THERAPEUTIC ACHIEVEMENT WITH LONG-TERM ORAL ANTICOAGULANTS IN POST- MYOCARDIAL INFARCTION PATIENTS

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THERAPEUTIC ACHIEVEMENT WITH LONG-TERM ORAL ANTICOAGULANTS IN POST- MYOCARDIAL INFARCTION PATIENTS

THERAPEUTISCH EFFECT VAN ORALE ANTICOAGULANTIA NA HARTINFARCT

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Cover: The optimal intensity for long-term oral anticoagulant therapy in post- myocardial infarction patients. - Cover designed by Hyacintha Kraidy.

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To my dearest parents

"So they may have life and have it abundantly"
American University of Beirut

CONTENTS

Introduction 9

Chapter 1 11
Long-term oral anticoagulant therapy after myocardial infarction.

Chapter 2 31
Methods of double-blind titration in the ASPECT trial of anticoagulant therapy for myocardial infarction patients.

Chapter 3 57
The ASPECT trial - data processing.

Chapter 4 75
Assessment of therapeutic achievement in a long-term anticoagulant trial in post-myocardial infarction patients.

Chapter 5 91
Optimal intensity of oral anticoagulant therapy in post-myocardial infarction patients.

Chapter 6 107
Stroke and long-term anticoagulant therapy in post-myocardial infarction patients.

Chapter 7 119
General discussion.

Appendices
Appendix-A. ASPECT main results 127
Appendix-B. ASPECT forms 141

Summary 165
Samenvatting 169
Woorden van dank 173
Curriculum Vitae 175

INTRODUCTION

Treatment with oral anticoagulant therapy entails a delicate balance between over- (risk of bleeding) and under- (risk of thrombemboli) anticoagulation. Therapy is therefore monitored to maintain its anticoagulant effect within a narrow range. The main aim of this research was to determine the optimal intensity of long-term anticoagulant therapy in 3404 post-myocardial infarction patients.

Chapter 1 gives a review of long-term clinical trials which assessed the merits of anticoagulant therapy in the secondary prevention of morbidity and mortality after myocardial infarction. This review includes the results of more than thirty trials reported in the literature in the past forty years, however, unpublished data or results of small trials, were not considered. Few of these trials were randomized, and the level of anticoagulation was properly maintained in only some of these studies. The results of most of these trials have failed to convincingly demonstrate the beneficial effects of long-term anticoagulant therapy as a secondary preventive measure and the use of such therapy has therefore remained controversial.

Chapters 2 and 3 describe the design and execution of the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial. The main results of this trial are submitted in Appendix-A. ASPECT was designed to be a randomized, double-blind, placebo controlled, multicentre trial which compared standard oral anticoagulant therapy with placebo with regards to mortality and cardiovascular events. Chapter 2 describes the design and procedures of the ASPECT trial in detail, in particular the methods for double-blind anticoagulant titration. Chapter 3 presents an outline of the data processing system as used in ASPECT. A standardized procedure which was developed for data handling insured a high level of data quality derived from the participating centres.

Chapters 4, 5 and 6 addresses the effectiveness and safety of oral anticoagulant therapy. Chapter 4 reviews various methods, previously described, to evaluate therapeutic achievement of anticoagulant therapy in the ASPECT trial. In Chapter 5, the optimal achieved intensity of anticoagulant therapy required to prevent recurrence of arterial thromboembolic and haemorrhagic complications was quantitatively evaluated with regard to the international normalized ratio (INR) intensity preceding the event, enabling the calculation of INR-specific incidence rates. The INR expresses the level of anticoagulant therapy in an internationally agreed term. It is the common term for the prothrombin time as measured in a patient on oral anticoagulant therapy. Chapter 6 gives a detailed description of the risk of stroke in the ASPECT population.

Finally, a discussion of the findings is provided in Chapter 7, followed by recommendations for further research.

CHAPTER ONE

LONG-TERM ORAL ANTICOAGULANT THERAPY AFTER MYOCARDIAL INFARCTION

AJ Azar and JW Deckers

INTRODUCTION

Among the multiple therapeutic interventions and publications in the past decades, few have given rise to as much controversy as the use of oral anticoagulant therapy in the prevention of re-infarction and death in survivors of myocardial infarction [1,2]. Following the discovery of dicumarol and other anticoagulant congeners, the use of these drugs came into clinical use in the late forties, at which time the need for randomized controlled clinical trials and blinding principles were not generally appreciated. Since then, a multitude of short and long-term clinical trials have been performed to evaluate the effectiveness of coumarin treatment for patients who had sustained a myocardial infarction [3]. Only few of these trials, however, were randomized and properly controlled [4]. The first largest non-randomized short-term clinical trial was conducted in 1948 when Wright assessed the benefits of dicumarol in the prevention of myocardial re-infarction [5]. This study, a non-randomized, open, short term trial of 6 weeks, inaugurated the anticoagulant era because a positive treatment for the reduction of mortality and myocardial infarction associated with dicumarol was reported [6]. The results of subsequent studies were also suggestive of possible benefits of long-term anticoagulant treatment, albeit against an increased risk of bleeding. The most recent Dutch ASPECT trial, the largest randomized, double-blind, placebo controlled, multicentre, clinical trial which evaluated the effectiveness of anticoagulant therapy in post myocardial infarction patients, was conducted to solve the anticoagulant controversy. ASPECT will be extensively described in this dissertation.

In this chapter, the discovery of anticoagulant factors will be described as well as their abundant use from the fifties until the early seventies, and a description of the major long-term clinical trials that assessed the benefits of anticoagulant therapy in the secondary prevention of myocardial infarction and associated morbidity and mortality will be presented.

THE ANTICOAGULANT FACTORS

Sweet clover disease

The anticoagulant era began in 1920 when farmers in the Dakota plains and Canada complained of the deaths of their cattle due to profused internal bleeding [7]. At that time, haemorrhagic disease was labelled in veterinary terms the 'sweet clover disease'[7,8]. The cattle consumed stacked sweet clover that flourished on poor soil used to substitute for corn.

In 1933 a Wisconsin farmer drove more than 300 kilometres to Karl Paul Link's laboratory: with him he had a can of uncoagulable milk and spoiled clover. Link, who once was a farmer himself, proceeded to find the cause of the disease. He wrote [7,8]:

> *"... on a Saturday afternoon in February 1933 ...while a blizzard was howling and the mercury was hovering near zero, a farmer from ... Wisconsin, some 190 miles ...the farmers name was Ed Carlson. The haemorrhagic sweet clover disease of cattle was rampant on his farm. He had fed sweet clover hay for years previously without encountering any difficulties ... Farmer Carlson's multiple evidence was a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover- the only hay he had to feed the cattle... He had to stop feeding that hay, and possibly transfuse those desperately sick cattle if he wanted to save them... I can still see him take off ... and his barn must have appeared to him like a trachureous and somber ocean ... Schoeffel stormed back and forth in the laboratory shouting ... "a farmer shtruggles nearly 200 miles in dis Sau-Wetter, driven by a shpectre and den has to go home vit promises dat might come true in five, ten, fifteen years, maybe never...Get some good hay-transfuse ... how can you do dat ven you haf no money ... Vat vill he find when he gets home ? Sicker cows ... vat vill dey haf on Monday? MORE DEAD COWS!! He has no udder hay to feed - he can't buy any."*

A few years thereafter, Roderick traced the cause of death of the cows by use of the Quick 1-stage method developed in 1935 by Armond Quick [8,9]. He found that the disease was due to congesting spoiled hay made from sweet clover. The improperly cured hay was found to produce a deficiency of a circulating procoagulant factor; prothrombin. Prothrombin converts to thrombin, one of the final steps in the coagulation pathway. The principal role of thrombin is to convert fibrinogen to fibrin which in turn combines to form a network. This network becomes a structured fibrin

clot that prevents excessive bleeding. The disease of the cows was reversed by stopping the feeding of the spoiled hay and substituting a vitamin K rich plant to their diet, such as alfalfa [7].

Discovery of Dicumarol

> *"Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it."*

The haemorrhagic agent which gave the sweet smell and bitter taste to the uncured hay was identified to be dicumarol by Campbell in Link's laboratory [7,10]. Coumarin upon oxidation and in the presence of formaldehyde converts to dicumarol. It was observed that the time between oral administration of dicumarol and its effect in each species tested took about one day with a cumulative effect following repeated administration with large individual variations. This lead to the conclusion that, to achieve optimal therapeutic effect, dosages needed to be individually adjusted [7]. Link and co-workers also synthesised other coumarin derivatives, including Warfarin, a compound that was subsequently used not only as oral anticoagulant in the battle against thrombosis in man but even more widely as a rodenticide.

The coagulation cascade

A dynamic equilibrium exists between the coagulation system and the fibrinolytic system. These systems are associated with the formation and degradation of fibrin within the blood vessels. With the occurrence of for instance a disruption of the endothelial layer, the haemostatic system triggers the coagulation cascade in a series of reactions to stop the bleeding while, at the same time, the fibrinolytic system is activated to prevent excessive coagulation. The various coagulation factors are synthesised in the liver and transported to the tissues by the blood. An uncontrolled haemostatic response may either lead to excessive bleeding or to fibrin formation at non-injured sites, and may thus reduce blood flow to important tissues such as the myocardium and the brain [11,12].

The intrinsic and the extrinsic pathways are the two major independent activation pathways involved in the activation of prothrombin to thrombin (see Figure 1.1) [13]. Contact activation initiates the intrinsic pathway by activation of factors XII (Hageman factor) to XIIa (activated Hageman factor) with the interaction of prekallikrein and high-molecular-weight kinogen (HMW Kinogen). Factor XIIa

activates factor XI which converts in a cascade the factors IX, VIII, X and V to their active forms [11,12]. Tissue activation starts the extrinsic coagulation pathway in a similar cascade like fashion, by separately activating factors VII, IX and X. Both pathways mediate thrombin formation from prothrombin. The final coagulation step is fibrin formation from fibrinogen under the influence of thrombin. The large fibrin fragments, the fibrin monomers, combine to form a network which in the presence of factor XIII (the fibrin stabilizing factor) and calcium becomes a structured fibrin clot. The production of the procoagulant factors II, VII, IX, and X, as well as the anticoagulant factors protein C and its co-factor protein S, depends on the availability of vitamin K, and is thus diminished in the absence of vitamin K [11]. Antithrombin III and proteins C and S are the most important natural coagulation inhibitors and help to balance the coagulation cascade [11,14].

Coumarin derivatives diminish the production of the vitamin K dependent coagulation factors by preventing their carboxylation as well as of the coagulation inhibitor proteins C and S [14-17]. These precursors of coagulation factors (PIVKAs: Protein Induced by Vitamin K Absence or Antagonists) circulate in the plasma but lack any coagulative properties [14,15,18]. Because the coumarin derivatives inhibit the synthesis of coagulation factors it takes some time before a new equilibrium at a lower coagulation level is reached.

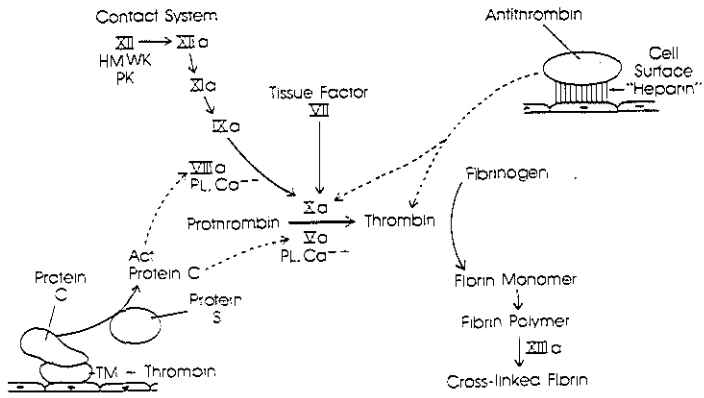

Figure 1.1 The coagulation cascade. Reproduced from Harrison's principles of internal medicine [11].

The most widely used test to control oral anticoagulant therapy is the one-stage prothrombin time test [14,16,19-24]. This test is sensitive to the reduction of three of the vitamin K dependent coagulation factors, i.e., factors II, VII and X [16] and measures the time needed for a plasma sample to clot when thromboplastin and calcium are added. Thromboplastin is a phospholipid-protein extract of tissue which contains the tissue factor and the phospholipid necessary to promote the activation of factor X by factor VII [16,20]. The prothrombin time is a measure of the extrinsic system coagulation activity [11,14,22]. The activated partial thromboplastin time, on the other hand, measures the intrinsic system coagulation activity and is used in patients on heparin therapy [11,14,22,25].

REVIEW OF LONG-TERM ANTICOAGULANT TRIALS

The therapeutic value of coumarin derivatives in the treatment of patients who suffer from deep venous thrombosis [1,15,26-29] and pulmonary embolism [16] is not disputed. In addition, prophylactic use of coumarin has been shown to prevent recurrent embolism secondary to intracardiac thrombi in patients with atrial fibrillation and enlarged left atria [16,30], or in patients with severely diminished left ventricular function [28]. Thromboembolic complications after major surgery [30,31] or after implantation of endovascular prosthetic materials [15,30,32-34] such as artificial heart valves, bifurcation prostheses or intracoronary stents are also prevented by oral anticoagulant therapy. However, the application of long-term anticoagulant therapy as a secondary preventive measure in patients who have sustained a myocardial infarction has remained controversial [20,28,35] although more than thirty randomized, non-randomized, blind and open trials have been reported in the literature. The results of the large clinical trials which assessed the benefits of long-term oral anticoagulant therapy after myocardial infarction will be reviewed in the following section.

Early trials (1950 - 1970)

In Norway, long-term anticoagulant therapy after myocardial infarction was introduced by Owren who described his initial clinical experience with coumarin in a group of 79 patients in 1948 [36]. In 1955, he subsequently published the results of active anticoagulant therapy with a duration of 1½ to 6 years in 247 patients. In 1957, Bjerkelund reported the effect of long-term dicumarol treatment in patients after recovery from acute myocardial infarction [36]. In that study, patients were assigned by ward to different treatment groups. Patients admitted to department 'seven' were assigned to the control group, patients admitted to department 'eight' were allocated

to long-term anticoagulant therapy, and patients admitted to department 'nine' were assigned to control or active therapy for alternating periods of approximately 6 months. On the whole, 118 patients were assigned to control and 119 to active therapy with a mean follow-up of 37 months. Mortality in placebo treated patients was 32.2% compared to 19.3% in the anticoagulated group, and the relative risk (RR) associated with anticoagulant therapy was 0.57 with a 95% confidence interval (CI) of 0.37 to 0.87. It was concluded that long-term anticoagulant therapy in the form of dicumarol reduced mortality. Myocardial infarction rates were also reduced [36] (39.8% in placebo and 21.8% after anticoagulant therapy (RR, 0.57; 95% CI 0.36,0.91)). These results as well as a summary of the findings of all long-term anticoagulant therapy in post myocardial infarction patients are presented in table 1.1.

Only few of these early trials were double-blind. The trial conducted by Borchgrevink in 1960 is a typical example of a randomized, single blind trial. This trial aimed to assess the merits of moderate versus intense long-term anticoagulant therapy which was measured using the prothrombin- proconvertin (P&P) method of Owren and Aas [37]. The patients studied were mainly suffering from angina, although a few had previously sustained a myocardial infarction [38]. The results of the trial were in favour of more intense anticoagulant therapy. In 1962, Harvald randomly allocated 315 post myocardial infarction patients by date of birth to either anticoagulant therapy (phenprocoumon or dicoumarol) or placebo [39]. Eighty five percent of the treated patients were found to be in the therapeutic range of 10%-25% on the basis of prothrombin time determinations. A lower death and re-infarction rates were detected in the treated group, but only during the first year. In addition, a higher risk of haemorrhagic complications was observed. The authors concluded that it was not justifiable to advise anticoagulant therapy routinely for long-term use after myocardial infarction.

The results of the first report of the working party to the British Medical Research Council (BMRC) in 1959 were in agreement with the positive findings of Bjerkelund previously described [38,40]. The drug phenindione was randomly given to 195 patients, and doses were adjusted to maintain the prothrombin time using brain thromboplastin 2-2.5 times the control values. The control group of 188 patients received low dose (1mg) phenindione which was insufficient to affect prothrombin time. Prothrombin times were only measured in the high dose group. The authors reported a lower death rate and a significant reduction in recurrent myocardial infarction during the three years of follow-up, against an increased risk of haemorrhagic episodes in the higher dose group. In their Second Report published in 1964, the mortality data at the end of 5 years were similar in both treatment groups, although the rate of reinfarction was less in the anticoagulant group [38,41,42]. One criticism of this investigation was that the trial was open and that the physicians, involved assessed the ECG's for reinfarction, knew the treatment being received and were thus not blinded.

In 1964, Aspenström allocated 131 patients in a non-randomized single blind study to receive either dicoumarol or placebo with a follow-up from 5 to 8 years [43]. The results of the study indicated a higher risk of cerebrovascular incidents in the anticoagulant group and no difference in mortality in the two groups.

Given these discrepant findings, long-term anticoagulant therapy in the prevention of ischemic heart disease was still controversial in the early sixties (Bjerkelund, 1957; Borchgrevink, 1960; Harvald, 1962; British Medical Research Council, 1959, 1964; and Aspenström, 1964). In addition, many physicians found the management of the anticoagulant treatment too demanding and therefore were abandoning its use [21]. The high frequency of haemorrhagic complications induced by anticoagulant therapy increased this controversy [36].

For this reason, in an attempt to reassess the values of long-term anticoagulant therapy, a second trial was conducted by Loeliger in the Netherlands, in 1967, the very first double-blind long-term anticoagulant trial [44]. In this relatively small study, 250 patients were randomly and in a double-blind manner allocated to receive either phenprocoumon or placebo. This trial achieved adequate therapeutic control: 68% of the patients had a Thrombotest value lying between 5%-10%. The mean daily dose of phenprocoumon was 2.8 mg. Death rates were similar in both treatment groups but reinfarction occurred more frequently in placebo as compared to the anticoagulated group (9.8% vs 1.6%). The authors emphasised that the favourable clinical outcome as well as the low rate of bleeding complications were the results of a high but stable intensity of hypocoagulability. In that same year, Lovel reported the results of a randomized trial in which 62 patients were allocated to heparin, 172 patients to phenprocoumon in doses aimed at reducing the prothrombin activity to between 15% and 30% of normal, and 178 patients to un-controlled low dose phenprocoumon. This trial demonstrated improved survival for the high dose group, but only over the first two years [45].

The final report of the Veterans Administration Cooperative Study was published in 1969 by Ebert [46]. In this study, patients were randomly allocated to receive either dicoumarol/warfarin or placebo and were followed for at least 2 years. The dose of warfarin was adjusted to maintain the one-stage prothrombin time, using human brain thromboplastin, between 2 to 2.5 times normal. Anticoagulant therapy was found to increase survival rate in the anticoagulated group during the first three years after an acute myocardial infarction. However, an increased risk of haemorrhagic episodes was observed.

In the same year, Sørensen published the results of a non-randomized trial with patients allocated to either dicoumarol or placebo depending on the day of admission. A 46% reduction in mortality was observed between the two groups in favour of anticoagulant therapy. A reduction in recurrent myocardial infarction was also reported in patients at least 60 years of age. The risk of haemorrhagic episodes was increased for the anticoagulated group.

Table 1.1 Results of long term anticoagulant therapy in post myocardial infarction patients

Author or study name (year)	country	design	mean follow-up	AC level (%in range)	treatment	No.	mortality (%) RR (95% C.I.)	recurrent MI (%) RR (95% C.I.)	extra-[1] cranial bleeding
Wright[2] (1948)	U.S.A.	non-randomized open	6 weeks	30-50 sec (Link-Shapiro)[3]	conventional vs dicumarol with or with-out heparin	368 432	23.9% - 15.0% 0.63 (0.4-0.84)	15.5% - 4.5% 0.28 (0.17-0.47)	22 - 53 -
Bjerkelund (1957)	Norway	non-randomized open	37 months	10%-20% P&P (46%)	no control dicumarol	118 119	32.2% - 19.3% 0.57 (0.37-0.87)	39.8% - 21.8% 0.57 (0.36-0.91)	8 - 37 -
Borgrevink (1960)	Norway	randomized single blind	17 months	10%-20% P&P (48%)	moderate vs intense anticoagulation	100 103	8.0% - 1.0% 0.12 (0.01-0.95)	13.0% - 1.9% 0.15 (0.035-0.65)	1 - 10 -
Harvald (1962)	Denmark	non-randomized open	31 months	10%-25% P&P (85%)	placebo vs phenprocoumon or dicoumarol	170 145	26.5% - 23.4% 0.89 (0.60-1.30)	39.4% - 35.9% 0.67 (0.50-0.90)	11 (38) 53 (102)
Medical Research Council (1959,1964)	U.K.	randomized open	25 months	doubling 1-stage PT (45%)	ineffective vs effective dose phenindione	188 195	21.3% - 14.9% 0.70 (0.45-1.1)	43.1% - 17.4% 0.41 (0.29-0.57)	10 - 80 -
Aspenstrom (1964)	Sweden	non-randomised singel blind	46 months	10%-25% P&P (69% P&P<30%)	ineffective vs effective dose dicoumarol	113 118	44.2% - 33.1% 0.75 (0.54-1.0)	45 events[4] 20 events[4]	17 (28) 56 (104)

Abbreviations:
AC, anticoagulant; No, number of patients per treatment group; RR, rate ratios; C.I., confidence intervals; MI, myocardial infarction; P&P, prothrombin-proconvertin; INR, international normalized ratio; PT, prothrombin time; TT, thrombotest.
[1]Number of patients and number of episodes (in brackets).
[2]This short term study has been included since it was the first large trial which assessed the merits of anticoagulant therapy in patients with an acute myocardial infarction.
[3]Modification of the Quick one-stage test.
[4]Number of patients with events not available.

Table 1.1 (contined) Results of long term anticoagulant therapy in post myocardial infarction patients

Author or study name (year)	country	design	mean follow-up	AC level (%in range)	treatment	No.	mortality (%) RR (95% C.I.)	recurrent MI (%) RR (95% C.I.)	extra-[1] cranial bleeding
Wasserman (1966)	U.S.A	randomised open	<36 months	10%-30% Quick 1-stage	no anticoagulant control vs warfarin	70 77	21.4% - 15.6% 0.73 (0.37-1.50)	-	6 - 13 -
Loeliger (1967)	Holland	randomised double blind	6 months	5%-10% TT (68.2%)	placebo vs phenprocoumon	122 128	9.0% - 6.3% 0.69 (0.29-1.67)	9.8% - 1.6% 0.16 (0.036-0.70)	1 - 17 -
Lovell (1967)	Australia	randomized open	18 months	15%-30% Prothrombin activity (67%)	ineffective vs effective dose phenprocoumon	178 172	21.9% - 19.2% 0.88 (0.58-1.32)	9.6% - 7.0% 0.73 (0.36-1.48)	0 - 48 -
U.S. veterans (1965,1969)	U.S.A	randomized sinlge blind	53 months	doubling 1-stage PT -	placebo vs dicoumarol or warfarin	359 388	31.8% - 30.9% 0.97 (0.79-1.20)	20.9% - 15.6% 0.75 (0.55-1.0)	- (11) - (72)
Sørensen (1969)	Denmark	non-randomized open	17 months	10%-30% P&P (74%)	placebo vs dicumarol	95 139	20.0% - 10.8% 0.54 (0.29-1.00)	39.0% - 5.0% 0.72 (0.12-0.62)	1 - 32 (34)
Meuwissen (1969)	Holland	randomized double blind	20 months	5%-15% TT (91%)	placebo vs phenprocoumon	70 68	11.4% - 1.5% 0.13 (0.017-1.0)	10.0% - 7.4% 0.74 (0.25-2.20)	0 - 7 (8)
Ritland (1969)	Norway	randomized open	12 months	20%-30% P&P (55%)	phenindione 3 mo. phenindione 12mo.	106 102	6.6% - 7,8% 1.17 (0.43-3.10)	8.5% - 4.9% 0.58 (0.20-1.66)	-
Seamen (1969)	U.S.A.	randomized double blind	73 months	10%-30% P&P (61%)	placebo vs phenindione	87 88	35.6% - 40.9% 1.15 (0.79-1.68)	37.9% - 40.0% 1.05 (0.72-1.52)	44 (96) 59 (179)

Table 1.1 (continued) Results of long term anticoagulant therapy in post myocardial infarction patients

Author or study name (year)	country	design	mean follow-up	AC level (% pts in range)	treatment	No.	mortality (%) RR (95% C.I.)	recurrent MI (%) RR (95% C.I.)	extra-cranial bleeding
Merskey (1974)	U.S.A.	randomized open	maximum 12 months	<10% TT (58%)	pacebo vs anticoagulant	153 175	23.5% - 16.6% 0.70 (0.45-1.09)	-	-
Breddin (1980)	German-Austrian	randomized open	24 months	5%-12% TT (58%)	placebo phenprocoumon	309 320	10.4% - 12.2% 1.18 (0.76-1.83)	8.1% - 5.0% 0.62 (0.34-1.13)	0 - 12 -
Sixty-Plus (1982)	Holland	randomized double blind	24 months	INR 2.7-4.5 (71.6%)	placebo vs acenocoumarin or phenprocoumon	439 439	15.7% - 11.6% 0.74 (0.53-1.04)	15.2% - 6.9% 0.45 (0.30-0.68)	- (10) - (84)
EPSIN group (1982)	France	randomized open	29 months	<35% prothrombin time (44%)	acetyl salycilic acid vs anticoagulant	651 652	11.1% - 10.3% 0.93 (0.68-1.27)	4.9% - 3.1% 0.62 (0.36-1.08)	35 (55) 104(171)
WARIS (1990)	Norway	randomized double blind	37 months	2.8-4.8 INR (67%)	placebo vs warfarin	607 607	20.3% - 15.5% 0.76 (0.60-0.98)	20.4% - 13.5% 0.66 (0.51-0.85)	- (25) - (52)
ASPECT (1992)	Holland	randomized double blind	37 months	2.8-4.8 INR (74%)	placebo vs acenocoumarin or phenprocoumon	1704 1700	11.1% - 10.0% 0.90 (0.73-1.11)	14.2% - 6.7% 0.47 (0.38-0.59)	17[5] - 56[5] -

[5]Number of patients with major extracranial bleeding.

Ritland [47] assessed the effect of 3 and 12 months anticoagulant therapy in patients who had survived their first myocardial infarction. Mortality and re-infarction rates were observed to be similar in both groups. These results may be attributed to the moderate anticoagulant intensity achieved.

The second Dutch trial that assessed long-term anticoagulant therapy after myocardial infarction was performed by Meuwissen in 1969 [6]. In a prospective double-blind trial, patients were randomly allocated to phenprocoumon or placebo. A significant decrease in mortality for the anticoagulated group was noted and only minor bleeding complications were observed in the anticoagulated group. The main drawback of this trial was the small number of patients. Nevertheless, the authors were convinced of the positive outcome and, at the end of the trial, switched all placebo patients to phenprocoumon treatment. In that era, the late sixties, long-term administration of oral anticoagulant therapy for patients suffering from myocardial infarction was increasingly being accepted by the medical community, at least in Europe [2,48]. In the United States of America long-term anticoagulant treatment for this indication was considered ineffective [50].

As an indication of the popularity of anticoagulant treatment in the Netherlands, Jordan, in 1949 founded the first anticoagulant control centre, the Thrombosis Centre which was build on voluntary basis [49]. Following this model, a nation-wide system of regionally centralized Thrombosis Centres for out-patients and home patients was subsequently established in the Netherlands [1].

Decline of the anticoagulant therapy (1970's)

Although the late sixties were considered as the anticoagulant era, long-term anticoagulant therapy was not yet very prominent during that time. Gifford, in 1969, was one of the first to comment on the poor methodological design of the early studies [51]. The positive findings were criticized because the trials were open, not properly randomized, historical controls were used and sample sizes were inadequate. On the other hand, the increased recognition of the role of thrombus formation in the pathogenesis of myocardial infarction was in favour of a more liberal use of anticoagulant therapy [41,52,59]. In an attempt to re-examine the controversy of this therapy, the International Anticoagulant Review Group (IARG), combined results of 9 published trials concerned with long-term anticoagulant administration in patients who had recovered from the acute phase of myocardial infarction in 1970 [35]. Treatment allocation of five of these trials were at random and the allocation method used was considered acceptable by the review group in the other four. In these 9 trials, the total number of patients at study amounted to 2487, 1230 in the anticoagulated and 1257 in the placebo group. Adequate level of anticoagulation was achieved in 50% of the trials only. Total mortality was 28.4% in the treated group and

30.5% in placebo. Based on the above, the IARG recommendations did not favour long-term anticoagulant therapy.

Chalmers and co-workers in 1977 also reviewed the evidence from 32 trials for short and long-term anticoagulant therapy. A total of 3854 patients were included in this analysis with 2106 patients in the anticoagulant group and 1748 placebo patients. A 21% mortality reduction was reported, but an increased risk of haemorrhages in the anticoagulated group (10.4% in the active treatment and 4.6% in placebo) [3]. The authors concluded that 'anticoagulant therapy is beneficial after acute myocardial infarction' and that 'further experimental trials would be unethical'. This review also reported a 50% reduction in thromboembolic episodes and re-infarctions. Chalmer's review and the pooled results of the IARG were criticized because both reports pooled trials of dissimilar study designs, protocols and anticoagulant quality [8,53]. The results of the same 32 trials were subsequently re-examined by Peto [54] as well as by Armitage [55]. Peto demonstrated a 53% (95% CI, 46% to 60%) mortality reduction for the non-randomized trials and a 20% mortality reduction for the randomized trials (95% CI, 5% to 35%). Armitage confirmed Peto's results.

Meanwhile, Germany, France, and The Netherlands remained unconvinced regarding the role of long-term anticoagulant therapy. The three following randomized trials were then conducted: (1) the German-Austrian Aspirin Trial in 1980 [56]; (2) the EPSIM group trial: Enquête de Prévention Secondaire de l'Infarctus du Myocarde in 1982 [57]; and (3) the Sixty Plus Re-infarction Study in 1982 [58,60,61].

The German-Austrian Aspirin Trial had one placebo and two active intervention groups: acetyl salicylic acid in 317 patients, phenprocoumon in 320 patients and placebo in 309 patients [41,56]. The trial was double-blind for acetyl salicylic acid and placebo and open for phenprocoumon. The dose of phenprocoumon was adjusted to maintain thrombotest levels between 5%-12% corresponding to an INR of about 2.5-5.0. Patients treated with acetyl salicylic acid received 1.5 g daily. No differences in mortality or myocardial infarction between the anticoagulant and placebo treatment groups was found but a trend in favour of aspirin. Also, a higher risk of haemorrhages in the group treated with anticoagulants as compared to placebo was observed. However, the results of this trial were disputed because of the definition of the end-points used, a combination of sudden death and myocardial infarction [4].

The EPSIM research group randomized patients admitted to coronary care units to anticoagulant therapy or aspirin [57]. A placebo group was not included for comparison. No marked differences between the two groups (11.1% mortality in aspirin and 10.3% on anticoagulant therapy) were observed. The negative findings were attributed to the inadequacy of anticoagulant therapy, since only 44% of the patients had a prothrombin time level below 35% prothrombin activity in a six months period.

The first two trials, the German-Austrian and that of the EPSIM research group, not only assessed the use of anticoagulant therapy but also of aspirin. There was no

substantial mortality reduction in the anticoagulated group as compared to placebo or to aspirin. This may have been the result of the inadequate anticoagulant control. Again, the long standing and bitter controversy regarding long-term anticoagulant therapy was not resolved by these trials.

The 'Sixty-Plus' Re-infarction Study of the Netherlands (1980)

One of the major criticisms regarding the previous anticoagulant trials in patients with a sustained myocardial infarction, repeatedly emphasised by Poller [62] as well as by the Dutch haematologist Loeliger [30,63], was that, in order to obtain beneficial effects of long-term anticoagulant control, adequately maintained therapeutic quality control with experienced dosage regulation should be maintained [63]. In Loeliger's historical review on the use of anticoagulant drugs, an INR range of 2.8-4.8 (equivalent to prothrombin time levels of 5% - 10%) was considered to be the optimum therapeutic range. Patients with values below that range are at higher risk for thrombus formation and, at levels above a ratio of 5.0, at increased risk for occurrence of severe bleeding complications [63]. Loeliger stressed the poor methodology in the earlier post myocardial infarction trials. In his opinion, the increased risk of haemorrhagic complications observed in the previous trials was also associated with the poor quality of thromboplastin used to measure the prothrombin time. Moreover, the findings of most of the previous trials lacked external validity because of unsolved agreement on the intensity of anticoagulant therapy needed to achieve beneficial effects [1,31].

In order to circumvene the problem of variability in the sensitivity of thromboplastin, an internationally standardized prothrombin time prolongation range was introduced [64-66]. According to this new standard, thromboplastin needed to be calibrated against the primary international reference preparation of thromboplastin established by the World Health Organization (WHO) in 1976. By definition, this thromboplastin displayed an International Sensitivity Index (ISI) of 1.0 [64,65]. All thromboplastin in use had to be calibrated against this reference preparation and be assigned an ISI. By means of the latter, prothrombin times are translated into times or ratios found with the primary international reference preparation [16,65,67]. The procedure is relatively simple: the patient's prothrombin time is divided by the normal prothrombin time, and the ratio raised to the ISI is the INR (INR = prothrombin ratio^{ISI}).

To reappraise the value of oral anticoagulant therapy and with the availability of the prothrombin time standardization, the 'Sixty-Plus' Reinfarction Study was initiated by the Federation of Dutch Thrombosis Centres in 1976. Six centralized Thrombosis Centres agreed to participate in this trial [58]. The Dutch investigation included patients who were receiving anticoagulant therapy following a documented myocardial infarction that had occurred at least 6 months earlier. Eight hundred and

seventy eight patients were randomly allocated in a double-blind manner to continue anticoagulant therapy (439 patients) with either phenprocoumon or acenocoumarol or to discontinue active treatment (439 patients). The double-blind character of the trial was maintained by having both groups continue with the same pattern of visits to the Thrombosis Centre for blood tests. Consequently, 'dosage adjustments' were consequently also made in the placebo group. Excluded from the trial were patients with increased bleeding tendency, thromboembolism, resistant hypertension, atrial fibrillation, malignancy, mental illnesses or on a waiting list for cardiac surgery. The Thrombotest, a reliable and standardized modification of the prothrombin time test, was used to control anticoagulant therapy. This trial indeed achieved adequate therapeutic control because 78% of patients on phenprocoumon were found to be between the therapeutic range (thrombotest 5%-10%, at that time corresponding to an INR range of 2.7-4.5 INR), and 63% for acenocoumarin. Data analysis was carried on "intention-to-treat" as well as "clinical efficacy". The former takes into account relevant events occurring between time of randomization and the end of observation period according to original treatment allocation without considering changes in trial therapy occurring during the trial process. The "efficacy" analysis only included events that occurred within 28 days after discontinuation of trial medication. The mean age of patients at study was 62 years. After a mean follow-up of 2 years, a 26% reduction in all cause mortality (placebo 15.7% and active therapy 11.6%) was found on "intention-to-treat". Reduction in myocardial infarction for active therapy was 54% (placebo 15.2% and active therapy 6.9%). Thromboembolic events occurred less frequently in the anticoagulated group, but mortality related to thromboembolic events was similar in both treatment groups. A thirty seven percent reduction in intracranial events (placebo 4.8%, and active therapy 3.0%) was observed. The incidence of major and minor bleeding was higher in the anticoagulated group (107 vs 35 in placebo). Seventy five percent of the bleeding events occurred in patients within target therapeutic range. There were no deaths associated with bleeding. It was concluded that intensive and stable anticoagulant therapy substantially reduced the risk of death, recurrent myocardial infarction and intracranial events in post myocardial infarction patients when the anticoagulant level was kept between 2.7-4.5 INR in the majority of patients [58]. The risk of bleeding associated with well controlled anticoagulant level was considered to be acceptable [58].

Pooling of trials

In an other, more recent attempt to debate the value of long-term anticoagulant therapy, Leizorovicz and Boissel pooled data from 7 long-term anticoagulant trials [68]. The 'Sixty-Plus' Re-infarction Study was not included in this review because this trial was not considered to be a study in which anticoagulant therapy had been

initiated. In this pooled review, a 21% mortality was reported for the placebo group compared to 18% for treated patients. The reinfarction rates were 14% under placebo and 10% under active treatment. The pooled review of Leizorovicz and Boissel was criticized by Loeliger in 1984, since the quality of oral anticoagulant therapy had not been considered. Loeliger, by pooling the results from 19 prospective controlled clinical trials in post myocardial infarction patients, concluded that the rate of myocardial infarction was lowered by two-third and mortality by 40% in those studies that were able to adequately maintain therapeutic quality control, i.e. to achieve a level of anticoagulant therapy between 2.5 to 5.0 INR. However, Loeliger's conclusions were based on "efficacy" basis rather than on "intention-to-treat" analysis. If the latter analysis had been performed, a lower beneficial effect of oral anticoagulant therapy would have been obtained. Despite these positive effects, long term anticoagulant therapy for patients with a sustained myocardial infarction was not recommended by many investigators [4,10,41].

The problem of long-term oral anticoagulant therapy remained unsolved. In European countries, such as the Netherlands, France and some parts of Germany, a substantial number of patients who had a myocardial infarction were still receiving long-term oral anticoagulant therapy, whereas such treatment had long been abandoned in other countries, including the United States of America [69] and the United Kingdom.

