Welcome to issue 32 of Atrial Fibrillation Research Review.

This issue begins with a report on the success of warfarin control in Queensland, with an observed mean time in therapeutic range of >80%, much better than the recommended 60% threshold. Research from Europe has reported high success rates for complete LAA closure with the WATCHMAN device in patients with high risks of stroke and bleeding, and with multiple comorbidities. Researchers from Norway have confirmed a J-shaped relationship between physical activity and AF risk; i.e. the lowest risk is seen with moderate levels of physical activity. The same paper also identified low resting heart rate as a risk factor for AF, and this was also reported in the final paper included in this issue, which confirmed a U-shaped relationship between resting heart rate and AF risk.

Your feedback and suggestions help in the choice of studies for inclusion in each issue, so please keep them coming.

Kind Regards,
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Quality of warfarin control in atrial fibrillation patients in South East Queensland, Australia

Authors: Bernaitis N et al.

Summary: These authors reviewed retrospective data from 3692 patients enrolled in Sullivan Nicolaides Pathology practice in Queensland to evaluate warfarin control and identify factors influencing time in therapeutic range. INR (international normalised ratio) tests were within the therapeutic range (2.0–3.0) for 73.6% of the patients. The mean time in therapeutic range was 81%, and a time in therapeutic range of >60% was seen in 97% of patients. Age, gender and socioeconomic factors did not influence time in therapeutic range.

Comment: One of the principal reasons for the preference of NOACs over warfarin is the reliability and predictability of anticoagulation – achieving close to 100% time in therapeutic range with NOACs is theoretically possible. We know from the large anticoagulant clinical trials that Australian centres achieve times in therapeutic range well above study averages, and this is confirmed in this retrospective ‘real-world’ analysis.


Abstract
Usefulness of CHADS\textsuperscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores in the prediction of new-onset atrial fibrillation

Authors: Saliba W et al.

Summary: This population-based research assessed the performance of the CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores for predicting new-onset AF in 1,062,073 patients aged ≥50 years without pre-existing AF at baseline from an Israeli health database. AF developed in 23,223 patients during 3,053,754 person-years of follow-up, giving an incidence rate of 0.76 per 100 person-years. The respective AF incidence rates for sequentially increasing CHADS\textsubscript{2}, CHA\textsubscript{2}DS\textsubscript{2}-VASc scores 0–9 were 0.17, 0.21, 0.49, 0.94, 1.65, 2.31, 2.75, 3.30, 4.09 and 6.71 per 100 person-years (p<0.001), with each point increase significantly increasing the likelihood of developing AF (HR 1.57 [95% CI 1.56–1.58]); a similar pattern was seen for CHADS\textsubscript{2} scores. CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc had respective areas under the receiver operating characteristic curves for predicting new-onset AF of 0.728 and 0.744.

Comment: This health database analysis of >1 million Israelis ≥50 years of age yielded an overall annual incidence of new-onset AF of 0.76%, with a clear relationship to CHA\textsubscript{2}DS\textsubscript{2}-VASc score — a 1.6-fold increase for every additional point.


Abstract

Implant success and safety of left atrial appendage closure with the WATCHMAN device

Authors: Boersma LVA et al., on behalf of the EWOLUTION investigators

Summary: This paper reported <30-day periprocedural outcomes for 1021 EWOLUTION registry patients with nonvalvular AF who had undergone LAA closure for stroke prevention; the patients had average CHADS\textsubscript{2}, CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED scores of 2.8, 4.5 and 2.3, respectively. 45.4% had a history of transient ischaemic attack, ischaemic stroke or haemorrhagic stroke and 62% were considered unsuitable for NOACs. The successful device deployment rate was 98.5%, with no flow or minimal residual flow achieved in 99.3% of implanted patients. There were 31 serious adverse events within 1 day of the procedure, affecting 26 patients. By day 30, 0.7% of the patients had died. Major bleeding requiring transfusion was the most frequent serious adverse event occurring within 30 days of LAA closure. Compared with NOAC-eligible patients, NOAC-eligible patients had a lower 30-day serious adverse event rate (0.5%) compared with NOAC-eligible patients (3.0%) (p=0.001).

