Atrial fibrillation and stroke: unrecognised and undertreated

When did you or your primary care physician last palpate your wrist to check for a regular heart rate? This simple action, followed by an electrocardiogram if the heart rate is irregular, might be crucial in preventing death and disability from ischaemic stroke, heart failure, or myocardial infarction. In this week's issue, we publish a clinical Series of three papers on atrial fibrillation ahead of the annual European Society of Cardiology (ESC) meeting held in Rome, Italy, Aug 27–31. Atrial fibrillation is estimated to affect 33 million people worldwide. But this figure is likely an underestimate since many people do not know that they have atrial fibrillation until they develop symptoms or present with an ischaemic thromboembolic stroke or systemic thromboembolism. The estimated lifetime risk of developing atrial fibrillation is 25%. A rising prevalence is largely due to an increase in the elderly population, but perhaps also due to a prevalence of risk factors, such as diabetes, hypertension, obesity, and alcohol consumption.

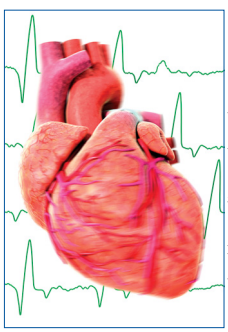
Even once diagnosed, as the first paper in our Series highlights, many people who should be on oral anticoagulation therapy for stroke prevention after appropriate risk assessment are not on any at all, are wrongly given aspirin (which is not effective), are on a suboptimum dose (especially when on the oral vitamin K antagonist warfarin), or are not adhering to the lifelong required treatment. Vitamin K antagonists have been shown to reduce stroke or systemic thromboembolism by 64% and all-cause mortality by 26%. The newer non-vitamin K antagonist oral anticoagulants, such as dabigatran, have an additional effect of 19% and 10% reduction, respectively, and might have a better adherence profile. The authors highlight the steps needed to reduce stroke burden by better recognising stroke risk, which is a continuum, and to make oral anticoagulant treatment the default unless low risk is truly shown. Once patients are deemed at low risk, they need to be regularly reviewed since their risk profile might change over time and anticoagulant therapy might then be indicated.

Stroke occurrence and death in patients in 47 countries 1 year after presenting to a hospital emergency department with atrial fibrillation have been assessed by Jeff Healey and colleagues, in a prospective registry study published online on Aug 8. 11% of more than 15 000 patients died within 1 year, predominantly from heart failure, and 4% had a stroke. Coexisting hypertension varied from 42% in India to 81% in eastern Europe. And, worryingly, 32% of patients in North America, western Europe, and Australia, and up to 70% of those in China, who should have been on anticoagulant therapy according to existing guidelines, were not. To prevent heart failure in those with symptomatic atrial fibrillation, heart rate control, and in some cases rhythm control, is the approach to take. The second and third papers in our Series review existing evidence for rate and rhythm control in atrial fibrillation.

Atrial fibrillation is also one of the ten potentially modifiable risk factors associated with acute stroke identified in the INTERSTROKE study, published in today's issue. Martin O'Donnell and colleagues show that the population attributable risk of atrial fibrillation for ischaemic stroke is 17·1% in western Europe, North America, and Australia. The ten potentially modifiable risk factors (hypertension, regular physical activity, apolipoprotein [Apo] B/ApoA1 ratio, diet, waist-to-hip ratio, psychosocial factors, smoking, cardiac causes including atrial fibrillation, alcohol consumption, and diabetes mellitus) accounted for 90·7% of the population attributable risk for stroke worldwide.

Atrial fibrillation is eminently modifiable as a risk factor for stroke and relatively easy to screen for. There is also now an increasing choice of effective oral anticoagulant therapy. What is needed is an increased recognition that this is not a benign disorder and that we have good evidence-based clinical risk assessment scores for both stroke risk and bleeding risk to give physicians and patients the confidence to make the right choices. The UK's National Institute for Health and Care Excellence has just this month included new indicators to help general practitioners improve the identification and management of atrial fibrillation and, next year, 30 practices across the UK will routinely test anyone older than 65 years for atrial fibrillation.

The new 2016 European Guidelines on cardiovascular disease prevention in clinical practice already recommend that anyone aged 65 years or older and anyone with diabetes mellitus is screened for atrial fibrillation by palpation followed by electrocardiogram if needed. More specific, new ESC guidelines on atrial fibrillation will be released and presented at the Rome conference. There are no excuses to ignore this common cardiac disorder. ■ *The Lancet*



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Atrial fibrillation 1

Stroke prevention in atrial fibrillation

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Lancet 2016; 388: 806–17

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This is the first in a Series of three papers about atrial fibrillation

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See Online for appendix

Atrial fibrillation is found in a third of all ischaemic strokes, even more after post-stroke atrial fibrillation monitoring. Data from stroke registries show that both unknown and untreated or under treated atrial fibrillation is responsible for most of these strokes, which are often fatal or debilitating. Most could be prevented if efforts were directed towards detection of atrial fibrillation before stroke occurs, through screening or case finding, and treatment of all patients with atrial fibrillation at increased risk of stroke with well-controlled vitamin K antagonists or non-vitamin K antagonist anticoagulants. The default strategy should be to offer anticoagulant thromboprophylaxis to all patients with atrial fibrillation unless defined as truly low risk by simple validated risk scores, such as CHA_2DS_2-VASc. Assessment of bleeding risk using the HAS-BLED score should focus attention on reversible bleeding risk factors. Finally, patients need support from physicians and various other sources to start anticoagulant treatment and to ensure adherence to and persistence with treatment in the long term.

Introduction

Ischaemic strokes related to atrial fibrillation usually result from cardioembolism of a large cerebral artery, and therefore tend to be larger (figure 1) and more frequently fatal or associated with greater disability than strokes from other causes.[1–3] However, strokes related to atrial fibrillation are largely preventable, because oral anticoagulants (OACs) are so effective. In meta-analyses,[4,5] vitamin K antagonists (VKAs; eg, warfarin) reduced stroke or systemic thromboembolism by 64% and all-cause mortality by 26% compared with placebo (five studies) or untreated controls (one study); the use of non-VKA OACs (NOACs) offers additional significant reductions of 19% and 10%, respectively, relative to warfarin.[4,5]

Several steps are needed to reduce the stroke burden associated with atrial fibrillation. The first is recognition of the risk of stroke in patients with atrial fibrillation, followed by risk assessment using simple risk scores such as CHA_2DS_2-VASc, and prescription of appropriate stroke prevention to all who are not at low risk of stroke. Second, a system is needed to recognise the pre-symptomatic phase of atrial fibrillation rather than wait for stroke to be the first clinical manifestation. Finally, measures are needed to achieve optimum treatment, including excellent international normalised ratio (INR) control if VKAs are used, excellent adherence to thromboprophylactic drugs (ie, VKAs or NOACs) as prescribed, and long-term persistence with treatment. In this paper, we provide an overview of all three aspects of stroke prevention in atrial fibrillation, in the hope that greater awareness will result in reduction of the overall ischaemic stroke burden associated with atrial fibrillation.

Search strategy and selection criteria

We searched MEDLINE and PubMed (date of last search May 2, 2016) using the following search terms: "atrial fibrillation", "warfarin", "dabigatran", "rivaroxaban", "apixaban", "edoxaban", "randomized trial", "real world", "cohort study", "registry", "stroke prevention", "stroke risk", and "bleeding risk", and checked reference lists from relevant articles. No publication time limits were specified, though preference was given to articles from the past 10 years and some highly cited older articles. This search primarily focused on studies to be included in the table, panel 2, and the appendix pp 14–25.

Atrial fibrillation as a cause of ischaemic stroke

Of all strokes with an established cause, over 85% are ischaemic strokes,[6] and the association of atrial fibrillation with ischaemic stroke of cardioembolic origin is well recognised.[7] Indeed, findings from recent population-based studies or stroke registries[8–12] consistently showed a substantial atrial-fibrillation-attributable risk of stroke, especially in the elderly; at least one in three to four patients with an ischaemic stroke, and over 80% of those with ischaemic stroke of cardioembolic type, also had atrial fibrillation (appendix p 5), suggesting an even stronger association of atrial fibrillation with stroke than previously thought. In over 25% of strokes related to atrial fibrillation, the stroke was the first manifestation of previously unknown atrial fibrillation, which in most cases could have been prevented by OAC treatment, had atrial fibrillation been detected before the stroke (appendix p 5).

Sometimes, even extensive post-stroke diagnostic testing does not elucidate the cause of the stroke (ie, large-vessel disease, cardioembolism, or small-vessel disease); such cryptogenic strokes comprise around 25% of all strokes.[13] In two randomised trials assessing various post-stroke cardiac rhythm monitoring strategies in patients with cryptogenic stroke,[14,15] previously unknown atrial fibrillation was eventually detected by prolonged monitoring in 30% of patients in the CRYSTAL-AF trial[14] and in 16% of patients with 30-day monitoring in the EMBRACE trial;[15] identification of atrial fibrillation after stroke would qualify patients for

secondary prevention using OACs instead of the standard non-atrial fibrillation post-stroke treatment, aspirin. In a meta-analysis of 50 studies,[16] atrial fibrillation was detected in 24% of patients after stroke by combined short-term and long-term monitoring. The optimum, cost-effective technique and duration of post-stroke monitoring beyond the first 24 h remains uncertain. At present, prolonged post-stroke monitoring is optional.

Replacement of the term cryptogenic stroke with the more explicitly defined embolic stroke of undetermined source (ESUS), a non-lacunar brain infarct without evident proximal arterial stenosis or cardioembolic sources, has been increasingly advocated.[17] A substantial proportion of patients with ESUS have paroxysmal atrial fibrillation.[17,18] The risk of stroke recurrence is high after incident ESUS.[17,18] Electrocardiographic documentation of atrial fibrillation is mandatory for OAC use in the context of stroke prevention.[19] In the CRYSTAL-AF[14] and EMBRACE[15] post-stroke monitoring trials, at least 75% of atrial fibrillation episodes were asymptomatic, which emphasises the unreliability of symptoms for detection of atrial fibrillation. Two ongoing randomised trials will compare the efficacy and safety of the NOACs dabigatran (RE-SPECT ESUS[20]) and rivaroxaban (NAVIGATE ESUS; NCT02313909) versus aspirin in unselected patients after ESUS, which might obviate the need for post-stroke monitoring.

Previous management of atrial fibrillation in patients presenting with stroke

Although most strokes related to atrial fibrillation can be prevented using OACs,[21] findings from contemporary registry-based and observational real-world reports from various geographical regions have consistently shown that OAC treatment is underused in patients with atrial fibrillation who are at risk of stroke.[22] No OAC is used in around a third of eligible patients with atrial fibrillation, and in over 50% of patients who receive warfarin the quality of anticoagulation control remains suboptimum.[23]

In the Canadian Stroke Registry,[24] only 10% of patients with known atrial fibrillation and acute ischaemic stroke were previously well managed on warfarin (an additional 29% were on subtherapeutic warfarin), whereas in secondary prevention (ie, those with a history of stroke) the percentages increased to 18% and 39%, respectively (appendix p 6). In the Adelaide Stroke Incidence Study,[10] warfarin had been prescribed before stroke in 27% of patients with previous atrial fibrillation (15% therapeutic and 12% subtherapeutic; appendix pp 3, 4). Findings from a registry of over 94 000 ischaemic strokes from Sweden[12] suggested that of all patients with ischaemic stroke, 20% had known but untreated or inadequately treated atrial fibrillation and 9% had previously unknown atrial fibrillation; in these patients stroke could have been prevented by either treatment with an OAC according to current guidelines or by screening for atrial fibrillation (appendix pp 3, 4). In the UK, according to the Sentinel Stroke National Audit Programme (SSNAP), there has been some improvement over previous anticoagulant treatment rates in patients with stroke with known atrial fibrillation over the past 3 years, but antiplatelet drugs, largely aspirin, were still the sole antithrombotic prescribed in 26% of patients in the 12 months ending March, 2016.

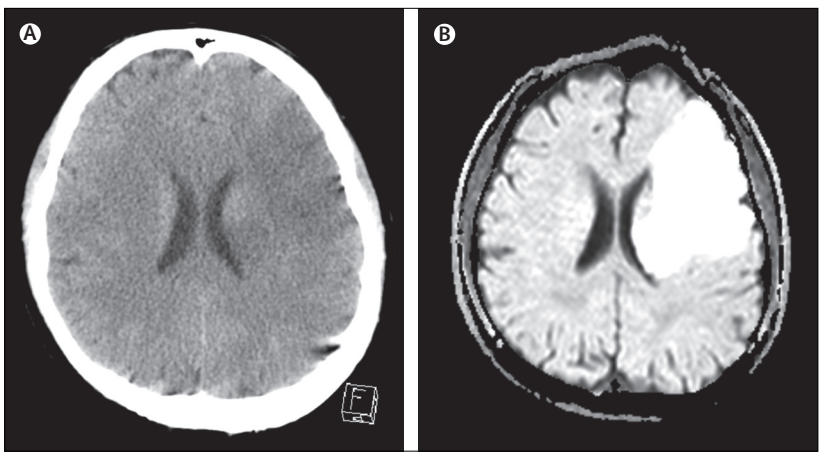

Figure 1: **Imaging of large middle cerebral artery cardioembolic stroke in a patient with atrial fibrillation**
(A) CT and (B) subsequent MRI from a 39-year-old man with large middle cerebral artery cardioembolic stroke.

For the **SSNAP data** see https://www.strokeaudit.org/results/clinical-audit/national-results.aspx

Aspirin is still widely misused for primary or even secondary stroke prevention in a quarter to a third of patients with atrial fibrillation who are eligible for OACs,[24,25] presumably because of misperception of efficacy and safety for stroke prevention in atrial fibrillation, which is likely to contribute to continuing underuse of anticoagulants.[26] Aspirin is neither effective nor safe as thromboprophylaxis for atrial fibrillation,[26] even possibly increasing stroke risk in elderly patients,[27] and has largely been removed from guidelines.[19,28,29] The consequence of aspirin misuse is evident in stroke registries (appendix pp 3, 4, 6), with a high proportion of atrial-fibrillation-related strokes occurring in patients treated only with aspirin, despite a $CHADS_2$ or CHA_2DS_2-VASc score of at least 2 (appendix pp 3, 4). Replacing aspirin with OACs, and prescribing OACs for the 20% of high-risk patients with known atrial fibrillation who receive no OAC treatment (appendix p 6) constitutes a simple solution to reduce the atrial fibrillation stroke burden, provided effective measures to close this evidence–treatment gap are implemented.

Finding unknown atrial fibrillation to prevent stroke

Almost 10% of all ischaemic strokes (representing >25% of strokes related to atrial fibrillation) occur simultaneously with first-detected atrial fibrillation. Measures to screen or case-find unknown asymptomatic atrial fibrillation, and then treat with OACs, should logically have a major effect on reducing stroke burden. The inbuilt assumptions are that unknown asymptomatic

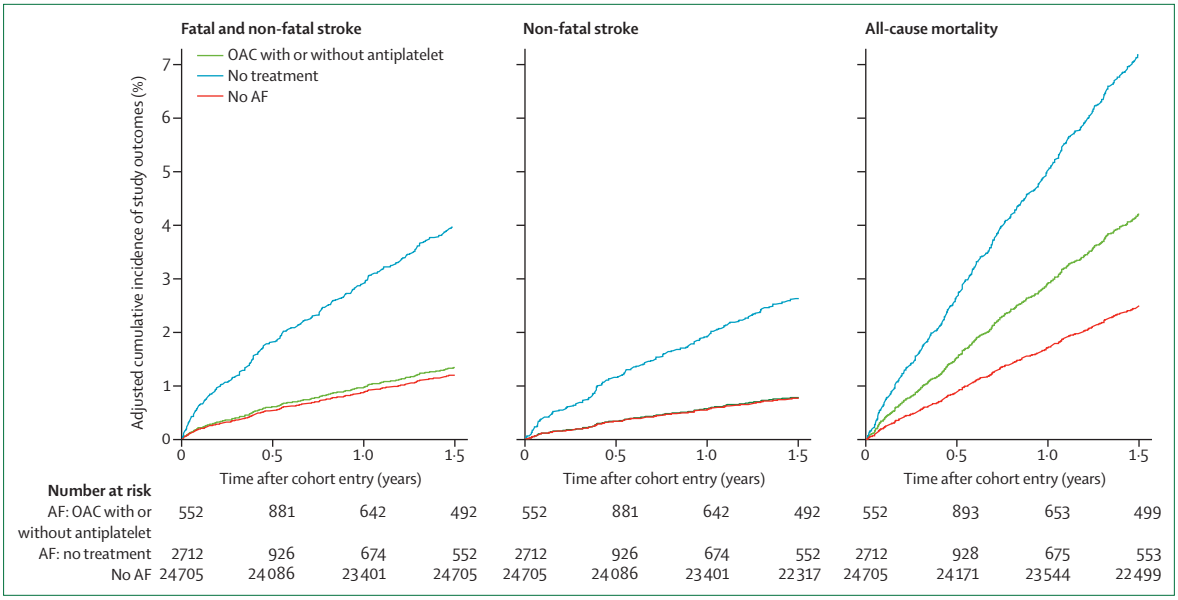

Figure 2: **Effect of treatment on incidentally detected atrial fibrillation**
AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.[21]

atrial fibrillation is common, and that prognosis of unknown asymptomatic atrial fibrillation is similar to that in the pivotal trials,[30] which included a small but unknown proportion of patients with incidentally detected atrial fibrillation (eg, during a routine clinic visit). Such pre-symptomatic atrial fibrillation has sometimes been assumed to have a benign prognosis.[31] In a study of asymptomatic incidentally detected atrial fibrillation in general practice, prognosis was far from benign, with a doubling of stroke and all-cause mortality compared with age-matched and sex-matched patients without atrial fibrillation.[32] Moreover, anticoagulant treatment reduced the stroke rate from 4% to 1% after only 1·5 years compared with no treatment; this rate is almost identical to that in matched controls without atrial fibrillation seen contemporaneously (figure 2).[21] A similar adverse prognosis of atrial fibrillation first discovered in the absence of symptoms was noted in Olmsted county (MN, USA).[33,34] In the EORP-AF registry,[35] patients who had never experienced symptoms actually had a worse prognosis than those with symptoms.

