ORIGINAL INVESTIGATION

Antithrombotic Treatment and the Incidence of Angina Pectoris

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Background: In primary prevention, anticoagulation with warfarin sodium to an international normalized ratio of 1.5 and 75 mg of aspirin per day each reduced the incidence of coronary heart disease (CHD). Effects on the development of angina pectoris and total CHD (resulting from angina, myocardial infarction, and coronary death) have been assessed, particularly in light of recent evidence that warfarin may have a "durable effect" on CHD through effects on the pathologic condition of the vessel walls involved.

Methods: The Thrombosis Prevention Trial was carried out in 5499 men aged 45 through 69 years who were at increased risk of CHD. The trial was factorial, with 1 group taking active warfarin and active aspirin, 1 taking active warfarin and placebo aspirin, 1 taking placebo warfarin and active aspirin, and 1 taking double placebo treatment. In addition to those with myocardial infarction and coronary death, men developing angina pectoris after entry to the trial were identified.

Results: Warfarin appeared to reduce the incidence of stable angina by 16% (95% confidence interval [CI], –14 to 38), although not significantly ($P=.26$), while aspirin increased the incidence by 39% (95% CI, 0 to 91) ($P=.05$). The incidence of stable angina was 37% (95% CI, –1 to 60) less in those taking warfarin than in those taking aspirin ($P=.05$). Warfarin reduced total CHD by 18% (95% CI, 4 to 30) ($P=.01$), while the reduction due to aspirin was 8% (95% CI, –10 to 22) ($P=.36$).

Conclusions: The results are compatible with the concept of a durable effect of warfarin on the chronic pathologic conditions underlying angina, although this has not been established with certainty. Further research is needed to confirm or refute our findings, because they carry potentially important implications for the primary prevention of CHD with the use of antithrombotic agents.

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THE THROMBOSIS Prevention Trial (TPT) was primarily concerned with the value of low-dose antithrombotic treatment in the primary prevention of major episodes of coronary heart disease (CHD), ie, myocardial infarction and coronary death, in middle-aged men at increased risk. We showed[1] that both low-intensity oral anticoagulation with warfarin sodium to an international normalized ratio of about 1.5 and 75 mg of aspirin per day in a controlled-release formulation each reduced the incidence of CHD by about 20%. Warfarin achieved this benefit almost entirely through a reduction in fatal episodes by 39%, while aspirin reduced nonfatal episodes by 32%. Combined treatment with warfarin and aspirin reduced all major CHD, fatal or nonfatal, by 34%. Major episodes are often the first clinical manifestation of CHD, but are frequently preceded by gradual changes in the vessel walls, to which thrombosis and atherogenesis may contribute and which lead to angina pectoris. Results from the Post Coronary Artery Bypass Graft Trial[2,3] indicate that low-dose warfarin may have a "durable effect" on the long-term processes underlying the eventual development of major events, because significant treatment effects with warfarin not seen during the trial treatment phase emerged on long-term follow-up—a 35% reduction in mortality ($P=.008$) and a 31% reduction in myocardial infarction ($P=.003$). Any such durable effect could be, at least partly, through an effect of warfarin delaying the progression of atheroma, which, in turn, would contribute to a delayed onset of angina and eventually to a reduction in major episodes.

Although the onset of angina was not a primary end point in our trial, we now describe the effects of the TPT treat-

PARTICIPANTS AND METHODS

A detailed description of participants and methods has been given elsewhere,[1,4] along with CONSORT guidelines.[5]

PARTICIPANTS

The trial was carried out through 108 group practices in the British Medical Research Council's General Practice Research Framework in men aged 45 through 69 years who were at an increased risk of CHD. At the screening, attended by 61 422 (66%) of the 93 446 invited, smoking history and family history of premature CHD were elicited, body mass index was calculated, blood pressure was measured, and blood was taken for total cholesterol, plasma fibrinogen, and plasma factor VII coagulant activity testing. These variables were weighted according to their association with CHD in the Northwick Park Heart Study.[6] Family history had not been recorded in this study, so a positive history given by entrants to the trial was assumed to increase risk by 50%. A score for each man was then calculated. Within each practice, those men in the top 20% of the risk score distribution, or in the top 25% in regions with particularly high CHD mortality rates, were considered to be eligible for the trial. Of the 10 557 men at increased risk and eligible for the treatment phase, 5499 (52%) entered the trial.

