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Editorial

A Risk Benefit Comparison of Targeted Anticoagulants

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Atrial fibrillation (AF) places a substantial clinical and economic burden on global health care systems [1]. Most patients with AF are at an increased risk of stroke and its other embolic complications. Traditionally, the vitamin K antagonist warfarin has been utilized in order to treat these conditions. Recently, common pathway inhibitors such as dabigatran, rivaroxaban, and apixaban have been approved for stroke prevention in non-valvular AF and as such, health care providers now have additional options. These new novel oral anticoagulants (NOAC) provide ease of delivery but add cost to our health care systems. A 2006 study surveying 119,000 United States (US) Medicare beneficiaries with AF found that the average total healthcare cost of AF without an adverse event was US$15,718 and with an event, the number escalated to US$43,937 [2]. In a climate of evolving cost restraints, the role of NOACs is as of yet indeterminate.

Despite having similar pathways, each NOAC has a unique clinical application. Dabigatran is a twice daily drug that is administered in 110 and 150 mg doses. The latter dosage was proven superior to warfarin with a 36% relative reduction of stroke. The lower dose was shown to be non-inferior to warfarin with respect to the primary endpoint [3]. In addition to stroke prevention, there are clear clinical benefits to using dabigatran as opposed to warfarin, particularly reduced rates of intracranial bleeding. However, the benefit of dabigatran may be outweighed by an increase in risk of gastrointestinal (GI) bleed and myocardial infarction (MI).

Rivaroxaban, a NOAC mechanistically different than dabigatran, inhibiting factor Xa, is a once daily drug. As compared to patients taking warfarin, those randomized to rivaroxaban were 21% less likely to suffer a stroke or embolic event [4]. There was no significant difference in bleeding events, though warfarin patients perished more frequently from bleeds, while rivaroxaban patients more frequently needed transfusions. This drug can be used safely with a lower dose in patients with renal insufficiency as it has two modes of clearance.

Finally, apixaban is a twice daily drug that impairs the clotting pathway in a similar fashion as rivaroxaban. In the ARISTOTLE study, there was a 21% risk reduction of the primary endpoint, ischemic or hemorrhagic stroke or systemic embolism, as well as a 31% risk reduction in all bleeding, which was primarily attributable to a reduction in intracranial bleeding with a trend towards reduction of GI bleeds [5]. However, the study comes with a caveat: patients eligible for inclusion only needed a $CHADS_2$ score of 1, a subgroup that accounted for approximately one-third of the study population. This lower risk subgroup would normally be treated with vitamin K antagonism, but were included in the study's final analysis anyway. As this population was included in the study, it is possible that patients with a $CHADS_2$ score of 1 may clinically benefit from apixaban, although the study was not powered to answer this question.

An important consideration in anticoagulant use is its total cost, including the actual medication, lab payments, clinic visits, transportation, and possible adverse events. In respect to medication alone, warfarin's cost per pill is exceptionally lower than any NOAC's cost per pill. Secondarily, the former needs to be monitored while the latter does not. Additionally, as shown above, NOACs pose a lower risk of serious adverse events, such as intracranial hemorrhage (ICH), which has been shown to cost on average US$47,640 per event. Other risks, like stroke and major bleeding cost US$32,900 and US$23,414 per event, respectively [1]. Since each NOAC carries either equivalent or less risk than warfarin, patients on the latter are more likely to have an extremely costly adverse event and thus be financially burdened. In sum, over a lifetime, warfarin costs the least, at US$77,813. Rivaroxaban, dabigatran, and apixaban were shown to cost US$78,738, US$82,719, and US$85,326, respectively. Furthermore, in this study, the quality of life (QOL) was inversely proportional to cost, meaning that apixaban offers the highest QOL while warfarin the lowest [6]. A possible explanation why warfarin costs the least is that warfarin patients die the more frequently, which obviously drives down the average cost.

One common critique of NOACs is a lack of reversal or antidote for the drugs. However, in July of 2014, the US Food and Drug Administration granted idarucizumab as a breakthrough drug for this clinical application. The antibody irreversibly binds to dabigatran, reversing its effects entirely, without toxicity to the patient. With this recent development, one can assume that other similar drugs are on the way, a substantial step in the use of NOACs.

In summary, the NOACs are at least equivalent to warfarin in preventing stroke and its complications. Each drug has its own clinical profile including dosage and clearance characteristics that allow clinicians to personalize the use of these drugs. In the future, it may become more apparent that the NOACs provide overall improvement of QOL at little increase in cost.

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