DOST

Evidence Summary on Apixaban, Dabigatran, and Rivaroxaban for the prevention of myocardial infarction, cerebrovascular disease, and other cardiovascular events among patients with nonvalvular atrial fibrillation

Service Line	Evidence Summary
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Background

What is atrial fibrillation?

Atrial fibrillation (AF) is a condition that causes the heart to beat irregularly. This occurs when abnormal electrical impulses disrupt the usual rhythm of the heart. The heart's upper chambers, the atria, contract haphazardly that the heart fails to pump blood efficiently. When this happens, blood can sometimes pool in the heart and form a clot, which can then travel to the brain and block the flow of blood causing a stroke. AF is also associated with an increased risk of myocardial infarction (MI), and AF patients have a significantly higher incidence of overall major adverse cardiovascular events. AF may be classified as nonvalvular in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair (January et al. 2014).

What is the standard of care for prevention of myocardial infarction, cerebrovascular disease and other cardiovascular events with atrial fibrillation?

Patients with atrial fibrillation have an increased risk of stroke and thromboembolism that is associated with a higher risk of recurrence and greater severity. According to the Stroke Society of the Philippines, based on their Handbook of Stroke 6th Ed, it is recommended for patients with non-valvular AF who have stroke risk factor/s to receive effective stroke prevention therapy with either well-controlled warfarin therapy or one of the direct oral anticoagulants (DOACs). Warfarin belongs to the group of anticoagulants which are blood thinners that prevent the formation of blood clots in the body. Commonly suggested anticoagulants include warfarin and heparin. Since 1954, warfarin has been the only drug approved for the prevention of stroke among AF patients.

Warfarin is currently listed in the Philippine National Formulary for prophylaxis and treatment of thromboembolic disorders (e.g., venous, pulmonary) and embolic complications arising from atrial fibrillation or cardiac valve replacement, as an adjunct to reduce risk of systemic embolism (e.g. recurrent MI, stroke) after myocardial infarction and acute coronary syndrome.

Meanwhile, DOACs are known as new/novel oral anticoagulants or non-vitamin K oral anticoagulants (NOACs) which were introduced as alternatives in oral anticoagulation therapy, particularly for oral vitamin K antagonists (VKA) such as warfarin.

What is the potential of dabigatran, rivaroxaban, and apixaban for the prevention of myocardial infarction and other cardiovascular events with atrial fibrillation?

Dabigatran, rivaroxaban, and apixaban come from a class of drugs called direct oral anticoagulants (DOACs). VKA therapy is safe and effective for oral anticoagulation, if the target time in therapeutic range (TTR) is achieved. However, this can be challenging for warfarin due to drug and food interactions and liver disease, resulting in either an increased risk of blood clotting due to undertreatment or bleeding due to overtreatment.

DOACs present as an alternative to VKA therapy as they produce a more predictable, less labile anticoagulant effect and are proven in Phase III clinical trials to be as safe as warfarin in terms of bleeding (Julia and James, 2017). Unlike warfarin, DOACs do not require frequent monitoring. These anticoagulants directly inhibit specific proteins within the coagulation cascade. Dabigatran is a direct thrombin inhibitor while rivaroxaban and apixaban are direct inhibitors of factor Xa.

There are different dosing regimens available for dabigatran, rivaroxaban and apixaban. According to the 2020 ESC Guidelines, the standard dose for DOACs are dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and apixaban 5 mg twice daily. Meanwhile, dabigatran has a lower dose of 110 mg while a reduced dose is available for rivaroxaban and apixaban at 15 mg and 2.5 mg, respectively. The considerations for the administration of lower dose of dabigatran, and reduced dose regimens of rivaroxaban, and apixaban are detailed in Appendix 2.

As of publishing this evidence summary, the DOACs are listed in the 21st WHO Essential Medicines List (2019) but not included in the latest Philippine National Formulary (8th ed.) (2018). The WHO expert committee recommended the addition of DOACs to the EML for prevention of stroke and systemic embolism in patients with valvular atrial fibrillation based on favorable efficacy and acceptable safety. The Committee noted that the DOACs demonstrated clinical benefits in terms of reduced mortality, reduced risk of stroke or systemic embolism, and were associated with fewer severe/major bleeding episodes compared to well-controlled warfarin in patients with NVAF. The use of DOACs may also have relevant health system benefits related to the infrastructure required for warfarin treatment monitoring, as they do not require laboratory monitoring.

Rationale of this evidence review

The Health Technology Assessment Council (HTAC) received the request from different proponents for the evidence review of dabigatran, rivaroxaban, and apixaban for consideration of their inclusion in the PNF. The three drugs are currently registered with the Philippine Food and Drug Administration (FDA).

In this evidence summary, we present the data on the efficacy, effectiveness, safety, and cost implications of DOACs compared to warfarin, and compared with each other for the prevention of myocardial infarction, cerebrovascular disease, and other cardiovascular events among patients with nonvalvular atrial fibrillation. The evidence considered in the review were the role of DOACs in clinical practice guidelines being used by relevant medical societies, the review of the WHO for the inclusion of DOACs in the EML, reviews on the efficacy, effectiveness and safety of DOACs when compared with each other, and the cost comparison and budget impact of the use of DOACs for the specified indication.

Policy Question

Should apixaban (2.5 mg and 5 mg film-coated tablet), dabigatran (110 mg and 150 mg capsule), or rivaroxaban (15mg and 20mg film-coated tablet) be included in the Philippine National Formulary for the prevention of myocardial infarction, cerebrovascular diseases and other cardiovascular events among patients with nonvalvular atrial fibrillation (NVAF) and NVAF patients with existing comorbidities?

Research Questions

Clinical Assessment

1. What is the comparative safety and efficacy of apixaban, dabigatran and rivaroxaban compared to warfarin in the prevention of myocardial infarction, cerebrovascular diseases and other cardiovascular events among patients with nonvalvular atrial fibrillation?
2. What is the comparative safety and efficacy between apixaban, dabigatran and rivaroxaban in the prevention of myocardial infarction, cerebrovascular diseases and other cardiovascular events:
    a. Among patients with nonvalvular atrial fibrillation?
    b. Among patients with nonvalvular atrial fibrillation and existing comorbidities?

Economic Assessment

1. What is the associated medication cost per patient of using dabigatran, rivaroxaban, and apixaban in preventing myocardial infarction, cerebrovascular diseases, and other cardiovascular events among patients with nonvalvular atrial fibrillation?
2. What is the total medication cost for the expected number of patients using dabigatran, rivaroxaban, and apixaban?
3. What is the 3-year budget impact to the government for the use of dabigatran, rivaroxaban, and apixaban?

Key Findings

The HTAC concluded with the following findings based on its decision framework as stipulated in Republic Act 11223 or the *Universal Healthcare Act*:

Criteria	
Clinical Efficacy, Effectiveness, and Safety	***Dabigatran, rivaroxaban and apixaban versus warfarin*** Dabigatran, rivaroxaban and apixaban are effective for the prevention of stroke and systemic embolism among patients with nonvalvular atrial fibrillation compared to warfarin, 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. In terms of safety, dabigatran, rivaroxaban and apixaban are associated with lower risk of bleeding compared to warfarin, 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. Moreover, large observational studies on real-world populations demonstrated that the risk of bleeding with dabigatran, rivaroxaban, and apixaban may be equivalent to or lower than the risk with warfarin. ***Dabigatran versus rivaroxaban versus apixaban among patients with nonvalvular atrial fibrillation*** ***Dabigatran versus rivaroxaban versus apixaban in clinical practice guidelines and Philippine FDA-approved indications*** Dabigatran, rivaroxaban, and apixaban are recommended for the prevention of cerebrovascular events (e.g. stroke) and cardiovascular events (e.g., myocardial infarction and systemic embolism) in patients with nonvalvular atrial fibrillation, as indicated in locally-adopted guidelines and approval by the Philippine FDA. While dabigatran, rivaroxaban, and apixaban have common contraindications such as pregnancy and lactation, high risk of bleeding, severe hepatic impairment (i.e. Child C liver cirrhosis), and creatinine clearance of <15 mL/min, some DOACs also have specific contraindications and recommendations.

Namely:

- dabigatran is contraindicated for patients with renal impairment and a creatinine clearance of 15-29 mL/min for which rivaroxaban and apixaban may serve as alternative DOACs;
- rivaroxaban is not recommended by guidelines for patients with Child B liver cirrhosis for which apixaban and dabigatran may serve as the alternative DOAC; and
- concomitant use of P-glycoprotein inhibitors such as ketoconazole is contraindicated with dabigatran and rivaroxaban for which apixaban may serve as an alternative.

Efficacy and safety of dabigatran versus rivaroxaban versus apixaban

In terms of the composite outcome of stroke and systemic embolism, the available evidence cannot determine the best choice intervention due to conflicting evidence between the studies. However, one real-world study with head-to-head comparison of DOACs (Lip et al., 2018) shows that apixaban is the best DOAC for this outcome.

In terms of stroke, the available evidence cannot determine the best choice intervention due to conflicting evidence between the studies but one real world study (Lip et al. 2018) shows that apixaban is the best DOAC for the outcome of stroke.

For the remaining efficacy outcomes of systemic embolism, all-cause mortality, and myocardial infarction there was no superior choice among the DOACs among the studies since only one of four studies included in the review reported these outcomes.

In terms of major bleeding, the available evidence is consistent with apixaban being the best among the DOACs for this safety outcome. In terms of gastrointestinal bleeding and intracranial hemorrhage, the available evidence cannot determine the best choice intervention due to conflicting evidence between the studies. However, of the three studies that reported these outcomes, one NMA (Lopez-Lopez et al. 2017) and one observational study (Lip et al., 2018) show that apixaban is the best DOAC in terms of gastrointestinal bleeding, while one observational study suggests that dabigatran is the best DOAC in terms of intracranial hemorrhage.

For the remaining safety outcomes of any bleeding and hemorrhagic stroke, there was no superior choice among the DOACs among the studies that reported these outcomes (e.g. two studies for any bleeding, and one study for hemorrhagic stroke).

Nevertheless, the evidence is limited due to the lack of head-to-head clinical trials that compared the direct oral anticoagulants among each other.

Dabigatran versus rivaroxaban versus apixaban among subgroups of patients with nonvalvular atrial fibrillation

Among subgroups of patients with nonvalvular atrial fibrillation, namely (1)

	patients with mild impairment (CrCl 50-80 mL/min) to moderate (CrCl 30-50 mL/min) impairment in renal function; (2) patients aged >75 years; (3) patients with heart failure; (4) NVAF patients with diabetes mellitus, the comparative safety and efficacy of DOACs cannot be determined due to having no sufficient evidence given the following: 1) the availability of only one study as basis for the evidence; and 2) the lack of head-to-head clinical trials of DOACs among subgroups of patients with NVAF.
Affordability and Viability	The cost minimization analysis showed that the associated medication cost per patient using the generic drug prices was ₱27,948.78 (₱78,748.78 if patients have AEs) for dabigatran, ₱27,418.80 for rivaroxaban (₱78,218.00 if patients have AEs), and ₱18,622.30 for apixaban (₱69,422.30 if patients have AEs). Apixaban was the least expensive treatment. Meanwhile, assuming once daily 5 mg dosing of warfarin and weekly INR monitoring, the cost of treatment per patient will amount to ₱29,417.15 (₱80,217.15 if patients have AEs). The computed total costs to be incurred by the government for 2023 associated with the use of DOACs (excluding the cost of adverse events) for the expected number of patients will be ₱6.17 B for dabigatran, ₱6.05 B for rivaroxaban, and ₱4.11 B for apixaban. Meanwhile, assuming once daily 5 mg dosing of warfarin and weekly INR monitoring, the cost of treatment for all patients will amount to ₱6.49 B. We recognize that, generally, there are higher rates of adverse events with warfarin compared to DOACs but we cannot directly compare the cost at the population level due to unavailability of data directly comparing these drugs within the same setting. The 3-year budget impact to the government of financing DOACs for the prevention of myocardial infarction, cerebrovascular diseases, and other cardiovascular events among patients with nonvalvular atrial fibrillation (excluding the cost of adverse events) is expected to be ₱19.84 B for dabigatran, ₱19.46 B for rivaroxaban, and ₱13.22 B for apixaban. Meanwhile, assuming once daily 5 mg dosing of warfarin and weekly INR monitoring, the 3-year budget impact of warfarin is ₱20.88 B.

HTA Council Preliminary 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.

Responsiveness to Disease Magnitude and Severity

In 2017, a total of 3.046 million new cases of atrial fibrillation (AF) were recorded worldwide. Compared to the incidence rate in 1997, the estimated incidence rate of atrial fibrillation in 2017 ramped up to 31%. It was estimated that in that year, the worldwide prevalence of AF was at 37,574,000 million cases or about 0.51% of the global population. It was evident that the highest burden was among the high socio-demographic index. Further, it was projected that by 2050, there will be an absolute increase in the cases of atrial fibrillation by more than 60% (Lippi et al, 2020). According to CDC (2022), atrial fibrillation increases with age; and generally, more women than men experience AF.

Even though AF is the most common sustained arrhythmia, data on AF in the Philippines remains scarce. In the Philippines, it was estimated that 2% of Filipinos aged 70 years and above have AF; and some risk factors contributing to its occurrence include hypertension, diabetes and high cholesterol (St. Luke's Medical Center, 2017). Patients with AF have a substantially elevated risk of stroke that is associated with a considerable risk of recurrence and more severe disability. A global survey on the frequency of atrial fibrillation-associated stroke found that among 175 respondents from the Philippines, 11% had an ischemic stroke event that is related to atrial fibrillation [mean age: 62 (SD: 0.50)] (Perera et al. 2016). Hence, stroke prevention through anticoagulant thromboprophylaxis is an important part of the management of atrial fibrillation.

Clinical Efficacy, Effectiveness, and Safety

This section consists of three parts: 1) evidence from clinical practice guidelines (CPGs) adopted by relevant medical societies and the Philippine FDA-approved indications on the use of DOACs for NVAF; 2) evidence from the WHO review on DOACs which was adopted in this assessment by the HTA Council in order to substantiate the clinical efficacy, effectiveness and safety of DOACs for the prevention of stroke and systemic embolism in patients with NVAF compared to the well-established standard of care (i.e., warfarin); and 3) evidence from a systematic search for network meta-analyses and observational studies that compared DOACs against each other to determine the superior DOAC in terms of clinical efficacy, effectiveness and safety.

A. Role of Direct Oral Anticoagulants in Clinical Practice Guidelines for the Management of Nonvalvular Atrial Fibrillation

To determine the role of DOACs in the prevention of myocardial infarction, cerebrovascular diseases and other cardiovascular events among patients with NVAF, relevant societies (i.e., Philippine Neurocritical Care Society, Philippine Heart Association, Stroke Society of the Philippines) were consulted on the clinical practice guidelines being used by the society as reference for this indication.

The Philippine Neurocritical Care Society (PNCS) adopted the 2012 science advisory on the use of oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation from the American Heart Association/American Stroke Association. Meanwhile, both the Philippine Heart Association (PHA) Pharmacotherapy Council and the Stroke Society of the Philippines (SSP) use international guidelines set by the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society and the European Society of Cardiology. In addition, the SSP also

refers to the 2021 European Heart Rhythm Association Practical Guide on the use of Non-Vitamin K Oral Anticoagulants in Patients with AF.

While all DOACs are indicated for the management of NVAF, the various CPGs have several considerations in recommending specific DOACs for special populations, i.e. those with existing conditions, or comorbidities. In regards to NVAF patients with special considerations or comorbidities, the CPGs recommend DOACs for the following subpopulations of NVAF: patients with mild-to-moderate chronic kidney disease (CKD), patients with peripheral artery disease, patients with advanced age, patients with high and low body weight, patients with thrombocytopenia, and patients with malignancy. Meanwhile, all DOACs are contraindicated for the following subpopulations: pregnant patients, patients with creatinine clearance (CrCl) <15 mL/min, and patients with Child-Turcotte-Pugh C liver disease or hepatic disease associated with clinically manifest coagulopathy and clinically relevant bleeding risk.

Notably, for patients with severe CKD or CrCl of 15-30 mL/min, dabigatran is contraindicated with all CPGs citing the primary elimination modality of dabigatran being renally excreted; while apixaban and rivaroxaban serve as alternative DOACs for this subpopulation (both apixaban and rivaroxaban are recommended by the ESC for this population while the EHRA and the AHA/ASA guidelines recommend apixaban only and rivaroxaban only, respectively.) For patients with Child-Turcotte-Pugh B liver disease, rivaroxaban is contraindicated in all CPGs based on available trials conducted among this subpopulation; while dabigatran and apixaban serve as alternative DOACs for this subpopulation. (American Heart Association/American Stroke Association, 2012; American College of Cardiology/American Heart Association/Heart Rhythm Society 2019; European Society of Cardiology, 2020; European Heart Rhythm Association Practical Guide, 2021).

The table below summarizes the recommendations of the reference clinical practice guidelines. The full details of the guidelines from each medical society along with the respective definition of the class (strength) of recommendation and level (quality) of evidence can be found in Appendix 1.