The Norwegian Warfarin Re-infarction (WARIS) study (1990)

Results of the large Norwegian Warfarin Re-Infarction Study (WARIS) were recently published [70]. The primary aim of the WARIS study was to assess whether long-term treatment with warfarin would result in a reduction of mortality for patients who had recovered from an acute myocardial infarction. WARIS was a prospective, randomized, double-blind, late entry study, with stratification of patients according to the use of beta-blockers. In order to protect the double-blinding, placebo prothrombin times were also monitored. The level of anticoagulation aimed at was 5%-10% thrombotest, corresponding to an INR of between 2.8-4.8. The size of the study was based on a biennial mortality on placebo of 12.5% and on a 35% reduction in mortality by warfarin. In order to achieve 80% power and 5% significance level, a total of 1200 patients were needed. The total planned study period was 5 years, and included 3 years of enrollment and 2 years of follow-up. Exclusion criteria were age over 75 years, use of anticoagulants, malignant disease, life expectancy shorter than 2 years, high risk of bleeding and residence outside the study area. The first patient was accrued in 1983. At the end of the study, 1214 patients had been randomized. Six hundred and seven patients were randomly allocated to placebo and 607 to Warfarin. Quality control using the cross-sectional approach revealed that two-thirds

of the patients were within the pre-set range. After a mean follow-up of 37 months, mortality was 123 in placebo-treated and 94 in warfarin-treated patients, a 24% mortality reduction in favour of the warfarin treated group on "intention-to-treat". A 34% reduction in recurrent myocardial infarctions (124 on placebo, 82 on warfarin), and 55% reduction in the occurrence of cerebrovascular accidents (44 on placebo and 20 on warfarin) was observed on "intention-to-treat". The incidence of major extracranial as well as intracranial bleeding was only 0.6% per year. The authors concluded that warfarin significantly reduced mortality and recurrent myocardial infarction in patients who had sustained an acute myocardial infarction [70].

Summary

In summary, the value of long-term anticoagulant therapy after myocardial infarction has been evaluated in a large number of trials. Most of the early studies lacked scientific control groups and their randomization techniques employed could be criticized. In addition, they faced laboratory control problems in that a number of different laboratory tests were used to monitor anticoagulant therapy. The most widely used test was the one-stage prothrombin time test, introduced by Quick in 1935. The thromboplastin used to measure prothrombin time was prepared by different methods and, consequently, their sensitivity to the reduction of vitamin-K dependent clotting factors varied significantly. Therefore, the different thromboplastin reagents used which resulted in the same prothrombin time often reflected different levels of anticoagulant effects [16].

In general, the studies reported in the sixties showed a non-significant reduction in mortality, but significantly less thrombo-embolism in the anticoagulated group. This was offset by a higher risk of haemorrhagic episodes. In the seventies debate over the effectiveness of long-term anticoagulant therapy was prominent, but only three major studies were performed: Breddin [56], EPSIM [57], The 'Sixty-Plus' Re-infarction Study [58]. The German-Austrian trial (Breddin et.al) and the EPSIM research group not only assessed the use of anticoagulant therapy but also that of aspirin. In both trials, anticoagulant therapy was as effective as aspirin in reducing mortality and morbidity for patients who had sustained a myocardial infarction. The Dutch 'Sixty-Plus' Re-infarction Study was carefully performed and controlled but, in reality, assessed the risk of discontinuation of long-term anticoagulant therapy in patients with a previous transmural myocardial infarction. Cessation of long-term anticoagulant therapy induces a 'hypercoagulable state' that is associated with increased risk for thromboembolic events [58]. Nevertheless, the positive findings of the "Sixty-Plus" study reopened the long standing debate of long-term use of oral anticoagulant therapy after acute myocardial infarction. The positive results of the Norwegian (WARIS) study were subsequently published in the early nineties. The

largest randomized, double-blind, placebo controlled, multicentre clinical trial primarily assessed the efficacy of long-term anticoagulant therapy in the prevention of mortality in patients who had sustained a recent myocardial infarction was initiated in the Netherlands.

Why the Dutch ASPECT trial?

The present policy of long-term anticoagulant therapy in the Netherlands is based on the results of the three Dutch double-blind trials performed in the late sixties and seventies (Loeliger, Meuwissen, and the 'Sixty-Plus' Reinfarction Study) [58]. The 'Sixty-Plus' Re-infarction Study, a well designed and controlled study, reported a positive result for long-term anticoagulant therapy in patients who had survived a myocardial infarction. These patients were on anticoagulant therapy for a median of six years, the time between the infarction and entry into the trial. However, the 'Sixty-Plus' study did not answer the question whether oral anticoagulant therapy is efficacious in patients with a more recent myocardial infarction. Indeed, the authors stated that: "..it is not known whether the patients included are a random sample of those with a first myocardial infarction or whether in the period between the first myocardial infarction and entry into the study (median 6 years) a selective mechanism had in effect weeded out all those but those patients for whom anticoagulant therapy was beneficial.." [58]. They concluded that patients who are on long-term anticoagulant therapy should continue treatment. Also, the study did not address the question of efficacy of long-term anticoagulant therapy, and no information was available for younger and female subjects since the population was over 60 years of age and 85% male. Finally, the trial did not provide information on the duration of oral anticoagulant therapy and the risk of bleeding episodes. Thus, the uncertainties regarding the value of long-term anticoagulant therapy in patients with a recent myocardial infarction continued to exist after forty years of intense debate [71].

It seemed appropriate that the original members of the 'Sixty-Plus' Re-infarction Study group decided to conduct a study in the Netherlands that would re-examine the efficacy of long-term anticoagulant therapy in the prevention of myocardial infarction and death. The first draft of the ASPECT protocol was approved in 1981 by the Federation of Dutch Thrombosis Centres and the ASPECT research group was founded under its auspices. Funds were limited at that time, but the 'Praeventiefonds' of the Netherlands agreed to finance the ASPECT trial in 1985. In April 1986, the first ASPECT patient was admitted and in December 1992 the last patient was enrolled, bringing the total number of randomized patients to 3404. All patients were followed until June 1992. The results of ASPECT are presented in appendix A of this dissertation.

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CHAPTER TWO

METHODS OF DOUBLE-BLIND TITRATION IN THE ASPECT TRIAL OF ANTICOAGULANT THERAPY FOR MYOCARDIAL INFARCTION PATIENTS

AJ Azar, JGP Tijssen, JW Deckers and J Lubsen

THE CLINICAL TRIAL

In general, efficacy of treatment can only be judged by comparing groups receiving different treatments. This protects against Muench's Second Law which stated that: " Results can always be improved by omitting controls" [1,2].

The concept of controlled clinical trials is not a new one. As pointed out by the late A. Lilienfeld, the first successfully conducted trial goes back to the Old Testament, Daniel verses 12 through 15. The king assigned to one group of children the kings meal, meat and wine, and, to a comparable group of children, vegetables and water. Both groups were observed for ten days. The health status of the two groups was measured by "our countenance be looked upon". It was observed that the countenance of the group of children on vegetables and water "appeared fairer and fatter in flesh than those on the king's diet" [3,4].

To allow inference about efficacy, the groups compared should indeed be comparable. This was recognised, for instance, by James Lind in 1747, in an experiment regarding the etiology and treatment of scurvy in sailors. The study consisted of six dietary regimens with two patients per treatment group. He wrote:

"... I took twelve patients in the scurvy on board of the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, living in a proper apartment for the sick in the fore-hold; and had one diet common to all... Two of these were ordered each a quarter cider a day. Two others took twenty-five gutts of elixir vitriol...Two others took two spoonful of vinegar ...Two of the worst ...were put under a course of sea water....Two others had each two oranges and one lemon given them every day...The two remaining patients took ... garlic, mustard seed, rad raphan, balsam of Per, and gum myrrh ... The consequences was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them being at the end of six days fit for duty..."

Lind inferred that citrus fruit was essential for curing and subsequently preventing scurvy on board ship [3,5]. Fifty years later, in 1795, this was recognized by the British Navy, which required the inclusion of limes or lime juice in the diet on board of ships. In our century, just after World War II in 1948, the first well designed and strictly conducted clinical trial with random allocation was that of the British Medical Research Council trial on the efficacy of streptomycin in the treatment of pulmonary tuberculosis [6-8].

The principles of controlled clinical trials were emphasized by Sir Austin Breadford Hill in the late fifties [8-13]. He stated that the first step in conducting a clinical trial is the random allocation of patients to the study groups [9,13]. Randomization is the key to proper trial design as it ensures comparability of groups by distributing low and high risk subjects equally, thus balancing treatment groups. This guarantees validity of comparison between treatment groups [1,8-10,14-20].

In addition to randomization, double-blinding should be implemented to ensure that patient and investigator alike assess the outcome for each treatment group in a comparable manner [1,11,19-21]. Blinding is required when knowledge of actual treatment by both patient and physician may affect the way the outcomes under study, or possible side effects, are reported [1,19]. The drug under study is compared to a reference treatment, usually to placebo, in order to eliminate (extraneous) placebo effect from the comparison [22]. The use of proper randomization techniques, blinding and placebo controls should all be part of the protocol, as has been repeatedly emphasized by clinicians, epidemiologists as well as statisticians [10,17].

In a randomized, double-blind, placebo controlled trial patients who satisfy the requirements of the experiment and who gave consent to participate are randomly allocated to either the experimental treatment or the reference treatment. In most instances, treatment is administered blindly, such that neither the physician, patient, or statistician are aware of treatment allocation. Trial treatment duration can vary from hours or weeks to years. Patients are recruited during a certain period of time and data on their outcome are continuously gathered and checked, usually by a coordinating centre. Finally, after the data have been checked and cleaned, a statistical analysis is performed and a report generated, in which the trial results are presented and disseminated to the medical world.

The term "clinical trial", or "therapeutic trial" is used interchangeably in the literature [23]. The main objective of a clinical trial is to evaluate to what extent a specific therapeutic intervention reduces the incidence of the disease under investigation, or alters the course of the disease in comparison to a reference treatment. The clinical trial in itself should be seen as a device that measures a treatment effect: the treatment effect is measured by comparing frequencies of disease outcomes [22].

Clinical trials, in most instances placebo controlled, form the final phase of drug development but are also performed when the drug is already on the market. Multicentre clinical trials are large and complex, often involving a number of

institutions and investigators. Adherence to a single protocol is of vital importance to unify the conduct of a multicentre trial between the various participating clinical centres [24,25]. At the same time, a proper organizational structure is necessary to oversee the conduct of the trial [26]. Indeed, the concept of a controlled clinical trial not only involves a design and analysis procedure, but also constitutes a broad management task with proper planning, implementation, development and quality control [27,28].

A trial is appropriate in situations when clinicians hold different opinions regarding efficacy of certain treatment regimens, in particular in the presence of large variations in clinical practice. As indicated in chapter I, one such situation is the use of long-term treatment of oral anticoagulant therapy after myocardial infarction. Oral anticoagulant therapy was introduced in clinical practice in the early fifties. However, the early trials on its efficacy were performed with inappropriate methodologies according to modern standards. The 'Sixty-Plus' Re-infarction Study [29] also did not settle the anticoagulant issue either because of its specific design (see chapter I). Thus, the controversy regarding the institution of long-term oral anticoagulant therapy in order to reduce morbidity and mortality after myocardial infarction has continued and a new long-term clinical trial was called for. The ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial was designed to be a randomized, double-blind, placebo controlled, large scale, multicentre trial that compared standard oral anticoagulant therapy with placebo. In this chapter, the design and procedures of the ASPECT trial and in particular the methods for double-blind anticoagulant titration are described.

THE ASPECT TRIAL

Objectives

The main objective of the ASPECT trial was to investigate whether long-term anticoagulant therapy initiated shortly after hospital discharge would reduce total mortality of post myocardial infarction patients. Secondary objectives were to evaluate whether long-term anticoagulant therapy would decrease the incidence of recurrent myocardial infarction and whether anticoagulant therapy would affect cerebrovascular events and the occurrence or the severity of haemorrhagic episodes.

Outline of trial design

ASPECT was a randomized, double-blind, placebo controlled, multicentre, clinical trial in patients who had been hospitalized for acute myocardial infarction, with two

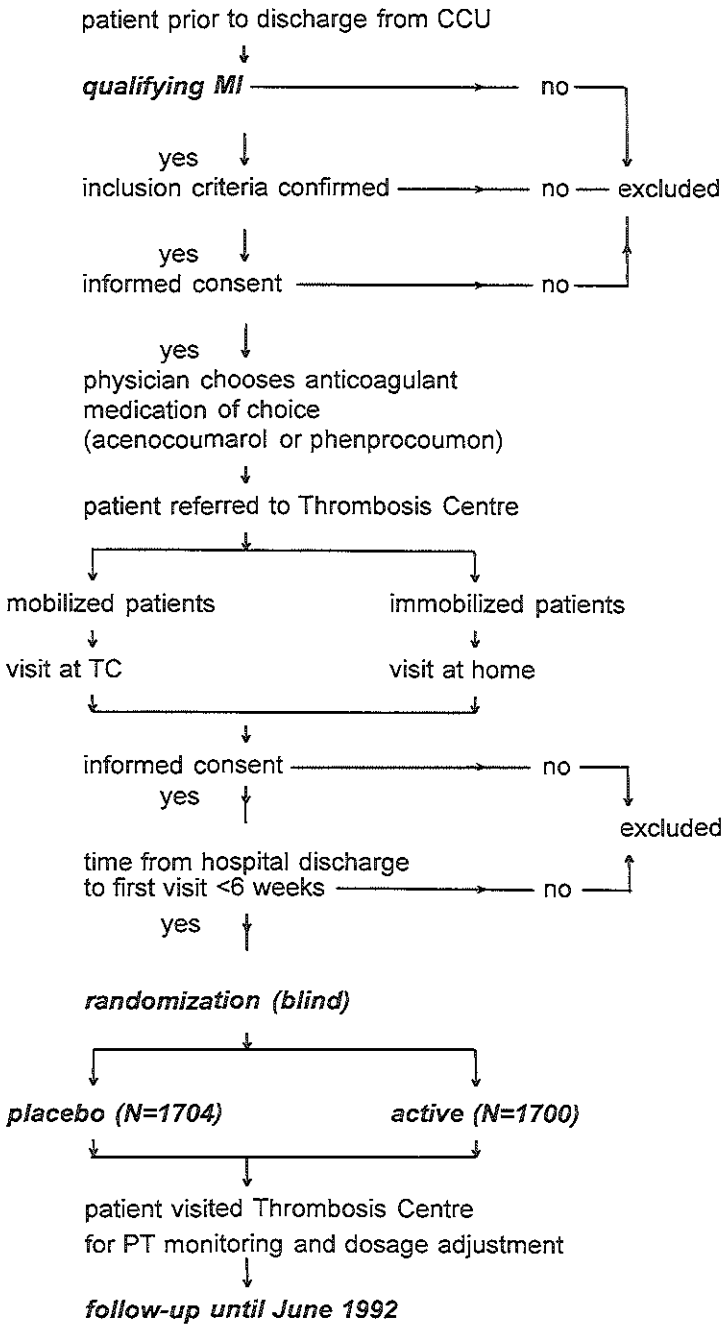


Figure 2.1 Flow chart of the ASPECT trial.
CCU, coronary care unit; TC, Thrombosis Centre; PT, prothrombin time

treatment arms: "active" anticoagulant therapy and matching placebo. Patients were eligible for entry up to six weeks after discharge from the hospital provided they met the selection criteria and had given informed consent. Treatment was initiated within four days after randomization and was continued until trial termination. Randomization was stratified by Thrombosis Centre according to the anticoagulant congener (acenocoumarin in tablets of 1 milligram (mg) or in tablets of 4 mg, or phenprocoumon in tablets of 3 mg) preferred or normally used by the referring cardiologist. Intensity of oral anticoagulant therapy was adjusted individually, guided by prothrombin time measurements. The target intensity was 10%-5% Thrombotest activity, equivalent to 2.8-4.8 international normalized ratio (INR) [30]. Therapeutic control was achieved by regular visits to the Thrombosis Centre for prothrombin time monitoring. Dosages and interval between visits for the placebo group were adjusted in such a manner that complete blindness of patient as well as treating physician was ensured.

While on trial medication, patients were not allowed to receive other anticoagulant or anti-platelet drugs. Patients in whom open anticoagulant therapy had been administered prior to randomization were requested to return this medication to their pharmacy.

Patients were recruited from September 1, 1986 until December 31, 1991. Data on mortality, cardiovascular events, cerebrovascular events and bleeding complications were gathered until June 30, 1992, for all patients irrespective of premature discontinuation of trial medication [Figure 2.1].

Patient selection

Inclusion and exclusion criteria

Prior to hospital discharge, male or female patients of any age with a transmural or non-transmural myocardial infarction were screened by the treating cardiologist for inclusion [appendix B.I]. The diagnosis of the qualifying myocardial infarction (or "index" infarction) was based on the presence of at least two of the following three criteria: (1) persistent chest pain typical for myocardial infarction; (2) at least one of the following cardiac enzymes raised to more than twice the upper limit of normal: creatine kinase (CK), MB iso-enzyme of creatine kinase (CK-MB), lactate dehydrogenase (LDH), alpha-hydroxybutyrate dehydrogenase (HBDH), serum glutamate oxalo-acetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT); and (3) evolving ST-T segment changes on the electrocardiogram.

Excluded were patients predisposed to bleeding or thromboembolism, such as those with a history of haemorrhagic diathesis, severe hepatic or renal insufficiency, severe hypertension not controlled by treatment, intracranial bleeding, surgery or

trauma of the cerebral nervous system within six weeks prior to hospital admission. Also excluded were patients with absolute indication for anticoagulant therapy, such as chronic or paroxysmal atrial fibrillation, left ventricular aneurysm, left ventricular thrombus (if known), rheumatic valve abnormality, venous or arterial thromboembolism, cardiomyopathy, or artificial cardiac valves. Patients on the waiting list for coronary bypass surgery and patients with known malignant disease, mental disorder, pregnancy, residence outside the study area or with other household members receiving active anticoagulant therapy were also not eligible.

Informed consent

Patients were informed by their referring cardiologist of the background and the objectives of the trial. Also, any possible side-effects associated with anticoagulant therapy, such as increased risk of bleeding episodes, were explained. Patients were also informed that therapy was initiated by random assignment to either placebo or verum. Patients were explicitly informed that they could refuse further participation and that they would receive normal standard care in that case.

The informed consent procedures were carried-out in full accordance with the principles of the "Declaration of Helsinki" [31]. Patients recruited to the trial gave their informed consent orally. The procedures were approved by the Ethical Committee of the participating hospitals. Informed consent was also extended to include permission for the Coordinating Centre to collect individual data on the clinical course. A guideline form was developed in which trial procedures were explained to the patient [appendix B.II]. Also provided was a form which described the follow-up schedules and the routine testing procedures of the Thrombosis Centres [appendix B.III]. The patient was given a 'patient card' which provided the information that the patient could be either on verum or placebo anticoagulant treatment. The patient was also given a telephone number to contact the Thrombosis Centre in cases of emergency.

Randomization and initiation of treatment

When a patient agreed to participate, the referring cardiologist notified the regional Thrombosis Centre and the Coordinating Centre. The referring cardiologist also indicated which anticoagulant congener should be given (acenocoumarin in tablets of 1 mg or in tablets of 4 mg, or phenprocoumon in tablets of 3 mg), if the patient were to be randomized to verum medication. Within four days up to a maximum of six weeks after notification by the cardiologist, the patient visited the Thrombosis Centre. Immobilized patients were visited at their home by a nurse. At this first visit, the patient was asked to confirm his previously given informed consent. If informed

consent was indeed confirmed, the next available randomization number was assigned to the patient.

The anticoagulant drugs and their matching placebo's were indistinguishable in appearance. Acenocoumarol was supplied by Ciba Geigy and phenprocoumon by Hoffmann-LaRoche. For each anticoagulant congener, bottles containing either verum or placebo were delivered to a local pharmacy in the cities where the Thrombosis Centres were located. The bottles contained a fixed number of tablets (acenocoumarin 1 mg: 400 tablets, 4 mg: 100 tablets, and phenprocoumon 3 mg: 100 tablets or matching placebo). The pharmacists were also provided with lists of treatment codes for each randomization number. For each randomization number, the pharmacist prepared a trial medication set of three bottles which contained, depending on treatment code, either verum or placebo. Upon the preparation of each set, the original label on each bottle was replaced by a new label which indicated the ASPECT randomization number (e.g. AMA0001), the anticoagulant congener 'MA' for Marcoumar® (phenprocoumon 3 mg) or placebo, or ASI0001, 'SI' for Sintrom® (acenocoumarin 4 mg) or placebo, or ASM0001, 'SM' for Sintrom mitis® (acenocoumarin 1 mg) or placebo), the number of tablets, and was marked "ASPECT medication trial". The pharmacists supplied the Thrombosis Centres with trial medication sets for each randomization number and provided additional sets if necessary.

After assignment of the randomization number, patient identifying information and the randomization number were entered into the Thrombosis Centre computer system. This moment was considered the time of initiation of trial medication and therefore the start of follow-up. The patient was seen at the Thrombosis Centre at the initial (i.e. randomization) visit (visit 1), after 4 to 7 days (visit 2), and subsequently on average once a week during the first month and once every 5 weeks thereafter. The patient was seen more frequently if complications occurred. Frequency and character of the visits were comparable to those of routine visits to the Thrombosis Centre. At each visit, the patient's history was taken, a blood sample was drawn and the dosages of the trial medication were adjusted. Dosage adjustment depended on the results of the prothrombin times which needed to be maintained between the normalized 105 and 180 seconds range corresponding to 10% and 5% or INR range of 2.8 and 4.8. The INR expresses the level of anticoagulation in an internationally agreed term. It is the common term for the prothrombin time as measured in a patient on oral anticoagulant therapy and normalized according to thromboplastin calibration standards [32]. The above range has been recommended as the target range for the prevention of arterial thrombosis by the Federation of Dutch Thrombosis Centres from the early 1970's onwards.

The Thrombotest reagent was used to determine the prothrombin time [33]. When a patient's plasma sample is added to the Thrombotest reagent, the clotting time only depends on the activity of factors II (prothrombin), VII (proconvertin) and X

(Stuart-Prower factor) [34,35]. In this chapter, as well as in all subsequent chapters, the clotting times obtained with Thrombotest are referred to as prothrombin times (PT). Based on the prothrombin time results, the dosages were calculated by the computer system and checked by the Thrombosis Centre physician in such a manner that an optimal therapeutic level was achieved: prothrombin times between the normalized 105-180 sec range.

The laboratory entered the prothrombin times into the Thrombosis Centre computer system. Under verum treatment prothrombin times ranged between 105 and 180 sec and under placebo medication the prothrombin time value was around 40 sec. For patients on verum the true prothrombin times at all visits were revealed to the Thrombosis Centre physician. In order not to break the double-blinding and in an attempt to obtain prothrombin times similar to verum, titration of placebo treated patients was simulated. The simulation program was developed by TRODIS and TDAS, two institutions responsible for installing and maintaining the anticoagulant dosage program at the participating Thrombosis Centres that employed their systems. The simulation program was automatically initiated at each visit. The range of the fake prothrombin times values was between 80 sec and 210 secs.

The algorithm was as follows: at the first visit of the ASPECT patient at the Thrombosis Centre, the factual prothrombin time were displayed unchanged both for patients assigned to verum and to placebo. At visit 2, a multiplication factor of 2 was given for patients on placebo matching phenprocoumon for those who used the TRODIS system. This was done since phenprocoumon takes a longer time than acenocoumarol to exert an effect. For placebo matching acenocoumarol, the simulation program was initiated at the second visit for TDAS users only. At all subsequent visits, both simulation programs were initiated for all anticoagulant congeners in placebo patients. The prothrombin times were displayed as follows: values below 45 sec were automatically multiplied by a multiplication factor related to the day of visit to the Thrombosis Centre, such that the range of those calculated values was between 80 sec and 210 sec. Beginning on January 1, the multiplication factor started at a value of 2.3 and increased daily with an increment of 0.1 until the maximum value of 4.7 was reached. The multiplication factor then decreased daily by 0.1 until the value of 2.3 was reached. This procedure was repeated until the end of the year. The transformed (fake) prothrombin times were stored, displayed and printed on all computer print-outs in which patients were identified as participants in ASPECT. However, the original prothrombin times could not be retrieved by either clinical Thrombosis Centre personnel or by computer professionals since they were overwritten by fake values. An example is illustrated here.

On January 8 a true prothrombin time value of 40 seconds was measured on the patient on his fifth visit to the Thrombosis Centre. This prothrombin time value was entered into the computer system and automatically transformed into a fake prothrombin time value of 120 seconds since a multiplication factor of 3.0 was applied

at that day. The 120 sec was consequently printed on all patient forms and the 40 sec was removed from the computer system. In order to avoid fake prothrombin times above the value of 210 sec, the simulation program for TRODIS users replaced values exceeding 55 sec with the value of 45 sec. Subsequently, the multiplication factor program was initiated. However, for TDAS users, the true prothrombin time was stored and displayed to the Thrombosis Centre's physician. A warning signal was displayed for placebo prothrombin times exceeding 55 sec for both TRODIS and TDAS systems and the patient was identified as a problem case. This procedure was developed in order to detect placebo patients inadvertently using verum. The multiplication factor program was also suppressed if vitamin K was administered for instance preceding a tooth extraction. Based on the prothrombin times (factual or fake), the computer system recommended a dose until the next visit, and, in case of a high prothrombin time value, recommended the case to be reviewed by the Thrombosis Centre physician who manually checked the prothrombin times and made a final decision on the dosage of trial medication until the next visit. In the whole process it was impossible for the patient, laboratory personnel, Coordinating Centre, and Data and Statistics Centre to be aware of treatment allocation.

The day following every subsequent visit, the patient was informed of the new anticoagulant dosage prescription and schedule until the next visit by mail. This information was given to the patient by telephone after the first visit. Visits were scheduled according to the normal routine procedures of the Thrombosis Centre. The computer system scheduled these visits, kept track of the amount of trial medication available to the patient and indicated when medication had to be issued and new supplies were needed.

Patients were encouraged to continue trial treatment until June 30, 1992. It was the right of the patient, the referring cardiologist or any other physician to discontinue trial medication for any reason at any moment. In case of an emergency, the cardiologist or any other physician could break the code by determining the prothrombin time value in his own laboratory. In the event of conditions in which trial medication had temporarily been discontinued, trial medication was resumed when possible. Patients who discontinued trial medication prematurely and were not placed on open anticoagulant therapy discontinued their regular visits to the Thrombosis Centre.

Data collection and follow-up

Entry of new patients was reported to the Coordinating Centre on a daily basis by the Thrombosis Centre [appendix B.IV). The patient's general practitioner and the referring cardiologist were also informed of the patients participation [appendix B.V]. Baseline information was gathered from the hospital records. Information on clinical

events was obtained either at the visits to the Thrombosis Centre or, in case patients had discontinued visiting the Thrombosis Centre, from the general practitioner. Additional information was gathered from the hospital records, if necessary.

Baseline information consisted of: age, sex, date of admission and discharge; data on previous medical history (angina pectoris, myocardial infarction, catheterisation, coronary bypass operation and percutaneous transluminal coronary angioplasty and cardiovascular risk factors: hypertension, presence of diabetes mellitus, family history and smoking habits); blood pressure and heart rate at admission and at discharge; peak blood haematology and bio-chemistry values during hospital stay (haemoglobin, haematocrit, thrombocyte count, enzyme values and cholesterol levels); Q-waves at discharge; ventricular tachycardia and fibrillation during the first 48 hours; heart failure graded according to the Killip classification (worst haemodynamic state during hospital stay); post infarction angina; second and third degree AV-block; extension of myocardial infarction; results from investigations during hospital stay (echocardiogram, radionuclide scan, ventriculography, coronary angiography, thallium perfusion scan and exercise test); interventions performed during hospital stay (percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, other cardiac or non-cardiac surgery, pacemaker implantation and cardioversion or defibrillation); cardiac thoracic ratio at discharge; and medications used during hospital stay and at discharge [appendix B.VI]. The last electrocardiogram (ECG) prior to hospital discharge was scored according to the Minnesota guidelines [36] and the Cardiac Infarction Injury Score [37] was obtained [appendix B.VII]. This reading of ECGs was performed by SEAL ('Stichting ECG-Analyse Leiden') in Leiden.

Follow-up data included detailed information on the following clinical events: death, hospital admissions, bleeding complications and discontinuation of trial medication. If a patient had died, information on time, cause and circumstances leading to death was collected. If a recurrent myocardial infarction was suspected, ECGs, data on occurrence of chest pain and cardiac enzyme values were obtained. If a cerebrovascular accident had occurred, relevant information on history and clinical course was obtained and a description of the CT-scan result by the neurologist or the radiologist was collected. If trial medication was prematurely discontinued, the date and reasons were recorded, as was subsequent antithrombotic treatment.

For patients under control of the Thrombosis Centre, all prothrombin times values were gathered, irrespective of discontinuation of trial medication. Patients were instructed to report any bleeding and were also specifically questioned about bleeding at each routine follow-up visit.

Outcome events

Definition of clinical events

Six major clinical events were considered: (1) death from any cause; (2) vascular event; (3) vascular death; (4) recurrent myocardial infarction (fatal or non-fatal); (5) cerebrovascular event; and (6) major bleeding. Vascular event was defined as vascular death or non-fatal myocardial infarction or non-fatal cerebrovascular event, whichever occurred first.

Vascular death included the following: 1) instantaneous or sudden death (all deaths occurring within 1 hour after onset of symptoms); 2) unobserved and unexpected death; 3) fatal recurrent myocardial infarction (death within 28 days after recurrent myocardial infarction, or the onset of symptoms of acute myocardial infarction with subsequent death); 4) death due to congestive heart failure (without a recent myocardial infarction within 28 days); 5) fatal cerebrovascular event; and 6) death due to extracranial bleeding. All other deaths were considered non-vascular.

Recurrent myocardial infarction was diagnosed when at least two of the following were present [38,39]: (1) a history of chest discomfort of at least 30 minutes duration; (2) serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme twice the upper limit of normal; or (3) the development of new Q-waves (lasting >0.03 seconds (sec) or of a Q-wave equivalent (R >0.03 sec in V1 and R/S >1 in V2)) on the standard 12-lead electrocardiogram (ECG) . The location of the recurrent myocardial infarction was determined from the ECG. Localisations were defined as follows: (1) anterior (septal) (leads V1, V2, V3, V4); (2) anterolateral (leads I, aVL, V5, V6); (3) inferior (leads II, III, aVF); and (4) undetermined. Patients with symptoms of acute myocardial infarction who subsequently died were categorised as fatal myocardial infarction.

Cerebrovascular events were diagnosed according to internationally accepted criteria for the assessment of cerebrovascular disease [40]. Brief attacks lasting less than 24 hours and leaving no residual symptoms were classified as TIA [40]. If death occurred within 24 hours, the case was classified as intracranial bleeding unless the findings on computed tomography (CT)-scanning indicated otherwise. Events lasting beyond 24 hours were specified as cerebral infarction or intracranial bleeding on the basis of CT-scanning, if available. If a CT-scan was not available the event was classified as unspecified. Of all cerebrovascular events the functional outcome was classified as death within 24 hour, death beyond 24 hours, survival with no disability, survival with mild disability (residual symptoms, but no impact on daily activities), survival with moderate disability (symptoms which significantly interfered with normal daily activities, with the patient being unable to live independently) or survival with severe disability (patient completely dependent in all activities of daily living).

A bleeding was considered major if it lead to death, was clinically suspected

or proven intracranial, or in cases of hospital admission for treatment of bleeding. All other bleeds including hospital admissions for diagnostic purposes were considered minor.

Classification of clinical events

The Mortality and Morbidity Classification Committee (MMCC) independently reviewed the clinical course of each of the above cases on the basis of a standardized patient report prepared by the trial coordinator. A narrative section describing the clinical course of the patient was complemented by a summary of all pertinent data (ECGs, enzyme values, description of the CT-scans, etc). Potential outcome events were reviewed irrespective of discontinuation of trial medication. The committee members were blinded to the patient's treatment allocation and were not informed of available prothrombin time measurements. The review was first carried out in writing [appendix B.VIII]. Cases which evoked differences of opinions were reviewed in plenary meetings. In the event of a cardiac complication the case was reviewed by the cardiology subcommittee and classified as acute myocardial infarction (see above definition), unstable angina pectoris, stable angina pectoris, rhythm disturbance, congestive heart failure, dissecting aneurysm, pericarditis, endocarditis, elective diagnostic procedures, non-cardiac chest pain, and aspecific chest pain. In the event of a neurological complication the case was reviewed by the neurology subcommittee. Diagnosis of intracranial haemorrhages were based on the findings on CT-scan or autopsy. In all other instances, the case was reviewed by the internal medicine subcommittee.

Definition of outcome events for trial medication effect assessment

The primary outcome event was death from all causes. Secondary outcome events were: (1) vascular event; and (2) vascular death; (3) recurrent myocardial infarction (fatal or non-fatal); (4) cerebrovascular event; and (5) major bleeding.

The main analysis consisted of a comparison of the incidence of the primary end-points in the trial medication groups. In this analysis, all randomized patients were included irrespective of previous discontinuation of trial medication ("intention-to-treat" analysis). Analysis involving secondary end-points were carried out as a supportive analysis. The occurrence of end-points was compared in terms of the hazard ratio; i.e, the risk of the outcome event per unit of time for patients assigned to anticoagulant treatment divided by the risk for those assigned to placebo. This analysis was based on a comparison of the time to first event or event free survival. Hazard ratios were obtained with the use of the Cox proportional-hazards model [41].

The precision of the hazard-ratio estimates were described by 95 percent confidence intervals obtained from the Cox model. For "intention-to-treat" analysis censoring was applied when the patient died or at the end of follow-up, on June 30, 1992. In a subsidiary analysis only those end-points that occurred while the patient was on trial treatment (or within 28 days after its cessation) were taken into account ("per-protocol" analysis).

Extracranial haemorrhages were reported by number of episodes. Episodes that led to hospital admission were separately indicated.

Intensity of treatment

Therapeutic anticoagulant quality control achieved by the various participating Thrombosis Centres was assessed by calculating the proportion of time spent by the patient within the prothrombin time target range of 105 sec - 180 sec corresponding to an INR range of 2.8-4.8. To this end, two methods were employed: (1) the 'cross-section-of-the-files' approach [34,35]; and (2) the cumulative methods [42]. The first method is based on a cross section through the total population and considered the last prothrombin time 6 months after the date of randomization. The second method considered all prothrombin times at 6 months from randomization until the end of trial or until the last visit to the Thrombosis Centre. Prothrombin times at 6 months were chosen since patients would have reached a stable condition at that time [34]. For both methods, all patients under control of the Thrombosis Centre, irrespective of discontinuation of trial medication, were included.

Trial size and interim analysis

Two types of errors had to be guarded against: type I (α) and type II (ß) errors. A type I error occurs when the trial is declared positive when in fact the biological difference between the anticoagulated and the control group is null. In ASPECT, a 5% significance level was set to guard against this type of error. The second type of error, type II, fails to declare a difference between the anticoagulated and control group when in fact they are different. The investigator must specify a priori the minimal relevant clinical difference to be detected with the desired probability (1 - ß) of reaching that difference. The probability (1 - ß) is referred to as the power of the test.

Sample size calculations were based on cumulative mortality. The estimated number of deaths needed and the estimated risk reduction in the control group were used to calculate the number of patients required. For a two-sided test with 5% significance level, power of 85%, and a 25% reduction in mortality by anticoagulant therapy, a total of 350 deaths were required. Under the assumption of a 10% biennial total mortality in the control group during an accrual period of 2 years and one year

Table 2.1 Cut off points for the one-sided p-value. The trial will be terminated at the respective interim evaluations if the one-sided p-value, calculated from the available data, is not between the corresponding limits.

Interim evaluation	lower boundary	upper boundary
interim 1	0.005	0.95
interim 2	0.005	0.88
interim 3	0.005	0.81
interim 4	0.014	0.74
interim 5	0.023	0.67
final analysis	0.032*	---

*This is not a formal boundary but the nominal level that makes the final results statistically significant at the 5% level.

Table 2.2 An example of results that precipitate early termination of ASPECT. It was assumed that mortality under placebo is as expected (column 3). Columns 4 and 5 give the number of deaths in the treated group which cause the p-value to be out of its boundaries.

