Use of warfarin in non-rheumatic atrial fibrillation: a commentary from general practice

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SUMMARY. Seven randomized trials published in the last six years have shown that warfarin reduces the risk of ischaemic strokes and death in patients with atrial fibrillation. The annual rates of major bleeding episodes in all these trials were low and, as a result, doctors in primary and secondary care are being encouraged to consider using warfarin for patients with atrial fibrillation unless there are obvious contraindications. However, the populations used in these studies were highly selected and rigorously monitored throughout the trial period to minimize the risk of bleeding in a way which probably could not be expected in routine primary care. Although the rates of major bleeding episodes were uniformly low, the rates of minor bleeding episodes were much higher and these could impact substantially on patients' views of the treatment and on the workload of the primary care team. Evidence is now at hand which allows the stratification of risk in patients with atrial fibrillation which should enable those who are at greatest risk to be considered for this form of treatment. Patients may develop risk factors over time which could render them unsuitable for continuation of warfarin therapy. The general practitioner is centrally placed to make the decision about initiating or continuing treatment or indeed stopping it. Several models for decision making in warfarin treatment from primary and secondary care are proposed.

Keywords: atrial fibrillation; anticoagulant agents; morbidity risk factors; risk reduction; literature reviews.

Introduction

SEVEN randomized trials published in the last six years have shown that warfarin reduces the risk of ischaemic strokes and death in patients with atrial fibrillation.[1-7] These are the Copenhagen study of warfarin and aspirin for the prevention of thromboembolic complications in atrial fibrillation (AFASAK),[1] the Boston area anticoagulation trial for atrial fibrillation (BAATAF),[2] the Canadian atrial fibrillation anticoagulation (CAFA) study,[3] the stroke prevention in atrial fibrillation (SPAF) study[4] and the stroke prevention in atrial fibrillation (SPINAF) study,[5] and the European atrial fibrillation trial (EAFT).[6] The seventh study is a second stroke prevention in atrial fibrillation study.[7] On the basis of these studies, editorials in peer reviewed journals have encouraged doctors to consider giving anticoagulant therapy to patients with atrial fibrillation, where there is no contraindication.[8,9] Other reviewers have been more cautious, expressing concern at the potential widespread use of warfarin in atrial fibrillation on the basis of trials with carefully selected study populations.[10] Clinical practice, however, has been slow to change in the light of these studies' findings.[11,12]

The results of the randomized trials attracted the attention of the National Health Service Management Executive, whose focus group research identified anticoagulant treatment for patients with atrial fibrillation as a key element in purchasing negotiations for regional health authority corporate contracts.[13]

In this review article the structure, execution and principal findings of the studies are compared; how the study settings relate to everyday general practice are considered; and the implications of these research results for primary care are assessed.

Warfarin in non-rheumatic atrial fibrillation

Over the past six years, randomized trials in Europe and North America have produced results supporting the use of warfarin in both primary and secondary prevention of stroke in patients with non-rheumatic atrial fibrillation.[1-7] Three trials have also reported on the effect of aspirin versus placebo. The design and results of these studies are summarized in Table 1. The authors of five primary prevention trials[1-5] have reported the findings of a collaborative meta-analysis of their results.[14] The estimates of the reduction in relative risk of stroke with warfarin are shown for each trial separately, and for all the trials combined in Figure 1. Similar data for aspirin are also shown in Figure 1. Results are significant if confidence intervals do not overlap zero. Overall, warfarin decreases the relative risk of stroke by 68%. In addition, the meta-analysis resolved other questions which had not been clearly answered by the individual trials. In particular, it was found that warfarin reduced the risk of both major and minor stroke. It was also shown to be equally effective in men and women.[14] The overall effect of aspirin was statistically significant but smaller: when data from both studies were combined, aspirin decreased the risk of stroke by 36% (Figure 1).

Within all the trials, the rate of serious complications from warfarin was remarkably low. In the meta-analysis, the annual rate of cerebral haemorrhage was 0.3% in patients treated with warfarin, and 0.1% in the control group. Taking these five studies together, 40 patients with atrial fibrillation would have to be given anticoagulant treatment for one year to prevent one stroke. For every 1000 patients treated for one year, between 15 and 50 episodes of ischaemic stroke or systemic embolism would be avoided, at a cost of between four and six major episodes of bleeding over the same period.

