.7** (P=0.001)	17.5 (-18.5-53.5)	0.954 NS

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; †, including placebo and other antiarrhythmics; NS, nonsignificant

APPENDIX 5.2

Appendix 5.2

Table (1) Population Characteristics of the Included Studies (Flecainide clinical trials)

Study name	*Age;mean years (range/±SD) (Flecainide/Control)*	*Weight (Kg)*	*Male*	*Female*	*Onset of acute AF (hours) (Flecainide/Control)*	*Left atrial diameter, mm (range) (Flecainide/Control)*	*Type of SVA; Flecainide/Control)*	*Cause of AF*	*Mean ventricular ejection fraction*	*Mean heart rate at entery (beats/min)*	*Mean blood pressure (mm Hg)*
Goy *et al.* 1985	64 (38-93)	-	31	19	8.5 (days) Converted; 5.3±9.8 (days) Nonconverted; 16.7±26.2 (days)	41.68 Converted; 40±11 Nonconverted; 46±11	AF; 39 AFL; 6 SVT; 5	Medical; 50	-	-	-
Borgeat *et al.* 1986	64 (16-92)	-	39	21	95±4/140±4 (days)	45±2/46±1	AF (30/30)	Medical; (30/30)	-	-	-
Crozier *et al.* 1987	55 (18-89)	-	31	19	< 24 hrs	NS	AF; 25 SVT; 15 AFL/PAT with AV block; 10	Medical; 50	-	-	-
Nathan *et al.* 1987	49 (17-79)	-	19	2	NS	NS	PAF (11) PAFL (10)	Medical; 21	-	PAF; 156±10 PAFL; 120±12	-
Crijns *et al.* 1988 (a)	62±14	-	12	8	< 24 hr 14 > 24 hr 6	NS	AF (20)	Medical; 20	-	117±26	-
Crijns *et al.* 1988 (b)	55±16	-	14	6	< 24 hr 13 > 24 hr 7	NS	AF (20)	Medical; 20	-	135±53	-
Gavaghan *et al.* 1988	61.9±7.3/61.8±12.7	-	24/20	5/7	67.6±41.4/61.8±12.7	NS	AF (25/24) AFL (4/3)	CABG surgery; (26/23) Valve replacement surgery; (3/4)	<0.5 in (5/4)	152±35.6 /168±44.4	-
Suttorp *et al.* 1989	59±12 60±13/58±11	-	19/13	1/7	< 24 hr (12/13) > 24 hr (8/7)	123±23/134±18	AF (17/17) AFL (3/3)	Medical; (20/20)	-	123±23/134±18	-
Wafa *et al.* 1989	63±7 61±8/66±5	-	15/11	0/3	58±19 (30-96)	NS	AF (15/12) AFL (0/2)	CABG surgery; (15/14)	-	151±15/144±10	-
Villani *et al.* 1990	44.4±1.9/46.6±1.8	-	12/12	7/6	-	42.6±3.4/43.5±4	PAF (19/18)	NS	-	121±12/114±16	-

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery pypass surgery; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; SVA, supraventricular arrhythmia; The values are given as control/treatment

Appendix 5.2

Table (1) Population Characteristics of the Included Studies (Flecainide clinical trials; continued)

Study name	*Age;mean years (range/±SD) (Flecainide/Control)*	*Weight (Kg)*	*Male*	*Female*	*Onset of acute AF (hours) (Flecainide/Control)*	*Left atrial diameter,mm (range) (Flecainide/Control)*	*Type of SVA; Flecainide/Control)*	*Cause of AF*	*Mean ventricular ejection fraction*	*Mean heart rate at entery (beats/min)*	*Mean blood pressure (mm Hg)*
Suttorp *et al.* 1990	59±14 58±15/61±13	-	15/19	10/6	< 24 hr (15/16) > 24 hr (10/9); the mean duration of AF (if >24 hrs) was 100.8±57.6/184.8±266	38±7/37±7	AF (20/20) AFL (5/5)	Medical; (25/25)	-	137±25/141±21	-
Donovan *et al.* 1991	60 (21-90) 61±13/59±11	-	72	30	8.7±13/7.3±9	-	Recent-onset AF (51/51)	Cardiothoracic surgery; (26/27) Cardiac disease; (25/24)	-	145±19/147±22	Systolic; 118±17 /122±17
Capucci *et al.* 1992	58±12/59±10/57±11	-	14/10/11	8/9/10	28±29.4/29.8±30.2/ 27±26.8	45±5/46±6/46±8	Recent-onset AF (22/19/21)	Medical; (22/19/21)	-	123±21/125±20 /122±14	-
Capucci *et al.* 1993	-	-	-	-	-	-	Recent-onset AF (41/43/61)	Medical; (41/43/61)	-	-	-

AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery pypass surgery; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; SVA, supraventricular arrhythmia; The values are given as control/treatment

Appendix 5.2

Table (2) Population Characteristics of the Included Studies (Amiodarone clinical trials)

Study name	*Age; mean years (range/±SD) (Flecainide/Control)*	*Weight (Kg)*	*Male*	*Female*	*Onset of acute AF (hours) (Flecainide/Control)*	*Left atrial diameter, mm (range) (Flecainide/Control)*	*Type of SVA; Flecainide/Control)*	*Cause of AF*	*Mean ventricular ejection fraction*	*Mean heart rate at entery (beats/min)*	*Mean blood pressure (mm Hg)*
Faniel *et al.* 1983	66.6	53	14	12	NS	NS	AF; 20 AFL; 6	Medical; 26	-	142	-
Strasberg *et al.* 1985	63	-	16	10	15 mins-48 hrs	42±8	AF; 16 PAF; 10	Medical; 26	-	143±17	129±31
Posada *et al.* 1988	54.5/56.9	-	-	-	≤ 7 days	55±4/48±8	AF; (14/22)	Medical; (14/22)	-	-	-
Bertini *et al.* 1990	68±7.35/Pr62. 58±11.54	-	7/9	8/15	60 min (25-840)	NS	AF; (12/16) SVT; (3/8)	Medical; (15/24)	-	145±25.91/ 148.5±30.73	Systolic; 139.33±20.6 /135.65±23.07 Diastolic; 90±11.45/ 83.9±11.96
Noc *et al.* 1990	71±9.6 (51-85)	-	15	9	20 mins-48 hrs	NS	PAF; 24	Medical; 24	-	125±27	-
McAlister *et al.* 1990	59±14/59±19	-	25/23	16/16	103±71/102±70 (hrs)	Normal or mild ↑; (24/24) Moderate or large ↑; (7/9) Unknown; (10/6)	AF; (29/27) AFL; (8/9) AF/AFL; (4/3)	Surgical and medical; (41/39) Surgical only; (35/36)	≥ 40%; (33/27) < 40%; (2/2) Unknown; (6/10)	125/124	Systolic; 117/115
Andrivet *et al.* 1993	58.5±3/58±1.9	-	12/18	9/7	< 24 hrs; (12/17) > 24 hrs; (9/8)	42±1.8/36.7±1.3	AF; (11/18) AFL; (5/2) AT; (2/2) AF+AFL; (0/2) AF+AT; (1/1) AFL+AT; (2/0)	Medical; (21/25)	-	137±5/130±5	-
Chapman *et al.* 1993	71±9/65±13	-	8/10	2/4	Not less than 1 hr	NS	AF; (7/9) AFL; (1/3) SVT; (2/2)	Medical; (10/14)	-	160±23/160±20 (SD)	Systolic BP (SD); 128±32/123±18
Contini *et al.* 1993	61.9 (48-77)	-	52	9	NS	NS	AF; 61	Surgical; 61	> 50%; 49 < 50%; 12	153.5±5.7	Systolic BP; 102±6.1 Diastolic; 64.5±2.7
Bellandi *et al.* 1993	61.36±11.87/ 65.15±11.89	-	104	92	53.16±46.51/ 56.97±48.13	41.87±3.57/42.18±3. 72	AF; (98/98)	Medical; (98/98)	-	135.06±16. 3/138.04±19.2	Systolic; 138.31±20.4 /141.6±21.06 Diastolic; 84.7±7.6/ 86.9±9.

Appendix 5.2

Table (2) Population Characteristics of the Included Studies (Amiodarone clinical trials; continued)

Study name	*Age; mean years (range/±SD) (Flecainide/Control)*	*Weight (Kg)*	*Male*	*Female*	*Onset of acute AF (hours) (Flecainide/Control)*	*Left atrial diameter,mm (range) (Flecainide/Control)*	*Type of SVA; Flecainide/Control)*	*Cause of AF*	*Mean ventricular ejection fraction*	*Mean heart rate at entery (beats/min)*	*Mean blood pressure (mm Hg)*
Cesar *et al.* 1994	56.27±13/ Q54.8±13/ Prc55.4±12	-	10/11/14	6/10/9	2.81±1.9/1.75±1.6/ 2.75±2.5	NS	AF; (16/21/23)	Medical; (16/21/23)	-	-	-
Cochrane *et al.* 1994	60.2/65.8	-	11/10	4/5	54/49 (hrs)	-	AF; (15/15)	CABG; (11/10) Aortic valve replacement; (3/3) Mitral valvotomy; (1/0) Combined procedures; (0/2)	-	146/144	116.7±3/126±2
Treglia *et al.* 1994	56.6±9.8/57.8±10.2	-	10/13	17/14	35.9±61.5/39.5±52.3	32.9±5.4/34.5±4.6	AF; (27/27)	Medical; (27/27)	-	150.4±19.3/ 153.4±18.1	110.4±18.6/ 100.2±18.3
Biasi *et al.* 1995	66.1±8/62.9±8	-	36/32	10/6	76.8±50.4/84±36	Enlarged; (13/11) Unknown; (9/6)	AF or AFL; (46/38)	Coronary surgery; (31/23) Valvular surgery; (15/15)	≥ 40%; (20/21) < 40%; (1/2) Unknown; (9/6)	131±23/ 139.4±22	98.5±10.7/ 95.38±12.3
Hou *et al.* 1995	70±8/70±6	60±11/ 61±11	22/21	4/3	14/4 hrs	47±10/49±9	AF; (20/19) AFL; (6/5)	Surgical; (3/4) Medical; (23/20)	-	157±20/163±26	-
Moran *et al.* 1995	67±15	73±15	15/11	6/10	≥ 1 hr	NS	AF; (11/15) AT; (4/2) AFL; (2/2) Reentry junctional tachycardia; (4/2)	Surgical; (11/10) Medical; (10/11)	-	153±23/151±16	Systolic; 123±23/130±33
Donovan *et al.* 1995	56±13/59±16/59±12	-	-	-	11.5±13.6/8.8±8.2/ 8.9±13.6	NS	AF; (32/34/32)	CABG surgery; (29) Valve replacement surgery; (7) Medical; (62)	-	121±28/ 129±21/134±22	Systolic; 120±17/124±22 123±19
Galve *et al.* 1996	60±13/61±11	-	27/28	13/11	25±32/18±35	42±7/42±8	AF (50/50)	Cardiac surgery; (8/9) Medical; (42/41)	34±7/32±7	147±24/141±24 (SD)	Systolic; 138±25/128±30
Larbuisson *et al.* 1996	67 (40-76)/66 (58-75)	73.5/72	20/17	2/1	Within one week after cardiac surgery	-	AF or AFL; (22/18)	CABG surgery; (19/16) Valve replacement surgery; (3/2) Medical; (8/10)	58 (32-78)/ 57 (30-80)	-	-