Interim	no. patients accrued	no. deaths placebo (expected)	no. deaths active (required)	no. deaths active (required)
interim 1	1000	15	3	26
interim 2	2000	40	20	51
interim 3	3000	80	51	92
interim 4	4000	120	89	130
interim 5	4000	165	131	173
final analysis	4000	200	166	----

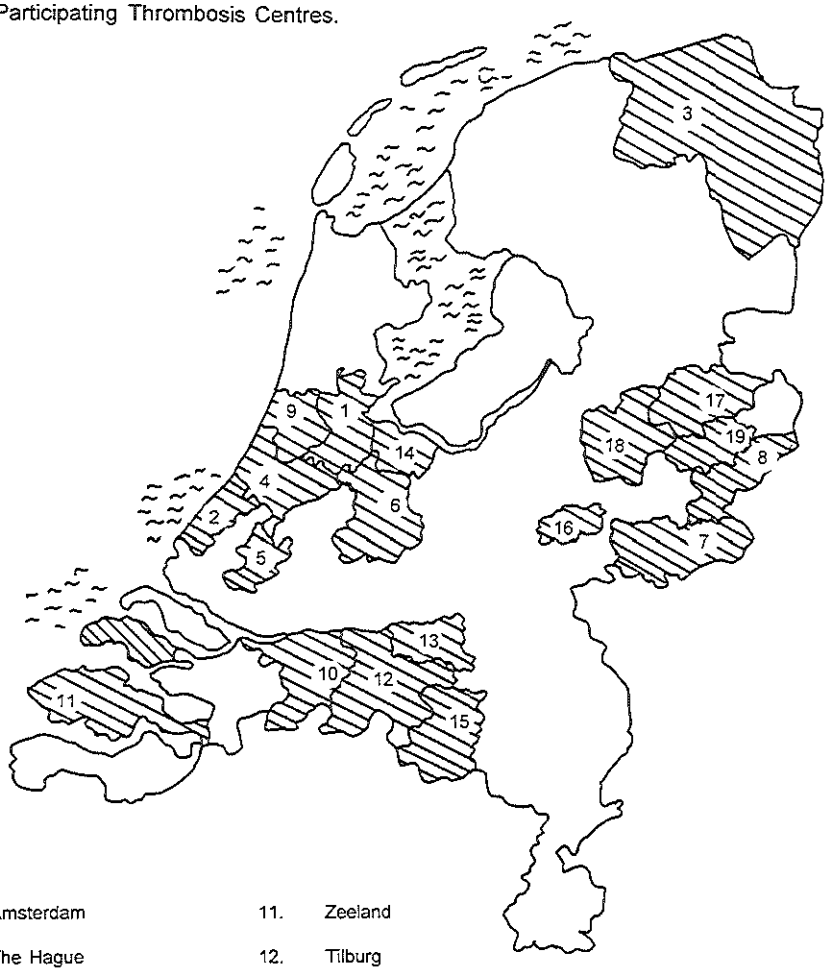
follow-up for all patients after the last patient had been enrolled, a total of 2000 patients per treatment group was estimated in the original design.

Since ASPECT was a long-term trial where patient entry and follow-up continued over a long period of time, there was an ethical obligation for the Data and Monitoring Committee (DMC) to monitor the unblinded data for evidence of adverse or beneficial trial medication effect every six months. A specific statistical stopping rule was designed before the trial was started [43]. The stopping rule is an aid in the decision making process and the DMC was entitled to deviate from the pre-specified stopping rule since secondary end-points and other relevant issues could influence the decision to terminate the trial.

The stopping rule of ASPECT stipulated early termination of the trial at the respective interim evaluations if the one-sided p-value, calculated from the available data was not within the limits given in Table 2.1. This would imply that at the third interim analysis the trial would be terminated and positive treatment effect reached when $p<0.005$; the trial would also be terminated but no treatment effect demonstrated in case of $p>0.81$. Table 2.2 shows the number of deaths in the anticoagulated group which would cause the p-value to be out of its boundaries based on the assumption that mortality in placebo is as expected. Thus, at the third interim analysis, with 3000 accrued patients and 80 deaths in placebo, the trial would be terminated and positive treatment effect reached in case of a maximum number of deaths of 51 in the anticoagulated group: the trial would also be terminated in case of 92 deaths in the anticoagulated group but treatment effect would not be reached.

A statistical stopping rule stipulates under which circumstances the trial will be prematurely terminated as in the case of a strong association between use of oral anticoagulant therapy and risk of dying. The stopping boundaries employed for the group sequential test were based on the one-sided p-value (log rank test) because a difference between placebo and anticoagulant therapy was not symmetrical. The selected procedure at a 5% significance level guaranteed a power of 84%, compared to the original value of 85% if no stopping rule had been employed [43]. As accrual was lower than anticipated, six interim analysis were performed on a yearly basis. By transforming the stopping rule to an 'α-spending scale' these transformations preserved the type I error rate of 5%. These modifications marginally affected the power [43]. The yearly interim reports were prepared by the data manager. The blinded data were handed over to the secretary of the DMC who had access to the patient allocation codes. In such a way the DMC was able to perform an independent statistical analysis on an annual basis.

Figure 2.2 Participating Thrombosis Centres.



1.	Amsterdam	11.	Zeeland
2.	The Hague	12.	Tilburg
3.	Groningen	13.	Den Bosch
4.	Leiden	14.	Hilversum
5.	Rotterdam	15.	Eindhoven
6.	Utrecht	16.	Arnhem
7.	Lichtenvoorde	17.	Almelo
8.	Enschede	18.	Deventer
9.	Haarlem	19.	Hengelo
10.	Breda		

Organization

Background and history

The idea for ASPECT was developed by investigators previously associated with the 'Sixty-Plus' Re-infarction Study. A provisional protocol was approved in 1981 by the Federation of Dutch Thrombosis Centres and the ASPECT research group was founded under its auspices. Initially this group consisted of the Policy Board and the Steering Committee. The first Policy Board meeting was held in 1982. A grant given by the Netherlands Thrombosis Foundation in 1984 enabled the development and finalization of the study protocol. Additional funds were made available by the 'Praeventiefonds' of the Netherlands by the end of 1985. In 1986, the Coordinating Centre was set up at the Rotterdam Thrombosis Centre and a Data and Statistics Centre was set-up at the Thoraxcentre, Rotterdam. Initially, six Thrombosis Centres including Amsterdam, Groningen, The Hague, Leiden, Rotterdam, and Utrecht agreed to participate. In the course of the trial, the number of participating Thrombosis Centres was extended to 19 [Figure 2.2]. These Thrombosis Centres, included Almelo, Arnhem, Breda, Den Bosch, Deventer, Eindhoven, Enschede, Haarlem, Hengelo, Hilversum, Lichtenvoorde, Middelburg, and Tilburg.

Research Group

The ASPECT Research Group consisted of the following units [Figure 2.3]: the Policy Board (which included the Data Monitoring Committee as a sub-committee), the Steering Committee, the Mortality and Morbidity Classification Committee, the Coordinating Centre, the Data and Statistics Centre, 62 participating Cardiology Departments and 19 participating Thrombosis Centres [appendix B.X]. The Cardiology Departments referred the eligible patients to the Thrombosis Centres who were responsible for providing the specified anticoagulant treatment to the patient. The Coordinating Centre together with the Data and Statistics Centre were responsible for proper data collection. The other Committees were established to guarantee proper conduct of the trial and quality of operations.

The Policy Board was composed of senior scientists in the fields of cardiology, internal medicine, pharmacology, thrombosis and haemostasis research, biostatistics, epidemiology and ethics. They were all appointed by the Federation of Dutch Thrombosis Centres. A representative from the 'Sick Funds', a representative from the National Institute for Public Health and those appointed by the pharmaceutical companies were non-voting members. The Policy Board was responsible for the scientific conduct of the trial. Its responsibilities included: (1) approval of the final version of the protocol; (2) approval of amendments; (3) monitoring the progress of

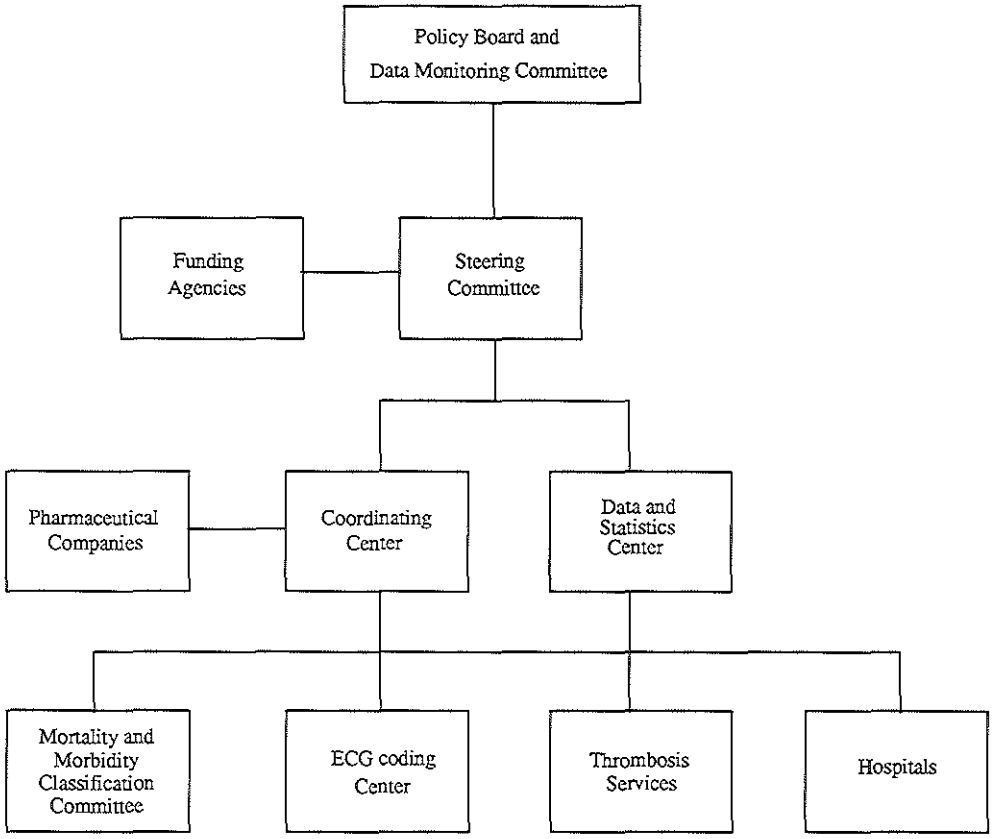


Fig. 2.3 ASPECT organisation chart

the trial; (4) advising in issues concerning study decisions and key issues regarding data analysis and publication procedures; and (5) to act upon recommendations of the Data Monitoring Committee with regards to early termination of the trial. The Board met annually from 1987 onwards. The last Policy Board meeting was held at the end of 1992 when the primary trial results were disseminated by the data-manager.

The Data Monitoring Committee (DMC) was a sub-committee of the Policy Board. It consisted of four representatives of the following disciplines: pharmacology, biostatistics, epidemiology and internal medicine. The primary responsibilities of the Data Monitoring Committee included monitoring the accumulating data for early evidence of treatment effects between placebo and anticoagulant group. In addition, the DMC reviewed the quality of operations at the Coordinating Centre, the Data and Statistics Centre and the participating Cardiology Departments and Thrombosis Centres. The committee met once every year, prior to the Policy Board meeting. The DMC was entitled to recommend early termination of the trial to the Policy Board. A DMC reporter with access to all patient codes but not involved in the actual execution of the trial was responsible for the preparation of the unblinded interim reports. The Steering Committee included representatives from each Thrombosis Centre, cardiologists, an epidemiologist and statistician. The Steering Committee was responsible for the execution of the trial at the operational level. Its responsibilities included: (1) selecting Thrombosis Centres and hospitals; (2) providing leadership to the Coordinating Centre and to the Data and Statistics Centre; (3) drafting, updating and maintaining the trial protocol; (4) reviewing the performances of the centres; (5) implementing modifications to the study design established by the policy Board; (6) resolving operational problems; and (7) preparing publications and final report submission. The Steering Committee met on a monthly basis during the first three years (1986 to 1989) and thereafter once every trimester.

The Mortality and Morbidity Classification Committee consisted of cardiologists, internists, pathologists and neurologists. Its members classified death reports, non-fatal cardiovascular episodes, cerebral vascular events and extracranial haemorrhagic bleeding. They were blinded to treatment assignment. The trial coordinator acted as secretary to the committee.

The Coordinating Centre was first located at the Rotterdam Thrombosis Centre (1986 through 1990) and thereafter at the Rotterdam Medical Research Group (Romeres). The Coordinating Centre staff consisted of a trial coordinator, a data manager and administrative staff for data collection and secretarial tasks. The centre was primarily responsible for: (1) maintaining communications among the participants and proper adherence to the study protocol; (2) distributing trial medications ; (3) data collection and quality control; (4) resolving day to day problems; and (5) providing patient reports to the Mortality and Morbidity Classification Committee.

The Data and Statistics Centre was located at the Clinical Epidemiology Unit

of the Thoraxcentre, University Hospital Dijkzigt, Rotterdam. The staff consisted of a data manager and a scientific computer programmer. The Data and Statistics Centre's main functions included: (1) reviewing the data forms; (2) informing the Coordinating Centre of outstanding data forms or incomplete and inconsistent data; (3) preparing, updating and maintaining the ASPECT computer database; (4) preparing the monthly reports submitted to the Steering Committee; and (5) preparing the interim reports and the final trial report submitted to the Policy Board Committee.

All committees, excluding the Data Monitoring Committee (DMC) and the DMC reporter were blinded to trial treatment and were not informed of the DMC interim results unless the trial was prematurely terminated.

Quality control

Treatment compliance and tablets control of randomized patients was accomplished by examining the value of the generated prothrombin times. Placebo patients who were accidentally administered verum tablets were detected by the Thrombosis Centre physician since prothrombin times exceeded 55 sec on these instances. The computer was programmed to automatically generate a warning signal for such cases. However, placebo patients who missed taking their tablets could not be identified. Verum patients who either were administered placebo tablets by accident or who missed taking their tablets were identified by the Thrombosis Centre physician since the generated prothrombin times were too low.

Funding agencies

ASPECT was conducted under the auspices of the Federation of Dutch Thrombosis Centres. It was funded by the 'Praeventiefonds' and the 'TromboseStichting' of the Netherlands. The anticoagulant drugs and their matched placebo tablets were supplied by Hoffmann-LaRoche, and Ciba Geigy, both from Basle, Switzerland. The funding agencies had staff representatives in the protocol committee.

DISCUSSION

Patient enrollment

" The common thread that runs through the recruitment experience is the first and foremost truth of Muench's Third Law, namely that the number of patients promised for a clinical trial must be divided by a factor of at least 10".

Muench's Third Law [17,44] was applicable for ASPECT. The patient intake was slower than anticipated. Initial recruitment was set originally from September 1, 1986 until September 1, 1988 with one year follow-up with a total of 4000 enrolled patients. However, due to lower than anticipated accrual rate, patient entry was extended until December 31, 1991 with six months follow-up for the last recruited patient. A total number of 3404 patients were then randomized. Low patient intake was attributed to new developments with respect to the institution of thrombolytic therapy and increased frequency of angioplasty in patients with an acute myocardial infarction. The following measures were taken to increase patient intake: (1) close monitoring of all participating centres; (2) presentations at medical meetings to acquaint the referral physicians with the trial design, purpose, and type of patients required; (3) news- letters to all Dutch cardiologists, with details on the trial progress and the number of patients admitted; (4) news articles in the medical and lay press to increase motivation and consequently patient accrual; (5) increasing the number of participating Thrombosis Centres and hospitals, for the former from six at the start of the trial to nineteen and for the latter from eighteen to sixty-two at the termination date; finally (6) small compensations were granted to all specialists for each randomized patient.

How was ASPECT blinded?

In order to insure the double blinding of ASPECT the following criteria were set forth by the Steering Committee: (1) patient, attending nurse, treating cardiologist, all committees excluding the Data Monitoring Committee (DMC) and the DMC reporter were not knowledgeable of treatment allocation; (2) a multiplication factor program was employed so that placebo prothrombin times were made similar to verum. For this reason, only Thrombosis Centres that provided computerized anticoagulant dosage prescriptions were eligible to participate in ASPECT.

However, one should not underestimate the difficulty of blinding a trial that involved dose titration with different anticoagulant congeners. The following problems can be visualized. For example, the prothrombin time could have been determined by any physician and knowledge of this value would have enabled the identification of treatment allocation. For this reason, the patient was requested to reveal to each attending physician the patient card that specified his or her enrolment in ASPECT as well as the importance of blinding. Dosage adjustment was performed by the Thrombosis Centre computer system by checking the factual prothrombin times with the given therapy (verum or placebo). If placebo factual prothrombin time values were greater than 55 sec then the multiplication factor program was not initiated but a warning signal was generated and consequently disclosure of trial medication. This safety measure was employed since prothrombin times exceeding 210 sec were an

indication for administration of vitamin K. The frequency of disclosure of treatment is not known since the factual prothrombin times were overwritten by fake values. The Thrombosis Centre personnel speculated that these cases did not exceed 1%. Finally and theoretically, a patient who pricked himself on successive days would be able to detect the given therapy. However, members of the Steering Committee speculated that such cases would be infrequent.

Justification for double-blind procedure

The first largest randomized clinical trial which assessed the benefits of Dicumarol in the prevention of myocardial infarction employed the alternate case method for patient recruitment [17,45]. Patients admitted on odd days of the month were allocated to anticoagulant therapy, and to placebo on even days. At the end of the trial it was noted that patients randomized to anticoagulant therapy out-numbered placebo, and the randomization scheme was therefore questioned. At that period of time, most physicians favoured anticoagulant therapy over placebo. Apparently, the physician rather than chance influenced treatment assignment; consequently, the comparability of the two groups and the validity of the results were questionable.

The nature of ASPECT required the evaluation of clinical observations made on individual patients with regard to the effect of oral anticoagulant therapy. These evaluations could be assessed either in an open or in a blind design. In an open design, the health effects or 'events' are assessed by a physician, aware of the treatment group the patient was randomized to. In such a trial, observation of a hard endpoint, such as total mortality, would not influence the outcome provided that randomization was properly accomplished and not influenced by decisions on treatment allocation, methods of data collection and bias in treatment compliance. However, evaluations of end-points relating to specific causes of death and definitions of myocardial infarction and cerebrovascular events could lead to investigation bias, since these are relatively subjective or 'soft' end-points. The knowledge of the physician to treatment assignment may influence the occurrence of the 'event' or the number of patients discontinuing trial medication. This might have been exerted in a conscious or subconscious manner.

The objective of a clinical trial is to collect data free from treatment related bias and treatment related side effects. Therefore, double-blinding was implemented in ASPECT with the use of a placebo in view of: (1) the subjectivity involved in defining the secondary outcomes; (2) to avoid bias during patient recruitment, data collection, data assessment; (3) to eliminate factors unintentionally associated with treatment; (4) to preserve the integrity of randomization; and (5) in view of the bias which could result from selected use of for instance beta blocking agents which have been shown to influence prognosis and decrease mortality in patients with myocardial infarction

[46,47].

Furthermore, to ensure maximum comparability between the treatment groups, double-blinding was also implemented with respect to the anticoagulant effect induced by the drugs compared, since anticoagulant therapy is not a fixed dose therapy. Therefore, dosages, frequency and time between visits for placebo were similar to those of patients in the anticoagulated group.

In summary, trial treatment was given in a double-blind manner, and neither the patient nor the treating physician were aware of the treatment the patient received. With regard to the physician, this method protected against favouring one therapy over the other and against distorting the trial by, for instance, by discontinuing study medication to some patients rather than others. The latter would have endangered the 'intention to treat' principle which took into account all events attributed to the treatment the patient was randomized to, irrespective of discontinuation of trial medication. Finally, both physician and patient would be unaware of the benefits or side-effects of therapy. In the context of ASPECT, the blinded Mortality and Morbidity Classification Committee assessed the health effects observed in the patients. Moreover, all committees and the Coordinating Centre, excluding the Data Monitoring Committee, remained blinded to treatment allocation to avoid bias in interpreting the interim and final results.

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CHAPTER THREE

THE ASPECT TRIAL - DATA PROCESSING

AJ Azar, GA van Es, R van Domburg and JW Deckers

INTRODUCTION

> *" One must go seek more facts, paying less attention to technics of handling the data and far more to the development and perfection of obtaining them".*
>
> *Bradford Hill, 1951*

The success of a clinical trial is dependent on its design, the ability of the physicians, the laboratory personnel and others involved to adhere to the predefined study protocol and the statistical techniques used for analyzing the collected data [1-4]. In addition, its success depends on the quality of the collected data. Collection of data should follow standardized methods [5] so as to avoid systematic errors and to minimize random errors. Therefore, the proper planning, development, implementation, and quality control are pre-requisites for its successful conduct [6,7].

A clinical trial does not only involve a design and analysis procedure but also constitutes a broad management task [6], including the development of the study protocol, patient recruitment, treatment, data collection, database management, follow-up, data analysis and submission of the final report [8,9]. Once the protocol is finalized and accepted by the various committees, the procedures therein described are used as the manual for actions, operations and definitions by the participating centre or, in studies in which no single centre can furnish the required number of a selected population, the various collaborating centres [3,10,11].

In ASPECT, computer systems were employed to assist in data processing [2,12,13]. Data processing was defined as: 1) data collection; 2) data management; and 3) data analysis. Observations and measurements made on individual patients were recorded on data forms [14]. These forms were designed such that recording information was facilitated and data to be collected was accurate, standardized and processible. Information gathered was subsequently entered, stored and ultimately validated in the ASPECT database [15,16]. Data management included the definition of the database structure, data entry, editing, monitoring, storage and retrieval (queering and report writing) [17,18]. In order to maximize the quality of the collected

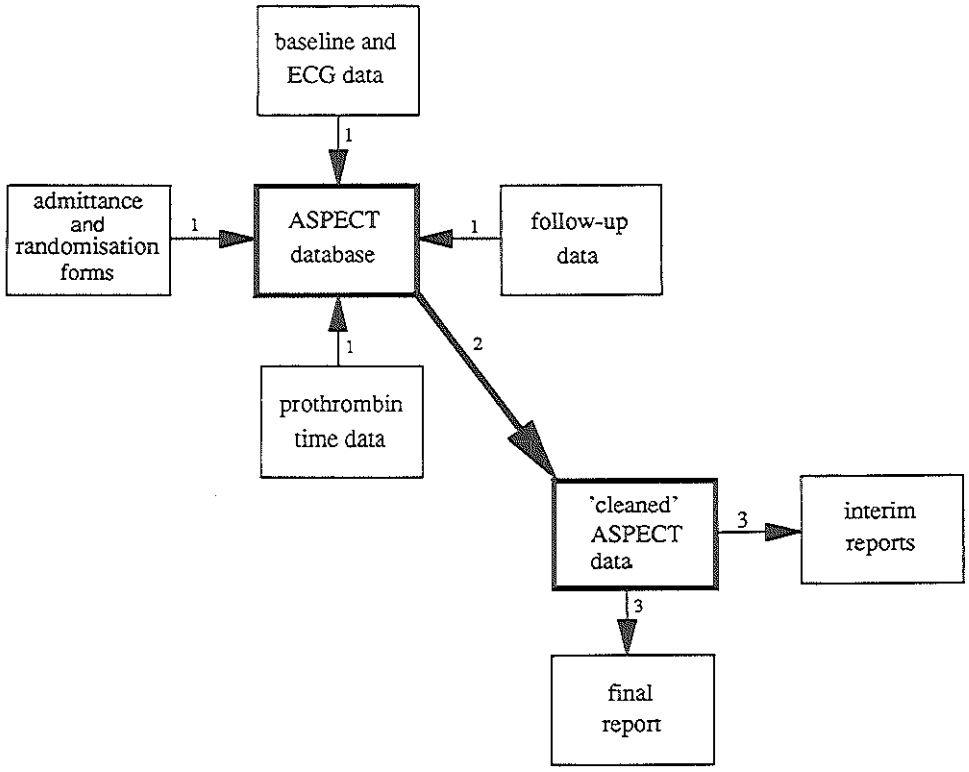


Figure 3.1 Flow of data in ASPECT. The data entry fields (1), quality control checks (2) and data analysis (3) are indicated.

information, data that was missing, incomplete or outside predefined boundaries was managed already at the collection phase [13,19,20]. Concurrent data collection was therefore employed. It is the method in which data collection, entry, storage, checks, and analysis are processed simultaneously. Concurrent data collection is essential for the optimization of data quality, since it allows for the early detection and correction of incomplete and out-of range data and facilitates the generation of periodic interim reports [10,15]. Such reports assisted the trial committees, in particular the Data and Monitoring Committee, in performing its task. Concurrent data collection therefore, assured accurate data by assisting in data collection, entry, monitoring, storage and retrieval [13,18]. Errors could occur either during the data-entry phase or could result from inconsistencies in the data. During data-entry, on-line interactive range and validity checks, such as in range dates, numbers and skipping of not applicable parameters were performed. Patient reports were generated after each data-entry session and were checked against the values on the medical records for keying or transcription errors. Edit queries were run in order to retrieve variables which showed inconsistencies during data entry. Data analysis, which involves the extraction of information from the data, was considered as a technique to verify the collected data [18] and ensured that errors made during the collection phase were early detected by adoption of this process.

In this chapter we will present an outline of the data processing system as employed in ASPECT. The system enabled us to achieve high level data quality derived from the various collaborating centres while maintaining proper blinding of trial treatment groups.

DATA PROCESSING

The most important role of the Data and Statistics Centre together with the Coordinating Centre, previously described in Chapter 2, was to process the trial data. To aid in data collection a variety of forms were designed by the Steering Committee: 1) Admittance and Randomization Forms; 2) Baseline and Electrocardiogram (ECG) Forms and (3) Follow-up Forms. In addition, prothrombin time data, submitted on diskettes, were collected as well. In the next section, a description of the processing of each of the above items is given. In Figure 3.1 the flow of data, quality control and data analysis for each of the above forms is described.

Admittance and Randomization data

Two different forms were designed for patient enrollment: Admittance and

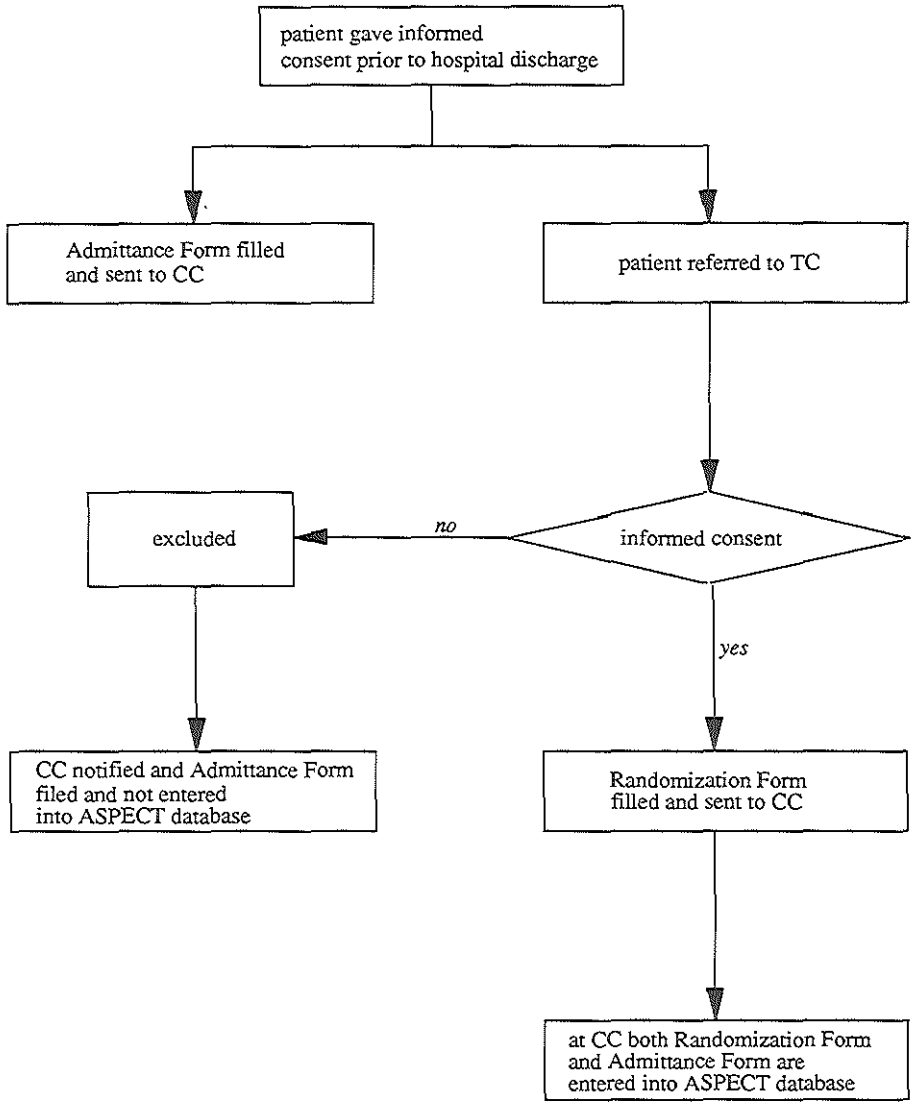


Figure 3.2 Flow chart for patient enrollment.
CC, Coordinating Centre; TC, Thrombosis Centre.

Randomization Forms. The flow for patient entry into ASPECT is described in Figure 3.2.

The Admittance Form was filled-out by the treating cardiologist prior to hospital discharge and prior to randomization, for patients who were eligible and had given oral informed consent for participation in ASPECT. This form contained information on the criteria for eligibility, the patient's sex, date of birth, anticoagulant congener to be used, the specialist's name, hospital and general practitioner's names and addresses, and name and address of the regional Thrombosis Centre [appendix B.I]. This form was sent to the Coordinating Centre.

The randomization form filled-out at the initial visit at the Thrombosis Centre was also sent to the Coordinating Centre. It included information on the Thrombosis Centre patient identification number, randomization number and date of randomization [appendix B.IV]. The patient's randomization number and date of randomization were subsequently entered into the Thrombosis Centre computer system. These patients, identified by the randomization number and the treatment code (verum or placebo), were tagged. As a matter of course, the randomization codes were not assessable to system users. The randomization number was subsequently printed on all computer generated patient forms.

Randomization numbers consisted of a seven digit sequence number, e.g., ASI0001. The first letter indicated the Thrombosis Centre name, e.g. 'A' indicated Amsterdam. The next two letters represented the registered trade name for the anticoagulant congener specified by the referring cardiologist: 'MA' for Marcoumar® (phenprocoumon 3 mg), 'SI' for Sintrom® (acenocoumarin 4 mg), and 'SM' for Sintrom mitis® (acenocoumarin 1 mg). The four digits represented the patient's sequence number. In the example above, ASI0001 was given to the first patient from Amsterdam who was assigned to Sintrom® or its placebo. A treatment allocation code (verum or placebo) was assigned to each randomization number according to a randomization list. Randomization lists, blocked in units of 10, were separately prepared for each Thrombosis Centre and for each anticoagulant congener. Therefore, with 19 Thrombosis Centres and 3 anticoagulant congeners, a total of 57 strata were formed. Table 3.1 shows the randomization numbers given to the ASPECT population.

For each randomized patient, the Admittance and the Randomization Forms were entered into the ASPECT database by the Coordinating Centre personnel. The Admittance Form was filed at the Coordinating Centre but not entered into the ASPECT database for those patients who withdrew their initially given consent during their first visit to the Thrombosis Centre. The Coordinating Centre identified patients by their randomization number and date of birth.

Table 3.1 Randomization numbers for the ASPECT population

	Thrombosis Centres	Marcoumar	Sintrom	Sintrom mitis
TDAS	Almelo	OMA 0001- 1000	OSI 0001- 0500	OSM 0001 - 1000
	Amsterdam	AMA 0001- 1000	ASI 0001- 0500	ASM 0001 - 1000
	Arnhem	FMA 0001- 1000	FSI 0001- 0500	FSM 0001 - 1000
	Den Bosch	NMA 0001- 1000	NSI 0001- 0500	NSM 0001 - 1000
	Deventer	KMA 0001- 1000	KSI 0001- 0500	KSM 0001 - 1000
	Eindhoven	CMA 0001- 1000	CSI 0001- 0500	CSM 0001 - 1000
	Groningen	GMA 0001- 1000	GSI 0001- 0500	GSM 0001 - 1000
	Haarlem	HMA 0001- 1000	HSI 0001- 0500	HSM 0001 - 1000
	Hengelo	IMA 0001- 1000	ISI 0001- 0500	ISM 0001 - 1000
	Hilversum	SMA 0001- 1000	SSI 0001- 0500	SSM 0001 - 1000
	Middelburg	MMA 0001- 1000	MSI 0001- 0500	MSM 0001 - 1000
	Rotterdam	RMA 0001- 1000	RSI 0001- 0500	RSM 0001 - 1000
TRODIS	Breda	BMA 0001- 1000	BSI 0001- 0500	BSM 0001 - 1000
	Den Haag	DMA 0001- 1000	DSI 0001- 0500	DSM 0001 - 1000
	Enschede	EMA 0001- 1000	ESI 0001- 0500	ESM 0001 - 1000
	Leiden	LMA 0001- 1000	LSI 0001- 0500	LSM 0001 - 1000
	Lichtenvoorde	VMA 0001- 1000	VSI 0001- 0500	VSM 0001 - 1000
	Tilburg	TMA 0001- 1000	TSI 0001- 0500	TSM 0001 - 1000
	Utrecht	UMA 0001- 1000	USI 0001- 0500	USM 0001 - 1000

Prothrombin time data

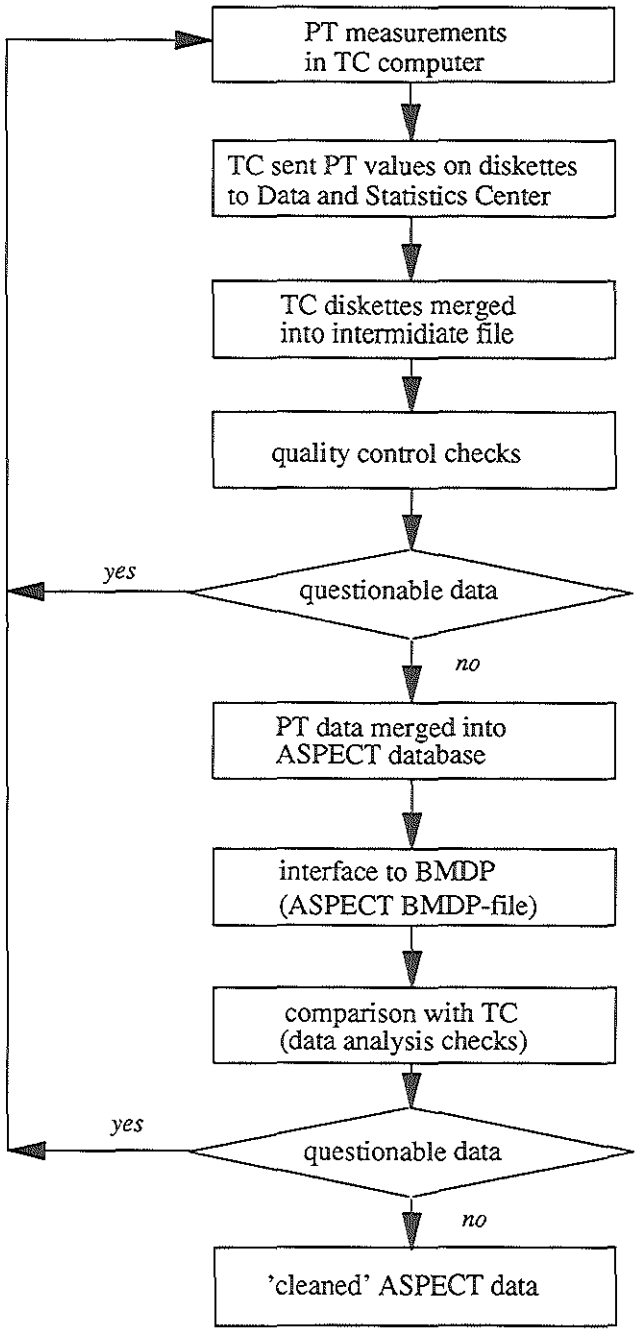
After assignment of the randomization number, the following procedures were routinely performed by the Thrombosis Centre. At regular intervals, the patient's blood sample was drawn to determine the prothrombin time. This is the time needed for a blood sample to clot when thromboplastin reagent is added [21]. The obtained prothrombin time was either entered automatically from the laboratory computer system or manually entered into the Thrombosis Centre computer system. In both cases, the laboratory personnel was unaware of the patient's participation in ASPECT since only the patient's name and Thrombosis Centre patient identification number were indicated on all blood samples.

Two treatment regimens were employed: "active" anticoagulant therapy (verum) or placebo. Under verum treatment prothrombin times are prolonged and should range from 105 seconds (sec) to 180 sec. Under placebo medication, however, the prothrombin time will not be influenced and will not lie in the magnitude of 40 sec. In order to insure the double blinding, described in Chapter 2, a procedure was developed which adjusted the prothrombin time values for placebo patients such that placebo fake prothrombin times were in the same range as those obtained in patients on active anticoagulant therapy. A special computer algorithm was developed for this purpose. For each ASPECT patient, this algorithm checked the randomization number with the medication code (verum or placebo). For verum patients, the factual prothrombin times were entered and stored in the computer system and displayed to the Thrombosis Centre physician. For placebo patients the true prothrombin times were simulated into fake values by a multiplication factor program (a more detailed description of the simulation program was given in Chapter 2).

The multiplication factor program was developed by two independent institutions, TRODIS and TDAS, responsible for installing and maintaining the simulation program at the respective Thrombosis Centres that employed their systems. The TRODIS system includes a central computer system linked to all its users and is primarily based on the pharmaco-kinetics of the coumarin used. TRODIS was adopted by 7 of the participating Thrombosis Centres. The TDAS system is a personal computer oriented system, and is developed on empirical grounds and trend analysis. TDAS was used by 12 of the participating Thrombosis Centres (Table 3.1). Because of the different dosage algorithms used in both systems, the multiplication factor program was implemented differently for each system.

For all randomized patients, irrespective whether trial medication was discontinued (as long as the patient visited the Thrombosis Centre), information on the prothrombin time values with the corresponding date was submitted biannually on diskettes to the Data and Statistics Centre. At the Data and Statistics Centre, the data were batch entered into an intermediary file. Screening queries were generated by the computer programmer who checked for data completeness and validity.

Figure 3.3 Flow chart for obtaining the prothrombin time measurements from the various participating Thrombosis Centres. Quality control checks are also represented. PT, prothrombin time; TC, Thrombosis Centre.