Table 1. Summary of recommendations of clinical practice guidelines on the use of direct oral anticoagulants for nonvalvular atrial fibrillation

Recommended Drugs for the following Population:	American Heart Association/American Stroke Association (2012)	American College of Cardiology/American Heart Association/Heart Rhythm Society (2019)	European Society of Cardiology (2020)	European Heart Rhythm Association Practical Guide (2021)
All NVAF patients	Warfarin *(Class I; Level A)*[1] Dabigatran *(Class I; Level B)*[1] Rivaroxaban *(Class IIa; Level B)*[1] Apixaban *(Class I; Level B)*[1]	Dabigatran *(Class I, Level: B)*[1] Rivaroxaban *(Class I, Level: B)*[1] Apixaban *(Class I, Level: B)*[1]	Dabigatran *(Class I, Level A)*[1] Rivaroxaban *(Class I, Level A)*[1] Apixaban *(Class I, Level A)*[1]	Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)*
Pregnant NVAF patients	*No recommendation*	*No recommendation*	Warfarin *(Class I, Level C)*[1]	*No recommendation*
NVAF patients with mild to moderate CKD (CrCl of >30 to <49 mL/min)	Dabigatran *(Class I, Level B)*[1] Rivaroxaban *(Class IIb; Level C)*[1] Apixaban* *(Class III; Level C)*[1] **Note: Apixaban should not be used if CrCl is <25 mL/min*	*No recommendation*	Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)*	Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)*
NVAF patients with severe CKD (CrCl of 15-30 mL/min)	Rivaroxaban* *(Class IIb; Level C)*[1] **Note: Reduced dose of rivaroxaban; Safety and efficacy of rivaroxaban has not been established in this population*	*No recommendation*	Rivaroxaban* *(No rating)* Apixaban* *(No rating)* **Note: Reduced dose of DOACs are feasible options for severe CKD*	Apixaban *(No rating)*
NVAF patients with peripheral artery disease[1]	*No recommendation*	*No recommendation*	Warfarin *(No rating)* Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)* *Note: No specific OAC therapy that is preferred**	*No recommendation*
NVAF patients with	*No recommendation*	*No recommendation*	Dabigatran *(No rating)*	Dabigatran *(No rating)*

[1] Definition of the class (strength) of recommendation and level (quality) of evidence can be found in Appendix 1

liver disease			Apixaban *(No rating)* *Note: All DOACs are contraindicated in patients with Child-Turcotte-Pugh C liver disease*	Apixaban *(No rating)* *Note: All DOACs are contraindicated in patients with hepatic disease associated with clinically manifest coagulopathy and clinically relevant bleeding risk (i.e., Child-Turcotte-Pugh C liver disease)*
NVAF patients in advanced age and frailty	*No recommendation*	*No recommendation*	Warfarin *(No rating)* Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)* *Note: NOACs were noted to have a better risk-benefit profile compared to warfarin despite lack of mention of their preference over warfarin*	Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)*
NVAF patients with high body weight	*No recommendation*	*No recommendation*	*No recommendation*	Warfarin *(No rating)* Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)* *Note: For patients with BMI of ≥40 kg/m^2, plasma level measurement with any of the NOACs or conversion to VKA therapy may be reasonable to be considered*
NVAF patients with low body weight	*No recommendation*	*No recommendation*	*No recommendation*	Warfarin *(No rating)* Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban* *(No rating)* **Note: Dose reduction is required for apixaban. Apixaban is the preferred choice for patients ≤60 kg due to evidence of safety and efficacy in this population and overall study*

				population.
Patients with NVAF and thrombocytopenia	*No recommendation*	*No recommendation*	*No recommendation*	Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)* *Note: Patients with thrombocytopenia with absolute platelet count of >50,000 µl should proceed NOAC therapy with caution. with absolute platelet count of >20,000 µl to <50,000 µl should proceed with great cation and consider half dose of NOACs for those with bleeding risk factor/s. NOACs are contraindicated for patients with >50,000 µl platelet count. .*
Patients with NVAF and malignancy	*No recommendation*	*No recommendation*	*No recommendation*	Warfarin *(No rating)* Dabigatran *(No rating)* Rivaroxaban *(No rating)* Apixaban *(No rating)*

B. Clinical Use of Direct Oral Anticoagulants Approved by the Philippine FDA

Dabigatran, rivaroxaban, and apixaban are all registered in the Philippine FDA for patients with NVAF for the prevention of cerebrovascular events and cardiovascular events. Based on the FDA-approved product label and inserts of dabigatran, rivaroxaban, and apixaban, DOACs are contraindicated for some patients based on co-morbidities or existing conditions.

Common contraindications

All DOACs are commonly contraindicated by the PH FDA for the following conditions due to lack of established safety:

- Patients with prosthetic heart valves
- Pregnancy and lactation
- Severe Hepatic Impairment (*i.e., Child-Turcotte-Pugh C*)
- Antiphospholipid syndrome (APS) (*in particular patients who are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I*)
- End-stage renal disease or patients undergoing dialysis (*i.e., CrCl <15mL/min*)
- Clinically significant active bleeding
- Patients with known hypersensitivity to the particular DOAC or any excipient of the product

Specific contraindications

In terms of drug interaction, rivaroxaban and dabigatran are contraindicated with the concomitant use of inhibitors of P-glycoprotein (*P-gp*), such as azole-antimycotics (*e.g. ketoconazole, itraconazole, voriconazole, and posaconazole*). Concomitant medication of apixaban with these drugs should be done with caution as it may increase apixaban exposure by 2-fold.

For hepatic disease associated with coagulopathy, rivaroxaban and apixaban are contraindicated due to clinically relevant risk of bleeding. Further, patients with moderate hepatic impairment (*Child Pugh B)* were more sensitive to rivaroxaban which resulted in a steeper pharmacokinetic/pharmacodynamic relationship between concentration and prothrombin time. Meanwhile, apixaban may be used with caution in patients with mild or moderate hepatic impairment *(Child Pugh A or B)* with no required dose adjustment. Dabigatran, on the other hand, has no specified contraindication for either hepatic disease associated with coagulopathy or mild to moderate hepatic insufficiency (*Child Pugh A or B*) noting no change in dabigatran exposure in this population.

For severe renal impairment with CrCl of <30 mL, dabigatran is contraindicated due to the observed prolongation of half-life in patients with impaired renal function in pharmacokinetic studies, as indicated in the product insert. However, apixaban and rivaroxaban can be used with caution in patients with severe renal impairment (*i.e., CrCl 15-29 mL/min*). In these patients, rivaroxaban is recommended to be used with caution while apixaban requires no dose adjustment.

C. WHO Review on the Inclusion of Direct Oral Anticoagulants in the WHO Model List of Essential Medicines

Methodology

The clinical review of WHO Expert Committee on the Selection and Use of Essential Medicines in 2019 was adopted for the evidence on the clinical efficacy/effectiveness and safety of DOACs compared to warfarin. The WHO Expert Committee on the Selection and Use of Essential Medicines evaluated evidence from two separate applications for the inclusion of DOACs in the essential medicines list (EML). The first application consisted of an updated systematic review and meta-analysis involving five randomized controlled trials of DOACs versus warfarin, a systematic literature review of 23 observational studies of DOACs versus warfarin, and a systematic review of 54 cost-effectiveness analysis studies of DOACs versus warfarin. The second application consisted of a meta-analysis of 8 systematic reviews and 13 randomized controlled trials of DOACs versus warfarin, 3 large observational studies on real world populations, and 2 systematic reviews of cost-utility analysis studies of DOACs versus warfarin. The WHO Expert Committee did not conduct an additional search or review any other additional studies apart from those submitted in the two applications. Only the summary of the results of the reviews were included in the document published by WHO.

Results of the Review

A total of 6 studies that were submitted as part of two applications were included in the clinical review of the WHO for the inclusion of DOACs in the WHO EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. These include 1) a systematic review of 5 randomized controlled trials (DiCesare et al., 2019a), 2) a meta-analysis of 8 systematic reviews and 13 randomized controlled trials (Neumann et al., 2019), 3) a systematic literature review of 23 observational studies (DiCesare et al., 2019b), 4) a prospective open cohort study (Vinogradova et al. 2018), 5) a propensity matched analysis (Li et al., 2017), and 6) a propensity score matched analysis (Lip et al., 2016). These studies were reviewed by the WHO but were not further detailed in their technical report.

WHO Recommendation

The WHO Expert Committee on the Selection and Use of Essential Medicines **recommended the addition of Dabigatran to the core list** of the EML for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of venous thromboembolism based on favorable efficacy and acceptable safety. It is currently listed with a **square box** which denotes that dabigatran is the representative of DOACs together with the identified **therapeutically equivalent alternatives (i.e., apixaban, edoxaban and rivaroxaban).** Moreover, these medicines have a similar overall benefit-risk profile compared to warfarin, are associated with a lower risk of major bleeding, and may be particularly beneficial in settings where warfarin monitoring is not available.

In terms of economic considerations, the WHO Expert Committee noted that DOACs have higher daily treatment costs than warfarin, but have been found to be a cost-effective intervention based on the results of systematic reviews of cost-effectiveness and cost-utility analysis among middle-high income to high income countries, with ICERs below the willingness-to-pay thresholds.

General Findings

- Efficacy: DOACs, compared to well-controlled warfarin, demonstrated clinical benefits in terms of reduced mortality, reduced risk of stroke or systemic embolism in patients with NVAF.
- Safety: DOACs are associated with fewer severe/major bleeding episodes compared to well-controlled warfarin in patients with NVAF.

Specific studies referred by the WHO review

Efficacy Outcomes

Outcome 1: Stroke/Systemic embolism

Table 2. Summary of studies included in the WHO review that evaluated the composite of stroke and systemic embolism outcomes of DOACs compared to warfarin.

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Warfarin		
DiCesare et al, 2019a	Updated meta-analysis of Ruff et al., 2014 including J-ROCKET AF trial k= 5 RCTs	DOACs were associated with a significantly **reduced risk of stroke and systemic embolism** in patients with nonvalvular atrial fibrillation (NVAF) [RR: 0.80 (95% CI 0.71 to 0.91), p=0.003] with absolute effect of 8 fewer events per 1000 (95% CI: 3 fewer to 11 fewer) compared with warfarin, based on high quality of evidence.
DiCesare et al, 2019b	Systematic literature review k= 23 observational studies	DOACs were associated with a **reduced risk of stroke and systemic embolism** compared with warfarin in patients with NVAF [RR: 0.79 (95% CI: 0.71 to 0.89), p<0.001]; absolute effect: 5 fewer events per 1000 (95% CI: 3 fewer to 7 fewer), based on very low quality of evidence (due to the evidence being based on 12 observational studies with heterogenous findings). Moreover, they noted that Dabigatran, Rivaroxaban, and Apixaban were each associated with a lower risk of stroke and systemic embolism when compared individually with warfarin.

Outcome 2: Stroke

Table 3. Evaluation of stroke outcomes in Neumann et al, 2019 that is included in the WHO review comparing DOACs with vitamin K antagonists.

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Vitamin K antagonists		

Neumann et al, 2019	Meta-analysis k= 8 SRs and 13 randomized trials	Use of DOACs compared to the use of vitamin K antagonists in individuals with NVAF was significantly associated with **decreased risk of stroke** [RR 0.83, (95%CI 0.72 to 0.96)]; absolute effect: 7 fewer events per 1000 (95%CI: 11 fewer to 4 fewer), based on high certainty of evidence.

Outcome 3: Mortality

Table 4. Evaluation of mortality outcomes in Neumann et al, 2019 that is included in the WHO review comparing DOACs with vitamin K antagonists.

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Vitamin K antagonists		
Neumann et al, 2019	Meta-analysis k= 8 SRs and 13 randomized trials	Use of DOACs compared to the use of vitamin K antagonists in individuals with NVAF was significantly associated with **decreased risk of mortality** [RR 0.90, (95%CI 0.85 to 0.94)], based on high certainty evidence.

Outcome 4: Systemic embolism

Table 5. Evaluation of systemic embolism outcomes in Neumann et al, 2019 that is included in the WHO review comparing DOACs with vitamin K antagonists.

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Vitamin K antagonists		
Neumann et al, 2019	Meta-analysis k= 8 SRs and 13 randomized trials	DOACs were found to **probably decrease the risk of systemic embolism** [RR 0.74 (95%CI 0.48 to 1.13)]; absolute effect: 1 fewer event per 1000 (95% CI: 1 fewer to 0 fewer), based on moderate certainty of evidence

Safety Outcomes

Outcome 1: Major Bleeding

Table 6. Summary of studies included in the WHO review that evaluated the major bleeding outcomes of DOACs compared to warfarin and vitamin K antagonists

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Warfarin		
DiCesare et al, 2019a	Updated meta-analysis of Ruff et al., 2014 including J-ROCKET AF trial k= 5 RCTs	DOACs were associated with a **significantly lower risk of major bleeding** compared with warfarin [RR 0.86 (95%CI 0.74 to 0.99) p=0.04]; absolute effect: 8 fewer events per 1000 (95%CI: 1 fewer to 16 fewer), based on the moderate quality of the evidence (downgraded due to inconsistency).
DOACs vs Vitamin K antagonists		
Neumann et al, 2019	Meta-analysis k= 8 SRs and 13 randomized trials	DOACs were found to **probably decrease the risk of major bleeding** [RR: 0.81(95% CI: 0.66 to 0.98)]; absolute effect: 11 fewer events per 1000 (95% CI: 20 fewer to 1 fewer), based on moderate certainty of evidence).

Outcome 2: Bleeding

Table 7. Summary of studies included in the WHO review that evaluated the bleeding outcomes of DOACs compared to warfarin

Author, Year	Study Design	Results and Interpretation by the WHO
DOACs vs Warfarin		
DiCesare et al, 2019b	Systematic literature review of 23 observational studies k= 23 observational studies	DOACs were associated with a **lower risk of bleeding** compared with warfarin in NVAF patients [RR: 0.72 (95% CI: 0.64 to 0.80). p<0.001]; absolute effect 9 fewer events per 1000 (95% CI: 6 fewer to 11 fewer), based on very low quality of evidence (due to the evidence being based on 17 observational studies with heterogeneous findings). Dabigatran, rivaroxaban, and apixaban were each associated with a lower risk of major bleeding when compared individually with warfarin.
Apixaban vs Warfarin		
Vinogradova et al., 2018	Prospective open cohort study N=156,005	There is a **lower risk of bleeding** with apixaban compared to warfarin [HR 0.69, 95%CI 0.54 to 0.79)] in patients with atrial fibrillation.
Li et al., 2017	Propensity matched analysis N=76,940	Apixaban showed a **lower risk of bleeding** [HR 0.60 (95%CI 0.54 to 0.65)] compared to warfarin. The quality of evidence not assessed.

Lip et al., 2016	Propensity score matched analysis N=45,361	Apixaban showed a **lower risk of bleeding** [HR 0.53, (95%CI: 0.39 to 0.71)] versus warfarin.
Dabigatran vs Warfarin		
Vinogradova et al., 2018	Prospective open cohort study N=156,005	There is **no significant difference** in the risk of bleeding associated with dabigatran vs warfarin [HR 0.87 (95%CI 0.72 to 1.04)] in individuals with NVAF. The quality of evidence not assessed.
Lip et al., 2016	Propensity score matched analysis N=45,361	Dabigatran showed a **lower risk of bleeding** [HR 0.69, (95%CI 0.50 to 0.96)] compared to warfarin in individuals with NVAF.
Rivaroxaban vs Warfarin		
Vinogradova et al., 2018	Prospective open cohort study N=156,005	There is **no significant difference** in the risk of bleeding associated with rivaroxaban vs warfarin [HR 1.12 (95%CI 0.99 to 1.26)] in individuals with NVAF. The quality of evidence not assessed.
Lip et al., 2016	Propensity score matched analysis N=45,361	There is **no significant difference** in the risk of bleeding associated with rivaroxaban vs warfarin [HR 0.98 (95%CI 0.83 to 1.17)] in individuals with NVAF.

D. Review of Network Meta-analysis and Observational Studies on the Comparison of DOACs versus DOACs

Methodology

Location and selection of studies

A search was conducted in one database (i.e., PubMed) on 21 October 2022 for systematic reviews, meta-analyses, and network meta-analyses comparing the efficacy, effectiveness, and safety of DOACs *(apixaban, dabigatran and rivaroxaban)* among each other for the prevention of myocardial infarction, cerebrovascular disease, and other cardiovascular events in patients with NVAF. The search was limited to studies published from 2019, which was the year of the WHO review on DOACs, until the date of the last search. Due to this search filter, all studies detected were reviews and meta-analyses that included only observational studies or pooled the results of both observational studies and randomized controlled trials (RCTs). Given the inherent biases of observational studies due to the presence of confounders and lack of randomization, together with the expected challenges in pooling the results of observational studies with different study designs and results of RCTs, the search was refined to only include systematic reviews and NMAs of RCTs.

