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Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter

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ABSTRACT

The stroke rate in atrial fibrillation is 4.5% per year, with death or permanent disability in over half. The risk of stroke varies from under 1% to over 20% per year, related to the risk factors of congestive heart failure, hypertension, age, diabetes, and prior stroke or transient ischemic attack (TIA). Major bleeding with vitamin K antagonists varies from about 1% to over 12% per year and is related to a number of risk factors. The $CHADS_2$ index and the HAS-BLED score are useful schemata for the prediction of stroke and bleeding risks.

Vitamin K antagonists reduce the risk of stroke by 64%, aspirin reduces it by 19%, and vitamin K antagonists reduce the risk of stroke by 39% when directly compared with aspirin. Dabigatran is superior to warfarin for stroke prevention and causes no increase in major bleeding. We recommend that all patients with atrial fibrillation or atrial flutter, whether paroxysmal, persistent, or permanent, should be stratified for the risk of stroke and for the risk of bleeding and that most should receive antithrombotic therapy. We make detailed recommendations as to the preferred agents in various types of patients and for

RÉSUMÉ

L'incidence annuelle de l'accident vasculaire cérébral (AVC) attribuable à la fibrillation auriculaire (FA) est de 4.5 %, causant la mort ou l'invalidité permanente dans plus de la moitié des cas. Cette incidence varie de moins de 1 % à plus de 20 % par année en fonction des facteurs de risque: insuffisance cardiaque, hypertension, âge, diabète et antécédents d'AVC ou d'ischémie cérébrale transitoire. Le risque d'hémorragie majeure sous traitement avec les antagonistes de la vitamine K varie entre 1 % et 12 % par année et s'avère lié à beaucoup d'autres facteurs. L'index de CHADS2 et le score HAS-BLED sont utiles pour la prédiction du risque d'AVC ou d'hémorragie. Le risque d'AVC est réduit de 64% avec le traitement aux antagonistes de la vitamine K et de 19% avec l'aspirine. Comparativement à l'aspirine, les antagonistes de la vitamine K réduisent ce risque de 39%. Le Dabigatran est supérieur à la warfarine pour la prévention du risque d'AVC sans augmentation du risque de saignement majeur. Nous recommandons que le risque d'AVC et de saignement majeur soit déterminé chez tous les patients avec FA ou flutter auriculaire (paroxystique, persistant ou permanent) et que la plupart reçoivent un traitement antithrombotique. Nos recommandations font état des agents antithrom-

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The disclosure information of the authors and reviewers is available from the CCS on the following Web sites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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the management of antithrombotic therapies in the common clinical settings of cardioversion, concomitant coronary artery disease, surgical or diagnostic procedures with a risk of major bleeding, and the occurrence of stroke or major bleeding. Alternatives to antithrombotic therapies are briefly discussed.

botiques à favoriser dans les contextes cliniques de cardioversion, maladie cardiaque athérosclérotique concomitante, procédures diagnostiques ou chirurgicales avec risque d'hémorragie majeure associée, et en cas d'AVC ou de saignement majeur. Les alternatives au traitement antithrombotique sont brièvement discutées.

Risk of Stroke

Risk factors and risk estimation schemes

In the 5 landmark randomized clinical trials of oral anticoagulants (OACs) among patients with nonvalvular atrial fibrillation (AF),[1-6] most of whom had no previous stroke or TIA, control subjects had a mean 4.5% annual incidence of stroke (range, 3%-7%), over half of which resulted in death or permanent disability.[7] The mean annual incidence of the composite of stroke or other systemic emboli was 5% (range, 3%-7.4%). These subjects had no contraindications to warfarin and no echocardiographic evidence of rheumatic valvular disease. The observed rates of stroke and other systemic embolism were similar to those reported in earlier cohorts[8] and likely are representative of individuals in the general population with AF and not receiving antithrombotic therapy. In the United States, the annual risk of stroke attributable to AF is 1.5% in the age group 50 to 59 years, rises to 23.5% in the age group 80 to 89 years, and overall is 15%.[9]

An overview of the randomized control trials of warfarin therapy in AF[7] determined that previous stroke or TIA, increasing age, history of hypertension, and diabetes were statistically significant multivariate predictors of stroke. Annual stroke risk ranged from 0 (patients younger than 60 years) to 1.3% (patients younger than 80 years with no other risk factors) and to 11.7% (patients with prior stroke or TIA). A recent systematic review[10] examined the evidence identifying independent risk factors for stroke as reported in 7 studies selected according to rigourously defined criteria. The absolute annual risk of stroke varied 20 fold among patients grouped by various risk factors. Independent risk factors for stroke were the same as those previously identified[7]: stroke or TIA (relative risk [RR] 2.5), age (RR 1.5/decade), history of hypertension (RR 2.0), and diabetes mellitus (RR 1.7). Female sex was an independent risk factor in 3 of 6 cohorts, but coronary artery disease and clinical congestive heart failure were not found to be independent risk factors in any of these studies. Even though congestive heart failure and reduced ejection fraction have been identified only as univariate risk factors,[7,10-12] they are included in current risk classification schemes.[13,14] The review[10] emphasized a variety of shortcomings of the studies, including inconsistencies in definitions of some of the risk factors, the use of antiplatelet therapies, and the stroke outcomes (ischemic strokes only, all strokes, strokes plus other systemic emboli, and strokes plus TIAs).

The $CHADS_2$ index[14] (see Table 1 for the components of the acronym) assigns 1 point each for congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for a history of stroke or TIA (Table 1). The scheme was validated and compared with 2 other schemes among 1733 Medicare beneficiaries aged 65 to 95 years who had been discharged from hospital with nonrheumatic AF and had not been prescribed warfarin. The $CHADS_2$ index was the most accurate predictor of stroke, with the annual stroke rate increasing by about 2.0% for each 1-point increase in $CHADS_2$ score (from 1.9% with a score of 0 to 18.2% with a score of 6). This scheme was also evaluated in comparison with several others among 2580 patients receiving aspirin in 6 prospective trials.[15] The $CHADS_2$ index identified increments in stroke risk similar to those identified in the prior validation and was better than the other schema at discriminating medium- and high-risk patients. Although a recent systematic review[16] of 12 risk stratification schemes noted that none has been compared in a single cohort of adequate size and diversity, the $CHADS_2$ index has appropriately become the favoured choice for determining risk of stroke and guiding choice of antithrombotic therapy.[13]

The European Society of Cardiology (ESC) has recently updated its guidelines for the management of AF[17] and has incorporated the new Birmingham 2009 schema (known by the acronym CHA_2DS_2-VASc) for the prediction of stroke risk.[18] The schema was validated and compared with standard criteria in a subset of 1577 patients documented in the Euro Heart Survey on AF population. The schema is similar to the $CHADS_2$, but gives 2 points for age of 75 years or older and 1 point for age between 65 and 74 years, 1 point for vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), and 1 point for female sex. The ESC recommends that the widely used and easily remembered $CHADS_2$ be applied first; only if the score is under 2 should the new schema be applied to further grade risk of stroke in patients at low risk. The degree of risk can be refined, and if any of the additional risk factors embodied in the CHA_2DS_2-VASc are present, the score will be increased and may influence the physician to choose more potent antithrombotic management. Conversely, if the score remains at 0, the patient is clearly at very low risk of stroke and may not require any antithrombotic agent. The ESC recommends that a patient

Table 1. The $CHADS_2$ score for estimating stroke risk in patients with atrial fibrillation according to the presence of major risk factors

	$CHADS_2$ risk criteria	Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age >75 years	1
D	Diabetes mellitus	1
S_2	(Prior) stroke or TIA	2

$CHADS_2$ score	Adjusted stroke rate, %/y (95% CI)
0	1.9 (1.2-3.0)
1	2.8 (2.0-3.8)
2	4.0 (3.1-5.1)
3	5.9 (4.6-7.3)
4	8.5 (6.3-11.1)
5	12.5 (8.2-17.5)
6	18.2 (10.5-27.4)

Data from Gage BF, et al.[14]

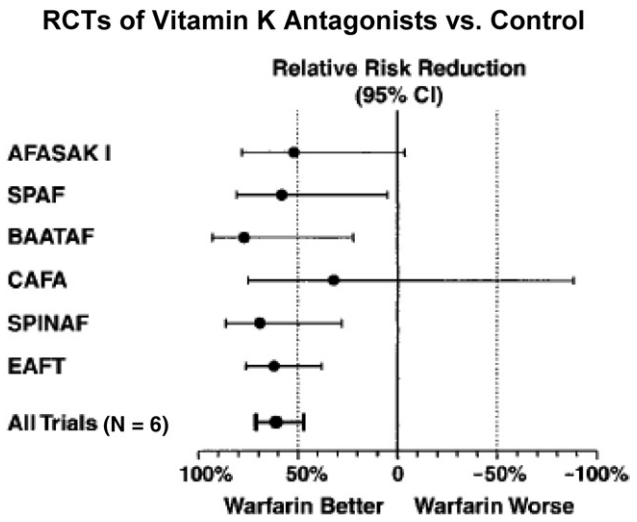

Figure 1. Randomized controlled trials (RCTs) of adjusted-dose warfarin (or other vitamin K antagonist in a small proportion of patients) vs placebo or no treatment. Point estimates of the relative risk reductions of stroke (ischemic plus hemorrhagic) with their associated 95% CIs are depicted for 5 trials of primary prevention and 1 of secondary prevention. The overall relative risk reduction is 64% (95% CI, 49%-74%). AFASAK, Atrial Fibrillation, ASpirin, AntiKoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation; EAFT, European Atrial Fibrillation Trial. Reprinted from Hart RG et al[26] with permission from Ann Intern Med.

with a score of 0 according to the CHA_2DS_2-VASc schema should receive either aspirin or no antithrombotic therapy, with the latter preferred; a patient with a score of 1 should receive either aspirin or OAC, with the latter preferred; and a patient with a score of 2 should receive OAC. This new schema may eventually be useful for patient management, but for the present, the CCS recommends ongoing use of the $CHADS_2$ schema.

