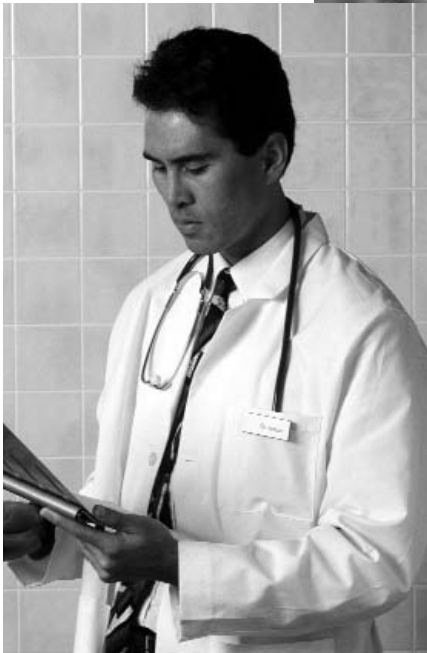
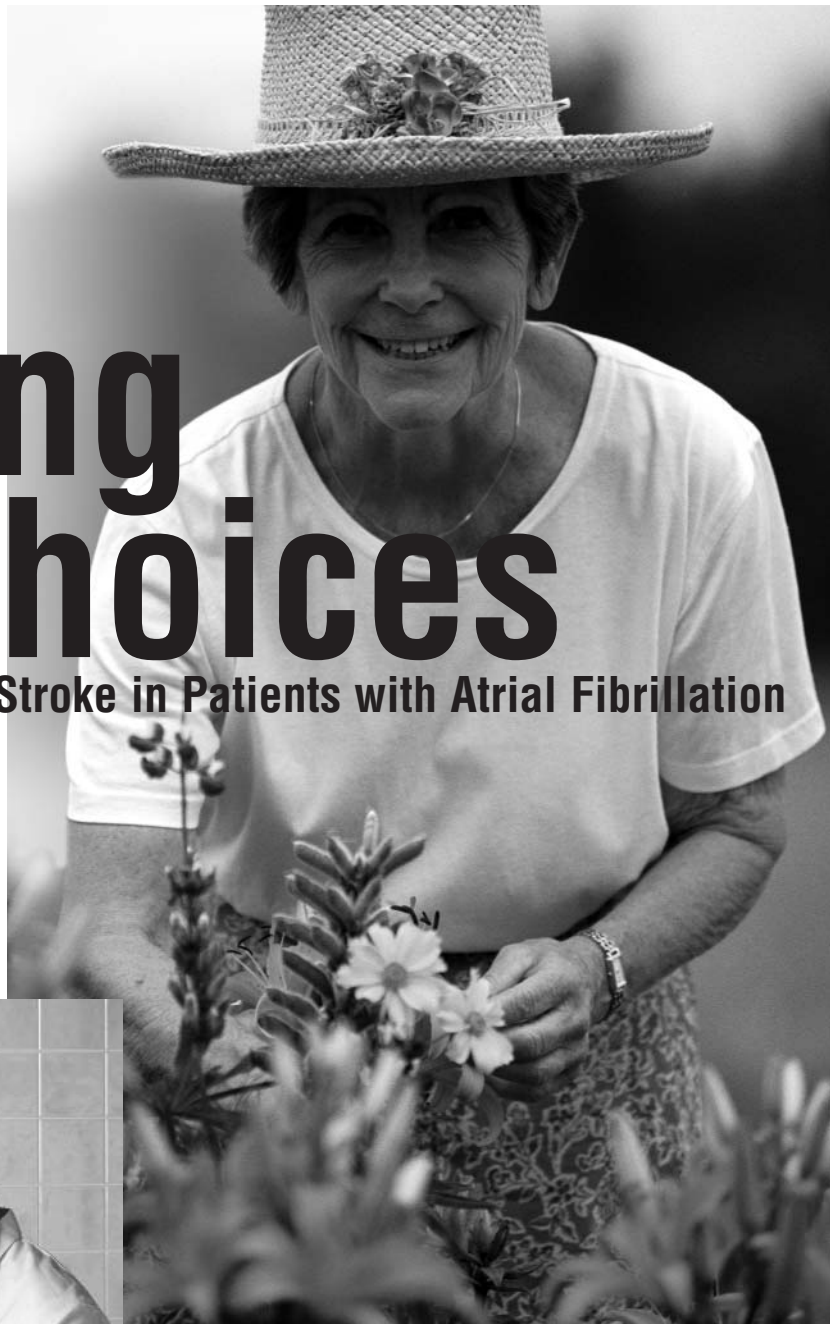


