Record of the Cardiovascular Advisory Committee Meeting held on 8 June 2022

Cardiovascular Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Cardiovascular Advisory Committee meeting; only the relevant portions of the meeting record relating to Cardiovascular Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Cardiovascular Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present:
Prof Tim Stokes (Chair)
Dr Andrew Aitken
Dr Dean Boddington
Prof Jennifer Martin
Prof Mark Webster
Dr Mayanna Lund
Dr Richard Medlicott
Dr Samuel Whittaker

Apologies:
Dr John Elliott

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Rivaroxaban for the prevention of major cardiovascular events	**Medium Priority**
• Empagliflozin for the treatment of congestive heart failure (CHF) with reduced ejection fraction (HFrEF), as add-on to CHF treatments	**High Priority**
• Prasugrel for the treatment of acute coronary syndrome (ACS)	**High Priority**

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Cardiovascular Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.3. The Cardiovascular Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cardiovascular Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cardiovascular Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Cardiovascular disease that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Cardiovascular disease that differ from the Cardiovascular Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Cardiovascular Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Cardiovascular disease.

4. Welcome and introduction

The committee welcomed Dr Mayanna Lund as a new member to the committee.

5. Record of Cardiovascular Advisory Committee meeting held Wednesday, May 8, 2019

5.1. The Advisory Committee reviewed the minutes of the Cardiovascular Advisory Committee meeting held on May 8, 2019 and agreed that the minutes be accepted.

5.2. The Chair noted that he did not attend the PTAC meeting held in February 2022 at which the application for empagliflozin for the treatment of heart failure was reviewed.

5.3. A member noted that they had acted as discussion lead for the application of empagliflozin for the treatment of heart failure at the February PTAC meeting.

6. Previous action points/recommendations made

None noted

7. Correspondence and Matters Arising

7.1. Correspondence was tabled from the Chair of the Cardiac Society of Australia and New Zealand (CSANZ) NZ Region, addressed to Professor Mark Weatherall Chair PTAC dated 16 July 2021. The correspondence requested that LDL cholesterol targets in special authority criteria for funded LDL cholesterol therapies be lowered to align with the latest CSANZ guidelines. This was noted by the Committee and referred to be part of the discussion in the Therapeutic Group Review.

7.2. Correspondence was tabled from the Heart Foundation addressed to the Medical Director Pharmac dated 10 June 2021. The correspondence requested that Pharmac review improved access to Fixed Dose Combination (FDC) hypertensive medicines. This was noted by the Committee and referred to be addressed as part of the Therapeutic Group Review.

8. Therapeutic Group and NPPA Review

Overall Summary

The Committee noted the significant increase in medicine costs for the group since the last review in particular the increase in spend on antithrombotic agents.

Alpha-adrenoreceptor blockers

8.1. The Committee noted that doxazosin remains the most commonly used agent in this category representing 87% of scripts and 63% of expenditure. The Committee also noted the delisting of terazosin in August 2021

8.2. The Committee noted that it appeared that the sole use of prazosin was for the management of PTSD-associated nightmares and it was no longer used as a cardiovascular agent.

Agents Affecting the Renin-Angiotensin System

8.3. The Committee noted the trend for greater utilisation of Angiotensin II receptor blockers (ARB) over Angiotensin Converting Enzyme inhibitors (ACEi), which was considered likely in part to the restrictions placed on cilazapril prescribing.

8.4. The Committee noted a prescriber preference for candesartan in the ARB category, with some reports of nightmares possibly attributable to the use of losartan. The Committee noted a possible supply risk with only two ARB agents listed and recommended that Pharmac investigate the possibility of listing a third ARB option.

8.5. The Committee noted the movement of patients to losartan with hydrochlorothiazide following the delisting of cilazapril with hydrochlorothiazide. The Committee considered that it would be desirable to have listed an alternate to the hydrochlorothiazide combination and recommended that Pharmac explore combination anti-hypertensive products that include other thiazide like agents such as indapamide and dihydropyridine calcium channel blockers. The Committee also noted that there can be titration difficulties with combination products leading to inappropriate dosing, however it was recognised that there is a strong need for combination therapies and there are pro-equity benefits to such medicines.