Questionable data files were returned to the respective Thrombosis Centres for further scrutiny. The files were re-checked and merged into the ASPECT database in the absence of ambiguities. Data were not only checked for completeness but also for plausibility. This was achieved by performing a statistical analysis on the data. The percent of time the patient's prothrombin time within the target range (2.8-4.8 INR) [21] was compared to therapeutic achievement usually attained in anticoagulated patients treated in that Thrombosis Centre. Discrepant results were discussed in a plenary meeting with the data manager and with the Thrombosis Centre. A new file was subsequently generated, recontrolled and eventually batch entered into the ASPECT database (Figure 3.3). The whole process made it impossible for the patient, laboratory personnel, Coordinating Centre and the Data and Statistics Centre to be aware of treatment allocation.

Baseline and ECG data

All baseline observations and 12-lead electrocardiogram (ECG) measurements made on individual patients were recorded on Baseline and ECG Forms. The collected data, specified in Chapter 2, were abstracted from the medical records of the participating hospitals. Relevant clinical information such as the last ECG were photocopied and stored at the Coordinating Centre. Nominal and ordinal measurements were coded on a Mark Sense Card. Other baseline information of the randomized patients were recorded on the Baseline Form. A total of 170 different variables at baseline was defined. The ECG Form was scored by SEAL ('Stichting ECG-Analyse Leiden') Department in Leiden. A total of 49 variables per ECG were inspected. A random sample of 39 ECG's were repeat coded by SEAL: the error rate of 3.2% which was found in this analysis was considered acceptable. Discrepant codings were primarily reviewed by the trial coordinator and when necessary discussed with SEAL. The final ECG was entered into the ASPECT database by the data manager. The data flow and quality control steps are represented in Figure 3.4.

Each Baseline Form was reviewed by the trial coordinator for correctness and completeness prior to entry into the ASPECT database. This was performed in order to reduce the volume of computer generated error messages. The Baseline Form was considered completed when all information was recorded. Data not available were coded as missing. The lag time between data acquisition and entry amounted on average to two months, with a range of 1 day to 11 months.

When the form was completed, the patient's seven digit randomization number was entered into the ASPECT database. The Coordinating Centre personnel entered both the Baseline and the ECG Forms. During data entry, computer edit checks defined by the database manager were performed that included: (1) on-line interactive range and validity checks, such as in range dates and numbers; (2) out of field data

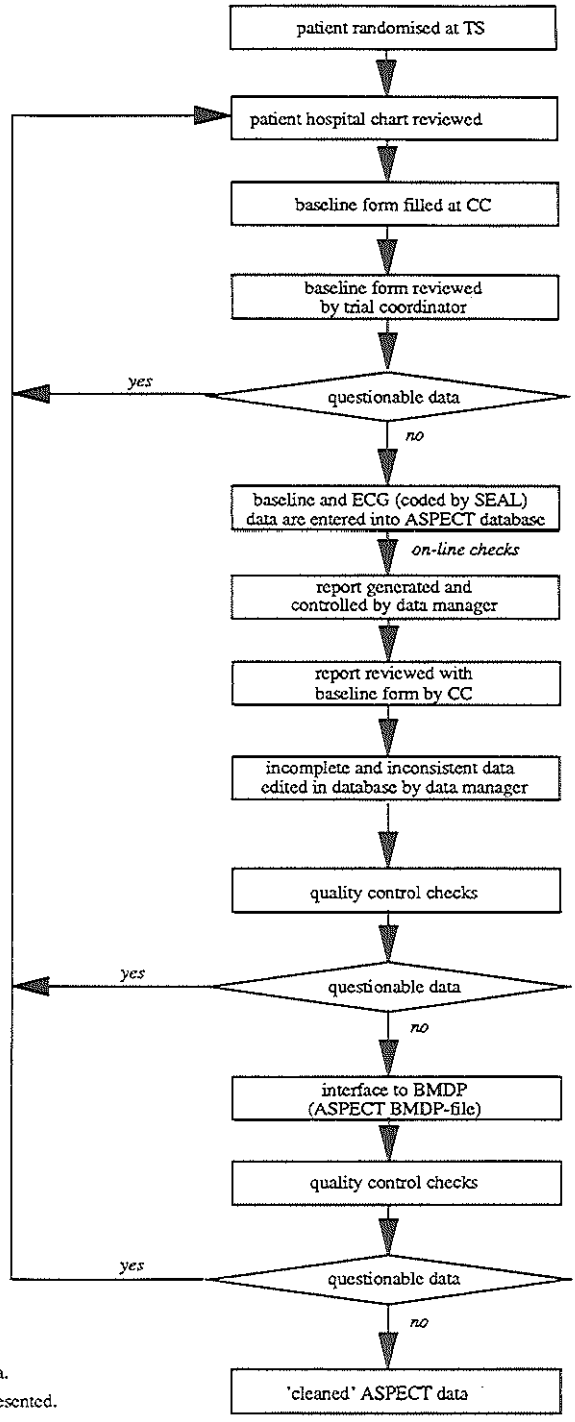


Fig. 3.4 Flow chart of baseline and ECG data.
Quality control checks are also represented.
TS, Thrombosis Service; CC, coordinating center.

checks, such as gender coded as 3 when only choices 1 or 2 were possible; (3) skipping of not-applicable questions, such as skipping exercise test data when no test was performed; and (4) syntax checks to differentiate between numeric and alphabetic characters, for instance typing a free text in place of a date. For on-line checks, the system alerted the user by an audible "beep" sound in case of out of range or inconsistent values. Values outside the pre-specified range were only entered after additional review. After each data entry session, patient reports were generated by the data manager. These were evaluated for completeness and consistency and further checked for keying or transcription errors against the values on the medical records by the Coordinating Centre personnel.

Screening queries retrieved variables which showed discrepancies during data entry. These included plausibility checks and inventory checks against prior data values. Internal protocol violation checks were also implemented. These were operations which triggered double defined variables and checked the values of variables derived from existing ones; as an example, the age of a subject was computed by subtracting date of randomization from date of birth. On various occasions, query generated programs were initiated to validate the entered items. Also, batch processing at the Data and Statistics Centre was performed to retrieve all missing and inconsistent data values. The resulting edit queries were sent to the Coordinating Centre for review. A hard copy was documented for data errors detected by manual or computer processing.

Massive updating of selected data items was occasionally performed. A retrospective revision of all patient files was performed in such cases. As an example, use of acetyl salicylic acid during index admission or at discharge was recorded as "use of aspirin: yes/no". At the end of the trial this was redefined into "use of aspirin during hospital stay: yes/no" or " use of aspirin at discharge: yes/no".

During the whole process of data entry, quality control and analysis, the Coordinating Centre personnel and the trial coordinator were only permitted to enter the raw data and extract data from the database. The data manager only had authority to alter data already entered.

Follow-up data

The Thrombosis Centres routinely keeps track of all complications occurring in patients under oral anticoagulant therapy. This procedure was also adopted for patients in the ASPECT trial. All complications referred to as 'events' were centrally collected at the Coordinating Centre from the monthly overviews supplied by the participating Thrombosis Centres on the 'Clinical Event Form'. A special form was designed to acquire information on patients who were no longer followed by the Thrombosis Centre [appendix B.IX]. A standardized yearly follow-up letter that

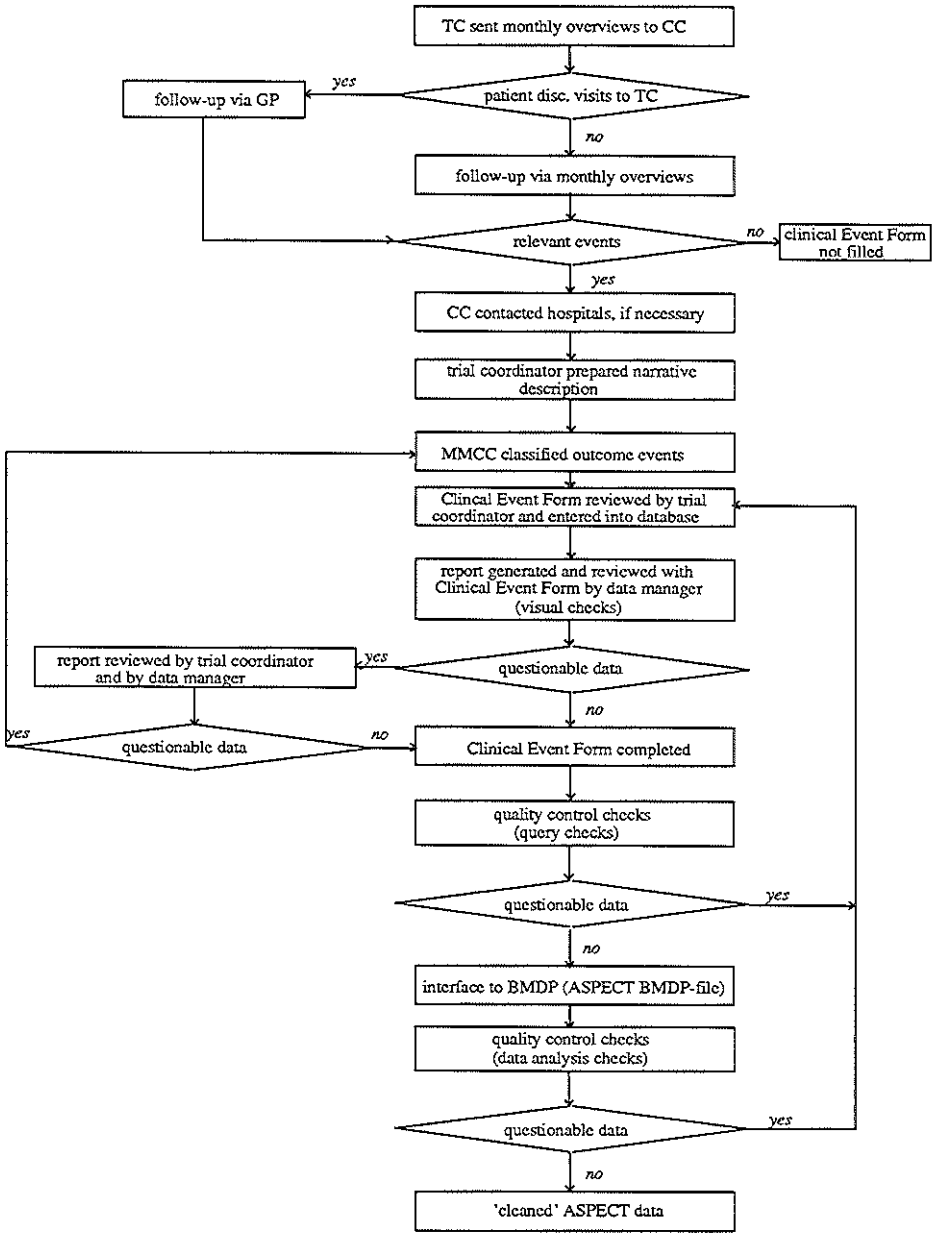


Figure 3.5 Flow chart of handling of events during follow-up. Quality control checks are also represented. TC, Thrombosis Centre; GP, general practitioner; disc. discontinued; CC, coordinating centre; MMCC, Mortality and Morbidity Classification Committee.

inquired on hospitalizations and complications was generated for this purpose by the data manager and sent to the general practitioners of these patients. Copies of relevant clinical information such as electrocardiograms and enzyme values determined during hospital stay were requested. Such ECG's were also scored by SEAL, Leiden, and entered into the ASPECT database. All events were classified and coded by the Mortality and Morbidity Classification Committee (MMCC). When consensus on the diagnosis was reached the Follow-up Form was entered into the ASPECT database by the trial coordinator. A patient report was then generated which was verified by the data manager for completeness and validity. Questionable data were reviewed in plenary meetings by the trial coordinator and the data manager and when necessarily returned to the MMCC for a final consensus. Also, query generated checks were performed by the data manager. These screening queries retrieved inconsistent data which were sent to the Coordinating Centre for inspection. The data were subsequently checked and edited in the ASPECT database. A BMDP-file was subsequently generated which was ready for analysis. Figure 3.5 shows the flow of handling of clinical events during follow-up. During the follow-up period which started on April 1986 for the first randomized patient and that ended six years later, any deficiencies in baseline collection were corrected prior to trial termination.

DATABASE MANAGEMENT SYSTEM

CLINT

The CLINT clinical trial management system was used for ASPECT [22]. The CLINT package was chosen because of the availability of the package at the Data and Statistics Centre and of the variety of functions provided by the package. It is specifically designed for clinical trials conducted at the Thoraxcentre, University Hospital, Dijkzigt, Rotterdam. The package is written in MUMPS (DSM Dec standard Mumps, MSM Micromumps and Data Tree) and is available in the Thoraxcentrum Utility System (TUS) mainframe computer where the ASPECT database was located. The database management system makes use of a hierarchial data structure with a varying number of records per patient.

The CLINT package allows for data acquisition, data processing, consistency and range checks. The system verifies data input by internally computerized checks which result in an accurate and complete database. Erroneous and missing data are therefore spotted early in the trial process.

The CLINT data dictionary, the heart of the system, contains information on the database structure and defines the forms, data files and follow-up records. Each field is specified by type, length, optimal value indicator, valid ranges, default values, definition of numeric, text or time variant data and skipping options [23,24]. The

system therefore describes and locates each data element in the system. CLINT can read, store and retrieve numeric, codes (such as gender with males coded as 1 and female as 2), character, text, dates and default data types. The data manager was responsible for organizing, defining and maintaining the data dictionary.

In long term clinical trials, variables are often inserted, modified or deleted. Changes in the variable names, their length, type and specification are also common. Additionally, new codes for a specific variable are inserted during the process of the trial. In ASPECT, the data dictionary was continuously updated. CLINT allowed for such modifications without massive restructuring of the database model.

The system could accept any number of input screens of varying lay-outs. Also, adding modules or variables to the data dictionary was possible. The system was able to design new screens from existing ones. This was functional considering the amount of comparable information gathered, as, for instance, follow-up data gathered at various time intervals. At the end of the study, some patients had data recorded on as many as 3000 to 4000 variables.

A special query language was used for report generation and simple data analysis. Direct interface to the BMDP statistical packages [25] was essential to generate the interim and final report [23]. Variables for each analysis were identified by the data manager and transferred for analysis. The definition of the data file, down loading of the desired variables from the database with an automatic format generation, group codes, and missing value definitions were processed interactively with variable down loading. Data management and data analysis on different computer systems led sometimes to inconveniences, but these were more than offset by the conveniences of interactive data entry and data management. Interim reports were prepared by the data manager on predefined dates. The reports included data summaries and exploratory analysis. These were submitted to the DMC reporter who was unblinded to the data and was not involved in the operations of the trial. The DMC together with the DMC reporter reviewed the unblinded data. Although the preparation of the interim reports at regular intervals was time consuming and tedious, it was essential to monitor for evidence of adverse or beneficial treatment effects during the course of the trial. The beneficial byproduct of these interim reports was an up-to date database in which extra quality control checks were performed by the Data and Statistics Centre on data level and independently by the DMC on medical plausibility [appendix A].

On the whole, CLINT is a database management system which was relatively easy to maintain and conveniently structured for ease of data retrieval and data management.

Database protection and security

The continuous flow of patient data, checks and edits hindered the ability to reproduce the database at any specific time. In order to reproduce the interim results, the ASPECT database was 'frozen', i.e. saved on tape by the data manager after each analysis.

The ASPECT database was protected against unauthorized users. In order to execute any function, the user had to have authorization before entry which included: the study name, password and function [24]. At the Data and Statistics Centre, Rotterdam, back-up copies of the database were made on a daily, weekly, monthly, and yearly basis. The daily, weekly, and monthly copies were saved on tape and stored in a safe at the Thoraxcentre; the yearly copy was stored at the Coordinating Centre.

DISCUSSION

The proper development, implementation, and maintenance of the large and complex ASPECT database required a major effort which depended on proper management once the protocol was finalized. The primary objective and function of the Data and Statistics Centre and the Coordinating Centre was to achieve data of high quality. Surprising as it may seem now, at that time, however, little information was available in the literature regarding standards for data quality control. There was a general agreement that quality control is important to assure accurate data, but no systematic, clear description on the issue was available [26].

We defined data processing objectives as one which insured high quality research data. The quality of data from the multicentre ASPECT trial was dependent on: (1) the quality of data submitted on each form; (2) the data entry procedures including record completeness, interactive system checks [11], consistency, plausibility and validity checks; [15,26-29]; (3) concurrent data processing, i.e. continuous and simultaneous revision of the data entered, altered, inserted or deleted; (4) the techniques used for data processing; and finally, (5) preparation of the interim and final reports.

1. The data forms were individually checked for completeness and consistency by the trial coordinator, prior to entry into the ASPECT database. The purpose was to detect transcription errors in order to reduce the volume of computer generated checks.
2. Single data entry error rates have been reported by other investigators to be exceptionally high [30]. For this reason, double data entry has been considered mandatory when a large number of data-entry people are involved [30]. Double-data entry could not be performed in ASPECT because of lack of budget. However, a

patient report was generated after each data-entry session. Data audit was therefore performed, involving an item-by item comparison of information recorded on the forms to that contained in the computer file of that form [31]. This was done by the Coordinating Centre staff. In that way, transcription errors and incompleteness in the computer files, if present, were detected early in the entry process. Therefore, we believe that double data-entry would not have decreased the error rate in a substantial or significant way.

3. The data-manager ran edit queries on the data in order to retrieve inconsistencies. Questionable data were returned to the Coordinating Centre for further scrutiny. We therefore used the technique of concurrent data processing [15] to facilitate the detection and correction of inconsistencies during the collection phase of the trial.

Data submitted directly on diskettes, the prothrombin time data, were batch entered into an intermediary file. These data were considered to be of high quality because of the million of patient years of experience of the Thrombosis Centres with this method. To validate the quality of the data batch entered, we analyzed each Thrombosis Centre separately and compared these results to those presented by the individual centres. The data were only merged into the ASPECT database when this process was satisfactory. In this manner, the technique of data-analysis was used to verify the data.

4. Use of a computer data management system can assist in data processing. However, data management problems tended to increase as the size and the duration of the trial became large. Automated computer assisted editing during data entry was effective in minimising errors. However, CLINT had no facility options to check whether previously entered data had been modified at a later stage. Therefore, ASPECT did not possess a system which contained options of tagging altered information and indicating the date, time, user's name as well as reason for editing. Such facility could have guarded the system against accidental modifications and damages. In some clinical trials, modified data are located in files different from the original data file, also called the 'master file' [32]. The use of such an organised description of past modifications to the study data, entitled an 'audit trial' of course to the retrieval of changes performed on the data [33]. In the case of ASPECT, all modifications could only be stored on hard copies and this procedure only increased the administrative task.

Also, the data management system should be controlled prior to operation. During its conception, CLINT, the database system used in the ASPECT trial, was a young package which substantially changed during the course of the trial. Although programming errors during the early phases of the trial occurred more frequently than during its later stages, the CLINT computer programmer was at our disposal and could assist in changes whenever necessary.

5. Finally, after data have been checked and cleaned, a statistical analysis is

performed and a report is generated [31]. This analysis is done in order to assess the comparison of the treatment groups for differences in outcome. In the ASPECT trial, data analysis and management were performed on different machines. CLINT was used for data-entry and management, and the BMDP statistical package was employed for data analysis. A direct interface to BMDP was available. Performing data management and data analysis on different machines was inconvenient and required continuous support by the CLINT computer programmer.

In short, the quality of findings is not only the function of the type of data generated at the centres, but also related to the manner in which these data were processed and analyzed [34,35]. The ASPECT data-base could be considered of high quality data because of the technique used in thieving out errors from the system. Concurrent data processing was applied in this process. Data collection, entry, monitoring, storage, retrieval and analysis were in this case processed simultaneously. Transcription errors were immediately detected by item-to-item comparison of information recorded on the forms to that contained in the computer file of that form. Screening were run to retrieve variables which showed inconsistencies during data entry. Finally, data-analysis was performed and a report generated in which the trial results were presented and checked independently by the Data Monitoring Committee for medical plausibility and completeness. This was performed on a yearly basis.

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CHAPTER FOUR

ASSESSMENT OF THERAPEUTIC ACHIEVEMENT IN A LONG-TERM ANTICOAGULANT TRIAL IN POST-MYOCARDIAL INFARCTION PATIENTSM

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SUMMARY

To obtain beneficial effects of long-term anticoagulant treatment and to reduce side effects associated with therapy, anticoagulant treatment should be maintained within a narrow defined therapeutic range. A number of approaches have been proposed to assess therapeutic quality control using the international normalized ratio (INR): (1) the 'cumulative-INRs' considered the number of INR values and the 'cross-section-of-the-files' considered the most recent INR obtained in each patient. The results expressed as a percentage of all INR values within therapeutic range; (2) an estimate of the percent of time each patient was within the therapeutic range, where the INR change occurred either directly after the first or half-way between visits; and (3) total volume of observation time of all patients categorised into classes of INR values assuming that INR values changed linearly between visits. These approaches were evaluated in 1700 post-myocardial infarction patients on active anticoagulant (acenocoumarol or phenprocoumon) therapy. Total treatment period comprised 3725 patient-years and 61,471 INR measurements. Target anticoagulant level was 2.8-4.8 INR. The data revealed that irrespective of the approach used, therapeutic achievement stabilized after 6 months of treatment. Under-anticoagulation decreased between the first and third month and was again lower after six months of treatment. Over-anticoagulation (INR>4.8) occurred between 8% to 10% at any time interval using approaches 1 and 2, and around 5% of the time using approach 3. Acenocoumarol was two and a half times more often outside the therapeutic range than phenprocoumon. TDAS® and TRODIS dosage systems provided similar levels of effectiveness.

It is concluded that, therapeutic achievement is recommended to be evaluated using the third approach, since it incorporates time and has the most realistic assumptions. This approach is also most suitable for assessing anticoagulant control, since calculation of incidence rates of events at different intensities can be made. Finally, the present data call for an improvement by the standard of control for patients during the first 3 months of anticoagulant treatment.

INTRODUCTION

The therapeutic effects of anticoagulants in the treatment of patients with deep venous thrombosis, pulmonary embolism, prosthetic heart valves, atrial fibrillation and heart failure are well established [1,2]. However, long-term anticoagulant therapy for secondary prevention in post-myocardial infarction patients remains controversial [1]. Anticoagulant therapy carries potential bleeding risks and therefore requires regular supervision by the clinician and demands patient compliance [3].

Prothrombin times have been used for many years to monitor therapy with orally administered coumarin derivatives. However, the thromboplastins used to measure prothrombin time was prepared by different methods and consequently their sensitivity to the reduction of the vitamin K dependent clotting factors varied significantly [1]. Therefore, similar prothrombin times often reflected in fact different levels of anticoagulant effects. At present, any prothrombin time established with any thromboplastin reagent can be translated in an internationally agreed norm: the international normalized ratio (INR) [4-8]. With this standardized INR, the intensity of anticoagulation can be compared not only between different anticoagulant clinics but also between studies on the therapeutic efficacy of anticoagulant therapy.

A number of methods have been described to evaluate efficacy of anticoagulant therapy. The purpose of the present analysis was to compare the merits of previously proposed methods, including those considering INR measurements only [9-19] methods expressing the time each patient's INR was within the therapeutic range expressed as a percentage of the total treatment time [20-23] as well as a recently suggested patient-time method [3,24,25]. The study population comprised 1700 participants in a secondary prevention trial of post-myocardial infarction patients with anticoagulant therapy. Since different anticoagulant congeners were employed in this trial, we were also able to compare therapeutic achievement with the anticoagulant congeners acenocoumarol to phenprocoumon. In addition, the therapeutic merits of two different dosage systems were evaluated.

METHODS

Study patients

The patients who took part in the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial comprised the study group. This trial has been described in detail elsewhere [see Chapter 2]. In short, ASPECT was a randomized, double-blind, placebo controlled, multicentre, clinical trial which compared anticoagulant therapy with matching placebo on mortality and

cardiovascular events in post-myocardial infarction patients.

Hospital survivors of acute myocardial infarction were screened for eligibility just prior to hospital discharge. Informed consent was obtained in all subjects. Patients were randomly assigned to treatment with oral anticoagulant therapy or to matching placebo. From September 1, 1986 until December 31, 1991, a total of 3404 patients entered the trial. Follow-up ended on June 30, 1992. The mean age of the patients was 61 years and 80% of the study population was male.

Oral anticoagulation and dose adjustment

The target anticoagulant range was 2.8 - 4.8 INR [26]. Individual dose adjustments were guided by the prothrombin time measurements obtained at regular intervals at one of the nineteen participating anticoagulant clinics, the Thrombosis Centres. Anticoagulant treatment consisted of phenprocoumon given in tablets of 3 milligram (mg), acenocoumarol in tablets of 1 mg or acenocoumarol in tablets of 4 mg.

At each follow-up visit at the Thrombosis Centre, the patient's history was taken and a blood sample was drawn to determine the prothrombin time. The prothrombin time is the time needed for a blood sample to clot when a small quantity of thromboplastin reagent is added [27]. The obtained prothrombin time was either entered automatically from the laboratory computer system or manually into the Thrombosis Centre computer system. Based on the results of the test, a proposal for a new dosage was calculated by the computer system which was subsequently checked by the Thrombosis Centre physician.

Calculation of the dosage adjustment at the Thrombosis Centres was performed by two independent systems: TRODIS and TDAS®. The dosage algorithm for TRODIS is primarily based on the pharmaco-kinetics of the coumarin used and was employed by 7 of the participating Thrombosis Centres [28]. TDAS® is primarily based on empirical grounds and trend analysis and was used by 12 of the participating Thrombosis Centres. More information of these dosage systems is submitted in the appendix.

Patients were seen at the initial (i.e. randomization) visit and on a weekly basis thereafter until the prothrombin time measurements were within the specified target range. The interval between visits was subsequently prolonged until a maximum period of eight weeks. Patients requiring frequent dosage adjustments were seen more regularly. While on trial medication, patients were advised not to take other anticoagulant or anti-thrombotic medication. At the end of trial on June 1992, trial medication was discontinued in all patients.

Assessment of therapeutic anticoagulant control

Therapeutic anticoagulant control was assessed using three different approaches.

In the first approach, which is 'INR-oriented', therapeutic achievement was assessed using two techniques: (1a) the 'cumulative INRs' [9-16] which considers the number of INR measurements within the target range expressed as a percentage of the total number of values obtained; (1b) the 'cross-section-of-the-files' technique [17-19], that only considered the most recent (within 56 days) INR obtained in each patient at pre-defined time intervals. The results of both techniques are expressed as a percentage of all INR values within the therapeutic range.

The second approach considered the number of weeks each patient's INR was under- (INR<2.8), within- (INR 2.8-4.8) or above- (INR>4.8) target therapeutic range. This approach produced an estimate of the percent of time each patient was within the defined ranges [20-23]. In order to allocate the exact time between INR measurements, it has been proposed to count the weeks preceding a visit as belonging to the INR of that visit [22], or to divide these weeks between the previous and subsequent visit [21]. Thus, in each of these two techniques, an abrupt change in INR, either at the time of the visit (technique 2a, 'initial-interval step'), or half-way between visits (technique 2b, 'mid-interval step') is assumed.

The third approach, which is 'patient-time' oriented, is a recently proposed modification of approach 2 [3,24,25]. In this approach, the total volume of observation time of all patients is categorized in classes of INR-values. In this approach a more realistic linear change of the INR between successive visits is assumed, and small increments in time (days) and in INR (0.1 INR) are used to allocate time between two INR determinations. Once the number of days is allocated to all these small INR classes, they can be grouped in larger categories or be divided in person-time within, above or under the therapeutic zone. Since the unit of measurement is patient-time, this approach is suitable for assessment of anticoagulant control, but also for the calculation of the incidence of events at different INR intensities, since the incidence rate is expressed as the number of events over the number of patient-years.

Data analysis

For obvious reasons, patients in the trial treated with placebo were not included in this analysis: their INR values were not based on actual measurements but were generated by a computer to simulate the real anticoagulation procedure. Measurements obtained after discontinuation of trial medication were excluded, i.e, patients who received open label anticoagulant therapy following trial medication discontinuation were not considered irrespective of the reason for cessation of trial

medication. In addition, in case the interval between two consecutive INR measurements exceeded 56 days, this time period was not included in the present analyses, since a linear change over this long period becomes unrealistic.

Calculation of therapeutic anticoagulant control was performed according to the descriptions above. As an example, therapeutic achievement was calculated using the three different approaches in a hypothetical patient with five INR determinations. The patient had an INR measurement of 2 on May 2, an INR value of 4 on May 8, an INR measurement of 3 on May 12, an INR of 5 on May 20, and an INR of 3 on May 22. Using technique 1a, the 'cumulative INRs', which considered INR determinations only, the patient was under-anticoagulated (INR <2.8) for 20% of the INR measurements, while he was within therapeutic range (2.8-4.8 INR) for 60% and over anticoagulated (INR>4.8) for 20% of the measurements. However, using the 'cross-section-of-the-files' technique 1b and considering the last INR value only, the patient in this case is considered to be within the therapeutic range for 100% of the measurements.

Approach 2 considered the percent of time the patient was within the therapeutic range and assumed that the change between two consecutive INR measurements occurred either immediately after the first (technique 2a) or half-way the interval (technique 2b). Using technique 2a, the patient in question had an INR value of 2 for 0 days, a value of 4 for 6 days, an INR value of 3 for 6 days, and of 5 for 8 days. The patient in question will be under anticoagulated for 0% of the time, within the therapeutic range for 60% of the time and over-anticoagulated for 40% of the time. Using the 'mid-interval step' technique 2b, the results would be: INR <2.8 for 15% of the time, INR 2.8-4.8 for 60% of the time and INR >4.8 for 25% of the time.

Approach 3 considered the number of patient-days within specific INR ranges and calculates the slope of the line between two consecutive INR measurements. These slopes are +0.33 for the first 6 days, -0.25 the next 4 days, +0.25 for the next 8 days, and -1.0 for the last two days. The INR measurements of the patient will thus increase daily with an increment of 0.33 from May 2 to May 8, then decreases with 0.25 until reaching the value of 3.0 on May 12, increases thereafter daily with 0.25 until May 20 and finally would decrease with an increment of 1.0, thus producing the different anticoagulation levels: INR <2.8 for 12% of the patient-time, INR 2.8-4.8 for 83% of the patient-time and INR >4.8 for 5% of the patient-time.

In order to investigate which variables independently predicted stability of anticoagulant therapy, multivariate modelling with logistic regression analysis was performed [29]. The following variables were entered in the model: anticoagulant congener (acenocoumarol vs phenprocoumon), dosage system (TDAS® vs TRODIS), age (categorised on the basis of the median value) and gender. The logistic model yields the odds ratio for each variable, adjusted for the other variables in the model. This odds ratio may be interpreted as the relative risk, i.e., the risk of

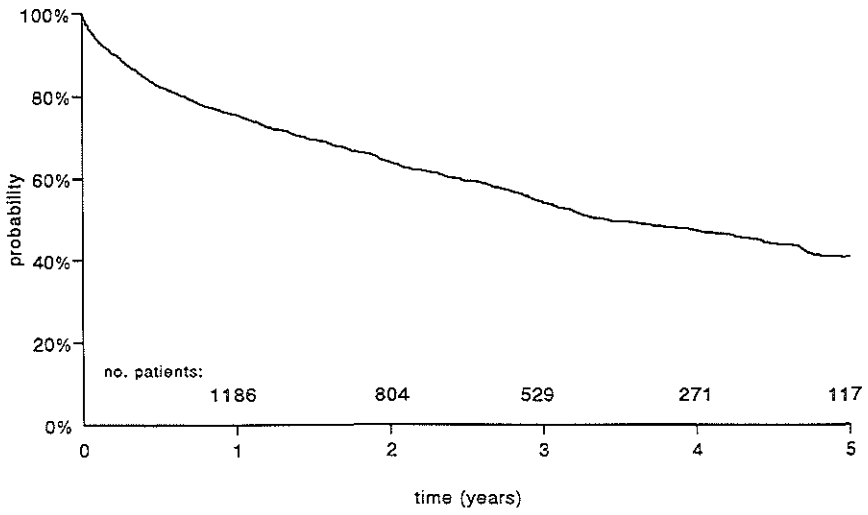
unstable anticoagulant therapy in the presence of the particular variable, relative to the risk in the absence of that variable. Confidence intervals were derived from the likelihood function.

RESULTS

A total of 61,471 INR measurements were performed during 3725 patient years of follow-up with a median of 30 determinations per patient (range from 1 to 140). In the first month following recruitment, the patients visited the Thrombosis Centre for a mean of 4.3 visits, while, on average, 2.2 visits per patient were made in the first to second month. After the third month INR determinations were made once in every month on average.

The number of patients alive and on trial medication during the course of the trial is presented in Figure 1. The duration of treatment ranged from 1 day to six years. The number of patients on trial medication gradually decreased with time. After one month following randomization, 94% of the patients were still receiving active anticoagulant therapy compared to 82% at 6 months and 64% at 2 years.

Figure 1: Time of discontinuation of trial medication



Intensity of anticoagulation was assessed using the three approaches following initiation of treatment (Table 4.1). The data revealed that, irrespective of the approach and technique used, therapeutic achievement stabilized after 6 months of treatment. The lowest percentage of INR measurements within target range (63%) were obtained with the INR-oriented 'cumulative' technique 1a, while the highest number (80%) was obtained with the INR-oriented 'cross-section-of-the-files' technique 1b. Approaches 2 and 3 yielded intermediate values. In the first month of treatment, a large number of INR measurements were below INR<2.8. This number was highest for the 'cumulative' technique 1a (51%) and lowest using the 'cross-section-of-the-files' technique 1b (29%). Using any approach and technique, under-anticoagulation decreased between the first and third month and was again lower after 6 months of treatment. Over-anticoagulation (INR>4.8) occurred between 8% to 10% at any time interval using approaches 1 and 2, and around 5% of the time using approach 3. Although there is no formal way to decide on the superiority of any of these approaches we have a preference for approach 3 on theoretical grounds. Therefore, all further analyses have been carried-out using this approach.

Table 4.1 Therapeutic achievement (2.8-4.8 INR) at different time intervals after initiation of anticoagulant therapy using the described methods

Approaches	Time (months)				Time (years)		Total
	0-1	1-3	3-6	6-12	1-2	2-3	
1a 'cumulative INRs'	41%	56%	64%	66%	67%	66%	63%
1b 'cs-of-the-files'	61%	76%	80%	81%	81%	80%	80%
2a 'initial-interval step'	45%	61%	67%	70%	71%	70%	70%
2b 'mid-interval step'	45%	63%	71%	74%	74%	74%	72%
3 'linear' change	47%	66%	76%	79%	80%	80%	77%

cs, cross-section.

Thirty eight percent of the patients were treated with acenocoumarol given in tablets of 1 mg, 7% to acenocoumarol in tablets of 4 mg and 55% to phenprocoumon in tablets of 3 mg (Table 4.2). Therapeutic achievement per anticoagulant congener is presented in Table 4.3. For both congeners, under-

Table 4.2 Distribution of patients per coumarin congener and dosage system

	Acenocoumarol	Phenprocoumon
TDAS (n=892)	492 (55%)	400 (45%)
TRODIS (n=808)	278 (35%)	530 (65%)
Total	770 (45%)	930 (55%)

Table 4.3 Therapeutic achievement per coumarin congener and dosage system

	TDAS		TRODIS		Total	
INR	Ac.	Ph.	Ac.	Ph.	Ac.	Ph.
< 2.8	23%	17%	30%	17%	25%	17%
2.8-4.8	72%	80%	66%	79%	70%	80%
>4.8	5%	3%	4%	4%	5%	3%

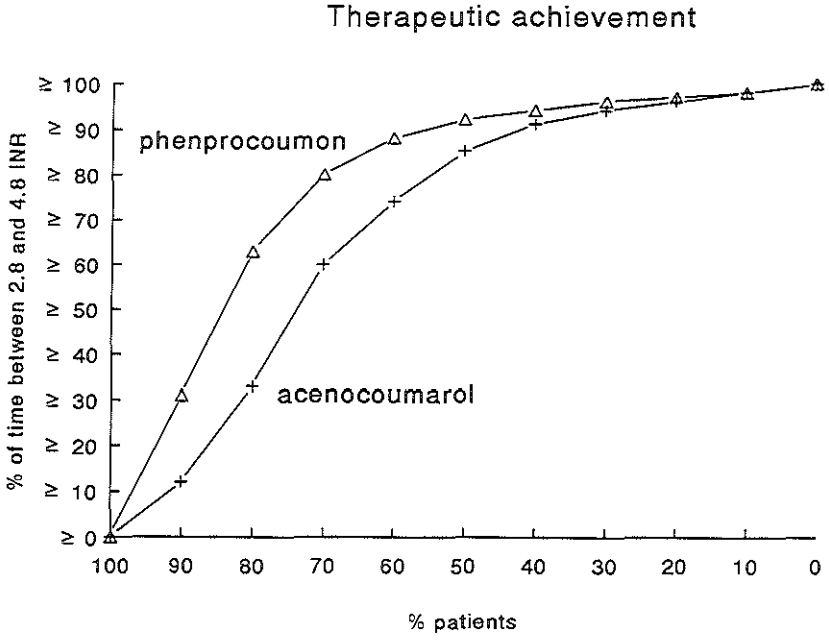
Ac., acenocoumarol; Ph., phenprocoumon.
The observation time for all patients, broken down by dosage system, is given as a percentage of the total observation time for each coumarin congener.

anticoagulation was observed to occur more frequently than over-anticoagulation irrespective of the dosage system used. Patients treated with acenocoumarol were within the therapeutic range 70% of the time compared to 80% for phenprocoumon. The therapeutic achievement for both congeners is graphically presented in Figure 4.2. The data illustrate that 60% of the patients treated with acenocoumarol were for at least 70% of the time within the target range, compared to 80% for those treated with phenprocoumon. In order to assess the independent contribution of the anticoagulant congeners to therapeutic achievement, patients were defined as stable when 70% of observation time was spent within therapeutic range, calculated using approach 3. The relative risk (RR) of unstable anticoagulation for patients treated with acenocoumarol compared to those treated with phenprocoumon was 2.5 with a 95% confidence interval (CI) of 2.0 to 3.3, after adjustment for possible confounding variables as described in the methods section.