As a result, a second search was conducted on 17 January 2023 for systematic reviews and network meta-analyses that answered the same research question. The filter for the date of publication was broadened to studies published from 2011, which was the year the Phase III RCT of apixaban, the most recently approved DOAC being studied in this review, was published. A study was considered if it met the following inclusion criteria: (1) the population of interest are patients with NVAF, (2) the interventions include all three DOACs of interest (i.e., apixaban, rivaroxaban, and dabigatran), (3) the study design is a network meta-analysis of randomized clinical trials, and (4) the study conducted head-to-head comparisons of a DOAC vs another DOAC. Although one of the review methods specified in the HTA Methods Guide is to adopt the latest and most comprehensive systematic review, upon full-text screening and quality assessment of the latest NMA that was detected in the search (Antza et al. 2019), the study concluded that no comparative conclusions should be drawn from the results of their NMA since there were no trials with direct head-to-head comparison included in the NMA and due to the presence of differences in the study characteristics of included RCTs and the violation of the transitivity rule. Hence, the NMA by Lopez-Lopez et al. (2017), which was the second most recent NMA following the study by Antza et al. 2019 with a more extensive search strategy and more RCTs, was also included in this review. Further, studies that focused on a specific subgroup of patients with NVAF (i.e. diabetic patients, patients with mild and moderate renal function, the elderly, and patients with heart failure) were also relevant and included in the review.

Cognizant of the usefulness of observational studies in determining the effectiveness of health technologies in the real world setting, the studies included in the SR-NMAs of observational studies detected in the initial search were screened for real-world evidence that can supplement the results of the NMA of RCTs. A study was included if it met all of the following criteria: (1) the study must compare dabigatran, rivaroxaban, and apixaban against each other, (2) the sample size of the observational study should be at

least 1000 patients per DOAC treatment arm, (3) the follow-up period should be at least 1 year, and (4) the sample size of each DOAC arm should be balanced.

Critical Appraisal

Network meta-analysis

The Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making appraisal tool by Jansen et al., 2014 was used to appraise the quality of the included network meta-analysis on DOACs among the general population with nonvalvular AF. The tool was designed to help assess the relevance and credibility of indirect treatment comparisons and network meta-analysis to help inform health care decision making. The questions on relevance will answer the extent to which the results of the NMA apply to the context for decision-making. Meanwhile, credibility is the extent to which the NMA validly answers the question the study is designed to answer. It has five domains (evidence base used, analysis, reporting quality and transparency, interpretation of results, and conflict of interest) that can be judged as *strong*/*neutral*/*weak*.

The results of the included network meta-analysis that was used for this evidence review was derived primarily from the statistical risk measures of pairwise comparisons (e.g., OR, HR, and RR), and not from the ranking analyses. Although all the SR-NMA studies conducted ranking analysis (e.g., SUCRA, rank probabilities, P-score ranking) for the interventions being evaluated in the NMA, the strength of evidence for this measure is considered not satisfactory for deriving conclusions on the hierarchy of interventions.

Key issues with the use of ranking outlined by Mbuagbaw et al. (2017) in the interpretation of ranking analysis were that the surface under the cumulative ranking curve (SUCRA) does not consider the magnitude of differences in effects between treatments; and that chance may explain any apparent difference between treatments, and SUCRA does not capture that possibility. Given the risk of misleading interpretations from ranking analysis, the reported odds ratios for pairwise comparisons were used in this evidence review for the interpretation of results.

Observational studies

The Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool by Sterne et al., 2016 was used to appraise the quality of the included observational studies that compared DOACs with each other among the general population with nonvalvular AF. The tool aims to measure the risk of bias in the outcomes (i.e. benefits or harms of interventions) of observational studies by emulating a hypothetical low risk of bias randomized controlled trial, in order to determine how much it deviates from the true outcome.

Results

Description of search results

Overall, there were a total of 8 studies included in this review: 4 studies that focused on the general NVAF population and 4 studies that focused on subgroups of patients with atrial fibrillation. Of the studies that focused on the general NVAF population, two were NMAs of RCTs (Antza et al. 2019 and Lopez-Lopez et al. 2017) while the other two were observational studies (Lip et al 2018 and Staerk et al 2018). Meanwhile, the studies that reviewed evidence for special populations with atrial fibrillation were all NMAs of RCTs (Hao Jin et al., 2020a, Deng et al., 2020, Hao Jin et al., 2020b and Hao Jin et al., 2021).

The search for NMAs of RCTs detected 85 studies which were then subjected to title and abstract screening following the set inclusion criteria described in the section above. The most recent NMA that passed the screening is the study by Antza et al. (2019) and is included in this review. However, due to the issues with the credibility of the NMA based on its critical appraisal and its conclusion that no comparative interpretations should be drawn from the results of their NMA, the second most recent NMA of RCTs that passed the inclusion criteria (Lopez-Lopez et al. 2017) was also included in the review. Additionally, the most recent studies that focused on any specific subgroup of NVAF patients were also deemed relevant to the review, resulting in the inclusion of 4 other studies - one NMA for each subgroup detected in the search. As for the inclusion of observational studies, the search and screening of references of the SR-MAs and SR-NMAs of observational studies detected only 2 studies that passed the inclusion criteria for observational studies described in the section above. The characteristics of each study are detailed in the table below.

For the search of SR-MAs and SR-NMAs that detected reviews that included observational studies or pooled results of observational studies and RCTs, a total of 7 studies were detected - 5 that focused on the general NVAF population and 2 that included special populations. However, the HTAC notes the following issues on the use of network meta-analyses of observational studies: 1) the transitivity assumption in conducting an NMA cannot be satisfied when observational studies are included since the studies being compared are inherently different from each other; 2) the available appraisal tool for NMAs are only applicable for NMAs that included RCTs; and 3) the evidence generated from good quality observational studies will still be less robust in comparison to the evidence from poor quality RCTs. Due to these concerns, the results of the NMAs of observational studies were not considered in the development of the HTAC recommendation and judgment on the comparative efficacy and safety of DOACs. However, the characteristics and results of these studies are still detailed in Table 8.

Table 8. Characteristics of studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban)

Author, Year Setting Study design	Population	Intervention/Comparator	Outcome	
			Efficacy	***Safety***
Network meta-analyses of randomized controlled trials				
Antza et al., 2019 *Multi-country NMA of RCTs (k=18)* *Follow-up period: 30 days to median of 2.8 years*	Patients with atrial fibrillation (N=78,796)	- Dabigatran 150 mg - Dabigatran 110 mg - Rivaroxaban 20 mg - Apixaban 5 mg - Edoxaban 60 mg - Warfarin	*Primary*: Stroke/systemic embolism *Secondary:* myocardial infarction, hemorrhagic stroke, ischemic stroke, all-cause mortality	*Primary*: Major bleeding *Secondary:* clinical relevant non-major bleeding, gastrointestinal bleeding
Lopez-Lopez et al., 2017 *Multi-country (including the Philippines) NMA of phase II and III RCTs (k=23)* *Follow-up period: 3 months to 30 months*	Patients with nonvalvular atrial fibrillation eligible for oral anticoagulation (N=94,656 patients)	- Apixaban 5 mg - Betrixaban - Edoxaban 60 mg - Rivaroxaban 20 mg - Dabigatran 150 mg - Dabigatran 110 mg - Vitamin K antagonist - Antiplatelet agent <150 mg - Antiplatelet agent ≥150 mg	All stroke, stroke or systemic embolism ischaemic stroke, haemorrhagic stroke, myocardial infarction, all-cause mortality,	All bleeding, minor bleeding, major bleeding, intracranial bleeding, gastrointestinal bleeding, and clinically relevant bleeding
Hao Jin et al., 2020a CKD/Renal Function Multi-country (including the Philippines) NMA with Phase III RCTs (k=9) *Follow-up period: Mean follow-up 1.8 years to 2.8*	Patients with atrial fibrillation and different levels of renal function (N=71,681)	- Dabigatran 110 mg - Dabigatran 150 mg - Edoxaban 30 mg - Edoxaban 60 mg - Apixaban 5 mg - Rivaroxaban 20 mg - Warfarin	Stroke or systemic embolism	Major bleeding

years				
Deng et al., 2020 Elderly > 75 Multi-country (including the Philippines) NMA of RCTs (k=5) *Follow-up period: Mean follow-up 1.8 years to 2.8 years*	Patients with NVAF who are aged ≥75 years (N=28,137 elderly patients)	- Apixaban 5 mg - Edoxaban 60 mg - Rivaroxaban 20 mg - Dabigatran 110 mg - Warfarin	Stroke or systemic embolism	Major bleeding
Hao Jin et al., 2020b Heart Failure Multi-country NMA of RCTs (k=9) *Follow-up period: Mean follow-up 1.8 years to 2.8 years*	Patients with AF with heart failure (N=28,025 patients)	- Apixaban 5 mg - Edoxaban 60 mg - Edoxaban 30 mg - Rivaroxaban 20 mg - Dabigatran 110 mg - Dabigatran 150 mg - Warfarin	Stroke or systemic embolism	Major bleeding
Hao Jin et al., 2021 Diabetes Mellitus *Network meta-analysis of phase III or IV RCTs (k=4)* *Follow-up period: Mean follow-up 1.8 years to 2.8 years*	Patients with AF with diabetes mellitus (N=13,319)	- Apixaban 5 mg (with some patients reduced to 2.5mg) - Edoxaban 60 mg - Rivaroxaban 20 mg (with some patients reduced to 15mg) - Dabigatran 110 mg - Dabigatran 150 mg - Warfarin	Stroke or systemic embolism	Major Bleeding
Observational studies				
Lip et al., 2018 *Retrospective observational*	Patients with atrial fibrillation (N=466,991)	- Apixaban 5 mg or 2.5 mg (n=108,852) - Rivaroxaban 15 mg or 20	Composite ischaemic stroke/systemic embolism	Major bleeding GI bleeding ICH

study *Follow-up period:* *Mean 168.7 days to 240.2 days* *Median 123 days to 156 days*	United States	mg (n=153,002) - Dabigatran 150 mg or 110 mg (n=37,724)	Ischaemic stroke Systemic embolism Hemorrhagic stroke	Other bleeding
Staerk et al., 2018 *Retrospective cohort study* *Follow-up period: 2 years*	Patients with an atrial fibrillation diagnosis naïve to anticoagulants and subsequently filled a prescription for an OAC (N=31,522) Denmark	- Apixaban 5 mg standard dose or 2.5 mg reduced dose (n=11,064) - Rivaroxaban 20 mg standard dose or 15 mg reduced dose (n=8,966) - Dabigatran 150 mg standard dose or 110 mg reduced dose (n=11,492)	Stroke / thromboembolism (TE) Ischaemic stroke	Major bleeding, intracranial bleeding and gastrointestinal bleeding

For the general NVAF population

Study characteristics

Overall, there were four (4) studies included for the assessment of DOACs among the general NVAF population. There were two network meta-analyses of phase II and phase III RCTs (Antza et al., 2019 and Lopez-Lopez et al., 2017) and two observational studies (Lip et al., 2018 and Staerk et al., 2018) which reviewed the efficacy, effectiveness, and safety of DOACs among patients with atrial fibrillation. The NMA included randomized controlled trials that were conducted in a multi-country setting that includes the Philippine setting. The follow-up period of the studies included in the NMA ranged from 30 days to 30 months while the follow-up period of the observational studies ranged from a median of 123 days to 2 years. The table above (Table 8) summarizes the characteristics of the network meta-analysis.

Quality of the SR-NMAs

Both SR-NMA studies that were included (Antza et al., 2019 and Lopez-Lopez et al., 2017) were deemed *sufficient* in terms of the relevance domain due to their reviews matching the desired research question using the appraisal tool by Jansen et al., 2014. In terms of credibility, Antza et al., 2019 was insufficient due to weaknesses in the following credibility domains: 1) *evidence base used* due to limitations in literature search, the lack of details on the baseline patient characteristics of included studies, and the lack of explanation for imbalance in treatment effect modifiers; 2) *analysis* due to the lack of attempt to minimize bias from difference in treatment effect modifiers, and non-performance of subgroup analysis or meta-regression; and 3) reporting quality and transparency due to the nonreporting of the impact of patient characteristics to the pooled results. Meanwhile, Lopez-Lopez et al., 2017 was deemed somewhat sufficient, due to two neutral strengths in terms of evidence base used and reporting quality and transparency. Details on the appraisal of these systematic review and network meta-analysis studies using the tool by Jansen et al. can be found in Appendix 3.

Quality of the Observational Studies

The study by Lip et al., 2018 had an overall moderate risk of bias arising from moderate *bias due to confounding* due to the presence of confounding factors that may have affected the results of the study but were controlled for using a valid and reliable statistical analysis. Meanwhile, Staerk et al., 2018 had an overall serious risk of bias arising from biases in the following domains: (1) serious bias due to confounding due to the self-reporting nature of important confounders (NSAID use or alcohol abuse) or the lack of controlling for other important confounders that were identified by the study (e.g., body weight, hemoglobin, international normalized ratio, serum creatinine, and CrCl), (2) moderate bias in classification of interventions due to lack of details on presence or imbalance of past interventions for patients with existing conditions; and (3) moderate bias in selection of the reported results due to reporting of absolute risk and absolute risk reduction rather than relative risks. Further details on the appraisal of observational studies using the ROBINS-I tool can be found in Appendix 4.

Results of the NMA and Observational studies (Efficacy outcomes)

Overall, in terms of efficacy outcomes, the reported odds ratios of the two network meta-analyses of RCTs and two real world observational studies showed that none of the DOACs was superior over the other. There was conflicting evidence among one NMA and two observational studies in terms of stroke. The NMA (Lopez-Lopez et al., 2017) concluded that there was inconclusive evidence among DOACs. Meanwhile, one observational study (Lip et al., 2018) found that apixaban is better than rivaroxaban which is better than dabigatran, while the other observational study reported that apixaban was comparable with dabigatran and rivaroxaban but the comparison between rivaroxaban and dabigatran is inconclusive. In terms of systemic embolism, one observational study (Lip et al., 2018) found that apixaban is better than rivaroxaban; there was inconclusive evidence for the comparisons left.

- For the outcome of composite stroke and systemic embolism, there was conflicting evidence between the NMAs and observational studies that reported this outcome. The two NMAs reported that dabigatran is better than rivaroxaban and inconclusive evidence for all other comparisons while the retrospective cohort study of Lip et al., 2018 found that apixaban is the best among the three drugs; while the study of Staerk et al., 2018 found that there was inconclusive evidence among DOACs for this outcome.
- In terms of myocardial infarction and all-cause death, only the study of Lopez-Lopez et al., 2017 reported results for these outcomes. The study found that for myocardial infarction, rivaroxaban is better than dabigatran but inconclusive evidence for all other comparisons while there was inconclusive evidence among the DOACs for all-cause death.

In addition, the four studies noted specific recommendations in their review. The study of Antza et al., 2019 cautioned that no comparative conclusions among DOACs should be inferred from their review. Both the studies of Antza et al., 2019 and Lopez-Lopez et al., 2017 concluded that head-to-head trials are needed to investigate further the efficacy of the drugs. Lastly, among the retrospective observational studies, Lip et al., 2018 noted that their head-to-head comparisons were for hypothesis generating only; hence, results of this study must be interpreted with caution while Staerk et al., 2018 concluded that randomized clinical trials are needed to evaluate the effectiveness and safety among DOACs.

Outcome 1: Stroke

Overall, one NMA and two observational studies had conflicting results. The NMA of Lopez-Lopez et al., 2017 showed that the comparative risks of all pairwise comparisons (i.e. rivaroxaban and apixaban, rivaroxaban and dabigatran, and dabigatran and apixaban) are inconclusive. Meanwhile, the study of Staerk et al., 2018 showed that the effectiveness of apixaban and dabigatran, and apixaban and rivaroxaban are comparable. On the other hand, the comparison between rivaroxaban and dabigatran in terms of the risk of stroke is inconclusive. Lastly, Lip et al., 2018 concluded that apixaban had lower risk for this outcome compared to rivaroxaban and dabigatran. The studies did not conduct analysis for heterogeneity. None of the included trials in the NMAs involved direct head-to-head comparison of DOACs.

In addition, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for stroke, dabigatran has the highest probability of ranking first (~78%), apixaban ranks second (40%), rivaroxaban on third rank (30%), warfarin ranks fourth (50%) and edoxaban, which is not part of the research questions, ranks fifth (40%).

Table 9. Results of studies comparing DOACs with each other (apixaban, dabigatran and rivaroxaban) for the efficacy outcome of stroke

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.83 (0.59 to 1.16) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Apixaban vs. Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 175 Dabigatran: 280	HR 0.69 (0.57-0.84)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Dabigatran (150 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 75 Dabigatran: 57	Absolute risk difference −0.03% (−0.47% to 0.35%)	Comparable	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Dabigatran (110 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 75 Dabigatran: 57	Absolute risk difference −0.01% (−0.52% to 0.53%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs*	Not indicated *Indirect comparison*	Not indicated	OR 1.01 (0.74 to 1.38) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

(k=23)					
Apixaban vs. Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 559 Rivaroxaban: 749	HR 0.85 (0.76-0.95)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Rivaroxaban (20 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 75 Rivaroxaban: 57	Absolute risk difference 0.09% (−0.22% to 0.39%)	Comparable	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Rivaroxaban (15 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 75 Rivaroxaban: 57	Absolute risk difference −0.23% (−0.81% to 0.38%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.22 (0.87 to 1.73) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Rivaroxaban: 57 Dabigatran: 60	Absolute risk difference −0.12% (−0.51% to 0.22%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (15 mg) vs Dabigatran (110mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Rivaroxaban: 57 Dabigatran: 60	Absolute risk difference 0.24% (−0.28% to 0.81%)	Inconclusive	Serious Risk of Bias from bias due to confounding

Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not applicable	Dabigatran: 281 Rivaroxaban: 232	HR 1.23 (1.04-1.47)	Favors rivaroxaban	Moderate risk of Bias from bias due to confounding

Outcome 2: Systemic Embolism

One observational study evaluated systemic embolism. Lip et al., 2018 concluded that apixaban was better than rivaroxaban but there was inconclusive evidence when apixaban was compared to dabigatran and dabigatran compared to rivaroxaban.