TRIAL TREATMENT

The trial, which was double-blind and placebo-controlled, began as a randomized comparison of warfarin and placebo (prefactorial), which accounts (see "Results" section) for the slightly larger number of men in the analyses following warfarin treatment than in the analyses following aspirin treatment.[1] The full trial was factorial in design, resulting in 4 treatment groups, ie, active warfarin and active aspirin, active warfarin and placebo aspirin, placebo warfarin and active aspirin, and placebo warfarin and placebo aspirin. Warfarin sodium was started at 2.5 mg/d and adjusted by increments or decreases of 0.5 mg/d or 1.0 mg/d at monthly intervals until the international normalized ratio was about 1.5. Dosage changes were matched in men taking placebo warfarin. Aspirin was given as 75 mg/d in a controlled-release formulation.

INCIDENT ANGINA

Men were followed up for a median of 6.8 years for major outcomes (myocardial infarction or coronary death), including those who withdrew from treatment while the trial was in progress. Incident angina was routinely ascertained while men were receiving trial treatment, but they were not followed up for angina if they withdrew. The median follow-up for systematic inquiry about angina was 5.0 years and virtually the same in all 4 treatment groups. A previous history of angina was elicited at screening, and those with angina at recruitment were excluded. Possible cases of incident angina were identified in several ways. First, the annual medical examination included a question about the onset of angina, and the research nurses in the practices reported cases as they arose in between annual examinations by the physician. In addition, and following the initial report of the Antiplatelet Trialists' Collaboration,[7] practices had been advised to initiate treatment of

Table 1. Criteria for Diagnosis of Incident Angina*

Definite (n = 128)	Probable (n = 76)	Doubtful (n = 15)
Coronary angioplasty or coronary artery bypass graft or Physician diagnosis (hospital or GP) and Antianginal therapy and At least 1 or more of the following: Ischemia on resting ECG Positive ECG stress test Angiogram showing atheroma Positive thallium scan Hospital admission for chest pain (or supportive consultant opinion) Subsequent myocardial infarction Autopsy evidence of coronary atheroma	Physician diagnosis (hospital or GP) and Antianginal therapy or At least 1 of the additional criteria under "Definite"	Physician diagnosis (hospital or GP) only or Diagnosis stated as uncertain even if antianginal therapy given

*GP indicates general practitioner; ECG, electrocardiogram.

ments on its development, with results that may have implications for aspirin and warfarin use. In addition, many trials now include the onset of angina and the use of interventions as outcomes, partly because angina represents a clinical development indicating a high risk of major events later and because interventions for angina may delay major episodes that might otherwise have occurred.

RESULTS

Results for angina are shown in **Table 2**. For summary purposes, and to avoid describing results for all 3 categories of certainty, most references are to the results for the combined category of definite and probable cases. For all cases of angina, ie, stable and unstable, and by analysis of main effects, warfarin appears to have reduced cases

angina with (nontrial) aspirin, which meant patients had to withdraw from trial treatment, so that these withdrawals were a further source of information about new cases. Second, the clinical notes of men withdrawn from the trial because of coronary artery bypass grafting or angioplasty were reviewed to identify those in whom angina was the indication and who had not already been ascertained. Third, the clinical notes of all 410 men who had experienced major CHD end points were reviewed to identify those who might have developed angina beforehand and who had not already been notified as having done so. Information was then collected about the basis for diagnosing angina in each patient, either from the general practitioner's notes or from hospital records. In all, 219 cases of apparent incident angina were identified, and these were classified as definite, probable, or doubtful, these decisions being made without knowledge of each man's trial treatment group. Criteria to be satisfied for the 3 categories are shown in **Table 1**, 128 cases (58%) being definite, 76 (35%) probable, and 15 (7%) doubtful (often, in this last group, only because of missing details required for inclusion in the definite or probable groups). Patients were also classified according to a physician's diagnosis as stable (161 [74%]), stable later becoming unstable (11 [5%]), unstable (9 [4%]), or unclassifiable (38 [17%]). The onset of angina occurred within less than 2 months of trial entry in 4 men (2%), between 2 and 6 months in 12 (5%), between 6 and 12 months in 17 (8%), and after more than 12 months in 186 (85%).

