Thrombosis prevention trial: follow-up study of practical implications

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SUMMARY

The impact of randomised controlled trials on subsequent practice has only occasionally been assessed. Doing so is particularly necessary when unusual and possibly controversial treatments are being used. The aim of this study was to assess the practical implications of the results of the placebo-controlled primary prevention thrombosis prevention trial, in which the active treatment regimens were combined warfarin and aspirin, warfarin alone, and aspirin alone. Both active agents were given in low doses. Decisions on post-trial management were sought about men who continued with randomly-allocated treatment until the trial ended.

The results of the trial appeared to have influenced decisions about future management. While aspirin was clearly the most frequent choice, a regimen involving warfarin was also used for a substantial proportion of men. Prior experience of acceptability, effectiveness, and safety probably played a significant part in decisions to continue with or switch to a warfarin-containing regimen. The findings may provide a measure of reassurance about the value of oral anticoagulation in other settings, particularly atrial fibrillation where, despite the results of trials showing major reductions in stroke, anticoagulation is underused.

Keywords: *warfarin; aspirin; coronary heart disease; disease management.*

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Introduction

THE factorial thrombosis prevention trial evaluated low intensity oral anticoagulation with warfarin to an International Normalised Ratio (INR) of 1.5 and low-dose aspirin (75 mg daily) for the primary prevention of coronary heart disease in middle-aged men at increased risk.[1] The trial was carried out in 108 practices in the Medical Research Council's general practice research framework. Warfarin reduced fatal events by 39% (and, consequently, mortality from all causes by 17%) but had no effect on non-fatal events. Aspirin reduced non-fatal events by 36% and was associated with a non-significant increase of 12% in fatal events. Combined treatment with both warfarin and aspirin reduced events, whether fatal or non-fatal, by 34%.

The results of the trial were presented to participating practices just before their publication. They were also summarised in letters to both the practices and the men who participated, together with the treatment group to which each man had been allocated. Practices were asked to discuss the trial's findings over the next two or three months with the men who were still taking their allocated treatment when the trial ended with a view to deciding about its practical implications for each individual.

Method

The trial, which was double-blind and placebo-controlled, was factorial in design. The four treatment groups were:

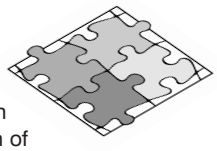
1. active warfarin and active aspirin;
2. active warfarin and placebo aspirin;
3. placebo warfarin and active aspirin; and
4. placebo warfarin and placebo aspirin.

When the trial ended, research nurses, in consultation with the doctors in the 40 practices that wished to continue or start on one of the trial's active regimens with supplies from the co-ordinating centre (for a limited period), sent in lists with the decisions for individual men reached after discussing the trial's results with them, i.e. (a) continue with treatment taken during the trial, (b) change from one active regimen to another, (c) change from placebo treatment in the trial to one of the active regimens or (d) discontinue treatment.

Results

In the 40 practices with precise information about decisions on future management there were 773 men (85%) out of 914 originally randomised and still on their allocated treatment. There was no information about the remaining 141 (15%) men for a variety of reasons; for example, men who did not attend for discussions about their continuing management. Of the 773 men, 156 (20%) did not continue on a trial regi-

HOW THIS FITS IN



What do we know?

Thus far, there is no other information on the use of warfarin in primary prevention of heart attacks.

What does this paper add?