Paroxysmal AF

The Stroke Prevention in Atrial Fibrillation (SPAF) trial[6] found similar annual rates of ischemic stroke in patients with "recurrent" (3.2%) and "chronic" (3.3%) AF. A report from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Warfarin (ACTIVE-W), based on 1202 patients with paroxysmal AF and 5495 with persistent or permanent AF, confirmed similar rates of thromboembolic events.[19] However, it is possible that the risk of stroke is less in patients whose episodes of AF are brief (<1 day) and self-terminating.[20] The short-term risk of stroke appears to be higher in patients with recent-onset AF than in those with AF that first occurred more than 1 to 2 years ago.[21,22] Among AF patients with prior stroke, the annual recurrence rate is about 12% without antithrombotic treatment.[7,23] Several case series reported recurrence rates of 0.1% to 1.3% per day during the first 2 weeks following a cardioembolic stroke.[24]

Thyrotoxicosis and hypertrophic cardiomyopathy

The risk of stroke in patients with thyrotoxic AF is substantial, although the mechanism and the relative role of congestive heart failure are uncertain. The risk of stroke is also substantial among patients with hypertrophic cardiomyopathy and AF. These risks have not been rigourously evaluated, and antithrombotic therapies for patients with AF and thyrotoxicosis or hypertrophic cardiomyopathy should be based on the presence of validated stroke risk factors.[9,13,17]

Atrial flutter

There is a widespread perception that the risk of stroke is less with atrial flutter than with AF. However, a retrospective analysis of a large database of elderly hospitalized patients found little difference in the risk ratios for atrial flutter (1.4) and AF (1.6).[25] By 8 years of follow-up, more than half the patients with atrial flutter had developed AF, and these patients were more likely to experience a stroke. The development of AF was more likely among patients with congestive heart failure, rheumatic heart disease, hypertension, and diabetes mellitus.

Trials of Antithrombotic Therapies

Oral vitamin K antagonists and antiplatelet agents

An overview[7] of the initial 5 randomized trials of oral vitamin K antagonists compared with no treatment found the incidence of ischemic stroke was reduced from 4.5% per year to 1.4% per year (relative risk reduction [RRR] 68%; 95% CI, 50%-79%; $P < .001$). The rate of major hemorrhage with vitamin K antagonists was 1.3% per year vs 1% per year in controls. The most recent meta-analysis of such trials[26] in-

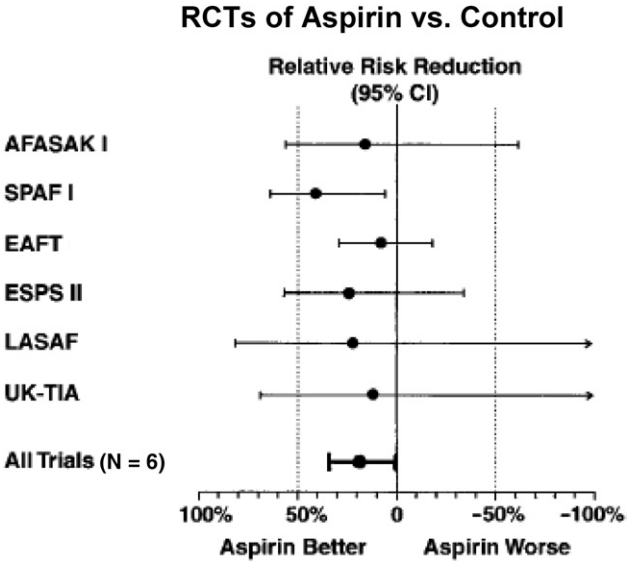

Figure 2. Randomized controlled trials (RCTs) of aspirin vs placebo or no treatment. Point estimates of the relative risk reductions of stroke (ischemic plus hemorrhagic) with their associated 95% CIs are depicted for 4 trials of primary prevention and 3 of secondary prevention. The overall relative risk reduction is 19% (95% CI, −1% to 35%). AFASAK, Atrial Fibrillation, ASpirin, AntiKoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study; LASAF, Low-dose Aspirin, Stroke, Atrial Fibrillation; UK-TIA, United Kingdom Transient Ischemic Attack; JAST, Japan Atrial fibrillation Stroke Trial. Reprinted from Hart RG et al[26] with permission from Ann Intern Med.

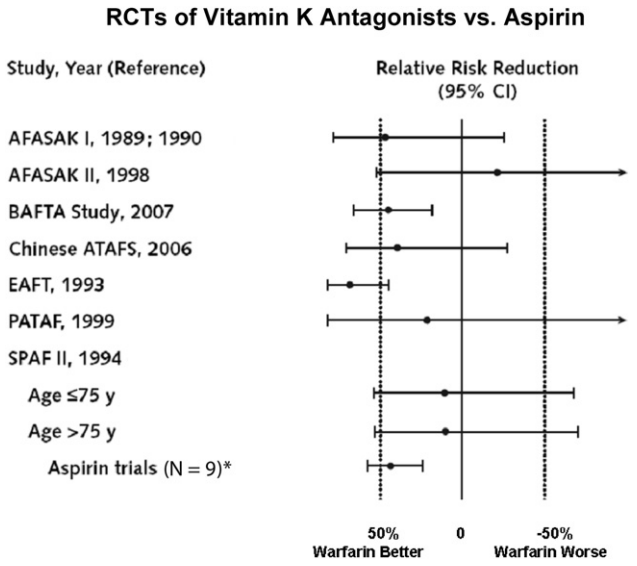

Figure 3. Randomized trials of adjusted-dose warfarin (or other vitamin K antagonist in a small proportion of patients) vs aspirin. Point estimates of the relative risk reductions of stroke (ischemic or hemorrhagic) with their associated 95% CIs are depicted for 7 trials of primary prevention and 1 of secondary prevention. The overall relative risk reduction is 39% (95% CI, 19%-53%). AFASAK, Atrial Fibrillation, ASpirin, AntiKoagulation; BAFTA, Birmingham Atrial Fibrillation Treatment of the Aged; Chinese ATAFS, Chinese Antithrombotic Therapy in Atrial Fibrillation; EAFT, European Atrial Fibrillation Trial; PATAF, Prevention of Arterial Thromboembolism in Atrial Fibrillation; SPAF, Stroke Prevention in Atrial Fibrillation. Reprinted from Hart RG et al[27] with permission from Ann Intern Med.

cluded 1 additional trial (of secondary prevention of stroke) and calculated an RRR of 64% (95% CI, 49% to 74%) for the more clinically meaningful outcome of all stroke (ischemic or hemorrhagic; Fig. 1). The absolute risk reduction (ARR) was 2.7% per year in primary prevention trials and 8.4% per year in the only secondary prevention trial. There was an excess of 0.3% per year (P = not significant) of major extracranial hemorrhage with vitamin K antagonist therapy but a statistically significant ARR of mortality of about 1.6% per year.

The overview included trials of aspirin vs no treatment[26] and reported an RRR for all stroke of 19% (95% CI, 1% to 35%; Fig. 2), with an ARR of 0.8% per year in primary prevention trials and 2.5% per year in secondary prevention trials. There were no significant differences in major extracranial hemorrhage or mortality. An update of this overview[27] assessed trials of vitamin K antagonists vs aspirin and reported an RRR for all stroke of 39% (95% CI, 19%-53%) in favour of vitamin K antagonists (Fig. 3), equivalent to an ARR of about 0.9% per year for primary prevention and 7% per year for secondary prevention. There were no significant differences in major extracranial hemorrhage or mortality. The inclusion of 3 further trials comparing vitamin K antagonists with other antiplatelet agents did not importantly alter the findings.

Warfarin adjusted to an international normalized ratio (INR) of 2 to 3 has been compared with various regimens of lower-dose warfarin plus aspirin[28] and to warfarin at lower intensity and low fixed dose,[29-31] but none of these regimens was as effective. It had been expected that in patients suitable for warfarin therapy, the combination of aspirin plus clopidogrel might be noninferior to warfarin for the prevention of stroke, while offering the advantages of less bleeding and greater convenience. However, the ACTIVE-W trial[32] found the RR for the composite outcome of stroke, non–central nervous system embolus, myocardial infarction, and vascular death was 1.44 (95% CI, 1.18-1.76; $P = .0003$) for the combination of clopidogrel plus aspirin (75 mg and 75-100 mg/d) vs warfarin (INR 2-3). Somewhat surprisingly, the RR for major bleeding was 1.10 (95% CI, 0.83-1.45) with the combination.

It had also been expected that in patients not suitable for warfarin therapy, the combination of aspirin and clopidogrel might be more effective than aspirin alone. The ACTIVE-A trial[33] did find that after a mean of 3.6 years, the risk of major vascular events was reduced by the combination (RR 0.89; 95% CI, 0.81-0.98; $P = .01$). However, major bleeding was increased by the combination (2.0% vs 1.3% per year; RR 1.57; 95% CI, 1.29-1.92; $P < .01$).

New non–vitamin-K-antagonist anticoagulants

Ximelagatran is an oral direct thrombin inhibitor with predictable and stable pharmacokinetics and relatively low potential for interactions with other drugs and with foods. Coagulation monitoring and dose adjustments are not required. This agent was evaluated in 2 large trials employing noninferiority designs.[34,35] In both, it was concluded that ximelagatran was noninferior to warfarin. The incidence of major bleeding was similar with the 2 agents, but all bleeding was significantly less with ximelagatran. However, both studies found a 6-fold excess of patients with elevations of alanine aminotransferase to greater than 3 times the upper limit of normal, usually within the first 6 months. The Food and Drug Administration did not approve the new agent, having concluded that the more convenient dose and monitoring regimens and less total bleeding did not outweigh concerns about hepatic toxicity and the inappropriately large noninferiority margins.

