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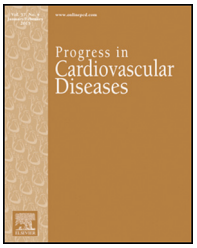

Oral Anticoagulant Therapy in Atrial Fibrillation Patients at High Stroke and Bleeding Risk

Tatjana S. Potpara[a,b], *Gregory Y.H. Lip*[a,c,*]

[a]*School of Medicine, Belgrade University, Belgrade, Serbia*
[b]*Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia*
[c]*University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom*

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ABSTRACT

Atrial fibrillation (AF) is associated with a 5-fold greater risk of ischemic stroke or systemic embolism compared with normal sinus rhythm. Cardioembolic AF-related strokes are often more severe, fatal or associated with greater permanent disability and higher recurrence rates than strokes of other aetiologies. These strokes may be effectively prevented with oral anticoagulant (OAC) therapy, using either vitamin K antagonists (VKAs) or non-vitamin K antagonist OACs (NOACs) such as the direct thrombin inhibitor dabigatran or direct factor Xa inhibitors rivaroxaban, apixaban or edoxaban. Most AF patients have a positive net clinical benefit from OAC, excluding those with AF and no conventional stroke risk factors. Balancing the risks of stroke and bleeding is necessary for optimal use of OAC in clinical practice, and modifiable bleeding risk factors must be addressed. Concerns remain over 'non-changeable' bleeding risk factors such as older age, significant renal or hepatic impairment, prior stroke(s) or prior bleeding event(s) and active malignancies. Such AF patients are often termed 'special' AF populations, due to their 'special' risk profile that includes increased risks of both thromboembolic and bleeding events, and due to fear of bleeding complications these AF patients are often denied OAC. Evidence shows, however, that the absolute benefits of OAC are the greatest in patients at the highest risk, and NOACs may offer even a greater net clinical benefit compared to warfarin particularly in these high risk patients.

In this review article, we summarize available data on stroke prevention in AF patients at increased risk of both stroke and bleeding and discuss the use of NOACs for thromboprophylaxis in these 'special' AF populations.

Atrial fibrillation (AF) is associated with a 5-fold greater risk of thromboembolic events compared with normal sinus rhythm (NSR).[1] Without treatment, approximately one in three AF patients would ultimately suffer an ischemic stroke, most often of cardioembolic or far less commonly of atherothrombotic origin.[2,3] Cardioembolic AF-associated events predominantly

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* Address reprint requests to Prof Gregory Y.H. Lip, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, United Kingdom.
E-mail address: g.y.h.lip@bham.ac.uk (G.Y.H. Lip).

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Abbreviations and Acronyms

AF = atrial fibrillation

ARR = absolute risk reduction

CKD = chronic kidney disease

CMB = cerebral microbleeds

CrCL = creatinine clearance

CV = cardiovascular

ESRD = end-stage renal disease

FFP = fresh frozen plasma

GI = gastrointestinal

HR = hazard ratio

ICH = intra cranial haemorrhage

INR = international normalised ratio

MRI = magnetic resonance imaging

NOAC = non-vitamin K antagonist oral anticoagulant

OAC = oral anticoagulant

OR = odds ratio

PCC = prothrombin complex concentrate

RR = relative risk

TTR = time in therapeutic range

VKAs = vitamin K antagonists

result from dissemination of thrombus formed in the left atrial appendage, and such strokes are often more severe, more fatal or associated with greater permanent disability and higher recurrence rates than strokes of other aetiologies.[3–5]

Cardioembolic AF-related strokes may be effectively prevented with oral anticoagulant (OAC) therapy, using either vitamin K antagonists (VKAs) or non-vitamin K antagonist OACs (NOACs) such as the direct thrombin inhibitor, dabigatran, or direct factor Xa inhibitors, rivaroxaban, apixaban or edoxaban.[6–10] Treatment with VKAs provides a positive net clinical benefit in almost all AF patients (excluding those with no conventional stroke risk factors), regardless of the bleeding risk level.[11,12] Compared with VKAs, NOACs may offer even a greater net clinical benefit, particularly in AF patients at increased risk of bleeding.[13,14]

