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- Cardioversion and quality of life/natural history of AF
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- US experience of LAA closure for stroke prevention in AF
- Causes of death in anticoagulated AF
- Bariatric surgery reduces new-onset AF risk

Abbreviations used in this issue:

AF = atrial fibrillation; CIED = cardiovascular implantable electronic devices; HR = hazard ratio; INR = international normalised ratio; LAA = left atrial appendage; NOAC = nonvitamin K oral anticoagulant; VKA = vitamin K antagonist.

Welcome to issue 36 of Atrial Fibrillation Research Review.

Research reporting fewer bleeding complications with uninterrupted dabigatran than with uninterrupted warfarin in patients undergoing AF ablation begins this issue. There is also a summary table to help with choosing oral anticoagulation for stroke prevention in nonvalvular AF, adapted from the two parts of an excellent consensus document. We have also included experiences from the US on LAA closure for preventing stroke in AF since the procedure was approved by the FDA in 2015. The final paper for this issue reports a reduced risk of new-onset AF in previously obese patients who have lost bodyweight following bariatric surgery.

Thank you for your feedback and suggestions – please keep them coming.

Kind Regards,

Dr Andrei Catanchin

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Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation

Authors: Callkins H et al., for the RE-CIRCUIT Investigators

Summary: Patients scheduled for catheter ablation of paroxysmal or persistent AF (n=704) were randomised to receive dabigatran 150mg twice daily or warfarin with a target INR of 2.0–3.0. 635 participants underwent ablation after 4–8 weeks of uninterrupted anticoagulation, which was continued for 8 weeks postablation. Compared with warfarin, dabigatran was associated with a lower incidence of major bleeding events during and up to 8 weeks postablation (primary endpoint; 1.6% vs. 6.9% [p<0.001]), fewer periprocedural pericardial tamponades, fewer groin haematomas and a similar incidence of minor bleeding events. One warfarin recipient experienced a thromboembolic event.

Comment: This important study strongly supports the periprocedural anticoagulation strategy some of us have been employing for some time (e.g. since Praxbind was released); AF ablation with uninterrupted Pradaxa. This approach could easily be applied to less invasive procedures (e.g. ablation for atrial flutter).

Reference: N Engl J Med; Published online March 19, 2017

Abstract

The role of cardiovascular implantable electronic devices in the detection and treatment of subclinical atrial fibrillation

Authors: Hess PL et al.

Summary: These authors noted that most studies to date have explored the consequences of subclinical AF using CIEDs (cardiovascular implantable electronic devices) (CIEDs); however, three trials are to assess the time to a first AF diagnosis in patients receiving a CIED for AF detection. Estimated HRs for stroke, which are currently limited to patients with a prior CIED, vary between 0.87 and 9.40. Stroke risk pathogenesis may include proximately causal factors, upstream risk activators and risk markers. Although subclinical AF treatment may be a useful stroke prevention strategy, there is no direct evidence of benefit from oral anticoagulation. Two ongoing trials are assessing the risks and benefits of NOACs among participants with a previously implanted CIED who are at high stroke risk, but who have not had a prior diagnosis of clinical AF. If a clinical benefit is proven, then further research will be required to evaluate the cost effectiveness of screening for and the treatment of subclinical AF.

Comment: This review highlights an important current issue as we see increasingly more AF detected through various means – not only pacemakers/ICDs and loop recorders, but also the explosion of ‘wearable technology’ that can already (and will be increasingly able to) detect AF. What we do with this information remains to be determined.


Abstract
Seasonal trends in atrial fibrillation episodes and physical activity collected daily with a remote monitoring system for cardiac implantable electronic devices

Authors: Censi F et al.

Summary: Remotely transmitted AF and daily physical activity monitoring data were analysed for 988 HomeGuide trial participants implanted with a pacemaker or implantable defibrillator. Seasonal trends were seen for both physical activity and AF incidence with an inverse correlation. A first-order autoregressive model revealed a regression coefficient of daily activity to AF incidence of −0.64 (p<0.0001); the cross-correlation coefficient reached its maximum values at ±180 day lags. Compared with summer months, winter months were associated with a 14.4% greater AF incidence and 14.7% less physical activity (p<0.0001 for both). A power spectral analysis showed weekly periodicity in physical activity, but not AF incidence, that corresponded to rest during festivities.

Comment: This fascinating study correlates daily physical activity and daily AF burden with a clear seasonal variation (less activity and more AF in winter, cyclical over 3.5 years) in almost 1000 patients, average age 68 years, with cardiac devices. While it’s possible that AF led to reduced activity, this wasn’t reflected in hospitalisation data and it’s more likely the reverse is true, although direct causality cannot be inferred from this analysis.

Reference: Int J Cardiol 2017;234:48–52

Abstract

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: parts 1 & 2

Authors: Diener H-C et al.

