

# Research Highlights

Highlights from the latest articles on atrial fibrillation



## Dabigatran: a RELY-able alternative to warfarin?

**Evaluation of:** Connolly SJ, Ezekowitz MD, Yusuf S *et al.*: Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361, 1139–1151 (2009).

Warfarin has been demonstrated to be effective in reducing stroke in high-risk patients with atrial fibrillation (AF) but is difficult to initiate, challenging to monitor and inconvenient for patients and practitioners alike. As the mainstay anticoagulant for the past 40 years, its specific limitations (dietary and drug interactions, and requirements for monitoring) has resulted in under-treatment of AF patients who are at high risk of stroke, particularly the elderly. However, the holy grail of stroke prevention in AF may be just around the corner with a new class of drug – the oral direct thrombin inhibitors – providing fixed dosing without the need to monitor, and with no known dietary and drug interactions.

Ximelagatran, the first oral direct thrombin inhibitor to undergo clinical trial in the Stroke Prevention using Oral Thrombin Inhibitor in AF (SPORTIF) studies [1], was withdrawn from further development owing to idiosyncratic hepatotoxicity, but was, nevertheless, shown to be similar, in terms of efficacy to warfarin in stroke reduction in high-risk AF patients. Importantly the SPORTIF studies demonstrated that this class of drug was effective in stroke reduction. Dabigatran, another oral direct thrombin inhibitor, has since been studied in the largest outcome study ever conducted in AF, and looks set to revolutionize care.

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study assessed the outcome in patients receiving either two different blinded doses (110 or 150 mg blinded dose) of dabigatran

or open-label warfarin for stroke prevention in AF, in the absence of valvular heart disease. The study recruited 18,113 patients in 44 countries and included patients considered to be at high risk for stroke (heart failure, previous stroke/transient ischemic attack, age 75 years and above or age 65 years and above with diabetes, hypertension or coronary artery disease).

The study fulfilled its primary end point, demonstrating that both doses of dabigatran were noninferior to warfarin in reducing the incidence of both ischemic and hemorrhagic stroke, and systemic embolism. The 150 mg dose was superior to warfarin in reducing stroke and systemic embolization by 34% (RR 0.66; 95% CI: 0.53–0.82,  $p < 0.001$ ). Importantly, the risk of major bleeding was no different for the 150 mg dose compared with warfarin, with the 110 mg dose exhibiting a 20% lower risk of major bleed ( $p = 0.003$ ). The 150 mg dose was, however, superior in respect of stroke or systemic embolization compared with the 110 mg dose ( $p = 0.005$ ).

The two doses are likely to be useful to the physician. The 110 mg dose may be well suited to the moderate-risk patient, where as in the patient with very high risk (e.g., previous stroke event), the higher bleeding risk may be acceptable given the reduction of stroke. Put simply, it provides the option of tiered therapy, which can be tailored to the individual with the knowledge that there is no increase in bleeding risk compared with warfarin.

### What is the downside?

There was an, as yet, unexplained higher rate of myocardial infarction with both doses of dabigatran compared with warfarin. Dabigatran is unsuitable for use in patients with severely impaired renal function (creatinine clearance  $<30$  ml/min) given that over 80% of the active drug is renally excreted. It is hoped that these

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### Financial & competing interests disclosure

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*No writing assistance was utilized in the production of this manuscript.*



concerns will be teased out in the ongoing safety follow-up study (RELY-ABLE).

There are further compounds on the horizon. Recently published data from a Phase II study with an alternative thrombin inhibitor (AZD0837) has also suggested it to be safe and well-tolerated compared with vitamin K antagonists [2].

It seems that dabigatran, already licensed in some countries for venous thrombosis prophylaxis, will also find a role in other uses of warfarin, such as venous thromboembolism. The RECOVER study demonstrated noninferiority with total bleeding events higher in the warfarin arm (HR 0.63;  $p = 0.002$ ) [3]. According to trial data, dabigatran promises to offer a reliable, efficacious and safe alternative to vitamin K antagonists for stroke prevention in patients with AF who are at high risk.

## References

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- 3 Schulman S, Kearon C, Kakkar AJ *et al.*: Dabigatran vs warfarin in the treatment of acute venous thromboembolism. *N. Engl. J. Med.* doi: 10.1056/NEJMoa0906598 (2009) (Epub ahead of print).

## Atrial selective therapy for AF: a further step forward

**Evaluation of:** Kowey PR, Dorian P, Mitchell LB *et al.*: Vernakalant hydrochloride for the rapid conversion of atrial fibrillation following cardiac surgery. *Circ. Arrhythm. Electrophysiol.* 2, 652–659 (2009).

Antiarrhythmic drugs currently available for cardioversion of atrial fibrillation (AF) often lack efficacy and are associated with significant side effects that may preclude their use in certain patient groups. The development of a new agent that is both safe and efficacious is long overdue.

