A case control study to identify and explore associations with sudden death and medications that can prolong the QT interval on the electrocardiograph.

by

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ABSTRACT

Background: In England and Wales over 5000 people die each year with a sudden death of ill-defined or unknown cause.

Aims: To explore the hypothesis that the use of drugs that can cause prolongation of the QT interval on the electrocardiograph are associated with an increased risk of sudden death from cardiac arrhythmia.

Methods: A community based, matched case control study used post mortem and primary care datasets. Cause of death was most likely due to cardiac arrhythmia. 789 cases were matched to 2357 controls for age, sex and cardiovascular disease at the GP practices. The International Registry for Drug-Induced Arrhythmias "Arizona" classification was used to separate drugs according to strength of QT prolongation.

Results: Conditions significantly associated with sudden death were used in the adjusted analysis. Overall risks were doubled for the registry drugs that were considered to pose the greatest risk but with considerable variation. The association with sudden death increased with concomitant use of registry drugs. Drugs used for psychiatric purposes were consistently strongly associated with sudden death.

Conclusion: Arizona registry classification is a poor predictor of sudden death. The linkage of the general practice research database to mortality data has the potential for a much larger sample for further study.

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ACE	Angiotensin converting enzyme
AV	Atrioventricular
CABG	Coronary artery bypass graft
CAST	Cardiac arrhythmia suppression trial
CHD	Coronary heart disease
CLR	Conditional logistic regression
CT	Computed tomography
EAD	Early after depolarisation
ECG	Electrocardiogram
GPRD	General Practice Research Database
HERG	Human ether a go go gene
ICD	International classification of diseases
IMD	Index of material deprivation
LREC	Local research ethical committee
MHRA	Medicines and Healthcare Agency Regulatory Authority
MI	Myocardial infarction
MREC	Multi centre research ethics committee
MRI	Magnetic resonance imaging
MSCT	Multi slice computed tomography
NIHSS	National institute of health stroke scale
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys
OR	Odds ratio
PCT	Primary Care Trust
PTCA	Percutaneous transluminal coronary angiography
SADS	Sudden arrhythmic deaths syndrome
SCD	Sudden cardiac death
SSA	Shared Service Agency
TCA	Tricyclic antidepressant
TdP	Torsades de pointes
VPD	Ventricular premature depolarisations
WHO	World Health Organisation

0 INTRODUCTION

This thesis describes a matched case-control study that identified and quantified associations between sudden cardiac death (SCD) from presumed cardiac arrhythmia and medications that prolong the QT interval on the electrocardiograph.

The background (Chapter 1) puts the study into context with previous work.

Chapter 2 states the aims of the study.

Chapter 3, the methods, describes in detail the design of the study, and the definition and selection of cases and controls and how information was obtained. It defines drug exposure as the independent variable. The process of obtaining ethical approval is described. There are short sections on matching and strategy for analysis.

Chapter 4 explores methodological issues relevant to this thesis. A reliability study measured the level of agreement between the two nurses that gathered the data. A comparison of surgeries that granted access to medical researchers with those that did not was done investigating whether they were single or multi handed and indices of deprivation for the catchment areas of surgeries. The third methodological study quantified the level of agreement between causes of death on mortality files and post mortem reports.

Chapter 5 describes the results of the case-control study with particular emphasis on associations between SCD and medications that can prolong the QT interval.

Chapter 6 discusses the findings of the thesis and attempts to put them into context with contemporary work by other researchers.

My role on the study

Before I started working on the study, the protocol had been written, ethical approval obtained and section 60 approval had been granted by the Department of Health for access to patient records.

I was employed as a research nurse to gather the data and also expressly to do an MPhil. I designed the database for the study and wrote all of the queries and reports. I planned and undertook all of my own analysis. To aid timely submission of my MPhil I used the data collected up to October 2006 whilst the case-control study continued for a longer period and thus had a larger number of cases.

1 BACKGROUND

1.0 Introduction to the background section

This chapter describes the epidemiology of sudden cardiac death (SCD) in the United Kingdom and worldwide and explores cardiological conditions that lead to SCD. There is a substantial section on medications that can directly and indirectly prolong the QT interval. Cases in this thesis had a post mortem report and there are sections that examine the accuracy of death certification and post mortem reporting in the UK and beyond.

When researchers write about sudden cardiac death they do not always mean the same thing. There are many definitions of sudden cardiac death, the broadest including death from myocardial infarction as well as arrhythmia. Narrower definitions exclude myocardial infarction and acute precipitating causes.

1.1 The epidemiology of sudden cardiac death

Search strategy

I used the medical database medline 1950 to April 6th 2009. The search strategy used the keywords “sudden” “cardiac” and “death” limited to epidemiology and gave 1553 references. A further limit to abstracts gave 1233 references of which there were 1049 articles in the English language. There were 264 full text articles. I used relevant papers and references to other relevant papers were followed up and incorporated into this thesis.

I used the Critical Skills appraisal Programme[1] (CASP) appraisal tool as a framework for evaluating studies although I did not do it formally as one would do for a systematic review. I reviewed case control and cohort studies from the major researchers investigating the association with sudden cardiac death and medication and I have quoted relevant study results. I have commented on the quality of relevant studies in my thesis with respect to the CASP guidelines.

1.1.1 Definition of sudden cardiac death

There are many definitions of sudden cardiac death (SCD) and there is ambiguity in the definition of SCD in clinical and public health practice. It is a matter of debate as to when an unexpected death should be called 'sudden' and how the cardiac origin of the death should be ascertained[2]. This background section will explore various broad definitions of sudden cardiac death as well as the much narrower definition of sudden cardiac death that defines the cases in this thesis.

Typically SCD is broadly defined as follows: 'Natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms or within 24 hours of having been observed alive and symptom free; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected[3] [4]. In practice, numerous criteria have been used to define sudden cardiac death in the medical literature. Sudden cardiac death is witnessed in only two thirds of cases making the diagnosis and time of onset difficult to establish[5].

One broad definition of SCD used by Zheng et al was to define SCD as deaths occurring out of the hospital or in the emergency room or as "dead on arrival" with an

underlying cause of death reported as a cardiac disease (ICD-9 code 390 to 398, 402, or 404 to 429)[6]. This analysis was based on 719,456 cardiac deaths among adults age 35 years or older in 1998 of which 456,076 were classified as sudden cardiac death.

In a letter to the editor Angelini pointed out that if SCD denotes any unexpected, cardiac death (which, by inference, would have been prevented by a pacemaker or an implantable defibrillator), it seems unreasonable to assume that SCD accounted for 63.6% of cardiac deaths in 1998, as claimed by Zheng[7]. He concluded that "what would indeed be important to identify is premature arrhythmic death". He stated that without consistent electrocardiographic monitoring and post mortem data, death certificates will not elucidate the true incidence of this event.

In this thesis the cases were people that had died from a presumed sudden cardiac arrhythmic death not due to an acute precipitating event such as a myocardial infarction. Every case had a post mortem report and individuals were excluded from being a case if there was evidence that death was due to any non cardiac cause or if they had an acute cardiac event that could trigger an arrhythmia such as a fresh coronary artery thrombus. This is an uncommon definition of SCD. In the section describing the epidemiology I will be using the broader definition of SCD based on the International Classification of Diseases version 10 codes.

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1.1.2 Incidence of SCD in the UK

The National Service Framework 2005 estimated the number of sudden cardiac deaths each year in the United Kingdom (UK) at 100,000[8]. A prospective survey of 83 coroners jurisdictions in England estimated that the frequency of deaths in apparently

healthy adults age 16 to 64 seen alive within 12 hours of death for whom there was no medical history of cardiac disease and for whom the post mortem report showed either a cardiac or no identifiable cause of death was 11 in 100,000[9]. An estimated 400 sudden cardiac deaths in the UK each year that occur in people under the age of 30 years are unexplained and thought to have a genetic basis[8].

1.1.3 Incidence Worldwide

Various estimates exist for the magnitude of sudden cardiac death in the general population of the United States. Figures based on primary cardiac arrest from first responder agencies and from death certificate data give estimates ranging from 184,000 to greater than 400,000 per year[4]. Thus in the general population of the United States the incidence of sudden cardiac death is about 1 death per 1000 head of population per year and as described below this figure holds for other developed nations.

A prospective cohort study using an integrated primary care database in the Netherlands reported an annual incidence of sudden out of hospital cardiac arrests of 0.92 cases per 1000 person-years (95% Confidence interval (CI): 0.85, 0.99). The study population comprised 249,126 subjects with a mean follow up of 2.54 years. In this period 4,892 deaths were identified, 582 of which were classified as (probable) sudden cardiac death[10].

It has been estimated that in the developed world sudden cardiac death is the largest cause of natural death accounting for 12-18% of total mortality and 50% of cardiac mortality. These figures are based on retrospective studies that may be an over-

estimate as described below. Sudden cardiac death accounted for 5.6% of the annual mortality of a population of 660,486 residents of Multnomah County, Oregon according to a prospective study[4] .Between 1 February 2002 and 31 January 2003, 353 residents suffered sudden cardiac death (incidence 53 of 100,000, median age 69 years, 57% male). An assessment of the validity of death certificate-based retrospective surveillance was made by comparing it with the prospective study results. It was found that retrospective death certificate-based surveillance significantly overestimated sudden cardiac death (1007 cases, incidence 153 of 100,000, median age 81 years, 51% male).

Sudden cardiac death rates were overestimated by 47% when derived from death certificates in a study that compared out of hospital sudden cardiac deaths derived from death certificates with physician adjudicated sudden cardiac deaths in the Framingham Heart Study from 1959 to 1999[11].

1.1.4 Incidence of sudden cardiac death by gender

The incidence of SCD is higher in men than in women, with men two to four times more affected than women when age is adjusted for. Most studies of primary cardiac arrest have reported a threefold higher incidence in men compared with women[12] but these studies have looked at data retrospectively. Prospective studies may reduce the sex discrepancy as shown in a study that found 43% of 353 sudden cardiac death cases were female[4]. A prospective study in the Netherlands that classified 582 people as having probable sudden cardiac death estimated the risk to be 2.3 fold higher in men than in women [10].

1.1.5 Change in sudden cardiac death rates over time

Temporal trends of the 358 sudden cardiac deaths in the original and offspring cohorts of the Framingham heart study from 1950 to 1999 have been examined. From the periods 1950-1969 to 1990-1999 sudden cardiac death rates decreased by 49%, (95% CI (28 %, 64%)). This decrease was seen in men and women, in subjects with and without a prior history of coronary heart disease, and in smokers and non-smokers[13].

The trend in subjects with and without heart disease may be evidence that the improvements in primary and secondary prevention have resulted in the decreasing occurrence of this event. Interventions aimed at reducing the frequency and severity of myocardial ischaemia, such as thrombolytic therapy and coronary artery bypass grafting, have been associated with decreased incidence of sudden cardiac death and reduced overall cardiac mortality[5].

1.1.6 Circumstances of sudden cardiac deaths

In the prospective study that identified 353 sudden cardiac deaths in the residents of Multnomah County Oregon 52% of them were witnessed. 82% of cardiac arrests took place at home of which 46% were witnessed. The place of death did not vary significantly when stratified by age or gender[4]

1.1.7 Onset of symptoms to death

Experience from ambulatory and coronary care unit monitoring indicates that the underlying mechanism in most sudden deaths is ventricular fibrillation[14]. This finding is supported by a study that showed that of 133 persons with spontaneous cardiac arrest attended by paramedics within 10 minutes, 100 (75%) had ventricular fibrillation as the initial rhythm and 33 (25%) had extreme bradycardia or asystole. The latter group of arrhythmias was characterised by sinus arrest or severe sinus bradycardia (90%) and complete A-V block (10%)[15].

1.1.8 Chances of survival from cardiac arrest

For those who suffer out-of-hospital cardiac arrest due to heart disease, survival rates are low, even in the setting of witnessed arrests in persons with ventricular fibrillation. ospital discharge rates of 20% have been reported from urban centres with the ability to provide rapid-response defibrillator equipped emergency medical services. Survival is highest when cardiopulmonary resuscitation (CPR) is started early, possibly because definitive procedures such as defibrillation, medications and intubation can be effectively applied[16]. However, national averages of successful resuscitation from out-of-hospital cardiac arrest due to heart disease are only between 1% and 2%[5]. This discrepancy could in part be due to people dying because they do not get prompt expert treatment.

A prospective community study over the two years 1994 and 1995 in the United Kingdom health districts of Brighton, South Glamorgan and York concluded that the chance of surviving a cardiac arrest in the community depends on whether it is witnessed and if so by whom and if there is a resuscitation attempt [17]. The main

outcome measure was survival to reach hospital and for 30 days after cardiac arrest in 1290 people less than 76 years of age. People whose cardiac arrests were witnessed by a doctor or paramedic had the greatest chance of survival with 35 out of 101 (35%) surviving. Out of 200 cardiac arrests witnessed by other members of the public 15 (7.5%) survived. Home cardiac arrests totalled 464 with 15 (2.0%) surviving. There were 525 cardiac arrests unwitnessed and none survived. The study found that there is an increased chance of surviving a cardiac arrest if it is witnessed by a person that is trained in the technique of resuscitation.

A prospective study in North America[4] also found that the survival rate was better if the sudden cardiac death occurred outside the home. This is likely to be related to a higher chance of the out-of-home sudden cardiac death being a witnessed event (70% of out of home SCDs were witnessed compared with 46% of in home SCDs). The study also found that there were no differences between genders with respect to overall survival rate.

1.1.9 Strategies to prevent sudden cardiac death

A prospective study of sudden cardiac arrest in casinos where trained security officers used automated external defibrillators in 105 cases with ventricular fibrillation resulted in a survival rate of 74% when defibrillation was started no later than 3 minutes after a witnessed collapse and 49% when defibrillation was started after more than 3 minutes[18]. A literature review concluded that early defibrillation is critical to improving survival and public access to defibrillation offer hope that further improvements in survival can be achieved.[19] The complexity of trigger mechanisms makes it difficult to achieve a reliable identification of high-risk patients. The number

of sudden cardiac deaths could be reduced by, firstly in patients with known heart disease by developing new methods to identify those who are at risk, secondly treat patients that do not have a diagnosis of heart disease according to risk factors for coronary disease and thirdly, improve the success rate of resuscitation by putting greater emphasis on the training of laypersons in basic and advanced life support techniques.

1.2 Causes of Sudden Cardiovascular Death

1.2.1 Post-Mortem findings

Cardiac arrhythmia was the most common cause of death in a study that evaluated the post mortem reports of four hundred and forty five sudden cardiac deaths, all of whom had evidence of at least moderate atherosclerosis[20]. Extensive coronary atherosclerosis is by far the most common pathological finding in patients who die suddenly[21]. One study concluded that coronary artery disease accounts for as much as 80% of sudden cardiac deaths[22]. Zheng et al found that of those people who were classified as dying of a sudden cardiac death, coronary heart disease (ICD-9 codes 410-414) was the underlying cause on 62% of death certificates. These conclusions were reached from an analysis of United States vital statistics mortality data from 1989 to 1998[6]. It has been shown that in nearly two thirds of cases, three coronary arteries showed more than 75% luminal obstruction[23]. The arteries with extensive atherosclerosis in victims of sudden cardiac death were the left anterior descending (96%), right coronary (79%), left circumflex (66%), and left main stem (34%). Vascular obstruction was generally found in both proximal and distal segments of the epicardial coronary arteries. In a study of 90 hearts, healed infarcts in the absence of

acute infarction were found in 37 (41%) and no infarct in 34 (38%) of sudden coronary deaths[24].

Post mortem studies of sudden cardiac death give consistent findings in line with an American study of the Framingham population which concluded that 85% of people greater than 40 years old that died from cardiac arrest had coronary artery disease, 10% had other structural cardiac abnormalities for example cardiomyopathy, hypertrophy or valvular disease leaving 5% with no macroscopic structural cardiac abnormality[25].

A study of 215 post mortem reports of sudden cardiac death cases in Southampton, England found that 51% had a previous MI[26].

An investigation of sudden cardiac deaths in London, England stated that at least 4% of sudden deaths are unexplained at autopsy and concluded that over half of sudden arrhythmic deaths (SADS) were likely to be due to inherited heart disease[27]. These SADS are a subset of those dying from SCD.

1.2.2 The problem of unrecognised heart disease

In approximately 40% to 50% of cases of cardiac arrest in the community there is no history of heart disease. The examination of the Framingham heart study data showed that 173 (48%) of the 358 sudden cardiac deaths were in subjects not treated for preceding coronary heart disease[13]. Thus unrecognised and therefore untreated heart disease is a major factor contributing to sudden cardiac death rates.

1.2.3 The increasing importance of sudden death in heart failure

Sudden death has become the dominant mode of death in heart failure taking over from worsening and progressive heart failure. With the development of drugs that primarily have modulation of the renin-angiotensin and sympathetic nervous systems as their mechanism the relative importance of progressive heart failure has decreased[28].

1.2.4 Common risk factors

The most powerful predictor of sudden cardiac death is poor left ventricular function. Other risk factors mirror those of coronary heart disease and include hypercholesterolaemia, hypertension, cigarette smoking, alcohol consumption, physical inactivity, obesity and diabetes [29 30].

A multivariate model developed using prospective data on 4120 middle-aged men from the Albany and Framingham studies estimated the probability of sudden cardiac death. The model took into account risk factors of body mass, cigarette smoking, hypertension, hyperlipidaemia and left ventricular hypertrophy by electrocardiographic criteria. There was a 16 fold increase in risk from the lowest to the highest risk group for people without recognised heart disease with the annual incidence of sudden cardiac death 0.7% in the highest subgroup[31].

The risk of sudden cardiac death varies over time among people with known heart disease. The highest risk of out-of-hospital cardiac arrest is in the first 6 months after a major cardiovascular event, such as a myocardial infarction or new onset heart failure and then declines rapidly over the next 18 months. Survivors of cardiac arrest

or patients with ventricular tachyarrhythmias in the convalescent phase of an acute myocardial infarction have an incidence of sudden cardiac death in the first year following a ventricular fibrillation episode of 15%.

Obesity is associated with an excessive occurrence of CHD, largely as a consequence of its association with atherogenic risk factors[32]. Obesity is more strongly correlated with sudden death incidence in men. Diabetes doubles the risk of atherosclerotic cardiovascular mortality with the rate for sudden death being slightly greater in women[33].

1.2.5 Arrhythmias

Sudden cardiac death is often preceded by arrhythmia. According to the National Service Framework guidelines, cardiac arrhythmia affects more than 700,000 people in England[8]. An arrhythmia may be caused by an inherited problem or by an acquired condition that disturbs the electrical impulses that regulate the heart. The heart may beat too slowly, too quickly, or in an irregular way. The symptoms experienced by patients include palpitations, loss of consciousness, dizziness and breathlessness. In extreme cases, certain types of arrhythmia can cause sudden cardiac death. Acquired heart disease is the most common factor predisposing a person to arrhythmias. The main causes are atherosclerosis, hypertension, previous myocardial infarction and inflammatory or degenerative conditions. The ischaemia, scarring or abnormal tissue deposits found with these diseases can cause tachycardias (originating in either the atria or ventricles) by causing cells to fire abnormally or by creating islands of electrically inert tissue so that impulses circulate in a re-entrant fashion around these areas.

A variety of other factors may predispose a person to develop arrhythmias. Prominent among them is the part of the autonomic nervous system that is involved in cardiovascular regulation. This control system alters the sinus rate. When sudden death occurs in the absence of evidence of organic heart disease it is conceivable that neurochemical and electrophysiological malfunction is responsible[34 35]. The National Service framework for the UK states that most sudden deaths in people under 30 years old are caused by inherited cardiomyopathies and arrhythmias[8].

1.2.5.1 Chemically induced arrhythmias

Many chemical agents may provoke arrhythmias, sometimes with serious consequences. Known factors include high or low blood and tissue concentrations of a variety of minerals, such as potassium, magnesium and calcium. These play a vital role in the conduction of impulses in the heart. Addictive substances, especially alcohol, cigarettes and recreational drugs notably cocaine, can also provoke arrhythmias as can various medications including those used to treat arrhythmia[36].

1.2.6 Cardiomyopathies

Hypertrophic cardiomyopathy can present at any age its prevalence is 0.2% and sudden death occurs in about 1% of patients annually[37]. About 70% of cases of hypertrophic cardiomyopathy are inherited as autosomal dominant with a high degree of penetrance and equal sex distribution. Hypertrophy of the ventricular septum occurs. The muscle fibres are short, thick and fragmented and there is fibrosis. About one third of cases have left ventricular hypertrophy[38]. Ventricular arrhythmias are common in patients in patients with either hypertrophic or diffuse cardiomyopathy [39].

Dilated cardiomyopathy results in an enlarged, flabby heart. It is associated with ventricular arrhythmias and sudden death. It may be idiopathic or caused by alcohol dependence, undiagnosed hypertension, viral infection, autoimmune disease and puerperal heart failure. Thyrotoxicosis may rarely present as dilated cardiomyopathy. There is also a rare X chromosome linked form[40].

Restrictive cardiomyopathy may be caused by a variety of conditions including iron storage diseases, scleroderma, amyloidosis and sarcoidosis. For sarcoid heart disease ventricular premature beats have been associated with sudden death[41].

1.2.7 Wolff-Parkinson-White Syndrome

In this condition, one or more accessory pathways are present that can cause paroxysmal tachycardia by contributing to accelerated conduction from the atrium to the ventricle. Although disabling arrhythmias afflict only a minority of these patients, sudden death has been reported[42 43].

1.2.8 Genetic Long QT syndrome

Prolongation of the QT interval is associated with ventricular arrhythmias, syncope, and sudden death. This syndrome may be acquired or congenital. Two rare clinical syndromes were originally recognised; firstly the Jervell-Lange-Neilson syndrome that is autosomal recessive, and symptoms also include deaf mutism[44], secondly the Romano-Ward syndrome which is autosomal dominant with normal hearing. As well as a prolonged QT interval, both syndromes are characterised with frequent syncopal attacks that are often provoked by emotional or physical stress. There is a high

mortality with 20% dying in the first year after the first syncope and 50% within 10 years. Several other genetic types have been identified corresponding to potassium and sodium ion dysfunction[45]. One of these is the Brugada syndrome, which is associated with an abnormality in a sodium ion channel gene. The syndrome is estimated to be responsible for at least 4% of all sudden deaths and the prevalence of the disease is estimated to be 5/10 000 inhabitants[46] It is more common in South Asian subjects. In a community based study in Japan the Brugada-type ECG was found in 98 of 13,929 study subjects (0.70%, 95% confidence interval [CI]: 0.57% to 0.86%). The typical coved-type with an rsR' pattern in V_1 lead ("typical" Brugada-type) was found in 0.12% of subjects (95% CI: 0.07% to 0.20%).

1.3 Drugs causing QT prolongation; direct and indirect mechanisms

1.3.1 Acquired Long QT syndrome

Acquired QT prolongation is most commonly drug induced or secondary to hypocalcaemia, hypomagnesaemia or hypokalaemia. Drug induced prolongation of the QT interval may cause life-threatening ventricular arrhythmia[47]. Antiarrhythmic drugs are often implicated especially quinidine, procainamide and disopyramide. Prolongation of the QT interval is part of the therapeutic benefit of drugs like amiodarone or sotalol but the drug should be stopped if the QT interval exceeds 500ms. Torsades de Pointes (TdP, a form of multi-focal ventricular tachycardia) may occur if the QT interval exceeds 500ms[48]. Several other types of drugs can also prolong the QT interval including some commonly prescribed antibiotics, antidepressants, diuretics, antifungals, antihistamines, antimalarials, diuretics, lipid-

lowering drugs, oral hypoglycaemics. They increase the QT interval by a variety of mechanisms.

1.3.2 Definition of QT interval and Corrected QT interval

The QT interval on the electrocardiogram (ECG) corresponds to the time taken to depolarise and repolarise the ventricular myocardium. The length of the QT interval is inversely proportional to heart rate. To remove the effect of heart rate, the QT interval is transformed (normalised) into a value known as the QTc interval. The c in QTc stands for correction. The most commonly used method for correcting the QT interval for heart rate is the one formulated by Bazett [49]. Bazett's formula is $QTc = QT/(\sqrt{RR})$, where QTc is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, (a single heart beat) measured in seconds. Bazett's formula over-corrects at high heart rates and under-corrects at low heart rates. There are several other more accurate methods, but they tend not to be used because they are complicated. The regression based approach is considered to be the most accurate[50]. The normal range of the QTc interval is 350 to 430 ms for men below 55 years and for women it is 350 to 450 ms[51]. QTc prolongation can be defined as QTc values above 450ms for men and 470ms for women. Both the QT and QTc intervals commonly exceed 500ms among subjects developing TdP [52].

1.3.3 QTc Prolongation and risk of sudden cardiac death

There is controversy about the mortality risk posed by QTc prolongation in the general population. This is because good quality epidemiological studies that have investigated the risk reached different conclusions.[53]

A recent prospective, population-based Rotterdam study of 6134 subjects age 55 years and older, that were enrolled and followed up for an average time of 6.7 years, demonstrated that subjects with an abnormally prolonged QTc interval, >450 ms in men, > 470 ms in women) were associated with a three-fold increased risk of sudden cardiac death after adjustment for relevant covariates, age, gender, body mass index, hypertension, cholesterol/high density lipoprotein ratio, diabetes mellitus, myocardial infarction, heart failure and heart rate[54]. Positive findings were also found in the longitudinal Zutphen study from the Netherlands involving middle- aged and elderly men[55] and from the Strong Heart Study[56] that enrolled American Indians and in the Cardiovascular Health Study of community dwelling elderly subjects [57]. The Caerphilly heart study indicated that QT dispersion is an independent predictor of cardiac death but that the QT maximum was not[58]. QT dispersion is defined as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12 lead ECG[59]. QT dispersion is a measure of myocardial repolarisation heterogeneity[60] and is predictive of ischaemia-related cardiac dysrhythmia in patients with ischaemic heart disease[61].

No association with baseline QTc prolongation and total mortality or sudden death was found in the population based Framingham study[62]. The Framingham study involved subjects aged 30 to 65 years with follow up extending over a 30 year period. The negative Framingham study is of particular concern because Framingham investigators have consistently provided excellent scientific studies.

The difference in the conclusions of the Rotterdam study and the Framingham study may be due to the difference between the ages at which subjects were enrolled. In the Framingham study the baseline electrocardiogram (ECG) was recorded in a majority of subjects at a relatively young age, probably before the development of subclinical cardiac disease whereas for the Rotterdam study the first of two baseline ECGs were recorded at age 55 years when subclinical disease is more likely to be present.

The Rotterdam investigators were able to show a dose response effect between the duration of the QTc interval (borderline and and abnormally prolonged categories relative to normal QTc prolongation) and the risk of sudden cardiac death in the entire population. This dose-response effect adds considerable strength and significance to the association of QTc prolongation and the risk of sudden cardiac death in older adults.