Summary/comment: This excellent consensus document (in two parts) suggests answers to the frequently posed question ‘which NOAC/dose is best for my patient?’ and merits further reading.

<table>
<thead>
<tr>
<th>Summary table:</th>
<th>First choice</th>
<th>Second choice</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable vascular disease</td>
<td>NOAC monotherapy</td>
<td>NOAC plus aspirin</td>
<td>No specific NOAC preference</td>
</tr>
<tr>
<td>Percutaneous coronary intervention/ stents</td>
<td>Low-dose NOAC recommended during concurrent anti platelet therapy</td>
<td></td>
<td>Dabigatran has good evidence for the low dose, further data are awaited for the other NOACs</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>Warfarin standard of care</td>
<td>&quot;NOACs are safe and effective alternatives, with practical advantages...&quot;</td>
<td>NOACs likely equivalent</td>
</tr>
<tr>
<td>Catheter ablation</td>
<td>Uninterrupted warfarin standard of care</td>
<td>Uninterrupted NOAC</td>
<td>RECURCUT had not been released at the time of writing; warfarin and dabigatran are reversible</td>
</tr>
<tr>
<td>Valvular AF (mechanical valves, moderate–severe mitral stenosis)</td>
<td>Warfarin standard of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other valve disease</td>
<td>Apixaban/rivaroxaban</td>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Warfarin with time in therapeutic range &gt;70%</td>
<td>Warfarin continuation is reasonable</td>
<td>Change to NOAC</td>
<td>No specific NOAC preference</td>
</tr>
<tr>
<td>CHA2DS-VASc score 1 (2 in females)</td>
<td>Consider dabigatran/apixaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single episode AF</td>
<td>Treat as for recurrent AF</td>
<td>May wait until AF recurs in borderline cases</td>
<td>No specific NOAC preference</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Apixaban/rivaroxaban</td>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>NOAC</td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>Acute stroke on anticoagulation</td>
<td>Measure anticoagulation intensity and consider thrombolysis</td>
<td>Catheter thrombectomy</td>
<td></td>
</tr>
<tr>
<td>After stroke/transient ischaemic attack</td>
<td>Anticoagulant after exclude haemorrhage</td>
<td>‘1-3-6-12 rule’</td>
<td></td>
</tr>
<tr>
<td>High risk of gastrointestinal bleeding</td>
<td>Apixaban 5mg twice daily or dabigatran 110mg twice daily</td>
<td>Dabigatran 150mg twice daily or rivaroxaban 20mg</td>
<td>Avoid concurrent antiplatelet use</td>
</tr>
<tr>
<td>Creatinine clearance 30–50 mL/min</td>
<td>Apixaban 5/2.5mg twice daily or rivaroxaban 15mg</td>
<td>Dabigatran 110mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>No anticoagulation</td>
<td>NOACs not recommended</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>Apixaban</td>
<td>Dabigatran 110mg twice daily or rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Any NOAC</td>
<td>No specific NOAC preference</td>
<td></td>
</tr>
<tr>
<td>Adherence issues</td>
<td>Probably NOAC; see paper</td>
<td>No specific NOAC preference</td>
<td></td>
</tr>
</tbody>
</table>


Abstract (part 1); Abstract (part 2)
PBS codes: Non-valvular atrial fibrillation – 4269. Other PBS codes differ – please refer to PBS Schedule.

Before prescribing, please review full Product Information available from Bristol-Myers Squibb Australia Pty Ltd by calling 1800 067 567.

MINIMUM PRODUCT INFORMATION ELIQUIS®

(2.5 mg and 5 mg tablets). Indications: For use in adult patients for VTE prevention after elective total hip or total knee replacement surgery; stroke and systemic embolism prevention with non-valvular atrial fibrillation (NVAF) with at least one additional factor for stroke; treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); prevention of recurrent DVT and PE.

Contraindications: Hypersensitivity to apixaban or tablet excipients; clinically significant active bleeding (intracranial, GI); impaired haemostasis; hepatic disease associated with coagulopathy and clinically relevant bleeding risk, severe hepatic impairment (Child-Pugh C); severe renal impairment (CrCl < 25 mL/min); organ lesion or conditions at risk of clinically significant major bleeding; strong inhibitors of both CYP3A4 and P-gp, concomitant anticoagulant treatments. See PI for details.

Precautions: Haemorrhage risk: existing conditions with increased bleeding risk; fall in haemoglobin or blood pressure – search for bleeding site; discontinue if severe haemorrhage or complications; consider treatment. Increased risk of thrombotic events after premature discontinuation when transitioning to warfarin (consider coverage with another anticoagulant); valvular heart disease; active cancer; acute pulmonary embolism in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy; patients with provoked VTE; ischaemic stroke; renal or hepatic impairment; strong inducers of both CYP3A4 and P-gp; concomitant NSAIDs; other anti-platelets or antithrombotic agents not recommended; spinal/epidural anaesthesia or puncture; indwelling catheters; neuraxial blockade; hip fracture surgery; pregnancy; lactation; children; elderly patients on concomitant acetylsalicylic acid; effects on clotting tests. See PI for details.