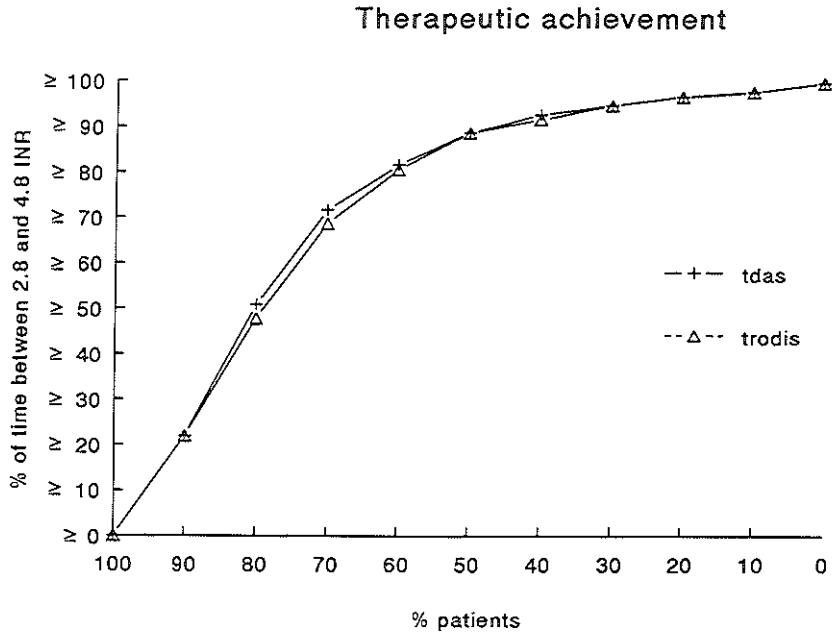
Of the 19 participating anticoagulant centres, 52% used TDAS® and 48% TRODIS dosage systems. Again, the percentage of patient-days within the optimal therapeutic range of 2.8-4.8 was calculated using approach 3 and is presented for both systems in Table 4.3. The therapeutic achievement within target range for both dosage systems is given in Figure 4.3. TDAS® and TRODIS systems provided similar levels of therapeutic effectiveness. Using the logistic regression model to control for the possible confounding variables, age and gender, and applying the same definition of stability as above, the relative risk of unstable anticoagulation associated with TDAS® was 1.20 (95% CI, 0.97 to 1.47).

DISCUSSION

The most common approach to characterize anticoagulant therapy is to count the number of times the prothrombin time lies within the therapeutic range expressed as percentage of the total determinations performed, known as the 'cumulative' approach ('INR-oriented' technique 1a). This approach was adopted by a number of investigators [9-16]. Although this approach has proven popular, its merits were questioned by Duxbury, who asserted that, since unstable patients have more measurements performed on them than stable patients, the results of the method are unrealistic and biased [21]. He proposed a method in which adequacy of anticoagulant therapy was expressed as the number of weeks each patient's INR was within the therapeutic range. This approach produced an estimate of the percent of the time each patient was within the therapeutic range [21]. This approach is oriented towards patient and time but assumed a sudden change in the INR between two consecutive visits (technique 2a), in Duxbury's proposal the change occurred half-way between these visits (technique 2b). This approach was not only used by Duxbury, but also by Raper in 1983 [23] and Coppelstone and



Legend to Figure 4.2.
Therapeutic achievement for the two anticoagulant congeners acenocoumarol and phenprocoumon. On the x-axis the percent of patients is indicated and on the y-axis the least percent of time the patient is within therapeutic range (2.8-4.8 INR). The graph indicates that 60% of the patients treated with acenocoumarol were for at least 70% of the time within therapeutic range as compared to 80% for those treated with phenprocoumon. Patients were defined as stable when at least 70% of their observation time was within therapeutic range. The rate of unstable anticoagulation for patients treated with acenocoumarol was 2.5 with a 95% confidence interval of 2.0 to 3.3.



Legend to Figure 4.3.
Therapeutic achievement for the two dosage system TDAS® and TRODIS is presented. On the x-axis the percent of patients is indicated and on the y-axis the least percent of time the patient is within therapeutic range (2.8-4.8 INR). The graph indicates that 70% of the patients are for at least 70% of the time within therapeutic range. Patients were defined as stable when at least 70% of their observation time was within therapeutic range. The rate of unstable anticoagulation associated with TDAS® was 1.20 with a 95% confidence interval of 0.97 to 1.47.

Roath in 1984 [22]. The technique suggested by Coppelstone and Roath is a modification of the latter in that it is assumed that the INR change between two consecutive visits took place immediately after the first [oac 22]. The obvious drawback of these techniques is that an abrupt change is unrealistic. A patient who has an INR below the therapeutic zone at the first visit, and above at the second visit, is assumed at no time to have had an INR within the target zone. This is unrealistic, since in changing from below to above the target zone, the patient must have spent some time within the therapeutic zone. The approach of Duxbury, Copplestone and Roath, is not suitable for centres without automated data facilities, and the 'cross-section-of-the files' (technique 1b) has been suggested for such centres [17-19]. This technique considered the last INR measured per patient, expressed as a percentage of all INR measurements within the therapeutic range. This technique was based on the assumption that the probability that a patient's prothrombin time is adequate at an arbitrary moment is equal to the proportion of time spent by the patient within the therapeutic range. This technique was employed by Broekmans and Loeliger in 1982 [19], van den Besselaar in 1988 [17] and Smith and Arnesen in 1990 [16]. A drawback of this technique is that it uses only a fraction of all INR measurements, i.e, a fraction of all available information. This is also its advantage: the technique may easily be implemented in non-computerized anticoagulant clinics. The 'patient-time' oriented approach, is a newly proposed modification to approach 2 [3,24,25] that is different in two aspects: the use of the 'linear' technique and the application of the concept of patient-time for the calculation of incidence rates. Although Duxbury, Copplestone and Roath did incorporate the concept of patient-time in their calculations, they tended to 'individualize it' by considering "percent of time a percentage of patients" was within the therapeutic range [22]. The 'linear' approach, has the obvious benefit over the previous approaches in that it recognises that a patient who is below the therapeutic zone at the first, and above target zone at the second visit, must have spent some time within the therapeutic zone. Finally, this approach has the potential to incorporate the calculation of incidence rate data which is a fundamental measure of disease.

In the present analysis, these approaches were compared in the large ASPECT cohort of 1700 anticoagulated post-myocardial infarction patients. Our findings show that the different approaches yield values ranging from 63% to 80% for INR values or patient-time within the therapeutic target zone. This illustrates that therapeutic quality control data from different studies can be compared only if the same approaches are used. Although we have no formal reason to consider the truth content of one approach to be better than the other, we have good arguments to favour approach number 3: the assignment of INR-time is more realistic than either any of the other approaches and the possibility to use the patient-time dimension for the calculation of incidence rates has obvious advantages. It should be emphasised that, using any approach, a substantial number of subjects were

under-anticoagulated in the first six months and that therapeutic achievement stabilised only after the first six months of treatment. In addition, under-anticoagulation was observed more frequently to occur than over anticoagulation. This finding indicates that physicians are more cautious regarding over-treatment than under-anticoagulation.

Three most recently conducted preventive trials [12,16,Appendix A] have now shown the highly beneficial effects of oral anticoagulant treatment in survivors of myocardial infarction. It seems likely that the positive results of these trials were the result of a high standard of anticoagulant monitoring (Sixty-Plus 72% of all INR within the target range, WARIS 67%, ASPECT 63%, all using the 'cumulative INRs' technique). This indicates first, the importance of quality control, and the application of comparable methods to express the quality in. Secondly, it may be noted that even in these carefully designed and performed trials, the target zone was not reached in a substantial part of the time. This illustrates the need for analysis on the basis of achieved level of intensity, and not on an intention-to-treat basis only [24, and see Chapter 5].

An interesting finding is that the long-acting anticoagulant phenprocoumon was associated with better therapeutic control than the short acting anticoagulant acenocoumarol. This finding has been reported by other investigators [30]. After correcting for dosage system, anticoagulant centre, age and gender, the results again indicated that patients treated with acenocoumarol were two and a half times more likely to be outside the therapeutic range than those treated with phenprocoumon.

The participating anticoagulant centres utilized either the TRODIS or the TDAS® dosage system. Use of the TRODIS system appeared to result in more stable anticoagulation than with the TDAS® system. It must be noted, however, that this may be a reflection of differences between centres, who all used only one of the two systems, rather than a true difference between the two dosage systems.

In conclusion, in this article we compared different approaches to assess therapeutic achievement, as well as therapeutic achievement for two frequently used anticoagulants and different anticoagulant dosage systems. The newly proposed approach ('patient-time') is recommended as the method of choice since it incorporates time and has the most realistic assumptions. This approach is also most suitable for assessing therapeutic anticoagulant control, since calculation of incidence rates of events at different intensities can be made. In addition, comparison of the therapeutic achievement of the two most used anticoagulant congeners in the Netherlands revealed that the short acting congener acenocoumarol was more likely to be outside the therapeutic range than the long acting phenprocoumon. However, comparison of the therapeutic achievement of the two dosage systems used in this country showed minor differences. Finally, the present data call for an improvement by the standard of control for patients during

the first 3 months of anticoagulant treatment.

APPENDIX

The participating Thrombosis centres utilize computers to establish the dosage for its patients under anticoagulant therapy. Two programs of dosage algorithms have been developed: TRODIS based on pharmacokinetic findings and TDAS®, on empirical grounds. Both programs are able to provide automated dosage prescription for at least 70% of the patients. Although, the physician checks the results of the computer generated out-puts, the dosage system makes use of predefined INR measurements preceding the visit, the interval between measurements and patient's relevant medical data. Details of the TRODIS dosage algorithm have been previously described by Wiegeman etal [28].

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CHAPTER FIVE

OPTIMAL INTENSITY OF ORAL ANTICOAGULANT THERAPY IN POST-MYOCARDIAL INFARCTION PATIENTS

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SUMMARY

Treatment with oral anticoagulant therapy entails a delicate balance between over- (risk of bleeding) and under- (risk of thromboemboli) anticoagulation. However, the optimal intensity of therapy in post-myocardial infarction patients required to prevent the occurrence of either event (thromboembolic and haemorrhagic) is not known. Here, incidence rates associated with specific international normalized ratio (INR) intervals were calculated for bleeding and thromboembolic complications in 3404 post-myocardial infarction patients enrolled in the ASPECT (Anticoagulants in the Secondary Prevention of Events) trial. Total treatment period was 7213 patient-years. Major bleeding occurred in 57 (0.8/100 patient-years) and thromboembolic complications in 397 patients (5.6/100 patient-years).

A Poisson regression analysis was performed to determine the independent risk of event associated with INR-specific intervals, after adjustment for possible confounding variables. Based on INR measurements obtained within 28 days from the event and relative to INR intensities below 2, the rate ratio of major bleeding associated with INR values between 2 and 3 was 0.2 with a 95% confidence interval (CI) of 0.1 to 1.3. The rate ratio was 0.6 at INR between 3 and 4. An 80% increase in bleeding risk was associated with INR measurements between 4 and 5, and 5 fold increase for INR values exceeding 5. The rate ratio of thromboemboli associated with INR values between 2 and 3 was 0.3 with a 95% CI of 0.2 to 0.6, a reduction of 70% compared with INR intensities below 2. An 80% reduction of thromboemboli was obtained at INR intensities between 3 and 4, as well as for INR intensities above the value of 5. The intensity of anticoagulant therapy at which the incidence of bleeding and thromboembolic complications was lowest was between the INR range 3.0-4.0. Other significant predictors for major bleeding and thromboemboli included higher levels of systolic blood pressure and age. Female patients showed a higher trend for bleeding than males.

These results suggest the optimal intensity of long-term anticoagulant therapy for post-myocardial infarction patients to lie between 3.0 and 4.0 INR.

INTRODUCTION

The narrow therapeutic range of oral anticoagulant therapy mandates careful and frequent monitoring of patients with conditions for which the therapeutic benefit of anticoagulant therapy has been established, i.e., in the treatment of patients with deep venous thrombosis, pulmonary embolism, atrial fibrillation, severely diminished left ventricular function, or in subjects who have undergone major surgery, or implantation of endovascular prosthetic materials [1]. However, in conditions in which the therapeutic value of long-term anticoagulant therapy is still controversial, the risk of life-threatening side effects, in particular that of bleeding complications, becomes an impediment to its widespread utilization [1-5]. One such condition is the use of anticoagulant therapy in the secondary prevention in patients after a myocardial infarction [2,6,7].

The findings of the three most recently performed post-myocardial infarction trials [8,9,Appendix A] suggested substantial benefits of long-term anticoagulant therapy in mortality by achieving lower rates of thromboembolic disorders including myocardial infarction and of cerebrovascular events. The trials demonstrated that intensive and stable anticoagulant therapy reduced the rate of reinfarction by 34% to 55% and cerebrovascular events by 40% to 55%. In these investigations, a high quality of anticoagulation was achieved, since 63% to 74% of the prothrombin time measurements were within the therapeutic international normalised ratio (INR) range between 2.5-5.0. Therapeutic quality control was expressed as the total number of INR measurements obtained, the so called 'INR-oriented' assessment of anticoagulant therapy (see Chapter 4).

Randomised trials conducted to compare two intensities of oral anticoagulant therapy offer little information on the optimal intensity of anticoagulant therapy, not only because the target level is arbitrarily chosen, but also because the intensity of anticoagulant therapy actually achieved is not taken into account [10]. Therefore, it is not known which intensity of anticoagulant therapy offers the optimal benefit-risk ratio, i.e., the optimal balance between prevention of thromboembolic events and bleeding complications.

In order to determine the optimal intensity of anticoagulant therapy, the occurrence of haemorrhagic as well as arterial thromboembolic complications were quantitatively evaluated with regard to the INR level preceding the event, enabling the calculation of INR-specific incidence rates. The study population comprised 3404 post-myocardial infarction patients randomised to anticoagulant therapy or placebo.

METHODS

Patients

Subjects who took part in the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial comprised the study group. This trial has been described in detail elsewhere [see Chapter 2]. In short, ASPECT was a randomized, double-blind, placebo controlled, multicentre, clinical trial which compared anticoagulant therapy with matching placebo on mortality and cardiovascular events in post-myocardial infarction patients.

Hospital survivors of acute myocardial infarction were screened for eligibility just prior to hospital discharge. After informed consent was obtained, patients were randomly assigned to treatment with oral anticoagulant therapy or to matching placebo. From September 1, 1986 until December 31, 1991, a total of 3404 patients entered the trial. The study population contributed 7213 patient years of follow-up.

Oral anticoagulation and dose adjustment

The target anticoagulant range was 2.8 - 4.8 INR [11-14]. Individual dose adjustments were guided by the prothrombin time measurements obtained at regular intervals at one of the 19 participating anticoagulant clinics. Anticoagulant treatment consisted of phenprocoumon, acenocoumarol or matching placebo tablets. Double-blinding was maintained at the anticoagulant clinics by employment of a computerized dosage algorithm that automatically converted (not prolonged) prothrombin times to sham values within therapeutic range in placebo treated patients.

At each follow-up visit to the anticoagulant clinic, a short history was taken and a blood sample was drawn for determination of the Thrombotest®, a modified prothrombin time test [15]. The prothrombin time is the time needed for a blood sample to clot when a small quantity of thromboplastin reagent is added. Patients were seen at the initial (i.e. randomization) visit and on a weekly basis thereafter until the prothrombin time measurements were within the specified target range. The interval between visits was subsequently prolonged until a maximum period of eight weeks. Patients requiring frequent dosage adjustments were seen more regularly. While on trial medication, patients were strongly advised not to take other anti-thrombotic (including anti-platelet) medication. At the end of trial on June 1992, trial medication was discontinued in all patients.

Definition of clinical events

The following clinical events were considered: major bleeding and thromboembolic complications.

Bleeding was considered major if: (1) it led to death; (2) was clinically suspected or proven intracranial (cerebrovascular event leading to death within 24 hours was considered to be caused by intracranial bleeding unless the findings on computed tomography (CT) scanning indicated otherwise. In all other instances, the diagnosis of an intracranial haemorrhage had to be confirmed by findings on CT-scan [16]); or (3) led to hospital admission for treatment of bleeding (hospital admission for diagnostic purposes only was not considered a criteria for major bleeding).

Thromboembolic complications included: (1) instantaneous or sudden death, occurring within 1 hour after onset of symptoms; (2) recurrent myocardial infarction documented by at least two of the following [17,18]: (a) history of chest discomfort of at least 30 minutes duration; (b) serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme exceeding twice the upper limit of normal; or (c) the development of new Q-waves (lasting >0.03 seconds (sec) or of Q-wave equivalent (R >0.03 sec in V1 and R/S >1 in V2)) on the standard 12-lead electrocardiogram (ECG). Myocardial infarction was also diagnosed when death occurred within 28 days after hospitalization for recurrent myocardial infarction; (3) cerebral infarction, classified according to internationally accepted criteria and diagnosed on the basis of the CT-scan findings; and (4) other arterial thromboembolic complications.

Information on clinical events was obtained directly from the patients when they visited the Thrombosis Centre or from their general practitioners. In case of hospitalization, additional information was retrieved from the hospital records. The diagnosis and classification of clinical events were established by the Mortality and Morbidity Classification Committee of the ASPECT trial who independently reviewed the clinical course of each case on the basis of a review of a standardized patient report. The committee members were blinded to treatment assignment and were not informed of actual prothrombin time measurements.

Assessment of optimal intensity

Incidence rates were calculated for different achieved intensities of anticoagulant therapy. To obtain the INR-specific incidence rate, data on the INR at the time of the untoward event, either bleeding or thromboembolic complications, for different intensities were entered in the numerator, while the denominator comprised the sum of observation times of all patients at each INR intensity. Patients who were treated

with placebo were included in the analysis, since their achieved INR intensity corresponding to 'lack' of anticoagulation is of course known and corresponds to INR less than 2, at the time of an event, as well as at all other times. INR-specific incidence rates were calculated for intervals of 0.5 INR. The optimal intensity of anticoagulant therapy will lie at the level at which the incidence of bleeding and thromboemboli is lowest, i.e., where the incidence of complications, whatever their type, is lowest.

'Numerator data: events'

The instantaneous INR measurement at the time of event (bleeding or thromboembolism) was retrospectively obtained from the hospital records. If the INR measurement was not available at the date of event, the last INR measurement obtained within a maximum period of 28 days prior to the event was considered. INR measurements were considered missing in all other instances. INR measurements of placebo patients were assumed to have a value of less than 2 at the time of event.

In a subsequent, more strict analysis, we only included events for which an INR measurement obtained no more than three days prior to the event was available, whereas all others were considered missing.

Patients were censored when an event was reached, after 28 days following cessation of trial medication or at the end of follow-up, on June 30, 1992, whichever occurred first. In case patients experienced more than one event, only the first was considered. Four patients with a major bleeding due to an invasive interventional procedure during hospitalization were not included in this analysis.

'Denominator data: INR-time'

The total number of patient days within INR-specific intervals was entered in the denominator (see Chapter 4). In order to calculate the time each patient was within an INR-specific range, we assumed that the INR changed linearly between visits (see Chapter 4). Patients who used placebo were considered to have INR measurement below 2 during the total period of follow-up.

Poisson regression analysis

A Poisson regression analysis [19] was used to calculate the relative risk of bleeding and thromboembolic events associated with INR-specific intervals after adjustment for age, sex, type of coumarin congener and blood pressure. Age and systolic blood pressure, measured during hospitalization for the index myocardial infarction, were categorized on the basis of the median value, i.e, below or above 60 years of age, and below or over 120 mmHg. The incidence rate ratios obtained from the model may be viewed as relative risks, i.e., the risk of event relative to the reference risk factor category controlling for the other risk factors. The precision of the rate ratio estimates were described by means of 95% confidence intervals obtained from the Poisson distribution. In all analyses, the incidence rate associated with INR values below 2 was used as reference.

Table 5.1 Selected demographic, baseline and randomisation characteristics

	Anticoagulant		Placebo		Total	
No. of patients (%)	1700	(100)	1704	(100)	3404	(100)
Mean Age,yr (SD)	61	(11)	61	(11)	61	(11)
Gender (%)						
Male	1370	(81)	1350	(79)	2720	(80)
Female	330	(19)	354	(21)	684	(20)
Trial medication (%)						
Phenprocoumon	930	(55)	935	(55)	1865	(55)
Acenocoumarol	770	(45)	769	(45)	1539	(45)
Mean SBP,mmHg (SD)	119	(16)	119	(16)	119	(16)

yr, year; SD, standard deviation; SBP, systolic blood pressure at hospital discharge.

RESULTS

A total of 1700 patients were randomised to anticoagulant therapy (with 3725 patient-years of follow-up) and 1704 to placebo (with 3488 patient-years of follow-up). The baseline characteristics of the patient groups are presented in Table 5.1. The mean age of the patients was 61 years, 80% were male, and 55% of the patients received phenprocoumon and 45% acenocoumarol. The mean follow-up per patient was 2.1 years. Within one year of randomization, 76% of the patients in the anticoagulant group were still receiving active therapy compared to 70% in placebo.

The incidence of major bleeding is shown in Table 5.2. Fifty-seven cases of major bleeding (0.8/100 patient-years) occurred, of which 51 in the anticoagulated (1.4/100 patient-years) and 6 in the placebo group (0.2/100 patient-years). Fatal bleeding (9 patients) was only observed in the anticoagulated group (0.2/100 patient-years). The most frequent sites of major extracranial bleeding were the gastro-intestinal tract (26 in the anticoagulated group and 2 in placebo) and 10 muscular haematoma in the anticoagulated group.

The incidence of thromboembolic events is presented in Table 5.3. A total number of 397 thromboembolic complications (5.6/100 patient-years) occurred of which 118 were fatal. One-hundred and twenty-seven thromboembolic events (3.4/100 patient-years) were observed in the anticoagulated group and 270 in placebo (7.9/100 patient-years). The major thromboembolic events included sudden death (69 patients), recurrent myocardial infarction (293 patients) and cerebral infarction (34 patients).

INR measurements obtained at hospital admission or within 3 days prior to the occurrence of major bleeding were available in 42 cases and within a time frame of 28 days in 55 patients. INR measurements within 3 days from thromboembolic complication were obtained in 294 patients and within 28 days in 375 patients. The total number of patient-years within INR-specific intervals for the combined event (bleeding and thromboemboli) were: 3559 patient-years (INR<2), 838 patient-years (INR 2-3), 1775 patient-years (INR 3-4), 564 patient-years (INR 4-5), and 82 patient-years (INR>5).

INR-specific incidence rates based on measurements obtained within 3 days for major bleeding and thromboembolic complication are presented in Figure 5.1. The incidence of thromboembolic complications was highest, 78 per 1000 patient-years, for anticoagulant intensities less than 2 INR. The incidence of thromboembolic events at anticoagulant intensities between 2 and 3 INR was 14 per 1000 patient-years, and amounted to 11 per 1000 patient-years for anticoagulant intensities within the range of 4 to 5 INR. On the other hand, the INR-specific incidence rate of bleeding was lowest, 2 per 1000 patient-years, at anticoagulant intensities less than 2 INR and increased to 19 per 1000 patient-years at anticoagulant intensities between 4 and 5 INR. The incidence of bleeding was

Table 5.2 Incidence of major bleeding during follow-up

	Anticoagulant (n=1700)	Placebo (n=1704)	Total
Intracranial bleeding	14	1	15
Fatal	7	0	7
Non-fatal	7	1	8
Extracranial bleeding	37	5	42
Fatal	2	0	2
Non-fatal	35	5	40
First major bleeding	51 (1.4/100py)	6 (0.2/100py)	57 (0.8/100py)

py, patient-years.

Table 5.3 Incidence of thromboembolic events during follow-up

	Anticoagulant (n=1700)	Placebo (n=1704)	Total
Sudden death	35	34	69
Recurrent MI	86	207	293
Fatal	16	31	47
Non-fatal	70	176	246
Cerebral infarction	6	28	34
Fatal	0	2	2
Non-fatal	6	26	32
Other arterial thrombo-emboli	1	4	5
First major thromboemboli*	127 (3.4/100py)	270 (7.9/100py)	397 (5.6/100py)

*Sudden death/recurrent MI/cerebral infarction/other arterial thromboemboli whichever event occured first. MI, myocardial infarction; py, patient-years.

highest, 66 per 1000 patient-years, at anticoagulant intensities exceeding 5 INR.

The optimal anticoagulant intensity

INR-specific incidence rates with corresponding 95% confidence intervals, based on INR measurements obtained within 3 days from event, are presented in Figure 5.2, for the combined events of bleeding as well as thromboemboli. The incidence of complications is observed to be highest at INR values below 2 and above 5. The intensity at which the INR-specific incidence rates of the curve is lowest is the optimal intensity: between 3 and 4 INR. When the analysis was repeated for INR measurements obtained within 28 days from the event, the optimal intensity remained essentially unchanged.

Results of the Poisson regression analysis, performed to determine the independent risk of event (bleeding or thromboembolic) associated with INR-specific intervals, after controlling for age, sex, systolic blood pressure at discharge and type of coumarin congener, are presented in Table 5.4. Based on INR measurements obtained within 28 days from the event and relative to INR intensities below 2, the rate ratio of major bleeding related to INR intensities between 2 and 3 amounted to 0.2 with 95% confidence interval (CI) of 0.1 to 1.3. The rate ratio was 0.6 at INR between 3 and 4, a reduction of 40% and the rate ratio of bleeding associated with INR measurements between 4 and 5 was 1.8, an increase of 80%. However, a five fold increase in the rate ratio of bleeding was observed in case INR measurements exceeded the value of 5.

On the other hand, the rate ratios of thromboemboli associated with INR intensities between 2 and 3 was 0.3 with a 95% CI of 0.2 to 0.6, a reduction of 70% compared with INR intensities below 2. An 80% reduction of thromboemboli was obtained at INR intensities between 3 and 4, as well as for INR intensities above the value of 5.

Other significant predictors for major bleeding and thromboemboli included higher systolic blood pressure and age. Female patients showed a higher trend for bleeding than males.

In all analyses, incidence rates based on INR measurements obtained within 3 days from the event were slightly higher than those achieved when the INR measurements were obtained within 28 days.

DISCUSSION

In this analysis involving over 7000 patient-years of follow up with almost 60 major bleedings and approximately 400 thromboembolic events, the optimal intensity of

Figure 5.1 inr specific incidence rates
(for bleeding and thromboembolic complications)
(inr within 3 days from event)

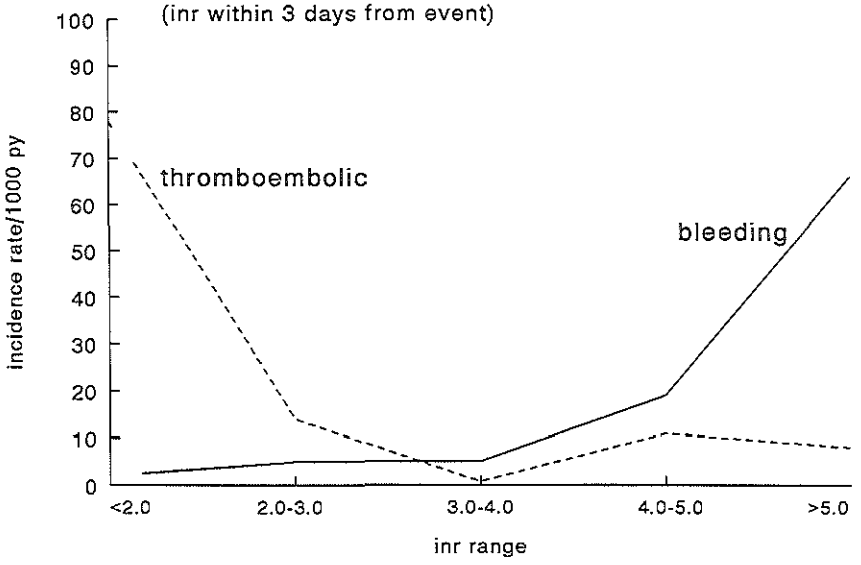

Figure 5.2 inr specific incidence rates
(inr within 3 days from event)

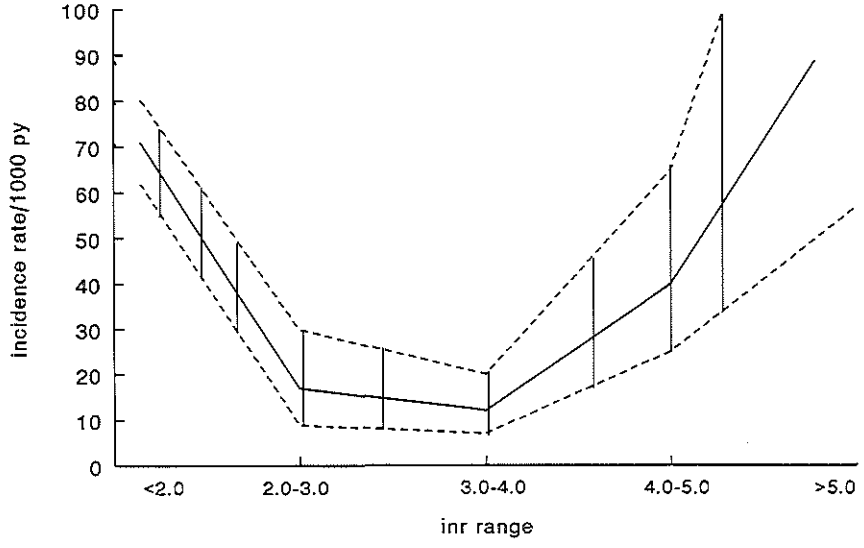

Table 5.4 INR-specific rate ratios for haemorrhagic and thromboembolic complications

	INR< 3 days* RR (95% CI)	INR< 28 days+ RR (95% CI)
	Haemorrhagic events	
INR		
<2	1.0 -	1.0 -
2-3	0.3 (0.1-3.3)	0.2 (0.1-1.3)
3-4	0.7 (0.1-5.4)	0.6 (0.1-2.4)
4-5	3.1 (0.4- 24)	1.8 (0.4-7.8)
>5	8.2 (1.0- 65)	4.9 (1.1- 22)
Age (years)		
< 60	1.0 -	1.0 -
≥ 60	1.9 (0.9-4.0)	1.5 (0.8-2.8)
Gender		
Male	1.0 -	1.0 -
Female	1.9 (0.9-3.7)	1.7 (0.9-3.2)
Anticoagulant congener		
Phenprocoumon	1.0 -	1.0 -
Acenocoumarol	1.0 (0.5-2.0)	0.9 (0.5-1.6)
SBP (mmHg)		
≤ 120	1.0 -	1.0 -
> 120	2.0 (1.0-3.8)	2.0 (1.1-3.6)
	Thromboembolic events	
INR		
<2	1.0 -	1.0 -
2-3	0.2 (0.1-0.6)	0.3 (0.2-0.6)
3-4	0.1 (0.1-0.4)	0.2 (0.1-0.5)
4-5	0.3 (0.1-1.2)	0.5 (0.2-1.0)
>5	0.2 (0.1-1.8)	0.2 (0.1-0.7)
Age (years)		
< 60	1.0 -	1.0 -
≥ 60	1.4 (1.0-2.0)	1.6 (1.2-2.1)
Gender		
Male	1.0 -	1.0 -
Female	1.1 (0.8-1.6)	1.1 (0.8-1.5)
Anticoagulant congener		
Phenprocoumon	1.0 -	1.0 -
Acenocoumarol	0.9 (0.4-2.1)	1.0 (0.7-1.5)
SBP (mmHg)		
≤ 120	1.0 -	1.0 -
> 120	2.6 (1.2-5.8)	3.3 (2.2-4.9)

*Last INR value within 3 days from event.
+Last INR value within 28 days from event.
INR, international normalised ratio; RR, rate ratio; CI, confidence interval; SBP, systolic blood pressure at hospital discharge.

anticoagulant therapy using a previously proposed method [10], involving the calculation of INR-specific bleeding and thromboembolic incidence rates, was evaluated. The optimal intensity, the intensity of anticoagulation at which the incidence of haemorrhages as well as thromboembolism was lowest, appeared to be located between INR 3.0 and 4.0. In this range, the risk of bleeding was relatively low, amounting to 5 major bleedingcomplications per 1000 treatment-years, while the reduction in thromboembolic complications, relative to INR intensities below 2, was still reduced by 70%.

The risk of bleeding associated with anticoagulant therapy, observed in patients with as well as without coronary heart disease, is well recognized and has fostered the conduct of several trials that compared the efficacy of different intensities of oral anticoagulant therapy [20-26]. So far, however, these trials have been unable to provide the "true" optimal anticoagulant intensity. The main reason of course is that achieved anticoagulant intensity are not constant and will invariably fluctuate around the pre-specified target level hinging on particular characteristics of the patient under treatment as well as on extraneous features related to the administration and monitoring of the therapy.

Given the acknowledged relation between incidence of bleeding complications and high anticoagulant intensities [20-27], it is surprising that few attempts have been made to quantify this association. In one recent population study [28], in which the achieved intensity of anticoagulant therapy was analyzed in 6814 patients, a 42% increase in the risk of major bleeding was reported for every INR rise. In an other recent analysis, a nested case control study of 565 patients starting outpatient therapy with warfarin by Landefeld et al, the odds ratio for major bleeding increased with increasing prothrombin time-to-control ratios [25]. In the present analysis, the risk of major bleeding gradually increased with elevation in the intensity of anticoagulation achieved. The risk was increased 80% when INR intensities were between 4 and 5 as compared to intensities below 2 INR, while the risk was increased almost five fold in case INR intensity exceeded 5.

Although it seems reasonable to assume an increased risk of thromboembolic events with less intense anticoagulation, this conclusion cannot easily be extracted from the literature. In addition to the previously mentioned methodological issues, the relatively small size of some studies is an other limiting factor. Evidence for strong effects of anticoagulant therapy on thromboembolic complications were obtained in placebo controlled post-myocardial infarction trials [8,9,Appendix A]. The results of the three most recently conducted preventive trials, the Sixty-Plus [8], WARIS [9] and ASPECT [Appendix A] convincingly demonstrated that substantial reduction in myocardial infarctions and cerebrovascular events, can be achieved with this type of therapy, in survivors of myocardial infarction. The intensity of treatment in the three trials was characterised by a prothrombin time prolongation of 2.5 to 5.0 INR. In the Dutch 'Sixty-Plus' Reinfarction study, the risk of recurrent

myocardial infarction was more than halved, while there was a suggestive trend toward fewer intracranial events (20 vs 12) in patients receiving anticoagulant therapy. In the Warfarin Reinfarction trial (WARIS), the risk of reinfarction was reduced by 34%, and that of cerebrovascular accidents by 55%, both highly significant. As in the current analysis, the incidence of bleeding in both trials was higher in the anticoagulated patients, but due to use of different definitions, the observed rates are not quite comparable.

One criticism of this analysis is that we were unable to obtain INR measurements at the time of the event in every instance. However, the association between intensity of anticoagulation and events would probably have been stronger if these measurements had been acquired at the moment of the incident in each patient. On the other hand, a relatively small number of events occurred at moderate INR intensities; our estimation of the best INR intensity may therefore be imprecise, and the optimal INR range is likely to be smaller than currently estimated.

In line with findings reported by others, the current analysis confirmed the independent contribution of higher systolic blood pressure [29] to increased bleeding tendency during anticoagulation therapy. This parameter was also associated with increased thromboembolic complications. Our results tend to confirm a recent observation [28] of a higher bleeding incidence in the elderly and females [28-30]. In contrast to findings of an other analysis that employed the same quantitative approach as currently described [28], we were unable to confirm the association of the use of acenocoumarol with increased bleeding tendency.

In conclusion, the optimal therapeutic range for long-term oral anticoagulant therapy has been a matter of intense debate for more than 30 years [3]. Findings in this large cohort provide a quantitative basis to locate the optimal therapeutic anticoagulant intensity within the INR range of 3.0 and 4.0. In this range, which is somewhat lower than targeted anticoagulant intensity in the most recent secondary prevention trials [31], the incidence of major bleeding during long-term anticoagulant therapy is relatively small while a substantial reduction in the rate of thromboembolic events is achieved.

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CHAPTER SIX

STROKE AND LONG-TERM ANTICOAGULANT THERAPY IN POST-MYOCARDIAL INFARCTION PATIENTS

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SUMMARY

In a randomized, double-blind, placebo controlled trial we studied 3404 post-myocardial infarction patients who suffered a stroke during long-term anticoagulant therapy. The duration of treatment ranged from 1 day to six years. Three years following randomization, 2% of the patients on anticoagulant therapy had a stroke compared to 4% in placebo. The incidence of stroke analyzed on "intention-to-treat" was 0.7 per 100 patient-years in the anticoagulant group and 1.2 per 100 patient-years in placebo, a hazard ratio (HR) of 0.60 with a 95% confidence interval (CI) of 0.40 to 0.90, a 40% reduction in the risk of stroke in the anticoagulated group. A total of 19 intracranial bleeding was observed. The risk of haemorrhages was 8 times greater for anticoagulated patients compared to placebo. Eight of the 17 bleedings were fatal in the anticoagulant group and no fatal haemorrhages occurred in placebo. A total of 15 cerebral infarctions occurred in the anticoagulated group and 43 in placebo. Of the 14 haemorrhagic strokes, 6 were within INR 3.0-4.0 and 8 with an INR>4.0. Of the 7 non-haemorrhagic strokes, 2 were at INR< 2, 3 within INR 3.0-4.0, 1 at INR>4.0, and no measurement was available in one patient. The total number of patients who died or were severely disabled as a result of cerebral stroke amounted to 13 in the anticoagulated group, compared to 18 in placebo.

