Welcome to the twelfth issue of Atrial Fibrillation Research Review.

One of two meta-analyses included in this issue pooled data from the pivotal phase 3 clinical trials investigating the oral anticoagulants for stroke prevention or systemic embolic events in patients with AF, and concluded that the oral anticoagulants have a favourable benefit-risk profile. The other meta-analysis showed that LAA occlusion devices are as effective as adjusted-dose warfarin and other anticoagulation strategies for preventing stroke in patients with nonvalvular AF. There are also analyses of other major clinical trials, including a subanalysis of the ROCKET-AF trial, which reported similar risks of major/nonmajor clinically relevant bleeding for rivaroxaban and warfarin in the trial participants, while a post hoc analysis of ARISTOTLE trial data showed the major CV events after cardioversion of AF were rare, with similar rates in the warfarin and apixaban arms.

I hope you find this issue stimulating reading, and I am looking forward to receiving your comments, feedback and suggestions.

Kind Regards,

Associate Professor John Amerena

Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation

Authors: Carrero JJ et al.

Summary: These researchers examined outcomes associated with warfarin treatment in relation to kidney function among patients with established CV disease and AF. Using data from a Swedish registry, the study included 24,317 survivors of an acute MI with AF and known serum creatinine levels, including 21.8% who were prescribed warfarin at discharge. A total of 51.7% of patients had moderate CKD or worse (estimated glomerular filtration rate <60 mL/min/1.73m$^2$). Compared with no warfarin use, warfarin was associated with a lower 1-year risk for the composite outcome of death, readmission due to MI or ischaemic stroke without a higher risk of bleeding. This association was observed in each CKD stratum (moderate, severe or end-stage CKD). The proportions of patients who developed the composite outcome, bleeding events, and the total of these two outcomes within 1 year from discharge date increased with the worsening of CKD categories, as did the rate at which these events occurred.

Comment: This observational study confirms the efficacy of warfarin in reducing recurrent ischaemic events after MI. This has been shown in the past, but long-term anticoagulation has never been widely used in this context due to excessive bleeding, especially with concomitant antiplatelet therapy. Bleeding was not increased in this study, which seems implausible, but it raises the possibility that it was overestimated in earlier studies, and we have no information as to the use of single or dual antiplatelet treatment with warfarin in this analysis.

Reference: JAMA 2014;311(9):919–28


Abbreviations used in this review:

AF = atrial fibrillation; CKD = chronic kidney disease; CV = cardiovascular; ECV = electrical cardioversion; GI = gastrointestinal; HR = hazard ratio; LA(A) = left atrial appendage; LV = left ventricular; MI = myocardial infarction; PCV = pharmacological cardioversion; RR = relative risk; TOE = transoesophageal echocardiography

STROKES SHATTER LIVES

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On this issue:

- Warfarin, CKD and outcomes after acute MI in AF
- Efficacy and safety of oral anticoagulants vs. warfarin in AF
- Contemporary real-life cardioversion of AF
- Aspirin vs. vitamin K antagonists guided by TOE in AF
- AF ±LV hypertrophy with ‘lenient’ rate- or rhythm-control
- LAA occlusion for stroke prophylaxis in nonvalvular AF
- Factors associated with major bleeding events
- Apixaban after cardioversion for AF
- AF recurrence and progression after catheter ablation of paroxysmal AF

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation

Authors: Ruff CT et al.

Summary: This meta-analysis of the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI-48 trials examined the relative benefit of oral anticoagulants in key patient subgroups and their effects on important secondary outcomes. Overall, 42,411 participants received an oral anticoagulant and 29,272 received warfarin. Oral anticoagulants reduced the risk of stroke or systemic embolic events by 19% compared with warfarin (RR 0.81 [95% CI 0.73–0.91; p=0.0001]), mainly due to a reduction in haemorrhagic stroke (0.49 [0.38–0.64; p<0.0001]). Oral anticoagulants also reduced all-cause mortality (RR 0.90 [95% CI 0.85–0.95; p=0.0003]) and intracranial haemorrhage (0.48 [0.39–0.59; p<0.0001]), but increased GI bleeding (1.25 [1.01–1.55; p=0.04]). There was no heterogeneity for stroke or systemic embolic events in important subgroups. Low-dose oral anticoagulant regimens showed similar reductions in stroke or systemic embolic events to warfarin and a more favourable bleeding profile, but more ischaemic strokes (RR 1.28 [95% CI 1.02–1.60; p=0.045]).

Comment: This comprehensive meta-analysis of the oral anticoagulant trials shows that the risk-benefit profile of the new agents is very favourable, except for GI bleeding. Given this, and other papers showing cost effectiveness of these new agents, I feel they will replace warfarin for most indications, except for patients with severe renal dysfunction or mechanical heart valves.


