ORIGINAL INVESTIGATION

Thrombosis Prevention Trial

Compliance With Warfarin Treatment and Investigation of a Retained Effect

Alicja R. Rudnicka, PhD; Deborah Ashby, PhD; Patrick Brennan, MSc; Tom Meade, MD

Background: The Thrombosis Prevention Trial was a primary prevention factorial trial that reported a reduction in the risk of coronary heart disease (CHD) with warfarin and/or aspirin. This article examines compliance (duration of treatment) with warfarin treatment and whether warfarin has a retained effect.

Methods: Risk of CHD while complying with warfarin treatment was compared with risk of CHD in all participants randomized to placebo. Simultaneously, risk of CHD in ex–warfarin users was compared with controls receiving placebo to determine the possiblility of a retained effect. A second analysis, preserving the advantage of randomization, estimated the potential increase in the time to a CHD event in patients randomized to active treatment compared with patients randomized to placebo, if all patients in both active and placebo groups had fully complied with the trial treatment.

Results: Risk of all CHD while complying with warfarin treatment was associated with a hazard ratio (HR) of 0.75 (95% confidence interval [CI], 0.60-0.94), which was lower than the HR obtained by intention-to-treat analysis (0.79; 95% CI, 0.65-0.96). Regarding fatal cases of CHD, the HR was 0.49 (95% CI, 0.32-0.75) while compliant with warfarin treatment, which is also lower than the HR obtained by intention-to-treat analysis (0.61, 95% CI, 0.43-0.85). Ex–warfarin users had a retained risk reduction of 23% for all CHD (0.77; 95% CI, 0.58-1.02) and of 34% for fatal events (0.66; 95% CI, 0.41-1.04). Expected survival time to a CHD event if patients randomized to warfarin had fully complied with treatment was 1.39 times greater (95% CI, 1.12-1.69) than if patients randomized to placebo had fully complied with placebo, whereas for fatal CHD the relative increase in survival time was 2.04 times greater for the former (95% CI, 1.43-2.86).

Conclusions: Full compliance with warfarin treatment may lower by 50% the risk of fatal CHD. There is also evidence of a retained effect. These results strengthen previous evidence of the potential benefits of low-intensity oral anticoagulation with warfarin.

Arch Intern Med. 2003;163:1454-1460

From the Department of Environmental and Preventive Medicine (Drs Rudnicka and Ashby), Medical Research Council Epidemiology and Medical Care Unit (Mr Brennan and Dr Meade), Wolfson Institute of Preventive Medicine, London, England.
The authors have no relevant financial interest in this article.

THE THROMBOSIS Prevention Trial[1] showed that both low-intensity anticoagulation with warfarin to a therapeutic international normalized ratio (INR) of about 1.5 and low-dose aspirin (75 mg/d) reduced the incidence of first episodes of coronary heart disease (CHD) in men at increased risk by approximately 20%. Aspirin treatment provided a 32% reduction in nonfatal events as well as a nonsignificant 12% increase in fatal events. Warfarin treatment reduced fatal events by 39% and nonfatal events by a nonsignificant 12%. The combined regimen of warfarin and aspirin reduced all events, fatal and nonfatal combined, by 34%. These results are from analyses by intention to treat. This means that all adverse events were analyzed in the groups to which the participants experiencing them had originally been randomly allocated, whether or not they withdrew from treatment during the trial or, having withdrawn, took a nontrial treatment for clinical indications (usually aspirin).

Since it is not possible to predict which first CHD events will prove fatal, the apparently marked effect of warfarin in reducing fatal events is potentially of considerable importance, and must be confirmed or refuted in other primary prevention trials. In the Thrombosis Prevention Trial, about half of the the participants withdrew from randomized treatment at some stage, although mostly later on, so that about two thirds of all person-years were spent in the allocated treatment. It would be useful if reliable data on the effect of full compliance with treatment could be established, eg, by confining analyses

to CHD events that occurred while the trial treatment was being adhered to. However, the pitfalls of on-treatment analyses are well known. They arise mainly from the possibility that withdrawal from treatment is influenced by characteristics associated with the risk of CHD; and if withdrawal rates differ between treatment groups, the groups are no longer strictly comparable, which may cause significant bias in the results.

