Atrial fibrillation: an update on management

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Summary
Atrial fibrillation carries a markedly increased risk of stroke and left ventricular dysfunction, and is associated with reduced quality of life.

In light of the potential for poor outcomes and the likely understated presence of silent atrial fibrillation, opportunistic screening should be carried out in general practice.

Modifying the risk factors for atrial fibrillation is the cornerstone of management with adjuvant drug therapy to help maintain sinus rhythm, control the ventricular rate and reduce the risk of cerebral thromboembolism.

The need for anticoagulant therapy can be assessed by using the revised CHA2DS2-VASc score. Direct oral anticoagulants are now preferred to warfarin in those who qualify for their use.

Catheter ablation is an effective option to improve survival in patients with left ventricular dysfunction. It also improves quality of life and reduces arrhythmia-related hospital admissions.

Introduction
Atrial fibrillation is the most common arrhythmia detected in clinical practice and accounts for over 30% of hospital admissions for cardiac rhythm problems. The burden of disease appears to be increasing with higher prevalence and rates of atrial fibrillation-related hospital admissions. This illustrates the need for a renewed approach to its management.

Epidemiology
The prevalence of atrial fibrillation in Australia is 2–4%, with a predominance in older people. This is likely to be an underestimation because silent atrial fibrillation (asymptomatic, subclinical) has not been taken into account. Most atrial fibrillation in Australia is non-valvular.

Atrial fibrillation is associated with a significant increase in the long-term risk of stroke (2–5-fold higher than matched patients without atrial fibrillation), heart failure, impaired quality of life and all-cause mortality. It is important for GPs to recognise the strong association of certain risk factors with atrial fibrillation. These predominantly include obesity, obstructive sleep apnoea, hypertension, valvular heart disease and genetic predisposition.

Classification of atrial fibrillation according to duration

| Paroxysmal | Episodes that last less than 7 days, whether they revert spontaneously or undergo direct current cardioversion. |
| Persistent | Episodes that continue for more than 7 days and do not self-terminate. |
| Long-standing | Continuous for more than 1 year, despite a rhythm-control strategy. |
| Permanent | When the patient and the treating physician decide to accept that the patient will remain in atrial fibrillation and will not attempt to achieve sinus rhythm. Often after a rhythm-control strategy has been unsuccessful. |

Keywords
antiarrhythmic drugs, anticoagulants, apixaban, catheter ablation, dabigatran, rivaroxaban, thromboembolism

Box 1 Classification of atrial fibrillation according to duration

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Opportunistic screening (pulse check and ECG) of all patients over the age of 65 years in general practice is now strongly recommended by international guidelines. This follows clear demonstrable benefits to increased quality-adjusted life-years and a reduced incidence of stroke.\textsuperscript{11,13} We may soon have eHealth tools like smartphone ECG devices which might contribute to higher detection rates of silent atrial fibrillation.\textsuperscript{14,15} However, more research is needed before the routine use of these tools. Also, we need more data to establish the burden of atrial fibrillation detected by these devices before starting therapy.

**Diagnostic work up**

An ECG is essential to confirm a diagnosis of atrial fibrillation. Additional investigations are needed to determine the cause. All patients should undergo a full blood count, urea and electrolytes and thyroid function tests. An echocardiogram should be performed to detect underlying cardiac abnormalities, such as valvular pathology, left atrial size and volume, as well as the presence of left ventricular dysfunction. In select patients who require acute rhythm control, transoesophageal echocardiography is performed to look for thrombus in the atria before attempting an electrical or pharmacological cardioversion.

**Risk stratification tools**

The CHA\textsubscript{2}DS\textsubscript{2}-VASc score is the most widely accepted tool for assessing risk of a stroke in clinical practice and is easy to use. It is endorsed by European\textsuperscript{13} and North American guidelines.\textsuperscript{16} The 2018 Australian atrial fibrillation guidelines recommend a ‘sexless’ version of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score, known as CHA\textsubscript{2}DS\textsubscript{2}-VA (Table 1).\textsuperscript{3} They recommend considering anticoagulation for a CHA\textsubscript{2}DS\textsubscript{2}-VA score of 1. In contrast, the North American guidelines recommend anticoagulation for a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of at least 2 in men and at least 3 in women.\textsuperscript{3,16} Other risk scores, including ATRIA and ORBIT, do not show major differences in predicting a high risk of stroke.

