Welcome to issue 33 of Atrial Fibrillation Research Review.

This issue begins with a meta-analysis looking at relationships between physical activity levels and risk of AF. ARISTOTLE trial data have been reanalysed further to explore how giving the full apixaban dosage to participants who met only one (rather than ≥2) of the three dose-reduction criteria impacted on stroke/systemic embolism and bleeding outcomes. A further analysis of ENGAGE AF-TIMI 48 trial data has confirmed the benefits of edoxaban over warfarin in patients who are at increased risk of falls. This issue concludes with another meta-analysis, this one evaluating the practice of adjuvant antarrhythmic drug use after AF ablation.

I hope these regular updates on AF-related research are proving informative and helpful in your everyday practice. I look forward to any feedback or suggestions you may have.

Kind Regards,
Dr Andrei Catanchin
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Differential association of exercise intensity with risk of atrial fibrillation in men and women

Authors: Mohanty S et al.

Summary: This was a meta-analysis of studies reporting on the relationship between exercise and AF risk. Pooled data from seven studies (n=93,995) revealed that a sedentary lifestyle was associated with a high risk of incident AF (OR 2.47 [95% CI 1.25–3.7]). Data from three trials (n=149,048, all women) showed that compared with a sedentary lifestyle, moderate and intense physical activity levels decreased the odds of developing AF (respective ORs 0.91 [95% CI 0.78–0.97] and 0.72 [0.57–0.88]). Data pooled from male study participants revealed that moderate physical activity was associated with a decrease in AF risk (OR 0.8133 [95% CI 0.26–1.004]), but vigorous physical activity increased the risk (3.30 [1.97–4.63]).

Comment: Continuing a recent theme and now accepted association, this meta-analysis confirms moderate physical activity reduces AF risk. Additionally, here, increasing intensity of exercise appears protective in women (as compared with men where it increases AF risk). Defining exactly what is intense exercise in men versus women in different age groups remains a challenge.

Reference: J Cardiovasc Electrophysiol 2016;27(9):1021–9

Abstract
Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation

Authors: Healey JS et al., on behalf of the RE-LY Atrial Fibrillation Registry and Cohort Study Investigators

Summary: This was a prospective study of a cohort of 15,400 registry patients from multiple countries presenting to emergency departments with AF or atrial flutter as a primary or secondary diagnosis; of 15,361 patients with complete follow-up, 1758 died within 1 year. Compared with patients with a secondary AF diagnosis, those with a primary AF diagnosis had a lower mortality rate (6% vs. 16% [p<0.0001]), and 1-year mortality among patients from South America was double that of patients from North America, western Europe or Australia (p<0.0001). The most common cause of death was HF (30%), while stroke was responsible for 8% of deaths. Among the 4% of patients who had a stroke by 1 year, a lower proportion had AF as a primary versus secondary diagnosis (3% vs. 5% [p<0.0001]). Patients from Africa, China and southeast Asia had the highest stroke rates (7–8%) and those from India had the lowest (<1%); the stroke rate was 3% for patients from North America, western Europe and Australia.

Comment: We have here another large global public health publication from the McMaster University group: 12-month stroke and mortality following presentation to ED with AF (either as a primary or secondary diagnosis). Complex explanations for the significant regional variation are possible, including risk factors not accounted for (e.g. smoking, obesity), economic and cultural differences and adequate anticoagulation and blood pressure control. We again see HF as a crucial factor.

Reference: Lancet 2016;388(10,050):1161–9

Abstract

Efficacy and safety of non-vitamin K antagonist oral anticoagulants after cardioversion for nonvalvular atrial fibrillation

Authors: Renda G et al.

Summary: This was a random-effects meta-analysis of postcardioversion safety of NOACs versus VKAs using trial data (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48 and X-VeRT) for 3949 participants who underwent 4900 electrical or pharmacological cardioversion procedures for AF. There was no significant difference between NOAC and VKA therapy for the risk of stroke/systemic embolism (risk ratio 0.84 [95% CI 0.34–2.04]) or major bleeding (1.12 [0.52–2.42]), nor was there any statistically significant heterogeneity among the trials.

Comment: Many of us have been performing cardioversion on NOAC-treated patients for a number of years, based on the RE-LY analysis of almost 2000 cardioversions and subsequent similar (although much smaller in number) reports from ROCKET-AF and ARISTOTLE; more recently, the prospective X-VeRT trial (rivaroxaban) randomised 1500 patients. The results of this meta-analysis clearly support the practice of cardioversion on NOACs.


