

## Direct oral anticoagulant: Looking beyond convenience

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Since the 2010 Food and Drug Administration approval of Dabigatran as the first non-vitamin-K antagonist oral anticoagulants or direct oral anticoagulants (DOACs) as it is now more commonly referred to, there has been much development in the field with increasing availability of different DOACs and an expansion in indications of use. In the prevention of thromboembolism in nonvalvular atrial fibrillation (NVAF), DOACs have overtaken warfarin, which has been first-line therapy since the 1950s. In the most recent 2023 guidelines by the American Heart Association (AHA) for the diagnosis and management of atrial fibrillation, there is a Class 1A recommendation for patients who are candidates for anticoagulation without mechanical heart valve or history of moderate-to-severe rheumatic mitral stenosis to be prescribed DOACs over warfarin to reduce the risk of mortality, stroke, systemic embolism and intracranial haemorrhage.<sup>1</sup> This stance is also echoed by the European Society of Cardiology guidelines in 2020,<sup>2</sup> and—closer to home—in the Asia Pacific Heart Rhythm Society 2017 Consensus.<sup>3</sup>

The reasons for these recommendations for DOACs are several fold.<sup>4</sup> First, they stem from the pivotal trials comparing individual DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) with warfarin, which showed non-inferiority or in some instances superiority to warfarin for the prevention of stroke or systemic embolism in patients with NVAF. Second, there are several added benefits compared to warfarin, including reduced risk of major bleeding (especially intracranial bleeding), quick onset and offset of action that precludes the need for regular bridging therapy during interruption, and no requirement for regular international normalised ratio (INR) monitoring. Of relevance to this study, DOACs have also been known to have less food and drug–drug interactions (DDIs).

In this issue of the *Annals*, Chen et al.<sup>5</sup> aimed to explore the impact of DDIs with DOACs in patients with NVAF through a nested case-control study utilising a national administrative database. In summary, the key findings of this study were (1) the concurrent use of DOACs with CYP3A4 and/or P-glycoprotein (P-GP) inducers increased the risk

of thromboembolic events; (2) interactions of DOACs with CYP3A4/P-GP inhibitors showed a marginal effect on reducing thromboembolic events; (3) distinct sex differences were noted with majority of the effects seen in males, as compared to females.

The authors should be applauded for highlighting a commonly overlooked aspect of DOACs and potential DDIs. This contrasts with warfarin whereby healthcare professionals are often more vigilant for such interactions. In the real world, this is particularly relevant for DOACs, as atrial fibrillation, which is inherently a degenerative condition, increases in incidence with age and affects a population where polypharmacy is prevalent.<sup>6</sup> With increasing adoption of guideline directed medical therapy,<sup>7</sup> the effects of DOACs and DDIs, if not addressed, would be amplified. Tellingly, Joosten et al. concluded in a recent randomised controlled trial (RCT), FRAIL-AF, that the switching of warfarin to a DOAC in frail older patients with NVAF was associated with more bleeding complications compared to continuing treatment with warfarin, without an associated reduction in thromboembolic complications.<sup>8</sup> This pragmatic RCT included the most vulnerable and yet increasingly relevant atrial fibrillation population, which has been largely excluded in clinical trials. While there may be several contributory factors that have led to this conclusion, the authors hypothesised that the potential benefit of DOACs may have tapered off in the elderly through a possible contributory factor of polypharmacy. This highlights the importance of addressing DOACs and its potential DDIs.

In this study, another interesting and potentially clinically relevant point raised is the sex differences noted with the effects predominantly seen in males. Of note, studies have demonstrated that women have higher levels of CYP3A4 protein tissue samples compared to men, and would metabolise drugs which are substrates of CYP3A4 more swiftly,<sup>9,10</sup> potentially resulting in reduced effects of such interactions on females compared to males. This will be work for further investigation.

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There are several limitations to this study. First, pertinent clinical information like renal and liver function status had been excluded from the case-control study. Given that DOACs are predominantly renally cleared but are also contraindicated in patients with moderate-to-severe liver cirrhosis, confounding interactions that could affect thromboembolic risks independent of the DDIs might not have been addressed with this study. Second, as acknowledged by the authors, the statistical power of analysis might be limited by its sample size for the various subgroup analyses. It is well known that there are differences in the metabolism of the various types of DOACs. Dabigatran is not metabolised by the CYP3A4 pathway, while rivaroxaban and apixaban are affected by strong CYP3A4 inducers and inhibitors, resulting in increased and decreased clearance, respectively. All DOACs are substrates of P-GP pathway. Despite these differences, while the overall DOAC group showed significant increase in thromboembolic events with the inducers, there were no significant differences with each of the individual types of DOAC. Third, the cohort had a significant difference in CHA<sub>2</sub>DS<sub>2</sub>VASc score with the case group having a higher score than the control group ( $5.6 \pm 2.9$  versus  $4.3 \pm 2.7$ ,  $P < 0.001$ ). This could potentially confound any difference observed and might require further analyses in future studies. Last, while the authors reported that the use of a DOAC concurrently with CYP3A4 and/or P-GP inhibitors had a marginal effect in reducing thromboembolic events with point estimates less than 1, only 1 out of 5 models showed statistical difference.

In summary, with the current best-practice recommendations and the relative ease of use of DOACs, the uptake of DOACs in the treatment of NVAf is predicted to continue to rise. Nonetheless, despite fewer food and DDIs compared with warfarin, healthcare professionals should pay particular attention to potential drugs that may affect DOACs' efficacy or increase its adverse effect profile, as this has been shown to impact on clinical outcomes. The AHA 2023 guidelines put forth a Class 1C recommendation for managing drug interactions in patients receiving DOAC with concomitant therapy with interacting drugs, especially CYP3A4 and/or P-GP inhibitors or inducers.<sup>1</sup> It is, thus, prudent to take into account the pharmacological properties of individual DOACs and the possible medication interactions. On an individualised patient basis, some considera-

tion may be afforded to the use of warfarin in such patients, especially in those with renal/hepatic impairment, given the ability to monitor and titrate INR levels.

**Keywords:** *cardiology, direct oral anticoagulants, epidemiology, nonvalvular atrial fibrillation, thromboembolism, vitamin-K antagonist oral anticoagulants*

### Disclosure

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