Management of atrial fibrillation: when are invasive approaches useful?

The management of atrial fibrillation extends from stroke prevention to rate or rhythm control strategies. The role of an invasive strategy is expanding and it remains important to identify suitable candidates early in the disease process.

Atrial fibrillation is the most common arrhythmia of clinical significance with reported global estimated age-adjusted incidence rates of 60.7 per 100 000 person-years in men and 43.8 in women (Chugh et al, 2014). The UK prevalence of atrial fibrillation has been reported as around 4% (Sudlow et al, 1998). It is anticipated that the prevalence of atrial fibrillation will increase dramatically over the next few decades because of the aging population, improved cardiovascular therapies and longer survival of patients with heart disease (Miyasaka et al, 2006).

Atrial fibrillation causes troublesome symptoms in approximately two thirds of affected individuals and doubles the mortality in both younger and older individuals (Benjamin et al, 1998). Atrial fibrillation independently increases the risk of stroke by up to fivefold (Wolf et al, 1991) and is an independent predictor for 30-day and 1-year mortality following ischaemic stroke (Marini et al, 2005). Individuals with atrial fibrillation are also at increased risk of heart failure (Wang et al, 2003). Atrial fibrillation is therefore associated with significant morbidity and mortality.

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The causative mechanism for atrial fibrillation-related stroke is thought to be embolism of thrombus from the left atrial appendage to the cerebral circulation. Oral anticoagulation with warfarin reduces the risk of stroke by about two thirds (Andersen et al, 2008). Novel oral anticoagulant agents are at least as effective as warfarin at preventing stroke with a lower risk of intracranial haemorrhage (Capodanno et al, 2013). All patients with a high risk of stroke without contraindications should therefore be treated with oral anticoagulant therapy (January et al, 2014). High stroke risk has been demonstrated in patients with a CHA_2DS_2 VASc score of ≥1 (*Table 1*) and therefore guidelines emphasize that anticoagulation should be considered in these patients (January et al, 2014). HAS-BLED score can be use to assess patients' annual bleeding risk which can help assess the benefit of anticoagulation for stroke prevention *vs* its associated risk (Pisters et al, 2010). Further to this, recurrent falls in elderly patients should not normally be considered a contraindication to anticoagulation. This is supported by a meta-analysis which determined that a patient with a 5% annual stroke risk from atrial fibrillation would need to fall 295 times in a year for the falls risk to outweigh the stroke reduction benefit of anticoagulation (Man-Son-Hing et al, 1999).

Table 1. The CHA_2DS_2 VASc risk scoring system

CHA_2DS_2 VASc	Score
Congestive heart failure or left ventricular ejection fraction ≤40%	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
Stroke, transient ischaemic attack or thromboembolism	2
Vascular disease	1
Age 65–74 years	1
Female	1

From Andersen et al (2008)

The management of atrial fibrillation has long been a debate between a rate control *vs* a rhythm control strategy. Although observational studies have suggested that achieving sinus rhythm reduces mortality (Pappone et al, 2003), randomized controlled trials have failed to demonstrate any difference in outcomes between rate control and rhythm control using conventional approaches (i.e. medication and electrical cardioversion) (Wyse et al, 2002; Carlsson et al, 2003). As rate control is therefore assumed to be non-inferior to rhythm control in terms of outcome, symptoms still play a fundamental role in deciding long-term management in these patients.

In patients with paroxysmal atrial fibrillation and symptoms the aim is to reduce the atrial fibrillation burden and maintain sinus rhythm. This can be achieved with the use of antiarrhythmic drugs or catheter ablation and there are pros and cons to either approach. Catheter ablation has a small up-front procedural risk with a major complication rate of 3–4% but with freedom from paroxysmal atrial fibrillation in approximately 70% of patients after a single procedure, rising to approximately 90% if allowing for a repeat procedure. With antiarrhythmic drugs there are side effects and often incomplete control of symptoms. If used as first line it seems the two approaches have similar outcomes in the medium term (Walfridsson et al, 2015). However, in those with symptomatic paroxysmal atrial fibrillation despite antiarrhythmic drugs, catheter ablation is superior to ongoing treatment with other antiarrhythmic drugs (Pappone et al, 2006; Stabile et al, 2006). In patients with persistent atrial fibrillation the management (rate or rhythm control) is also guided by symptoms.

