Long-term oral anticoagulant treatment after myocardial infarction

Results of the 'Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis' (ASPECT) trial

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Long-term oral anticoagulant treatment after myocardial infarction

Results of the 'Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis' (ASPECT) trial

Langdurige orale antistollingsbehandeling na een myocardinfarct

Resultaten van het 'Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis' (ASPECT) onderzoek

PROEFSCHRIFT

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aan de Erasmus Universiteit Rotterdam
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Contents

Publications and manuscripts based on the studies described in this thesis

Chapter 2
The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction.
Lancet 1994; 343:499-503.

Chapter 3
P.F.M.M. van Bergen, J.W. Deckers, J.J.C. Jonker, R.T. van Domburg, A.J. Azar, A. Hofman. Efficacy of long-term anticoagulant treatment in subgroups of post myocardial infarction patients.
British Heart Journal, in press.

Chapter 4
P.F.M.M. van Bergen, J.J.C. Jonker, J.W. Deckers, F.W.A. Verheugt, A. Hofman. Cumulative meta-analysis of long-term anticoagulant therapy after myocardial infarction.
Submitted.

Chapter 5
P.F.M.M. van Bergen, J.J.C. Jonker, G.P. Molhoek, P.H. van der Burgh, R.T. van Domburg, J.W. Deckers, A. Hofman. Characteristics and prognosis of non-participants of a multi-centre trial of long-term anticoagulant treatment after myocardial infarction.
Submitted.

Chapter 6
P.F.M.M. van Bergen, J.J.C. Jonker, B.A. van Hout, R.T. van Domburg, J.W. Deckers, A. Hofman. Costs and effects of long-term oral anticoagulant treatment after myocardial infarction.
Journal of the American Medical Association, in press.

Chapter 1

Rationale for long-term anticoagulant therapy after myocardial infarction

Introduction

Atherosclerosis

Despite the fact that mortality from cardiovascular diseases has declined considerably over the last decades, it still represents the leading cause of mortality and morbidity in industrialized countries.[1,2] Most clinical manifestations of cardiovascular disease share the underlying pathophysiological process of atherosclerosis. Atherosclerosis is a diseased state of the intima and media of medium to large sized arteries characterized by focal plaques preferentially located in areas of low shear. It is assumed that plaques origin from fatty streaks that are initiated by oxidation of low density lipoprotein.[3] Formation of fatty streaks may also follow initial injury from a wide range of agents including toxins, viral infections and intraluminal devices such as catheters. The subsequent inflammatory reactions induce smooth muscle proliferation by growth factor production from a wide range of cells including platelets, endothelial cells, macrophages, and other smooth muscle cells. The development of fatty streaks may already commence early in childhood and progress over a period of decades to become atherosclerotic plaques which contain lipid-filled foam cells, extracellular lipid and a layer of smooth muscle cells just beneath the endothelium.[4] Plaque growth is mediated by the proliferation of smooth muscle cells and extracellular connective tissue elements such as collagen, elastin, and proteoglycans. Growth factors derived from the interaction between platelets and the underlying artery wall further stimulates this process.[5,6] This process will lead to the formation of a fibrolipid plaque that constitutes a core of extracellular lipid separated from the media by smooth muscle cells and covered and separated from the lumen by a thick cap of collagen-rich fibrous tissue containing smooth muscle cells. Surrounding the lipid core are lipid-filled foam cells. Elevated coronary plaques may cause clinical symptoms when the plaque size is sufficient to obstruct the normal bloodflow, usually when it occupies more than 40 percent of

the original cross-sectional area of the lumen. As the result of a dynamic interplay between plaque vulnerability, possibly mediated through a process of inflammation, and external stresses the atherosclerotic plaque surface may eventually rupture.[7,8]

Coagulation cascade and anticoagulants

Rupture of atherosclerotic plaques is followed by exposure of the de-endothelialised vessel wall to the blood and release of tissue factor. Subsequently, in addition to platelet deposition in the injured area, the clotting system is activated. Mediated through activation of clotting factors V, VII, IX and X, prothrombin (factor II) is transformed into thrombin. Thrombin is the most powerful activator of the coagulation system. Not only does thrombin activate platelets to expose the procoagulant lipids in their membrane and to release factor V, it also activates factor VIII and the receptor of the von Willebrandfactor, thus enhancing a positive feed-back loop producing huge amounts of thrombin. Also, fibrinogen is converted into fibrin monomers that spontaneously polymerise to form long fibrin strands. Subsequently, thrombin also activates factor XIII, which serves to crosslink the fibrin monomers to form an insoluble fibrin network with platelets which results in the formation of a fixed and occlusive platelet-fibrin thrombus.[9]

Most of the various coagulant factors that are involved in the coagulation cascade are formed in the liver and transported in the blood. Factor VIII is formed elsewhere, probably in endothelial and lymphatic cells. Oral anticoagulants, usually consisting of coumarin derivatives, diminish the production of vitamin K dependent coagulation factors (factor II, VII, IX and X). Their close resemblance to vitamin K prevents the final, vitamin K dependent, carboxylation of the clotting factors II, VII, IX and X to become what are then called PIVKA's (Protein Induced by Vitamin K absence or Antagonist).[10] By competition with the naturally available amount of vitamin K, coumarins influence the ratio of PIVKA's and coagulation factors. As PIVKA's are unable to catalyse the coagulation cascade, the rate at

which prothrombin is activated decreases and the activation of thrombin and the subsequent formation of a thrombus are hampered.[11]

Thrombosis and myocardial infarction

Intraluminal thrombosis caused by rupture of an atherosclerotic plaque in a coronary artery may precipitate necrosis of myocardial tissue. The eminent role of thrombosis in the coronary arteries has for long been disputed, but was established when Dewood showed occlusive thrombosis in the majority of coronary angiographies during the acute phase of myocardial infarction.[12] The onset of acute infarction harbours several risks for fatal outcome. Electrical instability and pump failure contribute to the risk of death following acute myocardial infarction. However, following the recovery of the acute phase of myocardial infarction, patients remain at increased risk of death and arterial thrombo-embolism during many years.[13]

In view of the fact that recurrent acute thrombosis of the arterial vascular system represents the most frequent cause of cardiovascular complications after myocardial infarction, reduction of thrombin formation appears a rational way to prevent subsequent cardiovascular events. To test this hypothesis, the randomised, placebo-controlled, double-blind ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial was initiated in 1986. The aim of this trial was to assess the effects of long-term oral anticoagulant treatment on mortality and cerebro- and cardiovascular complications in hospital survivors of acute myocardial infarction. The main results of this trial are described in *chapter 2*. Since oral anticoagulant treatment is associated with an increased risk of bleeding, we investigated if it was possible to identify subsets of patients on the basis of clinical variables during admission that would have no benefit of anticoagulant treatment. The results of this subgroup analysis are presented in *chapter 3*. In *chapter 4*, results of earlier studies that assessed the merits of oral anticoagulant treatment in

post myocardial infarction patients are pooled to combine the statistical power of the studies in a cumulative meta-analysis. *Chapter 5* compares the prognostic factors and survival of ASPECT participants and eligible non-participants as to provide insight in the kind and magnitude of selection of patients for the ASPECT trial. Because oral anticoagulant treatment requires regular monitoring, it is generally thought to be expensive. In *chapter 6* the medical costs associated with the use of oral anticoagulant treatment after myocardial infarction in our study population are estimated and compared with the medical costs of placebo patients.

References

1. Thom TJ. International mortality from heart disease: Rates and trends. Int J Epidemiol 1989; 18(suppl 1):S20-8.
2. Sytkowski PA, Kannel WB, d'Agostino RB. Changes in risk factors and the decline in mortality from cardiovascular disease. N Engl J Med 1990; 322:1635-41.
3. Steinberg D, Parthasarathy S, Carew T, Khoo J, Witztum J. Beyond cholesterol. Modifications of low-density lipoprotein that increases its atherogenicity. N Engl J Med 1989; 320:915-24.
4. Stary H. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis 1989; 9:1-19.
5. Davies M, Woolf N, Rowles P, Pepper J. Morphology of the endothelium over atherosclerotic plaques in human coronary arteries. Br Heart J 1988; 60:459-64.
6. Burrig K. The endothelium of advanced arteriosclerotic plaques in human. Arterioscl Thromb 1991; 11:1678-89.
7. Falk E. Why do plaques rupture? Circulation 1992;86[suppl III]:III-30-III-42.
8. Van der Wal AC, Becker AE, Van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation 1994; 89:36-44.
9. Mann KG, Nesheim ME, Church WR, Haley P, Krishnaswamy S. Surface dependent reactions of the vitamin K-dependent enzyme complexes. Blood 1990; 76:1-16.
10. Stenflo J, Suttie JW. Vitamin K-dependent formation of gamma carboxyglutamic acid. Ann Rev Biochem 1977; 46:68-73.
11. Hemker HC, Muller AD. Kinetic aspects of the interaction of blood-clotting enzymes. VI. Localization of the site of blood-coagulation inhibition by the protein induced by vitamin K absence (PIVKA). Thromb Diath Haemorrh 1968; 20:78-87.

12. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980; 303:897-902.

13. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. Am J Cardiol 1979; 44:53-9.

Chapter 2

Effect of long-term oral anticoagulant therapy on mortality and cardiovascular morbidity after myocardial infarction

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Abstract

The use of long-term oral anticoagulant treatment after myocardial infarction remains controversial because of conflicting findings on mortality in previous trials and the increased risk of bleeding associated with anticoagulants.

We have carried out a randomised, placebo-controlled, double-blind, multi-centre trial in 3,404 hospital survivors of myocardial infarction. Eligible patients were randomly assigned to anticoagulant (acenocoumarol or phenprocoumon) or placebo treatment within 6 weeks after discharge. The target prothrombin time was 2.8-4.8 international normalised ratio. During mean follow-up period was 37 months (range 6-76 months), there were 170 deaths among 1,700 anticoagulant-treated patients and 189 in 1,704 placebo-treated patients (hazard ratio 0.90 [95% CI 0.73-1.11]). Anticoagulant treatment led to significant reductions by comparison with placebo treatment in recurrent myocardial infarction (114 vs 242 patients; hazard ratio 0.47 [0.38-0.59]) and cerebro-vascular events (37 vs 62; 0.60 [0.40-0.90]). Major bleeding complications were seen in 73 patients who received anticoagulants and 19 who received placebo.

We conclude that long-term anticoagulant treatment after myocardial infarction in low risk patients has a limited effect on mortality but achieves substantial benefit by reducing the risk of cerebro-vascular events and recurrent myocardial infarctions.

Introduction

Patients who have sustained myocardial infarction are at increased risk of subsequent cardiovascular morbidity and death.[1] After the discovery of the anticoagulant effect of coumarin derivatives, many clinical trials were carried out in the 1950s and 1960s to assess the efficacy of oral anticoagulants in the prevention of cardiovascular complications and death after myocardial infarction. The results of these trials were conflicting. Good results in some trials were questioned because of poor study design,[2-5] whereas inadequate anticoagulation in other trials could have obscured positive effects.[6] The debate was revived in 1980 by the Sixty Plus Reinfarction Study, which showed an increase in cardiovascular complications when long-term oral anticoagulant therapy after myocardial infarction was withdrawn.[7] Although that trial showed that withdrawal was detrimental, it provided no evidence that initiation of oral anticoagulant treatment after myocardial infarction was beneficial. A 1990 trial of post-infarction patients in Norway found substantial reductions in mortality (34%), and stroke (55%) with anticoagulant therapy by comparison with placebo.[8]

We report here the results of a randomised, double-blind, placebo-controlled trial that assessed the effect of long-term oral anticoagulant treatment on mortality in 3,404 hospital survivors of myocardial infarction. Secondary endpoints were vascular death, recurrent myocardial infarction, cerebro-vascular events and bleeding complications.

Patients and Methods

Design

Hospital survivors of acute myocardial infarction were enroled in the trial from 60 Dutch hospitals from between September, 1986, and December, 1991. Patients were required to have rises in cardiac enzyme activities at least to twice the upper limit of normal with a typical serial pattern. Criteria for exclusion were an indication for oral anticoagulant treatment (e.g. left ventricular thrombus or aneurysm, chronic atrial fibrillation, cardiomyopathy), anticoagulant therapy within the six months before the qualifying myocardial infarction, increased bleeding tendency, anticipated coronary revascularisation procedure, malignant disease with poor prognosis, mental disorder, pregnancy, or oral anticoagulant treatment of other household members.

After informed consent had been obtained at hospital discharge, the patient was referred to a regional thrombosis centre, a specialised centre for the monitoring of coumarin therapy of outpatients. At thrombosis centres patients were randomly assigned to treatment with a coumarin derivative or matching placebo. The choice of anticoagulant (acenocoumarol or phenprocoumon), was made before randomisation at the discretion of the referring cardiologist in consultation with the thrombosis centre. Trial medication was started as soon as possible after hospital discharge but not later than six weeks afterwards; it was continued until the end of the trial (June 30, 1992). After the randomisation visit the patient was seen at the thrombosis centre once or twice a week until the prothrombin time was within the target range of 2.8-4.8 international normalised ratio (INR).[9,10] At every visit to the thrombosis centre, a short history was taken and a blood sample was drawn for measurement of the prothrombin time by Thrombotest.[11] The time between visits was gradually lengthened to a maximum of eight weeks unless dose adjustment necessitated more frequent visits. A computer dose system at the thrombosis

centres made it possible to give identical dosage instructions and management of placebo and actively treated patients. Treatment allocation was double-blind. While on trial medication, patients were strongly advised not to take other anti-thrombotic medication. The study was approved by the Ethics Committees of the participating hospitals.

Clinical Events

The clinical events were death, recurrent myocardial infarction, cerebro-vascular events, and major bleeding. *Death* was classified as vascular or non-vascular. Vascular death included instantaneous or sudden death (all deaths occurring within 1 hour of onset of symptoms), unobserved and unexpected death, fatal recurrent myocardial infarction (death within 28 days after recurrent myocardial infarction), and death due to congestive heart failure, cerebro-vascular events, or extracranial bleeding. All other deaths were considered non-vascular. *Recurrent myocardial infarction* was diagnosed in the presence of at least two of a history of chest discomfort lasting longer than 30 min, serial cardiac enzyme pattern typical of myocardial infarction with at least one activity more than twice the upper limit of normal, or the development of new Q-waves (>0.03 s) on the standard 12-lead electrocardiogram. Patients who survived the onset of symptoms of an acute myocardial infarction for at least 1 h but died subsequently were classified as having suffered a recurrent myocardial infarction. *Cerebro-vascular events* were classified as infarction or bleeding on the basis of the computed tomography scan or, if this was not available, as unspecified. If death occurred within 24 h of the onset of an unspecified cerebro-vascular event, a diagnosis of intracranial bleeding was made.[12] Functional outcome at discharge of stroke survivors was classified as no disability, mild, moderate, or severe disability.[13] Cerebro-vascular lasting less than 24 h and leaving no residual symptoms were classified as transient ischaemic attacks. *Vascular event* was the composite endpoint of vascular death, recurrent

myocardial infarction, or cerebro-vascular event. *Major bleeding* was defined as intracranial or fatal bleeding or any bleeding that led to admission for hospital treatment. All events were reviewed by the members of the classification committee unaware of treatment allocation on the basis of a standard patient report.

Data Analysis

The primary endpoint was death from any cause and the secondary endpoints were vascular death, recurrent myocardial infarction, cerebro-vascular event, vascular event, and major bleeding. The main analysis considered all randomised patients irrespective of the actual therapy at the time of the endpoint ("intention-to-treat" analysis). In this analysis, the incidence of endpoints was compared in terms of the hazard ratio (the risk of the endpoint per unit of time for patients assigned to oral anticoagulant treatment divided by the risk for those assigned to placebo treatment). Hazard ratios were calculated by the Cox proportional-hazards model.[14] For intention to treat analysis, censoring was applied when the patient died or at the end of follow up on June 30, 1992. For the "per-protocol" analysis we included only endpoints that occurred while the patient was on trial medication or within 28 days after its withdrawal. The size of the trial was such that 10% mortality in the placebo group could be distinguished from 7.5% mortality in the anticoagulant group with 80% power and a two-sided P value less than 0.05. The Data Monitoring Committee once a year sought evidence of beneficial or adverse effects of therapy according to a predefined statistical stopping guideline.[15]

Quality control of the anticoagulant effect was assessed by two methods. The cumulative method assessed the proportion of all prothrombin times that were within the target range. The other method assessed the proportion of time patients spent with the INR within the target range by taking a cross-section of the prothrombin times at four predefined times.[16]

Results

Patients

Between Sept 1, 1986 and Dec 31, 1991 we randomised 3,404 patients from 60 hospitals in the Netherlands at 19 regional thrombosis. The mean follow-up period was 37 (6-67) months. No patient was lost to follow-up. There were no differences in base-line characteristics between the treatment groups (table 1). 9% of patients had had a previous myocardial infarction and 25% received thrombolytic agents during the index admission. ß-blockers were prescribed to 51% of the patients at discharge. More than 90% of patients underwent randomisation within 2 weeks of discharge, and the median time from discharge to randomisation was 4 days.

The coumarin chosen before randomisation was phenprocoumon in 55 patients in each group and acenocoumarol in 45 of each group.

In the actively treated group 5,241 patient-years of follow up were accumulated for the 1,700 patients; in the placebo group there were 5,200 patient-years of follow up for 1,704 patients.

During follow-up there were 170 deaths in the actively treated group and 189 in the placebo-treated group (table 2), a reduction of 10%. (hazard ratio 0.90 [95% CI 0.73-1.11]; table 3). There were 3 fatal episodes of extracranial bleedings (all gastrointestinal) in the anticoagulant group. Survival is shown in figure 1.

Anticoagulant treatment significantly reduced the risk of recurrent myocardial infarction (tables 2 and 3). More than one recurrent myocardial infarction occurred in 13 anticoagulated-treated and 34 placebo-treated patients. Anticoagulant treatment also reduced the risk of a first cerebro-vascular event (tables 2 and 3). Cerebral infarction occurred in 15 anticoagulant treated (2 fatal) and 43 placebo-treated patients (2 fatal) patients. However, cerebral haemorrhage was more common among anticoagulant treated patients (17 cases, 8 fatal) than among

Table 1. Baseline characteristics of the randomised patients.*

	AC (n=1700)	Placebo (n=1704)
Mean age (yr ±SD)	61 (±11)	61 (±11)
Male (%)	81	79
Randomization delay† (%)		
< 2 wk	92	94
2-4 wk	5	4
4-6 wk	3	2
Previous myocardial infarction (%)	9	9
Diabetes mellitus (%)	8	7
Current smokers (%)	53	52
Thrombolytic agents used (%)	25	25
Aspirin during admission (%)	28	28
Highest enzyme values (median and 25% -75% quartiles)‡		
CK	7.5 (4.3-13.2)	7.1 (4.1-12.4)
ASAT	4.6 (2.7- 7.6)	4.4 (2.6- 7.3)
LD	2.5 (1.7- 3.6)	2.4 (1.6- 3.5)
Q-wave infarction (%)§	77	77
Anterolateral	46	46
Inferoposterior	54	54
Killip class III or IV (%)‖	5	5
B-Blocking agents at discharge (%)	51	51
Coumarin congener (%)		
phenprocoumon	55	55
acenocoumarol	45	45

* No significant differences were detected for any of the comparisons shown.
AC denotes anticoagulants, CK creatine kinase, ASAT serum aspartate aminotransferase and LD lactate dehydrogenase.
†Time from hospital discharge to randomisation.
‡ Expressed as multiple of the upper limit of normal.
§Q-waves ≥0.03 sec and ≥0.1 mV.
‖Highest Killip or MIRU class reached in hospital.

placebo-treated patients (2 cases, neither fatal). Unspecified strokes occurred in 4 anticoagulant group (1 fatal) and 12 in the placebo group (6 fatal). Of the 25 survivors of stroke in the anticoagulated group, 7 (28%) were moderately or severely disabled at discharge, compared with 19 (39%) of the 49 survivors of stroke in the placebo group. There was a significant reduction with anticoagulation in the endpoint "vascular event" (tables 2 and 3).