One purpose of this article was to present a detailed approach to this problem. As far as possible, all potential sources of bias were identified and allowed for, and comparisons were made in a way that retained the benefits of randomization while permitting an assessment of the effect of full compliance. The rate of noncompliance with trial treatment is probably high in a long-term trial of warfarin, mostly because bleeding episodes, including minor ones, rightly or wrongly, are attributed to the medication, and also because of patients' reluctance for regular visits for INR checking and dose adjustments. Thus, compliance with warfarin treatment may be of greater importance than compliance with many other medications, and this justifies the special attention given to it in this article.

A second purpose was to determine whether there is any evidence of a retained benefit from warfarin treatment, ie, an effect beyond its short-term antithrombotic properties. This possibility has recently arisen from the Post Coronary Artery Bypass Graft trial,[2,3] which showed significant treatment effects with warfarin not seen during the trial treatment phase, but emerging on long-term follow-up (a 35% reduction in mortality [$P = .008$] and a 31% reduction in myocardial infarction [$P = .003$]). Such retained or durable effect could be attributable, at least partly, to warfarin's capacity to delay the progression of atheroma, a possibility supported by experimental studies.[4]

METHODS

PARTICIPANTS

Trial participants have been described in detail elsewhere and according to CONSORT (Consolidated Standards of Reporting Trials) criteria.[1] The trial was carried out through 108 group practices in the British Medical Research Council's General Practice Research Framework among men aged between 45 and 69 years who were at increased risk of CHD. Smoking history and family history of premature CHD were obtained, body mass index calculated, blood pressure measured, and blood taken for assessment of total cholesterol, plasma fibrinogen, and plasma factor VII coagulant activity. These variables were weighted according to their association with CHD in the Northwick Park Heart Study.[5] A score for each man was then calculated. Within each practice, men who were 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, a total of 5499 (52%) entered the trial.

TRIAL TREATMENT

The trial, which was double-blind and placebo controlled, included both warfarin and aspirin treatments and was factorial in design, resulting in 4 treatment groups who received the following: active warfarin and active aspirin (WA); active warfarin and placebo aspirin (W); placebo warfarin and active aspirin (A); and placebo warfarin and placebo aspirin (P). For each patient, warfarin treatment was started at a dose of 2.5 mg/d, and adjusted by increments or decreases of 0.5 mg/d or 1.0 mg/d at monthly intervals until his INR was about 1.5. Dose changes were matched in men taking placebo warfarin. Aspirin was given at a dose of 75 mg/d in a controlled-release formulation. The use of nontrial warfarin was infrequent. On the other hand, nontrial aspirin was used often, particularly by men who developed angina. Compliance and the possibility of a retained treatment effect due to aspirin are therefore not considered here. Withdrawal from any trial treatment was permanent, ie, treatment was not reintroduced subsequently.

FOLLOW-UP

Men were followed up for a median duration of 6.8 years for major outcomes (myocardial infarction or coronary death), including those who withdrew from treatment while the trial was in progress.[1] All CHD was defined as the sum of coronary deaths and fatal and nonfatal myocardial infarction. There were 410 events, of which 142 were fatal and 268 nonfatal. Stroke was a secondary outcome, of which 106 were fatal and 23 nonfatal.

STATISTICAL ANALYSIS

The treatment effect of warfarin is given by comparing results in the WA and W groups with those in the A and P groups.

Reasons for noncompliance with trial treatment were summarized overall and according to treatment allocation. Nearly all men who withdrew from randomized treatment nevertheless spent some time taking it and are therefore described as partially compliant rather than noncompliant. *Ex–warfarin users* refers to those allocated to active warfarin treatment after they had stopped taking the medication. *Fully compliant patients* or *full compliers* describe individuals who adhered to their randomized treatment for the entire duration of follow-up. Differences in baseline covariates were compared between full compliers and partial compliers. Withdrawal patterns from trial treatment overall and stratified by 2-year intervals were examined for active and placebo groups. The log odds of withdrawing from trial treatment (active or placebo) were examined with respect to the baseline covariates.