Comment: This contemporary registry enrolled patients unsuitable for anticoagulation and at high stroke and bleeding risk, and importantly, comes in the NOAC era. We are reminded there remains an important role for alternatives to anticoagulation (not just alternatives to warfarin).

Reference: Eur Heart J 2016;37(31):2465–74

Abstract

Physical activity, resting heart rate, and atrial fibrillation

Authors: Morseth B et al.

Summary: Associations of physical activity and resting heart rate with hospital-diagnosed AF were explored in 20,484 adults enrolled in the third prospective Tromsø Study survey in 1986–87. AF was diagnosed in 750 participants (70.5% men) over mean follow-up of 20 years (409,045 person-years). Compared with participants reporting low levels of physical activity, the risk of any AF was lower in those who reported moderate activity levels (adjusted HR 0.81 [95% CI 0.68–0.97]), but the risk was nonsignificantly higher in those who reported vigorous activity levels (1.37 [0.77–2.43]). Each 10 beats/min increase in resting heart rate was associated with a reduction in the risk of AF (adjusted HR 0.92 [95% CI 0.86–0.98]), with a resting heart rate of <50 beats/min being a significant risk factor for AF (p<0.05).

Comment: These findings are not new and add to the current knowledge base and accepted J-shaped relationship between exercise and AF; moderate exercise is beneficial but higher intensity/workload is less so. Different from previous reports, vigorous exercise did not actually increase the risk of AF in this study; resting heart rate <50 beats/min predicted AF.


Abstract

Blood pressure control and stroke or bleeding risk in anticoagulated patients with atrial fibrillation

Authors: Vermulapalli S et al.

Summary: This research explored associations of systolic BP and hypertension bracket with stroke risk in 14,256 ROCKET-AF trial participants receiving anticoagulation, among whom 55.8% and 34.6% had controlled and uncontrolled hypertension, respectively. Each 10mm Hg increase in systolic BP increased the risk of stroke or systemic embolism (adjusted HR 1.07 [95% CI 1.02–1.13]), and compared with no hypertension, there was a trend for an increased risk in patients with controlled (1.22 [0.89–1.66]) and uncontrolled hypertension (1.42 [1.03–1.95]; p=0.06). The major bleeding risk did not differ significantly between hypertensive brackets and did not vary significantly by systolic BP. Furthermore, systolic BP had no significant impact on the benefit of rivaroxaban versus warfarin for preventing stroke or systemic embolism (p=0.69 for interaction).

Comment: This large contemporary population of AF patients, by definition at high stroke and vascular risk (the ROCKET-AF study), were treated according to then best practice. The risk of stroke/systemic embolism rose significantly with each 10mm Hg increment in presenting BP.

Reference: Am Heart J 2016;178:74–84

Abstract

Effect of colchicine on the incidence of atrial fibrillation in open heart surgery patients

Authors: Tabbalat RA et al.

Summary: The END-AF randomised controlled trial enrolled consecutive patients with no AF history to undergo elective cardiac surgery with (n=179) or without (n=181) colchicine 12–24 hours preoperatively and continued until discharge from hospital; the in-hospital mortality rate was 3.3%. No significant difference was seen between the colchicine and no colchicine groups for AF lasting >5 minutes (primary endpoint; 14.5% vs. 20.5% [p=0.14]), but a significantly greater proportion of colchicine recipients experienced diarrhoea (24.6% vs. 5.5% [p<0.001]); the diarrhoea led to colchicine discontinuation in 52% of affected recipients.

Comment: Colchicine is used routinely as an anti-inflammatory agent for both treatment and prevention of pericarditis, and is used by some in catheter ablation procedures. While this is an effective strategy, the mechanisms of AF after cardiac surgery are complex and multifactorial, and colchicine is not effective as routine therapy.