The combination of coronary deaths, nonfatal myocardial infarction, and incident angina is described as *total CHD*. Five men developed angina during the prefactorial phase of the trial and subsequently entered the factorial phase, 3 of whom later had nonfatal myocardial infarcts and 1 died of CHD. They have been included in the analysis of the main effects of warfarin but omitted from analyses of the main effects of aspirin and of the 4 separate treatment groups. Forty-two men who had angina at entry to the trial and who were included in our earlier report,[1] 11 of whom later had a myocardial infarct, were omitted from all the present analyses. These omissions make virtually no difference to our previously reported results on coronary death and myocardial infarction, but mean that all those described herein as developing angina did so after entry to the trial (and no reports of angina developing after myocardial infarction were included).

STATISTICAL ANALYSES

Statistical methods have been fully described previously.[1] The main effect of warfarin is given by comparing results in the *active warfarin and active aspirin* and the *active warfarin and placebo aspirin* groups with those in the *placebo warfarin and active aspirin* and the *placebo warfarin* and *placebo aspirin* groups, with the addition of the few cases of incident angina in the prefactorial (warfarin only) stage, ie, comparing the *active warfarin* group with the *placebo warfarin* group. For aspirin, the *active warfarin and active aspirin* and the *placebo warfarin and active aspirin* groups are compared with the *active warfarin and placebo aspirin* and the *placebo warfarin and placebo aspirin* groups. For this report, *main* is used only in this technical sense. All results are based on intention to treat. Comparisons are reported as percentage reductions in the tables, and, where a reduction is negative, this is referred to as a positive increase in the text.

by 11% (95% confidence interval [CI], –17 to 32) ($P=.42$). There was a large, but only marginally significant increase in the incidence of angina in those taking aspirin than in those not, the percentage excess being 33% (95% CI, 0 to 77) ($P=.05$) in the definite and probable category, and being greatest, at 46%, among the definite cases. These results are based on larger numbers than direct comparisons of either active agent (warfarin or aspirin) with placebo in the separate groups (although these comparisons give similar results [data not shown] that are not statistically significant). There were fewer incident cases in those taking warfarin alone compared with aspirin alone, the difference being 31% (95% CI, –5 to 54) ($P=.08$). To confine the results only to cases in which a predominantly long-term, atherogenic process was involved, Table 2 also shows results omitting the 9 unstable cases (7 definite and 2 probable) and the 38 unclassified cases, among whom there were almost certainly some others with unstable onsets. By analysis of main effects and by comparison with all angina (stable and unstable), the apparent reduction due to warfarin on stable angina only is somewhat greater at 16% (95% CI, –14 to 38), although still not significant($P=.26$), while the increase due to aspirin is greater at 39% (95% CI, 0 to 91) and, once again, significant ($P=.05$). The difference between those taking warfarin alone and aspirin alone is now marginally significant, with 37% (95% CI, –1 to 60) fewer cases among those taking warfarin than taking aspirin ($P=.05$).

Table 3 shows results for total CHD, ie, the combination of coronary death, nonfatal infarction, and angina. Of those who developed angina, 36 later experienced major events but are included only once. Warfarin reduced total events by 18% (95% CI, 4 to 30) ($P=.01$), resulting from the large decrease due to warfarin in major fatal events, along with its possible effect on angina (Table 2) and its small (nonsignificant) reduction in major nonfatal events.[1] For aspirin, there was a reduction of about 8% (95% CI, –10 to 22) ($P=.36$), the net result of the reduction due to aspirin in major nonfatal events, the small (nonsignificant) increase in fatal events,[1] and the apparent increase in angina. (Results omitting unstable cases are not shown because the analysis in Table 3 concerns total CHD.)