Patients with pacemakers or similar implanted devices frequently have brief or even prolonged episodes of asymptomatic atrial fibrillation, and these have been associated with a more than doubling of the stroke risk, and a 5·5 times increase in the risk of subsequent atrial fibrillation.[36,37] Longer (>18 h) episodes of atrial fibrillation have the highest adverse prognosis.[36] Ongoing randomised trials of anticoagulant treatment of device-detected asymptomatic atrial fibrillation (eg, ARTESiA [NCT01938248] and NOAH [NCT02618577]) are investigating the role of two NOACs, apixaban or edoxaban, versus aspirin for the treatment of device-detected subclinical atrial fibrillation. Even excessive atrial ectopics or runs (defined as ≥20 beats) of atrial tachycardia without definitive atrial fibrillation carry a similar prognosis.[38] This finding, coupled with the only partial temporal association of stroke with device-detected atrial fibrillation episodes,[39–41] suggests that as well as being a risk factor for stroke, atrial fibrillation is also a powerful risk marker for an abnormal atrial or systemic substrate, which can lead to stroke.[42]

Screening or case finding in either the clinic or community will detect atrial fibrillation in 1·4% of patients on a single screen in those aged at least 65 years.[43] Using stepped screening with patient-activated handheld electrocardiograph (ECG) devices for 2 weeks in 75–76-year-olds detects atrial fibrillation in 3% of patients.[44] Opportunistic case finding using pulse palpation and ECG if irregular is as effective as systematic 12-lead electrocardiography, and is more cost-effective.[45] Hence, opportunistic clinic pulse screening forms the basis of guideline recommendations on screening.[19] Cheaper, faster, yet accurate devices providing automated atrial fibrillation diagnosis, including handheld single-lead ECGs,[44,46,47] blood pressure oscillometry,[48] and smartphone photoplethysmography,[49] are likely to improve the cost-effectiveness. Indeed, screening for unknown atrial fibrillation is likely to be cost-effective for stroke prevention,[46,50] and might lead to revisions of recommendations about screening for atrial fibrillation to prevent stroke.[30,51]

Stroke risk factors and risk stratification

Atrial fibrillation increases the risk of stroke and systemic thromboembolism, but the excess risk also depends on the presence of various additional risk factors, which

were defined from findings from the non-warfarin placebo or control arms of historical randomised trials done two decades ago[52] or from large observational epidemiological studies. There is good evidence of increased risk in patients with previous stroke or systemic embolism, age at least 65 years, recent decompensated heart failure (irrespective of ejection fraction; hence, heart failure with reduced or preserved ejection fraction, eg, hypertrophic cardiomyopathy),[53] moderate-to-severe left ventricular dysfunction on cardiac imaging, diabetes mellitus, hypertension, or vascular disease (ie, peripheral artery disease or previous myocardial infarction).[54] Female sex is probably a stroke risk modifier, with accentuation of risk in those older than 65 years or with at least one additional stroke risk factor.[55,56] The age threshold conferring excess stroke risk seems to be even lower (age ≥50 years) in east Asians.[57]

More recent attention has been directed towards defining the stroke risk associated with a single stroke risk factor, since not all risk factors carry equal weight, and risk in atrial fibrillation varies depending on clinical setting (eg, community based *vs* hospitalised) and according to ethnic origin[58] and availability of appropriate methods to establish event rates.[59] The evidence is compelling that even a single stroke risk factor confers an excess risk of thromboembolism and mortality (figure 3),[60–62] with a positive net clinical benefit for OAC treatment compared with aspirin or no antithrombotic treatment for such patients.[60,63]

The more common stroke risk factors have been incorporated into stroke risk stratification scores (appendix pp 7, 8), designed to help practical decision making in everyday practice. The most comprehensive review and comparison of stroke and bleeding risk scores is provided in the 2014 National Institute for Health and Care Excellence (NICE) guidelines,[28] which are based on systematic reviews, evidence appraisal, and cost-effectiveness. Risk scores based on clinical factors have modest predictive value for identifying high-risk patients, and additional refinement of clinical-factor-based scores to improve identification of high-risk patients can be made by the addition of biomarkers (eg, von Willebrand factor, natriuretic peptides, or troponin) and imaging (eg, cerebral or cardiac imaging).[64] Even then, *c* statistics (ie, how well a score predicts an event) suggest only modest discrimination despite addition of several biomarkers, but with additional costs and a major loss of simplicity and practicality for everyday clinical use.

Stroke risk is a continuum, and the artificial categorisation into low or high risk still leads to many patients with high-risk atrial fibrillation being under-treated. The default should be to use OACs to treat all patients with atrial fibrillation unless clearly defined as truly low risk. Hence, clinicians should be most concerned with identifying the very-low-risk patients who do not need thromboprophylaxis. The CHA_2DS_2-VASc score[65] is useful as a simple clinical score for easy

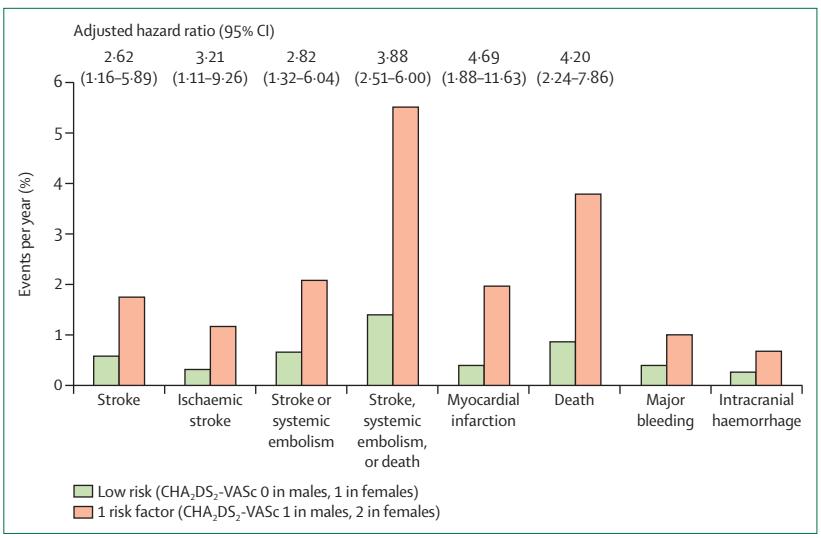

Figure 3: **Risk of stroke with a single additional risk factor**
Data from Fauchier and colleagues.[60]

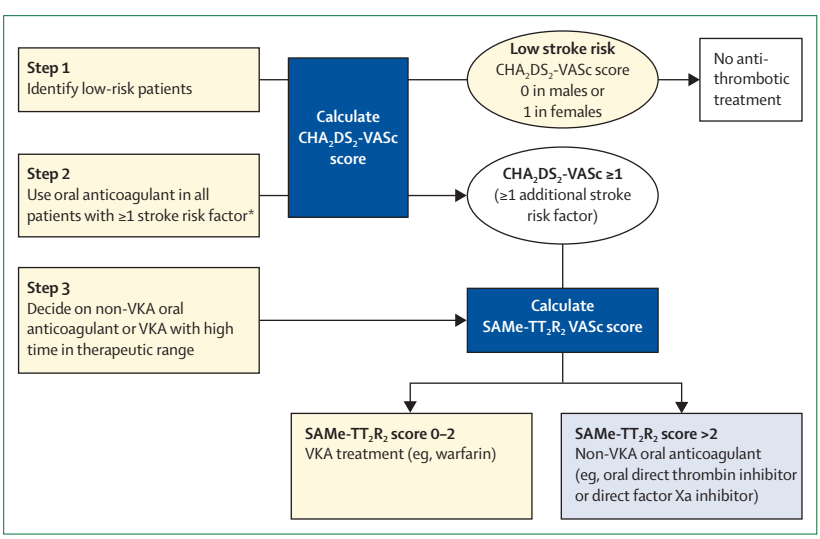

Figure 4: **Recommended decision pathway for treatment of newly diagnosed non-valvular atrial fibrillation**
VKA=vitamin K antagonist. *Also calculate the HAS-BLED score. If HAS-BLED ≥3, address the modifiable bleeding risk factors and plan a closer clinical follow-up.

initial identification of low-risk patients (CHA_2DS_2-VASc score 0 in males and 1 in females) who have stroke rates of 1% or lower per year, who do not need antithrombotic treatment.[59,66,67]

One common misperception is that paroxysmal atrial fibrillation carries a low risk of stroke, whereas in many studies the risk is almost identical to that of persistent or permanent atrial fibrillation, notwithstanding considerations of variable arrhythmia burden and associated risk factors, especially since patients with paroxysmal atrial fibrillation tend to be younger and have fewer risk factors. Guidelines recommend treating paroxysmal atrial fibrillation with OACs using identical rules as apply to persistent or permanent atrial

fibrillation;[19,68] unfortunately, in practice, this is often not done.[69]

Thromboprophylaxis in patients with atrial fibrillation

Guidelines recommend different approaches to thromboprophylaxis in atrial fibrillation. Some use CHA_2DS_2-VASc score in a categorical approach; for example, the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines[68] define patients with atrial fibrillation as low, moderate, or high risk, and recommend antithrombotic treatment on that basis. Patients at high risk are those with a CHA_2DS_2-VASc score of at least 2, for whom OACs are recommended; low risk are those with a CHA_2DS_2-VASc score of 0, for whom no antithrombotic treatment should be considered. For those with a CHA_2DS_2-VASc score of 1, OACs, aspirin, or no antithrombotic treatment can be chosen, depending on risk factors and patient values and preferences.

The 2014 NICE guidelines[28] and European Society of Cardiology guidelines[19] recommend that the initial step should be to identify low-risk patients (CHA_2DS_2-VASc score 0 in males, 1 in females) who do not need antithrombotic treatment. The next step is to offer effective stroke prevention with OACs (either VKAs with good quality anticoagulation control or NOACs) to those with at least one additional stroke risk factor. Since the default should be to give anticoagulants to all patients with atrial fibrillation unless defined as truly low risk, we recommend this simplified approach (figure 4), because the decision to provide anticoagulation is already made with at least one additional stroke risk factor irrespective of score value or the addition of biomarkers or imaging. Since patients with atrial fibrillation have high rates of hospital admission and risk stratification is not a static one-off process, low-risk patients should be regularly reviewed to establish whether risk has increased. Aspirin alone should not be offered for stroke prevention in atrial fibrillation.[26–28]

Bleeding risk assessment should also be part of the clinical decision-making process. In most cases, an elevated bleeding risk score should not be used as a reason to withhold anticoagulation, because stroke risk almost invariably outweighs serious bleeding risk, but patients at high risk of bleeding should be flagged up for more careful review and follow-up, especially in the era of electronic health record alerts, with prompt attention given to common reversible bleeding risk factors within the score.[70] These include uncontrolled hypertension; control of a known previous bleeding site, especially gastrointestinal; labile INRs if on a VKA; and excess alcohol or concomitant non-steroidal anti-inflammatory drug use.[71] The simplest and best validated score is HAS-BLED[72] (appendix pp 9, 10), which reliably predicts bleeding in patients on OACs (whether VKAs or other anticoagulants[73]), aspirin, or no antithrombotic treatment. HAS-BLED has also been validated in

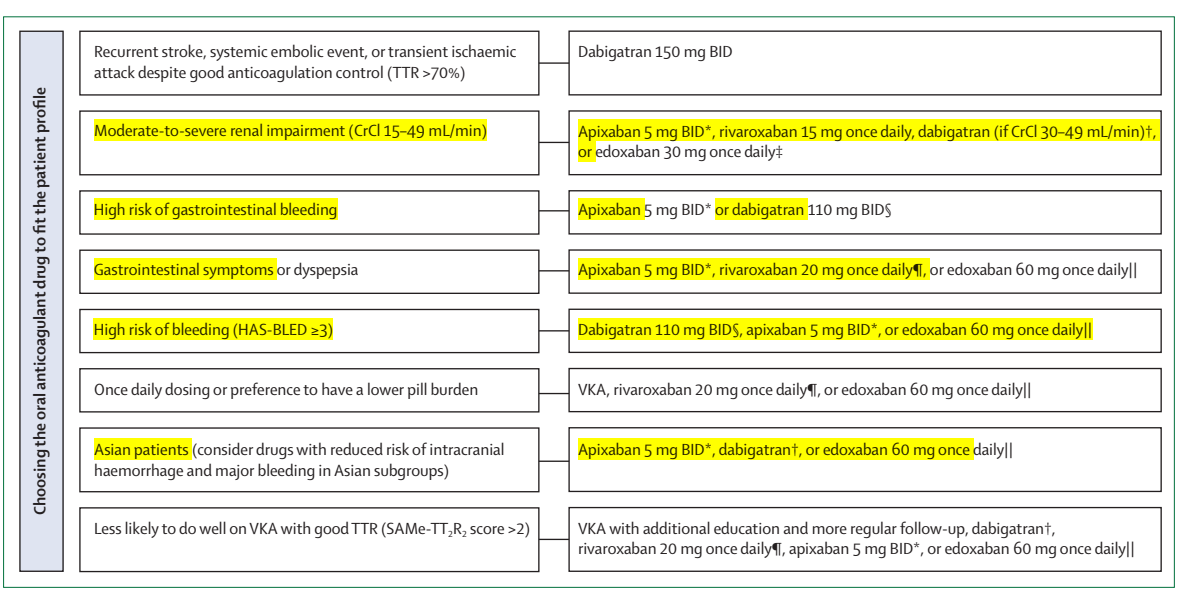

Figure 5: **Choice of oral anticoagulant drug to fit the patient profile**

A simplified schema to assist physician choice of anticoagulant (VKA or individual NOAC) according to patient characteristic. BID=twice daily. CrCl=creatinine clearance. NOAC=non-vitamin K antagonist oral anticoagulant. TTR=time in therapeutic range. VKA=vitamin K antagonist. *Reduced to 2·5 mg BID with two of three criteria from age ≥80 years, bodyweight ≤60 kg, or serum creatinine concentration ≥133 μmol/L. †110 mg BID for patients with a CrCl 30–49 mL/min (most countries, but not in the USA); in the USA only, 75 mg BID (available in the USA only) for patients with CrCl 15–29 mL/min (and only 150 mg BID dose available in the USA for CrCl >30 mL/min). ‡30 mg with CrCl 15–49 mL/min, P-glycoprotein inhibitors, or weight <60 kg. §110 mg BID dose not available in the USA for atrial fibrillation. ¶Reduced to 15 mg if CrCl 15–49 mL/min. ||Dose to be halved if the patient has any of the following: CrCl 15–49 mL/min, bodyweight ≤60 kg, or concomitant use of P-glycoprotein inhibitors.

non-atrial fibrillation populations, including venous thromboembolism and patients undergoing bridging therapy. Simpler scores that aim to provide information valid for both VKAs and NOACs are likely to inappropriately categorise many patients who subsequently bleed as low risk or substantially underestimate bleeding risks in VKA-treated patients by ignoring labile INR as a risk criterion.[74,75] More complex scores using biomarkers offer statistically improved prediction of high-risk patients, but are less simple for everyday clinical use and do not focus on the reversible bleeding risk factors.[70]

VKAs are effective and safe if well managed with good quality anticoagulation control, as shown by the time in therapeutic range (TTR) of over 70%.[76] However, a good TTR can be difficult to obtain in clinical practice, or in some populations such as Asians.[77] The control of VKAs is affected by several clinical features, and some common factors have been incorporated into the SAMe-TT_2R_2 score (appendix pp 9, 10).[78] Although prediction of the actual TTR is modest, the score is best used pragmatically to flag patients unlikely to do well on a VKA (score >2), because of labile INRs or poor TTR and the consequent risk of thromboembolism, death, or bleeding.[79,80] Such patients should be targeted for more regular review and follow-up; educational interventions and counselling, which improve TTR;[81] or use of NOACs.[82]

With availability of four NOACs in addition to VKAs, we can fit a particular drug to a patient's clinical profile,[83,84] by use of available evidence from large randomised trials and observational cohorts (figure 5 and discussed later). Various clinical considerations when choosing a particular type or dose of NOAC can be summarised by the mnemonic ABCDE: abnormally low weight (dose reduction might be needed); bleeding risk, especially previous or recent gastrointestinal bleeding; creatinine clearance (ie, renal function); drug interactions (eg, P-glycoprotein inhibitors); and elderly age (dose reduction might be needed).

