

## HTA Council Recommendation

### DOACs vs warfarin

Based on moderate to high quality of evidence from meta-analyses of systematic reviews and trials comparing DOACs to warfarin, DOACs are superior to warfarin in the prevention of the efficacy outcome of stroke and systemic embolism among patients with nonvalvular atrial fibrillation. In terms of safety, based on moderate to high quality of evidence from meta-analyses of systematic reviews and trials, and very low quality of evidence from systematic reviews of observational studies, DOACs are associated with a lower risk of bleeding. Moreover, large observational studies on real-world populations demonstrated that the risk of bleeding with apixaban, dabigatran, and rivaroxaban may be equivalent to or lower than the risk with warfarin.

### Apixaban vs Dabigatran vs Rivaroxaban

Overall, the evidence on the comparative efficacy, effectiveness, and safety of apixaban, dabigatran and rivaroxaban is limited due to the lack of head-to-head clinical trials that compared the direct oral anticoagulants among each other. However, based on the totality of available evidence from network meta-analysis of randomized clinical trials, observational studies, recommendations from clinical practice guidelines, and approved PH FDA indications, **the evidence cannot conclusively determine** which intervention among the DOACs is significantly superior to the other in all outcomes in terms of efficacy, effectiveness, and safety. While apixaban seems to be safest in terms of major bleeding, results of the NMAs and observational studies for the other relevant efficacy and safety outcomes are contradicting. Further, the specific recommendations of the DOACs based on PH-FDA approved indications and locally-adopted guidelines allow them to be used in certain populations where a DOAC is contraindicated for (i.e., rivaroxaban and apixaban can be used for patients with renal impairment where CrCl is between 15-29 mL/min for which dabigatran is contraindicated for, while dabigatran and apixaban can be used for patients with Child B liver cirrhosis where rivaroxaban is not recommended for). **Hence, it is deemed that apixaban, dabigatran, and rivaroxaban may be therapeutic alternatives for each other, depending on the clinical profile and treatment goals of the individual patient. This is consistent with the recommendation of the WHO Committee which considered these three drugs as therapeutically equivalent.**

**The HTAC recommends the government financing of dabigatran, rivaroxaban, and apixaban through their inclusion in the PNF on the basis of the following:**

- Apixaban, dabigatran and rivaroxaban all have additional clinical benefits in terms of efficacy and safety compared to the current standard of care which is warfarin.
- Among the three drugs, there is no conclusive evidence that will establish the superiority of one DOAC over the other in terms of clinical efficacy, effectiveness, and safety outcomes. Locally-adopted CPGs recognize the value of each DOAC for special populations for which a specific DOAC is contraindicated and another DOAC can serve as a therapeutically equivalent alternative for.
- Based on the CMA, apixaban is the least expensive treatment. However, we recognize the need to provide therapeutic alternatives for NVAf patients with several comorbidities and different clinical profiles.