Appendix 5.2

Table (3) Population Characteristics of the Included Studies (Sotalol clinical trials)

Study name	*Age;mean years (range/±SD) (Sotalol/Control)*	*Weight (Kg)*	*Male*	*Female*	*Onset of acute AF (hours) (Sotalol/Control)*	*Left atrial diameter,mm (range) (Sotalol/Control)*	*Type of SVA; (Sotalol/Control)*	*Cause of AF*	*Mean ventricular ejection fraction*	*Mean heart rate at entery (beats/min)*	*Mean blood pressure (mm Hg)*
Campbell *et al.* 1985	60.5±9.1/63.5±5.2	-	19/15	1/5	54.4±16/55.11±27.7 (hrs)	NS	AF; (19/19) AFL; (1/1)	CABG surgery (17/16) Valve replacement surgery (3/4)	> 50%; (18/18) < 50%; (2/2)	163±24/158±17	114±12/158±17
Teo *et al.* 1985	43±17	-	9	4	Acute AF; 742.4 (hrs) Chronic AF; 6.38 (years)	NS	Acute; AF, 3; AFL, 11; SVT, 1 Chronic; AF, 8; AFL, 2; SVT; 6	Surgical; (4), 3 valve replacement surgery, and 1 thoracic surgery Medical; (28)	-	-	-
Levy *et al.* 1986	47 (10-77)	-	16/16	7/7	8.2 hrs	NS	AF; (9/9) AFL; (4/4) Junctional tachycardia; (10/10)	Medical; (23/23)	-	153.7	Systolic; 101.96 Diastolic; 69.4
Janssen *et al.* 1986	58/ M 57.7/ C59.6	-	34/31/40	7/8/10	NS	NS	AF; (9/4 M) AFL; (2/0) PAF; (1/0)	GABG; (12/4)	≥ 30%	141±29.6/ 135±23.8	-
Denis *et al.* 1988	65.8±14.3	-	11	9	< 24 hrs	NS	AF; (8) AFL; (5) Junctional tachycardias; (5) Systolic tachycardias; (2)	Medical; (20)	-	-	-
Jordaens *et al.* 1991	41.7±5.5	71±4.9	19	24	3.3 hrs	NS	AFL; (1) AVNT; (30) CMT; (12)	Medical; (43)	-	180.5±6.7	Systolic; 118±6 Diastolic; 83.8±5.7
Hamer *et al.* 1993	23-54	-	3	3	NS	NS	PSVT; (6)	Medical; (6)	-	-	-
Halinen *et al.* 1995	54.9±12.7/53.2±15.3	-	21/19	12/9	12.4±10.8/11.8±11.5 (hrs); Median (9/7.3)	NS	PAF; (33/28)	Medical; (33/28)	-	119/125	-
Sung *et al.* 1995	SVT; 42 (19-72) AF; 63 (28-83)	80.5	62	31	SVT; Median (range); 0.25 (0.08-120) AF; 24 (0.08-144)	NS	SVT; (30/14) AF; (25/9) AFL; (9/5)	Medical; (64/29)	-	S; 1 mg/Kg; 135±7.5 S; 1.5 mg/Kg; 140±9.1 mg/Kg PL; 140±9.1	Systolic; 125 Diastolic; 78.9

• AF, atrial fibrillation; AFL, atrial flutter; CABG, coronary artery pypass surgery; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PSVT, paroxysmal supraventricular tachycardia; SVA, supraventricular arrhythmia; The values are given as control/treatmen; M, metoprolol; C, control; AVNT, atrioventricular nodal tachycardia; CMT, circus movement tachycardia

Appendix 5.2

Table (4) Cardiac diagnoses in noncardiac surgery patients (Flecainide clinical trials)

Study name	*Patients (n)*	*Valvular (Fle/Cont)*	*Hypertension (Fle/Cont)*	*Ischemic heart disease (Fle/Cont)*	*Thyroid (Fle/Cont)*	*Lone fibrillator (Fle/Cont)*	*Congenital heart disease (Fle/Cont)*	*Pericarditis (Fle/Cont)*	*Alcohol-associated (Fle/Cont)*	*CHF (NYHA class) (Fle/Cont)*	*Cardiomyopathy (Fle/Cont)*	*Miscellaneous (Fle/Cont)*
Goy *et al.* 1985	50	12	4	8	0	21	0	2	0	0	4	0
Borgeat *et al.* 1986	60	11	11	14	0	10	0	2	0	0	5	1
Crozier *et al.* 1987	50	2	3	12	0	13	0	0	0	0	2	18
Nathan *et al.* 1987	21	0	0	2	0	14	0	0	0	0	0	5
Crijns *et al.** (a) 1988	20	6	1	7	0	4	0	1	0	0	0	0
Crijns *et al.** (a) 1988	20	2	3	6	0	4	0	1	0	0	0	4
Suttorp *et al.* 1989	40	0/2	5/4	6/4	0	9/9	0/1	0	0	0	0	0
Wafa *et al.* 1989	29	1/1	0	15/14	0	0	0	0	0	0	0	0
Suttorp *et al.* 1990	50	4/3	2/2	7/7	0	10/12	0	0	0	0	0	1/2
Donovan *et al.* 1991	102	2	0	8/7	2	15	-	1	3	-	-	23
Capucci *et al.* 1992	62	0	7F/5P/7A	0	0	15F/19A/21P	0	0	0	Class I; 20F/18A/19P	0	0
Villani *et al.* 1990	37	-	-	-	-	-	-	-	-	-	-	-
Madrid *et al.* 1993	40/40	4	17	9	3	42	0	0	0	0	0	5
Capucci *et al.* 1994	181	0	21/25Pr/24P	5/4/5	0	32/32/33	0	0	0	0	0	0

NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Amio/Cont), the number of patients with a given cardiac diagnosis in flecainide (Fle) and control (Cont) group; others, including patients in active control group

Appendix 5.2

Table (5) Cardiac diagnoses in noncardiac surgery patients (amiodarone clinical trials)

Study name	*Patients (n)*	*Valvular (Amio/Cont)*	*Hypertension (Amio/Cont)*	*Ischemic heart disease (Amio/Cont)*	*Thyroid (Amio/Cont)*	*Lone fibrillator (Amio/Cont)*	*Congenital heart disease (Amio/Cont)*	*Pericarditis (Amio/Cont)*	*Alcohol-associated (Amio/Cont)*	*CHF (NYHA class) (Amio/Cont)*	*Cardiomyopathy (Amio/Cont)*	*Miscellaneous (Amio/Cont)*
Faniel *et al.* 1983	26	4	0	4	0	4	1	1	0	1	2	11
Strasberg *et al.* 1985	26	1	2	13	0	6	0	1	0	0	3	1
Posada *et al.* 1988	36	8/9	2/3	0/2	0	1/2	0	0	0	0	0/2	3/3
Bertini *et al.* 1990	15/24	0	6/11	0	0	9/13	0	0	0	0	0	0
Noc *et al.* 1990	NS	-	-	-	-	-	-	-	-	-	-	-
McAlister *et al.* 1990	41/39	21/19	0	19/17	0	0	0	0	0	0	0	1/3
Andrivet *et al.* 1993	21/25	3/5	1/1	0	0	16/18	0	0	0	0	0	1/1
Bellandi *et al.* 1993	98/98	23/20	21/19	22/24	0	21/24	0	0	0	0	5/6	6/5
Chapman *et al.* 1993	10/14	0	2/2	3/3	0	6/10	0	0	0	0/2	0/0	0
Contini *et al.* 1993	24	0	0	MI; 24	0	0	0	0	0	0	0	0
Cesar *et al.* 1994	16/21/23	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Cochrane *et al.* 1994	0	0	0	0	0	0	0	0	0	0	0	0
Treglia *et al.* 1994	54	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Biasi *et al.* 1995	17	0	0	MI inferior (6/4) MI anterior (3/4)	0	0	0	0	0	0	0	0
Donovan *et al.* 1995	62	6	5	18	0	15	0	0	7	0	0	11
Hou *et al.* 1995	23/20	4/3	3/3	6/5	0	5/4	0	2/1	0	II; (9/8) III; (3/5) IV; (14/11)	2/2	1/2
Moran *et al.* 1995	42	0	0	1/0	0	2/4	0	1/0	0	0	0	6/7
Galve *et al.* 1996	50/50	27	0	18	-	28/20	0	0	0	5/6	5	2
Larbuisson *et al.* 1996	NS	-	-	-	-	-	-	-	-	-	-	-

NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Amio/Cont), the number of patients with a given cardiac diagnosis in amiodarone (Amio) and control (Cont) group; others, including patients in active control group

Appendix 5.2

Table (6) Cardiac diagnoses in noncardiac surgery patients (Sotalol clinical trials)

Study name	*Patients (n)*	*Valvular (Sot/Cont)*	*Hypertension (Sot/Cont)*	*Ischemic heart disease (Sot/Cont)*	*Thyroid (Sot/Cont)*	*Lone fibrillator (Sot/Cont)*	*Congenital heart disease (Sot/Cont)*	*Pericarditis (Sot/Cont)*	*Alcohol-associated (Sot/Cont)*	*CHF (NYHA class) (Sot/Cont)*	*Cardiomyopathy (Sot/Cont)*	*Miscellaneous (Sot/Cont)*
Teo *et al.* 1985	28	5	0	5	4	3	1	0	1	0	0	9
Levy *et al.* 1986	23	5	0	1	0	10	2	1	0	0	2	4
Jordaens *et al.* 1991	43	NS	-	-	-	-	-	-	-	-	-	-
Hamer *et al.* 1993	6	0	0	0	0	6	0	0	0	0	0	0
Halinen *et al.* 1995	33/24	1/1	11/12	MI; 2/3 Angina; 3/7	0	9/1	0	0	7/4	0	0	0
Sung *et al.* 1995	93	0	22	12	0	45	0	0	0	10	0	0

NA, not available; CHF, congestive heart failure; NYHA class, New York Heart Association class; (Amio/Cont), the number of patients with a given cardiac diagnosis in sotalol (Sota) and control (Cont) group; others, including patients in active control group