From clinical trials to real-world practice

The efficacy of warfarin compared with placebo or aspirin for stroke prevention in patients with non-valvular atrial fibrillation was established almost 30 years ago (table).[4] In a meta-analysis[86] of eight more recent stroke prevention trials (2005–11), the pooled rate of residual stroke or systemic embolism in the warfarin arms was significantly lower than in earlier trials (1·66% *vs* 2·09%), probably because of improved management of warfarin treatment (mean TTR 63·6% *vs* 42–81%, and four of six earlier trials with a TTR <60%), whereas the rates of major bleeding (1·4–3·4%) and intracranial haemorrhage (ICH; 0·61%) were similar.[86]

Owing to many limitations (panel 1),[87] VKA treatment outside the trial setting is often suboptimal, and NOACs are increasingly used as a viable alternative. A meta-analysis[5] of four landmark NOAC trials in non-valvular atrial fibrillation revealed a significant 19% stroke risk

	Included trials	Number of patients	Comparison	Stroke or SE RR or HR (95%CI)	Major bleeding RR or HR (95%CI)	Gastrointestinal bleeding RR or HR (95%CI)	ICH RR or HR (95%CI)	All-cause mortality RR or HR (95%CI)
Meta-analyses of randomised controlled trials of antithrombotic treatments								
Hart et al (2007)[4]	5 primary, 1 secondary prevention trial	2900	Adjusted-dose warfarin *vs* placebo or no treatment	64% (49 to 74) RR reduction with warfarin	Not calculated	–66% (–235 to 18)*	6 *vs* 3 events	26% (3 to 43)
Hart et al (2007)[4]	12 trials	3647	Adjusted-dose warfarin *vs* antiplatelet treatment	39% (22 to 52) RR reduction with warfarin	Not calculated	–70% (–234 to 14)*	20 *vs* 7 events	9% (–19 to 30)
Hart et al (2007)[4]	7 trials	3990	Aspirin *vs* placebo or no treatment	19% (–1 to 35) RR reduction with aspirin	Not calculated	2% (–98 to 52)*	8 *vs* 4 events	14% (–7 to 31)
Ruff et al (2014)[5]	4 trials	42 411 on a NOAC, 29 272 on warfarin	NOACs *vs* adjusted-dose warfarin	Overall RR 0·81 (0·73 to 0·91); ischaemic stroke RR 0·92 (0·83 to 1·02); haemorrhagic stroke RR 0·49 (0·38 to 0·64)	RR 0.86 (0·71–1·00)	RR 1·25 (1·01 to 1·55)	RR 0·48 (0·39–0·59)	RR 0·90 (0·85 to 0·95)
Meta-analyses of observational studies of dabigatran *vs* warfarin								
Romanelli et al (2016)[85]	7 trials	197 348 on warfarin, 197 348 on dabigatran 150 mg, 11 305 on dabigatran 110 mg	Dabigatran 150 mg or 110 mg *vs* dose-adjusted warfarin	Dabigatran 150 mg HR 0·92 (0·84 to 1·10); dabigatran 110 mg HR 0·92 (0·72–1·18)	Not reported	Dabigatran 150 mg HR 1·23 (1·01 to 1·50); dabigatran 110 mg HR 0·91 (0·55 to 1·51)	Dabigatran 150 mg HR 0·44 (0·34 to 0·59); dabigatran 110 mg HR 0·49 (0·34–0·72)	Not reported

HR=hazard ratio. ICH=intracranial haemorrhage. NOAC=non-vitamin K antagonist oral anticoagulant. RR=relative risk. SE=systemic embolism. *Major extracranial bleeding.

Table: **Meta-analyses of randomised, controlled trials or observational studies on the efficacy and safety of antithrombotic treatments for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation**

Panel 1: **Essential features of vitamin K antagonists and non-vitamin K antagonist oral anticoagulants**

Vitamin K antagonists

- Slow onset and offset of action, with some thrombophilia during onset and offset
- Narrow therapeutic window (target INR 2·0–3·0)
- Several interactions with food and other drugs, which affect the anticoagulation intensity
- Variable dose response depending on the individual's genetic background
- INR-guided dosing necessitates regular INR monitoring and frequent dose adjustments
- TTR of >65–70% is vital for optimum stroke prevention
- Used in clinical practice for a long time; not expensive

Non-vitamin K antagonist oral anticoagulants

- Fast onset and offset of action; onset faster than offset
- Fixed once or twice daily dosing
- A few clinically relevant interactions with other drugs; no food interaction
- Stable, dose-related anticoagulant effect; no need for regular laboratory monitoring of anticoagulation intensity, but renal function assessment is mandatory at baseline and during follow-up, depending on baseline renal function
- Strict adherence to non-vitamin K antagonist oral anticoagulant treatment crucial for optimum efficacy
- Relatively new drugs, expensive, but cost-effective, in comparison with vitamin K antagonists

See appendix pp 11–17 for more details. INR=international normalised ratio. TTR=time in therapeutic range.

reduction versus VKAs, which was driven by the reduction in haemorrhagic stroke and no real change in ischaemic stroke; comparable safety in terms of major bleeding, with impressive reductions in ICH, at the cost of increased gastrointestinal bleeding; and a 10% reduction in all-cause mortality relative to warfarin (table and appendix pp 11–13). The efficacy and safety of NOACs over warfarin seems to be even greater in east Asians compared with non-Asians.[88]

Randomised trials provide the most objective evidence on a drug treatment, but the results might not be fully applicable to a range of real-world settings, because of the trial-specific inclusion and exclusion criteria. Notwithstanding some limitations, post-marketing observational studies, including prospective international registries and large administrative datasets, provide valuable complementary information on treatment performance in daily clinical practice. A meta-analysis of real-world observational studies on dabigatran versus warfarin for stroke prevention in non-valvular atrial fibrillation (table)[85] yielded results broadly consistent with the main RE-LY trial. Key findings from those studies are shown in panel 2 and the appendix (pp 14–17). In real-world studies of rivaroxaban with lower risk patients, compared with the pivotal ROCKET-AF trial, the rates of stroke, major bleeding, and death seemed to be lower,[89] but findings from more recent propensity-score-matched real-world studies with rivaroxaban consistently showed similar thromboembolism and bleeding risks to warfarin (appendix pp 14–17). In a large propensity-weighted analysis from a Danish nationwide cohort study,[90] no significant differences were found between NOACs and warfarin for ischaemic stroke, but the risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran than for warfarin. Warfarin and rivaroxaban had comparable annual bleeding rates.

Findings from large prospective international observational registries show that many patients with atrial fibrillation who are eligible for OACs because of high risk of stroke are still not treated with OACs, particularly the elderly or those at high risk of bleeding. Findings from registry studies highlight the gaps in daily clinical practice alluded to earlier, and identify the unmet needs regarding evidence-based guidance on optimum strategies for stroke prevention in some subsets of patients with atrial fibrillation.[22] Key findings and a detailed summary are shown in panel 2 and the appendix (pp 18–25).

Specific management considerations

Because of the overlap in stroke and bleeding risk factors, high-risk patients with atrial fibrillation are often denied OACs without an absolute contraindication. Elderly people[91] and most patients with a history of bleeding (eg, previous gastrointestinal bleeding with a healed culprit lesion) clearly benefit from OAC resumption.[92] Patients with atrial fibrillation after intracerebral haemorrhage or those with severe renal disease represent other high-risk groups that were excluded from randomised trials, but findings from observational studies suggest some benefit from OACs.[93–95]

Patients with atrial fibrillation undergoing percutaneous coronary intervention and stenting need a complex management strategy including OACs with single or dual antiplatelet treatment, to balance risk of stroke, recurrent ischaemia, or stent thrombosis against the risk of serious bleeding with combined treatment. Dependent on the patient risk profile and clinical setting (ie, acute coronary syndrome *vs* stable disease), triple treatment with OACs plus dual antiplatelet treatment, followed by OACs plus a single antiplatelet drug such as clopidogrel, should be used for the shortest period advisable.[96] Thereafter, OAC monotherapy (a NOAC or well-managed VKA) should continue.[96]

Catheter atrial fibrillation ablation is superior to medical treatment at eliminating clinical atrial fibrillation recurrences, but should not be used to avoid OAC treatment; the decision regarding long-term OAC use after ablation should be based on individual stroke risk and not the estimated procedural success.[97] Reports on the association of left atrial appendage isolation with appendage thrombus and stroke are conflicting, with results showing either improvement or a neutral effect, and there might even be a downside depending on the procedural details.[98] Two ongoing trials are investigating

Panel 2: **Key points regarding oral anticoagulant treatment for thromboprophylaxis in patients with non-valvular atrial fibrillation**

Key points from the landmark NOAC trials in patients with non-valvular atrial fibrillation*

- NOACs were superior to warfarin (dabigatran 150 mg or apixaban) or similarly effective as warfarin (dabigatran 110 mg, rivaroxaban, or edoxaban in both doses) at reducing stroke or systemic embolism.
- Stroke reduction was largely driven by the reduction in haemorrhagic stroke (significant for all NOACs *vs* VKAs) with minimal effect on ischaemic stroke, in which a significant reduction was only reported for dabigatran 150 mg.
- NOACs were either safer than warfarin (dabigatran 110 mg, apixaban, or edoxaban in both doses) or as safe as warfarin (dabigatran 150 mg or rivaroxaban) with respect to major bleeding.
- Apixaban was more effective than aspirin in the prevention of stroke or systemic embolism, with comparable safety (regarding major bleeding, haemorrhagic stroke, ICH, and gastrointestinal bleeding), and was better tolerated.

Key points from large real-world administrative dataset analyses of NOAC use[22]†

- Effectiveness and safety of dabigatran, rivaroxaban, and apixaban in real-world data were broadly consistent with findings from landmark trials; however, the ROCKET-AF study included higher-risk patients with more events than real-world studies.
- Gastrointestinal bleeding was the most common major bleeding event.
- ICH or fatal bleeding was rare.
- Risk of bleeding during OAC initiation is higher with warfarin than with dabigatran.

Key points from contemporary large observational international prospective registries‡

- OAC treatment for stroke prevention has increased in the past decade compared with earlier real-world data. Contemporary OAC use ranges from 45% in US general practice and 50% in Japan general practice, to 82% in European cardiologists and 87% in Japanese cardiovascular specialists.
- Cardiologists and electrophysiologists are more likely to prescribe OACs across all stroke risk strata than are internal medicine specialists or primary care physicians.
- OAC use is generally higher in Europe and Japan than in the USA.
- VKAs are still the most commonly used OACs in many regions.
- OACs are underused in eligible patients and overused in patients at truly low risk of stroke.
- Physician perception of stroke and bleeding risk often differs from the evidence-based guideline-recommended risk assessment tool estimate.
- The most common reason for OAC non-use is physician decision (real or perceived high bleeding risk, need or perceived need for concomitant antiplatelet treatment, paroxysmal or asymptomatic atrial fibrillation, only one stroke risk factor), followed by patient refusal.
- Permanent discontinuation of warfarin is common among patients with atrial fibrillation (20% to >50%), especially in incident users and young patients. Discontinuation is most commonly because of physician preference, patient refusal, or bleeding events.
- Antiplatelet treatment, mostly aspirin, is used in about a third of patients, frequently as the sole treatment, especially in elderly people. When concomitant with an OAC, only half have vascular disease.

ICH=intracranial haemorrhage. OAC=oral anticoagulant. NOAC=non-vitamin K antagonist oral anticoagulant. VKA=vitamin K antagonist. *See appendix (pp 14–17) for a detailed summary of the trials and complete list of references. †See appendix (pp 14–17). ‡See appendix (pp 18–25).

early rhythm control (EAST; NCT01288352) or atrial fibrillation ablation versus antiarrhythmic drug treatment (CABANA; NCT00911508) on long-term risk of stroke and death.

Percutaneous left atrial appendage occlusion using the WATCHMAN, Amplatzer Cardiac Plug, or WaveCrest device or the Lariat endocardial and epicardial ligation technique might be an alternative for patients with atrial fibrillation who are at high risk of both stroke and bleeding or with contraindications to OACs; however, interventional cardiologists need to be trained in the procedure, and patients must receive dual antiplatelet treatment for at least 6 weeks after the procedure.[99]

Modifiable cardiovascular risk factors (eg, hypertension, obesity, dyslipidaemia, obstructive sleep apnoea, physical inactivity, and smoking) are important contributors to atrial fibrillation substrate progression and increased atrial fibrillation burden. Emerging evidence shows that aggressive risk factor management is likely to improve symptoms and reduce atrial fibrillation recurrence, thus facilitating rhythm control in patients with or without atrial fibrillation catheter ablation.[100,101] Lifestyle interventions are likely to favourably affect cardiovascular outcomes, but whether these will reduce stroke remains to be established.

Population-centred or patient-centred interventions

Nurse-led clinics are an attractive possibility to improve uptake of stroke prevention strategies. In a randomised trial of 712 patients,[102] appropriate OAC prescription increased from a high base of 83% in the usual care

group to 99% in the nurse-led clinic. Although cardiovascular death and hospital admissions were both significantly reduced by the intervention, stroke was infrequent, with only 1% of patients having stroke in 22 months of follow-up, and was not significantly different between groups in this well-managed patient cohort. Another approach is to link population screening for unknown atrial fibrillation with screening for known but untreated atrial fibrillation, referring such individuals to a cardiology team to prescribe OACs.[44]

Marketing of NOACs has probably resulted in a rise in the proportion of eligible patients receiving anticoagulation; after introduction of NOACs in the UK, the proportion of patients with a CHA_2DS_2-VASc score of at least 2 starting anticoagulants for atrial fibrillation increased from 41% to 65%.[103] Patient support groups (eg, Atrial Fibrillation Association and StopAfib.org) also have a part to play in increasing patient awareness of atrial fibrillation and its attendant stroke risk, and reducing reluctance to start OACs.

For the **Atrial Fibrillation Association** see http://www.afa.org.uk

For the **StopAfib.org** see http://www.StopAfib.org

A neglected aspect of stroke prevention is ensuring that patients who start OACs continue to take the treatment indefinitely. Unfortunately, persistence with OACs, or rather non-persistence, is a major issue; 21–50% of patients discontinue VKAs by 1 year after inception.[103] Findings from many studies have shown lower persistence with warfarin than a single NOAC. In one study,[103] persistence with warfarin was significantly lower than with NOACs at 1 year (65% *vs* 83%; appendix p 2). This difference in persistence of drug treatment is likely to be a major factor in strokes related to atrial fibrillation, because cessation of VKAs more than doubles the stroke risk, with a peak in the first year after cessation, and a high absolute increase for at least 3 years after cessation.[104] In view of the shorter half-life with NOACs, poor patient adherence also translates to a higher risk of stroke and mortality despite overall good adherence to these drugs.[105,106] Therefore, greater efforts are needed to support the patient to increase adherence and continue OACs long term, whether with decision aids, educational measures, or patient counselling.[81,107]

Future directions

Increasing awareness of the role of unrecognised atrial fibrillation should accelerate efforts to detect atrial fibrillation before stroke has occurred and institute effective thromboprophylaxis with OACs. Widespread recognition of the role of undertreatment of atrial fibrillation in causation of ischaemic stroke will be of crucial importance to focus efforts to close the evidence–treatment gap for OACs, and replace aspirin with OACs in the therapeutic armamentarium. Basic and clinical research is needed to better understand the pathological atrial substrate leading to cardioembolism for which atrial fibrillation is likely to be a marker. In the longer term, efforts should be directed at primary prevention of atrial fibrillation, which might need similar lifestyle modifications as advocated for prevention of coronary heart disease.

Contributors

BF drafted, collated, and revised the manuscript. TSP did the literature searches. TSP and GYHL drafted and revised the manuscript.

Declaration of interests

BF has received research grants to undertake investigator-initiated studies from Bristol-Myers Squibb/Pfizer, Bayer, and Boehringer Ingelheim; has been a consultant for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Servier, AstraZeneca, and Gilead; and has been a speaker for Bayer, Bristol-Myers Squibb/Pfizer, and AstraZeneca. TSP has been a consultant for Bayer, AstraZeneca, and Pfizer; and a speaker for Bayer, Pfizer, and AstraZeneca. GYHL has been a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi Sankyo; and a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo.

Acknowledgments

We thank Alistair Corbett for providing the stroke images in figure 1, and James Leyden and Leif Friberg for providing additional information on antiplatelet treatment for appendix figure 2 (pp 3, 4) from the studies they led.

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Atrial fibrillation 2

Rate control in atrial fibrillation

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Lancet 2016; 388: 818–28

See Editorial page 731

This is the second in a Series of three papers about atrial fibrillation

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Control of the heart rate (rate control) is central to atrial fibrillation management, even for patients who ultimately require control of the rhythm. We review heart rate control in patients with atrial fibrillation, including the rationale for the intervention, patient selection, and the treatments available. The choice of rate control depends on the symptoms and clinical characteristics of the patient, but for all patients with atrial fibrillation, rate control is part of the management. Choice of drugs is patient-dependent. β blockers, alone or in combination with digoxin, or non-dihydropyridine calcium-channel blockers (not in heart failure) effectively lower the heart rate. Digoxin is least effective, but a reasonable choice for physically inactive patients aged 80 years or older, in whom other treatments are ineffective or are contraindicated, and as an additional drug to other rate-controlling drugs, especially in heart failure when instituted cautiously. Atrioventricular node ablation with pacemaker insertion for rate control should be used as an approach of last resort but is also an option early in the management of patients with atrial fibrillation treated with cardiac resynchronisation therapy. However, catheter ablation of atrial fibrillation should be considered before atrioventricular node ablation. Although rate control is a top priority and one of the first management issues for all patients with atrial fibrillation, many issues remain.