Contemporary real life cardioversion of atrial fibrillation

Authors: Crijns HJGM et al.

Summary: The RHYTHM-AF registry study evaluated the real-world use of ECV and PCV in 3940 symptomatic patients with recent-onset AF, 75% of who underwent cardioversion; the mode of which varied significantly. Over 2 months of follow-up, sinus rhythm was restored in 89.7% of participants by ECV and in 69.1% after PCV. In patients not undergoing cardioversion during admission, 34% spontaneously converted to sinus rhythm within 24 hours. ECV was most successful in patients pretreated with antiarrhythmic drugs (mostly amiodarone). PCV was enhanced by class Ic antiarrhythmic drugs; the conversion rate with amiodarone was similar to that with rate-control drugs. Females and those with paroxysmal and first detected AF, as well as those without previous ECV, responded well to PCV. The median duration of hospital stay was 16.2 hours for ECV patients and 24.0 hours for PCV patients. Chronic maintenance of sinus rhythm was enhanced in patients taking long-term antiarrhythmic drugs, β-blockers or renin-angiotensin system inhibitors.

Comment: This analysis of the RECORD-AF study is instructive, as it showed both ECV and PCV were quite effective, especially with class Ic drugs (flecainide) and in patients with paroxysmal and first detected AF. Although amiodarone was the most frequently administered drug in this study (and in Australian emergency departments) to try to revert AF, it did not offer much more than rate control, so its use should be discouraged given its toxicity.


STREAMLINED AUTHORITY CODE 4269 for stroke prevention in non-valvular atrial fibrillation

PBS Information: Authority required (STREAMLINED) for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation and one or more risk factors for developing stroke or systemic embolism. Authority required (STREAMLINED) for prevention of venous thromboembolism in a patient undergoing total hip replacement or total knee replacement. Refer to PBS Schedule for full authority information.

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Aspirin versus vitamin K antagonist treatment guided by transoesophageal echocardiography in patients with atrial fibrillation

Authors: Dinh T et al., for the TIARA investigators

Summary: Patients with nonvalvular AF and a moderate risk of stroke (mean CHADS2-VASc score 2.1; n=238) were randomised to receive aspirin or adjusted vitamin K antagonist therapy after thrombogenic features in the atria and aorta had been excluded by TOE in this pilot study. The respective composite primary endpoint event rates (stroke, major bleeding, peripheral embolism, all-cause mortality) over mean follow-up of 1.6 years were 3.2% and 6.1% in the aspirin and vitamin K antagonist arms (p<0.0001 for noninferiority).

Comment: This study tested whether aspirin was as effective as warfarin in preventing stroke in patients who did not have LAA thrombus on TOE and in whom anticoagulation would conventionally have been recommended. It amazes me that this got ethical approval, and I predict no further studies will be done testing this hypothesis, given the paucity of data that aspirin has any meaningful effect in reducing stroke and the current advice by NICE that aspirin not be used in stroke prevention in nonvalvular AF.

Reference: Heart 2014;100(7):563–8
http://heart.bmj.com/content/100/7/563.abstract

Outcomes in atrial fibrillation patients with and without left ventricular hypertrophy when treated with a lenient rate-control or rhythm-control strategy

Authors: Badhuka AO et al.

Summary: These researchers analysed echocardiographic data for LV hypertrophy in 2105 participants from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, among who 332 died during 6 years of follow-up. Severely increased LV mass was significantly associated with all-cause mortality for all participants and those in the rhythm-control arm (respective adjusted HRs 1.34 [95% CI 1.01–1.79; p=0.045] and 1.61 [1.09–2.37; p=0.016]), and CV hospitalisations in patients with heart failure with preserved and decreased LV systolic function (1.8 [1.0–3.2; p=0.03] and 2.4 [1.1–5.2; p=0.02]), while (any) increased LV mass was significantly associated with CV hospitalisations among participants who received ‘lenient’ rate-control (1.72 [1.05–2.82; p=0.03]), but not those who received ‘strict’ rate-control.

Comment: This interesting study showed that LV hypertrophy was an independent predictor of mortality in AF, and that the groups who seemed to do worse were those with LV hypertrophy who had a rhythm-control approach or a lenient rate-control strategy. These results may have been due to proarrhythmia associated with the use of antiarrhythmic agents in patients with structural heart disease and a rhythm control approach, or due to reduced diastolic filling with lenient rate control in patients whose ventricular diastolic function was already compromised.

Reference: Am J Cardiol 2014;113(7):1159–65
http://www.ajconline.org/article/S0002-9149(14)00047-2/abstract

Percutaneous left atrial appendage occlusion for stroke prophylaxis in nonvalvular atrial fibrillation

Authors: Bajaj NS et al.

