Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation.

Edvardsson, N; Juul-Möller, Steen; Omblus, R; Pehrsson, K

Published in:
Journal of Internal Medicine

DOI:
10.1046/j.1365-2796.2003.01159.x

2003

Journal of Internal Medicine 2003; **254**: 95–101

Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation

N. EDVARDSSON[1], S. JUUL-MÖLLER[2], R. ÖMBLUS[3] & K. PEHRSSON[4]
From the [1]Division of Cardiology, Sahlgrenska University Hospital, [2]Malmö University Hospital, [3]Bristol-Myers Squibb Bromma; and [4]Karolinska University Hospital; Stockholm, Sweden

Abstract. Edvardsson N, Juul-Möller S, Ömblus R, Pehrsson K (Sahlgrenska University Hospital, Malmö University Hospital, Bristol-Myers Squibb Bromma; and Karolinska University Hospital; Stockholm, Sweden). Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. *J Intern Med* 2003; **254:** 95–101.

Objectives. To assess the optimal stroke prevention treatment for patients with atrial fibrillation (AF) and a low–medium risk (≤4%) of stroke.

Design. A total of 668 patients with persistent or permanent AF, without an indication for full dose and with adequate rate control on sotalol, were randomized to warfarin 1.25 mg + aspirin 75 mg daily (W/A, 334 patients) or no anticoagulation (C, 334 patients). The mean follow-up period was 33 months. The protocol intended to verify a 37% relative risk reduction provided a 4% stroke incidence in the C group.

Results. The stroke incidence was less in the W/A group, although the reduction was not statistically significant (W/A 9.6% versus C 12.3%). Four haemorrhagic strokes were identified, two in each group. Secondary end-points were transient ischaemic attacks (TIA) (W/A 3.3% versus C 4.5%), all cause mortality (W/A 9.3% versus C 10.8%), cardiovascular morbidity (W/A 17.7% versus C 22.2%) and the combination of stroke + TIA (W/A 11.7% versus C 16.5%). Bleedings were documented in 19 versus four patients (W/A 5.7% versus C 1.2%) ($P = 0.003$), although none fatal. Sinus rhythm (SR) was recorded occasionally in 68 patients (W/A 9.6% versus C 10.8%). The stroke incidence tended to be higher in those with SR than without, 16.2% versus 10.4%.

Conclusions. Our results were inconclusive, but consistent with a small beneficial effect of W/A for reduction of stroke and major vascular events in AF patients at moderate risk. The low-dose regiment produced, however, a significantly increased risk of bleedings. Documented SR occasionally recorded may represent a subpopulation that warrants full dose warfarin.

Keywords: atrial fibrillation, low-dose warfarin and aspirin, stroke prevention.

Introduction

Patients with atrial fibrillation (AF) have an increased risk for stroke. This risk, however, depends on the coexistence of certain risk factors such as high age, valvular disease, hypertension, diabetes mellitus, previous ischaemic stroke, and congestive heart failure [1–6]. Patients with chronic AF, aged 60 or younger and without any other risk factor for ischaemic stroke (lone AF) have a very low-risk for stroke (<0.5% annually), whilst patients with one or more of these risk factors have a risk of >8% annually [1, 7–10]. The risk of stroke has been found to be increased by almost six times in nonrheumatic AF compared with controls [8, 9]. The general prevalence of chronic AF is close to 1%, but increases from <0.5% in age groups younger than 50 years to >8% in individuals over 80 years of age [8].

Anticoagulation treatment with warfarin in patients with chronic AF with an international

normalized ratio (INR) between 2 and 3 reduces the risk of ischaemic stroke by two-thirds [10]. At the same time, this regimen imposed a risk of serious bleedings such as cerebral haemorrhage of 1.3% annually [1] besides other major bleedings requiring hospital treatment (2.5%) [11]. Prophylactic treatment with aspirin in doses of 325 mg once daily results in a relative reduction of the risk of ischaemic stroke by 18% to a cost of 1.5% fatal or major bleeds annually [12]. Patients with chronic AF and a yearly risk of ischaemic stroke exceeding 4% should be considered for anticoagulant treatment.