Dabigatran is an oral direct thrombin inhibitor that is licensed for use in Canada and the United States. It was compared with warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[36] in which 18,113 patients with AF (mean $CHADS_2 = 2.1$) were randomized to dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, or warfarin (INR 2-3) and followed for a median of 2.0 years. The mean time in the therapeutic range for warfarin was 64%. Rates of discontinuation of therapy by 2 years were 16.6% for warfarin, 20.7% for dabigatran 110 mg, and 21.2% for dabigatran 150 mg. Approximately 20% of subjects were taking aspirin in addition to their study drug. The rates of the principal outcome of all stroke (ischemic or hemorrhagic) or non–central nervous system embolus were 1.69% per year with warfarin, 1.53% per year with dabigatran 110 mg (RR 0.91; 95% CI, 0.74-1.11; $P < .001$ for noninferiority), and 1.11% per year with dabigatran 150 mg (RR 0.66; 95% CI, 0.53-0.82; $P < .001$ for superiority; Fig. 4). The RR of stroke or systemic embolus for dabigatran 150 mg vs 110 mg was 0.73 (95% CI, 0.58-0.91; $P = .005$). The rates of major bleeding were 3.36% per year with warfarin, 2.71% per year with dabigatran 110 mg (RR vs warfarin 0.8, $P = .003$), and 3.11% per year with dabigatran 150 mg (RR vs warfarin 0.93, $P = .31$ and RR vs dabigatran 110 mg 1.16, $P = .052$). The rates of the net clinical benefit outcome (a composite of stroke, systemic em-

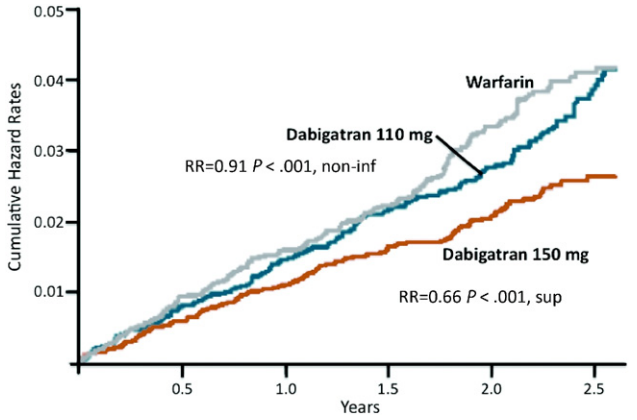

Figure 4. Cumulative hazard rates (y-axis) vs time in years (x-axis) for the primary outcome of stroke (ischemic or hemorrhagic) or systemic embolism, according to treatment group (dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, or warfarin [INR 2-3]). RR, relative risk. Reprinted from Connolly SJ, et al[36] with permission from N Engl J Med, © Massachusetts Medical Society.

bolism, pulmonary embolism, myocardial infarction, death, or major bleeding) were 7.64% per year with warfarin, 7.09% per year with dabigatran 110 mg (RR vs warfarin 0.92; 95% CI, 0.84-1.02), and 6.91% per year with dabigatran 150 mg (RR vs warfarin 0.91; 95% CI, 0.82-1.00). Hence, in this group of patients with clear indications for warfarin therapy, dabigatran 110 mg twice daily was associated with rates of stroke and systemic embolism similar to those associated with warfarin, but with a rate of major hemorrhage that was lower. Compared with warfarin, dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism and a similar rate of major hemorrhage. Compared with dabigatran 110 mg, the 150-mg dose was associated with lower rates of stroke and systemic embolus but a strong trend toward more major hemorrhage.

The data for the comparative beneficial and harmful effects of dabigatran vs warfarin among patients with AF are derived only from RE-LY and a relatively small pilot study (Prevention of Embolic and ThROmbotic events in patients with persistent atrial fibrillation).[37] However, RE-LY enrolled over 18,000 patients. The recommendations made by previous national guidelines exercises have been based on a total of 2900 patients in the randomized trials of warfarin vs control, 3990 patients in the trials of aspirin vs control, and 3647 patients in the trials of warfarin vs aspirin. The results of RE-LY and studies of other newer anticoagulants, as they are published, must be taken into account in all subsequent guidelines exercises.

Although dabigatran 110 mg twice daily was found to be as effective as warfarin and caused less major bleeding, and dabigatran 150 mg twice daily was found to be more effective than warfarin and with a similar risk of major bleeding, additional considerations are necessary in arriving at sensible recommendations for use. The subjects all had at least 1 risk factor for stroke (mean $CHADS_2$ was 2.0), and patients with CrCl <30 mL per minute and any condition that increased the risk of bleeding were excluded. Dyspepsia was twice as common in the dabigatran groups, gastrointestinal bleeding was more common, and patients receiving dabigatran discontinued study therapy almost 50% more often in the first year of therapy than did those receiving warfarin. Although there was a trend to a reduction of the composite clinical outcome in the dabigatran groups, there was a trend to more frequent myocardial infarction with dabigatran, which was significant at the 150-mg dose. There was no hint of greater hepatic toxicity with dabigatran than with warfarin, but the total clinical experience extends to only a mean of 2 years, and careful long-term follow-up data are needed. Dabigatran tablets are much more costly than warfarin, but rigourous cost-effectiveness analyses will be needed to assess total costs.

We recommend that when an OAC is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin. Possible exceptions would include patients with a propensity to dyspepsia, gastrointestinal bleeding, or both and those at substantial risk of coronary events (see more detailed discussion under the heading Coronary Artery Disease). The dose of 150 mg twice a day is preferable to 110 mg twice a day, except in patients of low body weight, decreased renal function, or at increased risk of major bleeding.

Idraparinux is a specific inhibitor of activated factor X, which may be given in a fixed, weekly subcutaneous injection without coagulation monitoring. This agent was compared with vitamin K antagonists (INR 2-3) in the AMADEUS trial of 4576 patients.[38] The trial was stopped early because of excess clinically relevant bleeding with idraparinux (19.7% vs 11.3% per year, $P < .0001$), at which point idraparinux was noninferior for the principal outcome of all stroke or systemic embolism (hazard ratio 0.71; 95% CI, 0.39-1.30; $P = .007$). Elderly patients and those with renal insufficiency were more at risk of excess bleeding, but clearly at the dose regimen tested, idraparinux would not be a suitable alternative to vitamin K antagonist therapy in AF patients.

There are several available oral, direct-acting factor Xa inhibitor drugs that have proven effective and safe in studies of deep venous thrombosis and offer promise in the setting of AF. In the Apixaban Versus ASA to Reduce the Rate Of Embolic Stroke (AVERROES) trial,[39] apixaban (5 mg twice a day) was compared with aspirin (81-324 mg daily) among patients with AF at more than very low risk of stroke in whom vitamin K antagonist therapy was unsuitable. The trial was terminated for early efficacy in 2010. In the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial,[40] apixaban (5 mg twice a day) is being compared with warfarin (INR 2.5) among patients at somewhat higher risk of stroke. The expected enrollment is 15,000 patients, with completion in 2010. In the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial,[41] which enrolled over 14,000 patients, rivaroxaban (20 mg/d) was compared to warfarin (INR 2.5) among patients with AF at risk of stroke and suitable for warfarin therapy. Rivaroxiban was noninferior to warfarin for the principal outcome of all stroke or systemic embolus.

Atrial flutter

Although there are no rigourous prospective data on the incidence of stroke among patients with atrial flutter, nor are there randomized trials of the value of anticoagulation, it is generally recommended that patients with atrial flutter be risk stratified and treated in the same manner as patients with AF.[9,13]

Table 2. The HAS-BLED score for estimating the risk of major bleeding among AF patients

Clinical characteristic	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (eg, age >65 yr)	1
Drugs or alcohol (1 point each)	1 or 2

Risk factor score	Major bleeds (%/y)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

Data from Pisters R, et al.[46]

Risk of Hemorrhage

The efficacy of any antithrombotic therapy for the prevention of ischemic stroke must be balanced against the risk of major hemorrhage, particularly cerebral hemorrhage, which is often fatal. In each of the initial randomized trials of antithrombotic therapies, the principal outcome was the composite of ischemic stroke or systemic embolus. Although hemorrhage and the subsets of intracranial and intracerebral hemorrhage were generally reported, the net benefit for major clinical outcomes was not always clear. More recent trials and overviews have focused on the principal outcome of all stroke (ischemic plus hemorrhagic) or systemic embolus, a more meaningful outcome for patients and treating physicians. The incidence of extracranial major hemorrhage (usually without long-term sequellae among survivors) can be subjectively compared to the reduced incidence of all stroke in order to reach conclusions about the net patient benefits of antithrombotic therapies.

The risk of hemorrhage depends on the specific antithrombotic agent (including dose and monitoring) and on a variety of patient characteristics. The risks of hemorrhage are lowest with either aspirin (75-325 mg/d) or clopidogrel (75 mg/d) alone, higher when they are combined, higher still with dabigatran 110 mg twice a day, and highest with dabigatran 150 mg per day and vitamin K antagonists, which carry similar risks. When vitamin K antagonists are used, the bleeding risk depends on the INR, the quality of monitoring, the duration of therapy (the risk is higher during the initial few weeks of therapy), and the stability of dietary and other factors that may alter the INR at a given dose of the chosen agent. The risk of bleeding is likely to be higher in common clinical practice than in the rigourous setting of a clinical trial or a dedicated, expert anticoagulation service.

For most patients who are candidates for warfarin, an INR range of 2.0 to 3.0 with a target of 2.5 appears optimal.[9,13] In a large cohort of patients, the risk of ischemic stroke, severity of stroke, and mortality rose sharply when INR fell to 1.5 to 1.9, but the risk of intracranial hemorrhage did not rise until INR values exceeded 3.9.[42] A recent meta-analysis[43] of studies that assigned hemorrhagic and thromboembolic events in patients taking anticoagulants to discrete INR ranges found that 44% of hemorrhages occurred when INRs were above the therapeutic range, 48% of thromboembolic events took place when INRs were below it, and the mean proportion of events that occurred when the patient's INR was outside the therapeutic range was higher in the studies of shorter follow-up. Patients with a previous TIA or minor stroke may benefit from a somewhat higher INR of 2.0 to 3.5, with a target of 3.0.[13,17,44] Patients at higher risk of cerebral hemorrhage, particularly those older than 75 years, may benefit from a somewhat lower INR range of 1.6 to 2.5, with a target of 2.0,[13] although protection against ischemic stroke drops off sharply when INRs fall below this target.

The HEMORR$_2$HAGES scheme[45] was developed from 3 previously published prediction rules, a recent systematic review, and a formal literature search. The scheme allotted 2 points for a previously documented episode of bleeding and 1 point each for hepatic or renal disease, ethanol abuse, malignancy, age >75 years, reduced platelet count or function, rebleeding risk, hypertension (uncontrolled), anemia, genetic factors (CYP 2C19 SNPs), excessive falls (including neuropsychiatric disease), and stroke. When compared with the 3 earlier prediction rules in a population of elderly patients with AF[45] who were receiving warfarin, aspirin, or no antithrombotic therapy, the new scheme provided good discrimination among patients with an annual risk of hospitalization for hemorrhage while receiving warfarin, which ranged from 1.9% to 12.3%.

