ATRIAL FIBRILLATION
Supporting information

This guideline has been prepared with reference to the following:

NICE. Atrial fibrillation: diagnosis and management. 2021. London. NICE

https://www.nice.org.uk/guidance/ng196

January CT, Wann SL, Calkins H 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: e125–e151

https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665

Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50:e1-e88

https://academic.oup.com/ejcts/article-lookup/doi/10.1093/ejcts/ezw313

You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e531S-75S

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278056/

Immediate treatment

The risk of stroke should be assessed using the CHA_2DS_2VASc score?

The European Society of Cardiology, American College of Cardiology, American Heart Association, Heart Rhythm Society and American College of Chest Physicians all currently recommend the use of CHA_2DS_2VASc score for stroke risk assessment in atrial fibrillation patients, with some variations regarding the C (congestive heart failure) and V (vascular disease) components (Chai, 2020).

A study of thromboembolic risk (TR) in 7329 anticoagulated AF patients (Lip, 2010) tested the predictive value of CHADS2, Framingham, NICE 2006, American College of Cardiology/American Heart Association/European Society of Cardiology 2006, the 8th American College of Chest Physicians guidelines and the CHA2DS2-VASc schemes. Comparison of schemes demonstrated variable classification of AF patients into risk strata, although c-statistics for TE were broadly similar among the schemes tested and varied between 0.575 (NICE 2006) and 0.647 (CHA2DS2-VASc). CHA2DS2-VASc classified 94.2% as being at high risk, whereas most other schemes categorized two-thirds as being at high risk. Of the 184 TR events, 181 (98.4%) occurred in patients identified as being at high risk by the CHA2DS2-VASc scheme. There was a stepwise increase in TR with increasing CHA2DS2-VASc score (P (trend) < 0.0001), which had the highest HR (3.75) among the tested schemes. The negative predictive value (ie, the percent categorized as "not high risk" actually being free from TR) for CHA2DS2-VASc was 99.5%. The authors concluded that, of the contemporary stroke risk stratification schemes, the CHA2DS2-VASc scheme correctly identified the greatest proportion of AF patients at high risk, despite the similar predictive ability of most schemes as evidenced by the c-statistic.

A systematic review examined the risk of ischemic stroke for patients with atrial fibrillation and CHA2DS2-VASc score of 0, 1, or 2 not treated with oral anticoagulation (Joundi et al, 2016). The authors found that the summary estimate for the annual risk of ischemic stroke was 1.61% (95% CI 0%-3.23%) for CHA2DS2-VASc score of 1, meeting the theoretical threshold for using novel oral anticoagulants (0.9%), but below the threshold for warfarin (1.7%). The summary incident risk of ischemic stroke was 0.68% (95% confidence interval 0.12%-1.23%) for CHA2DS2-VASc score of 0 and 2.49% (95% confidence interval 1.16%-3.83%) for CHA2DS2-VASc score of 2. The authors concluded that those with CHA2DS2-VASc score of 1 may be considered for a novel oral anticoagulant, but because of the high heterogeneity in the reviewed studies, the decision should be based on individual patient characteristics.

Chao TF, Nedeljkovic MA, Lip HYH et al. Stroke prevention in atrial fibrillation: comparison of recent international guidelines. Eur Heart J Suppl. 2020;22(Suppl O):O53-O60.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7753747/

Joundi RA, Cipriano LE, Sposato LA et al. Ischemic Stroke Risk in Patients With Atrial Fibrillation and CHA2DS2-VASc Score of 1: Systematic Review and Meta-Analysis. Stroke 2016;47:1364-7

Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke 2010;41;2731-8
http://stroke.ahajournals.org/content/41/12/2731.long

Evidence Level: III

Once reversion to sinus rhythm occurs, atrial fibrillation/flutter responds to long term prophylaxis with propafenone or flecainide in patients with no evidence of ischaemic heart disease?
A 2019 systematic review found moderate-certainty evidence from five RCTs indicated that propafenone reduced atrial fibrillation recurrences by about a third (RR 0.67, 95% CI 0.61 to 0.74) [Valembois, 2019]. The same review found high-certainty evidence from four RCTs that flecainide reduced atrial fibrillation recurrences by about a third (RR 0.65, 95% CI 0.55 to 0.77).