Interactions with other Medicines: inducers and inhibitors of both CYP3A4 and P-gp. See PI for details.

Adverse Effects: Most common: anaemia, haemorrhage (including eye, GI, rectal, gingival), haematoma, haematuria, epistaxis, contusion, nausea, menorrhagia. Others include: thrombocytopenia, hypotension, thrombosis, intra-abdominal, haemorrhagic, mouth, vaginal, suture-associated, vein, catheter-related, urethral incision site, post-procedural bleeding, haemorrhage, platelet count increased or abnormal, fibrinogen increased, wound secretion, haemoptysis, hyperviscosity. See PI for details.

Dosage and Administration: VTE prevention: 2.5 mg twice daily. Start 12 to 24 hours after surgery. Take for 32 to 38 days. DVT/PE treatment: 10 mg twice daily for 7 days, followed by 5 mg twice daily. Prevention of recurrent DVT/PE: 2.5 mg twice daily after at least 6 months of treatment for DVT/PE. See PI for details. Bristol-Myers Squibb Australia Pty Ltd ABN 31 004 333 322. Level 2, 4 Nexus Court, Mulgrave VIC 3170 Australia. Pfizer Australia Pty Ltd. 38–42 Wharf Road, West Ryde NSW 2114 Australia.† Registered trademark. Bristol-Myers Squibb Australia Pty Ltd

PBS Information: Authority required (STREAMLINED). Refer to PBS Schedule for full authority information.

ELIQUIS PROTECTS PATIENTS WITH NVAF, DVT AND PE FROM THROMBOEMBOLIC EVENTS†‡1–3

† In adult patients with NVAF and at least one additional risk factor for stroke
‡ In adult patients with symptomatic proximal DVT or PE

NVAF, non-valvular atrial fibrillation; SE, systemic embolism; DVT, deep vein thrombosis; PE, pulmonary embolism; RRR, relative risk reduction.

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eliquis.com.au
Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation

Authors: Staerk L et al.

Summary: NOACs were compared with VKAs for stroke/thromboembolism or intracranial bleeding risk in a Danish cohort of 43,229 patients registered with AF, including 42% VKA recipients, 29% dabigatran recipients, 13% rivaroxaban recipients and 16% apixaban recipients, with respective mean CHADS2, VASc scores of 2.9, 2.7, 3.0 and 3.1. Over follow-up of 2 years, there were 1054 stroke/thromboembolic events and 261 intracranial bleeds. Compared with the standardised 1-year absolute risk of stroke/thromboembolism for VKAs of 2.01%, the respective absolute risk differences for dabigatran, rivaroxaban and apixaban did not differ significantly. In contrast, compared with the standardised 1-year absolute risk of intracranial bleeding with VKAs of 0.60%, dabigatran and apixaban were associated with significantly lower absolute risk differences (−0.34% [95% CI −0.47% to −0.21%] and −0.20% [−0.38% to −0.01%]), but the absolute risk difference for rivaroxaban was not significantly different.

Comment: In this large Danish real-world registry, NOAC efficacy was similar to warfarin but times in therapeutic range and INRs are not provided and we know this country performs exceptionally well in this respect. The other important information not provided relates to dosing of the NOACs, specifically the appropriateness of low-dose prescribing.


Abstract

Cardioversion and subsequent quality of life and natural history of atrial fibrillation

Authors: Pokorney SD et al., for the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Investigators

Summary: These researchers analysed data from patients who had undergone cardioversion and propensity-matched noncardioverted patients in a 3:1 ratio from the prospective ORBIT-AF registry. Among 9642 patients, 8% underwent 906 cardioversions over median follow-up of 12 months. Compared with noncardioverted patients, cardioverted patients had higher rates of 1-year cardiovascular-related hospitalisation (43% vs. 21%; adjusted HR 2.2 [95% CI 1.8–2.6]) and sinus rhythm at both first and second follow-up visits (36% vs. 27% [p=0.042]); the findings for first-time cardioverted patients were similar. Neither symptom improvement nor symptomatic progression differed significantly between cardioverted and noncardioverted patients (34% vs. 42% and 15% vs. 4%). Cardioversion was associated with AF progression after cardioversion and after first cardioversion (respective odds ratios 1.6 [95% CI 1.2–2.2] and 2.7 [p<0.001]). Only 18% of patients who were not previously on an antiarrhythmic started such treatment postcardioversion, <5% underwent ablation, and 22% stopped their antiarrhythmic agent.