Major bleeding complications were more common in the anticoagulant group than in the placebo treated group. Gastro-intestinal bleedings accounted for about half of the extracranial major bleedings episodes.

Table 2. Incidence of major clinical events during follow-up ("intention-to-treat" analysis)

	AC	Placebo	
Number of patients	1700	1704	
Years of follow-up	5241	5200	
	Events (event rate)	Events (event rate)	HR (95% C.I.)†
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)
Recurrent MI	114 (2.3/100py)	242 (5.1/100py)	0.47 (0.38-0.59)
Cerebro-vascular event	37 (0.7/100py)	62 (1.2/100py)	0.60 (0.40-0.90)
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)

HR, hazard ratio; CI, confidence interval; py, patient-years; MI, myocardial infarction.
†Endpoints 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/cerebro-vascular event whichever event occurred first.
§Intracranial/extracranial bleeding whichever event occurred first.

Table 3. Contribution of events to clinical endpoints

	AC	Placebo
	Number of Events	
Vascular death	134	142
Instantaneous/Sudden	*57*	*43*
Unobserved/Unexpected	*12*	*21*
Recurrent MI	*24*	*40*
Congestive heart failure	*27*	*30*
Cerebro-vascular event	*11*	*8*
Extracranial bleeding	*3*	*0*
Cerebro-vascular event	37	62
Intracranial bleeding	*17*	*2*
Cerebral infarction	*15*	*43*
Unspecified	*4*	*12*
Transient ischaemic attack	*2*	*6*
Major extracranial bleeding	56	17
Gastrointestinal	*33*	*8*
Muscular	*8*	*1*
Other	*15*	*8*

MI, myocardial infarction.

Event-free survival, including the occurrence of major bleeding, is shown in figure 2. At 3 years of follow-up event-free survival was significantly higher in the anticoagulant group than in the placebo group 83 vs 76% $p < 0.0001$, log-rank test). The findings of the per-protocol analyses are given in table 4.

Table 4. Incidence of major clinical events during follow-up ("per protocol" analysis)*

	AC	Placebo	
Number of patients	1700	1704	
Years of follow-up	3725	3488	
	Events (event rate)	Events (event rate)	HR (95% C.I.)†
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)
Recurrent MI	86 (2.3/100py)	207 (6.1/100py)	0.41 (0.32-0.53)
Cerebro-vascular event	24 (0.6/100py)	42 (1.2/100py)	0.57 (0.34-0.93)
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)

HR, hazard ratio; CI, confidence interval; py, patient-years; MI, myocardial infarction.
*Endpoints 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/cerebro-vascular event whichever event occurred first.
§Intracranial/extracranial bleeding whichever event occurred first.

Table 5. Reasons for discontinuation of trial medication

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

By the cumulative method to assess adequacy of the anticoagulant treatment (57,634 measurements), 62% of prothrombin times were within the target range; 29% were below 2.8 INR and 9% were above 4.8 INR. By the cross-sectional method (1,172 measurements) we calculated that for 74% of patients' time, coagulation was within the therapeutic range (< 2.8 INR for 20% and > 4.8 INR for 6% of the time). The commonest reasons for discontinuation of study medication are shown in table 5. After 3 years about half of the patients in each group had discontinued trial medication, mostly for non-medical reasons. Overall, patients were on trial medication for 71% of time in the anticoagulant group and for 67% in the placebo group.

Discussion

We have found that long-term oral anticoagulant treatment has only a moderate effect on mortality but strongly reduces cardiac and cerebro-vascular morbidity after myocardial infarction. The 10% mortality reduction we observed is much smaller than the 24% reduction in the Norwegian trial.[8] In that trial mortality after mean follow-up of 3 years in placebo-treated patients was 20%, compared with 11% in our trial. The better outcome in our placebo-treated patients may be due to better left-ventricular function at baseline,[17,18] or to recent improvements in medical care during the acute phase of (recurrent) myocardial infarction, leading to a lower fatality rate.[19-21] The significant reduction in recurrent myocardial infarction in anticoagulant-treated patients accords with previous reports; it is due mainly to a much lower rate of non-fatal reinfarction.

The increased risk of haemorrhagic stroke associated with long-term oral anticoagulant treatment has probably contributed to its limited use after myocardial infarction.[22,23] Although we observed a higher rate of haemorrhagic stroke in anticoagulant-treated patients, overall stroke incidence was reduced by 40% mainly because of a 65% lower rate of ischaemic stroke. Altogether, the incidence of fatal stroke in the two groups was similar, but the proportion of stroke survivors with moderate or severe disability at discharge was higher in placebo group. Thus, though the number of strokes in this trial was low, we suggest that anticoagulant treatment reduces the frequency of non-fatal stroke and improves subsequent functional outcome.

The 35% reduction in vascular events by oral anticoagulant treatment is equivalent to the prevention of 3 vascular events per 100 patient-years at the cost of one major bleeding event. The rate of bleeding complications (1.5 per 100 patient-years) is similar to findings of previous studies.[8,24] The consistency of these data confirms the relative safety of long-term anticoagulant therapy with an INR range of 2.8-4.8,

provided adequate quality of oral anticoagulant treatment is achieved.

It is difficult to assess the clinical impact of such diverse events as bleeding and thrombo-embolic complications. In an attempt to estimate the relative importance of such complications, Braunwald et al. have proposed an "unsatisfactory-outcome" endpoint score,[25] to which cardiovascular complications during follow-up contribute an arbitrary weight varying from one (death) to zero (no events). If we use this weighting system for the major endpoints, the score was 24% lower in the anticoagulant group than in the placebo group. Although it was primarily intended to compare the effects of different thrombolytic agents, we believe that this score supports our findings.

Since this trial did not include patients treated with aspirin, no efficacy estimates for the comparison of anticoagulant and aspirin treatment can be derived from our data. The efficacy of long-term oral anticoagulant treatment and of aspirin after myocardial infarction has been directly compared in a few trials,[26,27] but interpretation is limited by the open design and small size of these trials. Also, results may have been affected by poor quality of anticoagulation. We believe that a trial is now warranted that directly compares the efficacy and safety of long-term aspirin and coumarin treatment in a large group of patients who have sustained myocardial infarction.

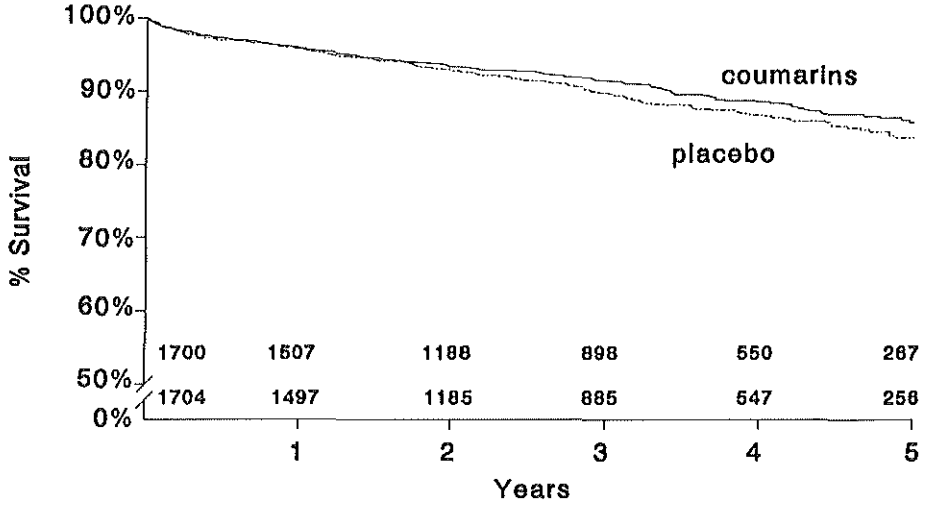

Figure 1. Kaplan-Meier curves for death from any cause, according to assigned therapy. Numbers denote patients at risk (anticoagulated patients in top).

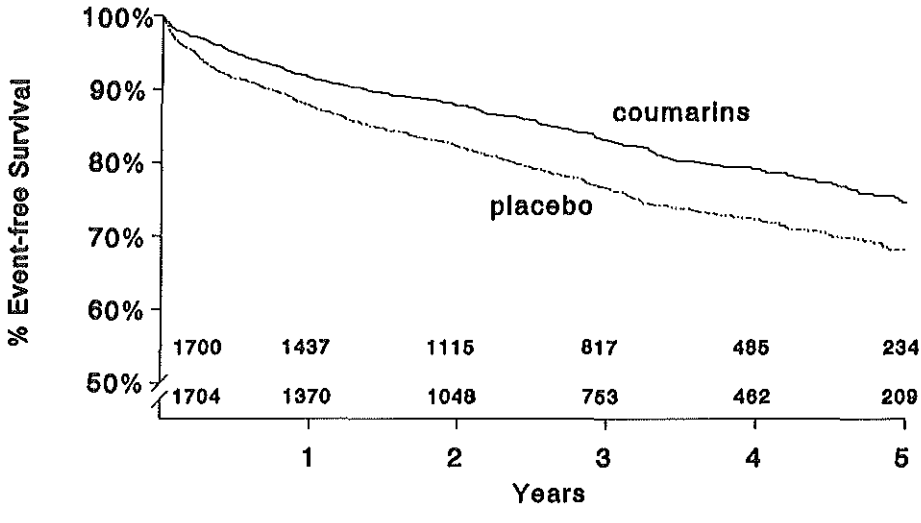

Figure 2. Kaplan-Meier curves for death, non-fatal myocardial infarction, non-fatal cerebro-vascular event or major bleeding, whichever occurred first, according to assigned therapy.

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References

1. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. Am J Cardiol 1979; 44:53-9.
2. Merskey C, Drapkin A. Anticoagulant therapy after myocardial infarction; Analytical review. Blood 1965; 25:567-96.
3. Gifford RH, Feinstein AR. A critique of methodology in studies of anticoagulant therapy for acute myocardial infarction. N Eng J Med 1969; 280:351-7.
4. Gross H, Vaid AK, Levine HS, et al. Anticoagulant therapy in myocardial infarction. Am J Med 1972; 52:421-4.
5. Goldman L, Feinstein AR. Anticoagulants and myocardial infarction. The problems of pooling, drowning and flooting. Ann Intern Med 1979; 90:92-4.
6. Loeliger EA. Letter to the Editors. Eur J Clin Pharmacol 1984; 25:137-9.
7. The Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant treatment in elderly patients after myocardial infarction. Lancet 1980; ii:989-93.
8. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-52.
9. Loeliger EA. The optimal therapeutic range in oral anticoagulation. History and proposal. Thromb Haemostas 1979; 42:1141-52.
10. Loeliger EA, Poller L, Samana M, et al. Questions and answers on prothrombin time standardization in oral anticoagulant control. Thromb Haemostas 1985; 54:515-7.
11. Owren PA. Thrombotest. A new method for controlling anticoagulant treatment. Lancet 1959; ii:754-8.
12. Phillips LH, Whisnant JP, Reagan TJ. Sudden death from stroke. Stroke 1977; 8:393-5.
13. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients.

Stroke 1988; 19:512-7.

14. Cox DR. Regression models and life tables. J Stat Soc 1972; 34:187-202.
15. Van Es G, Tijssen JGP, Lubsen J. Early termination of clinical trials with prolonged observation of individual patients: a case study.
Stat Med 1987; 6:927-37.
16. Besselaar van den AMHP, Meer van der FJM, Gerrits-Drabbe CW. Therapeutic Control of Oral Anticoagulant Treatment in the Netherlands.
Am J Clin Path 1988; 90:685-90.
17. Norris RM, Caughey DE, Deening LW, Mercer CJ, Scott JP. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. Lancet 1970; ii:485-8.
18. The Multicenter Postinfarction Research group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983; 309:331-6.
19. ISIS-2 Collaborative group. A randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. Lancet 1988; ii;349-60.
20. GISSI. Effectiveness of intravenous thrombolytic therapy in acute myocardial infarction. Lancet 1986; i:397-402.
21. Pfeffer MA, Braunwald E, Moyé LA et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992; 327:669-77.
22. Wintzen AR, Jonge de H, Loeliger EA, Bots GTAM. The risk of intracerabral hemorrhage during oral anticoagulant treatment: a population study.
Ann Neurol 1984; 16:553-8.
23. Franke CL, Jonge de H, Swieten van JC, Op de Coul AAW, Gijn van J. Intracerebral hematomas during anticoagulant therapy.
Stroke 1990; 21:726-30.
24. Risks of long-term oral anticoagulant treatment in elderly patients after myocardial infarction. Second report of the Sixty Plus Reinfarction Study Research Group.
Lancet 1982; i:64-8.

25. Braunwald E, Cannon CP, McCabe CH. An approach to evaluating thrombolytic therapy in acute myocardial infarction; the 'unsatisfactory outcome' end point. Circulation 1992; 86:683-87.
26. Breddin K, Loew D, Lechner K, Ueberla K, Walter E. Secondary prevention of myocardial infarction: a comparison of acetylsalicylic acid, placebo and phenprocoumon. Haemostasis 1980; 9:325-44.
27. The E.P.S.I.M. Research group. A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction. N Eng J Med 1982; 307:701-8.

Chapter 3

Efficacy of long-term anticoagulant therapy in subgroups of post myocardial infarction patients

British Heart Journal, in press

Abstract

Determination of clinical variables that identify subsets of patients who do not benefit from anticoagulant treatment could preclude them from unnecessary exposure to the potentially adverse effects of treatment.

We analyzed the effect of anticoagulant treatment in subgroups of hospital survivors of myocardial infarction according to age, gender, history of hypertension, previous myocardial infarction, smoking habits, diabetes mellitus, Killip class, anterior location of infarction, thrombolytic therapy, and ß-blockers on the occurrence of recurrent myocardial infarction, cerebro-vascular event, vascular event (the composite endpoint of reinfarction, cerebro-vascular event and vascular death) and death from any cause.

None of the investigated subgroups of patients showed significantly lesser beneficial effect from treatment for any of the clinical endpoints. The effect of treatment with respect to vascular event appeared to be smaller in females compared to men (-11% vs -45%) and in diabetics compared to non-diabetics (-14% vs -42%). In a multivariate analysis higher age, previous myocardial infarction, diabetes mellitus, the use of thrombolytic agents and heart failure during admission were independently associated with an increased occurrence of cardiovascular complications during follow-up.

The relative benefit of long-term oral anticoagulant therapy in survivors of myocardial infarction is not modified by known prognostic factors for cardiovascular disease.

Introduction

Patients who survive an acute myocardial infarction carry an increased risk of arterial thrombo-embolism. Recent clinical trials have proven that long-term oral anticoagulant treatment with a target international normalised ratio (INR) of 2.8-4.8 reduces the incidence of such complications.[1,2] However, oral anticoagulant treatment has also been associated with an increased risk of bleeding complications which can sometimes be fatal or cause severe disability as in the case of intracranial haemorrhage.[3-5] Determination of clinical variables that identify subsets of patients who do not benefit from anticoagulant treatment could preclude them from unnecessary exposure to the potentially adverse effects of treatment. Results of a recent subgroup analysis of the Warfarin Re-infarction Study indicated that the presence of diabetes mellitus and previous myocardial infarction could offset the beneficial effect of long-term warfarin treatment. In addition, it was also suggested that older patients had a relatively smaller benefit from treatment.[6] The ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial investigated the effect of protracted anticoagulant treatment relative to placebo in hospital survivors of myocardial infarction. In view of the results of the WARIS subgroup analysis and their important implications we performed a subgroup analysis of the ASPECT patients.

Methods

Patients

The present analysis is based on data of patients enroled in the ASPECT (Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis) trial. Details of this randomised, double-blind, placebo-controlled trial that assessed the efficacy of long-term anticoagulant therapy after myocardial infarction have been published previously.[2] In short, the ASPECT trial comprised 3,404 hospital survivors of an

acute myocardial infarction who were randomised between September 1, 1986 and December 31, 1991 to oral anticoagulant therapy with a coumarin derivative (phenprocoumon or acenocoumarol) or matching placebo within on average 4 days of discharge. To become eligible, patients required a cardiac enzyme level elevation of at least twice the upper reference limit. Patients with an indication for oral anticoagulant therapy (e.g. chronic atrial fibrillation, left ventricular thrombus or aneurysm, or cardiomyopathy), or who were on anticoagulant treatment within a period of six months preceding the qualifying myocardial infarction, with increased bleeding tendency, anticipated revascularisation procedure, malignant disease with poor prognosis, mental disorder, pregnancy, or other household members receiving oral anticoagulant therapy were not eligible. Oral anticoagulant therapy was adjusted individually, with a prothrombin's target range of 2.8-4.8 INR. Treatment allocation was double-blind. Trial medication was continued until the end of the trial follow-up on June 30, 1992. The median duration of follow-up was 37 months. The major clinical outcome events were as follows: death occurred in 170 of the 1,700 anticoagulated patients and in 189 of the 1,704 placebo patients, a reduction of 10% (95% confidence interval -11 to 27%). Recurrent myocardial infarction was observed in 114 anticoagulated patients versus 242 placebo patients, a reduction of 53% (41 to 62%) and cerebro-vascular event in 37 anticoagulated patients versus 62 placebo patients, a reduction of 40% (10 to 60%). Any vascular event occurred in 239 anticoagulated patients versus 366 placebo patients, a reduction of 35% (24 to 45%). The study was approved by the ethical committees of the participating hospitals and all patients had given oral informed consent.

Events

The following endpoints were considered: recurrent myocardial infarction, cerebro-vascular event, vascular event and death from any cause. *Recurrent myocardial infarction* was defined as a history of chest discomfort with a duration

exceeding 30 minutes and serial enzyme pattern typical for myocardial infarction with at least one cardiac enzyme exceeding twice the upper reference limit, or the development of new Q-waves (>0.03 secs) on the standard 12-lead electrocardiogram. Patients who survived the onset of symptoms of an acute myocardial infarction for at least one hour and died subsequently were also classified as having suffered a recurrent myocardial infarction. *Cerebro-vascular event* included haemorrhagic and ischaemic stroke and transient ischaemic attack. *Vascular event* was defined as the composite endpoint of either vascular death, recurrent myocardial infarction or cerebro-vascular event. All clinical events were blindly classified by a Mortality and Morbidity Classification Committee.

Data Analysis

Effect estimates of anticoagulant treatment in subgroups of variables known to affect long-term prognosis were calculated using the Cox model with the endpoint as the independent variable. Differences in effect of anticoagulant treatment in subgroups were investigated by the introduction of interaction terms in the model. In addition, interaction with anticoagulant therapy on the respective outcome events was assessed by a statistical comparison of the difference of coefficients associated with anticoagulant therapy. The same variables were also introduced in a multivariate Cox proportional-hazards model to assess their independent association using the predefined endpoint as the independent variable. The following variables were considered for inclusion in the model: anticoagulant treatment, age, gender, smoking status on admission, diabetes (defined as a history of diabetes with hypoglycaemic medication at discharge), history of hypertension, previous myocardial infarction, highest Killip class during admission, anterior location of infarction, administration of thrombolytic agents, and the use of ß-blockers at discharge.

All analyses were performed according to the "intention-to-treat" principle. *P*-values < 0.05 were considered significant.