How do the studies relate to general practice?

As far as general practice is concerned the salient questions about the design and execution of these studies are:

- Are the characteristics of the populations studied comparable with the general population who may be offered this form of anticoagulation in primary care in the United Kingdom?
- Is the type of follow up carried out in these studies to ensure compliance feasible in day to day general practice?

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Table 1. Summary of randomized trials of warfarin and aspirin in patients with non-rheumatic atrial fibrillation.

Study (year), country	Design	Comparison of	Setting	Duration (years)	Target	Person years of follow up	Annual event rate		Relative risk of warfarin (%)
							Placebo	Warfarin	
AFASAK (1989), Denmark[1]	Randomized Double blind aspirin/placebo	Warfarin, aspirin and placebo	OPD[a]	2.0	2.8–4.2 INR	398	4.8	1.4	*71*
BAATAF (1990), USA[2]	Randomized Controlled Unblinded	Warfarin versus aspirin	OPD	2.3	1.2–1.5 PTR	435	2.9	0.4	*86*
CAFA (1991), Canada[3]	Randomized Placebo controlled Double blind	Warfarin versus placebo	OPD[b]	2.5	2.0–3.0 INR	241	3.7	2.1	*43*
SPAF (1991), USA[4]	Randomized aspirin/placebo Double blind	Warfarin versus placebo. Aspirin versus placebo	OPD	1.3	1.3–1.8 PTR	245	7.4	2.3	*67*
SPINAF (1992), USA[5]	Randomized Placebo controlled Double blind	Warfarin versus placebo	OPD	1.7	1.2–1.5 PTR	483	4.3	0.9	*79*
EAFT (1993), Netherlands[6]	Randomized Secondary prevention trial	Warfarin versus aspirin versus placebo	OPD	2.3	2.5–4.0 INR	517	17.0	8.0	*53*

OPD = outpatient department. INR = international normalized ratio. PTR = prothrombin time ratio. [a]Echocardiography laboratory. [b]University centres.

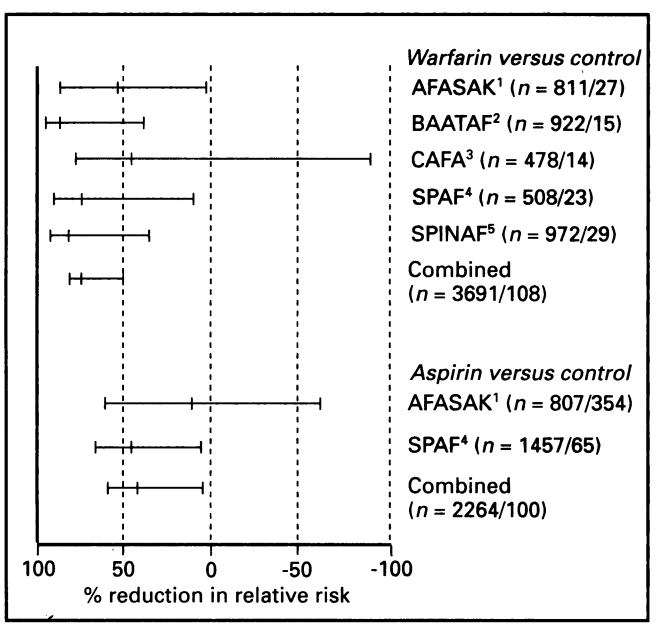

Figure 1. *Efficacy of warfarin and of aspirin compared with control, in separate studies and in studies combined, where positive percentage reduction is better and negative percentage reduction is worse (n = number of patient years studied/number of stroke events). Original source of figure:* Archives of Internal Medicine *1994; 154: 1449-1457.*[14] *© Copyright 1994, American Medical Association.*

- Is the classification of complications relevant to general practice ?
- Is warfarin safe in the long term?
- Is it possible to stratify risk and thus individualize therapy in general practice?

Study populations

The trials[1-7] enrolled mainly older patients (mean age 69 years), both men and women, who had verifiable evidence of atrial fibrillation on echocardiogram, and who had no contraindication to warfarin treatment. Almost half of the subjects had a history of hypertension, and nearly a quarter had a history of angina. One fifth had a history of congestive heart failure, and 14% of diabetes.