The new ESC guidelines for management of AF[46] suggest the use of a new schema for the prediction of bleeding risk (Table 2). It is based on the presence of hypertension, abnormal liver or renal function, history of stroke or bleeding, labile INRs, elderly age (>65 years), and concomitant use of drugs that promote bleeding or excess alcohol use (HAS-BLED is the acronym)[46] and was derived from the Euro Heart Survey on AF. The proposed schema relies on fewer and more readily obtained risk factors than earlier schemata do and performs at least as well as the HEMOR$_2$RHAGES schema in the prediction of bleeding events. Documentation of a HAS-BLED score allows the clinician to assign the patient a risk of major bleeding ranging from about 1% (score 0-1) to 12.5% (score 5) and can be useful in decisions about the relative risks of stroke vs major bleeding with various antithrombotic therapies. Patients at high risk of major bleeding warrant caution in the use of antithrombotic therapies and closer monitoring and follow-up. We suggest the use of this new schema as a simpler alternative to the HEMOR$_2$RHAGES schema.

RECOMMENDATION

We recommend that all patients with AF or AFL (paroxysmal, persistent, or permanent) should be stratified using a predictive index for stroke (eg, CHADS$_2$) and for the risk of bleeding (eg, HAS-BLED) and that most patients should receive antithrombotic therapy (Strong Recommendation, High-Quality Evidence).

We recommend that patients at very low risk of stroke (CHADS$_2$ = 0) should receive *aspirin* (75-325 mg/d) (Strong Recommendation, High-Quality Evidence).

We recommend that patients at low risk of stroke (CHADS$_2$ = 1) should receive *OAC* therapy (either warfarin [INR 2 to 3] or Dabigatran) (Strong Recommendation,

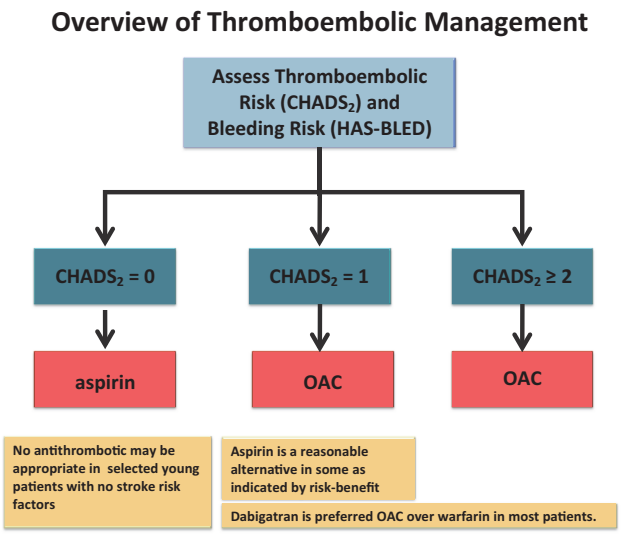

Figure 5. A summary of our recommendations for thromboembolic management guided by the $CHADS_2$ score. See Tables 1 and 2 for definitions of $CHADS_2$ and HAS-BLED. OAC, oral anticoagulant.

High-Quality Evidence). We suggest, based on individual risk-benefit considerations, that aspirin is a reasonable alternative for some (Conditional Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places relatively greater weight on the absolute reduction of stroke risk with both warfarin and dabigatran compared with aspirin and less weight on the absolute increased risk for major hemorrhage with an OAC compared with aspirin.

We recommend that patients at moderate risk of stroke ($CHADS_2 \geq 2$ should receive *OAC* therapy (either warfarin [INR 2-3] or Dabigatran) (Strong Recommendation, High-Quality Evidence).

We suggest that when OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of *dabigatran 150 mg* by mouth twice a day is preferable to a dose of *110 mg* by mouth twice a day (exceptions discussed in text) (Conditional Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a relatively high value on the greater efficacy of dabigatran during a relatively short time of follow-up, particularly among patients who have not previously received an OAC; the lower incidence of intracranial hemorrhage; and its ease of use—and less value on the long safety experience with warfarin.

Figure 5 is a flow chart outlining our recommendations for the choice of antithrombotic therapy.

Recent practice guidelines[9,13] stress the importance of appropriate antithrombotic therapy for AF, and yet practice surveys indicate that rates of compliance range from rather low[47-51] to reasonably high.[52]

Selected Clinical Settings

Elderly patients

Advanced age (>75 years) has been consistently noted as a risk factor for both ischemic stroke and major hemorrhage, particularly intracranial. Hylek et al[53] reported a series of 472 patients aged ≥65 years (153 patients aged ≥80 years), with electrocardiogram-verified AF, newly started on warfarin at the study institution, and managed by the on-site anticoagulation clinic. Anticoagulation control was very good, with 56% of person-time within the INR range of 2.0 to 3.0, 29% below 2.0, 11% within 3.0 to <4.0, and only 2% ≥4.0. Even within this optimized setting, the rate of major hemorrhage (100% follow-up) was 7.2 per 100 patient-years (intracranial hemorrhage 2.5 per 100 patient-years). The incidence of major hemorrhage was 13.1% for patients aged ≥80 years vs 4.75% for those <80 years. The risk during the first 90 days of therapy was 3 times that of the remainder of the year. The risk of major hemorrhage was increased 20 times among patients with an INR > 4.0. Most of the intracranial bleeds occurred in patients aged ≥75 years. The rate of major hemorrhage was higher in patients with higher $CHADS_2$ scores. In contrast, the Birmingham Atrial Fibrillation Treatment of the Aged study[54] found that in patients aged >75 years, warfarin was more efficacious than aspirin in preventing all strokes (ischemic plus hemorrhagic) and did not cause more major extracranial hemorrhage (1.4% per year with warfarin vs 1.6% per year with aspirin). The lower bleeding risk may be attributable to more restrictive patient selection for a clinical trial than for the Hylek survey and to the fact that 40% of them had been taking warfarin safely prior to entering the trial. A more recent cohort study found an annual incidence of major extracranial bleeding of 1.3% with careful INR management.[55] These observations point to the challenges in choosing the optimal antithrombotic therapy for very elderly patients in order to ensure a favourable risk-benefit ratio.[56] For those with no stroke risk factors other than age ≥75 years, some guidelines have recommended consideration of aspirin in preference to warfarin.[13] Nevertheless, ischemic stroke, with its dire consequences, is relatively frequent, and the competing risk of intracranial hemorrhage with warfarin may be acceptable. If warfarin is to be used, great care must be taken to rigourously maintain the selected therapeutic INR with frequent monitoring in the first 3 months and more often than the "standard" monthly interval subsequently.

Cardioversion

Although the randomized trials have shown no improvement in major outcomes, including thromboembolism, with a rhythm control strategy vs rate control, individual patients may gain symptomatic benefit and even long-term freedom from AF after electrical or pharmacologic cardioversion. The strongest predictor of initial and persistent success with cardioversion is short duration of the AF before cardioversion. In general, it may be expected that AF occurring in conjunction with surgery (see accompanying article titled "Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery"[57]), viral illness, alcohol excess, or in association with thyrotoxicosis or pulmonary embolus has a high likelihood of reversion with persistence of sinus rhythm if there has been resolution of the precipitating cause. Successful and sustained reversion to sinus

rhythm is associated with relatively young age and freedom from underlying heart disease. Some patients have intolerable symptoms and poor exercise tolerance during AF and may prefer attempted rhythm control to rate control. The rate of initial success in restoring sinus rhythm is high, but in the contemporary Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, vigorous efforts to establish and sustain sinus rhythm resulted in prevalences of only 82.5%, 73.3%, and 62.6% at 1, 3, and 5 years, respectively.[58]

Stroke risk with cardioversion

Cardioversion is appropriate for selected patients with AF or AFL,[57,58] necessitating consideration of the possibility of associated thromboembolism. A well-designed prospective cohort study reported a reduction of postcardioversion systemic embolism of from 5.3% to 0.8% among anticoagulated patients.[59] These observations have been supported by several published case series.[13] Two more-recent studies reported remarkably similar incidences of cerebral embolization among patients receiving OAC in the setting of electrical cardioversion.[60,61] It is generally believed that a newly formed thrombus will become organized and adherent to the left atrial wall within 2 weeks of formation. Transesophageal echocardiography (TEE) reveals that in the majority of patients, thrombus resolves, rather than simply becoming firmly adherent to the wall of the left atrium or left atrial appendage.[62] Accordingly, it is generally recommended that documented systemic anticoagulation at therapeutic levels be instituted at least 3 weeks before cardioversion.[9,13] An analysis that pooled data from 32 studies found that 98% of thromboembolic events occurred within 10 days of cardioversion of AF or flutter.[63] However, evidence exists that even after successful electrical cardioversion, atrial contraction may not normalize for weeks when AF has been present for some time,[64,65] and therefore maintenance of anticoagulation for at least 4 weeks after cardioversion seems prudent.[9,13] If AF or AFL persists or recurs after attempted cardioversion, or if symptoms suggest that the presenting AF or AFL has been recurrent, antithrombotic therapy should be continued indefinitely with either aspirin or OAC as appropriate. If normal sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy depends on the risk of stroke, and in difficult cases, the practitioner may require expert consultative advice. There is no evidence that the incidence of thromboembolism is less with pharmacologic than with electrical cardioversion,[66,67] and accordingly, it is generally recommended that anticoagulant management should not differ.[13] New-onset AF is generally not thought to warrant anticoagulation if cardioversion is undertaken within 48 hours of its onset, based on case series showing an incidence of thromboembolism $<1\%$[9,13,68,69] without OAC. Even when the duration of the current episode of AF is <48 hours, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or TIA), it would be appropriate to delay cardioversion to allow the patient to receive OAC for 3 weeks before the procedure and to continue indefinitely. Following attempted cardioversion, if AF persists or recurs or if symptoms suggest the presenting AF or AFL has been recurrent, antithrombotic therapy (OAC or aspirin) should be commenced and continued indefinitely. If normal sinus rhythm is achieved and sustained, the need for ongoing antithrombotic therapy depends on the risk of stroke. (See accompanying article titled "Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department."[70])

Atrial flutter

Retrospective studies of patients with atrial flutter undergoing cardioversion suggest that the risk of thromboembolism may not be importantly different from that for patients with AF.[68,69] Case series note a very low incidence of thromboemboli when patients with atrial flutter are adequately anticoagulated prior to cardioversion.[69-71] It is generally recommended that patients with atrial flutter who are to be cardioverted receive an anticoagulant regimen identical to that for patients with AF.[9,13,17]

Emergency cardioversion

Emergency cardioversion may be required because of ischemia or hemodynamic compromise in some situations and should not be delayed, even if the AF has been present for more than 48 hours and the patient is not already anticoagulated. In such a situation, concomitant anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) may offer some benefit, but there are no published evaluations. (See accompanying article titled "Management of Recent-Onset Atrial Fibrillation and Flutter in the Emergency Department."[70])

RECOMMENDATION

We recommend that *hemodynamically stable* patients with AF or AFL of $\geq$*48 hours or uncertain duration* for whom electrical or pharmacologic cardioversion is planned should receive therapeutic OAC therapy (warfarin [INR 2-3] or dabigatran) for 3 weeks before and at least 4 weeks post-cardioversion.