The results of this study indicated that long-term anticoagulant therapy substantially reduced the risk of stroke in post-myocardial infarction patients. The increased risk of bleeding complications associated with anticoagulant therapy was offset by a marked reduction in ischemic events.

INTRODUCTION

Myocardial infarction survivors have an increased risk of thromboembolic events, that has been estimated at approximately 5% to 8% in the first year, including stroke [1]. Administration of long-term anticoagulant therapy may reduce the number of such events [2]. However, an estimated 10 times increase in risk of bleeding during such treatment has been reported [2-7]. Approximately 50% of these bleedings are fatal [4]. The presence of some factors, including hypertension, older age, and trauma, has been associated with an increased risk of stroke [6].

The results of the three conducted post-myocardial infarction trials [8,9, Appendix A] indicated a 40% to 55% reduction in the risk of stroke in patients treated with anticoagulant therapy for a mean duration of 2 to 3 years as compared with placebo. The intensity of anticoagulant therapy in the three trials was targeted at 2.5 to 5.0 international normalised ratio (INR). The number of intracranial bleedings was higher in the anticoagulated group, but intracranial infarctions were more common in the placebo group. Fatal intracranial bleeding was only observed in the anticoagulated group in two of the three trials [9, Appendix A].

The purpose of this report is to describe the risk of stroke for post-myocardial infarction patients treated with long-term anticoagulant therapy. In addition, we aimed to examine the relation between the risk of intracranial haemorrhage or infarction and the intensity of anticoagulant therapy. The study population comprised 3404 patients randomised to anticoagulant therapy or placebo.

METHODS

Patients

We studied post-myocardial infarction patients who took part in the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial. This trial has been described in Chapter 2. In short, ASPECT was a randomized, double-blind, placebo controlled, multicentre clinical trial which compared anticoagulant therapy with matching placebo on mortality and cardiovascular events in post-myocardial infarction patients.

Hospital survivors of acute myocardial infarction were screened for eligibility just prior to hospital discharge. Informed consent was obtained in all subjects. Patients were randomly assigned to treatment with oral anticoagulant therapy or to matching placebo. From September 1, 1986 until December 31, 1991, a total of 3404 patients entered the trial. The study population contributed 10441 patient years of follow-up.

Oral anticoagulation and dose adjustment

The target anticoagulant range was 2.8 - 4.8 INR [10-14]. Individual dose adjustments were guided by the so called prothrombin time measurements obtained at regular intervals at one of the participating anticoagulant clinics. Anticoagulant treatment consisted of phenprocoumon, acenocoumarol or matching placebo tablets. Double-blinding was maintained by conversion of the actual prothrombin time values of placebo treated patients to values within therapeutic range by a computerized dosage algorithm at the anticoagulant clinic.

At each follow-up visit to the anticoagulant clinic, a short history was taken and a blood sample was drawn for determination of the prothrombin time test. The prothrombin time is the time needed for a blood sample to clot when a small quantity of thromboplastin reagent is added [12]. Patients were seen at the initial (i.e. randomization) visit and on a weekly basis thereafter until the prothrombin time measurements were within the specified target range. The interval between visits was subsequently prolonged until a maximum period of eight weeks. Patients requiring frequent dosage adjustments were seen more regularly. While on trial medication, patients were strongly advised not to take other anti-thrombotic medication. At the end of trial on June 1992, trial medication was discontinued in all patients.

If available, prothrombin time measurements immediately before the haemorrhagic and non-haemorrhagic episode were obtained. Otherwise, the last measurement within a maximum time frame of 28 days prior to the stroke was registered.

Clinical events

Stroke was diagnosed according to internationally accepted criteria for the assessment of cerebrovascular disease [15]. Brief attacks lasting less than 24 hours and leaving no residual symptoms were classified as transient ischemic attacks (TIA) [15]. If neurological death occurred within 24 hours, the case was classified as intracranial bleeding unless findings on computed tomography (CT)-scanning indicated otherwise. Events lasting beyond 24 hours were specified as cerebral infarction or intracranial bleeding on the basis of CT-scanning, if available. If a CT-scan was not available the event was classified as unspecified.

The functional outcome of all cerebrovascular events was classified as death within 24 hour, death beyond 24 hours, survival with no disability, survival with mild disability (residual symptoms, but no impact on daily activities), survival with moderate disability (symptoms which significantly interfered with normal daily activities, with the patient being unable to live independently) or survival with severe

Table 6.1. Selected demographic, baseline and randomisation characteristics

	AC		Placebo		Total	
	No.	(%)	No.	(%)	No.	(%)
	1700	(100)	1704	(100)	3404	(100)
Age (years)						
< 55	507	(30)	490	(29)	997	(29)
55 - 65	536	(32)	573	(33)	1109	(33)
> 65	657	(38)	641	(38)	1298	(38)
Gender						
Male	1370	(81)	1350	(79)	2720	(80)
Female	330	(19)	354	(21)	684	(20)
Previous MI*						
No	1543	(91)	1554	(91)	3097	(91)
≤ 1 year	25	(1)	18	(1)	43	(1)
> 1 year	132	(8)	132	(8)	264	(8)
Previous use of AC*						
No	1665	(98)	1660	(98)	3325	(98)
≤ 1 year	5	(0)	7	(0)	12	(0)
> 1 year	30	(2)	37	(2)	67	(2)
Hematocrit						
< 45	913	(54)	876	(51)	1789	(53)
≥ 45	735	(43)	767	(45)	1502	(44)
not available	52	(3)	61	(4)	113	(3)
Beta-blockers	867	(51)	869	(51)	1736	(51)
Acetyl salicylic acid+	118	(7)	104	(6)	222	(7)
Mean SBP, mmHg (SD)	119	(16)	119	(16)	119	(16)
History of DM	134	(8)	125	(7)	259	(8)
Current smokers	894	(53)	888	(52)	1782	(52)

AC, anticoagulant group; MI, myocardial infarctions, SBP, systolic blood pressure at discharge, DM, diabetes mellitus, SBP, systolic blood pressure at discharge.

*Prior to the qualifying myocardial infarction.

+Discontinued at randomization.

#Reported in the patient's medical history.

disability (patient completely dependent in all activities of daily living).

Information on clinical events was obtained directly from the patients when they visited the Thrombosis Centre or from their general practitioners. In case of hospitalization, additional information was retrieved from the hospital records. The diagnosis and classification of clinical events was made by three neurologists who independently reviewed the clinical course of each case on the basis of an independent review of a standardized patient report. The committee members also registered and coded all neurological admissions. The members were blinded to treatment assignment and were not informed of actual prothrombin time measurements. Other neurological non-vascular complications diagnosed in the course of the trial included: cerebral tumour (11 patients), Guillain-Barré, hernia nucleus pulposus (20 patients), amyotrophic lateral sclerosis (11 patients), and polyneuropathy (3 patients).

Data Analysis

A comparison between the anticoagulated and placebo groups with respect to the incidence of stroke was made in terms of the hazard ratio, i.e., the risk of stroke per unit time for patients randomly assigned to oral anticoagulant therapy divided by the risk for those randomly assigned to placebo. Hazard ratios were obtained with the use of the Cox proportional-hazards model [16]. The precision of the hazard-ratio estimates were described by 95 percent confidence intervals obtained from the Cox model. For "intention-to-treat" analysis, all randomized patients were included irrespective of previous discontinuation of trial medication. Censoring was applied when the patient died, had a stroke, or at the end of follow-up, on June 30, 1992. In a subsidiary analysis only those strokes that occurred while the patient was on trial treatment (or within 28 days after its cessation) were taken into account ("per-protocol" analysis).

RESULTS

A total of 1700 patients were randomised to anticoagulant therapy and 1704 to placebo. The mean follow-up was 3.1 years. Demographics data, smoking habits, medical history and medication used during hospitalisation are presented in Table 6.1. The median age of the patients was 61 years, 80% of the study population were men, 8% were known to have or treated for diabetes mellitus, and 7% were given acetylsalicylic acid prior to enrolment which was discontinued at randomisation.

The incidence of stroke analyzed on 'intention-to-treat' and 'per-protocol' analysis is presented in Table 6.2. Based on the total observation time ('intention-to-

Table 6.2 Incidence of stroke in the ASPECT trial

	Anticoagulant (1700)	Placebo (1704)	HR (95% CI)
		"intention-to-treat"	
Patient-years of follow-up	5241	5200	
First stroke	37 (0.7/100py)	62 (1.2/100py)	0.60 (0.4-0.9)
intracranial bleeding	17	2	
fatal	8	0	
non-fatal	9	2	
cerebral infarction	15	43	
fatal	2	2	
non-fatal	13	41	
Transient ischemic attack	2	6	
fatal	0	0	
non-fatal	2	6	
unspecified	4	12	
fatal	1	6	
non-fatal	3	6	
		"per protocol"	
Patient-years of follow-up+	3725	3488	
First stroke	24 (0.6/100py)	42 (1.2/100py)	0.57 (0.34-0.93)
intracranial bleeding	14	1	
fatal	7	0	
non-fatal	7	1	
cerebral infarction	6	28	
fatal	0	2	
non-fatal	6	26	
Transient ischemic attack	1	6	
fatal	0	0	
non-fatal	1	5	
unspecified	3	7	
fatal	1	1	
non-fatal	2	6	

HR, hazard ratios; CI, confidence intervals; py, patient-years.-treat')

99 patients were diagnosed as having a stroke. The incidence of stroke in the anticoagulated group was 0.7 per 100 patient-years and in placebo 1.2 per 100 patients-years, a hazard ratio (HR) of 0.60 with a 95% confidence interval (CI) of 0.40 to 0.90, a 40% reduction in the risk of stroke in the anticoagulated group.

The risk of haemorrhages was 8 times greater for anticoagulated patients compared to placebo. Of the 17 intracranial bleeding in the anticoagulated group, 15 were diagnosed on the basis of a CT-scan (9 intracerebral, 3 subdural, 3 subarachnoidal). Eight of the 17 bleedings were fatal: 6 were diagnosed by a CT-scan (3 intracerebral, 2 subdural and 1 subarachnoidal) and two were diagnosed on the basis of death within 24 hours. Of the two intracranial bleedings in the placebo group, one was subdural and one undefined. No fatal intracranial bleeding occurred in the placebo group. The functional outcome of the 9 anticoagulated patients who survived the intracranial bleeding was as follows: 2 were not disabled, 4 mildly disabled, 1 moderately while 2 patients were severely disabled. Two placebo patients who suffered an intracranial bleeding were not disabled.

The incidence of cerebral infarction was approximately 3 times greater in the placebo than the anticoagulated group. The functional outcome of the 13 anticoagulated patients who survived the intracranial infarction was: 5 were not disabled, 4 mildly and 4 moderately disabled. No severely disabled patients occurred in the treated group. For the 41 placebo patients who survived the infarction, the numbers were: 11 not disabled, 13 mildly disabled, 8 moderately and 9 severely disabled.

Six patients in treated and 18 in placebo group had an unspecified event or transient ischemic attack. Six fatal events occurred in placebo compared to one in anticoagulated group. The functional outcome of the 3 non-fatal unspecified strokes in the anticoagulated group were: 2 were not disabled, and 1 mildly. For the 6 placebo patients who survived, the numbers were: 3 not disabled, 1 mildly disabled, 1 moderately and 1 severely disabled.

When all strokes was combined the following figures were obtained: the number of patients who died or were severely disabled amounted to 13 in the anticoagulated group, compared to 18 in placebo. When moderately disabled was combined the figures were: 18 in the anticoagulated group compared to 27 in placebo.

The distribution of time from randomization to onset of stroke is presented in Figure 6.1, analyzed on intention-to-treat. The duration of treatment ranged from 1 day to six years. After 3 years following randomization 2% of the patients on anticoagulant therapy had a stroke compared to 4% in placebo.

Trial treatment was discontinued in 1655 patients (768 after anticoagulant therapy and 887 in placebo). Reasons for discontinuation were: death (194 patients: 91 anticoagulant therapy and 103 placebo); non-fatal cerebrovascular event (44 patients: 12 anticoagulant therapy and 32 placebo); non-fatal myocardial infarction

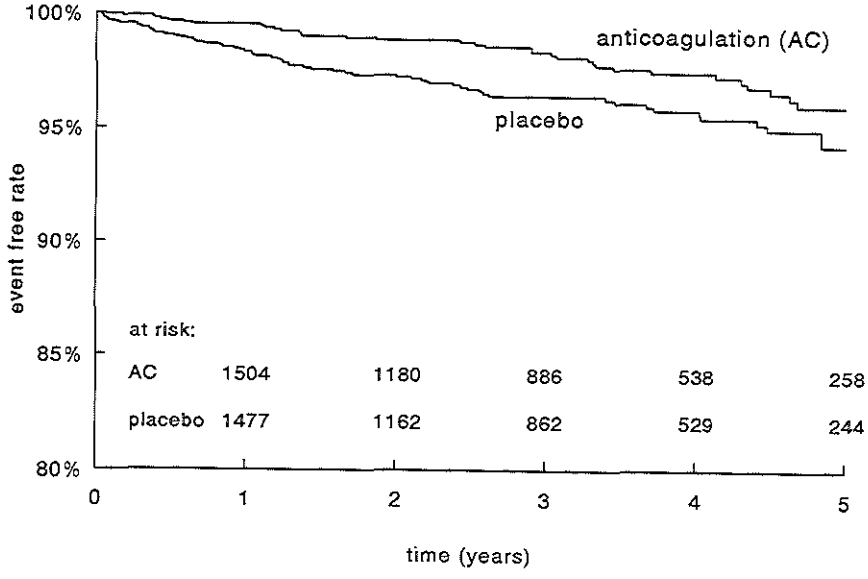
(155 patients: 31 anticoagulant therapy and 124 placebo); non-fatal extracranial bleeding (92 patients: 81 anticoagulant therapy and 11 placebo); and patient, physician' refusal, change of address or other reasons (1170 patients: 553 anticoagulant therapy and 617 placebo).

Among the 24 patients with a stroke in the actively treated group, prothrombin times were obtained as measured shortly before (17 patients) or within one month prior to the stroke (21 patients). Of the 14 haemorrhagic strokes, 6 were within INR 3.0-4.0 and 8 with an INR>4.0. Of the 7 non-haemorrhagic strokes, 2 were at INR< 2, 3 within INR 3.0-4.0, 1 at INR>4.0, and no measurement was available in one patient.

Of the 33 patients who had a stroke after discontinuation of trial medication, antiplatelet agents were used by 2 patients with a cerebral infarction and anticoagulants by 5: one with a cerebral infarction, 3 an intracranial haemorrhage and one a TIA.

Figure 6.1 Event free (all strokes)

(n=3404)



DISCUSSION

The results of this study indicated that long-term anticoagulant therapy substantially reduced the risk of stroke in post-myocardial infarction patients. Although an increased risk in bleeding complications were reported, this was offset by a marked reduction of ischemic events.

A comparison of strokes observed in the two most recently published secondary preventive trials is given in Table 6.3. The 'Sixty-Plus' reinfarction trial randomly allocated patients already treated with oral anticoagulant therapy to continuation of treatment (439 patients), or to discontinuation of treatment (439 patients) [2,8]. All patients were followed for at least two years. The Warfarin Reinfarction trial (WARIS) was carried-out in 1214 patients with a recent myocardial infarction who were randomised to either anticoagulant therapy or placebo. Patients were followed for a mean duration of three years [9]. The incidence of stroke in all three trials was thus reduced by 40% to 55% in favour for the anticoagulant group. The incidence in the anticoagulated group in the ASPECT population was lowest (0.7 per 100 patient-years) and highest (1.4/100 patient-years) in the 'Sixty-Plus' trial. The incidence of stroke in placebo group was similar for both 'Sixty-Plus' and WARIS (2.3/100 patient-years) and was again lowest in ASPECT (1.2/100 patient-years). In the 'Sixty-Plus' trial a substantial higher number of deaths was observed as compared to the other two studies. This may be attributed to not only the selection of patients in these trials but also to new treatment modalities, i.e., developments with respect to the institution of thrombolytic therapy and increased frequency of revascularization in patients with myocardial infarction in the eighties.

In all three trials, characterised by the intensity of treatment of a prothrombin time prolongation of 2.5 to 5 INR, intracranial bleeding occurred more frequently in the anticoagulated group than in placebo. In the treated group, at least 50% of the intracranial bleedings were fatal. The rate of haemorrhagic stroke (fatal or non-fatal) in the anticoagulated group was 0.3/100 patient-years for both WARIS and ASPECT, and was higher (1.0/100 patient-years) in the 'Sixty-Plus' trial. For placebo treated patients the risk was lowest in WARIS (0 patients), the risk amounted to 0.04/100 patient-years in ASPECT and was again highest (0.1/100 patient-years) in the 'Sixty-Plus' trial.

A total of 35 haemorrhagic strokes were observed in the three trials: 32 in the anticoagulated group of which 17 were fatal, and 3 in placebo of which 1 was fatal. The risk of haemorrhagic stroke observed in the three trials in the treated group was 0.4/100 patient-years and in placebo of 0.04/100 patient-years. Thus, the incidence of haemorrhagic stroke in the anticoagulated patients was 10 times higher than in untreated patients. Furthermore, about 50% of the haemorrhagic strokes were fatal. In two population studies conducted in the Netherlands, a similar 8 to 10 times increase in the risk of intracranial haemorrhage in long-term anticoagulated patients

Table 6.3 Incidence of stroke in the 'Sixty-Plus' and WARIS trials*

	Anticoagulant	Placebo	HR (95% CI)	Anticoagulant	Placebo	RR (95% CI)
	Sixty-Plus			*WARIS*		
No. of patients	439	439		607	607	
Patient-years of follow-up†	878	878		1872	1872	
Stroke	12 (1.4/100py)	20 (2.3/100py)	0.60 (0.30;1.21)	20 (1.1/100py)	44 (2.4/100py)	0.45 (0.23;0.76)
intracranial bleeding	9	1		6	0	
fatal	5	1		4	0	
non-fatal	4	0		2	0	
non-haemorrhagic	2	13		14	44	
fatal	1	5		0	10	
non-fatal	1	8		14	34	
unspecified	1	6		-	-	
fatal	0	0				
non-fatal	1	6				

RR, rate ratios; CI, confidence intervals; py, patient-years.

older than 50 years compared to the total population was reported [4,6]. In addition, the risk of fatal haemorrhagic stroke was reported to be at least 50% [2-4,6,7].

Non-haemorrhagic strokes (excluding the category unspecified) occurred more frequently in placebo than in the anticoagulated group. Fatal non-haemorrhagic stroke occurred more often in untreated patients than in treated patients in two of the three studies [2,9] and occurred equally in both treatment groups in the present trial. A total of 31 non-haemorrhagic strokes occurred in the three trials in the anticoagulated group compared with 100 in placebo. A combined incidence was observed of 0.4/100 patient-years in the treated group compared with 1.3/100 patient-years in placebo. This finding indicates that untreated patients have at least a three fold increased risk of non-haemorrhagic stroke compared to treated patients.

When the incidence of non-haemorrhagic and unspecified strokes are combined, an incidence of 0.4/100 patient-years to 0.7/100 patient-years occurred in the anticoagulated group compared with 1.2/100 patient-years to 2.4/100 patient-years in placebo. A total of 36 events occurred in the three trials in the anticoagulated group compared with 118 in placebo. The respective incidence of treated and untreated patients will be 0.5/100 patient-years and 1.5/100 patient-years. The data again indicate at least a 3 fold increase risk for untreated patients compared to treated patients.

The overall outcome of patients treated with anticoagulation is better than for placebo, despite the ten fold risk in bleeding for the treated patients. The functional outcome for patients treated with anticoagulants resulted in 13 deaths or severely disabled compared to 18 patients in placebo. For the anticoagulant group 18 patients were moderately to severly (inlcuding deaths) disabled compared to 27 in placebo.

The rate of intracranial bleeding has been reported to occur more frequently at higher anticoagulant intensities [3,6,17-22, see Chapter 5] and that of infarction at lower intensities [2,21,22, see Chapter 5]. The therapeutic range for the dutch trials was 2.5-5 INR. In our study, we observed that at INR intensities between the range 3 and 4, 4 haemorrhages occurred, above the value of 4, eight haemorrhages and only two at intensities above 4.8 INR.

In conclusion, long-term anticoagulant therapy substantially reduces the risk of stroke in post-myocardial infarction patients. Although the rate of intracranial bleeding, the most serious complication of anticoagulant therapy, is increased 10 fold, this is more than offset by a marked reduction in ischemic events of comparable functional outcome.

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CHAPTER SEVEN

GENERAL DISCUSSION

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INTRODUCTION

Initial enthusiasm for anticoagulant therapy was dampened in the seventies and eighties for reasons associated with problems inherent to the institution of anticoagulant therapy itself, as well as to the upcoming popularity of antiplatelet therapy in the form of aspirin. Early anticoagulant therapy faced major control problems in that different laboratory tests were used to monitor intensity of treatment. The thromboplastins used to measure the prothrombin time were prepared by different methods, and, consequently their effect on the reduction of the vitamin K dependent clotting factors varied significantly [1]. Therefore, whilst different thromboplastins employed in the controls resulted in the same prothrombin time, they represented different intensities of anticoagulant effects. An international scheme of prothrombin time standardization based on international reference preparations and a uniform method of reporting of results was only introduced in 1976 [2]. The international normalized ratio (INR) system is based on a quantitative assessment of the responsiveness of a thromboplastin as explained in Chapter I. With this standardized INR, the therapeutic efficacy of anticoagulation achieved can be compared not only between different anticoagulant clinics but also between studies.

The optimal therapeutic range for anticoagulant therapy was consequently advised by three expert groups: The British Society of Haematology (BSH) (1984, 1990), European consultants who met in Leuven (1985), and the two consensus meetings of the American College of Chest Physicians/ National Heart and Lung Institute ACCP/NHLBI (1986, 1989) [3] (Table 7.1).

Table 7.1. Recommended therapeutic INR ranges for anticoagulant therapy in post-myocardial infarction patients

British Society of Haematology (1984, 1990)	3.0 - 4.5 INR
European consultants, Leuven (1985)	3.0 - 4.5 INR
ACCP/NHLBI (1986, 1989)	2.0 - 3.0 INR

Table 7.2. Major events in the three recently conducted trials on long-term anticoagulant therapy in post myocardial infarction patients

	Sixty-Plus		WARIS		ASPECT		Total	
	AC	PL	AC	PL	AC	PL	AC	PL
No. of patients	439	439	607	707	1700	1704	2745	2750
No. patient-years	878	878	1872	1872	5241	5200	7991	7950
Death (/100 py)	51 (5.8)	69 (7.9)	94 (5.0)	123 (6.5)	170 (3.2)	189 (3.6)	315 (3.9)	381 (4.8)
MI (/100 py)	29 (3.3)	64 (7.3)	82 (4.4)	124 (6.9)	114 (5.1)	242 (2.3)	225 (2.8)	400 (5.0)
Stroke (/100 py)	12 (1.4)	20 (2.3)	20 (1.1)	44 (2.4)	37 (0.7)	62 (1.2)	69 (0.9)	126 (1.6)

AC, anticoagulant group; PL, placebo group. MI, myocardial infarction

Table 7.3. Distribution of end-points in the different anti-thrombotic trial

		% Reduction		
	No. of patients	Mortality	Re-infarction	Stroke
Anticoagulant trials				
Sixty-Plus (1980)	878	26	55	40
WARIS (1990)	1214	24	34	55
ASPECT (1993)	3404	10	53	40
Aspirin trials[*]				
Elwood (1974)	1239	22	-	-
CDPA (1976)	1529	30	12	-10
Elwood (1979)	1682	17	50	-
Breddin (1980)	626	17	33	-
AMIS (1980)	4524	-10	18	45
PARIS I (1980)	2026	17	25	45
PARIS II (1986)	3128	2	53	38

MI, myocardial infarction.
[*]percent reduction indicated for non-fatal myocardial infarction and non-fatal stroke.

The lower recommended range in North America can be explained by the higher incidence of bleeding complications previously observed during anticoagulant therapy in the United States, due to lack of prothrombin time standardisation as previously discussed and less efficiently organised monitoring network.

Recently conducted clinical trials

Recommendations by the BSH and the European consultants were to a large extent influenced by the results of the Dutch 'Sixty-Plus' Reinfarction study [4], with a target INR range between 2.7 and 4.5. Although the 'Sixty-Plus' trial suggested substantial benefits of long-term anticoagulant therapy with regard to mortality, myocardial infarction and cerebrovascular events, the results were criticised since it assessed the value of discontinuation of long-term therapy. On the other hand, the positive findings of the trial did provide a challenge to physicians who had abandoned the use of anticoagulant therapy. The findings of the three most recently [4,5, Appendix A] conducted trials are summarized in Tables 7.2 and 7.3. These indicate that the risk of mortality is reduced by 10% to 26%, of reinfarction by 34% to 55% and of stroke by 40% to 55%.

ANTICOAGULANTS OR ASPIRIN ?

Further to the three most recently anticoagulant trials, pooled analysis of data from other anticoagulant trials demonstrated reduction in mortality in favour of anticoagulant therapy varying from 14% to 40% [6-10], and in myocardial infarction from 44% to 65% [6,10] (Table 7.4). The review by Chalmers [6] which included all randomized trials on anticoagulant therapy in the acute phase of myocardial infarction, had been criticised because it had pooled trials of very dissimilar study design. Peto and Armitage [7,8] reanalysed the data using more rigorous statistical methods and reported comparable results of those of Chalmers. Leizorovicz [9] considered only long-term anticoagulant trials. Loeliger [10] selected long-term anticoagulant trials with similar anticoagulant intensities (INR 2.5-5), and reported the largest reductions in mortality and reinfarction. In the present pooled analysis of the three most recent trials, all randomised, double-blind placebo controlled and with INR between 2.5 and 5.0, a reduction in mortality of 19%, in myocardial infarction and stroke of 44% was found (Table 7.4).

How do these data compare to those obtained with anti-platelet agents, in particular that of aspirin ? The randomised double-blind, placebo controlled trials which evaluated the effect of aspirin at doses of 300 to 1,500 milligrams/day in post-myocardial infarction are summarized in Table 7.3 [11]. The time between index

infarction and entry into the trial ranged from one week to seven years, with the majority of patients recruited within one year. Trial duration varied from one to four years. The reduction in mortality ranged from 2% to 30%, in non-fatal myocardial infarction from 12% to 53% and in non-fatal stroke from 10% to 45% (Table 7.3). The pooled results of the trials [12], totalling more than 15,000 patients, demonstrated a reduction in vascular mortality of 13%, in non-fatal reinfarction of 31%, in non-fatal stroke of 42%, and in vascular events (defined as first occurrence of either myocardial infarction, stroke or death) of 25% (Table 7.4).

Table 7.4. Pooling of the different anti-thrombotic trials

		% Reduction		
	No. of trials	Mortality	Re-infarction	Stroke
Anticoagulant trials				
Chalmers (1977)	32	21	55	-
Peto (1978)	32	20	-	-
Armitage (1980)	32	20	-	-
Leizorovicz (1983)	7	14	-	-
Loeliger (1984)	9	40	65	-
Azar (1993)	3	19	44	44
Aspirin trials				
Antiplatelet Group* (1988)	10	13	31	42

*Cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke.

Until present, only two prospective trials have been conducted which directly compared long-term use of anticoagulant therapy with aspirin: The German-Austrian trial (Breddin) [13] and 'Enquete de Prevention Secondaire de l'Infarctus du Myocarde' (EPSIM) [14]. The Breddin trial had three intervention groups: aspirin 1,500 mg/day (317 patients) or matching placebo (309 patients), and phenprocoumon (320 patients). The trial was double-blind for aspirin and placebo

and open for phenprocoumon. The mean follow-up was two years. A total of 39 deaths occurred in the anticoagulant group compared to 32 in placebo and 27 in aspirin. The EPSIM group randomized patients to anticoagulant therapy (652 patients) or aspirin 500 mg/day (651 patients). The mean follow-up was 29 months. A total of 67 deaths were reported in the anticoagulant group as compared to 72 in aspirin. Although in both trials aspirin was as effective as anticoagulant therapy in reducing mortality and morbidity, the intensity of anticoagulant therapy was poorly controlled. In addition, the small number of patients (and endpoints) make these findings inconclusive.

The optimal intensity of anticoagulant therapy

The previously presented recommendation of the British Society of Haematology (1984, 1990), the European consultants, Leuven (1985) and the ACCP/NHLBI (1986, 1989) were based on trials conducted to assess the efficacy of treatment in prevention of mortality and vascular events, and on trials which compared different intensities of treatment. So far, however, these trials did not provide the optimal anticoagulant intensity. One reason is that the achieved anticoagulant intensity is not constant and invariably fluctuates around the targeted level hinging on characteristics of the patient as well as on extraneous features related to the administration and monitoring of the therapy. As described in Chapter 5, the optimal intensity of anticoagulant therapy was evaluated with use of INR specific incidence rates of bleeding as well as thromboembolic complications. On the basis of that analysis, involving over 7000 patient-years of follow up with almost 60 major bleeding and approximately 400 thromboembolic events, the optimal intensity of anticoagulation at which the incidence of haemorrhages as well as thromboembolism was lowest is situated between an INR range of 3.0 and 4.0. In that range, the risk of bleeding was relatively low, amounting to 5 major bleeding complications per 1000 treatment-years, while the reduction in thromboembolic complications amounted to 70% [Figure 7.1]. It should be noted that the advised 3.0 to 4.0 INR range is lower than that advocated by the BSH and Leuven group and higher than the American guidelines.

EPICRISIS

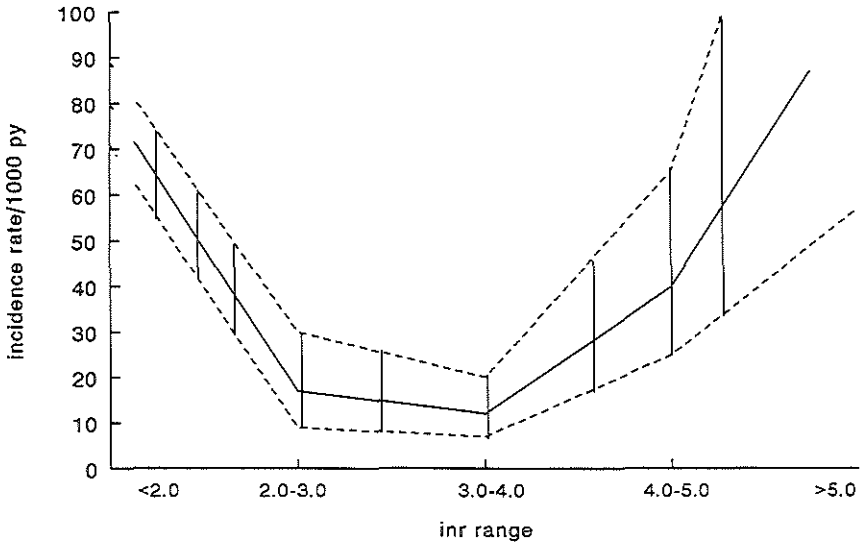
It is obvious that anticoagulant treatment with coumarin derivatives as well as with the antiplatelet agent aspirin result in a substantial reduction in mortality, myocardial infarction and stroke in survivors of myocardial infarction. Admittedly, the reduction in mortality in ASPECT [Appendix A] was relatively modest compared to that found

in WARIS [5] and the Sixty-Plus trial [4]. This finding is probably related to the selection of the patients, survivors of an uncomplicated myocardial infarction at relatively low risk of subsequent events. Furthermore, new treatment modalities such as thrombolytic therapy and revascularization procedures, both associated with improved survival, have changed relative to the two previous trials. Nevertheless, in ASPECT, reductions in recurrent myocardial infarction of 53% (95% confidence interval 41%, 62%) and vascular events (reduction 35%, 95% confidence interval 24%, 45%) were more substantial than that established in the pooled results of the Anti-platelet Trialists group (reduction in myocardial infarction 31%, 95% confidence interval 26%, 36%, in vascular events 25%, 95% confidence interval 21%, 29% respectively) and, although this comparison is based on indirect evidence, are suggestive of a more pronounced effect of anticoagulant therapy.

Although the direct costs of anticoagulant therapy are higher than that of aspirin, by approximately hfl 500,– per patient-year of treatment, these are not prohibitive compared to other medical regimens. The more obvious advantage of aspirin over anticoagulant therapy is its ease of use, and the frequent monitoring necessarily associated with anticoagulant therapy could well impede its widespread utilization.

Figure 7.1 inr specific incidence rates

(inr within 3 days from event)



With the growing realization that modification of platelet function simultaneously with fibrin formation may be more effective than either process on its own [15], the worth of the concurrent use of aspirin and anticoagulants in low doses is currently being investigated in other trials [16]. Recent data have identified elevated levels of factor VII as a risk indicator for increased cardiovascular disease incidence [16]. Since low dose anticoagulant therapy decreases levels of factor VII, this treatment modality is also being investigated in the British Thrombosis Prevention Trial. However, on the basis of our findings, it is unlikely that anticoagulant therapy with intensity of INR < 3 will be effective in the prevention of thromboembolic complications.

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APPENDIX-A

ASPECT's final analysis

Characteristics of patients randomized

from 01.04.86 to 31.12.91 with follow-up until 30.06.92

Prepared by:

Aida J. Azar, M.P.H.

Rotterdam, 7 November 1992

Table of contents:

Table 1. Thrombosis centers 2

Table 2. Selected demographic and clinical baseline characteristics 3

Table 3. Electrocardiographic baseline characteristics (last ECG before discharge) 4

Table 4. Maximum activities of creatine kinase and serum glutamate oxalotransaminase 5

Table 5. Use of anticoagulants, aspirin and thrombolytic drugs during index admission 6

Table 6. Complications during index admission 7

Table 7. Cardiac medications at hospital discharge 8

Table 8. Non-cardiac medications at hospital discharge 8

Table 9. Risk factors 9

Table 10. Randomization characteristics 9

Table 11. Incidence of patients with major clinical events during follow-up ("on intention to treat") 10

Table 12. Incidence of patients with major clinical events during follow-up ("per protocol") 11

Table 13. Why and when trial medication was discontinued in the study groups 12

Table 14. Invasive procedures after randomization 13

Table 15. Prothrombin time measurements 13

Figure 1. Survival curve for all patients (N=3404) 14

Figure 2. Event free curve for all patients (N=3404) 14

Table 1. Thrombosis centers

	AC		Placebo		Total	
No. of patients*	1700	100%	1704	100%	3404	100%
Amsterdam	218	13%	220	13%	438	13%
The Hague	143	8%	146	9%	289	8%
Groningen	102	6%	105	6%	207	6%
Leiden	174	10%	172	10%	346	10%
Rotterdam	133	8%	129	8%	262	8%
Utrecht	211	12%	213	13%	424	12%
Lichtenvoorde	45	3%	47	3%	92	3%
Enschede	171	10%	179	10%	350	10%
Haarlem	132	8%	128	8%	260	8%
Breda	34	2%	38	2%	72	2%
Middelburg	129	7%	128	7%	257	7%
Tilburg	30	2%	30	2%	60	2%
Den Bosch	26	2%	25	1%	51	2%
Eindhoven	17	1%	15	1%	32	1%
Arnhem	57	3%	55	3%	112	3%
Almelo	5	0%	3	0%	8	0%
Hilversum	47	3%	47	3%	94	3%
Deventer	14	1%	12	1%	26	1%
Hengelo	12	1%	12	1%	24	1%

AC, anticoagulant group.
*Patients randomized prior to 1 January 1992 with follow-up until 30 June 1992.

Table 2. Selected demographic and clinical baseline characteristics

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
Age (years)						
< 55	507	30%	490	29%	997	29%
55 - 65	536	32%	573	33%	1109	33%
> 65	657	38%	641	38%	1298	38%
Gender						
Male	1370	81%	1350	79%	2720	80%
Female	330	19%	354	21%	684	20%
Previous MI*						
No	1543	91%	1554	91%	3097	91%
≤ 1 year	25	1%	18	1%	43	1%
> 1 year	132	8%	132	8%	264	8%
Previous use of AC*						
No	1665	98%	1660	98%	3325	98%
≤ 1 year	5	0%	7	0%	12	0%
> 1 year	30	2%	37	2%	67	2%

AC, anticoagulant group; MI, myocardial infarctions.
*Prior to the qualifying myocardial infarction.

Table 3. Electrocardiographic baseline characteristics

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
New Q-waves (clinician's opinion)						
no	528	31%	594	35%	1122	33%
yes	1172	69%	1110	65%	2282	67%

No. of available ECGs*
(last ECG before discharge)

	AC		Placebo		Total	
Heart rate (min^{-1})	1692	100%	1694	100%	3386	100%
< 60	233	14%	258	15%	491	15%
60 - 80	1233	73%	1253	74%	2486	73%
> 80	219	13%	179	11%	398	12%
not available	7	0%	4	0%	11	0%
Q-waves+						
Anteroseptal	497	29%	515	30%	1012	30%
Lateral	98	6%	83	5%	181	5%
Inferior/posterior	708	42%	711	42%	1419	42%
None	389	23%	385	23%	774	23%
Q-waves (M-C)$						
1.1.n	464	27%	434	26%	898	26%
1.2.n	479	28%	480	28%	959	28%
1.3.n	313	19%	315	19%	628	19%
None	435	26%	464	27%	899	27%
not available	1	0%	1	0%	2	0%

AC, anticoagulant group; M-C, Minnesota-coding.
*18 ECGs were missing.
+Q-waves $\geq$0.03 sec and $\geq$0.1 mV; anteroseptal leads V_1, V_2, V_3, V_4 or V_5; lateral leads I, aVL or V_6;inferior/posterior leads II, III, aVF and R>0.03 secs in V_1 and R/S in V_2. ECGs with more than one location are included in the highest of the above categories.
$Measure of the severity of the Q-wave.