Results obtained from the intention-to-treat analysis (ITT) are given for comparison with the on-treatment analysis 1 (OT1); the latter shows the ratio of the risk while compliant with warfarin treatment to the risk in all patients randomized to placebo as a measure of the treatment effect of warfarin on patients while compliant. Another analysis using risk while complying with placebo as denominator gave virtually identical results.

The on-treatment analysis 2 (OT2) shows the ratio of the risk in ex–warfarin users to the risk in all patients randomized to placebo as a direct measure of any retained protection from active warfarin. These 2 effects were modeled simultaneously using a Cox proportional hazard model that included the main effect of adhering to active treatment (OT1) and a time-updated variable indicating previous participation in active treatment (OT2). The results are expressed as hazard ratios (HRs). Results from ITT, which included all patients randomly allocated to a warfarin group whether or not they were compliant, will contain the contribution of any retained effect of warfarin. Thus, if there were no such effect, the HR from ITT would be diluted (closer to 1.0) compared with the HR from OT1.

A sensitivity analysis was performed to assess the impact of redefining compliance on estimates of OT1 and OT2. Patients who had been off treatment for up to 1, 3, 6, or 12 months

Table 1. Reasons for Withdrawing From Trial Treatment According to Randomized Allocation

Reason	Treatment Allocation, No. (%)		Total, No. (%)
	Placebo	Active	
Hypertension	36 (2)	26 (1)	**62** (2)
Bleeding	132 (8)	205 (12)	**337** (10)
Other serious disease	272 (16)	247 (14)	**519** (15)
Incompatible drugs	111 (6)	118 (7)	**229** (7)
Alcohol abuse	18 (1)	32 (2)	**50** (1)
Other*	918 (54)	918 (53)	**1836** (53)
Fatal or nonfatal CHD	163 (10)	117 (7)	**280** (8)
Fatal or nonfatal stroke	35 (2)	39 (2)	**74** (2)
Death from other cause	28 (2)	37 (2)	**65** (2)
Total	**1713 (100)**	**1739 (100)**	**3452 (100)**

Abbreviation: CHD, coronary heart disease.
*Including mainly nonspecific reasons: some patients left the area (4%), their clinic closed (4%), or they had transient ischemic attacks (<1%).

were included as compliers in OT1, and this redefined ex–warfarin users as those who had been off treatment for at least 1, 3, 6, or 12 months.

Finally, a method to allow for the time spent on active treatment was chosen. An accelerated life model proposed by Robins and Tsiatis[6] was used to determine what the survival increase would have been if everyone in the active treatment group had been fully compliant to the end of the study, and nobody in the placebo group had received active treatment. Korhonen et al[7] adapted this model in which the treatment effect is proportional to the time spent on treatment and assumed that withdrawal from trial treatment, as was the case in this trial, is permanent (active treatment is not reintroduced at a later date). In our trial survival time is the time from randomization to a CHD event (the sum of coronary deaths and fatal and nonfatal myocardial infarction). The model is based on the notion of a treatment-free survival time, ie, what the survival time to the first CHD event would have been in the absence of active treatment. The treatment effect is estimated on the assumption that treatment-free survival times are equally distributed between randomized groups. Treatment-free survival time was directly observed for men in the placebo group who died or had a terminating adverse event prior to the end of the study's observation period—it was assumed that the placebo group did not have access to active treatment. However, because most men were still alive and event free at the end of the trial, recensoring of the data had to be performed.[7] In this analysis, the treatment effect was the increase in time to a CHD event in patients randomized to active treatment compared with patients randomized to placebo, if all patients in both active and placebo groups had fully complied with trial treatment. Causes of death other than CHD are censored; thus, when this technique is applied to a particular cause of death, the change in survival time is that observed if no other cause is acting. This method has the advantage of using information on all end points, and of preserving randomization since all events are assigned to the originally allocated treatment group.