Reference: Am Heart J 2016;178:102–7

Abstract
Established standards in anticoagulation therapy

A long history of clinical use in the prevention and treatment of venous thrombosis and pulmonary embolism\(^2\)\(^,\)\(^4\) reduces the relative risk of stroke by 64% in patients who have atrial fibrillation compared to placebo or no treatment\(^5\)\(^\dagger\) (1 meta-analysis: number needed to treat for 1 year to prevent 1 stroke is 37 (for primary prevention) and 12 (for secondary prevention).

Weekly treatment cost of warfarin 10mg/day – $12.54\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)

\(^{\dagger}\) 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\(^1\)\(^,\)\(^6\)


PBS Information: This product is listed on the PBS as an antithrombotic agent.
Left atrial thrombus resolution in atrial fibrillation or flutter

Authors: Lip GYH et al., on behalf of the X-TRA study and CLOT-AF registry investigators

Summary: This abstract reported the findings of: i) the prospective X-TRA trial, in which participants with nonvalvular AF or atrial flutter and LA/LAA thrombus received rivaroxaban for 6 weeks; and ii) the retrospective observational CLOT-AF registry of thrombus-related outcome data after standard anticoagulant treatment for 3–12 weeks in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus. In X-TRA, the rate of thrombus resolution on transoesophageal echocardiography was 41.5%, and the rate of thrombus resolution or reduction was 60.4%. The reported thrombus resolution rate in CLOT-AF was 62.5%; this appeared better in Western European than Eastern European countries (68.0% vs. 56.5%).

Comment: Many of us have been using NOACs for anticoagulation in the presence of LA thrombus and, anecdotally at least, this has been as effective as standard therapy with enoxaparin (Clexane)/warfarin. A thrombus reduction/resolution rate of 60% at 6 weeks is not quite what we see in clinical practice and may not be reassuring enough for some, but comparable with the comparison study.


Association between heart rate at rest and incident atrial fibrillation

Authors: Skov MW et al

Summary: The relationship between resting heart rate and incident AF was explored by analysing digital electrocardiograms from 281,451 primary-care patients in the Copenhagen Electrocardiographic Study. AF occurred in 15,666 participants (lone AF in 1631) during median follow-up of 8.4 years. Compared with a reference resting heart rate of 66–72 beats/min, resting heart rates of 50–51 beats/min were associated with an increased risk of incident AF (adjusted HR 1.16 [95% CI 1.06–1.27]), and there was a dose-dependent increase in risk with resting heart rates >72 beats/min peaking at 95–120 beats/min (1.36 [1.26–1.46]); these associations were accentuated for the risk of lone AF (1.48 [1.19–1.84] and 1.84 [1.47–2.30], respectively). There was also an almost linear increase in the risk of death from any cause as resting heart rate increased, and rates of 50–51 beats/min significantly increased the likelihood of requiring pacemaker implantation (adjusted HR 1.80 [95% CI 1.46–2.21]).

Comment: Slower as well as faster resting heart rates predict AF (through a number of different mechanisms) – i.e. a U-shaped relationship. Additionally, perhaps not surprisingly, resting bradycardia predicted pacemaker insertion. Finally, as has been taught for centuries, increasing resting heart rate is associated with increasing all-cause mortality.


Trajectories of cardiovascular risk factors and incidence of atrial fibrillation over a 25-year follow-up

Authors: Norby FL et al

Summary: CV risk factor trajectories were evaluated for 2456 patients with incident AF and 6414 matched controls from the ARIC study, and the association of these trajectories with the incidence of AF was explored in 10,559 individuals free of AF at baseline. There were abrupt increases in the prevalences of stroke, myocardial infarction and heart failure as time to AF diagnosis shortened, and compared with controls, individuals who developed AF had more CV risk factors >15 years before diagnosis. Distinct trajectories for the assessed CV risk factors were identified. In general, individuals with trajectories denoting long-term CV risk factor exposure were at increased AF risk even when adjustments for single measurements of CV risk factors had been made.

Comment: We already know AF is associated with CV disease in general as well as the presence of individual CV risk factors (e.g. hypertension, smoking). This analysis links this risk back to risk factor presence >15 years earlier, highlighting the importance of lifestyle and other measures to control/reduce risk factors for benefits potentially decades in the future.