Given that rate control seems to have a non-inferior outcome to rhythm control, in most instances rate control will be attempted first and rhythm control reserved for those who remain symptomatic despite this. This decision will also be tempered by the likelihood of an ablation strategy being successful. When deciding on the most appropriate management approach for patients with atrial fibrillation it is important to take into account existing comorbidities and also the patient's wishes. Further to this, clinicians must be prepared to reassess over time in case a change in strategy is required.

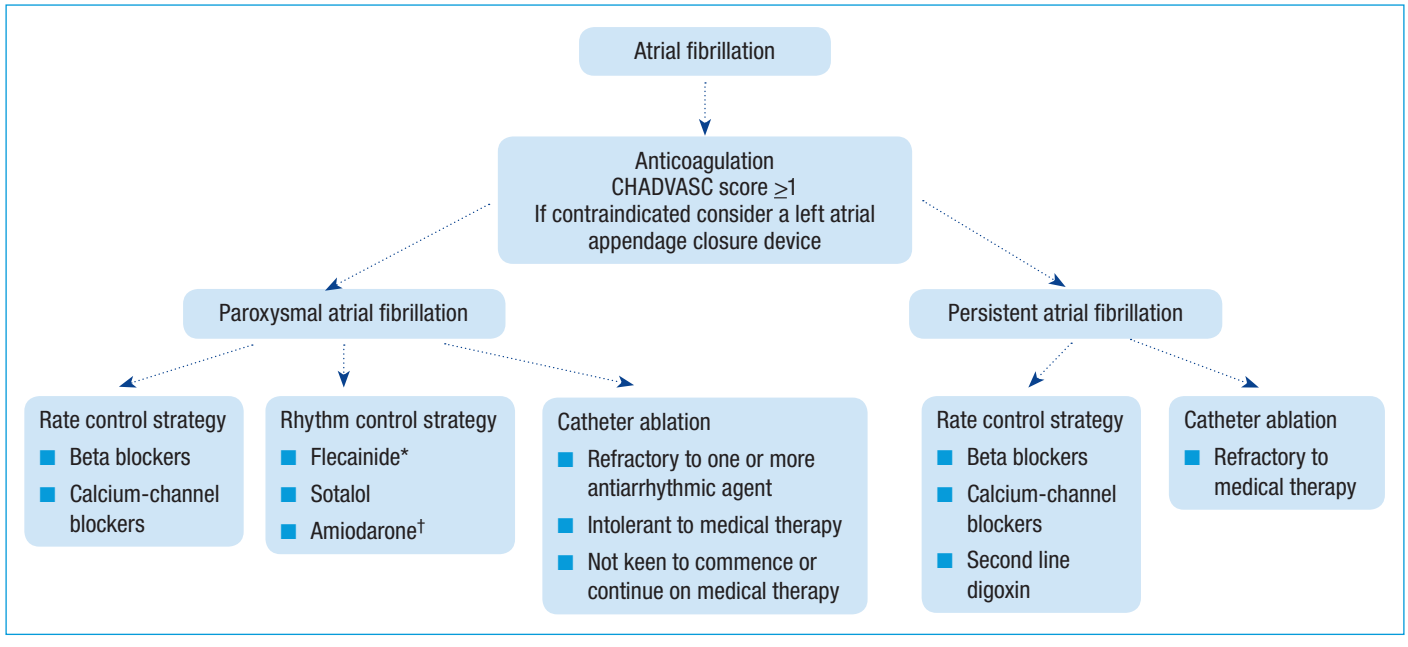
Treatment

Figure 1 outlines treatment strategies for atrial fibrillation.

Anticoagulation

All patients with atrial fibrillation should have stroke risk assessed at the point of diagnosis to evaluate their risk of ischaemic cerebrovascular events. Without a significant HAS-BLED score or contraindications anticoagulation should be commenced in those deemed to be high risk (January et al, 2014). Stroke risk is currently calculated most commonly using the CHA_2DS_2 VASc score. In those with a CHA_2DS_2 VASc score of 0 there is no indication for anticoagulation unless the patient is being considered for electrical cardioversion or catheter ablation. Women with no other risk factors are not at elevated risk of stroke and hence do not score a point for gender alone – therefore female gender alone is not an indication for anticoagulation. Furthermore, antiplatelet agents appear to have little if any effect on stroke risk and are now thought to have no role in stroke prevention for atrial fibrillation-related stroke. Therefore, if patients are at low risk and do not require anticoagulation, or are at risk but have a contraindication to anticoagulation, antiplatelets still have no role. There is still immense interest in refining stroke risk and recent work using a composite of clinical

Figure 1. Treatment strategies for atrial fibrillation. *Given together with an atrioventricular nodal blocker, i.e. beta blocker or calcium-channel blocker. †Avoid long-term in view of side-effect profile, unless there is a lack of an alternative.



