Atrial fibrillation

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ABSTRACT

- The incidence and prevalence of atrial fibrillation are increasing because of both population ageing and an age-adjusted increase in incidence of atrial fibrillation.
- Deciding between a rate control or rhythm control approach depends on patient age and comorbidities, symptoms and haemodynamic consequences of the arrhythmia, but either approach is acceptable.
- Digoxin is no longer a first-line drug for rate control: β-blockers and verapamil and diltiazem control heart rate better during exercise.
- Anti-arrhythmic drugs have only a 40%–60% success rate of maintaining sinus rhythm at 1 year, and have significant side effects.
- The selection of optimal antithrombotic prophylaxis depends on the patient's risk of ischaemic stroke and the benefits and risks of long-term warfarin versus aspirin, but is independent of rate or rhythm control strategy.
- Ischaemic stroke risk is best estimated with the $CHADS_2$ score (Congestive heart failure, Hypertension, Age ⩾ 75 years, Diabetes, 1 point each; prior Stroke or transient ischaemic attack, 2 points).
  - For patients with valvular atrial fibrillation or a $CHADS_2$ score ⩾ 2, anticoagulation with warfarin is recommended (INR 2–3, higher for mechanical valves) unless contraindicated or annual major bleeding risk > 3%.
  - Aspirin or warfarin may be used when the $CHADS_2$ score = 1.
  - Aspirin, 81–325 mg daily, is recommended in patients with a $CHADS_2$ score of 0 or if warfarin is contraindicated.
- Stroke rate is similar for paroxysmal, persistent, and permanent atrial fibrillation, and probably for atrial flutter.

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Atrial fibrillation (AF) is the most common sustained arrhythmia, and is associated with increased cardiovascular morbidity and mortality, and preventable stroke. The incidence and prevalence of AF rise with age, with a prevalence of 8% in people older than 80 years.[1] In addition, the age-adjusted incidence in the Framingham study increased significantly from the 1960s to the 1980s, and has increased further from 1980 to 2000.[2] This may be due in part to the population increase in obesity and obstructive sleep apnoea.[3]

AF can be classified as either a first-detected episode or recurrent AF (> 2 episodes), and further subclassified as paroxysmal (self-terminating, usually < 24 hours), persistent (sustained > 7 days), or permanent. AF becomes permanent when cardioversion is unsuccessful or has not been attempted.

Here we summarise updated concepts in the management of AF as recently published in the revised guidelines of the American College of Cardiology, American Heart Association and European Society of Cardiology (ACC/AHA/ESC).[4]

Prevention of AF

Use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,[5] and statins may reduce the incidence of AF, as may fish oils, which alter atrial membrane composition.[4] After cardiac surgery, where postoperative AF occurs in about 25% of patients, pretreatment with β-blockers, sotalol, amiodarone, and statins has been shown to reduce the incidence.[4,6,7]

Strategic objectives in the management of AF

Objectives in the management of AF are to:

- identify and treat associated or causative factors — this may abort the arrhythmia;
- decide on "rate control or rhythm control", and implement treatment either to control heart rate or to achieve and maintain sinus rhythm; and
- prevent thromboembolism, balancing the risk of stroke against the risk of bleeding on warfarin.

Identification of associated or causative factors

AF is most commonly caused by hypertension, ischaemic heart disease, heart failure, valvular heart disease, and thyrotoxicosis, but other treatable causes exist (Box 1). The minimal clinical evaluation comprises a history, physical examination, electrocardiography, transthoracic echocardiography, and blood tests of thyroid, renal and hepatic function. Additional tests may be required to exclude other conditions according to clinical suspicion.

Rate or rhythm strategy

Most patients with AF require control of the heart rate for symptomatic relief, and to prevent tachycardia-induced cardiomyopathy. Digoxin is no longer the drug of first choice for rate control (I/C; see Box 2 for key to evidence levels);[4] β-blockers are the most effective agents for monotherapy, followed by verapamil and diltiazem,[8] as these drugs control both exertional and resting heart rate (I/B).

The decision to attempt cardioversion and maintain sinus rhythm, rather than just control heart rate, depends on the long-term frequency and hazards of AF, and risks of cardioversion and antiarrhythmic therapy. Older patients (> 65 years) with recurrent persistent AF at high risk of stroke ($CHADS_2$ score ⩾ 1, see "Stroke risk stratification" below) have similar outcomes (stroke or mortality) with either rate or rhythm control, and a trend towards fewer hospitalisations for those managed with rate control.[9] Rate control is more suitable for older patients with asymptomatic persistent or permanent AF, whereas young patients with highly symptomatic paroxysmal AF may require rhythm control.

