Management of atrial fibrillation: recommendations from NICE

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, affecting up to 2% of the general population. Its prevalence increases with age. The aims of treatment for atrial fibrillation are essentially two-fold (Stewart et al, 2001):

1. Preventing complications of thromboembolism, the most important of which is stroke
2. Alleviating symptoms by controlling heart rate or through restoring normal sinus rhythm.

In recent years, there has been new evidence in the management of atrial fibrillation and National Institute for Health and Care Excellence (NICE, 2014) has released new guidelines on atrial fibrillation to reflect the current thinking. A detailed review on the subject has previously been published by this journal (Nijjer and Lefroy, 2012). This article summarizes the more extensive web-based guidance, highlighting the new changes recommended by National Institute for Health and Care Excellence, examining the rationale behind it and also discussing how this will impact practice of hospital doctors.

Preventing complications

Preventing complications has two components: assessment of risk and treatment.

Thromboembolic risk stratification

Stroke prevention forms one of the main facets of atrial fibrillation management. In 2006, National Institute for Health and Care Excellence recommended stratifying patients into high, moderate and low risk for consideration of thromboprophylaxis. It also advocated the use of the CHADS2 scoring system (*Table 1*).

The latest National Institute for Health and Care Excellence guidance is in line with the European Society of Cardiology 2012 update (Camm et al, 2012) where there is a paradigm shift away from identifying high-risk patients towards encouraging anticoagulation in most patients unless they are truly low risk, i.e. <65 years with no risk factors. Stroke risk should be actively assessed in all patients with atrial fibrillation and atrial flutter and, as a new addition to the guidelines, in all patients who have undergone a successful DC cardioversion, recognizing that recurrence of subclinical atrial fibrillation poses a continuing risk.

It is worth commenting on stroke risk in atrial flutter. Most patients with atrial flutter also have episodes of atrial fibrillation. An interesting observation by the Mayo Clinic group noted that when compared to lone atrial fibrillation (after age and sex adjustment), patients with lone flutter in fact had a higher rate of thromboembolism (hazard ratio 2.6) (Halligan et al, 2004). Patients with flutter should be risk stratified like patients with atrial fibrillation.

The CHADS2 score has clear limitations; it does not include common stroke risk factors like vascular disease and it was derived from a historical dataset where stroke risk factors were not consistently defined or systematically recorded. The system has now been replaced with the CHA2-DS2-VASc scoring system (*Table 2*) which largely teases out the risk in the lower scoring groups, making it a more comprehensive tool. In addition, risk factors from the CHADS2 scoring system were mainly identified from trial cohorts whereas CHA2-DS2-VASc was derived from a real-world cohort of patients with atrial fibrillation (Lip et al, 2010).

The National Institute for Health and Care Excellence (2014) guidance now recommends anticoagulation for people with a CHA2-DS2-VASc score of 2 and consideration of anticoagulation if they have a score of 1. The initiation of anticoagulation has to take bleeding risk into account. This leads to another new aspect of the guidelines where bleeding risk is being considered. *Figure 1* illustrates the different options for thromboprophylaxis in patients with atrial fibrillation.

Table 1. CHADS2 scoring system

Congestive heart failure	1
Hypertension (blood pressure >140/90 mmHg or treated hypertensive)	1
Age ≥75 years	1
Diabetes mellitus	1
S2 Prior stroke, transient ischaemic attack or thromboembolism	2

Bleeding risk stratification

The National Institute for Health and Care Excellence (2014) guidance recommends use of the HAS-BLED score to assess the risk of bleeding in people who are starting or have started anticoagulation (*Table 3*). A HAS-BLED score of 3 or more indicates a high risk of bleeding and the patient should have regular reviews.