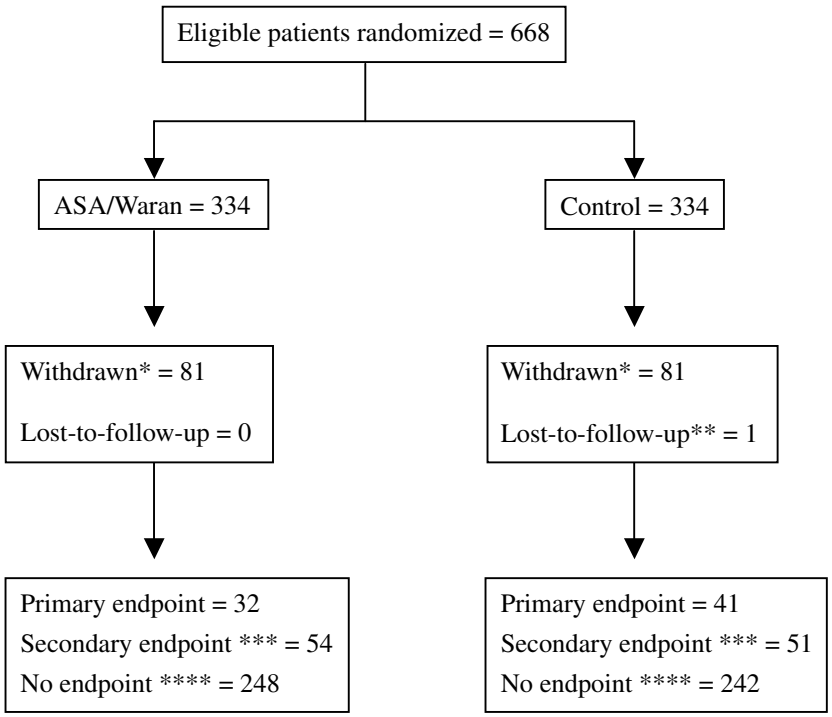
This indicates that an intermediate-risk population with chronic AF exists, i.e. the link between lone AF and high-risk patients. These patients may be treated with aspirin only, according to the present guidelines [13], standing an ischaemic stroke-risk of <4% annually.

Low-dose aspirin (75 mg) has been shown to provide a 25% relative reduction of the risk of ischaemic stroke in patients with stable angina pectoris and in transient ischaemic attacks (TIA) and/or minor stroke [14, 15]. The combination of low-dose aspirin and fixed low-dose warfarin (1.25 mg daily) has been shown to be inferior to full-dose warfarin in patients with medium to high-risk for ischaemic stroke [16]. However, this combination may be justified in patients in whom full-dose warfarin is not indicated.

The aim of the study was to investigate the effect of 75 mg aspirin in combination with 1.25 mg of warfarin once daily on the incidence of stroke and bleedings in patient with chronic AF judged to have an intermediate risk (4%) of ischaemic stroke.

Material and methods

The design was randomized open-label controlled trial carried out at 62 out-patient clinics in Sweden between 1995 and 1998. The study comprised 668 patients, 416 men and 252 women, aged 58–98 years, mean 73 years (Fig. 1). For one patient



* Withdrawn from assigned therapy, but still followed up for the intention-to-treat analysis

** For one of the "withdrawn" patients only survival data was available

*** Secondary endpoint without primary endpoint

**** Completed trial without primary or secondary endpoint

Fig. 1 Patients and event flow.

only survival data was available. Characteristics of the study population are depicted in Table 1.

Eligible patients were all men and women aged 60 years or older with electrocardiographic documentation of persistent or permanent AF in the preceding 4 weeks without prosthetic heart valves, significant valvular diseases, previous stroke or TIA, and other requirements for or contraindications to aspirin or warfarin therapy. Other exclusion criteria were severe heart failure (NYHA III/IV), bradycardia of <60 beats min^{-1} (bpm), severe hypertension [systolic blood pressure (SBP) > 190 mmHg and/or diastolic blood pressure (DBP) >110 mmHg], S-potassium (<3.6 mmol L^{-1} and >5.2 mmol L^{-1}), chronic obstructive lung disease, primary liver disorder, known bleeding disorder, thyreotoxicosis and impaired renal function (S-creatinine >200 μmol L^{-1}). Patients with ischaemic heart disease receiving aspirin were also excluded.