1.3.4 Possible mechanisms of observed risk association between QTc prolongation and sudden cardiac death

The simplest explanation is that QTc prolongation, whatever the cause, is proarrhythmic, and this alone is sufficient to increase the probability of sudden arrhythmic cardiac death. Another possibility is that the length of the QTc interval is just a marker for the severity of underlying sub-clinical cardiac disease and that the risk is related to the underlying cardiac problem. The authors of the Rotterdam study tried to adjust for covariate risk factors, but perhaps adjustment was not complete. A third possibility is that the QTc prolongation in the general adult population is due to genetic variability, with the increased risk of sudden cardiac death being a direct consequence of gene-related QTc prolongation. Furthermore it is possible that the presence of one or more ion-channel gene polymorphisms could cause minor

alterations in ion-channel function contributing to a modest prolongation in cardiac repolarisation and an increased probability for fatal arrhythmias. For example, a D85N polymorphism in the KCNE1 gene, the beta-subunit of the I_{Ks} has been associated with drug-induced QTc prolongation. The frequency of this polymorphism is approximately 2% to 3% in the general population. By itself this polymorphism might have only minimal effects on the QTc duration in a general population. However, the presence of additional unrecognised ion-channel polymorphisms may have additive effects on the QTc duration such that individuals that carry several of these polymorphisms, might be at increased risk of sudden cardiac death[63]. Such polymorphisms are being investigated as modifier genes to explain the normal variation in the QTc interval that exists among healthy individuals[64].

Investigations into the genetic contributions to rhythm and conduction disorders have found genes or loci associated with primary rhythm and conduction disorders such as familial atrial fibrillation and atrio-ventricular block[65]. Some cardiac muscle problems such as cardiomyopathy, predispose to arrhythmia and have documented genetic components.

1.3.5 The clinical significance of a long QT interval

The lengthening of the QT interval on the ECG is a significant finding because it is associated with Torsade de Pointes (TdP), which is a dangerous polymorphic ventricular arrhythmia that can lead to sudden death.

About 70% of patients who develop TdP have a prolonged QT interval. In contrast, only a few patients with prolonged QT interval go on to develop TdP [66] [67]. Therefore

despite the association it cannot be claimed that a prolonged QT interval causes TdP or sudden death. This will be discussed further with respect to specific drugs.

For patients with TdP the most common QT interval or QTc is 600ms to 649ms. Other measures have been proposed to supplement QTc measurement and allow better prediction of risk of dysrhythmia such as QT dispersion which is the maximum difference in QTc values on a 12 lead ECG. This is considered to be a measure of heterogeneity and a predictor of dysrhythmia [68].

1.3.6 Cardiac cells

It is necessary to have an understanding of the properties and behaviour of cardiac cells before discussing the mechanisms by which drugs cause QT prolongation. Cardiac cells exhibit a charge capable of changing throughout the cardiac cycle. The mechanism that allows this dynamic process is the flow of positively charged ions (cations) in or out of the cell. During the resting state the cell is polarised. Its interior is negatively charged (-90mV) with respect to the exterior. The potassium ion (K+) is the dominant cation inside the cell. Its continuous outward movement through the cell membrane is what maintains the intracellular negativity. Like all living cells, the inside of the cardiac myocyte has a negative charge. This results in a voltage difference across the cell membrane called the transmembrane potential. Unlike most other cells, cardiac myocytes are excitable. When appropriately stimulated, channels in the cell membrane open, allowing ions to flow across the cell membrane. This results in the cardiac action potential. There are three main components to the action potential: depolarisation, repolarisation, and a resting phase[69].

During repolarisation, the cardiac membrane potential returns to normal. During this phase, the myocytes cannot contract (refractory period). The resting phase is the period between action potentials. During the resting phase most myocytes have no net movement of ions across the cell membrane. In some cells, however, the resting phase is associated with a gradual increase in transmembrane potential (phase 4 activity). When this potential is high enough, the appropriate channels open and spontaneous depolarisation begins. The property of cells to increase transmembrane potential during the resting phase is called *automaticity*. This is the mechanism whereby the normal cardiac impulse is generated. Cells in the sinus node usually have the fastest phase 4 and initiate the cardiac impulse. The phases of this process are summarised in fig 1.

Fig 1. Phases of the cardiac action potential

Phase 0 is depolarisation of the myocyte when sodium channels in the cell membrane open and positively charged sodium ions enter it, causing a rapid change in the transmembrane potential. This depolarisation spreads to adjacent cells and corresponds to ventricular depolarisation seen as the QRS complex on the ECG [70].

Phase 1 corresponds to a period of rapid initial repolarisation, which is brief. The sodium influx in the fast channels has ended and the recovery process is now in place by the opening of transient outward potassium channels with efflux of potassium ions.

Phase 2 is known as the plateau phase. There is reduction of the efflux of potassium ions and in addition Calcium ions (Ca^{++}) and Sodium ions (Na^{+}) are moving into the cell. The flow of outward currents through delayed potassium rectifier channels is almost equalled by inward flow of current through calcium slow channels. The return of the cell to its resting state is delayed. Calcium entry promotes contractibility.

Phase 3 marks the return of the cell to negativity, which occurs because of the continued loss of potassium from the cell at a faster rate, and the ending of the opposing inward currents carried by Na^{+} and Ca^{++}. There are at least three distinct delayed Potassium rectifier currents.

Phase 4 marks the return of the resting membrane potential of –90mV. Following Na, calcium will more slowly begin crossing the cell membrane (slow calcium channels). Repolarisation occurs as the cell recovers its intracellular negativity by the outward movement of K^{+} ions[71].

Many medications can cause acquired long QT syndrome including, antibiotics, antidepressants, antifungals, antihistamines, antimalarials, diuretics, heart

medications, lipid-lowering drugs, oral hypoglycaemics and psychotropic drugs. They increase the QT interval by a variety of mechanisms which are discussed below.

1.3.7 Antiarrhythmic drugs

The Cardiac Arrhythmia Suppression Trial (CAST) showed that treatment with class 1c antiarrhythmic agents to suppress post myocardial infarction ventricular arrhythmias paradoxically increased mortality from sudden cardiac death[72]. This trial was designed to test the hypothesis that suppression of ventricular premature complexes (VPDs) in survivors of acute myocardial infarction would reduce arrhythmic death risk. Instead, a preliminary finding from CAST was that the encainide and flecainide groups had a 3.6 fold increase in arrhythmic death compared with their placebo group. These unfortunate results were especially surprising in that the CAST population represented patients in whom the risk of arrhythmic death was thought to be low. Subsequent studies came to similar conclusions for 1a, 1b, and pure class 3 antiarrhythmic drugs.

Antiarrhythmic drugs bind to sites on cell walls and affect ion channel function by causing them to remain open or closed at any given time. These drugs can also promote arrhythmias and some of them can directly cause lengthening of the QT interval. The standard classification of antiarrhythmic drugs was developed by Singh and Vaughan Williams based upon the drug's electrophysiological mechanisms of action. Class 1 medications exert their effects by blocking the sodium channel [73] and are divided into 3 subgroups, 1a, 1b and 1c. Of particular interest to this thesis are the class 1A and class 3 drugs because they prolong repolarisation. Classes 1B, 1C and 2

do not prolong repolarisation. The actions of all four classes are summarised below (Table 1).

Table 1 Singh-Vaughan Williams Classification of anti-arrhythmic medication

Class	Action	Drugs
1	Sodium Channel Blockade	
1A	High potency as sodium channel blockers. Blockade also of potassium channels. Prolong repolarization, (lengthen QT interval)..	Quinidine, procainamide, disopyramide
1B	Lowest potency as as sodium channel blockers. Little, if any change, in action potential. Shorten repolarization (decrease QT) interval).	Lidocaine, mexiletine, tocainide, phenytoin
1C	Most potent sodium channel blockers. Little effect on repolarization (QT interval does not change).	Encainide, flecainide, propafenone, moricizine(?)
2	Beta-Adrenergic Blockade, slowing sinus rhythm, prolong PR interval. No effect on QT interval.	Propanolol, esmolol, acebutolol, *l*-sotalol
3	Block outward potassium conductance, prolonging the QT interval.	Amiodarone, bretylium, *d*,*l*-sotalol, ibutilide
4	Calcium Channel Blockade, slowing sinus rhythm, prolong PR interval.	Verapamil, diltiazem, bepridil
Miscel laneous	Miscellaneous Actions	Adenosine, digitalis, magnesium

1.3.8 Antiarrhythmic drug action

Class 1 drugs enhance the fast inward depolarising Na+ current albeit in a variety of ways. Class 1A depresses phase 0, slows conduction and prolongs repolarisation and thus can directly prolong the QT interval. Quinidine is the most widely used antiarrhythmic drug that can induce TdP[74].

The Class 3 drugs are potassium channel blockers. They can prolong the QT interval and initiate early after depolarisations and precipitate torsades de pointes. These drugs

traverse the lipid bilayer as neutral molecules and equilibrate in the cytosol as positively charged molecules. In the resting state, the activation gate of the K^+ channel remains closed. Upon depolarisation the activation gate opens and the drug enters the vestibule to block the channel. The channel then enters a long lasting closed state (inactivation), which increases the affinity of drug binding. Upon depolarisation, the activation gate closes (deactivation) and traps the drug within the channel vestibule. On subsequent depolarisations the channel is not available to conduct K+ because the drug remains bound [75] [76] [77]. Potassium currents may be voltage gated or ligand activated. Of particular importance are the delayed rectifier (rapid) I_{kr} and the delayed rectifier (slow) I_{ks}. Disruption to these channels can cause long QT syndrome. Class 3 agents include amiodarone, sotalol and dofetilide. Amiodarone is much less likely to cause torsades de pointes than other drugs with a similar QT prolonging effect such as sotalol, procainamide and disopyramide [78] [79]. It is interesting to note that Amiodarone decreases QTc dispersion. Many class 1A drugs (primarily Na^+ channel blockers) also show significant K^+ channel blocking behaviour.

1.3.9 Non-antiarrhythmic drug action

1.3.9.1 Anti-psychotic medication

It is not just antiarrhythmics that can directly cause QT lengthening. It is now apparent that most conventional and atypical antipsychotics can cause dose-related prolongation of the corrected QT interval (QTc), although there are important differences in the potency of individual agents[80]. Antipsychotic drugs, particularly thioridazine of the phenothiazine family, primarily block the rapid component of the delayed rectifier K^+ channel (I_{kr}) causing lengthening of the myocyte action potential, QTc interval prolongation, early after depolarisations (EADs) and TdPs [81]. Important

QT prolongation has been observed in people taking thioridazine or droperidol [82]. Thioridazine has now been withdrawn from the market as have sertindole and droperidol [83]. Chlorpromazine has been associated with a variety of ECG changes including QT prolongation[84] and sudden death[85] [86]. Other non-phenothiazine antipsychotics may also cause cardiac abnormalities including QTc prolongation. Pimozide moderately prolongs QTc even at low daily doses and has been linked to several sudden deaths both in clinical use[87] and in overdose[88]. Haloperidol has been associated with prolonged QTc and TdP at higher clinical doses and in overdose and has been associated with sudden death[89]. Antipsychotics share little more than their overall therapeutic effects: they differ importantly in pharmacology and widely in chemical structure. Because of this, it is unlikely that all antipsychotics have the same effects on myocardial ion channels or on QT interval, or have similar pro-dysarrhythmic potential. New electrophysiological and epidemiological data suggest there may not be a clear-cut cause–effect relationship between QTc prolongation and the development of ventricular tachyarrhythmias for all atypical antipsychotics. For at least one of these agents (sertindole), counterbalancing mechanisms may act to reduce the risk of proarrhythmic activity arising as a result of QTc prolongation.

The mechanisms by which different antipsychotics affect cardiac conduction are complex and probably numerous. They share the ability to antagonise the rapid component of the delayed rectifier I_{kr} current[90] . I_{kr} is encoded by the human ether-a-go-go related gene (HERG) and experiments using HERG-transfected or cloned cells suggest a direct antagonistic effect for drugs such as haloperidol[91], sertindole [92], thioridazine and chlorpromazine[93], amongst others[94] [95]. Some antipsychotics may

also interfere with cardiac calcium and sodium channels. How these different effects contribute to QT changes and the risk of TdP or sudden cardiac death remains unclear.

1.3.9.2 Antidepressants

Tricyclic antidepressants (TCAs) act primarily on sodium influx during phase 0 (sodium fast channel). In overdose, TCAs may induce widening of the QRS complex[96]. TCAs may secondarily affect calcium influx (calcium slow channel) and potassium efflux during phase 3 – thereby lengthening the QT interval. Thus, TCAs may cause QT interval prolongation both by widening the QRS complex and by delaying repolarisation. The secondary effects of TCAs and the primary effects of thioridazine-like drugs may act together to lengthen the QT interval and stimulate TdP. Because the time taken for repolarisation is the major component of the QT interval, drugs impacting on it are more likely to significantly increase the QT interval than are drugs widening the QRS complex alone.

1.3.9.3 Cisapride

Cisapride is an oral prokinetic drug which is known to prolong the QT interval and cause TdP[97]. It is thought to be responsible for several cases of sudden death. It is likely that it does this in the same direct way as the class 1A antiarrhythmic procainamide to which it is structurally very similar. Cisapride also stimulates serotonin-4 receptors which can result in cardiac chronotropic activity and it has been postulated that this may be responsible for QT prolongation[98]. Cisapride was removed from general distribution in July 2000[99].

1.3.9.4 Other drugs

Other non-antiarrhythmic potassium channel blocking drugs that can directly prolong the QT interval include terfenadine[100], erythromycin [101] [102], and cocaine [103] [104]. The adverse effects of terfenadine appeared to depend on concentration, occurring at supraclinical doses or at normal doses in patients also taking drugs that inhibit cytochrome P-450 drug metabolism-such as imidazole antifungals and some macrolide antibiotics[105].

Some antibiotics (such as macrolides and fluoroquinolones), antimalarials and imidazole antifungal agents can cause QT prolongation and torsades de pointes [106] [107] [108] [109]. Torsades de pointes is rare and does not occur with all antimicrobials that prolong the QT interval. Intravenous erythromycin prolongs the QT interval, causes dispersion of recovery across the ventricular wall, and occasionally induces torsades de pointes. Quinine prolongs the QT interval at standard doses, as does halofantrine particularly when it is combined with mefloquine. Ketoconazole prolongs the QT interval by directly blocking I_{kr} and by delaying the cytochrome P-450 dependent mechanism of other drugs that prolong the QT interval.

I have described that I_{kr} blockade is an important mechanism for acquired long QT syndrome. It is worth emphasising that it occurs with a variety of unrelated drugs, including class 3 antiarrhythmics, quinidine, cisapride, terfenadine, astemizole, bepredil, sulphamethoxiazole, erythromycin and ketoconazole.

1.3.10 Indirect mechanisms of QT prolongation

There are many ways by which a drug can indirectly cause lengthening of the QT interval.

The overuse of diuretics can result in the loss of ions. A reduction of extra-cellular K^+ concentration can cause the resting membrane potential of cardiac cells to become closer to the threshold level that a cell must reach in order to complete depolarisation. Thus cardiac cells are more likely to respond to an approaching wave front of activation. When this happens cells are said to become more excitable. Such cells are more likely to fire off spontaneously causing early after depolarisations (EADs) causing arrhythmia. Hypocalcaemia is also associated with a prolonged QT interval. The loss of magnesium ions (Mg^{++}) can reduce the efficiency of the repolarisation process because it is a component (with Adenosine Triphosphate ATP) in the active process of pumping sodium ions out and potassium into the cell that occurs in action potential phase 4.

Drug interactions play a major role in causing QT prolongation and may also increase the risk of TdP. Drugs may interact by the following mechanisms 1) One drug may decrease the clearance of another drug that prolongs the QT interval resulting in an increase in its plasma concentration 2) Two drugs may cause QT prolongation independently with an additive effect, or 3) a drug may both decrease the clearance of the drug that prolongs the QT interval and prolong the QT interval itself.

Several drugs that can directly cause QT prolongation are metabolised by the cytochrome p450 (CYP) enzyme which consists of several isoenzymes . One of these

isoenzymes is CYP 3A. Thus medications that inhibit CYP 3A can indirectly cause a prolonged QT interval by elevating active drug levels. Torsades de pointes, a life-threatening ventricular arrhythmia associated with QT prolongation, can occur when these CYP3A inhibitors are coadministered with drugs that can directly lengthen the QT interval and are metabolised by CYP3A such as terfenadine, astemizole, cisapride or pimozide [110]. It has also been reported that grapefruit juice is a clinically important inhibitor of CYP3A. Drug interactions that lead to increased concentrations of cisapride can cause QT interval prolongation and ventricular arrhythmia[111].

Drugs that inhibit the CYP 3A system include the anti-arrhythmic, amiodarone macrolide antibiotics, (clarithromycin and erythromycin) antidepressants, (fluoxetine, setraline and fluvoxamine), antifungals, (fluconazole, ketoconazole and itraconazole) and others such as diltiazem.

About 5% – 10% of Europeans are poor metabolisers (pharmokinetic factor) [112]. The CYP isoenzyme 2D6 is most commonly involved. The Pfizer 054 study assessed the potential for metabolic inhibitors such as paroxetine to induce QTc interval prolongation by increasing antipsychotic drug levels. The metabolic pathways inhibited in the Pfizer 054 study were 2D6 (paroxetine) for thioridazine, risperidone, and haloperidol; 3A4 (ketoconazole) for ziprasidone, quetiapine, and haloperidol; and 1A2 (fluvoxamine) for olanzapine. Aripoprazole is metabolised by both 2D6 and 3A4 pathways[113].

Erythromycin can interact with many other drugs, usually by interfering with their hepatic metabolism through the cytochrome p450 enzyme system as indicated above. Particularly important is its concomitant use with astemizole and terfenadine which

has been associated with long QT, TdP and sudden death[114]. In addition there is some evidence that erythromycin may itself cause action potential prolongation by altering sodium channel function, like the class 1A antiarrhythmics[115].

1.3.11 Additional factors contributing to QT interval prolongation

There are non-drug factors that contribute to QT interval prolongation. The QTc interval varies throughout the 24 hour cycle, with night time values about 20 ms longer than daytime measurements. Changes in sympathetic and parasympathetic (autonomic) tone determine these differences[116] [117]. At birth, QTc interval measurements are the same for male and female infants[118]. Before puberty, the QT intervals and the patterns of ventricular repolarization in boys and girls are similar. At puberty, in boys the QT interval shortens, and a typical male pattern of ventricular repolarization develops[119]. At puberty the male QTc interval shortens by about 20 ms. This androgen driven difference remains until ages 50 to 55 years when, coincident with a decline in male testosterone levels, sex differences in QTc measurements narrow. We would expect 45% of cases of TdP to occur in women based on the usual cardiovascular risk factors; however, about 70% of cases are found in women. Elderly men and women tend to have longer QT interval measurements than their younger counterparts even when free of cardiovascular disease[120]. The QT prolonging effects of hypokalaemia, hypomagnesaemia and hypocalcaemia caused by overuse of diuretics have been discussed. Other factors can bring about these conditions including excessive vomiting and diarrhoea. Postprandial states, intensive exercise and agitation, Anorexia nervosa and anti-obesity surgery can also lower K^+ levels. Liver disease can lead to inhibition of the cytochrome P450 system resulting in

reduced metabolism and thus increased concentration of QT interval prolonging drugs.

1.3.12 QT prolonging drugs Conclusion

Many drugs have been associated with QT prolongation and some have been linked to TdP and sudden death. It may not be clear for some medications if there is a direct relationship between the extent of drug-induced QT prolongation and the risk of dysrhythmia or death, although this is often assumed on firm theoretical and observational grounds. Drug induced QT prolongation is a common observation and the outcome can be death thus, the development of new drugs should include procedures to detect this side effect.

In clinical practice, the adverse effects of QT prolonging drugs can be prevented by not exceeding the recommended dose; by restricting the dose in patients with pre-existing heart disease or other risk factors; and by avoiding concomitant administration of drugs that inhibit drug metabolism or excretion, prolong the QT interval or produce hypokalaemia. The potassium concentration should be checked regularly and potassium sparing diuretics should be preferred[121].

1.4 Death Certification in the United Kingdom

1.4.1 The importance of Death certification

Death certification is important because it is the most practical reflection of the level of health in populations. It provides the basis for testable hypotheses concerning the determinants of variation of the causes of death. These determinants are used to define health problems, to identify the emerging problems of public health and to monitor

the efficacy of health programs. Thus, death certification has a crucial role to play in strategic health planning. In the United Kingdom, there is a legal requirement to record deaths. Thus, the advantage of mortality statistics over other statistics relating to health is that they are more generally available. Critically, their validity depends on their completeness and accuracy[122].

1.4.2 The certification and registration of death

When a death occurs the registered medical practitioner concerned is required by law to issue a medical certificate of the cause of death. The certificate must state the date that the deceased was last seen alive, whether the body was seen after death, the length of time between onset of disease and death and if the certified cause of death is based on post-mortem evidence. This certificate is given to the "qualified informant" who is most usually a close relative of the deceased. This person must attend the Registrar's office to give, orally, details of place and date of death, name, sex, date and place of birth of the deceased, and the deceased person's occupation and place of residence. If no qualified informant is available the medical practitioner must send the certificate by post to the local Registrar of Deaths. Returns on deaths are sent weekly to the Office for National Statistics (ONS) for processing, where the "International Statistical Classification of Diseases and Related Conditions" is used to code the cause of death. A copy is sent to the Director of Public Health of the health district in which the dead person resided[123].

1.4.3 The role of the Coroner

There are more than half a million deaths each year in England and Wales, 70% of bodies are cremated and 30% are buried [124]. Of the half million deaths each year in England and Wales 45% are referred to the coroner[125]. The coroner must enquire into deaths associated with accidental, violent, unnatural and sudden causes.

1.4.4 History of death certification

The format of medical certificates has changed over time. The most radical change occurred in 1927 when a two part medical certificate was introduced: in the first part the doctor recorded the disease or condition leading directly to death and causes antecedent to it, while the second part was reserved for other significant conditions contributing to the death, but not related to the disease or condition causing it. From 1940 onwards the entry in the first part of the certificate was taken to be the underlying cause of death. Before then the underlying cause of death was selected by the General Register Office using a complicated set of rules, in which conditions of various types were given an arbitrary order of precedence, regardless of the order in which they were specified on the medical certificate[126].

Further changes to the methods of identifying the underlying cause of death occurred in 1984 when the Office of Population, Censuses and Surveys (OPCS) adopted a broader interpretation of that previously used, of a World Health Organisation (WHO) coding rule that when the cause of death in the first part of the death certificate was a direct sequel condition mentioned in the second part, the latter condition should be preferred as the cause of death. This resulted in an artificial decrease in the numbers of deaths from certain causes (e.g. bronchopneumonia) and corresponding increases in

other causes (e.g. chronic conditions such as diseases of the nervous system and mental disorders). The anomaly was reversed in 1993, when an overhaul of OPCS's computer systems led to the introduction of an automated system for coding, developed by the US National centre for health statistics, which followed the internationally agreed interpretation of the WHO's rules for selecting the underlying cause of death [126].

Old age has been permitted as a cause of death since 1985 for people over 70 years. It was introduced because causes of death for the very elderly in terminal decline were being used and it was found that it was common practice to put bronchopneumonia as cause of death which had the effect of over-estimating the true effect of bronchopneumonia on mortality.

The method that is chosen to arrive at the underlying cause of death is influential in deciding the eventual outcome. Changes in the method of certifying deaths have changed over time and remain subject to change so that historic mortality data files are not strictly comparable.

1.4.5 Arriving at the underlying cause of death

The certification of the cause of death falls into two sections. Part 1 is in three subsections and asks for the direct cause of death. Part 2 asks for the significant condition contributing to death, if any.

The underlying cause of death is the condition that triggered the chain of events that led to the patient’s death, without which death would not have occurred.

It is important to know that the underlying cause of death must be written in the lowest completed line of part 1 of the certificate. Coders at the ONS make the assumption that the certifier has followed this practice; in which case the “general rule” in coding the cause of death applies. In guidelines issued by the World Health Organisation, this general rule must be overridden in certain circumstances, most commonly when the completion of Part 1 of the certificate does not follow a proper clinical sequence of events. Under these circumstances, coders follow other rules that allow them to select the underlying cause of death.

In many cases it is not appropriate to complete all 3 lines in part 1 because an immediate or antecedent cause of death may not be identifiable in all cases. An underlying cause of death can stand alone as the only completed line in part 1.

Diseases are coded according to the International Classification of Diseases (ICD). Every disease has a code number. The coding system is in operation throughout the world and allows a translation of different medical terms. This standardisation allows a comparison between different health authorities and countries. About every 10 years there is a revision.

These issues concerning the certification of the cause of death and its coding are important because they determine ultimately the content of population level mortality data.

1.4.6 Assessing data quality

Mortality notification has the advantage that it refers to a clearly identifiable event and is legally required. However some data may be unreliable because human witnesses differ in their reliability. If the qualified informant is only distantly involved in the life of the deceased then the information given by them may lack accuracy. Doctors also differ in their reliability. The medical reason given for death is subject to uncertainty, being based largely on clinical opinion in many cases.

Various methods have been used to evaluate the quality of the cause of death statistics[127]. Traditionally, post-mortem findings were deemed as the gold standard to evaluate the accuracy of cause of death certification. However, because of the biased selection of cases and the decreasing number of post-mortems, fewer and fewer evaluation studies have used post-mortem findings as the standard[128]. The consensus of a panel of physicians has also been used as a method to evaluate the quality of death certification[129]. Most of the studies using this method were large cohort studies or randomised clinical trials and wanted to assure that the end point was not biased. Physician review as the standard has the disadvantage of being time consuming and costly[130 131].

1.4.7 Common errors

British Home Office guidelines state …

"The most frequently occurring errors in the completion of certificates are: -

(a) Failure to complete all questions in full

(b) Incorrect completion of forms

(c) Illegible handwriting; and

(d) Discrepancies between forms as to the date and time of death"[132].

Physicians sometimes make the mistake of putting the mode of death on death certificates, possibly because medicine is often aimed at treating this. The mode of death should not appear on death certificates because of the lack of aetiological specificity[133]. Modes of death are physiological derangements or biochemical disturbances produced by causes of death. Examples include various arrhythmias,, cardiopulmonary failure, sepsis, and hypovolaemic shock. The cause of death, on the other hand, is aetiologically specific. Examples include diabetes mellitus, cerebrovascular infarction, lung cancer, and alcoholic liver cirrhosis.

Other common errors include putting the causes of death in the wrong order and entering two or more diagnoses in the same line in the death certificate [134] [135] [136].

The certifying physician may include erroneous information on certificates in an effort to conceal diagnoses that might cause distress to family members[137] [138]. Maudsley and Williams found that 18.5% of family physicians surveyed would consider modifying a death certificate for this reason. The percentage of death certificates affected in this way is not known.