To date, there is no systematic way to quantify and balance bleeding *vs* stroke risk in deciding if anticoagulation is appropriate. As a general rule of thumb, patients

Table 2. CHA2-DS2-VASc scoring system

Congestive heart failure	1
Hypertension (blood pressure >140/90 mmHg or treated hypertensive)	1
A2 Age ≥75 years	2
Diabetes mellitus	1
S2 Prior stroke, transient ischaemic attack or thromboembolism	2
Vascular disease (e.g. myocardial infarction, peripheral vascular disease)	1
Age 65–74 years	1
Sc Sex category (female)	1

Dr Wei Yao Lim *is Cardiology Registrar and* **Dr Fakhar Khan** *is Cardiology Consultant, at The Heart Hospital, University College London Hospitals, London W1G 8PH*

Correspondence to: Dr WY Lim (weiyaolim@nhs.net)

with atrial fibrillation with high thromboembolic risk (CHA2-DS2-VASc ≥2) should be anticoagulated.

This scoring system does not help rule out anticoagulation but rather it identifies modifiable risk factors where clinicians can intervene to reduce bleeding risk.

Antiplatelet therapy

A major change to treatment has been the shift away from the use of aspirin for stroke prevention alone because of the limited evidence on aspirin efficacy in stroke prevention. In fact, data from the BAFTA study indicate that the risk of major bleeding or intracranial haemorrhage was similar for both aspirin and warfarin (Mant et al, 2007). In 2006, aspirin was recommended for patients who had a moderate (CHADS2 = 1) stroke risk but the 2014 guidelines categorically state not to offer aspirin monotherapy for stroke prevention to people with atrial fibrillation.

In a person who has a CHA2-DS2-VASc score of 2 or above and cannot have warfarin or direct oral anticoagulants, the combination of aspirin and clopidogrel can be considered but not encouraged. This recommendation is derived from Connolly et al (2009b) who showed that dual antiplatelet combination was more effective than aspirin alone, but carries a greater risk of major bleeding.

Figure 1. Thromboprophylaxis in patients with atrial fibrillation. INR = international normalized ratio.

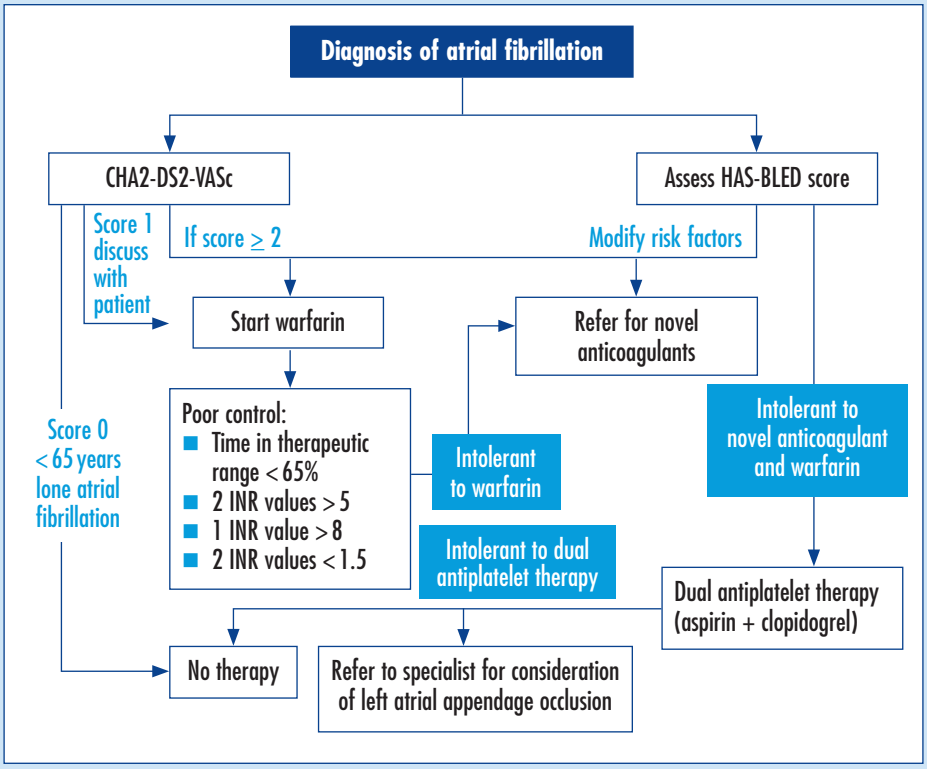


Table 3. HAS-BLED score

Hypertension (>160 mmHg systolic)	1
Abnormal renal or liver function (1 point each) (dialysis/transplant/cirrhosis/ bilirubin 2X/aspartate transaminase/alanine transaminase X3 normal)	1 or 2
Stroke	1
Bleeding history or disposition (anaemia)	1
Labile international normalized ratio (time in therapeutic range <60%)	1
Elderly (>65 years)	1
Drugs (non-steroidal anti-inflammatory drugs or antiplatelets) and alcohol (>8 units per week) (1 point each)	1 or 2