Bleeding risk can be estimated using the HAS-BLED score (Table 2).\textsuperscript{17} Although higher bleeding risk scores can be used to alert the patient and the doctor, they should not discourage anticoagulation. The net benefit to the patient usually favours stroke prevention with anticoagulation over the risk of major bleeding.\textsuperscript{3} This requires shared decision making with the patient after discussing the risks and benefits of the treatment strategy.

**Treatment strategies**

The management of atrial fibrillation revolves around stroke prevention, aggressive risk-factor management, and acute and long-term rate or rhythm control. Catheter ablation may also be considered.

### Table 1  The CHA\textsubscript{2}DS\textsubscript{2}-VA score

| Risk factor | Definition                                                                 | Points |
|-------------|---------------------------------------------------------------------------|--------|
| C           | Congestive heart failure which includes:                                   | 1      |
|             | • symptomatic HFrEF and HFpEF                                             |        |
|             | • moderately–severely reduced left ventricular function in the absence of previous symptoms |        |
| H           | Hypertension – whether or not blood pressure is currently elevated         | 1      |
| A           | Age ≥75 years                                                              | 2      |
| D           | Diabetes                                                                   | 1      |
| S           | Previous stroke or transient ischaemic attack or history of systemic thromboembolism | 2      |
| V           | Presence of vascular disease:                                             | 1      |
|             | • previous myocardial infarction, or                                       |        |
|             | • peripheral arterial disease, or                                          |        |
|             | • complex aortic atheroma or plaque on imaging                            |        |
| A           | Age 65–74 years                                                            | 1      |

Oral anticoagulation therapy to prevent stroke and systemic embolism is recommended in patients with non-valvular atrial fibrillation whose CHA\textsubscript{2}DS\textsubscript{2}-VA score is ≥2 (high quality of evidence), unless there are contraindications to anticoagulation, and should be considered strongly if CHA\textsubscript{2}DS\textsubscript{2}-VA score is 1 (moderate quality of evidence).\textsuperscript{3}

HFpEF heart failure with preserved ejection fraction
HFpEF heart failure with reduced ejection fraction
Source: reference 3
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Stroke prevention
Anticoagulation reduces the relative risk of stroke by around 70% in patients with atrial fibrillation. The options include warfarin or direct oral anticoagulant drugs such as factor Xa inhibitors – apixaban and rivaroxaban – and the direct thrombin inhibitor dabigatran. Aspirin is no longer recommended as an alternative.

Direct oral anticoagulants are recommended as first-line therapy over warfarin in patients with non-valvular atrial fibrillation, provided there are no absolute contraindications to their use (see Box 2).18 Dose reduction of direct oral anticoagulants may also be required depending on patient characteristics (see Table 3).1 Direct oral anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolism in these patients and have significantly lower rates of major haemorrhage.19 Evidence is lacking for their use in patients with mitral stenosis or a metallic valve replacement, hence warfarin is the drug of choice to prevent systemic thromboembolism in this population.

For those receiving warfarin, INR should be measured by routine laboratory tests at least weekly initially and then monthly. Dose modifications of warfarin should be aimed at maintaining the INR between 2 and 3. When switching from warfarin to a direct oral anticoagulant, after warfarin is stopped, the direct oral anticoagulant can be started when the INR is less than 2.18

The expert consensus is that patients with concurrent atrial fibrillation and ischaemic heart disease undergoing percutaneous coronary intervention should receive triple therapy with aspirin, clopidogrel and anticoagulation for as short a time as possible (no longer than six months immediately post percutaneous coronary intervention in stable coronary artery disease). They should then continue dual therapy with clopidogrel and anticoagulation for at least 12 months after percutaneous coronary intervention before considering stopping antiplatelet therapy and continuing anticoagulation as monotherapy.20-23 Current evidence does not support substituting clopidogrel with the newer P2Y12 antiplatelet drugs prasugrel and ticagrelor.