Echocardiography was recommended but not mandatory. If no exclusion criteria were met all patients received sotalol to attain homogeneity for heart rate modulation and the dosage was openly adjusted during a 2-week run-in period to obtain a heart rate at rest between 60 and 100 bpm and with a QTc (QT interval corrected for heart rate) of <0.52 s after heart rate modulation.

The patients were then randomized by central telephone randomization either to warfarin 1.25 mg/day (fixed dose) in combination with aspirin 75 mg/day (W/A) or to no anticoagulation. The latter group served as controls (C). At each contact, these patients were instructed not to take aspirin or any other antiplatelet drug. The mean follow-up period (randomization date to end of the study) for the patients was 33 months (range 14–45) and included out-patient visits at 1, 6 and thereafter every 6 months. At each visit, heart rate and blood pressure were measured and a 12-lead resting electrocardiogram (ECG) was recorded with the patient supine, the cardiac rhythm was obtained as well as the QTc interval.

Plasma was obtained from each patient randomized to warfarin/aspirin for determination of the INR 1 month after randomization and thereafter annually. The sensitivity of the INR analyses stopped in many cases at 1.3 and any value below could not be further determined. (This meant that apart from frequency count no details on INR values could be obtained.)

The primary end-point was stroke. Computer tomography (CT) verification was mandatory to differentiate between ischaemic and haemorrhagic stroke. Secondary end-points were TIA, all cause mortality, cardiovascular morbidity, acute myocardial infarction, peripheral embolism and any reported bleeding that warranted exclusion from the trial as specified by the protocol.

Adverse events were recorded by the clinician at each visit. In addition, all patients were interviewed by phone at month 3 and every 6 months thereafter to record any suspected or manifest events. All events were verified and confirmed by the steering committee.

All patients gave their written informed consent. The study was approved by all involved local ethics committees after evaluation of the Ethics Committee of the Göteborg University, and by the Swedish Medical Products Agency.

Table 1 Characteristics of the study population ($n = 668$, mean + SD)

	Warfarin + aspirin	Controls
Men, *n* (%)	214 (64)	202 (61)
Age (years)	72 ± 7	73 ± 7
Age range (years)	53–90	58–90
Length (cm)	173 ± 9	173 ± 9
Weight (kg)	79 ± 14	79 ± 14
Systolic blood pressure (mmHg)	145 ± 19	146 ± 19
Diastolic blood pressure (mmHg)	85 ± 8	85 ± 9
Heart rate (bpm)	78 ± 12	77 ± 12
Q wave in ECG, *n* (%)	29 (9)	33 (10)
Mean QT (ms)	385 ± 46	389 ± 43
QTc (ms)	438 ± 50	441 ± 40
Ejection fraction (%)	51 ± 10	51 ± 9
Echocardiography, *n* (%)	216 (65)	200 (60)
International normalized ratio (INR) > 1.3 (%)[a]	(9)	Not applicable

[a]Includes all samples taken after randomization.

Statistics

All data are based on an intention-to-treat analysis. For additional information, an efficacy and safety analysis per protocol was also performed, i.e. patients on active treatment. The results of the 'per protocol' analysis was consistent with the results of the intention-to-treat analysis. All comparisons of time to event variables were performed applying log-rank tests and Cox regression analysis. Hazard ratios

(HR) with two-sided 95% confidence intervals (CIs) were calculated. All statistical tests were performed as two-sided, at the 5% significance level. The tool for data base management was Medlog® (Crystal Bay, NV, USA) and the statistical analysis software was SPSS®, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Efficacy

Primary end-point Stroke was verified in 73 of 667 patients (10.9%), with 9.6% in W/A versus 12.3% in C group ($P = 0.28$, log-rank test) (Table 2). Four of these were haemorrhagic strokes, two in each arm.

Stroke was slightly more common in women than in men [13.5% vs. 9.4% (NS)].

Stroke occurred in 54 of 499 patients whilst they were on treatment per protocol, all of them ischaemic. The occurrence of stroke per protocol did not differ from the intention-to-treat analysis.

Secondary end-points Transient ischaemic attacks occurred in 26 patients (3.9%) [3.3% vs. 4.5%, in W/A versus C arm, NS] (Table 2). The combined end-point stroke + TIA appeared to be less common in the W/A arm [11.7% vs. 16.5% in C, $P = 0.087$, log-rank test]. Neither was there any differences regarding cardiovascular morbidity, acute myocardial infarction or peripheral embolism.