Introduction

Atrial fibrillation is associated with stroke, heart failure, and death.[1] Atrial fibrillation itself might be treated to reduce symptoms, improve quality of life, prevent cardiovascular morbidity and mortality, and avert iatrogenic consequences of unnecessary treatment. The first step in the assessment of a patient with atrial fibrillation is to identify and treat associated medical disorders and have a strategy to correct issues related to haemodynamic instability.

Aside from anticoagulation to prevent stroke, two main treatment strategies (not necessarily exclusionary) have emerged: rate control and rhythm control. The aim of rate control is to regulate the ventricular (heart) rate during atrial fibrillation (but not adversely affect the rate during sinus rhythm), reduce or eliminate symptoms, improve haemodynamics, prevent heart failure, and reduce the risk of adverse cardiovascular outcomes. The aim of rhythm control is to achieve and maintain sinus rhythm. Pharmacological rhythm control is only moderately effective in maintaining sinus rhythm, has potential adverse effects, and does not cure atrial fibrillation; it can postpone or reduce atrial fibrillation recurrences but rarely eliminates atrial fibrillation.[2] So far, to our knowledge, no trials comparing rhythm to rate control strategies have shown that rhythm control is superior to rate control alone in terms of major cardiovascular outcomes: morbidity, mortality, and quality of life.[3–9] The absence of a recorded beneficial effect of rhythm control treatments could be related to the little ability of these approaches to maintain sinus rhythm ranging between 39% and 63% during follow-up of 2·3–3·5 years, but additional reasons for not finding a benefit might also exist. In the past 10 years, atrial catheter ablation procedures to restore and maintain sinus rhythm have improved substantially and have an increased success rate. Atrial fibrillation catheter ablation is superior to antiarrhythmic drugs for rhythm control in paroxysmal atrial fibrillation.[10–13] Although less effective than in patients with paroxysmal atrial fibrillation, catheter ablation can also be done successfully in patients with symptomatic persistent or long-standing (>1 year) persistent atrial fibrillation.[14] Implementation of atrial ablation in rate versus rhythm control trials might change outcomes in favour of rhythm control therapy but this effect has not yet been shown. The Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST; ClinicalTrials.gov, number NCT01288352)[15] and the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA; ClinicalTrials.gov, number NCT00911508) randomly assigned patients to rate control or early atrial catheter ablation. Outcomes in cardiovascular morbidity and mortality will be available within several years. These trials will provide contemporary results as to whether catheter ablation of atrial fibrillation is accompanied by a reduction of morbidity and mortality. If these trials report positive results, guidelines for treatment of atrial fibrillation and the choice between rhythm control and rate control might change.

However, on the basis of the present available data, accepting atrial fibrillation with treatment aimed at reducing symptoms and preventing heart failure,

Search strategy and selection criteria

We identified data for this Series paper by searching MEDLINE, Current Contents, PubMed, and references from relevant articles using the search terms "atrial fibrillation" and "rate control". We considered data published in English between Jan 1, 1980, and June 30, 2016.

especially in elderly patients without any symptoms or only minor symptoms, is reasonable.[1,16] A rate control strategy can achieve this outcome; it is easier than rhythm control to institute and manage, and is associated with a lower rate of serious adverse events and fewer hospital admissions.[17]

The value of rate control as a treatment for atrial fibrillation

Atrial fibrillation can have important haemodynamic and symptomatic consequences. During atrial fibrillation, the atria fail to eject blood properly and do not contribute to the stroke volume, reducing cardiac output by 20–30% or more.[18] The irregular and usually fast ventricular rate further reduces ventricular filling and stroke volume.[19,20] Both the rhythm irregularity and the reduced stroke volume cause symptoms and contribute to the development or worsening of heart failure.[19] The reduction in stroke volume will become even more substantial at faster heart rates.[20] Reduced cardiac output can be exacerbated in patients with heart failure who have preserved or reduced left ventricular ejection fractions and can cause substantial clinical deterioration.[21] Persistent rapid rates can also worsen or even cause a tachycardia-induced cardiomyopathy.[22]

There are four situations in which to consider rate control treatment (figure 1, 2). First, rate control is background (so-called adjunctive) treatment for nearly all patients with atrial fibrillation, even when a rhythm control strategy is attempted, because during relapses of atrial fibrillation well controlled heart rates are crucial. Rate control is the approach of choice for patients with new-onset or so-called acute atrial fibrillation and for patients with acute recurrences, even if rhythm control has been tried. Second, rate control can be a first choice treatment for patients who do not require sinus rhythm (eg, patients older than 80 years with no or minor symptoms).[1,16] Present data suggest that only oral anticoagulants,[23,24] and not rhythm control treatments,[3–9] have been associated with improved survival in atrial fibrillation. Therefore, the main reason to use a rhythm control strategy at present is to reduce symptoms. Third, rate control is the only option when rhythm control, including atrial fibrillation ablation, fails. Finally, rate control is the treatment of choice for patients in whom the risks of restoring sinus rhythm outweigh the benefits (eg, in patients with brady–tachy syndrome who do not need pacing during atrial fibrillation). For patients who fit into these categories, rate control is reasonable but treatment has to be personalised with a shared decision-making approach for every patient.[25,26]

The definition of rate control and what the guidelines recommend

Rate control in atrial fibrillation is an adequate and appropriate ventricular rate that reduces symptoms and enables exercise. Rate control should prevent bradycardia

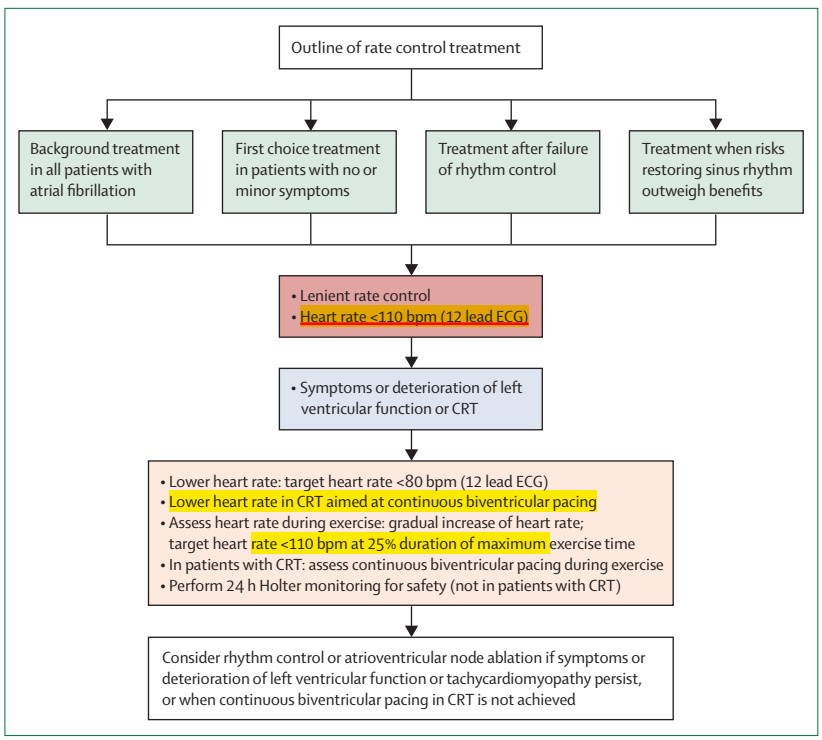

Figure 1: **Outline of rate control treatment**
bpm=beats per min. ECG=electrocardiogram. CRT=cardiac resynchronisation treatment.

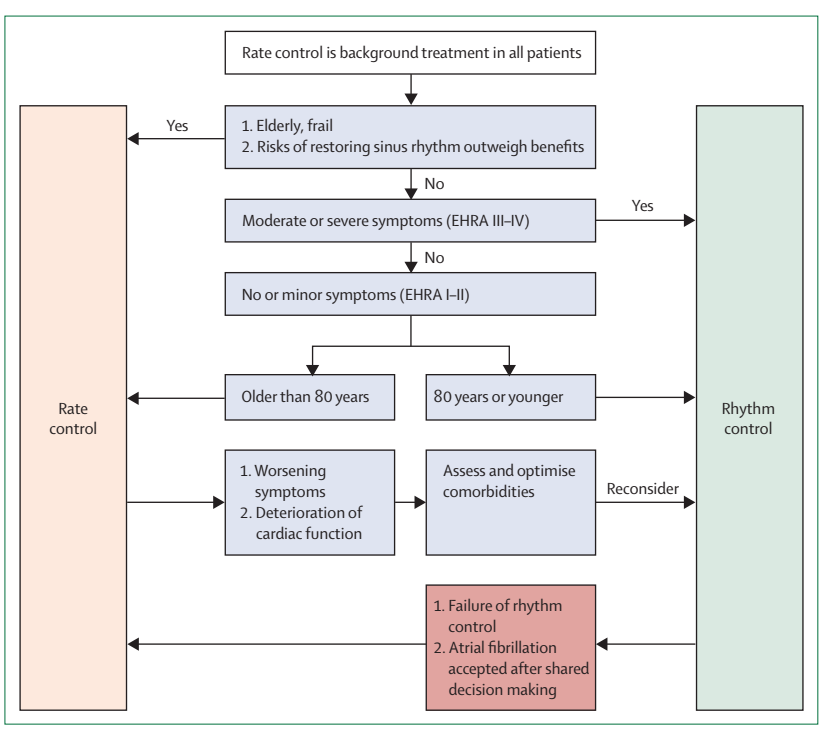

Figure 2: **Decision tree of timing and patient selection for rate control treatment**
EHRA=European Heart Rhythm Association classification.

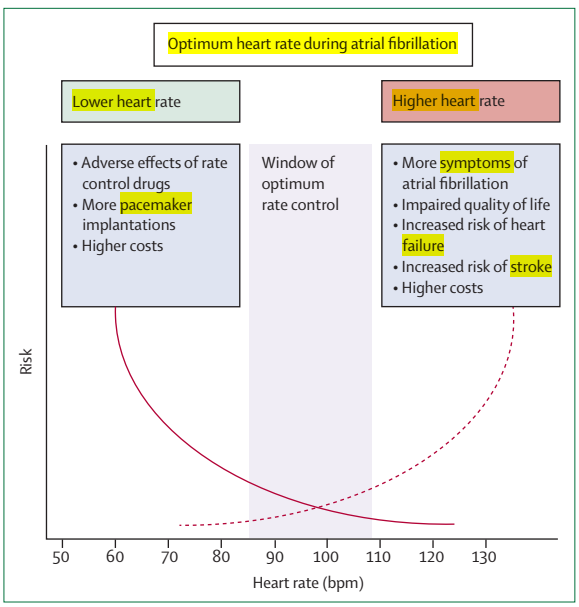

Figure 3: **Advantages and disadvantages of slow and fast heart rate management during atrial fibrillation**
Note that both slow and fast heart rate approaches might eventually increase costs albeit for different reasons. bpm=beats per min.

and reduce the risk of tachycardia-induced cardiomyopathy and worsening heart failure. But what is meant by "adequate" rate control?[27] Adequate rate control can be defined as the appropriate heart rate to supply the necessary cardiac output for specific physiological demands and to prevent adverse consequences. Heart rates that are too fast or too slow create problems (figure 3).[28]

However, to maintain physiological needs ventricular rates might need to be faster in atrial fibrillation than in sinus rhythm because the atria are not contributing to cardiac output. The ventricular rate in atrial fibrillation might not always translate to a proper heart rate during sinus rhythm for patients with paroxysmal atrial fibrillation. Furthermore, an adequate heart rate for one patient might not be adequate for others; for example, patients with heart failure and preserved left ventricular ejection fractions often need low heart rates to enable diastolic filling.[18]

Previous atrial fibrillation guidelines recommended heart rates in atrial fibrillation that were as low as those recommended for sinus rhythm (ie, resting heart rates of 60–80 beats per min [bpm] and 90–115 bpm during moderate exercise).[29] However, these recommendations were not based on randomised trials investigating rate control strategies. Only one randomised trial[17] has assessed the optimum heart rate in atrial fibrillation. RACE II[17] randomly assigned 614 patients with permanent atrial fibrillation and a resting ventricular rate of more than 80 bpm to lenient rate control (resting heart rate <110 bpm) or strict rate control (target resting heart rate <80 bpm and <110 bpm during moderate exercise). Lenient rate control was non-inferior to strict rate control regarding the development of cardiovascular morbidity and mortality, symptoms, quality of life, and atrial and ventricular remodelling.[17,30,31] Although the trial aimed to assess the effect of faster and slower heart rates in atrial fibrillation, it was not a mechanistic study on heart rate-specific outcomes. Rather, the trial compared two distinct clinical rate control strategies: one of which could be described as maintenance of current ventricular rate-slowing therapy; the other aimed at achieving strict rate control. Heart rate differences between both groups were moderate, but the strategies were completely different. Compared with the strict control strategy, the lenient rate control strategy was easier to achieve, necessitating fewer and lower doses of drugs to control heart rate, and it was more convenient because it required fewer hospital visits.

Since the RACE II trial data became available, the European Society of Cardiology atrial fibrillation guidelines have adopted the lenient rate control strategy as the first-choice approach in asymptomatic patients with atrial fibrillation and patients with minor symptoms of atrial fibrillation as long as the cardiac function remains preserved.[1] In the case of symptom persistence, deterioration of cardiac function, or cardiac resynchronisation therapy necessitating continuous biventricular pacing, a stricter rate control approach is recommended (figures 1, 2). After achievement of the stricter heart rate target, a 24 h Holter monitor is recommended to assess safety (ie, to identify bradycardia or pauses [not in patients with a cardiac resynchronisation therapy device]). However, atrial fibrillation guidelines from the American College of Cardiology, American Heart Association, and Heart Rhythm Society lean towards more stringent rate control and recommend a strict rate control approach as class IIA recommendation (resting heart rate <80 bpm) in symptomatic patients.[16] A lenient rate control strategy (resting heart rate <110 bpm) could be reasonable as long as patients remain asymptomatic and have preserved left ventricular systolic function (class IIB). The 2014 Canadian guidelines recommend a resting heart rate of less than 100 bpm and the assessment of heart rate during exercise in patients with associated symptoms during exercise.[32]

For patients who have atrial fibrillation and heart failure with a preserved or reduced ejection fraction, the optimum target for ventricular rate control is unknown. The 2016 European Society of Cardiology heart failure guidelines recommend a moderately lenient rate control approach in patients with atrial fibrillation and heart failure, aiming at a resting heart rate of 60–100 bpm.[33] The 2009 American College of Cardiology and American Heart Association heart failure guidelines advocate a target ventricular rate of less than 80–90 bpm at rest and less than 110–130 bpm during moderate exercise.[34]

However, despite these guideline recommendations, clinical judgment of the individual patient remains of utmost importance. Rate control in any given patient requires consideration of their activity level and symptoms, the type of atrial fibrillation (paroxysmal, persistent, or permanent), the patient's age, underlying disorders, the presence of heart failure, and previous attempts at medical management; assessment of the relation, in the individual, between ventricular function and heart rates in atrial fibrillation; and reconsideration of ablation of atrial fibrillation itself if not considered before. In some instances, fast heart rates are required to simply maintain exercise tolerance, and sometimes a fast heart rate is required for medical conditions as well, such as with heart failure ("lower is not always better").[35]

Slow heart rates in patients with heart failure and reduced left ventricular ejection fractions have been associated with increased mortality.[35,36] Sometimes symptoms such as fatigue and reduced exercise are caused by a heart rate that is too slow initiating bradycardia and chronotropic incompetence. In that case, either rate-controlling drugs should be reduced, if possible, or a pacemaker should be implanted. However, for persistent symptoms and to prevent tachycardia inducing or mediating cardiomyopathy, the reverse can be the case. No one formula can integrate the best approach to optimum treatment in the individual patient, but one important message is that a lenient approach to rate control is easy, safe, and effective in many patients and should be considered as the initial approach.

Rate control treatments

Pharmacological rate control treatments

A golden rule of rate control is to observe and think before beginning a treatment because the heart rate during atrial fibrillation could indicate specific disorders needing further management. In the absence of drug treatment, the heart rate during atrial fibrillation might signify illnesses such as hyperthyroidism with very fast ventricular rates, or conduction system disease with slow rates. The response to treatment can unmask specific disorders. If rates are uncontrollable, heart failure or hyperthyroidism might be present. Conversely, atrioventricular block and ventricular escape rhythms after initiation of rate control could represent conduction system disease or lead to unavoidable pacemaker implantation, especially in elderly people with the brady–tachy syndrome.

The ventricular rate during atrial fibrillation is determined by the intrinsic conduction characteristics (dromotropic effect) of the atrioventricular node and sympathetic and parasympathetic activity. Three types of drugs are widely used to reduce the ventricular rate during atrial fibrillation: β blockers, non-dihydropyridine calcium-channel antagonists, and cardiac glycosides (digoxin). The choice of rate-controlling drugs, alone or in combination, depends on symptoms, comorbidities, and potential side-effects (figure 4).