Sinus rhythm probably does confer a benefit, particularly for patients with heart failure. However, because drugs are relatively ineffective at long-term maintenance of sinus rhythm (60% in sinus rhythm at 1 year on amiodarone and 40% with sotalol),[9] and have significant cardiac and extra-cardiac toxicities, including ventricular tachycardia and pulmonary fibrosis, this benefit is negated. A rhythm control strategy is therefore associated with

1 Causes and predisposing factors for atrial fibrillation

Reversible causes of atrial fibrillation

Drugs

- Alcohol
- Caffeine

Surgery

- Cardiac, pulmonary, oesophageal, or general surgery

Endocrine disorders

- Hyperthyroidism
- Phaeochromocytoma

Inflammatory atrial disease

- Pericarditis
- Myocarditis

Atrial pressure elevation

- Pulmonary embolism

Atrial fibrillation with associated heart disease

Atrial pressure elevation

- Hypertension (particularly when left ventricular hypertrophy is present)
- Valvular heart disease (mitral or tricuspid valve disease)
- Myocardial disease leading to systolic or diastolic dysfunction (ischaemic cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy)
- Intracardiac tumours or thrombi

Atrial ischaemia

- Coronary artery disease

Congenital heart disease

- Atrial septal defect

Infiltrative atrial disease

- Amyloidosis
- Age-induced atrial fibrotic changes
- Haemochromatosis
- Endomyocardial fibrosis
- Primary or metastatic disease in or adjacent to the atrial wall

Electrophysiological abnormalities

- Enhanced automaticity (focal atrial fibrillation)
- Conduction abnormality (re-entry)

Atrial fibrillation without associated heart disease

- Idiopathic "lone" atrial fibrillation

Atrial fibrillation associated with medical conditions

Atrial dilatation

- Obesity
- Sleep apnoea

Neurogenic

- Subarachnoid haemorrhage
- Major ischaemic stroke

Familial atrial fibrillation ◆

2 Recommendation and evidence codes

Codes are presented as Recommendation class/Evidence level according to the ACC/AHA/ESC 2006 classification scheme.[4]

Recommendation classes

I: There is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective.

II: There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

IIa: Weight of evidence/opinion is in favour of usefulness/efficacy.

IIb: Usefulness/efficacy is less well established by evidence/opinion.

III: There is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful.

Levels of evidence

A: Data from multiple randomised clinical trials or meta-analyses.

B: Data from a single randomised trial or non-randomised studies.

C: Consensus opinion of experts, case studies, or standard of care. ◆

frequent AF recurrences, which may be asymptomatic, and places the patient at risk of stroke unless continuously treated with effective antithrombotic prophylaxis.

Cardioversion

Electrical cardioversion remains the mainstay for conversion of persistent AF to sinus rhythm, but there are significant issues of anticoagulation, as discussed below. Cardioversion can also be achieved with amiodarone and flecainide, but up to two-thirds of paroxysmal episodes revert spontaneously within 24 hours. Use of flecainide as a "pill in the pocket" (an oral dose taken at the onset of symptoms) is now endorsed for infrequent highly symptomatic AF (IIb/C).[4] However, concomitant use of atrio-ventricular nodal slowing drugs is advised, and first use recommended in hospital while monitored. Flecainide is also contraindicated with structural heart disease.