RESULTS

At 5 years, 4360 men (79%) were still in the trial. Of the 2158 in the placebo warfarin arms of the trial (A and P), 62% were still adhering to their trial treatment; and of the 2202 in the active warfarin arms (WA and W), 60% were still adhering to their trial treatment. **Table 1** summarizes reasons for withdrawing from trial treatment prior to the end of the study. Apart from the slightly higher proportion of men who withdrew because of bleeding episodes in the active warfarin treatment arm (12% vs 8% receiving placebo), and an awareness that warfarin treatment led to fewer CHD events, reasons for withdrawing were similar between the active treatment and placebo groups. The **Figure** shows that the times at which patients in the active warfarin treatment and placebo groups withdrew were also much the same.

Table 2 shows that, apart from a significantly higher proportion of smokers among the partial compliers, mean values for characteristics recorded at trial entry were similar for compliers and partial compliers in each of the active and placebo groups. Logistic regression also indicated age as a weak confounder regarding withdrawal from trial treatment (details not given). Although the average age in full and partial compliers was similar, nonetheless the odds of withdrawing from trial treatment increased marginally across quintiles of age.

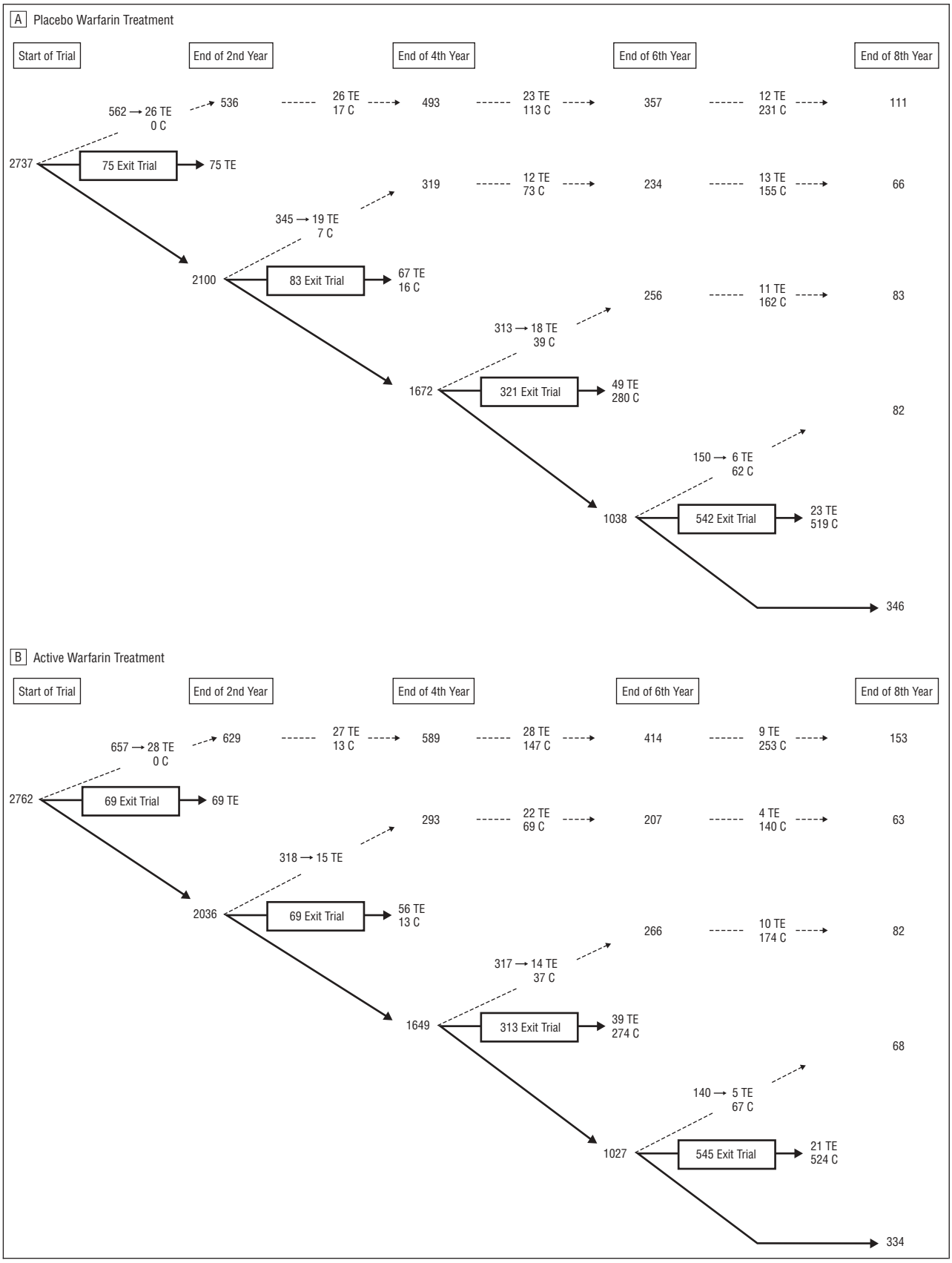
Table 3 shows that, in partial compliers, times spent on or off treatment were similar in the active and placebo groups.