Table 10. Results of studies comparing DOACs with each other (apixaban, dabigatran and rivaroxaban) for the efficacy outcome of systemic embolism

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Apixaban vs Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 7 Dabigatran: 18	HR 0.44 (0.18-1.06) *No heterogeneity reported*	Inconclusive	Moderate Risk of Bias from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 26 Rivaroxaban: 62	HR 0.47 (0.29-0.74)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not applicable	Dabigatran: 18 Rivaroxaban: 23	HR 0.80 (0.43-1.48)	Inconclusive	Moderate Risk of Bias from bias due to confounding

Outcome 3: Stroke/Systemic Embolism

Overall, the best choice of treatment for this outcome cannot be determined with the included studies as the studies have conflicting results. The two NMAs of RCTs concluded that dabigatran is better than rivaroxaban while there is inconclusive evidence when apixaban was compared to dabigatran and rivaroxaban. Meanwhile, one retrospective observational study (Lip et al., 2018) concluded that apixaban is the best among the DOACs while there is inconclusive evidence when dabigatran was compared to rivaroxaban. The other observational study (Staerk et al., 2018) concluded that there is a comparable difference when rivaroxaban was compared with dabigatran while there is inconclusive evidence when apixaban was compared with dabigatran and rivaroxaban. No study reported heterogeneity for this outcome. None of the included trials in the NMAs involved direct head-to-head comparison of DOACs.

In addition, both NMAs of RCTs also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis of Lopez-Lopez et al., 2017 showed that for stroke/systemic embolism, dabigatran has the highest probability of ranking first (90%), apixaban ranks second (60%), edoxaban, which is not part of the research questions, is at 3rd rank (40%), rivaroxaban on 4th rank (40%) and warfarin ranks fifth (90%) and antiplatelet on rank 6 (100%).

Meanwhile, the ranking of interventions by Antza et al., 2016 using P-score ranking showed that for stroke/systemic embolism, dabigatran 150 mg has the highest probability of ranking first (97%), apixaban ranks second (75%), rivaroxaban on third rank (54%), dabigatran 110 mg ranks fourth (45%) and warfarin, is at rank five (21%).

Table 11. Results of studies comparing DOACs with each other (apixaban, dabigatran and rivaroxaban) for the efficacy outcome of composite stroke/systemic embolism

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.82 (0.62 to 1.08) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Apixaban vs. Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 215 Dabigatran: 333	HR 0.72 (0.60-0.85)	Favors apixaban	Moderate Risk of Bias from bias due to confounding

Apixaban (5 mg) vs. Dabigatran (110 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.87 (0.66 to 1.14) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Apixaban (5 mg) vs. Dabigatran (150 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 1.20 (0.90 to 1.60) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 148 Dabigatran: 102	Absolute Risk Difference 0.25% (−0.33% to 0.72%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Dabigatran (110 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 148 Dabigatran: 102	Absolute Risk Difference 0.28% (−0.43% to 1.10%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not applicable	Apixaban: 710 Rivaroxaban: 1,008	HR 0.80 (0.73-0.89)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Rivaroxaban (20 mg)					

Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.90 (0.70 to 1.16) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 148 Rivaroxaban: 107	Absolute Risk Difference 0.24% (−0.20% to 0.68%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Rivaroxaban (15 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Apixaban: 148 Rivaroxaban: 107	Absolute Risk Difference 0.08% (−0.77% to 1.97%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.11 (0.87 to 1.41) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Dabigatran (110 mg) vs Dabigatran (150 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 1.38 (1.10-1.74) I^2= 0%	Favors dabigatran 150 mg	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Dabigatran vs Rivaroxaban					

Lip et al 2018 *Retrospective observational study*	Not applicable	Dabigatran: 334 Rivaroxaban: 309	HR 1.10 (0.95-1.23)	Inconclusive	Moderate Risk of Bias from bias due to confounding
Dabigatran (110 mg) vs Rivaroxaban (20 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 1.04 (0.80 to 1.35) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Dabigatran (150 mg) vs Rivaroxaban (20 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.75 (0.57 to 0.99) I^2= 0%	Favors dabigatran 150 mg	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.35 (1.03 to 1.78) *No heterogeneity reported*	Favors dabigatran	Somewhat sufficient credibility of the study
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Rivaroxaban: 107 Dabigatran: 102	Absolute risk difference 0.00% (−0.50% to 0.44%)	Comparable	Serious Risk of Bias from bias due to confounding

Rivaroxaban (15mg) vs Dabigatran (110mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not applicable	Rivaroxaban: 107 Dabigatran: 102	Absolute risk difference 0.19% (–0.60% to 0.98%)	Inconclusive	Serious Risk of Bias from bias due to confounding

Outcome 4: All-cause death

Only the study of Lopez-Lopez et al., 2017 evaluated results for this outcome and concluded that there are inconclusive risks of all-cause death among all three drugs. None of the included trials in the NMAs involved direct head-to-head comparison of DOACs.

In addition, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for all-cause death, rivaroxaban has the highest probability of ranking first (55%), apixaban and dabigatran ranks second, both with 30% probability, edoxaban, which is not part of the research questions is tied with apixaban at third rank (20%), dabigatran and apixaban on fourth rank (20%), warfarin ranks fifth (60%) and antiplatelet on rank six (70%).

Table 12. Results of studies comparing DOACs with each other (apixaban, dabigatran and rivaroxaban) for the efficacy outcome of all-cause death

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.00 (0.84 to 1.19) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017	Not indicated	Not indicated	OR 0.94 (0.76 to 1.17) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

Network meta-analysis of phase II and III RCTs (k=23)					
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated	Not indicated	OR 0.94 (0.74 to 1.18) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

Outcome 5: Myocardial infarction

Only the study of Lopez-Lopez et al., 2017 evaluated results for this outcome and concluded that rivaroxaban is better than dabigatran while there is inconclusive evidence among the comparisons left (i.e. dabigatran vs apixaban and rivaroxaban vs apixaban). None of the included trials in the NMAs involved direct head-to-head comparison of DOACs.

Meanwhile, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for myocardial infarction, rivaroxaban has the highest probability of ranking first (60%), apixaban ranks second (40%), warfarin at third rank (40%), edoxaban which is not part of the research question on fourth rank (28%), dabigatran ranks fifth (50%) and antiplatelet on rank six (60%).

Table 13. Results of studies comparing DOACs with each other (apixaban, dabigatran and rivaroxaban) for the efficacy outcome of myocardial infarction

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of*	Not indicated *Indirect*	Not indicated	OR 1.48 (0.98 to 2.22) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

phase II and III RCTs (k=23)	*comparison*				
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.92 (0.63 to 1.34) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.62 (0.41 to 0.93) *No heterogeneity reported*	Favors rivaroxaban	Somewhat sufficient credibility of the study

Results of the SR NMA and Observational studies (Safety outcomes)

Overall, in terms of the safety outcomes, the reported odds ratios of the two network meta-analyses of RCTs and hazard ratios of the two real world observational studies showed that apixaban had lower risks in terms of major bleeding when compared to rivaroxaban and dabigatran. Meanwhile, other pairwise comparisons showed inconclusive evidence for the same outcome. In terms of gastrointestinal bleeding, one NMA (Lopez-Lopez et al., 2017) and one observational study (Lip et al., 2018) showed that apixaban is the first choice of treatment while one observational study (Staerk et al., 2018) found comparable results between apixaban and dabigatran, and apixaban and rivaroxaban. Two studies (Lopez-Lopez et al., 2017 and Staerk et al., 2018) reported the comparative risks for GI bleeding between rivaroxaban and dabigatran to be inconclusive while one observational study (Lip et al., 2018) reported that dabigatran is associated with lower risk compared to rivaroxaban. In terms of other bleeding and hemorrhagic stroke, the study of Lip et al., 2018 found that apixaban and dabigatran were better than rivaroxaban. For intracranial hemorrhage, one NMA (Lopez-Lopez et al., 2017) and one observational study (Lip et al., 2018) found that there is inconclusive evidence among the three drugs; while one observational study showed that dabigatran is better than apixaban and rivaroxaban, while rivaroxaban and apixaban are comparable. Lastly, for clinically relevant bleeding, the study of Lopez-Lopez et al., 2017 found that apixaban is better than rivaroxaban while there is inconclusive evidence among the other comparisons left.

In addition, as mentioned above, individual recommendations from four different studies noted that: (1) no comparative conclusions should be drawn from their study (Antza et al., 2019), (2) further head-to-head trials are needed to conclude for the efficacy of DOACs and (3) the head-to-head comparison of DOACs must be interpreted with caution (Lip et al., 2018).

Outcome 1: Major bleeding

Overall, all studies included found that apixaban is the best choice of treatment in terms of major bleeding. The two NMAs of RCTs concluded that apixaban is better than rivaroxaban and dabigatran while there is inconclusive evidence when rivaroxaban was compared to dabigatran. Meanwhile, the two observational studies were consistent that rivaroxaban was the worst for this outcome. The study of Lip et al 2018 found that apixaban is better than rivaroxaban and dabigatran while dabigatran is better than rivaroxaban. Meanwhile, the study of Staerk et al. 2018 found that apixaban and dabigatran are better than rivaroxaban but there was inconclusive evidence when apixaban and dabigatran are compared with each other. Further, all comparisons for this outcome with significant heterogeneity did not conduct subgroup analysis to investigate the reasons for heterogeneity. None of the included trials in the NMAs involved direct head-to-head comparison between DOACs.

In addition, the included NMA of RCTs also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis of Lopez-Lopez et al., 2017 showed that for major bleeding, apixaban has the highest probability of ranking first (~85%). Dabigatran has the highest probability of ranking third and rivaroxaban at fifth. The ranking of interventions by Antza et al., 2016 using P-score ranking showed that apixaban ranked as the first-choice treatment for major bleeding with the highest

P-score of 0.80. The ranking for the next interventions are as follows: dabigatran 110 mg, dabigatran150, warfarin, and rivaroxaban 20 mg, with P-scores of 0.58, 0.29, 0.13, and 0.09, respectively.

Table 14. Results of studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) for the safety outcome of major bleeding

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.33 (1.09 to 1.62) *No heterogeneity reported*	Favors apixaban	Somewhat sufficient credibility of the study
Apixaban vs. Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 571 Dabigatran: 832	HR 0.78 (0.70-0.87)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Dabigatran (110 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.87 (0.70 to 1.07) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Apixaban (5 mg) vs. Dabigatran (150 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect*	Not indicated	OR 0.75 (0.61 to 0.92) I^2= 0%	Favors apixaban	Insufficient credibility of the study due to weaknesses in the evidence base used,

	comparison				analysis, and reporting quality and transparency
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 154 Dabigatran: 114	Absolute risk difference 0.40% (−0.09% to 0.85%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Dabigatran (110 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 128 Dabigatran: 170	Absolute risk difference −0.19% (−1.04% to 0.72%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 1,948 Rivaroxaban: 3,981	HR 0.55 (0.53-0.59)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Rivaroxaban (20 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.68 (0.55 to 0.83) I^2= 0%	Favors apixaban 5 mg	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 154 Rivaroxaban: 175	Absolute risk difference −0.54% (−0.99% to −0.05%)	Favors apixaban 5 mg	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Rivaroxaban (15 mg)					
Staerk et al. 2018	Not	Apixaban: 128	Absolute risk difference	Favors apixaban 2.5 mg	Serious Risk of Bias

Retrospective cohort study	indicated	Rivaroxaban: 104	−1.27% (−2.19% to −0.22%)		from bias due to confounding
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.45 (1.19 to 1.78) *No heterogeneity reported*	Favors apixaban 5 mg	Somewhat sufficient credibility of the study
Dabigatran (110 mg) vs Dabigatran (150 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.86 (0.74 to 1.00) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Dabigatran: 836 Rivaroxaban: 1,190	HR 0.71 (0.65-0.78)	Favors dabigatran	Moderate Risk of Bias from bias due to confounding
Dabigatran (110 mg) vs Rivaroxaban (20 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.76 (0.63 to 0.96) I^2= 0%	Favors dabigatran 110 mg	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency

Dabigatran (150 mg) vs Rivaroxaban (20 mg)					
Antza et al., 2019 *Network meta-analysis of RCTs (k=18)*	Not indicated *Indirect comparison*	Not indicated	OR 0.91 (0.74 to 1.11) I^2= 0%	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.10 (0.90 to 1.34) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 175 Dabigatran: 114	Absolute risk difference 0.93% (0.38% to 1.45%)	Favors dabigatran 150 mg	Serious Risk of Bias from bias due to confounding
Rivaroxaban (15mg) vs Dabigatran (110mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 175 Dabigatran: 114	Absolute risk difference 1.08% (0.03% to 2.09%)	Favors dabigatran 110 mg	Serious Risk of Bias from bias due to confounding

Outcome 2: Gastrointestinal bleed

There were conflicting results among the three studies that reported this outcome. The study of Lopez-Lopez et al., 2017 found that apixaban is better than rivaroxaban and dabigatran while there is inconclusive evidence when rivaroxaban and dabigatran were compared with each other. Meanwhile, the study of Lip et al 2018 reported that apixaban is the best in preventing GI bleeding. The study of Staerk et al. 2018 found that apixaban is comparable with dabigatran and rivaroxaban while there is inconclusive evidence when

rivaroxaban was compared to dabigatran. None of the included trials of the NMAs involved direct head-to-head comparison between the DOACs.

Meanwhile, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for GI bleeding, antiplatelet therapy has the highest probability of ranking first (~40%), apixaban and dabigatran ranks second (30%), edoxaban and apixaban at third rank (~35% and 30%, respectively), edoxaban which is not part of the research question and apixaban on fourth rank (~35% and 30%, respectively), rivaroxaban ranks fifth (80%) and warfarin on rank six (99%).

Table 15. Results of studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) for the safety outcome of gastrointestinal bleed

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.71 (1.21 to 2.43) *No heterogeneity reported*	Favors apixaban 5 mg	Somewhat sufficient credibility of the study
Apixaban vs Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 294 Dabigatran: 508	HR 0.66 (0.57-0.76)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Dabigatran (150 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 71 Dabigatran: 64	Absolute risk difference −0.05% (−0.42% to 0.29%)	Comparable	Serious Risk of Bias from bias due to confounding

Apixaban (2.5 mg) vs. Dabigatran (110 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 50 Dabigatran: 98	Absolute risk difference −0.68% (−1.35% to −0.02%)	Favors apixaban 2.5 mg	Serious Risk of Bias from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 952 Rivaroxaban: 2,239	HR 0.48 (0.44-0.52)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Rivaroxaban (20 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 71 Rivaroxaban: 72	Absolute risk difference −0.20% (−0.50% to 0.10%)	Comparable	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Rivaroxaban (15 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 50 Rivaroxaban: 53	Absolute risk difference −0.87% (−1.58% to −0.15%)	Favors apixaban 2.5 mg	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.66 (1.19 to 2.33) *No heterogeneity reported*	Favors apixaban 5 mg	Somewhat sufficient credibility of the study

Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Dabigatran: 510 Rivaroxaban: 675	HR 0.77 (0.68-0.86)	Favors dabigatran	Moderate Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.97 (0.71 to 1.33) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 72 Dabigatran: 64	Absolute risk difference 0.15% (−0.24% to 0.51%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (15mg) vs Dabigatran (110mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 72 Dabigatran: 64	Absolute risk difference 0.20% (−0.55% to 0.96%)	Inconclusive	Serious Risk of Bias from bias due to confounding

Outcome 3: Other bleeding

Only one study (Lip et al 2018) evaluated this outcome and concluded that between apixaban and rivaroxaban, apixaban is better at preventing other bleeding while in comparing dabigatran and rivaroxaban, dabigatran showed better safety results. Further, the comparative risk of apixaban and dabigatran for other bleeding was inconclusive.

Table 16. Results of studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) for the safety outcome of other bleeding

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Apixaban vs Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 235 Dabigatran: 302	HR 0.88 (0.74-1.04)	Inconclusive	Moderate Risk of Bias from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 836 Rivaroxaban: 1,680	HR 0.57 (0.52-0.61)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Dabigatran: 304 Rivaroxaban: 495	HR 0.62 (0.54-0.72)	Favors dabigatran	Moderate Risk of Bias from bias due to confounding

Outcome 4: Intracranial hemorrhage

There was conflicting evidence among the three studies that reported this outcome. The study of Lopez-Lopez et al., 2017 and Lip et al 2018 found that there was inconclusive evidence among the three drugs. Meanwhile, one retrospective cohort study (Staerk et al. 2018) concluded that dabigatran is better than apixaban and rivaroxaban in preventing ICH while apixaban and rivaroxaban are found to be comparable with each other. None of the included trials in the NMAs involved direct head-to-head comparisons between the DOACs.

In addition, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for clinically relevant bleeding, apixaban has the highest probability of ranking first (90%), edoxaban, which is not part of the research question, ranks second (80%), warfarin tanks third (~58%), rivaroxaban ranks fourth (60%), and dabigatran ranks sixth (~78%).