Making Choices

Treatments to Prevent Stroke in Patients with Atrial Fibrillation



Physician's Manual

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Purpose of the decision aid

In the last few years new, and sometimes confusing, information has become available about the efficacy of warfarin and aspirin for stroke prevention in patients with atrial fibrillation. Sometimes the decision about the optimal stroke prevention therapy for a patient with atrial fibrillation is not easy and can depend upon the patient's preference. The purpose of the decision aid is to present patients with up-to-date and easy to understand information about this topic. The decision aid is intended to help patients:

- understand what it means to have a stroke;
- understand their risk of stroke if they take no antithrombotic therapy;
- understand the benefits and risks of aspirin therapy;
- understand the benefits and risks of warfarin therapy;
- clarify the personal importance of the benefits and risks of each alternative;
- identify any questions they wish to discuss with their physician; and
- be better able to discuss the treatment options with their physician.

Purpose of this physician's manual

This physician's manual is intended to:

- provide you with a summary of the format and content of the decision aid;
- provide you with the scientific justification for the information presented in the decision aid; and
- prepare you for any questions your patients may have about warfarin and aspirin therapy for stroke prevention in atrial fibrillation.

Format of the decision aid

This decision aid is in the form of an audiobooklet, consisting of a booklet (written to a Grade 8 reading level), an audiotape and a personal worksheet. There are different booklets depending upon the patients' risk of stroke. The risk stratification scheme that is used is shown in Appendix 1. Your patient falls into one of stratum A, B, C, or D. The tape guides the patients through the information in the booklet, and provides them with more details than are in the booklet. Patients can use the audiobooklet at any time and place that is convenient for them. They can stop the tape at any time, can replay sections, and can share the audiobooklet with friends and relatives. The personal worksheet helps patients to weigh the benefits and risks of aspirin and warfarin therapy, record questions that they would like to discuss with their physician, and indicate which therapy (warfarin, aspirin or neither) they are inclined to take. It is clearly indicated that this decision should be made together with their physician.

Presentation of probabilities

About half of the strokes that occur in patients with atrial fibrillation are minor, and half are major. In the audiobooklet patients are presented with explicit descriptions of the consequences of having a 'typical' minor or major stroke, as well as a gastrointestinal bleed (the most common major side-effect of warfarin and aspirin). We believe that this information is required in order for patients to make an informed decision.

Patients are presented with information about the probability of a stroke and major gastrointestinal bleed using 100 "faces". Coloured "sad faces" are used to indicate the patients who will have a stroke or a major bleed. Dark blue is used to indicate a major stroke, light blue a minor stroke and red a major bleed. The information is framed in both a positive and negative way (e.g. "Your chance of having a stroke in the next 2 years is 8%. This means that there is a 92% chance that you will not have a stroke").

Risk of stroke in patients with atrial fibrillation

Patients with atrial fibrillation have an increased risk of stroke. About 75% of the strokes are felt to be cardioembolic (either originating in the left atrium or ventricle). Since most patients with atrial fibrillation also have other risk factors for stroke (e.g. hypertension, diabetes and vascular disease) it is not surprising that the other 25% of strokes arise from non-cardiac sources (e.g. carotid stenosis, atheromata in the aortic arch, or disease in the intracranial vessels).