Table 7.a Summary of subgroup analyses

Flecainide clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(a) Type of active control											
Fle vs Propafenone	0-3	2	2	66/68	65.1% (5.7); (53.8-76.3)	50% (6.1); (38.1-61.9)	14.1 (-2.4-30.4)	1.7 (NS)	0.96 (0.33)	-	-
Fle vs Propafenone	3-8	2	2	66/68	78.9% (5); (69-88.7)	67.5% (5.5); (56.7-78.4)	11.9 (-2.8-26.5)	1.6 (NS)	1.26 (0.26)	-	-
Fle vs Verapamil	0-3	2	2	41/26	63.6% (7.5); (49-78.2)	6.1 (4.6); (-3-15.2)	57.4 (40.2-74.7)	6.5**	1.02 (0.3)	-	-
Fle vs Amiodarone	0-3	2	2	56/51	62.7% (6.02); (50-75.4)	27.7% (6.02); (15.9-39.6)	34 (16.7-51.5)	3.9**	3.7 (0.054)	34.97 (1.5-68.5)	2.05*
Fle vs Amiodarone	3-8	2	2	56/51	82.3% (4.9); (72.8-91.9)	50.9% (6.8); (37.4-64.2)	29.6 (12.7-46.5)	3.43**	7* (0.01)	30.9 (-13.9-75.8)	1.4 (NS)
Fle vs Amiodarone	8-24	1	1	22/19	95% (4.4); (86.8-104.2)	89.5% (7); (75.7-103.3)	5.98 (-10.3-22.3)	0.72 (NS)	-	-	-
Fle vs Quinidine	0-3	1	1	30/30	56.7% (9)	0	56.7% (9)	6.3**	-	-	-
Fle vs Quinidine	3-8	1	1	30/30	66.7% (8)	60% (8)	6.7 (-17-30.99)	0.5 (NS)	-	-	-
Fle vs Digoxin+Disopyramide	0-3	1	1	29/27	65.5% (8.9)	29.6 (8.9)	35.9 (38.9-74.4)	2.9**	-	-	-
Fle vs Digoxin+Disopyramide	3-8	1	1	29/27	75.9% (7.9)	63 (9)	12.9 (-11.1-36.9)	1.1 (NS)	-	-	-
Fle vs Digoxin+Disopyramide	8-24	1	1	29/27	86.2% (0.06)	88.9 (0.06)	-2.7 (-19.9-14.6)	-0.3 (NS)	-	-	-
Fle vs Sotalol	0-3	1	1	6/6	50% (20.5)	50% (20.5)	0 (-56.6-56.6)	0 (NS)	-	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 5.2

Table 7.a Summary of subgroup analyses (continued)

Flecainide clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(b) Type of arrhythmia:											
i. Versus placebo											
AF	0-3	5	5	167/183	72.6% (66.4-78.8)	16.3% (10.7-21.8)	67.3 (60.3-74)	18.7**	56.9** (0)	51.7 (22.7-80.7)	3.5**
AF	3-8	5	5	167/183	82.8% (77.4-88.3)	37.3% (30-44.5)	65.7 (58.7-72.9)	18.2**	72** (0)	47.4 (14.8-80.1)	2.85**
AF	8-24	1	1	19/18	94.7% (84.7-104.8)	27.8% (7.1-48.5)	67 (44-90)	5.7**	-	-	-
AFL	-	-	-	-	-	-	-	-	-	-	-
PSVT	-	-	-	-	-	-	-	-	-	-	-
ii. Versus others#											
Versus Propafenone											
AF	0-3	2	2	78/81	73.7% (4.7); (64.6-82.9)	51.9% (5.5); (41-62.7)	16.8 (2.15-31.4)	2.3*	2.9 (0.1)	-	-
AF	3-8	1	1	58/61	77.6% (5.5); (66.9-88)	72% (5.7); (60.9-83.4)	5.5 (-10-21)	0.7 (NS)	-	-	-
AFL	0-3	1	1	5/5	20% (17.9); (-15-55)	40% (21.9); (-2.9-83)	-20 (-75-35)	-0.7 (NS)	-	-	-
Versus Verapamil											
AF	0-3	1	1	17/17	82.4% (9.2); (64-100.5)	5.9% (5.7); (-5-17)	76.5 (55.2-97.8)	7**	-	-	-
AFL	0-3	1	1	3/3	0%	0%	0	-	-	-	-
PSVT	0-3	1	1	6/6	50% (20.4); (10-90)	16.7% (15.2); (-13-46.5)	33.3 (-16.6-83)	1.3 (NS)	-	-	-
Versus Quinidine											
AF	0-3	1	1	30/30	56.7% (9); (39-74)	0%	56.7 (38.9-74)	6.3**	-	-	-
AF	3-8	1	1	30/30	66.7% (8.6); (49.8-83.5)	60% (8.9); (42.5-77)	6.7 (-17.7-31)	0.54 (NS)	-	-	-

Appendix 5.2

Table 7.a Summary of subgroup analyses (continued)

Flecainide clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	P_T *(SE); (95% CI)*	P_C *(SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(c) Cause of arrhythmia											
i. Versus placebo											
Cardiac surgery group	0-3	1	1	26/27	61.5% (9.5); (42.8-80.2)	18.5% (7.5); (3.9-33.2)	43.2 (19.3-66.8)	3.5**	-	-	-
Cardiac surgery group	3-8	1	1	26/27	69.2% (9.1); (51.5-86.97)	37% (9.3); (18.8-55.3)	32.2 (6.8-57.6)	2.5**	-	-	-
Noncardiac surgery (medical) group	0-3	4	4	107/124	76.8% (3.7); (69.7-84)	13.2% (3.2); (6.9-19.6)	73.8 (66.1-81.6)	18.6**	41.6** (0)	56.3	3.3**
Noncardiac surgery (medical) group	3-8	4	4	107/124	86.8% (3.1); (80.6-92.9)	32.4% (4.5); (23.6-41.2)	74.93 (67.2-82.7)	18.9**	38.9** (0)	56.6	3.5**
Noncardiac surgery (medical) group	8-24	4	4	107/124	86.8% (3.1); (80.6-92.9)	31.7% (4.1); (23.6-39.8)	50.4 (39.6-61.2)	9.2**	4.5** (0.2)	49.8	7.2**
ii. Versus others#											
Versus Digoxin+Disopyramide											
Cardiac surgery group	0-3	1	1	29/27	65.5% (8.8); (48-82.8)	29.6% (8.8); (12.4-46.9)	35.9 (11.5-60.3)	2.9**	-	-	-
Cardiac surgery group	3-8	1	1	29/27	75.9% (7.9); (60.3-91)	63% (9.3); (44.7-81.2)	12.9 (-11-36.9)	1.05 (NS)	-	-	-
Cardiac surgery group	8-24	1	1	29/27	86.2% (6.4); (73.7-98.8)	88.9% (6); (77-100.1)	-2.7 (-19.9-14.6)	-0.3 (NS)	-	-	-
Versus Quinidine											
Noncardiac surgery (medical) group	0-3	1	1	30/30	56.7% (9); (39-74)	0%	56.7 (38.9-74)	6.3**	-	-	-
Noncardiac surgery (medical) group	3-8	1	1	30/30	66.7% (8.6); (49.8-83.5)	60% (8.9); (42.5-77)	6.7 (-17.7-31)	0.54 (NS)	-	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 5.2

Table 7.a Summary of subgroup analyses (continued)
Flecainide clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T(SE); (95% CI)*	*P_C(SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(d) Route of administration											
ii. Versus placebo											
IV route only	0-3	2	2	85/83	57.6% (5.4) (47.2-68.2)	16.9% (4.1); (8.9-24.9)	39.8 (26.5-53)	5.9**	0.43 (0.5)	-	-
IV route only	3-8	2	2	85/83	67.1% (5.1); (57.1-77)	43% (5.3); (32.6-53.4)	23.7 (9.2-38.1)	3.2**	1.7 (0.2)	-	-
Orally	0-3	3	3	82/100	80.7% (3.9); (72.9-88.4)	15.6% (3.96); (7.8-23.4)	77.9 (69.7-86.3)	18.4**	33.7**	60.2 (19.5-100.8)	2.9**
Orally	3-8	3	3	82/100	89.5% (3.3); (83-96)	32.2% (5.1); (22.2-42)	79 (70.9-87)	19**	27**	64.7 (30-99.3)	3.7**
Orally	8-24	3	3	82/100	89.5% (3.3); (83-96)	31.3% (4.6); (22.4-40)	54 (42.4-66)	9**	1.97 (0.372)	-	-
ii. Versus others#											
Versus Amiodarone											
IV route only	0-3	1	1	34/32	58.8% (8.4); (42.3-75.4)	40.6% (8.7); (23.6-57.6)	18.2 (-5.5-41.9)	1.5 (NS)	-	-	-
IV route only	3-8	1	1	34/32	67.6% (8); (51.9-83.4)	59.4% (8.7); (42.4-76.4)	8.3 (-14.9-31.4)	0.7 (NS)	-	-	-
Orally	0-3	1	1	22/19	68.2% (9.9); (48.7-87.6)	15.8% (8.4); (-0.6-32.2)	52.4 (26.9-77.8)	4**	-	-	-
Orally	3-8	1	1	22/19	90.0% (6.13); (78.9-102.9)	36.8% (11.1); (15.2-58.5)	54.1 (29.3-78.9)	4.3**	-	-	-
Versus Quinidine											
IV + Orally	0-3	1	1	30/30	56.7% (9); (39-74)	0%	56.7 (38.9-74)	6.3**	-	-	-
IV + Orally	3-8	1	1	30/30	66.7% (8.6); (49.8-83.5)	60% (8.9); (42.5-77)	6.7 (-17.7-31)	0.54 (NS)	-	-	-
Versus Verapamil											
IV only	0-3	1	1	35/20	65.7% (8); (50-81)	5% (4.9); (-4.6-14.6)	60.7 (42-79)	6.5**	-	-	-
Orally	0-3	1	1	6/6	50%	16.7%	33.3 (-16.6-83)	1.3 (NS)	-	-	-