Table 4 shows the effect of complying with warfarin treatment. The numbers of adverse events are lower with OT1 than with ITT because only those occurring while patients were on treatment were included. The HR for all CHD is 0.75 (95% CI, 0.60-0.94) with OT1, compared with 0.79 (0.65-0.96) with ITT. For fatal CHD the HR is 0.49 (95% CI, 0.32-0.75) with OT1, compared with 0.61 (95 % CI, 0.43-0.85) with ITT—a reduction of 51% compared with one of 39%, although the 95% CIs overlap. Adjustment for smoking and age made virtually no difference with OT1.

Table 5 shows results obtained with OT2, which assessed the possibility of a retained effect of warfarin. In the unadjusted analysis, ex–warfarin users maintained a reduction in all CHD events of about 14% (HR, 0.86; 95% CI, 0.66-1.15), though this is less than the HR obtained with ITT, and a reduction of 17% in fatal events (HR, 0.83; 95% CI, 0.53-1.30). Adjustment for smoking and age noticeably reduced rather than increased the HRs, so that the reduction in fatal events was 34% (HR, 0.66; 95% CI, 0.41-1.04) and of marginal statistical significance, as was the adjusted value of 23% reduction in risk for all CHD.

Table 6 shows the sensitivity analysis and suggests that any retained effect lasts for at least 1 year, since ex–warfarin users who had been off treatment for at least 12 months still appeared to retain some benefit (albeit the CIs are quite wide).

Table 7 shows the results that would be obtained with fully compliant patients during the trial using the accelerated failure time model. One interpretation of the accelerated life model results is that the survival time of an individual on active treatment is a multiple of the survival time that man would have experienced taking placebo. For example, a full complier's expected survival time without experiencing a CHD event is 1.39 times greater than that of patients always taking placebo, and for fatal



At the start of the trial 2737 men were randomized to placebo (A) and 2762 to active warfarin treatment (B). Within the first 2 years there were 69 terminating events in the warfarin group while participants were taking treatment; of the 657 who withdrew from warfarin treatment, 28 experienced a terminating event. Thus, entering the second year of the trial, 629 participants had withdrawn from warfarin treatment and 2036 were fully compliant. Dashed lines follow partial compliers and solid lines full compliers. TE indicates terminating events; C, censoring.

