



EDITORIALS

Which anticoagulant for stroke prevention in atrial fibrillation?

New rank order of available drugs will help guide clinicians and patients.

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The mainstay of therapy for non-valvular atrial fibrillation (the most common cardiac arrhythmia in clinical practice) is antithrombotic treatment to reduce the risk of stroke. Atrial fibrillation causes a local and systemic thromboembolic state, increasing the risk of stroke approximately fivefold.¹ Use of anticoagulants is guided by risk stratification tools, most commonly the CHA₂DS₂-VASc score.² The recent evolution of direct acting oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban has helped overcome some of the shortcomings of vitamin K antagonists,³⁻⁶ including an increased risk of intracranial bleeding and a need for continuous monitoring.⁷ The new drugs also offer more treatment options for patients. Work reported by López-López and colleagues (doi:10.1136/bmj.j5399) in this issue provides robust evidence to help patients and clinicians choose between anticoagulants based on efficacy, safety, and cost effectiveness.⁸

Derived from a systematic review of the literature, the authors used data from almost 95 000 patients from 23 randomised controlled trials to conduct a network meta-analysis and cost effectiveness analysis of all antithrombotic drugs approved for prevention of stroke in patients with atrial fibrillation. The authors found that many DOACs reduced the risk of stroke or systemic embolism compared with warfarin, but some had more favourable profiles than others when compared with each other. All DOACs had a lower risk of all cause mortality than warfarin, and most reduced the risk of major and intracranial bleeding compared with warfarin. The authors concluded that apixaban 5 mg twice daily was the best treatment option for most outcomes, and was cost effective.

A number of similar syntheses and analyses have already been published. Informed by this evidence, the general consensus is that DOACs are as effective as warfarin for prevention of stroke in patients with atrial fibrillation, and almost always have a more favourable safety profile in trials. The most similar analysis, published in 2012, ranked apixaban 5 mg twice daily and dabigatran 150 mg twice daily as the safest and most cost effective options.⁹ However, López-López and colleagues take their research to the next level and provide an up to date comprehensive analysis. No other study has analysed data from

this many randomised controlled trials while providing direct and indirect comparisons, efficacy data, safety data (including an exhaustive list of outcomes), cost effectiveness, and a rank order from best to worst for all included drugs. Importantly, representatives from two patient groups helped design, conduct, report, and interpret the study - and were included as authors.

Although tempting, findings such as these should not be the only consideration when choosing an anticoagulant in the management of non-valvular atrial fibrillation. Shared decision making will also be informed by patient preference, issues of convenience, and factors such as age and personalised risk-benefit profiles that might favour one drug over another.

For patients with atrial fibrillation, removing the constant monitoring and dose adjustment required with warfarin may encourage self-management and improve quality of life and adherence to treatment. For carers of patients who are frail or have cognitive dysfunction, the improved safety profile of DOACs can provide reassurance.

However, caution is required when attempting to identify a best treatment in comparison with others. One or more DOACs may be contraindicated in some patients, and the use of warfarin is still warranted. Patient specific factors may also prevent the use of any DOAC (renal disease for example) and warfarin remains an effective treatment. This should not be forgotten. As the authors acknowledge, clinicians and patients now need clear guidance on first, second, and third line DOACs for stroke prevention, and when other drugs, including warfarin, should be used. Post marketing studies are currently ongoing, and will help evaluate the real world benefits and risks of DOACs relative to warfarin and to each other. The study conducted by López-López and colleagues adds to this growing body of knowledge. Their findings are important and increasingly so, owing to the exponential rise in the worldwide prevalence of atrial fibrillation currently being observed.¹⁰

If the evidence was strengthened further with head to head trials of DOACs (designed with patient involvement from the start), clinical practice, including clinical guidelines, could be altered accordingly. It's already clear that DOACs are at least as effective as warfarin, safer to use and, of course, easier for

patients. However, in transferring the new findings into practice, a pragmatic strategy of shared decision making that takes full account of patient specific characteristics and preferences is more appropriate than following a blanket recommendation that one anticoagulant is best and should be prescribed over all others. One anticoagulant may not fit all.

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- 1 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;359:983-8. doi:10.1161/01.STR.22.8.983 pmid:1866765.
- 2 Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;359:2893-962. doi:10.1093/eurheartj/ehw210 pmid:27567408.
- 3 Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;359:1139-51. doi:10.1056/NEJMoa0905561 pmid:19717844.
- 4 Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;359:981-92. doi:10.1056/NEJMoa1107039 pmid:21870978.
- 5 Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;359:883-91. doi:10.1056/NEJMoa1009638 pmid:21830957.
- 6 Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;359:2093-104. doi:10.1056/NEJMoa1310907 pmid:24251359.
- 7 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;359:857-67. doi:10.7326/0003-4819-146-12-200706190-00007 pmid:17577005.
- 8 López-López J, Sterne J, Higgins J, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost-effectiveness analysis. *BMJ* 2017;359:j5399.
- 9 Wells G, Coyle D, Cameron C, et al. *Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation*. CADTH Therapeutic Reviews, 2012.
- 10 Ball J, Carrington MJ, McMurray JJV, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;359:1807-24. doi:10.1016/j.ijcard.2012.12.093 pmid:23380698.

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