Welcome to issue 35 of Atrial Fibrillation Research Review.

The issue begins with researchers who concluded that AF in STV can only be predicted by the presence of heart disease, history of AF and nature of the STV, and not by the presence of HF, advanced age, diabetes or vascular disease. A meta-analysis of cohort studies reporting on the use of VKAs in patients with AF on haemodialysis found a trend for a reduced ischaemic stroke risk, but this appeared to be countered by an increase in bleeding risk, with no resultant impact on mortality. Registry data from GARFIELD-AF were examined to describe changes in antithrombotic therapy prescribing patterns during 2010–2015, including an increased use of NOACs, as would be expected. This issue concludes with the development and validation of a tool (AF-CVS) for predicting risk of ECV failure or AF recurrence in patients with acute AF.

I hope you find these and the other selected research interesting, and I look forward to any feedback you may have.

Kind Regards,

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### Predictive of atrial fibrillation in patients with supraventricular tachyarrhythmias treated with catheter ablation or not. Classical scores are not useful

**Authors:** Brembilla-Perrot B et al.

**Summary:** The frequency of AF over mean 3 years of follow-up and its predictors were assessed in 4169 patients referred for SVT; 1388 and 205 patients had typical and atypical atrioventricular nodal re-entrant tachycardia, respectively, 329 had atrioventricular re-entrant tachycardia over a concealed accessory pathway, 1321 had atrial flutter and 976 had pre-excitation syndrome. Ablation of SVT was performed in 2949 patients. AF occurred in 469 patients. A multivariable analysis revealed that AF risk during follow-up was increased by AF development prior to ablation, a history of AF, the nature of the SVT (atrial flutter) and the presence of heart disease, but not the presence of HF, advanced age, diabetes or vascular disease. AF was weakly but significantly prevented by ablation.

**Comment:** AF is very common in patients who have had atrial flutter (regardless of the management of atrial flutter), and is related to other SVTs and in particular the presence of accessory pathways. The earlier in life the electrophysiological abnormality is corrected, the higher likelihood of reducing future AF – in this study successful catheter ablation reduced subsequent AF (albeit modestly).

**Reference:** Int J Cardiol 2016;220:102–6

### Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation

**Authors:** Nielsen PB et al.

**Summary:** This propensity-weighted Danish study assessed the clinical effectiveness and safety of apixaban 2.5mg (n=4400), dabigatran 110mg (n=8875) and rivaroxaban 15mg (n=3476) versus warfarin (n=38,893) in patients with nonvalvular AF who had not previously received an oral anticoagulant. Apixaban was associated with a higher 1-year ischaemic stroke/systemic embolism rate than dabigatran, rivaroxaban and warfarin (4.8% vs. 3.3%, 3.5% and 3.7%, respectively), and was the only NOAC with a trend for an increased risk compared with warfarin (respective HRs 1.19 [95% CI 0.96–1.49], 0.89 [0.77–1.03] and 0.89 [0.69–1.16] for apixaban, dabigatran and rivaroxaban). Dabigatran, but not apixaban or rivaroxaban, was associated with a lower risk of bleeding than warfarin (respective HRs 0.80 [0.70–0.92], 0.96 [0.73–1.27] and 1.06 [0.87–1.29]).

**Comment:** These same authors analysed full-dose NOACs versus warfarin last year – here we see real-world data on reduced-dose NOACs. Accepting these are registry data with their inherent limitations, albeit for >50,000 subjects, we see dabigatran 110mg twice daily having a favourable safety profile (as in RE-LY), apixaban 2.5mg twice daily trending towards reduced efficacy (appropriateness of dose reduction unknown) and rivaroxaban 15mg essentially neutral.

**Reference:** BMJ 2017;356:j510

### Abbreviations used in this issue:

- AF = atrial fibrillation
- BMI = body mass index
- ECV = electrical cardioversion
- HF = heart failure
- HR = hazard ratio
- NOAC = nonvitamin K oral anticoagulant
- PVI = pulmonary vein isolation
- RFA = radiofrequency ablation
- SVT = supraventricular tachycardia
- VKA = vitamin K antagonist
Assessment of use vs discontinuation of oral anticoagulation after pulmonary vein isolation in patients with atrial fibrillation

Authors: Sjölander S et al.

Summary: This retrospective analysis of Swedish registry data from 1175 patients with AF and >1 year of follow-up data investigated warfarin discontinuation following PVI; the patients’ mean CHA2DS2-VASc score was 1.5. The proportion of patients stopping warfarin within the first year following PVI was 39.6%. Among patients with a CHA2DS2-VASc score ≥2, those who stopped warfarin had a higher rate of ischaemic stroke than those who continued warfarin (1.6% vs. 0.3% per year [p=0.046]). The risk of stroke was significantly increased by discontinuing warfarin in patients with a CHA2DS2-VASc score ≥2 and in those who had experienced a prior ischaemic stroke (respectively HRs 4.6 [95% CI 1.2–17.2] and 13.7 [2.0–91.9]).