β blockers block sympathetic (β1-receptor) activity in the atrioventricular node and thus slow the ventricular rate. Side-effects include cold extremities, broncho-constriction, impotence, and fatigue. In patients with heart failure and reduced left ventricular ejection fractions, β blockers are recommended because large randomised controlled trials showed significant reduction in the rates of morbidity and mortality in patients randomly assigned to β blockers. However, for patients with atrial fibrillation these data are not so robust.[37,38] The reason for this is uncertain but it might be that β blockers in patients with atrial fibrillation slow the ventricular rate too much. Perhaps lower β blocker dosing, accompanied by faster heart rates, would be associated with better outcomes.[35,36]

Non-dihydropyridine calcium-channel antagonists slow atrioventricular node conduction by blocking calcium channels, thereby increasing the refractory period of the atrioventricular node. Constipation and peripheral oedema are side-effects associated

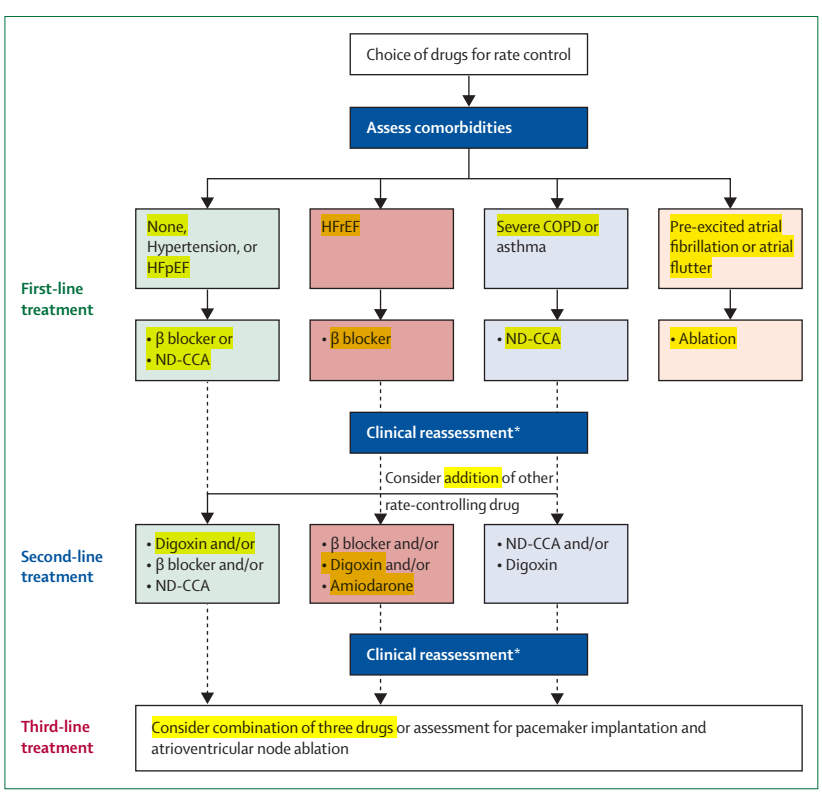

Figure 4: **Flow chart on initiating rate control**
Solid lines represent best options and dashed lines represent second options, which might not be needed. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. COPD=chronic obstructive pulmonary disease. ND-CCA=non-dihydropyridine calcium-channel antagonists. *Clinical reassessment includes exclusion of underlying triggers: ischaemia, heart failure, severe valve disease, hyperthyroidism, anxiety, and others.

with non-dihydropyridine calcium-channel blockers. Calcium-channel blockers are contraindicated in patients with heart failure and reduced left ventricular ejection fractions because of negative inotropic effects and adverse survival characteristics. These drugs might also reduce blood pressure because of their vasodilating effects.

Digoxin, presumably through tonic increase in parasympathetic activity, reduces atrioventricular conductance. Digoxin is not effective in patients with a high sympathetic drive (ie, physically active or critically ill patients). Adverse effects of digoxin include gastrointestinal complaints, bradycardia, and tachycardia, including life-threatening ventricular arrhythmias. Digoxin is cleared by the kidney, has a narrow therapeutic range, and interacts with other drugs (eg, verapamil or specific antibiotics). Therefore, cautious use of low-dose digoxin is suggested in older patients, in patients with renal insufficiency, and patients with concomitant use of drugs that could raise digoxin concentrations. Assessment of the digoxin plasma concentration can help in dose finding.[39]

Data continue to emerge questioning the safety of digoxin in atrial fibrillation but whether the safety issues relate to the drug or the type of patient (ie, presence of comorbidities) treated with digoxin is unclear. Conflicting data on cardiovascular outcomes from patients with atrial fibrillation who used digoxin have been reported, predominantly derived from post-hoc analyses. An early analysis from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial reported that digoxin was independently associated with increased mortality in patients with atrial fibrillation.[40] Later analyses of AFFIRM reported conflicting results of its effect on prognosis.[41,42]

Meta-analyses and retrospective analyses confirmed that digoxin in patients with atrial fibrillation is associated with an increased mortality risk,[43,44] but neutral effects were also reported.[45–49] A meta-analysis[50] showed no increased mortality in patients with atrial fibrillation and heart failure, but did in patients with atrial fibrillation without heart failure. Nevertheless, it is difficult to ascribe adverse outcomes to digoxin alone because patients who take digoxin often have several comorbidities and have not responded to other treatments. Digoxin use has decreased, most importantly because there is no evidence that digoxin is an effective rate-controlling drug during exercise.[51] However digoxin is still frequently instituted in patients with heart failure and reduced left ventricular ejection fractions alone or in combination with a β blocker (although less often than before).[51]

Sotalol and amiodarone also have negative dromotropic effects.[52] Sotalol is a β blocker with additional class III antiarrhythmic effects.[53,54] The additional class III effect of sotalol can prolong the QT interval, thereby causing life-threatening arrhythmias (ie, torsades de pointes). As such, sotalol is not recommended solely for rate control.[55,56] Amiodarone remains restricted to a small subset of patients because of its extensive non-cardiac adverse effects[57,58] (ie, critically ill patients and those with [acute] heart failure in whom β blockers and digoxin are insufficient to reduce the heart rate adequately).[59] Chronic rate control data for amiodarone are very limited.[52] Dronedarone also has negative dromotropic characteristics.[60] However because of its ability to increase the risk of stroke, heart failure, and cardiovascular death in patients with permanent atrial fibrillation, dronedarone is contraindicated in permanent atrial fibrillation.[61]

Which rate-controlling drugs for which patients?

Many studies have compared different drugs to achieve either acute or chronic rate control. However, the quality of these studies is low, especially because of the low number of patients included in the trials and short follow-up.

Acute rate control is recommended in patients with severe haemodynamic distress or in patients who are very symptomatic. However, the optimum heart rate target is not investigated and should be judged on clinical grounds. The target is usually a heart rate of less than 100 bpm, guided by haemodynamic and symptomatic improvement. For patients with heart failure and reduced left ventricular ejection fractions, amiodarone might be a good option for acute treatment because β blockers are often—and calcium channel blockers are always—contraindicated in the acute situation, and digoxin is often ineffective.[59]

For chronic rate control, no strong recommendations for drug choices can be provided. The choice of drug or drugs depends on the presence of heart failure with preserved or reduced left ventricular ejection fractions, comorbidities, and lifestyle (figure 4, table). Two of the more interesting studies compared several drugs in the same patients in a random sequence, assessing heart rates as the primary outcome. One study included 12 patients with permanent atrial fibrillation and used 24 h Holter monitoring and a treadmill exercise test to assess heart rates.[62] Drug regimens included digoxin 0·25 mg, diltiazem 240 mg, atenolol 50 mg, digoxin 0·25 mg and diltiazem 240 mg, and digoxin 0·25 mg and atenolol 50 mg. The most effective treatment, defined as the treatment with the lowest heart rate during 24 h Holter monitoring and exercise, was the combination of atenolol and digoxin.

The RATAF study was a randomised, crossover study comparing four rate-controlling drugs in 60 symptomatic patients with permanent atrial fibrillation without heart failure or reduced left ventricular ejection fractions, and with increased plasma concentrations of N-terminal pro-B-natriuretic peptide. The rate-controlling drugs were metoprolol 100 mg/day, diltiazem 360 mg/day, verapamil 240 mg/day, and carvedilol 25 mg/day.[63–65] Diltiazem seemed to be most effective

	Intravenous administration	Usual oral maintenance dose	Contraindicated
β blockers*			
Metoprolol tartrate	2·5–5 mg intravenous bolus over 2 min; up to four doses	25–100 mg twice a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Metoprolol XL (succinate)	NA	50–400 mg once a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Bisoprolol	NA	1·25–20 mg once a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Atenolol	NA	25–100 mg once a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Esmolol	500 μg/kg intravenous bolus over 1 min, followed by 50–300 μg/kg per min	NA	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Nebivolol	NA	2·5–10 mg once a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Carvedilol	NA	3·125–50 mg twice a day	In case of asthma institute β1 blockers; contraindicated in acute heart failure and history of severe bronchospasm
Non-dihydropyridine calcium channel antagonists			
Verapamil	2·5–10 mg intravenous bolus over 2 min	40 mg twice a day to 480 mg (extended release formulations) once a day	Contraindicated in HFrEF; adapt doses in hepatic and renal impairment
Diltiazem	0·25 mg/kg intravenous bolus over 2 min, then 5–15 mg/h	60 mg three times a day to 360 mg (extended release formulations) once a day	Contraindicated in HFrEF; adapt doses in hepatic and renal impairment
Digitalis glycosides			
Digoxin	0·5 mg intravenous bolus (0·75–1·5 mg over 24 h in divided doses)	0·0625–0·25 mg once a day	Contraindicated in WPW; high plasma levels associated with increased mortality; check renal function before starting and adapt dose in patients with chronic kidney disease
Digitoxin	0·4–0·6 mg	0·05–0·3 mg once a day	Contraindicated in WPW; high plasma levels associated with increased mortality; check renal function before starting and adapt dose in patients with chronic kidney disease
Others			
Amiodarone	300 mg intravenous diluted in 250 mL 5% dextrose over 30–60 min (preferably via central venous cannula), followed by 900–1200 mg intravenous over 24 h diluted in 500–1000 mL via a central venous cannula	200 mg once a day	Long QT syndrome

NA=not applicable. HFrEF=heart failure with reduced ejection fraction. WPW=Wolff-Parkinson-White syndrome. *Some other β blockers are also available but not recommended as specific rate control therapy in atrial fibrillation and are therefore not mentioned (eg, propranolol and labetolol).

Table: **Drugs for rate control in atrial fibrillation**

in reducing the ventricular rate. Arrhythmia-related symptoms were reduced by diltiazem and verapamil, but not by β blockers. Diltiazem and verapamil preserved exercise capacity and reduced levels of NT-pro-B-natriuretic peptide, whereas metoprolol and carvedilol both reduced the exercise capacity and increased plasma levels of NT-pro-B-natriuretic peptide. These data might encourage clinicians to use non-dihydropyridine calcium-channel blockers more often.[66,67]

Although this strategy has never been investigated, in patients with a low burden of self-terminating paroxysmal atrial fibrillation, so-called pill-in-the-pocket rate control could be an option to control ventricular rate at the very moment of a relapse. Such a strategy precludes continuous rate-controlling drug treatment.

Non-pharmacological rate control treatment

Non-pharmacological rate control treatment (eg, atrioventricular node ablation and implantation of a pacemaker) can control the ventricular rate when heart failure develops or progresses, patients remain symptomatic, drugs fail, or drug-related adverse effects necessitate drug discontinuation.[1,16] Ablation of the atrioventricular node with pacemaker insertion should be restricted until, and only if, it is absolutely necessary. Before doing so, catheter ablation of atrial fibrillation always should be considered.

Atrioventricular node ablation is a simple procedure with a low complication rate and low long-term mortality.[68] The procedure usually does not worsen left ventricular function although worsening can occur due to continuous right ventricular pacing, especially if the baseline left ventricular function is not normal.[69] However, atrioventricular node ablation renders patients pacemaker-dependent.

The choice of pacing treatment (right ventricular or biventricular pacing with or without implantable defibrillator) will depend on individual patient charac-

teristics, including left ventricular ejection fraction.[70–72] Biventricular pacing instead of right ventricular pacing should be considered in patients with heart failure and reduced left ventricular ejection fractions.

Appropriate programming of the pacemaker is essential. Rate adjustments are required in the first few weeks after ablation. To prevent life-threatening ventricular arrhythmias, the lower rate should be set at 80–90 bpm immediately after the ablation.[73] Over the ensuing month, the pacing rate may be lowered. Although the optimum settings remain a matter of contention, especially in patients with heart failure and preserved left ventricular ejection fractions, low rates (lower rate of 50–60 bpm) are indicated to allow appropriate diastolic filling. Proper adjustments for paced rate response have not been tested. Atrioventricular node modification has been attempted but has not found its way into clinical practice because it is successful for only a minority of patients in whom it is tried.

Monitoring of rate control

Although no specific recommendations suggest monitoring is necessary for patients in whom a rate control approach is anticipated or instituted, in patients who are symptomatic, assessment of the ventricular heart rate at rest and during exercise is recommended. Heart rate during moderate exercise is particularly worth assessing. An immediate rapid increase in heart rate is often associated with symptoms and might necessitate an increase of rate-controlling drugs.[74] After institution of strict rate control, 24 h Holter monitoring should be considered for safety reasons (eg, assessing the occurrence of pauses; figure 1). The same holds when symptoms develop or persist. In patients who have atrial fibrillation-related symptoms during activity, the adequacy of heart rate control can be assessed during an exercise test or with use of a loop recorder.

Rate control in patients with implantable cardioverter-defibrillators and cardiac resynchronisation therapy devices

Atrial fibrillation can lead to inappropriate shocks in patients with implantable cardioverter-defibrillators.[75] Therefore in these patients, a stricter rate control approach is warranted, or at least drugs to prevent very fast conducted atrial fibrillation. Adequate programming of the implantable cardioverter-defibrillators can further reduce the risks of inappropriate shocks.[76] Programming adjustments could include higher ventricular tachycardia or fibrillation thresholds (detection thresholds >200 bpm) and longer detection durations.[77]

Intercurrent or permanent atrial fibrillation can interfere with the outcome of cardiac resynchronisation therapy in patients with heart failure, reduced left ventricular ejection fractions, and atrial fibrillation.[78,79] The incidence of atrial fibrillation in patients undergoing cardiac resynchronisation therapy implantation is high (up to 30%), thus justifying careful analysis of device diagnostics, 12-lead electrocardiograms, and Holter recordings.[80] The absolute goal in patients having cardiac resynchronisation therapy is to achieve 100% biventricular pacing. If atrial fibrillation is present and interferes with biventricular pacing despite medical management, atrioventricular nodal ablation or atrial fibrillation ablation should be considered. Although not specifically tested in patients with atrial fibrillation receiving cardiac resynchronisation therapy, a small study[81] reported that pulmonary vein isolation is superior to atrioventricular node ablation with biventricular pacing for quality of life and 6 min-walk distance in patients with heart failure, reduced left ventricular ejection fractions, and drug-refractory paroxysmal or persistent atrial fibrillation.

Exercise testing or rate response programming based on histogram data might help determine the effective percentage of biventricular pacing during episodes of atrial fibrillation. If pharmacological rate control proves ineffective, atrioventricular node ablation should be done. Atrioventricular node ablation, as compared with pharmacological rate control, has been associated with a reduction in all-cause mortality, mainly by reducing cardiovascular mortality, and improvements in New York Heart Association class when compared with medical rate control treatment only.[82] As mentioned earlier, atrioventricular node ablation has the disadvantage of pacemaker dependency.[83] The proper rate to pace at rest and with exercise remains unknown.

Rate control in specific patient groups

Atrial flutter

All rate control criteria for atrial fibrillation also apply to atrial flutter. However, adequate rate control is more difficult to achieve in patients with atrial flutter, especially during episodes of exertion when rates increase abruptly, perhaps due to the lack of concealed conduction in the atrioventricular node that occurs with atrial fibrillation. Catheter ablation of atrial flutter is now recommended as the first-line treatment with the best success rate; complications are rare and late recurrences uncommon.[84]

Postoperative atrial fibrillation

Atrial fibrillation is the most common complication after cardiac surgery, occurring in up to 30% of the patients. The peak incidence of postoperative atrial fibrillation occurs between postoperative days 2 and 4. Ventricular rate control is recommended in postoperative atrial fibrillation, for which β blockers are the most effective treatment.[1] Studies assessing the optimum rate have not been done. Generally, the haemodynamic situation and symptoms guide treatment. Intravenous rate-controlling drugs are necessary in haemodynamically unstable patients.

Patients treated with class IC antiarrhythmic drugs

It is recommended that rate-controlling drugs are used concomitantly with class IC antiarrhythmic drugs (flecainide and propafenone) because of the propensity for class IC antiarrhythmic drugs to convert atrial fibrillation to atrial flutter, which in turn might then be conducted rapidly to the ventricles (ie, to avoid the so-called proarrhythmic effect).[1,85]

Wolff-Parkinson-White syndrome

After an episode of atrial fibrillation, catheter ablation of the accessory pathway is recommended as first-choice therapy.[86] When pre-excitation is present, β blockers, non-dihydropyridine calcium-channel antagonists, digoxin, and adenosine are contraindicated.