Table 4. Maximum activities of creatine kinase and serum glutamate oxalotransaminase

CK	AC		Placebo		Total	
	1700	100%	1704	100%	3404	100%
< 200%*	103	6%	108	6%	211	6%
200% - 500%	407	24%	427	25%	834	25%
500% - 1000%	523	31%	544	32%	1067	31%
1000% - 2000%	417	25%	397	23%	814	24%
> 2000%	182	10%	160	10%	342	10%
not available	68	4%	68	4%	136	4%

AC, anticoagulant group; CK, creatine kinase.
*Maximal values during index admission are expressed as percentages of the upper reference limit.

ASAT/SGOT	AC		Placebo		Total	
	1700	100%	1704	100%	3404	100%
< 200%*	237	14%	263	15%	500	15%
200% - 500%	668	39%	684	40%	1352	40%
500% - 1000%	517	30%	503	30%	1020	30%
1000% - 2000%	204	12%	184	11%	388	11%
> 2000%	25	1%	20	1%	45	1%
not available	68	4%	50	3%	118	3%

AC, anticoagulant group; ASAT/SGOT, serum glutamate oxalotransaminase.
*Maximal values during index admission are expressed as percentages of the upper reference limit.

Table 5. Use of anticoagulants, aspirin and thrombolytic drugs during index admission

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
Coumarin derivatives						
No	254	15%	255	15%	509	15%
Yes	1446	85%	1449	85%	2895	85%
Heparin i.v.						
No	1348	79%	1367	80%	2715	80%
Yes	352	21%	337	20%	689	20%
Neither coumarin nor heparin	205	12%	204	12%	409	12%
Aspirin						
No	1224	72%	1227	72%	2451	72%
Yes	474	28%	475	28%	949	28%
Unknown	2	0%	2	0%	4	0%
Thrombolytic i.v.						
No	1281	75%	1285	75%	2566	75%
Yes	419	25%	419	25%	838	25%
SK	307	73%	325	78%	632	76%
rtPA	75	18%	55	13%	130	15%
apsac	37	9%	38	9%	75	9%
other	0	0%	1	0%	1	0%
Thrombolytic i.c.						
No	1682	99%	1683	99%	3365	99%
Yes	18	1%	21	1%	39	1%

AC, anticoagulant group; i.v., intravenous ≥ 10,000 units/day; i.c., intracoronary; sk, streptokinase; rtPA, alteplase; apsac, anistreplase.

Table 6. Complications during index admission

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
VT/VF < 24 h						
No	1478	87%	1485	87%	2963	87%
Yes	222	13%	219	13%	441	13%
VT/VF > 24 h						
No	1664	98%	1666	98%	3330	98%
Yes	36	2%	38	2%	74	2%
Heart failure*						
Class I	1115	66%	1124	66%	2239	66%
Class II	489	29%	487	29%	976	29%
Class III	70	4%	68	4%	138	4%
Class IV	26	1%	25	1%	51	1%
2° AV-block						
No	1658	98%	1667	98%	3325	98%
Yes	42	2%	37	2%	79	2%
3° AV-block						
No	1634	96%	1637	96%	3271	96%
Yes	66	4%	67	4%	133	4%
Extended infarction						
No	1662	98%	1665	98%	3327	98%
Yes	38	2%	39	2%	77	2%

AC, anticoagulant group; VT/VF, ventricular tachycardia or ventricular fibrillation; AV, atrio-ventricular.
*Highest KILLIP or MIRU class reached in hospital.

Table 7. Cardiac medications at hospital discharge

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
Cardiac glycoside	108	6%	102	6%	210	6%
Diuretics	379	22%	380	22%	759	22%
Beta-blockers	867	51%	869	51%	1736	51%
Long-acting nitrates	644	38%	623	37%	1267	37%
Calcium antagonists	284	17%	302	18%	586	17%
ACE-inhibitors	160	9%	146	9%	306	9%
Antiarrhythmic drugs	58	3%	54	3%	112	3%
Nitroglycerin sublingual	759	45%	744	44%	1503	44%
Acetyl salicylic acid*	118	7%	104	6%	222	7%
Other	12	1%	19	1%	31	1%

AC, anticoagulant group.
*Discontinued at randomization.

Table 8. Non-cardiac medications at hospital discharge

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
Sedatives	173	10%	155	9%	328	10%
Analgetics	40	2%	54	3%	94	3%
Antidiabetics	102	6%	93	5%	195	6%
Antibiotics	36	2%	23	1%	59	2%
Pulmonary drugs	95	6%	65	4%	160	5%
Gastrointestinal drugs	115	7%	113	7%	228	7%
Corticosteroids	50	3%	49	3%	99	3%
Thyroid drugs	10	1%	20	1%	30	1%
Other drugs	99	6%	109	6%	208	6%

AC, anticoagulant group.

Table 9. Risk factors at admission

	AC		Placebo		Total	
No. of patients	1700		1704		3404	
Hypertension*	389	23%	395	23%	784	23%
History of Diabetes Mellitus	134	8%	125	7%	259	8%
Family history†	278	16%	305	18%	583	17%
Current smokers	894	53%	888	52%	1782	52%

AC, anticoagulant group.
*Reported in the patient's medical history.
†Myocardial infarction of first or second degree family members.

Table 10. Randomization characteristics

	AC		Placebo		Total	
No. of patients	1700	100%	1704	100%	3404	100%
Trial medication*						
Phenprocoumon	930	55%	935	55%	1865	55%
Acenocoumarol						
4 mg	127	7%	138	8%	265	8%
1 mg	643	38%	631	37%	1274	37%
Randomization delay†						
< 2 weeks	1565	92%	1599	94%	3164	93%
2 - 4 weeks	82	5%	67	4%	149	4%
4 - 6 weeks	53	3%	37	2%	90	3%
not available	0	0%	1	0%	1	0%

AC, anticoagulant group.
*Patients are randomized to placebo or true medication after the physician has determined the type of medication.
†Interval between hospital discharge and randomization.

Table 11. Incidence of patients with major clinical events during follow-up ("on intention-to-treat")*

	AC group (n=1700)	Placebo (n=1704)	HR (95%C.I.)+
Total patient years of follow-up	5241	5200	
	no. of events		
Death from any cause	170 (3.2/100py)	189 (3.6/100py)	0.90 (0.73-1.11)
Vascular death	134 (2.5/100py)	142 (2.7/100py)	0.94 (0.75-1.20)
Instantaneous/Sudden	57	43	
Unobserved/Unexpected	12	21	
Recurrent MI	24	40	
Congestive heart failure	27	30	
Cerebrovascular event	11	8	
Extracranial bleeding	3	0	
Non vascular death	36	47	
First recurrent MI	114 (2.3/100py)	242 (5.1/100py)	0.47 (0.38-0.59)
One MI	101	208	
Two MIs	12	28	
Three MIs	1	5	
Four MIs	0	1	
First cerebrovascular event	37 (0.7/100py)	62 (1.2/100py)	0.60 (0.40-0.90)
Intracranial bleeding	17	2	
Cerebral infarction	15	43	
Transient ischemic attack	2	6	
Unspecified	4	12	
Vascular event+	239 (4.8/100py)	366 (7.9/100py)	0.65 (0.55-0.76)
Major bleeding$	73 (1.4/100py)	19 (0.4/100py)	3.87 (2.33-6.41)
Major extracranial bleeding	56	17	
Macroscopic haematuria	2	0	
Genital tract bleeding	1	0	
Haematoma >10 cm	4	1	
Epistaxis >30 min	2	2	
Gastrointestinal	33	8	
Respiratory tract	2	1	
Muscular	8	1	
Haemarthrosis	0	0	
Other	4	4	

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.
*Censoring was applied when the patient died or by the end of follow-up (30 June 1992).
+The hazard ratio estimates are indicated.
+Vascular death/myocardial infarction/cerebrovascular event whichever event occurred first.
$Intracranial/extracranial bleeding whichever event occurred first.

Table 12. Incidence of patients with major clinical events during follow-up ("per protocol")*

	AC group (n=1700)	Placebo (n=1704)	HR(95% C.I.)+
Total patient years of follow-up	3725	3488	
	no. of events		
Death from any cause	91 (2.4/100py)	105 (3.0/100py)	0.86 (0.65-1.14)
Vascular death	81 (2.2/100py)	99 (2.8/100py)	0.81 (0.61-1.09)
Instantaneous/Sudden	35	34	
Unobserved/Unexpected	10	17	
Recurrent MI	16	31	
Congestive heart failure	10	14	
Cerebrovascular event	8	3	
Extracranial bleeding	2	0	
Non vascular death	10	6	
First recurrent MI	86 (2.3/100py)	207 (6.1/100py)	0.41 (0.32-0.53)
First cerebrovascular event	24 (0.6/100py)	42 (1.2/100py)	0.57 (0.34-0.93)
Intracranial bleeding	14	1	
Cerebral infarction	6	28	
Transient ischemic attack	1	6	
Unspecified	3	7	
Vascular event#	163 (4.4/100py)	305 (9.0/100py)	0.53 (0.44-0.64)
Major bleeding$	55 (1.5/100py)	6 (0.2/100py)	9.05 (3.90-21.0)
Major extracranial bleeding	42	5	
Macroscopic haematuria	1	0	
Genital tract bleeding	1	0	
Haematoma >10 cm	4	0	
Epistaxis >30 min	1	1	
Gastrointestinal	26	2	
Respiratory tract	0	0	
Muscular	6	0	
Haemarthrosis	0	0	
Other	3	2	

HR, hazard ratio; CI, confidence interval; MI, myocardial infarction.
*End-points occurring while the patient was on trial medication (or within 28 days after its cessation).
+The hazard ratio estimates are indicated.
#Vascular death/myocardial infarction/cerebrovascular event whichever event occurred first.
$Intracranial/extracranial bleeding whichever event occurred first.

Table 13. Why and When trial medication was discontinued in the study medication groups

Variable	AC	Placebo
No. of permanent discontinuations	768	887
Reasons for discontinuation		
deaths	91	103
Non-fatal cerebrovascular event	12	32
Non-fatal myocardial infarction	31	124
Non-fatal extracranial bleeding*	81	11
Patient's refusal	165	170
Physician's refusal	12	14
Change of address	75	70
Other	301	363
% of patients still alive and still on medication		
at 3 mo	89	85
at 6 mo	82	79
at 1 yr	76	70
at 2 yr	64	59
at 3 yr	54	48
at 4 yr	48	41

MI, myocardial infarction.
*Major or minor bleeding.

Table 14. Invasive procedures after randomization

	AC	Placebo	Total
Angiography	340	440	780
Angioplasty	71	94	165
Bypass surgery	128	142	270
Pacemaker	14	23	37
Thrombolysis	24	69	93

Table 15. Prothrombin time measurements*

INR	Cumulative approach (n=57,634)	'Cross-section-of-the files' (n=1172)
<2.8	29%	20%
2.8-4.8	62%	74%
>4.8	9%	6%

INR, international normalized ratio.
*Verum patients up to discontinuation of trial medication.

figure 1: survival curve (on 'intention-to-treat')

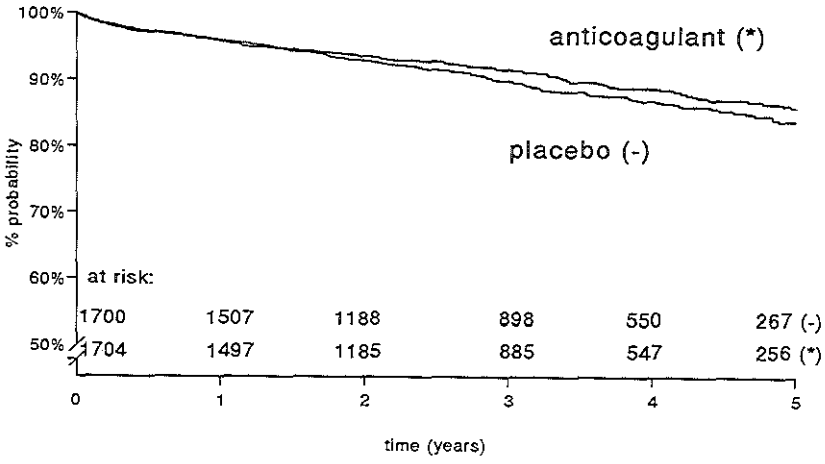
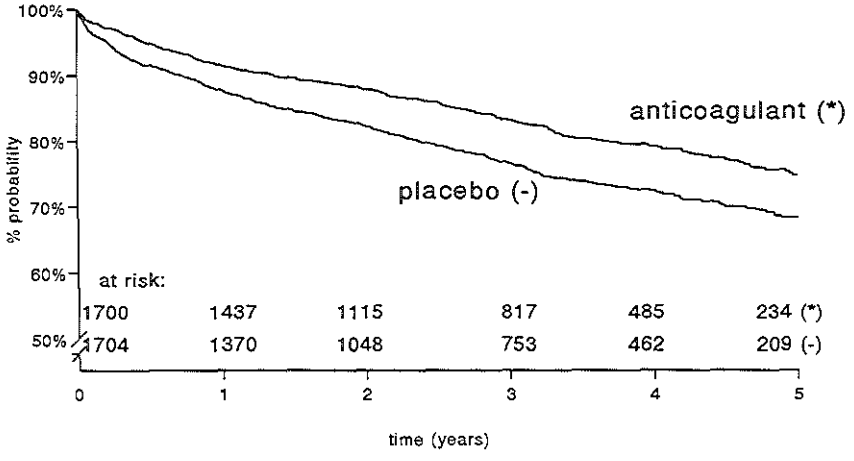


figure 2: event free survival



APPENDIX-B

APPENDIX B.I

LEEFTIJDSGRENS VAN
75 JAAR
IS VERVALLEN !

Ruimte afslagplaatje

TOELATINGSFORMULIER ASPECT-ONDERZOEK

Vul dit formulier bij ontslag in voor *iedere patiënt* bij wie in het ziekenhuis de diagnose *'acuut myocard infarct'* is gesteld.

Vul dit formulier volledig in, tenzij door u één van de volgende vragen is beantwoord middels het aankruisen van een hokje gevolgd door [stop].
Dit betekent dan dat de patiënt niet in het onderzoek wordt opgenomen.
Het formulier behoeft dan niet meer verder te worden ingevuld.
Wel dient het formulier ook in dit geval ondertekend te worden (zie hieronder) en opgestuurd naar het coördinatie centrum, teneinde het aantal van deelname uitgesloten patiënten te kunnen berekenen.

Indien geen identificatieplaatje van de patiënt aanwezig is, s.v.p. de volgende gegevens hieronder noteren.

2. Geslacht : M/V (doorhalen wat niet van toepassing is)

3. Geboortedatum : _____/_____/_____ (dag/maand/jaar)

4. Opnamedatum : _____/_____/_____ (dag/maand/jaar)

Behandelend arts : _____

Ziekenhuis -naam : _____

-plaats : _____

Datum : _____/_____/_____ (dag/maand/jaar)

Adres coördinatie centrum:

ASPECT

ASPECT - onderzoek,
Glashaven 68,
3011 XK Rotterdam.

INCLUSIECRITERIUM

	Ja	Nee
5. Toonden de *hartenzymen* het karakteristieke *infarctpatroon*, met tenminste één enzym meer dan 2X de normaalwaarde?	☐	☐ [stop]

EXCLUSIECRITERIA

*6a. Bestaat er een *strikte indicatie* voor *orale anticoagulantia* behandeling?	☐ [stop]	☐
Zo ja, welke? _____		
*6b. Bestaat er een *strikte contraindicatie* voor orale anticoagulantia-behandeling?	☐ [stop]	☐
Zo ja, welke? _____		
7. Heeft patiënt een andere *ernstige ziekte* dan het cardiale lijden?	☐ [stop]	☐
Zo ja, welke? _____		
8. Heeft in de *6 maanden vóór de ziekenhuisopname* orale antistollingsbehandeling plaatsgehad?	☐ [stop]	☐
9. Heeft een *ander lid van het huishouden* een antistollingsbehandeling?	☐ [stop]	☐
10. Staat patiënt op de *wachtlijst voor coronary bypass operatie* of *coronairangioplastiek (PTCA)*?	☐ [stop]	☐
11. Zijn er moeilijkheden te verwachten t.a.v. een goede *medewerking* (b.v. langdurig verblijf buiten de huidige woonplaats)?	☐ [stop]	☐
12. Wilt u de patiënt tot de studie toelaten?	☐	☐ [stop]
Zo nee, waarom? _____		
13. Is toestemming verkregen?	☐	☐ [stop]

INFARCTGEGEVENS

14. Ontstonden nieuwe *Q-golven* (≥0.03 sec.) of *Q-golf equivalenten* (R≥0.03 sec. in V1 en RS-ratio ≥1 in V2) in het ziekenhuis?	Ja	Nee
15. Ontstond *ventrikeltachycardie* of *ventrikelfibrilleren* in het ziekenhuis?		
< 24 uur na opname	Ja	Nee
> 24 uur na opname	Ja	Nee

*16. Wat was in het ziekenhuis de slechtste (hoogste) klasse vlgs *Killip* of *MIRU*?

I ☐
II ☐
III ☐
IV ☐

*17. Hoe is bij ontslag de validiteitsscore volgens *NYHA* t.a.v.

a: dyspneu
I ☐
II ☐
III ☐
IV ☐

b: angina pectoris
I ☐
II ☐
III ☐
IV ☐

18. Wat is de *cardiothoracale ratio* (CTR) *bij ontslag*, indien bepaald?

(Geef hierbij de absolute waarden aan.) (_____/_____)

19. Blijft patiënt onder uw controle? Ja Nee

Zo nee, in welk ziekenhuis? _____

Meld patiënt aan als ASPECT-patiënt bij de trombosedienst*
en stuur dit formulier op naar het coördinatie centrum.

---

* zie toelichting aan de linkerzijde.

ASPECT – onderzoek, Glashaven 68, 3011 XK Rotterdam, 010 - 411 20 74

juli 1991

Geachte mevrouw/mijnheer,

Bij u is vastgesteld dat u een hartinfarct heeft gehad. Een hartinfarct wordt meestal veroorzaakt door een afsluiting van één van de bloedvaten die het hart zelf van bloed voorzien. Antistollingsmiddelen zijn medicijnen die "bloedverdunnend" werken waardoor de kans op een nieuwe afsluiting en daarmee een volgende hartinfarct zou kunnen worden verminderd. Behandeling met antistollingsmiddelen heeft als nadeel dat soms bloedingen kunnen ontstaan.

Tot op heden bestaat echter onvoldoende zekerheid dat langdurige behandeling met antistollingsmiddelen inderdaad een gunstige werking heeft op het voorkómen van een volgende hartinfarct. Zo komt het dat een gedeelte van de hartinfarctpatiënten in Nederland op dit moment antistolling krijgt als nabehandeling en een ander gedeelte niet. Daarom wordt op dit moment onderzoek gedaan naar het nut van deze behandeling. Dit onderzoek heet kort en bondig **ASPECT**, en deze letters staan voor: **A**nticoagulants in the **S**econdary **P**revention of **E**vents in **C**oronary **T**hrombosis. Een groot aantal ziekenhuizen neemt aan dit onderzoek deel dat wordt uitgevoerd in samenwerking met de Federatie van Nederlandse Trombosediensten.

In dit belangrijke onderzoek krijgt de helft van de patiënten antistollingstabletten en de andere helft tabletten die eruit zien als antistollingstabletten maar niet het antistollingsmiddel bevatten (z.g. placebo-tabletten). U noch uw hartspecialist zullen weten welke tabletten u krijgt. Alleen op deze wijze kan een juiste indruk worden verkregen over het nut van antistolling na een hartinfarct. Wij verwachten momenteel dat het onderzoek nog ongeveer 1 jaar gaat duren. Na beëindiging van het ASPECT-onderzoek zal uw specialist op basis van de verkregen resultaten beslissen over eventuele voortzetting van de antistollingsbehandeling.

Indien u aan dit onderzoek wilt meedoen, wordt voor u een afspraak gemaakt bij de dichtstbijzijnde trombosedienst. De trombosedienst zal de gebruikelijke controles uitvoeren en u regelmatig van nieuwe tabletten voorzien. Van de trombosedienst krijgt u ook informatiemateriaal dat voor de antistollingsbehandeling belangrijk is.

De controles op de trombosedienst staan los van controle afspraken of poliklinische afspraken die uw specialist met u maakt.

Wanneer u toestemming geeft, behoudt u natuurlijk het recht om zich te allen tijde uit het onderzoek terug te trekken.

Bent u bereid om aan dit onderzoek mee te doen?

APPENDIX B.III

ATAL Stichting Amsterdamse Trombosedienst en Artsenlaboratorium
Jan Tooropstraat 138 - 1061 AD Amsterdam

Direktie: A. Jeletich-Bastiaanse, arts - Drs. J. L. J. Smit, klinisch-chemicus

Ref. Datum.

Aan de deelnemers van het ASPECT-onderzoek

Geachte heer/mevrouw

In het ziekenhuis hebt u besloten deel te nemen aan het z.g. ASPECT-onderzoek. De achtergronden en het doel van dit onderzoek zijn tijdens uw ziekenhuisopname aan u uitgelegd. Voor de volledigheid treft u hierbij nog een exemplaar aan van het patiënten-informatieformulier. Bij de aanmelding bij de Trombosedienst is voor u een z.g. onderzoeksnummer gekozen, bestaande uit 3 letters en 4 cijfers (bijv. LMA 0021).

Graaag wil ik u nog enkele praktische richtlijnen geven voor een goed verloop van het ASPECT-onderzoek:

1. Draag de aan u uitgereikte ASPECT-informatiekaart ALTIJD bij u. Laat deze kaart zien bij bezoeken aan huisarts en specialisten.
2. De trombosedienst zorgt ervoor dat u steeds nieuwe antistollingstabletten krijgt. Bij het eerste bezoek aan de trombosedienst krijgt u 2 potjes met antistollingstabletten, met vermelding van uw onderzoeksnummer op het etiket. Indien één potje dreigt leeg te raken, wilt u dan kontakt opnemen met de trombosedient zodat bij het volgende bezoek aan de trombosedienst u een nieuw potje met tabletten kunt krijgen.
   Dit betekent dat u geen antistollingstabletten mag gebruiken die door uw eigen apotheek zijn verstrekt!
   Bij een ziekenhuisopname dient u óók uw eigen antistollingstabletten te blijven gebruiken.
3. Na elke controle door de trombosedienst ontvangt u een doseringskalender waarop staat aangegeven hoeveel tabletten u per dag dient in te nemen. Op deze doseringskalender staat uw onderzoeksnummer vermeld.
4. Het ASPECT-onderzoek duurt tot ongeveer april 1992. Tot die tijd blijft u de antistollingstabletten gebruiken die u door de trombosedienst worden verstrekt.
   Tijdens het ASPECT-onderzoek zijn u geen beperkingen opgelegd. Dit betekent o.a. dat u gewoon op vakantie kunt gaan. Wel is het dan van belang dat u voldoende antistollingstabletten meeneemt voor die vakantie.

Mocht u nog vragen hebben dan kunt u dit bespreken met de zuster van de trombosedienst.

Met vriendelijke groeten,
Stichting ATAL,

A. Jeletich-Bastiaanse, arts

Trombosedienst : telefoon 020-11 49 11
Artsenlaboratorium : telefoon 020-11 38 11
Postrekening : 28559
Bank : Morgan Labouchere N.V. Amsterdam, rek.nr. 26.20.26.848

APPENDIX B.IV

ROTTERDAMSE TROMBOSEDIENST

Geb.datum : _____

Adres : _____ Ziekenfonds: _____

Woonplaats : _____ Partikulier: _____

Postcode : _____ Tel.nr.pat.: _____ Huisarts : _____

Gezonden door: _____

ASPECT-nummer: _____

==========

INDICATIES

o 110 Hartinfarct vraag ook hiernaar:--> o 001 ASPECT

o 120 Recidief o 421 Trombose v/d vena centralis retinae (oog)

o 130 Angina pectoris o 600 Cerebrale vaataandoeningen (hersenen)

o 410 Trombose v/d diepe vaten o 210 Atrium/boezemfibrilleren

o 416 recidief Trombose onder AS o 710 Hartklepprothese

o 430 Oppervlakkige tromboflebitis o 800 Profylactisch

o 140 Aneurysma cordis/aortae o 730 Coronair bypass

geopereerd ja/nee o 540 Arteriële embolie in de

o 520 Atherosclerose grote circulatie

o 760 gedotterd geopereerd ja/nee

o 700 Vaat-operaties (veneus Bypass) o 550 Longembolie

Bij opnieuw patiënten reden van opname navragen!

- Ontslag ziekenhuis/thuis begonnen datum: _____
- Eerder bij de trombosedienst onder behandeling ja/nee
- Leverfunktiestoornis ja/nee HB : _____
- Nierfunktiestoornis ja/nee HT : _____
- Tensie/bloeddruk _____/_____ Tromb: _____
- Welk preparaat: Sintrommitis/Marçoumar*)
- Post of aan huis bezoeken datum: _____ wijk nr. _____

*) Sintrom 4 mg. gaat uit de handel!

Rotterdam Paraaf

9048.sta

APPENDIX B.V

De Weledelgeleerde

Rotterdam, 26 februari 1991

Betreft:
Geboren:

Zeer geachte collega ,

Bij deze deel ik u mee, dat bovengenoemde patiënt(e) toestemming heeft gegeven om aan het ASPECT-onderzoek deel te nemen.

Het ASPECT-onderzoek is een gerandomiseerd, placebo gecontroleerd onderzoek naar het effect van langdurige behandeling met antistolling na een recent myocardinfarct.

Ik wil u verzoeken om in het geval dat uw patiënt(e) wederom in een ziekenhuis wordt opgenomen mij zonodig informatie te verschaffen over deze heropname.
Hetzelfde geldt voor het geval dat uw patiënt(e) komt te overlijden.

Verder is het voor u van belang te weten dat uw patiënt(e) de antistollingsmedicatie van ons krijgt zodat ik u wil vragen geen andere antitrombotische medicijnen (aspirine, sulfinpyrazon of dipyridamol) voor te schrijven.

Bij voorbaat mijn hartelijke dank.

Met vriendelijke groet,

APPENDIX B.VI

STUDIE NR. .....

ASPECT STUDIE NR. .....

Datum randomisatie : _ / _ / _

Datum opname : _ / _ / _

Datum ontslag : _ / _ / _

Opname SBD : _____ mmHg
DBD : _____ mmHg

Opname HF : _____ /min

Ontslag SBD : _____ mmHg
DBD : _____ mmHg

Ontslag HF : _____ /min

Hb : _____ mmol/l
Ht : _____ %
Trombo's : _____ x 10^9 /l
Cholesterol : _____ mmol/l
(max.opn./ontsl.)

CTR (bij ontslag) : __ / __

EDV : _____ mm

EF : _____ %
EF : _____ %
EDV : _____ ml/m²

HF rust : _____ /min
HF max. : _____ /min
SBD rust : _____ mmHg
SBD max. : _____ mmHg
Max. inspanning : _____ Watt
Norm. inspanning : _____ Watt

Ingevuld datum : _ / _ / _
naam :
Afgewerkt datum : _ / _ / _
naam :

Let op, bij invulling beslist 2B potlood gebruiken!

	<ja	<nee	<onbekend
OPNAME.			
Q of Q-equivalenten			
VT/VF in zkh. < 24 uur			
> 24 uur			
decomp.cordis in zkh. I			
vlgs. Killip/MIRU II			
III			
IV			
dyspneu bij ontslag I			
II			
III			
IV			
AP bij ontslag I			
II			
III			
IV			
andere complicaties geen			
tweede gr. AV			
derde gr. AV			
uitbreiding MI			
overig			
OAC behandeling			
VERRICHTINGEN:			
Echo			
EDV vergroot			
hypokinesie/akinesie			
dyskinesie			
Radionuclidescan			
Ventriculografie			
EDV vergroot			
hypokinesie/akinesie			
dyskinesie			
Coronairangiografie			
> 50% vernauwing: geen			
LM			
LAD			
(L) CX			
RCA			
Trombolytica i.v.			
Trombolytica i.c.			
Thallium perf.scan			
PTCA			
Bypass chirurgie			
Overige card. chirurgie			
Overige chirurgie			
Pacemaker			
Cardioversie/defibrillatie			
Inspanningsproef			
reden van stoppen: AP			
dyspneu			
overig pat. bepaald			
door arts bepaald			
ritmestoornissen			
onbekend			
ST-segment: onveranderd			
elevatie			
depressie			
heparine > 10.000 E/dag		[N]	

	<ja	<nee
ENZYMEN:		
CK bepaald		
max:		
ref:		
CK-MB bepaald		
max:		
ref:		
LDH bepaald		
max:		
ref:		
A-HBDH bepaald		
max:		
ref:		
SGOT-ASAT bepaald		
max:		
ref:		
SGPT-ALAT bepaald		
max:		
ref:		
ONTSLAGMEDICATIE:		
digitalis		
diuretica		
beta-blockers		
langw. nitraten		
Ca-antagonisten		
art. vaatverwijders		
anti-aritmica		
overig		
VOORGESCHIEDENIS:		
AP ≤4 wkn		
> 4 wkn		
Oud MI < 1 jr		
> 1 jr		
Catheterisatie < 1 jr		
> 1 jr		
Bypass chir. < 1 jr		
> 1 jr		
PTCA < 1 jr		
> 1 jr		
antiplaatjes middelen < 1 jr		
> 1 jr		
antistolling < 1 jr		
> 1 jr		
reden antistolling: MI		
CVA		
DVT/LE		
overig		
blanko		
overig		
onbekend		
RISICOFACTOREN:		
geen		
hypertensie		
diabetes mellitus		
familieanamnese		
roken		
DIVERSEN:		
Kopie ontslagbrief		
Ontslag E.C.G.		
Kopie lab.uitslagen		

APPENDIX B.VII

STUDIE NR.....

ASPECT STUDIE NR.....

DATUM: ___/ ___/ ___

Toelichting:

frequentie > 5 afronden naar boven in veelvoud van 10

ECG KENMERKEN

ECG kwaliteit - goed - ☐ matig - ☐ slecht - ☐

Kamerfrekwentie - < 40 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | 110 | 120 | >

CIIS-SCORE.....

1. Q AVL (msec) - 0 | 10 | 20 | 30 | 40 | 50

2a. T pos. AVL < 1/2 mm, ≥ 3 mm - N | J

2b. T neg. AVL (mm) - 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8

3. neg. deflectie QRS AVR (mm) - 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 20

4. T neg. AVR (mm) - 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8

5. QR II of AVF ≥ 1/5 - N | J

6. Q III of R (niet na QI) AVL ≥ 40 msec - N | J

7. T neg. III > 1 mm - N | J

8. T pos. V1 > 2 mm - N | J

9. R V2 ≤ 3 mm, ≥ 14 mm - N | J

10. T neg. V2 ≥ 1/4 mm - N | J

11. Q/R V3 > 1/20 - N | J

12. S V5 < 2 mm - N | J

MINNESOTA-CODE.....

1. Q golf - N | 1.1 | 1.2 | 1.3 | 1.4 | 1.5 | 1.6 | 1.7
- 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 2.6 | 2.7 | 2.8
- 3.1 | 3.2 | 3.3 | 3.4 | 3.5 | 3.6

2. as - N | 1 | 2 | 3 | 4 | 5

3. R top - N | 1 | 2 | 3 | 4

4. ST segment - N | 1.1 | 1.2
- 2 | 3 | 4

5. T top - N | 1 | 2 | 3 | 4

6. AV geleiding - N | 1 | 2 | 3 | 4 | 5 | 6 | A

7. IV geleiding - N | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8

8. N = normaal sinusritme (50 ≤ HF ≤ 100
? = ritme niet te beoordelen

8. aritmieën - N | 1.1 | 1.2 | 1.3 | 1.4 | 1.5
2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | ?

9. N = geen "codeerbare" diversen
3.1 = RAO: rechter atrium overbelasting
3.2 = LAO: linker atrium overbelasting

9. diversen - N | 1 | 2
- 3.1 | 3.2
- 4.1 | 4.2
- 5
6.1 | 6.2

LOKALISATIE Q-GOLVEN.....

(Q ≥ 0,03 sec. en ≥ 0,1 mV)

afleiding: I - N | J | NTB
II - N | J | NTB
III - N | J | NTB

afleiding: AVR - N | J | NTB
AVL - N | J | NTB
AVF - N | J | NTB

Bij normale ijk: 0,1 mV = 1 mm
bij halve ijk : 0,1 mV = 0,5 mm.

codeer "J" indien Q ≤ 0,03 sec. of ≥ 0,1 mV
codeer "N" indien Q < 0,03 sec. of < 0,1 mV
codeer "NTB" indien niet te beoordelen

V1 - N | J | NTB
V2 - N | J | NTB
V3 - N | J | NTB

V4 - N | J | NTB
V5 - N | J | NTB
V6 - N | J | NTB

Q-GOLF EQUIVALENTEN .....

R > 0,03 sec en ≥ 0,1 mV in V1 - N | J | NTB

R/S ratio ≥ 1 in V2 - N | J | NTB

bij normale ijk: 0,1 mV = 1 mm
bij halve ijk : 0,1 mV = 0,5 mm

Let op, bij invulling beslist 2B potlood gebruiken!

aker/thorax 86.2

ZIEKENHUISOPNAME CARDIAAL APPENDIX B.VIII

ASPECT-nummer: ..... Naam beoordeler: .....

Eventn ..... Opnamedatum: ...../...../..... Ontslagdatum: ...../...../.....

Is de hoofddiagnose inderdaad cardiaal?

o ja

o nee: Indien neen geef aan naar wie deze opname dan verstuurd dient te worden:

o Neuroloog o Internist o Retour Coördinatiecentrum

HOOFDDIAGNOSE

o A. Myocardinfarct

- o 1 Overleden onder klinisch beeld
- o 2 Aanwezigheid van tenminste 2 van de 3 onderstaande mogelijkheden
  - o a pijn op de borst
  - o b stijging van de hartenzymen (CK. CK-MB. LDH. HBDH. ALAT. ASAT) met ten minste één enzym groter dan 2x de bovengrens van de normaalwaarde.
  - o c ontstaan Q-golf groter dan 0.03 sec. (of R groter dan 0.03 sec. in V1 en RS ratio groter dan 1 in V2)

Geef locatie infarct: (aanwezigheid van Q-golven in minstens 2 afleidingen)

- o 1 antero (septaal) (V1-V4)
- o 2 anteroseptaal op basis van ST-T en/of T-golf veranderingen
- o 3 anterolateraal (V5, V6, 1, AVL)
- o 4 anterolateraal op basis van ST-T en/of T-golf veranderingen
- o 5 inferoposterior (II, III, AVF)
- o 6 inferoposterior op basis van ST-T en/of T-golf veranderingen
- o 7 niet te bepalen

o B. Onstabiele Angina Pectoris

- o 1 AP in rust
- o 2 Progressieve AP d'effort
- o 3 Nieuwe AP d'effort
- o 4 Geen onstabiele AP
- o 5 AP met hartenzymstijging > 1 maar < 2

o C. Stabiele Angina Pectoris

- o 1 ja
- o 2 nee

o D/ Anders

- o 1 Ritme / geleidingsstoornis
- o 2 Pompfunctiestoornis
- o 3 Aneurysma dissecans
- o 4 Pericarditis
- o 5 Endocarditis
- o 6 Electieve opname voor cardiale diagnostiek/ verrichting
- o 7 Overige in de thorax gesitueerde pijnklachten van niet cardiale oorzaak
- o 8 Aspecifieke "pre-cordiale klachten"
- o 9 Geen van bovenstaande

COMPLICATIES (meerdere mogelijkheden)

- o 1 Cerebro vasculair accident
- o 2 Extracraniële arteriële thromboëmbolie
- o 3 Extracraniële veneuze thromboëmbolie
- o 4 Anders
- o 5 Geen

VERRICHTINGEN (meerdere mogelijkheden) /door CC ingevuld

- o 1 Angiografie
- o 2 Thrombolyse
- o 3 Coronair angioplastiek
- o 4 Coronaire bypass operatie
- o 5 Pacemaker implantatie
- o 6 Overig cardiaal invasief
- o 7 Geen

Geef complicaties van verrichtingen (meerdere mogelijkheden)

- o 1 Overlijden
- o 2 Myocardinfarct
- o 3 Bloeding
- o 4 Extracraniële arteriële thromboëmbolie
- o 5 Extracraniële veneuze thromboëmbolie
- o 6 Cerebraal
- o 7 Overig
- o 8 Geen

Is de patiënt overleden?

o 1 Ja Datum: ...../...../.....

o 2 Neen

Indien ja. geef acute omstandigheden aan:

- o 1 Instantane dood
- o 2 Plotseling (minder dan 1 uur na ontstaan van klachten)
- o 3 Niet geobserveerd. onverwacht
- o 4 Ritmestoornis geobserveerd
- o 5 Pompfunctie stoornis
- o 6 Tijdens verrichting
- o 7 Bloeding
- o 8 Extracraniële arteriële thromboëmbolie
- o 9 Extracraniële veneuze thromboëmbolie
- o 10 Cerebraal
- o 11 Overig cardiaal
- o 12 Overig

Is de medicatie gestaakt? /door CC ingevuld

o 1 Ja Datum: ...../...../.....

o 2 Nee

o 3 Eerder gestaakt

Indien ja. vervolgmedicatie na staken ASPECT medicatie:

- o 1 Antistolling
- o 2 Plaatjes aggregatieremmer
- o 3 Geen antitrombotische medicatie
- o 4 Onbekend

o Hervatting ASPECT medicatie

o ja Datum: ...../...../.....

o nee

o Deze episode dient besproken te worden

HANDTEKENING. _____

(ZIEKENHUISOPNAME) EXTRA-CRANIELE BLOEDING

ASPECT-nummer: ..... Naam beoordeler: .....