Comment: This study strongly supports current guidelines: the usual approach to anticoagulation in dialysis patients with AF by most nephrologists is to avoid warfarin because of the significant risk of bleeding outweighing the benefits, supported by the findings here. Whether a NOAC, in particular apixaban (which is permitted in haemodialysis patients in the US FDA labelling) would give a favourable risk-benefit profile in these patients remains to be studied.

Reference: JAMA Cardiol 2017;2(2):146–52

Abstract

Non-permanent atrial fibrillation and oral anticoagulant therapy are related to survival during 10 years after first-ever ischemic stroke

Authors: Baturova MA et al.

Summary: These researchers evaluated the impact of AF type and oral anticoagulant therapy on 10-year outcomes in 336 registry patients with a first-ever ischaemic stroke, 44 and 65 of whom had permanent and recurrent AF, respectively. There were 200 deaths during follow-up. AF was an independent predictor of all-cause mortality (HR 1.52 [95% CI 1.14–2.04]), particularly permanent AF (1.86 [1.29–2.69]). Compared with patients without AF, the mortality risk was not significantly different for patients with recurrent AF receiving oral anticoagulant therapy (HR 0.73 [95% CI 0.38–1.39]), but it was in those with permanent AF receiving oral anticoagulant therapy (1.57 [0.92–2.67]) and more so if they were not receiving oral anticoagulant therapy (2.28 [1.38–3.77]).

Comment: With respect to anticoagulation, we manage paroxysmal AF in the same way as persistent AF. In these stroke patients, the best outcomes were seen with warfarinised paroxysmal AF and the worst with nonwarfarised persistent AF (NB, terminology here: ‘recurrent’ means paroxysmal and ‘permanent’ means persistent).

Reference: Int J Cardiol 2017;232:134–9

Abstract

Asymptomatic versus symptomatic episodes in patients with paroxysmal atrial fibrillation via long-term monitoring with implantable loop recorders

Authors: Simantirakis EN et al.

Summary: This research in 30 consecutive patients with paroxysmal AF who received an implantable loop recorder looked at ECG differences between symptomatic and asymptomatic episodes of AF and identified parameters related to the appearance of symptoms; there were 82 episodes from 25 patients that were evaluable. Compared with asymptomatic episodes of AF, symptomatic episodes were associated with a significantly faster mean heart rate (142.48 vs. 95.71 beats/min [p<0.001]) and significantly lower heart rate variability (92.62 vs. 150.06 msec [p<0.001]). During mixed asymptomatic-symptomatic episodes, the mean heart rate for the symptomatic period was significantly faster than for the asymptomatic period (141.88 vs. 102.91 beats/min [p<0.001]) and mean heart rate variability was significantly lower (87.33 vs. 173.55 msec [p=0.003]). No significant correlations were seen between patient characteristics and the clinical presentation of AF.

Comment: This interesting study complements what we see in clinical practice – patients with more physiological heart rates in AF are less likely to be symptomatic, and with good ventricular rate control, many patients can become unaware of their arrhythmia. In particular, note the patients who reported symptoms during rapid rates but not during controlled rates.


Abstract

Vitamin K antagonists for stroke prevention in hemodialysis patients with atrial fibrillation

Authors: Van Der Meersch H et al.

Summary: This was a systematic review and meta-analysis of 12 prospective or retrospective cohort studies (n=17,380) reporting ischaemic stroke and bleeding rates in patients with AF undergoing haemodialysis, including 4010 who had received VKAs. Patients treated with VKAs had a low mean CHADS2 or CHA2DS2-VASc score (1.7–2.75), and in time the therapeutic range or mean international normalised ratio was generally low. Treatment with VKAs was associated with a trend for a lower ischaemic stroke risk (HR 0.74 [95% CI 0.51–1.06]) but a significantly higher bleeding risk (1.21 [1.03–1.43]), with no effect on mortality risk (1.00 [0.92–1.09]). Data from four studies showed a nonsignificant increased risk of haemorrhagic stroke with VKA exposure (HR 1.93 [95% CI 0.93–3.98]).

Comment: The usual approach to anticoagulation in dialysis patients with AF by most nephrologists is to avoid warfarin because of the significant risk of bleeding outweighing the benefits, supported by the findings here. Whether a NOAC, in particular apixaban (which is permitted in haemodialysis patients in the US FDA labelling) would give a favourable risk-benefit profile in these patients remains to be studied.

Reference: Am Heart J 2017;184:37–46

Abstract

Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation

Authors: Nielsen JC et al., for the MANTRA-PAF Investigators

Summary: This paper reported 5-year outcomes from the MANTRA-PAF trial, which randomised patients with paroxysmal AF to RFA (evaluable n=125) or antiarrhythmic drug therapy (evaluable n=120) as first-line treatment; 227 participants had Holter recording data and those assigned to the antiarrhythmic drug arm were more likely to have used a class I or III antiarrhythmic agent (87.33 vs. 173.55 msec [p=0.003]).

Comment: Although the initial MANTRA-PAF results suggested catheter ablation and antiarrhythmic drugs were equally effective at rhythm control, many larger studies and meta-analyses have clearly shown the superiority of ablation over pharmacotherapy across multiple variables; this longer term analysis supports this.