1.4.8 Quantification of error

The Shipman enquiry third report of 14 July 2003 cited a study that showed only 55% of death certificates were of an acceptable standard[139]. In 1993 Jordan and Bass [140] reported that 31.9% of a sample of death certificates completed at a Canadian tertiary

care teaching hospital contained errors. The highest percentage of inaccurate completion occurred in the Department of Medicine, with 40.3% of certificates classified as unacceptable because of major errors. Other studies have shown that 16% to 33% of sampled death certificates contain major errors in the Cause of Death statement[141] [142]. The rate of major discrepancies in autopsy series has been found to be as high as 30%[143]. A study designed to assess the efficacy of an educational program identified major errors in 32.9% of 146 certificates prior to the intervention. Significant improvement followed after the intervention with major errors decreasing to 15.7% of 83 certificates[144]. A less successful educational program that did not show a significant improvement had a pre-intervention major error percentage of 22.4% and a post intervention major percentage of 15.1%[145].

The final step in the certifying process is coding by a trained person, known as a nosologist. It is thought to be objective and accurate[146].

1.4.9 Error in sudden death in epilepsy (sudep)

The United Kingdom National Sentinel Clinical Audit of Epilepsy-related Death [147] reviewed the records of individuals who died from an epilepsy related death, in the United Kingdom, between September 1999 and August 2000. During that time 2412 deaths were reported where epilepsy was mentioned somewhere on the death certificate.

They found that certification of death (with or without post-mortem) was inconsistent and, in some cases inappropriate. Of deaths certified without post-mortem as due to epilepsy, 38% were sudden and/or not witnessed and should have been subject to

post-mortem. They reported that 87% of 439 deaths involving a post-mortem were inadequately investigated. The main problems were with further investigations and certification. Not all pathologists requested further investigations and the procedures tend to be non-standardised. These investigations are important to eliminate other causes of death.

The audit concluded that death certification was inadequate in 41% of deaths involving a post-mortem. The reasons included:

- Phrasing of the cause of death. This was very variable. Although the term SUDEP has been in use since 1997, it was cited on the death certificate in just 10% of audited cases.

- A cause was often cited (e.g. asphyxia, aspiration of stomach contents, status epilepticus) despite a lack of pathological evidence.

- In some cases, every medical condition the person had was listed on the death certificate, even if this had not contributed to the death.

- In general, problems with certification highlighted the difficulty of establishing the true number of epilepsy-related deaths from certification data.

1.4.10 Conclusion to death certification section

Many commentators are of the opinion that death certification should be standardised. The Shipman Inquiry recommended that “the separate system of certification prior to

cremation should be abolished"[148]. Death certification needs reform as does the coronial system.

1.5 Accuracy of Post-Mortem reporting

Post-Mortem examination is considered to be the gold standard for the critique of medical practice, providing a quality control tool for the retrospective evaluation of diagnoses and treatment. The post-mortem facilitates new insights into the pathogenesis of disease and effects of therapy, gives feedback to clinical research protocols, provides epidemiological information and occasionally consoles grieving families that death was inevitable[149].

A large amount of evidence has been gathered to directly evaluate the accuracy of death certification using the post mortem report as the reference standard. It is not so easy to assess the accuracy of the post mortem report because there is no other gold standard. There are some highly objective tests such as medical imaging that can be usefully employed as well as comparison studies that assess inter-rater reliability between pathologists.

1.5.1 Post-mortem rates

The post-mortem rate has been declining for decades[150] causing a reduction in determining the accuracy of clinical diagnosis. There is a tendency for the discrepancy rate between clinical diagnosis and post mortem to increase with age, probably because of the greater difficulty in making correct clinical diagnoses due to lack of clear symptoms and the presence of multiple pathologies[151].

To address concerns about declining autopsy rates in a large academic medical centre in America, a quality improvement service was set up that sought to increase the visibility of the service and improve reporting and increase the amount and quality of the data[152]. This resulted in an increase in the autopsy rate and an improvement in clinician perception of the service.

1.5.2 The importance of the post-mortem report

Many studies highlight the importance of the post mortem report.

A one year prospective study of 568 deaths in England and Wales that had the aim of determining whether the cause of death could be accurately predicted without the need for a post mortem examination, recommended that it could not and thus that the present system be continued [153]. Some natural diseases were frequently misdiagnosed, although ischaemic heart disease was found to be the most common and most accurately predicted cause of death. Before post mortem, pathologists predicted a cause of death in 61% to 74% of cases depending on the body being viewed in the mortuary or evaluated as a paper exercise. After post mortem it was found that the cause of death was only predicted correctly in 39% and 46% of cases. This study highlights the inaccuracies inherent in stating a cause of death without post-mortem.

Post mortem reports sometimes identify causes of death not predicted from medical history, as illustrated in the following two studies. An investigation of 63 deaths occurring in a hospital after cardiac surgery concluded that the post mortem examination identified an undiagnosed cause of death in a significant minority of patients 8 (12.7%). In another study, it was revealed that post-mortem examination of 110 patients who died following thoracic surgery showed an unsuspected cause of

death in 34 (31%)[154]. The authors stated that post-mortem remained the gold standard method for attributing cause of death.

Post mortem reporting can identify drifting of medical diagnoses as shown by a comparison of ante mortem (in vivo) and post mortem diagnoses of coronary heart disease at a university hospital for 1965, 1975 and 1985[155]. The post mortems showed that there was a gradually rising trend in both true positive and false negative ante mortem diagnoses. The implications were that there would be a progressive lowering of the counted numbers of coronary heart disease in official figures. The authors stated that "improvements in clinical accuracy are needed before vital statistics data are accepted at face value and analysed for biological explanation".

Suspected causes of death and main clinical diagnoses were determined and compared with findings at post-mortem examination in 97 patients who died in the Gloucestershire Royal Hospital intensive care unit[156]. Complete agreement was found in 74 (76.3%). Discrepancies fell into 4 main groups; unrecognised haemorrhage 7, myocardial infarction 5, thromboembolic disease 5 and infectious complications 4. Important diagnostic discrepancies were found in 19.6% of patients who had a post mortem. The authors conclude that "despite technological advances in intensive care medicine the post mortem examination continues to have an important role in auditing clinical practice and diagnostic performance".

1.5.3 Limitations and inaccuracies of the post-mortem report

Post mortem reports sometimes contain errors. One high profile example concerns work of the pathologist who concluded that a victim of Dr Harold Shipman had died

of natural causes despite hospital doctors recording in the medical records that Dr Shipman had given his patient an injection of 20 mg of morphine when she had a severe asthma attack at her home. Morphine causes respiratory depression and would have exacerbated the asthma. Home office pathologist Dr Kenneth Scott told the General medical council that the pathologist had made key mistakes in his post mortem report[157].

Limitations of the post mortem examination have been identified in several studies. The Hammersmith hospital, London reviewed death certificates following post mortem of 123 patients who had cardiac valve prosthesis found that prostheses were recorded in only 43 (35%) of them [158]. The authors point out that these errors may lead to inaccurate reporting of the number of valves that fail.

Post-mortem reports from 1994-1996 and 1998-2000 in Ireland that were available for 245 sudden infant deaths found that the reporting quality was below the minimum accepted standard in 55.5% of cases [159]. The quality of autopsy was at its best when performed in regional centres. The finding of additional pathological information was significantly related to the extent of the post mortem.

Studies have shown that myocardial infarction has been recorded as the cause of death even when no active coronary lesion is present[160]. In this thesis this would have the effect of reducing the number of sudden deaths available to us because we exclude myocardial infarction deaths. Studies have shown that tests can be useful to detect sudden death from coronary thrombosis[161 162].

Additional tests can be helpful in detecting other conditions such as infection and anaphylaxis[163].

1.5.4 Comparison of medical imaging with conventional autopsy

Imaging techniques have a significant role in autopsy practice. They can identify many causes of death such as traumatic brain injury or disseminated cancer. They can locate a projectile within the body and show its path through soft tissue. They can answer specific questions, such as, whether there is a cardiac air embolus in a person who has suffered neck trauma[164]. Modern imaging methods such as photogrammetry, optical surface and radiological CT/MRI scanning in combination have produced full 3-dimensional representations of internal body structures. In 2005 for the first time this technology was used to document forensic relevant injuries of the human body in combination with vehicle damages[165]. Other examples include post mortem angiographic method used in detecting coronary artery bypass graft (CABG)[166], multi-slice computed tomography (MSCT) and magnetic resonance imaging (MRI) for head and neck structures [167] and the human arterial system including intracranial and coronary arteries enabling identification of vascular pathologies such as calcification, stenosis and injury[168]. Medical imaging findings in hanging and manual strangulation compared with autopsy concluded that MSCT and MRI revealed strangulation signs concordantly with forensic pathology findings[169].

However medical imaging has limitations. A study that assessed the accuracy of post mortem MRI found that it was not able to accurately image coronary artery lesions or to differentiate thrombus from clot and pulmonary oedema from pneumonic exudates[170]. When stenosis of the coronary arteries is identified with imaging there is

still doubt that it is the cause of death[171]. Supplementing the image with a clinical history and an external examination of the body may still not remove the need for an autopsy[172].

Thus, although imaging can identify some abnormalities relevant to sudden death further studies are needed to correlate MRI with post mortem findings before MRI alone can make a reliable cause of death.

1.5.5 Conclusion to accuracy of post-mortem reporting

There is no reference standard to judge the post mortem because the post mortem is the reference standard. However the post mortem report is subject to inaccuracies, some due to poor individual practice and others systemic.

Imaging technology is useful in enhancing the post mortem report and picking out some of its flaws. For some conditions imaging technology can be better than the dissection of the body.

Accurate post mortem reporting is essential to maintain and improve clinical practice and it has been shown that the accuracy of post mortem reporting improves when frequency increases.

1.6 Summary of Chapter 1

Sudden death is an important cause of mortality. Chapter one of this thesis has demonstrated that there are case reports and pharmacological evidence to show that drugs that can prolong ventricular repolarisation or cause torsades de pointes can

contribute to the mortality from sudden death. I have described the important clinical factors that make people more likely to suffer this type of death. In addition I have explored evidence whether deaths identified as sudden cardiac by post mortem report have been accurately classified.

We know how many sudden deaths occur each year but we do not know how many of them are caused by medications that affect cardiac conduction, therefore we do not know how many cases of sudden death could be prevented by more judicious prescribing. This thesis has the aim of identifying drugs associated with sudden death. This study could inform further research on this topic by identifying medications and combinations of medications that are strongly associated with sudden death.

In chapter two I will state the aims and of the study and in chapter three I will give a detailed description of the methods that I used to try to achieve those aims.

2 AIMS

2.1 The aim of the study

The aim of the study was to investigate the hypothesis that the use of drugs that can cause prolongation of the QT interval on the electrocardiograph are associated with an increased risk of sudden death from probable cardiac arrhythmia.

2.2 Objectives

1. To determine the extent of individual risk of sudden death in association with treatment by drugs which tend to prolong the electrocardiograph QT interval as specified in the International Registry for Drug-induced Arrythmias maintained by the University of Arizona, Tucson, Arizona, United States of America[173].

2. To examine possible differences in risk of sudden death between major registry drug classes.

3. To assess possible differences in risk between individuals with and without established coronary heart disease.

3 METHODS

3.1 Demographics of study areas

The study was performed in the Birmingham, Solihull, Nottingham and Coventry Primary Care Trust areas. According to the 2001 census, cases were drawn from a combined population of 1,744,440 people out of which 977, 087 (56%) reside in Birmingham, 300,848 (17.2%) in Coventry, 266,988 (15.3%) in Nottingham and 199,517 (11.4%) in Solihull. Details of the age and background of people resident in those areas at the time of the census are summarised in the fig 2 below.

Fig 2. Age and ethnic characteristics of study areas.

Solihull has the greatest proportion of people 75 years and older 15,271 (7.7%), followed by Coventry 22,341 (7.4%), Birmingham 68,079 (7.0%) and Nottingham (18,333 (6.9%).

White people are the predominant racial group in all populations accounting for 77.7% of the total. We did not categorise cases or controls according to race. We can describe the racial mix of the areas from which cases were obtained.

Birmingham has a white population of 687,406 (70.35%). The largest minority ethnic group in Birmingham is Pakistani (10.65%) followed by Indian (5.71%) and Black Caribbean (4.9%).

Coventry has a white population of (83.98%). The largest minority group in Coventry is Indian (8.04%) followed by Pakistani (2.05%) and Black Caribbean, 3,314 (1.1%).

Nottingham has a white population of (84.91%). The largest ethnic minority group is Pakistani (3.64%) followed by Black Caribbean (3.44%) and Indian (2.28%).

Solihull is 94.6% white with the largest ethnic minority group Indian (1.82%).

3.2 Design of the study

The design was a community based matched case-control study. The case-control study is a type of analytical study because the differences between cases and controls

can be regarded as potentially causal. Matching eliminates factors already known to be associated with the outcome. Thus it has an advantage over ecological and prevalence studies for which no causal link can be concluded.

The case control design was chosen because sudden death is a rare event with an incidence of approximately 1 per thousand cases in the population of developed nations, because it is informative, quicker and less expensive than the alternative prospective design and because there were no United Kingdom based databases available that combined drug data with post mortem reports and mortality data to use in a cohort design.

3.3 Case definition

Cases were defined as individuals aged 20 to 84 years who had died suddenly in the community and who had a post mortem report in which the cause of death was consistent with a cardiac arrhythmia.

3.4 Case selection

Mortality files for all individuals who had died from the start of the study in August 2003 and for whom a post-mortem examination was undertaken on behalf of the coroner's office were obtained on a monthly or quarterly basis from 1st September 2003 to 1st October 2006 from the Primary Care Trusts for Birmingham, Solihull, Coventry and Nottingham. The mortality files stated which individuals died in the community and which did not. I discarded all individuals that did not die in the community and then assessed the remaining records to identify suitable cases. A key

aspect of this thesis was the steps that were taken to select cases because they enabled the identification of arrhythmic deaths with a high degree of probability.

Individuals were excluded if their deaths occurred when they were less than 20 years of age or over 85 years.

This community based study had at the outset the intention to exclude all hospital deaths The mortality files record the place were people die and if the death of an individual was recorded as occurring in hospital then they were excluded. This exclusion criterion was applied to ensure that the study was community based. People who were dead on arrival at hospital were excluded because their deaths were recorded as hospital deaths. Thus the mortality files may have underestimated the number of community based deaths by recording some of them as hospital deaths.

Cases were chosen according to the principle that their cause of death may have been due to a cardiac arrhythmia. Cardiac arrhythmia does not leave defining evidence in the body so in order to identify these people a clear set of criteria was used to rule out other causes of death. These criteria were applied to the mortality files, which record the 1a, 1b, 1c and 2 causes of death. Individuals who had a known non-cardiovascular cause of death such as road traffic accident, suicide, pneumonia or stroke were excluded. Also excluded were cardiac causes of death, which may have been due to a mechanism other than death from cardiac arrhythmia in the absence of acute coronary artery thrombosis. Hence we excluded deaths from acute coronary artery thrombosis, myocardial infarction, haemopericardium, left ventricular aneurysm and heart failure. This is a narrower definition than that normally applied to SCD and thus could be

called SCD of probable arrhythmic cause. The original proposal was to include deaths from MI and analyse these as a separate group, but the funders did not agree to fund this element. Thus, patients with an MI were excluded even though MIs are known to cause arrhythmias.

3.5 Exclusions from post-mortem reports

The application of the above criteria left a set of provisional cases.

Post mortem reports for provisional cases were obtained either from patient written records at the shared service agencies for the primary care trusts or on request from the Coroners' offices. The additional information provided by the post mortem report would result in the exclusion of a provisional case if it were judged that there was evidence for a cause of death not compatible with that due to a cardiac arrhythmia.

3.6 Definition of cardiovascular disease in this thesis

Cases were categorised into one of two types, cardiovascular and non-cardiovascular and matched to controls categorised in the same way. This decision was taken because people with cardiovascular disease have an increased risk of sudden death and if not taken, the study would have classified as cases a much greater proportion of people (compared with controls) that had a history of cardiovascular disease. This would not be informative because it is already established that individuals with cardiovascular disease are at much greater risk of sudden death. There would also be a danger of confounding because some of the drugs that can prolong the QT interval are likely to be associated with both sudden death and cardiovascular disease. Thus matching for previously identified cardiovascular disease was an attempt to eliminate confounding factors in the design stage.

3.7 Criteria for being classified as having cardiovascular disease

Cases and controls were categorised as having cardiovascular disease if they were taking medication for a cardiovascular condition or if any of the following criteria obtained from the medical notes applied:

-any previous myocardial infarction;

-any previous coronary revascularisation (PTCA/CABG);

-a diagnosis of angina with medical treatment;

-cardiac valve disease;

-heart failure on drug treatment;

-hypertension on drug treatment;

-cardiomyopathy;

-dysrhythmic treatment.

If any one of the above conditions held, then that would be enough to justify a classification of cardiovascular disease. Any individual could meet one, several or all of the cardiovascular conditions. People were not graded according to severity of cardiovascular disease. Hypertension was included because it is classified as a cardiovascular disease albeit much milder than others such as myocardial infarction. Diabetes and dyslipidaemia were not included because these conditions are not classified as CVD, although because of the strong association between Diabetes Mellitus and CVD many patients are managed similarly.

3.8 Criteria for not having cardiovascular disease

Cases were classified as not having cardiovascular disease simply if they did not meet the criteria above. Thus they were not taking cardiovascular drugs and had no history of cardiovascular disease.

3.9 Process of obtaining controls

Each case was matched to three controls at the general practice at which the case was registered. This was an efficient way of obtaining controls.

Suitable controls were obtained by running a database search on the computerised medical notes. This process was straightforward and efficient. In order to exclude control patients that had moved away, people who had failed to consult their general practitioner within the previous 2 years were not included in the study. This step was essential to remove the bias of erroneously recording controls having fewer medications (none for people that have moved away) than cases.

Cases and controls were matched for sex, age to within 5 years and cardiovascular disease. Researchers used the surgery medical records database to select the controls on the basis that they were the closest in age to the case, providing the other matching criteria were satisfied. At large general practices it was possible to match controls very closely for age, often to within a few days. At small single handed practices the difference would be weeks, months and occasionally years.

The process of manually selecting controls as in this thesis can introduce bias. The requirement to select the 3-controls nearest in age to the case (whilst matching for

CVD and gender) removed the possibility of selection bias. However, when matching for the broad definition of cardiovascular disease I was more likely to obtain the more prevalent hypertension rather than the rarer, more severe, less prevalent cardiovascular diseases such as MI.

3.10 Sources of medical information for cases and controls

Medical information was collected for cases and controls from two sources, the general practice computerized database and the written medical notes.

The medical notes for the cases were usually seen at the shared service agency where they had been sent following the death of the person and less frequently at the general practice if they had not yet been sent away.

It was not always possible to have access to the written medical notes of some cases, whilst the computerized medical notes were available for every case and control and were always viewed.

3.11 Strategy for viewing medical notes

Researchers proceeded on the basis that if written notes were viewed for cases then they must be viewed for every control for that case. If it was not possible to view written notes for a case then the written notes for a control were not viewed even though they were available. This policy avoided information bias.

It was not always possible to view written notes on cases because the PCTs were not always able to provide them.

3.12 Information obtained at GP surgeries

The date of birth and sex of all cases and controls was recorded, as was the date of death of each case. The names of all drug prescriptions including dosage, frequency and route of administration in the periods 0-7, 8-30 and 31-90 days prior to the death of each case were recorded. Information for the controls was also obtained for these periods up to the date of death of their case. Information for the controls after the date of death of their case was not collected because such information could not occur for the cases because of their death.

People who are ill are more likely to visit their doctor. Thus the dates and type of all general practice and hospital consultations in the 90 days prior to the death of the case were recorded to obtain a measure of morbidity.

Information was obtained on the presence of cardiac conditions that are known to contribute to an increased risk for sudden death. This is detailed in fig 3.

Fig 3. Cardiovascular conditions

(1) Has the patient ever had a myocardial infarction and if so the date of the last one.

(2) Treated angina in the last 3 years.

(3) Ever had a coronary artery revascularization operation. Coronary artery bypass graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA)

(4) Heart failure in the past year.

(5) Treated hypertension within the past 3 years.

(6) Sinus bradycardia in the past year.

(7) Heart block in the past year.

(8) Atrial fibrillation in the past year.

Additional information that could contribute to sudden death was also recorded. Amongst these were the presence of electrolyte concentrations in the blood which predispose to QT prolongation such as low potassium (hypokalaemia), low calcium (hypocalcaemia) and low magnesium, (hypomagnesaemia) defined as lower than normal laboratory results. Also recorded was the presence of case reported conditions that are associated with sudden death; epilepsy, unexplained syncope, dizziness, liver disease, renal disease, syncope and recreational drug misuse.

3.13 Method for ascertaining sudden death risk with QTc prolonging medication

3.13.1 Drug exposure definition

The exposure was defined as the use of QTc prolonging drugs, as specified in the most recent version of the International Registry for Drug-induced Arrythmias maintained by the University of Arizona, Tucson, Arizona, United States of America [173]. They have classified QT prolonging drugs into four categories. Types 1, 2 and 4 are mutually exclusive. Type 3 includes every drug in types 1,2 and 4 and in addition includes some drugs that are not categorised as type 1,2 or 4. Not all of the drugs appearing on the registry are licensed, marketed or prescribed in the United Kingdom and of those drugs that are, not all were prescribed to patients on this study.

3.13.2 Index date definition

Every case was matched without exception to exactly 3 controls, constituting a set. For every individual in a set, an index date was defined to be the date of death of the

case. All medications taken by cases and controls were categorised as taken in the period 0-7 days prior to death of case, 8-30 days prior to death of case and 31-90 days prior to death of case.

3.13.3 Classification of medications that can affect the QT interval

The registry classifications are as follows:

Type 1. Drugs that are generally accepted to have a risk of causing Torsades de Pointes.

Type 2. Drugs that in some reports have been associated with Torsades de Pointes and/or QT prolongation but at this time lack substantial evidence for causing Torsades de Pointes.

Type 3. Drugs to be avoided for use in patients with diagnosed or suspected congenital long QT syndrome. Drugs in lists 1, 2 and 4 are also included here.

Type 4. "Drugs that, in some reports have been weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended doses and in patients without other risk factors (eg, concomitant QT prolongation drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome and concomitant drugs that inhibit metabolism).

3.13.3.1 Registry type 1 drugs

Type 1 medications are of the greatest importance to this study because they constitute the strongest exposure. Type 1 medications prescribed to people in this study were drawn from macrolide antibiotics, antiarrhythmics, antipsychotics and antinausea classes..

Table 2: Registry type 1 drugs

Macrolide anti-biotics	Clarithromycin, Erythromycin
Anti-arrhythmics	Amiodarone, Disopyramide, Sotalol
Anti-psychotics	Chlorpromazine, Haloperidol, Thioridazine
Anti-Nausea	Domperidone

Macrolide antibiotics are usually prescribed for one week whereas other medications are typically prescribed as monthly repeats. Thus use was defined as current for macrolide antibiotics if they were prescribed within 7 days of the death of the case and use was defined as current for drugs that are prescribed monthly if they were prescribed within 30 days of the death of the case.

3.13.3.2 Registry type 2 drugs

Type 2 medications are drawn from many drug classes. Examples of type 2 medication are alpha blockers, dopaminergic, anti-arrythmic, diuretic, antibiotic, anti-mania, anti-hypertensive, anti-psychotic, anti-cancer, muscle relaxant and vasodilator drugs (Table 3).

Table 3 Registry type 2 drugs

Alpha1 blocker	Alfuzosin
Dopaminergic	Amantadine
Anti-arrythmic	Flecainide
Diuretic	Indapamide
Anti-biotic	Levofloxacin, Ofloxacin
Anti-mania	Lithium
Anti-hypertensive	Nicardipine
Anti-psychotic	Quetiapine Risperidone
Anti-cancer	Tamoxifen
Muscle relaxant	Tizanidine
Phosphodiesterase	Vardenafil
Anti-depressant	Venlafaxine

3.13.3.3 Registry type 4 drugs

Type 4 drugs are drawn from a wide variety of classes. Type 4 drugs prescribed to individuals on the sudden death study consist of tricyclic antidepressants, other anti-depressants, anti-biotics and anti-fungal.

Table 4 Registry type4 drugs

Tricyclic anti-depressant	Amitriptyline, Clomipramine, Dosulepin Imipramine, Trimipramine
Other anti-depressant	Citalopram, Fluoxetine, Paroxetine Sertraline
Antibiotic	Ciprofloxacin, Trimethoprim
Antifungal	Itraconazole

3.13.3.4 Registry "type 3 only" drugs (not type1, type 2 or type 4)Type 3 medications include all drugs in lists 1, 2 and 4 as well as medications that are uniquely classified as type 3. "Type 3 only" medications prescribed to people in this

thesis belonged to bronchodilator, decongestant, sympathomimetic, appetite suppressant and bladder antispasmodic classes.

Table 5 Registry "type 3 only drugs" (not type1, type 2 or type4)

Bronchodilators	Salbutamol Terbutaline
Decongestants	Ephedrine Pseudoephedrine
Sympathomimetics	Salmeterol
Appetite Suppressants	Sibutramine
Bladder anti-spasmodic	Tolterodine

3.14 Obtaining approvals and subsequent difficulties

3.14.1 MREC approvals

Initial MREC approval was granted by the West Midlands on the 30 April 1999. Following submission of a revised protocol in November 2000, West Midlands MREC re-approved the study on the 3 January 2001. They again re-approved the study on the 7 June 2004 ref MREC/98/7/58.

3.14.2 LREC approvals

In April 2000 funding approval was received from the Wellcome Trust. LREC approvals were obtained from City hospital and East Birmingham in December 2000 and in January 2001 from North Birmingham and South Birmingham. In April 2001 approval was obtained from Solihull LREC.

3.14.3 Pilot study

At the end of December 2000 and beginning of 2001 cases were identified from the Birmingham Coroner's records for a one-month pilot period. Controls were sought from general practices at which cases were registered and data extraction piloted.

3.14.4 Permissions from PCTs outside the Birmingham area

Permission was granted to conduct the study at the Primary Care Trusts (PCTs) of Birmingham, Solihull, Coventry and Nottingham. It was necessary to obtain the approval of the directors of public health and the research and development departments of the Primary Care Trusts. The Primary Care Trusts insisted that the researchers that would be looking at medical notes be subject to a Criminal Records Bureau (CRB) check and when this was successfully concluded the research nurses were granted honorary contracts.

The information officers at the four Primary Care Trusts agreed to supply mortality records for all deceased patients from August 2003 until the conclusion of the study. The files were sent, in encrypted form as either a database or a spreadsheet. Researchers identified provisional cases from the files.

The shared service agencies (SSAs) granted permission to researchers to view the medical notes of deceased patients on their premises. In addition to clinical information the written notes often contained the post mortem reports.