The risk of stroke in the average patient with non-rheumatic atrial fibrillation on no antithrombotic therapy is about 5% per year (10% over 2 years). This risk varies considerably depending upon the characteristics of the patient. The most important clinical factors that increase the risk of stroke in a patient with atrial fibrillation are:

- * a previous transient ischemic attack (TIA), stroke, or systemic arterial embolism (even if it occurred many years ago);
- * increasing age;
- * poor left ventricular function (clinically or on echocardiogram); and
- * high blood pressure (systolic BP >160 mm Hg) or history of hypertension.

Transthoracic echocardiograms are often ordered in patients with atrial fibrillation. The most important echocardiographic finding that increases the risk of stroke in patients with atrial fibrillation is poor left ventricular function. It was previously thought that increased left atrial size was an important risk factor, but we now believe that left atrial size does not add very much clinically important, independent information to the clinical risk factors mentioned above[4]. Because the role of transesophageal echocardiography in the management of patients with atrial fibrillation is not known, it is not considered in our risk stratification scheme.

We have developed a risk stratification scheme to estimate the risk of stroke of patients with atrial fibrillation (see Appendix 1), which divides patients into four risk categories. This risk stratification scheme is adapted from the current American College of Chest Physicians recommendations [2]. Four different audiobooklets have been developed, and the patient receives the audiobooklet that fits his or her clinical profile. Thus, in the audiobooklet, the patients will be presented with information about the risk of stroke that is tailored to them.

Information in the audiobooklet

In the last few years a number of high quality randomized trials evaluating the benefits and risks of warfarin and aspirin in patients with atrial fibrillation have been published. Unfortunately, the average follow-up in most trials was relatively short (1 to 2 years). It is generally assumed that the benefits and risks of warfarin and aspirin stay constant with longer follow-up, but this is not known for sure. Certainly, when patients with atrial fibrillation are placed on either warfarin or aspirin, the usual intent is to treat them indefinitely, or until side-effects or contraindications arise.

In the audiobooklet patients are presented with information about their risk of stroke and major hemorrhage during the next two years. We feel that this is a reasonable compromise between the relatively short follow-up in the clinical trials, and the reality that these medications are usually given for prolonged periods of time.

Efficacy of warfarin

Seven randomized trials have compared warfarin with either placebo or control [5-11]. The results are remarkably consistent: a relative risk reduction in stroke of about 65% [1,5,12]. It appears that this risk reduction applies to patients with different baseline risks of stroke. For example, warfarin will decrease the risk of stroke in a patient with a 12% risk of stroke to about 4% ($12\% \times 0.35$), and will decrease the risk of stroke in a patient with a 2% risk of stroke to less than 1% ($2\% \times 0.35$).

The target International Normalized Ratio (INR) used in the various studies was different. It is clear that an INR above 3.5 leads to an increased risk of hemorrhage [13-15], and an INR below 1.5 to 2.0 is much less effective at preventing strokes [16-17]. Thus, at the present time a target INR of 2.0 to 3.0 for most patients seems reasonable, and is the current recommendation of the American College of Chest Physicians [2].

It is always important to consider the generalizability of the results of clinical trials to the "real world". All of the randomized trials had personnel dedicated to the study, and the patients were compliant volunteers. Therefore, the 65% reduction with warfarin may slightly over-estimate its effectiveness in usual clinical practice. On the other hand, no techniques were used in the trials that are not available in usual clinical practice, and it is likely that diligent physicians will achieve similar results in compliant patients.

Efficacy of aspirin

The results of randomized trials evaluating the efficacy of aspirin are not as consistent as those of warfarin. There are two types of trials from which information can be gained: randomized trials comparing aspirin with placebo, and randomized trials comparing aspirin with warfarin.