> Patients who seem to be high risk for anticoagulation ought to be reviewed by a heart rhythm specialist before simply accepting a high stroke risk off anticoagulation.

characteristics and plasma biomarkers (NT-proBNP and high sensitivity troponin) has shown great promise (Hijazi et al, 2016). Systems incorporating clinical characteristics, plasma biomarkers and possibly imaging may yet change the process of risk stratification dramatically and this field will likely move quickly over the coming years.

Approximately 90% of intracardiac thrombus in patients with atrial fibrillation forms in the left atrial appendage. Percutaneous left atrial appendage closure devices were therefore established as an alternative to systemic anticoagulation (Holmes et al, 2014). In 2009 the landmark PROTECT AF trial demonstrated non-inferiority of percutaneous left atrial appendage closure compared to warfarin for stroke prevention in patients at high risk of stroke (Holmes et al, 2009). As with any preventative procedure there is an up-front procedural risk with a major complication rate in the region of 5%, with similar subsequent protection from stroke similar to oral anticoagulation but without the associated increase in bleeding risk.

With improvements to technology and increasing operator experience procedural safety continues to improve, making appendage closure look increasingly attractive (Reddy et al, 2011). Currently appendage closure is recommended for patients with atrial fibrillation who have a significant risk of thromboembolism (CHA_2DS_2 VASc score ≥ 1) but have an increased risk of bleeding with oral anticoagulation. Depending on the data that emerge and what health-care systems are prepared to fund, the indications may widen and this could progress to a situation where it is offered as an alternative simply guided by patient choice. With the availability of novel oral anticoagulants and left atrial appendage occlusion, patients who seem to be high risk for anticoagulation ought to be reviewed by a heart rhythm specialist before simply accepting a high stroke risk off anticoagulation.

Medical therapy

After the first and most important question 'Is anticoagulation required?' one must then consider rate control and rhythm control. Rather than consider these separate options, physicians are now encouraged to review these separately as the second and third management decisions. In all patients with atrial fibrillation it is important to control the ventricular rate which can be achieved with drugs such as beta-blockers or calcium-channel blockers. If these fail to control rate in isolation, digoxin can be added as second line.

In those with paroxysmal atrial fibrillation and symptoms despite rate control, the uses of antiarrhythmic drugs such as flecainide or sotalol help reduce atrial fibrillation burden. Flecainide should usually be prescribed with an atrioventricular nodal blocker to avoid rapidly conducted atrial flutter, whereas sotalol also has some beta-blocker action. Amiodarone can be used as an alternative if these are not effective or they are contraindicated. However, long-term use is difficult to justify because of amiodarone's side-effect profile. For those with persistent atrial fibrillation, medications alone are unlikely to restore sinus rhythm and a rhythm control strategy will require either DC cardioversion or catheter ablation.

Electrical cardioversion

Although electrical cardioversion of persistent atrial fibrillation is almost always successful acutely, atrial fibrillation recurs in the first month in 25–60% of patients (Fetsch et al, 2004). Therefore, it is commonplace to perform electrical cardioversion on antiarrhythmic drugs such as amiodarone to increase the chances of patients maintaining sinus rhythm for a meaningful period of time. Although cardioversion can provide symptom relief in the short term, if it is clear that symptoms are caused by atrial fibrillation, then clinicians are increasingly opting for invasive treatment such as catheter ablation or atrioventricular node ablation from the outset.

