Technology Guidance

Non-vitamin K antagonist oral anti-coagulation agents (NOACs)

for preventing stroke and systemic embolism in non-valvular atrial fibrillation

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Rivaroxaban 15 mg and 20 mg tablets, and apixaban 2.5 mg and 5 mg tablets for preventing stroke and systemic embolism in patients with NVAF and:
  - CHA_2DS_2-VASc score of 1 or more for men; and
  - CHA_2DS_2-VASc score of 2 or more for women.

Rivaroxaban and apixaban should not be used in patients with valvular AF (especially rheumatic mitral stenosis), or patients with prosthetic heart valves.

Subsidy status

Rivaroxaban 15 mg and 20 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication.

Apixaban 2.5 mg and 5 mg tablets are recommended for reclassification from MAF to the MOH Standard Drug List (SDL).

SDL subsidy or MAF assistance do not apply to any strengths of dabigatran.

Updated: 1 Jul 2022

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of non-vitamin K antagonist oral anti-coagulation agents (NOACs – apixaban, rivaroxaban, and dabigatran) for preventing stroke and systemic embolism in NVAF in August 2016. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with the Ministry of Health NOACs Working Group members. Published clinical and economic evidence was considered in line with the registered indications for each NOAC agent.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

1.4. Manufacturers of apixaban and dabigatran, which were not recommended for subsidy at the August 2016 meeting due to unacceptable cost effectiveness or budget impact, were invited to submit revised price proposals, which the Committee considered in April 2018.

1.5. Manufacturers of apixaban and rivaroxaban, which were listed on MAF, were invited to submit price proposals for their products to be reclassified to SDL, which the Committee considered in November 2021.

Clinical need

2.1. In 2016, the Committee recognised that the prevalence of AF and the risk of stroke related to AF both increase as the population ages. Clinicians confirmed that NOACs and warfarin were first-line treatment options in local practice for preventing stroke and systemic embolism in people with NVAF.

2.2. In August 2021, the Committee noted that there had been a significant increase in prescribing and use of NOACs in public healthcare institutions since rivaroxaban and apixaban were subsidised in 2017 and 2018, respectively.

Clinical effectiveness and safety

3.1. At the meeting in 2016, the Committee agreed that warfarin was the appropriate comparator for NOACs for people with NVAF who required anticoagulation.

3.2. The Committee acknowledged that warfarin, an effective treatment to prevent stroke, was associated with frequent drug-drug interactions, dietary restrictions, and the need for regular monitoring.

3.3. The Committee considered the clinical evidence from pivotal trials of the NOACs (ARISTOTLE [apixaban], RE-LY [dabigatran] and ROCKET-AF [rivaroxaban]) versus warfarin. It noted that apixaban (5 mg twice daily, 2.5 mg twice daily in some patients), dabigatran (150 mg twice daily and 110 mg twice daily), and rivaroxaban (20 mg daily, 15 mg daily in some patients) were as effective as warfarin in preventing stroke and systemic embolism.

3.4. In particular, the Committee noted better safety experienced with NOACs compared to warfarin with respect to reducing intracranial haemorrhage (ICH). Although the absolute risk reductions in ICH were small (ranging from 0.2% to 0.5% per year, or two to five ICH events avoided for every 1,000 patients treated per year), the Committee concurred with the clinical experts that this benefit was clinically significant because of the high morbidity and mortality associated with ICH.

3.5. The Committee noted the lack of head-to-head trials comparing all three NOACs. It noted that:

- the population in the study comparing rivaroxaban with warfarin (ROCKET-AF) had a higher mean baseline CHADS2 score, and a higher proportion of patients had comorbidities (heart failure, diabetes, and hypertension) than the population in RE-LY or ARISTOTLE; and
- a lower proportion of patients in the apixaban study (ARISTOTLE) took concomitant aspirin compared to those in RE-LY or ROCKET-AF.

3.6. The Committee considered that the differences in baseline characteristics between study populations could lead to difficulties in interpreting the results of any indirect treatment comparison.

3.7. The Committee concluded that the NOACs could be considered comparable with no clinically important differences in outcomes.

3.8. In August 2021, the Committee reviewed local real-word data which showed patient outcomes data were consistent with clinical trial findings, with the use of NOACs leading to improved patient outcomes including reduced rates of stroke, systemic embolism, mortality, intracranial haemorrhage and gastrointestinal bleeding compared to warfarin.