There was no standardization in the exclusion criteria among the randomized trials, and the rate at which patients were excluded in some of the studies does give some concern about the extrapolation of the results to the general population with atrial fibrillation. For example, in the SPINAF trial 7982 patients were initially considered eligible, but 93% were excluded, of whom 30% had 'chronic alcoholism, or a psychiatric or social condition rendering the patient unsuitable for anticoagulation'.[5] A further 20% of the patients excluded, 1605 in total, were deemed ineligible according to undefined administrative criteria.

In the SPAF study, 18 376 people were initially identified as eligible, but only 3% were entered into the warfarin treatment arm of the study.[4] Of all patients in the study nearly 1000 were excluded because the investigators could not be sure they could be followed up, and over 1700 refused to enter once invited. A separate list of exclusion criteria was applied to the 703 patients entered into the study, but not assigned to anticoagulant therapy. Of this group of 703 patients, one third at this stage refused anticoagulant therapy, and 6% were excluded because of 'repeated falls or unstable gait predisposing to head trauma'.[4]

As a rule, patients entered into these trials represented a population with atrial fibrillation who were at very low risk of bleed-

ing on warfarin, and were most likely to comply with treatment and be amenable to follow up. Despite this, quite large percentages in all the trials were withdrawn from warfarin therapy after entering the trials: 38% in the AFASAK study,[1] 10% in the BAATAF study,[2] 26% in the CAFA study,[3] 11% in the SPAF study,[4] 31% in the SPINAF study[5] and 21% in the EAFT study.[6] The largest number of withdrawals occurred in the AFASAK trial, which was the closest to being a community study comparable to a UK primary care population.[1]

Compliance and monitoring

During the studies patients were vigorously monitored in a hospital outpatient setting, and underwent repeated physical examinations for side effects of warfarin treatment. Should this type of follow up be expected in primary care?

The clearest description of follow up came from the Copenhagen AFASAK study, where each patient had clinical check ups twice in the first six months and then every six months.[1] Complete physical examination was undertaken and echocardiography was carried out to determine left atrial size. During the second year, echocardiographic evidence of continuing atrial fibrillation was confirmed. Similar rigorous follow up is recorded in the BAATAF study where patients had to complete health questionnaires regularly and had their responses checked in telephone consultations with study nurses.[2] In the SPAF and EAFT trials, clinical checks were conducted on the study patients three- and four-monthly, respectively.[4,6] It is unlikely that comparably rigorous follow up would be the norm in routine general practice. While rigorous follow up within a research project is expected, it is likely that this contributed to the uniformly low level of episodes of major bleeding found in the studies. In patients for whom such follow up could not be promised, could similarly low major complication rates be assured?

Regarding anticoagulation, blood tests in all studies were carried out at monthly intervals, which probably fits with the schedule in most general practices. However, the control of international normalized ratios or prothrombin time ratios proved difficult even in these carefully controlled trial conditions. The percentage of days on which anticoagulation control was either lower than the lower limit, or greater than the upper limit for each study is shown in Table 2.

Classification and rates of complications

Although the tight control of anticoagulation may have proved difficult the overall annual rate of proven cerebral haemorrhage — the most drastic result of poor control — was uniformly low in all the studies (0.3% in patients treated with warfarin, and 0.1% in the control group). The annual rate of major bleeding episodes in each study is shown in Table 2. Bleeding episodes in the studies were classified as major or minor, but there was no consensus about the definitions of these terms. The majority of the studies suggested that a major bleeding episode was one necessitating hospital admission, surgery, a blood transfusion, or a combination of the three. All other bleeding events were classified as minor. But in the BAATAF study, an episode of minor bleeding included an event requiring a transfusion of fewer than four units of blood, which many would consider serious.[2]

The importance of episodes of minor bleeding is given relatively little consideration in review articles and commentaries on these studies. The percentage of patients in each study who had an episode of minor bleeding is shown in Table 2. These events would almost certainly come to the notice of doctors in primary care, and would have to be investigated.

The distinction between episodes of major and minor bleeding in these studies is characterized by a secondary care perspective. What represents minor bleeding in these studies would certainly be worrying for patients and probably generate considerable anxiety within primary health care teams. For example, otherwise innocuous complaints like haematuria, epistaxis, or menorrhagia, if reported by telephone by a patient taking warfarin, would probably result in one or two home visits by the general practitioner, at least one emergency international normalized ratio request and very possibly further assessments by the district nurse if the patient was housebound.