Table 2. Baseline Characteristics of Full and Partial Compliers*

Characteristic	Full Compliers			Partial Compliers		
	All	On Active Treatment	Taking Placebo	All	On Active Treatment	Taking Placebo
Age, y	57.2 (6.6)	57.3 (6.7)	57.2 (6.5)	57.5 (6.8)	57.4 (6.9)	57.5 (6.7)
Systolic BP, mm Hg	139 (18)	139 (18)	139 (18)	139 (19)	139 (18)	138 (19)
BMI	27.4 (3.5)	27.3 (3.4)	27.4 (3.6)	27.4 (3.7)	27.5 (3.8)	27.3 (3.6)
Cholesterol, mg/dL	247 (39)	247 (39)	247 (39)	247 (39)	247 (39)	244 (39)
Fibrinogen, g/L	3.01 (0.57)	3.03 (0.56)	3.01 (0.57)	3.05 (0.61)	3.03 (0.60)	3.07 (0.61)
Factor VII, % of standard	115 (32)	115 (31)	116 (31)	116 (32)	116 (32)	115 (32)
Smokers, %	37	37	38	46	45	46
Family history of CHD, %	16	16	16	15	14	15

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); BP, blood pressure; CHD, coronary heart disease.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.02586.

*Values are given as mean (SD) unless otherwise indicated.

Table 3. Median Time in Years On and Off Trial Treatment

	Active Treatment		Placebo	
	On	Off	On	Off
All full compliers	6.6	. . .	6.6	. . .
All partial compliers	2.5	3.7	2.8	3.6

Table 4. Risk of CHD Event While Complying With Warfarin Treatment (OT1 Analysis) Compared With Risk in ITT Analysis*

	ITT		OT1	
	Events, No.	HR (95% CI)	Events, No.	HR (95% CI)
All CHD	410	0.79 (0.65-0.96)	345	0.75 (0.60-0.94)
Fatal CHD	142	0.61 (0.43-0.85)	117	0.49 (0.32-0.75)
Nonfatal CHD	268	0.90 (0.71-1.15)	228	0.91 (0.69-1.19)
Strokes	106	1.15 (0.78-1.68)	88	1.20 (0.79-1.84)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat analysis; OT1, on-treatment analysis 1.

*Differences in results from the 2 analyses are due to fewer events in partial compliers randomized to the warfarin group. The number of events was the same with both analyses in the placebo group.

CHD there is more than a doubling. Both 95% CIs exclude 1.00 for these results. If the treatment-free survival times follow an exponential distribution under full compliance, the estimate from this model is equivalent to that obtained from a Cox proportional hazard model. The inverse of the values in Table 7 give survival time as 28% less for patients always on placebo than for those always on active treatment for all CHD, whereas for fatal CHD, expected survival time is 51% less for patients taking placebo. These estimates are specifically for survival time until a CHD event, as other causes of death are censored. It appears that active warfarin treatment may marginally decrease the time to a stroke event, although this result is not statistically significant. This may be due to the inclusion of individuals taking aspirin and warfarin who had an increased risk of cerebral hemorrhage.[1]

COMMENT

The potential difficulties and misleading implications of on-treatment analyses are widely appreciated. It may, however, be short-sighted to overlook the use of on-treatment analyses altogether, particularly—as was the case in this trial—when the ITT indication of an effect on fatal episodes is large, and a similar trial is unlikely to be carried out in the foreseeable future. We have taken detailed account of any possible effects of differences between treatment compliers and partial compliers. Apart from episodes of bleeding and differences in numbers of CHD events arising from the warfarin treatment effects, reasons for withdrawing from trial treatment were similar in the warfarin and placebo groups, and the numbers of patients withdrawing at different stages were also similar. The median times spent on and off treatment by partial compliers were much the same in those initially randomized to active or placebo treatment. Adjustment for 2 differences in baseline characteristics between full and partial compliers, particularly smoking but also age, made almost no difference in the OT1 analysis, which demonstrated a greater protective effect compared with ITT against fatal CHD. Compliance with warfarin is associated with greater protection, particularly from fatal CHD. Adjustment for confounders actually increased rather than reduced the indication of retained benefit with active warfarin, a result that may be partly due to allowance for the adverse effect of smoking. However, we recognize that these steps may not have allowed for all possible biases. For example, men withdrawing from trial treatment may have a better prognosis than full compliers even after smoking and age are taken into consideration, and this would explain, at least in part, the OT2 results on the retained effect. However, the relative survival time analysis (Table 7) preserves the benefit of randomization in attributing all adverse CHD events to the group to which each participant was originally randomized. This analysis suggests that full compliance could have effects suggested by OT1.