Eventn°: .....

Is de hoofddiagnose inderdaad extracraniële bloeding?

o ja

o nee: indien neen geef aan naar wie deze opname dan verstuurd dient te worden:
o Neuroloog o Cardioloog o Retour Coördinatiecentrum

Heeft de extracraniële bloeding geleid tot ziekenhuisopname?

o ja Opnamedatum: ...../...../..... Ontslagdatum: ...../...../.....

o nee Datum van gebeurtenis: ...../...../.....

HOOFDDIAGNOSE

o 1	Macroscopische haematurie rode urine (stolsels)	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 2	Bloeding tr. genitalis geen haematurie, geen menstrueel bloedverlies	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 3	Bloeding conjunctiva rood oog met onver-anderde visus	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 4	Bloeding huid 10 cm. of multipel	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 5	Bloeding neus 30 min. of med. behandeld	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....

o 6	Bloeding tr.digestivus haematemesis, melaena, rect. bloedverlies, pos. benzidine	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 7	Bloeding tr. resp. hemoptöe, geen neus- bloeding	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 8	Bloeding spier pijnlijke zwelling, (bewegingsbeperking) retroperitoneale bloeding, buikwand haematoom	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 9	Bloeding gewricht hydrops gewricht met haematoom of met bloed bij punctie	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 10	Bloeding intra-oculair incl. oogfundusbloeding (excl.retinopathie)	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....
o 11	Bloeding anders niet anders te classi- ficeren, wel specificeren	diagnostische bloeding	o 1 neen o 2 ja	Onderliggend lijden .....

.....

.....

ZIEKENHUISOPNAME INTRACRANIEEL

ASPECT-nummer: ..... Naam beoordeler: .....

Eventn°: .....

Is de hoofddiagnose inderdaad neurologisch ?

o 1 Ja

o 2 Neen

o 3 Onzeker

Indien neen, geef aan aan wie deze opname gestuurd dient te worden:

o Cardioloog o Internist o Retour Coördinatiecentrum

Heeft de gebeurtenis geleid tot ziekenhuisopname?

o ja Opnamedatum: ...../...../..... Ontslagdatum: ...../...../.....

o nee Datum van gebeurtenis: ...../...../.....

I. Cerebrale gebeurtenissen: CT-scan aanwezig

o A/ Hersenbloeding

- o 1 Intracerebraal
- o 2 Arachnoïdaal
- o 3 Subduraal
- o 4 Epiduraal

Afloop:

- o 1 Overleden < 24 uur
- o 2 Overleden > 24 uur (.....dagen)
- o 3 Niet overleden en niet invaliderend
- o 4 Niet overleden en gering invaliderend
- o 5 Niet overleden en matig invaliderend
- o 6 Niet overleden en ernstig invaliderend

o B/ Herseninfarct

Afloop:

- o 1 Overleden < 24 uur
- o 2 Overleden > 24 uur (.... dagen)
- o 3 Niet overleden en niet invaliderend
- o 4 Niet overleden en gering invaliderend
- o 5 Niet overleden en matig invaliderend
- o 6 Niet overleden en ernstig invaliderend

o C/ Niet te beoordelen

II. Acute cerebrale gebeurtenissen: geen CT-scan aanwezig

Afloop:

o 1 Overleden < 24 uur

o 2 Overleden > 24 uur (.....dagen)

o 3 Genezen < 24 uur

o 4 Genezen > 24 uur (.....dagen)

o 5 Niet overleden en niet invaliderend

o 6 Niet overleden en gering invaliderend

o 7 Niet overleden en matig invaliderend

o 8 Niet overleden en ernstig invaliderend

III. Spinale pathologie (bloeding of infarct)

o 1 Ja

o 2 Neen

o 3 Mogelijk

IV. Overige neurologische aandoening

o 1 Ja: _____

o 2 Neen

Is de patiënt overleden?

o 1 Ja Datum: ...../...../.....

o 2 Neen

Is de medicatie gestaakt? /door CC ingevuld

o 1 Ja Datum: ...../...../.....

o 2 Nee

o 3 Eerder gestaakt

Indien ja, vervolgmedicatie na staken ASPECT medicatie:

o 1 Antistolling

o 2 Plaatjes aggregatieremmer

o 3 Geen antitrombotische medicatie

o 4 Onbekend

o Hervatting ASPECT medicatie

o ja Datum: ...../...../.....

o nee

o Deze episode dient besproken te worden

HANDTEKENING: _____

ZIEKENHUISOPNAME OVERIG / INTERN

ASPECT-nummer: ..... Naam beoordeler: .....

Eventn°: .....

Is de hoofddiagnose inderdaad overig?

o ja

o nee; Indien neen geef aan naar wie deze opname dan verstuurd dient te worden:

o Neuroloog o Cardioloog o Retour Coördinatiecentrum

Heeft de gebeurtenis geleid tot ziekenhuisopname?

o ja Opnamedatum: ...../...../..... Ontslagdatum: ...../...../.....

o nee Datum van gebeurtenis: ...../...../.....

HOOFDDIAGNOSE

o 1 Extracraniële arteriële thromboëmbolie
o 2 Extracraniële veneuze thromboëmbolie
o 3 Perifeer arterieel vaatlijden
o 4 Tractus respiratorius aandoening
o 5 Tractus digestivus aandoening
o 6 Tractus urogenitalis aandoening
o 7 Intoxicatie
o 8 Overige tractus
o 9 Electieve chirurgie
o 10 Trauma
o 11 Suïcide
o 12 Homocide
o 13 Geen diagnose te stellen

STAKEN MEDICATIE (zonder ziekenhuisopname)

ASPECT-nummer: ..... Naam beoordeler: .....

Eventn°: ..... Datum staken medicatie: ...../...../.....

Medicatie gestaakt in verband met:

o 1 Weigering patient zonder verdere medische reden
o 2 Verhuizing
o 3 Weigering huisarts/specialist zonder expliciete reden
o 4 Boezemfibrilleren
o 5 Recent ontstane angina pectoris
o 6 Progressie stabiele angina pectoris
o 7 Thoracale klachten
o 8 Overig cardiaal
o 9 Onvermogen de medicatie behoorlijk in te nemen
o 10 Aneurysma cordis

o Overige indicatie voor antistolling: .....
o Overige contraindicatie voor antistolling: .....
o Overig, a.u.b. specificeren: .....

o Verandering van medicatie: Datum: ...../...../.....
  o 1 Antistolling
  o 2 Plaatjesaggregatieremmers
  o 3 Geen antitrombotische medicatie
  o 4 Onbekend

o Hervatting ASPECT medicatie
o ja Datum: ...../...../.....
o nee

HANDTEKENING: _____

EXTRAMURAAL OVERLIJDEN (inclusief verpleeghuis- en bejaardenhuisopnamen)

ASPECT-nummer: ..... Naam beoordeler: .....

Event n ..... Datum overlijden: ...../...../.....

Geef de doodsoorzaak

o 1 Instantane dood (zonder voorafgaande specifieke klachten)
o 2 Plotseling en onverwacht (minder dan 1 uur na ontstaan klachten)
o 3 Klinisch beeld recidief infarct (langdurige pijn, ECG's in ambulance)
o 4 Niet geobserveerd, onverwacht
o 5 Pompfunctiestoornis
o 6 Overig cardiaal
o 7 Trauma
o 8 Suïcide
o 9 Homicide
o 10 Overig
o 11 Niet te bepalen

Reden staken medicatie?

o 1 Extramuraal overlijden
o 2 Eerder gestaakt

HANDTEKENING _____

APPENDIX B.IX

ASPECT - onderzoek, Glashaven 68, 3011 XK Rotterdam, 010 - 411 20 74 - 414 86 44, tst. 46

datum

ons kenmerk
onderwerp

Geachte collega,

Uw patient(e) is met zijn¦haar toestemming opgenomen in het ASPECT-onderzoek. Inmiddels is de behandeling via de thrombosedienst gestaakt. Een verdere registratie van het klinisch beloop is echter voor het onderzoek van belang. Via de thrombosedienst kunnen deze gegevens niet meer achterhaald worden.

Zou u zo vriendelijk willen zijn door middel van het bijgevoegde formulier ons informeren over het verdere klinische verloop en eventuele antitrombotische vervolgmedicatie?
Een antwoordenveloppe is bijgesloten. Vanzelfsprekend zullen de door u verstrekte gegevens als medisch geheim worden behandeld.

Mocht u vragen hebben met betrekking tot het onderzoek dan kunt u zich wenden tot ondergetekende, tel.:010-4112074.

Bij voorbaat hartelijk dank voor uw medewerking.

Met vriendelijk groet,

ASPECT - onderzoek, Glashaven 68, 3011 XK Rotterdam, 010 - 411 20 74 - 414 86 44, tst. 46

datum

ons kenmerk
onderwerp
Betreft:

Datum laatste controle:....|....|....

I. Is patient(e) na bovengenoemde datum nog in een ziekenhuis opgenomen geweest? ja|nee
Indien ja:

Eerste opname:
-Datum opname:...|...|... -Datum ontslag:...|...|...
-Ziekenhuis naam:..... -Specialist naam:.....
-Ontslagdiagnose:

Tweede opname:
-Datum opname:...|...|... -Datum ontslag:...|...|...
-Ziekenhuis naam:..... -Specialist naam:.....
-Ontslagdiagnose:

Indien meer dan twee ziekenhuisopnamen hebben plaatsgevonden, s.v.p. op andere zijde vermelden.

II. Patient(e) is: in leven|overleden (datum:...|...|...)
Patient(e) is overleden in: o ziekenhuis t.w.:.....
o verpleegtehuis t.w.....
o thuis of elders

Omschrijf s.v.p. onderstaand de omstandigheden waaronder de patient(e) is overleden.

BLKFUP|AZAR|90

N.B: Gebruikt patient(e) Aspirine? ja|nee, zo ja, sedert: (datum) ...|...|...

Opmerkingen:

Datum:...|...|... Naam:.....

APPENDIX B.X

Participating centers (with numbers of patients randomized and principal investigators):

Almelo: *Twenteborg Ziekenhuis:* (8) J.I. Darmanata, M.D., Ph.D., B.J.L. de Rode M.D., Amstelveen: *ziekenhuis Amstelveen*: (3) Joh. Büller M.D., J.P. van Mantgem M.D. Ph.D., Amsterdam: *Academisch Medisch Centrum*: (5) B.J.M. Delemarre M.D., B. van Vlies M.D., Ph.D., *Andreas ziekenhuis*: (63) A. Hillebrand M.D., Ph.D., J.E. Japikse M.D., A. Vermeulen M.D., Ph.D., *A.Z. Vrije Universiteit*: (201) prof. F.W.A. Verheugt M.D., Ph.D., *Boerhaave kliniek*: (11) E.D.E. Bialoglowski M.D., *Boven IJ ziekenhuis*: (31) L.J. Jansen M.D., A.D. Overdijk M.D., Ph.D., R.J. van Woersem, M.D., *St. Lucas ziekenhuis*: (37) I.M. Hellemans M.D., B.L.E. Lutterman M.D., E.S. Nieuwendijk M.D., Ph.D., W.G. de Voogt M.D., *Slotervaart ziekenhuis*: (42) R.H. Bakker M.D., J.E. Schreuder M.D., Arnhem: *Ziekenhuis Rijnstate*: (81) A.J. Hameleers M.D., L.H.J. van Kempen M.D., Ph. D., W. van Lommel M.D., R. van Nieuwenhuizen M.D., R.D. Rijneke M.D., P.W.J. Stolwijk M.D., Blaricum: *Gooi Noord*: (57) Th. W. Donkerloo M.D., R. van Stralen M.D., A.A. de Winter M.D., Breda: *Ziekenhuis De Baronie*: C.J.F.M. Middelhof M.D., D.N. van Paassen M.D., R. Sloos M.D., P.D. Tan M.D., *St. Ignatius*: (27) H.M.A. Corbeij M.D., P.H.J.M. Dunselman M.D., Ph.D., J.A.M. te Riele M.D., R.P. Wielenga M.D., Delft: *Reinier de Graaf Gasthuis*: (17) D. Rehorst M.D., H.A. Schippers M.D., E.G.M. Stassen M.D., A.J.A.M. Withagen M.D., Den Bosch: *Carolus ziekenhuis*: (22) R.A.M. van Langeveld M.D., H.H. Tan M.D., E.C.M. Schavemaker, M.D., *Willem Alexander ziekenhuis*: (31) W.F.A. Blans M.D., E. Krivka M.D., Den Haag: *Leijenburg ziekenhuis*: (128) P.B. den Bakker M.D., G.A. van der Kleij M.D., Ph.D., C.M. Sparling M.D., Ph.D., J.W.J. van Wesemael M.D., *Het Rode Kruis ziekenhuis*: (27) P.N.M. Buhre M.D., M. van Rossem M.D., Deventer: *Deventer Ziekenhuizen*: (24) L.H.M. Bouwens M.D., H. Groeneveld M.D., D.J.A. Lok M.D., F.C.W. Tietge M.D., Eindhoven: *Catharina ziekenhuis*: (14) J.J.R.M. Bonnier M.D., P. Borsje M.D., M.I.H. el Gamal M.D., H.R. Michels M.D., T.H.F. Relik M.D., *Diaconessenhuis*: (10) B.L. van Brussel M.D., D. Hendriks M.D., L. Relik-van Wely M.D., *St. Sint Joseph ziekenhuis*: (8) A.H. Bosma M.D., M.C. Huige M.D., L.C. Slegers M.D., R.F. Visser M.D., Enschede: *Medisch Spectrum Twente*: (351) P.H. van der Burgh M.D., K. Huisman M.D., B.A.M. Kauer M.D., C. Kroon M.D., G.P. Molhoek M.D., J.C. Poortermans M.D., A.J.M. Timmermans M.D., L.R. van der Wieken M.D., Goes: *Oosterschelde ziekenhuis*/ Zierikzee: *Zweedse Rode Kruis ziekenhuis*: (246) J.A.J. de Boo M.D., E. Bruins, M.D., M. Drenth M.D., A.J. van den Hoorn M.D., A.H. Liem M.D., H.W.O. Roeters van Lennep M.D., Groningen: *A.Z. Groningen*: (65) J.F. May M.D., Ph.D., J.W. Viersma M.D., Ph.D., *Diakonessenhuis*: (82) J.H. Bennekers M.D., P.J.L.M. Bernink M.D., Ph.D., J.F. Oostenrijk M.D., Hk. de Vries M.D., Ph.D., *R.K. Ziekenhuis*: (60) H.G.H. Kok M.D., E. Laverman M.D., L.E.J.M. Schrijvers M.D., Haarlem: *Elisabeth's Gasthuis*: (69) A.J. Funke Küpper M.D., Ph.D., G. Kan M.D., Ph.D., P. Kloppenburg M.D.(deceased), K.H. Romijn M.D., M.A.H.W. Schöttelndreier M.D., G.J.E. Verdel M.D., *Spaarne Ziekenhuis*: (227) A. ten Hove Jansen M.D., H.H. Kruijswijk M.D., Ph.D., Mr. E.J. Müller M.D., J.C.L. Wesdorp M.D., *St. Joannes de Deo*: (15) T.W.G. Veenbrink M.D., Hengelo: *Streekziekenhuis Midden-Twente*: (26) T. Austermann-Kaper M.D., D.F. Brune M.D., J.J.J. Bucx M.D., S.A.M. Said M.D., Hilversum: *Streekziekenhuis Hilversum*: (49) F. van Bemmel M.D., F.A. van Erven M.D., Ph.D., K.L. Liem M.D., R.R.A.P. Webb M.D. (deceased), F.N. Wempe M.D., Leiden: *A.Z. Leiden*: (131) H.A. Bosker M.D., C. Begeman, M.D., V. Manger Cats M.D., Ph.D., *Diaconessenhuis*: (26) S.A.G.J. Witteveen M.D., Ph.D., Leiderdorp: *St. Elisabeth ziekenhuis*: (172) J.M.H. Moorrees M.D., C. van Rees M.D., Ph.D., T.L. See M.D., Leidschendam: *St.Antoniushove*: (78) J.W.G. Draulans M.D., P. de Groot M.D., H.J.A. Paalman M.D., Middelburg: *Sti. Streekziekenhuis Walcheren*: (11) E.G.H.J.M. Kamerbeek M.D., Nieuwegein: *St. Antonius ziekenhuis*: (95) C.A.P.L. Ascoop M.D., Ph.D., E.T. Bal M.D., J.M.P.G. Ernst M.D., Ph.D., W. Jaarsma M.D. Ph.D., N.M. van Hemel M.D., Ph.D., J.H. Kingma M.D., Ph.D., E.G. Mast M.D., H.W.M. Plokker M.D., Ph.D., M.J. Suttorp, M.D., Oosterhout: *St. Joseph*: (3) D.M. Prenger M.D., F.Schuitemaker M.D., Overveen: *Marine hospitaal*: (9) W.F. van Marion M.D., A.D.J. Verburg M.D., Raamsdonksveer: *Sti. Streekziekenhuis Dongemond*: (15) B.A. van der Wal M.D., J.A. van Wissen M.D., Rotterdam: *A.Z. Rotterdam-Dijkzigt*: (76) A.H.M.M. Balk M.D., K. Meeter M.D., Ph.D., prof. M.L. Simoons M.D., Ph.D., *Bergweg ziekenhuis*: (39) W.M. Muijs van den Moer M.D., B.J. van den Berg, M.D., *St. Clara ziekenhuis*: (23) F.M.A. Harms M.D., L. de Jonge M.D., R. Wardeh M.D., *Van Dam-*

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SUMMARY

The therapeutic effects of anticoagulants in the treatment of patients with deep venous thrombosis, pulmonary embolism, prosthetic heart valves, atrial fibrillation and heart failure are well established. However, long-term anticoagulant therapy for secondary prevention of morbidity and mortality in post-myocardial infarction patients remains controversial. Anticoagulant therapy carries potential bleeding risks and therefore requires continuous anticoagulant monitoring by the clinician and demands patient compliance. However, the relation of bleeding and thromboembolic complications to intensity of anticoagulant therapy has not yet been investigated. In this thesis, the optimal intensity of long-term anticoagulant therapy in preventing the occurrence of thromboembolic as well as haemorrhagic complications in 3404 post-myocardial infarction patients was assessed.

Chapter 1 reviewed the value of long-term anticoagulant therapy after myocardial infarction based on more than thirty trials which have been reported in the literature in the past 40 years. The early studies were performed with inappropriate methodologies and demonstrated a non-significant reduction in mortality. Beneficial effects in reduction of thromboembolic complications were offset by a higher risk of haemorrhagic episodes. These studies also faced laboratory control problems in that different laboratory tests were used to monitor intensity of treatment. However, at present, any prothrombin time established with any thromboplastin reagent can be translated into an internationally agreed norm, the international normalised ratio (INR).

In the seventies, debate over the effectiveness of long-term anticoagulant therapy was prominent but, in that decade, only three randomized controlled studies were performed: Breddin, EPSIM and 'Sixty-Plus'. The first two studies failed to demonstrate a reduction in mortality by use of oral anticoagulant therapy. In both trials aspirin was as effective as anticoagulant therapy in reducing mortality and morbidity, however anticoagulant control was relatively poor and the small size of the trials makes the findings inconclusive. The 'Sixty-Plus' trial did demonstrate a positive treatment effect of oral anticoagulant therapy as compared to placebo. In this trial 72% of the patients were within 2.7-4.5 INR. The merits of the "Sixty-Plus' study were debated by many because of its specific design: it assessed the value of discontinuation of long-term therapy rather than of its initiation. Nevertheless, the positive findings of this study reopened the long standing debate of long-term use of oral anticoagulant therapy after myocardial infarction.

Subsequently, results of the carefully performed WArfarin Re-Infarction Study (WARIS) was published in 1990. A total of 607 patients were assigned to warfarin

and 607 to placebo. Mean follow-up was over three years. The results clearly demonstrated the benefits of oral anticoagulant therapy in patients surviving an acute myocardial infarction in preventing death: mortality in placebo was 123 compared to 94 in patients treated with warfarin (24% reduction). In addition, the rate of myocardial re-infarction was reduced by 34% and stroke by 55%. Anticoagulant control was adequate: 67% of the patients had values within the range of 2.8-4.8 INR.

The results of the largest randomized, double-blind, placebo controlled, multicentre ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial are given in Appendix A. ASPECT compared oral anticoagulant therapy (acenocoumarol or phenprocoumon) in 1700 patients to placebo in 1704 patients surviving an acute myocardial infarction with a mean follow-up of three years. A total of 170 deaths in actively treated group compared to 189 in placebo was observed (10% reduction in mortality), the rate of myocardial re-infarction was reduced by 53%, stroke by 40% and vascular event by 35%. These beneficial effects were offset by a 10 fold increase in the incidence of major bleeding for the actively treated group (55 in the actively treated group and 6 in placebo). Anticoagulant control was adequate: 63% of the patients had INR measurements within 2.8-4.8 INR.

Chapters 2 and 3 described in detail the methods for double-blind anticoagulant titration as employed in ASPECT. Anticoagulant therapy is not a fixed dose therapy but patients who use these drugs have to visit the anticoagulant clinic regularly for INR monitoring and dosage adjustments. Placebo patients also visited the clinics and fake INR values were obtained in this group. Similarly, dosage adjustments were made for this group just as in patients on active therapy. This method ensured the double-blind collection of data and thereby prevention of information bias.

Chapter 4 reviewed the different approaches to assess therapeutic quality control using the INR: (1) the 'cumulative-INRs' considered the number of INR values and the 'cross-section-of-the-files' considered the most recent INR obtained in each patient. The results are expressed as a percentage of all INR values within therapeutic range; (2) an estimate of the percent of time each patient was within the therapeutic range, where the INR change occurred either directly after the first or half-way between visits; and (3) total volume of observation time of all patients categorised into classes of INR values assuming that INR values changed linearly between visits. These approaches were evaluated in the ASPECT patients on active anticoagulant therapy. Total treatment period comprised 3725 patient-years and 61,471 INR measurements. The data revealed that, irrespective of the approach used, therapeutic achievement stabilized after 6 months of treatment. Under-anticoagulation decreased between the first and third month and was again lower after six months of treatment. Over-anticoagulation (INR>4.8) occurred between 8%

to 10% at any time interval using approaches 1 and 2, and around 5% of the time using approach 3. TDAS® and TRODIS dosage systems provided similar levels of effectiveness. Therapeutic achievement is recommended to be evaluated using the third approach, since it incorporates time and has the most realistic assumptions. This approach is also most suitable for assessing anticoagulant control, since incidence rates of events at different intensities can be calculated. Finally, the present data call for an improvement by the standard of control for patients during the first 3 months of anticoagulant treatment.

Chapter 5 proposed a method to determine the optimal intensity of long-term anticoagulant therapy required to prevent the occurrence of thromboembolic and haemorrhagic complications. This involved the calculation of incidence rates associated with specific INR intervals for both events (bleeding or thromboembolic) in the ASPECT population. Total treatment period was 7213 patient-years. Major bleeding occurred in 57 (0.8/100 patient-years) and thromboembolic complications in 397 patients (5.6/100 patient-years). A Poisson regression analysis was performed to determine the independent risk of event associated with INR-specific intervals, after adjustment for possible confounding variables. Based on INR measurements obtained within 28 days from the event and relative to INR intensities below 2, the rate ratio of major bleeding associated with INR values between 2 and 3 was 0.2, while 0.6 at INR between 3 and 4, an 80% increase in bleeding risk was observed for INR between 4 and 5, and 5 fold increase for INR values exceeding 5. A reduction of 70% in the rate of thromboemboli associated with INR values between 2 and 3 was observed compared with INR intensities below 2, an 80% reduction at INR intensities between 3 and 4, as well as for INR intensities above the value of 5. The intensity of anticoagulant therapy at which the incidence of bleeding and thromboembolic complications was lowest was between 3.0-4.0 INR. Other significant predictors for major bleeding and thromboemboli included higher levels of systolic blood pressure and age. Female patients showed a higher trend for bleeding than males. These results suggest the optimal intensity of long-term anticoagulant therapy for post-myocardial infarction patients to lie between 3.0 and 4.0 INR.

Chapter 6 presented a detailed description of the 99 ASPECT patients with stroke including intracranial bleeding, cerebral infarctions, unspecified and transient ischemic attacks. Three years following randomization, 2% of the patients on anticoagulant therapy had a stroke compared to 4% in placebo. The incidence of stroke analyzed on "intention-to-treat" was 0.7 per 100 patient-years in the anticoagulant group and 1.2 per 100 patient-years in placebo, a hazard ratio (HR) of 0.60 with a 95% confidence interval (CI) of 0.40 to 0.90. A total of 19 intracranial bleeding was observed. The risk of haemorrhages was 8 times greater for anticoagulated patients compared to placebo. Eight of the 17 bleedings were fatal in the anticoagulant group and no fatal haemorrhages occurred in placebo. A total

of 15 cerebral infarctions occurred in the anticoagulated group and 43 in placebo. The total number of patients who died or were severely disabled as a result of cerebral stroke amounted to 13 in the anticoagulated group, compared to 18 in placebo. The results indicated that long-term anticoagulant therapy substantially reduced the risk of stroke in post-myocardial infarction patients. The increased risk of bleeding complications associated with anticoagulant therapy was offset by a marked reduction of ischemic events.

SAMENVATTING

Het therapeutisch effect van anticoagulantia bij de behandeling van patienten met diep veneuze thrombose, long-embolie, kunstkleppen, atrium fibbrilleren en hartfalen is onomstreden. Echter, de langdurige behandeling van patienten die een hartinfarct hebben overleefd is nog steeds controversieel. Antistollings behandeling verhoogt het bloedingsrisico en vereist een voortdurende bewaking door de arts en goede therapie-trouw van de patient. In dit proefschrift wordt, gebaseerd op de gegevens van 3404 post-infarct patienten, een advies opgesteld over de optimale intensiteit van de behandeling met antistolling in de preventie van zowel tromboembolische als bloedings complicaties.

Hoofdstuk 1 geeft een overzicht van de waarde van behandeling met antistolling na het hartinfarct gebaseerd op de resultaten van meer dan dertig therapeutische experimenten die in de afgelopen veertig jaar zijn gerapporteerd in de literatuur. De eerste studies, die nog niet volgens juiste methoden werden uitgevoerd, toonden een niet significante reductie in sterfte en een voordelige effect het terugdringen van thromboembolische complicaties aan; deze werden echter geneutraliseerd door een hoger bloedings risico. Verder hadden deze studies te kampen met problemen betreffende de eenduidigheid van de laboratorium waarden, omdat verschillende laboratorium bepalingen werden gebruikt om de intensiteit van antistolling te controleren. Tegenwoordig is het echter mogelijk om elke bloedingstijd die met een thromboplastine reagent is bepaald om te rekenen in een internationaal erkende norm: de International Normalized Ratio (INR).

In de zeventiger jaren vond een uitgebreide discussie plaats over de effectiviteit van langdurige behandeling met antistolling, maar er werden slechts drie gerandomiseerde, gecontroleerde studies uitgevoerd: Breddin, EPSIM en 'Zestig Plus'. De eerste twee studies slaagden er niet in om een afname in sterfte door het gebruik van orale anticoagulantie aan te tonen. In beide therapeutische experimenten was de behandeling met aspirine even effectief in het terugdringen van mortaliteit en morbiditeit als de behandeling met antistolling; de bewaking van de antistolling was echter relatief slecht. Bovendien was de omvang van de experimenten niet afdoend. Het Zestig Plus onderzoek toonde wel een positief behandelingseffect aan voor anticoagulantia in vergelijking met placebo. In dit onderzoek bevond 72% van de patienten zich binnen de 2.7-4.5 INR. De verdienste van het 'Zestig Plus' onderzoek werd door velen aangevochten vanwege het specifieke ontwerp van deze studie: eerder werd de waarde van het continueren van behandeling met antistolling aangetoond dan het starten van deze behandeling. Desalniettemin, de positieve bevindingen van dit onderzoek heropenden het reeds

lang durende debat over de langdurige behandeling van antistolling na het hartinfarct.

Vervolgens werden in 1990 de resultaten van de omzichtig uitgevoerde WArfarine Re-Infarct Studie (WARIS) gepubliceerd. In totaal werden 607 patienten toegewezen aan een behandeling met warfarine, en 607 aan placebo. De gemiddelde duur van de vervolgperiode was drie jaar. De resultaten toonden overduidelijk de voordelen van orale behandeling met antistolling aan op het voorkomen van de dood bij patienten die een acuut hartinfarct hadden overleefd: de sterfte in de patientengroep behandeld met placebo was 124, in vergelijking met 94 doden in de met warfarine behandelde groep (een afname van 24%). Het aantal recidief infarcten werd met 34% gereduceerd, de cerebro-vasculaire accidenten met 55%. De bewaking van de antistolling was afdoende: 67% van de patienten had waarden binnen de 2.8-4.8 INR.

De resultaten van het grootste gerandomiseerde dubbelblinde placebo-gecontroleerde onderzoek, genaamd ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis), worden weergegeven in Appendix A. ASPECT vergeleek 1700 patienten behandeld met antistolling tegen 1704 patienten behandeld met placebo. Alle patienten hadden een hartinfarct overleefd; de gemiddelde vervolgperiode was 3 jaar. In de aktief behandelde groep werden 170 doden geteld in vergelijking tot 189 doden in de placebo-groep (een 10% afname in sterfte). Het aantal recidief infarcten werd gereduceerd met 53%, cerebro-casculaire accidenten met 40%, en alle vasculaire complicaties met 35%. De keerzijde werd gevormd door een tienvoudige verhoging in het optreden van ernstige bloedingen in de aktief behandelde groep (55 tegen 6). De bewaking van antistolling was afdoende: 63% van de patienten had INR waarden binnen de 2.8-4.8.

In de hoofdstukken 2 en 3 worden de methoden, die in ASPECT zijn toegepast met betrekking tot de dubbelblinde titratie van de antistolling, in detail beschreven. In de behandeling met antistolling wordt geen vaste dosering gebruikt. Patienten die deze behandeling ondergaan moeten de thrombose dienst regelmatig bezoeken om de INR waarde te laten bepalen en desgewenst de dosering aan te laten passen. Patienten behandeld met placebo bezochten eveneens de trombose dienst, waarbij er nep-waarden voor deze patienten groep werden bepaald. Op vergelijkbare wijze werd zo de dosering in deze groep aangepast. De methode verzekerde het dubbelblinde karakter van de gegevensverzameling en voorkwam daardoor informatie bias.

Hoofdstuk 4 bespreekt de verschillend benaderingen om met behulp van de INR een kwaliteitsbewaking van de antistollings behandeling te verkrijgen: (1) de "cumulative INR's" beschouwt het totaal aantal INR waarden, en de "cross-section-on-files" beschouwt de laatst verkregen INR waarde van iedere patient. De resultaten worden uitgedrukt als het percentage van alle INR waarden binnen het

therapeutisch gebied; (2) een schatting van het percentage van de tijd die een patient binnen het therapeutisch gebied verbleef, waarbij de verandering in INR waarde of direct na het eerste bezoek of midden tussen de twee bezoeken in plaatsvond; (3) het totale "volume" van de geobserveerde tijd die patienten doorbrengen in een bepaalde INR waarde, aannemende dat de INR waarden lineair over de tijd veranderen. Deze drie benaderingen werden geevalueerd aan de hand van de aktief behandelde patienten in ASPECT. De totale behandelings periode omvatte 3725 patientjaren en 67471 INR waarden. De gegevens toonden aan dat, onafhankelijk van de gebruikte methode, de intensiteit waarin de patienten ontstold waren na zes maanden van behandeling stabiliseerde. Het aantal patienten met een te lage intensiteit van antistolling verminderde tussen de eerste en de derde maand, en was wederom kleiner na zes maanden. Onafhankelijk van de tijd kwam een te hoge intensiteit van antistolling (INR > 4.8) voor in 8% tot 10% van de gevallen na gebruikmaking van de benaderingen 1 en 2, en in 5% van de gevallen na gebruikmaking van benadering 3. De TDAS and TRODIS doserings systemen leverden vergelijkbare niveaus van effectiviteit op. De derde benadering wordt aanbevolen om het therapeutisch succes van de antistollings behandeling te evalueren, omdat deze benadering gebaseerd is op de meest realistisch aannames en bovendien de factor tijd in beschouwing neemt. Ten slotte laten de gepresenteerde gegevens zien dat een verbetering van de standaard bewaking van de behandeling met antistolling gedurende de eerste drie maanden wenselijk is.

In hoofdstuk 5 wordt een methode om de optimale intensiteit van langdurige behandeling met antistolling in post-infarct patienten, die nodig is om het optreden van tromboembolische en bloedings complicaties te voorkomen, onderzocht. Dit vond plaats met behulp van incidentie rates van beide complicaties, geassocieerd met bepaalde INR intervallen. De totale behandelings periode omvatte 7213 patientjaren. Ernstige bloedingen kwamen voor in 57 (0.8/100 patientjaren) en tromboembolische complicaties in 397 patienten (5.6/100 patientjaren). Een Poisson regressie analyse werd uitgevoerd om, na correctie voor mogelijke confounders, het onafhankelijke risico van de INR-specifieke intervallen op de genoemde complicaties vast te stellen. Gebaseerd op de INR metingen verkregen binnen 28 dagen voor de complicaties en gerelateerd aan INR intensiteiten onder de 2, bedroeg het relatieve risico van ernstige bloedingen geassocieerd met INR waarden tussen 2 en 3 0.2, vervolgens 0.6 bij INR waarden tussen 3 en 4, 1.8 bij INR waarden tussen 4 en 5, en 5 bij INR waarden groter dan 5. Op vergelijkbare (maar omgekeerde) wijze nam het (relatieve) risico op thrombo-embolische complicaties toe met afnemende INR intervallen. De intensiteit van de behandeling met antistolling waarbij de incidentie van zowel bloedingen als tromboembolische complicaties het laagst bleek, was in het INR interval 3.0-4.0. Andere significante voorspellers van ernstige bloedingen en tromboembolieen waren hogere systolische bloeddruk en leeftijd. Vrouwelijke patienten vertoonden een verhoogd risico op bloedingen in vergelijking met mannen.

De resultaten suggereren dat de optimale intensiteit van langdurige behandeling met antistolling bij post infarct patienten tussen de 3.0 en 4.0 INR ligt.

In hoofdstuk 6 wordt een uitvoerige beschrijving gegeven van de 99 ASPECT patienten met een CVA, waaronder intracraniele bloedingen, herseninfarcten, niet-gespecificeerde en kortstondige ischemische aanvallen gerekend worden. Drie jaar na randomisatie kreeg 2% van de patienten behandeld met antistolling een cerebrovasculair accident in vergelijking met 4% van de patienten behandeld met placebo. De incidentie van CVA's, geanalyseerd op basis van het "intension-to-treat" principe, bedroeg 0.7 per 100 patientjaren in de antistollings groep en 1.2 per 100 patientjaren in de placebo groep. Dit resulteerde in een hazard ratio van 0.60, met een 95% betrouwbaarheidsinterval van 0.40 tot 0.90. In totaal werden 19 intracraniele bloedingen waargenomen. Het risico op bloedingen was 8 maal zo groot in patienten behandeld met antistolling vergeleken met patienten behandeld met placebo. Acht van de 17 bloedingen in de antistollings groep waren dodelijk; in de placebo groep kwamen geen dodelijke bloedingen voor. In de antistollings groep kwamen 15 en in de placobo groep kwamen 43 herseninfarcten voor. Het aantal patienten dat overleed of ernstig gehandicapt raakte door een cerebrovasculair accident bedroeg 13 in de antistollings groep en 18 in de placebo groep. De resultaten geven aan dat langdurige behandeling met antistolling het risico op een CVA in postinfarct patienten aanzienlijk verlaagt. Het verhoogde risico op bloedings complicaties geassocieerd met antistollings behandeling werd (meer dan) gecompenseerd door een afname van het aantal ischemische complicaties.

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CURRICULUM VITAE

Aida J. Azar was born on 14 december 1961 in Beirut, Lebanon. In June 1980 she obtained from the International College of Beirut, the Baccalaureate Part II, Section Experimental Science. From the American University of Beirut, she acquired the degrees of Bachelor of Science, major in Biology (June 1983), and a Master of Public Health degree, concentration in Epidemiology-Biostatistics (June 1985). During her residency training at the American University of Beirut (1984), she assisted in a research project conducted by the Faculty of Health Sciences sponsored by the Ford Foundation. This project provided information on the health needs of the residents of the city of Beirut. In September 1985 she left Lebanon to settle in her mother's birth place, the Netherlands. During the first three months, she was a Research Assistant for the University of Rotterdam (Erasmus), sponsored by the Netherlands Interuniversity Cardiology Institute. The study involved the determinations of the effects of recanalization in acute myocardial infarction. Since january 1986, she was the data-manager for the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial. ASPECT related the effects of long-term oral anticoagulant therapy on the prognosis of patients who had survived a myocardial infarction. ASPECT was funded by the 'Praeventiefunds' of the Netherlands. The Data and Statistics Centre was located at the Clinical Epidemiology Unit, department of Cardiology, Thoraxcentre, Erasmus University of Rotterdam. Moreover, she was a methodological and statistical consultant for staff members of the Thoraxcentre, Erasmus University of Rotterdam.

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