Warfarin is effective and can be managed safely. The survey has shown that an appreciable number of men wished to continue with a warfarin-containing regimen after the trail although most opted for aspirin.

men. Of these, 90 (58%) discontinued one of the three active regimens while the remaining 66 (42%) had been on double placebo treatment. A total of 617 (80%) of the 773 men therefore continued with, or started on, an active regimen as shown in Table 1. Of the 278 men who remained on their active trial treatment, there were 76 (27%) on the double active regimen i.e. warfarin and aspirin, 62 (22%) on the warfarin regimen, and 140 (50%) on aspirin. A further 223 men on one active treatment changed to another; in other words, 48 (22%) changed to double active treatment from either warfarin alone or aspirin alone (details not shown), 12 (5%) changed to warfarin (from either combined treatment or aspirin alone) and 163 (73%) changed to aspirin (from either combined treatment or warfarin alone). Thus, although most changes were from a warfarin-containing regimen to aspirin alone, just over a quarter decided on a warfarin-containing regimen. Of the 116 men on placebo who took up active treatment, nine (8%) started on combined treatment, 4 (3%) started on warfarin alone and 103 (89%) started on aspirin alone, a lower proportion thus starting on a warfarin-containing regimen than for those continuing with an active treatment.

Discussion

The 40 practices were able to give precise information about post-trial intentions for 85% of the men still on their originally allocated treatment when the trial ended. Of these, 80% decided to continue or start on one of the active regimens. Among those deciding to continue with the same regimen, half (50%) continued on a warfarin-containing regimen with slightly more (27%) continuing on combined treatment with warfarin and aspirin, compared with those (22%) continuing on warfarin alone. Half (50%) decided to continue with aspirin alone. Among those deciding on a change from one active regimen to another, 73% chose aspirin. The remaining 27% consisted of 22% changing to combined treatment and 5% changing to warfarin only. At first sight, the higher proportions continuing on, or changing to, combined treatment with both warfarin and aspirin compared with warfarin only is surprising. A partial explanation may be appreciation of the larger effect in reducing events (fatal and non-fatal combined) attributable to combined treatment than to warfarin alone (or aspirin) and also experience during the trial itself that combined treatment could be managed acceptably and safely. Thus, for men already on one of the active regimens, both the doctors and the men themselves may have felt confident about changing to combined treatment, which they knew by then to be more effective than either of the single active treatments. Conversely, 66 (36%) of the 182 (116+66) who had been on double placebo and who decided against further treatment may perhaps have done so partly because they realised they had not had the reassuring practical experience of a warfarin regimen; of those who had been on placebo and did take up active treatment, only 11% chose one of these regimens, the large majority (89%) choosing aspirin. However, it is probable that some doctors and men would have restarted or started on aspirin anyway, i.e. independently of the trial's findings.

Prior experience with the warfarin-containing regimens by the men in the trial as well as by the doctors and nurses seems to have been influential in decisions to continue with or change to one of these regimens. In this respect, our study differs from the context of others in which men with, for example, atrial fibrillation, have generally not had previous experience of different antithrombotic regimens and thus understandably tend to express preferences for aspirin.[2] Our results come from practices with extensive experience of the use of low intensity oral anticoagulation. While they are strictly applicable only in the context of primary prevention, they and the trial's main results[1] may provide a measure of reassurance about the value (clinical and financial), acceptability, safety and practicalities of oral anticoagulation in other settings. This may particularly apply to atrial fibrillation where, despite the results of trials showing major reductions in stroke, anticoagulation is underused. These trials used higher mean INRs than we did; however, the principle that anticoagulation can be managed effectively in general practice on a larger scale than hitherto nevertheless seems applicable.

References

1. The Medical Research Council's General Practice Research Framework (1998). 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. Taylor FC, Cohen H, Ebrahim S. Systemic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. *BMJ* 2001; **322:** 321-326.

Table 1. Men on randomly allocated treatment throughout the trial and continuing the same active treatment, changing active treatment or starting active treatment. Excludes 156 men who did not continue with a trial regimen (see text).

Treatment	Warfarin and aspirin	Warfarin	Aspirin	Total
Same treatment *n* (%)	76 (27)	62 (22)	140 (50)	278 (100)
Change of active treatment (to regimen shown) *n* (%)	48 (22)	12 (5)	163 (73)	223 (100)
Change from placebo to active treatment *n* (%)	9 (8)	4 (3)	103 (89)	116 (100)