Table 7.a Summary of subgroup analyses (continued)
Flecainide clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(e) Duration of arrhythmia:											
i. Versus placebo											
> 24 hrs	0-3	1	1	22/21	68.2% (48.7-87.6)	28.6% (9.2-47.9)	39.6 (12.2-67)	2.8**	-	-	-
> 24 hrs	3-8	1	1	22/21	95.5% (86.7-104.2)	47.62% (26.3-68.98)	47.8 (24.8-70.9)	4.1**	-	-	-
< 24 hrs	0-3	2	2	36/68	57.7% (47.2-68.2)	16.93% (8.9-24.9)	39.8 (26.5-53.13)	5.9**	0.43 (0.5)	-	-
< 24 hrs	3-8	2	2	36/68	67.1% (57.1-77.1)	43% (32.6-53.4)	23.7 (9.2-38.14)	3.2**	1.74 (0.2)	-	-
ii. Versus others#											
< 24 hrs	0-3	3	3	70/57	81.7% (73.4-90.2)	45.6% (31.4-59.8)	63.3 (51.96-74.6)	10.96**	27.2** (0)	-	-
> 24 hrs	0-3	7	8	114/110	64.5% (56.1-72.9)	25.3% (16-34.5)	45.8 (35.1-56.5)	8.4**	5.8 (0.6)	-	-
> 24 hrs	3-8	7	8	114/110	79.13% (72.2-86)	47.6% (38.7-56.4)	27.98 (16.4-39.6)	4.7**	12.2 (0.09)	-	-
> 24 hrs	8-24	7	8	114/110	87.8% (69-82.9)	75.97% (69-82.9)	7.1 (-1.9-16.1)	1.5 (NS)	3.2 (0.87)	-	-
Overall analysis											
Versus placebo	0-3	5	5	167/183	72.6% (66.4-78.8)	16.3% (10.7-21.8)	67.3 (60.3-74)	18.7**	56.9** (0)	51.7 (22.7-80.7)	3.5**
Versus placebo	3-8	5	5	167/183	82.8% (77.4-88.3)	20.96% (15.7-26.2)	58.4 (66.2-53)	14.7**	53** (0)	46.9 (17.3-53)	3.11**
Versus placebo	8-24	5	5	167/18	82.8% (77.4-88.3)	36.3% (29.5-43)	42 (32.9-51.2)	9.02**	14** (0.007)	41.3 (23.9-58.7)	4.6**
Versus others#	0-3	8	8	215/150	63.7% (57.7-69.6)	25% (19.4-30.6)	39.02 (31.2-46.82)	9.8**	25.3** (0.003)	36.3 (22.5-50.1)	5.1**
Versus others#	3-8	8	8	215/150	71.7% (66.1-77.3)	58.6% (51.4-65.9)	26.3 (18.4-34.1)	6.5**	31.1** (0.0003)	25.9 (10.5-41.5)	3.3**
Versus others#	8-24	8	8	215/150	82.5% (78-87)	92.7% (78.5-95)	15.8 (8.6-22.6)	4.4**	32.14** (0.0002)	16.4 (2.3-30.5)	2.3**

Appendix 5.2

Table 7.b Summary of subgroup analyses

Amiodarone clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of compari-son*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*	*OR (95% CI)*	*statistic for effect*	*Q statistic (P)*
(a) Type of active control														
Am vs Propafenone	0-3	4	4	110/107	6.8% (2.2); (2.5-11.3)	16.6% (2.3); (12-21.1)	-6.5 (-12.9_-0.1)	-1.997*	16.7 (0.001)	-22 (-44.7-0.09)	-1.95*	0.24 (0.13-0.5)	-4.2**	1.5 (NS)
Am vs Propafenone	3-8	4	4	110/107	22.5% (3.7); (15-29.8)	63.8% (4.2); (55-72)	-29.1 (-41.1_-17)	-4.75**	5.45 (0.145)	-	-	0.29 (0.16-0.5)	-4.3**	6.13 (NS)
Am vs Propafenone	8-24	4	4	166/154	80.8% (3.1); (74.8-86.8)	86.7% (2.6); (81.5-91.9)	-3.6 (-11.8-4.6)	-0.85 (NS)	6.4 (0.04)	2.7 (-15.6-20.9)	0.29 (NS)	0.92 (0.5-1.63)	-0.3 (NS)	6.9* (0.03)
Am vs Digoxin	0-3	3	3	91/89	35.3% (4.9); (25.8-44.9)	20.96% (4.3); (12.5-29.4)	14.8 (1.98-27.6)	2.3*	4.5 (0.1)	-	-	2 (1.07-3.9)	2.2*	3.23 (0.2)
Am vs Digoxin	3-8	3	3	91/89	60.3% (5); (50.5-70.2)	48.3% (5.3); (38-58.7)	11.6 (-2.7-25.9)	1.6 (NS)	3.2 (0.2)	-	-	1.6 (-0.9-2.8)	1.5 (NS)	2.97 (0.23)
Am vs Digoxin	8-24	3	3	91/89	80.7% (3.8); (73.3-88)	62.8% (4.9); (53.1-72.5)	11.76 (-0.8-24.3)	1.8 (NS)	1.3 (0.5)	-	-	1.7 (0.87-3.2)	1.5 (NS)	2 (0.4)
Am vs Flecainide	0-3	2	2	51/56	27.7% (6); (15.9-39.6)	62.7% (6); (50-75.4)	-34 (-51.5_-16.7)	-3.9**	3.7 (0.05)	-34.97 (-68.5_-1.5)	-2.05*	0.3 (0.14-0.62)	-3.2**	2.9 (0.09)
Am vs Flecainide	3-8	2	2	51/56	50.7% (6.8); (37.4-64.2)	82.3% (4.9); (72.8-91.9)	-29.6 (-46.6_-12.7)	-3.4**	6.9957 (0.0096)	-30.9 (-75.8-13.9)	-1.4 (NS)	0.3 (0.004-1.9)	-1.3 (NS)	5.8* (0.02)
Am vs Flecainide	8-24	2	2	51/56	77.5% (5.5); (66.8-88.3)	88.9% (3.9); (81.3-96.5)	-6.7 (-20.1-6.6)	-0.99 (NS)	0.03 (0.86)	-	-			
Am vs Quinidine	0-3	2	2	69/84	29.2% (5.3); (18.7-39.7)	25.8% (4.2); (17.6-34)	3.2 (-10-16.5)	0.5 (NS)	2.9 (0.09)	-	-	1.3 (0.6-2.63)	0.6 (NS)	3.9* (0.05)
Am vs Quinidine	3-8	1	1	53/63	41.5% (6.8); (28.2-54.8)	58.7% (6.2); (46.6-70.9)	-17.2 (-35.2-0.8)	-1.9 (NS)	-	-	-	0.67 (0.4-1.2)	-1.4 (NS)	-
Am vs Procainamide	0-3	2	2	26/37	50% (9.8); (30.8-69)	48.6% (8.2); (32.5-64.7)	1.3 (-23.7-26)	0.1 (NS)	0.007 (NS)	-	-	1.05 (0.39-2.8)	0.1 (NS)	0.007 (NS)
Fle vs Digoxin+Diso-pyramide	0-3	1	1	29/27	65.5% (8.9)	29.6 (8.9)	35.9 (38.9-74.4)	2.9**	-	-	-	4.1 (1.5-12)	2.7**	-
Am vs Cibenzoline	0-24	1	1	21/25	71.4% (9.8)	72% (0.1)	-0.57 (-26.7-25.6)	-0.04 (NS)	-	-	-	0.97 (0.3-3.5)	-0.04 (NS)	-
Am vs Mg Sulfate	0-3	1	1	21/21	28.6% (9.8)	33.3% (10)	-4.7 (-32.7-23.2)	-0.33 (NS)	-	-	-	0.8 (-1.5-1.08)	-0.33 (NS)	-

Table 7.b Summary of subgroup analyses (continued)

Amiodarone clinical trials (continued)

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(b) Type of arrhythmia:											
i. Versus placebo											
AF	0-3	3	3	101/103	28.8% (4.4); (20-37.4)	25.2% (4.3); (16.8-33.5)	4.5 (-7.7-16.6)	0.72 (NS)	2.74 (0.3)	-	-
AF	3-8	3	3	101/103	51.4% (4.9); (41.7-61)	50.5% (4.9); (40.9-60)	0.8 (-12.8-14.4)	0.11 (NS)	0.69 (0.41)	-	-
AF	8-24	1	1	50/50	56% (7); (42.2-69.8)	50% (7); (36-63.9)	6 (-13.5-25.5)	0.6 (NS)	-	-	-
ii. Versus others#											
Versus Digoxin											
AF	0-24	3	3	85/84	83% (3.6); (75.9-90)	63% (5); (53-73)	11.3 (-1.5-24)	1.7 (NS)	1.2 (NS)	-	-
AFL	0-24	1	1	6/5	83.3% (15.2); (53.5-113.5)	60% (21.9) (17.1-102.9)	23.3 (-28.9-75.6)	0.8 (NS)	-	-	-
Versus Quinidine											
AF	0-1	1	1	16/21	50% (12.5); (25.5-74.5)	71.4% (9.9); (52-90.8)	-21.4 (-52.6-9.8)	-1.3 (NS)	-	-	-
Versus Procainamide											
AF	0-24	1	1	7/9	71% (17); (37.9-104.9)	55.6% (16.6); (23-88)	15.9 (-30.7-62)	0.7 (NS)	-	-	-
AFL	0-24	1	1	1/3	50% (50); (-48-148)	0	-50 (-148-48)	-1 (NS)	-	-	-
PSVT	0-24	1	1	2/2	95% (15.4); (64.8-125)	95% (15.4); (64.8-125)	0 (-42.7-42.7)	0 (NS)	-	-	-
Versus Propafenone											
AF	0-3	2	2	39/43	25% (12.5); (0.5-49.5)	81.3% (9.8); (62-100)	-2.9 (-9.9-4.2)	-0.8 (NS)	11.9** (0.001)	-26 (-80.9-28.9)	-0.93
AF	3-8	2	2	39/43	13.7% (5); (3.1-24.4)	64.5% (6.8); (51-78)	-43.6 (-62_-25.5)	-4.7**	0.97 (NS)	-	-
AFL or AF	0-3	2	2	68/56	19% (4.8); (9.8-28.4)	44.6% (6.6); (31.6-57.7)	-25.5 (-41.6_-9.5)	-3.12**	0.004 (NS)	-	-

Table 7.b Summary of subgroup analyses (continued)

Amiodarone clinical trials (continued)

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(c) Cause of arrhythmia											
i. Versus placebo											
Cardiac surgery group	-	-	-	-	-	-	-	-	-	-	-
Noncardiac surgery (medical) group	0-3	1	1	19/21	15.8% (0.08)	28.6% (9.8)	-12.8 (-38-12.6)	-1 (NS)	-	-	-
Noncardiac surgery (medical) group	3-8	1	1	19/21	89.5% (7)	47.6% (0.1)	41.9 (16.4-67.3)	3.24**	-	-	-
ii. Versus others#											
Versus Propafenone											
Cardiac surgery group	0-3	2	2	68/56	27.7% (5); (17.7-37.8)	48% (6.6); (35.2-61)	-18.3 (-34.8_-1.8)	-2.2*	1.7 (0.2)	-	-
Cardiac surgery group	3-8	2	2	68/56	81% (4.7); (71.8-90.4)	67.9% (6.2); (55.6-80.1)	13 (-2.3-28.5)	1.7 (NS)	0.044 (NS)	-	-
Noncardiac surgery (medical) group	0-3	2	2	42/51	3.4% (2.5); (-1.6-8.4)	12.9% (2.4); (8-17.6)	-2.9 (-9.9-4)	-0.8 (NS)	10.3** (0.001)	-21.7 (-68-24.7)	-0.92 (NS)
Noncardiac surgery (medical) group	3-8	2	2	42/51	16.5% (5.5); (5.8-27.2)	74.5% (5.5); (63.7-85)	-41 (-58.5_-23.6)	-4.6**	0.33 (0.4)	-	-
Noncardiac surgery (medical) group	8-24	2	2	42/51	75.8% (3.7); (68.6-83)	88.6% (2.8); (83-94)	-11 (-20_-2)	-2.4*	0.35 (0.6)	-	-
Versus Flecainide											
Noncardiac surgery (medical) group	0-3	1	1	19/22	15.8% (8.4); (-0.6-32.2)	68.2% (9.9); (48.7-87.6)	-52.4 (-77.8_-26.9)	-4**	-	-	-
Noncardiac surgery (medical) group	3-8	1	1	19/22	36.8% (11); (15-58.5)	90.9% (6); (78.9-102.9)	-54 (-78.9_-29.3)	-4.3**	-	-	-
Noncardiac surgery (medical) group	8-24	1	1	19/22	89.5% (7); (75.7-103.4)	95.5% (4); (86.8-104.2)	-6 (-22.3-10.3)	-0.7 (NS)	-	-	-
Versus Digoxin											
Cardiac surgery group	0-3	1	1	15/15	26.7% (11.4); (4.3-49)	20% (10.3); (-0.2-40)	6.7 (-23.5-36.8)	0.4 (NS)	-	-	-
Cardiac surgery group	3-8	1	1	15/15	60% (12.6); (35-85)	60% (12.6); (35-85)	0 (-35-35)	0 (NS)	-	-	-