Six studies have compared aspirin with placebo. The relative risk reductions in stroke ranged from 11% to 44% [5-7,18-20]. When these trials were combined in a meta-analysis [12], the relative risk reduction was 22%, which is very similar to the 25% found in a large meta-analysis of all randomized trials of aspirin therapy in patients with different types of vascular disease [21].

Thus, using a relative risk reduction of 20 to 25% from aspirin for all patients seems to best reflect current knowledge. However, five trials have compared warfarin with aspirin [5,6,11,22,23]. Combining these data, warfarin is more efficacious in preventing stroke in patients with non-rheumatic atrial fibrillation (36% relative risk reduction versus aspirin) [12].

The dose of aspirin used in the studies varied between 50mg and 325mg a day. The current recommended dose is 325mg of enteric coated aspirin a day [2].

Because aspirin has relatively few side-effects, does not require monitoring and is only taken once a day, we believe that the results of the studies of aspirin are reflective of what happens in actual practice.

Efficacy of combination of fixed low-dose warfarin and aspirin

Two recent studies [16,22] have shown that adjusted dose warfarin (to maintain an INR of 2.0 to 3.0) is markedly superior to the combination of fixed low-dose warfarin (INR 1.2-1.5) and aspirin (300 to 325 mg per day) in reducing the risk of stroke in patients with atrial fibrillation (relative risk reductions 61% and 74%). Therefore the use of combination therapy with low dose warfarin and aspirin is NOT recommended for stroke prophylaxis in patients with atrial fibrillation.

Side-effects of warfarin

The major side-effect of warfarin therapy is bleeding, which can be characterized as major or minor. Major bleeding is usually defined as bleeding that is severe enough to require hospital admission, blood transfusion, or a bleed that leaves residual sequelae. Although relatively rare, intracranial hemorrhage is the bleed that is associated with the most morbidity. However, in the audiobooklet patients are not told about intracranial hemorrhages, because these bleeds have been counted as strokes in the description of the efficacy of warfarin. Our assumption is that patients are more concerned about the frequency of disabling strokes, rather than whether the stroke is hemorrhagic or non-hemorrhagic.

By far the most common type of major hemorrhage is bleeding into the gastrointestinal tract. Therefore, in the audiobooklet the consequences of an upper gastrointestinal bleed are described in considerable detail. Because it is not practical to describe all of the potential types of major bleeds, it is indicated that the description of a gastrointestinal bleed is representative of what it would be like to have a major bleeding episode.

Some patients have major bleeding episodes even if they are not on warfarin. Therefore, when presenting patients with the risk of major bleeding on warfarin therapy, it is important that they are provided with the excess bleeds associated with warfarin therapy. This information can be derived from three sources: a) randomized trials in patients with atrial fibrillation comparing warfarin with placebo or control, b) randomized trials in patients with atrial fibrillation comparing warfarin with aspirin, and c) cohort studies of patients in anticoagulation clinics who are taking warfarin. These studies provide somewhat different estimates of the excess rate of major hemorrhage due to warfarin therapy. We will briefly review the available studies, and then justify our choice of an excess annual rate of major hemorrhage of 2% per year due to warfarin (or 4% over two years). Remember that for this decision aid we are only interested in non-CNS major bleeds, since intracranial hemorrhages are counted as strokes.

In the randomized trials of patients with atrial fibrillation comparing warfarin with control, the excess annual rate of major bleeding ranged from more bleeds in the control group in one study [7], to 2% more in the warfarin group in another study [5]. If one averages the excess rate of major bleeds in all of the studies, it is around 0.5 to 1.0% per year. In the studies comparing warfarin with aspirin, the warfarin-treated patients had an excess risk of major bleeding of 0.2% per year [12]. The likelihood of bleeding with warfarin is directly related to the intensity of anticoagulation: in the

randomized clinical trials, virtually all of the major bleeds were seen in patients with INRs in excess of 3.0 [24]. In general, cohort studies report greater rates of major bleeds ranging from 0.6% per year to 5% per year [25-34].