Following attempted cardioversion,

If AF or AFL persists or recurs or if symptoms suggest that the presenting AF or AFL has been recurrent, the patient should have antithrombotic therapy continued indefinitely (using either OAC or aspirin, as appropriate).

If sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapy should be determined on the basis of the risk of stroke, and in selected cases expert consultation may be required (Strong Recommendation, Moderate-Quality Evidence).

We recommend that hemodynamically stable patients with AF or AFL of known duration 48 hours may undergo cardioversion without prior or subsequent anticoagulation. However, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or TIA), cardioversion should be delayed, and the patient should receive OAC for 3 weeks before and at least 4 weeks post-cardioversion.

Following attempted cardioversion,

If AF or AFL persists or recurs or if symptoms suggest that the presenting AF or AFL has been recurrent, antithrombotic therapy (OAC or aspirin, as appropriate) should be commenced and continued indefinitely.

If normal sinus rhythm is achieved and sustained for 4 weeks, the need for ongoing antithrombotic therapyshould

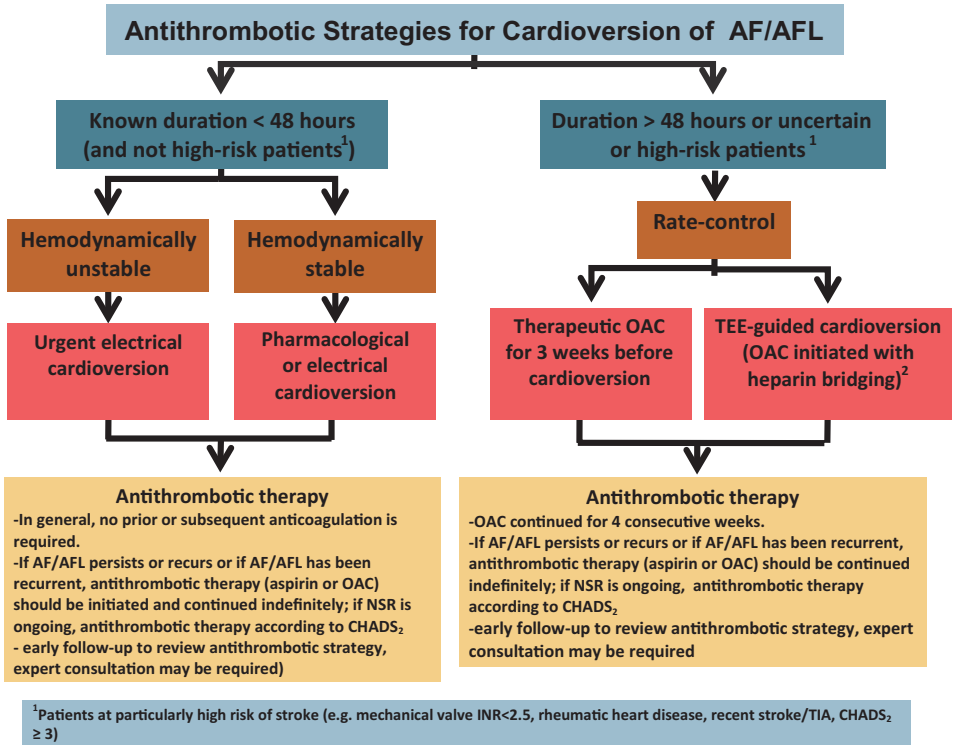

Figure 6. A summary of our recommended strategies for antithrombotic therapy in conjunction with cardioversion. $CHADS_2$, please see Table 1; INR, international normalized ratio; NSR, normal sinus rhythm; OAC, oral anticoagulant; TEE, transesophageal echocardiography; TIA, transient ischemic attack.

be determined on the basis of the risk of stroke according to $CHADS_2$ score, and in selected cases expert consultation may be required (Strong Recommendation, Moderate-Quality Evidence).

We suggest that hemodynamically unstable patients with AF or AFL who require emergency cardioversion be managed as follows:

If the AF or AFL is of known duration 48 hours, the patient may generally undergo cardioversion without prior anticoagulation. However, if the patient is at particularly high risk of stroke (eg, mechanical valve, rheumatic heart disease, recent stroke, or TIA), the patient should receive IV UFH or LMWH before cardioversion if possible, or immediately thereafter if even a brief delay is unacceptable, and then be converted to OAC for at least 4 weeks post-cardioversion.

If the AF or AFL is of ≥48 hours or of uncertain duration, we suggest the patient receive intravenous UFH or LMWH before cardioversion if possible, or immediately thereafter if even a brief delay is unacceptable. Such a patient should then be converted to OAC for at least 4 weeks post-cardioversion.

Following attempted cardioversion, the guidelines for subsequent antithrombotic therapy are identical to those for the management of hemodynamically stable patients undergoing cardioversion (Conditional Recommendation, Low-Quality Evidence).

Figure 6 is a flow chart outlining our recommendations for antithrombotic therapy in conjunction with cardioversion.

Transesophageal echocardiography guidance

The potential role of TEE to rule out the presence of atrial thrombi and the avoidance of anticoagulation was studied in several case series. An overview of these studies[71] reported that patients with no atrial thrombus who then underwent electrical cardioversion had an unacceptably high incidence of embolization by comparison with anticoagulated patients in separate case series. It is generally accepted that the absence of thrombi on TEE does not eliminate the requirement for a period of 4 weeks of anticoagulation following cardioversion.

The Assessment of Cardioversion Utilizing Echocardiography (ACUTE) was a multicentre randomized prospective of trial of 1222 patients with AF of more than 2 days' duration.[60] Patients were assigned to therapy guided by TEE findings or to conventional management. Patients assigned to TEE were anticoagulated at therapeutic levels (typically with UFH intravenously for 24 hours or warfarin [INR = 2-3] for 5 days) prior to attempted cardioversion. If TEE showed no thrombus, the patient underwent cardioversion and continued on anticoagulant therapy for 4 weeks. If thrombus was detected, warfarin was given for 3 weeks, TEE was repeated, and if the thrombus had resolved, cardioversion was performed and warfarin continued for 4 weeks. If thrombus was still detected after 3 weeks of anticoagulation, no cardioversion was attempted, but warfarin was continued for 4 weeks further. The patients randomized to no TEE received warfarin for 3 weeks precardioversion and a further 4 weeks post-cardioversion. There was no significant difference between the TEE and the no-TEE groups in the rate of embolic events or prevalence of sinus rhythm. The TEE group had fewer total hemorrhagic events, most of them

minor. Right or left heart thrombi were identified in 13.8% of patients who underwent TEE. Of those patients with thrombi detected, 88.2% had a thrombus in the left atrial appendage. Among those patients with atrial thrombi detected, the value of repeat TEE after the initial 3 weeks of anticoagulation is uncertain.[72] The investigators subsequently reported the results of a small randomized controlled trial which found no difference in safety outcomes between UFH and enoxaparin for the acute anticoagulation phase.[73] In centres where TEE is readily available and the interpretations reliable, a TEE-guided management strategy may safely shorten the time to cardioversion by comparison with standard anticoagulant regimens. The cost-effectiveness of such an approach depends very much on local and national patterns of practice and cost structures.

RECOMMENDATION

We suggest that hemodynamically stable patients with AF or AFL of ≥48 hours or of unknown duration may undergo cardioversion guided by TEE (following the protocol from the Assessment of Cardioversion Utilizing Echocardiography trial as detailed in the text) (Conditional Recommendation, High-Quality Evidence).

Coronary Artery Disease

The clinician managing a patient with AF must often deal with concomitant coronary artery disease in the settings of primary prevention, stable coronary artery disease, an acute coronary syndrome (ACS), or percutaneous coronary intervention (PCI). There is good evidence for the use of aspirin for primary prevention,[74,75] for aspirin or clopidogrel for stable coronary artery disease,[76] for aspirin supplemented by clopidogrel for up to 1 year following an ACS (with or without PCI[77-86]) and for PCI (both elective[83,84] and post-ACS[80]). Warfarin alone or in combination with aspirin is less effective than aspirin plus clopidogrel for patients post-PCI.[81,82] There is considerable evidence from randomized controlled trials, that for primary prevention among patients at high risk of coronary events, low-intensity warfarin (INR 1.5) is as effective as aspirin for the prevention of coronary events,[87] and for secondary prevention following myocardial infarction, warfarin alone (INR 2.8-4.8)[88] or warfarin (INR 2-2.5) plus aspirin (75-100 mg)[89,90] is at least as efficacious as aspirin alone in reducing subsequent coronary events.[91] There has been no rigourous comparison of warfarin vs the combination of aspirin and clopidogrel.

The benefits of antithrombotic therapies for the primary prevention of coronary events must be balanced against the risks of major bleeding attributable to both aspirin and vitamin K antagonists. Although viewpoints vary, once the annual risk of a coronary event exceeds 1% to 1.5%, antithrombotic therapy is likely to confer more benefit than harm.[75,92] Among patients with known coronary artery disease, ACS, or recent PCI, the benefits of appropriate antithrombotic therapy strongly outweigh the harms. Both aspirin and warfarin are appropriate for the primary prevention of coronary events in those patients at higher risk and for secondary prevention in most patients with known coronary artery disease. Accordingly, when such patients also have AF or AFL, it seems reasonable to choose the most appropriate antithrombotic therapy for the prevention of stroke with the expectation that the chosen therapy will also be protective against coronary events. For primary prevention of coronary events and for stable coronary artery disease, when the risk of stroke is very low ($CHADS_2 = 0$), aspirin would be appropriate because of its lower bleeding risk and greater ease of administration. When the risk of stroke is higher ($CHADS_2 \geq 1$), warfarin would be appropriate, instead of aspirin.