Table 7.b Summary of subgroup analyses (continued)

Amiodarone clinical trials (continued)

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of compari-son*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(d) Route of administration											
i. Versus Placebo											
IV route only	0-3	2	2	82/82	33.8% (5.2); (23.6-43.98)	24.4% (4.7); (15-33.7)	9.6 (-4-23.3)	1.4 (NS)	0.4 (0.6)	-	-
IV route only	3-8	2	2	82/82	54.9% (5.5); (44.2-65.7)	51% (5.5); (40.5-62)	3.7 (-11.6-18.9)	0.47 (NS)	0 (1)	-	-
IV route only	8-24	1	1	50/50	56% (7); (42-69.8)	50% (7); (36-63.9)	6 (-13.5-25.5)	0.6 (NS)	-	-	-
Orally	0-3	1	1	19/21	15.8% (0.08)	28.6% (9.8)	-12.8 (-38-12.6)	-1 (NS)	-	-	-
Orally	3-8	1	1	19/21	89.5% (7)	47.6% (0.1)	41.9 (16.4-67.3)	3.24**	-	-	-
ii. Versus others#											
Versus Flecainide											
IV route only	0-3	1	1	32/34	40.6% (8.7); (23.6-57.6)	58.8% (8.4); (42-75.4)	-18.2 (-41.9-5.5)	-1.5 (NS)	-	-	-
IV route only	3-8	1	1	32/34	59.4% (8.7); (42-76)	67.6% (8); (51.9-83.4)	-8.3 (-31-14.9)	-0.7 (NS)	-	-	-
Orally	0-3	1	1	19/22	53.8% (0.09)	16.7% (0.08)	-52.4 (-77.8_-26.9)	-4**	-	-	-
Orally	3-8	1	1	19/22	60.3% (5)	48.3% (5.3)	-54 (-78.9_-29.3)	-4.3**	-	-	-
Orally	8-24	1	1	19/22	80.7% (3.8)	62.8% (4.9)	11.8 (-0.8-24.3)	1.8 (NS)	-	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Table 7.b Summary of subgroup analyses (continued)

Amiodarone clinical trials (continued)

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(e) Duration of arrhythmia:											
i. Versus placebo											
> 48 hrs	0-3	1	1	19/21	15.8% (0.08)	28.6% (9.8)	-12.8 (-38-12.6)	-1 (NS)	-	-	-
> 48 hrs	3-8	1	1	19/21	89.5% (7)	47.6% (0.1)	41.9 (16.4-67.3)	3.24**	-	-	-
< 48 hrs	0-3	1	1	51/53	40% (0.09)	25% (7.7)	15.6 (-7.1-38.3)	1.35 (NS)	-	-	-
< 48 hrs	3-8	1	1	51/53	59.4% (8.7)	56.3% (8.8)	3.13 (-21.1-27.3)	0.25 (NS)	-	-	-
ii. Versus others#											
Versus Digoxin											
> 48 hrs	0-3	1	1	15/15	26.7% (11.4); (4.3-49)	20% (10.3); (-0.2-40)	6.7 (-23.5-36.8)	0.4 (NS)	-	-	-
> 48 hrs	3-8	1	1	15/15	60% (12.6); (35-85)	60% (12.6); (35-85)	0 (-35-35)	0 (NS)	-	-	-
> 48 hrs	8-24	1	1	15/15	86.7% (8.8); (69.5-103.9)	80% (10.3); (59.8-100)	6.7 (-19.9-33)	0.5 (NS)	-	-	-
< 48 hrs	0-3	1	1	26/24	53.8%	16.7%	37 (12.8-61.5)	3**	-	-	-
< 48 hrs	3-8	1	1	26/24	73.1%	41.7%	31.4 (5.3-57.5)	2.4*	-	-	-
< 48 hrs	8-24	1	1	26/24	92%	70.8%	11.8 (-0.8-24)	1.8 (NS)	-	-	-
Versus Propafenone											
> 48 hrs	0-24	1	1	98/98	80.6% (3.99); (72.8-88)	90.8% (2.9); (85-96.5)	-10.2 (-19.9_-0.5)	-2.1*	-	-	-
< 48 hrs	0-3	2	2	42/51	3.4% (2.5); (-1.6-8.4)	12.9% (2.4); (8-17.6)	-2.9 (-9.9-4)	-0.8 (NS)	10.3** (0.001)	-21.7 (-68-24.7)	-0.92 (NS)
< 48 hrs	3-8	2	2	42/51	16.5% (5.5); (5.8-27.2)	74.5% (5.5); (63.7-85)	-41 (-58.5_-23.6)	-4.6**	0.33 (0.4)	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 5.2

Table 7.c Summary of subgroup analyses

Sotalol clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T(SE); (95% CI)*	*P_C(SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(a) Type of arrhythmia:											
i. Versus placebo											
AF	0-3	2	2	34/18	32.3% (8); (16.6-48.1)	11.1% (10.5); (-9.4-31.6)	26.4 (5.9-46.9)	2.5**	0.35 (0.6)	-	-
AFL	0-3	2	2	13/9	30.5% (12.7); (5.5-55.4)	15.96% (12.2); (-7.8-39.8)	12.97 (-22.2-48.1)	0.7 (NS)	0.001 (0.98)	-	-
PSVT	0-3	3	3	76/46	81.8% (4); (73.8-89.7)	10.23% (4.4); (1.6-18.9)	63.1 (50-76.1)	9.5**	0.04* (0.03)	58.5 (32.9-84)	4.5**
ii. Versus others#											
AF	0-3	3	3	62/51	34.2% (4.6); (25-43.2)	42% (7); (28.3-56)	13.7 (-0.9-28.2)	1.8 (NS)	27.99**	17.3 (-29.6-64.2)	0.73 (NS)
AF	3-8	3	3	62/51	61.7% (4.7); (52.4-71)	76.4% (5.8); (65-87.83)	-16.4 (-31.2_-1.5)	-2.15*	14**	-8.1 (-52-35.9)	-0.36 (NS)
AF	8-24	3	3	62/51	74.3% (5); (64.5-84.2)	85.7% (6.6); (72.8-98.7)	-18.7 (-29.2_-8.2)	-3.5**	4.2 (0.123)	-	-
AFL	0-3	1	1	1/1	0.5% (0.5); (-48-1.5)	0.5% (0.5); (-48-1.5)	0 (-1.39-1.39)	0 (NS)	-	-	-
PSVT	0-3	2	2	12/12	50% (14.4); (21.7-78.3)	28.6% (12.2); (4.7-52.5)	18.8 (-18.7-56.2)	0.98 (NS)	0.75 (0.4)	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Table 7.c Summary of subgroup analyses (continued)

Sotalol clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(b) Cause of arrhythmia											
i. Versus placebo											
Noncardiac surgery (medical) group	0-3	3	3	123/73	62.2% (4.1); (54.3-70.2)	13.99% (4.9); (4.4-23.6)	47.1 (36.34-57.8)	8.6**	7.1* (0.03)	47.4 (27.1-67.6)	4.6**
Cardiac surgery group	-	-	-	-	-	-	-	-	-	-	-
ii. Versus others#											
Cardiac surgery group	0-3	2	2	31/24	74.2% (7.9); (58.8-89.6)	50% (11.2); (28.1-71.9)	51.2 (31.7-70.6)	5.15**	5.7* (0.02)	49.3 (2.5-9.6)	2.1*
Cardiac surgery group	3-8	2	2	31/24	87.7% (5.9); (76.2-99.2)	76.6% (8.4); (60.1-93.1)	11.1 (-10.3-32.5)	1.02 (NS)	1.53 (0.22)	-	-
Cardiac surgery group	8-24	2	2	31/24	87.7% (5.9); (76.2-99.2)	94.4% (4.7); (85.2-103.6)	-7.3 (-23.7-9.1)	-0.87 (NS)	0.4 (0.53)	-	-
Noncardiac surgery (medical) group	0-3	3	3	45/40	17.2% (5.3); (6.8-27.6)	33.2% (7.3); (18.9-47.43)	-13.5 (-31.8-4.8)	-1.45 (NS)	4.5 (0.11)	-	-
Noncardiac surgery (medical) group	3-8	3	3	45/40	29.7% (6.6); (16.7-42.7)	57.3% (7); (43.6-71)	-29.99 (-49_-10.9)	-3.1**	9.6** (0.01)	-8.5 (-61.7-44.7)	-0.31 (NS)
Noncardiac surgery (medical) group	8-24	3	3	45/40	48.9% (7.5); (34.3-63.5)	72.7% (5.8); (61.3-84.1)	-23.4 (-42_-4.83)	-2.5*	0.12* (0.03)	-5.8 (-51.7-40.1)	-0.25 (NS)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Table 7.c Summary of subgroup analyses (continued)

Sotalol clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(c) Route of administration											
i. Versus Placebo											
IV route only	0-3	3	3	123/73	62.2% (4.1); (54.3-70.2)	13.99% (4.9); (4.4-23.6)	47.1 (36.34-57.8)	8.6**	7.1* (0.03)	47.4 (27.1-67.6)	4.6**
Orally	0-3	-	-	-	-	-	-	-	-	-	-
ii. Versus others#											
IV route only	0-3	1	1	20/20	75% (9.6); (56-93.97)	50% (11.2); (28.1-71.9)	25 (-3.99-53.99)	1.69*	-	-	-
IV route only	3-8	1	1	20/20	85% (7.98); (0.7-1.01)	80% (8.9); (62.5-97.5)	5 (-18.5-28.5)	0.42 (NS)	-	-	-
IV route only	8-24	1	1	20/20	85% (7.9); (69.4-100.6)	95% (4.9); (85.4-104.6)	-10 (-28.3-8.3)	-1.07 (NS)	-	-	-
Orally	0-3	3	4	50/38	24.7% (4.9); (15-34.3)	33.2% (7.3); (18.93-47.4)	14.6 (-0.4-29.6)	1.9 (0.06)	32.3**	20.9 (-34.6-76.3)	0.7 (NS)
Orally	3-8	3	4	50/38	52.3% (5.3); (41.9-62.6)	56.8% (6.7); (43.6-70)	-21.5 (-39.4_-3.6)	-2.4*	15.9**	3.6 (-46-53.2)	0.14 (NS)
Orally	8-24	3	4	50/38	68% (5.7); (56.9-79)	74.4% (5.5); (63.6-85)	-16 (-32.7-0.5)	-1.9 (0.06)	7.9*	-0.67 (-35.9-34.6)	-0.04 (NS)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 5.2

