Sir,

Direct thrombin inhibitors potentially have advantages over vitamin K antagonists (VKAs) like early onset of action, less drug interactions and therapeutic effect which is predictable. This may relieve the physician and patient stress of regular prothrombin time (PT) with INR monitoring and one can avoid the traditional overlap of heparin and warfarin to build up anticoagulation. The disadvantage is that direct thrombin inhibitors have a shorter half life so the patient needs to very strictly adhere to the drug while warfarin has a half life of about 40 hours which may come to rescue as embolic phenomenon due to atrial fibrillation (AF) is acute event.

Dabigatran Etexilate was tested in phase II PETRO trial (prevention of embolic and thrombotic events in patients with persistent AF) which was a double blind, dose escalating trial (50,150 and 300 BID). The identified doses were carried forward in RE-LY trial (Randomised Evaluation of Long Term Anticoagulant Therapy, Warfarin, compared with Dabigatran) in 18,113 patients where dabigatran in dose of 110 mg and 150 mg twice daily was compared with dose adjusted warfarin. RE-LY trial concluded that dabigatran 150 mg BD was superior to warfarin in preventing stroke and non-inferior to warfarin with regard to major bleeding while dabigatran 110 mg BD was superior to warfarin with regard to major bleeding and non -inferior to warfarin in preventing stroke. There was a low incidence of intracranial haemorrhage with both the doses but an increase in myocardial infarction with 150 mg BD dosing. RE-LY trial is extending anticoagulation for another 28 months in upcoming RELY-ABLE study. Dabigatran has a 2 hour onset of action and a half life of 14-17 hours.

Rivaroxaban has 2.5-4 hour onset of action and 5-9 hours of half life in healthy individuals and 9-13 hours in elderly individual. The ROCKET-AF (Rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) trial, a double blind trial included 14,264 patients and compared 20 mg once daily rivaroxaban with dose adjusted warfarin, that showed rivaroxaban is non- inferior to warfarin in prevention of stroke or systemic embolism and intracranial haemorrhage and fatal bleeding has been less frequent in rivaroxaban group.

Apixaban 2.5 mg BID was compared with aspirin (81-324 mg QD) in AVERROES (Apixaban versus Acetylsalicylic acid(ASA) to prevent strokes) trial which included more than 6000 patients who were unsuitable for warfarin. The study showed superiority of apixaban over aspirin in stroke prevention without increased bleeding risk. The ARISTOTLE phase III study (Apixaban for prevention of stroke in subjects with atrial fibrillation) includes over 18000 patients and compares apixaban 5 mg BD to warfarin(INR-2-3) for stroke prevention with a median CHADS2 score of 2. The results proved that apixaban was superior to warfarin in stroke prevention with a decrease in bleeding risk and a decrease in mortality. Apixaban has 3 hour onset of action and 8-15 hours of half life.
Other direct thrombin inhibitors with proven efficacy over warfarin in non valvular AF include betrixaban (EXPLORE-xa study comparing 40, 60 or 80 mg betrixaban vs. warfarin (INR 2-3). The ENGAGE AF TIMI 48 using edoxaban 30 or 60 mg once daily vs. warfarin (INR 2-3) is still ongoing. YM-150 (Daraxeban) has been tested in OPAL-1 and OPAL-2 trial in a dose of 30-120 mg once daily has shown to be safe and well tolerated with no serious adverse effects.

Warfarin will continue to be the drug of choice in valvular AF patients for now as it is yet to be tested in this subset of patients. However, there are some concerns over the use of direct thrombin inhibitors in patients with non-valvular AF: Shorter half life of direct thrombin inhibitors makes patients compliance extremely important in AF. In patients with failed therapy, we won’t have INR levels which can guide us for optimal management. Till specific antidotes are developed for these drugs, reversal will be a big issue. Dose adjustment in hepatic and renal dysfunction and higher cost of these drugs compared to warfarin are of concern.

References