The impact of bleeding on quality of life was assessed in a subpopulation of the BAATAF trial.[15] This analysis showed that while patients taking warfarin did not, at the outset, perceive themselves to be any less healthy than a comparable group not receiving warfarin, this view changed markedly in the event of even minor bleeding.

Apart from the obvious distress to the patient who experiences a complication, these episodes of bleeding have important cost implications. In the Swedish national prospective study, it was calculated that if the annual complication rate of warfarin treatment (episodes of major bleeding) exceeded 1.3%, a net expense in health care provision would result.[16] Only two of the six randomized trials in this series achieved bleeding rates within this limit.[1,2] The Canadian study CAFA showed a rate of fatal or serious bleeding of 2.5%, despite excluding 94% of the population.[3] The true cost implications of serious haemorrhage are difficult to estimate. The direct costs of hospitalization for a woman with a gastrointestinal bleed on warfarin are easily calculated. But if that woman looks after a frail husband who requires nursing home care as a result of his partner's admission to hospital, substantial additional costs to society will also be incurred which are not accounted for in a cost-effectiveness analysis which adopts the perspective of the health service.

Table 2. Percentage of study days where anticoagulant control fell outside stated range, annual rate of major bleeding episodes and percentage of patients with minor episodes.

	% of days where INR/PTR		Bleeding episodes	
Study	Below lower limit	Above higher limit	Annual rate of major (%)	% of patients with minor
AFASAK[1]	*0.6*	*26*	*1.2*	-[a]
BAATAF[2]	*9*	*8*	*0.4*	*17.9*
CAFA[3]	*40*	*17*	*2.5*	*16.0*
SPAF[4]	*5*	*23*	*1.5*	-[a]
SPINAF[5]	*29*	*15*	*1.3*	*24.6*
EAFT[6]	*32*	*9*	*2.8*	*20.9*

INR = international normalized ratio. PTR = prothrombin time ratio. [a]Not reported.

Safety of warfarin in the long term

All the existing trials in this series were conducted for a shorter period than planned because of the stopping rules relating to the demonstration of efficacy. Within their study environment, and within their carefully selected populations, they provided a compelling body of evidence supporting the use of warfarin in nonrheumatic atrial fibrillation. There will now never be long term trials of this type, so the continuation of anticoagulant therapy beyond the three-year mark becomes a matter of clinical judgement for the individual practitioner.

Is warfarin safe in the long term? This question is difficult to answer from the literature because studies differ markedly in methodology, some took place in the 1970s and early 1980s when monitoring was different, patient mix might have been different, and concomitant therapy might have acted as a confound-

ing variable. The findings of the main studies reporting episodes of major and minor bleeding during anticoagulant treatment are shown in Table 3. The long term complication rates of warfarin from long term observations are shown in Table 4. It is acknowledged that there are methodological inconsistencies in introducing results from observational studies for different conditions using different monitoring criteria for comparison with the atrial fibrillation studies, but the advice for general practitioners deriving from these studies is to offer patients warfarin in the long term. It is therefore appropriate to look to the existing literature on the subject, while acknowledging that much of it does not adhere to the experimental gold standard.

Table 3. One-year bleeding rates during anticoagulant therapy reported in 10 studies.

First author, study dates	Design	No. of patients	Target	Annual rate of bleeding (%)	
				Major	Minor
Forfar 1970–77[17]	Observational	501	1.8–2.6 PTR	*0.7*	-[a]
Sixty plus reinfarction group 1980–82[18]	RCT	439	2.7–4.5 INR	*2.6*	*0.9*
Hull 1982[b,19]	RCT	49	1.5–2.0 PTR	*4.1*	*18.0*
Petitti 1970–80[20]	Observational	370	-[a]	*18.0*	-[a]
Gurwitz 1978–86[21]	Observational	321	-[a]	*5.0*	*23.0*
Turpie 1988[b,22]	RCT	108	2.5–4.0 INR	*4.6*	*9.3*
Levine 1962–80[23]	Review	588	Varies	*7.0*	*22.0*
Levine 1971–83[23]	Review	405	Varies	*2.4*	*3.2*
Levine 1967–82[23]	Review	189	Varies	*4.7*	*11.0*
Landefeld 1977–85[24]	Observational	562	1.2–1.5 1.5–2.0 PTR	*12.0*	*9.0*

PTR = prothrombin time ratio. RCT = randomized controlled trial. INR = international normalized ratio. [a]Not reported. [b]Three-month study.