Table 7.c Summary of subgroup analyses (continued)

Sotalol clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T(SE); (95% CI)*	*P_C(SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
(d) Duration of arrhythmia:											
i. Versus placebo											
< 24 hrs	0-3	3	3	123/73	62.2% (4.1); (54.3-70.2)	13.99% (4.9); (4.4-23.6)	47.1 (36.34-57.8)	8.6**	7.1* (0.03)	47.4 (27.1-67.6)	4.6**
> 24 hrs	0-3	-	-	-	-	-	-	-	-	-	-
ii. Versus others#											
< 24 hrs	0-3	3	3	50/38	24.7% (4.9); (15-34.3)	33.2% (7.3); (18.93-47.4)	14.6 (-0.4-29.6)	1.9 (0.06)	32.3**	20.9 (-34.6-76.3)	0.7 (NS)
< 24 hrs	3-8	3	3	50/38	52.3% (5.3); (41.9-62.6)	56.8% (6.7); (43.6-70)	-21.5 (-39.4_-3.6)	-2.4*	15.9**	3.6 (-46-53.2)	0.14 (NS)
< 24 hrs	8-24	3	3	50/38	68% (5.7); (56.9-79)	74.4% (5.5); (63.6-85)	-16 (-32.7-0.5)	-1.9 (0.06)	7.9*	-0.67 (-35.9-34.6)	-0.04 (NS)
> 24 hrs	0-3	1	1	20/20	75% (9.6); (56-93.97)	50% (11.2); (28.1-71.9)	0.25 (-3.99-53.99)	1.69*	-	-	-
> 24 hrs	3-8	1	1	20/20	85% (7.98); (0.7-1.01)	80% (8.9); (62.5-97.5)	5 (-18.5-28.5)	0.42 (NS)	-	-	-
> 24 hrs	8-24	1	1	20/20	85% (7.9); (69.4-100.6)	95% (4.9); (85.4-104.6)	-10 (-28.3-8.3)	-1.07 (NS)	-	-	-

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 5.2

Table 7.c Summary of subgroup analyses (continued)

Sotalol clinical trials

Type of comparison	*Time interval (hrs)*	*No. of trials*	*No. of comparison*	*No. of patients*	*P_T (SE); (95% CI)*	*P_C (SE); (95% CI)*	*RD(%) (95% CI)*	*Z*	*Q statistic (P)*	*RD(%) (95% CI)*	*Z*
Overall analysis											
Versus placebo	0-3	3	3	123/73	62.2% (4.1); (54.3-70.2)	13.99% (4.9); (4.4-23.6)	47.1 (36.34-57.8)	8.6**	7.1* (0.03)	47.4 (27.1-67.6)	4.6**
Sot vs Other drugs (all)	0-3	4	5	70/58	34.9% (4.4); (26.4-43.6)	38.2% (6); (26.2-50)	16.8 (3.5-30)	2.5*	32**	21.8 (-19.5-63)	1.04 (NS)
Sot vs Other drugs (all)	3-8	4	5	70/58	34.98% (4.4); (26.4-43.6)	65.2% (5.4); (54.7-75.7)	-11.8 (-26-2.5)	-1.62 (NS)	18.9**	2.5 (-32.6-37.5)	0.14 (NS)
Sot vs Other drugs (all)	8-24	4	5	70/58	73.7% (4.6); (64.6-82.7)	82.4% (4); (74.6-90)	-10.8 (-22.9-1.3)	-1.75 (NS)	8.8 (0.07)	-7.3 (-26.9-12.4)	-0.7 (NS)

RD, risk difference; 95% CI; 95% confidence interval; P_T and P_C, pooled percentages of patients remaining in sinus rhythm in treatment and control groups; Q statistic, test of heterogeneity, * statistically significant $P < 0.05$; ** highly statistically significant $P < 0.01$; NS, nonsignificant

Appendix 6.2

Table (1) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up

Trial (1): Ceremuzynski *et al.* 1992

Time interval (weeks)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
4	9	305	0.9700	0.9700	0.00992	11	308	0.9643	0.9643	0.01058
8	1	296	0.9970	0.9672	0.01034	4	297	0.9865	0.9866	0.01226
12	0	295	1	0.9672	0.01034	2	293	0.9932	0.9932	0.01301
16	1	295	0.9966	0.9639	0.01082	3	291	0.9897	0.9897	0.01404
20	1	294	0.9959	0.9600	0.01135	4	288	0.9861	0.9861	0.01527
24	3	293	0.9904	0.9508	0.01251	2	284	0.99293	0.99293	0.01584
28	1	290	0.9965	0.9475	0.01289	1	282	0.9965	0.9965	0.01611
32	2	289	0.9931	0.94098	0.01362	3	281	0.9893	0.9893	0.01689
36	1	287	0.9968	0.9380	0.01393	2	278	0.9928	0.9928	0.01739
40	1	286	0.9962	0.9344	0.01429	1	276	0.9964	0.9964	0.01762
44	0	285	1	0.9344	0.01429	0	275	1	1	0.01762
48	0	285	1	0.9344	0.01429	0	275	1	1	0.01762
52	0	285	1	0.9344	-	0	275	1	1	0.01762
Total events	19					33				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (1) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up (continued)

Trial (2): Navarro-Lopez *et al.* 1993

Time interval (months)	Amiodarone group					Placebo group					Metoprolol group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1				1	1	
6	1	115	0.99	0.99	0.0093	1	123	0.99	0.99	0.009	6	130	0.956	0.956	0.0179
12	0	107	1	0.99	0.0093	1	113	0.992	0.983	0.012	1	116	0.989	0.945	0.0201
18	2	106	0.979	0.97	0.0163	4	112	0.967	0.950	0.020	0	113	1	0.945	0.0201
24	1	105	0.992	0.963	0.0182	2	107	0.976	0.928	0.024	2	112	0.984	0.930	0.0228
30	0	100	1	0.963	0.0182	1	102	0.995	0.923	0.025	5	107	0.954	0.888	0.0287
36	0	81	1	0.963	0.0182	0	75	1	0.923	0.025	3	78	0.954	0.847	0.0344
Total events	4					9					17				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (1) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up (continued)

Trial (3): BASIS 1993

Time interval (Months)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
12	3	98	0.9667	0.9667	0.01812	11	114	0.9	0.9	0.0281
24	6	89	0.9310	0.9	0.03097	5	94	0.944	0.85	0.034
36	5	84	0.9389	0.845	0.0374	11	87	0.871	0.74	0.042
48	5	80	0.9335	0.789	0.04211	2	82	0.973	0.72	0.043
60	5	76	0.9298	0.733	0.04546	2	78	0.972	0.7	0.044
72	2	66	0.9681	0.71	0.04679	10	72	0.857	0.6	0.048
84	1	51	0.9859	0.7	0.04759	4	48	0.917	0.55	0.0499
96	3	37	0.9143	0.64	0.05414	3	44	0.945	0.52	0.0508
102	0	37	1	0.64	0.05414	5	26	0.827	0.43	0.0570
Total events	31					53				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (1) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up (continued)

Trial (4): Garguichevich *et al.* 1995

Time interval (Days)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
30	1	57	0.98125	0.98125	0.01797	2	49	0.95	0.95	0.031135
60	1	56	0.98089	0.9625	0.02516	1	46	0.9868	0.9375	0.034624
90	0	55	1	0.9625	0.02516	0	45	1	0.9375	0.034624
120	0	55	1	0.9625	0.02516	2	45	0.9600	0.9	0.043067
150	0	55	1	0.9625	0.02516	1	44	0.9722	0.875	0.047437
180	0	55	1	0.9625	0.02516	0	43	1	0.875	0.047438
210	0	55	1	0.9625	0.02516	3	43	0.9286	0.8125	0.055869
240	2	55	0961039	0.9250	0.03486	2	40	0.9539	0.775	0.059719
270	0	55	1	0.9250	0.03486	0	38	1	0.775	0.059719
300	1	55	0.97297	0.9000	0.03948	1	38	0.9762	0.7566	0.061367
330	1	50	0.98556	0.8870	0.04178	0	37	1	0.7566	0.061367
360	0	50	1	0.8870	0.04178	2	37	0.9418	0.7125	0.064718
Total events	6					14				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (2) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which did not report the number of patients remaining at risk during the follow-up (continued)

Trial (1): Nicklas *et al.* 1991

Time interval (Days)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
50	4	49	0.925	0.925	0.03763	4	52	0.925	0.925	0.03653
100	2	47	0.9459	0.875	0.04684	1	48	0.9865	0.913	0.03919
150	2	43	0.9571	0.838	0.05237	1	47.45	0.9863	0.9	0.04160
180	1	41	0.9851	0.825	0.05397	0	46.8	1	0.9	0.04160
200	0	40	1	0.825	0.05397	0	46.8	1	0.9	0.04160
250	0	40	1	0.825	0.05397	1	46.8	0.9861	0.888	0.04382
300	2	40	0.9394	0.775	0.059402	0	46.15	1	0.888	0.04382
350	1	38	0.9677	0.750	0.061628	2	46.15	0.9578	0.85	0.04952
360	1	37	0.9667	0.725	0.063579	2.6	44.2	0.9412	0.8	0.05547
400	1	35	0.9655	0.700	0.065275	2.625	42	0.9375	0.75	0.05998
450	0	34	1	0.700	0.065275	1.9	39	0.9507	0.713	0.06267
500	0	34	1	0.700	0.065275	0.68	37	0.9818	0.7	0.06349
Total events	14					15.6				
Total reported	14					9				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (2) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which did not report the number of patients remaining at risk during the follow-up (continued)