Catheter ablation for AF

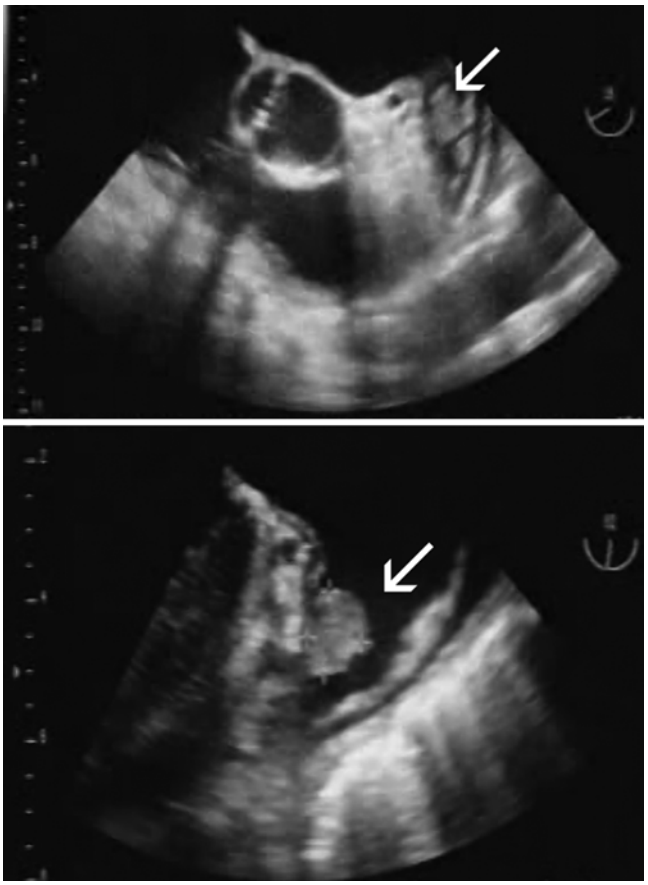
This procedure involves application of radiofrequency ablation to electrically isolate the pulmonary veins, with or without other lesions to attempt cure of AF. Success rates are variable, but approximate 75%, although this may require multiple procedures.[10] If AF recurs, episodes may be less symptomatic or asymptomatic. Catheter ablation is associated with a 3%–6% risk of major complications, including pulmonary vein stenosis, thromboembolism, and the rare (0.6%) but often fatal atrio-oesophageal fistula. It is safest and most successful in patients younger than 70 years with paroxysmal AF for whom anti-arrhythmic therapy has been ineffective and who have a left atrial diameter <5 cm and left ventricular ejection fraction $>40\%$. Greater understanding of the mechanisms underlying AF may increase the efficacy of this procedure, but currently ablation is not applicable to the large numbers of elderly patients who develop this arrhythmia.

Prevention of thromboembolism

AF predisposes to the formation of blood clots within the left atrium (LA) and particularly the left atrial appendage (LAA) (Box 3), and these may embolise to the systemic circulation. Consequently, AF is an independent risk factor for cardioembolic ischaemic stroke. Although most strokes in people with AF are embolic from the LA/LAA, about a quarter may originate elsewhere — from the left ventricle, heart valves, and extracranial and intracranial arteries. Cardioembolic strokes in patients with AF are typically larger, associated with higher early mortality, and occur in older patients compared with strokes in patients with sinus rhythm (Box 4).

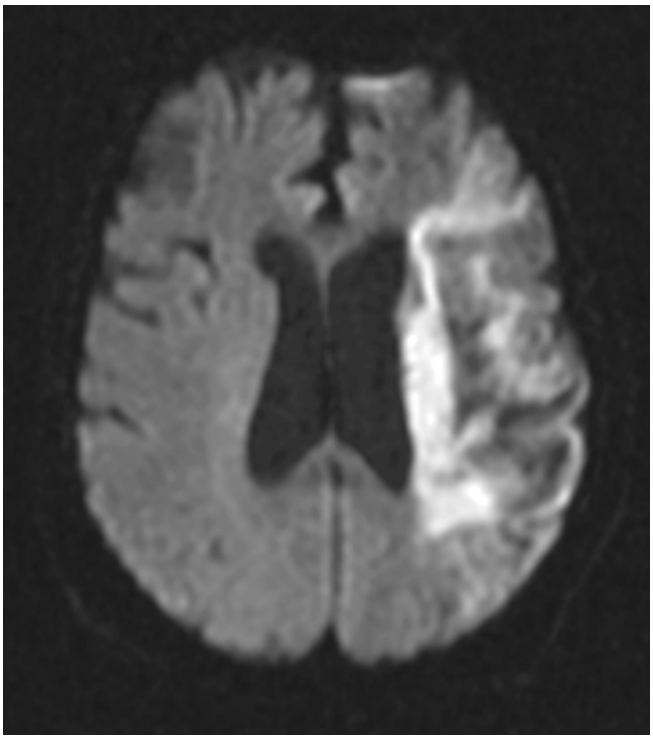
Optimal thromboprophylaxis for patients with AF is individualised and requires an assessment of:

3 Left atrial appendage thrombus on transoesophageal echocardiography



Top panel: basal short axis view across the aortic valve, showing the thrombus in the left atrial appendage (arrow).
Bottom panel: magnified mid-oesophageal two-chamber view, showing the large thrombus in the left atrial appendage (arrow). ◆

4 Diffusion-weighted magnetic resonance imaging scan



The image shows a large area of mixed high and low signal, consistent with haemorrhagic infarction in the left frontal and parietal lobes, following embolic occlusion of the upper division of the left middle cerebral artery in a patient with atrial fibrillation. ◆

- the patient's risk of thromboembolism, particularly ischaemic stroke;
- the potential benefits of anticoagulant compared with antiplatelet therapy;
- the competing risk of major haemorrhage with antithrombotic therapy; and
- the patient's preference.

There is considerable evidence from trials to guide estimates of the risk of stroke, and the potential benefits of either anticoagulant or antiplatelet therapy, but the risk of major haemorrhage is much more difficult to assess, with less evidence to inform decisions, which therefore remain subjective. The patient must be an active partner in the decision on whether to take an anticoagulant for life. This takes some time to explain, as the patient must have a clear understanding of both potential risks and benefits.

Risk of stroke

Among patients with non-valvular AF, the risk of ischaemic stroke averages 5% per year (range, 3%–8%), about 3–5 times that of people in sinus rhythm.[11] However, the risk is greatly influenced by individual patient characteristics (Box 5). For patients with lone AF (younger than 60 years with no clinical history or echocardiographic signs of cardiopulmonary disease), the cumulative risk of stroke over 15 years is very low (about 1.3%).[12] For patients with non-valvular AF, the strongest independent predictor of stroke is prior stroke or transient ischaemic attack (TIA) (relative risk [RR], 1.9–3.7), which increases the annual risk of subsequent stroke to about 12% per year with no antithrombotic therapy, and about 10% per year with aspirin.[13] Increasing age increases the annual risk of stroke from 1.5% in ages 50–59 years to 23% in those aged 80–89 years.[11] Other independent risk factors for ischaemic stroke are heart failure with systolic dysfunction, hypertension, and diabetes mellitus (Box 5).[14]

Stroke risk stratification for non-valvular AF

The revised guidelines promote the simple $CHADS_2$ score to estimate stroke risk. This is an acronym for an index that gives 1 point for Congestive heart failure, Hypertension, Age $\geqslant$ 75 years, and Diabetes mellitus, and 2 points for prior Stroke/TIA. This score successfully distinguishes between patients at high risk and those at low risk of stroke (Box 6).[15-17]

Antithrombotic therapy

Valvular AF

Rheumatic mitral valve disease with AF carries a 17-fold increased risk of stroke and requires anticoagulation with warfarin (international normalised ratio [INR], 2–3) (I/A). AF in patients with prosthetic valves also requires anticoagulation, usually with a higher INR target dependent on type of valve.

5 Prognostic factors for ischaemic stroke and systemic embolism in patients with non-valvular atrial fibrillation

High-risk factors	Moderate-risk factors	Less validated or weaker-risk factors
• Previous stroke, transient ischaemic attack or embolism • Mitral stenosis • Prosthetic heart valve	• Age > 75 years • Hypertension • Heart failure • Diabetes mellitus • Left ventricular ejection fraction < 35%	• Female • Age 65–74 years • Coronary artery disease • Thyrotoxicosis

Non-valvular AF

Warfarin or aspirin

Adjusted-dose warfarin reduces the relative risk of stroke by 62%,[18] with absolute risk reductions of 2.7% per year for primary prevention and 8.4% per year for secondary prevention. Major extracranial bleeding is increased by warfarin therapy (absolute risk increase, 0.3% per year).[18] Aspirin is less efficacious, with only 22% relative risk reduction, and absolute risk reductions of 1.5% and 2.5% per year for primary and secondary prevention, respectively.[19] Aspirin appears to prevent non-disabling non-cardioembolic ischaemic strokes more than disabling cardioembolic strokes.[19] Treating 1000 patients with AF for 1 year with oral anticoagulant rather than aspirin would prevent 23 ischaemic strokes while causing 9 additional major bleeds.