3.14.5 Subsequent general practioner committee objections

Despite being granted MREC approval by the West Midlands on the 30 April 1999 the study was not able to proceed due to a number of objections to the protocol by some Birmingham doctors sitting on the Local Medical Committee of general practitioners who were concerned that patient confidentiality would be compromised. They objected to researchers' collecting information from the medical notes of the living controls without the consent of those patients. Some general practitioners were also concerned that the Data Protection Act of 1998 prevented them from allowing researchers to access patient notes without patient consent.

3.14.6 Section 60 approval

3.14.6.1 Obtaining Section 60 approval

In order to persuade the Birmingham general practitioners committee to co-operate with the study a decision was taken by the research team to apply for section 60 approval. Section 60 approval was a legal provision that allowed researchers to access patient medical notes without seeking the permission of either patients or their relatives and allows general practices lawful permission to give this access; the hope was that this would ameliorate the concerns of the general practitioner local committee.

A submission was made to the Department of Health on the 11 June 2002 seeking support under section 60 of the Health and Social Care Act 2001 to allow access to patient identifiable data.

The argument was put forward that people who refuse to act as a control may differ in some important respects from those that participate. In particular, individuals that are being treated with conditions to which are attached a social stigma are more likely to refuse to take part in medical studies. Some of these conditions are associated with medications that can prolong the QT interval such as mental illness. If the study were to proceed solely taking consented controls then systematic bias could occur which would cast doubt on the results and conclusions of the study. It would not be possible to evaluate how strong any such bias would be.

Section 60 approval from the Department of Health was granted on the 26 July 2002 registration number 001/02/02 subject to the following three conditions:

(1) Research nurses should be allowed to examine patient records in order that anonymous data can be collected for use by the study team.

(2) Information about the research should be displayed in practice waiting rooms.

(3) The research nurses responsible for examining patient records should have a contractual obligation of confidentiality.

Confirmation of the approval was included on the register of activities carried out with section 60 support.

3.14.7 Eventual approval by the Birmingham GPs local medical committee

Once section 60 approval was obtained a further submission was made to the Birmingham general practitioners committee who removed their objections.

3.14.8 Objections to the study from some individual GP surgeries

After permission was granted by each PCT for the study to commence and the Birmingham general practitioners committee had removed their objections all GPs were written to ask for their co-operation. The letter asked the senior partners to allow research nurses onto their premises to view patient medical records held in written form and on the computerised database. They were told that when a case was identified from the mortality files a member of the team would telephone the practice manager to ask for permission to attend the surgery to obtain the clinical information. They were asked to reply to us only if they had an objection. Only 8 objections were received at this stage. However more objections were obtained after surgeries were contacted when they had a case. The majority of medical practices (approx 90%) eventually gave their permission. Those that did not give their permission were most often single-handed practices. The stated reasons for not taking part were lack of time, computers and office space.

3.14.9 Birmingham and Solihull change their permission to view medical notes

From the outset of the study we could obtain written medical notes at the SSAs' for almost all of the cases. Those few medical notes that we could not look at were those

that could not be found by the SSA because they were lost or because the general practice had not yet released them.

Fifteen months after we started gathering data, Birmingham and Solihull SSA decided that we could no longer view medical notes without paying an expensive fee. This meant that we no longer had access to the medical notes and the post mortem reports at the SSA.

3.14.10 The effect of no longer being able to view post mortem reports

Post mortem reports for most cases were available with the medical notes at the shared service agency for the first 18 months of data collection. Those not available were requested from the coroners' office. Post mortem reports were effectively denied to us when the Birmingham and Solihull SSA levied their charge.

We assessed the impact of no longer being able to view post mortem reports with a review of those that we had at that time. Of 356 post-mortem reports representing 71% of the collected cases we concluded that we would lose 10 (3%) additional cases that would not have been eliminated on viewing just mortality file data alone. In view of this small gain of additional information it was decided not to request post-mortem reports from the coroner.

3.15 Case-Matching

3.15.1 Case-matching in general

Cases are people with the outcome variable. The selection of cases requires a suitable case definition. Care is needed that bias does not arise from the way in which cases

are selected. In general it is better to use incident rather than prevalent cases because unlike prevalence, incidence is not influenced by factors that determine the duration of the outcome variable. The outcome variable in this thesis is probable sudden death from cardiac arrhythmia which is a clearly defined incident outcome variable.

Controls are people that do not have the outcome variable. Controls were selected independently of the exposure variables.

Case control studies identify past exposure to suspect causative factors and by comparing cases with controls estimate an odds ratio. To avoid bias, the exposures of cases and controls should be measurable with the same accuracy[174].

3.15.2 Matching in this thesis

Matching is a way of negating or reducing the effects of confounding variables through the process of ensuring that cases and controls are similar with respect to them.

This thesis matched 3 confounding variables in the design stage: age, sex and presence of cardiovascular disease because they are strong independent risk factors for sudden death.

There are other risk factors such as individual cardiovascular conditions, severity of cardiovascular disease, alcohol abuse and severe obesity and arguably many others but we limited the matching to just 3 criteria because there would not be enough statistical power in a study with the number of cases that the researchers expected to

obtain (about 1000) to analyse the subgroups. Information on other risk factors was gathered with the intention of controlling for them in the analysis and we did that.

Matching strategy includes elements of design and analysis. In principle matching can be used in any analytic study design. However it can be difficult, expensive and time-consuming to find a comparison group because potential controls may have to be excluded before finding one with the required set of characteristics[175].

This thesis matched on age, sex and presence of cardiovascular disease thus there were four (2x2) combinations to consider when matching a case to a control. If additional factors had been matched then the process would have become progressively more difficult.

3.15.3 Avoiding overmatching

There are additional reasons to avoid matching to more than 3 factors. Excessive matching causes controls to be very similar to cases which can lead to important exposure factors being missed because they are approximately equally prevalent between the groups. Overmatching will reduce statistical efficiency if the matched variable is associated with the exposure but not the disease. Validity will be compromised if matching is done on a path variable between exposure and disease.

The researchers were also aware that a decision to match to more than 3 factors would have resulted in a loss of cases for which a full matching was not possible, causing a further reduction in statistical power. An additional consideration was that there

would be an increase in the cost of researchers' time when matching for extra subgroups.

3.15.4 Matching to more than one control to increase statistical power

When the number of cases is limited as in this thesis, the statistical power of the study to detect a real difference if it exists can be increased by matching to more than one control per case (referred to as R : 1 matching) where R is the number of controls per case. This thesis matched every case to 3 controls.

As R increases the cost of obtaining additional controls remains the same but the increase in statistical power declines so researchers have the problem of deciding on the optimum point to stop. The general consensus amongst researchers is that it is not worth matching to more than 4 controls per case[176].

There is a hidden problem with obtaining extra controls for a study where the subjects are elderly. The population age structure is pyramidal, thus if large numbers of controls are obtained per case the average age of controls could become significantly younger than that of the cases.

3.15.5 Other advantages of matching

There are some circumstances when matching is highly desirable or even necessary. Matching in this thesis was a very efficient way to obtain controls. Matching to individuals in the same general practice enabled us to control for provision of health care. Unknown confounders cannot be controlled except when they are fortuitously highly correlated with those variables that are matched.

3.15.6 Disadvantages of matching

There are some serious disadvantages of matching. It is impossible to evaluate the effect of the matched factor on the outcome. Matching results in a greater similarity between cases and controls with respect to their exposure histories and this has the potential to cause an underestimate of the true association between exposure and disease.

Stratified analysis cannot easily be used with matched data to control for additional confounders. In this thesis additional confounders were adjusted in the conditional logistic regression analysis but the effective sample size is reduced because the analysis is based on discordant pairs.

3.15.7 Analysis of matched data

Table 6 illustrates the presentation of data for the analysis of a 1 : 1matched-pair case-control study. Unlike the two-by-two table for unmatched data, in which each cell represents the number of individuals with a certain exposure and disease status, the cells for a matched study denote the number of pairs that fall into each category. Thus cell ‘e’ indicates the number of pairs in which both the case and control are exposed and so on. In a matched-pair analysis the estimate of the magnitude of the association between the exposure and disease is based entirely on the ratio of the discordant pairs. So for the table above the odds ratio is $OR = f / g$. The appropriate null hypothesis for 1 : 1 matching is that the expected values of ‘f’ and ‘g’ are equal ie $= (f + g) / 2$. If we have sufficient numbers a chi-squared test leads to $\chi^2 = (f – g)^2 / (f + g)$.

This is known as McNemar's test. The test statistic is compared with a χ^2 distribution with 1 degree of freedom and a confidence interval can be calculated[174].

$$95\%\ CI = OR^{(1 \pm 1.96/\chi)}$$

Table 6 Presenting data for matched pairs case control studies

		Controls	
		Exposed	Not Exposed
Cases	Exposed	e	f
	Not Exposed	g	h

3.16 Strategy for Analysis

3.16.1 Statistical Power in this study

Statistical tables were studied before the start of the study to inform the number of matched sets that would be required for different levels of significance, power, relative risk and proportion exposed. Thus about 500 sets (where each case is matched to 3 controls as in this study) are needed to detect a relative risk of 1.5 where the proportion exposed is 0.1, the significance is 0.05 and the power is 80%[177].

From the start of the study I was confident that more than 500 sets could be obtained but it was not possible to determine in advance an accurate figure for effect size for any given medication. It was also not possible to know before data collection began the proportion of cases or controls that would be on medications of interest.

The analysis for this thesis is based on 789 sets. I used PASS statistical software to show that with this number of sets I could detect an odds ratio of 1.47 at a power of 80% and significance level of 0.05 where the proportion of individuals exposed is 0.1.

3.16.2 Measure of effect size

Conditional logistic regression odds ratios were calculated because they are the appropriate measure of effect size for this matched case-control design.

3.16.3 Software used for analysis

Stata 7 was used to calculate conditional logistic regression odds ratios. SPSS version 14 was used for other analysis.

3.16.4 Adjustments for covariates

Comparisons were made between the use of suspect drugs of all classes for all cases and controls. Covariates that were imbalanced between cases and controls were identified and adjusted in the analysis of medications. This analysis was also done after stratifying for cardiovascular disease. Adjustment was made for those conditions that were shown to be significantly associated with sudden death, namely myocardial infarction, heart failure, low serum potassium, heart block, atrial fibrillation, epilepsy, syncope, impaired liver function, recreational drug abuse and alcohol abuse.

3.16.5 Drug Comparisons in time periods

Data obtained on prescribing in the 3 designated periods, 0-7 days, 8-30 days and 31-90 days gave an additional means of checking the validity of the findings, the expectation being of reduced differences in the proportions using suspect drugs between cases and controls more distantly from the event.

4 Exploring methodological issues

4.1 Study 1 Comparison between raters

I undertook two separate comparisons, one for electronic medical databases and the other for paper notes to assess the agreement of information obtained by data collectors and to assess their accuracy.

4.1.1 Introduction to the comparison study

Two experienced research nurses extracted the information for the study from computerised medical records and written medical records. The level of agreement between the nurses was assessed through a comparison of data extracted from the same information source. There would be cause for concern if the level of agreement for extracted data were to be poor, as this would also cast doubt on its accuracy.

4.1.2 A review of comparison studies in the literature

A review of the literature was undertaken to understand how comparison studies were done, the number of cases reviewed, how agreement was measured, the levels of agreement that were obtained and the importance that the levels of agreement had for those studies. Keywords entered into medical database search engines were nurse inter-rater reliability, medical notes, medication, agreement and concordance. Papers that had comparison studies on cardiovascular disease and medication were the most relevant.

A study with the aim of assessing the quality of care between hospitals for congestive heart failure and pneumonia via a review of medical notes confirmed diagnoses with clinical data from medical records. To assess the inter-rater reliability of nurse

abstracters, 32 random hospital records abstracted by one nurse were re-abstracted by two more nurses. Nurses were asked to score the thoroughness of history taking and physical examination by physicians, the use of common tests for patients with appropriate indications and the use of standard therapies. Intra-class correlation coefficients were 0.64 to 0.95 demonstrating very good to excellent agreement[178].

A review of the medical records of 420 patients in New York who had received a diagnosis of heart failure was used to evaluate the care that they received. Reviewers looked at medications, problems, progress, consultation letters, hospital discharge data, emergency department visits, laboratory results, radiographic data and old records from other physicians. To measure consistency across reviewers a second blinded record review was completed using 45 patient records selected randomly. The kappa statistic was used to assess inter-rater reliability for each review criterion. For these analyses 8 measures were used. The authors gave the 4 highest ratios, which vary from 0.57 for the measurement of left ventricular ejection fraction to the prescribed trial of angiotensin converting enzyme (ACE) inhibitors (0.80). The authors did not report information on the lowest 4 kappa figures other than they were less than 0.57[179]. The authors commented that heart failure is over diagnosed in primary care.

The level of agreement between two physicians was evaluated in a study in which both physicians independently of each other extracted data from recorded interviews of two patients. The encounter for each new patient visit had 63 data elements and the encounter for each of the follow-up interviews had 27 data elements. The results were in agreement on 92.2% of the elements with a kappa statistic of 0.82 overall, 0.9 for

one patient and 0.65 for the other indicating a moderate to high degree of concordance[180].

A study that sought to evaluate the reliability and validity of estimating the National Institute of Health Stroke Scale (NIHSS) from medical records compared handwritten notes from the medical records of 39 patients and their NIHSS stroke scores estimated by 6 raters blinded to the actual scores. Estimated scores were compared among raters with the actual measured scores. Inter-rater reliability was excellent with an intra-class correlation coefficient of 0.82[181].

Agreement among 8 American research nurses, as calculated by the kappa statistic were found to be generally high for a study that sought to assess the validity of the medical record and patient questionnaire for measuring delivery of different health services[182].

Kappa scores were found to be poor to moderate in a study that looked at the reliability of medical record review for estimating death from medical errors. They varied from 0.40 to 0.41 for adverse events and from 0.19 to 0.23 for negligent adverse events. The study relied on nurse and physician reviews of medical records to detect the errors[183].

A study evaluated the inter-group and intra-group reliability of a scoring tool for the appropriateness of medication for use in primary care. The tool was scored by two groups of evaluators for each drug. There were 211 drugs taken by 30 patients each taking at least 5 drugs. The overall kappa scores between groups were moderate and the kappa scores within groups were good[184].

A study that had the aim of evaluating factors associated with child asthma medication reported that agreement between physicians and caregivers for reported medication was 78% with a kappa of 0.54; 95% confidence interval: 0.45-0.63 [185].

Varying levels of agreement exist when comparing medical record with patient interview and pharmacy with kappa scores between 0.38 and 0.70 for a study that reported on medications in 2267 interviews, 1936 medical records, and 457 pharmacy records[186]. Greater levels of agreement were obtained for a prospective population based cohort study of people older than 55 years of age, with 80.6% agreement, the highest for B adrenoceptor blocking agents with kappa statistics of 0.97 for atenolol and metoprolol [187].

4.1.3 Conclusion to the comparison study literature search

For studies to have validity it is important that the information obtained is both accurate and reliable. There is no gold standard to assess the accuracy of the information that can be obtained. In general, reliability studies should be done early to identify problems with data collection and interpretation. It is rarely sensible to compare the results from different comparison studies because they are usually measuring different outcomes or the same outcome in different ways or measuring different populations as demonstrated above.

4.1.4 The Kappa statistic

The simplest way to measure agreement is to calculate a percentage and this is often done. Many researchers prefer to give the kappa statistic because it corrects for chance. The kappa statistic can be used for two purposes, firstly to test rater independence and secondly to quantify the level of agreement between raters. The second use of kappa is used in this study. The kappa statistic is considered to be appropriate for testing whether agreement exceeds chance for binary and nominal ratings and so can be applied to the sudden death study because all of the diagnostic information is binary. Kappa can also be applied to assess agreement about medication for names of drugs, dosages and time periods given.

The kappa calculation uses a term called the proportion of chance (or expected agreement). This is the proportion of times raters would agree by chance alone and it assumes that raters are statistically independent.

Kappa scores vary between –1 and +1 that is between perfect disagreement and perfect agreement. A kappa score of 0 signifies that agreement is no better than chance. A scale has been proposed to describe the level of concordance… agreement 0 - 0.20, “poor”; 0.21 – 0.40, “fair”; 0.41 – 0.60, “moderate”; 0.61 – 0.80, “substantial”; 0.81 – 1.00 “almost perfect”. [188] .

Kappa has several flaws that are relevant to this study. It does not make distinctions between various types and sources of disagreement. Disagreement can exist simply because raters have interpreted information differently.

Kappa scores are seldom comparable across studies, procedures or populations because they are influenced by trait prevalence and base rates. Kappa scores for the comparison study in this thesis vary between the different diagnoses even when the total number of errors is the same because of the distribution of those scores in the 2x2 contingency table.

Kappa values obtained from samples with different base rates fluctuate and so may not be comparable thus if sample base rates differ from population base rates the result may not be generalisable. [189].

There is wide disagreement about the usefulness of kappa statistics to assess rater agreement. Kappa statistics should not be viewed as the unequivocal standard or default way to quantify agreement; one should use and interpret this controversial statistic cautiously and one should consider alternative methods of agreement such as the intraclass correlation or log odds ratio and make an informed choice[190].

4.1.5 Comparison study methods

4.1.5.1 Electronic database comparison study

To assess the agreement on information held on medical practice electronic databases between the two nurse data extractors, computerised medical records for 28 deceased individuals from 6 general practitioner surgeries were abstracted by one nurse and were later re-abstracted by the other. Each record was viewed at the General Practitioner surgery at which the individual was registered and patient diagnoses, blood test results and medications were recorded. Both nurses were trained in data

abstraction and had previous experience in other studies. Only one of them had worked on a previous cardiology study.

4.1.5.2 Paper notes comparison study

To assess agreement on information held on written medical notes a second data extraction was done by the same 2 nurses on a different group of 24 patients from written medical records held at the Nottingham Shared Service Agency. Patient diagnoses and blood test results were recorded but not medications because few surgeries record medications in the written notes.

4.1.5.3 Clinical information obtained

The nurses recorded the presence or absence of 8 cardiovascular conditions, namely if the patient had ever had a myocardial infarction, treated angina within past 3 years, ever had a coronary revasculation, heart failure in past year, treated hypertension in past 3 years, sinus bradycardia in past year, heart block in past year and atrial fibrillation in past year. Also recorded was the presence or absence of 3 non-cardiovascular conditions namely, ever had epilepsy, renal abnormalities in past year and liver abnormalities in past year and 2 symptoms that could be indicative of a cardiovascular condition, that is unexplained dizziness and unexplained syncope both in the past 1 year. They also recorded the presence of 4 blood results namely hypokalaemia, hypocalcaemia, hypomagnesaemia and hyperkalaemia all within the past year.

4.1.5.4 Medication information obtained

The nurses recorded the names and dosage of all prescribed non-topical medications that were taken by the case in the 3 months prior to death. The dates of prescription, and length of time for which they were prescribed were viewed on the databases and from this information the nurses were able to record if the drug had been taken 7 days, 1 month or 3 months prior to the death of the case.

4.1.6 Results

The results of the agreement of diagnostic criteria for the computerised database extraction on 28 cases are summarised in the table 7 with more detail for that of cardiovascular status in table 8. The result of the computer extraction for medication is given in table 9. The results of diagnostic criteria extracted from paper notes on a separate group of 24 cases are given in table 10 with more detail of cardiovascular status in table 11.

With regard to the computerised database agreement for diagnoses on 28 cases (Table 7), the worst agreement levels existed for atrial fibrillation, heart failure and hypertension. The worst kappa score was a moderate 0.47 which occurred for the diagnosis of atrial fibrillation one year prior to death where both raters agreed that 1 case had it and 25 cases did not (one rater identified 3 cases and the other rater identified just 1 case). A moderate level of agreement (0.53) existed also for heart failure where the raters agreed that 3 cases had it and 21 did not. (one rater identified 7 cases and the other rater agreed on just 3 of them). The third worst kappa score was 0.65 for hypertension where the raters agreed that 11 cases had it and 12 did not (one nurse identified 16 cases of hypertension and the other agreed on 11 of them).

No individuals were identified by either of the raters as having myocardial infarction or heart block. There was perfect agreement (kappa = 1) for cardiovascular status, 18 of the 28 cases were classified as cardiovascular by both data extractors (Table 8) despite diagnoses of cardiovascular subclasses not being in perfect agreement.

For comparison of paper notes, kappa scores varied between substantial and perfect (Table 10). The raters agreed that 16 people could be classified as being cardiovascular cases and 6 could not, thus not agreeing about the cardiovascular status of 2 of them, for a kappa score of 0.80. There was perfect agreement for 3 cardiovascular conditions “ever had a coronary revasculation”, “sinus bradycardia in past year” and “atrial fibrillation” in past year”. The worst level of agreement existed for heart failure for which there was a moderate kappa score of 0.63. One rater identified 4 individuals as having heart failure and the other rater agreed on just two of them. This was because the nurse that had worked on previous cardiology studies was able to recognise drugs given to people in heart failure and classify them accordingly in the absence of heart failure being mentioned in the medical notes. Thus heart failure was the cardiovascular condition that overall had the least agreement on both computerised database and paper notes. Furthermore it was the same rater that identified the most heart failure in the computer as well as paper notes study. There was excellent agreement for the paper notes extraction of the 4 blood tests there being only 1 blood test for 1 case on which the raters disagreed.

The agreement for medications was evaluated according to three criteria, name of prescribed drug, dosage and time period prior to the death of the case (Table 9). The

percentage agreement for drug name was 92%, agreement on dosage was 97% and agreement on time period was 91%.

Table 7 Computerised database agreement for diagnoses on 28 cases

Diagnosis	Differences	% agreement	Kappa score
Cardiovascular	0	100	1
Myocardial infarction	0	100	1
Angina	2	92.86	0.7083
Coronary revascularisation	1	96.43	Not calculable
Heart failure	4	85.71	0.5294
Hypertension	5	82.14	0.6534
Sinus bradycardia	1	96.43	Not calculable
Heart block	0	100	1
Atrial fibrillation	2	92.86	0.4716
Epilepsy	1	96.43	0.7812
Renal	0	100	1
Liver	0	100	1
Unexplained dizziness	0	100	1
Unexplained syncope	1	96.43	Not calculable
Hypokalaemia	0	100	1
Hypocalcaemia	0	100	1
Hypomagnesaemia	0	100	1
Hyperkalaemia	1	96.43	0.65

Table 8 Computerised database agreement for cardiovascular status on 28 cases

		Rater 1	**Rater 1**
		Cardiovascular	**Non-Cardiovascular**
Rater 2	Cardiovascular	18	0
Rater 2	Non-Cardiovascular	0	10

Table 9 Computerised database agreement for medication on 28 cases

	Drug name	Dosage for agreed drugs	Time period for agreed drugs
Agree	178	172	458
Disagree	16	6	47
% agreement	92%	97%	91%

Table 10 Paper notes diagnoses for a separate group of 24 cases

Diagnosis	Differences	% agreement	Kappa score
Cardiovascular	2	92%	0.7983
Myocardial infarction	1	96%	0.8333
Angina	1	96%	0.8333
Coronary revascularisation	0	100%	1
Heart failure	2	92%	0.625
Hypertension	1	96%	0.9032
Sinus bradycardia	0	100%	1
Heart block	1	96%	Not calculable
Atrial fibrillation	0	100%	1
Epilepsy	1	96%	Not calculable
Renal	0	100%	1
Liver	0	100%	1
Unexplained dizziness	1	96%	Not calculable
Unexplained syncope	0	100%	1
Hypokalaemia	1	96%	Not calculable
Hypocalcaemia	0	100%	1
Hypomagnesaemia	0	100%	1
Hyperkalaemia	0	100%	Not calculable

Table 11 Paper notes agreement for cardiovascular status on 24 cases

		Rater 1	**Rater 1**
		Cardiovascular	**Non-Cardiovascular**
Rater 2	Cardiovascular	16	1
Rater 2	Non-Cardiovascular	1	6

4.1.7 Discussion

4.1.7.1 Computerised database

Kappa scores varied between moderate and perfect. Given the small sample of 28 cases, confidence intervals are wide and a few errors can cause kappa scores to plummet dramatically.

The nurse rater that identified the greatest number of hypertensive subjects also identified the least number of heart failure cases as well as the least number of atrial fibrillation cases. Thus although it is relatively easy to identify cardiovascular cases, as shown by the perfect agreement for overall cardiovascular status it is more difficult to agree on the diagnoses for cardiovascular subclasses.

Given that one nurse was more experienced than the other in recognising heart failure and the difficulty in classifying heart failure as noted by James et al [179] it is understandable that this diagnosis had one of the worst levels of agreement. For the diagnosis of hypertension one rater had a policy of classifying an individual as having this condition only if they saw the written diagnosis whereas the other rater also looked out for appropriate treatment.

It became clear in a later briefing that the main reason for disagreement on diagnoses between nurses was the interpretation of the information in the medical record. For example how does one interpret the criteria “atrial fibrillation in the period one year prior to death”? Clearly there is no problem if the diagnosis is in the notes, especially if backed up by relevant treatment; but what if the diagnosis was 18 months prior to death? One rater may decide that the criteria had not been met but another may decide that it had been if the subject had been receiving relevant treatment such as warfarin or aspirin. But those treatments can be used for other conditions so a judgement would have to be made on the presence of those other conditions and the likelihood of the patient being treated for them. It is likely that agreement would have been better if the wording of the criteria had been more explicit such as “ever had a diagnosis of atrial fibrillation”. Another important consideration is that one of the nurses had extracted and interpreted cardiovascular information for a previous trial and it would not be surprising if this greater experience led to her diagnoses being more accurate.

For the blood results hypokalaemia, hyperkalaemia, hypocalcaemia and hypomagnaesaemia there was only 1 case, when comparing computerised notes, on which the raters disagreed.

Agreement was excellent for those conditions where the criteria were unambiguous.

4.1.7.2 Paper notes

There is perfect agreement for the paper notes diagnosis of atrial fibrillation and moderate agreement for the computerised database extraction which could be due to

the small sample size so that the moderate agreement hinged on only two individuals for which there was disagreement.

Heart failure was the cardiovascular condition that overall had the least agreement on both computerised database and paper notes comparison and this was because of the difference in experience of the nurses and the difficulty of the diagnosis. The same rater identified the most heart failure in the computer as well as the paper notes study. The bias in the classification of cases as having heart failure does not alter the classification of cases as cardiovascular.

There was excellent agreement for the paper notes extraction of the 4 blood tests there being only 1 blood test for 1 case in the paper notes on which the raters disagreed.

Agreement was excellent for both database and paper notes extraction of unambiguous data.

After a review of the medical records of 52 individuals (28 computer records, 24 paper records) the raters disagreed about the cardiovascular status of only two of them thus it is essential to define clearly the criteria.

For both computerised and paper notes, extraction agreement was excellent for those conditions where the criteria were unambiguous.