Percutaneous left atrial appendage occlusion may be considered as an option in patients with atrial fibrillation at increased risk of stroke who have contraindications to long-term anticoagulation. This is because of the propensity for bleeding or poor drug tolerance.24

### Table 2  The HAS-BLED score

| Risk factor | Clinical characteristic | Points |
|-------------|-------------------------|--------|
| H           | Hypertension            | 1      |
|             | • systolic blood pressure >160 mmHg |        |
| A           | Abnormal liver OR kidney function | 1 each |
|             | • dialysis/renal transplantation/serum creatinine ≥200 mmol/L | |
|             | • cirrhosis or bilirubin 2x upper limit of normal with AST/ALT/ALP 3x upper limit normal | |
| S           | Stroke                  | 1      |
| B           | Bleeding                | 1      |
|             | • history of bleeding or a bleeding diathesis | |
| L           | Labile INRs             | 1      |
| E           | Elderly                 | 1      |
|             | • >65 years             |        |
| D           | Drugs OR alcohol        | 1 each |
|             | • concomitant use of antiplatelets/NSAIDs | |
|             | • ≥8 drinks/week        |        |

HAS-BLED score ≥3 is considered as a high-risk of bleeding

ALP alkaline phosphatase
ALT alanine aminotransferase
AST aspartate aminotransferase
NSAIDs non-steroidal anti-inflammatory drugs
Source: reference 17
Rate control versus rhythm control

To date, randomised controlled trials do not suggest superiority of one strategy over the other.\textsuperscript{25}

**Rhythm control**

Rhythm control may be given priority for:

- those with underlying left ventricular dysfunction
- highly symptomatic patients in spite of rate-control therapy
- patient preference (some patients may not want to remain on rate-control drugs because of their symptoms or intolerance to the drugs)
- paroxysmal or early persistent atrial fibrillation.

In the acute setting, any patient who is haemodynamically unstable should undergo immediate synchronised electrical cardioversion. When the patient is haemodynamically stable, acute rhythm control may be desired if they are symptomatic or if it is their first episode with an onset of less than 48 hours. Flecainide and amiodarone are the two drugs available for acute pharmacological cardioversion.\textsuperscript{26}

In patients with haemodynamically stable atrial fibrillation lasting more than 48 hours, or of unknown duration, acute rhythm control should be ideally attempted only after anticoagulation for three weeks. Anticoagulation should be continued for at least four weeks after cardioversion. It is still reasonable to attempt an acute cardioversion, only after the transoesophageal echocardiogram has excluded a left atrial thrombus.\textsuperscript{26}

Drugs with the strongest evidence for long-term rhythm control are amiodarone, flecainide and sotalol. Given its high adverse-effect profile, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.\textsuperscript{3} Flecainide can be started in patients with structurally normal hearts (confirmed with an echocardiogram) who do not have underlying coronary artery disease. Treatment should be started at 50 mg twice a day and titrated up to a maximum dose of 150 mg twice a day, depending on tolerance. Patients should be concomitantly prescribed an atrioventricular nodal blocking drug (e.g. metoprolol) in conjunction with flecainide. Sotalol is also an option for patients intolerant to amiodarone and flecainide. However, the QT interval should be closely monitored, and sotalol is relatively contraindicated in patients with chronic renal impairment.

**Rate control**

Treatment options for acute rate control are beta blockers, non-dihydropyridine calcium channel antagonists and amiodarone. Again, amiodarone is reserved for patients who are highly symptomatic with known left ventricular dysfunction when other drugs could be contraindicated.

First-line therapies for long-term rate control, in patients without left ventricular dysfunction, are beta blockers (e.g. metoprolol), non-dihydropyridine calcium channel blockers (e.g. verapamil), or digoxin (with monitoring of serum concentrations). The

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**Box 2** Absolute contraindications to direct oral anticoagulants

| Severe renal impairment: |
|-------------------------|
| • CrCl <30 mL/min with dabigatran |
| • CrCl <15 mL/min with apixaban* |
| • CrCl <15 mL/min with rivaroxaban* |
| Liver impairment e.g. cirrhosis (Child Pugh C) |
| Current active bleeding or coagulopathy |
| Previous life-threatening haemorrhage while on a direct oral anticoagulant |
| Documented previous anaphylaxis to a direct oral anticoagulant |

* International European guidelines approve the use of apixaban and rivaroxaban in patients with CrCl as low as 15 mL/min, however this is not reflected in Australian guidance (see Table 3).