Warfarin versus clopidogrel plus aspirin

Warfarin (INR, 2–3) is superior to clopidogrel 75 mg plus aspirin 75–100 mg for prevention of vascular events in patients with AF at high risk of stroke ($CHADS_2$ score ⩾ 1), reducing the annual risk of stroke from 5.6% with dual antiplatelet therapy to 3.9% with warfarin (RR, 0.69; 95% CI, 0.57–0.85).[20] However, these results apply primarily to patients previously exposed to warfarin therapy. For patients new to both treatments, post hoc analysis found the benefits of warfarin were not well defined. In routine practice, the superiority of warfarin could be negated by poor INR control, whereas the major bleeding rate associated with clopidogrel plus aspirin may approximate that of warfarin.

Warfarin combined with antiplatelet therapies

Combinations of oral anticoagulants plus antiplatelet agents for AF have not generally shown reduced risks of haemorrhage or augmented efficacy over adjusted-dose oral anticoagulation alone.

Risk of bleeding

Low rates of major haemorrhage in the trials are unlikely to reflect common practice. Predictors of major bleeding include increasing age, hypertension, elevated INR, and previous cerebral ischaemia,[21,22] as well as combining antiplatelet agents with anticoagulation and use of dual antiplatelet therapy.[23]

Adjusted odds ratios associating drug use with gastrointestinal bleeding are between 1 and 2 for low dose aspirin, clopidogrel and warfarin alone, but corresponding figures for aspirin in combination with clopidogrel or warfarin are 7.4 and 5.3, respectively.[24]

Keeping the INR < 3, lowering blood pressure to below 135 mmHg systolic, and avoiding antiplatelet drugs decreases intracranial haemorrhage.[23]

Who should receive antithrombotic therapy?

The threshold of stroke risk where the benefit of anticoagulation exceeds the risk is controversial, but is somewhere between 3% and 5% per year, depending on the bleeding risks and preferences of the patient. This equates to a $CHADS_2$ score of ⩾ 2 (Box 6). Patients with a $CHADS_2$ score of 0 do not require anticoagulation, and can be managed with aspirin 81–325 mg (I/A). The recommendations for those with a $CHADS_2$ score of 1 now state that either aspirin or warfarin may be used (IIa/B).

The value of echocardiography as a prime determinant of the need for chronic anticoagulation in patients with AF is limited, because it has not been established whether the absence of echocardiographic prognostic factors identifies a low-risk group of patients who could safely avoid anticoagulation.

Treatment gap

Newly diagnosed or prior AF occurs in 15%–38% of patients presenting with ischaemic stroke, and increases mortality and disability (Professor G Donnan, NEMESIS study, personal communication).[25] Therapeutic anticoagulation reduces the risk of disabling stroke; however, only about 10%–20% of patients with known AF are adequately anticoagulated immediately before their stroke.[26,27] In a recent study, a third of patients with AF were on no treatment at the time of stroke, a third were on antiplatelet treatment, and a quarter were on warfarin with subtherapeutic INR; only one-eighth were on adequate warfarin at the time of the stroke.[26]

6 Stroke risk in patients with non-valvular AF not treated with anticoagulation, according to the $CHADS_2$ score[16]

Prognostic factors	Relative risk	$CHADS_2$ score
Congestive heart failure (EF < 35%)	1.4	1
History of hypertension	1.6	1
Age ⩾ 75 years	1.4	1
Diabetes mellitus	1.7	1
Stroke or TIA in past	2.5	2

Relative risk refers to comparison of patients with AF to patients without these prognostic factors. AF = atrial fibrillation. EF = ejection fraction. TIA = transient ischaemic attack.

$CHADS_2$ Score	Patients (n = 1733)	Adjusted stroke rate (%/year) (95% CI)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

The adjusted annual stroke rate was derived from multivariate analysis assuming no aspirin use. ◆

The reasons for undertreatment with antithrombotic agents are complex, but include a lack of knowledge about trials and guidelines,[27] perceived "potential contraindications", and fear of bleeding. Warfarin use increases in patients reviewed by cardiologists and by younger GPs.[27]

Elderly patients with AF

Elderly patients with AF have a greater net benefit from anticoagulation, at the expense of an increased risk of major haemorrhage.[28,29] Cognitive function, falls risk, compliance, access to INR testing facilities, drug interactions due to polypharmacy, and the required changes in diet and lifestyle must be taken into account before committing an elderly patient to indefinite anticoagulation.