It would be surprising if full compliance were not associated with a greater benefit than partial compliance since, for most medicines, full compliance ensures a continuing pharmacological effect. Three other

Table 5. Risk of CHD Event in Ex–Warfarin Users Unadjusted and Adjusted for Smoking and Age (OT2 Analysis) Compared With ITT Analysis*

	ITT		OT2 (Unadjusted) Ex-Warfarin		OT2 (Adjusted) Ex-Warfarin, HR (95% CI)
	Events, No.	HR (95% CI)	Events, No.	HR (95% CI)	
All CHD	410	0.79 (0.65-0.96)	293	0.86 (0.66-1.15)	0.77 (0.58-1.02)
Fatal CHD	142	0.61 (0.43-0.85)	113	0.83 (0.53-1.30)	0.66 (0.41-1.04)
Nonfatal CHD	268	0.90 (0.71-1.15)	180	0.89 (0.62-1.27)	0.83 (0.58-1.18)
Strokes	106	1.15 (0.78-1.68)	67	1.04 (0.60-1.80)	0.81 (0.47-1.41)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; OT2, on-treatment analysis 2.
*Differences in results from the 2 analyses are due to fewer events in ex–warfarin users. The number of events was the same with both analyses in the placebo group.

Table 6. Sensitivity Analysis for Differing Definitions of On and Off Warfarin Treatment*

	OT1: Full Compliers (0 mo) and Up to Specified No. of Months Without Warfarin Treatment (On Warfarin)				
	0	≤1	≤3	≤6	≤12
All CHD	0.75 (0.60-0.94)	0.77 (0.62-0.96)	0.78 (0.63-0.97)	0.79 (0.64-0.98)	0.79 (0.64-0.98)
Fatal CHD	0.49 (0.32-0.75)	0.52 (0.35-0.79)	0.54 (0.36-0.81)	0.55 (0.37-0.81)	0.53 (0.36-0.79)
Nonfatal CHD	0.91 (0.69-1.19)	0.92 (0.71-1.20)	0.92 (0.71-1.20)	0.94 (0.72-1.22)	0.95 (0.74-1.23)
Strokes	1.20 (0.79-1.84)	1.23 (0.81-1.86)	1.20 (0.79-1.83)	1.23 (0.81-1.86)	1.26 (0.84-1.89)
	OT2: Months Without Warfarin Treatment (Ex-Warfarin)				
	>0	≥1	≥3	≥6	≥12
All CHD	0.86 (0.66-1.15)	0.83 (0.62-1.10)	0.81 (0.60-1.08)	0.78 (0.58-0.98)	0.77 (0.56-1.06)
Fatal CHD	0.83 (0.53-1.30)	0.77 (0.49-1.23)	0.73 (0.45-1.19)	0.74 (0.45-1.22)	0.80 (0.48-1.33)
Nonfatal CHD	0.89 (0.62-1.27)	0.86 (0.60-1.24)	0.85 (0.59-1.23)	0.81 (0.55-1.19)	0.74 (0.49-1.14)
Strokes	1.04 (0.60-1.80)	1.00 (0.57-1.75)	1.04 (0.60-1.82)	0.97 (0.54-1.74)	0.87 (0.46-1.64)

Abbreviations: CHD, coronary heart disease; OT1, on-treatment analysis; OT2, off-treatment analysis.
*Data are given as unadjusted hazard ratio (95% confidence interval). In OT1, patients were classified as full compliers up to 1, 3, 6, or 12 months without treatment. In OT2; ex–warfarin users include patients off treatment for at least 1, 3, 6, or 12 months.