4.1.7.3 Agreement for medication

The agreement for medications was evaluated according to three criteria, name of prescribed drug, dosage and time period prior to the death of the case (Table 9). Percentage agreement over 90% is considered to be acceptable[191]. A percentage agreement of 92% for drug name was found. Agreement on dosage and time period prior to the death of the case was evaluated only for those drugs that both raters had identified as being prescribed. The comparison of dosage was made only for those medications that both raters had agreed were given to the respective case and was 97%. In order to assert that a drug had been prescribed to individuals in any of the three time periods prior to death, a calculation had to be made by each rater which took into account the date of death of the case, the dates on which drugs had been prescribed, the total numbers of tablets prescribed and the number of tablets to be taken each day. An error of 1 day in the calculation can make a difference when declaring that a case had a drug in a time period explaining why agreement was the lowest of the drug criteria at 91%. Kappa scores were not done for individual medications because of the small numbers of cases that received even the most commonly prescribed drug.

4.1.8 Conclusion

There was perfect agreement for the classifications cardiovascular and non-cardiovascular. There was a good to perfect (kappa = 1) level of agreement for most diagnoses and never less than moderate and when moderate were for conditions that required interpretation. Thus we can be sure that the raters were almost always seeing the same information but sometimes experienced difficulties when they had to make a

judgement. It is helpful to data extractors if their instructions are worded as unambiguously as possible.

There is evidence of bias between the raters for the classification of some cardiovascular conditions, most notably heart failure and hypertension due to differences in training and experience. Fortunately there is no evidence of bias between cases and controls in this thesis because the same nurse viewed notes for both cases and the associated controls.

This thesis collected data using both electronic and paper records. Therefore actual agreement is likely to be higher than the kappas recorded here.

4.2 Study 2: Compliance characteristics of participating practices

Most surgeries and general practitioners granted access to study investigators for the purpose of viewing medical notes. As doctors who decline to take part in research are widely believed to differ from those that do, I explored the characteristics of GPs who did and who did not allow access to their patient records.

4.2.1. Compliance characteristics of surgeries and GPs

I stratified the decisions by surgeries that I approached for permission to view medical notes according to whether they were single handed or not and present it below (Table 12). Single handed general practices were more than twice as likely to refuse access 21/75(28.0%) compared with doctors working in multi-handed practices

33/276(12.0%). There was a significant difference between single handed and group surgeries t = 11.6, p = 0.001.

Table 12 Comparing single handed with group surgeries

	Compliers n (%)	**Non-Compliers n (%)**	**Total**
Single handed surgeries	54 (72.0%)	21 (28.0%)	75 (100%)
Group surgeries	243 (88.0%)	33 (12.0%)	276 (100%)

I found that the GP decisions to assist with the study were taken at surgery level. Out of a total 1210 general practitioners working in the 351 surgeries that I approached for access to medical notes, 1083 (89.5%) doctors worked in surgeries that granted access.

4.2.2 Compliance characteristics of surgeries with respect to deprivation scores

Deprivation scores were obtained for individual practices and summary statistics generated to compare compliant with non-compliant surgeries (Table 13). Townsend deprivation scores are calculated from four census variables, namely percentages for unemployment, car ownership, overcrowding and non-owner occupied housing. Index of Material Deprivation (IMD) scores are based on income deprivation, employment deprivation, health deprivation and disability, education skills and training deprivation, barriers to housing and services, living environment deprivation and crime A positive deprivation score for an area would indicate that the area is relatively deprived; a negative figure that the area is relatively better off.

Table 13 Compliance characteristics of surgeries with respect to deprivation scores

	Number of GPs per practice	Practice List Size	Townsend 2001	IMD 2000 Score	IMD 2004 Score
Compliers mean (SD)	3.7 (2.4)	6115 (3527)	4.3 (5.1)	38.5 (19.5)	36.9 (19.0)
Refusers mean (SD)	2.4 (1.6)	4418 (2862)	5.0 (5.7)	39.9 (19.5)	35.6 (17.9)

* IMD Index of multiple deprivation

Table 13 shows that deprivation scores are positive irrespective of compliance characteristics which indicates that sudden cardiac death occurs more often in areas of social deprivation. The mean number of general practitioners was significantly larger at compliant practices, $t = 3.83$, $p = 0.0002$. The mean practice list size at surgeries that refused access was significantly smaller than that at compliant surgeries, $t = 3.34$, $p = 0.0009$. Differences were not significant between complier and refuser surgeries for mean Townsend 2001 score, $t = 0.911$, $p = 0.36$, nor were they significant for IMD 2000 scores, $t = 0.49$, $p = 0.63$ or for mean IMD 2004 scores $t = 0.47$, $p = 0.64$. Thus there is no clear difference in terms of social deprivation between surgeries that comply and those that do not.

Refusal to allow access could not be due to GP workload or to lack of administrative support because the research nurse did all of the data extraction which took about one hour for each case control set and only required access to a computer at a time convenient to the surgery.

4.3 Study 3 Post Mortem reports

4.3.1 Introduction

Provisional cases were individuals who had a post mortem report and met the case definition on examination of the mortality files. The study team sought to further strengthen the case definition by examining post-mortem reports from the Birmingham coroner's records in order to identify and exclude any unsuitable cases. The supportive coroner who was a collaborator on the study proposal retired prior to its start and his successor would not grant access to post mortem reports.

Fortunately we were able to view many but not all post mortem reports at the PCTs although copies were missing for some deceased individuals. Later, 16 months into the study researchers were also prevented from viewing reports at the shared service agency for Birmingham and Solihull PCTs, when they decided to levy a charge to view written medical information. Researchers were able to sometimes view a copy of the post mortem report at the GP surgery at which the case was registered

To prevent a considerable loss of cases it was decided to explore whether we could accept individuals for whom post mortem reports were not available for scrutiny.

4.3.2 Aims

The purpose of the study was to address the following questions:

1. How successful were study investigators in obtaining access to post mortem reports?

2. What proportion of individuals who would be classifiable as cases on mortality file data would be excluded after taking the additional information that is in post mortem reports into account?

4.3.3 Methods

To address question 1 researchers recorded on the study database if a post mortem report had been viewed.

To address question 2, a study team consisting of a consultant cardiologist and senior lecturer in medicine compared the levels of agreement for 1a, 1b, 1c, and 2 causes of death for 96 cases between, mortality file data and post mortem reports obtained from surgeries.

4.3.4 Results

The study team were able to obtain access to the post mortem reports of 463 (58.7%) cases out of the total 789. Although every one of the remaining 326 (41.3%) cases had a post mortem report investigators were not able to view them.

The 96 cases for which photocopied post mortem reports were available met the eligibility criteria according to the causes of death on their mortality files but 4 (4.17%) of them were excluded after assessment of the post mortem report.

There was a very good level of agreement between causes of death on post mortem report and public health mortality file data. There were seven “cause of death” errors, one of them in the 1a cause of death category, three in the 1b causes of death category

and three in the 2 cause of death category. One of the errors in the 1b cause of death category had the potential for a case misclassification (Fig 4).

One can probably make the assumption that the cause of death recorded on the post mortem is correct and the cause of death appearing on the mortality file is copied from it so when the two differ the error is in the mortality file. The disagreements in the causes of death between post mortem and mortality file data for the seven cases that have differences are explored in more detail for each case below.

Fig 4. Differences between post mortem report and mortality file causes of death

Case 1 the mortality file missed out “hypertension” from the post mortem 1b cause of death “coronary artery atherosclerosis and stenosis and hypertension”.

Case 2 the mortality file missed out “diabetes mellitus” from the post mortem 1b cause of death of chronic mitral valvar disease, systemic hypertension and diabetes mellitus.

Case 3 the mortality file missed out “with thrombosis” from the post mortem 1b cause of death of “coronary artery disease with thrombosis”.

Case 4 the mortality file missed out “hypertension” from the post mortem section 2 cause of death.

Case 5 the mortality file missed out “extensive oedema of lungs” from the post mortem section 2 cause of death.

Case 6 the 1a cause of death on the mortality file was “sudden adult death syndrome” whereas that on the post mortem report was “unascertained”.

Case 7 the mortality file had an insertion error in section 2 cause of death of “chronic obstructive airways disease, diabetes mellitus and hyperthyroidism” instead of no phrase.

4.3.5 Discussion

I believe that the disagreement for case 3 had the potential for a misclassification and thus I consider it to be a serious error because the study excluded deceased individuals from being a case if they had a coronary thrombosis. The disagreements for the other 6 cases would not affect the decision to include them as cases so I would classify these errors as minor.

This study was concerned with the level of agreement between post mortems and mortality file data, not with how well the pathologists followed the guidelines for entering the causes of death on the post mortem reports. The instructions state that there should be only one diagnosis for each of 1a, 1b, and 1c causes of death. In this respect I observed that it was very common for pathologists to disregard the guidelines and I showed some examples for the cases above.

For those post mortem reports that were viewed, the majority were seen at the PCT premises. Only a minority of medical practices scanned post mortem reports into their computers. It would be of benefit to researchers if more surgeries were to adopt this practice

It was possible to view post mortem reports for 463 (58.7%) cases. It is possible that the study would have lost a small number of the 326 other cases if their post mortem reports had been available and the best estimate of the number that would have been lost would be 326 multiplied by proportion that was lost on review by the study team (4.17%), (table 4) that is 15 of them. It is unlikely that this relatively small loss would have had an impact on the findings of this thesis.

4.4 Summary of Chapter 4

In chapter 4 I have explored aspects of the methods of this study. In study 1 I measured the agreement between myself and the other nurse for the extraction of information from patient medical records held at general practitioner surgeries in computerised database and paper form. I found it to be acceptable. Study 2 assessed the compliance characteristics of general practitioners and found that single handed surgeries (compared with group surgeries) were significantly less likely to grant researchers access to patient records. Study 3 stated the number of post mortem reports viewed and quantified the agreement between the causes of death on mortality files compared with the causes of death on post mortem files for the same individuals. It also quantified the number of provisional cases that would be excluded after taking into consideration the additional information held on post mortem reports into account.

5 Results

5.1 Characteristics of cases and controls

All 789 cases were successfully matched to 3 controls. Males outnumbered females by a ratio of 2:1. More than half of the cases (56.1%) had a documented history of heart disease. Close matching for age was achieved with the average age 67.80 (SD 12.71) for cases and 67.79 (SD 12.70) for controls (Table 14).

Table 14 Summary of matching factors, age, sex and cardiovascular disease

	Cases n (%)	**Controls n (%)**
Males n %	524 (66.4%)	1572 (66.4%)
Females n %	265 (33.6%)	795 (33.6%)
History of cardiovascular disease n %	443 (56.1%)	1329 (56.1%)
No history of cardiovascular disease n %	346 (43.9%)	1038 (43.9%)
Age (mean, SD)	67.80 (12.71)	67.79 (12.70)
Age <20.0	0	0
Age 20.0 – 30.0	6 (0.76%)	18 (0.76%)
Age 30.0 – 40.0	22 (2.79%)	65 (2.75%)
Age 40.0 – 50.0	55 (6.97%)	164 (6.93%)
Age 50.0 – 60.0	120 (15.21%)	361 (15.25%)
Age 60.0 – 70.0	174 (22.05%)	520 (21.97%)
Age 70.0 – 80.0	288 (36.50%)	864 (36.50%)
Age >80.0	124 (15.72%)	375 (15.84%)

5.2 Summary of previous medical conditions according to case control status

Proportionally more cases than controls had a history of myocardial infarction, heart failure, low potassium, atrial fibrillation, epilepsy, syncope, impaired liver function,

drug misuse and alcohol abuse. Conditional logistic regression odds ratios (OR) to measure effect size were calculated and 95% confidence intervals (95% CI) to measure the statistical reliability of this estimate were calculated (Table 15).

Table 15 Summary of previous medical conditions by group

Medical diagnosis	**Cases n (%)**	**Controls n (%)**	**Odds ratio (OR)**	**95%Confidence interval (95% CI)**
Previous myocardial infarction	83 (10.5%)	164 (6.9%)	1.71*	1.27, 2.30
Angina	107 (13.6%)	297 (12.5%)	1.11	0.86, 1.44
Coronary revasculation	20 (2.5%)	89 (3.8%)	0.65	0.39, 1.08
Heart failure	85 (10.8%)	103 (4.4%)	3.22*	2.29, 4.52
Hypertension	399 (50.6%)	235 (52.2%)	0.73	0.51, 1.03
Low serum Potassium	22 (2.8%)	18 (0.8%)	4.08*	2.10, 7.90
Low serum Calcium	3 (0.4%)	6 (0.3%)	1.50	0.36, 6.00
Low serum Magnesium	0 (0.0%)	1 (0.0%)	-----	----------
Bradycardia	8 (1.0%)	16 (0.7%)	1.52	0.64, 3.60
Heart block	7 (0.9%)	9 (0.4%)	2.45	0.88, 6.81
Atrial fibrillation	58 (7.4%)	102 (4.3%)	1.91*	1.33, 2.73
Epilepsy	46 (5.8%)	33 (1.4%)	4.26*	2.71, 6.70
Syncope	16 (2.0%)	26 (1.1%)	1.97*	1.02, 3.82
Dizziness	36 (4.6%)	98 (4.1%)	1.11	0.75, 1.65
Impaired renal function	49 (6.2%)	113(4.8%)	1.37	0.95, 1.99
Impaired liver function	26 (3.3%)	27 (1.1%)	3.0*	1.73, 5.21
High Serum Potassium	24 (3.0%)	54 (2.3%)	1.36	0.83, 2.24
Drug misuse	8 (1.0%)	3 (0.1%)	11.08*	2.34, 52.57
Alcohol abuse	100 (12.7%)	48 (2.0%)	8.59*	5.75, 12.82

* significant at $\alpha = 0.05$.

Conditions found to be significantly associated with sudden death were used to adjust for the strength of the effect size between sudden death and medications (section 5.5).

5.3 Analysis of consultations

Table 16 counts the number of consultations given to individuals and cannot be analysed using conditional logistic regression unlike tables 17, 18 and 19 which count the number of individuals given at least one consultation. For the latter three tables crude conditional logistic odds ratios were calculated. They were not adjusted because there was no need to control for confounding variables in this analysis. My goal was to find if there was a link between consultation and sudden death irrespective of disease.

5.3.1 Comparison of GP and hospital consultations in 3 months prior to death of the case

The number and type of consultations for each individual in the three months prior to the death of the cases were recorded (Table 16).

Table 16 Comparison of GP and hospital consultations in 3 months prior to death of the case

	Consultations for Cases N	**Consultations for Cases Mean (SD)**	**Consultations for Controls N**	**Consultations for Controls Mean (SD)**
GP	1337	1.69 (2.30)	3969	1.68 (1.96)
Hospital clinic	261	0.33 (0.75)	820	0.35 (0.81)
Hospital admission	63	0.08 (0.32)	70	0.03 (0.19)

Cases have a significantly greater mean number of hospital admissions than controls t = 5.40, $p < 0.0001$. There is no significant difference between cases and controls for mean number of GP clinic conditions, t = 0.15, p = 0.88 or hospital clinic consultations, t = 0.84, p = 0.43.

5.3.2 General Practitioner Consultations

There are 497 cases and 1,544 controls that had at least one GP consultation in the 3 months prior to the death of the case (Table 17). Conditional logistic regression odds ratios, significance values and confidence intervals were generated. There was no significant association with sudden death and occurrence of at least one GP consultation in the 3 months prior to death of the case. Analysing separately the samples with a history of cardiac disease and no history of cardiac disease does not alter this finding.

Table 17 General Practitioner Consultations

	Cases N	**Controls N**	**OR**	**95% CI**	**p**
Non Cardiac	157	497	0.90	0.70, 1.15	0.403
Cardiac	340	1047	0.88	0.68, 1.15	0.356
All	497	1544	0.89	0.74, 1.07	0.214

OR; Conditional logistic regression odds ratio.

5.3.3 Hospital Outpatient Consultations

There is no significant association with sudden death and hospital outpatient consultations in the 3 months prior to death of the case. Analysing separately the cardiac and non cardiac samples makes no difference to the findings (Table 18).

Table 18 Hospital Outpatient Consultations

	Cases N	**Controls N**	**OR**	**95% CI**	**p**
Non Cardiac	145	390	1.19	0.93, 1.51	0.164
Cardiac	57	165	1.05	0.75, 1.46	0.796
All	202	555	1.14	0.93, 1.38	0.200

OR; Conditional logistic regression odds ratios.

5.3.4 Hospital admissions

Admissions to hospital within 3 months of death are significantly associated with sudden death in cardiac patients, odds ratio 3.28 (2.11, 5.08) (Table 19).

Table 19 Hospital admissions

	Cases N	**Controls N**	**OR**	**p**	**95% CI**
Non Cardiac	12	18	2.08	0.057	0.98, 4.43
Cardiac	42	39	3.28*	< 0.001	2.11, 5.08
All	54	57	2.98*	< 0.001	2.0, 4.26

OR; Conditional logistic regression odds ratios.
* significant at $\alpha = 0.05$.

5.4 Medications

Cases on average take significantly more medication than controls, $t = 5.66$, $p < 0.0001$. Cases take a mean of 4.82 (sd = 4.20) and controls a mean of 3.97 (sd = 3.45) medcations.

5.5 Results for drug exposures

Using a conditional logistic regression model I calculated odds ratios (OR) for the association of sudden death with current use of registry QT prolonging drugs and I also calculated them adjusted for significant medical conditions. Current use was defined as prescription 0-7days for antibiotics and 0-30 days for other drugs. To explore the impact of cardiovascular disease on these associations I then stratified for cardiovascular disease and calculated the corresponding odds ratios.

5.5.1 Registry type 1 drugs

Registry type 1 drugs consist of macrolide antibiotics for which current use is prescription in the period 0-7 days prior to death of index case and other drugs for which current use is prescription 0-30 days.

5.5.1.1 Current use of macrolide antibiotics

The risk of sudden cardiac death was significantly increased for erythromycin users, non adjusted OR 7.5 (1.46, 38.66) and adjusted OR 8.67 (1.46, 38.66). Sudden death risk was not significantly increased for combined macrolide use. No cases took clarithromycin so it was not possible to calculate an odds ratio or a confidence

interval. Numbers of exposed individuals are very small and so confidence intervals are wide which reflects the great imprecision in these estimates (Table 20).

Table 20 Current use of macrolide antibiotics

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Clarithromycin	0	4	-----	-----	----	----------
Erythromycin	5	2	7.5*	1.46, 38.66	8.67*	1.50, 49.92
Macrolides	**5**	**6**	**2.5**	**0.76, 8.19**	**2.42**	**0.68, 8.63**

OR; Conditional logistic regression odds ratios.
* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.1.1.1 Current use of macrolide antibiotics stratified for cardiovascular disease

As there were only 2 prescriptions of antibiotics for non-cardiovascular patients, both for control patients, it is not possible to find if an association with sudden death exists.

In cardiovascular patients the risk of sudden cardiac death was significantly increased for erythromycin users, non-adjusted OR 7.5 (1.46, 38.66) and adjusted 8.67 (1.50 49.92) and for combined macrolide use non adjusted OR 3.75 (1.01 13.96) and adjusted 4.40 (1.08 17.91) (Table 21).

Table 21 Current use of macrolide antibiotics for cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Clarithromycin	0	2	-----	------	-----	----------
Erythromycin	5	2	7.5*	1.46 38.66	8.67*	1.50, 49.92
Macrolides	**5**	**4**	**3.75***	**1.01 13.96**	**4.40***	**1.08, 17.91**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope impaired liver function, drug misuse and alcohol abuse.

5.5.1.2 Current use of non-macrolide type 1 drugs

Unadjusted odds ratios significantly above 1 are found for amiodarone OR 2.6 (1.24, 5.46) and haloperidol OR 6.0 (1.10, 32.76). On combining drugs, significant unadjusted odds ratios are found for antiarrhythmics 1.89 (1.03, 3.47) and antipsychotics 3.86 (1.44, 10.36) and all 2.09 (1.31, 3.34).

After adjustment; only combined antipsychotic use remained significantly associated with sudden death OR 3.65 (1.17, 11.40) (Table 22).

Table 22 Current use of non-macrolide type 1 drugs

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#95% CI**
Amiodarone	13	15	2.6*	1.24, 5.46	1.70	0.74, 3.89
Disopyramide	0	1	----	-------	--------	----------
Sotalol	4	11	1.09	0.35, 3.43	0.93	0.28, 3.07
Antiarrhythmics	**17**	**27**	**1.89***	**1.03, 3.47**	**1.34**	**0.68, 2.61**
Chlorpromazine	3	5	1.8	0.43, 7.53	1.83	0.31, 10.73
Haloperidol	4	2	6.0*	1.10, 32.76	3.74	0.54, 25.83
Thioridizine	2	0	----	------	-------	----------
Antipsychotics	**9**	**7**	**3.86***	**1.44, 10.36**	**3.65***	**1.17, 11.40**
Domperidone	4	9	1.33	0.41, 4.33	1.32	0.41, 4.34
Type 1 (excluding Macrolides)	**30**	**43**	**2.09***	**1.31, 3.34**	**1.64**	**0.98, 2.73**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.1.2.1 Current use of non macrolide type 1 drugs for patients without cardiovascular disease

For people that do not have a diagnosed cardiovascular condition there is a significant association between sudden death and current use of antipsychotic medication, adjusted OR 4.5 (1.27, 15.95) and unadjusted OR 4.97 (1.15, 21.55). When the anti-nausea drug domperidone is included there is a weakened unadjusted significant association for all combined OR 3.0 (1.05, 8.55) (Table 23).

For non cardiovascular patients the combined type 1 antipsychotic medication is significantly associated with sudden death both before and after adjustment. When domperidone is also taken into account the crude odds ratio is significant but not the adjusted one.

Table 23 Current use of non macrolide type 1 drugs for patients without cardiovascular disease

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#95% CI**
Chlorpromazine	3	3	3.0	0.61, 14.86	3.07	0.43, 21.80
Haloperidol	1	1	3.0	0.19, 47.96	1.96	0.05, 84.83
Thioridizine	2	0	-------	--------	----------	----------
Antipsychotics	**6**	**4**	**4.5***	**1.27, 15.95**	**4.97***	**1.15, 21.55**
Domperidone	1	3	1.0	0.10, 9.61	1.13	0.17, 11.01
Type 1 (excluding Macrolides)	**7**	**7**	**3.0***	**1.05, 8.55**	**3.04**	**0.93, 9.91**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.1.2.2 Current use of non macrolide type 1 drugs for patients with cardiovascular disease

There is a significant association between sudden death and amiodarone, unadjusted OR 2.6 (1.24, 5.46) but not between sudden death and sotalol. Both drugs are prescribed to control arrhythmia (Table 24).

No significant association can be found between sudden death and current use of antipsychotic medication but this could be because the number of prescriptions is small.

On combining drugs, significant unadjusted odds ratios are found for antiarrhythmics 1.89 (1.03, 3.47) and all type 1 drugs 1.92 (1.14, 3.23). After adjustment no significant odds ratios are obtained.

Table 24 Current use of non macrolide type 1 drugs for patients with cardiovascular disease

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Amiodarone	13	15	2.6*	1.25, 5.46	1.70	0.74, 3.89
Disopyramide	0	1	-------	----	----	--------
Sotalol	4	11	1.09	0.35, 3.43	0.93	0.28, 3.07
Anti arrhythmics	**17**	**27**	**1.89***	**1.03, 3.47**	**1.34**	**0.68, 2.61**
Chlorpromazine	0	2	-------	----	----	---------
Haloperidol	3	1	9.0	0.94, 86.52	4.71	0.45, 49.45
Thioridizine	0	0	----------	----	----	--------
Anti psychotics	**3**	**3**	**3.0**	**0.61, 14.86**	**2.29**	**0.39, 13.45**
Domperidone	3	6	1.5	0.38, 6.00	1.41	0.35, 5.69
Type 1 (excluding Macrolides)	23	36	1.92*	1.14, 3.23	1.43	0.81, 2.52

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.1.3 Use of type 1 drugs in time periods (0-7, 8-30, 31-90) days prior to death of index case

I calculated unadjusted odds ratios for use of type 1 medications in time periods (0-7, 8-30, 31-90) days prior to death of index case (Appendix 1).Apart from macrolide antibiotics there is very little difference between the numbers of medications prescribed in the three time periods and the associated odds ratios because with few exceptions the same people are being counted in all of them.No individual had received more than one type 1 drug in period 0-7 or period 8-30 days One control has received more than one type 1 drug (domperidone and erythromycin) in period 31-90 days. No Case has received more than one type 1 drug.There was a significant association with amiodarone, combined anti-arrhythmics, combined anti-psychotics and combined type 1 medication in all time periods.

To quantify the temporal nature of drug exposure in terms of risk of sudden death I compared drug use in 3 defined time periods (0-7, 8-30, 31-90 days) (Table 29).

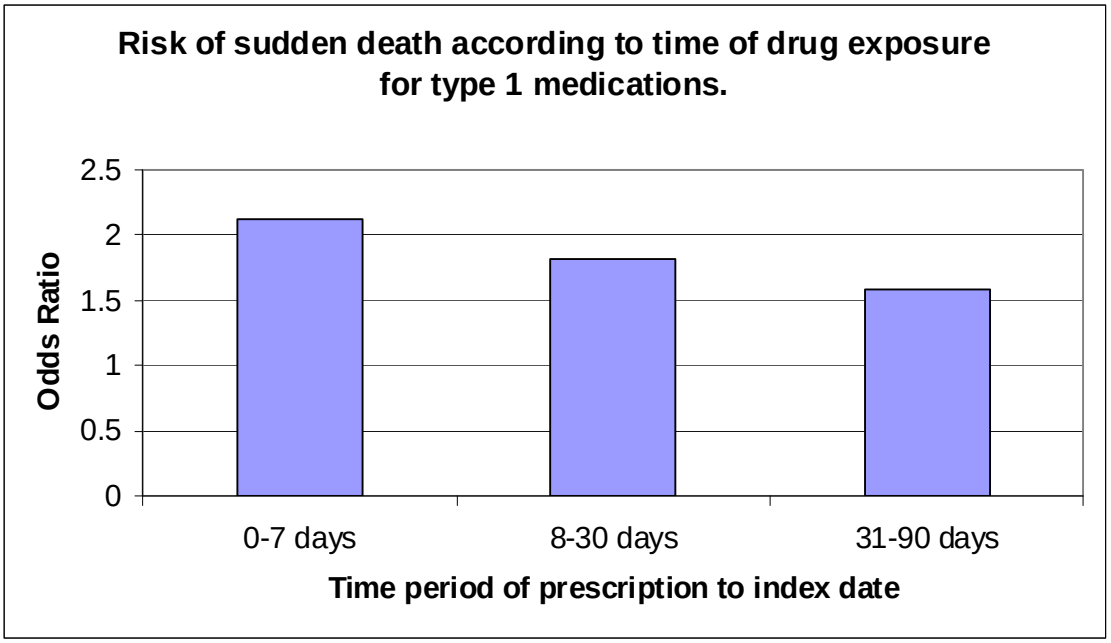
Significant associations with sudden death and type 1 medications are found in all three time periods. The hypothesis that medications are contributing to death is supported if odds ratios increase with approaching index date of death. This trend is clearly seen in the table 25 and associated graph (fig 5) for combined type 1 medications.