In the setting of elective PCI, aspirin plus clopidogrel are required for optimal prophylaxis against stent thrombosis. If the patient also has AF with a risk of stroke that is very low to low ($CHADS_2 \leq 1$), then aspirin plus clopidogrel would be appropriate for a minimum of 1 month for a bare metal stent, 3 months for a sirolimus drug-eluting stent, or 6 months for a paclitaxel drug-eluting stent; subsequently, $CHADS_2 = 0$ patients might continue on aspirin alone, and $CHADS_2 = 1$ patient might stay on aspirin plus clopidogrel or be switched to warfarin. If the risk of stroke is higher ($CHADS_2 \geq 2$), OAC is required for adequate stroke prophylaxis. Hence, for optimal prophylaxis against both stroke and coronary events, a period of therapy with a combination of aspirin, clopidogrel, and OAC ("triple antithrombotic therapy") may be required, even though the risk of bleeding is considerably increased by this combination.[93] Whereas the optimal duration of dual antiplatelet therapy post-PCI for patients without AF is up to 12 months, the duration of triple therapy in patients with AF is uncertain and should be decided on the basis of balancing the likely risks of a stent-related event vs the risk of bleeding. Those patients at particularly high risk of bleeding should be considered for the use of a bare metal stent rather than a drug-eluting stent, with the triple therapy continued for only 1 month.

Following an episode of ACS, aspirin plus clopidogrel appear optimal for up to 1 year. If the patient also has AF with a risk of stroke that is very low to low ($CHADS_2 \leq 1$), then aspirin plus clopidogrel would be appropriate for up to 1 year; subsequently, $CHADS_2 = 0$ patients might continue on aspirin alone, and $CHADS_2 = 1$ patients might stay on aspirin plus clopidogrel or be switched to warfarin. If the risk of stroke is higher ($CHADS_2 \geq 2$), warfarin is required for adequate stroke prophylaxis. Hence, for optimal prophylaxis against both stroke and coronary events, a period of therapy with combination aspirin, clopidogrel, and warfarin may be required, as for the patients with elective PCI. Whereas the optimal duration of dual antiplatelet therapy post-ACS for patients without AF is up to 12 months, the duration of triple therapy in patients with AF should be decided based on balancing the likely risks of a stent-related event vs the risk of bleeding. There are no randomized trials to guide the decisions, but it might be reasonable to prescribe 1 month of triple therapy, followed by up to 1 year of a combination of warfarin plus clopidogrel or warfarin plus aspirin, followed by warfarin alone as suggested in other guidelines.[91] The issues regarding antithrombotic therapies for patients with coronary artery disease plus AF have been extensively evaluated in recent evidence-based guidelines.[9,13,84,86,93]

In the RE-LY trial, although the net clinical benefit outcome (a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding) was in favour of dabigatran 150 mg (hazard ratio 0.91; 95% CI, 0.82-1.00; $P = .04$), there was a higher incidence of myocardial infarction with dabigatran (hazard

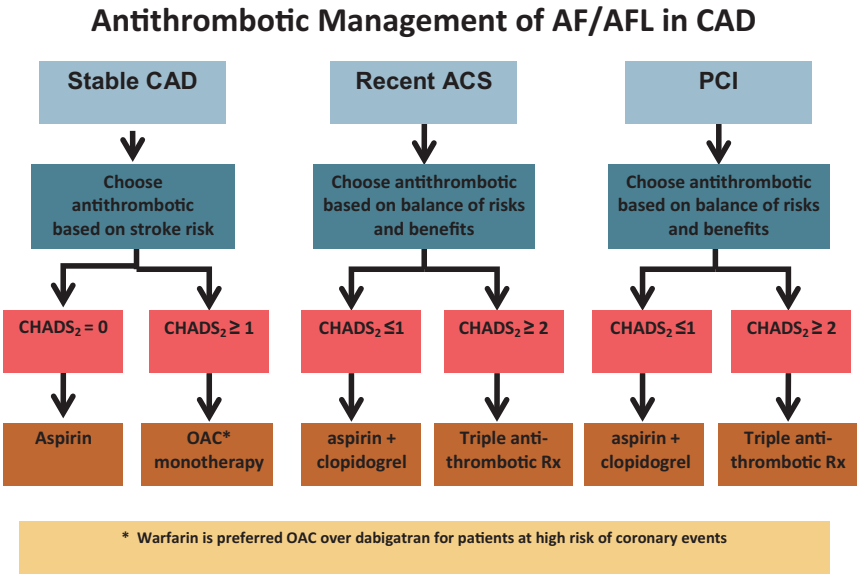

Figure 7. A summary of our recommendations for antithrombotic management in settings of coronary artery disease. ACS, acute coronary syndrome; CAD, coronary artery disease; $CHADS_2$, see Table 1; OAC, oral anticoagulant; PCI, percutaneous coronary intervention.

ratio 1.38; 95% CI, 1.00-1.91; $P = .048$). There has not yet been a trial of dabigatran to evaluate the agent for the primary or secondary prevention of coronary events. Given the known benefits of warfarin for the reduction of coronary events, which can be substantial in those patients at higher risk, when OAC is indicated to prevent stroke in those who have AF and are also at high risk of a coronary event (eg, those without evidence of coronary artery disease whose Framingham risk is ≥2% per year, those with stable coronary artery disease with high risk features, and those with or ACS in recent months), it seems prudent to recommend warfarin in preference to dabigatran.

RECOMMENDATION

We suggest that patients with AF or AFL who have stable coronary artery disease should receive antithrombotic therapy selected on the basis of their risk of stroke (aspirin for $CHADS_2 = 0$ and OAC for $CHADS_2 \geq 1$). Warfarin is preferred over dabigatran for those at high risk of coronary events (Conditional Recommendation, Moderate-Quality Evidence).

We suggest that patients with AF or AFL who have *experienced ACS* or who have *undergone PCI* should receive antithrombotic therapy selected on the basis of a balanced assessment of their risks of stroke, of recurrent coronary artery events, and of hemorrhage associated with the use of combinations of antithrombotic therapies, which in patients at higher risk of stroke may include aspirin plus clopidogrel plus OAC (Conditional Recommendation, Low-Quality Evidence).

Figure 7 is a flow chart outlining our recommendations for the management of antithrombotic therapy in the setting of coronary artery disease.

Invasive Procedures

When a patient receiving an OAC or antiplatelet agent is to undergo a surgical or diagnostic procedure that has a risk of major bleeding, the risk of a thromboembolic event occurring while the antithrombotic agent is reduced or stopped must be weighed against the goal of a reduced risk of major bleeding.[94,95] We suggest that such patients be stratified as to their risk of stroke, which can range from <1% to >20% per year. If there is a very low to moderate risk of stroke ($CHADS_2 \leq 2$), the antithrombotic agent should be discontinued before the procedure (aspirin or clopidogrel for 7-10 days, warfarin for 5 days if the INR was in the range of 2-3, and dabigatran for 2 days). Once post-procedure hemostasis is established (about 24 hours), the antithrombotic therapy should be reinstated. If the risk of bleeding from the procedure is low, the clinician might choose to continue the antithrombotic agent uninterrupted.

On the other hand, if there is a particularly high risk of stroke (eg, prosthetic valve, recent stroke or TIA, rheumatic valve disease, $CHADS_2 \geq 3$) or of other thromboembolism (eg, Fontan procedure), some form of antithrombotic therapy should be continued until as close to the time of the procedure as is judged to be safe in terms of the risk and consequences of procedural bleeding, and it should be reinstated as soon as hemostasis is established post-procedure. Consideration should be given to the risk of major bleeding from the procedure in determining the antithrombotic regimen. It is likely that most potentially hemorrhagic dental procedures, if undertaken with appropriate surgical skill and the use of hemostatic mouthwash, can be done without discontinuing warfarin, provided the preoperative INR is under 3.0.[96] Cataract extraction and minor dermatologic procedures may also be done without interrupting warfarin.[95] A randomized controlled trial is currently underway by a group of Canadian investigators who are comparing the strategies of uninterrupted warfarin vs bridging UFH or

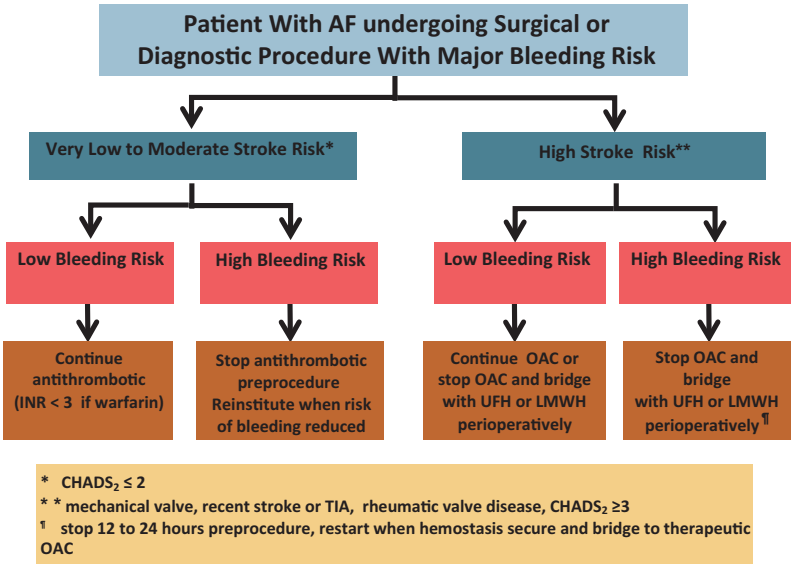

Figure 8. A summary of our recommendations for management of antithrombotic therapies in patients undergoing surgical or diagnostic procedures with a risk of major bleeding. AF, atrial fibrillation; $CHADS_2$, see Table 1; INR, international normalized ratio; LMWH, low molecular weight heparin; OAC, oral anticoagulant; TIA, transient ischemic attack; UFH, ultrafractionated heparin.

LMWH in the mangement of patients having a cardiac arrhythmia device implanted.[97]

RECOMMENDATION

We suggest that patients with AF or AFL who are receiving aspirin, clopidogrel, or OAC and are scheduled for a surgical or diagnostic procedure carrying a risk of major bleeding be stratified by their risk of stroke:

If there is a *very low to moderate risk of stroke* ($CHADS_2$ ≤2), patients should have their antithrombotic agent discontinued before the procedure (aspirin or clopidogrel for 7-10 days, warfarin for 5 days if the INR was in the range of 2-3, and dabigatran for 2 days). Once postprocedure hemostasis is established (about 24 hours), the antithrombotic therapy should be reinstated (Conditional Recommendation, Low-Quality Evidence).