Vernakalant is a novel, atrium-selective, early-activating  $K^+$  and frequency-dependent  $Na^+$  channel blocker whose antiarrhythmic efficacy in AF was established in the atrial arrhythmia conversion trial (ACT) I – a Phase III, double-blind placebo-controlled trial [1]. This study demonstrated a highly significant difference in the rate of successful cardioversion in those treated with vernakalant when compared with placebo (51.7 vs 4%,  $p \leq 0.001$ ). In those with recent onset of AF, the median

time to conversion was 11 min. ACT III produced similar results in a further 276 patients [2].

The recently published ACT II trial adds to the previously published data, confirming efficacy and safety for vernakalant's use in managing AF between 24 h and 7 days after cardiac surgery. In this second trial, similar results were obtained, with 47% of patients reverting to sinus rhythm at 90 min compared with 14% with placebo ( $p \leq 0.001$ ).

The drug was generally well tolerated in all three studies. There were three deaths in ACT I; however, these were thought to be unrelated to the study drug – it is worth noting that there was no increase in episodes of ventricular proarrhythmia, despite a mild increase in the QT interval. Transient hypotension was the most commonly reported adverse event; this was always short-lived and only two patients required further intervention (intravenous fluid).

The company manufacturing vernakalant released a promising press report in December stating that the latest study had met its primary end point [101]. This was a

direct head-to-head comparison with amiodarone. The data are not yet available, but eagerly awaited.

In summary, the currently available agents for rapid restoration of sinus rhythm in the emergency department or postoperative setting remain moderately efficacious at best. These studies demonstrate the efficacy, safety and speed of this novel, atrium-selective agent in these AF patients. The oral form is entering Phase III development and its use in rhythm control is being explored.

## References

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- 2 Kowey PR, Roy D, Pratt CM *et al.*: Efficacy and safety of Vernakalant hydrochloride injection for the treatment of atrial fibrillation after valvular or coronary artery bypass surgery. *Circulation* 116, II636–II637 (2007).



## Website

- 101 A Phase III superiority study of vernakalant vs amiodarone in subjects with recent onset atrial fibrillation (AVRO)  
<http://clinicaltrials.gov/ct2/show/NCT00668759>

# PUFA in AF: more hype than hope

**Evaluation of:** Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC: Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation following coronary artery bypass surgery: a randomized, double blind, placebo controlled clinical trial. *Circ. Arrhythm. Electrophysiol.* 3(1), 46–53 (2010).

Atrial fibrillation (AF) postcoronary artery bypass graft (CABG) remains a significant problem, occurring in up to 65% of patients and associated with longer hospitalizations and poor mortality outcome. Therefore, there has been huge interest to reduce postoperative AF. Omega-3 polyunsaturated fatty acid (PUFA) may have potential for preventing AF through its anti-inflammatory, antifibrotic and antiarrhythmic properties. A previous open-labeled study using (n-3 PUFA) eicosapentenoic acid and docosahexenoic acid did demonstrate a reduction in CABG AF [1]. This has led to several randomized controlled trials examining the role of PUFA in the prevention of postoperative AF. This report by Saravanan and colleagues describes the findings of a single-center, randomized double-blind

placebo-controlled study investigating the effect of short-term n-3 PUFA supplementation in patients undergoing CABG (minimum treatment of 5 days) in the occurrence of AF. Phospholipid n-3 PUFA levels were measured in serum at study entry, at surgery and in right atrial appendage tissue at surgery. Postoperative continuous ECG monitoring was performed for a minimum of 5 days. The primary outcome was the occurrence of at least 30 s of AF. Secondary outcome measures were clinical AF, AF dependency and hospital stay. The study was adequately powered to detect a reduction of 55% in the primary end point. A total of 103 patients completed the study (51 in the placebo group and 52 in the n-3 PUFA group). Both groups were comparable in terms of baseline characteristics and n-3 PUFA levels were higher in serum and right atrial tissue in the active treatment group. There was, however, no significant difference between groups in the primary outcome of AF (95% CI: 6–30%,  $p = 0.28$ ), in any of the secondary outcomes or in AF free survival. Rather, there was a trend towards more AF in the n-3 PUFA group. Therefore, the authors concluded that n-3 PUFA given at a dose of 2 g/day increased the n-3 PUFA content of atrial

tissue but did not reduce the incidence of AF in the 5 days following CABG. It should be noted that similar negative findings have recently been reported in another randomized placebo-controlled trial involving 170 CABG patients treated with PUFA prior to operation [2]. Taking the findings of these two studies together, questions are raised regarding the potential of PUFA in post-CABG. The results of ongoing, large-scale studies will help define the role of PUFA [101].

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## Website

- 101 Omega-3 Fatty acids for prevention of post-operative atrial fibrillation (OPERA)  
<http://clinicaltrials.gov/ct2/show/NCT00970489>