Assessing anticoagulation control

There has been more focus now on ensuring that patients who are on warfarin are adequately anticoagulated. National Institute for Health and Care Excellence (2014) recommends calculating a person's time in the therapeutic range over a maintenance period of at least 6 months, excluding measurement during the first 6 weeks. Stroke prevention is most effective when time in the therapeutic range is >70%. Apart from improving the quality of international normalized ratio (INR) control, patients who are not able to achieve a good time in the therapeutic range could be considered for alternative stroke prevention strategies.

Poor anticoagulation control within a 6-month period is defined by National Institute for Health and Care Excellence as:

- 2 INR values >5
- 1 INR value >8
- 2 INR values <1.5
- Time in the therapeutic range <65%.

Direct oral anticoagulants

One of the main groups of drugs that have in part have been the impetus for change in stroke prevention are the direct oral anticoagulants. National Institute for Health and Care Excellence published the first of three technology appraisals on the use of the direct oral anticoagulants in 2012 (National Institute for Health and Care Excellence, 2012). Although cost is often perceived as a barrier, National Institute for Health and Care Excellence has concluded that direct oral anticoagulants are cost-effective within their licensed indications.

There are currently three direct oral anticoagulants available: dabigatran, rivaroxaban and apixaban. They are proven in clinical trials to be as effective and in some cases superior to warfarin in patients with non-valvular atrial fibrillation. For stroke prevention in patients with atrial fibrillation, all three direct oral anticoagulants can be started in patients who have risk factors and would qualify for warfarin. *Table 4* illustrates the evidence for and dosing of these three drugs.

Direct oral anticoagulants are associated with fewer bleeding complications than warfarin. However, in the event of major bleeding, there is no specific antidote to reverse the effects. The mainstay of treat-

Table 4. Direct oral anticoagulants: dosage and evidence

Name	Dose	Evidence
Dabigatran	150 mg twice daily, 110 mg twice daily (renal dose)	RE-LY (Connolly et al, 2009a)
Rivaroxaban	20 mg once daily, 15 mg once daily (renal dose)	ROCKET-AF (Patel et al, 2011)
Apixaban	5 mg twice daily, 2.5 mg twice daily (renal dose)	ARISTOTLE (Granger et al, 2011)

ment is largely supportive. There are some studies in healthy volunteers and animals suggesting the use of prothrombin complex concentrate, activated prothrombin complex concentrate or factor VIIa to treat major haemorrhage with limited clinical outcome data (Siegal and Cuker, 2013).

Renal impairment is one of the contraindications to the use of direct oral anticoagulants. Its use depends on the degree of renal impairment (calculated using creatinine clearance) and the type of direct oral anticoagulants. Direct oral anticoagulants should not be used in patients with a creatinine clearance of < 15 ml/min. If a patient's creatinine clearance falls to between 15 and 29 ml/min, dabigatran is contraindicated as it has the highest renal excretion but apixaban and rivaroxaban can be use at a reduced dose (*Table 4*).

Routine monitoring is not required for patients taking direct oral anticoagulants as there is currently no lab test that can reliably measure their concentration. The manufacturers of dabigatran recommend yearly monitoring of renal function as 80% of the drug is renal excreted.

It is important to note that direct oral anticoagulants are not to be used in patients with mechanical prosthetic valves. A phase 2 study of dabigatran in prosthetic metallic valve patients was stopped early because of an increased risk of stroke and bleeding in the dabigatran group (Eikelboom et al, 2013).

