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New Frontiers and Treatment Paradigms for Stroke Prevention in Atrial Fibrillation

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Atrial fibrillation (AF) is a major public health burden worldwide, and its prevalence is set to increase owing to widespread population ageing, especially in rapidly developing countries such as Indonesia. Patients with AF are reported to have a five-fold increased risk of stroke; moreover, compared with the other identified risk factors for stroke (hypertension, heart failure, and coronary heart disease), AF has the strongest association.

Burden of Atrial Fibrillation

Systemic thromboembolism is the most severe complication of AF. It accounts for about 15–20 % of ischaemic strokes. AF-related stroke was cardiac in origin; thrombi form in the left atrial appendage and embolize, causing ischaemic stroke. Besides, AF-related strokes were associated with a poor prognosis as more than 50 % of the survivors remain with a severe deficit, and recurrence may be as high as 12 % per year. AF could in fact drive a prothrombotic or hypercoagulable state, by virtue of its fulfilment of Virchow's triad for thrombogenesis (blood stasis, endocardial dysfunction/damage, and abnormal haemostasis). Therefore, antithrombotic therapy has become an established method of preventing stroke in patients with AF.

Vitamin K antagonist (VKA)

Current guidelines for the management of AF recommend the use of the risk-prediction model CHADS₂-VASc to guide decisions about anticoagulation treatment. Vitamin K antagonists (VKAs) are highly effective for the prevention of stroke, mainly of ischemic origin, in patients with AF, resulting in a 64% risk reduction compared with placebo and a 37% risk reduction compared with antiplatelet therapy. For this reason, VKAs are currently recommended in all AF patients at moderate to high risk for stroke or systemic embolism (SE). However, VKAs have significant limitations, particularly their unpredictable anticoagulant response and numerous food and drug interactions, mandating regular laboratory monitoring. These limitations make treatment with VKAs problematic for many patients; as a result, only about half of all potentially eligible AF patients are treated with VKAs. In the multinational GARFIELD study of patients with AF from Australia, Brazil, Canada, East Asia, Mexico, and Western Europe, 40.7% of patients with a CHADS₂-VASc score ≥ 2 were not receiving anticoagulation.

Antiplatelet therapy

Acetylsalicylic acid has been widely used as an agent for stroke prophylaxis in patients with AF. Until recently, guidelines recommended ASA therapy only in patients with non-valvular AF who are considered at low risk of stroke, or in whom VKA therapy is contraindicated. A comparison of antiplatelets (including clopidogrel, triflusal, and indobufen as well as ASA) with VKA therapy in the meta-analysis by Hart et al. revealed that adjusted-dose warfarin reduced the RR of all stroke by 37% (95% CI 23 –48) compared with antiplatelet therapy (180 vs. 282 events in 8946 patient-years). The modest effect of antiplatelet agents on stroke risk may be more due to the inhibition of platelet thrombi in the carotid and cerebral arteries than the inhibition of cardiogenic thrombi that occur in AF. However, it is likely that the lower bleeding risk with antiplatelet agents compared with that of VKAs (albeit at the cost of reduced efficacy) remains their key attraction.

Novel oral anticoagulants (NOACs)

Over the last several years, novel oral anticoagulant drugs (NOACs), including direct thrombin inhibitors and factor Xa inhibitors, have been developed. These drugs have the potential to address some of the limitations of VKAs. These agents have fewer food and drug interactions and a more predictable anticoagulant effect, thus allowing fixed dosing without the need for laboratory monitoring. Furthermore, their shorter half-life may produce additional advantages, eg, if temporary interruption is required for a surgical procedure or in the case of an hemorrhagic complication.

In one meta-analysis, the results of clinical trials carried out with 4 NOACs were combined. These drugs present some important differences in terms of mechanisms of action, 1 drug (dabigatran etexilate) is a direct thrombin inhibitor and 3 drugs (rivaroxaban, apixaban, and edoxaban) are direct factor Xa inhibitors. Moreover, there are some differences in the mechanisms of excretion, in their mean half-lives, and in the drug-drug interactions, among others. NOACs were pooled to perform a comparison with vitamin K antagonists, calculating pooled relative risks (RRs) and associated 95% confidence intervals (CIs). There were 12 studies (3 administering dabigatran, 4 administering rivaroxaban, 2 administering apixaban, and 3 administering edoxaban) enrolling a total of 54 875 patients. NOACs significantly reduced total mortality (5.61% versus 6.02%; RR, 0.89; 95% CI, 0.83– 0.96), cardiovascular mortality (3.45% versus 3.65%; RR, 0.89; 95% CI, 0.82– 0.98), and stroke/systemic embolism (2.40% versus 3.13%; RR, 0.77; 95% CI, 0.70 – 0.86). There was a trend toward reduced major bleeding (RR, 0.86; 95% CI, 0.72–1.02) with a significant reduction of intracranial hemorrhage (RR, 0.46; 95% CI, 0.39 – 0.56). No difference in myocardial infarction was observed.

Conclusion

Current VKA therapy is highly effective at preventing stroke in patients with non-valvular AF. However, this benefit is offset by the likelihood of bleeding associated with its use, as well as the need for regular coagulation monitoring because of high inter- and intra-subject variability and a sensitivity to drug

interactions. Newer oral anticoagulants have the potential to simplify stroke prevention in patients with AF. Rates of stroke and systemic embolism with the newer agents were at the very least comparable to those of warfarin. Favourable bleeding profiles compared with warfarin were reported across the trials, and there was an indication of reduced mortality compared with warfarin. The newer agents may therefore overcome the limitations associated with VKAs and provide an alternative to agents like warfarin. Collectively, the new agents may also lead to improved adherence to clinical guidelines when oral anticoagulation is the recommended option.

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SURAT PERNYATAAN

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Adalah benar bahwa saya sebagai Peneliti / Peneliti Utama pada karya ilmiah tersebut di atas yang merupakan publikasi dalam bentuk ***Prosiding Kegiatan Ilmiah Nasional WECOC 26th 2014***. Publikasi tersebut tidak menggunakan manusia maupun hewan sebagai subjek penelitian dan telah sesuai dengan kaidah dari komite etik. Penulis besar berharap agar penilai bekernan mereviu dan memberikan penilaian terhadap karya ilmiah tersebut diatas.

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dr. Sunu Budhi Raharjo, PhD, Sp.JP(K)



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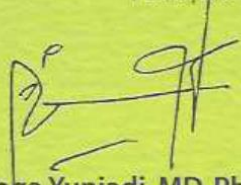
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