Balancing the stroke and bleeding risks is necessary for optimal use of OAC in clinical practice,[15–19] and modifiable bleeding risk factors such as poorly controlled hypertension, low quality of VKA treatment (as reflected through labile international normalised ratios [INRs]), co-medication (e.g., antiplatelet or non-steroidal anti-inflammatory drugs) or alcohol abuse must be corrected.[20,21] Concerns remain over 'non-changeable' bleeding risk factors such as older age, significant renal or hepatic disease, prior stroke(s) or prior bleeding event(s) and malignancy. Such AF patients are often termed 'special' AF populations, due to their 'special' risk profile that includes increased risks of both thromboembolic and bleeding events.[17] In these populations the use of OAC might be challenging and more data are needed to better define optimal stroke prevention and diminish often unjustified underuse of OAC in the high-risk AF patients.[22]

In this review article, we summarize available data on stroke prevention in AF patients at increased risk of both stroke and bleeding and discuss the use of NOACs for thromboprophylaxis in these 'special' AF populations.

Elderly patients with AF

Over a half of AF patients are >75 years old.[23] Advancing age is amongst the strongest independent stroke risk factors, with relative risk (RR) of 1.5 per decade (95% confidence interval [CI], 1.3–1.7)[24,25] and stroke rates of up to 36.2% at age of 80–89 years.[26] The lifetime AF-related stroke incidence sharply increases during the sixth decade of life, reaching the threshold for OAC at 65 years even in the absence of other risk factors.[17–19]

Recently a significant overall decline in the annual stroke rates (from 2.09% to 1.66%, $p < 0.001$) in AF patients taking warfarin has been reported, but the risk was still higher in elderly (≥75 years) compared with younger patients.[27] The rates of warfarin-related major bleeding (including intracranial haemorrhage [ICH]) also increased with ageing (from 4.7% in those younger than 80 years to 13.1% per 100 patient-years in older patients),[28] and each year at least 1% of the latter are hospitalised due to gastrointestinal (GI) bleeding.[29] VKAs are often underused in older AF patients[30,31] and, when warfarin is prescribed, those ≥80 years old were more likely to discontinue the drug within the first year of treatment (26%).[28]

A recent report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry suggests that antiplatelet therapy (mainly aspirin, alone or in combination with OAC) is still frequently prescribed in clinical practice (30.7%), particularly in patients at high risk of stroke (as measured by the CHA_2DS_2-VASc score of ≥2) or bleeding (the use of antiplatelet drugs increased from 8.7% in patients with a HAS-BLED = 0 to 29.4% in those with a HAS-BLED = 4).[32] This persistent misperception of lower bleeding risk with aspirin compared to OAC most likely stems from results of the historical randomised trials on warfarin vs. aspirin for stroke prevention in AF.[6] A meta-analysis of participants aged ≥75 years showed a 2.2% lower risk of ischemic stroke at the cost of a 1.7% greater risk of major bleeding with warfarin, but older patients were significantly under-represented in those trials.[33]

In contrast to these historical data, a contemporary, adequately powered, randomised, controlled trial on adjusted-dose warfarin (target INR of 2.0–3.0) vs. aspirin 75 mg daily for stroke prevention in elderly AF patients (all ≥75 years old, mean age 81.5 years) showed no significant difference in the rates of haemorrhagic strokes (0.5% vs. 0.4%), other ICH (0.2% vs. 0.1%) or extracranial bleeding (1.4% vs. 1.6%) with warfarin vs. aspirin (all $p > 0.05$).[23] Overall, there was no difference in the annual rates of major bleedings (1.9% vs. 2.0%, RR 0.97; 95% CI, 0.53–1.75), and the primary endpoint of fatal or disabling stroke, other ICH or arterial embolism was significantly reduced by warfarin in comparison to aspirin (RR 0.48; 95% CI, 0.28–0.80, $p = 0.003$), with no significant interaction between age and treatment.[23] Aspirin was also associated with more adverse events (including bleeding) than warfarin in another trial on octogenarians with AF.[34]

In the absence of formal contraindications, warfarin is often denied to older AF patients due to concerns such as frailty and the risk of falling, or anticipated non-adherence to therapy (secondary to the need for regular INR monitoring or cognitive impairment)[35–37] resulting in a poor quality of warfarin therapy as measured by the time in therapeutic