Left atrial appendage occlusion

The left atrial appendage is considered the main site of thrombus formation in patients with atrial fibrillation. This led to the development of percutaneous closure devices as an alternative to anticoagulation. The WATCHMAN and Amplatzer are two devices available.

However, there is insufficient evidence on the efficacy of left atrial appendage occlusion. When the National Institute for Health and Care Excellence (2014) guidance was published, there was only a single paper (Holmes et al, 2009) showing that percutaneous closure of left atrial appendage was non-inferior to warfarin in stroke prevention but a peri-procedural hazard was identified.

The PREVAIL study (Holmes et al, 2014) once again demonstrated left atrial appendage occlusion as non-inferior to warfarin but was still associated with higher risk of pericardial effusions requiring surgical repair and pericardiocentesis.

The ongoing Amplatzer cardiac plug trial (Park et al, 2011) will hopefully shed more light on the subject. Hence, National Institute for Health and Care Excellence does not recommend left atrial appendage occlusion as an alternative to anticoagulation and this can only be considered if patients do not tolerate long-term anticoagulation after a careful discussion of the benefits and risk.

Treating symptoms

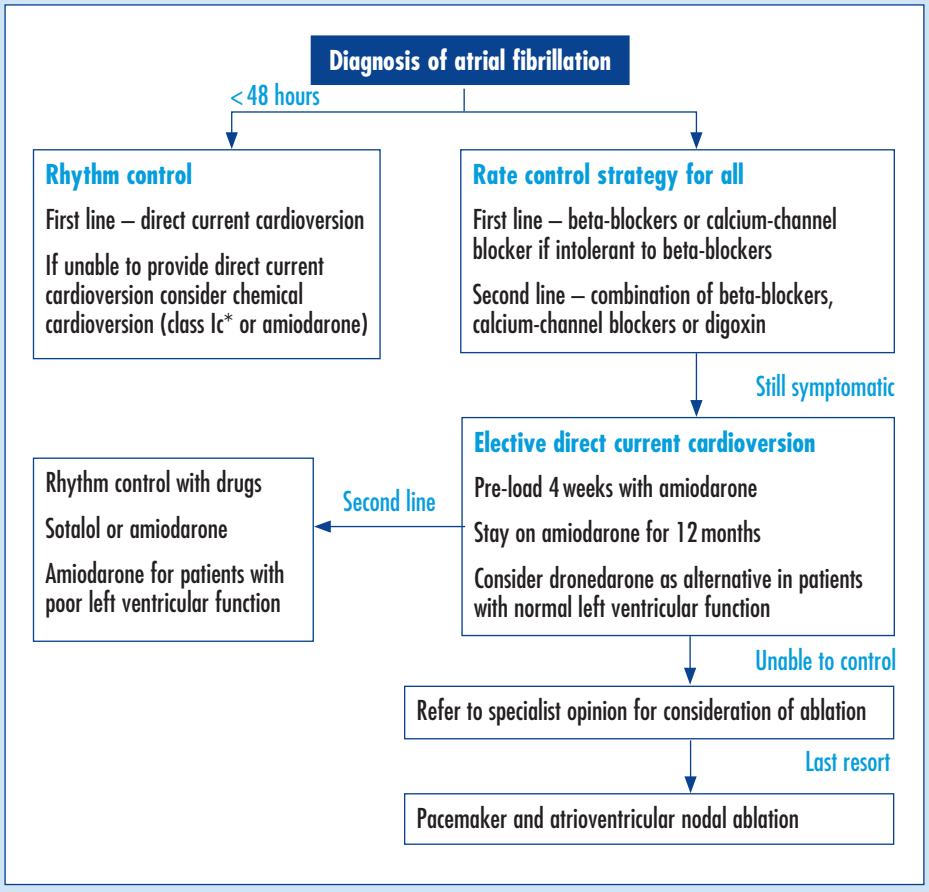
Figure 2 shows the treatment strategies available for atrial fibrillation.

