Advances in therapy for atrial fibrillation

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Two epidemiological studies have demonstrated that the lifetime prevalence of atrial fibrillation (AF) among people aged 40 years or more is roughly one in four [1,2]. AF increases in prevalence with age, ranging from 0.5% in people aged 50–59 years to almost 9% in those aged 80 years or more, and is associated with a high risk of morbidity and mortality from heart failure, stroke and thromboembolic complications [3]. In addition, when strokes do occur in association with AF, patients have a substantial mortality, morbidity, disability and longer hospital stays [3].

In patients with AF there are two important decisions to make:

- Whether to employ a rate- or rhythm-control strategy;
- What antithrombotic regimen to utilize.

For younger, symptomatic patients, and those with paroxysmal or persistent AF (<1 year duration), a rhythm-control strategy to restore and maintain sinus rhythm may be the preferred option, but cardioversion and antiarrhythmic drugs are not without their problems, as discussed by Fitzmaurice [4], Singh and Singh [5], and others in this themed issue of *Therapy*. The other, perhaps more important consideration given the associated thromboembolic complication of AF, is whether or not to anticoagulate patients. Currently, guidelines recommend anticoagulation for patients at high risk of stroke and aspirin for those at low risk. However, the antithrombotic treatment recommendations for those patients at moderate risk, often the majority of patients based on current stroke risk stratification schema, are ambiguous, suggesting either aspirin or warfarin. Despite the evidence from clinical trials that thromboprohylaxis with warfarin significantly reduces the incidence of stroke and mortality [101], such therapy still remains grossly underutilized. This underutilization is due, in part, to the inherent difficulties associated with warfarin, such as the inconvenience of regular monitoring, interactions with drug/alcohol/diet, difficulties managing therapeutic international normalized ratios (INRs) and dose adjustments, all of which have led to the development of novel anticoagulants; the forerunner, dabigatran, is discussed by several of the authors in this themed issue. There are also several other 'new' oral anticoagulants currently under examination in clinical trials, such as rivaroxaban, apixaban, AZD0837, DU-176 and so on, and we eagerly await the results of these trials. These are exciting times in the management of AF, with the emergence of promising new antiarrhythmic drugs, vernakalant and dronedarone, and novel oral anticoagulants, such as dabigatran, among others.

This themed issue provides an excellent overview of the evidence regarding the current rhythm-control strategies and antithrombotic management options for patients with AF, as well as the exciting new antiarrhythmic and anticoagulant drugs that are emerging, which will hopefully transform the management of AF, in particular antithrombotic therapy.

Four review articles cover a diverse range of topics from gender differences in AF to new perspectives in the mechanisms of AF. Kühne and Conen's excellent review of gender differences in AF provides an insight into the epidemiology of AF in women, describing the risk factors associated with AF among women and focusing on the implications of female gender in the presentation and management of AF [6]. Evidence suggests that women have poorer AF-related outcomes, which may be associated with gender differences in the treatment of AF, although the authors conclude that the pathophysiological mechanisms to explain gender differences in AF are missing and further studies are needed.

The benefits and complications of ablation therapy for AF are comprehensively reviewed by Shin and Deneke, who suggest that whilst the treatment is very effective, efficacy needs to be improved [7]. Singh and Singh then review emerging drugs for the management of AF, including rhythm-control and oral anticoagulation. Their article focuses mainly on two new antiarrhythmic drugs, vernakalant and dronedarone [5]. Vernakalant and the results of the three Atrial Arrhythmia Conversion Trials (ACT) [8–10], also discussed in the Research

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Highlights by Elder *et al.* [11], seem a viable option for the pharmacological conversion of AF, but currently await final FDA approval. The evidence from the ATHENA trial [12] suggests that dronedarone is associated with a significant reduction in cardiovascular hospitalizations or death (mainly driven by a reduction in AF-related hospitalizations), although results from the ANDROMEDA trial [13] mean that dronedarone is absolutely contraindicated in patients with recent symptomatic or decompensated heart failure. This excellent review also briefly discusses two new oral anticoagulants: tecarfarin, a structural analog of warfarin, and the direct oral thrombin inhibitor, dabigatran, the latter of which is discussed in more detail in the Research Highlights by Elder *et al.* [11] and in the two Editorials by Sullivan and Olshansky [14], and Fauchier *et al* [15].