Table 25 Comparing use of combined type 1 drugs in time periods (0-7, 8-30, 31-90 days)

	Cases N	Controls N	OR	95% CI	p value
All Type 1 (0-7 days)	33	47	2.12*	1.36, 3.32	0.001
All Type 1 (8-30 days)	31	51	1.82*	1.17, 2.85	0.008
All Type 1 (31-90 days)	35	67	1.58*	1.04, 2.38	0.030

OR; Conditional logistic regression odds ratios.
* significant at $\alpha = 0.05$.

Fig 5. Risk of sudden death according to time of drug exposure for type 1 medications



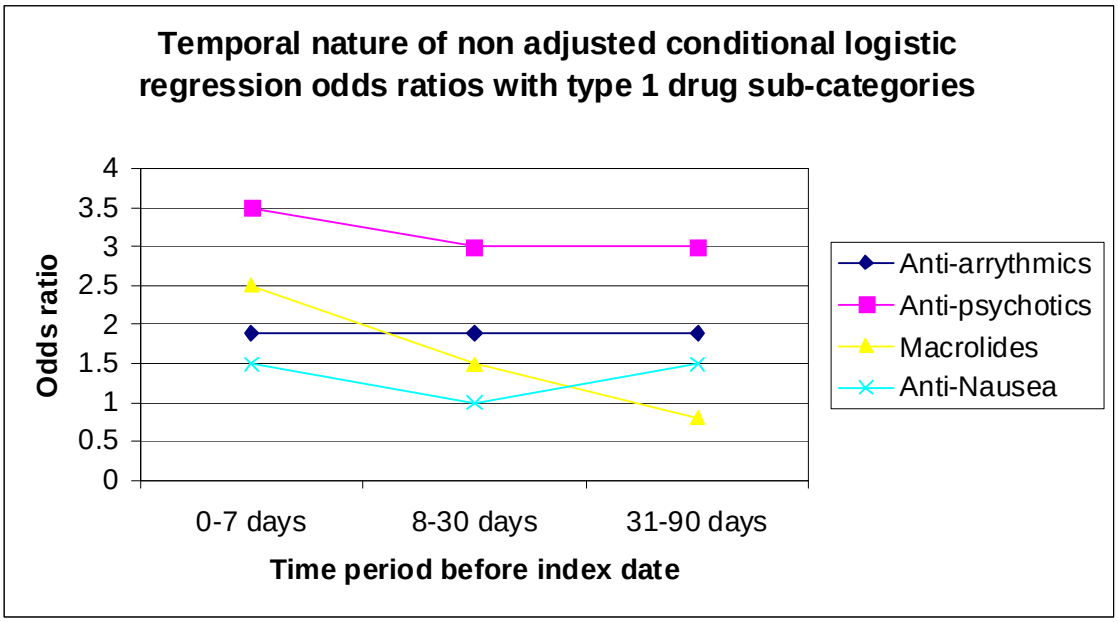
The trend for odds ratios for combined type 1 medications to become greater the closer to the index date was further investigated by examining subcategories of type 1 drugs. The increase is mostly due to macrolide antibiotic use and to a lesser extent

antipsychotic use. Antiarrythmics and the antinausea domperidone show very little variation in their use over the three time periods (Table 26) & (Fig 6).

Table 26 All type 1 medication subcategories (Non-adjusted)

	Antiarrythmics OR, (95%CI)	**Antipsychotics** OR, (95%CI)	**Macrolides** OR, (95%CI)	**Anti-Nausea (Domperidone)** OR, (95%CI)
0-7 days	1.89(1.03, 3.47)	3.5(1.18, 10.4)	2.5(0.76, 8.19)	1.5(0.45, 4.98)
8-30 days	1.89(1.03, 3.47)	3.0(1.05, 8.56)	1.5(0.45, 4.98)	1.0(0.27, 3.69)
31-90 days	1.89(1.03, 3.47)	3.0(1.05, 8.56)	0.8(0.35, 1.89)	1.5(0.45, 4.98)

Fig 6.Risk of sudden death according to time of drug exposure for subcategories of type 1 medications



5.5.2 Current use of registry type 2 drugs

A very significant association $p< 0.001$ is found with sudden cardiac death and the anti-psychotic drug risperidone adjusted OR 6.0 (2.57, 14.02), unadjusted OR 6.02 (2.48, 14.64) (Table 27).

No evidence exists of an association with sudden death for current use of grouped type 2 medications.

There was one prescription for the antibiotic levofloxacin in the period 0-7 days prior to death of the case which can be included in the 0-30 days table that defines current use for type 2 drugs.

Several individuals have received more than 1 type 2 drug in the period 0-30 days prior to the death of the index case.

Table 27 Current use of type 2 drugs

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**# Adjusted 95% CI**
Alfuzosin	3	27	0.33	0.10, 1.10	0.37	0.11, 1.27
Amantadine	1	0	-----	-----	----	--------
Flecainide	1	3	1.00	0.10, 9.61	1.01	0.10, 11.55
Indapamide	12	50	0.71	0.37, 1.35	0.91	0.47, 1.77
Levofloxacin	0	1	-----	-----	----	---------
Lithium	4	8	1.42	0.45, 4.98	1.29	0.38, 4.41
Nicardipine	1	2	1.5	0.14, 16.54	2.36	0.20, 27.12
Quetiapine	0	3	----	-----	-----	-----
Risperidone	16	8	6.00*	2.57, 14.02	6.02*	2.48, 14.64
Tamoxifen	1	11	0.27	0.04, 2.21	0.28	0.04, 2.18
Tizanidine	0	1	----	-----		------
Vardenafil	0	5	----	-----	----	------
Venlafaxine	5	9	1.67	0.56, 4.97	2.26	0.70, 7.25
Type 2 (0-30 days)	**42**	**120**	**1.05**	**0.73, 1.51**	**1.19**	**0.81, 1.74**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.2.1 Current use of type 2 drugs for non cardiovascular disease

No significant associations between sudden death and type 2 medication given to non cardiovascular patients can be detected (Table 28).

Two non-cardiovascular cases and four non-cardiovascular controls are on two type 2 drugs.

Table 28 Current use of type 2 drugs for non-cardiovascular patients

	Cases N	**ControlsN**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Alfuzosin	1	10	0.30	0.04, 2.34	0.34	0.04, 2.72
Amantadine	1	0	------	------	------	--------
Levofloxacin	0	1	---	----	------	--------
Lithium	3	7	1.29	0.33, 4.97	1.18	0.30, 4.69
Risperidone	4	8	1.5	0.45, 4.98	1.63	0.47, 5.65
Tamoxifen	0	4	-----	------	------	--------
Tizanidine	0	1	-----	--------	------	--------
Vardenafil	0	2	------	-------	------	--------
Venlafaxine	1	5	0.60	0.70, 5.14	1.03	0.11, 9.35
Type 2 (0-30 days)	**8**	**34**	**0.68**	**0.31, 1.48**	**0.74**	**0.33, 1.65**

adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.2.2 Current use of type 2 drugs for cardiovascular patients

There are 12 cardiovascular cases and no cardiovascular controls on risperidone (Table 29) and this is indicative of an association between sudden death and the

current use of risperidone. It is not possible to calculate an odds ratio because of the presence of the zero.

There are no significant associations with sudden death and any other type 2 drug given to people who are classified as having cardiovascular disease.

No cardiovascular case is on more than one type 2 drug. Four cardiovascular controls are on more than one type 2 drug.

Table 29 Current use of type 2 drugs for cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Alfuzosin	2	17	0.35	0.08, 1.53	0.38	0.08, 1.80
Flecainide	1	3	1.0	0.10, 9.61	1.08	0.10, 11.55
Indapamide	12	50	0.710	0.37, 1.35	0.91	0.47, 1.77
Lithium	1	1	3.0	0.19, 47.96	1.92	0.11, 33.06
Nicardipine	1	2	1.5	0.14, 16.54	2.36	0.20, 27.12
Quetiapine	0	2	------	--------	-----	--------
Risperidone	12	0	-----	--------	-----	---------
Tamoxifen	1	7	0.43	0.05, 3.48	0.45	0.05, 3.68
Vardenafil	0	3	-------	-------	-----	--------
Venlafaxine	4	4	3.0	0.56, 4.97	3.48	0.80, 15.22
Type 2 (0-30 days)	**34**	**85**	**1.22**	**0.80, 1.84**	**1.42**	**0.92, 2.20**

adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.2.3 Use of type 2 medications in time periods (0-7, 8-30, 31-90) days prior to death of index case

I calculated non adjusted odds ratios for use of type 2 medications in time periods (0-7, 8-30, 31-90) days prior to death of index case (Appendix 2).

There is very little difference between the numbers of medications prescribed in the three time periods and the associated odds ratios, because as for type 1 medications, with few exceptions the same people are being counted in all of them. Some cases and controls were prescribed more than 1 type 2 drug in all time periods.

I compared the risk of sudden death associated with registry type 2 medications in the three time periods (Table 30). The hypothesis that medications are contributing to death is supported if odds ratios are significant and increase in the time period that is closest to the index date. Odds ratios are not significant and there is no evidence of a trend with grouped type 2 medications in the table.

Table 30 Risk of sudden death according to time of type 2 drug exposure

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Type 2 (0-7 days)	39	116	1.01	0.69, 1.47	0.962
Type 2 (8-30 days)	40	119	1.01	0.70, 1.46	0.962
Type 2 (31-90 days)	42	141	0.91	0.63, 1.30	0.590

5.5.3 Registry type 4 drugs

Registry type 4 drugs consist of antibiotics and antifungals for which current use is prescription in the period 0-7 days prior to death of index case and other drugs for which current use is prescription 0-30 days.

There were 10 prescriptions for ciprofloxacin, 8 for trimethoprim and none for itraconazole in this period.

5.5.3.1 Current use of type 4 antibiotics

There was no evidence of an association with sudden death and current use of type 4 antibiotics (Table 31).

One individual received both type 4 antibiotics in the time period 0-7 days prior to death of the index case.

Table 31 Current use of type 4 antibiotics

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95%CI**
Ciprofloxacin	2	8	0.75	0.16, 3.53	0.54	0.11, 2.73
Trimethoprim	3	5	1.80	0.43, 7.53	1.29	0.26, 6.52
Antibiotics	5	12	1.15	0.39, 3.35	0.80	0.27, 2.77

adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

There was no evidence of an association with sudden death and current use of type 4 antibiotics for non cardiovascular patients (Table 32).

Table 32 Current use of type 4 antibiotics for non cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95%CI**
Ciprofloxacin	0	2	--------	----------	--------	----------
Trimethoprim	1	0	--------	----------	--------	----------
Antibiotics	1	2	1.5	0.14, 16.54	1.5	0.14, 16.54

adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

There was no evidence of an association with sudden death and current use of type 4 antibiotics for cardiovascular disease patients (Table 33). One individual received both type 4 antibiotics in the time period 0-7 days prior to death of the index case.

Table 33 Current use of type 4 antibiotics for cardiovascular disease patients

	Cases N	Controls N	OR	95% CI	#Adjusted OR	#Adjusted 95%CI
Ciprofloxacin	2	6	1.00	0.20, 4.95	0.69	0.13, 3.71
Trimethoprim	2	5	1.20	0.23, 6.19	0.70	0.10, 4.98
Antibiotics	4	10	1.21	0.37, 3.99	0.74	0.20, 2.80

adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.3.2 Current use of type 4 antidepressants

Antidepressant medications account for every type 4 drug where current use is defined to be the period 0-30 days.

Crude odds ratios that indicate a significantly increased risk of sudden death are obtained for current use of citalopam 2.05 (1.01, 4.16), fluoxetine 3.11 (1.46, 6.65), paroxetine 3.0 (1.25, 7.21) and for combined type 4 medications 2.12 (1.55, 2.90) (Table 34).

After adjustment, fluoxetine remains significantly associated with sudden death OR 2.68 (1.12, 6.38) and so do combined type 4 medications OR 1.87 (1.33, 2.64) although the associations are less strong. Dosulepin which was not significantly associated with sudden death before adjustment becomes so after adjustment OR 2.41 (1.07, 5.44). Citalopram and paroxetine are no longer significantly associated with sudden death after adjustment (Table 34).

It is not possible to calculate an odds ratio for nortriptyline or trimipramine because of a zero in either the numerator or the denominator. Imipramine is the only drug that has an odds ratio less than 1 but there have only been 5 prescriptions.

One case has taken two type 4 drugs in the period 0-30 days.

Table 34 Current use of type 4 antidepressants

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Amitriptyline	14	30	1.45	0.77, 2.74	1.41	0.73, 2.75
Citalopram	13	19	2.05*	1.01, 4.16	1.54	0.69, 3.47
Clomipramine	2	4	1.5	0.27, 8.19	1.69	0.29, 9.76
Dosulepin	12	18	2.15	0.99, 4.67	2.41*	1.07, 5.44
Fluoxetine	14	14	3.11*	1.46, 6.65	2.68*	1.12, 6.38
Imipramine	1	4	0.75	0.08, 6.71	0.77	0.09, 6.93
Nortriptyline	0	1	-----	----------	------	--------
Paroxetine	10	10	3.0*	1.25, 7.21	2.24	0.83, 6.06
Sertraline	6	9	2.0	0.71, 5.62	1.75	0.55, 5.56
Trimipramine	1	0	----	----------	------	--------
Type 4 (Anti-depressant)	**72**	**109**	**2.12***	**1.55, 2.90**	**1.87***	**1.33, 2.64**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

Crude odds ratios that indicate a significantly increased risk of sudden death are obtained in non cardiovascular disease patients for current use of sertraline OR 7.5 (1.46, 38.66) and combined anti-depressants OR 2.23 (1.37, 3.65). Sertraline is the only type 4 antidepressant that shows such a significant result for non cardiovascular patients but this may be due to chance as it works in the same way as other type 4 antidepressants. Following adjustment the association for combined use remains significant OR 1.92 (1.12, 3.31) (Table 35).

Table 35 Current use of type 4 antidepressants for non-cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95%CI**
Amitriptyline	7	12	1.75	0.69, 4.44	1.92	0.72, 5.11
Citalopram	5	7	2.14	0.68, 6.75	1.78	0.46, 6.84
Clomipramine	1	3	1.0	0.10, 9.61	1.45	0.14, 14.51
Dosulepin	4	6	2.0	0.56, 7.09	2.11	0.59, 9.63
Fluoxetine	6	6	3.0	0.97, 9.30	2.38	0.59, 9.63
Imipramine	1	2	1.5	0.14, 16.54	1.5	0.14, 16.54
Nortriptyline	0	0	-----	-------	------	--------
Paroxetine	1	5	0.6	0.07, 5.14	0.34	0.03, 3.46
Sertraline	5	2	7.5*	1.46, 38.66	4.19	0.73, 24.02
Trimipramine	1	0	-----	---------	-----	--------
Type 4 (Anti-depressant)	**30**	**43**	**2.23***	**1.37, 3.65**	**1.92***	**1.12, 3.31**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

Crude odds ratios that indicate a significantly increased risk of sudden death are obtained in cardiovascular disease patients for current use of fluoxetine, paroxetine and combined anti-depressants (Table 39). After adjustment the association for paroxetine remains significant OR 4.67 (1.35, 16.13) as does that for combined use OR 1.83 (1.18, 2.87). The association with fluoxetine after adjustment is no longer significant (Table 36).

Table 36 Current use of type 4 antidepressants for cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Amitriptyline	7	18	1.17	0.49, 2.79	1.11	0.44, 2.77
Citalopram	8	12	2.0	0.82, 4.89	1.43	0.52, 3.94
Clomipramine	1	1	3.0	0.19, 47.96	2.16	0.13, 35.97
Dosulepin	8	12	2.25	0.85, 6.01	2.65	0.91, 7.69
Fluoxetine	8	8	3.21*	1.16, 8.92	2.89	0.95, 8.81
Imipramine	0	2	-----	--------	-------	------
Nortriptyline	0	1	----	--------	------	-----
Paroxetine	9	5	5.4*	1.81, 16.11	4.67*	1.35, 16.13
Sertraline	1	7	0.43	0.05, 3.48	0.61	0.07, 5.25
Trimipramine	0	0	----	----------	-------	------
Type 4 (Anti-depressant)	**42**	**66**	**2.04***	**1.35, 3.08**	**1.83***	**1.18, 2.87**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.3.3 Use of type 4 medications in time periods (0-7, 8-30, 31-90) days prior to death of index case

I calculated non adjusted odds ratios for use of type 4 medications in time periods (0-7, 8-30, 31-90) days prior to death of index case (Appendix 3). Risperidone is strongly associated with sudden death in every period. The difference between the numbers of medications prescribed in the three time periods is mainly due to antibiotic prescription. For antidepressant use with few exceptions the same people are being counted in all three time periods. Some cases and controls were prescribed more than 1 type 4 drug.

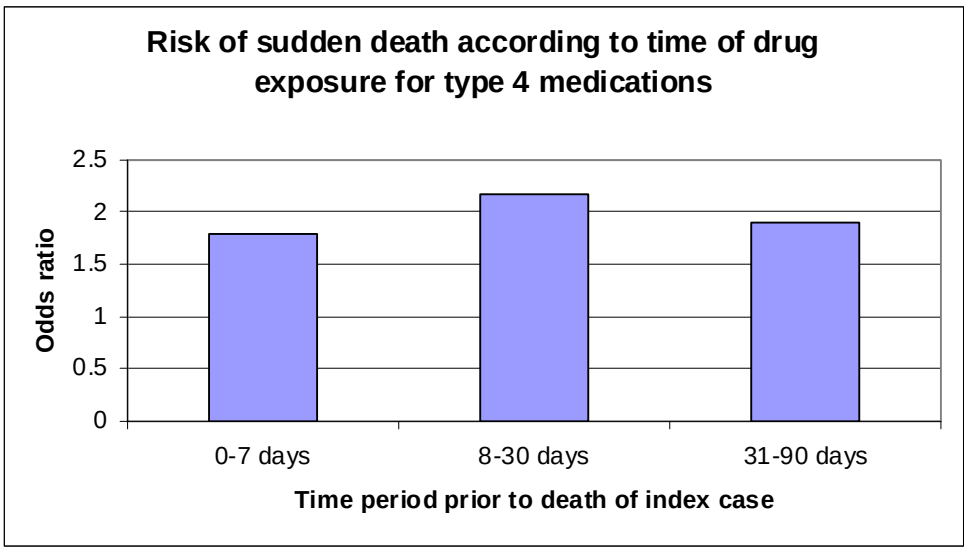
I have compared the risk of sudden death associated with registry type 4 medications in the three time periods (Table 37 & Fig 3). Odds ratios are significant. There was no temporal trend in odds ratio with sudden death and type 4 medication (Table 37) & (Fig 7).

Table 37 Risk of sudden death according to time of type 4 drug exposure

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Type 4 (0-7 days)	66	117	1.78	1.29, 2.44	<0.001*
Type 4 (8-30 days)	82	122	2.16	1.61, 2.91	<0.001*
Type 4 (31-90 days)	85	145	1.89	1.42, 2.51	<0.001*

* significant at $\alpha = 0.05$.

Fig 7. Risk of sudden death according to time of drug exposure for type 4 medications



5.5.4 Current use of type 3 only drugs (not type1, type 2 or type 4)

Conditional logistic regression crude odds ratios that are significantly associated with sudden death are obtained for salmeterol OR 1.62 (1.06, 2.47), inhaled salbutamol OR 1.37 (1.04, 1.77) and combined type 3 only medication OR 1.40 (1.10, 1.78) (Table 38). After adjustment only combined drug use remains significant OR 1.35 (1.0, 1.74)

Odds ratios for terbutaline and oral salbutamol are raised but not significantly. Few individuals take them.

It may be that the odds ratios above 1 seen with most type 3 only drugs are because of the association between sudden death and respiratory disease.

Many cases and controls receive more than one type 3 only medication

Table 38 Current use of type 3 only drugs (not type 1, type 2 or type 4)

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Ephedrine	1	0	----	-------	--------	--------
Pseudoephedrine	1	4	0.75	0.08, 6.71	0.58	0.05, 6.18
Salbutamol (Oral)	8	13	1.85	0.77, 4.45	1.96	0.77, 4.98
Salbutamol (Inhaler)	88	198	1.37*	1.04, 1.77	1.31	0.99, 1.74
Salmeterol	35	67	1.62*	1.06, 2.47	1.49	0.96, 2.32
Sibutramine	0	1	-----	-------	------	------
Terbutaline	8	15	1.63	0.68, 3.90	1.81	0.71, 4.63
Tolterodine	5	12	1.25	0.44, 3.55	1.47	0.47, 4.58
Type 3 only (0-30 days)	**112**	**252**	**1.40***	**1.10, 1.78**	**1.35***	**1.04, 1.74**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

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5.5.4.1 Comparing current single use of salbutamol and salmeterol with joint use

Non adjusted odds ratios for current use of combined salbutamol and salmeterol are significant OR 1.66 (1.03, 2.69). Odds ratios are not significant for single use (either in oral form or inhaler or both but excluding salmeterol) of salbutamol 1.30 (0.96, 1.76) or single use (that is salmeterol but not salbutamol)of salmeterol 1.41 (0.61, 3.27) Most people receiving salmeterol are also taking salbutamol so numbers of people taking salmeterol and not salbutamol are relatively small (Table39).

Table 39 Comparing current single use of salbutamol and salmeterol with joint use

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Salbutamol inhaler and oral only (0-30) days	67	159	1.30	0.96, 1.76	0.090
Salmeterol only (0-30) days	8	17	1.41	0.61, 3.27	0.421
Salbutamol and Salmeterol (0-30) days	**27**	**50**	**1.66***	**1.03, 2.69**	**0.039**

5.5.4.2 Current use of type 3 only drugs for non-cardiovascular patients

There are no significant associations between sudden death and type 3 medications given to people that are classified as not having cardiovascular disease (Table 40).

Table 40 Current use of type 3 only drugs for non-cardiovascular patients

	Cases N	Controls N	OR	95% CI	#Adjusted OR	#Adjusted 95% CI
Ephedrine	0	0	-------	-------	-------	--------
Pseudoephedrine	1	2	1.5	0.14, 16.54	2.07	0.18, 24.4
Salbutamol (Oral)	0	6	------	-------	------	-------
Salbutamol (Inhaler)	24	64	1.14	0.70, 1.85	1.33	0.81, 2.19
Salmeterol	9	28	0.96	0.45, 2.06	1.06	0.49, 2.30
Sibutramine	0	0	-------	-------	-----	-------
Terbutaline	2	5	1.20	0.23, 6.19	0.99	0.18, 5.29
Tolterodine	2	6	1.00	0.20, 4.95	2.01	0.39, 10.45
Type 3 only (0-30 days)	28	85	0.99	0.63, 1.54	1.18	0.75, 1.87

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.4.3 Current use of type 3 only drugs for cardiovascular patients

Significant non adjusted odds ratios are found in cardiovascular patients with oral salbutamol OR 3.43 (1.24, 9.45), inhaled salbutamol OR 1.51 (1.09, 2.09), salmeterol OR 2.15 (1.27, 3.64) and combined type 3 only drugs OR 1.63 (1.22, 2.18). After

adjustment all these odds ratios become smaller but with the exception of inhaled salbutamol remain significant (Table 41).

Table 41 Current use of type 3 only drugs for cardiovascular patients

	Cases N	**Controls N**	**OR**	**95% CI**	**#Adjusted OR**	**#Adjusted 95% CI**
Ephedrine	1	0	------	-------	-------	-----
Pseudoephedrine	0	2	------	-------	-------	-----
Salbutamol (Oral)	8	7	3.43*	1.24, 9.45	3.29*	1.12, 9.61
Salbutamol (Inhaler)	64	134	1.51*	1.09, 2.09	1.30	0.93, 1.84
Salmeterol	26	39	2.15*	1.27, 3.64	1.79*	1.03, 3.11
Sibutramine	0	1	----	-------	-----	---------
Terbutaline	6	10	1.86	0.65, 5.26	2.50	0.79, 7.89
Tolterodine	3	6	1.5	0.38, 6.00	1.16	0.25, 5.29
Type 3 only (0-30 days)	**84**	**167**	**1.63***	**1.22, 2.18**	**1.43***	**1.05, 1.95**

* significant at $\alpha = 0.05$.
# adjusted for previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse.

5.5.4.4 Use of type 3 only drugs in time periods (0-7, 8-30, 31-90) days prior to death of index case

I calculated unadjusted odds ratios for use of type 3 only medications in time periods (0-7, 8-30, 31-90 days) prior to death of the index case (Appendix 4).

There is very little difference between the numbers of medications prescribed in the three time periods and the associated odds ratios because with few exceptions the

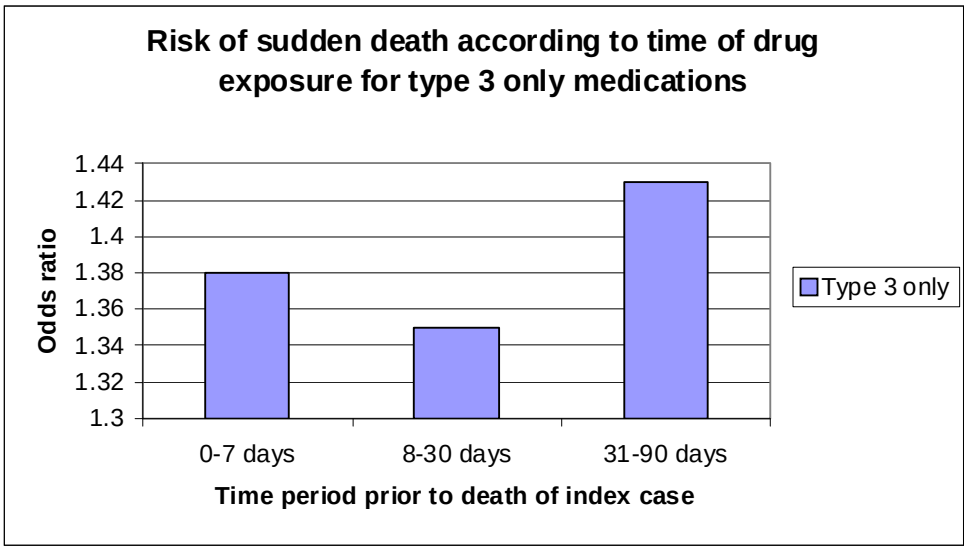
same people are being counted in all of them. Some cases and controls were prescribed more than one type 3 only drug. Significant associations with sudden death for salbutamol inhaler and salmeterol and combined type 3 only medication were found in all time periods.

I compared odds ratios in the 3 defined time periods (0-7, 8-30, 31-90 days. I found no evidence of a trend for increased association with type 3 only medication and sudden death (Table 42) & (Fig 8).