Results

Patients

Baseline characteristics of the patients are presented in Table 1. No differences were observed between the therapy groups for any of the baseline variables. In both treatment groups, 9% of the patients had suffered a previous myocardial infarction before enrolment, while approximately 25% of the patients was treated with thrombolytic agents. In either group, 5% of the patients had suffered moderate to severe heart failure during hospital admission.

Table 1. Baseline characteristics of randomised patients, according to therapy group.

	Placebo (n=1700)	Anticoagulants (n=1704)
Mean age (yr ±SD)	61 (± 11)	61 (± 11)
Male (%)	79	81
Randomization delay† (%)		
< 2 wk	94	92
2-6 wk	6	8
Previous myocardial infarction (%)	9	9
Diabetes mellitus (%)	7	8
Current smokers (%)	52	53
Thrombolytic agents used (%)	25	25
Highest enzyme values as ratio of reference (median and 25% -75% quartiles)‡		
CK	7.1 (4.1-12.4)	7.5 (4.3-13.2)
ASAT	4.4 (2.6- 7.3)	4.6 (2.7- 7.6)
LD	2.4 (1.6- 3.5)	2.5 (1.7- 3.6)
Q-wave infarction (%)§		
No	23	23
Yes	77	77
Anterolateral	46	46
Inferoposterior	54	54
Killip class III or IV (%)‖	5	5
B-Blocking agents at discharge (%)	51	51

AC denotes anticoagulated, CK creatine kinase, ASAT serum aspartate aminotransferase and LD lactate dehydrogenase.
†Time from hospital discharge to randomization.
‡ Expressed as multiple of the upper limit of normal.
§Q-waves ≥0.03 sec and ≥0.1 mV.
‖Highest Killip or MIRU class reached in hospital.

Treatment effect in subgroups

The relative effects of anticoagulant treatment within subgroups on the occurrence of various outcome events are shown in Tables 3 through 6. Relative reductions and statistical limits within subgroups are graphically displayed in Figures 1 through 4. The effect of treatment on reinfarction over the strata was fairly homogeneous, with some attenuation of the treatment effect in women and patients with prior myocardial infarction (Table 3). For instance, the risk (hazard) of recurrent myocardial infarction associated with anticoagulant therapy in women was 0.59 (95% confidence intervals 0.36, 0.96), indicating a risk reduction of 41% relative to an observed risk reduction of 59% in men. Anticoagulant treatment appeared to have a smaller effect on cerebro-vascular events in patients with diabetes or hypertension but, due to the lower incidence of cerebro-vascular complications, the confidence intervals of the effect estimates were wider than for recurrent myocardial infarction (Table 4). This was in particular true for the number of cerebro-vascular events in subjects aged below 65 years. Obviously, the composite diagnosis vascular event included the highest number of endpoints (Table 5). The calculated effect estimates suggested a particularly modest effect of treatment in women (risk reduction 11%, 95% CI -25%, 36%) and in patients with diabetes mellitus (risk reduction 14%, 95% CI -36%, 45%), compared to risk reductions of 45% in men and 42% in non-diabetics, respectively.

Anticoagulant treatment was not associated with a significant mortality reduction in any of the subgroups, although the effect estimate reached borderline significance in patients without clinical signs of acute heart failure, i.e. Killip class 1 (Table 6).

Interaction of subgroups with treatment

Introduction of interaction terms in the model provided no evidence for interaction of the selected variables with the effect of anticoagulant treatment for any of the endpoints. In accordance with these results, no effect modification could be

demonstrated in patients with previous myocardial infarction, diabetes and female gender by comparison of the coefficients in these subgroups.

Predictors of events

Results of the multivariate analysis are presented in Table 2. After adjustment, anticoagulant treatment was associated with a 56% lower incidence of recurrent myocardial infarction (Relative Risk 0.44, 95% Confidence Interval 0.35, 0.55). Previous myocardial infarction, higher age, the presence of diabetes and the use of thrombolytic therapy were significantly associated with a higher incidence of recurrent myocardial infarction during follow-up. In a similar way, anticoagulant treatment was associated with a 39% lower incidence of cerebro-vascular events, while increasing age and diabetes were independent predictors of this outcome. The strongest predictors of death were higher age, diabetes, heart failure and previous myocardial infarction, while the use of ß-blockers proved to be protective towards mortality.

Table 2. Adjusted risk estimates (and 95% confidence intervals) of prognostic factors in post myocardial infarction patients

	Recurrent MI RR (95% CI)		Cerebro-vascular Event RR (95% CI)		Vascular Event RR (95% CI)		Mortality RR (95% CI)	
Anticoagulant therapy	0.44	(0.35,0.55)	0.61	(0.40,0.92)	0.61	(0.52,0.72)	0.90	(0.73,1.11)
Age (increment of 1 year)	1.02	(1.01,1.03)	1.05	(1.03,1.08)	1.03	(1.02,1.04)	1.07	(1.05,1.08)
Previous MI	2.00	(1.47,2.64)	1.08	(0.57,2.07)	1.79	(1.43,2.26)	1.67	(1.25,2.23)
Diabetes	1.45	(1.03,2.05)	2.32	(1.39,3.90)	1.59	(1.24,2.04)	1.34	(0.96,1.85)
Thrombolysis	1.42	(1.09,1.85)	0.69	(0.36,1.32)	1.01	(0.82,1,25)	0.73	(0.53,1.02)
Killip class > 1	1.02	(0.81,1.28)	0.88	(0.58,1.36)	1.22	(1.03,1.45)	1.67	(1.35,2.08)
ß-Blockers	0.97	(0.78,1.21)	1.29	(0.85,1.95)	0.86	(0.73,1.07)	0.70	(0.56,0.87)
Male gender	1.10	(0.84,1.45)	0.72	(0.46,1.14)	1.00	(0.81,1.21)	1.06	(0.82,1.37)
Smoking	1.06	(0.85,1.33)	0.95	(0.61,1.48)	1.00	(0.84,1.19)	1.09	(0.86,1.36)
Hypertension	1.06	(0.82,1.37)	1.19	(0.76,1.87)	1.11	(0.91,1.34)	1.16	(0.90,1.48)
Anterior infarction	0.91	(0.71,1.17)	0.96	(0.60,1.53)	1.04	(0.87,1.26)	1.08	(0.75,1.37)

RR: Relative Risk, CI: Confidence Interval

Table 3. Effect of anticoagulant treatment on Recurrent Myocardial Infarction in subgroups.

VARIABLE	RECURRENT MYOCARDIAL INFARCTION					
	PLACEBO (%)		ANTICOAGULANTS (%)		HR (95% CI)	
	no. of events / no. of patients					
Age (yr)						
<55	59/490	(12.0)	30/507	(5.9)	0.47	(0.30-0.74)
55-65	82/623	(13.1)	34/601	(5.7)	0.42	(0.28-0.63)
>65	101/591	(17.0)	49/591	(8.3)	0.45	(0.32-0.64)
Sex						
Male	194/1350	(14.4)	87/1369	(6.4)	0.41	(0.32-0.54)
Female	48/354	(13.6)	26/330	(7.9)	0.59	(0.36-0.96)
Current Smoking						
No	118/816	(14.5)	58/806	(7.2)	0.48	(0.35-0.66)
Yes	124/888	(14.0)	55/893	(6.2)	0.42	(0.30-0.57)
Diabetes						
No	216/1579	(13.7)	100/1565	(6.3)	0.45	(0.35-0.57)
Yes	26/125	(20.8)	13/134	(9.7)	0.43	(0.22-0.85)
Medical history of Hypertension						
No	178/1309	(13.6)	92/1310	(7.0)	0.49	(0.38-0.64)
Yes	64/395	(16.2)	21/389	(5.4)	0.32	(0.19-0.52)
Previous Myocardial Infarction						
No	208/1554	(13.4)	90/1542	(5.8)	0.42	(0.32-0.54)
Yes	34/150	(22.7)	23/157	(14.6)	0.64	(0.36-1.05)
Killip Class						
I	151/1124	(13.4)	75/1114	(6.7)	0.48	(0.36-0.64)
≥II	91/580	(15.7)	38/585	(6.5)	0.39	(0.27-0.58)
Anterior infarction*						
No	186/1286	(14.5)	83/1299	(6.4)	0.42	(0.32-0.55)
Yes	56/418	(13.4)	30/400	(7.5)	0.54	(0.34-0.85)
Thrombolytic Therapy						
No	178/1285	(13.9)	87/1280	(6.8)	0.47	(0.36-0.61)
Yes	64/419	(15.3)	26/419	(6.2)	0.39	(0.24-0.61)
ß-blockers						
No	128/835	(15.3)	56/833	(6.7)	0.42	(0.31-0.58)
Yes	114/869	(13.1)	57/866	(6.6)	0.48	(0.34-0.66)

HR; Hazard Ratio, * defined by Q wave > 0.03 sec in V2, V3 or V4.

Table 4. Effect of anticoagulant treatment on Cerebro-vascular Event in subgroups.

VARIABLE	CEREBRO-VASCULAR EVENT					
	PLACEBO (%)		ANTICOAGULANTS (%)		HR (95% CI)	
	no. of events / no. of patients					
Age (yr)						
<55	3/490	(0.6)	7/507	(1.4)	2.26	(0.57-8.98)
55-65	19/623	(3.0)	11/601	(1.8)	0.61	(0.29-1.30)
>65	40/591	(6.8)	19/591	(3.2)	0.45	(0.26-0.78)
Sex						
Male	40/1350	(2.0)	24/1369	(1.8)	0.58	(0.35-0.98)
Female	22/354	(6.2)	13/330	(3.9)	0.65	(0.32-1.30)
Current Smoking						
No	40/816	(4.9)	20/806	(2.5)	0,51	(0.30-0.89)
Yes	22/888	(2.5)	17/893	(1.9)	0.75	(0.39-1.43)
Diabetes						
No	52/1579	(3.3)	27/1565	(1.7)	0.52	(0.32-0.83)
Yes	10/125	(8.0)	10/134	(7.5)	0.91	(0.37-2.23)
Medical history of Hypertension						
No	45/1309	(3.4)	24/1310	(1.8)	0.52	(0.31-0.86)
Yes	17/395	(4.3)	13/389	(3.3)	0.81	(0.39-1.69)
Previous Myocardial Infarction						
No	54/1554	(3.5)	34/1542	(2.2)	0.63	(0.41-0.97)
Yes	8/150	(5.3)	3/157	(1.9)	0.35	(0.09-1.35)
Killip Class						
I	38/1124	(3.3)	25/1114	(2.2)	0.61	(0.39-1.10)
≥II	24/580	(4.1)	12/585	(2.1)	0.48	(0.25-0.94)
Anterior infarction*						
No	45/1286	(3.5)	29/1299	(2.2)	0.63	(0.39-1.02)
Yes	17/418	(4.1)	8/400	(2.0)	0.50	(0.20-1.13)
Thrombolytic Therapy						
No	55/1285	(4.3)	33/1280	(2.6)	0.60	(0.38-0.92)
Yes	7/419	(1.7)	4/419	(1.0)	0.56	(0.16-1.97)
ß-blockers						
No	27/835	(3.2)	19/833	(2.3)	0.70	(0.38-1.28)
Yes	35/869	(4.0)	18/866	(2.1)	0.51	(0.28-0.91)

HR; Hazard Ratio, * defined by Q wave > 0.03 sec in V2, V3 or V4.

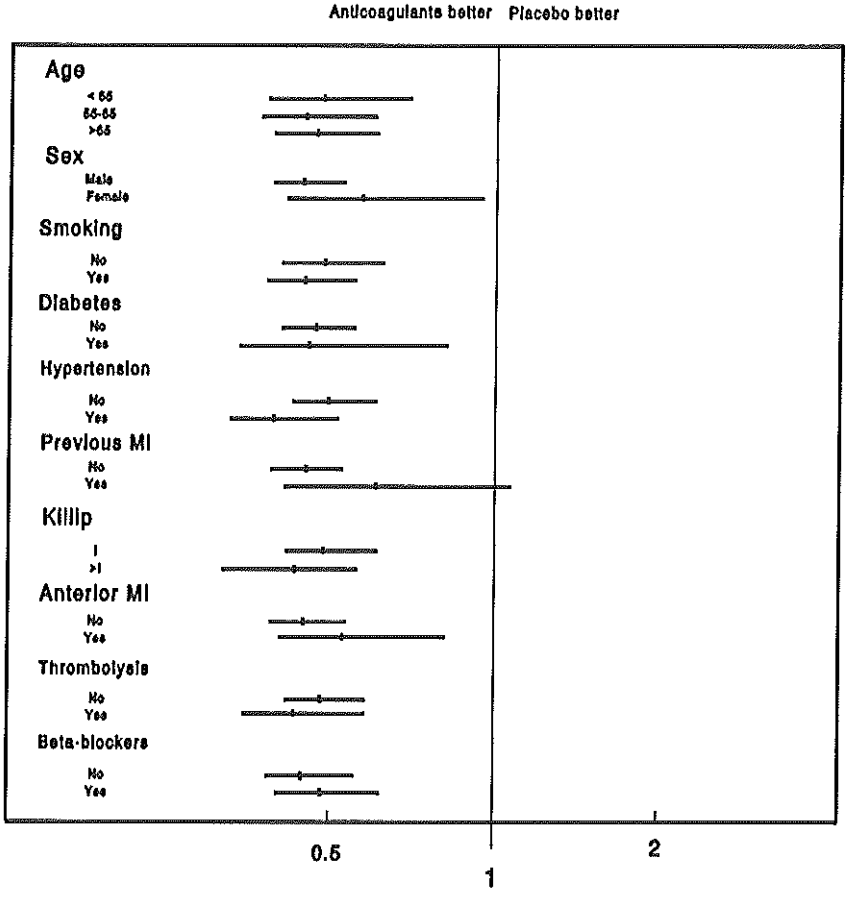

Figure 1. Effect estimates (vertical bars) and confidence intervals (horizontal bars) of oral anticoagulant treatment with respect to recurrent myocardial infarction in clinically defined subgroups of patients.

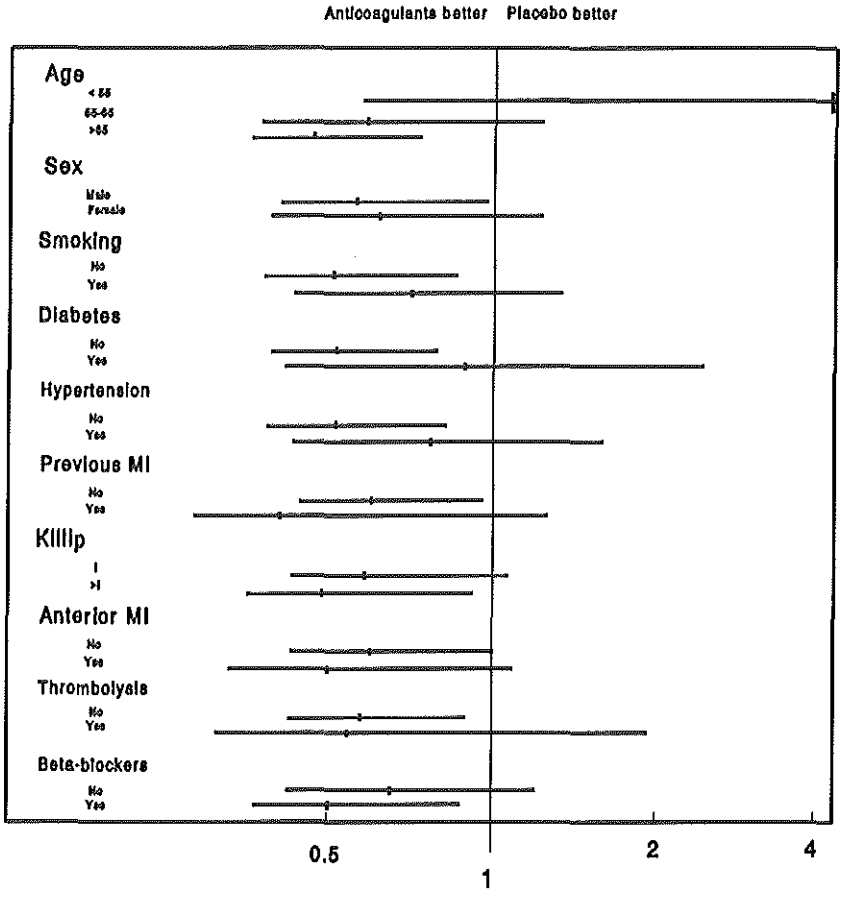

Figure 2. Effect estimates and confidence intervals of oral anticoagulant treatment with respect to cerebro-vascular event in clinically defined subgroups of patients.

Table 5. Effect of anticoagulant treatment on Vascular Event in subgroups.

VARIABLE	VASCULAR EVENT					
	PLACEBO (%)		ANTICOAGULANTS (%)		HR (95% CI)	
	no. of events / no. of patients					
Age (yr)						
<55	76/490	(15.5)	42/507	(8.3)	0.50	(0.34-0.74)
55-65	120/623	(19.3)	72/601	(12.0)	0.61	(0.45-0.82)
>65	170/591	(28.8)	124/591	(21.0)	0.65	(0.52-0.83)
Sex						
Male	286/1350	(21.2)	172/1369	(12.6)	0.55	(0.45-0.67)
Female	80/354	(22.6)	66/330	(20.0)	0.89	(0.64-1.25)
Current Smoking						
No	190/816	(23.3)	131/806	(16.3)	0.67	(0.53-0.84)
Yes	176/888	(19.8)	107/893	(12.0)	0.56	(0.44-0.72)
Diabetes						
No	327/1579	(20.7)	200/1565	(12.8)	0.58	(0.49-0.70)
Yes	39/125	(31.2)	38/134	(28.4)	0.86	(0.55-1.36)
Medical history of Hypertension						
No	275/1309	(21.0)	177/1310	(13.5)	0.49	(0.38-0.64)
Yes	91/395	(23.0)	61/389	(15.7)	0.32	(0.19-0.52)
Previous Myocardial Infarction						
No	310/1554	(19.9)	202/1542	(13.1)	0.62	(0.52-0.75)
Yes	56/150	(37.3)	36/157	(22.9)	0.55	(0.36-0.84)
Killip Class						
I	224/1124	(19.9)	130/1114	(11.7)	0.55	(0.44-0.69)
≥II	142/580	(24.5)	108/585	(18.5)	0.71	(0.55-0.91)
Anterior infarction						
No	273/1286	(21.2)	169/1299	(13.0)	0.58	(0.47-0.70)
Yes	93/418	(22.2)	69/400	(17.3)	0.73	(0.53-1.01)
Thrombolytic Therapy						
No	290/1285	(22.6)	200/1280	(15.6)	0.65	(0.54-0.78)
Yes	76/419	(18.1)	38/419	(9.0)	0.47	(0.32-0.70)
ß-blockers						
No	198/835	(23.7)	138/835	(16.6)	0.66	(0.53-0.82)
Yes	168/869	(19.3)	100/866	(11.5)	0.56	(0.43-0.72)

HR; Hazard Ratio, * defined by Q wave > 0.03 sec in V2, V3 or V4.

Table 6. Effect of anticoagulant treatment on Mortality in subgroups.