The molecular basis of alternations in sacroplasmic reticulum Ca^{2+} handling in AF and their potential therapeutic implications is the focus of a review by Wehrens *et al* [16]. It has been suggested that changes in the sacroplasmic reticulum Ca^{2+} homeostasis might contribute to a reduced contractile function and promote arrhythmogenesis in the atria. Pharmacological inhibition of aberrant SR Ca^{2+} release might be a promising new strategy for the treatment of AF.

Fitzmaurice controversially asks whether there is a role for cardioversion in the modern management of AF in a Perspective article [4]. He argues for the abolition of electrical cardioversion in the routine management of AF, given that several randomized controlled trials of rate- versus rhythm-control (AFFIRM, STAF, HOT CAFE) [17] have all demonstrated that electrical cardioversion does not confer a mortality benefit over rate-control and that the antiarrhythmic drugs needed to maintain sinus rhythm may actually be associated with increased mortality. He asserts that the place for electrical cardioversion is in the acute setting or for those who remain symptomatic despite optimal medical therapy, where long-term anticoagulant therapy should also be continued.

The management of thromboembolism in AF patients is the focus of an Editorial by Sullivan and Olshansky, highlighting the importance of stroke risk stratification with newer schema, such as CHA_2DS_2-VASc [18], to identify patients who may benefit from oral anticoagulation. This Editorial highlights the inherent difficulties associated with warfarin therapy: maintenance of a therapeutic INR, increased risk of bleeding, underutilization of warfarin, to name but a few, resulting in the journey to discover an alternative to warfarin, the most promising of which to date is dabigatran. Some of the advantages of the latter drug over warfarin (fixed dose, no monitoring and rapid anticoagulant effect) but also some of the problems that may limit its applicability (dyspepsia, price/affordability for patients, safety/efficacy in AF patients with acute coronary syndromes requiring percutaneous coronary intervention ± stent, and patient willingness to switch from a stable, established oral anticoagulation), should it be granted FDA approval, are discussed.

Another Editorial discusses the controversial topic of the most appropriate antithrombotic treatment for AF patients with a $CHADS_2$ score of 1, who are defined as being at 'moderate risk' of stroke with an annual stroke risk of 2–4% [3], where current guidelines recommend either aspirin or warfarin [3,19,20,101]. This Editorial by Fauchier *et al.* [15] examines the risks and benefits of anticoagulation in such patients, drawing upon *post hoc* analyses from recent antithrombotic trials in AF patients where the evidence for the benefit of warfarin among such patients is conflicting. They argue for refinement of stroke risk stratification to prevent the majority of patients being defined as moderate risk, where current treatment guidance is dependent on physician discretion, patient preference and development of bleeding risk predictors.

Finally, in the Research Highlights section, Elder *et al.* focus on some recent drug developments for use in AF patients [11]. First, they examine the results of the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study [21], where dabigatran 150 mg twice daily or 110 mg, a direct oral thrombin inhibitor, were compared with warfarin. The RE-LY study demonstrated that dabigatran 150 mg twice daily had superior efficacy to warfarin, with a similar bleeding risk, whilst dabigatran 110 mg twice daily demonstrated a similar efficacy to warfarin but with a significant reduction in major bleeding, particularly intracranial hemorrhage, compared with warfarin [21]. Second, they discuss vernakalant, an atrial-selective early activating potassium and frequency-dependent sodium channel blocker. The ACTs (I–III) [9–11] have demonstrated the efficacy and safety of vernakalant in AF patients, and we currently await the results of the AVRO trial, where vernakalant is being tested in a head-to-head comparison with amiodarone. The third paper reviewed by Elder *et al.* concerns the use of polyunsaturated fatty acids in the prevention of postoperative

AF. Although existing results are disappointing, we await the results of larger randomized controlled trials to define the role of polyunsaturated fatty acids in postcoronary artery bypass graft patients.