Warfarin use is very unlikely in patients older than 85 years, despite evidence of its safety in selected patients.[30] Aiming for an INR of 2 may be a reasonable benefit–risk trade-off for primary prevention in elderly patients with non-valvular AF,[4] although usual practice is to give aspirin in the very elderly.

Paroxysmal compared with permanent AF

The annual stroke risk is similar for patients with paroxysmal and permanent AF,[19] so recommendations on antithrombotic therapy apply to both (IIa/B).

Atrial flutter

Although data on atrial flutter are sparse, anticoagulation guidelines are the same as for AF (I/C).

Anticoagulation before and after cardioversion

Stroke may occur at the time of cardioversion because of expulsion of an atrial thrombus, and up to 4–6 weeks after because of atrial stunning, a reversible mechanical dysfunction. This period mandates anticoagulation therapy (IIa/B), as stroke has been associated with subtherapeutic INR. There are two basic strategies for elective cardioversion. The first is to anticoagulate for at least 3 weeks before and 4–6 weeks after elective cardioversion. The second strategy obviates the need for prior anticoagulation, and involves a pre-procedure transoesophageal echo (TOE) to exclude the presence of LA/LAA thrombus. After cardioversion, patients must be anticoagulated with heparin or enoxaparin followed by warfarin or enoxaparin as above (IIa/B).

Management of interruption of anticoagulation before and after surgery

Patients with AF undergoing surgery have competing problems of surgical bleeding when anticoagulated and thrombotic risk when off warfarin. The individual patient's stroke risk is most useful in guiding management. Patients at high risk (eg, valvular AF) should receive either heparin or enoxaparin until the day of surgery, and recommence heparin or enoxaparin and usual warfarin at the earliest safe time postoperatively to minimise thrombotic and bleeding complications. Expert haematology advice is often useful. Patients at low or intermediate risk of stroke ($CHADS_2$ score of $\leqslant 1$) may have usual antiplatelet/anticoagulant temporarily withheld with minimal risk (IIb/C).

Anticoagulation after ablation

Asymptomatic recurrences of AF occur in 10% of patients and complicate the decision regarding continuation or cessation of warfarin. Many electrophysiologists recommend continued anticoagulation after a successful procedure if the $CHADS_2$ score predicates this.

New antithrombotic agents

Ximelagatran, a direct thrombin inhibitor, has equivalent efficacy to warfarin in AF, but has been withdrawn because of hepatotoxicity. A large trial with a similar drug, dabigatran, is in progress. The AMADEUS trial, which compared once-weekly subcutaneous idraparinux with warfarin, has recently been stopped because of an excess in bleeding rate in the idraparinux group. Large trials comparing oral anti-factor Xa drugs with warfarin are planned.

When dual antiplatelet therapy and warfarin are both required

Patients on warfarin for AF may require additional antiplatelet therapy, such as after angioplasty. There is little evidence to guide management of anticoagulation and antiplatelet therapy in this context, and there is considerable variability in the approach taken by cardiologists.[31] A balance is needed between preventing stent thrombosis and stroke, and minimising bleeding risk. In the absence of warfarin, dual antiplatelet therapy is required for longer with drug-eluting than bare metal stents (1 year, compared with about 4 weeks).[32,33] When the presentation is an acute coronary syndrome, clopidogrel is beneficial for up to 1 year. Patients with a $CHADS_2$ score $\leqslant 1$ may have adequate protection against stroke during this time with antiplatelet drugs, and warfarin may be resumed thereafter. Patients with a $CHADS_2$ score $\geqslant 2$ or valvular AF may require a limited period with triple therapy until one or both antiplatelet drugs can be safely ceased (IIb/C).

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Competing interests

Saul Freedman received an honorarium for being on the AstraZeneca international advisory board for ximelagatran, a drug which has been removed from the market for liver toxicity as mentioned in the article. Graeme Hankey is a member of the executive committee of the rivaroxaban in atrial fibrillation trial (Johnson & Johnson Pharmaceutical Research and Development, USA), the steering committee of the atrial fibrillation trial of monitored, adjusted dose vitamin K antagonist, comparing efficacy and safety with unadjusted SanOrg 34006/idraparinux (AMADEUS) trial (Sanofi Aventis), and the stroke advisory committee of atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE) trial (Sanofi Aventis). He was a member of international and national advisory boards for ximelagatran (AstraZeneca), for which he received honoraria and travel expenses to attend meetings.

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