Because of the intensive follow-up and the low risk (for bleeding) and compliant patients entered into the randomized trials, it is very likely that these rates under-estimate the rate of bleeding in usual clinical practice. Therefore, we believe that the best estimate of the likelihood of a major non-CNS bleed in atrial fibrillation patients on warfarin is 2% per year (or 4% over 2 years). This represents the average risk of a major bleed in the cohort studies, and is a rate similar to that found in two of the randomized trials comparing warfarin with control or placebo[2,13].

The effect of age upon the bleeding rate is controversial, but there is some suggestion that it may be higher in older patients [11,25]. Therefore, in the text of the audiobooklet it is indicated that the rate of bleeding is probably higher in patients older than 75 and lower in patients younger than 60, without providing different rates for different ages. We also take the opportunity to emphasize that careful control of INR lowers the risk of major bleeding.

Minor bleeding episodes on warfarin therapy such as easy bruising and epistaxis occur much more frequently than major hemorrhage. These are described in the audiobooklet. The costs and inconveniences of warfarin therapy are also described.

Side-effects of aspirin

Enteric-coated aspirin at a dose of 325mg a day is generally well tolerated. Most patients with atrial fibrillation have been on aspirin for various ailments in the past, and they therefore know whether or not they develop abdominal symptoms such as nausea and epigastric distress on aspirin. In the audiobooklet it is indicated that the frequency of these symptoms is doubled in patients on aspirin compared with those not on aspirin. The risk of a major bleeding episode on 325mg of enteric-coated aspirin daily in elderly patients is unknown, but appears to be very low given the results in the randomized placebo-controlled trials (which tested various doses of aspirin). The best estimate appears to be approximately a 0.5% excess over two years, [7,35-39] and this is what is presented to the patients in the decision aid.

Presenting the choices to your patient

Patients are presented with a summary of the frequency of stroke and major bleeding for the three options; warfarin, aspirin, or neither. They are then asked to fill out a sheet called "Weighing my own pros and cons". In this worksheet they are asked to indicate: if there are any factors in their medical history which would increase their risk of bleeding; the importance they place on the amount of stroke protection provided by warfarin and aspirin, the importance of the risks and disadvantages of the two therapies; any questions they may have; their preferences regarding who should make this decision, and whether they are leaning towards taking warfarin, aspirin or neither. They are asked to bring this sheet with them at the time of their next visit to their physician, to use as a tool to guide the decision about which therapy they will take.

We welcome your feedback!

We hope that this decision aid will facilitate communication between yourself and your patients in whom antithrombotic therapy for atrial fibrillation is being contemplated. Please provide us with your feedback about what you liked and did not like about this audiobooklet, and whether or not you and your patients found it useful. It is likely that the audiobooklet will be modified in the future as more information about antithrombotic therapy for atrial fibrillation becomes available, and your comments will help us improve the new version.

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Appendix 1: Risk of stratification scheme used in the decision aid

The information about the likelihood of stroke over two years that is provided to your patient will depend upon his or her risk factors. He or she will receive an audiobooklet which contains one of the following four risks. The figures represent the risk of stroke over two years of follow-up.

RISK	No Therapy	Aspirin	Warfarin
A. LOW < 65 years old, no hypertension, no left ventricular dysfunction (clinically or on echocardiogram), no previous TIA/stroke/systemic arterial embolism.	2%	1.5%	1%
B. MEDIUM 65-75 years old, no hypertension, no left ventricular dysfunction (clinically or on echocardiogram), no previous TIA/stroke/systemic arterial embolism.	4%	3%	2%
C. HIGH <75 years old, and hypertension or left ventricular dysfunction (clinically or on echocardiogram) <u>OR</u> > 75 years old without risk factors	12%	9%	4%
D. VERY HIGH >75 years old, and hypertension or left ventricular dysfunction (clinically or on echocardiogram) <u>OR</u> Any age and previous TIA/stroke/systemic arterial embolism.	20%	16%	7%



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