Patients with the brady–tachy form of sick sinus syndrome

In patients with brady–tachy syndrome (ie, sick sinus syndrome, and paroxysmal atrial fibrillation with high ventricular rates), dual-chamber, rate-modulated pacemaker implantation in combination with rate-controlling drugs might help to prevent symptoms. Little research on heart rate control has been dedicated to these patients. However, high heart rates during atrial fibrillation have been associated with increased hospital admissions and symptoms.[87] Pacemaker diagnostics can help to monitor heart rates during atrial fibrillation in these patients and institute adequate heart rate control.

What is new in rate control?

The response to rate control treatment might be genotype-dependent. The success of specific types of β blockers could depend on the presence of the β1-adrenoceptor (ADRB1) Arg389Gly polymorphism. The underlying mechanism is that the mutation induces loss of function of the β1-receptor, mediated by reduced cyclic-adenosine monophosphate production. Available data show that patients with the homozygous Arg389 genotype were more resistant to pharmacological rate control using different β blockers than patients with Gly389 genotypes.[88,89] However, this finding might not be the case for all β blockers because this polymorphism did not affect the heart rate-lowering effect of bisoprolol and bucindolol.[89,90] As such, data are still sparse but patient-tailored treatment might also become dependent on genotype.

An interesting new rate control strategy is to pace the atrioventricular node. A 2015 study[91] showed the feasibility of high frequency atrioventricular node stimulation to reduce the ventricular rate in patients with atrial fibrillation given cardiac resynchronisation therapy. Atrioventricular node stimulation increased the ventricular intervals by more than 25% in 81% of the patients acutely.[91] Future research is warranted but this treatment approach could become useful in patients with atrial fibrillation given cardiac resynchronisation therapy and in patients with atrial fibrillation given a dual-chamber, rate-modulated pacemaker.

Conclusions

Rate control in atrial fibrillation (ie, the appropriate rate to supply the necessary cardiac output for specific physiological demands and prevent adverse consequences) is a crucial part of atrial fibrillation management. However, serious gaps in knowledge exist making broad recommendations difficult for all clinical circumstances. Rate control is background treatment for all patients with atrial fibrillation, including those receiving treatment with a rhythm control strategy. A lenient approach to rate control is easy, safe, and effective for many patients, and should be considered as the initial approach for patients with few symptoms and who are at low risk for this approach. A stricter rate control approach is adopted when symptoms persist or deterioration of the left ventricular function occurs. Patients with acute onset of atrial fibrillation, brady–tachy syndrome, cardiac resynchronisation therapy devices, or implantable cardioverter defibrillators each require special attention. Atrioventricular node ablation has a role as a treatment of last resort but the optimum target heart rate at rest and with exertion remains uncertain. In patients with atrial fibrillation, catheter ablation should always be considered. Although rate control is one of the first management issues in all patients with atrial fibrillation, and has been studied in detail, many issues remain to be clarified.

Contributors

ICVG searched the scientific literature; designed the review, figures, and table; and wrote the manuscript. MR and HJGMC critically reviewed the manuscript. BO designed the review, searched the scientific literature, and wrote the manuscript.

Declaration of interests

ICVG reports the research grant from Medtronic to University Medical Center Groningen. BO reports speaking and consultant fees from Lundbeck and Daiichi Sankyo, and consulting fees from On-X. MR and HJGMC declare no competing interests.

Acknowledgments

We acknowledge support from the Netherlands Cardiovascular Research Initiative: an initiative supported by the Netherlands Heart Foundation, CVON 2014–9: "Reappraisal of Atrial Fibrillation: interaction between hyperCoagulability, Electrical remodelling, and Vascular destabilization in the progression of AF (RACE V)" (ICVG, MR, HJGMC).

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Atrial fibrillation 3

Rhythm control in atrial fibrillation

Jonathan P Piccini, Laurent Fauchier

Many patients with atrial fibrillation have substantial symptoms despite ventricular rate control and require restoration of sinus rhythm to improve their quality of life. Acute restoration (ie, cardioversion) and maintenance of sinus rhythm in patients with atrial fibrillation are referred to as rhythm control. The decision to pursue rhythm control is based on symptoms, the type of atrial fibrillation (paroxysmal, persistent, or long-standing persistent), patient comorbidities, general health status, and anticoagulation status. Many patients have recurrent atrial fibrillation and require further intervention to maintain long term sinus rhythm. Antiarrhythmic drug therapy is generally recommended as a first-line therapy and drug selection is on the basis of the presence or absence of structural heart disease or heart failure, electrocardiographical variables, renal function, and other comorbidities. In patients who continue to have recurrent atrial fibrillation despite medical therapy, catheter ablation has been shown to substantially reduce recurrent atrial fibrillation, decrease symptoms, and improve quality of life, although recurrence is common despite continued advancement in ablation techniques.

Lancet 2016; 388: 829–40

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This is the third in a Series of three papers about atrial fibrillation

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Reasons to choose a rhythm control strategy

Atrial fibrillation affects 33 million individuals worldwide,[1] and increases risk of stroke, heart failure, and death, and also impairs quality of life. Accordingly, the goals of care in atrial fibrillation include the prevention of stroke, control of the ventricular rate, and minimisation of symptoms to improve quality of life.[2–4] Although some patients' symptoms are relieved with ventricular rate control alone, many require restoration and maintenance of sinus rhythm—referred to as rhythm control. The decision to pursue rhythm control is an individualised one and is based on symptoms, the type of atrial fibrillation (paroxysmal, persistent, or long-standing persistent), patient comorbidities, general health status, and anticoagulation status. The burden and severity of atrial fibrillation-related symptoms should drive the decision to choose a strategy that aims to restore or maintain sinus rhythm rather than accept continued atrial fibrillation with rate control alone. Finally, not only are present rhythm and symptoms considered, but the age of the patient is also important. Unopposed atrial fibrillation over many decades might have adverse health consequences in younger patients, including in those who are aysmptomatic.

Acute rhythm management for atrial fibrillation

The acute evaluation and management of patients presenting with atrial fibrillation is mainly focused on the improvement of cardiac haemodynamics and the provision of protection against thromboembolic events, such as stroke and systemic embolism. Both inappropriately tachycardic ventricular rates and irregularity of the cardiac rhythm can lead to symptoms or haemodynamic impairment, particularly in patients with abnormal ventricular filling (eg, diastolic function). The severity of atrial fibrillation symptoms should be the key factor in the decision to do a cardioversion and restore sinus rhythm. Patients with haemodynamic compromise require urgent cardioversion. Patients with a rapid ventricular rate require acute rate control and potentially acute rhythm management.

Prevention of thromboembolism

Stroke prevention treatment in the form of oral anticoagulation is recommended for electrical and pharmacological cardioversion of atrial fibrillation lasting longer than 48 h in duration because restoration of sinus rhythm is associated with an increased risk of stroke or systemic embolism. However, even shorter periods of atrial fibrillation (>12 h) might be associated with a measurable and significant risk of stroke.[5] Oral anticoagulation with vitamin K antagonist or a non-vitamin K antagonist anticoagulant should be continued for a minimum of 4 weeks after cardioversion because of the risk of thromboembolism in the setting of left atrial appendage contractile dysfunction (ie, atrial stunning) after cardioversion. On the basis of guideline recommendations, patients with risk factors for stroke (CHA_2DS_2-VASc score ≥1) should continue lifelong oral anticoagulation regardless of the present rhythm status or maintenance of sinus rhythm. Unless adequate anticoagulation has been documented for 3 weeks or

Search strategy and selection criteria

We searched MEDLINE, PubMed, and major conference proceedings with the search terms "atrial fibrillation", "rhythm control", "cardioversion", "antiarrhythmic", and "catheter ablation". We also searched proccedings from the American Heart Association Scientific Sessions, American College of Cardiology, European Society of Cardiology, Heart Rhythm Society, and Cardiostim Scientific Sessions. Finally, guideline documents about management of atrial fibrillation across major cardiovascular societies were also searched and reviewed from January, 2006 to June, 2016.

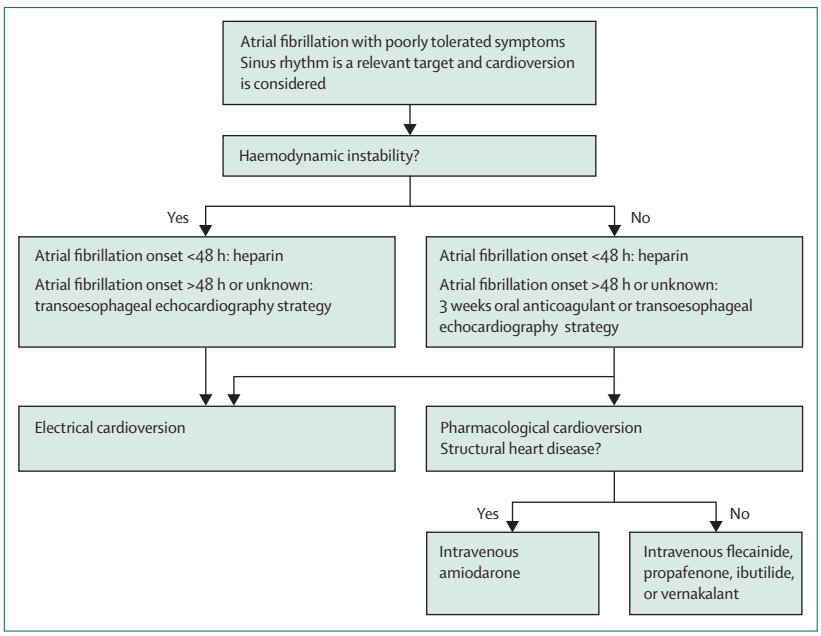

Figure 1: **Management algorithm for acute rhythm control in atrial fibrillation**

atrial fibrillation is definitively known to be less than 48 h in duration, a transoesophageal echocardiogram should be done to ensure there are no atrial or appendage thrombi before attempting to cardiovert (figure 1).[2,4,6,7]

Direct current cardioversion

Direct current cardioversion is a very effective means of terminating atrial fibrillation and restoring sinus rhythm. Pretreatment before direct current cardioversion treatment with antiarrhythmic medications such as flecainide, propafenone, sotalol, or amiodarone, increases the probability of restoring sinus rhythm.[8,9] The use of biphasic rather than monophasic external defibrillators allows the use of lower energy (lower joules) and greater cardioversion efficacy. Results from clinical trials have shown that anteroposterior electrode placement is more effective than anterolateral placement.[10] When initial shocks are unsuccessful and do not terminate atrial fibrillation, the electrodes should be repositioned and cardioversion repeated. A postcardioversion electrocardiogram and adequate monitoring are required after the procedure before the patient can leave the hospital safely.

The risk of stroke is highest in the first 72 h after cardioversion and most events occur within 10 days of the procedure.[4] Minor skin burns can occur. In patients with sinus node dysfunction, transient or prolonged sinus arrest can occur. In particular, the presence of substantial bradycardia before cardioversion or high doses of atrioventricular nodal blockers should alert the clinician to an increased risk of postconversion pauses or asystole. Cardioversion-related arrhythmias, such as ventricular tachycardia or fibrillation, are very rare with synchronised shocks but can arise in the presence of hypokalaemia, hypomagnesaemia, digoxin toxicity, or improper synchronisation. The risks related to sedation or anaesthesia can include transient hypoxia, hypoventilation, or hypotension. Patients with implanted pacemakers and defibrillators should have their device interrogated after direct current cardioversion to ensure normal device function.

Pharmacological cardioversion

Although many atrial fibrillation episodes terminate spontaneously within hours or days, other episodes can persist for longer. When atrial fibrillation symptoms persist despite adequate rate control or when rhythm control is desired, restoration of sinus rhythm with cardioversion is advised. Unlike direct current cardioversion, pharmacological cardioversion of atrial fibrillation with bolus administration of an antiarrhythmic drug obviates the need for conscious sedation. However, the success rate for pharmacological cardioversion is lower when compared with direct current cardioversion. Success rates are highest when the atrial fibrillation is relatively short lived (generally <48 h duration). The anticipated conversion rate with approved drugs is 50% or more within 15–120 min. Most patients undergoing pharmacological cardioversion require continuous clinical and ECG monitoring during drug administration and afterwards, particularly because of the risk of proarrhythmic events such as ventricular arrhythmia, sinus node arrest, or atrioventricular block.[2–4]

Intravenous flecainide (2 mg/kg over 10 min) is effective (67–92% at 6 h) in restoring sinus rhythm, particularly in patients with atrial fibrillation lasting less than 24 h.[2] Most patients convert to sinus rhythm within the first hour after dosing. In the case of intravenous propafenone (2 mg/kg over 10–20 min), the expected conversion rate is 53–98% and the time to conversion varies from 30 min to 2 h.[11] Class Ic antiarrhythmics, such as flecainide and propafenone, should be avoided in patients with underlying heart disease and abnormal ventricular function or ischaemia. Owing to its weak β blocking effect, propafenone should be avoided in patients with severe obstructive lung disease. From a comparative standpoint, one study[12] has shown higher conversion rates to sinus rhythm of flecainide compared with propafenone (90% *vs* 72%). Flecainide and propafenone have limited efficacy for conversion of persistent atrial fibrillation and atrial flutter.

Ibutilide is a class III antiarrhythmic drug used for pharmacological cardioversion and is usually administered in one or two infusions of 1 mg over 10 min, with 10 min between doses. Most patients convert within 30 min, but overall conversion rates are 50% across several randomised trials.[13] Ibutilide prolongs the QT interval and carries a small but notable,

	Mechanism	Electrocardiographic effects and monitoring	Elimination	Dosing	Drug interactions	Contraindications
Class Ic*						
Flecainide	Blocks fast inward sodium channels	Prolongs PR and QRS; ECG 3 days after initiation and dose escalation	$T_{1/2}$ 13–19 h; hepatic 2/3; renal 1/3	50–150 mg twice daily	Increases digoxin levels	Ischaemic or structural heart disease; sinus node dysfunction, 2nd or 3rd degree atrioventricular block or bundle branch disease without a pacemaker
Propafenone	Blocks fast inward sodium channels; mild β blocker and L-type channel blockade	Prolongs PR and QRS; ECG 3 days after initiation and dose escalation	Variable; $T_{1/2}$ (2–10 h and up to 32 h in slow metabolisers); hepatic	150–300 mg three times daily	Increases digoxin and warfarin levels	Ischaemic or structural heart disease; asthma; sinus node dysfunction, 2nd or 3rd degree atrioventricular block or bundle branch disease without a pacemaker; potent CYP2D6 inhibitor or inducers
Class III†						
Sotalol	Racemic mixture: d-sotalol is a β blocker and l-sotalol inhibits I_{Ks}	Prolongs QT; ECG monitoring during initiation and QTc assessment every 3 months; renal function every 3 months	$T_{1/2}$ 12 h; renal	80–160 mg twice daily	Avoid concomitant QT prolonging drugs; antacids containing aluminium oxide and magnesium hydroxide decrease absorption	Asthma; creatinine clearance <40 mL/min; left ventricular dysfunction; QTc >450 ms; sinus bradycardia; <50 bpm, second or third degree atrioventricular block without a pacemaker
Dofetilide	Inhibits rapid component of delayed rectifier K current	Prolongs QT; ECG monitoring during initiation and QTc assessment every 3 months; renal function every 3 months	$T_{1/2}$ 10 h; 50% renal	125–500 μg every 12 h	Contraindicated with verapamil, cimetidine, trimethoprim, megestrol; prochloroperazine hydrochlorothiazide, ketoconazole; avoid QT prolonging drugs	Creatinine clearance <40 mL/min; QTc >440 ms
Multichannel blockers‡						
Amiodarone	Inhibits sodium, potassium, and long-lasting type calcium channels, and β-adrenergic receptors	Prolongs PR, QRS, and QT intervals; liver and thyroid function tests at baseline and every 6 months; pulmonary function testing with diffusing capacity of carbon dioxide at baseline and with symptoms; annual ophthalmological exam	$T_{1/2}$ 25–110 days; hepatic	Load then maintenance dose of 100–400 mg daily	Impairs warfarin metabolism, increases digoxin levels, simvastatin dose should not exceed 20 mg per day	Avoid in those with advanced lung disease; severe hepatic impairment; thyroid dysfunction
Dronedarone	Inhibits sodium, potassium, and long-lasting type calcium channels and β-adrenergic receptors	Prolongs PR, QRS, and QT intervals; renal and liver function testing at baseline and every 6 months	$T_{1/2}$ 13–19 h; hepatic	400 mg twice daily	Increases digoxin levels, contraindicated with potent CYP3A4 inducers or inhibitors	Permanent atrial fibrillation; recent decompensated or advanced heart failure (NYHA class III–IV); QTc >500 ms; severe hepatic impairment

$T_{1/2}$=half-life. bpm=beats per min. ECG=electrocardiogram. I_{Ks}=the rapid component of the delayed rectifier potassium current. NYHA=New York Heart Association. *Impair impulse formation and prolong action potential duration through inhibition of fast sodium channels. †Prolong action potential and refractoriness through inhibition of I_{Ks}. ‡Antiarrhythmic drugs with substantial blockade of multiple ion channels.