Table 4. Long term complication rates of warfarin.

First author, date	Calculation	Duration (years)	Annual rate of bleeding episode (%)	
			Major	Minor
Pettiti 1986[20]	Actuarial probability	5	*41.0*	-[a]
Gurwitz 1988[21]	Not stated	4	*12.0*	*37.0*
Wickramsinghe 1988[25]	Incidence	3.9(mean)	*10.0*	-[a]
Fihn 1993[26]	Cumulative incidence	8	*28.0*	*40.0*

[a]Not reported.

Within this body of literature, the observations of Forfar[17] and Petitti and colleagues[20] have important lessons for the general practitioner. Petitti and colleagues published a 10-year study of patients on long term warfarin therapy and concluded that the longer the duration of therapy, the more likely were the medically important complications. They calculated that from one week through five years, the probability of major haemorrhage increased 'almost linearly'.[20] In Forfar's seven-year observational analysis of haemorrhage in patients on long term warfarin, there was no cumulative risk in the first three years of treatment, but the trend increased between four and seven years of treatment. Forfar identified patients on warfarin for more than three years as a new at-risk group.[17] There must, therefore, be some concern that the low bleeding rates achieved in the short term trials may not be sustained in the long term.

Hospital or general practice-based warfarin monitoring?

Bath and colleagues were among the first in the UK to show that, despite what they describe as overwhelming evidence to support the use of warfarin, clinical practice was not changing.[27] Both physicians in secondary care and general practitioners seem reluctant to initiate warfarin therapy for seemingly eligible patients with atrial fibrillation. In one small review, fewer than half of cardiologists and geriatricians were likely to prescribe warfarin for patients with atrial fibrillation and dilated cardiomyopathy or aortic valve disease.[28]

General practitioners vary in their willingness to undertake anticoagulation monitoring, and in some practices do not offer this service, directing patients to the hospital clinic.[29] This may cause practical problems in older patients who may be unwilling or unable to attend such a clinic. Some haematologists are calling for substantial programmes to educate and guide general practitioners.[29] Others argue the case that introducing anticoagulation in atrial fibrillation be considered a health promotion strategy.[30]

Some doctors in hospital medicine argue for more resources for outpatient anticoagulant clinics. Yet the evidence is not altogether convincing that hospital based anticoagulant clinics run without problems. One large review published in 1993 showed that about a fifth of patients who presented at one anticoagulant clinic had done so unexpectedly, with no referral explanation from the hospital doctor, and that in only three quarters of the hospital case notes was the referral to the warfarin clinic recorded. Nearly one 10th who attended the clinic had no hospital records.[31]

Control achieved by hospital clinics is not always satisfactory, with fewer than 50% of results falling within the therapeutic range in one study, and nearly one third of patients classed as 'poorly controlled' in another.[32,33] Hospital anticoagulant clinics are often staffed by junior doctors who change frequently: in Pell and colleagues' study 10 junior doctors rotated through the study clinic in three years.[34] Indeed, the main finding of the study was of superior therapeutic control of warfarin in general practice over the three-year period, although it was far from ideal in either setting. Relatively few published studies compare secondary and primary care performance in this context.

Risk stratification in non-rheumatic atrial fibrillation

The issue of risk stratification has been considerably clarified by the results of the second stroke prevention in atrial fibrillation study (SPAF 2), and the meta-analysis of the first five randomized trials.[7,14] In the SPAF 2 trial, 1100 patients were randomized

to receive 325 mg aspirin daily, or warfarin adjusted to an international normalized ratio of 2.0–4.5 in two parallel randomized trials involving patients younger than 75 years, and those aged 75 years and over.[7] In the younger group, warfarin decreased the absolute rate of primary events (strokes) by 0.7%, while in the older age group, this decrease was nearly double (1.2%). In this trial, aspirin was as effective as warfarin in preventing total or disabling strokes. Warfarin was superior in preventing ischaemic strokes, but was associated with an increase in haemorrhagic strokes, which in general are more disabling.[35]

A key contribution of the SPAF 2 study was to show that three clinical variables independently predicted a higher risk of thromboembolism in patients with atrial fibrillation: hypertension, congestive heart failure within the past three months, and previous thromboembolism, with relative risks of 2.2, 2.6 and 2.1, respectively. If one of these three conditions coexists, the risk of stroke in such patients increases from 2.5% per year (no risk factors), to 7.2% per year. If two or all of the factors are present, the yearly risk of stroke increases to 17.6%.