Mortality

Altogether 67 patients died during the follow-up, but the all cause mortality did not differ between the two treatment arms (9.3% W/A versus 10.8% C). Fatal strokes occurred in nine of the 73 stroke patients within 1 week after the onset of stroke, six in the W/A group and three in the C group. One month after the stroke the mortality figures in these two groups was 7 and 4, respectively. Sudden death occurred in 14 patients, all men, but there was no difference between the two treatment arms, six (1.8%) in the W/A-arm and eight (2.4%) in the C-arm. Cardiovascular mortality occurred in 46 patients (6.9%) with 23 patients in each arm.

Additional observations

Sinus rhythm (SR) was recorded at any time during the study in 68 patients, 32 (W/A) versus 36 (C) (9.6% vs. 10.8%). This happened more often in women than in men (15.5% vs. 7%). Eleven versus 16 patients relapsed to AF later in the study, slightly more often in women, 15 versus 12 men. At the end of the study 47 patients had SR, 24 (W/A) versus 23 (C), 7.2% vs. 6.9%.

Of the 73 strokes, 11 (16.2%) occurred in patients who had SR at any time during the study, and in nine patients (19.1%) in those with SR at the end of the study.

The incidence of stroke tended to be more common in those patients with occasionally recorded SR than in those without (16.2% vs. 10.4%, NS).

Prognostic factors for stroke

In complementary analyses, prognostic variables potentially correlated with the risk of stroke were studied. Initially, each of the variables age (>65),

Table 2 Primary and secondary end-points

	Warfarin + aspirin, *n* (%)	Controls, *n* (%)	Hazard ratio (95% CI)	*P* (log-rank test)
Primary end-point				
Stroke	32[a] (9.6)	41[b] (12.3)	0.78 (0.49–1.23)	0.28
Secondary end-points				
Transient ischaemic attacks (TIA)	11 (3.3)	15 (4.5)	0.73 (0.33–1.58)	0.42
All cause mortality	31 (9.3)	36 (10.8)	0.86 (0.53–1.40)	0.55
Cardiovascular morbidity	59 (17.7)	74 (22.2)	0.76 (0.52–1.10)	0.14
Acute myocardial infarction	14 (4.2)	18 (5.4)	0.77 (0.38–1.55)	0.46
Peripheral embolism	5 (1.5)	5 (1.5)	0.99 (0.29–3.42)	0.99
Stroke + TIA	39 (11.7)	55 (16.5)	0.70 (0.46–1.05)	0.09
All reported bleedings	19 (5.7)	4 (1.2)	5.11 (1.75–15.0)	0.003

The mean follow-up period (randomization date to end of the study) was the same for both treatment groups, i.e. 33 months (range 14–45).
[a]Six patients died within 1 week and seven in total after 1 month.
[b]Three patients died within 1 week and four in total after 1 month.

sex, previous stroke or TIA, SR, history of hypertension, SBP >160 and diabetes mellitus was studied separately with respect to the risk of stroke. The only variable having a statistically significant impact on the stroke risk was SBP >160, with a HR (95% CI) of 2.12 (1.27–3.55) ($P = 0.004$). For the other variables, the hazard ratios were all greater than 1, ranging from 1.38 to 1.88, but none of the ratios were statistically apart from 1. Including the whole set of prognostic factors listed above together with study treatment (W/A or C) in a Cox regression model does not alter the results substantially, SBP >160 was still the only statistically significant risk factor with HR 1.95 (1.14–3.33) ($P = 0.014$). In this model, W/A treatment was associated with a risk reduction to 0.79 (0.50–1.26) ($P = 0.32$), in close accordance with the primary analysis.

Safety

According to intention-to-treat, bleedings were more common in the W/A group, 19 versus four patients, in all 3.4% (5.7% vs. 1.2%, $P = 0.003$, log-rank test). Per protocol, there were 19 bleedings in the W/A group and one in the C group, $P < 0.001$. Two of the patients in the W/A group had an INR between 2 and 3. All remaining patients had a value below 2.

No case of torsades de pointes or other proarrhythmia were documented during the study.