Rate control

In 2006, National Institute for Health and Care Excellence gave equal weighting to both rate control and rhythm control but the 2014 guidelines reflect a shift in favour of a rate control strategy. National Institute for Health and Care Excellence now recommend rate control as first-line strategy for all people with atrial fibrillation. Rhythm control can be considered in those with atrial fibrillation with a reversible cause, heart failure caused by atrial fibrillation or new onset atrial fibrillation.

The landmark AFFIRM study showed no overall difference in terms of mortality

Figure 2. Treatment strategies for atrial fibrillation. *Class Ic drugs (flecainide and propafenone) only to be used if no coronary artery disease and structurally normal heart.



in either strategy (Wyse et al, 2002). However, the rate control arm was associated with lower rates of hospitalization and adverse drug effects.

The agents recommended for rate control have not changed. Beta-blockers or rate-limiting calcium-channel blocker monotherapy remains first line and combination therapy is considered with any two of a beta-blocker, calcium-channel blocker or digoxin if symptoms are poorly controlled. The main change is that amiodarone is not to be offered as long-term rate control, largely because of the potential for adverse effects with prolonged exposure. Digoxin can be offered as first line in patients with non-paroxysmal atrial fibrillation who are sedentary.

Rhythm control

In addition to what has previously been mentioned, rhythm control is considered in people with symptomatic atrial fibrillation or poorly controlled rate after attempting a rate control strategy. Drugs used in this strategy include the class Ic (flecanide and propafenone) and class III (amiodarone, sotalol) antiarrhythmic agents. As the current guideline mainly favours electrical cardioversion to restore sinus rhythm, there is no clear mention which drug should be used as first line. Sotalol and amiodarone are equally efficacious in converting atrial fibrillation into sinus rhythm (Singh et al, 2005). It is worth noting that sotalol at a low dose is essentially a beta-blocker and only manifests its class III properties at doses above 240 mg. Its side-effect profile is more favourable than that of amiodarone. However, sotalol is contraindicated in patients with uncontrolled congestive cardiac failure and who have a long QT interval.

Maintaining sinus rhythm

A standard beta-blocker is recommended for the maintenance of sinus rhythm. Amiodarone can be considered for patients with left ventricular impairment or heart failure. In the 2014 guidelines, class I agents are mentioned as options for restoring sinus rhythm but have fallen out of favour for long-term maintenance. In fact the 2014 National Institute for Health and Care Excellence guidelines specifically state that class I antiarrhythmic agents should not be offered to patients with coronary artery disease or structural heart disease. The recommendation is likely extrapolated from data derived from post-myocardial infarction antiarrhythmic trials, which showed a harmful effect of these drugs. However, class I agents can still be use for chemical cardioversion in the younger patient with no coronary artery disease and a structurally normal heart.

Dronedarone is a new addition since 2006 and is recommended for maintenance of sinus rhythm after successful cardioversion or in people with paroxysmal atrial fibrillation. It is not to be used in patients with permanent atrial fibrillation. This is a second-line therapy usually after failure to control atrial fibrillation with beta-blockers and in patients who have at least one of the following risk factors: uncontrolled hypertension despite two different drug classes, diabetes mellitus, history of transient ischaemic attack, stroke or systemic embolism, left atria >50 mm and age >70 years. It is essential to note that dronedarone is contraindicated in patients with left ventricular systolic dysfunction as it increases mortality in these patients (Køber et al, 2008). Dronedarone is also not effective in controlling ventricular rhythm disturbances and liver function tests should be monitored with its use.

Cardioversion

In the new guidelines, electrical cardioversion is preferred over chemical cardioversion in patients whose atrial fibrillation has lasted for more than 48 hours. They also recommend commencing amiodarone 4 weeks before and up to 12 months after electrical cardioversion to maintain sinus rhythm. The efficacy of long-term maintenance of sinus rhythm is greater in patients pre-loaded with amiodarone.