Abstract

Before prescribing please review PBS and Product Information in the primary advertisement in this publication.

Axipaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine

Authors: Alexander JH et al., for the Axipaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) Investigators

Summary: This secondary analysis of the ARISTOTLE trial set out to investigate the effects of the standard 5mg twice daily dosage on stroke/systemic embolism and bleeding that was received by participants meeting only one of the three dose-reduction criteria; participants who met ≥2 of the criteria were reduced to 2.5mg twice daily in the trial. Compared with participants meeting none of the dose-reduction criteria (n=13,356), those who met one of the criteria (n=3966) had higher rates of stroke/systemic embolism (HR 1.47 [95% CI 1.20–1.81]) and major bleeding (1.89 [1.62–2.20]). The benefit associated with axipaban 5mg twice daily (n=8665) versus warfarin (n=8657) in terms of less stroke/systemic embolism was similar between participants with one versus no dose-reduction criterion (HRs 0.94 vs. 0.77 [p=0.06 for interaction]), as was the benefit in terms of major bleeding (0.68 vs. 0.72 [p=0.71 for interaction]). The patterns were similar for each dose-reduction criterion and across ages, bodyweights, creatinine levels and creatinine clearance.

Comment: Axipaban (Elquis) is the most frequently underdosed NOAC in Australia and worldwide; i.e. unwarranted use of the 2.5mg twice daily dosage, leading to inadequate anticoagulation in up to 40% of patients in real-world data. This study should reassure prescribers the full dose is equally effective and safe in patients with one dose-reduction criterion and the reduced dose should be reserved for those patients with 2 or more of age >80 years, weight <60kg and creatinine level >133 µmol/L.


Abstract

Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis

Authors: Walkey AJ et al.

Summary: These authors analysed retrospective claims data for a cohort of 38,582 patients with AF who had been hospitalised with sepsis to assess clinical practice patterns and risk of stroke and bleeding associated with use of parenteral anticoagulants at doses greater than used for venous thromboembolism prophylaxis; 13,611 of the patients received parenteral anticoagulants, and hospital parenteral anticoagulant use for AF during sepsis varied (median 33%). CHA2DS2-VASc scores performed poorly for discriminating ischaemic stroke risk during sepsis (C statistic 0.526). Propensity score-matched analyses of 27,010 patients revealed no significant difference between parenteral anticoagulant recipients versus nonrecipients for in-hospital ischaemic stroke rate (1.3% vs. 1.4%; relative risk 0.94 [95% CI 0.77–1.15]), but parenteral anticoagulant recipients had a higher clinically significant bleeding rate (8.6% vs. 7.2%; 1.21 [1.10–1.32]). There was no significant difference in parenteral anticoagulation-associated ischaemic stroke risk between patients with pre-existing versus newly diagnosed AF (relative risk 1.12 vs. 0.85 [p=0.31 for interaction]).

Comment: Sepsis and critical illness is not infrequently complicated by AF, which would usually prompt us to administer anticoagulation. This retrospective claims database analysis suggests no significant benefit (and possible harm by way of increased bleeding), but it should be noted this is not a prospective randomised study, which is needed in order to delineate this issue further.

Reference: JAMA Cardiol 2016;1(6):682–90

Abstract

Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy

Authors: Providencia R et al.

Summary: This was a systematic review of 14 studies, with a meta-analysis of five, reporting on the safety and efficacy of AF catheter ablation in patients with versus without hypertrophic cardiomyopathy. There was a low risk of procedure-related adverse events. Compared with patients without hypertrophic cardiomyopathy, those with hypertrophic cardiomyopathy had lower rates of freedom from AF/atrial tachycardia relapse after a single procedure (38.7% vs. 49.8% [p=0.03]) and after ≥1 procedure (51.8% vs. 71.2% [p=0.0006]), and they were significantly more likely to require repeat procedures or antiarrhythmic drugs to prevent arrhythmia relapse. Sensitivity analyses suggested similarity in outcomes for patients with hypertrophic cardiomyopathy with less dilated atria and paroxysmal AF and the general population.

Comment: AF ablation in hypertrophic cardiomyopathy patients is generally accepted to be less effective than in those without hypertrophic cardiomyopathy because these patients have considerably more substrate disease. On the other hand they are frequently highly symptomatic, present with cardiac failure, and are less likely to respond to antiarrhythmic drugs.