The ECGs of all 14 patients who died suddenly did not show any prolonged QTc values in the ECGs preceding the event.

Withdrawals

The number of patients who interrupted any treatment (sotalol, aspirin (ASA) or warfarin) was 81 (24.3%) in each treatment arm. There was no difference with regard to gender. Withdrawals were decided by the investigator in the vast majority of cases. Altogether 28 patients were withdrawn because of a new need for either warfarin (12 patients) or ASA (16 patients), as judged by the investigator. Three patients belonging to the sotalol group spontaneously started ASA treatment and became withdrawals.

Discussion

The risk of ischaemic stroke amongst people with AF averages about 5% per year, but with wide, clinically important variations (0.5–12% per year) amongst identifiable subpopulations of patients with AF [1, 7, 17, 18]. Estimating the risk of stroke for individual patients with AF is a crucial factor in the decision to provide adequate anticoagulation therapy. The threshold risk of stroke in these patients that warrants oral anticoagulation remains controversial and the opinion is divided regarding routine use of oral anticoagulation for those with intermediate risk of stroke, e.g. those between 2 and 6%.

We identified an intermediate risk population, in whom we expected a 0.5–4% stroke incidence per year and in whom the positive effects of full dose warfarin would be out-weighed by its increased risk of bleedings. Our control group also permitted the study of natural course of a patient population at low–medium risk.

The aim of the study was to show a relative 37% reduction based on the assumption of an end-point incidence of 4% per year. In reality, after 33 months we concluded that the stroke incidence in our control group was 3.3% per year, proving that the population included was indeed an intermediate population, although with a little lower stroke incidence than expected. The study was designed to randomize 1200 patients, who should be followed for 4 years. This would provide 144 primary end-points. During the course of the study the number of untreated eligible patients turned out to be lower than anticipated and the inclusion period stopped when 668 patients were included. The lower patient inclusion that anticipated in combination with the lower stroke incidence than expected may explain why the considerable relative reductions in this study failed to reach statistical significance.

The combined treatment with aspirin 75 mg and warfarin 1.25 mg provided no better prophylaxis against stroke than no treatment in this low to medium-risk population. The hazard ratios were 0.78 (stroke), 0.73 (TIA) and 0.70 (stroke + TIA). A benefit-risk analysis on an intention-to-treat basis showed that 18 strokes were saved at a cost of 15 bleedings requiring treatment. There was no excess of haemorrhagic stroke in the treatment group, two versus two patients in the control arm. The results are in agreement with previous studies with this low-dose regimen (16). However, our study is the first to provide a comparison versus no treatment, whereas other studies compared various active treatments in all arms.

All patients were recruited to the study on the assumption of a chronic AF. Prior to randomization all had at least two consecutive ECGs during a minimum of 1 month with AF. An interesting observation was the presence of SR during follow-up at predefined ECG controls in 68 patients, 41 of whom had also SR at the end of the study. In patients who had SR at any time during the follow-up the stroke incidence was higher than in those with only documented AF, 16% vs. 10%. Episodes with SR and stroke were more frequently seen in women, implying that conversion to SR after long-standing AF increases the risk for stroke. This may represent a subpopulation at especially high risk for stroke, necessitating full-dose warfarin.

The major limitation of the study is that the number of eligible patients included in the study did not reach the number that was anticipated. In spite of that we believe that some observations in this study may be potentially important and therefore worthwhile to report.

In conclusion, in this first comparison between a fixed combination of low-dose warfarin + aspirin and no anticoagulation in patients with chronic AF and with an intermediate risk of stroke no significant risk reductions were found, in spite of hazard ratios of 0.78 (stroke), 0.73 (TIA), 0.70 (stroke + -TIA). The low-dose regimen produced, however, a significantly increased risk of bleedings. Documented SR at any time in this group of patients with chronic AF may represent a subpopulation that warrants full-dose warfarin.

Conflict of interest statement

The study was financially supported by Bristol-Myers Squibb and one of the authors (R. Ömblus) was during the study employed at that company.

