INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Brief: *Direct Oral Anticoagulants in Atrial Fibrillation*
-November 2024-

Background:
In 2017, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review for the use of direct oral anticoagulant (DOAC) agents to prevent stroke for candidate patients with atrial fibrillation, adding apixaban to the IHS National Core Formulary (NCF) for this purpose. The current review summarizes safety and effectiveness data accruing during the past 7 years, but ultimately resulted in **no modifications** to the IHS NCF.

Discussion:
The US prevalence of atrial fibrillation (AF) is estimated to be >6 million persons, correlates with older age among other factors,[1,2] and confers a 5-fold increase in stroke risk above baseline. It is implicated in 1 in 4 strokes overall.[3] In California, American Indian patients have been shown to have a higher incidence of AF than other ethnicities/races, & have an ischemic stroke rate 38% higher than the combined average of all other groups with AF.[4] A 2023 retrospective analysis of US Native Medicare beneficiaries revealed a 12% all-cause annual mortality rate for those with AF.[5]

Since FDA approval of dabigatran in 2010, DOACs have gradually supplanted warfarin for most AF patients in the US.[6] However, exclusion or under-representation of selected groups in the four randomized, controlled trials (RCTs) forming the basis for approval of the currently available agents has led to further subgroup analysis of those pivotal trials and an accumulation of observational and RCT data examining these groups. There have been no head-to-head RCTs comparing DOACs for any indication.

Chronic kidney disease: Most patients with a CrCl < 25-30 were excluded from the original 4 RCTs. A 2023 meta-analysis of patient-level data from these trials showed that comparative reductions in stroke and intracranial hemorrhage associated with DOAC use vs. warfarin grew larger as CrCl decreased, approaching 25 ml/min.[7] A 2024 retrospective analysis of 7,000 patients with Stage 4/5 chronic kidney disease and AF showed apixaban was associated with a 47% lower risk of major bleeding vs warfarin (IR: 1.5 vs 2.9 per 100 person-years; sub-distribution hazard ratio [sub-HR], 0.53 [95% CI: 0.39-0.70]) and rivaroxaban was associated with a 65% higher risk of major bleeding (IR: 4.9 vs 2.9 per 100 person-years; sub-HR, 1.65 [95% CI: 1.10-2.48]).[8] A separate 2024 meta-analysis of 38 observational studies of patients with AF receiving dialysis suggested that apixaban is non-inferior to warfarin in reducing embolism but with less major bleeding. No anticoagulation also emerged as a non-inferior option given the high bleeding risk with any OAC.[9]

Liver disease: In 2023, evaluation of a US-based claims database of 20 million people yielded 10,209 patients with chronic liver disease and AF, 29% of whom had cirrhosis. Overall, DOAC use vs. warfarin was associated with a 36% reduction in ischemic stroke/ systemic embolism (SE) (95% CI: 0.46-0.90) and 31% less major bleeding (95% CI: 0.58-0.82). Indirect comparison showed apixaban and rivaroxaban to be similarly effective for reducing stroke and all-cause death, but compared with apixaban, rivaroxaban initiators had higher risk of hospitalization for major and for GI bleeding (HR 1.59 [95% CI: 1.18–2.14] and 2.12 [95% CI: 1.52– 2.98], respectively). In patients with cirrhosis, DOAC users compared to warfarin users had similar rates of stroke, but a significant 25-30% reduced risk for all-cause death and major bleeding.[10]

Valvular heart disease: Patients with hemodynamically significant valvular disease, including prosthetic valves, were excluded from the pivotal DOAC RCTs. A retrospective cohort study of 56,336 adults with AF and valvular heart disease from 2021 showed that DOAC use (vs. warfarin) was associated with lower risk for ischemic stroke/ SE (HR 0.64 [95% CI: 0.59 to 0.70]) and for major bleeding (HR 0.67 [95% CI: 0.63 to 0.72]). Among the 7,700 patients with mitral stenosis, DOAC users had lower risk for ischemic stroke/ SE (HR 0.74, 95% CI: 0.58-0.94) and major bleeding (HR 0.75, 95% CI: 0.63-0.89).[11] In counterpoint, INVICTUS was a 2022 randomized non-inferiority trial of rivaroxaban vs warfarin performed in 4,500 adults with AF and rheumatic heart disease and a mitral valve area of ≤ 2 cm^2. A composite of stroke, SE, MI, or death from vascular or unknown causes was more common in the rivaroxaban group (HR 1.25; 95% CI: 1.10 to 1.41), with reduced mean survival time.[12] Other analyses have suggested the risk of stroke or bleeding is similar between DOACs and warfarin in patients with moderate to severe mitral stenosis, and ongoing trials seek to clarify this further.

Coronary artery disease: Evidence suggests that in patients with stable coronary disease and AF, including those having had ACS or PCI ≥ 12 months prior, DOAC monotherapy without an antiplatelet agent is adequate for secondary prevention of recurrent ACS. In a 2024 RCT comparing edoxaban alone to dual therapy with an antiplatelet there were similar rates of a composite of major ischemic events in the trial groups, but less frequent excessive bleeding with monotherapy (HR 0.34; 95% CI: 0.22 to 0.53).[13] A separate meta-analysis of 20 observational studies comprising 47,451 patients showed an oral anticoagulant (OAC) + single antiplatelet therapy (SAPT) vs. OAC alone was associated with

higher total bleeding (RR 1.50; 1.20-1.88), without lower MACE (RR 1.10; 0.97-1.24); a subgroup analysis showed similar results for both vitamin K antagonists (VKAs) and DOACs.[14] Guidelines from both the European Society of Cardiology (2024) and the American Heart Association/ American College of Cardiology (2023) favor OAC monotherapy in this group.[15, 16]

Older age and frailty: A 2022 meta-analysis of the pivotal 4 DOAC RCTs using patient-level data demonstrated that while DOAC efficacy in stroke prevention rises compared to warfarin with older age, their relatively lower bleeding risk also rises, becoming comparable for those >75 years of age.[17] An open-label RCT published in 2024 examined 1,330 frail patients aged ≥75 years with AF to measure the effect of switching to a DOAC in patients receiving stable treatment with a VKA. Compared to those continuing VKA treatment, there were more clinically significant bleeding events in the group switching to a DOAC, without a compensatory reduction in thromboembolic events.[18]

Pharmacoeconomics: Though individual DOACs are far more expensive than warfarin in the US, overall cost of care for patients with AF could theoretically be lower due to reduced need for monitoring, reduced stroke risk, and reduced major bleeding. This was demonstrated in a 2021 prospective cohort study of 48,000 patients with AF treated with an OAC and dually enrolled in the US Veterans Affairs healthcare system and fee-for-service Medicare. Over a 3-year period, the mean individual cost of care in 2018 dollars was >$25,000 lower in patients treated with a DOAC compared with warfarin (vs. an average 3-year cost for all patients of approximately $72,000).[19]

Findings:

DOACs have become the standard of care for the treatment of most patients with AF at high risk of thromboembolism since FDA approval of the four agents in current use. The most current US and European guidelines reflect the findings of subsequent subgroup analyses over the last decade. DOAC use is contraindicated for patients with mechanical heart valves, moderate-severe mitral stenosis, recent implantation of a bioprosthetic valve, high risk drug interactions, and those with thrombotic antiphospholipid syndrome. Their role is uncertain in AF patients with comorbidities such as LV thrombus, catheter-associated deep vein thrombosis, and cerebral venous sinus thrombosis.[20]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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