VARIABLE	MORTALITY					
	PLACEBO (%)		ANTICOAGULANTS (%)		HR (95% CI)	
	no. of events / no. of patients					
Age (yr)						
<55	24/490	(4.9)	13/507	(2.6)	0.51	(0.26-1.02)
55-65	50/623	(8.0)	47/601	(7.8)	1.01	(0.67-1.52)
>65	115/591	(19.5)	109/591	(18.4)	0.95	(0.70-1.29)
Sex						
Male	144/1350	(10.7)	122/1369	(8.9)	0.82	(0.64-1.04)
Female	45/354	(12.7)	47/330	(14.2)	1.18	(0.78-1.79)
Current Smoking						
No	109/816	(13.4)	94/806	(11.7)	0.89	(0.67-1.17)
Yes	80/888	(9.0)	75/893	(8.4)	0.91	(0.66-1.25)
Diabetes						
No	170/1579	(10.8)	144/1565	(9.2)	0.85	(0.68-1.07)
Yes	19/125	(15.2)	25/134	(18.7)	1.19	(0.65-2.19)
Medical history of Hypertension						
No	146/1309	(11.1)	121/1310	(9.2)	0.81	(0.64-1.04)
Yes	43/395	(10.9)	48/389	(12.3)	1.16	(0.76-1.76)
Previous Myocardial Infarction						
No	156/1554	(10.0)	143/1542	(9.3)	0.92	(0.73-1.16)
Yes	33/150	(22.0)	26/157	(16.6)	0.73	(0.43-1.24)
Killip Class						
I	98/1124	(8.7)	72/1114	(6.5)	0.73	(0.54-1.00)
≥II	91/580	(15.7)	97/585	(16.7)	1.06	(0.79-1.42)
Anterior infarction						
No	133/1286	(10.3)	121/1299	(9.3)	0.90	(0.70-1.15)
Yes	56/418	(13.4)	48/400	(12.0)	0.88	(0.59-1.30)
Thrombolytic Therapy						
No	166/1285	(12.9)	148/1280	(11.6)	0.88	(0.70-1.11)
Yes	23/419	(5.5)	21/419	(5.0)	0.94	(0.51-1.72)
ß-blockers						
No	93/835	(11.1)	91/833	(10.9)	1.00	(0.73-1.32)
Yes	49/869	(5.6)	42/866	(4.9)	0.85	(0.56-1.30)

HR; Hazard Ratio, * defined by Q wave > 0.03 sec in V2, V3 or V4.

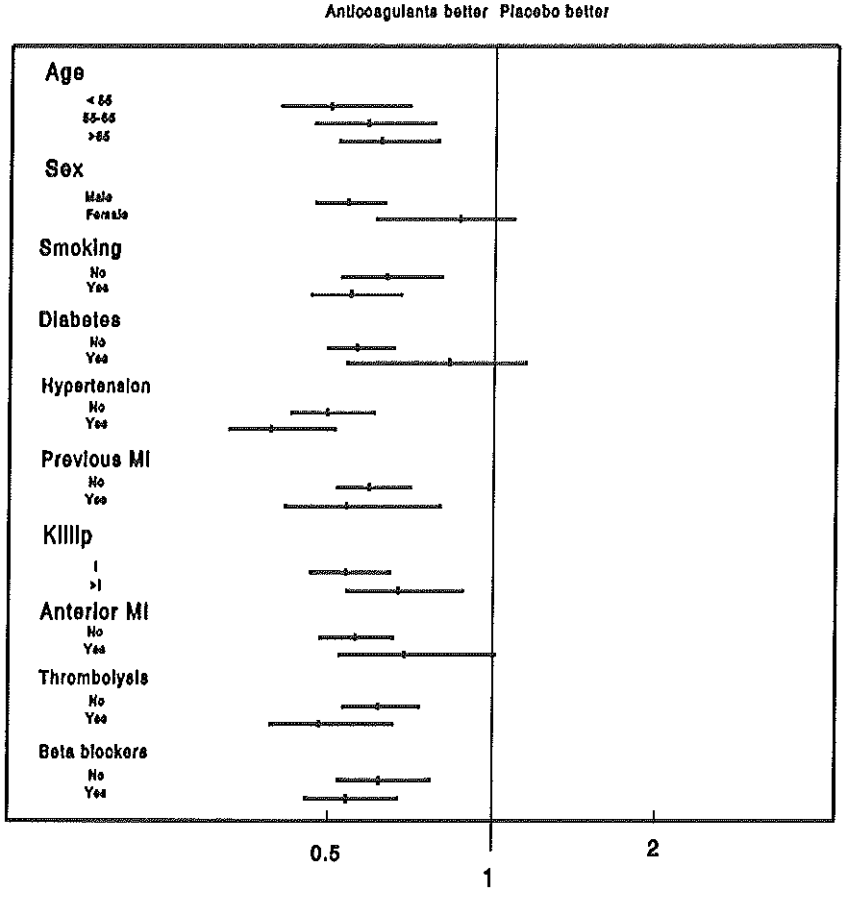

Figure 3. Effect estimates and confidence intervals of oral anticoagulant treatment with respect to vascular event in clinically defined subgroups of patients.

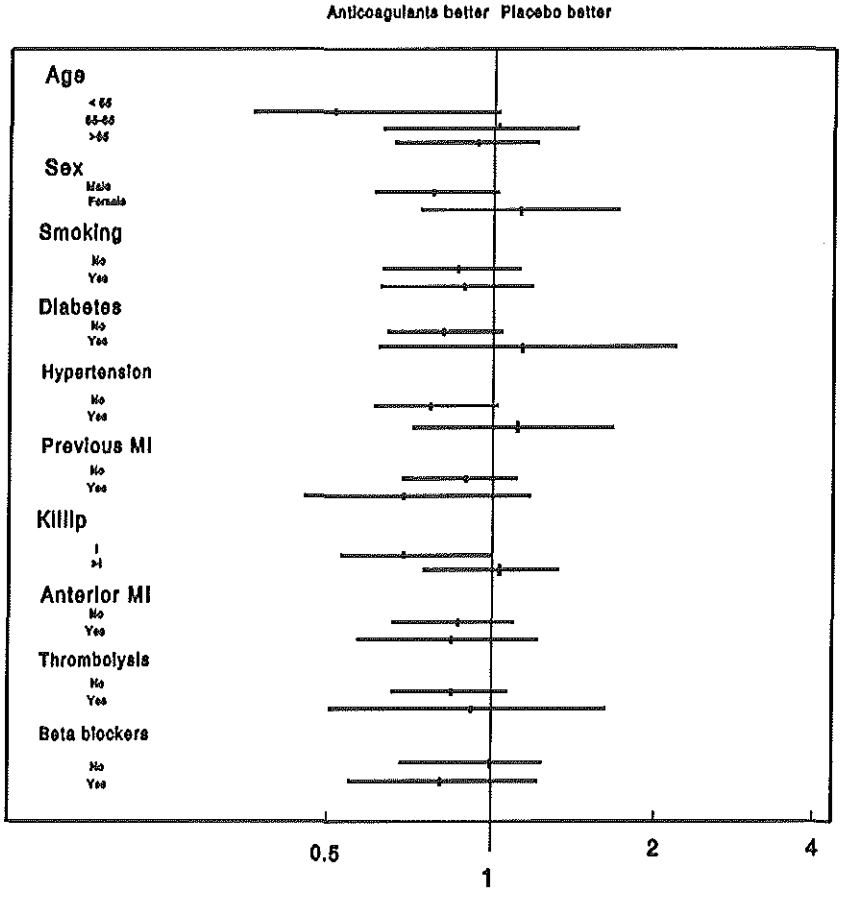

Figure 4. Effect estimates and confidence intervals of oral anticoagulant treatment with respect to mortality in clinically defined subgroups of patients.

Discussion

From the findings of this subgroup analysis it appears that the relative effect of long-term oral anticoagulant treatment on various thrombo-embolic endpoints after myocardial infarction does not differ in a statistically significant manner among subgroups of patients. Nevertheless, our data suggest that anticoagulant treatment may be less efficacious with respect to the prevention of vascular events in females and diabetics.

Some limitations of subgroup analysis should be noted at this point to clarify these results. Foremost, statistical power in subgroups may be negatively affected by the small number of patients or endpoints available for analysis, as in this case with respect to stroke. Also, when several subgroups are investigated without prior hypothesis, multiple testing may increase the risk of false positive results merely by chance. Further, the clustering of risk factors with a negative impact on outcome in particular subgroups of patients may confound the treatment effect as well. Therefore, results of subgroup analyses should always be interpreted with caution. In our subgroup analysis, both the introduction of interaction terms and the comparison of the coefficients in the subgroups of females and diabetics failed to show interaction, indicating that the suggested limited benefit could simply be the result of chance.

In spite of their potentially important clinical implications, subgroup analyses of anticoagulant treatment after myocardial infarction are scarce, probably because only a few trials were of sufficient size to permit such an analysis. The International Anticoagulant Review Group addressed this problem by pooling data of nine controlled studies.[7] Interestingly, this study also reported a small treatment effect of anticoagulation in women.

We did not establish interaction of previous myocardial infarction with the effect of anticoagulant treatment on mortality or recurrent myocardial infarction. These

findings are in accordance with the results of the Veterans Administration Study[8] but are distinct from the outcome of the subgroup analysis of the Warfarin Re-infarction Study. Moreover, in that study recurrence of myocardial infarction was not reduced by anticoagulant treatment in the presence of diabetes.[6] As discussed earlier, our findings point to an (not significantly) attenuated effect of anticoagulant treatment with respect to vascular events in patients with diabetes mellitus but no interaction was demonstrated with respect to recurrent myocardial infarction alone. Although similar in design, the WARIS trial showed a much higher overall event rate of cardiovascular endpoints than the ASPECT trial, which in part could explain these disparities in outcome of the respective subgroup analyses.

A multivariate analysis was performed to identify variables that showed an independent association with the selected endpoints, but one should recognize that these associations pertain only to the patient group under investigation as any patient population of a clinical trial may be subjected to selection bias. Our multivariate analysis confirmed the association of increasing age, previous myocardial infarction, diabetes and clinical signs of heart failure during admission with cardiovascular morbidity and mortality after myocardial infarction,[10-12] and the beneficial effect of ß-blockers.[13,14] The lack of the previously reported association of variables such as thrombolysis and anterior infarction with mortality probably resulted from selection of low risk patients in this trial, although the effect estimate of thrombolysis corresponds with earlier findings.[15-18]

In view of the fact that none of the considered variables showed a significant modification of treatment effect it may be argued that all patients have equal relative benefit from anticoagulant treatment. Although this in itself may be a valid statement, multivariate analysis revealed a number of distinct features that may refer to patients who may carry an increased risk for subsequent cardiovascular events. In this respect it is of particular importance to notice that thrombolysis confers a profound reduction in mortality during the acute phase but may otherwise

increase the risk of recurrent myocardial infarction after hospital discharge.

In summary, the results of this analysis suggest that the effects of anticoagulant treatment after myocardial infarction are not modified in clinically defined subgroups of patients while certain features characterize patients who carry an increased risk of cardiovascular complications.

References

1. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-52.
2. The ASPECT research group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Lancet, 1994; 343:499-503.
3. Levine MN, Raskob G, Hirsch J. Haemorrhagic complications of long-term anticoagulant therapy. Chest 1986; 89(2)suppl:16S-25S.
4. Fogelholm R, Eskola K, Kiminkinen T, Kunnamo I. Anticoagulant treatment as a risk factor for primary intracerebral haemorrhage. J Neurol Neurosurg Psychiatry 1992; 55:1121-4.
5. Wintzen AR, Jonge H de, Loeliger EA, Bots GTAM. The risk of intracerebral haemorrhage during oral anticoagulant treatment: a population study. Ann Neurol 1984; 16:553-8.
6. Smith P, Arnesen H, Abdelnoor M. Effects of long-term anticoagulant therapy in subgroups after acute myocardial infarction. Arch Intern Med 1992; 152:993-7.
7. International Anticoagulant Review Group. Collaborative analysis of long-term anticoagulant administration after acute myocardial infarction. The Lancet 1970; i:203-9.
8. Ebert RV, Borden CW, Hipp HR, Holzman D, Lyon AF, Schnaper H. Long-term anticoagulant therapy after myocardial infarction. JAMA 1969; 207:2263-67.
9. British Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. BMJ 1964; 2:837-43.
10. Norris RM, Caughey DE, Mercer CJ, Scott PJ. Prognosis after myocardial infarction. Six year follow-up. Br Heart J 1974; 36:786-90.
11. Merrilees M, Scott PJ, Norris RM. Prognosis after myocardial infarction: results of 15 year follow up. BMJ 1984; 288:356-9.

12. Martin CA, Thompson PL, Armstrong BK, Hobbs MST, de Klerk N. Long-term prognosis after recovery from myocardial infarction: a nine year follow-up of the Perth Coronary Register. Circulation 1983; 68:961-9.
13. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction.
N Engl J Med 1981; 304:801-7.
14. Beta-blocker Heart Attack Study Research group. A randomised trial of propanolol in patients with acute myocardial infarction.
JAMA 1982; 247:1707-14.
15. Stone PH, Raabe DS, Jaffe AS, Gustafson N, Muller JE, Turi ZG et al. Prognostic significance of location and type of myocardial infarction: independent adverse outcome associated with anterior location. J Am Coll Cardiol 1988; 11:453-63.
16. Geltman EM, Ehsani AA, Campbell MK, Schechtman K, Roberts R, Sobel BE. The influence of location and extent of myocardial infarction on long-term ventricular dysrythmia and mortality. Circulation 1979; 60:805-14.
17. ISIS-2 Collaborative group. A randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. Lancet 1988; ii; 349-60.
18. Simoons ML, Vos J, Tijssen JGP, Vermeer F, Verheugt FWA, Krauss H, Manger Cats V, et al. Long-term benefit of thrombolytic therapy.
J Am Coll Card 1989; 14: 1609-15.

Chapter 4

Cumulative meta-analysis of long-term anticoagulant treatment after myocardial infarction

Abstract

The efficacy of long-term anticoagulant treatment in patients after myocardial infarction has been investigated in numerous trials over the past decades. As most trials were of insufficient size to supply convincing results we have carried out a cumulative meta-analysis of 15 prospective follow-up studies that compared long-term anticoagulant treatment with standard therapy.

Data of consecutive studies were combined according to an intention-to-treat analysis with the Mantel-Haenszel method for assessment of relative risk. Death from all causes, recurrent myocardial infarction and cerebro-vascular stroke were assessed in 4,294 patients discharged after myocardial infarction on anticoagulant treatment and compared with 4,125 patients on reference therapy.

Long-term anticoagulant therapy reduced mortality with 10% (relative risk 0.90; 95% confidence interval 0.81-0.99), recurrent myocardial infarction with 43% (0.57; 0.50-0.64), and stroke with 45% (0.55; 0.40-0.65) in randomised trials. Statistical significance was reached for mortality in 1994, for reinfarction in 1964 and for stroke in 1990.

This cumulative meta-analysis provides evidence for a moderate reduction in mortality and a substantial reduction in recurrent myocardial infarctions and cerebro-vascular events by long-term oral anticoagulant treatment in patients after myocardial infarction.

Introduction

A large number of trials on long-term oral anticoagulant treatment after myocardial infarction has been conducted over the last 40 years, but the controversy regarding the efficacy of this mode of therapy has not been resolved.[1-19] Based on results of small sized trials showing inconclusive results with respect to mortality and recurrence of myocardial infarction, some investigators concluded that long-term oral anticoagulant therapy after hospital discharge was not effective.[14,15,21,24,25] However, when the results of the Sixty Plus trial showed a detrimental effect of cessation of long-term oral anticoagulants after myocardial infarction,[16] it was suggested that new trials were in order to settle the issue.[22] A study in Norwegian patients in 1990 showed a significant 24% mortality reduction and a substantial reduction in thrombo-embolic events.[19] Yet, the recent ASPECT trial comprising over 3,400 Dutch patients showed a non-significant 10% mortality reduction.[20]
In view of these ambiguous results, we performed a cumulative meta-analysis to assess the efficacy of long-term oral anticoagulant treatment for reduction of mortality and morbidity after myocardial infarction.

Methods

Selection of studies

Studies, reported in English, on the efficacy of long-term oral anticoagulant therapy in hospital survivors of myocardial infarction were identified by Medline searches from January 1963 to June 1, 1994 (keywords: 'myocardial infarction'; 'anticoagulants'), and by reviewing reference lists of relevant papers. We selected studies with a prospective follow-up design in which treatment was initiated within six months following myocardial infarction and in which a comparison was made to standard therapy or placebo. Consequently, trials with a randomisation window of

more than six months,[8,16] with a reference group treated with antiplatelet drugs,[18] and with enrolment of patients with other forms of coronary disease such as unstable angina pectoris,[3,6] were excluded. A total of 15 prospective follow-up studies remained available for analysis. Subsequent to this selection, three sets of studies were formed: a first set comprised all 15 studies that met the selection criteria described above; a second group included all randomised trials; a third set consisted of randomised, double-blind and placebo-controlled trials.

Statistical methods

For each study the number of patients and endpoints in each treatment group were assessed. The relative risk and the 95% confidence interval (CI) of the event rate associated with anticoagulant treatment were calculated for each individual study. Subsequently, a cumulative meta-analysis was performed using the Mantel-Haenszel method.[23] Overall 95% confidence intervals estimates were calculated by the test-based method according to Miettinen.[33] Endpoints considered separately in this meta-analysis were total mortality, recurrent myocardial infarction and cerebro-vascular event. All studies were analyzed according to the intention-to-treat principle.

Results

Study populations

Details of the selected 15 studies are presented in Table 1. The following coumarin derivatives were used: dicoumarol, phendione, phenprocoumon, warfarin and acenocoumarol. In some trials an ineffective dose of the coumarin derivative was employed instead of placebo for comparison with anticoagulant therapy.[2,5,9] Various methods were applied to measure the intensity of anticoagulant therapy.

Table 1. Characteristics of studies that assessed the effect of long-term anticoagulant therapy after myocardial infarction

Study No.	First author	Year of publication	Design	Follow-up (months)	Treatment	Target Range (% in range)
1.	Bjerkelund[1]	1957	non randomised open	37	conventional vs dicoumarol	10-20% P&P (46%)
2.	MacMillan[2]	1960	randomised open	13	ineffective vs effective dicoumarol	Doubling 1-stage PT (unknown)
3.	Harvald[4]	1962	non randomised open	31	placebo vs phenprocoumon or dicoumarol	10-25% P&P (85%)
4.	B.M.R.C.[5]	1964	randomised open	25	ineffective vs effective phenindione	Doubling 1-stage PT (46%)
5.	Conrad[7]	1964	randomised double-blind	10	placebo vs phenprocoumon	1.5 time 1-stage PT (82%)
6.	Lovell[9]	1967	randomised open	18	ineffective vs effective phenprocoumon	15-30% Prothrombin activity (67%)
7.	Ebert[10]	1969	randomised single blind	53	placebo vs dicoumarol or warfarin	Doubling 1-stage PT (82%)
8.	Sørensen[11]	1969	non randomised open	17	placebo vs dicoumarol	10-30%, P&P (74%)
9.	Meuwissen[12]	1969	randomised double-blind	20	placebo vs phenprocoumon	5-15%, TT (91%)
10.	Ritland [13]	1969	randomised open	12	phendione 3 months vs phendione 12 months	10-25%, P&P (80%)
11.	Seaman[14]	1969	randomised double-blind	73	placebo vs phenindione	10-30%, P&P (61%)
12.	Merskey[15]	1974	randomised open	12	placebo vs anticoagulant	< 10%, TT (58%)
13.	Breddin[17]	1980	randomised open	24	placebo vs phenprocoumon	5-12%, TT (58%)
14.	Smith[19]	1990	randomised double-blind	37	placebo vs warfarin	5-10%, TT (67%)
15.	ASPECT[20]	1994	randomised double-blind	37	placebo vs phenprocoumon or acenocoumarol	5-10%, TT (74%)

P&P: Prothrombin-Proconvertin-Stuart factor activity, PT: Prothrombin time, TT: Thrombo Test

The target range for optimal therapy varied considerably as did the proportion of patients with the INR in the target range. The mean follow-up ranged from 12 months to 53 months.