Table 17. Results of studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) for the safety outcome of any intracranial hemorrhage

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.96 (0.58 to 1.60) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Apixaban vs Dabigatran					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 77 Dabigatran: 85	HR: 1.04 (0.76-1.42)	Inconclusive	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Dabigatran (150 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 23 Dabigatran: 10	Absolute risk difference 0.18% (0.01% to 0.34%)	Favors dabigatran 150 mg	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Dabigatran (110 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 23 Dabigatran: 10	Absolute risk difference 0.26% (−0.06% to 0.59%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Apixaban (5mg)					

Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.55 (0.97 to 2.49) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 272 Rivaroxaban: 375	HR: 0.86 (0.73-1.00)	Inconclusive	Moderate Risk of Bias from bias due to confounding
Apixaban (5 mg) vs. Rivaroxaban (20 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 23 Rivaroxaban: 28	Absolute risk difference −0.05% (−0.24% to 0.12%)	Comparable	Serious Risk of Bias from bias due to confounding
Apixaban (2.5 mg) vs. Rivaroxaban (15 mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Apixaban: 23 Rivaroxaban: 28	Absolute risk difference −0.13% (−0.55% to 0.28%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.61 (0.96 to 2.72) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

Rivaroxaban (20mg) vs Dabigatran (150mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 28 Dabigatran: 10	Absolute risk difference 0.23% (0.06% to 0.41%)	Favors dabigatran 150 mg	Serious Risk of Bias from bias due to confounding
Rivaroxaban (15mg) vs Dabigatran (110mg)					
Staerk et al. 2018 *Retrospective cohort study*	Not indicated	Rivaroxaban: 28 Dabigatran: 10	Absolute risk difference 0.39% (−0.002% to 0.79%)	Inconclusive	Serious Risk of Bias from bias due to confounding
Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 85 Rivaroxaban: 115	HR: 0.75 (0.57-1.00)	Inconclusive	Moderate Risk of Bias from bias due to confounding

Outcome 5: Hemorrhagic stroke

One observational study (Lip et al., 2018) reported the results for this outcome. The study found that both apixaban and dabigatran are better at preventing hemorrhagic stroke than rivaroxaban. Meanwhile, the comparative risk of hemorrhagic stroke between apixaban and dabigatran is inconclusive.

Table 18. Results of SRs/MA/NMA studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) that evaluated the safety outcome of hemorrhagic stroke

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
Apixaban vs Dabigatran					
Lip et al 2018 *Retrospective*	Not indicated	Apixaban: 34 Dabigatran: 35	HR: 1.09 (0.69-1.74)	Inconclusive	Moderate Risk of Bias

observational study					from bias due to confounding
Apixaban vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Apixaban: 130 Rivaroxaban: 306	HR 0.73 (0.59-0.91)	Favors apixaban	Moderate Risk of Bias from bias due to confounding
Dabigatran vs Rivaroxaban					
Lip et al 2018 *Retrospective observational study*	Not indicated	Dabigatran: 35 Rivaroxaban: 57	HR 0.63 (0.41-0.96)	Favors dabigatran	Moderate Risk of Bias from bias due to confounding

Outcome 6: Clinically relevant bleeding

One NMA of RCTS compared all three DOACs for this outcome. The study found that apixaban is better than rivaroxaban while the comparative risks of clinically relevant bleeding between apixaban and dabigatran, and dabigatran and rivaroxaban are inconclusive. The study did not analyze for heterogeneity. None of the included trials in the NMAs involved direct head-to-head comparison between the DOACs.

In addition, the study of Lopez-Lopez et al., 2017 also estimated the probabilities of all treatments being at each possible rank and presented the results with rankograms. The findings from the rank probability analysis showed that for clinically relevant bleeding, apixaban has the highest probability of ranking first (~75%), warfarin ranks second (~75%) , edoxaban, which is not part of the research question ranks third (60%), dabigatran and rivaroxaban both have similar probability of ranking 4th (~30% for both) and 5th (40% for both), while antiplatelet which is not part of the research question ranks last (50%)

Table 19. Results of SRs/MA/NMA studies comparing DOACs with each other (Apixaban, Dabigatran and Rivaroxaban) that evaluated the safety outcome of clinically relevant bleeding

Study	Number of	Number of	Effect size (95% CI)	Interpretation	Quality of

	studies	Events			Evidence
Dabigatran (150mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 2.32 (0.74 to 8.63) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study
Rivaroxaban (20mg) vs Apixaban (5mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 1.53 (1.33 to 1.75) *No heterogeneity reported*	Favors apixaban	Somewhat sufficient credibility of the study
Rivaroxaban (20mg) vs Dabigatran (150mg)					
Lopez-Lopez et al., 2017 *Network meta-analysis of phase II and III RCTs (k=23)*	Not indicated *Indirect comparison*	Not indicated	OR 0.66 (0.18 to 2.07) *No heterogeneity reported*	Inconclusive	Somewhat sufficient credibility of the study

For special NVAF populations

Study characteristics

There were 4 NMAs of Phase III or IV RCTs which reported the efficacy and safety of DOACs in special populations of patients with atrial fibrillation: Hao Jin et al. 2020a, an NMA of 9 studies in AF patients with different renal function levels; Deng et al. 2020, an NMA of 5 RCTs in elderly patients (≥75 years of age) who have AF; Hao Jin et al. 2020b, an NMA of 9 studies in AF patients with heart failure; and Hao Jin et al. 2021, an NMA of 4 studies in patients with AF comorbid with diabetes mellitus. All NMAs included the pivotal Phase III RCTs of direct oral anticoagulants for patients with AF (i.e., RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-TIMI 48). None of the included trials in the NMAs involved direct head-to-head comparison between DOACs. The follow-up period of the RCTs included in the NMAs ranged from 1.8 to 2.8 years. See (*Table 1*) for the summary of characteristics of the studies included.

Quality of the SRs

Two of the four studies (Hao Jin et al., 2020a and Deng et al., 2020) were deemed insufficient while the other two (Hao Jin et al., 2020b and Hao Jin et al. 2021) were sufficient. Hao Jin et al., (2020)a, which focused on AF patients with different renal function levels, was found to be insufficient due to weakness in domains for analysis and interpretation due to the following reasons: 1) lack of attempt to minimize bias due to differences in treatment effect modifiers, 2) lack of analysis to investigate interstudy heterogeneity, and 3) the authors did not specify which analysis (whether SUCRA from ranking or pairwise comparison) was used for the study's conclusion. Deng et al., (2020) had weaknesses in the domain for evidence base used due to the lack of discussion on the differences in the distribution of important treatment effect modifiers such as stroke risk and bleeding risk across the studies; the domain for analysis due to the lack of attempt to minimize bias due to the imbalance in the distribution of treatment effect modifiers through subgroup analysis or meta-regression; and the domain for reporting quality and transparency due to the lack of discussion on the impact of important patient characteristics on the results of the NMA). Lastly, Hao Jin et al., (2020)b which focused on AF patients with heart failure and Hao Jin et al. (2021) which focused on AF patients with diabetes mellitus were both found to have sufficient credibility. While both studies had some issues on the interpretation of results, it was not enough to conclude that the credibility of the studies were insufficient. None of the studies reported conflict of interest which was deemed as a strong domain for all of them.

Results of the SRs (Efficacy outcomes)

In terms of efficacy outcomes, almost all pairwise comparisons yielded inconclusive results except for patients with mild impairment in renal function (CrCl 50-80mL/min) (Hao Jin et al., 2020a) in which dabigatran 150 mg was found to lower risk of stroke compared to dabigatran 110 mg. In patients with heart failure, it was stated in Hao Jin et al., 2020b that apixaban and dabigatran 150 mg were more likely to be the choice to prevent stroke or systemic embolism, even though pairwise comparisons between DOACs yielded inconclusive results. It is however worthy to note that participants from RE-LY and ARISTOTLE trials which dealt with dabigatran and apixaban respectively–had lower CHADS2 scores compared to participants from other trials, which might partly explain the lower rate of stroke or systemic embolism for participants given dabigatran and apixaban.

Outcome 1: Stroke/Systemic Embolism

NVAF patients with different renal function levels

According to Hao Jin et al., (2020)a, for patients with normal renal function (CrCI>80mL/min), there is inconclusive evidence on the comparison of risks of stroke/systemic embolism among the DOACs. For patients with mild impairment of renal function (CrCI 50-80mL/min), dabigatran150 showed lower risk of stroke/systemic embolism compared to dabigatran 110 mg (OR: 0.73, 95%CI: 0.53-0.99). Meanwhile, there is inconclusive evidence in the risk of stroke/systemic embolism for all other comparisons of DOACs vs DOACs. Lastly, in patients with moderate impairment in renal function (CrCI 30-50mL/min), there is inconclusive evidence in pairwise comparisons among DOACs. The heterogeneity of the study was analyzed with the $\tau 2$ or Tau^2 test . For the efficacy result, heterogeneity was deemed to be low ($\tau 2$ = 0.13, 0.04–0.43).

Cumulative ranking curve analysis was performed to come up with probability rankings of DOACs based on SUCRA for the different patient subgroups. For patients with normal renal function (CrCI>80mL/min), dabigatran 150 mg had the highest probability of being the most effective drug (90%), followed by dabigatran 110 mg (68%), while apixaban (66%), rivaroxaban (59%) and warfarin (47%) came in third, fourth, fifth, respectively. In patients with mild impairment in renal function (CrCI 50-80mL/min), edoxaban was ranked first (98%), followed by dabigatran 150 mg (74%), apixaban (64%), rivaroxaban, (40%), dabigatran 110 (23%), and warfarin (9%). Lastly, for patients with moderate impairment in renal function (CrCI 30-50mL/min), dabigatran 150 mg had the highest probability of being the most effective drug (95%), followed by apixaban (66%), dabigatran 110 mg (53%), rivaroxaban (51%), edoxaban (50%), and warfarin (27%).

NVAF patients in elderly patients

Deng et al. 2020 did not find any conclusive evidence in terms of risk of stroke/SE in head-to-head comparisons of DOACs in elderly NVAF patients aged ≥75 years. The heterogeneity of the study was analyzed and the results showed that the heterogeneity of the study was low (I^2 = 26%).

The study also performed rank probabilities to reflect the hierarchy of each intervention. The findings from the rank probability analysis showed that for the outcome of stroke and systemic embolism among elderly NVAF patients, apixaban had the highest probability to be the first-choice treatment, with a ranking probability of 41%, followed by rivaroxaban and dabigatran 110 mg, (34% and 24%, respectively), having the highest ranking probability for second- and third-choice treatment.

NVAF patients with heart failure

The study by Hao Jin et al., (2020)b concluded that apixaban and dabigatran 150 mg were more likely to become the choice for preventing stroke or systemic embolism in patients with AF and heart failure. However, based on the pairwise comparisons of apixaban, rivaroxaban, and dabigatran 150 mg and 110 mg, there is inconclusive evidence in terms of the efficacies of the

DOACs against the composite outcome of stroke and systemic embolism. The heterogeneity of the study was analyzed with the $\tau 2$ or Tau^2 test . For the efficacy results, heterogeneity was deemed to be low ($\tau 2$ = 0.13, 0.04–0.43).

The study also conducted a cumulative ranking curve (SUCRA) analysis to determine the probability of finding the most efficacious treatment in terms of stroke and systemic embolism prevention. The findings from the rank probability analysis showed that for the outcome of stroke and systemic embolism among NVAF patients with heart failure, there is a high probability that dabigatran 150 mg would rank first as the most effective drug with 82%, followed by apixaban (81%), edoxaban 60 mg (57%), and rivaroxaban (52%); while dabigatran 110 mg (30%) did not exhibit superiority in the prevention of the efficacy outcome as noted by the study.

NVAF patients with diabetes mellitus

The study by Hao Jin et al. 2021 did not find any conclusive evidence to determine the comparative risk for stroke/SE for all DOAC treatment comparisons. The heterogeneity of the study was analyzed. For the outcome of stroke/SE, heterogeneity was deemed to be low (I^2= 0.13, 95% CrI 0.04-0.44).

The study also conducted a cumulative ranking curve (SUCRA) analysis which showed that for the outcome of stroke and systemic embolism among NVAF patients with diabetes mellitus, there is a high probability that dabigatran 150 mg would rank first with 88%, followed by apixaban at second rank (63%), dabigatran 110 mg at third rank (59%), rivaroxaban at fourth rank (51%), edoxaban, which is not part of the research question, at fifth rank (31%), and warfarin at sixth rank (9%).

Table 20. Results of studies among special subpopulations for the efficacy outcome of composite of stroke/systemic embolism

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of Evidence
NVAF patients with different renal functions					
Hao Jin et al., 2020a CKD/Renal Function Multi-country NMA including Phase III RCTs (k=9) Note: Indirect evidence was used for DOAC vs. DOAC comparison	**Normal Renal Function (CrCl >80mL/min)** Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2 Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 *Indirect comparison*	Not indicated	Dabigatran$_{150}$ vs Dabigatran$_{110}$: OR 0.80 (0.48, 1.30)	Inconclusive	Insufficient credibility of the study due to weaknesses in analysis and interpretation
			Apixaban vs Dabigatran$_{110}$: OR 1.00 (0.59, 1.90)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{110}$: OR 1.10 (0.62, 2.00)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: OR 1.30 (0.73, 2.40)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{150}$: OR 1.40 (0.76, 2.50)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.00 (0.66, 1.70)	Inconclusive	
	Mild Impairment in Renal Function (CrCl 50-80mL/min)	Not indicated	Dabigatran$_{150}$ vs Dabigatran$_{110}$: OR 0.73 (0.53, 0.99)	Favors dabigatran 150 mg	
			Apixaban vs Dabigatran$_{110}$:	Inconclusive	

	Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2 Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 *Indirect comparison*		OR 0.78 (0.52, 1.20)		
			Rivaroxaban vs Dabigatran$_{110}$: OR 0.91 (0.63, 1.30)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: OR 1.10 (0.71, 1.60)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{150}$: OR 1.30 (0.85, 1.90)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.20 (0.80, 1.70)	Inconclusive	
	Moderate Impairment in Renal Function (CrCl 30-50mL/min) Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2	Not indicated	Dabigatran$_{150}$ vs Dabigatran$_{110}$: OR 0.66 (0.43, 1.00)	Inconclusive	
			Apixaban vs Dabigatran$_{110}$: OR 0.92 (0.54, 1.60)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{110}$: OR 1.00 (0.62, 1.70)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: OR 1.40 (0.79, 2.40)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{150}$: OR 1.50 (0.91, 2.60)	Inconclusive	
			Rivaroxaban vs Apixaban:	Inconclusive	

	Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 *Indirect comparison*		OR 1.10 (0.69, 1.80)		
			Note: Overall the results showed that the heterogeneity of the study was low, having an τ2 of 0.13.		
Elderly NVAF patients (≥75 years)					
Deng et al. 2020 *NMA of multi-country Phase III randomized controlled trials (k=5)* *Note: DOAC vs DOAC comparison used indirect evidence*	Rivaroxaban vs. Dabigatran 110 mg: 3 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Apixaban: 3 *Indirect comparison*	Not indicated	Apixaban vs Dabigatran$_{110}$: HR 0.81 (0.29, 2.30)	Inconclusive	Insufficient credibility of the study due to weaknesses in the evidence base used, analysis, and reporting quality and transparency
			Rivaroxaban vs Dabigatran$_{110}$: HR 0.84 (0.32,1.90)	Inconclusive	
			Rivaroxaban vs Apixaban: HR 1.00 (0.38, 2.50)	Inconclusive	
			Note: Overall the results showed that the heterogeneity of the study was low, having an I-squared of 26%.		
NVAF patients with heart failure					
Hao Jin et al. 2020b NMA of Phase III randomized controlled trials (k=9)	Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran: 2	Not indicated	Dabigatran$_{150}$ vs Dabigatran$_{110}$: OR 0.74 (0.50, 1.10)	Inconclusive	Sufficient credibility of the study
			Apixaban vs Dabigatran$_{110}$: OR 0.76 (0.47, 1.20)	Inconclusive	

Note: DOAC vs DOAC comparison used indirect evidence	Rivaroxaban vs. Dabigatran: 2 Rivaroxaban vs. Apixaban: 2 *Indirect comparison*		Rivaroxaban vs Dabigatran$_{110}$: OR 0.91 (0.59, 1.40)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: OR 1.00 (0.62, 1.70)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{150}$: OR 1.20 (0.78, 1.90)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.20 (0.81, 1.80)	Inconclusive	
			Note: Overall the results showed that the heterogeneity of the study was low, having an τ2 of 0.13.		
NVAF patients with diabetes mellitus					
Hao Jin et al. 2021 *SR-NMA of multi-country RCTs (k=4)* *Note: DOAC vs DOAC comparison used indirect evidence*	Dabigatran 150 mg vs. Dabigatran 110 mg$_0$: 1 Apixaban vs. Dabigatran: 2 Rivaroxaban vs. Dabigatran: 2 Rivaroxaban vs. Apixaban: 2 *Indirect comparison*	Not indicated	Dabigatran$_{10}$ vs Dabigatran$_{110}$: RR 1.20 (0.81, 1.90)	Inconclusive	Sufficient credibility of the study
			Rivaroxaban vs Dabigatran$_{150}$: RR 1.30 (0.82, 2.10)	Inconclusive	
			Rivaroxaban vs Apixaban: RR 1.10 (0.71, 1.70)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: RR 1.20 (0.72, 2.00)	Inconclusive	
			Apixaban vs Dabigatran$_{110}$: RR 0.99 (0.60, 1.60)	Inconclusive	
			Dabigatran$_{110}$ vs Rivaroxaban: RR 0.93 (0.59, 1.50)	Inconclusive	
			Note: Overall the results showed that the heterogeneity of the study was		

			low, having an τ2 of 0.13.		