Trial (2): The CASCADE Investigators 1993

Time interval (years)	Amiodarone group					Class IA group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
1	10.3	113	0.909	0.91	0.027086	26.45	115	0.77	0.77	0.039243
2	10.2	102.83	0.9010989	0.82	0.036241	9.2	88.55	0.8961	0.69	0.043128
3	6.8	92.66	0.9268293	0.76	0.040253	15	79.35	0.8116	0.56	0.046289
4	11.3	85.88	0.8684211	0.66	0.044615	4.6	64.4	0.9286	0.52	0.046588
5	3.4	74.58	0.9545455	0.63	0.045465	7	59.8	0.8846	0.46	0.046476
6	11.3	71.19	0.8412698	0.53	0.046983	7	52.9	0.8696	0.4	0.045683
7	0	59.89	1	0.53	0.046983	0	46	1	0.4	0.045683
8	0	59.89	1	0.53	0.046983	0	46	1	0.4	0.045683
Total events	53					69				
Total reported	38					55				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (2) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which did not report the number of patients remaining at risk during the follow-up (continued)

Trial (3): Doval *et al.* (GESICA) 1994

Time interval (Days)	Amiodarone group					Control group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
90	21.3	260	0.918182	0.918182	0.0169982	25.6	256	0.9	0.9	0.01875
180	19	238.7	0.920842	0.8455	0.022414	31.4	230.4	0.86367	0.7773	0.02600
270	17.7	219.8	0.919338	0.7773	0.025802	13.97	199	0.92979	0.7227	0.027978
360	10.6	202	0.947331	0.73636	0.027325	13.96	185	0.924525	0.6682	0.029429
450	14.2	191.45	0.92593	0.68182	0.028886	17.5	171.6	0.897959	0.6	0.030607
540	16.548	177.3	0.90666	0.61818	0.030129	15.4	153.6	0.9	0.54	0.031141
630	5.897	160.73	0.96333	0.5955	0.030437	17	138.3	0.875426	0.4727	0.031197
720	0	154	1	0.9955	0.030437	0	121	1	0.4727	0.031197
Total events	105					135				
Total reported	87					106				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (2) Approximation of total mortality events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which did not report the number of patients remaining at risk during the follow-up (continued)

Trial (4): Singh *et al.* (STATCHF) 1995

Time interval (Months)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
12	64.4	336	0.8084	0.8084	0.02147	61.96	338	0.8167	0.8167	0.021045
24	36.8	260	0.8586	0.694	0.02539	35	263	0.8669	0.7080	0.025009
36	32	175	0.8164	0.5666	0.02903	35.55	178	0.8003	0.5667	0.029166
48	12	101	0.8825	0.5	0.03397	21	95	0.7793	0.4416	0.033134
51	1	33	0.97	0.485	0.03388	5	39	0.8719	0.3850	0.037322
Total	146					158				
Total reported	131					143				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (3) Estimation of total mortality events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (1): Nicklas *et al.* 1991

Time interval (Days)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
50	5	49	0.89796	0.89796	0.04324	6	52	0.88462	0.8846	0.04431
100	2	44	0.9546	0.85714	0.04999	0	46	1	0.8846	0.04431
150	2	42	0.9524	0.81633	0.05532	0	46	1	0.8846	0.04431
180	0	40	1	0.81633	0.05532	0	46	1	0.8846	0.04431
200	0	40	1	0.81633	0.05532	0	46	1	0.8846	0.04431
250	0	40	1	0.81633	0.05532	0	46	1	0.8846	0.04431
300	2	40	0.9500	0.77551	0.05961	1	46	0.9783	0.8654	0.04733
350	1	36	0.9722	0.75397	0.06172	2	46	0.9565	0.8278	0.05222
360	1	26	0.9615	0.72497	0.06581	0	4	1	0.8278	0.05222
400	1	25	0.96	0.69597	0.06927	0	2	1	0.8278	0.05222
450	0	24	1	0.69597	0.06927	0	2	1	0.8278	0.05222
500	0	24	1	0.69597	0.06927	0	2	1	0.8278	0.05222
Total events	14					9				
Total reported	14					9				
RMSE‡	0.01486					0.246416				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (3) Estimation of total mortality events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (2): The CASCADE Investigators 1993

Time interval (years)	Amiodarone group					Class IA group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
1	13	113	0.88496	0.88596	0.03	40	115	0.65217	0.65217	0.0444
2	7	100	0.93000	0.82300	0.0359	14	75	0.81333	0.53043	0.0465
3	5	83	0.93976	0.77343	0.0400	23	61	0.62295	0.33043	0.0439
4	7	49	0.85714	0.66294	0.0517	7	38	0.81579	0.26957	0.0414
5	2	42	0.95238	0.63137	0.0538	11	31	0.64516	0.17391	0.0354
6	4	40	0.90000	0.56823	0.05695	11	20	0.45000	0.07826	0.0251
7	0	10	1	0.56823	0.05695	0	9	1	0.07826	0.0251
8	0	10	1	0.56823	0.05695	0	9	1	0.07826	0.0251
Total events	38					106				
Total reported	38					106				
RMSE‡	0.012009					0.59207				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (3) Estimation of total mortality events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (3): Doval *et al.* (GESICA) 1994

Time interval (Days)	Amiodarone group					Control group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
90	23	260	0.91154	0.91154	0.01761	23	256	0.91016	0.91016	0.01787
180	16	237	0.93249	0.85	0.02215	25	181	0.86188	0.78444	0.02797
270	14	187	0.92513	0.786364	0.02622	11	156	0.92949	0.72913	0.03057
360	9	146	0.93836	0.737889	0.02916	11	145	0.92414	0.67382	0.03248
450	10	137	0.92701	0.684029	0.03162	14	134	0.89552	0.60342	0.03410
540	11	127	0.91339	0.624782	0.03355	11	120	0.90833	0.54811	0.03482
630	4	116	0.96552	0.603238	0.03408	11	100	0.89000	0.48782	0.03542
Total events	87					106				
Total reported	87					106				
RMSE‡	0.005704					0.003526				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (3) Estimation of total mortality events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (4): Singh *et al.* (STATCHF) 1995

Time interval (Months)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
6	28	336	0.91667	0.91667	0.015078	29	338	0.9142	0.9142	0.0152
12	23	245	0.90612	0.83061	0.021873	24	309	0.9223	0.8432	0.0198
18	11	215	0.94884	0.78812	0.024218	17	241	0.9295	0.7837	0.0231
24	21	192	0.89063	0.70192	0.027935	17	221	0.9231	0.7234	0.0255
30	23	171	0.865497	0.60751	0.030331	-	-	-	-	-
36	11	148	0.925676	0.56235	0.030331	23	204	0.8873	0.6419	0.0277
42	6	137	0.956204	0.53773	0.031214	17	181	0.9061	0.5816	0.0287
48	8	131	0.938931	0.50489	0.031392	16	138	0.8841	0.5142	0.0299
Total	131					143				
Total reported	131					143				
RMSE‡	0.011837					0.004157				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (4) Approximation of sudden death events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up (continued)

Trial (1): Garguichevich *et al.* 1995

Time interval (Days)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
30	2	57	0.967	0.967	0.02366	1	49	0.98	0.98	0.02
60	0	55	0.99969	0.9667	0.02377	0	48	0.98	0.98	0.02
90	0	55	1	0.9667	0.02377	2	48	0.94	0.94	0.0339
120	0	55	1	0.9667	0.02377	1	46	0.92	0.92	0.0388
150	0	55	1	0.9667	0.02377	0	45	0.92	0.92	0.0388
180	0	55	1	0.9667	0.0238	1	45	0.90	0.9	0.0429
210	0	55	1	0.9667	0.0238	1	44	0.88	0.88	0.0465
240	2	55	0.9597	0.92778	0.0343	1	43	0.85	0.85	0.0511
270	0	53	0.99997	0.92775	0.0343	1	40	0.83	0.83	0.0538
300	0	53	1	0.92775	0.0343	0	40	0.83	0.83	0.0538
330	0	53	1	0.92775	0.0343	1	40	0.81	0.81	0.0562
360	0	53	1	0.92775	0.0343	1	39	0.789	0.789	0.0585
Total events	4					10				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Table (4) Approximation of sudden death events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which reported the number of patients remaining at risk during the follow-up (continued)

Trial (2): Singh *et al.* (STATCHF) 1995

Time interval (Months)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
12	27	336	0.92	0.9200	0.0148	31	338	0.909	0.909	0.01565
24	13	260	0.95109	0.8750	0.0187	23	263	0.9131	0.83	0.02129
36	15	175	0.91429	0.8000	0.02520	10	178	0.9398	0.78	0.02489
48	8	101	0.91675	0.7334	0.031959	10	95	0.8975	0.70	0.03299
54	1	33	0.95446	0.7000	0.040438	1	39	0.9714	0.68	0.03709
Total	64					75				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (5) Approximation of sudden death events, and variance of survival curve estimate by actuarial or life-table method in amiodarone trials which did not reported the number of patients remaining at risk during the follow-up (continued)

Trial (1): Doval *et al.* (GESICA) 1994

Time interval (Days)	Amiodarone group					Control group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
90	8	260	0.97	0.97	0.010579	13	256	0.95	0.95	0.013622
180	5	252	0.9794	0.95	0.013519	13	243.2	0.9437	0.90	0.018750
270	7	247	0.9699	0.92143	0.016688	10	230.3	0.9556	0.86	0.021687
360	5	240	0.9767	0.9	0.018603	2	219.43	0.9884	0.85	0.022319
450	9	233	0.9603	0.8643	0.021250	13	217.6	0.9412	0.80	0.025002
540	9	225	0.9603	0.83	0.023302	4	204.8	0.9821	0.7857	0.025648
Total	44	216	1	0.83	0.023302	54.8				
Total reported	32					39				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate

Appendix 6.2

Table (6) Estimation of sudden death events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (1): Doval *et al.* (GESICA) 1994

Time interval (Days)	Amiodarone group					Control group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
90	12	260	0.95385	0.95385	0.01301237	11	256	0.95703	0.957031	0.0126742
180	3	248	0.98790	0.94231	0.01446001	9	173	0.94797	0.907244	0.0201358
270	5	245	0.97959	0.92308	0.01652573	7	160	0.95625	0.867552	0.0242068
360	4	195	0.97949	0.90414	0.01870306	2	147	0.986395	0.855748	0.0252754
450	5	149	0.96644	0.87380	0.02246443	9	145	0.93793	0.802633	0.0292578
540	3	97	0.96907	0.84678	0.02664273	1	136	0.99265	0.796731	0.0296319
Total events	32					39				
Total reported	32					39				
RMSE‡	0.00756					0.002445				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (6) Estimation of sudden death events, and number of patients remaining at risk at beginning of the interval by curve fitting

Trial (2): Singh *et al.* (STATCHF) 1995

Time interval (Months)	Amiodarone group					Placebo group				
	d_i†	n_i£	P_i§	S_i¶	SE_i¥	d_i†	n_i£	P_i§	S_i¶	SE_i¥
0			1	1				1	1	
6	22	336	0.934524	0.934524	0.013495	16	338	0.9526627	0.9526627	0.01155082
12	8	314	0.974522	0.910714	0.015557	19	322	0.9409938	0.8964497	0.01657220
18	7	306	0.977124	0.889881	0.017078	10	248	0.9596774	0.8603025	0.01945069
24	5	200	0.975000	0.867634	0.019333	9	211	0.9573459	0.8236072	0.02213545
30	10	195	0.948717	0.8231399	0.022896	7	184	0.9619565	0.7922743	0.02425532
36	3	115	0.973913	0.8016667	0.025435	10	159	0.9371069	0.7424457	0.02737368
42	6	106	0.943396	0.7562893	0.029992	4	149	0.9731544	0.7225143	0.02839499
48	3	100	0.970000	0.7336006	0.031825	0	0	0	0	0
Total	64					75				
Total reported	64					75				
RMSE‡	0.011837					0.003656				