COMMENT

Compared with myocardial infarction and sudden coronary death, the onset of angina is usually gradual and difficult to date precisely, and it represents the transition from an asymptomatic to a symptomatic stage of a long-term process chiefly due to long-term changes in the vessel walls. Because angina is a strong risk factor for major events later, it is useful to consider whether and, if so, to

Table 2. Onset of Angina by Certainty of Diagnosis*

	Prefactorial		Factorial Groups				Main Effect			
							Warfarin†		Aspirin	
	Warfarin (n = 217)	Placebo (n = 200)	Active Warfarin and Active Aspirin (n = 1269)	Active Warfarin and Placebo Aspirin (n = 1260)	Placebo Warfarin and Active Aspirin (n = 1252)	Double Placebo (n = 1259)	Yes (n = 2746)	No (n = 2711)	Yes (n = 2521)	No (n = 2519)
Angina Pectoris										
Definite	4	6	39	21	31	27	64	64	70	48
Reduction (95% CI), %				33 (–16 to 61) (*P* = .15)			1 (–39 to 30) (*P* = .94)		–46 (–110 to –1) (*P* = .04)	
Definite + probable	5	10	55	37	53	44	97	107	108	81
Reduction (95% CI), %				31 (–5 to 54) (*P* = .08)			11 (–17 to 32) (*P* = .42)		–33 (–77 to 0) (*P* = .05)	
Definite + probable + doubtful	7	13	58	38	57	46	103	116	115	84
Reduction (95% CI), %				34 (1 to 56) (*P* = .04)			12 (–14 to 32) (*P* = .32)		–37 (–80 to –4) (*P* = .03)	
Stable Angina Pectoris										
Definite	3	5	28	12	24	18	43	47	52	30
Reduction (95% CI), %				50 (1 to 75) (*P* = .04)			10 (–36 to 40) (*P* = .63)		–73 (–171 to –11) (*P* = .01)	
Definite + probable	4	9	42	28	44	34	74	87	86	62
Reduction (95% CI), %				37 (–1 to 60) (P = .05)			16 (–14 to 38) (*P* = .26)		–39 (–91 to 0) (*P* = .05)	
Definite + probable + doubtful	4	11	45	29	47	36	78	94	92	65
Reduction (95% CI), %				39 (3 to 61) (*P* = .03)			18 (–10 to 39) (*P* = .19)		–41 (–93 to –3) (*P* = .03)	

*Data are given as number of patients unless otherwise indicated. CI indicates confidence interval.
†Includes prefactorial cases.

Table 3. Onset of Total Coronary Heart Disease (Coronary Deaths, Nonfatal Myocardial Infarction, and Angina) by Certainty of Angina Diagnosis*

	Prefactorial		Factorial Groups				Main Effect			
							Warfarin†		Aspirin	
	Warfarin (n = 217)	Placebo (n = 200)	Active Warfarin and Active Aspirin (n = 1269)	Active Warfarin and Placebo Aspirin (n = 1260)	Placebo Warfarin and Active Aspirin (n = 1252)	Double Placebo (n = 1259)	Yes (n = 2746)	No (n = 2711)	Yes (n = 2521)	No (n = 2519)
Definite	32	42	97	98	103	128	227	273	200	226
Reduction (95% CI), %				5 (–23 to 28) (*P* = .68)			18 (3 to 31) (*P* = .02)		12 (–6 to 26) (*P* = .19)	
Definite + probable	32	46	112	113	123	141	257	310	235	254
Reduction (95% CI), %				9 (–17 to 28) (*P* = .46)			18 (4 to 30) (*P* = .01)		8 (–10 to 22) (*P* = .36)	
Definite + probable + doubtful	34	49	115	114	127	143	263	319	242	257
Reduction (95% CI), %				11 (–14 to 30) (*P* = .35)			19 (5 to 30) (*P* = .009)		6 (–11 to 20) (*P* = .47)	

*Data are given as number of patients unless otherwise indicated.
†Includes prefactorial cases.

what extent its onset may be affected by antithrombotic and other treatments. In the case of warfarin, assessing its effect on stable angina provides another approach to identifying a possible durable effect.