Table 42 Comparing use of combined type 3 only drugs in time periods (0-7, 8-30, 31-90 days)

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Type 3 only (0-7days)	108	245	1.38*	1.08, 1.76	0.010
Type 3 only (8-30 days)	107	248	1.35*	1.05, 1.72	0.017
Type 3 only (31-90 days)	115	254	1.43*	1.13, 1.82	0.003

Fig 8. Risk of sudden death according to time of drug exposure for type 3 only medications



5.5.5 Exploring study results for confounding

Significant associations between sudden death and medications may be due to confounding with factors related to medical conditions that provoke prescription of medication. To take into account these medical conditions it is useful to compare results for registry QT prolonging drugs with medications that are not on the registry that are prescribed for the same medical conditions.

5.5.5.1 Comparing macrolide antibiotics with penicillin antibiotics

It is possible that the association between sudden death and erythromycin use is confounded with infection. I explored this possibility by comparing macrolides with an antibiotic group that does not cause Torsades de Pointes. I chose penicillins because, as is the case with macrolides, they are typically prescribed for chest infection and if confounding exists it is likely to be to the same extent for both antibiotic groups.

There is a significantly high nonadjusted odds ratio for flucloxacillin 3.25 (1.08, 9.75) but not for amoxicillin 1.16 (0.63, 2.12) or for grouped penicillins 1.52 (0.91, 2.53) (Table 43). These results are similar to that of the macrolides.

It is not unusual to obtain a significant odds ratio for an individual medication. Small numbers of individuals on drugs give imprecise results.

Table 43 Risk of sudden death with current use of penicillin antibiotics

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amoxicillin	15	39	1.16	0.63, 2.12	0.633
Ampicillin	1	1	3.0	0.19, 47.96	0.437
Flucloxacillin	7	7	3.25*	1.08, 9.75	0.036
Phenoxymethylpenicillin	1	1	3.0	0.19, 47.96	0.437
TOTAL	23	46	1.52	0.91, 2.53	0.107

* significant at $\alpha = 0.05$

One case and two controls were on more than one penicillin drug in the period 0-7days prior to death of the case.

5.5.5.1.1 Risk of sudden death with use of combined penicillin antibiotics within the three time periods

I calculated odds ratios for sudden death for the grouped penicillins in the time periods prior to death (Table 44) and for grouped macrolides and compared them (Fig 9).

Odds ratios are not significant for grouped penicillins in any time period. There is a trend for increased association with sudden death nearer the index case date of death.

Table 44 Risk of sudden death with use of combined penicillin antibiotics within the three time periods

	Cases N	**Controls N**	**OR**	**95% CI**		**p value**
0-7 days	23	46	1.52	0.91,	2.03	0.107
8-30 days	29	78	1.12	0.72,	1.74	0.605
31-90 days	37	127	0.87	0.56,	1.26	0.459

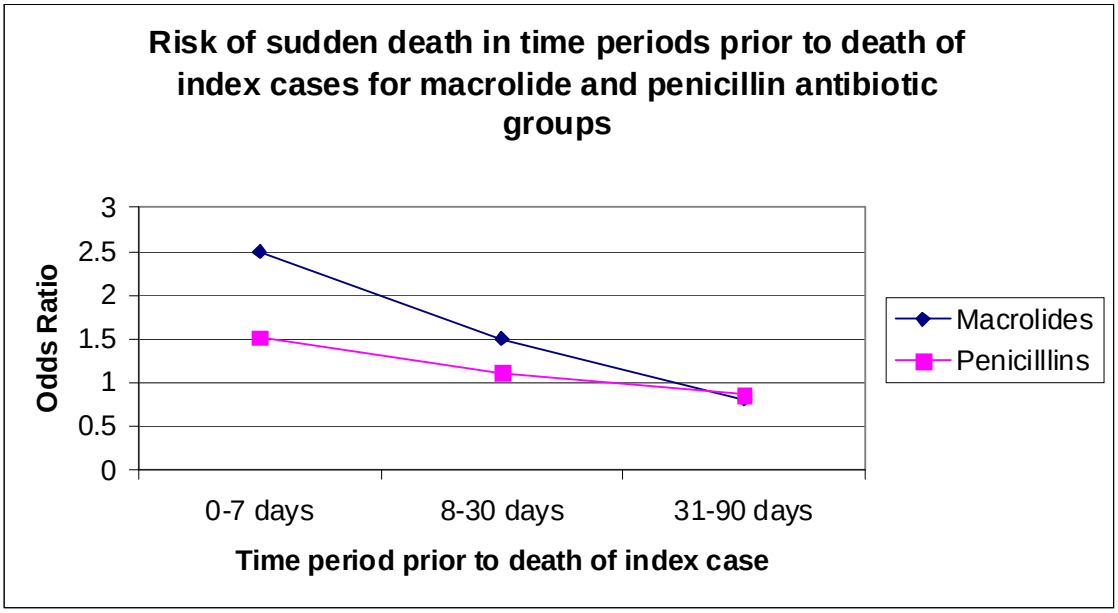
Table 45 Risk of sudden death with use of combined macrolide antibiotics within the three time periods

Odds ratios are not significant for grouped macrolides in any time period. There is a trend for increased association with sudden death nearer the index case date of death.

	Cases N	Controls N	OR	95% CI	p value
0-7 days	5	6	2.5	0.76, 8.19	0.130
8-30 days	4	8	1.5	0.45, 4.98	0.508
31-90 days	7	26	0.81	0.35, 1.89	0.626

Odds ratios are not significant for grouped macrolides or penicillins in any time period. Both grouped antibiotics show a trend for increased association with sudden death nearer the index case date of death. This trend is more pronounced for macrolides.

Fig 9. Comparing risk of sudden death between macrolides and penicillins according to time of drug exposure



5.5.5.2 Comparing anti-arrhythmics

I compared current use of registry type 1 anti-arrhythmics that are associated with torsades de pointes with those that are not (Table 47). Non adjusted odds ratios significantly greater than zero were found for current use of the type 1 anti-arrhythmic amiodarone OR 2.6 (1.24, 5.46) and for grouped type 1 anti-arrhythmics OR 1.89 (1.03, 3.47) (Table 46).

No significant effect was found for current use of the anti-arrhythmic flecainide OR 1.0 (0.10, 9.61) or for verapamil OR 0.43 (0.17, 1.14) or for grouped comparator anti-arrhythmics OR 0.48 (0.2, 1.17).

Table 46 Risk of sudden death with current use of anti-arrhythmics

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amiodarone	13	15	2.6*	1.24, 5.46	0.012
Disopyramide	0	1	----------	----------	----------
Sotalol	4	11	1.09	0.35, 3.43	0.882
Type1 Antiarrhythmics	**17**	**27**	**1.89***	**1.03, 3.47**	**0.040**
Flecainide	1	3	1.0	0.10, 9.61	1.0
Verapamil	5	33	0.43	0.17, 1.14	0.091
Combined comparator antiarrhythmics	**6**	**36**	**0.48**	**0.2, 1.17**	**0.107**

* significant at $\alpha = 0.05$

5.5.5.3 Comparing type 1 anti-psychotic medications

To explore confounding confounding by mental illness I compared registry type 1 anti-psychotics with antipsychotic medications that are not generally accepted to have a risk of causing Torsades de Pointes (Table 47).

A significantly raised odds ratio was found for current use of the registry type 1 drug haloperidol OR 6.0 (1.10, 32.76) and for grouped type 1 antipsychotics OR 3.86 (1.44, 10.36).

Chlorpromazine and thioridazine are phenothiazines. The closest comparator to them in this thesis is fluphenazine and prochlorperazine because they are also phenothiazines which is why I chose them.

There are no significant odds ratios for any single or grouped comparator drug. Fluphenazine amd prochlorperazine are group 3 phenothiazines which are typically prescribed for nausea and vertigo rather than psychosis and thus are not an ideal comparator.

Table 47 Risk of sudden death with current use of registry type 1 antipsychotics with comparator antipsychotics

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Chlorpromazine	3	5	1.8	0.43, 7.53	0.421
Thioridizine	2	0	----------	----------	----------
Haloperidol	4	2	6.0*	1.10, 32.76	0.039
Type 1 Antipsychotics	**9**	**7**	**3.86***	**1.44, 10.36**	**0.007**
Fluphenazine	1	2	1.5	0.14, 16.54	0.741
Prochlorperazine	8	21	1.14	0.51, 2.59	0.748
Flupentixol	3	2	4.5	0.75, 26.9	0.099
All Comparators	**12**	**25**	**1.44**	**0.72, 2.87**	**0.299**

* significant at $\alpha = 0.05$

5.5.5.4 Comparing Type 2 anti-psychotic medications

A highly significant unadjusted odds ratio was obtained for risperidone 6.0 (2.57 14.02) and for quetiapine and risperidone combined 4.36 (2.03 9.40) A highly significant odds ratio was obtained for comparator drugs amisulpride 18.0 (2.17 149.5) and for olanzapine 5.14 (2.02, 3.06) and for both both amisulpride and olanzapine combined 6.75 (2.94, 15.52) (Table 48).

Table 48 Risk of sudden death with current use of registry type 2 antipsychotic medication compared with non registry antipsychotics

	Cases N	**Controls N**	**OR**	**P value**	**95% CI**	**p value**
Quetiapine (type2)	0	3	-------	-------	----------	----------
Risperidone (type2)	16	8	6.0*	0.000	2.57, 14.02	0.000
TOTAL	**16**	**11**	**4.36***	**0.000**	**2.03, 9.40**	**0.000**
Amisulpride (comparator)	6	1	18.0*	0.007	2.17, 149.5	0.007
Olanzapine (comparator)	12	7	5.14*	0.001	2.02, 13.06	0.001
TOTAL	**18**	**8**	**6.75***	**0.000**	**2.94, 15.52**	**0.000**

* significant at $\alpha = 0.05$

5.5.5.5 Comparing Arizona type 4 antidepressant medications

Significant unadjusted odds ratios were obtained for citalopram, fluoxetine, paroxetine and for combined use (Table 34).

The most commonly prescribed anti-depressant comparator in this sample is escitalopram. Results for the comparator drug are similar to individual type 4 antidepressant drugs. The odds ratio for escitalopram was raised but not significantly (Table 49).

Table 49 Risk of sudden death with use of a comparator antidepressant medication

	Cases N	Controls N	OR	95% CI	p value
Escitalopram	4	7	1.71	0.50, 5.86	0.390

5.5.6 Effect of taking more than one QT prolonging registry medication

Individuals taking more than 1 QT prolonging drug may be exposed to an additive effect. The hypothesis that QT prolonging drugs are associated with sudden death is supported if associations between sudden death and multiple medication use are found and weakened if it is not because if our hypothesis is correct we would expect a dose response effect.

There are proportionally more cases than controls on 1 or more QT prolonging medications. The difference increases as the number of medications increases (Table 50).

Table 50 Risk of sudden death with increasing concommittent current use of all registry QT prolonging medication

Number Medications	Cases n (%)	Controls n (%)	Ratio (%cases/%controls)
5	1 (0.1%)	0 (0.0%)	-----
4	4 (0.5%)	2 (0.1%)	6.0
3	16 (2.0%)	22 (0.9%)	2.18
2	55 (7.0%)	111 (4.7%)	1.49
1	180 (22.8%)	437 (18.5%)	1.24

I compared concommittent use of Arizona QT prolonging drugs with non Arizona drugs.

5.5.6.1 Effect of taking more than one non registry medication

For non registry drugs there is an increasing trend from one to seven drugs for cases to have proportionally more concomitant prescriptions. From seven to seventeen drugs there is no trend (Table 51).

Table 51 Risk of sudden death with increasing concomitant current use of all non registry drugs

Number Medications	Cases n (%)	Controls n (%)	Ratio (%cases/%controls)
> 15	7 (0.89%)	3 (0.13%)	7.00
15	6 (0.76%)	2 (0.08%)	9.00
14	6 (0.76%)	10 (0.42%)	1.80
13	4 (0.51%)	3 (0.13%)	4.00
12	12 (1.5%)	29 (1.2%)	1.24
11	15 (1.9%)	43 (1.8%)	1.05
10	30 (3.8%)	40 (1.7%)	2.25
9	36 (4.6%)	67 (2.8%)	1.61
8	42 (5.3%)	118 (5.0%	1.07
7	53 (6.7%)	125 (5.3%)	1.27
6	61 (7.7%)	188 (7.9%)	0.97
5	64 (8.1%)	215 (9.08%)	0.89
4	88 (11.2%)	271 (11.5%)	0.97
3	76 (9.6%)	244 (10.3%)	0.93
2	72 (9.1%)	244 (10.3%)	0.89
1	37 (4.7%)	266 (11.2%)	0.42
0	180 (22.81%)	499 (21.08%)	1.08

5.5.7 Summary of principal results

Type 1 drugs are those with the greatest risk of torsades de pointes and they were associated with a doubling of mortality. Type 2 drugs, which have the next highest level of risk did not have a significantly raised odds ratio. A doubling of mortality was associated with type 4 medications, which are considered to have the least risk.

The majority of individual drugs in all registry classes had odds ratios greater than unity but in every class there were drugs that had odds ratios under that.
The most important finding is that drugs used for psychiatric purposes are associated consistently with sudden death. These drugs occur in all registry categories accounting largely for the unexpectedly strong effect in the type 4 drug class.

Anti-psychotic medications had the strongest association with mortality. Significant effects for combined use of chlorpromazine, haloperidol and thioridazine and for single use of risperidone remained high after adjustment.

Significant associations were found with combined use of anti-depressant medication and with single use of citalopam, dosulepin, fluoxetine and paroxetine.

There was an increase in the magnitude of effect from type 4 anti-depressant to types 1 and 2 anti-psychotic medication.

There was a significant association of sudden death with the type 1 macrolide erythromycin.

A strong trend was found for increasing association with sudden death nearer the index case date of death for combined macrolide antibiotic use and only a weak trend for the comparator combined use of penicillins.

A strong significant effect was evident for the non-adjusted analysis of current use of combined Arizona type 1 antiarrhythmics, the major contribution due to amiodarone. These drugs were given only to patients that were classified as having cardiovascular disease. After adjustment no significant odds ratios were obtained. There was no evidence of effect with comparator antiarrhythmics.

The association with sudden death increased with concommittent use of Arizona QT prolonging medication. There were proportionally more cases than controls on 1 or more QT prolonging medication. These differences increased steadily in magnitude as number of medications per person increased.

6 Discussion.

This chapter summarises the findings of this thesis and puts them into the context of the published literature.The strengths and limitations of the thesis are discussed and I will make recommendations.

6.1 The findings of this thesis

6.1.1 Exposure definition

The exposure was defined as the use of QTc prolonging drugs, as specified in the International Registry for Drug-induced Arrythmias maintained by the Georgetown University[173]. This is an internationally recognised register, which ensures there is general agreement about the categories of drugs used in the analysis.

6.1.2 Antipsychotics

6.1.2.1 Current use of anti-psychotics

Anti-psychotic medications were associated with the highest levels of mortality. For atypical antipsychotics, crude and adjusted associations were found with individual and combined drugs. There were only sixteen prescriptions for current use of typical antipsychotics and significance was obtained for the crude association between sudden death and haloperidol and the crude and adjusted association for combined antipsychotics.

6.1.2.2 Stratifying antipsychotics for cardiovascular disease

Combined use of chlorpromazine, haloperidol and thioridazine resulted in higher significant odds ratio in patients without cardiovascular disease but risk was not significantly raised in patients with cardiovascular disease. The opposite was true for

risperidone. It could be that these differences can be explained by drug prescribing habits or it could be that they are due to imprecise estimates because of the small number of prescriptions.

6.1.2.3 Comparing antipsychotic use

A powerful significant effect was found for current use of grouped registry type 1 antipsychotics. These drugs are are associated with Torsades de Pointes. It is possible that the association between sudden death and antipsychotic use is confounded by the conditions for which they are prescribed. To explore this possibility I compared type 1 antipsychotics with medications that are not generally accepted to have a risk of causing Torsades de Pointes. The comparator drugs were fluphenazine, prochlorperazine, and flupentixol. I did not find evidence of a significant effect for any single or grouped comparator drug. The group 3 phenothiazines are typically prescribed for nausea and vertigo rather than psychosis and they are often prescribed in low doses for these conditions and thus are not an ideal comparator.

6.1.2.4 Antipsychotics; comparison with other studies

The most important finding of this thesis was that medication associated with the greatest risk of sudden cardiac death was prescribed for serious mental illness. This is in line with the conclusions of other researchers.

A population based case control study in Holland that made use of a database with medical records from 150 general practitioners identified 554 cases of sudden cardiac death in a period of just over 6 years up to April 2001. The study found that current use of antipsychotic medication was associated with a 3 fold increase in risk of

sudden cardiac death and that the risk was highest in users of butyrophenone antipsychotics typified by haloperidol[192]. Risk of sudden cardiac death was highest among recent users but remained elevated during long term use. This latter finding could indicate confounding with conditions related to antipsychotic drug use. The design of this study, its numbers and results were similar to that found in my thesis. The authors recognised that people with serious mental illness are at a higher risk of death than people in the general population and adjusted, as I did, for known risk factors. They also adjusted for history of myocardial infarction, angina, heart failure, hypertension and alcohol abuse as well as for additional factors, cerebrovascular and cardiovascular ischaemia, diabetes mellitus, arrhythmia, hypercholesterolaemia, and smoking. It is notable that the results of this study are broadly in line with the results of this thesis despite some differences in identified covariates. Many of the covariates are associated with each other which results in a law of diminishing returns when adding extra covariates to the model.

A retrospective cohort study of 1487 sudden cardiac deaths in Medicaid employees in Tennessee USA found an odds ratio of 2.39 (95% confidence interval, 1.77-3.22) for antipsychotics. The authors found an increased risk for patients on antipsychotics that have cardiovascular disease OR 3.53 (95% CI, 1.66-7.51). I did not obtain this increased risk for cardiovascular patients in my thesis. Confidence intervals, overlapping with that in my thesis, are wide, reflecting lack of precision.

The authors also found a lower risk for former use OR 1.20 (95% CI, 0.91-1.58), an analysis that I could not do because I did not have information on patients taking medication beyond 3 months prior to death of case[193].

A Dutch population based case control study comprised 775 cases of sudden cardiac death and 6297 controls matched for age, gender, date of sudden death, and general practice. They found that the use of non-cardiac QTc-prolonging drugs in a general population is associated with an increased risk of sudden cardiac death[194]. The Dutch group had more cases taking Arizona type 1 medication but the differences were not great. This thesis agrees with the conclusion of the Dutch group that current use of antipsychotic QTc-prolonging drugs are associated with a significantly increased risk of sudden cardiac death.

The findings in this thesis of significant effects before and after adjustment for combined use of chlorpromazine, haloperidol and thioridazine and single use of risperidone were expected because odds ratios for haloperidol and risperidone have been linked to high rates of cardiac arrest[195].

6.1.2.5 Atypical antipsychotics

This thesis found a very strong association with the atypical antipsychotics risperidone and olanzapine and sudden cardiac death. The strength of my findings were surprising because risperidone, a type 2 drug, is not classified in the Arizona QT prolonging drug registry as a type 1 drug, the category considered to have the greatest risk and olanzapine is not categorised at all. It is unlikely that these results have arisen by chance because of the statistically high odds ratios. I could conclude that it is probably not plausible to believe that the strong association with sudden cardiac death and atypical antipsychotics is due to the direct action on cardiac tissue because it is not classified in the highest risk category. Alternatively, we should be mindful that we would expect fewer case reports linking the newer antipsychotics to sudden death

because they have been in use relatively recently. The very high odds ratios may be due to doctors selectively prescribing atypical antipsychotics to patients at higher risk. We may be seeing a strong confounding effect with factors associated with mental illness although this confounding effect was not noticeable with type 2 comparator drugs, venlafaxine or lithium. To try to remove the potential confounding effect of psychotic illness I also calculated the odds ratio of sudden death for the non QT prolonging drugs amisulpride and olanzapine with the same indication. I found powerful significant effects for amisulpride and olanzapine which were of similar magnitude to quetiapine and risperidone. These results imply the presence of strong confounding effects.

Epidemiological studies have reported raised risk of sudden cardiac death in patients taking atypical antipsychotics. A retrospective cohort study in Pennsylvania USA that involved 22,890 patients aged 65 years and older who received antipsychotic medication between 1994 and 2003 found that both atypical and conventional antipsychotic drugs were associated with a significantly high risk of death and that the risk of death was significantly greater in patients receiving the conventional medication[196]. A population based retrospective cohort study in Canada of 27,259 matched pair adults with dementia found that new use of atypical antipsychotics was associated with a statistically significant increase in the risk for death 30 days after initial dispensing but that this risk was less than that of conventional antipsychotics[197]. Risperidone[198] and olanzapine[199] have been shown to prolong cardiac repolarisation and are likely to enhance risk for QT prolongation and proarrhythmia in patients under conditions of impaired drug elimination such as renal or hepatic insufficiency and those taking interacting drugs.

On stratifying for cardiovascular disease this thesis found a very significant finding with risperidone and sudden cardiac death in cardiovascular patients. No significant effect was found with non-cardiovascular patients. This finding may have arisen because of a confounding effect of cardiovascular disease. In other studies risperidone with weight gain in the first year of treatment leading to increased risk of cardiovascular disease[200]. This weight gain is greater than that associated with the older generation of antipsychotics.

All antipsychotics are associated with sudden death in people with and without CVD. My finding that risperidone was more closely associated with SCD in CVD patients may indicate that alternative drugs should be used, however all antipsychotic drugs are a problem. This thesis is a case control study with very small numbers and findings need to be confirmed in cohort studies.

A recently published Tennessee Medicaid retrospective cohort study has found that current users of typical and atypical antipsychotic drugs had significantly higher incident rate ratios of SCD, approximately double that of non users and that there was no significant difference between typical and atypical drugs[201]. As in my thesis, deaths occurred outside of hospital. Sudden cardiac death was defined as a sudden pulseless condition that was fatal, that was consistent with a ventricular tachyarrhythmia, and that occurred in the absence of a known noncardiac condition as the proximate cause of the death. The end point excluded deaths of patients who had been admitted to the hospital, deaths that were not sudden, and deaths for which there was evidence of an extrinsic cause (e.g., drug overdose), a noncardiac cause (e.g., pneumonia), or a cardiac cause that was not consistent with a ventricular

tachyarrhythmia (e.g., heart failure). The primary analysis included 44,218 and 46,089 baseline users of single typical and atypical drugs respectively and 186,600 matched nonusers so was considerably more powered than my thesis. This increasing body of evidence regarding atypical antipsychotics supports my findings.

6.1.3 Antidepressants

6.1.3.1 Current use of antidepressants

Significant crude odds ratios were found for single use of citalopam, fluoxetine and paroxetine. After adjustment fluoxetine and dosulepin were significantly associated with sudden death. The significant adjusted result for dosulepin may be a chance finding due to the small number of prescriptions. I combined drug prescriptions to increase statistical power and found significant associations with sudden death before and after adjustment. The effect was diminished after adjustment which was expected because the effect of confounding variables was reduced.

I found that the association with sudden death and the selective serotonin reuptake inhibitor antidepressants (SSRIs) was as great as that with tricyclic antidepressants. A plausible mechanism exists because blockade of the HERG channel has been found for both drug classes, in the tricyclic antidepressant doxepin[202] and the SSRIs fluoxetine[203] and citalopram[204].

I had taken care to eliminate confounding with suicide by not choosing as cases people that had died in this way as identified by coroners post mortem. and recorded on the mortality files.

6.1.3.2 Stratifying antidepressants for cardiovascular disease

Crude and adjusted odds ratios were significant for combined use of antidepressants at similar levels in both cardiovascular and non cardiovascular patients. Paroxetine and fluoxetine were significantly associated with sudden death in cardiovascular patients; the association with paroxetine but not fluoxetine remained significant after adjustment. Sertraline was found to be significantly associated with sudden death in non cardiovascular patients before adjustment but not after. Numbers are small at the level of most individual drugs so the estimates of effect size lack precision.

A significant association between sudden cardiac death and depression is expected regardless of stratification for cardiovascular disease because a systematic review showed that depression confers a relative risk between 1.5 and 2.0 for the onset of coronary artery disease in undiagnosed individuals[205]. The review also concluded that depression in patients with existing coronary artery disease confers a relative risk between 1.5 and 2.5 for cardiac morbidity and mortality.

6.1.3.3 Comparing antidepressant use

I compared risk of sudden death between current use of Arizona type 4 anti-depressants and the comparator drug escitalopram. Combined odds ratios for Arizona type 4 anti-depressant drugs showed a significant effect whereas that for escitalopram, although raised thus indicating confounding, did not show such a strong effect.

An important result of this study is the consistency of the association between psychiatric medication and sudden death and the increase in magnitude from non-QT

prolonging comparator anti-depressant to Arizona type 4 anti-depressant to anti-psychotic.

6.1.3.4 Depression antidepressants and sudden cardiac death

Major depressive disorder affects approximately one sixth of the general population during their lifetime[206] An important finding of this thesis was that current use of antidepressants was associated with one of increased risk of SCD. This result is in agreement with other researchers. Meta-analyses of retrospective studies have shown an association between depression and fatal CHD or MI with a hazard ratio of 1.81 (95% CI: 1.53 to 2.15) over 10.8 years in 124,509 individuals[207] and with a hazard ratio of 1.64 (95% CI: 1.29 to 2.08) in 36,549 individuals[208]. The former study concluded that because of biased availability of adjustments, incomplete adjustments and reverse causality, depression could not be established as an independent risk factor.

An important question is how much confounding in the connection with antidepressant use and SCD is due to depression. I would expect confounding with depression because individuals with depression have diminished cardiac vagal control and may be at risk of ventricular arrhythmias[209]. Depression has been shown to be an independent risk factor for all cause mortality after acute MI in a subset of 358 depressed patients matched to 408 nondepressed patients followed up for 30 months on the ENRICHD clinical trial[210].

Recent prospective studies have been published that show a relationship with antidepressants and sudden cardiac death. Whang et al[211] studied 63,469 women in

the Nurses Health Study without baseline coronary disease, stroke, or malignancy for cardiovascular events on follow-up between 1992 and 2004. Questionnaires were administered every 2 years. The authors found that major depression and antidepressant use predicted nonfatal MI, sudden cardiac arrest, and fatal CHD events on multivariate analysis. Hazard ratios were stronger for fatal than for nonfatal events. Stepwise regression analysis found a hazard ratio between major depression or antidepressant use and sudden cardiac arrest of 2.33 (95% CI: 1.47 to 3.70, $p < 0.001$). Proportional hazards models showed that antidepressant use alone provided a higher hazard ratio for sudden cardiac arrest of 3.34 (95% CI: 2.03 to 5.50). The study indicates that there is an aetiological link between depression, treatment of depression and cardiovascular outcomes and provides evidence that depression is predominantly associated with sudden cardiac arrest via the use of antidepressant drugs. The relationship between antidepressants and sudden death could be due to an increase in ventricular arrhythmias.

Further recent work in a population based study that followed up 970 randomly selected individuals for 10 years, concluded after adjustment for age, sex, Framingham CVD risk score and depression that tricyclic antidepressant use was associated with an increased risk of coronary heart disease events (adjusted hazard ratio, 2.10; 95% CI. 1.09 – 4.06)[212]. The Tennessee Medicaid study showed increased risk for tricyclic antidepressants that was dose related[213].