Results of the SRs (Safety outcomes)
Outcome 2: Major bleeding

Almost all pairwise comparisons among DOACs resulted in inconclusive evidence for the prevention of major bleeding except in the following patients: (1) with normal renal function (CrCI>80mL/min) according to Hao Jin et al., (2020)a which favored dabigatran 110 mg over rivaroxaban and in patients, (2) with moderate impairment in renal function (CrCI 30-50mL/min) wherein apixaban turned out to be greater than dabigatran 110 and 150mg and rivaroxaban, and lastly (3) with heart failure patients in which apixaban was favored over rivaroxaban.

NVAF patients with different renal functions

According to Hao Jin et al., (2020)a, for patients with normal renal function (CrCI>80mL/min), dabigatran 110 mg was associated with a decreased risk in major bleeding compared to rivaroxaban (OR: 0.49, 95%CI: 0.31-0.75). In contrast, differences among the other DOACs pairwise comparisons were inconclusive for the aforementioned patient group. Meanwhile, for patients with mild impairment in renal function, all pairwise comparisons among DOACs yielded inconclusive evidence in terms of the safety of DOACs against the composite outcome of major bleeding. On the other hand, for patients with moderate impairment in renal function (CrCI 30-50mL/min), it was found that dabigatran 110 mg (OR: 2.0, 95%CI: 1.3-3.0), dabigatran 150 mg (OR 2.1, 95%CI: 1.4-3.1) and rivaroxaban (OR: 2.0, 95%CI: 1.3-3) increased the risk of major bleeding in contrast to apixaban. Pairwise comparisons among other DOACs for patients with moderate renal impairment all showed inconclusive evidence in the prevention of major bleeding. The heterogeneity of the study was analyzed with the $\tau 2$ or Tau^2 test . For the efficacy result, heterogeneity was deemed to be low ($\tau 2 = 0.13, 0.04–0.44$).

With regard to the rank probability analysis using SUCRA, in patients with normal renal function (CrCI>80mL/min), edoxaban 30 mg, which is not included in the research question, placed first as the safest drug (99%), followed by dabigatran 110 mg (78%), edoxaban 60 mg (66%), apixaban (47%), dabigatran 150 mg (40%), warfarin (19%), and rivaroxaban (2%). In patients with mild impairment in renal function (CrCI 50-80mL/min), edoxaban 30 mg (99%) came in first, followed by dabigatran 110 mg (70%), apixaban (69%), edoxaban 60 mg (43%), dabigatran 150 mg (36%), and rivaroxaban (20%). Lastly, for patients with moderate impairment in renal function (CrCI 30-50mL/min), edoxaban 30 mg (98%) also came in first as the safest drug, followed by apixaban (85%), edoxaban 60 mg (64%), rivaroxaban (30%), dabigatran 110 mg (27%), warfarin (24%), and dabigatran 150 mg (22%).

NVAF patients in elderly patients

Deng et al. 2020 had inconclusive evidence for pairwise comparisons of DOACs in terms of major bleeding for elderly patients with NVAF. The heterogeneity of the study was analyzed and the results showed that the heterogeneity of the study was low ($I^2 = 26\%$).

The findings from the rank probability analysis showed that for the outcome of major bleeding among elderly NVAF patients, apixaban had the highest probability to be the first-choice treatment, with a ranking probability of 71%,

followed by, dabigatran (19%), warfarin (48%), edoxaban (9%) and rivaroxaban (70%) respectively having the highest ranking probability for all succeeding ranks.

NVAF patients with heart failure

The study by Hao Jin et al., (2020)b concluded that apixaban and dabigatran 150 mg were more likely to become the choice for preventing major bleeding in patients with AF and heart failure. Based on the pairwise comparisons of the DOACs of interest included in their review (i.e., apixaban, rivaroxaban, and dabigatran 150 mg and 110 mg), apixaban is associated with lower risk of major bleeding compared to rivaroxaban. As for all other pairwise comparisons, there was inconclusive evidence detected among the DOACs in terms of their safety in preventing major bleeding. The heterogeneity of the study was analyzed with the $\tau 2$ or Tau^2 test . For the safety result, heterogeneity was deemed to be low ($\tau 2 = 0.13$, 0.04–0.44).

The findings from the rank probability analysis using SUCRA showed that for the outcome of major bleeding among NVAF patients with heart failure, there is a high probability that edoxaban 30 mg (99%) would rank first, apixaban would rank second as the safest drug among the DOACs of interest with 71%, followed by edoxaban 60 mg (59%), dabigatran 150 mg (55%), dabigatran 110 mg (44%), warfarin (12%) and rivaroxaban (10%). Dabigatran 110 mg and rivaroxaban were noted by the study to be inferior to other drugs in terms of preventing major bleeding.

NVAF patients with diabetes mellitus

Hao Jin et al. 2021 found that all pairwise comparisons of DOACs are inconclusive. For the outcome of major bleeding , heterogeneity was deemed to be low (I^2= 0.13, 95% CrI 0.04-0.43).

Cumulative ranking curve (SUCRA) analysis was performed for the major bleeding outcome, as detailed in the previous section. The findings showed that for the outcome of major bleeding in NVAF patients with diabetes mellitus, edoxaban would rank first with 94%, followed by dabigatran 110 (59%) rivaroxaban (52%), apixaban (47%), warfarin (38%), and dabigatran 150 mg (11%).

Table 21. Results of studies among special subpopulations for the safety outcome of composite major bleeding

Study	Number of studies	Number of Events	Effect size (95% CI)	Interpretation	Quality of evidence
NVAF patients with different renal functions					
Hao Jin et al., 2020a CKD/Renal Function Multi-country NMA including Phase III RCTs (k=9)	**Normal Renal Function (CrCl >80mL/min)** Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2 Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 Indirect comparison	Not indicated	$Dabigatran_{110}$ vs $Dabigatran_{150}$: OR 0.71 (0.50, 1.00)	Inconclusive	Insufficient credibility of the study due to weaknesses in analysis and interpretation
			Apixaban vs $Dabigatran_{110}$: OR 1.30 (0.87, 2.00)	Inconclusive	
			$Dabigatran_{110}$ vs Rivaroxaban: OR 0.49 (0.31, 0.75)	Favors dabigatran 110	
			Apixaban vs $Dabigatran_{150}$: OR 0.95 (0.63, 1.40)	Inconclusive	
			Rivaroxaban vs $Dabigatran_{150}$: OR 1.50 (0.97, 2.20)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.50 (1.00, 2.30)	Inconclusive	
	Mild Impairment in Renal Function (CrCl 50-80mL/min) Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2	Not indicated	$Dabigatran_{150}$ vs $Dabigatran_{110}$: OR 1.20 (0.95, 1.50)	Inconclusive	
			Apixaban vs $Dabigatran_{110}$: OR 1.00 (0.74, 1.30)	Inconclusive	
			Rivaroxaban vs $Dabigatran_{110}$: OR 1.20 (0.92, 1.70)	Inconclusive	
			Apixaban vs $Dabigatran_{150}$:	Inconclusive	

	Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 Indirect comparison		OR 0.85 (0.63, 1.10)		
			Rivaroxaban vs Dabigatran$_{150}$: OR 1.10 (0.78, 1.40)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.20 (0.92, 1.70)	Inconclusive	
	Moderate Impairment in Renal Function (CrCl 30-50mL/min) Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran 110 mg: 2 Rivaroxaban vs. Dabigatran 110 mg: 2 Apixaban vs Dabigatran 150 mg 2 Rivaroxaban vs Dabigatran 150 mg: 2 Rivaroxaban vs. Apixaban: 2 Indirect comparison	Not indicated	Dabigatran$_{110}$ vs Dabigatran$_{150}$: OR 1.00 (0.79, 1.30)	Inconclusive	
			Apixaban vs Dabigatran$_{110}$: OR 0.50 (0.33, 0.74)	Favors apixaban	
			Rivaroxaban vs Dabigatran$_{110}$: OR 0.98 (0.66, 1.50)	Inconclusive	
			Apixaban vs Dabigatran$_{150}$: OR 0.49 (0.33, 0.72)	Favors apixaban	
			Rivaroxaban vs Dabigatran$_{150}$: OR 0.96 (0.64, 1.40)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 2.00 (1.30, 3.00)	Favors apixaban	
			Note: Overall the results showed that the heterogeneity of the study was low, having an τ2 of 0.13.		
Elderly NVAF patients (≥75 years)					
Deng et al. 2020 *NMA of multi-country*	Rivaroxaban vs. Dabigatran 110 mg: 3 Apixaban vs. Dabigatran 110 mg: 2	Not indicated	Apixaban vs Dabigatran$_{110}$: HR 0.64 (0.27,1.50)	Inconclusive	Insufficient credibility of the study due to
			Rivaroxaban vs Dabigatran$_{110}$:	Inconclusive	

Phase III randomized controlled trials (k=5)	Rivaroxaban vs. Apixaban: 3 Indirect comparison		HR 1.20 (0.63, 2.40)		weaknesses in the evidence base used, analysis, and reporting quality and transparency
			Rivaroxaban vs Apixaban: HR 1.90 (0.89, 4.30)	Inconclusive	
			Note: Overall the results showed that the heterogeneity of the study was low, having an I^2 of 26%.		
NVAF patients with heart failure					
Hao Jin et al. 2020b NMA of Phase III randomized controlled trials (k=9)	Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran: 2 Rivaroxaban vs. Dabigatran: 2 Rivaroxaban vs. Apixaban: 2 Indirect comparison	Not indicated	$Dabigatran_{150}$ vs $Dabigatran_{110}$: OR 0.94 (0.70, 1.30)	Inconclusive	Sufficient credibility of the study
			Apixaban vs $Dabigatran_{110}$: OR 0.85 (0.58, 1.20)	Inconclusive	
			Rivaroxaban vs $Dabigatran_{110}$: OR 1.20 (0.89, 1.60)	Inconclusive	
			Apixaban vs $Dabigatran_{150}$: OR 0.90 (0.62, 1.30)	Inconclusive	
			Rivaroxaban vs $Dabigatran_{150}$: OR 1.30 (0.95, 1.70)	Inconclusive	
			Rivaroxaban vs Apixaban: OR 1.40 (1.10, 1.90)	Favors apixaban	
			Note: Overall the results showed that the heterogeneity of the study was low, having an $\tau 2$ of 0.13.		

NVAF patients with diabetes mellitus					
Hao Jin et al. 2021 *SR-NMA of multi-country RCTs (k=4)*	Dabigatran 150 mg vs. Dabigatran 110 mg: 1 Apixaban vs. Dabigatran: 2 Rivaroxaban vs. Dabigatran: 2 Rivaroxaban vs. Apixaban: 2 Indirect comparison	Not indicated	Rivaroxaban vs Dabigatran$_{150}$: RR 0.84 (0.61, 1.20)	Inconclusive	Sufficient credibility of the study
			Apixaban vs Dabigatran$_{150}$: RR 0.85 (0.60, 1.20)	Inconclusive	
			Rivaroxaban vs Apixaban: RR 0.99 (0.71, 1.40)	Inconclusive	
			Dabigatran$_{150}$ vs Dabigatran$_{110}$: RR 0.82 (0.64, 1.00)	Inconclusive	
			Apixaban vs Dabigatran$_{110}$: RR 1.00 (0.73, 1.50)	Inconclusive	
			Rivaroxaban vs Dabigatran$_{110}$: RR 0.97 (0.70, 1.40)	Inconclusive	
			Note: Overall the results showed that the heterogeneity of the study was low, having an τ2 of 0.13.		

Cost-effectiveness

Apixaban, dabigatran, and rivaroxaban were deemed to be superior over warfarin. Meanwhile, the clinical judgment for apixaban versus dabigatran versus rivaroxaban was deemed therapeutically equivalent in terms of both safety and efficacy with each DOAC being treatment alternatives for each other depending on the patient's clinical profile and treatment goals. Hence, cost-effectiveness was performed via cost-minimization analysis and will therefore be discussed under affordability and viability which includes a comparative costing analysis.

Affordability and Viability

The estimated 1-year and 3-year budget impact of covering warfarin, apixaban, dabigatran and rivaroxaban for the targeted population show that all three drugs will incur a large impact to the budget for the Philippines. Nevertheless, in this cost minimization analysis, apixaban had the lowest cost of the treatment regimen for patients with NVAF. Meanwhile, dabigatran and rivaroxaban had similar costs of treatment. Warfarin had the highest cost which was driven by both the cost of the drug regimen and the cost of weekly INR monitoring. The detailed budget impact analysis was discussed below.

A. Costing Analysis

Summary of costing inputs and assumptions

For the costing analysis, the three DOACs (i.e., dabigatran, apixaban, and rivaroxaban) and warfarin were compared with each other. There were two scenarios assumed in the analysis: first, all target users will not experience any adverse events and second, all target users will experience all adverse events (i.e., major bleeding and intracranial hemorrhage).The direct medical cost items included the: (1) cost of the drug regimen; (2) cost of INR monitoring for those under warfarin treatment only, and (3) the cost of management of adverse events associated with the use of oral anticoagulants at a third-party payer/government perspective for one year for the second scenario. According to consulted societies (Philippine Heart Association, Stroke Society of the Philippines, and the Philippine Neurocritical Society), the use of oral anticoagulants for the prevention of myocardial infarction and cerebrovascular events is indefinite and individualized, and should be continued as long as risk factors for stroke persists. For the purpose of this costing analysis, the treatment cost for one year is assumed for the comparison between dabigatran, apixaban, rivaroxaban and warfarin (assuming once daily treatment with 5mg). Treatment regimen for the four drugs and other relevant costs associated with the oral anticoagulation therapy were also consulted with the aforementioned societies. From these, the final costing outputs were the total cost of treatment regimen per patient and for all expected users.

The unit cost of warfarin was taken from the 2022 DPRI, while for dabigatran, rivaroxaban, and apixaban the generic prices were used. To capture this, initial prices excluding VAT from the 2022 list price were submitted by their respective innovator drug manufacturers. However, since the patent of the three brands have already expired in the Philippines and since there are branded generic products of the three DOACs registered with the Philippine Food and Drug Administration, a costing analysis for the scenario wherein the generic price was used for the unit cost of the drugs was conducted. For apixaban, the generic price exclusive of VAT was provided by its generic drug product manufacturer, while for dabigatran and rivaroxaban, a 40% projected price reduction was applied to the cost of their respective innovator drug. This assumption was based on a consultation with the DOH Pharmaceutical Division. All DOACs are given in an outpatient setting and while for

those under warfarin treatment, outpatient INR monitoring performed once weekly or 52 times a year was included in this analysis. Further, unlike VKA oral anticoagulants, no laboratory and diagnostic tests are required for the DOACs, according to expert opinion. Lastly, the cost of management of major bleeding and intracranial hemorrhage, which are adverse events associated with the use of DOACs, were taken from PhilHealth medical case rates (ICD code D68.3: hemorrhagic disorder due to circulating anticoagulants; and ICD code I60.6: subarachnoid hemorrhage from other intracranial arteries). Tables 22 and 23 below indicate the unit costs and assumptions used in the analysis.

In addition, in the scenario where all target users were assumed to experience the serious adverse events, major bleeding and intracranial hemorrhage, an additional cost due to hospitalization was included. Based on the PhilHealth case rates, additional costs are equivalent to ₱12,800.00 and ₱38,000.00, respectively.

In this costing analysis, the total number of expected patients was based on the updated clinical pathway for the management of atrial fibrillation followed in the local setting according to SSP and PHA (European Society of Cardiology, 2020) wherein OAC is considered and recommended for AF patients with CHA_2DS_2VASc score of $\geq$1 for males and $\geq$2 for females, respectively. This was computed using the following: (1) Philippine data from the Global Burden of Disease Study in 2017 on atrial fibrillation (Dai et al., 2020) which reported an age-standardized prevalence of atrial fibrillation of 371.0 per 100,000 individuals ages 20 years and above, and (2) data from a nationwide sample cohort study in South Korea (Kim et al. 2017) which reported the proportion of NVAF patients (93.60%) among patients with atrial fibrillation and were strongly recommended for anticoagulation therapy for stroke prevention. Additionally, the team used the data from the GARFIELD-AF Global study and calculated the percentage of NVAF patients for whom OAC is both considered and recommended (i.e. 91.57%).

Overall results per target user

Overall, the total cost of treatment per patient which includes only the the generic prices of the drug regimen were ₱27,948.78 for dabigatran, ₱27,418.80 for rivaroxaban, ₱18,622.30 for apixaban and ₱29,417.15 for warfarin. If the patient experiences adverse events such as major bleeding and intracranial hemorrhage, the total cost of treatment per patient will increase to ₱78,748.78 for dabigatran, ₱78,218.00 for rivaroxaban, ₱69,422.30 for apixaban and ₱80,217.15 for warfarin.