The diagnosis of angina is often notoriously difficult to establish with certainty.[8] We have therefore avoided any rigid, single definition and have shown results according to different levels of certainty. Diagnostic accu-

Table 4. Overview of Trials of Aspirin and Incident Angina*

Source	Men, %	Mean Age, y	Mean Follow-up, y	Aspirin			Placebo			Odds Ratio (95% Confidence Interval)
				Angina	Participants	Rate per 1000 Person-Years	Angina	Participants	Rate per 1000 Person-Years	
US Physicians' Health Study[14]	100	53.1	4.9	278	10 859	5.2	247	10 879	4.6	1.13 (0.95-1.35)
Thrombosis Prevention Trial[1]	100	57.5	6.4	108	2521	6.7	81	2519	5.1	1.35 (1.00-1.81)
Primary Prevention Project[15]	42	64.4	3.6	74	2226	9.1	96	2269	11.6	0.78 (0.57-1.06)

*Data are given as number of patients unless otherwise indicated. Test for heterogeneity, $P = .03$.

racy is improved by inquiring about angina on several occasions,[8] which we were able to achieve because the physicians asked about it at each annual medical examination over a median of 5.0 years. Because of the close and frequent contacts of trial participants with their health care teams and the different ways in which possible cases of new angina were ascertained, it is probable that most cases were identified during follow-up, when information on angina was systematically available on all men. There is no obvious way in which any incomplete ascertainment could have occurred differentially by trial treatment group. The double-blind placebo-controlled nature of the trial makes it unlikely that diagnoses (either by general practitioners or in hospitals) were biased by knowledge of treatment group or, particularly, whether treatment was with a warfarin- or aspirin-containing regimen, even when a report of bleeding might have suggested that a man was taking 1 of the 3 active regimens. In most men (85%), angina occurred more than a year after entry to the trial, so that treatment would have had time to exert an effect. Exclusion of the 9 unstable angina cases and the 38 unclassified cases (among whom there were almost certainly some other unstable cases) omitted those in whom there was probably a significant acute, thrombotic component.[9]

Results for stable cases only, ie, those predominantly due to long-term processes affecting the vessel walls, are somewhat clearer than for all cases (Table 2). The possible reduction in stable angina in the warfarin group is 16% (although not significant), and the increase apparently due to aspirin is 39% (95% CI, 0 to 91) ($P = .05$). The difference between those taking warfarin alone and those taking aspirin alone is 37% (95% CI, –1 to 60) ($P = .05$), so it is possible that the incidence of angina is truly lower in those taking warfarin than in those taking aspirin.

There appears to have been little research on the effect of warfarin on angina or on the long-term vessel wall changes in CHD (as distinct from major end points such as myocardial infarction and coronary death). However, warfarin reduces thrombin production, which may affect atherogenesis in several ways. These include its ability to form fibrin and platelet aggregates, to stimulate the production of tissue plasminogen activator and plasminogen activator inhibitor-1. This sequence of events may lead to atherogenic fibrin degradation products and to the production of interleukin 1β by macrophages, thereby inducing the expression of the intracellular adhesion molecule 1 and the proliferation of vascular smooth muscle.[10] A study in patients undergoing transesophageal echocardiography has reported that those with more severe grades of aortic atheroma receiving oral anticoagulants subsequently experienced a significantly lower mortality rate than those treated with aspirin,[11] which, although not from a randomized trial, accords with our finding[1] on mortality. The recent findings from the Post Coronary Artery Bypass Graft trial[3] might be, at least in part, due to some of these effects.