The era of ablation

Left atrial ablation is recommended in patients with both paroxysmal and persistent atrial fibrillation. However, it is only offered if drug treatment is unsuitable or has failed to control symptoms. This is in contrast with the European Society of Cardiology guidelines for paroxysmal atrial fibrillation where catheter ablation can be considered as first line. Data from the MANTRA-AF (Cosedis Nielsen et al, 2012) and RAAFT II (Wazni et al, 2005) trials showed better symptomatic control in the ablation group. Although ablation can be both clinically and cost effective in selected patients with paroxysmal atrial fibrillation, often more than one procedure is required. In patients with persistent atrial fibrillation, the success rates are much lower despite multiple attempts and National Institute for Health and Care Excellence has likely taken into account the clinical cost effectiveness of ablation as a first-line strategy under these circumstances.

National Institute for Health and Care Excellence (2014) recommends that surgical ablation should be considered in patients with symptomatic atrial fibrillation undergoing cardiac surgery. Surgical ablation is cost effective and carries a very good long-term outcome, but remains a complex procedure with the risk of serious complications (Abreu Filho et al, 2005; Lamotte et al, 2007).

Pace and ablate

Atrioventricular node ablation and pacemaker insertion features in the National Institute for Health and Care Excellence (2014) guidelines. This should be a last resort as it is an irreversible process. National Institute for Health and Care Excellence recommendations for this treatment differ for both paroxysmal and persistent atrial fibrillation.

TOP TIPS

- Assess stroke and bleeding risk using CHA2-D2-VASc and HAS-BLED scores for all patients with atrial fibrillation.
- Have a low threshold for starting anticoagulation.
- Consider direct oral anticoagulants in appropriate patients.
- If rate control is ineffective consider rhythm control favouring electrical direct current cardioversion.
- In cases of difficult to control atrial fibrillation speak to cardiology early to consider invasive therapy, e.g. ablation or a pace and ablate strategy.

In patients with persistent atrial fibrillation, this strategy can be considered in symptomatic patients despite optimal medical therapy or left ventricular dysfunction thought to be caused by high ventricular rates. National Institute for Health and Care Excellence also recommend a repeat assessment of symptoms after the insertion of a pacemaker and further optimization of drug therapy to ascertain if ablation is still required. Owing to the higher success rates of left atrial ablation in patients with paroxysmal atrial fibrillation than those with persistent atrial fibrillation, the guidelines recommend that atrial fibrillation ablation should be considered in patients with paroxysmal atrial fibrillation before a pacemaker and atrioventricular nodal ablation strategy.

Conclusions

The National Institute for Health and Care Excellence (2014) guidelines are a much-needed update to guide physicians through the management of the most common sustained cardiac arrhythmia with an increasing prevalence mainly in an elderly population. The guidelines advise a global risk assessment for all patients to encompass bleeding risk as well as risk for stroke prevention and encompass our better understanding of the lack of efficacy of antiplatelets in stroke prevention. Treatment options are now wider, with newer anticoagulant drugs that provide effective alternatives for patients in whom warfarin may be ineffective, and the emphasis is very much on a rate-controlling strategy. Catheter ablation continues to have an important role and can be very effective as an early approach in selected patients with paroxysmal atrial fibrillation but the emphasis remains on medical therapy in the first instance. **BJHM**

Conflict of interest: none.

KEY POINTS

- Stroke prevention and symptom control are the two main facets of management of atrial fibrillation.
- Stroke risk needs to be comprehensively evaluated but bleeding risk cannot be ignored.
- Antiplatelets lack efficacy and anticoagulation with warfarin or direct oral anticoagulants should be used in all except truly low risk patients.
- Rate control is now the preferred strategy.
- If rhythm control is considered, electrical cardioversion is preferred to chemical cardioversion.
- Invasive electrophysiology is gathering evidence and is a useful adjunct to current modalities of treatment.