Overall results for all target users

We recognize that, generally, there are higher rates of adverse events with warfarin compared to DOACs, but the cost at the population level cannot be directly compared due to the unavailability of data directly comparing these drugs within the same setting. Hence, the total cost for all target users had two scenarios: 1) all patients will not experience AEs, and 2) all patients will experience AEs.

For all target users who will not experience any adverse events, the computed total costs incurred to the government (using generic prices) for the target population are as follows: ₱6.17B for dabigatran, ₱6.05 B for rivaroxaban, ₱4.11 B for apixaban and ₱6.49 B for warfarin.

Meanwhile, for the second scenario wherein all target users will experience all adverse events (i.e., major bleeding and intracranial hemorrhage) the computed total costs incurred to the government (using generic prices) for the target population are as follows: ₱17.38 B for dabigatran, ₱17.26 B for rivaroxaban, ₱15.32 B for apixaban and ₱17.70 B for warfarin.

Table 22. Costing analysis for the use of DOACs vs warfarin for the population of nonvalvular atrial fibrillation who are recommended and considered for OAC therapy and who will not experience any adverse events

Parameter	Intervention			Comparator	Remarks/Assumptions	Reference
	Dabigatran 150 mg tablet	Rivaroxaban 20 mg tablet	Apixaban 5 mg tablet	Warfarin 5 mg tablet		
Part 1: Cost of drug regimen						
A=Unit cost of drug	₱ 38.29	₱ 75.12	₱ 25.51	₱17.91	Apixaban: List price without VAT from the generic drug manufacturer Rivaroxaban and Dabigatran: Assumption of 40% discount from the price of the innovator drug Warfarin: 2022 DPRI	Dabigatran, Rivaroxaban - submission from innovator drug manufacturer Apixaban - submission from branded generic drug manufacturer 2022 DPRI
B=Frequency of use per day	2	1	2	1	From the recommended dosing regimen from trials CPGs Assumption of once daily warfarin treatment (adjusted dose)	Consultation with societies: PNCS and PHA Clinical trials: Connolly et al., 2009 [RE-LY trial], Patel et al. 2011 [ROCKET-AF trial], Granger et al. 2011 [ARISTOTLE trial]

C=Duration of drug regimen	365	365	365	365	Maintenance dose, assumed for one year of treatment	
A*B*C=Total cost of drug regimen per user (D)	₱ 27,948.78	₱ 27,418.80	₱ 18,622.30	₱ 6,537.15		
Part 2: Cost of other medical cost						
Cost of monitoring (E)	₱ 0.00	₱ 0.00	₱ 0.00	₱ 440.00		Philippine Heart Center, Division of Laboratory Medicine
Frequency of INR monitoring per year (F)	0	0	0	52	Assuming once weekly INR monitoring (HTAC expert input)	
E*F-Total cost of monitoring (G)	₱ 0.00	₱ 0.00	₱ 0.00	₱ 22,880.00		
Part 3: Cost of treatment regimen for all target users						
D+G=Cost of treatment regimen per patient (H)	₱ 27,948.78	₱ 27,418.80	₱ 18,622.30	₱ 29,417.15		
Part 4: Cost of treatment regimen for all target users						
Total target number of users **(I)**	220,693	220,693	220,693	220,693	Global Burden of Disease 2017 (Dai et al. 2020) Prevalence: - 2017 counts of atrial fibrillation in the Philippines: 228, 680 (196,287 to 261,928) - 2017 Age-standardized rate per 100,000 people:	Personal communication with societies, 2022: PNCS and PHA Dai et al., 2020 PSA projected population for July

					371.0 (315.8 to 425.1) Philippine projected population for 2023: 69,403,992 (PSA, Age ≥20) Proportion of NVAF patients among those with AF: 93.60% (Kim et al. 2017) Proportion of NVAF patients for whom OAC is recommended and considered: 91.57% (GARFIELD AF GLOBAL)	2023 Kim et al. 2017 GARFIELD AF GLOBAL
I*H=TOTAL COST OF TREATMENT FOR ALL TARGET USERS	**₱6,168,100,104.54**	**₱6,051,137,228.40**	**₱4,109,811,253.90**	**₱6,492,159,084.95**		

Table 23. Costing analysis for the use of DOACs vs warfarin for the population of nonvalvular atrial fibrillation who are recommended and considered for OAC therapy and who will experience all adverse events

Parameter	Intervention			Comparator	Remarks/Assumptions	Reference
	Dabigatran 150 mg tablet	Rivaroxaban 20 mg tablet	Apixaban 5 mg tablet	Warfarin 5 mg tablet		
Part 1: Cost of drug regimen						
A=Unit cost of drug	₱ 38.29	₱ 75.12	₱ 25.51	₱17.91	Apixaban: List price without VAT from the generic drug manufacturer Rivaroxaban and	Dabigatran, Rivaroxaban - submission from innovator drug manufacturer

					Dabigatran: Assumption of 40% discount from the price of the innovator drug Warfarin: 2022 DPRI	Apixaban - submission from branded generic drug manufacturer 2022 DPRI
B=Frequency of use per day	2	1	2	1	From the recommended dosing regimen from trials CPGs Assumption of once daily warfarin treatment (adjusted dose)	Consultation with societies: PNCS and PHA Clinical trials: Connolly et al., 2009 [RE-LY trial], Patel et al. 2011 [ROCKET-AF trial], Granger et al. 2011 [ARISTOTLE trial]
C=Duration of drug regimen	365	365	365	365	Maintenance dose, assumed for one year of treatment	
A*B*C=Total cost of drug regimen (D)	₱ 27,948.78	₱ 27,418.80	₱ 18,622.30	₱ 6,537.15		
Part 2: Cost of other medical costs						
2.1 Cost of management of AEs						
Cost of management of major bleeding (E)	₱ 12,800.00	₱ 12,800.00	₱ 12,800.00	₱ 12,800.00	Assuming cost to the government for the management of major bleeding after anticoagulation	PhilHealth case rates (D68.3), 2017
Cost of management of intracranial	₱ 38,000.00	₱ 38,000.00	₱ 38,000.00	₱ 38,000.00	Assuming cost to the government for the	PhilHealth case rates (I60.6), 2017

hemorrhage (F)					management of intracranial hemorrhage after anticoagulation	
2.2. Cost of monitoring						
Cost of monitoring (E)	₱ 0.00	₱ 0.00	₱ 0.00	₱ 440.00		Philippine Heart Center, Division of Laboratory Medicine
Frequency of INR monitoring per year (F)	0	0	0	52	Assuming once weekly INR monitoring (HTAC expert input)	
E*F-Total cost of monitoring (G)	₱ 0.00	₱ 0.00	₱ 0.00	₱ 22,880.00		
Part 3: Cost of treatment regimen per patient						
D+H+I=Cost of treatment regimen per patient (with major bleeding and intracranial hemorrhage) **(J)**	₱ 78,748.78	₱ 78,218.80	₱ 69,422.30	₱ 80,217.15		
Part 4: Cost of treatment regimen for all target users						
Total target number of users **(L)**	220,693	220,693	220,693	220,693	Global Burden of Disease 2017 (Dai et al. 2020) Prevalence: - 2017 counts of atrial fibrillation in the Philippines: 228, 680 (196,287 to 261,928) - 2017	Personal communication with societies, 2022: PNCS and PHA Dai et al., 2020 PSA projected population for July

					Age-standardized rate per 100,000 people: 371.0 (315.8 to 425.1) Philippine projected population for 2023: 69,403,992 (PSA, Age ≥20) Proportion of NVAF patients among those with AF: 93.60% (Kim et al. 2017) Proportion of NVAF patients for whom OAC is recommended and considered: 91.57% (GARFIELD AF GLOBAL)	2023 Kim et al. 2017 GARFIELD AF GLOBAL
J*L=TOTAL COST OF TREATMENT FOR ALL TARGET USERS	**₱17,379,304,504.54,**	**₱17,262,341,628.40**	**₱15,321,015,653.90**	**₱17,703,363,484.95**		

B. Budget Impact Analysis

The budget impact analysis over a 3-year horizon was performed using data from sources indicated in Annex II. The incidence of atrial fibrillation in the Philippines for 2024 and 2025 were derived using the 2017 incidence rate of atrial fibrillation and the percentage change in age-standardized rates from 1990 to 2017 from Global Burden of Disease Study in 2017 on atrial fibrillation (Dai et al., 2020). The proportion of patients with non-valvular atrial fibrillation (NVAF) among those with atrial fibrillation was derived from Kim et al. 2017. Finally, for the expected number of NVAF patients to receive oral anticoagulation therapy (i.e., dabigatran, rivaroxaban, apixaban, or warfarin), the locally-adopted clinical pathway submitted by the SSP and PHA was used where OAC is considered and recommended for AF patients with CHA_2DS_2VASc score of ≥1 for males and ≥2 for females. For the purpose of this 3-year budget impact analysis, patients are assumed to be on anticoagulation therapy for a lifetime duration.

For the first scenario wherein all target users will not experience any adverse events, the estimated total cost of treatment (using generic prices) for 3 years with dabigatran, rivaroxaban, apixaban, and warfarin for 3 years is ₱19.84 B, ₱19.46 B, ₱13.22 B, and ₱20.88 B, respectively.

Meanwhile for the second scenario wherein all target users will experience adverse events (i.e., major bleeding and intracranial hemorrhage), the estimated total cost of treatment for 3 years with dabigatran, rivaroxaban, apixaban, and warfarin for 3 years is ₱55.89 B, ₱55.51 B, ₱49.27 B, and ₱56.93 B respectively.

Table 24. Three-year budget analysis for the use of DOACs vs warfarin for the population of nonvalvular atrial fibrillation who are recommended and considered for OAC therapy and will not experience any adverse events

Parameter/Year	Intervention			Comparator	Remarks	Reference/s
	Dabigatran	***Rivaroxaban***	***Apixaban***	***Warfarin***		
Cost of treatment per patient per year	₱27,948.78	₱27,418.80	₱18,622.30	₱29,417.15	From costing analysis	
Number of patients (2023)	220,693	220,693	220,693	220,693	Total number of patients who will take DOACs: Projected number of patients with atrial fibrillation with CHA_2DS_2VASc score of ≥1 for males and ≥2 for females on anticoagulation therapy in the Philippines in 2023. Estimated using the prevalence data from the GBD Study from 1990 to 2017, data on prevalence of AF patients with different CHA_2DS_2VASc scores.	Personal communication with societies, 2022: PNCS and PHA Dai et al., 2020 PSA projected population for July 2023 Kim et al. 2017 GARFIELD AF GLOBAL
Number of patients (2024)	236,643	236,643	236,643	236,643		
Number of patients (2025)	252,370	252,370	252,370	252,370		
Total Cost of Treatment Regimen for all users in billions						
Total cost (2023)	₱6.17 B	₱6.05 B	₱4.11 B	₱6.49 B	N/A	N/A
2024	₱6.61 B	₱6.49 B	₱4.41 B	₱6.96 B	N/A	N/A
2025	₱7.05 B	₱6.92 B	₱4.70 B	₱7.42 B	N/A	N/A
TOTAL COST FOR 3 YEARS (in billion [B] ₱)	**₱ 19.84 B**	**₱ 19.46 B**	**₱ 13.22 B**	**₱ 20.88 B**	N/A	N/A

Table 25. Three-year budget analysis for the use of DOACs for the population of nonvalvular atrial fibrillation who are recommended and considered for OAC therapy and will experience all adverse events

Parameter/Year	Intervention			Comparator	Remarks	Reference/s
	Dabigatran	*Rivaroxaban*	*Apixaban*	*Warfarin*		
Proportion of total users who are will experience all adverse events	100%	100%	100%	100%	Scenario assumption	
Cost of treatment regimen per patient (with ICH and major bleeding)	₱78,748.78	₱78,218.80	₱69,422.30	₱80,217.15	From costing analysis	
Number of patients (2023)	220,693	220,693	220,693	220,693	Total number of patients who will take DOACs: Projected number of patients with atrial fibrillation with CHA_2DS_2VASc score of ≥1 for males and ≥2 for females on anticoagulation therapy in the Philippines in 2023. Estimated using the prevalence data from the GBD Study from 1990 to 2017, data on prevalence of AF patients with different CHA_2DS_2VASc scores.	Personal communication with societies, 2022: PNCS and PHA Dai et al., 2020 PSA projected population for July 2023 Kim et al. 2017 GARFIELD AF GLOBAL
Number of patients (2024)	236,643	236,643	236,643	236,643		
Number of patients (2025)	252,370	252,370	252,370	252,370		
Total Cost of Treatment Regimen for all users in billions						
Total cost (2023)	₱17.38 B	₱17.26 B	₱15.32 B	₱17.70 B	N/A	N/A
2024	₱18.64 B	₱18.51 B	₱16.43 B	₱18.98 B	N/A	N/A
2025	₱19.87 B	₱19.74 B	₱17.52 B	₱20.24 B	N/A	N/A
TOTAL COST FOR 3 YEARS	**₱ 55.89 B**	**₱ 55.51 B**	**₱ 49.27 B**	**₱56.93 B**	N/A	N/A

(in billion [B] ₱)						

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Appendix 1. Clinical practice guidelines on the use of direct oral anticoagulants for patients with nonvalvular atrial fibrillation

Table A1. Summary of recommendations of international CPGs adopted by the Philippine medical societies for the prevention of stroke/systemic embolism among patients with NVAF.

Recommendations	Classification of Recommendation/ Level of Evidence
2012 American Heart Association/American Stroke Association Recommendations *(adopted by the Philippine Neurocritical Care Society (PNCS)* The 2012 recommendations indicated that the following drugs are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF: - Warfarin *(Class I; Level A)* - Dabigatran *(Class I; Level B)* - Apixaban *(Class I; Level B)* - Rivaroxaban *(Class IIa; Level B)* The following were recommendations specific to the use of **dabigatran** for the prevention of first and recurrent stroke: - Dabigatran 150 mg twice daily is an efficacious alternative to warfarin in patients with nonvalvular AF and at least 1 additional risk factor who have creatinine clearance (CrCl) >30 mL/min *(Class I; Level B)* - Dabigatran is not recommended in patients with a CrCl <15 mL/min since there is no data for patients with more severe renal failure *(Class III; Level C)* The following were recommendations specific to the use of **rivaroxaban for the prevention of first and recurrent stroke**: - In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), Rivaroxaban 20 mg/d is reasonable as an alternative to warfarin *(Class IIa; Level B)*. - In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), with a CrCl of 15 to 50 mL/min, 15 mg of Rivaroxaban daily may be considered; however, its safety and efficacy have not been established *(Class IIb; Level C)*. - Rivaroxaban should not be used if the CrCl is <15 mL/min *(Class III; Level C)*. The following were recommendations specific to the use of **apixaban** for the prevention of first and recurrent stroke: ● Apixaban 5 mg twice daily is an efficacious alternative to aspirin or warfarin in patients with NVAF who have at least 1 additional risk factor and no more than 1 of the following characteristics: a) Age ≥80 years; b) weight ≤60 kg; c) serum creatinine ≥1.5 mg/dL *(Class I; Level B)*.	*Class (Strength) of Recommendation:* ● *Class 1: Strong benefit over risk* ● *Class IIa: Moderate benefit over risk* ● *Class IIb: Weak benefit over risk* ● *Class III: No benefit* ● *Class III: Harm; Strong risk over benefit* *Level (Quality) of Evidence:* ● *Level A: High-quality evidence from more than 1 RCT, Meta-analyses of high-quality RCTs, One or more RCTs corroborated by high-quality registry studies* ● *Level B:* ○ *B-R: (Randomized) Moderate-quality evidence from 1 or more RCTs, Meta-analyses of moderate-quality RCTs* ○ *B-NR: (Non-Randomized): Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, and Meta-analyses of such studies* ● *Level C:* ○ *C-LD (Limited data): Randomized or nonrandomized observational or registry studies with limitations of design or execution' meta-analyses of such studies; physiological or mechanistic studies in human subjects* ○ *C-EO (Expert opinion): Consensus of expert opinion based on clinical experience*

● Apixaban 2.5 mg twice daily may be considered as an alternative to aspirin or warfarin in patients with NVAF who have at least 1 additional risk factor and ≥2 of the following criteria: a) Age ≥80 years; b) weight ≤60 kg; c) serum creatinine ≥1.5 mg/dL (*Class IIb; Level C).* ● Apixaban should not be used if the CrCl is <25 mL/min *(Class III; Level C).*	
2019 American College of Cardiology/American Heart Association/Heart Rhythm Society Guidelines The AHA/ACC/HRS guidelines on the management of atrial fibrillation recommended the following options of oral anticoagulants (OAC) for patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women: ● Warfarin *(Class 1, Level of Evidence: A)* ● Dabigatran *(Class 1, Level of Evidence: B)* ● Rivaroxaban *(Class 1, Level of Evidence: B)* ● Apixaban *(Class 1, Level of Evidence: B)* As for nonvalvular atrial fibrillation (NVAF), which is AF in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve, the guidelines recommended DOACs over warfarin in DOAC-eligible AF patients without moderate or severe mitral stenosis or a mechanical heart valve *(Class 1, Level of Evidence: A)*.	
European Society of Cardiology (2020) Guidelines for the diagnosis and management of atrial fibrillation ***NOACs in patients with nonvalvular atrial fibrillation*** Recommendations for the prevention of thromboembolic events in atrial fibrillation (AF) ● OAC is **recommended** for stroke prevention in AF patients with CHA_2DS_2-VASc score ≥2 in men or ≥3 in women *(Class 1, Level A)* ● OAC should be **considered** for stroke prevention in AF patients with a CHA_2DS_2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences *(Class IIa, Level B)* ● For stroke prevention in atrial fibrillation patients who are eligible for OAC, NOACs such as Apixaban, Dabigatran, edoxaban and Rivaroxaban are recommended in preference to Vitamin K antagonists such as warfarin (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis) *(Class 1, Level A)* ● In patients on VKAs with low time in international normalized ratio (INR) therapeutic range (e.g. time in therapeutic range (TTR) <70%), recommended options are: - Switching to a NOAC but ensuring good adherence and persistence with therapy *(Class 1, Level B)*	**Class of Recommendation:* ● *Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective* ● *Class II: Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the given treatment or procedure* ○ *Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy* ○ *Class IIb: Usefulness/efficacy is less well established by evidence/opinion.* ● *Class III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.* **Level of Evidence:* ● *Level A: Data derived from multiple randomized*