Comment: These findings are not necessarily surprising; cardioversion as rhythm control is usually temporary and additional strategies are required (antiarrhythmic drugs and/or catheter ablation). However, cardioversion can be very useful even in the short term (e.g. to help determine symptoms or confirm asymptomatic AF) and this can guide ongoing management.

Reference: Am Heart J 2017;185:59–66

Abstract

Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation

Authors: Bahit MC et al.

Summary: These authors reported on nonmajor bleeding and clinical outcomes for 18,140 ARISTOTLE trial participants with AF who received ≥1 dose of study drug. The nonmajor bleeding rate was greater than the major bleeding rate (12.1% vs. 3.8%) and, similar to major bleeding, was less frequent among apixaban recipients than warfarin recipients (6.4 vs. 9.4 per 100 patient-years; adjusted HR 0.69 [95% CI 0.63–0.75]). Haematuria (16.4%), epistaxis (14.8%), gastrointestinal bleeding (13.3%), haematura (11.5%) and bruising/ecchymosis (10.1%) were the most frequent forms of nonmajor bleeds. Apixaban and warfarin recipients who experienced nonmajor bleeds had similar medical or surgical intervention rates (24.7% vs. 24.5%), but there were trends for warfarin recipients to be more likely to change their antithrombotic therapy (58.6% vs. 50.0%) or permanently discontinue study drug (5.1% vs. 3.6% [p=0.10]). Independent associations were seen between clinically relevant nonmajor bleeding and increased risks of overall death (adjusted HR 1.70 [95% CI 1.32–2.18]) and subsequent major bleeding (2.18 [1.56–3.04]).

Comment: It’s easy to accept nonmajor bleeding as ‘part of taking an anticoagulant’; however, as this study shows, even ‘minor’ bleeding is not benign and predicts adverse outcomes including mortality. Nonmajor bleeding was significantly less frequent with apixaban than warfarin.

Reference: Heart 2017;103(8):623–8

Abstract

Post-approval U.S. experience with left atrial appendage closure for stroke prevention in atrial fibrillation

Authors: Reddy VY et al.

Summary: Acute procedural performance and complication rates were reported for all 3822 LAA closure procedures performed in the US for stroke prevention in patients with nonvalvular AF since FDA approval in March 2015. The implantation success rate was 95.6% and the median procedure time was 50 minutes. Of the 382 physicians performing these implantations, 71% were new, nonclinical trial implanters who performed 50% of the procedures. The procedural complication rates were 1.02% for pericardial tamponade (three cases were fatal), 0.78% for procedure-related stroke, 0.24% for device embolisation and 0.078% for procedure-related mortality.

Comment: The bulk of ‘real-world data’ in AF has been about NOACs. Catheter-directed LAA closure is not only an alternative to warfarin but an alternative to anticoagulation, and has been performed in Australia for almost 10 years, based on the original WATCHMAN device studies. In this US analysis, we see overall acceptable results, but methods are not quite ideal.

Reference: J Am Coll Cardiol 2017;69(3):253–61

Abstract
Bariatric surgery and the risk of new-onset atrial fibrillation in Swedish obese subjects

Authors: Jamaly S et al.

Summary: The impact of bariatric surgery on new-onset AF risk was explored in the prospective SOS (Swedish Obese Subjects) cohort study of 2000 obese individuals with sinus rhythm and no history of AF who underwent bariatric surgery matched to 2021 obese control subjects who received usual care. Median follow-up was 19 years. Compared with controls, the patients who underwent bariatric surgery had a significantly lower rate of first-time AF (12.4% vs. 16.8%; HR 0.71 [95% CI 0.60–0.83]). The benefit was greater for younger versus older patients (p<0.001 for interaction) and those with a higher versus lower diastolic blood pressure (p=0.028 for interaction).

Comment: In the last few years we have seen that effective treatment of obesity can reduce AF and its symptoms — here we have evidence that weight reduction may actually act as ‘primary prevention’ of AF, in this case via bariatric surgery, which effectively achieved sustained weight reduction of 25% at 1 year, 17% at 10 years and 18% at 20 years (compared with no reduction in controls).

Reference: J Am Coll Cardiol 2016;68(23):2497–504

Abstract

The impact of bariatric surgery on new-onset AF risk was explored in the prospective SOS (Swedish Obese Subjects) cohort study of 2000 obese individuals with sinus rhythm and no history of AF who underwent bariatric surgery matched to 2021 obese control subjects who received usual care. Median follow-up was 19 years. Compared with controls, the patients who underwent bariatric surgery had a significantly lower rate of first-time AF (12.4% vs. 16.8%; HR 0.71 [95% CI 0.60–0.83]). The benefit was greater for younger versus older patients (p<0.001 for interaction) and those with a higher versus lower diastolic blood pressure (p=0.028 for interaction).