Effect on mortality

Mortality data of each of the 15 selected studies are shown in Table 2. A statistically significant reduction in mortality was reported in three studies.[1,2,19] The cumulative relative risks of mortality in the three sets of studies are shown in Table 3. The total number of subjects in the anticoagulated group and control group comprised 4,294 patients versus 4,125 patients in the set of prospective studies, 3,891 patients versus 3,742 patients in the randomised trials and 2,515 patients versus 2,502 patients in the randomised, double-blind, placebo-controlled trials. The cumulative relative risk of mortality associated with anticoagulant treatment in all 15 prospective studies was 0.87 (95% CI 0.79-0.95), in the 12 randomised trials 0.90 (0.81-0.99) (Figure 1) and in the randomised, double-blind placebo-controlled trials 0.85 (0.74-0.98).

Effect on recurrent myocardial infarction

Since two studies did not report the number of recurrent infarctions,[14,15] the number of subjects for analysis of this endpoint comprised 4,031 anticoagulated patients and 3,952 reference patients in prospective studies. The relative risk for recurrent infarction associated with oral anticoagulant treatment did not reach statistical significance in eight of thirteen studies (Table 4). The cumulative relative risk was 0.59 (0.53-0.66) for all prospective studies. The 10 randomised trials that reported on recurrent infarction showed a slightly lower cumulative relative risk of 0.57 (0.50-0.64), as illustrated in Figure 2. Four trials that were conducted with a randomised, double-blind, placebo-controlled design yielded a cumulative relative risk of 0.55 (0.47-0.64).

Table 2. Relative risk of mortality associated with long-term anticoagulant therapy in hospital survivors of myocardial infarction in individual studies. Numbers denote events per total number of patients in each treatment group.

Study No.	Anticoagulant group	Reference group	Individual RR (95% CI)	
1. Bjerkelund	24/119	42/118	0.57	(0.37-0.87)
2. MacMillan	8/27	0/23	--	--
3. Harvald	34/145	45/170	0.89	(0.60-1.30)
4. B.M.R.C.	29/195	40/188	0.70	(0.45-1.08)
5. Conrad	9/52	8/34	0.74	(0.31-1.72)
6. Lovell	33/172	39/178	0.88	(0.58-1.32)
7. Ebert	120/385	114/350	0.96	(0.77-1.18)
8. Sørensen	15/139	19/95	0.54	(0.29-1.01)
9. Meuwissen	1/68	8/70	0.13	(0.02-1.00)
10. Ritland	8/102	7/106	1.19	(0.45-3.16)
11. Seaman	36/88	31/87	1.15	(0.79-1.68)
12. Merskey	18/175	10/86	0.88	(0.43-1.83)
13. Breddin	39/320	32/309	1.18	(0.76-1.83)
14. Smith	94/607	123/607	0.76	(0.60-0.98)
15. ASPECT	170/1700	189/1704	0.90	(0.74-1.10)

RR: Relative Risk, CI: Confidence Interval, --: not available

Table 3. Cumulative relative risk of mortality in the presence of long-term oral anticoagulant therapy in hospital survivors of myocardial infarction.

Study No.	Prospective studies		Randomised trials		Randomised, Double-blind Placebo-controlled trials	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
1. Bjerkelund	0.57	(0.37-0.87)				
2. MacMillan	0.72	(0.49-1.07)				
3. Harvald	0.80	(0.61-1.06)				
4. B.M.R.C.	0.77	(0.61-0.97)	0.86	(0.57-1.29)		
5. Conrad	0.77	(0.60-0.96)	0.83	(0.58-1.20)	0.74	(0.31-1.72)
6. Lovell	0.79	(0.65-0.96)	0.85	(0.65-1.12)		
7. Ebert	0.86	(0.74-0.99)	0.91	(0.77-1.08)		
8. Sørensen	0.84	(0.73-0.96)				
9. Meuwissen	0.82	(0.71-0.94)	0.88	(0.75-1.04)	0.46	(0.22-.098)
10. Ritland	0.83	(0.72-0.95)	0.89	(0.76-1.05)		
11. Seaman	0.85	(0.75-0.97)	0.92	(0.79-1.08)	0.90	(0.64-1.26)
12. Merskey	0.86	(0.75-0.97)	0.92	(0.80-1.07)		
13. Breddin	0.88	(0.78-1.00)	0.95	(0.83-1.09)		
14. Smith	0.85	(0.76-0.95)	0.90	(0.79-1.01)	0.80	(0.66-0.98)
15. ASPECT	0.87	(0.79-0.95)	0.90	(0.81-0.99)	0.85	(0.74-0.98)

RR: Relative Risk; CI: Confidence Interval

Table 4. Relative risk of recurrent myocardial infarction associated with long-term anticoagulant therapy in hospital survivors of myocardial infarction in individual studies. Numbers denote events per total number of patients in each treatment group.

Study No.	Anticoagulated group	Reference group	Individual RR (95% CI)	
1. Bjerkelund	22/119	38/118	0.57	(0.36-0.91)
2. MacMillan	6/27	4/23	1.28	(0.41-3.98)
3. Harvald	52/145	67/170	0.91	(0.68-1.21)
4. B.M.R.C.	34/195	81/188	0.40	(0.29-0.57)
5. Conrad	9/52	6/34	0.98	(0.38-2.51)
6. Lovell	12/172	17/178	0.73	(0.36-1.48)
7. Ebert	60/385	73/350	0.75	(0.55-1.02)
8. Sørensen	7/139	18/95	0.27	(0.12-0.61)
9. Meuwissen	5/68	7/70	0.74	(0.25-2.20)
10. Ritland	5/102	9/106	0.58	(0.20-1.66)
13. Breddin	16/320	25/309	0.62	(0.34-1.13)
14. Smith	82/607	124/607	0.66	(0.51-0.85)
15. ASPECT	114/1700	242/1704	0.47	(0.38-0.58)

RR: Relative Risk, CI: Confidence Interval

Table 5. Cumulative relative risk of recurrent myocardial infarction in the presence of long-term oral anticoagulant therapy in hospital survivors of myocardial infarction.

Study	Prospective studies		Randomised trials		Randomised, Double-blind Placebo-controlled trials	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
1. Bjerkelund	0.57	(0.36-0.91)				
2. MacMillan	0.65	(0.43-0.98)	1.28	(0.41-3.98)		
3. Harvald	0.80	(0.63-1.02)				
4. B.M.R.C.	0.63	(0.52-0.76)	0.45	(0.33-0.61)		
5. Conrad	0.64	(0.53-0.77)	0.49	(0.37-0.66)	0.98	(0.38-2.51)
6. Lovell	0.65	(0.54-0.77)	0.53	(0.40-0.69)		
7. Ebert	0.67	(0.58-0.79)	0.62	(0.50-0.75)		
8. Sørensen	0.65	(0.55-0.75)				
9. Meuwissen	0.65	(0.56-0.75)	0.62	(0.51-0.76)	0.86	(0.42-1.76)
10. Ritland	0.65	(0.56-0.75)	0.62	(0.51-0.75)		
13. Breddin	0.64	(0.56-0.74)	0.62	(0.51-0.75)		
14. Smith	0.65	(0.57-0.74)	0.63	(0.55-0.74)	0.68	(0.54-0.86)
15. ASPECT	0.59	(0.53-0.66)	0.57	(0.50-0.64)	0.55	(0.47-0.64)

RR: Relative Risk; CI: Confidence Interval

Effect on stroke

Risk reductions with respect to cerebro-vascular events are shown in Table 6. Eight studies reported on the incidence of stroke in sufficient detail for risk estimate calculation. The cumulative relative risk was 0.51 (0.38-0.68) for all prospective studies, 0.56 (0.41-0.76) for randomised trials and 0.54 (0.39-0.73) for randomised, double-blind, placebo-controlled trials (Table 7).

Table 6. Relative risk of stroke associated with long-term anticoagulant therapy in hospital survivors of cerebro-vascular stroke in individual studies. Numbers denote events per total number of patients in each treatment group.

Study No.	Anticoagulated group	Reference group	Individual RR (95% CI)	
1. Bjerkelund	0/119	1/118	--	--
3. Harvald	2/145	11/170	0.21	(0.05-0.95)
4. B.M.R.C.	3/195	1/188	2.89	(0.30-27.6)
8. Sørensen	2/139	6/95	0.23	(0.05-1.10)
10. Ritland	0/102	1/106	--	--
13. Breddin	1/320	1/309	0.97	(0.06-15.4)
14. Smith	20/607	44/607	0.45	(0.27-0.76)
15. ASPECT	37/1700	62/1704	0.60	(0.40-0.89)

RR: Relative Risk, CI: Confidence Interval, --: not available

Table 7. Cumulative relative risk of stroke in the presence of long-term oral anticoagulant therapy in hospital survivors of myocardial infarction.

Study No.	Prospective studies		Randomised trials		Randomised, Double-blind Placebo-controlled trials	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
1. Bjerkelund	--					
3. Harvald	0.19	(0.05-0.72)				
4. B.M.R.C.	0.42	(0.15-1.15)	--			
8. Sørensen	0.35	(0.15-0.79)				
10. Ritland	0.33	(0.15-0.75)	1.47	(0.25-8.82)		
13. Breddin	0.36	(0.17-0.79)	1.30	(0.29-5.83)		
14. Smith	0.43	(0.28-0.65)	0.51	(0.32-0.82)	--	
15. ASPECT	0.51	(0.38-0.68)	0.56	(0.41-0.76)	0.54	(0.39-0.73)

RR: Relative Risk; CI: Confidence Interval, -- indicates the first available study for analysis

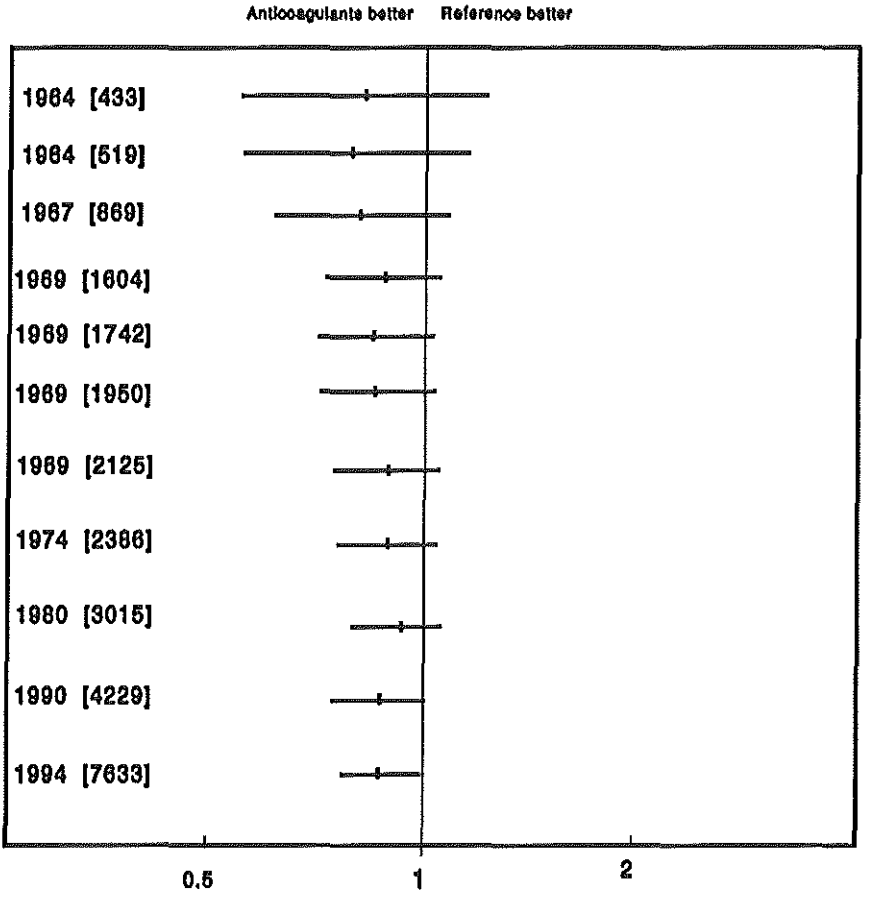

Figure 1. Cumulative relative mortality risk after myocardial infarction in the presence of oral anticoagulant treatment. The years of publication of randomised trials are depicted and the cumulative number of patients is shown between brackets.

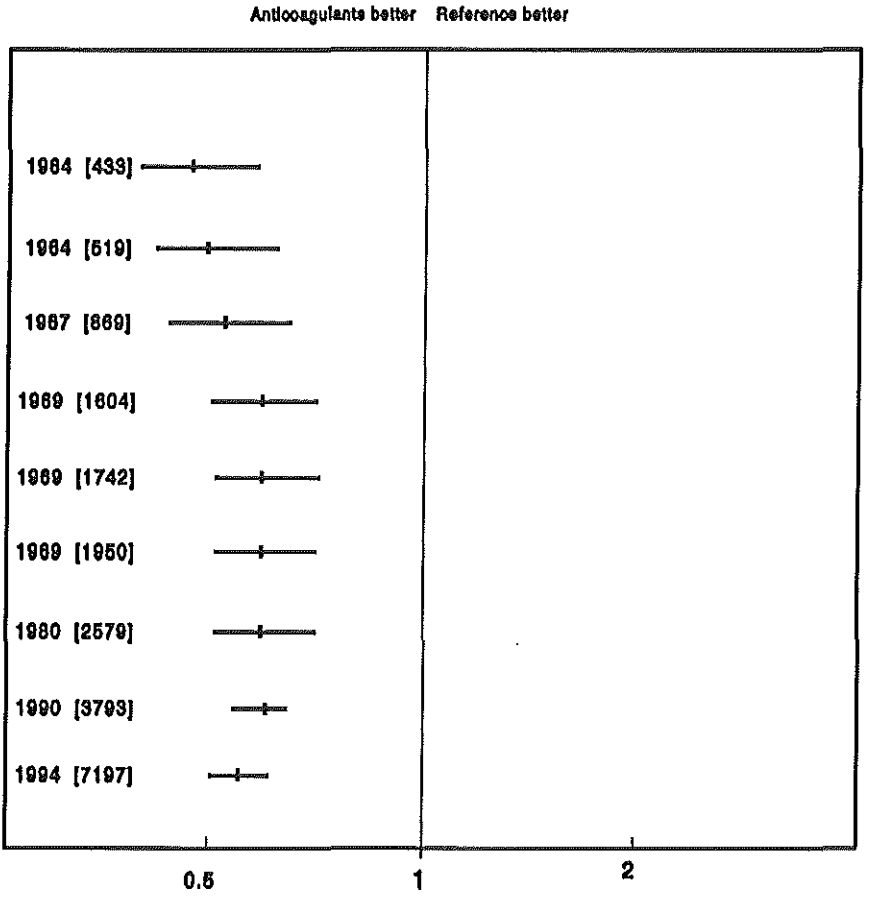

Figure 2. Cumulative risk of recurrence after myocardial infarction in the presence of oral anticoagulant treatment. The years of publication of randomised trials are depicted and the cumulative number of patients is shown between brackets.

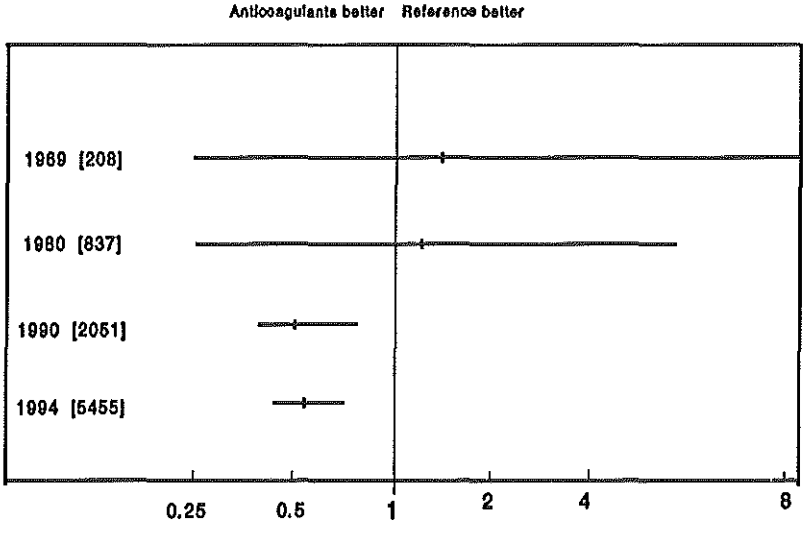

Figure 3. Cumulative relative risk of stroke after myocardial infarction in the presence of oral anticoagulant treatment. The years of publication of randomised trials are depicted and the cumulative number of patients is shown between brackets.

Discussion

This meta-analysis provides evidence for a 10% reduction in total mortality by anticoagulant treatment after myocardial infarction, a 43% reduction in fatal and non-fatal recurrent myocardial infarctions and a 45% reduction in cerebro-vascular events in randomised trials. Statistical significance for prevention of mortality has been established in 1994 while efficacy for prevention of reinfarction was established in 1964 and for prevention of stroke in 1990. The meta-analyses that included studies with a non-randomised design or that were restricted to trials with a double-blind design showed similar results.

Although a cumulative meta-analysis of clinical trials has an advantage over standard meta-analysis in that it shows the temporal compilation of evidence with respect to a typical treatment effect, it has the same flaws as any meta-analysis. Results may be affected by selection bias,[29,30] as well as by the methodology of selected studies.[31,32] and in this particular case, the quality of treatment. The current selection criteria have therefore been defined upfront and the studies that were considered not eligible for analysis have been listed. Also, the studies that were included in the present meta-analysis were clustered according to methodology. Interestingly, the summarised effect estimates of anticoagulant therapy on mortality and recurrent myocardial infarction in the various sets of studies showed only small differences. It should be noted however that 90% of patients of prospective studies participated in randomised trials.

The 10% mortality reduction in the present analysis differs from previous meta-analyses, that usually reported higher mortality reductions. The International Anticoagulant Review Group was the first to pool data from several studies.[27] Results in 2,487 patients from nine studies, four of which were not randomised, were confined to improved survival during the first years after myocardial infarction in males with a history of angina pectoris. Following the publication of a

number of small to moderately sized trials, a pooled analysis of seven randomised trials in 1983 reported a 28% mortality reduction and a 45% reduction in recurrent myocardial infarction.[28] Trials that involved patients using low dose anticoagulant therapy as a reference group were excluded in that analysis. A recent paper on meta-analyses of different treatments after myocardial infarction also reported a higher mortality reduction but differed from the present analysis because it included the Sixty Plus trial.[23] Finally, the large contribution (45% of the patients) by the recently conducted ASPECT trial that showed only a 10% reduction in mortality may also have attributed to the disparity in mortality reductions with previous meta-analyses. However, as clearly shown in the tables, exclusion of this trial would only affect the confidence intervals but not the effect estimate of the combined results. We therefore assume that the differences in results of various reports has resulted to a large extent from the selection of studies.

In summary, we conclude that this cumulative meta-analysis provides evidence for a substantial and consistent reduction in recurrent myocardial infarction, a substantial reduction in cerebro-vascular stroke and a moderate but significant reduction in mortality by long-term anticoagulant therapy in post myocardial infarction patients.

Acknowledgment

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References

1 Bjerkelund CJ. The effect of long term treatment with dicoumarol in myocardial infarction: a controlled clinical study. Acta Med Scand Suppl 1957; 330:13-212.

2. MacMillan RL, Brown KWG, Watt DL. Long-term anticoagulant treatment after myocardial infarction. Can Med Assoc J 1960; 83:567-70.