- Efforts to improve TTR (e.g. education/counseling and more frequent INR checks) *(Class IIa, Level B)* Recommendations for secondary prevention in AF patients after acute ischemic stroke ● In AF patients with an ischemic stroke or transient ischemic attack (TIA), long-term secondary prevention of stroke using OAC is recommended if there is no strict contraindication to OAC use, with a preference for NOACs over VKAs in NOAC-eligible patients *(Class 1, Level A)* ***NOACs in other special populations with nonvalvular atrial fibrillation*** Recommendation for management of AF during pregnancy ● Therapeutic anticoagulation with heparin or VKA according to the stage of pregnancy is recommended for patients with AF *(Class 1, Level C)* Recommendation for management of AF patients with severe chronic kidney disease (CKD) ● In patients with mild-to-moderate CKD (CrCl 30-49 mL/min), the same considerations for stroke risk assessment and choice of OAC may apply (i.e., NOACs such as Apixaban, Dabigatran, edoxaban and Rivaroxaban are recommended in preference to Vitamin K antagonists such as warfarin for OAC-eligible patients) ● The reduced dose regimens of Rivaroxaban, edoxaban and Apixaban are feasible options for severe CKD (CrCl 15-30 mL/ min). However, there are no RCTs that evaluate the efficacy and safety of OAC in this population, and observational data question the benefit of OAC in this patient population. Recommendation for management of AF patients with peripheral artery disease ● Patients with stable vascular disease should be prescribed OAC, unless contraindicated. Those with stable vascular disease (arbitrarily defined as no new vascular event in the past 12 months) should be managed with OAC alone. The CPG did not identify the specific OAC therapy that is preferred for this population. Recommendation for management of AF patients for gastrointestinal disorders ● Overall, NOAC use is associated with an increased risk of gastrointestinal bleeding but in patients treated with Apixaban or Dabigatran 110 mg the risk is similar to warfarin. ● AF patients with liver disease have an increased bleeding risk. Despite the lack of data in RCTs as this subpopulation was excluded from trials, observational studies did not raise concerns regarding the use of NOACs in advanced hepatic disease. ● All NOACs are contraindicated in patients with Child-Turcotte-Pugh C hepatic dysfunction ● Rivaroxaban (but not apixaban or dabigatran) is not recommended in patients in the	*clinical trials or meta-analyses.* ● *Level B: Data derived from a single randomized clinical trial or large non-randomized studies.* ● *Level C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.*

Child-Turcotte-Pugh B or C category Recommendation for management of AF in the elderly and frail ● Evidence from RCTs, meta-analyses, and large registries support the use of OAC in the elderly and frail population. NOACs appear to have a better overall risk–benefit profile compared with warfarin	
2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) in Patients with Atrial Fibrillation NOACs are approved for stroke prevention in 'non-valvular' AF. The term 'non-valvular AF' refers to AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis (usually of rheumatic origin), which were exclusion criteria for all phase III NOAC vs. warfarin trials in AF. ***NOACs in patients with nonvalvular atrial fibrillation*** ● After the indication for OAC is established, NOACs are preferred over VKAs in all NOAC-eligible AF patients. ***NOACs in other special populations with nonvalvular atrial fibrillation*** Recommendation for patients with atrial fibrillation mild or moderate chronic kidney disease (CrCl of >30 mL/min) ● Renal function should preferably be estimated by calculating the creatinine clearance (CrCl) using the Cockcroft-Gault method. Consideration of NOACs *based on renal function* are summarized as follows: ○ In patients with CrCl of ≥50 mL/min to <90 mL/min, the recommended options are: ■ Dabigatran 150 mg/110 mg ■ Rivaroxaban 20 mg ■ Apixaban 5 mg/2.5 mg ○ In patients with CrCl of ≥30 mL/min to <50 mL/min, the recommended options are: ■ Dabigatran 150 mg/110 mg ■ Rivaroxaban 15 mg ■ Apixaban 5 mg/2.5 mg Recommendation for patients with severe chronic kidney disease (CrCl of 15–29 mL/min) ● In view of the individual NOACs pharmacokinetics, dose-reduction criteria, and available evidence from RCTs, the use of either apixaban or edoxaban may be preferable in these patients, but direct head-to-head comparisons are missing. Given the important limitation of observational studies,	None used in the guidelines

further randomized RCT-based data are urgently required for these difficult patients. <u>Recommendation for patients with end-stage CKD (CrCl of <15 mL/min and/or dialysis)</u> ● The efficacy and safety of NOACs in patients with end-stage renal dysfunction is unclear and subject to ongoing studies. ● Given the lack of strong evidence, the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization. Patients need to be informed of the lack of data as well as the 'off label' character of whichever strategy or drug is chosen, including the uncertain benefit and the increased risk of complications. <u>Recommendation for patients with liver disease</u> ● Recent registry data indicate that even in patients with AF and various degrees of accompanying liver disease, NOACs may be associated with a lower incidence of bleeds and overall mortality. The NOAC use recommendation in liver disease based on Child-Turcotte-Pugh score is as follows: ○ All NOACs are contraindicated in patients with hepatic disease associated with clinically manifest coagulopathy and clinically relevant bleeding risk (i.e., Child Class C cirrhosis) ○ Rivaroxaban should not be used in AF patients with Child B liver cirrhosis due to a >2-fold increase in drug exposure in these patients ○ Dabigatran, apixaban, and edoxaban may be used with caution in patients with Child B cirrhosis ○ Normal dose of NOACs may be used for Child A cirrhosis <u>Recommendation for patients in advanced age and frailty</u> ● NOACs are preferred over VKAs or no OAC intervention among older patients <u>Recommendation for patients in high- and low body weights</u> ● *High Body Weight* ○ For patients with BMI of <40 kg/m^2, any of the NOACs may be used. ○ For patients with BMI of ≥40 kg/m^2, NOACs should be used with caution. Plasma level measurements with any of the NOACs or conversion to VKA therapy may be reasonable to be considered. ● *Low Body Weight* ○ For patients with BMI of 12.5 to 17.5 kg/m^2, dose reduction is required for apixaban or edoxaban, but not for rivaroxaban or dabigatran. Factor Xa inhibitors (i.e., apixaban or edoxaban) may be the preferred choice for patients ≤60 kg due to its consistent efficacy	

and safety for both underweight patients and overall study population. If on dabigatran or rivaroxaban, plasma level measurements should be considered. <u>Recommendation for patients with thrombocytopenia</u> ● In addition to the absolute number of platelets the dynamics of the platelet count (bulleted list below), the underlying reason for thrombocytopenia, and special risk factors (including the likelihood of dysfunctional platelets as well as other coagulation abnormalities) need to be considered. Given the lack of a large evidence base for guidance, the decision for NOAC treatment needs to follow an individualized, team-based approach including the patient and his/her needs and expectations. ○ Patients with an absolute platelet count of >50,000 µl should proceed NOAC therapy with caution. Close clinical and platelet count monitoring is advised. ○ Patients with an absolute platelet count of >20,000 to 50,000 µl should proceed NOAC therapy with great caution. Patients should undergo very close clinical and platelet count monitoring. Half-dose NOAC should be considered especially for those with ≥1 bleeding risk factor. ○ Patients with absolute platelet count of <20,000 µl, NOAC therapy should be avoided due to risk of spontaneous bleeding <u>Recommendation for patients with atrial fibrillation and malignancy</u> ● Overall, anticoagulation with NOACs may appear as a valid option in patients with AF and malignancy based on the few available data from RCTs as well as using extrapolations from cancer-related VTE treatment. Antithrombotic therapy in patients with AF suffering from a malignancy needs a dedicated interdisciplinary team approach. ○ The recommended choice of anticoagulants among patients with atrial fibrillation and malignancy are: (1) NOACs (unless opted against by multidisciplinary team such as for a patient with active GI cancer); (2) low molecular weight heparin (LMWH); and (3) VKA.	

Appendix 2. Standard dose and special considerations on dosing of DOACs

	DABIGATRAN	RIVAROXABAN	APIXABAN
Standard dose	**150 mg twice daily**	**20 mg once daily**	
Lower dose	**110 mg twice daily** ● Age ≥80 years ● Age ≥75 years (PHL FDA product insert) ● Concomitant use of verapamil, or ● Increased bleeding risk		
Reduced dose		**15 mg once daily** ● CKD patients with CrCl of 15 - 49 mL/min	
For NVAF patients with thrombocytopenia with platelet count: 20,000 - 50,000 / ul	Consider half-dose NOAC specially if ≥ 1 bleeding risk factor		

Appendix 3. Appraisal of included network meta-analyses using the Jansen tool

Table A2. Critical Appraisal of Antza et al. 2019

Domain	Answer	Remarks
Relevance	Sufficient	The study matched the PICO RQ of the assessors
Evidence base used	Weakness	Weak due to limitations in the literature search, no reporting of baseline patient characteristics, and no explanation of the imbalance in treatment effect modifiers
Analysis	Weakness	No reported actions to minimize the bias due to differences in treatment effect modifiers, or subgroup analysis or meta-regression analysis was performed
Reporting quality and transparency	Weakness	Although almost all other elements were included in the report, the study did not report the impact of patient characteristics to the pooled outcomes
Conclusion/Interpretation	Strength	The study conclusion was in line with the findings in the analysis and there was proper admission of its various limitations
Conflict of interest	Strength	No identified conflict of interest
OVERALL CREDIBILITY	**Insufficient due to weaknesses in the evidence base used, analysis, and reporting quality of the study.**	

Table A3. Critical Appraisal of Lopez-Lopez et al. 2017

Domain	Judgment	Remarks
Relevance	Sufficient	Matched our PICO and interventions studied are used in the treatment of the condition in the local setting.
Evidence base used	Neutral	Identified all relevant trials, interventions formed one connected network, no selective reporting, systematic differences in treatment effect modifiers were identified before discussion of results

		However, studies with high risk of bias for blinding of participants and staff (open label trial) were also included
Analysis	Strength	Preserved within-study randomization, minimized the bias due to imbalance in the distribution of treatment effect modifiers, and provided a valid rationale for using a fixed-effects model
Reporting quality and transparency	Neutral	Reported almost all key elements except for the individual results of the 23 included RCTs
Conclusion/Interpretation	Strength	Overall results were coherent across the study and conclusions included the limitation of the study
Conflict of interest	Strength	Potential conflicts of interest were addressed properly
OVERALL CREDIBILITY	**Somewhat sufficient** because of strong evidence in relevance analysis and interpretation but weak evidence in reporting quality and neutral strength in terms of credibility.	

Table A4. Critical Appraisal of Hao Jin et al. 2020a (Different renal function levels)

Domain	Judgment	Remarks
Relevance	Sufficient	The PICO is in line with the identified research question of the assessors
Evidence base used	Neutral	Although the study included an open-label clinical trial indicating possibility of performance bias, the NMA identified the important treatment effect modifiers across the included studies hence, the judgment.
Analysis	Weakness	There was a lack of attempt to minimize bias due to differences in treatment effect modifiers or analyze the effect of treatment effect modifiers present among studies
Reporting quality and transparency	Strength	All necessary information were presented in the study
Conclusion/Interpretation	Weakness	The authors did not specify which analysis results (i.e. if from SUCRA ranking, HR results, or pairwise results) was used for the study's conclusion

Conflict of interest	Strength	There were no conflicts of interest
OVERALL CREDIBILITY	**Insufficient** due to weakness in terms of analysis and interpretation	

Table A5. Critical Appraisal of Deng et al. 2020 (Elderly >75 years)

Domain	Judgment	Remarks
Relevance	Sufficient	The study matches with the PICO of interest for the clinical appraisal of DOACs for AF patients with existing conditions (i.e. elderly).
Evidence base used	Weakness	The study authors identified differences across studies in terms of length of follow-up, age, attrition, and sex in the table of baseline characteristics. However, these were deemed inadequate since the distribution of important treatment effect modifiers such as stroke risk (CHADSVASC), bleeding risk, across studies was not detailed prior to the discussion of the results.
Analysis	Weakness	Heterogeneity was not further discussed nor represented through data analysis and the methods used for assessing heterogeneity were unclear. No subgroup analysis or meta-regression were conducted to minimize the bias due to the imbalance in the distribution of treatment effect modifiers.
Reporting quality and transparency	Weakness	Lack of accounting/analysis for differences in patient characteristics across the different studies
Conclusion/Interpretation	Strength	Overall results were coherent across the study and conclusions included the limitation of the study
Conflict of interest	Strength	No conflict of interest
OVERALL CREDIBILITY	**Insufficient** because of weaknesses in the ff. domains: credibility (missing important treatment effect modifiers), analysis (no attempt at minimizing bias through meta-regression), and reporting quality and transparency (nonreporting of the impact of important patient characteristics on the results of the NMA)	

Table A6. Critical Appraisal of Hao Jin et al. 2020b (Heart failure)

Domain	Judgment	Remarks

Relevance	Sufficient	SR is applicable to our setting because it matches our PICO and the interventions studied are used in the treatment of the condition in the local setting.
Evidence base used	Neutral	Due to the inclusion of an open-label clinical trial indicating performance bias, and discussion on the differences in important treatment effect modifiers between the studies (Table 3).
Analysis	Strength	Effects of the differences in pre-specified confounders and whether a fixed-effect or random-effect model is more appropriate for the analysis were investigated.
Reporting quality and transparency	Strength	All relevant data were included in the manuscript
Conclusion/Interpretation	Weakness	Discussion and conclusion parts were unclear due to varying results and conclusions
Conflict of interest	Strength	No conflict of interest
OVERALL CREDIBILITY	**Sufficient**	

Table A7. Critical Appraisal of Hao Jin et al. 2021 (Diabetes mellitus)

Domain	Judgment	Remarks
Relevance	Sufficient	The PICO included in the review, and context of the review are relevant to the current research question.
Evidence base used	Neutral	Identified all relevant trials, interventions formed one connected network, no selective reporting, systematic differences in treatment effect modifiers were identified before discussion of results. However, an open-label clinical trial was included which may indicate performance bias.
Analysis	Strength	Preserved within-study randomization, study investigated the effects of the differences in pre-specified confounders and investigated whether a fixed-effect or random-effect model is more appropriate for the analysis.

Reporting quality and transparency	Strength	All necessary information were presented in the study
Conclusion/Interpretation	Weakness	Conclusions were not coherent with the reported results.
Conflict of interest	Strength	No potential COI.
OVERALL CREDIBILITY	**Sufficient**	

Appendix 4. Appraisal of the included observational studies using the ROBINS-I tool

Table A8. Critical Appraisal of Lip et al. 2018

Domain	Answer	Remarks
Bias due to confounding	Moderate	There were residual confounders not considered and no further detailing on the switch / discontinuation date.
Bias in selection of participants into the study	Low	The authors made sure to clearly outline the characteristics of patients to be included in the study, as well as the data on the follow-up.
Bias in classification of interventions	Low	Interventions were clearly defined and identified throughout the study.
Bias due to deviations from intended interventions	Low	No probable deviations in the intended intervention group.
Bias due to missing data	Low	No missing data from the start to analysis date.
Bias in measurement of outcomes	Low	Low risk of bias due to study design
Bias in selection of the reported result	Low	Authors were consistent in using the outcome measurements, as well as in the reporting of the results in different subgroups.
OVERALL BIAS	Low / Moderate/ Serious / Critical / NI	

Table A9. Critical Appraisal of Staerk et al. 2018

Domain	Judgment	Remarks
Bias due to confounding	Serious	At least one known important domain was not appropriately measured (NSAID or alcohol abuse) or not controlled for (body weight, haemoglobin, international normalized ratio, serum creatinine and CrCl).
Bias in selection of participants into the	Low	All participants who would have been eligible for the target trial were included in the study

study		and for each participant, start of follow up and start of intervention coincided.
Bias in classification of interventions	Moderate	The study is a database cohort study and study authors may not have been able to capture differences/imbalances in past interventions especially for those with existing conditions
Bias due to deviations from intended interventions	Low	No deviations since follow-up period was censored upon date of shift or discontinuation.
Bias due to missing data	Low	Data were reasonably complete
Bias in measurement of outcomes	Low	Outcomes can be measured objectively
Bias in selection of the reported result	Moderate	Study only reported absolute risk and absolute risk reduction rather than relative risks.
OVERALL BIAS	Low / Moderate / Serious / Critical / NI	