Valembois L, Audureau E, Takeda A et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev. 2019 Sep 4;9:CD005049
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005049.pub5/full

Evidence Level: I

Rate control affords greater clinical benefit than rhythm control?
A systematic review and meta-analysis of 8 RCTs in a total of 7499 patients (Caldeira, 2012) found no significant differences in the effects of rate and rhythm control on any outcome: all-cause mortality (RR: 0.95; CI: 0.86-1.05), cardiovascular mortality (RR: 0.99; CI: 0.87-1.13), arrhythmic/sudden death (RR: 1.12; CI: 0.91-1.38), ischaemic stroke (RR: 0.89; CI: 0.52-1.53), systemic embolism (RR: 0.89; CI: 0.69-1.14) and major bleeding (RR: 1.10; CI: 0.89-1.36). Another systematic review (Al-Khatib, 2014) which found 16 RCTs comparing rate versus rhythm control found no statistical difference with regard to effect on all-cause mortality (OR: 1.34 CI: 0.89 – 2.02), cardiac mortality (OR: 0.96 CI: 0.77 – 1.20) and stroke (OR: 0.99 CI: 0.76 – 1.30).
A 2023 systematic review found that “early” rhythm therapy was linked to a lower risk of all-cause mortality, cardiovascular mortality, stroke, and heart failure hospitalization compared with the rate control. The review identified two RCTs, one retrospective analysis of RCTs, and four observational studies. Compared with rate control, early rhythm control has been linked to lower all-cause mortality [risk ratio (RR), 0.76; 95% CI 0.69 to 0.83]. The early rhythm control group was also associated with a lower risk of cardiovascular mortality (RR, 0.68; 95% CI 0.63 to 0.74), stroke (RR, 0.77; 95% CI 0.67 to 0.87), and heart failure hospitalization (RR, 0.74; 95% CI 0.59 to 0.93). No significant difference in nights spent in hospital per year, acute coronary syndrome, major bleeding, and cardiac arrest/ventricular arrhythmia was found between the groups.

Al-Khatib SM, LaPointe NMA, Chatterjee R et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: A systematic review. Ann Intern Med 2014. 160, 760-773.

Caldeira D, David C, Sampaio C. Rate versus rhythm control in atrial fibrillation and clinical outcomes: updated systematic review and meta-analysis of randomized controlled trials. Arch Cardiovasc Dis 2012;105:226-38
http://www.sciencedirect.com/science/article/pii/S1875213611003639

Han S, Jia R, Cen Z et al. Early rhythm control vs. rate control in atrial fibrillation: A systematic review and meta-analysis. Front Cardiovasc Med. 2023;10:978637
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9939510/

Evidence Level: I

Oral anticoagulation is appropriate for patients with sustained or paroxysmal AF, if the risk of stroke is deemed to outweigh the risk of bleeding?
A randomised trial in 973 patients aged 75 and over (Mant, 2007) compared warfarin (n=488; Target INR 2-3) to aspirin (n=485; 75 mg/d) for stroke prevention in AF. Follow-up was for a mean of 2.7

years (SD 1.2). In the warfarin group there were 24 primary events (21 strokes, 2 other intracranial haemorrhages, 1 systemic embolus) vs 48 primary events (44 strokes, 1 other intracranial haemorrhage, 3 systemic emboli) in the aspirin group (yearly risk 1.8% vs 3.8%, RR 0.48, 95% CI 0.28 – 0.80, p=0.003; absolute yearly RR 2%, 95% CI 0.7-3.2).
A Cochrane review of 8 trials in 9598 patients (Aguilar, 2007) found that oral anticoagulation reduced stroke and other major vascular events by about one third when compared with antiplatelet therapy.
There is emerging evidence for the overall clinical benefits of using novel oral anticoagulants instead of Warfarin in the prevention of stroke in AF patients. (Dentali 2012) The recent ARISTOTLE trial (Wallentin 2013) for example, randomized 18 201 patients with atrial fibrillation to the new oral direct factor Xa inhibitor, apixaban, 5 mg twice daily or warfarin for at least 12 months and found that in the total population, the primary outcome of stroke or systemic embolism was 1.27% in the apixaban group compared to 1.6% in the warfarin. It also caused less major bleeding and reduced mortality.
A 2015 systematic review found that Novel oral anticoagulants (NOACs) reduced the risk of stroke and Stroke and systemic embolism (SEE) compared with warfarin (rate ratios [RRs] range from 0.78-0.82) (Lin et al, 2015). Relative to SSE, NOACs demonstrated a smaller benefit for ischemic stroke (dabigatran 110 mg, RR 1.08; edoxaban, 1.00; apixaban, 0.99). On the contrary, aspirin was associated with a significantly higher risk of SSE, ischemic stroke, and mortality than warfarin or NOACs (RR > 1), particularly in older elderly. Regarding safety, medium-dose aspirin (100-300 mg daily) and aspirin/clopidogrel combination showed an increased risk of MB compared with warfarin (RR 1.17 and 1.15, respectively), as per dabigatran 150 mg and rivaroxaban in older elderly (RR 1.17 and 1.12, respectively). Among the NOACs, dabigatran 150 mg conferred greater gastrointestinal bleeding risk compared with warfarin (RR 1.51), whereas rivaroxaban (RR 0.73) demonstrated less benefit of reduced intracranial bleeding than other NOACs (RRs range 0.39-0.46). Lower rates of SSE and intracranial bleeding were observed with the NOACs compared with warfarin. Dabigatran 150 mg and rivaroxaban were associated with higher rates of MB in older elderly.