If there is a *particularly high risk of stroke* (eg, mechanical valve, recent stroke or TIA, rheumatic valve disease, $CHADS_2$ ≥3) or of other thromboembolism (eg, Fontan procedure), further consideration should be given to the risk of major bleeding from the procedure:

If there is an *acceptable perioperative bleeding risk* (ie, risk of stroke outweighs risk of bleeding), patients should have OAC therapy continued perioperatively or have their OAC discontinued before the procedure and be bridged with LMWH or UFH perioperatively (Conditional Recommendation, Low-Quality Evidence).

If there is a *substantial risk of major and potentially problematic bleeding* (ie, risk of bleeding and risk of stroke are both substantial), patients should have their OAC discontinued before the procedure, with LMWH or UFH bridging until 12 to 24 hours preprocedure. Once postprocedure hemostasis is established (about 24 hours), the OAC should be reinstated with LMWH or UFH bridging (Conditional Recommendation, Low-Quality Evidence).

Figure 8 is a flow chart outlining our recommendations for the management of antithrombotic therapy in patients undergoing invasive procedures.

Stroke Management in Patients With AF

Among AF patients experiencing a stroke, the high rate of recurrence suggested that there was some urgency in initiating anticoagulation after the occurrence of embolic stroke. The International Stroke Trial Collaborative Group randomized 18,451 patients with ischemic stroke within 24 hours of onset to subcutaneous unfractionated heparin (5000 IU twice a day or 12,500 IU twice a day), aspirin 300 mg per day, both, or neither and maintained for 14 days or until prior hospital discharge.[24] CT scan was performed to exclude intracranial hemorrhage when possible and was mandatory in comatose patients. Among the 3169 patients with AF, both doses of heparin were significantly more effective for the prevention of recurrent stroke of ischemic or unknown type but resulted in significantly more symptomatic intracranial hemorrhage. There was no significant difference among the regimens in the rate of the composite outcome of recurrent stroke or symptomatic intracranial hemorrhage or in the rate of all-cause mortality. Patients with AF had a higher mortality than did patients without AF (16.9% vs 7.5%), probably because of greater mean age and larger cerebral infarcts. The rate of recurrence, within 14 days, of stroke of ischemic or unknown type was 3.9% among patients with AF, considerably lower than that reported in earlier studies but still higher than in patients without AF in this study. The results indicate that heparin is not indicated in the acute management of embolic stroke among

patients with AF. Published guidelines for the management of stroke in a patient with AF[98-100] are based on extrapolations from clinical trials[97,101] and include recommendations for the use of intravenous rtPA for selected patients within 3 hours of onset. Patients who receive rtPA should not receive any antiplatelet or anticoagulant therapy for at least 24 hours subsequently. If there is no evidence of hemorrhage on urgent CT scan, and yet the patient is not to receive fibrinolytic therapy, the patient should begin aspirin 325 mg per day immediately thereafter, with conversion to OAC after 14 days, or sooner if the infarct size is small and the patient is normotensive. If the clinical and computed tomography picture are consistent with a TIA, then immediate heparin therapy may be acceptable. If stroke occurs in a patient with AF or AFL who is already receiving anticoagulation, the drug should be stopped and intracranial hemorrhage should be excluded. If intracranial hemorrhage is present, the anticoagulation should be reversed, and subsequent decisions to resume anticoagulation should be made after reassessment of the risks of embolism and the risks of recurrent intracranial hemorrhage. For those without intracranial hemorrhage, it would be reasonable to start aspirin 325 mg per day when the INR falls below 1.5 and to restart the anticoagulant at day 14, or sooner if the infarct is small and the patient is normotensive.[98,99] If warfarin is chosen as the anticoagulant, meticulous attention should be given to maintenance of the INR in the range of 2 to 3. A double-blind randomized trial[102] of LMWH vs aspirin (160 mg/d) among patients with acute ischemic stroke and AF showed a trend to more recurrent ischemic stroke in the LMWH group (odds ratio 1.13; 95% CI, 0.57-2.24), supporting the strategy of early administration of aspirin to such patients in preference to heparin.

RECOMMENDATION

We recommend that patients with AF or AFL who experience a stroke be managed acutely according to the published guidelines of the American Heart and American Stroke Associations[100] (Strong Recommendation, Moderate-Quality Evidence).

Hemorrhage on OAC Therapy

The major determinants of OAC-induced bleeding are the INR, patient characteristics, and the concomitant use of drugs that interfere with hemostasis. The acute management of hemorrhage in a patient receiving OAC requires a graded response according to published guidelines,[103] beginning with the immediate measurement of the INR, stopping the OAC, and assessment of the severity of hemorrhage. If there is major bleeding, vitamin K may be given intravenously, and if the bleeding is life threatening, vitamin K should be accompanied by fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa. If the INR is elevated and no explanatory pathology is found, it may be appropriate to restart the OAC, attempting to maintain the INR in the usual therapeutic range with intensified monitoring and attention to patient factors that can increase the INR in the setting of a given dose of OAC. If the bleeding is not life threatening and occurs with an INR in the therapeutic range, once pathology is ruled out and if the $CHADS_2$ score is ≥ 2, it may be appropriate to reinstitute the OAC, attempting to maintain a therapeutic INR.

RECOMMENDATION

We suggest that patients with AF or AFL who experience hemorrhage while on OAC therapy be managed according to the practice guidelines of the American College of Chest Physicians[103] (Conditional Recommendation, Low-Quality Evidence).

Pharmacogenomics

Eventually, pharmacogenomic algorithms may allow more rapid and safe determinations of initial warfarin dosage, particularly among patients whose warfarin requirements are particularly low or high.[104] For the present, routine genetic testing is not advised in the management of therapy with a vitamin K antagonist.

Alternatives to Antithrombotic Therapies

Rhythm control and stroke risk

An overview[105] of the 5 trials that compared the strategies of rhythm vs rate control in AF found a mortality of 13.0% with rate control vs 14.6% with rhythm control (odds ratio 0.87, $P = .09$). The rates of ischemic stroke and major hemorrhage were similar. The AFFIRM trial[58] is by far the largest, mandated anticoagulation (INR 2.0-3.0) in the rate-control group (85% maintained warfarin) and strongly encouraged in the rhythm-control group, while allowing cessation at the physician's discretion if sustained sinus rhythm was achieved (70% maintained warfarin). Ischemic stroke occurred at an annual rate of about 1% in each group, and in most instances the patient was either off warfarin or the INR was <2.0. The authors concluded that continuous anticoagulation is warranted in all patients with AF and 1 or more risk factors for stroke, whether or not sinus rhythm appears to be restored and maintained, and this approach is recommended by consensus groups.[9,13]

Left atrial radiofrequency ablation is increasingly used as a rhythm control approach to treat AF, raising questions about the role of long-term OAC therapy in such patients.[106] The issues are the risk of dislodgement of left atrium thrombus during the ablation procedure, bleeding in association with the invasive procedure, creation of thrombogenic areas of left atrium endothelial damage, and the risk of embolization during long-term follow-up. Recommendations are generally weak and based on evidence of low or very low quality.[106] TEE is advised immediately preprocedure to ensure there is no important left atrium thrombus. In general, the procedure is performed with the patient adequately anticoagulated, either by sustaining the preprocedure warfarin (usually allowing the INR to fall to the lower end of the therapeutic range) or with use of bridging LMWH both before and after the procedure. In the latter case, UFH is given with access to the left atrium. The UFH or LMWH are discontinued at the completion of the procedure, and the sheath is removed when the ACT returns to a safe level. Parenteral anticoagulation is reinitiated within

hours of the sheath removal and maintained until therapeutic anticoagulation is reestablished with warfarin or dabigatran, which is continued for at least 3 months. Long-term OAC should continue if AF recurs. In the presence of sustained normal sinus rhythm, OAC should be discontinued only if the long-term risk of stroke is low ($CHADS_2$ score <2). (See further details in the accompanying article titled "Catheter Ablation of Atrial Fibrillation and Flutter."[106])

Left atrial appendage-directed interventions

A range of surgical procedures focused on curing AF have been developed and reported during the past 20 years.[107] Left atrial appendage removal or occlusion may be done in an attempt to lower the risk of thromboembolism as part of a Cox Maze procedure or as an adjunct to another cardiac surgical procedure. Only case series are available in the literature, with levels of success very specific to individual centres and the indications uncertain. The long-term risk of stroke after such procedures appears to be low, but the requirement for long-term OAC is unclear, and advice should be provided by the expert centre conducting the arrhythmia surgery. A Canadian collaborative group is currently conducting a pilot study evaluating left atrial appendage occlusion in conjunction with various cardiac surgical procedures (clinicaltrials.gov, NCT00908700). (See detailed discussion in the accompanying article titled "Surgical Therapy for Atrial Fibrillation."[108])

Percutaneous closure of the left atrial appendage was evaluated in a randomized, noninferiority comparison of conventional warfarin vs the Watchman occluding device and subsequent discontinuation of warfarin.[109] The composite primary outcome (any stroke, cardiovascular or unexplained death, or systemic embolism) at a mean of 18 months was nonsignificantly less in the Watchman group (RR = 0.62; 95% CI, 0.35-1.25), and the device was concluded to be noninferior to conventional warfarin therapy. However, there were relatively few events, the follow-up was short, there are substantial learning curve considerations, and the antithrombotic regimen used with the device was complex and changing. Additional, adequately powered studies, particularly in patients at higher risk of stroke, are needed for adequate assessment of this new technique.