3. Borchgrevink CF. Long-term anticoagulant therapy in coronary heart disease. Acta Med Scand 1960; 359[suppl]:7-52.

4. Harvald B, Hilden T, Lund E. Long-term anticoagulant treatment after myocardial infarction. Lancet 1962; ii:626-30.

5. British Medical Research Council. An assessment of long-term anticoagulant administration after cardiac infarction. BMJ 1964; 2:837-43

6. Aspenström G, Korsan-Bengsten K. A double blind study of dicoumarol prophylaxis in coronary heart disease. Acta Med Scand 1964; 176:563-75.

7. Conrad LL, Kyriacopoulos JD, Wiggins CW, Honick GL. Prevention of recurrences of myocardial infartion: a double-blind study of the effectiveness of long-term oral anticoagulant treatment. Arch Intern Med 1964; 114:348-58.

8. Loeliger EA, Hensen A, Kroes F, et al. A double-blind trial of long-term anticoagulant treatment after myocardial infarction. Acta Med Scand 1967; 182:549-66.

9. Lovell RR, Denborough MA, Nestel PJ, Goble AJ. A controlled trial of long-term treatment with anticoagulants after myocardial infarction in 412 male patients. Med J Aust 1967; 2:97-104.

10. Ebert RV, Borden CW, Hipp HR, et al. Long-term anticoagulant treatment after myocardial infarction: final report of the Veterans Administration cooperative study. JAMA 1969; 207:2263-7.

11. Sørensen OH, Friis T, Jørgensen AW, Jørgensen MB, Nissen NI. Anticoagulant treatment of acute coronary thrombosis. Acta Med Scand 1969; 185:65-72

12. Meuwissen OJ, Vervoorn AC, Cohen O, Jordan FL, Nelemans FA. Double blind trial of long-term anticoagulant treatment after myocardial infarction. Acta Med Scand 1969; 186:361-8.

13. Ritland S, Lygren T. Comparison of efficacy of 3 and 12 months anticoagulant therapy after myocardial infarction. A controlled clinical trial. Lancet 1969; i:122-4.
14. Seaman AJ, Griswold HE, Reaume RB, Ritzmann L. Long-term anticoagulant prophylaxis after myocardial infarction: first report.
N Engl J Med 1969; 281:115-9.
15. Merskey C, Drapkin A. Long-term anticoagulant therapy after myocardial infarction. JAMA 1974; 230:208-9
16. The Sixty Plus Reinfarction Study Research Group. A double-blind trial to assess long-term oral anticoagulant treatment in elderly patients after myocardial infarction. Lancet 1980; ii:989-93.
17. Breddin K, Loew D, Lechner K, Uberla K. Walter E. Secondary prevention of myocardial infarction: a comparison of acetylsalicylic acid, placebo and phenprocoumon. Haemostasis 1980; 9:325-44.
18. The E.P.S.I.M. Research group. A controlled comparison of aspirin and oral anticoagulants in prevention of death after myocardial infarction.
N Eng J Med 1982; 307(12):701-8.
19. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-52.
20. The ASPECT trial research group. Effect of long-term anticoagulant therapy on mortality and cardiovascular morbidity after myocardial infarction.
Lancet 1994; 343:499-503.
21. Frishman WH, Ribner HS. Anticoagulation in myocardial infarction: Modern approach to an old problem. Am J Card 1979; 43:1207-13.
22. Mitchell JRA. Anticoagulants in coronary heart disease-retrospect and prospect.
Lancet 1981; i:257-62.
23. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction.
N Engl J Med 1992; 327:248-54.
24. Goldman RJ, Gore JM, Dalen JE, Alpert JS. Long-term anticoagulant therapy after acute myocardial infarction. Editorials. Am Heart J 1985; 109(3):616-22.

25. Resnekov L, Chadiak J, Hirsch J, Lewis HD. Antithrombotic agents in coronary artery disease. Chest 1989; 95[suppl 2]:52-72.
26. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992; 327:248-54.
27. International Anticoagulant review group. Collaborative analysis of long-term anticoagulant administration after acute myocardial infarction. Lancet 1970; i:203-9.
28. Leizorovicz A, Boissel JP. Oral anticoagulants in patients surviving myocardial infarction. A new approach to old data. Eur J Clin Pharmacol 1983; 24:333-6.
29. Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. Stat Med 1987; 6:245-50.
30. L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987; 107:224-33.
31. Yenicek M. Meta-analysis in medicine. Where we are and where we want to go. J Clin Epidemiol 1989; 42:35-44.
32. O'Rourke K, Detsky AS. Meta-analysis in medical research: strong encouragement for higher quality in individual research efforts. J Clin Epidemiol 1989; 42:1021-4.
33. Miettinen OS. Estimability and estimation in case-referent studies. Am J Epidemiol 1976; 103:226-35.

Chapter 5

Characteristics and prognosis of non-participants of a multi-centre trial of long-term anticoagulant therapy after myocardial infarction

Abstract

Participants of a randomised trial may differ from eligible non-participants as a result of selection. We studied the distribution of prognostic factors and survival in eligible patients of a multi-centre trial of long-term oral anticoagulant treatment after myocardial infarction.

All hospital survivors of myocardial infarction in one participating clinical centre of a multi-centre, randomised, double-blind, placebo-controlled trial of long-term anticoagulant treatment after myocardial infarction were screened for entry criteria. Subsequently, prognostic factors and survival of participants were compared with eligible but not randomised patients.

The 350 participants were younger and were more often of male gender and more often smokers compared with 587 non-participants. Non-participants had more frequently suffered a previous myocardial infarction and were treated more often with diuretics and ACE-inhibitors, suggesting a higher proportion of patients with chronic heart failure in this group. Age, previous myocardial infarction and the use of diuretics at discharge were independent predictors of mortality, consent showed no association.

Our findings indicate that participants of a clinical trial have a better prognosis during the first years following myocardial infarction compared to eligible non-participants as a result of a higher prevalence of cardiovascular riskfactors associated with mortality in the non-participants.

Introduction

If only a proportion of eligible patients is enroled in a trial, the distribution of risk factors and prognosis in the study population may not be similar to non-participants.[1-3] Although the features of the study population may be well described by the entry criteria of the trial, some unforseen or unknown factors may lead to differences in the distribution of riskfactors between participants and non-participants.[4,5] Knowledge of dissimilarities in the distribution of riskfactors in the population of participants and non-participants may therefore help to evaluate possible sources of bias and elucidate the generalisability of the effects of treatment as observed in the trial. In this study we have compared prognostic factors and survival of participants and non-participants from two primary referral hospitals that took part in a large, randomised, double-blind, placebo-controlled trial of the efficacy of long-term oral anticoagulant treatment after myocardial infarction.

Methods

Data of participants were obtained from the Dutch 'Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial.[6] Between September 1986 and January 1992, 3,404 myocardial infarction survivors were recruited by 60 hospitals and randomised to oral anticoagulant treatment or matching placebo following their hospital discharge. Subjects were followed for a median period of 37 months at one of 19 participating thrombosis centres, specialised in the computerised monitoring of oral anticoagulant therapy. Trial medication was continued until the end of the trial follow-up, on June 30, 1992. Results of the trial were as follows: death occurred in 170 of the 1,700 anticoagulated patients as compared to 189 of the 1,704 placebo patients, a reduction of 10% (95% Confidence Interval -11 to 27%). Recurrent myocardial

infarction was observed in 114 anticoagulated patients versus 242 placebo patients, a reduction of 53% (41 to 62%) and cerebro-vascular event in 37 anticoagulated patients versus 62 placebo patients, a reduction of 40% (10 to 60%). Major bleeding complications were seen in 73 anticoagulated and in 19 placebo patients.

For the present comparison one participating clinical institution in Enschede was selected. This centre commenced participation on April 1, 1987 and continued patient enrollment until December 31, 1991 when the trial was ended. Following completion of the trial, the medical registration department of the centre was asked to identify all patients who were discharged alive with the clinical diagnosis 'myocardial infarction' (International Code of Disease 410, 9th version) during the intake period of the trial. Identified patients were then screened for entry criteria of the ASPECT trial, i.e. proven myocardial infarction with creatine kinase levels exceeding twice the upper reference level. Patients were subsequently screened for the presence of exclusion criteria, i.e. anticoagulant treatment on admission, residency outside the trial area, left ventricular dyskinesia or aneurysm on echocardiography or angiography, anticipated revascularisation procedure, indication or contra-indication for oral anticoagulant therapy, malignant disease with poor prognosis and mental disorder.

The following data were collected from medical records of selected patients: age, gender, history of previous myocardial infarction, administration of thrombolytic agents, highest Killip class during admission, third degree AV-block, discharge medication (diuretics, ß-blockers and ACE-inhibitors), antithrombotic medication at discharge (oral anticoagulants and aspirin), as well as risk factors for cardiovascular disease (current smoking, diabetes, history of hypertension, family history of coronary disease). If available, results of echocardiography and angiography during admission were collected for the assessment of ventricular function and coronary anatomy. Results of echocardiography were considered until 6 weeks after discharge if echocardiography was not performed during admission.

For all patients vital status was determined at the end of the follow-up of the trial on June 30, 1992.

Data analysis

For comparison of discrete data between groups the chi-square test was used. Unpaired t-test was employed for continuous variables. Clinical variables such as age, gender, the use of thrombolytics, ACE-inhibitors, diuretics, ß-blokkers, and trial participation and cardiovascular riskfactors such as smoking, previous myocardial infarction, Killip class >1 and hypertension were inserted in a Cox proportional-hazards model to assess their independent association with mortality.

Results

Between April 1, 1987 and December 31, 1991, 2,072 patients were discharged after admission for acute myocardial infarction. Of these, 350 were enrolled in the trial. Of the remaining 1,722 patients, 1,135 patients were not considered eligible for reasons listed in Table 1. Most patients were excluded because of residency outside the trial region. Other frequent reasons for exclusions were the use of anticoagulants on admission and a diagnosis of myocardial infarction that did not satisfy the selection criteria. The remaining 587 patients constituted the group of eligible but not randomised patients that was compared to the 350 participants.

Table 1 Reasons for exclusion of enrolment in the ASPECT trial

Patients discharged alive after MI	**2072**	
Randomised in ASPECT	350	
Available (%)	1722	(100.0)
Reasons for non eligibility:		
- Residence outside the study region (%)	302	(17.5)
- Anticipated revascularisation (%)	107	(6.2)
- CK < 2 fold increase (%)	257	(14.9)
- Anticoagulant treatment on admission (%)	231	(13.4)
- Contraindication for OAC (%)	31	(1.8)
- Indication for OAC (%)	29	(1.7)
- Dyskinesia or aneurysm (%)	81	(4.7)
- Carcinoma (%)	7	(0.4)
- Mental disorder (%)	22	(1.3)
- Missing data (%)	68	(3.9)
Number of eligible but not randomised patients	**587**	(33.4)

CK, creatine kinase, OAC, oral anticoagulants

Characteristics of the non-participants and participants are given in Table 2. On average, non-participants were significantly older and more often of female gender and more of them had sustained a previous myocardial infarction. In addition, fewer of the non-participants smoked cigarettes while diuretics and ACE-inhibitors were more frequently prescribed at discharge.

Mortality was significantly higher in non-participants than in participants. At the end of follow-up mortality amounted to 12% in participants and 20% in non-participants. Crude survival curves of participants and non-participants are

presented in Figure 1.

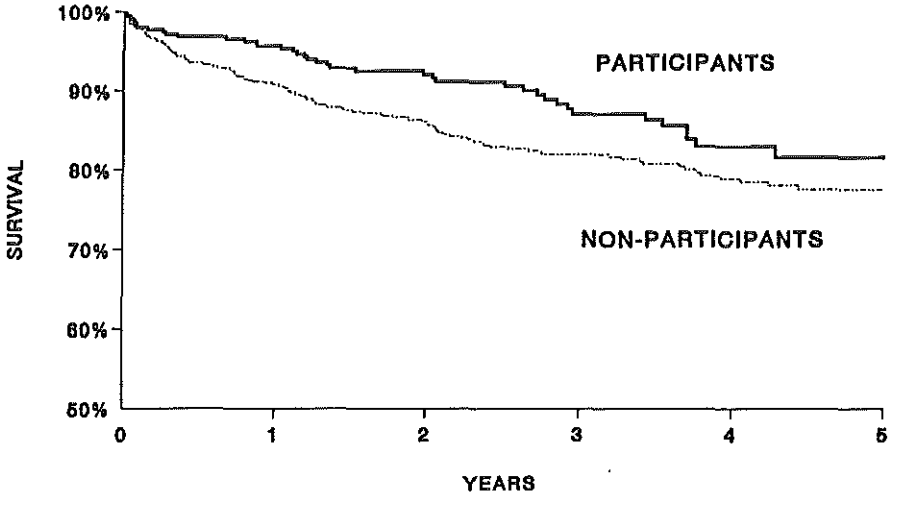

Figure 1. Survival in participants and non-participants.

Table 2 Characteristics at baseline of participants and non-participants

Variable	non-participants	participants	*P*-value
Number of patients	587	350	
Age, mean yr±SD	64	59	<0.0001
Male	63.5	83.4	<0.0001
Previous MI	12.4	8.3	0.048
Killip >1	30.5	33.7	0.28
Total AV-block	5.5	3.7	0.229
Risk factors			
Current smoking	44.8	58.9	<0.0001
Fam. history	4.9	6.3	0.380
Diabetes	10.1	8.6	0.455
Hypertension	20.6	19.7	0.741
Thrombolysis	29.1	32.6	0.245
Medication at discharge			
Diuretics	34.8	16.8	<0.0001
ACE inhibitors	17.4	10.6	<0.005
Beta-blockers	39.0	36.3	0.406
Anticoagulants	76.5	50.0	<0.0001
ASA	8.2	--	
Echocardiography performed	63.0	56.9	0.061
EDV > 55 mm	24.6	17.6	0.055
Akinesia	80.8	79.5	0.854
LV angiography performed	12.8	10.6	0.314
EDV> 55 mm	5.3	8.1	0.568
Akinesia	82.7	83.8	0.882
Coronary angiography performed	14.1	11.1	0.187
One vessel disease	59.0	53.8	0.589
Two vessel disease	25.3	33.3	0.356
Three vessel disease	9.6	10.3	0.915

AC: Anticoagulants, ASA: Aspirin

Because prognosis of both patient groups was determined by similar clinical variables and cardiovascular risk factors, a multivariate Cox analysis was performed in the combined population with trial participation as a covariate. The results of this analysis are presented in Table 3. After adjustment for the other prognostic factors, participation in the trial was no longer independently associated with improved outcome. Survival of patients in strata defined by age and use of diuretics are shown in Figure 2 and 3; the curves illustrate that survival in participants and non-participants is comparable in the various strata.

Table 3. Relative risk (and 95% confidence intervals) of factors associated with mortality

	RR	(95% CI)
Age (increment of 1 year)	1.04	(1.03,1.06)
Diuretics	2.10	(1.46,2.97)
Diabetes	1.95	(0.26,2.94)
Previous MI	1.60	(1.07,2.40)
Thrombolysis	0.44	(0.25,0.76)
Beta Blockers	0.60	(0.40,0.90)
Non participation	1.07	(0.72,1.61)

RR: Relative Risk, CI: Confidence Interval

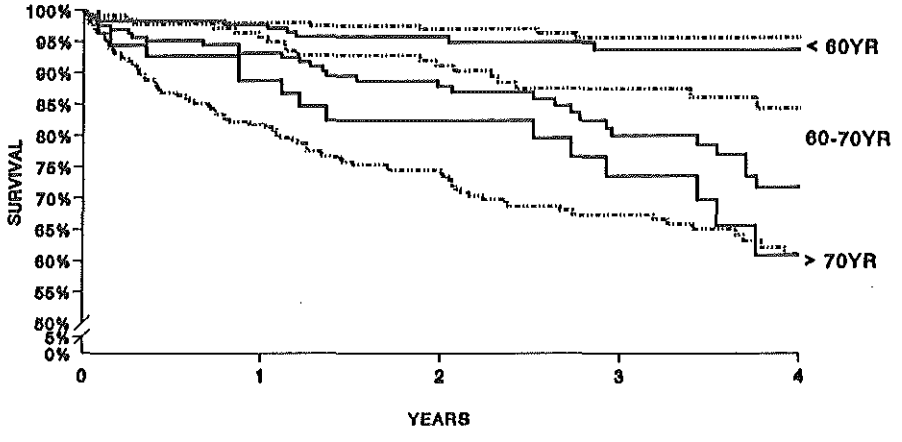

Figure 2. Survival according to age. Straight lines indicate participants, dotted lines indicate non-participants.

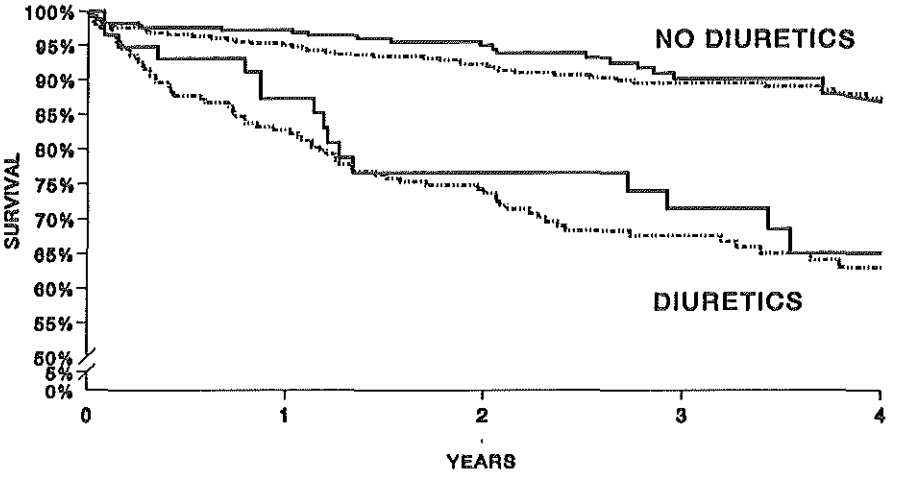

Figure 3. Survival according to the use of diuretics. Straight lines indicate participants, dotted lines indicate non-participants.

Discussion

This analysis demonstrates that participants of our multi-centre trial differed significantly from eligible non-participants with respect to important prognostic factors and, subsequently, survival. Higher age and the higher prevalence of clinical variables associated with left ventricular dysfunction such as previous myocardial infarction and the use of medication proved explanatory for the impaired prognosis of non-participants during the first years following myocardial infarction.

Despite the potentially important implications of disparities between participants and non-participants of a trial, only few trials have previously supplied data in sufficient detail to allow such a comparison.[7] Recently, the investigators of the Warfarin Re-infarction Study explored the demographical and clinical variables of non-participants.[8,9] In agreement with our findings, the authors demonstrated that higher age, female gender, previous myocardial infarction and the use of diuretics was more frequently present in non-participants. However, in contrast with our findings only age was found to be associated with mortality whereas our data indicate that previous myocardial infarction and the use of diuretics also independently predicted death.[10] Also, stratification according to these variables in our trial generally counterbalanced the disparity in mortality between participants and non-participants, suggesting that non-cardiovascular comorbidity had contributed only little to the difference in prognosis between these patient groups.[11]

Although reasons for non-participation of a trial may vary and be quite personal, including poor motivation, low mobility and saturation with focusing on disease,[9,12] the high proportion of non-participants who were discharged with oral anticoagulants (80%) in this trial clearly shows that refusal to participate was not based on ineligibility for anticoagulant treatment. The higher proportion of patients among non-participants with enlarged left ventricles on echocardiography illustrates the

higher prevalence of left ventricular dysfunction that may have partly resulted from the higher incidence of previous myocardial infarction. These data suggest that the higher risk of mortality during the early years after myocardial infarction of non-participants is largely related to complications associated with chronic heart failure.[12]

Our analysis is constrained by a few limitations. For practical reasons we have restricted this investigation to only one of the participating clinical centres. Also, due to the particular organisation of Dutch thrombosis centres in many different regions, patients who resided outside the region had to be excluded for analysis. The influence of these restraints cannot be quantitated. However, the selected centre represented the only clinical centre in the district of this particular thrombosis centre and had a primary referral function for the region. As the prognosis of participants from this hospital was similar to that of other participants of the ASPECT trial, it seems reasonable to assume that the results of this analysis are representative for the general post myocardial infarction population.