†, No. of deaths at the end of the interval
£, No. of pts at risk at the beginning of the interval
§, Probability of surviving interval
¶, Actuarial (Kaplan-Meier) survival estimate subsequent to interval (extracted from graph)
¥, Standard error of the Kaplan-Meier estimate
‡, Residual mean square error

Appendix 6.2

Table (7) Meta-analytic log-rank OR of total mortality in amiodarone randomised clinical trials

Sensetivity analysis subgroups	3 months	6 months	12 months	18 months	24 months	36 months	48 months	60 months	72 months	84 months	96 months	102 months
(1) Trials with completely censored data (N=4)												
Log-rank OR (Z)	1.14, 0.25 (NS)	0.63, -1.32 (NS)	0.54, -2.53**	-	0.598, -2.4**	0.58, -2.78**	0.63, -2.4**	0.68, -2.03*	0.63, -2.6**	0.61, -2.8**	0.63, -2.7**	0.598, -3**
95% CI for the OR	0.399-3.3	0.32-1.25	0.33-0.87	-	0.39-0.9	0.39-0.85	0.43-0.92	0.47-0.99	0.44-0.89	0.43-0.86	0.45-0.89	0.43-0.83
(1.1) Ceremuzynski 1992 and Garguichevich 1995 only												
Log-rank OR (Z, P)	0.58, -1.5 (NS)	0.497, -2.43**	0.52, -2.67**	-	-	-	-	-	-	-	-	-
95% CI for the OR	0.29-1.19	0.28-0.87	0.32-0.84	-	-	-	-	-	-	-	-	-
(1.2) Navarro-Lopez 1993 and Pfisterer 1993												
Log-rank OR (Z, P)	-	-	0.38, -1.96*	-	0.6, -1.7 (NS)	0.53, -2.28**	-	-	-	-	-	-
95% CI for the OR	-	-	0.14-1.001	-	0.3-1.14	0.3-0.9	-	-	-	-	-	-
(2) Trials with partially censored data (N=4)												
Log-rank OR (Z, P)	0.89, -0.4 (NS)	0.83, -1.2 (NS)	0.9, -0.8 (NS)	0.86, -1.4 (NS)	0.9, -1.6 (NS)	0.83, -1.9 (NS)	0.78, -2.6**	-	-	-	-	-
95% CI for the OR	0.52-1.53	0.6-1.13	0.71-1.17	0.69-1.07	0.696-1.04	0.69-1.01	0.65-0.94	-	-	-	-	-
(3) Trials with data generated by curve fitting (N=3)												
Log-rank OR (Z, P)	1.04, 0.14 (NS)	0.84, -1.02 (NS)	0.9, -0.6 (NS)	0.89, -1.1 (NS)	0.89, -1 (NS)	0.87, -1.4 (NS)	0.87, -1.4 (NS)	-	-	-	-	-
95% CI for the OR	0.61-1.78	0.61-1.17	0.7-1.19	0.71-1.1	0.72-1.103	0.7-1.07	0.72-1.06	-	-	-	-	-
(4) Trials with completely censored data and Trials with partially censored data (N=7)												
Log-rank OR (Z, P)	0.76, -1.3 (NS)	0.73, -2.2*	0.78, -2.29**	0.77, -2.8**	0.78, -2.8**	0.76, -3.23**	0.74, -3.7**	0.75, -3.6**	0.73, -3.8**	0.73, -3.9**	0.73, -3.9**	0.72, -4.1**
95% CI for the OR	0.494-1.17	0.56-0.97	0.63-0.97	0.63-0.93	0.65-0.93	0.64-0.896	0.63-0.87	0.64-0.88	0.62-0.86	0.62-0.85	0.62-0.86	0.62-0.85
(5) Trials with completely censored data and Trials with data generated by curve fitting (N=7)												
Log-rank OR (Z, P)	0.8, -0.79 (NS)	0.74, -2.08*	0.78, -2.21*	0.77, -2.5**	0.797, -2.4*	0.78, -2.7**	-	0.796, -2.5**	0.78, -2.8**	0.77, -2.9**	0.78, -2.9**	0.76, -3.1**
95% CI for the OR	0.55-1.29	0.56-0.98	0.63-0.97	0.63-0.94	0.66-0.96	0.66-0.94	-	0.67-0.95	0.65-0.93	0.65-0.92	0.65-0.92	0.64-0.91

* statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Appendix 6.2

Table (8) Meta-analytic log-rank OR of sudden death in amiodarone randomised clinical trials

Sensetivity analysis subgroups	3 months	6 months	12 months	18 months	24 months	36 months	48 months	54 months
(1) Trials with completely censored data (N=2)								
Log-rank OR (Z, P)	0.55 (-0.65, NS)	0.34 (-1.4, NS)	0.7 (-1.4, NS)	-	0.66 (-2.23*)	0.75 (-1.7, NS)	0.75 (-1.78, NS)	0.76 (-1.76, NS)
95% CI for the OR	0.09-3.3	0.08-1.54	0.43-1.14	-	0.46-0.95	0.54-1.05	0.55-1.03	0.6-1.03
(2) Trials with partially censored data (N=1)								
Log-rank OR (Z, P)	0.59 (-1.5, NS)	0.49, -2.2*	0.6 (-1.83, NS)	0.75 (-1.42, NS)	-	-	-	-
95% CI for the OR	0.25-1.4	0.26-0.92	0.38-1.03	0.497-1.12	-	-	-	-
(3) Trials with data generated by curve fitting (N=3)								
Log-rank OR (Z, P)	1.08 (0.2, NS)	0.97 (-0.15, NS)	0.8 (-1.5, NS)	0.73 (-1.8, NS)	0.72 (-2.1*)	0.79 (-1.6, NS)	0.81 (-1.5, NS)	-
95% CI for the OR	0.47-2.5	0.6-1.6	0.52-1.1	0.5-1.03	0.53-0.98	0.59-1.06	0.6-1.07	-
(4) Trials with completely censored data and Trials with partially censored data (N=7)								
Log-rank OR (Z, P)	0.59 (-1.32, NS)	0.46 (-2.6**)	0.67 (-2.3*)	0.73 (-2*)	0.695 (-2.53**)	0.75 (-2.1*)	0.75 (-2.2*)	0.75 (-2.2*)
95% CI for the OR	0.27-1.29	0.26-0.83	0.47-0.94	0.53-0.99	0.53-0.92	0.58-0.98	0.58-0.97	0.58-0.97
(5) Trials with completely censored data and Trials with data generated by curve fitting (N=7)								
Log-rank OR (Z, P)	0.96 (-0.11, NS)	0.88 (-0.6, NS)	0.69 (-2.1*)	0.67 (-2.4*)	0.67 (-2.6**)	0.74 (-2.1*)	0.75 (-2.1*)	0.76 (-2*)
95% CI for the OR	0.45-2.04	0.56-1.4	0.48-0.98	0.48-0.93	0.498-0.91	0.56-0.98	0.57-0.99	0.58-0.995

* statistically significant (P<0.05); ** highly statistically significant (P<0.01)

Appendix 6.2

Table (9) The pooled survival rates of total mortality in amiodarone clinical trials

Time point (months)	Censored pooled with partially censored trials		Censored pooled with curve fitting trials		Censored trials only	Curve fittig trials only
	Amiodarone	Placebo	Amiodarone	Placebo	Amiodarone	Amiodarone
1	97.6 (69.8)	95.7 (69)	-	-	97.6 (69.8)	-
2	95.1 (56.3)	93.8 (55.9)	-	-	96.5 (96.5)	-
3	92.9 (48.2)	92.3 (48)	92.2 (48)	91.9 (47.9)	96.5 (69.5)	88.4 (66.5)
4	91.7 (55.3)	91.7 (67.7)	-	-	96.3 (69.4)	-
5	91.6 (55.3)	89.9 (54.7)	-	-	96 (69.3)	-
6	90.98 (42.7)	88.5 (42)	91 (38.9)	88.96 (38.5)	96.7 (56.8)	85.9 (53.5)
7	90.7 (54.99)	87.3 (53.9)	-	-	95.5 (69)	-
8	89.4 (54.6)	85 (53.3)	-	-	93.3 (68.3)	-
9	87.4 (53.97)	79.2 (51.4)	-	-	93 (68.2)	-
10	86.4 (53.7)	84 (52.9)	84 (45.9)	85.6 (46.3)	91.7 (67.7)	78 (62.5)
11	84.96 (53)	82.9 (52.6)	-	-	91 (67.5)	-
12	85.87 (32.8)	81.2 (34.1)	85.9 (32.8)	82.1 (34.2)	94.3 (48.6)	78.9 (44)
15	75.7 (50)	65.2 (57)	-	-	-	-
18	73.6 (49.5)	69 (48)	78 (39.5)	77 (39.3)	95 (67)	69.7 (48.2)
24	77 (39.3)	69.2 (41.6)	77.5 (39.4)	70 (41.9)	93 (68)	69.8 (48)
36	75 (43.4)	71.4 (48.8)	75.6 (43.5)	66.2 (40.7)	89.9	65 (57)
48	62.7 (45.7)	54.7 (52.3)	-	-	-	57.3 (53.5)
60	59.8 (44.7)	48.8 (49.4)	-	-	-	-
72	60.7 (55)	-	-	-	-	-
84	60.3 (54.9)	-	-	-	-	-
96	57.99 (53.8)	-	-	-	-	-
102	64 (80)	-	-	-	-	-
Test of homogeneity	NS	NS	NS	NS	NS	NS

The standard error of the pooled rate is shown in brackets; NS, nonsignificant

Appendix 6.2

Table (10) The pooled survival rates of sudden death in amiodarone clinical trials

Time point (months)	Censored pooled with partially censored trials		Censored pooled with curve fitting trials	
	Amiodarone	Placebo	Amiodarone	Placebo
3	96.8 (69.8)	94.5 (68.7)	96 (69.3)	94.8 (68.9)
6	95.8 (69.2)	90 (67.1)	94.8 (56.2)	91.9 (55.4)
9	92.5 (68)	84.5 (65)	92.5 (68)	84.8 (65)
12	91.6 (55)	84.6 (53)	91.4 (55.2)	84.5 (53)
18	-	80.7 (63.5)	86.8 (65.9)	82.7 (64.3)
24	85.2 (65.3)	-	-	-
Test of homogeneity	NS	NS	NS	NS

The standard error of the pooled rate is shown in brackets; NS, nonsignificant

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