Table 1: **Antiarrhythmic drugs used to maintain sinus rhythm in patients with atrial fibrillation**

important risk of polymorphic ventricular tachycardia. Thus, ibutilide is less frequently used and not widely available. When ibutilide is used, patients should be monitored for a minimum of 6 h or until the QTc returns to baseline.[14]

Vernakalant targets multiple ion channels, including the atrial selective acetylcholine-activated potassium current ($I_{K,Ach}$) and was approved for pharmacological cardioversion by the European Medicines Agency in 2010. In clinical trials, vernakalant converted 51% of patients with short duration atrial fibrillation (3 h to 7 days) with a median time to conversion of 10 min.[15,16] The initial dose is 3 mg/kg dose over 10 min and a second infusion of 2 mg/kg can be given if atrial fibrillation persists after 10 min. Patients should be monitored for 2 h after infusion to monitor for proarrhythmia and other potential complications.

Amiodarone is used infrequently compared with other antiarrhythmic medications for the purposes of acute pharmacological cardioversion. The approximate conversion rate at 24 h in patients treated with placebo was 40–60%, with an increase to 80–90% after amiodarone treatment.[17] In contrast to the previously mentioned medications, digoxin, verapamil, sotalol, and β blockers are not effective for acute cardioversion of atrial fibrillation.

Pill-in-the-pocket approach

An underused but effective and convenient treatment for select ambulatory patients with atrial fibrillation is, as needed, on-demand oral pharmacological cardioversion (ie, so-called pill-in-the-pocket treatment). This therapeutic approach might be ideal in highly symptomatic patients with infrequent (eg, between once per month and once

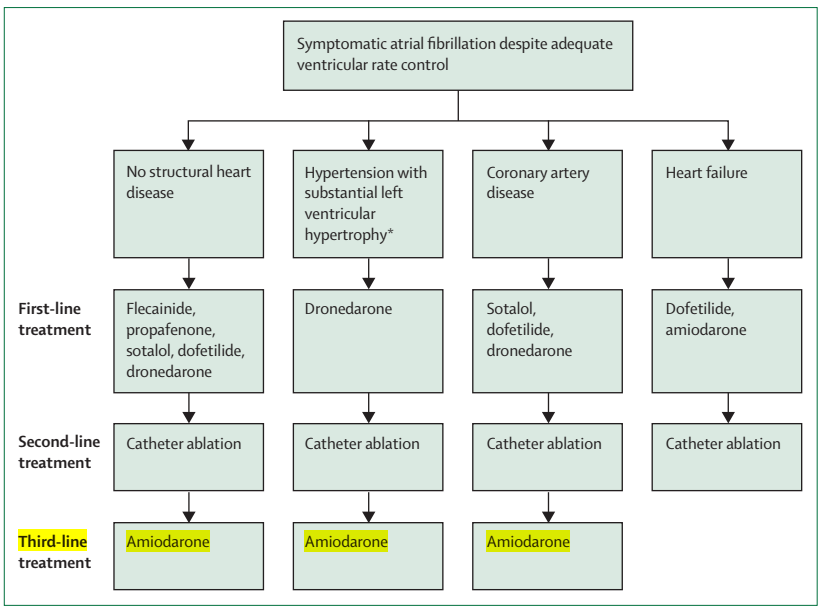

Figure 2: **Antiarrhythmic drug selection for the maintenance of sinus rhythm in patients with atrial fibrillation**
*Substantial left ventricular hypertrophy is defined as a wall thickness of more than 1·4 cm.

per year) recurrences of atrial fibrillation who do not have any structural heart disease or other contraindications to class Ic treatment. Before outpatient treatment can be started, the efficacy and safety of oral treatment should be shown in the hospital. Patients should be instructed to take flecainide (200–300 mg) or propafenone (450–600 mg) when symptoms of atrial fibrillation occur. Both drugs have similar efficacy. On rare occasions, conversion of atrial fibrillation to atrial flutter with one to one atrioventricular conduction can occur and cause syncope. In one clinical trial,[18] oral propafenone or flecainide was administered safely out of hospital with 94% effectiveness. Only one in 569 episodes resulted in atrial flutter with rapid conduction.[18]

Pharmacological drugs

Antiarrhythmic drugs to maintain sinus rhythm

When atrial fibrillation recurs and impairs quality of life, rhythm control is needed to restore and maintain sinus rhythm. There is no evidence that antiarrhythmic drug treatment improves survival and neither rate nor rhythm control strategies have been shown to be superior to one another. Thus, the focus of rhythm control with antiarrhythmic treatment is on symptom control and improvement of quality of life. Oral drug treatment is considered first-line therapy for long-term outpatient rhythm control. Antiarrhythmic drug treatments maintain sinus rhythm by stabilising cardiac myocyte membranes or by prolonging action potential durations either through impairing impulse formation (class I) or prolongation of refractoriness (class III). These medications have been typically referred to by their mechanism of action (Vaughan-Williams classification); however, the reality is that most antiarrhythmic drugs act through several mechanisms (table 1). The selection of an antiarrhythmic drug for a patient is principally guided by drug safety, because antiarrhythmic drugs often pose substantial risks of toxicity in some patient groups (figure 2).

Patients without structural heart disease have the most options for antiarrhythmic drug therapy. This includes patients with hypertension but no evidence of substantial left ventricular hypertrophy (defined as a wall thickness of ≤1·4 cm).[19] In these patients, class Ic treatment with flecainide or propafenone is often preferred because of their good efficacy and the patients' ability to start the drug on an outpatient basis.[4,20,21] Patients treated with sustained release propafenone 325 mg twice daily, have a 41% risk of recurrence at 1 year compared with 68% in those treated with placebo.[21] Class Ic antiarrhythmic drugs are not recommended in patients with structural heart disease because of concerns for ventricular proarrhythmia and increased mortality.[22] Thus, patients should undergo a stress test to exclude coronary ischaemia before starting flecainide or propafenone treatment. Finally, because of the risk of 1:1 conduction of atrial flutter, optimal treatment should include concomitant β-blocker or non-dihydropyridine calcium channel blocker treatment.

Class III antiarrhythmic drugs, including sotalol and dofetilide (available in the USA), prevent atrial fibrillation by prolonging refractoriness, and as a result, prolong the QT interval. Patients started on these medications should not be on any other QT prolonging drugs. Although there is some debate, most experts agree that class III drugs should be started on an inpatient basis to monitor the QT interval and any potential arrhythmia. These drugs are renally cleared and should not be used in patients with a creatinine clearance of less than 40 mL/min. Class III antiarrhythmic drugs are reverse-use dependent, which means that their channel blockade and electrophysiological effects are amplified in those with slow heart rates. Thus, the risk of proarrhythmia can be accentuated when patients stop atrial fibrillation and restore sinus rhythm with a much slower ventricular rate, particularly at heart rates less than 50 beats per min. Risk factors for ventricular proarrhythmia and torsades in patients treated with class III antiarrhythmic drugs include bradycardia, female sex, renal impairment, and left ventricular hypertrophy.[23]

Dronedarone is the most recent oral antiarrhythmic medication to be approved for the treatment of atrial fibrillation that has been shown to decrease the risk of cardiovascular admissions to hospitals in patients with non-permanent atrial fibrillation.[24,25] The drug is a benzofuran derivative that has less toxicity and less efficacy than the more potent amiodarone.[26] Dronedarone can be started as an outpatient but it should be avoided in

patients with permanent atrial fibrillation or recent or advanced symptomatic heart failure because of concerns for increased mortality.[27,28]

In patients with structural heart disease, including left ventricular dysfunction or symptomatic heart failure, antiarrhythmic drug treatment selection is challenging, particularly because of the small number of medications without substantial safety concerns in this population. Although dofetilide is a guideline recommended therapy for patients with atrial fibrillation and heart failure,[4] in most parts of the world, the only drug available is amiodarone. Although amiodarone is highly effective,[20,26] it is associated with important safety concerns, including thyroid toxicity, neurological toxicity, hepatic, and pulmonary toxicity. Many of amiodarone's adverse effects are dose dependent, so every attempt should be made to use as low a dose as possible. For many patients with atrial fibrillation, therapeutic success can be achieved with 100 mg daily. It is possible that the best rhythm control strategy in patients with heart failure might be to avoid membrane active antiarrhythmic drugs altogether. In the AATAC randomised trial,[29] patients with heart failure and reduced ejection fraction showed better maintenance of sinus rhythm and lower mortality when treated with catheter ablation than those treated with amiodarone.

Development of newer more effective membrane active antiarrhythmic medications targeting ion channels is challenging because of the risks of proarrhythmia.[30] As a result, there are increased efforts to identify drug targets that can reverse or slow the atrial remodelling that promotes atrial fibrillation.[31,32] Another important opportunity to improve pharmacological rhythm control is pharmacogenetic guidance.[33] The GENETIC-AF trial (NCT01970501) is evaluating whether or not genotype directed β-blocker therapy with bucindolol can provide effective rhythm control without conventional membrane active antiarrhythmic medication.

Upstream therapy

Although attempts to prevent recurrent atrial fibrillation and maintain sinus rhythm often focus on antiarrhythmic drug therapy or catheter ablation, these interventions do not target the underlying causative processes that lead to left atrial fibrosis and enlargement, which cause atrial fibrillation. There are a number of modifiable risk factors for the development of atrial fibrillation, including hypertension, obstructive sleep apnoea, increased body-mass index, coronary artery disease, and hyperglycaemia.[2] For example, sleep apnoea is associated with more extensive atrial fibrosis and doubled rates of recurrence after catheter ablation.[34,35] However, reductions in body-mass index,[36] blood pressure, and improved glycaemic control lead to less frequent atrial fibrillation.[37] Treatment of non-atrial fibrillation illness and comorbidity is often suboptimal and can also lead to progression of atrial fibrillation.[38] So-called upstream pharmacotherapies are prescribed to reverse or arrest the maladaptive pathophysiological processes that lead to atrial fibrosis and enlargement. Unfortunately, results with renin–angiotensin–aldosterone system inhibition have been mixed.[2,39] Although the anti-inflammatory properties of statin therapy might[40] or might not[41] be efficacious for the prevention of postoperative atrial fibrillation, evidence is insufficient for their use in the prevention of atrial fibrillation.[2] Based on the present evidence, lifestyle modification seems to have a large impact on the risk of atrial fibrillation whereas upstream drug therapy has not been particularly effective.[37]

Catheter ablation to maintain sinus rhythm

Indications and patient selection

After the discovery of ectopic impulses that initiate atrial fibrillation,[42,43] catheter ablation was developed to isolate and eliminate ectopic triggers of atrial fibrillation or modify the susceptible atrial substrate. There have been many improvements in the safety and efficiency of catheter ablation for atrial fibrillation management in the last decade.[44] In terms of maintenance of sinus rhythm, catheter ablation is more effective than antiarrhythmic drug therapy in selected patients with medically refractory atrial fibrillation.[45,46] Catheter ablation is particularly effective in younger patients (<65 years) with paroxysmal atrial fibrillation, without substantial atrial enlargement and when the procedure is done in experienced centres. In these settings, multiple clinical trials have reported a reduced number of arrhythmia episodes and fewer symptoms related to atrial fibrillation.[44,47] However, at present, there is no firm evidence that catheter ablation of atrial fibrillation significantly reduces the risk of mortality, stroke, or heart failure. Ongoing large randomised clinical trials, such as CABANA (Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; NCT00911508) and EAST (Early Therapy of Atrial Fibrillation for Stroke Prevention Trial; NCT01288352) will provide new insights and establish whether catheter ablation of atrial fibrillation provides significant reduction in stroke and death when compared with drug therapy for rate or rhythm control. Moreover, these trials will help to establish whether early rhythm control therapy with contemporary strategies can lower the incidence of stroke, cardiovascular death, or heart failure, compared with standard management.[48] The highly awaited results of these studies will help to establish whether catheter ablation provides benefit beyond the reduction of symptoms, which is currently the main purpose and indication for atrial fibrillation ablation.

When a rhythm control strategy is chosen, atrial fibrillation ablation is useful to treat symptomatic paroxysmal atrial fibrillation that is refractory to at least one class I or class III antiarrhythmic drug.[2,4,44–46,49] In some cases, atrial fibrillation ablation might be used as a first-line rhythm control strategy before the use of

	Number of patients	Atrial fibrillation pattern	Age (years)	Ablation as a first-line therapy	Ablation method	Outcome: sinus rhythm at 1 year		
						Ablation	AAD	p value
Krittayaphong et al (2003)[54]	30	Paroxysmal, persistent	55 (45–65; ablation); 47 (32–62; AAD)	No	Radiofrequency, PVI with LA lines; with CTI ablation and RA lines	79%	40%	0·02
Wazni et al (RAAFT study; 2005)[55]	70	Mainly paroxysmal	53 (45–61; ablation); 54 (46–62; AAD)	Yes	Radiofrequency, PVI	87%	37%	<0·001
Stabile et al (CACAF study; 2006)[52]	245	Paroxysmal, persistent	62 (53–71; ablation); 62 (52–72; AAD)	No	Radiofrequency, PVI with LA lines; with or without CTI ablation	56%	9%	<0·001
Oral et al (2006)[56]	245	Persistent	57 (48–66)	No	Radiofrequency, CPVA	70%	4%	<0·001
Pappone et al (APAF study; 2006)[57]	198	Paroxysmal	55 (45–65; ablation); 57 (47–67; AAD)	No	Radiofrequency, CPVA with CTI ablation	86%	22%	<0·001
Jais et al (A4 study; 2008)[58]	112	Paroxysmal	51 (40–62)	No	Radiofrequency, PVI with or without LA lines; with or without CTI ablation	89%	23%	<0·001
Forleo et al (2008)[59]	70	Paroxysmal, persistent	63 (54–72; ablation); 65 (59–71; AAD)	No	Radiofrequency, PVI with or without LA lines; with or without CTI ablation	80%	43%	0·001
Wilber et al (Thermocool study; 2010)[60]	167	Paroxysmal	56 (ablation); 56 (AAD)	No	Radiofrequency, PVI with or without LA lines with or without CFAEs; with or without CTI ablation with or without RA lines	66%	16%	<0·001
Cosedis Nielsen et al (MANTRA-PAF study; 2012)[21,51]	294	Paroxysmal	56 (ablation); 54 (AAD)	Yes	Radiofrequency, circumferential PVI with voltage abatement	85%	71%	0·01
Packer et al (STOP-AF study; 2013)[61]	245	Paroxysmal	57 (ablation); 56 (AAD)	No	Cryoablation, PVI; with or without LA lines	69·9%	7·3%	<0·001
Morillo et al (RAAFT2 study; 2014)[50]	127	Mainly paroxysmal	56 (ablation); 54 (AAD)	Yes	Radiofrequency, circumferential PVI with electrical isolation	45%	28%	0·02
Mont et al (SARA study; 2014)[53]	146	Persistent	55 (ablation); 55 (AAD)	No	Radiofrequency, PVI with or without LA lines with or without CFAEs	70%	44%	0·002
Di Biase et al (AATAC study; 2016)[29]	203	Persistent with heart failure, LVEF <40%, ICD	62 (ablation); 60 (AAD)	No	Radiofrequency, PVI with or without LA posterior wall isolation with or without LA lines with or without CFAEs with or without SVC isolation	70%	34%	<0·001

Data are median (range). AAD=antiarrhythmic drugs. PVI=pulmonary vein isolation. LA=left atrial. CTI=cavotricuspid isthmus. RA=right atrial. RAAFT=Radiofrequency Ablation Atrial Fibrillation Trial. CACAF=Catheter Ablation for the Cure of Atrial Fibrillation study. CPVA=circumferential pulmonary vein ablation. APAF=Ablation for Paroxysmal Atrial Fibrillation study. A4=atrial fibrillation ablation versus antiarrhythmic drugs. CFAE=complex fractionated atrial electrogram. MANTRA-PAF=Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation. STOP-AF=Sustained Treatment Of Paroxysmal Atrial Fibrillation. SARA=Study of Ablation Versus Antiarrhythmic Drugs in Persistent Atrial Fibrillation. AATAC=Ablation *vs* Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure. LVEF=left ventricular ejection fraction. ICD=International Classification of Diseases. SVC=superior vena cava.

***Table 2*: Key results from randomised clinical trials of AF ablation compared with antiarrhythmic drugs[2]**

antiarrhythmic drugs after a proper evaluation of the risk and benefits of antiarrhythmic and ablation therapy. This treatment strategy is usually reserved for those patients who express reluctance to long-term antiarrhythmic drug therapy because of the risks of proarrhythmia and other adverse effects.[50,51] In patients with persistent atrial fibrillation with substantial symptoms, atrial fibrillation ablation might be useful when atrial fibrillation is refractory to antiarrhythmic drugs or when these drugs are not well tolerated.[4,9,52,53] In patients with so-called long-standing atrial fibrillation (persistent atrial fibrillation with >12 month duration) the effectiveness of atrial fibrillation ablation is less well established with a substantial risk of recurrent atrial fibrillation.

The decision to pursue atrial fibrillation ablation depends on several factors, including the type or pattern of atrial fibrillation, left atrial size, the severity of symptoms, the presence of associated cardiovascular disease, the presence or absence of systolic dysfunction, the patient's previous history of treatment, the estimated risk of complications, and patient preference.[44] It is noteworthy that most patients assessed in clinical trials of atrial fibrillation ablation were young and healthy with paroxysmal atrial fibrillation, in which antiarrhythmic drugs were previously unable to maintain sinus rhythm (table 2). The effectiveness of atrial fibrillation ablation in the longer term across broader patient populations encountered in clinical practice is an active area of investigation, particularly in elderly patients (>75 years) with long-standing persistent atrial fibrillation and underlying structural heart disease.[4,44] However, early studies in older individuals and randomised studies in patients with heart failure have been promising.