In patients with other comorbidities beyond atrial fibrillation which can cloud whether symptoms are related to atrial fibrillation or not, electrical cardioversion can be a useful 'diagnostic test' to determine whether symptoms are genuinely related to atrial fibrillation (i.e. whether symptoms are improved in sinus rhythm). This can be particularly useful for insidious symptoms such as fatigue or breathlessness. Increasingly electrical cardioversion is being used in this way as a diagnostic test to guide definitive therapy, rather than a destination in itself. Repeated cardioversions may in fact delay definitive treatment with catheter ablation which very much impacts on the chances of success with this. Really there is no reason patients should have repeated electrical cardioversions without planning definitive therapy. Therefore, where ablation is likely to be the best option it should be considered early. The inability to achieve sinus rhythm during electrical cardioversion had been assumed by some to mean that success from catheter ablation is unlikely; however, a small prospective study has demonstrated that catheter ablation in those with unsuccessful cardioversion has a success rate of 59% (Lü et al, 2013).

Catheter ablation

The management of atrial fibrillation has moved beyond medical therapy with a larger proportion of patients now being referred for catheter ablation (National Institute for Cardiovascular Outcomes Research, 2015). Improved technology, greater operator skills and better

understanding of the mechanism of atrial fibrillation have all contributed to improved success rates.

In randomized controlled trials catheter ablation is more effective than antiarrhythmic drugs in eliminating paroxysmal atrial fibrillation (Pappone et al, 2006; Stabile et al, 2006). Further to this, non-randomized studies have suggested that achieving long-term maintenance of sinus rhythm in unselected patients with paroxysmal or persistent atrial fibrillation through catheter ablation results in reduced mortality and morbidity, mainly as a result of reduced heart failure and ischaemic cerebrovascular events (Hunter et al, 2012; Bunch et al, 2013b). In those with heart failure, restoration of sinus rhythm by catheter ablation improves B-type natriuretic peptide levels, functional capacity and ejection fraction compared to rate control medical therapy (Hunter et al, 2014). A recent randomized trial compared catheter ablation to amiodarone for rhythm control in patients with atrial fibrillation and heart failure and showed reduced heart failure events and improved mortality with definitive restoration of sinus rhythm with ablation (Di Biase et al, 2016).

Success rates, allowing for a second procedure in a significant proportion, have been reported close to 90% in those with paroxysmal atrial fibrillation but lower for persistent atrial fibrillation at approximately 70–80% depending on the patient (*Table 2*) (Bhargava et al, 2009; Hunter et al, 2010; Ouyang et al, 2010; Medi et al, 2011; Rostock et al, 2011; Weerasooriya et al, 2011). Certain predictors, particularly in persistent atrial fibrillation, are used to guide the likely success from catheter ablation which is used to rationalize patient selection for these procedures. Duration of persistent atrial fibrillation seems to be a particularly important factor as success rates within the first 6 months of persistent atrial fibrillation are very similar to those for paroxysmal atrial fibrillation, but tail off markedly after more than 2 years in persistent atrial fibrillation (Tilz et al, 2012). There is accumulating evidence that delaying definitive treatment by ablation with repeated electrical cardioversion and other medical treatments very much impacts on the chances of maintaining sinus rhythm long-term (Bunch et al, 2013a) – catheter ablation is certainly more effective when used early in the disease process.

Left atrial size has also been shown to predict arrhythmia recurrence (*Table 3*) (Richter et al, 2006; Berruezo et al, 2007; Arya et al, 2010; Ouyang et al, 2010; Wokhlu et al, 2010; Weerasooriya et al, 2011; Scherr et al, 2015). A linear relationship with left atrial size and atrial fibrillation recurrence has been demonstrated (Berruezo et al, 2007), with the chances of maintaining sinus rhythm long term falling for those with a left atrial diameter >5 cm. Significant structural heart disease and in particular severe left ventricular impairment may also reduce the chances of lasting success, particularly for those with persistent atrial fibrillation (Ullah et al, 2016). This is difficult since patients with atrial fibrillation and heart failure may have the most to gain. Specialist input from an electrophysiologist will help to identify which patients ought to be considered for catheter ablation.