Reference: Heart 2017;103(5):388–76

Abstract
Atrial Fibrillation Research Review™

Established standards in anticoagulation therapy

A long history of clinical use in the prevention and treatment of venous thrombosis and pulmonary embolism 1,2

Reduces the relative risk of stroke by 64% in patients who have atrial fibrillation compared to placebo or no treatment 5+

Weekly treatment cost of warfarin 10mg/day – $12.54 3,7,8

meta-analysis: number needed to treat for 1 year to prevent 1 stroke is 37 (for primary prevention) and 12 (for secondary prevention)

Based on April 2016 non-concession card PBS (maximum price to consumer) and medicare benefits schedule for 2 x prothrombin pathology tests/month

Established guidelines for warfarin reversal and bridging anticoagulation therapy 1,6

Before prescribing please review Product Information available via www.aspenpharma.com.au/products or call 1300 659 646


PBS Information: This product is listed on the PBS as an antithrombotic agent.
Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation

Authors: Camm AJ et al., for the GARFIELD-AF Investigators

Summary: GARFIELD-AF prospectively enrolled 39,670 patients with newly diagnosed nonvalvular AF into four sequential cohorts for the periods of 2010–2011 (n=5500), 2011–2013 (n=11,662), 2013–2014 (n=11,462) and 2014–2015 (n=11,046) to study antithrombotic therapy patterns. The median CHA2DS2-VASc score across the four cohorts was 3. The proportion of patients on anticoagulant therapy increased between the earliest and latest cohort by ~15%. More specifically, the use of NOACs with or without antiplatelets increased, while use of VKAs, with or without antiplatelet therapy, and antiplatelet monotherapy both declined. Most patients with a CHA2DS2-VASc score ≥2 received anticoagulants, and this increased over time due mainly to increased prescribing of NOACs. Men, elderly patients, those of Asian ethnicity, those with dementia, nonsteroidal anti-inflammatory drug users and current smokers were more frequently prescribed a NOAC than a VKA, whereas those with cardiac, vascular or renal comorbidities were more likely to be prescribed a VKA.

Comment: We continue to receive insights into recent/current global AF management practices from the GARFIELD registry. The main finding here is that guideline-directed practice is increasing, with more patients receiving anticoagulation (NOACs more so than warfarin) and, appropriately, much less aspirin use.


Abstract

Predicting unsuccessful electrical cardioversion for acute atrial fibrillation (from the AF-CVS score)

Authors: Jaakola S et al.

Summary: These authors used FinCV study data from 3716 ECVs in participants with acute AF to derive a clinical risk stratification tool for identifying patients who were at high risk for an unsuccessful outcome. A multivariate analysis identified the following five predictors for an increased risk of cardioversion failure or AF recurrence within 30 days (composite endpoint): i) age (odds ratio 1.31 [1.13–1.52]); ii) not a first AF (1.55 [1.19–2.02]); iii) HF (1.52 [1.08–2.13]); iv) vascular disease (1.38 [1.11–1.71]); and v) prior AF ≤1 month before ECV (2.31 [1.83–2.91]). These were included in the risk prediction tool, AF-CVS, which had a c-index value of 0.67 (p=0.84), AF-CVS scores of >5 (high risk) and <3 (low risk) were associated with composite endpoint rates of ~40% and ~10%, respectively, in both the derivation cohort and a validation cohort that included 1997 ECVs.

Comment: This interesting scoring system supports our clinical intuition and what we know about AF (e.g. an older patient with recurrent AF after recent cardioversion is highly likely to have further AF) and should guide our decision to further perform cardioversion or institute other rhythm control approaches.


Abstract

Genetic obesity and the risk of atrial fibrillation: causal estimates from Mendelian randomization

Authors: Chatterjee NA et al.

Summary: Using genetic predictors of BMI, these researchers explored its association with AF in 51,646 individuals of European ancestry without AF at baseline from seven prospective population-based cohorts. During cohort mean follow-up periods of 7.4–19.2 years, 4178 cases of incident AF were recorded. Two genetic instruments, namely FTO genotype (rs1558802) and a BMI gene score comprising 39 SNPs, were significantly associated with both BMI (0.43 kg/m² per A-allele [p=0.001] and 1.05 kg/m² per unit increase [p<0.001]) and incident AF (relative HRs 1.07 [95% CI 1.02–1.11] per A-allele and 1.11 [1.05–1.18] per unit increase). Age- and sex-adjusted instrumental variable HR estimates for a causal association between BMI and incident AF were 1.15 (95% CI 1.04–1.26) and 1.11 (1.05–1.17) per kg/m² for FTO and BMI gene score, respectively, both of which were consistent with the meta-analysed estimate between observed BMI and AF (1.05 [1.04–1.06] per kg/m² [p<0.001]); these findings were not significantly altered by multivariable adjustments.

Comment: Obesity is widely accepted as an important risk factor for AF and weight loss has been shown to improve symptoms as well as rhythm control. Here we see two genetic testing variables that are associated with obesity to predict BMI and also to predict AF. Reducing the overweight/obesity epidemic is likely to also reduce future AF.

Reference: Circulation 2017;135(8):741–54

Abstract