Acknowledgments

The authors are grateful for the stimulating collaboration with Bengt Jahnmatz and participating principal investigators. *Investigators* (in order of recruited patients): C. Höglund, S. Juul-Möller, L. Warselius, G. Cronsten, L. Sandström, R. Zlatewa, N. Edvardsson, B.-O. Ericsson, K. Pehrsson, S. Ekdahl, L. Hjelmaeus, B. Larsson, S. Grimfors, B. Atmer, J. Carlsson, P. Löfdahl. S. Strid, B. Bartholdsson, C. Pater, S.-Å. Falk, P. Möller, E. Basilier, P.-Å. Boström, F. Wagner, K. Ångman, F. Andersson/B. Friberg, S. Berglund/C. Zedigh, P. Brunmark, U.-B. Ericsson, C.-A. Svensson, D. Hagström, D. Lundblad, C. Fabian, B. Fredriksson, L.-O. Hemmingsson, Å. Sjöstrand, G. Ulvenstam, R. Watz/H. Lindvall, S. Wide, A. Sköld, A. Tisell, S Jensen, J. Kjellberg, J. Kobosko, L.-E. Larsson, C.M. Mölstad, S. Qittenbaum, A. Torp, S. Andersson, H. Brodersson/J. Ellström, T. Fraser, U. Hollertz, H. Jonsson, B. Ullman/M. Frick, A. Drejare, T. Lindén, E. Loogna/L. Svensson, L. Persson, G. Strömblad, C. Påhlsson, S. Thorsén, A. Dahlberg.

The SAFT Study Group was constituted as follows:
Executive committee. N. Edvardsson, S. Juul-Möller, K. Pehrsson, and R. Ömblus (Bristol-Myers Squibb).
Study monitors. G. Forsberg, M. Gagner, B. Jahnmatz, K. Lindqvist, B. Petersson, R. Ömblus.
Data handling. K. Torstensson.
Study statistician. M. Ålenius
Secretary. G. Forsberg

References

1 Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized clinical trials. *Arch Intern Med* 1994; **154:** 1949–57.
2 Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: a prospective study of 1066 patients from three clinical trials. *Arch Intern Med* 1998; **158:** 1316–20.
3 Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation I: clinical features in patients at risk. *Ann Intern Med* 1992; **II6:** 1–5.
4 Stoke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation II: Echocardiographic features in patients at risk. *Ann Intertn Med* 1991; **I:** 6–12.
5 Stroke Prevention in Atrial Fibrillation Investigators. Risk factors for thromboembolism during aspirin therapy in atrial fibrillation. *J Stroke Cerebrovasc Dis* 1995; **5:** 147–57.
6 Hart RG, Pearce LA, McBride R *et al.* Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 particpants in the SPAF I–III clinical trials. *Stroke* 1999; **30:** 1223–9.
7 Kopecky SL, Gersh BJ, McGoon MD *et al.* The natural history of lone atrial fibillation: a population-based study over three decades. *N Engl J Med* 1987; **317:** 669–74.
8 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contribution to stroke in the elderly. *Arch Intern Med* 1987; **147:** 1561–4.
9 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; **22:** 983–8.

10 Albers GW. Atrial fibrillation and stroke. Three new studies, three remaing questions. *Arch Intern Med* 1994; **154:** 1443–8.
11 Gullöv A, Koefoed B, Petersen P. Bleeding complications to long-term oral anticoagulant therapy. *J Thomb Thrombolysis* 1994; **1:** 17–25.
12 Antithrombotic Trialist's Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.
13 Fuster V, Ryden LE, Asinger RW *et al.* ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. *Eur Heart J* 2001; **22:** 1852–1923.
14 Juul-Möller S, Edvardsson N, Jahnmatz B *et al.* Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992; **340:** 1421–5.
15 The SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. *Lancet* 1991; **338:** 1345–9.
16 McBride R. Adjusted-dose warfarin versus low-intensity, fixes doses warfarin plus aspirin for high-risk patients with atrial fibrillation: stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet* 1996; **348:** 633–8.
17 Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from three randomized trials. *Arch Intern Med* 1997; **157:** 1237–40.
18 Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; **131:** 492–501.

Received 19 September 2002; revision received 20 February 2003; accepted 13 March 2003.

Correspondence: S. Kenneth Pehrsson MD PhD, Department of Cardiology, Karolinska Hospital, 171 76 Stockholm, Sweden (fax: 08-31-10-44; e-mail: k_pehrsson@hotmail.com).