Abreu Filho CAC, Lisboa LAF, Dallan LAO et al (2005) Effectiveness of the maze procedure using cooled-tip radiofrequency ablation in patients with permanent AF and rheumatic mitral valve disease. *Circulation* **112**(9 suppl): 120–5

Camm AJ, Lip GY, De Caterina R et al; ESC committee for practice (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* **33**(21): 2719–47 (doi: 10.1093/eurheartj/ehs253)

Connolly SJ, Ezekowitz MD, Yusuf S et al; RE-LY Steering Committee and Investigators (2009a) Dabigatran vs. warfarin in patients with atrial fibrillation. *N Engl J Med* **361**: 1139–151 (doi: 10.1056/NEJMoa0905561)

Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S (2009b) Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* **360**: 2066–78 (doi: 10.1056/NEJMoa090130)

Cosedis Nielsen J, Johannessen A, Raatikainen P et al (2012) A randomized comparison of radiofrequency ablation and antiarrhythmia drug therapy as first line treatment in paroxysmal atrial fibrillation. *N Engl J Med* **367**(17): 1587–95 (doi: 10.1056/NEJMoa1113566)

Eikelboom JW, Connolly SJ, Brueckmann M et al (2013) Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* **369**: 1206–14 (doi: 10.1056/NEJMoa1300615)

Granger CB, Alexander JH, McMurray JJ et al; ARISTOTLE Committees and Investigators (2011) Apixaban vs. warfarin in patients with atrial fibrillation. *N Engl J Med* **365**: 981–92 (doi: 10.1056/NEJMoa1107039)

Halligan SC, Gersh BJ, Brown RD Jr et al (2004) The natural history of lone atrial flutter. *Ann Intern Med* **140**: 265

Holmes DR, Reddy VY, Turi ZG et al (2009) Percutaneous closure of the left atrial appendage vs. warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised noninferiority trial. *Lancet* **374**: 534–42 (doi: 10.1016/S0140-6736(09)61343-X)

Holmes DR Jr, Kar S, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY (2014) Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL study. *J Am Coll Cardiol* **64**(1): 1–12 (doi: 10.1016/j.jacc.2014.04.029)

Køber L, Torp-Pedersen C, McMurray JJ et al (2008) Increased mortality after dronaderone therapy for severe heart failure. *N Engl J Med* **358**(25): 2678–87 (doi: 10.1056/NEJMoa0800456)

Lamotte M, Annemans L, Bridgewater B et al (2007) A health economic evaluation of concomitant surgical ablation for atrial fibrillation. *Eur J Cardiothorac Surg* **32**(5): 702–10

Lip GYH, Nieuwlaat R, Pisters R et al (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor based approach: the Euro Heart survey on atrial fibrillation. *Chest* **137**: 263–72 (doi: 10.1378/chest.09-1584)

Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E (2007) 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* **370**: 493–503

National Institute for Health and Care Excellence (2012) Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. Technology Appraisal 249. www.nice.org.uk/guidance/ta249/resources/guidance-dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-pdf (accessed 15 June 2015)

National Institute for Health and Care Excellence (2014) Atrial fibrillation: the management of atrial fibrillation. CG180. www.nice.org.uk/guidance/cg180/resources/guidance-atrial-fibrillation-the-management-of-atrial-fibrillation-pdf (accessed 15 June 2015)

Nijjer SS, Lefroy DC (2012) Atrial fibrillation. *Br J Hosp Med* **73**(5): C69–73 (doi: 10.12968/hmed.2012.73.Sup5.C69)

Park JW, Bethencourt A, Sievert H et al (2011) Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv* **77**: 700–6 (doi: 10.1002/ccd.22764)

Patel MR, Mahaffey KW, Garg J et al; ROCKET AF Investigators (2011) Rivaroxaban vs. warfarin in nonvalvular atrial fibrillation. *N Engl J Med* **365**: 883–91 (doi: 10.1056/NEJMoa1009638)

Siegal DM, Cuker A (2013) Reversal of novel oral anticoagulants in patients with major bleeding. *J Thromb Thrombolysis* **35**(3): 391–8 (doi: 10.1007/s11239-013-0885-0)

Singh BN, Singh SN, Reda DJ et al (2005) Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* **352**(18): 1861–72

Stewart S, Hart CL, Hole DJ, McMurray JJ (2001) Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. *Heart* **86**: 516–21

Wazni OM, Marrouche NF, Martin DO et al (2005) Radiofrequency ablation vs antiarrhythmic drugs as firstline treatment of symptomatic atrial fibrillation: A randomized trial. *JAMA* **293**: 2634–40

Wyse DG, Waldo AL, DiMarco JP et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* **347**: 1825–33