**Table 3** Dose adjustment of direct oral anticoagulants in non-valvular atrial fibrillation

| Direct oral anticoagulant | Clinical factors | Dose adjustment |
|---------------------------|------------------|-----------------|
| Apixaban                  | At least two of: |
|                           | • serum creatinine ≥133 micromol/L |
|                           | • age ≥80 years |
|                           | • weight ≤60 kg |
|                           | 5 mg twice a day to 2.5 mg twice a day |
| Rivaroxaban               | At least one of: |
|                           | • CrCl 30–49 mL/min |
|                           | • combination with dual antiplatelet therapy |
|                           | 20 mg daily to 15 mg daily |
| Dabigatran                | At least one of: |
|                           | • CrCl 30–50 mL/min |
|                           | • age ≥75 years |
|                           | • combination with dual antiplatelet therapy |
|                           | 150 mg twice a day to 110 mg twice a day |

CrCl creatinine clearance

Source: reference 3

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CrCl creatinine clearance

Source: reference 3
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RACE II trial remains the most recent comprehensive evaluation of strict control. It found that a lenient approach – heart rate target <110 beats per minute – was not associated with worse outcomes than a stricter approach of <80 beats per minute at rest or <110 beats per minute with exercise. In patients with left ventricular dysfunction who are not being considered for rhythm control, or who have failed rhythm control, first-line rate control therapy would be with beta blockers which have survival benefit in heart failure (e.g. bisoprolol, carvedilol, controlled-release metoprolol or nebivolol), or digoxin. Non-dihydropyridine calcium channel blockers are contraindicated in patients with left ventricular dysfunction.

Risk-factor management

Aggressive management of intercurrent risk factors like obesity, obstructive sleep apnoea, hypertension, diabetes, heart failure, valvular heart disease and excess alcohol is important. Long-term sustained weight loss reduces the burden of atrial fibrillation and maintains sinus rhythm. The Australian guidelines therefore endorse intensive weight loss (at least 10% of body weight) with a target body mass index below 27 kg/m². Exercise is also recommended as it improves aerobic capacity and reduces disease burden. The CARDIO-FIT study showed that arrhythmia-free survival with and without rhythm-control strategies was greatest in patients with high cardiorespiratory fitness compared to adequate or low cardiorespiratory fitness.

Australian guidelines recommend:

- blood pressure no more than 130/80 mmHg at rest, and 200/100 mmHg with exercise
- continuous positive airway pressure therapy if the apnoea–hypopnea index is at least 15/hour
- an HbA1c of no more than 6.5% (48 mmol/mol)
- lipid targets as per the cardiovascular risk profile
- smoking cessation
- no more than three standard drinks of alcohol per week.

Catheter ablation

Catheter ablation delivers radiofrequency energy resulting in isolation of the pulmonary veins and other contiguous venous structures. It has been shown to be a successful therapy in patients with atrial fibrillation. The subgroups that benefit most appear to be patients with paroxysmal and persistent atrial fibrillation who are symptomatic and those with left ventricular dysfunction. Catheter ablation also significantly improves quality of life and is associated with significantly fewer hospital admissions. It is important to discuss with the patient that procedural success rates vary and 20–30% of people may require a second procedure within 12 months. Major complication rates from the procedure are 1–7% and are related to the experience of the operator and the centre. The decision to do catheter ablation should be made after a detailed discussion between the patient and the cardiac specialist.

Conclusion

Treatment strategies for atrial fibrillation include stroke prevention, risk-factor management, rate and rhythm control, and catheter ablation. These have reduced the morbidity and mortality associated with this condition. However, there is growing literature on various aspects of atrial fibrillation management necessitating constant updates for physicians.