Endpoints and techniques for atrial fibrillation ablation

The recognition that atrial fibrillation might be initiated by premature beats arising from the pulmonary veins promoted the development of interventional procedures designed to prevent atrial fibrillation recurrence by eliminating these arrhythmogenic triggers at their sites of origin.[42] Strategies targeting the pulmonary veins act as the therapeutic foundation for most patients treated

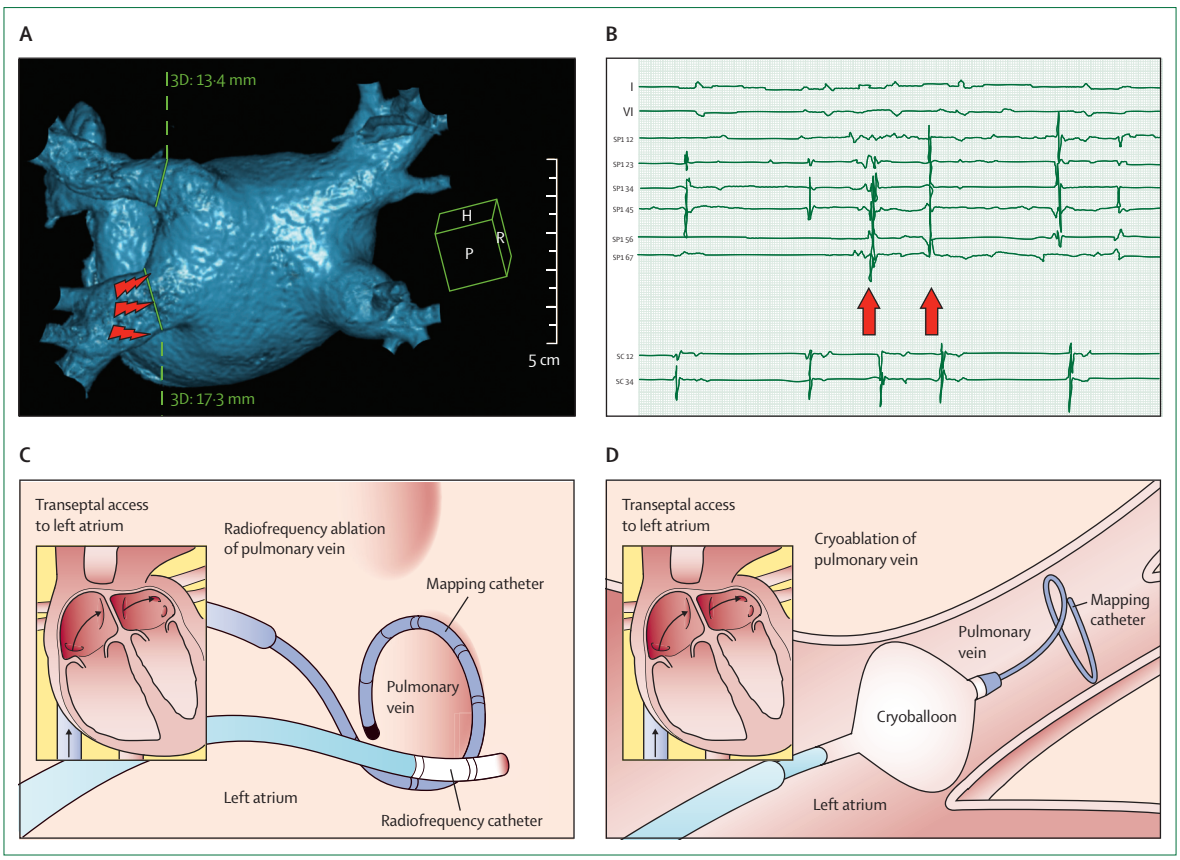

Figure 3: **Methods of ablation for pulmonary veins triggering atrial fibrillation**
(A) A 3D CT scan with a posterior view of left atrium and the four pulmonary veins. Firing initiating atrial fibrillation might come from pulmonary veins (red arrows on left inferior pulmonary vein). (B) An electrogram recorded by a multipolar catheter inserted in the left inferior pulmonary vein and shows depolarisation when premature atrial beats initiate at this site (red arrows). (C) The traditional approach of a radiofrequency catheter ablation system, delivering a series of point-by-point lesions to the antra of pulmonary veins using heat-energy with assistance from a 3D navigational system. (D) The more recent approach with a cryoballoon system and a single-shot approach in which the balloon delivers freezing temperatures at the same site. Adapted from Kuck et al.[63]

with atrial fibrillation ablation, in which electrical isolation and dissociation of the pulmonary veins from the left atrium is the goal.[44] In the event that a non-pulmonary vein trigger is observed, additional focal ablation or isolation can be considered at this site. Common non-pulmonary vein triggers include, but are not limited to, the posterior left atrial wall, superior vena cava, and the interatrial septum. More extensive ablation might be proposed in patients with non-paroxysmal atrial fibrillation. Substrate modification, which targets the atrial tissue that sustains (rather than triggers) atrial fibrillation, often involves the creation of linear lesions on the atrial roof, posterior wall, mitral isthmus, or targeting of areas of complex fractionated electrograms or rotors.[44] Although substrate ablation is often associated with improved efficacy, it is also associated with higher risks of atrial proarrhythmia, such as macrorentrant left atrial flutters. Despite the rationale for more extensive substrate modification, well-conducted clinical trials have not shown superiority of more extensive ablation.[62] Thus, the role of substrate modification remains controversial and much debated.

The most common energy source used in studies assessing catheter ablation for treatment of atrial fibrillation has been radiofrequency energy. More recently, balloon catheters that deliver cryoablation have been developed, allowing relatively easy pulmonary vein isolation compared with the more labour-intensive method of point-by-point ablation with radiofrequency (figure 3).[61,63] Although use of cryoballoon ablation is increasing in frequency, use of radiofrequency ablation remains the most common method worldwide. Other methods using different energy sources have been developed and are in various stages of development or clinical use, or both.

Recurrence of atrial fibrillation after catheter ablation

Recurrence of atrial fibrillation is not uncommon in the first 3 months after atrial fibrillation ablation but does not preclude long-term benefit. Accordingly, early recurrence is often best managed with medical therapy and cardioversion rather than early redo procedures or more aggressive ablation in this early phase.[4,44] Recurrence of atrial fibrillation after the third month

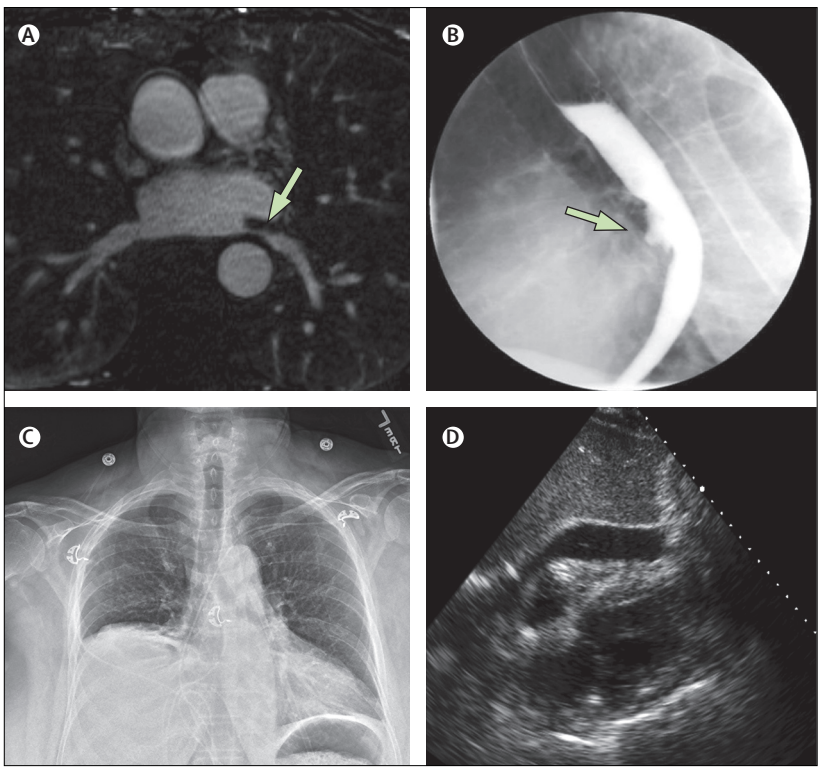

Figure 4: **Complications of atrial fibrillation ablation**
(A) Stenosis of the right upper pulmonary vein as shown by CT of the left atrium. (B) Barium swallow showing oesophageal ulceration after catheter ablation.[76] (C) Right hemidiaphragm elevation after right phrenic nerve paralysis sustained during radiofrequency ablation. (D) Echocardiography of a haemodynamically significant pericardial effusion with evidence of right ventricular compression and tamponade.

can indicate recovery of pulmonary vein conduction, and this can be an appropriate indication to repeat ablation or continue or reinitiate antiarrhythmic drugs if symptoms remain poorly tolerated.[64] Another important factor influencing recurrence rates after ablation is operator experience. Available data suggest that higher operator procedure volumes are associated with lower rates of atrial fibrillation recurrence and adverse events.[65,66] Although early data with these modalities have been promising, definitive comparative randomised trials are needed.

Long-term outcomes after atrial fibrillation ablation are suboptimal. 5 years after the procedure, only 25–30% of patients remain free from atrial fibrillation after a single ablation procedure.[67,68] Several developments in ablation technology offer promise to improve long-term outcomes, including contact-force sensing, alternative ablation modalities, and mapping and ablation of rotors.[69,70]

Anticoagulation therapy periablation

Because of the risks of periprocedural thromboembolism during ablation in the left atrium, patients undergoing catheter ablation of atrial fibrillation require preprocedural, intra-procedural, and post-procedural anticoagulation. Heparin is used during the procedure and is ideally administered before transeptal catheterisation to minimise thromboembolic risk.[71] Preoperative warfarin is continued uninterrupted throughout the procedure to minimise bleeding and thromboembolic risk.[72] Non-vitamin K antagonists might be interrupted shortly before the procedure and resumed 4–6 h afterwards, although uninterrupted non-vitamin K antagonist anticoagulants might be non-inferior to warfarin.[73] It is important to note that catheter ablation should not be done in an attempt to liberate patients from long-term anticoagulation.[4] Oral anticoagulation should be continued for a minimum of 2–3 months after ablation and thereafter should be on the basis of the patient's underlying risk for stroke (ie, CHA_2DS_2-VASc score ≥1 in men and ≥2 in women) rather than the rhythm status of the patient.[44,74] Patients at high risk for stroke who discontinue anticoagulation after catheter ablation of atrial fibrillation do have a higher risk of thromboembolic stroke than those who continue anticoagulation.[75]

Complications after atrial fibrillation catheter ablation

Although catheter ablation is a safe and effective rhythm control therapy, complications can occur (figure 4). Overall, the proportion of major complications with atrial fibrillation ablation is 4–5% and the risk of all-cause death is 1–2 in 1000.[77] Most complications present during the intraoperative or immediate postoperative period. These complications include access site-related bleeding or vascular complications, pericardial effusion, and tamponade (1–3%), transient ischaemic attack or stroke (1%), or pulmonary congestion due to volume overload.[44,78,79] Due to the proximity of the phrenic nerve to the right-sided pulmonary veins, catheter ablation can cause phrenic nerve paralysis, which is usually temporary but can persist for several months or longer. Phrenic nerve paralysis is more common with cryoballoon ablation (3%) than with radiofrequency ablation (<0·5%).[63]

Other complications can present after the ablation, including delayed pericardial tamponade. The most feared and severe complication of catheter ablation is atrio-oesophageal fistula formation, which is rare (one in 2500) but fatal in more than 50% of cases. Patients with atrio-oesophageal fistula usually present 10–14 days after ablation with symptoms that can include odynophagia, fever, and stroke-like symptoms.[80] Patients who present with dyspnoea after catheter ablation should be assessed for pulmonary vein stenosis. Although less common with contemporary ablation techniques (<0·5% of all cases),[77] pulmonary vein stenosis can still occur, particularly in patients who have undergone multiple atrial fibrillation catheter ablation procedures. Less commonly, patients can present with haemoptysis, or with an unexplained cough. This diagnosis can be made with lung ventilation scanning, CT scans, or cardiac magnetic resonance venography.[81]

Surgical ablation

Complete isolation of the pulmonary veins and other atrial structures can be achieved with surgical ablation techniques by transmural radiofrequency or cryothermal lesions. With traditional cut and sew techniques as used in the Cox maze procedure, it is possible to isolate the pulmonary veins, right and left atrial appendages, and extend lesions to the mitral annulus and coronary sinus. Persistence of sinus rhythm can be noted in 75–95% of the patients up to 15 years after surgery.[82] In patients who require mitral valve surgery, concomitant Cox maze isolation can result in a prognosis similar to that of patients initially in sinus rhythm.[83] The procedure is complex, associated with additional risk of complications, and thus is not widely performed.[2,4] As described previously, alternative sources of energy (eg, radiofrequency, cryoablation, and high-intensity focused ultrasound) can create lines of block in the atria without traditional cut and sew incisions, allowing less time-consuming and less complex procedures.[84,85] Although surgical ablation is controversial, it should be considered in patients with atrial fibrillation undergoing cardiac surgery.[44] Direct comparison clinical trials are needed to further clarify the optimal method of ablation in patients with advanced or long-standing persistent atrial fibrillation.

Populations with special circumstances

Heart failure

When rhythm and rate control strategies are compared in patients with atrial fibrillation and heart failure with reduced ejection fraction, neither strategy has been found to lead to superior outcomes.[86] Efforts to restore and maintain sinus rhythm are particularly challenging in patients with heart failure.[86] However, patients with heart failure who have less atrial fibrillation suffer less severe functional impairment and restoration of sinus rhythm after catheter ablation leads to improved ventricular function and exercise capacity.[87,88] As mentioned previously, antiarrhythmic options are scarce in patients with heart failure and carry risks of toxicity. However, the potential for pharmacogenetic-guided β-blocker therapy and improved outcomes associated with catheter ablation raises the possibility of more efficacious therapies in the future.[29,89]

Chronic kidney disease

Potential problems in patients with chronic kidney disease include reduced ability to excrete drugs or their metabolites, increased sensitivity to medications (particularly those bound to albumin in hypoalbuminaemic states), diminished tolerance of side-effects (particularly in the elderly), and loss of efficacy. Dosing of antiarrhythmic drugs should be based on the estimated creatinine clearance as indicated in the package insert. Several equations can be used for this purpose, each with advantages and limitations. Patients with chronic kidney disease should receive, when possible, the same treatment as those with normal renal function. However, dose adjustment for creatinine clearance is often needed for antiarrhythmic drugs, most of which have narrow therapeutic windows.[90]

Left ventricular hypertrophy

The presence of left ventricular hypertrophy complicates antiarrhythmic drug selection and subsequent therapy. Patients with left ventricular hypertrophy have an increased risk of proarrhythmia,[91] although one observational study suggests that the use of class Ic and class III antiarrhythmic drugs in patients with persistent atrial fibrillation and left ventricular wall thickness greater than or equal to 1·4 cm was not associated with increased mortality when compared with those given amiodarone.[92] Nonetheless, guidelines recommend avoidance of class Ic and class III drugs in patients with substantial left ventricular hypertrophy due to concerns for increased ventricular proarrhythmia.[2]

Postoperative atrial fibrillation

Postoperative atrial fibrillation is a common clinical problem affecting 30–50% of patients after cardiovascular surgery and is associated with considerable morbidity and mortality.[2] Multiple interventions have been shown to decrease the risk of postoperative atrial fibrillation, including β-blocker therapy and antiarrhythmic drug therapy, such as amiodarone.[93] Generally, these interventions are more effective when they are administered before surgery. Neither rate nor rhythm control has shown net clinical advantage for the treatment of postoperative atrial fibrillation and therefore, treatment decisions should be individualised and patient centred.[94]

Conclusion

Rhythm control therapy to maintain sinus rhythm is an important component of arrhythmia management in patients with atrial fibrillation. Although neither ventricular rate nor rhythm control has been established as superior, rhythm control is an important strategy to improve symptoms, functional status, and quality of life in patients with atrial fibrillation. Antiarrhythmic drug therapy remains a first-line treatment for maintenance of sinus rhythm. Catheter ablation leads to improved outcomes in patients who have not been successful with antiarrhythmic drug therapy and is an increasingly used therapy for rhythm control.

Declaration of interests

JPP received grants for clinical research from the Agency for Healthcare Research and Quality, ARCA biopharma, Boston Scientific, Gilead, Johnson & Johnson, ResMed, and St Jude Medical, and is a consultant to Bayer Healthcare, BMS/Pfizer, Janssen Pharmaceuticals, and Medtronic. LF serves on a consultant or advisory board for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic, and Novartis, and receives honoraria for speakers bureau from Bayer, BMS/Pfizer, Boehringer Ingelheim, Boston Scientific, and Medtronic. JPP is supported (in part) by funding from the Agency of Healthcare Research and Quality through cooperative agreement number 1U19 HS021092.

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