In summary, this analysis suggests that differences in the distribution of cardiovascular risk factors associated with impaired left ventricular function account almost entirely for the differences in prognosis between participants and non-participants of a trial in post myocardial infarction patients during the first years following acute myocardial infarction.

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References

1. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: The Framingham study. Ann N.Y. Acad. Sci. 1963; 107:539.
2. Doll R, Hill AB. Mortality in relation to smoking: Ten years' observation of British doctors. BMJ 1964; i:1399.
3. Gordon T, Moore FE, Shurtleff D, Dawber TR. Some epidemiologic problems in the long-term study of cardiovascular disease. Observations on the Framingham study. J Chronic Dis. 1959; 10:186-206.
4. Bergstrand CF, Vedin A, Wilhelmson C, Wilhelmsen L. Bias due to non-participation and heterogenous sub-groups in population surveys. J. Chronic dis. 1983; 36:725-8.
5. Criqui MH, Barret-Connor E, Austin M. Differences between respondents and non-respondents in a population based cardiovascular disease study. Am J Epidemiol 1978; 108:367-72.
6. Aspect research group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Lancet 1994; 343:499-503.
7. Charlson ME, Horwitz RI. Applying results of randomised trials to clinical practice: impact of losses before randomisation. BMJ 1984; 289:1281-4.
8. Smith P., Arnesen P, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-52.
9. Smith P, Arnesen H. Non-respondents in a post-myocardial infarction trial: characteristics and reasons for refusal. Acta Med Scand 1988; 223:537-42.
10. Smith P, Arnesen H. Mortality in non-consenters in a post-myocardial infarction trial. J Int Med 1990; 228:253-56.
11. Greenfield S, Aronow HU, Elashoff RM, Waternabe D. Flaws in mortality data. J Am Med Assoc 1988; 260:2253-5.
12. Vogt TM, Ireland CC, Black D, Camel G, Hughes G. Recruitment of elderly volunteers for a multicenter clinical trial. The SHEP pilot study. Controlled clinical trials 1986; 7:118-33.

Chapter 6

Cost and effects of long-term anticoagulant therapy after myocardial infarction

Journal of the American Medical Association

Abstract

Although the costs associated with monitoring are often mentioned as a major drawback of this mode of therapy, to date no attempts have been made to estimate the costs of long-term anticoagulant treatment relative to its benefits.
We have performed cost-effectiveness analysis, based on the costs of hospital stay during readmissions, costs related to major cardiological interventions and costs of oral anticoagulant treatment.

The costs of oral anticoagulant treatment were estimated at Dfl. 394 per patient year. Placebo patients stayed 18,830 days in the hospital as compared to 15,083 days for anticoagulated patients. Average costs per patient of medical care during follow-up were estimated at Dfl. 10,784 for placebo patients and Dfl. 9,878 for anticoagulated patients.

It is concluded that costs of long-term oral anticoagulant treatment after myocardial infarction are outweighed by the costs of prevented clinical events.

Introduction

The efficacy of long-term oral anticoagulant treatment in hospital survivors of myocardial infarction has recently been investigated in two randomised, double-blind, placebo-controlled trials. Both trials demonstrated a substantial reduction in cardiovascular complications after myocardial infarction as a result of protracted anticoagulant therapy.[1,2] However, long-term anticoagulant treatment is also associated with distinct disadvantages. First, patients on anticoagulant treatment have an increased risk of major bleeding, the incidence of which is estimated at 1 to 3 events per 100 patient-years of treatment.[3,4] Second, to maintain the patient's prothrombin time within the target range, oral anticoagulant treatment requires regular monitoring to adjust dosage of anticoagulants individually.[5] Although the costs associated with monitoring are often mentioned as a major drawback of this mode of therapy, to date no attempts have been made to estimate the costs of long-term anticoagulant treatment relative to its benefits.

Based on the data from the recent Anticoagulation in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial, we have calculated costs and benefits of long-term anticoagulant treatment in post myocardial infarction patients from the societal perspective.

Methods

Study Population

Results of the randomised, double-blind, placebo-controlled ASPECT trial have been reported elsewhere.[2] In short, between September 1986 and January 1992, 3,404 survivors of myocardial infarction were selected from 60 Dutch hospitals for randomisation after a median of 4 days of discharge to oral anticoagulant therapy

or matching placebo. Patients were followed for a mean period of 37 months at one of 19 participating outpatient clinics (thrombosis centres), specialized in the computerized monitoring of oral anticoagulant treatment. No patient was lost to follow-up. The major clinical outcome events were as follows: death occurred in 170 of the 1,700 anticoagulated patients and in 189 of the 1,704 placebo patients, a reduction of 10% (95% confidence interval -11 to 27%). Recurrent myocardial infarction was observed in 114 anticoagulated patients versus 242 placebo patients, a reduction of 53% (41 to 62%), and cerebro-vascular events in 37 anticoagulated patients versus 62 placebo patients, a reduction of 40% (10 to 60%). Major bleeding complications were seen in 73 anticoagulated and 19 placebo patients (relative risk 3.9, 95% confidence interval 2.3 to 6.4)

Assessment of medical care

The present analysis is based on the assessment of all actually observed days of hospitalization and the number of the following interventions: angiography, angioplasty, coronary bypass surgery, the use of thrombolytic agents and oral anticoagulant treatment. Data from hospital admissions during follow-up were obtained from the medical records. All events were blindly classified by the Morbidity and Mortality Classification Committee. Medical care was subdivided into care for vascular events, that are likely to be affected by anticoagulant treatment, and non-vascular events. The vascular events considered here are: recurrent myocardial infarction (and the use of thrombolytic agents), unstable angina pectoris, cardiological interventions (i.e. angiography, angioplasty and coronary bypass surgery), stroke, bleeding complications and arterial or venous thrombo-embolism.

Non-vascular events included hospital admissions for various reasons ranging from pneumonia to elective surgery. No costs were assigned to fatal events that occurred outside the hospital. Indirect costs for patient time and out-of-pocket costs for

patients were not included.

Calculation of costs of hospital care

The number of events and medical care as observed in the trial were multiplied with the estimates of unit costs. Unit costs of hospital care were calculated following the guidelines of the Dutch Ministry of Health in 1993 on costs of health care programmes, which include all costs of hospitalization, i.e. hotel, overhead and medical care costs. The costs of one day in hospital was estimated at Dfl. 773 per day, irrespective of the intensity of care provided, except for costs of additional cardiologic interventions.[6] In addition, costs of cardiologic interventions were estimated on the basis of a weighted average of published unit costs estimates in Dutch hospitals, i.e. Dfl. 3,000 for angiography, Dfl. 5,000 for angioplasty and Dfl. 20,000 for coronary bypass surgery which were appended to the costs associated with the hospitalization.[7] Costs of thrombolytic agents (75% streptokinase, 25% r-tPA) administered during hospital admissions were estimated at Dfl. 500.

Costs of anticoagulant treatment

Costs of oral anticoagulant treatment were calculated from the average rates of monitoring by thrombosis centres in the Netherlands and the costs of anticoagulant medication in 1990. These costs include all procedures of monitoring i.e. getting test results to the patient and advising the patient to adjust the anticoagulant dose. With 17.3 visits on average per year for monitoring and average costs of Dfl. 12.65 per visit, a total cost of Dfl. 219 per patient-year was adopted. Additionally, costs of the anticoagulant drug supply were estimated at Dfl. 175 per patient-year. Consequently, total costs for anticoagulant treatment including monitoring and drug supply amounted to Dfl. 394 per patient-year.

Results

Patients in both treatment groups were similar with respect to characteristics at baseline (Table 1). The number of patients with evidence of impaired left ventricular function such as previous myocardial infarction and high Killip class was low.

Table 1. Baseline characteristics of the randomised patients, according to assigned therapy.

	Anticoagulation	Placebo patients
Number of patients	1700	1704
Mean age (yr ±SD)	61 (±11)	61 (±11)
Male (%)	81	79
Previous myocardial infarction (%)	9	9
Diabetes mellitus (%)	8	7
Thrombolytic agents used (%)	25	25
Aspirin during admission (%)	28	28
Killip class III or IV (%)*	5	5
B-Blocking agents at discharge (%)	51	51

* Highest Killip or MIRU class reached in hospital.

Reasons for hospital admissions are shown in Table 2. After a mean follow-up of 37 months, placebo patients had spent 3,747 more days in hospital as compared to anticoagulated patients. The largest difference in hospital stay between the groups, 2,056 days, resulted from admissions for acute myocardial infarction. The second largest difference, 1,002 days, resulted from admissions for unstable angina. The mean period of hospital stay for the different categories of admissions was very

similar in both patient groups. Placebo patients more often underwent emergency angiography and angioplasty (Table 2). Days of hospitalization related to emergency interventions are not presented because they are incorporated in the hospital stay of the associated event. Hospital days associated with bleeding included all extra-cranial bleeding complications leading to hospital admission, while hospital days related to intra-cranial bleeding complications are included in those concerning stroke.

Table 2. Hospital admissions and associated hospital stay ("intention-to-treat" analysis)

	Anticoagulation		Placebo	
Number of patients	1,700		1,704	
Patient-years of follow-up	5,241		5,200	
	no. of events (total number of days in hospital)			
Vascular events:				
Recurrent MI	110	(1,556)	255	(3,612)
Thrombolysis	25		74	
Unstable angina	216	(2,498)	267	(3,500)
Angiography				
Elective	260	(1,008)	293	(1,074)
Emergency	80		147	
Angioplasty				
Elective	53	(312)	52	(286)
Emergency	18		42	
Bypass surgery				
Elective	89	(1,638)	100	(1,652)
Emergency	39		42	
Cerebro-vascular event	33	(752)	49	(1,080)
Bleeding	64	(737)	21	(224)
Arterial or venous thromboembolism	15	(178)	23	(363)
Non vascular events	484	(6,404)	521	(7,039)
Total		(15,083)		(18,830)

MI, myocardial infarction, ( ) total number of hospital days.

The cumulative number of days in the hospital regardless of the reason for admission for both groups according to the assigned treatment is presented in Figure 1. Total costs are shown in Table 3. Costs have also been discounted at 5%.

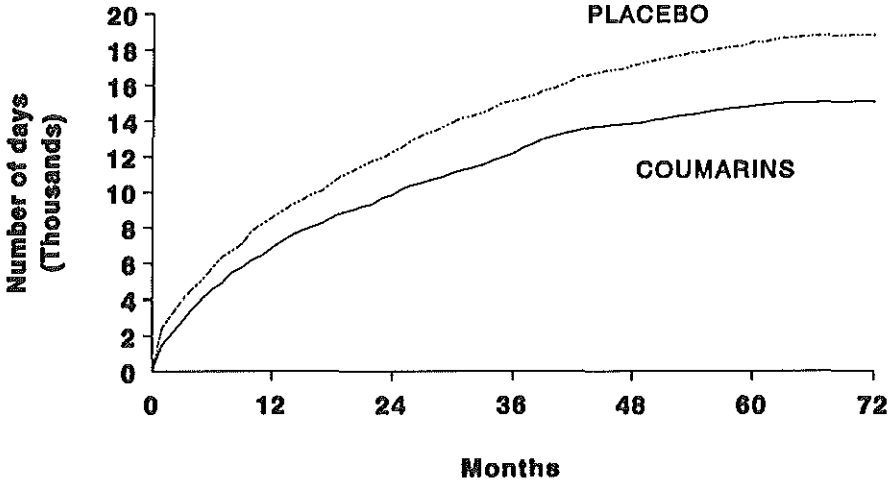

Figure 1. Cumulative number of days in the hospital, according to assigned therapy.

Table 3. Costs of medical treatment per treatment group

	Anticoagulation	Placebo
Vascular events:		
Recurrent MI	1,202,788	2,792,076
Thrombolysis	12,500	37,000
Unstable angina pectoris	1,930,954	2,705,500
Angiography	1,799,184	2,150,202
Angioplasty	596,176	691,078
Bypass surgery	3,826,174	4,116,996
Cerebro-vascular event	581,296	834,840
Bleeding	569,701	173,152
Arterial or venous thromboembolism	137,594	280,599
Non-vascular events	4,950,292	5,441,147
Anticoagulant treatment	2,064,954	
Total	17,671,613	19,222,590
Average costs per patient	10,395	11,281
Discounted at 5%	9,878	10,784

MI; myocardial infarction, costs expressed in Dutch guilders, 1 USD=1.80 Dfl.

The highest disparity in costs of medical care in favour of anticoagulated patients was the result of the higher number of admissions for recurrent myocardial infarction in placebo patients. The highest single contribution in costs of interventions for vascular events was due to coronary bypass surgery in both patient groups.

The total discounted costs for medical care of anticoagulated patients was Dfl. 1,584,093 lower than costs for medical care of placebo patients. Anticoagulant

treatment was associated with 220 (37%) fewer admissions for thrombo-embolic complications and 43 (200%) more admissions for bleeding complications as compared to placebo. Average medical costs during follow-up for anticoagulant patients were Dfl. 886 lower than for placebo patients. When costs are discounted at 5% per year the expected savings are estimated at Dfl. 896.

Sensitivity analysis

To examine whether reasonable variations in our assumptions would seriously affect the calculations, we analyzed how changes in costs of baseline variables would affect the principal outcome. The results of changes in costs of each distinct variable are presented in Table 4. This table shows that the largest effect on average costs of medical care would result from variations in the costs of hospitalization if costs of interventions and anticoagulation were unchanged. It also indicates that reduction of the costs of hospital stay would minimize the economic benefit of anticoagulation. If we would assume an average hospital stay of 7 days for unstable angina pectoris and recurrent myocardial infarction (instead of the number observed in the trial of 13 and 14 days, respectively), the benefit in average costs of anticoagulated patients would decrease to Dfl. 123, nonetheless still in favour of anticoagulation. All other variations in costs of contributing variables, including costs of anticoagulant treatment, would only marginally affect the average costs.

Changes in costs of anticoagulant treatment would affect average costs of medical care less than changes in costs of bypass surgery. The average costs of medical treatment would only become equal if billing figures of anticoagulant treatment would almost double to Dfl. 690 per patient year.

Table 4. Effect on discounted average costs of medical care by changes of the baseline variables by - and + 30%

	Anticoagulation			Placebo	
Discounted average costs in this analysis	9,878			10,784	
Estimation of average costs of medical care per patient if each individual variable would vary 30% around the projected costs.					
Variable	Number	New average costs (-30%)	(+30%)	Number	New average costs (-30%)	(+30%)
Hospital days (Dfl. 773)	15,083	(7,933)	(11,823)	18,830	(8,364)	(13,204)
Angiography (Dfl. 3,000)	340	(9,698)	(10,058)	440	(10,552)	(11,017)
Angioplasty (Dfl. 5,000)	71	(9,815)	(9,940)	94	(10,701)	(10,867)
Bypass surgery (Dfl. 20,000)	128	(9,426)	(10,330)	142	(10,284)	(11,284)
Anticoagulant treatment (Dfl. 394/year)	5,241	(9,554)	(10,201)			

Discussion

When the merits of long-term oral anticoagulant treatment are discussed, high costs of treatment are usually mentioned among the drawbacks inhibiting its large scale application. Our data not only indicate that this notion should be rejected but also that anticoagulant treatment during a mean period of three years after myocardial infarction would save approximately Dfl. 896, equivalent to approximately 519 USD, per patient compared to placebo. The largest contribution to the savings in costs of medical care associated with anticoagulant treatment resulted from the substantial reduction in the rate of recurrent myocardial infarction and related cardiological interventions.

Since the costs associated with hospitalization contribute the most to the total costs, variations in costs of hospital stay would have the most marked influence on the disparity in medical costs between anticoagulated and placebo patients. Nevertheless, even if the average hospital stay for coronary thrombo-ischaemic events were halved (or anticoagulant treatment would be half as efficacious in the prevention of these events), the economic benefit of anticoagulation would still remain. Moreover, it should be noted that this analysis did not consider costs of concomitant medication in ambulant patients and indirect costs, such as absence from work. Since these costs are likely to be positively related to the number of hospital admissions, their consideration would probably further augment costs in placebo patients.

The costs of anticoagulant treatment in this analysis are based on the Dutch situation where monitoring of long-term anticoagulant treatment of outpatients is executed through a unique and efficient network of specialized thrombosis centres. Billing levels for anticoagulant treatment may therefore differ quite substantially from other countries such as the United States. However, costs of other forms of medical care are likely to be equally more expensive. For example, costs of

angioplasty in the United States have recently been estimated at USD 9,000, about three times the unit costs in Holland. If we assume all costs of medical care (including costs of anticoagulant treatment) in the United States to be double of those in Holland, the savings by anticoagulant treatment would also double. The sensitivity analysis illustrates the effect on total costs if the estimated costs of any individual variable would differ considerably fro the true costs. Even so, costs of anticoagulant treatment could almost be doubled in the present analysis before a break-even point in medical costs for both patient groups was reached.

This cost-effectiveness analysis of long-term anticoagulant treatment compares favourably to other interventions for myocardial infarction, usually presented as costs estimates per year of life gained.[8-10] As recent improvements in the medical care of myocardial infarction have improved long-term survival,[11-13] non-fatal events following myocardial infarction will constitute a larger proportion of medical costs in future health care. Our analysis shows that application of anticoagulant treatment even in a low risk population of post myocardial infarction patients with only a moderate incidence of non-fatal thrombo-embolic complications will provide economic benefit.

Despite these transparent results, the implications of this analysis for clinical practice are constrained as the costs and effects of anticoagulant treatment are not compared to alternative antithrombotic drugs such as aspirin. Aspirin has also been shown to reduce thrombo-embolic events after myocardial infarction, although possibly not as efficacious as coumarins, without the need for monitoring.[14,15] A proper evaluation of the economic aspects requires a direct comparison between both therapies. Awaiting the results of such a comparison of treatment strategies, we conclude that long-term oral anticoagulant treatment is cost-effective for the prevention of cardiovascular complications after myocardial infarction.

References

1. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-52.
2. The ASPECT research group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Lancet 1994; 343:499-503.
3. Second report of the Sixty Plus Reinfarction Study Research group. Risks of long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Lancet 1982; i:64-8.
4 Meer van der FJM, Rosendaal FR, Vandenbroucke JP, Briët E. Bleeding complications in oral anticoagulant therapy: an analysis of risk factors. Arch Intern Med 1993; 153:1557-62.
5. Loeliger EA. Laboratory control, optimal therapeutic ranges and therapeutic quality control in oral anticoagulation. Acta Haematol 1985; 74:125-31.
6. Rutten FFH, Van Ineveld BM, Van Ommen R, Van Hout BA, Huijsman R. Kostenberekening bij gezondheidszorgonderzoek; richtlijnen voor de praktijk (costs in health care research; practicle guidelines). Ministry of Health, Rijswijk, The Netherlands 1993.
7. Van den Brand M, van Halem C, van den Brink F, de Feyter P, Serruys P, Suryapranata H, et al. Comparison of costs of percutaneous transluminal coronary angioplasty and coronary bypass surgery for patients with angina pectoris. Eur Heart J 1990; 11:765-71.
8. Vermeer F, Simoons ML, De Zwaan C, Van Es G, Verheugt FWA, Van der Laarse A, et al. Cost benefit analysis of early thrombolytic treatment with intracoronary streptokinase. Br Heart J 1988; 59:527-34.
9. Simoons ML, Vos J, Martens LL. Cost-utility analysis of thrombolytic therapy. Eur Heart J 1991; 12:694-9.
10. Goldman L, Sia STB, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta adrenergic antagonists after acute

myocardial infarction. N Engl J Med 1988; 319:152-7.