Conflict of interest: none declared

REFERENCES

1. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol 2013;167:807-24. https://doi.org/10.1016/j.ijcard.2013.02.039
2. Briffa T, Hung J, Knuiman M, McQuillan B, Chew DP, Eikelboom J, et al. Trends in incidence and prevalence of hospitalization for atrial fibrillation and associated mortality in Western Australia, 1995-2010. Int J Cardiol 2016;208:19-25. https://doi.org/10.1016/j.ijcard.2016.01.196
3. Brierie D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, et al.; NHFA CSANZ Atrial Fibrillation Guideline Working Group. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ 2018;27:1209-66. https://doi.org/10.1016/j.hlc.2018.06.014
4. Raja DC, Kapoor A. Epidemiology of atrial fibrillation - an Indian perspective. J Assoc Physicians India 2016;64(Suppl):7-10.
5. Pathak RK, Mahajan R, Lau DH, Sanders P. The implications of obesity for cardiac arrhythmia mechanisms and management. Can J Cardiol 2015;31:203-10. https://doi.org/10.1016/j.cjca.2014.10.027
6. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-31. https://doi.org/10.1016/j.jacc.2014.09.028
7. Enriquez A, Antzelevitch C, Bismah V, Baranchuk A. Atrial fibrillation in inherited cardiac channelopathies: from mechanisms to management. Heart Rhythm 2016;13:1878-84. https://doi.org/10.1016/j.hrrthm.2016.06.008
8. Lau DH, Schotten U, Mahajan R, Antic NA, Hatem SN, Pathak RK, et al. Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications. Eur Heart J 2016;37:1573-81. https://doi.org/10.1093/eurheartj/ehv575
9. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet 2016;388:806-17. https://doi.org/10.1016/S0140-6736(16)31257-0
10. Sanna T, Diener HC, Paszmary RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al.; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478-86. https://doi.org/10.1056/NEJMoa1315600
11. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalil F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. Europace 2015;17:1023-9. https://doi.org/10.1093/eurheartj/ehv083

12. Lowres N, Neuback L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. Thromb Haemost 2013;110:215-22. https://doi.org/10.1160/TH13-02-0165

13. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Barfod D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962. https://doi.org/10.1093/eurheartj/ehw210

14. William AD, Kanbour M, Callahan T, Bhagava G, Varma N, Ricard K, et al. Assessing the accuracy of an automated atrial fibrillation detection algorithm using smartphone technology: The iREAD Study. Heart Rhythm 2018;15:1561-S. https://doi.org/10.1016/j.hrthm.2018.06.037

15. Turakhia MP, Desai M, Hedlin H, Rajmane A, Talati N, Ferris T, et al. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the Apple Heart Study. Am Heart J 2019;207:66-75. https://doi.org/10.1016/j.ahj.2018.09.002

16. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140:e225-51. https://doi.org/10.1161/CIR.0000000000000665

17. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY, et al. The 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100. https://doi.org/10.1378/chest.10-0134

18. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al.; European Heart Rhythm Association. Left atrial appendage closure-indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. Europace 2015;17:642-6. https://doi.org/10.1093/europace/euv069

19. Chatterjee S, Sardar P, Lichtstein E, Mukherjee D, Alkatib S. Pharmacologic rate versus rhythm-control strategies in atrial fibrillation: an updated comprehensive review and meta-analysis. Pacing Clin Electrophysiol 2013;36:322-33. https://doi.org/10.1111/j.1540-8159.2012.03515.x

20. Chevalier P, Durand-Dubief A, Burri H, Cucherat M, Korkian G, Touboul P. Amiodarone versus placebo and class IC drugs for cardioversion of recent-onset atrial fibrillation: a meta-analysis. J Am Coll Cardiol 2003;41:255-62. https://doi.org/10.1016/S0735-1097(02)02705-5

21. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, et al.; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73. https://doi.org/10.1056/NEJMoa1001337

22. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). J Am Coll Cardiol 2015;65:2159-69. https://doi.org/10.1016/j.jacc.2015.03.002

23. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIORespiratory Fitness on arrhythmia recurrence in obese patients with atrial fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol 2015;66:985-96. https://doi.org/10.1016/j.jacc.2015.06.488

24. Ganesan AN, Nandali S, Luker J, Pathak RK, Mahajan R, Twomey D, et al. Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: a systematic review of efficacy and effect on ejection fraction. Heart Lung Circ 2015;24:270-80. https://doi.org/10.1111/hlc.12442

25. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordens L, et al.; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-27. https://doi.org/10.1056/NEJMo1707855

26. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnsen TD, Poole JE, et al.; CABA NA Investigators. Effect of catheter ablation vs antihypertensive drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABA NA randomised clinical trial. JAMA 2019;321:1275-85. https://doi.org/10.1001/jama.2019.0693

27. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, et al.; CABA NA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABA NA randomized clinical trial. JAMA 2019;321:1275-85. https://doi.org/10.1001/jama.2019.0693

28. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovani R, et al.; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-22. https://doi.org/10.1056/NEJMo1406288