Lin L, Lim WS, Zhou HJ et al. Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis. J Am Med Dir Assoc. 2015;16:e1-19

Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2007, 3. CD006186
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD006186.pub2/full

Dentali F, Riva N, Crowther M et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012; 126: 2381-91
http://circ.ahajournals.org/content/126/20/2381.long

Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493-503

Wallentin L,Lopes RD,Hanna M et al. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Circulation 2013; 127: 2166-76
http://circ.ahajournals.org/content/127/22/2166.full

Evidence Level: I

What is the relationship between hypokalaemia and atrial fibrillation (AF)?
In a prospective, observational, case-control study in 2402 cardiac surgery patients (Wahr, 1999), preoperative serum potassium levels < 3.5 mmol/L were predictive of postoperative atrial fibrillation/flutter (OR 1.7; 95% CI 1.0-2.7).
Cases of similarly low serum potassium levels associated with AF have been reported in association with Brugada syndrome (Notarstefano, 2005), Conn's syndrome (Porodko, 2001) and in patients undergoing haemodialysis (Korzets, 2001).
The relationship between hypokalaemia and AF has also been noted in experimental animal studies (Tribulova, 1999).

Korzets A, Ori Y, Herman M. Serum potassium levels and atrial fibrillation in haemodialysis patients. Nephrol Dial Transplant 2001;16:1090
http://ndt.oxfordjournals.org/content/16/5/1090.long

Notarstefano P, Pratola C, Toselli T, et al. Atrial fibrillation and recurrent ventricular fibrillation during hypokalemia in Brugada syndrome. Pacing Clin Electrophysiol 2005;28:1350-3

Porodko M, Auer J, Eber B. Conn's syndrome and atrial fibrillation. Lancet 2001;357:1293-4

Tribulova N, Manoach M, Varon D, et al. Hypokalemia-induced ultrastructural, histochemical and connexin-43 alterations resulting in atrial and ventricular fibrillations. Gen Physiol Biophys 1999;18(Suppl 1):15-8

Wahr JA, Parks R, Boisvert D, et al. Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. JAMA 1999;281:2203-10
http://jama.jamanetwork.com/article.aspx?articleid=190409

Evidence Level: III

Catheter ablation therapy should be considered in patients unresponsive to drug treatment?
The 2016 guidance from the European Society of Cardiology states that "catheter ablation of AF is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy" (Kirchhof, 2016).
The optimal rhythm management strategy for people with non-paroxysmal (persistent or long-standing persistent) atrial fibrilation is currently not well defined. Antiarrhythmic drugs have been the mainstay of therapy. But recently, in people who have not responded to antiarrhythmic drugs, the use of ablation (catheter and surgical) has emerged as an alternative to maintain sinus rhythm to avoid long-term atrial fibrillation complications (Nyong, 2016).
A systematic review of 3 RCTs (261 participants) compared catheter ablation with antiarrhythmic drugs for non-paroxysmal atrial fibrillation (Nyong, 2016). The evidence showed that catheter ablation was superior to antiarrhythmic drugs in achieving freedom from atrial arrhythmias (RR 1.84, 95% CI 1.17 to 2.88), reducing the need for cardioversion (RR 0.62, 95% CI 0.47 to 0.82), and reducing cardiac-related hospitalisation (RR 0.27, 95% CI 0.10 to 0.72) at 12 months follow-up. There was substantial uncertainty surrounding the effect of catheter ablation regarding significant bradycardia (or need for a pacemaker) (RR 0.20, 95% CI 0.02 to 1.63), periprocedural complications, and other safety outcomes (RR 0.94, 95% CI 0.16 to 5.68). Another systematic review found that catheter ablation was also superior than antiarrhythmic drugs as a first line treatment for patients with paroxysmal atrial fibrillation (Saglietto, 2021). Six RCTs were included in this review. Catheter ablation was associated with lower recurrences of atrial tachyarrhythmias (RR 0.58, 95% CI 0.46 to 0.72), consistent across the two types of ablation energy (radiofrequency, RR 0.50, 95% CI 0.28 to 0.89; cryoenergy, RR 0.60, 95% CI 0.50 to 0.72). Similarly, catheter ablation was related to less symptomatic arrhythmic recurrences (RR 0.46, 95% CI 0.27 to 0.79). Overall, adverse events did not differ.

Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50:e1-e88
https://academic.oup.com/ejcts/article-lookup/doi/10.1093/ejcts/ezw313

Nyong J, Amit G, Adler AJ et al. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. Cochrane Database Syst Rev. 2016;11:CD012088.
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012088.pub2/full

Saglietto A, Gaita F, De Ponti R et al. Catheter Ablation vs. Anti-Arrhythmic Drugs as First-Line Treatment in Symptomatic Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Front Cardiovasc Med. 2021:8
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8175669/

Evidence Level: I

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