Summary: This was a systematic review and analysis of 17 observational studies reporting percutaneous LAA closure device implantation in a total of 1052 patients followed for 1586.4 person-years. The adjusted incidence rates of stroke, major bleeding, peripheral embolism, all-cause mortality over mean follow-up of 1.6 years were 3.2% and 6.1% in the aspirin and vitamin K antagonist arms (p<0.0001 for noninferiority).

Comment: This study tested whether aspirin was as effective as warfarin in preventing stroke in patients who did not have LAA thrombus on TOE and in whom anticoagulation would conventionally have been recommended. It amazes me that this got ethical approval, and I predict no further studies will be done testing this hypothesis, given the paucity of data that aspirin has any meaningful effect in reducing stroke and the current advice by NICE that aspirin not be used in stroke prevention in nonvalvular AF.

Reference: Heart 2014;100(7):563–8
http://heart.bmj.com/content/100/7/563.abstract

Factors associated with major bleeding events

Authors: Goodman SG et al.

Summary: These authors reported additional safety results from the ROCKET-AF trial, which compared rivaroxaban with warfarin and showed risks of similar stroke/systemic embolism and the principal safety endpoint of major/nonmajor clinically relevant bleeding (14.9 vs. 14.5 events per 100 patient-years; HR 1.03 [95% CI 0.96–1.11]). This analysis showed that major bleeding risk increased with age, but without any difference between treatments across age categories (p=0.59 for interaction). Compared with participants free of major bleeding (n=13,455), those who experienced major bleeds (n=781) were more likely to be older, current/prior smokers, have GI bleeding, mild anaemia and a lower calculated creatinine clearance, and were less likely to be female or have a prior stroke/transient ischaemic attack. Independent associations were seen between increased major bleeding risk and increasing age, baseline diastolic blood pressure ≥90mm Hg, history of chronic obstructive pulmonary disease or GI bleeding, prior aspirin use and anaemia, while female gender and diastolic blood pressure <90mm Hg were associated with a decreased risk.

Reference: J Am Coll Cardiol 2014;63(9):891–900
http://tinyurl.com/x9hmsh

www.researchreview.com.au

www.acra2014.com.au
Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation

Authors: Flaker G et al.

Summary: This post hoc analysis of ARISTOTLE trial data assessed the major clinical and thromboembolic event risks after cardioversion for AF in apixaban versus warfarin recipients; the respective numbers of cardioversions in the apixaban and warfarin arms were 265 and 275. The mean times to the first cardioversion in the warfarin and apixaban arms were 243 and 251 days, respectively, with 75% of all cardioversions undertaken during the first year. No strokes or systemic emboli were seen during 30 days of follow-up among participants who underwent cardioversion. One participant from each arm experienced an MI, one from each arm experienced a major bleed, and two from each arm died.

Comment: This analysis of ARISTOTLE trial data showed that it is safe to perform direct current cardioversion in patients who have received at least 3 weeks of apixaban, with no significant difference in postcardioversion stroke or mortality compared with warfarin. Similar results have been published with dabigatran and rivaroxaban, suggesting it is safe to use oral anticoagulants in this context, and given the logistic advantages over warfarin in planning timing of direct current cardioversion, I feel they will be increasingly used in this way.

Reference: J Am Coll Cardiol 2014;63(11):1082–7
http://content.onlinejacc.org/article.aspx?articleID=1765172

Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation

Authors: Takigawa M et al.

Summary: These researchers investigated the incidences of recurrent AF and progression to persistent AF after catheter ablation for paroxysmal AF in 1220 consecutive patients. After an average of 1.3 procedures, the 5-year AF recurrence-free survival probabilities after the first and final catheter ablations were 59.4% and 81.1%. During median follow-up of 47.9 months after initial catheter ablation, progression from paroxysmal to persistent AF was seen in 15 participants (0.3% per year). Significant predictors of AF recurrence were AF history duration (HR 1.03 [p<0.0001]), number of ineffective antiarrhythmics (1.09 [p=0.005]) and LA diameter indexed by body surface area (LADI; 1.05 [p=0.001]), and significant predictors of progression to persistent AF were age (1.12 [p=0.0001]) and LADI (1.26 [p=0.0006]). AF progression did not occur for up to 10 years after initial catheter ablation in participants aged ≤65 years and an LADI of ≤24.0 mm²/m².

Comment: This study looking at freedom from AF after ablation suggests that the younger the patient and the less the LA structural changes, the more successful ablation was in ‘curing’ AF, although repeated procedures were often necessary. We await with interest the results of the CABANA study, which is examining the role of ablation as early rather than delayed treatment for AF.

http://circarrhyecp.ahajournals.org/content/7/2/267.full

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