11. Simoons ML, Vos J, Tijssen JGP, Vermeer F, Verheugt FWA, Krausse XH, et al. Long-term benefit of thrombolytic therapy.
J Am Coll Card 1989; 14:1609-15.
12. ISIS-2 Collaborative group. A randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. Lancet 1988; ii;349-60.
13. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction.
N Engl J Med 1992; 327:669-77.
14. Antiplatelet trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. BMJ 1988; 296:320-31.
15. Antiplatelet trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.
BMJ 1994; 308:81-106.

Chapter 7

General discussion

General discussion

The ASPECT trial has demonstrated that long-term anticoagulant treatment after myocardial infarction very effectively reduces the incidence of arterial thrombo-embolic events. The moderate effect of oral anticoagulant treatment on mortality can best be explained by examining the contributing causes of vascular death in the trial (chapter 2). The majority of deaths in both groups have been categorized as being either sudden/instantaneous, unobserved/unexpected (which are also most likely to be sudden in onset) or due to congestive heartfailure. As these conditions are more likely to be the result of electrical instability and end-stage ischemia as the result of coronary heart disease rather than coronary thrombosis, anticoagulant treatment would not be expected to yield any effect on these endpoints. As suggested in *chapter 2*, an additional plausible explanation for the modest reduction in mortality would lie in the improved treatment of acute myocardial infarction over the last years leading to a reduced fatality rate.

Although a reduction of coronary thrombotic events by the use of coumarin derivatives could be anticipated in the light of the pathogenesis of arterial sclerosis and coronary thrombosis, most of the trials that have been conducted in the past to investigate the effect of anticoagulant treatment in hospital survivors of myocardial infarction failed to show conclusive results. As demonstrated in *chapter 4*, this inability to provide unequivocal results in individual trials predominantly resulted from insufficient sample sizes. Since the statistical power of a trial largely depends on the number of endpoints, most trials were by definition inadequate in size or follow-up to show the true effect of long-term oral anticoagulant treatment. Combination of all available data according to predefined selection criteria corroborated the results of the ASPECT trial. As demonstrated in *chapter 5*, patients selected for the ASPECT trial differed favourably with respect to the presence of adverse prognostic factors relative to patients who met all the criteria for the trial

but were not randomised. This analysis suggests that selection bias has occurred in the ASPECT trial, favouring patients with better prognosis to participate. A higher participation of patients with impaired prognosis in our trial might have resulted in an higher prevalence of unfavourable prognostic factors, such as previous myocardial infarction, and presumably also in an higher incidence of clinical events. As a consequence, the incidence density rates of the ASPECT trial would probably resemble much closer those of the WARIS trial. However, the investigators of the WARIS trial provided evidence that their population too differed favourably from the general eligible population with respect to mortality,[1] which makes it impossible to speculate about the effect of selection on the number of clinical endpoints in both trials.

An important clinical consideration concerns the identification of patients in whom the effect of long-term oral anticoagulant treatment is less or absent. In *chapter 3* data have been presented that indicate that women and diabetics have only limited benefit of treatment. The presence of diabetes mellitus has previously been shown to interact with the effects of oral anticoagulant treatment in a subgroup analysis of the WARIS trial.[2] Although the results of subgroup analyses should be viewed with caution, the confirmation of this finding in two separate analyses certainly warrants careful consideration before prescribing long-term oral anticoagulant treatment to this particular category of patients. However, more data are needed to substantiate this finding since statistical tests failed to provide evidence of interaction in either subgroup. We have also provided data to suggest that prior myocardial infarction, higher age and the administration of thrombolytic agents during the acute phase of myocardial infarction are independent predictors of cardiovascular complications during follow-up and can therefore identify a subset of patients who may have more benefit from oral anticoagulant treatment.

Although the presently available data suggest that administration of anticoagulant treatment after myocardial infarction has a profound effect on the occurrence of

major clinical events, this mode of therapy is practically constrained as a result of the need of monitoring. While the acceptability of the burden of this procedure is largely and mostly a personal matter, the associated costs are an issue of concern to the society at large. It is therefore important to be informed on the costs and benefits of long-term oral anticoagulant treatment. Our data indicate that application of long-term oral anticoagulant treatment cuts total costs of medical care as compared to placebo treatment. This remarkable result is mainly due to a large reduction in coronary thrombo-ischemic events and associated hospital stay in anticoagulated patients. As our population comprised low-risk patients with a consequently low incidence of thrombo-embolic complications and mortality, it may be speculated that selection of patients who are at higher risk of thrombo-embolic complications would even further improve the cost-effect ratio of anticoagulant therapy.

In summary, our findings support the conclusion that long-term oral anticoagulant therapy after myocardial infarction is associated with a substantial and clinically relevant reduction of thrombo-embolic complications in low risk patients, that the magnitude of this effect is not modified in subgroups of clinically defined post myocardial infarction patients, perhaps with the exception of diabetics, and that this type of therapy is cost effective relative to placebo during the early years after myocardial infarction.

Further research

The conclusions given above are restricted to the effect of oral anticoagulant treatment compared to placebo. The favourable effects of aspirin in acute ischaemic heart disease in previous studies have formed a rational for its administration during the acute phase of myocardial infarction.[3-5] Recent clinical trials have also pointed to a beneficial effect of antiplatelet drugs beyond the acute phase of ischaemic heart disease.[6,7] The common pathogenesis of unstable angina pectoris

and myocardial infarction has facilitated the application of aspirin for both indications. During coronary thrombosis, both activation of thrombin and platelets occur.[8] Subsequent coronary artery thrombi vary in composition from predominantly platelet aggregates in the vessel wall to mainly fibrin accumulation in the lumen. A recent study concluded that fibrin formation and platelet activation are probably equally important in the early hours of myocardial infarction.[9] Aspirin irreversibly acetylates platelet cyclo-oxygenase and thereby prevents conversion of arachidonate to cyclic endoperoxides, hence blocking thromboxane A2 synthesis. This process differs from thrombin induced aggregation of platelets which is unaffected by aspirin. Therefore, inhibition of thrombin is expected both to reduce platelet aggregation and activation of the coagulation cascade, thereby adding to the effect of aspirin on the dynamic process of coronary thrombosis. Otherwise, elevated factor VII coagulant activity, VIIc, has been associated with the risk of ischemic heart disease.[10] It is in particular this procoagulant clotting factor which activity is most rapidly and extensively reduced by coumarin derivatives. On theoretical grounds, oral anticoagulants would have the additional advantage of decreasing the thrombin-mediated platelet aggregation and the generation of factor VIIc, thereby boosting the antithrombotic profylaxis with aspirin. Based on the current knowledge of the pathogenesis of coronary thrombosis, combination of both anticoagulant and antiplatelet drugs seems an rational approach for further reduction of thromboembolic complications after myocardial infarction. Since combination of full dose anticoagulant treatment (with target INR 2.8-4.8) and antiplatelet medication is associated with an unacceptable risk of bleeding,[11,12] combination of a low dose of either drug appears an appealing route for further research. Some studies have already suggested that the combination of both antithrombotic drugs may have a synergistic effect.[13,14] Recent data have also confirmed that a combination of low-dose aspirin and coumarin may not increase the risk of bleeding.[15] and that the combination of aspirin and low intensity anticoagulation may further reduce

recurrent events in the early phase of acute ischaemia compared to aspirin alone.[16] However, the magnitude of the clinical effect and the incidence of bleeding complications of a long-term low-dose combination of both drugs after acute ischaemic heart disease are yet unknown. We therefore stress the need for further clinical trials that compare antiplatelet strategy with anticoagulant treatment and the combination of low intensity oral anticoagulant and low dose aspirin treatment.

References

1. Smith P, Arnesen H. Mortality in non-consenters in a post-myocardial infarction trial. J Int Med 1990; 228:253-56.
2. Smith P, Arnesen H, Abdelnoor M. Effects of long-term anticoagulant therapy in subgroups after acute myocardial infarction.
   Arch Intern Med 1992; 152:993-97.
3. ISIS-2 Collaborative group. A randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. Lancet 1988; ii; 349-60.
4. Lewis HD, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina; results of a Veteran's Administration Cooperative Study.
   N Engl J Med 1983; 309:396-403.
5. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both, in unstable angina. Results of a Canadian multicentre trial. N Engl J Med 1985; 313:1369-75.
6. Meyer A, Verheugt FWA, Werter CJPJ, Lie KI, Pol JMJ van der, Eenige MJ, van. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Circulation 1993; 87:1524-30.
7. The RISC group. Risk of myocardial infarction and death during treatment with low-dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990; 336:827-30.
8. Gulba DC, Bathels M, Westhoff-Bleckj M, Jost S, Rafflenbeul W, Daniel WG, Hecker H, Lichtlen PR. Increased thrombin levels during thrombolytic therapy in acute myocardial infarction. Relevance for the success of therapy.
   Circulation 1991; 83:937-44.
9. Rapold HJ, Haeberli A, Kuemmerli H, Weiss M, Baur HR, Straub WP. Fibrin formation and platelet activation in patients with myocardial infarction and normal coronary arteries. Eur Heart J 1989; 10:323-33.

10. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principle results of the Northwick Park Heart Study. The Lancet 1986; ii:533-37.
11. Pettitti DB, Strom BL, Melmon KL. Prothrombin time ratio and other factors associated with bleeding in patients treated with warfarin. J Clin Epidemiol 1989; 42:759-64.
12. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993; 153:1665-70.
13. Turpie AGG, Gent M, Laupacis A, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med; 329:524-9.
14. Meade TW. Low-dose warfarin and low-dose aspirin in the primary prevention of ischemic heart disease. Am J Cardiol 1990; 65:7C-11C.
15. Meade TW, Roderick PJ, Brennan PJ, Wilkes HC, Kelleher CC. Extra-cranial bleeding and other symptoms due to low dose aspirin and low intensity oral anticoagulation. Tromb Haemost 1992; 68;1-6.
16. Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Circulation 1994; 89:81-8.

Chapter 8

Summary en samenvatting

SUMMARY

This thesis describes the results of studies that have been initiated to assess the effects of long-term oral anticoagulant therapy in hospital survivors of myocardial infarction.

Chapter 1 supplies a short introduction to the process of atherosclerosis which may lead to coronary thrombosis following rupture of a plaque. Prevention of thrombotic complications by inhibition of the activated coagulation cascade by coumarin derivatives forms the rational for the ASPECT trial. In *chapter 2* the results with respect to the main endpoints of the ASPECT trial are described. Oral anticoagulant therapy with an INR of 2,8-4,8 was given to 1,700 patients following discharge after acute myocardial infarction and compared to 1,704 patients taking placebo medication during a mean period of three years. A 10% reduction [95% CI -11% to 27%] in mortality was observed, a 53% reduction [41% to 62%] in recurrent myocardial infarction and a 40% reduction [10% to 60%] in stroke in patients assigned to anticoagulant therapy compared to placebo. Serious bleeding complications occurred fourfold more [95% CI 2,3-6,4] frequently in anticoagulated patients. In *chapter 3* the efficacy of oral anticoagulant treatment in subgroups is described. Subgroups were formed according to age, gender, smoking, diabetes, hypertension, previous MI, heart failure during admission, anterior MI, thrombolysis and beta-blockers. The relative reduction of clinical events by long-term oral anticoagulant treatment did not differ significantly amongst subgroups although the reduction in vascular events appeared lower in women and diabetics. On the other hand, higher age, prior myocardial infarction and thrombolytic therapy were associated with a higher incidence of cardiovascular complications whereas beta-blockers were associated with lower mortality. *Chapter 4* describes the compilation of evidence on the efficacy of oral anticoagulant therapy to reduce death, recurrent myocardial infarction and stroke in patients after

myocardial infarction. In a cumulative meta-analysis it is demonstrated that the use of long-term oral anticoagulant treatment in hospital survivors led to a significantly 10% [95% CI 1% to 19%] reduction in mortality, a 43% [36% to 50%] reduction in recurrent myocardial infarction and a 45% [35% to 60%] reduction in stroke. The results described in *chapter 5* indicate that participants in the ASPECT trial were younger, more often of male gender and used less frequently diuretics and ACE inhibitors compared to eligible but not randomised non-participants. Some of these variables are indicators of left ventricular dysfunction, suggesting that eligible non-participants generally had a worse left ventricular function compared to participants of the ASPECT trial. Older age, previous myocardial infarction and the use of diuretics were independent predictors of mortality in our patients. Thrombolytics and beta-blockers were associated with a lower mortality. Participation showed no association with mortality. Stratification according to the use of diuretics and age almost neutralized the difference in mortality between participants and non-participants. It is therefore concluded that the difference in prognosis between participants and non-participants may have resulted from disparity in these prognostic factors. *Chapter 6* presents the estimated costs of anticoagulant treatment and hospitalization in anticoagulated patients versus costs of hospitalization in placebo patients. It is demonstrated that the costs associated with long-term oral anticoagulant treatment are outweighed by the reduction in medical costs of anticoagulated patients. We therefore concluded that long-term oral anticoagulant treatment is cost-effective compared to placebo in the early years after myocardial infarction.

Samenvatting

Dit proefschrift geeft de resultaten van het 'Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis' (ASPECT) onderzoek weer, dat is uitgevoerd om meer duidelijkheid te verkrijgen over het effect van langdurig voortgezette orale antistollingsbehandeling bij patiënten die een hartinfarct hebben doorgemaakt.

Hoofdstuk 1 geeft een beschrijving van het proces van atherosclerose dat in een gevorderd stadium aanleiding kan geven tot trombosevorming in een kransslagader gevolgd door een hartinfarct. Tevens wordt in het licht van de ontstaanswijze van het hartinfarct ingegaan op het mogelijk nuttige effect van antistollings behandeling hetgeen aanleiding was voor het uitvoeren van het ASPECT-onderzoek.

In *Hoofdstuk 2* worden de belangrijkste resultaten van het ASPECT-onderzoek beschreven. Bij 1700 patiënten werd na gemiddeld 4 dagen na ontslag uit het ziekenhuis begonnen met antistollingsbehandeling bij een trombosedienst. Deze patiënten zijn vergeleken met 1704 patiënten die werden behandeld met placebo. Patiënten die deelnamen aan het onderzoek hadden in vergelijking met recente, eerdere onderzoeken betrekkelijk weinig prognostisch ongunstige parameters. Na een gemiddelde deelnameduur van ruim drie jaar was de sterfte bij patiënten die een antistollingsmiddel gebruikten 10% lager [95% Betrouwbaarheids Interval -11 tot 27%], het optreden van een hartinfarct 53% [95% BI 41 tot 62%] en van een CVA 40% [95% BI 10 tot 60%] in vergelijking met patiënten die placebo gebruikten. Ernstige bloedingscomplicaties traden echter vier maal vaker [95% BI 2,3 tot 6,4] op bij patiënten die antistolling gebruikten.

In *Hoofdstuk 3* wordt het effect beschreven van antistollingsbehandeling in verscheidene subgroepen patiënten. Subgroepen van patiënten werden gevormd aan de hand van leeftijd, geslacht, hoge bloeddruk, eerder hartinfarct, roken, diabetes, hartfalen, voorwand hartinfarct, trombolyse en ß-blokkers. Uit de analyse bleek dat

het effect van antistollingsbehandeling op de vermindering van het aantal cardiovasculaire complicaties in de verschillende groepen patiënten in het algemeen vergelijkbaar was. Een niet significant geringer effect van antistollingsbehandeling op het optreden van vasculaire gebeurtenissen werd gezien bij diabetici en vrouwen. Leeftijd, een eerder hartinfarct en het gebruik van trombolytica bleken geassocieerd met het vaker optreden van cardiovasculaire complicaties na ontslag uit het ziekenhuis. Het gebruik van ß-blokkers bleek daarentegen de kans op sterfte te verlagen.

In *Hoofdstuk 4* wordt aan de hand van een zogenaamde cumulatieve meta-analyse getracht de resultaten van eerdere onderzoeken naar het effect van langdurige antistollings behandeling na een hartinfarct te bundelen. Bij deze analyse bleek dat een significante reductie in sterfte van 10% [95% BI 1 tot 19%], een reductie in recidief hartinfarcten van 43% [95% BI 36 tot 50%] en in CVA's van 45% [95% BI 35 tot 60%] werd bereikt indien de resultaten van de gerandomiseerde onderzoeken werden samengevoegd.

Uit de resultaten van een onderzoek dat wordt beschreven in *Hoofdstuk 5* bleek dat in de groep van patiënten die voldeden aan de insluitingscriteria, maar om onbekende redenen niet deelnamen aan het onderzoek meer ouderen en vrouwen voorkwamen en dat meer patiënten diuretica en ACE-remmers gebruikten in vergelijking met patiënten die wel aan het ASPECT-onderzoek deelnamen. Enkele van deze parameters zijn indirecte indicatoren van een slechtere hartwerking. Leeftijd, het gebruik van diuretica, diabetes en een eerder hartinfarct bleken geassocieerd te zijn met een verhoogde sterftekans terwijl trombolytica en ß-blokkers geassocieerd bleken met een verlaagde kans op sterfte. Deelname aan het onderzoek bleek niet gerelateerd met sterfte. Na indeling van deelnemers en niet-deelnemers aan de hand van leeftijd en het gebruik van diuretica bleek het verschil in sterfte tussen beide groepen patiënten sterk verminderd. Hieruit werd geconcludeerd dat het verschil in sterfte tussen deelnemers en niet-deelnemers

waarschijnlijk het gevolg was van het verschil in de aanwezigheid van prognostisch ongunstige cardiovasculaire factoren.

In *Hoofdstuk 6* worden de kosten geschat van de antistollingsbehandeling en de ziekenhuis opnamen met daaraan gerelateerde cardiologische ingrepen bij patiënten die antistolling gebruikten en vergeleken met de medische kosten van ziekenhuisopnamen van patiënten die placebo gebruikten. De totale kosten van medische behandeling, inclusief de antistollingsbehandeling, van antistollingspatiënten waren lager dan de kosten welke de behandeling van placebopatiënten met zich meebracht. Dit was voornamelijk het gevolg van minder opnamen wegens hartinfarct en instabiele angina pectoris (hartkramp). Wel hadden antistollings patiënten iets meer kosten als gevolg van het optreden van bloeding. Deze uitkomsten geven aan dat langdurige antistollingsbehandeling gedurende de eerste jaren na een hartinfarct kosten-effectief is.

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Curriculum vitae

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He started his medical studies at the University of Amsterdam in 1977 and obtained his medical degree in 1986. Subsequently, he worked as a research fellow on a project of DNA-analysis of patients with autoimmune disease at the Central Laboratory for Bloodtransfusions in Amsterdam. Following a six months period at a pharmaceutical company, he has been a research fellow at the department of Internal Medicine II of the University Hospital Dijkzigt in Rotterdam, were he was involved in the research of diagnosis and treatment of deep venous thrombosis. From 1988 till 1994 he has been coordinator of the ASPECT trial. At present he is a resident of internal medicine in the Rijnland hospital in Leiderdorp (head: W.J. van Amstel) until Januari 1996 when he will start his fellowship cardiology in the St. Antonius hospital (head: N.M. van Hemel) in Nieuwegein.