Table 2. Success rates for single and multiple catheter ablation procedures for paroxysmal and persistent atrial fibrillation

Reference	Enrolment period	Type of atrial fibrillation	Cohort size	Ablation strategy	Follow-up (months)	Success at 1 year for single procedure %	Success at max. follow up for single procedure %	Multi procedure success at max. follow up %
Bhargava et al (2009)		Paroxysmal	728	Radiofrequency pulmonary vein isolation	57 ± 17		77.6	92.4
		Persistent and permanent	676	Radiofrequency pulmonary vein isolation	57 ± 17		67.2	84
Hunter et al (2010)	2001–6	Paroxysmal	151	Radiofrequency pulmonary vein isolation	32.4 (2.4–88.8)	30		86
		Persistent	134	Radiofrequency pulmonary vein isolation + linear lesions	32.4 (2.4–88.8)	40		68
Ouyang et al (2010)	2003–4	Paroxysmal	161	Radiofrequency pulmonary vein isolation	4.8 (0.33–5.5)	78	46.6	79.5
Medi et al (2011)		Paroxysmal	100	Radiofrequency pulmonary vein isolation	39 ± 10	86	49	82
Rostock et al (2011)		Persistent	395	Radiofrequency pulmonary vein isolation	27 ± 7	27		79
Weerasooriya et al (2011)	2001–2	Paroxysmal and persistent	100	Radiofrequency pulmonary vein isolation	Max 60	40	29	63

Table 3. Predictors for atrial fibrillation recurrence following catheter ablation

Reference	Predictors for atrial fibrillation recurrence post catheter ablation	Hazard ratio, odds ratio and relative risk; 95% confidence intervals	Follow up
Scherr et al (2015)	Failure to terminate atrial fibrillation during index procedure	3.83; 2.1–7.1, *P*<0.001	Median 70 months (60–81)
	Left atrial diameter ≥50 mm	2.08; 1.08–4.02, *P*=0.03	
	Continued atrial fibrillation duration ≥18 months	1.87; 1.04–3.39, *P*=0.04	
Arya et al (2010)	Left atrial diameter ≥5 mm	4.6; 2.6–9.1, *P*<0.0001	Max. 1 year
	Arterial hypertension	4.6; 2.6–9.1, *P*=0.003	
	Atrial fibrillation duration >21 months	0.13; 0.06–0.51, *P*=0.002	
Wokhlu et al (2010)	Diabetes	1.9; 1.3–2.9, *P*=0.002	Mean 3 years ± 1.9
	Persistent atrial fibrillation	1.6; 1.2–2.0, *P*<0.001	
Hunter et al (2010)	Persistent atrial fibrillation	*P*<0.01	Median 32.4 months (2.4–88.8)
	Female sex	*P*<0.05	
	Structural heart disease	*P*<0.01	
Weerasooriya et al (2011)	Persistent atrial fibrillation	1.9; 1–3.5, *P*=0.046	Max. 5 years
	Valvular heart disease	6.0; 2–17.6, *P*=0.001	
	Non-ischaemic dilated cardiomyopathy	34; 6.3–182.1, *P*<0.0001	

Based on the above evidence the existing guidelines have moved from a class IIA to a class I recommendation for catheter ablation in patients with symptomatic paroxysmal atrial fibrillation refractory to one or more antiarrhythmic drug, or when medical therapy is contraindicated as a result of comorbidities or intolerance (January et al, 2014). Guidelines also recognize a place for catheter ablation as first line in selected patients. As the success rate for ablation of persistent atrial fibrillation is lower than that for paroxysmal atrial fibrillation with a greater need for repeat procedures, the guideline recommendations remain a IIA classification. Owing to the beneficial effect seen in those with heart failure, catheter ablation is recommended in selected patients with left ventricular dysfunction (January et al, 2014).

Targeting pulmonary veins, aiming to isolate them electrically with encircling lines of scar, has been the cornerstone of catheter ablation for atrial fibrillation since its inception in the late 1990s (Pappone et al, 2000). This has conventionally been performed using point by point application of radiofrequency energy, but there are now circular catheters emitting radiofrequency energy around their circumference, and others that are balloon-based systems for applying laser energy or freezing (so-called 'cryo-energy'). The latter of these technologies, the cryoballoon, is the most widely used alternative to conventional point-by-point radiofrequency ablation, because it is at least as safe and successful as radiofrequency ablation and can be performed in under an hour as a day case procedure (Hunter et al, 2015; Kuck et al, 2016). The major complication rates associated with catheter ablation are approximately 3–4% and include vascular access complications (1%), cardiac tamponade (1%), stroke (0.2%), pulmonary vein stenosis (0.1%), phrenic nerve damage (0–2% depending on the technology used) and aorto-oesophageal fistula formation (< 0.1%) and death (0.1%) (Aldhoon et al, 2013).