Analysis of the pooled data from the first five randomized trials shows that among the control patients, risk factors that predicted stroke on multivariate analysis were increasing age, a history of hypertension, a history of diabetes, and a history transient ischaemic attacks.[14] What this means is that doctors can now assess the risk of stroke in individual patients with atrial fibrillation.

Those with only atrial fibrillation who are aged less than 60 years may not require any prophylaxis because of their extremely low risk of stroke. Patients aged less than 75 years without hypertension, congestive heart failure or thromboembolism could reasonably be offered aspirin rather than warfarin. In the SPAF and the AFASAK trials aspirin contributed to a risk reduction of over 50% in patients with hypertension, but apparently conferred no benefit in normotensive patients. This does not fit with other data on the value of aspirin in preventing stroke, and the issue needs further clarification, which may come with the publication of ongoing trials.[36,37] On the basis of these trials, warfarin appears to reduce substantially the risk of stroke in all other individuals with atrial fibrillation who do not have a contraindication to the treatment.

The current state of knowledge about stroke prevention in atrial fibrillation allows doctors to adopt a policy of risk stratification based on clinical and echocardiographic factors, with individually tailored treatment.

Shared clinical decisions

Identifying those at risk in a practice can be simply done by reviewing those patients on digoxin, and the pulse rate and rhythm of all patients aged 75 years and over can be recorded at the annual check. For those patients where warfarin is indicated, a strong case can now be made for clear, substantive collaboration between patient, general practitioner and specialist which can operate in several ways.

It is quite possible for risk stratification and the subsequent choice of prophylaxis to be carried out within primary care, where many of the new cases of atrial fibrillation may be discovered opportunistically. The contribution of the general practitioner would be to assess the overall suitability of the patient for anticoagulant therapy, given the echocardiographic findings, and risk profiles. Accordingly, echocardiography, which can influence the choice of aspirin against warfarin should be available as an open access facility to general practitioners.[38] The complete profile would include an up to date knowledge of risk factors using personal knowledge of the patient's medical history, the home, and the person's social habits. This will include, for example alcohol consumption, but also factors like the presence of a telephone in the house. Should the absence of a telephone in the home be a contraindication to warfarin treatment? Crucially, these risk factors will have to be reviewed periodically, as risk factors will vary with time. For example an elderly person living alone, with some visual impairment represents a wholly different clinical decision from a fit elderly grandmother living with her children and grandchildren in one house. In elderly populations (those aged 75 years and over), deafness is present in nearly one third,[39] and dementia in 5%.[40] Visual impairment from all causes increases with age. Thus, the decision to continue warfarin treatment in someone who develops one of these conditions could change: is it safe to continue to advise a patient by telephone about a change in dose when that patient may be too deaf to hear what is being said on the telephone, has visual acuity insufficient to read the labels on the tablet bottle or has a memory deficit which could make compliance less reliable?

An alternative model would involve shared assessment between primary and secondary care, with echocardiograms and comorbidity aiding the specialists in reaching a recommendation, to which the general practitioner's personal knowledge of the patient's circumstances would be complementary. Finally, the crucial role of the general practitioner will be to explain these considerations to the patient, and empower that person to come to a proper decision to accept or decline the treatment.

Conclusion

In summary, a very convincing body of evidence now exists which shows that in carefully selected people, treatment with warfarin exerts a protective influence from stroke at least up to three years of treatment. Continuing treatment for periods longer than that remains a matter of clinical judgement. The decision to initiate warfarin therapy should be the result of true collaboration between the patient, general practitioner, and specialist. Risk factors should be clearly calculated to identify those patients who would benefit from aspirin in preference to warfarin. Further studies are needed from primary care to establish the safety of anticoagulant therapy in the long term, especially in an elderly population, and to clarify the role of aspirin and the value of low dose warfarin in atrial fibrillation.

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