Abstract

Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in Asians with nonvalvular atrial fibrillation

Authors: Chan Y-H et al.

Summary: This retrospective analysis of health insurance data from consecutive Taiwanese patients with nonvalvular AF reported thromboembolic, haemorrhagic and fatal events associated with rivaroxaban (n=3916; 87% low-dose) and dabigatran (n=5921; 90% low-dose) versus warfarin (n=5251); follow-up was ≤11 months. Compared with warfarin, rivaroxaban and dabigatran were both associated with significantly lower risks of ischaemic stroke/systemic embolism (respective p values 0.0004 and 0.0006), intracranial haemorrhage (0.0007 and 0.0005) and all-cause mortality (p<0.0001 for both). There was no significant difference between rivaroxaban and dabigatran for the risk of ischaemic stroke/systemic embolism, intracranial haemorrhage, myocardial infarction or mortality; rivaroxaban was associated with a higher risk of hospitalisation for gastrointestinal bleeding (p=0.0418), but significance was lost in an on-treatment analysis (p=0.5783).

Comment: Warfarinised Asian patients have a significantly higher bleeding risk (including intracranial bleeding) than non-Asians, prompting a lower target international normalised ratio. This Taiwanese health insurance database analysis compared low-dose rivaroxaban or dabigatran with warfarin, and the results are in favour of NOAC use in this population.

Reference: J Am Coll Cardiol 2016;68(13):1389–401

Abstract

Independent commentary by Dr Andrei Catanchin, a cardiologist/electrophysiologist specialising in the management of AF and other arrhythmias in private practice in Melbourne. Dr Catanchin has a particular expertise in the management of AF and other rhythm disorders. He performs catheter ablation for AF and other arrhythmias, implants pacemakers and ICDs (defibrillators) and his research interests include alternatives to warfarin in AF management.
Edoxaban versus warfarin in atrial fibrillation patients at risk of falling

Authors: Steffel J et al.

Summary: This prespecified analysis of the ENGAGE AF-TIMI 48 trial, which compared edoxaban with warfarin, focussed on participants with (n=900; 4.3%) versus without increased risk of falling. Participants at risk of falling were of greater median age (77 vs. 72 years [p<0.001]) and had more comorbidities. Participants at increased risk of falling were more likely to experience a bone fracture due to falling (adjusted HR 1.86 [95% CI 1.49–2.33]), major bleeding (1.30 [1.04–1.64]), life-threatening bleeding (1.67 [1.11 to 2.50]) and were more likely to die from any cause (1.45 [1.23–1.70]), but they were not at increased risk of ischaemic events, including stroke/systemic embolic event (1.16 [0.89–1.51]). There was no evidence of treatment interactions for efficacy and safety outcomes; edoxaban was associated with greater absolute overall risk reductions in severe bleeding events and all-cause mortality compared with warfarin.

Comment: Well-known warfarin studies have shown the risk-benefit analysis in AF patients at high risk of falls to lie strongly in favour of anticoagulation, and these patients are usually at even higher risk of stroke than those at standard risk of falls). The same is shown here with this NOAC (factor-Xa inhibitor; not available in Australia).

Reference: J Am Coll Cardiol 2016;68(11):1169–78

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Antiarrhythmic therapy as an adjuvant to promote post pulmonary vein isolation success

Authors: Goldenberg GR et al.

Summary: This was a meta-analysis of eight prospective trials including 1991 patients with paroxysmal AF and 967 with persistent AF, among whom class IC-III antiarrhythmic drug therapy for 6–12 weeks started after initiation of ablation (n=1502) was compared with no such treatment (n=1450); follow-up was 1.5–17 months after stopping medication. No significant difference was seen between antiarrhythmic-treated and nontreated patients for arrhythmia recurrence (30.69% vs. 33.79%; OR 0.86 [95 % CI 0.71–1.06]), but a trend for less atrial arrhythmia recurrence was seen among participants who mostly received amiodarone (OR 0.60 [0.34–1.09]).

Comment: We continue antiarrhythmic drugs following AF ablation to prevent early AF recurrence and to promote atrial healing and remodelling in sinus rhythm. While this approach is effective at reducing early recurrence (in fact we sometimes see a higher AF burden immediately postablation due to inflammation), this meta-analysis confirms the lack of any medium- to long-term benefit.

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