Cost effectiveness

4.1. ***Cost-minimisation among the NOACs***
Given all three NOACs were considered comparable, the Committee agreed a cost-minimisation approach was appropriate for selecting the lowest-priced NOAC for subsidy consideration. It noted at the 2016 meeting that rivaroxaban, which had the lowest cost, was the most cost-effective option.

4.2. In April 2018, following a revised price proposal for apixaban, the Committee agreed the cost of apixaban was reasonable and could be considered an acceptable use of healthcare resources. Dabigatran remained at a higher cost compared with rivaroxaban and apixaban and was the least cost-effective option.

4.3. In November 2021, following price proposals from the manufacturers for apixaban and rivaroxaban to be reclassified from MAF to SDL, the Committee noted that apixaban, was the most cost-effective NOAC based on a cost-minimisation approach. At the proposed price, the Committee considered that a SDL listing was appropriate to benefit more patients and improve outcomes.

4.4. ***Cost-effectiveness of NOACs versus warfarin***
The cost-effectiveness model compared the NOACs to warfarin for stroke prevention in NVAF over a lifetime period. The Committee noted that at the prices proposed by the manufacturers, the base case incremental cost-effectiveness ratio (ICER) for NOACs compared with warfarin would fall in the range of less than $15,000 per quality-adjusted life-year (QALY) gained. It agreed that the ICERs were within an acceptable range of cost-effectiveness in sensitivity analyses. The Committee accepted that NOACs were a cost-effective treatment option compared with warfarin for stroke prevention in Singapore.

Estimated annual technology cost

5.1. In April 2018, the Committee estimated around 4800 people in Singapore would benefit from government assistance for rivaroxaban and apixaban. The annual cost impact was estimated to fall in the range of SG$3 million to SG$5 million at the prices proposed by the manufacturers. Given the ageing population, the local prevalence of AF, and the risk for AF-associated stroke increasing with age, the Committee expected that patient numbers would likely increase over time.

5.2. The Committee acknowledged the uncertainty surrounding the annual cost impact calculations and noted that the true rate of people switching from warfarin to a NOAC, or from one NOAC to another was difficult to accurately predict. In November 2021, the Committee considered that the annual cost impact could increase to more than SG$5 million if apixaban was listed on SDL for all registered indications.

Additional considerations

6.1. The Committee agreed that NOACs should not be used in people with valvular AF (especially rheumatic mitral stenosis), or people with prosthetic heart valves, given they have not been well-studied in clinical trials. The Committee also considered that inappropriate or off-label use of NOACs was currently low and not expected to increase significantly following SDL listing.

Recommendations

7.1. Based on evidence presented in 2016, the Committee recommended rivaroxaban 15 mg and 20 mg tablets be listed on the MAF for preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) who meet certain clinical conditions, given its superior reduction in ICH and acceptable cost-effectiveness at the price proposed by the manufacturer, compared with warfarin.

7.2. In April 2018, the Committee also recommended apixaban 2.5 mg and 5 mg tablets be listed on the MAF in line with the same clinical criteria as rivaroxaban, following an acceptable price reduction offered by the manufacturer.

7.3. In November 2021, the Committee recommended apixaban 2.5 mg and 5 mg tablets be reclassified from MAF to SDL. At the price proposed by the manufacturer, the Committee recommended rivaroxaban 15 mg and 20 mg tablets be retained on the MAF in line with the existing clinical criteria.

VERSION HISTORY

Guidance on non-vitamin K antagonist oral anti-coagulation agents (NOACs) for preventing stroke and systemic embolism in non-valvular atrial fibrillation

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1.	**Publication of guidance (rivaroxaban listed on MAF)**	
	Date of Publication	3 May 2017
2.	**Amendment to redact cost information**	
	Date of Publication	5 Feb 2018
3.	**Guidance updated to extend MAF listing to apixaban**	
	Date of Publication	1 Oct 2018
4.	**Guidance updated to reclassify apixaban from MAF to SDL**	
	Date of Publication	1 Jul 2022

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 25 August 2016, 18 August 2017, 26 April 2018, 18 August 2021 and 9 November 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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