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References

1. Boston Area Anticoagulation Trial of Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505-11.
2. Connolly SJ, Laupacis A, Gent M, et al; for CAFA Study Coinvestigators. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991;18:349-55.
3. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992;327:406-12.
4. Petersen P, Boysen G, Godtfredsen J, et al. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet 1989;i:175-9.
5. Petersen P, Boysen G. Letter to editor. N Engl J Med 1990; 323:482.
6. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation study: final results. Circulation 1991;84:527-39.
7. Atrial Fibrillation Investigators. Risk factors for stroke and efficiency of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449-57.
8. Wolf PA, Dawber TR, Thomas E Jr, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. Neurology 1978;28:973-7.
9. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation. Chest 2008;133:546S-92S.
10. The Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546-54.
11. Stroke Prevention in Atrial Fibrillation Investigation. Prevention of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. Ann Intern Med 1992;116:1-5.
12. Stroke Prevention in Atrial Fibrillation Investigation. Prevention of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. Ann Intern Med 1992;116:6-12.
13. Fuster V, Rydén LE, Cannon AS, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. Circulation 2006;114:257-354.
14. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.
15. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation 2004;110:2287-92.
16. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. Stroke 2008;39:1901-10.
17. Camm AJ, Kirchof P, Lip GYH, et al. Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31:2369-429. Available at http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf. Accessed December 15, 2010.
18. Lip GYH, Nieuwlaat R, Pisters R, Lane DR, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263-72.
19. Hohnloser SH, Pajitnev D, Pogue J, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticaogulation or combined antiplatelet therapy: an ACTIVE W substudy. J Am Coll Cardiol 2007;50:2156-61.
20. Hart RG, Pearce LA, Rothbart RM, et al. for Stroke Prevention in Atrial Fibrillation Investigators. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. J Am Coll Cardiol 2000; 35:183-7.

21. Petersen P, Godtfredsen J. Embolic complications in paroxysmal atrial fibrillation. Stroke 1986;17:622-6.

22. Wolf PA, Kannel WB, McGee DL, et al. Duration of atrial fibrillation and eminence of stroke: the Framingham Study. Stroke 1983;14:664-7.

23. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. Lancet 1993;342:1255-62.

24. Saxena R, Lewis S, Berge E, Sandercock PAG, Koustaal PJ; for International Stroke Trial Collaborative Group. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. Stroke 2001;32:2333-7.

25. Biblo LA, Yuan Z, Quan KJ, Mackall JA, Rimm AA. Risk of stroke in patients with atrial flutter. Am J Cardiol 2001;87:346-9.

26. Hart RG, Pearce LA, Aguilare MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.

27. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. Ann Intern Med 2007;147:590-2.

28. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. Lancet 1994;343:687-91.

29. Gullov AL, Koefoed BG, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs. adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Arch Intern Med 1998;158:1513-21.

30. Pengo V, Zasso A, Barbero F, et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in non-rheumatic atrial fibrillation. Am J Cardiol 1998;82:433-7.

31. Hellemons BS, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomized controlled trial comparing two intensities of coumarin with aspirin. BMJ 1999;319:958-64.

32. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. Lancet 2006;367:1903-12.

33. ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.

34. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of thromboembolism in patients with nonvalvular atrial fibrillation (SPORTIF III); a randomized trial. Lancet 2003;362:1691-98.

35. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690-8.

36. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

37. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol 2007;100:1419-26.

38. Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet 2008;371:315-21.

39. A phase III study of apixaban in patients with atrial fibrillation (AVERROES). ClinicalTrials.gov identifier: NCT00496769. Available at: http://clinicaltrials.gov/ct2/show/NCT00496769. Accessed December 15, 2010.

40. Apixaban for the prevention of stroke in subjects with atrial fibrillation (ARISTOTLE). ClinicalTrials.gov identifier: NCT00412984. Available at: http://clinicaltrials.gov/ct2/show/NCT00412984. Accessed December 15, 2010.

41. Randomized, double-blind study comparing once daily oral rivaroxaban with adjusted-dose oral warfarin for the prevention of stroke in subjects with non-valvular atrial fibrillation. ClinicalTrials.gov identifier: NCT00403767. Available at: http://clinicaltrials.gov/ct2/show/NCT00403767. Accessed December 15, 2010.

42. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-26.

43. Oake N, Fergusson DA, Forster AJ, van Walraven C. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. Can Med Assoc J 2007;176:1589-94.

44. European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med 1995;333:5-10.

45. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151:713-9.

46. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100.

47. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol 2005;46:1729-36.

48. Rowan SB, Bailey DN, Bublitz CE, Anderson RJ. Trends in anticoagulation for atrial fibrillation in the U.S.: an analysis of the national ambulatory medical care survey database. J Am Coll Cardiol 2007;49:1561-5.

49. Glazer NL, Dublin S, Smith NL, et al. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. Arch Intern Med 2007;167:246-52.

50. Simpson SR, Wilson C, Hannaford PC, Williams D. Evidence for age and sex differences in the secondary prevention of stroke in Scottish primary care. Stroke 2005;36:1771-5.

51. Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006;37:1075-80.

52. Nieuwlaat R, Capucci A, Lip GYH, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2006;27:3018-26.

53. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007;115:2689-96.

54. Mant J, Hobbs R, Roalfe A, et al; BAFTA investigators. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the

Aged Study, BAFTA): a randomized controlled trial. Lancet 2007;370:493-503.

55. Poli D, Antonucci E, Grifoni E, et al. Bleeding risk during oral anticoagulation in patients older than 80 years. J Am Coll Cardiol 2009;54: 999-1002.

56. Wyse DG. Bleeding while starting anticoagulation for thromboembolism prophylaxis in elderly patients with atrial fibrillation. Circulation 2007;115:2684-6.

57. Mitchell LB, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: prevention and treatment of atrial fibrillation following cardiac surgery. Can J Cardiol 2011;27:91-7.

58. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.

59. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. Am J Cardiol 1969;23:208.

60. Klein AL, Grimm RA, Murray RD, et al. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411-20.

61. Seidel K, Ramekaen M, Drogemuller A, et al. Embolic events in patients with atrial fibrillation and effective anticoagulation: value of transesophageal echocardiography to guide direct-current cardioversion: final results of the Ludwigschafen Observational Cardioversion Study. J Am Coll Cardiol 2002;39:1436-42.

62. Collins LJ, Silverman DI, Douglas PS, Manning WJ. Cardioversion of nonrheumatic atrial fibrillation: reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution. Circulation 1995;92:160-3.

63. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. Am J Cardiol 1998;82:1545-7, A8.

64. Manning WJ, Silverman DI, Keightly CS, et al. Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: final results of a prospective 4.5 year study. J Am Coll Cardiol 1995;25:1354-61.

65. Padraig GO, Puleo PR, Bolli R, et al. Return of atrial mechanical function following electrical cardioversion of atrial dysrhythmias. Am Heart J 1990;120:353-9.

66. Lown B. Electrical reversion of cardiac arrhythmias. Br Heart J 1967;29: 469-89.

67. Goldman M. The management of chronic atrial fibrillation: indications and method of conversion to sinus rhythm. Prof Cardiovasc Dis 1959; 2:465-79.

68. Weigner MJ, Caulfield TA, Danias PG, et al. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. Ann Int Med 1997;126: 741-5.

69. Gallagher MM, Hennessy BJ, Edvardsson N, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. J Am Coll Cardiol 2002;40:926-33.

70. Stiell IG, Macle L, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol 2011;27:38-46.

71. Elhendy A, Gentile F, Khandheria BK, et al. Thromboembolic complications after electrical cardioversion in patients with atrial flutter. Am J Med 2001;111:433-8.

72. Moreyra E, Finkelhor RS, Debul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. Am Heart J 1995;129:71-5.

73. Klein AL, Jasper SE, Katz JF, et al. The use of enoxaparin compared to unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion: Assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) II randomized multicentre study. Eur Heart J 2006;27:2858-65.

74. Berger JS, Roncaglioni MC, Avanzini F, et al. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006;295:306-13.

75. Sanmuganathan PS, Ghaharamani P, Jackson PR, et al. Aspirin for the primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart 2001;85:265-71.

76. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.

77. Yusuf S, Zhao F, Mehta S, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.

78. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-89.

79. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.

80. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-tern therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527-33.

81. Rubboli A, Milandri M, Castelvetri C, et al. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting: clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. Cardiology 2005;104:101-6.

82. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary stenting. N Engl J Med 1998;339:1665-71.

83. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624-9.

84. Steinhubl SR, Berger PB, Mann JT, et al. Early and sustained dual antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411-20.

85. Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease. Chest 2008;133:776S-814S.

86. King SB, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI guideline update for percutaneous coronary intervention. Circulation 2008;117:261-95.

87. 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; 351:233-41.

88. Smith P, Arneson H, Holme I. The effect of warfarin on mortality and reinfection after myocardial infarction. N Engl J Med 1990;323:499-503.

89. Hurlen N, Abdelnoor M, Smith P, et al. Warfarin, aspirin or both after myocardial infarction. N Engl J Med 2002;347:969-74.

90. Fiore LD, Ezekowitz MD, Brophy MT, et al. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of myocardial infarction: primary results of the CHAMP study. Circulation 2002:105:557-63.

91. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. J Am Coll Cardiol 2003;41:62S-9S.

92. Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease. Chest 2008;133:776S-814S.

93. Lip GYH, Huber K, Andreotti F, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting. Throm Haemost 2010;103:13-28.

94. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997;336:1506-11.

95. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy. Chest 2008;133:299S-339S.

96. Patatanian E, Fugate SE. Hemostatic mouthwashes in anticoagulated patients undergoing dental extraction. Ann Pharmacotherapy 2006;40:2205-10.

97. Birnie D, Healey JS, Krahn A, et al. Bridge or continue Coumadin for device surgery: a randomized controlled trial rationale and design. Curr Opin Cardiol 2008;24:82-7.

98. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. Chest 2008;133:630S-69S.

99. Broderick J, Connolly S, Feldman E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update. Stroke 2007;38:2001-23.

100. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke. Stroke 2007;38:1655-711.

101. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial: indications for early aspirin. Stroke 2000;31: 1240-9.

102. Berge E, Abdelnoor M, Nakstad PH, Sandset PM; on behalf of HAEST Study Group. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. Lancet 2000;355:1205-10.

103. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment. Chest 2008;133: 257S-98S.

104. International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009;360:753-64.

105. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs. rhythm control in patients with atrial fibrillation: a meta-analysis. Arch Int Med 2005;165:258-62.

106. Verma A, Macle L, Cox JL, Skanes AC, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. Can J Cardiol 2011;27:60-6.

107. Calkins H, Brugada J, Packer D, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendation for personnel, policy, procedures and follow-up. Europace 2007;9:335-79.

108. Pagé P, CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: surgical therapy. Can J Cardiol 2011;27:67-73.

109. Holmes DR, Reddy V, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet 2009;374:534-42.