Driving better decision-making in healthcare

Novel oral anticoagulants (NOACs)

*for the prevention of 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 15mg and 20mg film-coated tablets for preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and
  - CHA₂DS₂-VASc score of 1 or more for men, and
  - CHA₂DS₂-VASc score of 2 or more for women.

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

**Subsidy status**

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

Subsidies do not apply to two other novel oral anticoagulants (NOACs), apixaban and dabigatran.

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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 NOACs for the prevention of stroke and systemic embolism in NVAF. The Agency for Care Effectiveness conducted the evaluation, with inputs from the Ministry of Health NOACs Working Group members.

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
   - 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.

Clinical Need

2.1 The Committee recognised that:
   - the prevalence of AF is growing as the population ages and the risk of stroke related to AF increases with age; and
   - NOACs and warfarin were considered first-line treatment for the prevention of stroke and systemic embolism in people with NVAF.
Clinical effectiveness and safety

3.1 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 (5mg twice daily, 2.5 twice daily in some patients), dabigatran (150mg twice daily and 110mg 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 the benefit of better safety conferred by all the NOACs over warfarin in reducing intracranial hemorrhage (ICH). Although the absolute risk reductions in ICH were small (ranging from 0.2% to 0.5% per year, or about 2 to 5 ICH events avoided for every 1,000 patients treated per year), the Committee concurred with the clinical experts that this benefit was clinically significant, due to the high morbidity and mortality associated with ICH.

3.5 The Committee noted the lack of head-to-head trials comparing all 3 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;
- there was a lower proportion of patients in the apixaban study (ARISTOTLE) taking concomitant aspirin compared to those in RE-LY or ROCKETH-AF.

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

3.7 Therefore, the Committee concluded that the NOACs could be considered comparable with no clinically important differences in outcomes.
Cost effectiveness

Cost-minimisation among the NOACs

4.1 Given all 3 NOACs were considered comparable, the Committee agreed a cost-minimisation approach was appropriate to select the lowest priced NOAC for subsidy consideration. It noted that the manufacturer of rivaroxaban had offered the lowest price. As a result, the Committee did not recommend the other two NOACs (apixaban and dabigatran) for subsidy given their higher cost prices compared with rivaroxaban.

Cost-effectiveness of NOACs versus warfarin

4.2 The cost-effectiveness model compared the NOACs to warfarin for stroke prevention in NVAF over a lifetime period. The Committee noted that at a selling price of $3.08 per day, the base case incremental cost-effectiveness ratio (ICER) for NOACs compared with warfarin would fall in the range of less than SGD 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 The Committee estimated that around 3,500 people in Singapore would benefit from Government assistance for rivaroxaban. The cost impact was estimated to fall in the range of $3 to $5 million per year in the near term. It was noted that, owing to the ageing population, the prevalence of AF and the risk for stroke with AF increasing with age, the patient numbers would increase over time.

5.2 The Committee also noted that the cost estimates were based on various assumptions. The exact rate of people switching from warfarin, aspirin or no treatment to NOAC can be difficult to predict as clinical knowledge evolves and new technologies are introduced.
Additional considerations

6.1 The Committee agreed that the NOACs should not be used in people with valvular AF (especially rheumatic mitral stenosis), or people with prosthetic heart valves, given these people have not been well-studied in clinical trials. In view of the potential for inappropriate use of NOACs, the Committee recommended listing on the MAF rather than on the Standard Drug List.

Recommendation

7.1 The Committee recommended rivaroxaban 15mg and 20mg film-coated tablets for listing on the MAF for preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) who meet certain clinical conditions, on the basis of its superior reduction in ICH and acceptable cost-effectiveness at the price proposed by the manufacturer compared with warfarin.

7.2 Apixaban and dabigatran were not recommended for subsidy due to their higher cost prices compared with rivaroxaban that were not justified by the benefits they provide over rivaroxaban.

About the Agency

The Agency for care effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. When using the guidance, the responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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