With shorter procedure duration and low procedural risk, particularly with the cryoballoon ablation, the authors' and other centres have started performing pulmonary vein isolation procedures for atrial fibrillation in a district general hospital setting, using the simpler setup and proximity to day case hospital beds to perform a higher volume of cases as day cases. The authors' unit has performed over 200 ablations in such a setting over the last year. This model is arguably the future for provision of simple pulmonary vein isolation for atrial fibrillation, helping increase capacity and improving access for patients while at the same time freeing up tertiary centre space for more complex procedures.

The long-term use of anticoagulation after catheter ablation remains controversial. There are two arguments for continuation of anticoagulation regardless of an apparent cure by catheter ablation: first, it is likely that patients continue to have a small amount of asymptomatic atrial fibrillation from time to time whether they know it or not, and second it is still not entirely clear whether atrial fibrillation causes stroke or is simply a marker of increased stroke risk. Data suggest that the rate of stroke after successful catheter ablation of atrial fibrillation is very low (Hunter et al, 2012). However, randomized studies investigating the impact on stroke risk are ongoing. Therefore catheter ablation procedures should not be performed with the aim of discontinuing anticoagulation therapy. Guidelines currently recommend ongoing anticoagulation in those with significant stroke risk as for patients with ongoing atrial fibrillation (January et al, 2014).

Pace and ablate strategy

For patients with troublesome symptoms despite medical management, an alternative to catheter ablation attempting to cure atrial fibrillation is pacemaker implantation and atrioventricular node ablation. This has been associated with improved quality of life compared to continued antiarrhythmic treatment (Lim et al, 2007). It seems to be most effective for patients who are unable to achieve good rate control with medications, although the regularisation of heart rate alone may improve symptoms to some extent. The advantage to this approach is that it is low risk and has a fairly guaranteed outcome. The disadvantage compared

to curative catheter ablation is that it does not restore sinus rhythm and therefore may not resolve symptoms fully, and it requires a pacemaker. In real life this approach is often used for those who are frail and are thought not suitable for curative ablation, for those in whom ablation is unlikely to be successful, or in those whom catheter ablation has already been unsuccessful.

If the ejection fraction is ≤35% then it is important to ensure patients receive a cardiac resynchronization therapy device to prevent progression to heart failure with persistent right ventricular pacing (Brignole et al, 2013). Indeed in cardiac resynchronization therapy patients with persistent atrial fibrillation, rapidly conducted atrial fibrillation not responsive to atrioventricular node blocking drugs compromises the percentage of biventricular pacing. Outcomes appear to be worse for cardiac resynchronization therapy patients even when biventricular pacing percentage is <98% and in these patients atrioventricular node ablation should be strongly considered. This reduces all-cause and cardiovascular mortality and improves New York Heart Association functional class compared to sole medical therapy (Ganesan et al, 2012). It is a quick and simple day case procedure with a complication rate approaching 0%.

Conclusions

Atrial fibrillation is a common arrhythmia and its prevalence is rising. Catheter ablation is an effective treatment in symptomatic patients particularly when used early in the disease process (i.e. paroxysmal or early persistent atrial fibrillation). Difficult decisions often emerge with regards to rhythm control in patients with significant structural heart disease and heart failure in particular. Early review by an electrophysiologist is essential to obtain the best outcome for those who might benefit from catheter ablation. The single most important factor in management of atrial fibrillation remains stroke prevention. With the risk scoring algorithms to decide who is at risk, education programmes to make sure physicians act, and the advent of novel oral anticoagulants and left atrial appendage closure as alternatives to warfarin, it is hoped that more patients will be treated appropriately to prevent atrial fibrillation-related stroke. **BJHM**

Conflict of interest: none.

KEY POINTS

The management priorities for all patients with atrial fibrillation are:

- Assess stroke risk and treat if high risk.
- Ensure ventricular rate is controlled in atrial fibrillation.
- If symptomatic despite rate control consider rhythm control.
- Selection for rhythm control is guided by symptoms.
- Catheter ablation is best considered early in the disease process when it is most effective.
- Repeated electrical cardioversions is not a valid approach to managing atrial fibrillation.
- Heart rhythm specialists should work directly with GPs and other specialties to reach patients early.
- With novel oral anticoagulants and appendage closure there are many options for stroke prevention and complex patients should see a heart rhythm specialist.

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