Studies on aspirin do not, until perhaps recently, suggest that it beneficially affects either the long-term pathologic processes of CHD or the onset of angina pectoris. Ranke et al[12] carried out high-resolution duplex carotid ultrasound testing for carotid artery atherosclerosis in 27 participants in the Low Dose Aspirin Trial on Restenosis After Angioplasty in patients with stenoses in lower limb arteries. The carotid plaque area was unchanged with 900 mg/d of aspirin but increased "markedly" in those taking 50 mg/d. These results are compatible with a benefit due to a high, but not a low, dosage of aspirin, as in our trial in the latter instance, although they come from an observational study in a small selected subgroup of patients. An autopsy study claimed a lower prevalence of atherosclerosis in patients with a history of arthritis of more than 8 years (but not of 8 years or less) who had taken aspirin, compared with a control group, but included symptomatic outcomes, such as myocardial infarction and stroke, and pathological findings.[13] We have found a significant increase in incident angina of about 33% due to aspirin, or somewhat more if only stable angina is considered (Table 2). The US Physicians' Health Study, comparing those taking 325 mg of aspirin on alternate days vs placebo in a double-blind randomized trial, has reported that, in contrast to its immediate and sustained effect on myocardial infarction, aspirin conferred no long-term benefit on the development of angina pectoris,[14] perhaps marginally, but not significantly, increasing its incidence. On the other hand, the Collaborative Group of the Primary Prevention Project in Italy[15] has recently reported a nonsignificant 22% reduction in angina due to a 75-mg/d regimen of aspirin (including patients undergoing interventions). **Table 4** summarizes the findings on aspirin and angina from the 3 studies with data on this association. The only significant effect is the increase due to aspirin in the TPT. However, there is significant heterogeneity between the 3 trials, possibly because of the characteristics of those recruited into each of them. Any effect of aspirin on total CHD depends chiefly on the

substantial reduction in nonfatal major events, which has been reported by all but one[16] of the primary prevention trials. Other trials besides the TPT have described little or no effect of aspirin on fatal events in primary prevention,[17,18] on which the balance of aspirin on total CHD also depends, although the Italian trial[15] indicates a reduction in these events and in those that are nonfatal.

This study has dealt with the possible effects of antithrombotic therapy on angina, with the finding (suggested elsewhere[14] as well) that aspirin may not only be ineffective but also may increase its incidence. However, we emphasize the clear value of aspirin on the risk of myocardial infarction in primary and secondary prevention. In addition, the combination of low-dose aspirin and low-intensity anticoagulation with warfarin seems to reduce the risk of fatal events, which is not entirely clear for aspirin alone, and of nonfatal events. Consequently, the incidence of all major CHD events may be reduced by about a third, so that the combination should perhaps be used more frequently when primary prevention by antithrombotic measures in those at particular risk is under consideration.

In summary, the point estimates for our results on taking warfarin for stable angina (Table 2) are compatible with the concept of a durable effect of warfarin in reducing the incidence of angina on the assumption that this is due to chronic, long-term processes. However, the findings were not significant, and the CIs indicate that the incidence may increase, as with aspirin. A difference between the Post Coronary Artery Bypass Graft trial and the TPT is that benefit in the former was not apparent until after trial treatment had ceased, whereas any effect of warfarin on angina in the TPT (if this actually occurred) was seen during the trial treatment. However, compared with primary prevention, more intensive anticoagulation may be necessary to achieve the short-term antithrombotic effect of warfarin in settings other than primary prevention. Warfarin reduced all major events in the TPT by 20%,[1] which is compatible with the magnitude of its effect on all major events in secondary prevention trials, so the distinction between its effects on fatal and nonfatal events in the TPT may not be relevant in assessing its overall effect on the sum of major events and angina. Our results suggest that the incidence of stable angina is about a third lower in those taking warfarin than aspirin and clearly need to be confirmed or refuted, but if warfarin has advantages over aspirin and if it has a durable and an antithrombotic effect, the case for considering its use in primary (and secondary) prevention is strengthened. In the TPT, taking low-dose warfarin was no more hazardous than taking 75 mg of aspirin per day,[1] and the feasibility of dosage monitoring is improving with near-patient testing and self-testing methods similar to those used in diabetes mellitus, so regimens of this kind may be more practicable than is often assumed.

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