approaches also suggest the possibility of a retained effect of warfarin. One is the indication from the Post Coronary Artery Bypass Graft trial[2,3] already referred to, in which a significant reduction in events was observed after discontinuation of warfarin treatment. Second, the fact that no benefit was observed during treatment in the Post Coronary Artery Bypass Graft trial could perhaps be due to the relatively low intensity of anticoagulation achieved at the secondary prevention stage. This might have precluded the short-term, antithrombotic effect of warfarin necessary in the more thrombogenic context of secondary prevention. At the same time, compared with the less thrombogenic setting of primary prevention, as in our trial. A retained effect on the vessel wall might partly be the reason for the striking benefit observed later on, which could be explained by pathways through which warfarin might slow the development of vessel wall changes.[4] Third, there is suggestive, although weak, evidence that warfarin may reduce the incidence of angina pectoris, on the assumption that angina (other than unstable angina) is mainly due to vessel wall changes.[4]

Warfarin is more inconvenient to use than aspirin because of the need to establish the individual doses required for particular intensities of anticoagulation. At the low therapeutic INR (1.5) aimed for in the Thrombosis Prevention Trial, warfarin appears to be no more hazardous than low-dose aspirin so far as bleeding is concerned.[1] Careful monitoring must be ensured, but it does not have to be very frequent once a stable dose has been reached. It is not clear why warfarin in the Thrombosis Prevention Trial reduced fatal events of CHD to a much greater extent than nonfatal events. This difference was statistically significant[1] and an explanation has been suggested.[8] It could have been due to chance, however, considering that the difference is out of line with the results of secondary prevention trials of warfarin, in which effects on fatal and nonfatal events have been similar. We suggest that because of the obvious value of the primary prevention of CHD, the possibilities raised here of an even greater benefit following full rather than partial compliance, and of a retained effect, should not be overlooked.

Table 7. Relative Survival Time to CHD Events: Active Treatment vs Placebo*

	Relative Survival Time (95% CI)
All CHD	1.39 (1.12-1.69)
Fatal CHD	2.04 (1.43-2.86)
Nonfatal CHD	1.14 (0.91-1.43)
Strokes	0.88 (0.67-1.19)

Abbreviations: CHD, coronary heart disease; CI, confidence interval.
*Relative survival time for patients in active treatment vs patients taking placebo is the ratio of their time to a CHD event if all patients in both groups had fully complied with randomized treatment.

Accepted for publication August 30, 2002.

This trial was funded by the Medical Research Council and the British Heart Foundation, London, England; DuPont Pharma, Wilmington, Del; and Bayer Corporation, Leverkusen, Germany. GlaxoSmithKline, Uxbridge, England, and Boehringer-Ingelheim Ltd, Bracknell, England, provided warfarin free of charge during the pilot stage. DuPont Pharma provided warfarin and Bayer Corporation provided aspirin free of charge during the main trial.

We thank the men in the trial and the physicians and nurses in the participating practices. We gratefully acknowledge the help of many other physicians, nurses, and laboratory and administrative staff in the Medical Research Council Epidemiology and Medical Care Unit. We thank Susan Purdon for initial statistical methodological discussions. We thank the reviewers for their constructive comments on the manuscript.

Corresponding author and reprints: Alicja R. Rudnicka, PhD, Department of Environmental and Preventive Medicine, Wolfson Institute of Preventive Medicine, Charterhouse Square, London EC1M 6BQ, England (e-mail: a.r.rudnicka@qmul.ac.uk).

REFERENCES

1. The Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet*. 1998;351:233-241.
2. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153-162.
3. Knatterud GL, Rosenberg Y, Campeau L, et al. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. *Circulation*. 2000;102:157-165.
4. Knottenbelt C, Brennan PJ, Meade TW. Antithrombotic treatment and the incidence of angina pectoris. *Arch Intern Med*. 2002;162:881-886.
5. Meade TW, Mellows S, Brozovic M, et al. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet*. 1986; 2:533-537.
6. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using a rank preserving structural failure time model. *Comm Stat A*. 1991;20:2609-2631.
7. Korhonen PA, Laird NM, Palmgren J. Correcting for non-compliance in randomized trials: an application to the ATBC study. *Stat Med*. 1999;18:2879-2897.
8. Born GVR. Effects of aspirin and warfarin on fatal and non-fatal heart attacks [letter]. *Lancet*. 1999;354:1472.