

## Beyond warfarin: The advent of new oral anticoagulants

Sir,

We congratulate the authors for their well-drafted article published in the 2015 November issue of the Indian Journal of Radiology and Imaging.<sup>[1]</sup> We read the article entitled "Beyond warfarin: The advent of new oral anticoagulants" with interest and would like to humbly highlight few of our observations and comments from our experience.

1. Majority of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) have shown their efficacy over Vitamin K anticoagulants, but with few major limitations including a lack of antidote to reverse hemorrhage and overdose in emergent situations. However, the expedited approval of a new reversal agent for dabigatran by the Food and Drug Administration in October 2015 deserves a special mention in this context. Praxibind (idarucizumab) is a monoclonal antibody that has been approved for the reversal of anticoagulant effects of dabigatran during emergent surgical procedures and in life-threatening or uncontrolled bleeding situations. Similarly, andexanet alfa (a recombinant form of Factor Xa) that reverses the anticoagulant effect of Factor Xa inhibitors has been studied in Phase I and II clinical trials, and is currently being investigated in Phase III trials<sup>[2]</sup>
2. The authors mentioned that there is twice the risk of major gastrointestinal (GI) bleeding with both apixaban and dabigatran. The RE-LY trial showed similar rates of major hemorrhage (especially GI bleeding) with 150 mg dose of dabigatran in comparison to warfarin.<sup>[3,4]</sup> However, we beg to defer for apixaban as we tend to prefer it in our practice as an initial choice of anticoagulant for patients with a history of GI bleeding. The ARISTOTLE study

- showed reduced bleeding rates according to Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for severe bleeding and thrombolysis in myocardial infarction (TIMI) criteria for major bleeding<sup>[5]</sup>
3. Edoxaban is the most recently approved (January 2015 in the United States and June 2015 in Europe) Factor Xa inhibitor that needs special mention among the list of novel anticoagulants mentioned in this article. It has the best time to peak effect (1–2 h) and provides option for once-daily dosing. ENGAGE AF-TIMI 48 trial compared its efficacy with warfarin in patients with atrial fibrillation. It was found to be non-inferior to warfarin for stroke or systemic embolism risk reduction and with significantly reduced risk of any major bleeding.<sup>[6]</sup> The risk of all-cause mortality and major bleeding of edoxaban versus warfarin was significantly reduced with edoxaban 30 mg dose, but was similar or increased with edoxaban 60 mg dose. Of note, the study showed that patients with creatinine clearance of >95 ml/min had higher rates of ischemic stroke as compared to warfarin, likely due to its 50% renal excretion, resulting in black box warning of edoxaban in the United States
  4. One of the major advantages of NOACs as compared to warfarin has been better food–drug interaction and minimal drug–drug interactions. As described by the authors, dabigatran etexilate is the prodrug that is a substrate of P-glycoprotein (P-gp) efflux transporter, whereas rivaroxaban is metabolized by cytochrome P450 enzymes and acts as a substrate of P-gp transporters. However, we beg to defer with the authors regarding the drug interactions for apixaban because it acts

as a substrate of CYP3A4 and P-gp transporters. Concomitant usage of either inhibitors or inducers of CYP3A4 and P-gp transporters will increase or decrease the exposure to apixaban, respectively<sup>[7]</sup>

5. Authors have summarized the pharmacokinetics and modes of clearance of NOACs. They tend to mention the clearance of rivaroxaban as GI heavy, which seems to be discordant as per the pharmacokinetic literature of the particular drug. Elimination of rivaroxaban from the human body is primarily renal excretion (66%) and the rest tends to be metabolized in the liver followed by fecal excretion (33%)<sup>[8]</sup>
6. Finally, the authors have briefly covered the termination of NOACs prior to elective surgical procedure in their article. They mentioned that NOACs could be stopped 48 h prior to the surgical procedure without the need for bridging therapy. Although this theory beholds for most of the bread and butter cases, this could not be portrayed as a generalized concept, especially for complex cases that need further clarification for stopping and restarting the anticoagulants during the peri-operative period. In general practice, it is recommended to evaluate the bleeding risk involved in the surgical procedure and hold anticoagulants for at least 4–6 half lives.<sup>[9]</sup> We prefer to hold dabigatran 1–2 days prior to surgery in patients with creatinine clearance >50 ml/min, whereas 3–5 days prior for patients with creatinine clearance <50 ml/min. Rivaroxaban and apixaban could be discontinued 24 h prior to the procedure, whereas apixaban should be withheld 48 h prior to procedures with moderate to high risk of clinically relevant bleeding.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

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Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/0971-3026.190428

**Cite this article as:** Malhotra K, Khunger M. Beyond warfarin: The advent of new oral anticoagulants. *Indian J Radiol Imaging* 2016;26:419-20.