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Bibliography

1 Heeringa J, van der Kuip DAM, Hofman A *et al.*: Prevalence, incidence and lifetime risk of atrial fibrillation: The Rotterdam study. *Eur. Heart J.* 27, 949–953 (2006).

2 Lloyd-Jones DM, Wang TJ, Leip EP *et al.*: Lifetime risk for development of atrial fibrillation: The Framingham Study. *Circulation* 110, 1042–1046 (2004).

3 Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ: Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 285, 2864–2870 (2001).

4 Fitzmaurice DA: Is there a role for cardioversion in the management of atrial fibrillation? *Therapy* 7(2), 159–162 (2010).

5 Singh D, Singh S: Emerging drugs for atrial fibrillation. *Therapy* 7(2), 125–132 (2010).

6 Kuhne M, Conen D: Atrial fibrillation in women. *Therapy* 7(2), 139–146 (2010).

7 Shin D-I, Deneke T: Ablation catheters for atrial fibrillation: benefits and complications. *Therapy* 7(2), 133–138 (2010).

8 Roy D, Rowe BH, Stiell IG *et al.*: A randomized, controlled trial of RSD1235, a novel antiarrhythmic agent, in the treatment of recent onset atrial fibrillation. *J. Am. Coll. Cardiol.* 44, 2355–2361 (2004).

9 Roy D, Pratt CM, Torp-Pedersen C *et al.*: Vernakalant hydrochloride for rapid conversion of atrial fibrillation: a Phase 3, randomized, placebo-controlled trial. *Circulation* 117, 1518–1525 (2008).

10 Kowey P, Dorian P, Mitchell LB *et al.*: Vernakalant hydrochloride for the rapid conversion of atrial fibrillation following cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ. Arrhythm. Electrophysiol.* (2009) (Epub ahead of print).

11 Elder DHJ, Pauriah M, Choy A, Lang CC: Research highlights. *Therapy* 7(2), 121–123 (2010).

12 Hohnloser SH, Crijns HJ, van Eickels M *et al.*: Effect of dronedarone on cardiovascular events in atrial fibrillation. *N. Engl. J. Med.* 360, 668–678 (2009).

13 Kober L, Torp-Pedersen C, McMurray JJ *et al.*: Increased mortality after dronedarone therapy for severe heart failure. *N. Engl. J. Med.* 358, 2678–2687 (2008).

14 Sullivan RM, Olshansky B: Managing thromboembolic risk in patients with atrial fibrillation: are we approaching a new frontier? *Therapy* 7(2), 107–110 (2010).

15 Fauchier L, Gorin L, Babuty D: How should we treat patients with atrial fibrillation and a $CHADS_2$ score of 1? *Therapy* 7(2), 111–115 (2010).

16 Wehrens XHT, Ather S, Dobrev D: Role of abnormal sarcoplasmic reticulum function in atrial fibrillation. *Therapy* 7(2), 147–158 (2010).

17 Boos CJ, Lane DA, Lip GYH: Chronic atrial fibrillation. *Clin. Evid. (Online)* pii:0217 (2008).

18 Lip GY, Nieuwlaat R, Pisters R, Lane D, Crijns H: 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(2) 263–272 (2009).

19 Fuster V, Rydén LE, Cannom DS *et al.*: ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 114, e257–e354 (2006).

20 Singer DE, Albers GW, Dalen JE *et al.*: Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 133, S546–S592 (2008).

21 Connolly SJ, Ezekowitz MD, Yusuf S *et al.*: RE-LY Steering Committee and Investigators: Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361, 1139–1151 (2009).

Website

101 Atrial fibrillation. National clinical guideline for management in primary and secondary care (2006) www.guideline.gov/summary/summary.aspx?doc_id=9629&mode=full&ss=15