SSRI antidepressants have not been associated with sudden death in the literature until recently. Previous studies indicated that they were safe. The SSRI sertraline did not prolong the QT interval or elevate mortality in patients with acute coronary syndrome

in a 24 week follow up period[214]. A case control study that had 1080 cases and 4256 controls concluded that SSRI use but not tricyclic use correlated with protection from a subsequent MI in inpatients that had a first MI[215]. Other studies gave cause for concern, SSRIs had been linked with ventricular arrhythmias, QT interval prolongation and arrhythmia[216] and increased mortality[217] in some small clinical studies. A randomised control trial that randomised 2481 post MI patients to treatment with SSRIs and cognitive behaviour therapy found that although the depression was improved the risk of death or recurrent MI was not affected[218]. The Nurses Health Study[211] found that 61% of patients prescribed antidepressants used SSRIs and the authors stated that there was no difference in the results for SSRIs and other antidepressant drugs.

Thus, recent evidence implying an aetiological link between both TCA and SSRI antidepressants and SDC are in agreement with my thesis.

6.1.4 Antiarrhythmics

6.1.4.1 Current use of antiarrhythmics

Significantly increased odds ratios were found for current use of the anti-arrhythmic amiodarone and for grouped registry type 1 anti-arrhythmics but not between sudden death and sotalol. Doctors tend to prescribe sotalol to patients at low risk because it has toxic effects. Sotalol is a beta blocker and this class of drug is known to have cardio-protective properties[219].

6.1.4.2 Comparing antiarrhythmics

I compared risk of sudden death between current use of Arizona type 1 anti-arrhythmics, amiodarone, sotalol and disopyramide which are medications associated with torsades de pointes, and non type 1 anti-arrhythmics, flecainide and verapamil and found no evidence of effect with comparator anti-arrhythmics, suggesting that the QT prolonging action increases risk of sudden death. Finding comparator drugs was difficult because of low numbers of prescriptions and because of the different mechanisms of action of the drugs such as verapamil which has a calcium channel blocking effect and is used in the treatment of angina and hypertension. These difficulties mean that the comparisons may not be robust.

6.1.5 Macrolides

6.1.5.1 Current use of macrolides

There were only eleven current prescriptions for macrolide antibiotics, seven for erythromycin and four for clarithromycin. Current use of erythromycin was significantly associated with sudden death before and after adjustment however no

significant association was found with grouped macrolides. Erythromycin in this thesis was only given to cardiovascular patients so it was not possible to stratify macrolides according to CVD status The results for current use of macrolides are not robust given such small numbers.

6.1.5.2 Temporal patterns in drug use

Changes in the numbers of prescriptions in the three month period prior to deaths of cases were apparent only for drugs prescribed on a weekly basis given for short term conditions, particularly antibiotics. Drugs that were prescribed continuously for longer periods of time such as psychiatric medication showed no significant changes in association with sudden death in the 3 month period for which data was collected.

6.1.5.3 Temporal patterns in drug use in macrolide antibiotics

I found that there was a significant association of sudden death with erythromycin in the period 0-7 days prior to death of case and no significant association in the period 8-30 days or 31-90 days. If this trend of increasing association nearer to death of index case was caused by the QT prolonging effect of erythromycin then we could expect to see a similar pattern with clarithromycin but no such pattern was found, possibly because there were even fewer prescriptions for clarithromycin. If the trend was confounded by infection then it would be expected to be found in the non QT prolonging penicillin drugs. Such a trend was evident but it was more pronounced for grouped macrolides than for grouped penicillins. Odds ratios were not significant for the penicillins.

The confounding effect of infection was limited by the study design which chose cases that were community dwelling adults who did not die of respiratory disease. I would expect that any remaining confounding effect due to infection would apply equally to macrolide and penicillin antibiotic use. Thus the finding of a more pronounced trend for increased use of macrolide antibiotic use nearer to date of death of index case compared with penicillin use requires an explanation. It could be due to QT prolonging effect of macrolide antibiotics.

6.1.5.4 Macrolides; a comparison with other studies

This study found that current use of macrolide antibiotics was associated with one of the greatest risks of sudden cardiac death. However only seven patients had been prescribed erythromycin so the result is very imprecise. The association between sudden death and erythromycin is in agreement with that of other researchers; the Tennessee Medicaid cohort study showed that current use of erythromycin was associated with a doubling of risk[220]. They found, as I did, that there was no significant increase in the risk of sudden death among those who were currently using the comparator drug amoxicillin.

A recently published study prospectively identified 1678 cases of sudden cardiac death in a 4 year period in Portland USA concluded that QTc prolonging drugs were predictors of SCD in coronary artery disease[221]. Subjects with known non-cardiac causes of death were excluded and cases were required to have documented coronary artery disease. A particular strength of the study was that cases had an ECG before and unrelated to the occurrence of SCD. A particular weakness of the study was that cases were on average 6 years older than controls and thus confounding with age

could have occurred. SCD was defined as a sudden unexpected pulseless condition of likely cardiac origin and if unwitnessed, SCDs were deaths within 24 hours of last being seen alive and in a normal state of health.

6.1.6 Dose response effects

The presence of a dose response effect is an indication, although not by itself sufficient, that an effect exists between exposure and outcome. I found that the risk of sudden death increased with concomitant use of Arizona QT prolonging medication. There were proportionally more cases than controls on 1 or more QT prolonging medication. These differences increased steadily in magnitude as the number of medications increases. There is also an increasing trend for cases to have proportionally more concomitant prescriptions for non Arizona medications which implies that prior to death cases were more sick than controls.

Summary statistics show that on average cases are prescribed more medication than controls. There is also a greater range of prescribed medication for cases. Odds ratios significantly associated with sudden death are therefore more likely.

6.2 Do people actually take the medicine that they are prescribed?

Patients do not always take the medications that they are prescribed. A cross sectional observational study in America that had the aim of assessing the accuracy of medication histories for prescription, over the counter and herbal medicines for patients taking at least 5 medicines, concluded that little is known about the accuracy of computerised medication lists. Patient medical records do not identify medications

that patients are being prescribed but are not taking, nor do they identify medications that patients buy over the counter at pharmacies[222].

Poor compliance has been found in elderly patients[223] and elderly patients with heart failure with shortcomings in patients' knowledge regarding prescribed medication, despite efforts to give adequate information[224]. Compliance with medication regimens is worse for psychiatric disorders compared with physical disorders and worse for antipsychotic drug use compared with antidepressant use[225].

The implication for this study is that if there is an association between sudden cardiac death and QT prolonging medication then a high rate of non-adherence to medication is likely to artificially reduce the association between sudden death and QT prolonging drugs unless factors associated with poor adherence are linked to sudden cardiac death which if so could cause a bias leading to a stronger association with sudden death. People may be less likely to adhere to their medication for conditions when they do not perceive themselves as being ill, for example hypertension. Non adherence in drugs that are protective against SCD could increase death rates.

6.3 Internal validity and generality

Internal validity depends on study design, the measurements taken, the care with which they were done and the consideration of alternative explanations for perceived causal relationships. Generalisability is the extent to which research findings can be applied to a population and relies on internal validity.

The design was a case control study which is the weakest type of analytical study and although it can identify associations between exposure and outcome it cannot by itself be used as evidence to justify a causal relationship. It does however fulfil some of the criteria of causation[226]. The outcome, sudden cardiac death, cannot precede exposure. Significant strong associations were found with individual drugs and drugs grouped within classes. The concomitant use of medications was associated with increased risk. The hypothesis was plausible although the results were not always in accord with it. Alternative explanations for study findings were explored. The findings of this study were mostly consistent with the work of other researchers.

Every case had their cause of death verified by a post mortem report. Matching in the design and adjustment in the analysis increased the strength and the power of the analysis. Methodological issues around data gathering were explored and although mostly reassuring, some problems around diagnoses of medical conditions in GP medical notes were identified and resolved. The issue of confounding was explored in detail and alternative explanations explored through comparing drug results with non-QT prolonging comparators prescribed for similar indications. The cases and controls were drawn from four PCT areas in the Midlands, a large and ethnically diverse population of almost two million people with a predominantly white ethnic group. This population is more ethnically diverse than most other United Kingdom areas. Study results may be less generalisable to a population with a different ethnic mix.

6.4 Strengths and weaknesses of the study

A great strength of this study is that every case had a post-mortem report which is the reference standard for determining cause of death. Thus the error associated with

death certification data was greatly reduced. I was also able to obtain and analyse most post mortem reports to verify that the stated cause of death of the cases was accurate and consistent with cardiac arrhythmia.

A major weakness of the study was that because of the small number of individuals prescribed QT prolonging drugs it was underpowered to find associations with many individual medications. Confidence intervals are wide reflecting the imprecision of the estimates. Precision was improved but still often remained poor after analysing drugs combined in their classes. Numbers were often too small to justify the breakdown into the CVD and non CVD subgroups. I have done the analyses to explore the data and to compare with other studies.

It was a serious omission not to collect data on other known confounders such as diagnosis of mental illness, smoking and diabetes.

It is not possible to completely eliminate confounding from case control studies so it is not possible to say with certainty if significant findings with medication in this thesis are associated with risk or are due to confounding factors.

Matching in the design stage of the study eliminated the confounders, age and sex and mitigated against cardiovascular disease. This study obtained a perfect matching for sex and an extremely good matching for age with three days difference between mean average age of cases and controls.

There were limitations to matching for cardiovascular diseases because controls were not matched to cases on the basis of any individual cardiovascular condition or combination of cardiovascular conditions. Hypertension was by far the most common cardiovascular disease which led to a high prevalence of it in both cardiovascular cases and controls. Controls were more likely than cases to be put into the cardiovascular group on the basis of having hypertension. Cases were more likely to have serious cardiovascular conditions.

It cannot be assumed that there is equality for sudden death risk between the different cardiovascular disease subgroups. Neither can it be assumed that equality for sudden death risk exists within the subclasses, for example one person's hypertension may be more severe than another's. Therefore in the design stage the study did not control for sudden death risk with respect to the severity of cardiovascular disease between or within the cardiovascular subgroups. The imperfect matching for cardiovascular disease was addressed in two ways. Firstly significant associations with cardiovascular disease were identified and subsequently adjusted in the analysis. Secondly the inclusion of a subgroup without diagnosed CVD enabled a comparison between the cardiovascular and non cardiovascular subgroups.

Strong associations were found with sudden death and previous MI, heart failure, low serum potassium, atrial fibrillation, epilepsy, syncope, impaired liver function, drug misuse and alcohol abuse. All significant associations were used as covariates in the analysis. Odds ratios in the adjusted analysis were generally lower than those in the crude analysis which indicated that researchers had been successful in identifying and controlling for confounding factors beyond matching. Adjusted analysis did not

materially alter the combined odds ratios between sudden death and drugs in the Arizona registry classes.

I undertook many analyses but did not undertake multiple test adjustments. Bonferroni adjustments would in principle be possible[227] but given that there were 153 individual and combined tests for current use of Arizona drugs, they would only allow comparison with p values below 0.00034 to be significant[228] and would thus be of doubtful value given the reduction in power in an already underpowered study. In addition the main analyses were for the four Arizona groupings.

Data on epilepsy was collected to determine if we could find an association with sudden unexplained death; we did find an association. It has been estimated that about 30% of patients in the United Kingdom following seizure are given a diagnosis of epilepsy when syncope or arrhythmia is the appropriate diagnosis[229].

Cases are clearly more ill than controls, they are prescribed more medication, have more hospital visits and suffer in greater numbers with almost all cardiovascular conditions, notably past history of myocardial infarction and heart failure. These conditions make them more at risk of suffering a sudden death. However it is possible that doctors prescribe drugs with less risk to people that are sicker and thus considered to be more vulnerable to side effects.

6.5 Conclusions

My thesis identified and explored associations with medications that can affect cardiac conduction and sudden death and compared its findings with those of other

studies. Risk of sudden unexplained death from non cardiac drug treatment was concentrated in drugs used for psychiatric conditions. The argument that my findings may represent causal effects is strengthened by my further analysis that showed that differences were reduced but not eliminated after adjustment of odds ratios to take account of confounding diseases and because the separate analysis of individuals that had no prior clinical evidence of heart disease also mainly reduced but did not remove risks.

The associations between sudden death and prior disease found in this thesis and by others[29 30] indicate that cardiovascular disease was an important confounder for the association with QT prolonging drugs but in general with the exception of risperidone, adjustment in the analysis did not materially alter the results. It is possible that the risk of sudden death with the newer SSRI antidepressants and atypical antipsychotics is confounded by targeted prescribing of these drugs instead of the older drugs that have known toxicity. A strength of this thesis is that the cause of death was confirmed by post mortem examination for all cases, unlike other studies[194 213 220] that investigated the association between SCD and QT prolonging drugs. Prevalence for torsades de pointes is greater in women than in men so the unexpectedly high proportion of males in my thesis may be because men are more likely than women to have a post mortem[230].

6.6 Implications for clinicians and policymakers

Although a causal relationship for an association between QT prolonging medication and SCD has not yet been proved, the observational evidence is increasing thus there is a need for prescribers to focus on risk factor management. The prescriber's role is

vital in deciding whether the benefit of prescribing medication is greater than the risk. Ultimately the purpose of epidemiological research into the effects of pharmaceutical agents is to identify and quantify benefit and risk. Researchers have a duty to inform all members of the team involved in the prescribing and administering of medication about the possible adverse effects of medications as well as their benefits to enable them to make the best possible decisions.

It is important that prescribers are aware which drugs can prolong ventricular repolarisation and cause Torsades de pointes and know that the risk of these side effects varies between individuals according to sex, age and medical conditions. Excessive use of QT prolonging medication in any individual should be avoided provided that suitable alternative medications are available. In this context the role of the Medicines and Healthcare products Regulatory Agency (MHRA) is vital[231]. It is responsible for issuing graded alerts to healthcare professionals and organisations and publishes in print and online. The MHRA works with the Department of Health to promote healthcare policy such as enabling trained nurses and pharmacists to become prescribers and to help patients make better choices with better information and improved labelling. The MHRA is responsible for pharmacovigilance. Healthcare professionals and patients are able to report side effects through the MHRA Yellow Card Scheme and this information is shared with pharmaceutical companies. It is important that all prescribers are trained and are fully aware of pharmacovigilence procedures.

6.7 Recommendations

Case control studies are not capable of calculating absolute risk, which can be obtained from a cohort study. Recent cohort studies[211 212] have provided evidence for an aetiological link between antidepressant use and sudden cardiac death. There is a need for further large cohort studies to test if findings are consistent with the case control studies in the literature. A cohort study could use routinely collected data connected to mortality data. The linkage of the general practice research database (GPRD) which contains the anonymised medical records of patients registered at more than 480 practices throughout the United Kingdom to mortality data gives the potential of a much larger sample for further study of individual drugs because the GPRD is the largest and most validated database of its kind in the world. The relationship between QT prolonging medication and sudden cardiac death may only be finally decided by randomised controlled trials of QT versus non QT medication.

APPENDIX 1

Use of type 1 medications in periods 0-7, 8-30 and 31-90 days before death of index case

Table 52 Use of type 1 medications in 0-7 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amiodarone	13	15	2.6*	1.24, 5.46	0.012
Sotalol	4	11	1.09	0.35, 3.43	0.882
Disopyramide	0	1	----	----------	----
Antiarrhythmics	**17**	**27**	**1.89***	**1.03, 3.47**	**0.040**
Clarithromycin	0	4	----	----------	----
Erythromycin	5	2	7.5*	1.46, 38.66	0.016
Macrolides	**5**	**6**	**2.5**	**0.76, 8.19**	**0.130**
Chlorpromazine	3	5	1.8	0.43, 7.53	0.421
Haloperidol	2	1	6.0	0.54, 66.2	0.143
Thioridizine	2	0	----	----------	----
Antipsychotics	**7**	**6**	**3.5***	**1.18, 10.4**	**0.024**
Domperidone	4	8	1.5	0.45, 4.98	0.508
All Type1 (0-7 days)	**33**	**47**	**2.12***	**1.36, 3.32**	**0.001**

* significant at $\alpha = 0.05$.

Table 53 Use of type 1 medications in 8-30 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amiodarone	13	15	2.60*	1.24, 5.46	0.012
Sotalol	4	11	1.09	0.35, 3.43	0.882
Disopyramide	0	1	----	----------	----
Antiarrhythmics	**17**	**27**	**1.89***	**1.03 3.47**	**0.040**
Clarithromycin	1	2	1.5	0.14, 16.5	0.741
Erythromycin	3	6	1.5	0.38, 6.00	0.566
Macrolides	**4**	**8**	**1.5**	**0.45, 4.98**	**0.508**
Chlorpromazine	2	5	1.2	0.23, 6.19	0.827
Haloperidol	3	2	4.5	0.75, 26.3	0.099
Thioridizine	2	0	----	----------	----
Antipsychotics	**7**	**7**	**3.0***	**1.05, 8.56**	**0.040**
Domperidone	3	9	1.0	0.27, 3.69	1.0
All Type1 (8-30 days)	**31**	**51**	**1.82***	**1.17, 2.85**	**0.008**

* significant at $\alpha = 0.05$.

Table 54 Use of type 1 medications in 31-90 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amiodarone	13	15	2.6*	1.24, 5.46	0.012
Sotalol	4	11	1.09	0.35, 3.43	0.882
Disopyramide	0	1	----	----------	----
Antiarrhythmics	**17**	**27**	**1.89***	**1.03, 3.47**	**0.040**
Clarithromycin	2	5	1.2	0.23, 6.19	0.827
Erythromycin	5	21	0.72	0.27, 1.92	0.507
Macrolides	**7**	**26**	**0.81**	**0.35, 1.89**	**0.626**
Chlorpromazine	2	5	1.2	0.23, 6.19	1.0
Haloperidol	3	2	4.5	0.75, 26.93	0.099
Thioridizine	2	0	----	----------	----
Antipsychotics	**7**	**7**	**3.0***	**1.05, 8.56**	**0.040**
Domperidone	4	8	1.5	0.45, 4.98	0.508
All Type1 (31-90 days)	**35**	**67**	**1.58***	**1.04, 2.38**	**0.030**

* significant at $\alpha = 0.05$.

APPENDIX 2

Use of type 2 medications in periods 0-7, 8-30 and 31-90 days before death of index case

Table 55 Use of type 2 drugs in 0-7 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Alfuzosin	2	26	0.23*	0.05, 0.97	0.046
Amantadine	1	0	----	----------	----
Flecainide	1	3	1.00	0.10, 9.61	1.00
Indapamide	12	48	0.74	0.39, 1.41	0.362
Levofloxacin	0	1	----	----------	----
Lithium	4	8	1.5	0.45, 4.98	0.508
Nicardipine	1	2	1.5	0.14, 16.54	0.741
Ofloxacin	0	0	----	----------	----
Quetiapine	0	3	----	----------	----
Risperidone	14	8	5.25*	2.02, 12.51	0.000
Tamoxifen	1	11	0.27	0.04, 2.11	0.214
Tizanidine	0	0	----	----------	----
Vardenafil	0	4	----	----------	----
Venlafaxine	5	9	1.67	0.56, 4.97	0.360
Type2 (0-7 days)	**39**	**116**	**1.01**	**0.69, 1.47**	**0.962**

* significant at $\alpha = 0.05$.

Table 56 Use of type 2 drugs in 8-30 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Alfuzosin	3	27	0.33	0.10, 1.10	0.071
Amantadine	1	0	----------	----------	----------
Flecainide	1	3	1.0	0.10, 9.61	1.0
Indapamide	11	50	0.65	0.33, 1.26	0.202
Levofloxacin	0	0	---------	----------	----------
Lithium	4	8	1.5	0.45, 4.98	0.508
Nicardipine	1	2	1.5	0.14, 16.54	0.741
Ofloxacin	0	0	---------	----------	----------
Quetiapine	0	3	---------	----------	----------
Risperidone	15	8	5.63*	2.38, 13.27	0.000
Tamoxifen	1	11	0.27	0.04, 2.21	0.24
Tizinadine	0	1	---------	----------	----------
Vardenafil	0	5	---------	----------	----------
Venlafaxine	5	9	1.67	0.56, 4.97	0.360
Type2 (8-30 days)	40	119	1.01	0.70, 1.46	0.962

* significant at $\alpha = 0.05$.

Table 57 Use of type 2 drugs 31-90 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Alfuzosin	5	29	0.52	0.20, 1.34	0.173
Amantadine	1	0	-------	----------	----------
Flecainide	1	3	1.0	0.10, 9.61	1.0
Indapamide	10	53	0.55	0.28, 1.10	0.092
Levofloxacin	0	2	-------	----------	----------
Lithium	4	8	1.5	0.45, 4.98	0.508
Nicardipine	1	2	1.5	0.14, 16.54	0.741
Ofloxacin	0	7	-------	----------	----------
Quetiapine	0	2	-------	----------	----------
Risperidone	14	8	5.10*	2.13, 12.51	0.000
Tamoxifen	1	12	0.25	0.03, 1.92	0.183
Tizinadine	0	1	-------	----------	----------
Vardenafil	0	6	-------	----------	----------
Venlafaxine	5	8	1.875	0.61, 5.73	0.270
Type2 (31-90 days)	40	130	0.92	0.64, 1.32	0.647

* significant at $\alpha = 0.05$.

APPENDIX 3

Use of type 4 medications in periods 0-7, 8-30 and 31-90 days before death of index case

Table 58 Use of type 4 drugs in 0-7 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amitriptyline	13	29	1.39	0.72, 2.69	0.323
Ciprofloxacin	2	8	0.75	0.16, 3.53	0.716
Citalopram	11	18	1.83	0.87, 3.89	0.113
Clomipramine	2	4	1.5	0.27, 8.19	0.640
Dosulepin	10	17	1.89	0.82, 4.33	0.134
Fluoxetine	10	14	2.20	0.96, 5.05	0.062
Imipramine	1	4	0.75	0.08, 6.71	0.797
Itraconazole	0	0	----	----------	----
Nortriptyline	0	1	----	----------	----
Paroxetine	9	9	3.00	1.19, 7.56	0.020*
Sertraline	6	9	2.0	0.71, 5.62	0.188
Trimethoprim	3	5	1.80	0.43, 7.53	0.421
Trimipramine	1	0	----	----------	----
Type4 (0-7 days)	**66**	**117**	**1.78**	**1.29, 2.44**	**0.000***

* significant at $\alpha = 0.05$

Table 59 Use of type 4 drugs in 8-30 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amitriptyline	14	29	1.50	0.79, 2.85	0.215
Ciprofloxacin	4	10	1.26	0.39, 4.10	0.704
Citalopram	13	18	2.17	1.06, 4.42	0.034*
Clomipramine	2	4	1.5	0.27, 8.19	0.640
Dosulepin	12	18	2.15	0.99, 4.67	0.052
Fluoxetine	14	13	3.23	1.52, 6.87	0.002*
Imipramine	1	4	0.75	0.08, 6.71	0.797
Itraconazole	0	0	----------	----------	---------
Nortriptyline	0	1	----------	----------	---------
Paroxetine	10	9	3.33	1.35, 8.20	0.009*
Sertraline	5	9	1.67	0.56, 4.97	0.360
Trimethoprim	8	10	2.40	0.95, 6.08	0.065
Trimipramine	1	0	----------	----------	----------
Type4 (8-30 days)	**82**	**122**	**2.16**	**1.61, 2.91**	**0.000***

* significant at $\alpha = 0.05$.

Table 60 Use of type 4 drugs in 31-90 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Amitriptyline	18	34	1.64	0.92, 2.91	0.093
Ciprofloxacin	6	13	1.38	0.53, 3.64	0.510
Citalopram	15	15	3.00	1.47, 6.24	0.003*
Clomipramine	2	4	1.50	0.27, 8.19	0.640
Dosulepin	12	19	2.02	0.94, 4.34	0.070
Fluoxetine	14	13	3.23	1.52, 6.87	0.002*
Imipramine	1	4	0.75	0.08, 6.71	0.797
Itraconazole	0	1	----------	----------	----------
Nortriptyline	0	1	----------	----------	----------
Paroxetine	9	11	2.45	1.02, 5.92	0.046*
Sertraline	5	9	1.67	0.56, 4.97	0.360
Trimethoprim	6	25	0.72	0.30, 1.76	0.470
Trimipramine	1	1	3.0	0.19, 47.96	0.437
Type4 (31-90 days)	**85**	**145**	**1.89**	**1.42, 2.51**	**0.000***

* significant at $\alpha = 0.05$.

APPENDIX 4

Results for all type3 only drugs in all time periods are shown below.

Table 61 Use of type 3 drugs in 0-7 days before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Ephedrine	1	0	-----	----------	-----
Pseudoephedrine	1	2	1.50	0.14, 16.54	0.741
Salbutamol (Oral)	8	12	2.00	0.82, 4.89	0.129
Salbutamol (Inhaler	85	195	1.35*	1.03, 1.77	0.029
Salmeterol	34	66	1.59*	1.04, 2.45	0.033
Sibutramine	0	1	-----	----------	-----
Terbutaline	7	14	1.50	0.61, 3.72	0.381
Tolterodine	4	11	1.09	0.35, 3.43	0.882
Type 3 only (0-7days)	**108**	**245**	**1.38***	**1.08, 1.76**	**0.010**

* significant at $\alpha = 0.05$.

Table 62 Use of type 3 only drugs in 8-30 days within death of index case before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Ephedrine	0	0	----	----------	-----
Pseudoephedrine	1	4	0.75	0.08, 6.71	0.797
Salbutamol (Oral)	7	13	1.62	0.64, 4.05	0.306
Salbutamol (Inhaler	84	196	1.33*	1.01, 1.74	0.042
Salmeterol	35	66	1.64*	1.07, 2.52	0.022
Sibutramine	0	1	----	----------	------
Terbutaline	8	14	1.75	0.72, 4.24	0.217
Tolterodine	5	12	1.25	0.44, 3.55	0.675
Type 3 only (8-30 days)	**107**	**248**	**1.35***	**1.05, 1.72**	**0.017**

* significant at $\alpha = 0.05$.

Table 63 Use of type 3 only drugs in 31-90 days before death of index case before death of index case

	Cases N	**Controls N**	**OR**	**95% CI**	**p value**
Ephedrine	0	0	---	----------	-----
Pseudoephedrine	0	6	---	----------	-----
Salbutamol (Oral)	8	10	2.4	0.95, 6.08	0.065
Salbutamol (Inhaler	89	198	1.40*	1.07, 1.82	0.014
Salmeterol	40	70	1.78*	1.19, 2.66	0.005
Sibutramine	0	1	---	----------	---
Terbutaline	8	13	1.89	0.77, 4.66	0.166
Tolterodine	5	14	1.07	0.38, 3.04	0.893
Type 3 only (31-90 days)	**115**	**254**	**1.43***	**1.13, 1.82**	**0.003**

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