8.6. The Committee noted that it was not important whether combination medicines contained either an ACEi or ARB as the Renin-Angiotensin System agent.

8.7. The Committee noted the continued growth in the use of sacubitril with valsartan, observing that there was higher use at a younger age in Māori patients compared to non-Māori. It was considered that the need to make frequent visits to primary care is a limiting factor to higher utilisation by Māori relative to need. The Committee considered that there was potential for additional growth in the use of sacubitril with valsartan, however access to echocardiography assessment may have limited uptake. The Committee noted that the treatment of heart failure had become complicated, with it being difficult and time consuming to optimise an individual patient's treatment regime. The Committee indicated that the current special authority criteria for sacubitril with valsartan are still appropriate.

8.8. The Committee noted that there had been considerable communication to the health sector regarding the planned discontinuation of cilazapril and the need for prescribers to transition patients and that prescribers were slowly moving patients to alternative agents. It was considered that the proposed listing of ramipril would provide another good alternative for the remaining cilazapril patients to transition to.

Antiarrhythmics

8.9. The Committee noted that there had been limited growth in the use of antiarrhythmic agents with the exception of flecainide, which accounts for 62% of cost within the category, noting that a competitive process leading to a brand change in July 2019 had reduced the total cost of this agent. The Committee noted that flecainide is predominantly driven by cardiologist prescribing with increased use of echocardiography leading to more confident use of the agent. The Committee noted that atrial fibrillation is increasing in the population, leading to increased demand.

Antihypotensives

8.10. The Committee noted the increased use of midodrine, which is the only agent in this category, attributing this to an ageing population.

Beta-adrenoreceptor Blockers

8.11. The Committee noted that several agents in this category have been delisted since the last committee meeting (celiprolol, pindolol, timolol), due to difficulties securing long-term supply combined with low patient numbers. The Committee noted that the ease of use of bisprolol fumarate had contributed to its increased use in deference to agents such as carvedilol.

Calcium Channel Blockers

8.12. The Committee noted the continued growth in the utilisation of calcium channel blockers, and also noted that felodipine and diltiazem are the most frequently prescribed agent in this category. The Committee noted that there had been considerable difficulty in maintaining supply of both diltiazem and nifedipine following market withdrawal by respective suppliers. Members considered it important that a full range of presentations of these agents is maintained.

8.13. The Committee reviewed data showing the prescribing of combinations of anti-hypertensive agents and noted that a significant number of patients are currently prescribed separate ACE/ARB + calcium channel blockers. Members recommended that it would be appropriate to investigate the potential to fund a combination product which covered these agents.

Centrally acting agents

8.14. The Committee noted that clonidine, which represents the majority of volume and cost in this category, is mainly used off-label in the treatment of mental health conditions (e.g., ADHD) rather than for the treatment of hypertension.

Diuretics

8.15. The Committee noted an increase in the use of the potassium sparing diuretics spironolactone and eplerenone, and the growth in the use of chlortalidone and indapamide in the thiazide and related diuretic category. Members considered that the latter may be due to a greater awareness of greater efficacy for these agents over bendroflumethiazide.

Lipid-Modifying Agents

8.16. The Committee noted the decline in the use of the statin simvastatin and the growth in the use of atorvastatin. Members considered this decline was due to the greater efficacy of atorvastatin, and that it would likely continue.

8.17. The Committee noted the listing of the statin rosuvastatin in December 2021. Members considered that current estimates of uptake may be low, that the special authority criteria implemented were appropriate, and recognised the need to ensure access was targeted to those of greatest need due to the relative cost of rosuvastatin versus other funded statins. However, Members considered that the presence of special authority criteria does have the effect of dampening demand.

8.18. The Committee noted that the use of ezetimibe and fibrates have gone out of favour in Australia, Members also considered that the role of ezetimibe was less relevant now that the high-potency statin rosuvastatin was funded. The Committee also considered that there remains a significant clinical need for a PSCK9 inhibitor for patients with hyperlipidaemia that cannot be adequately controlled with existing

funded lipid modifying agents. Members requested that regional variation in the use of fibrates be explored.

Nitrates

8.19. The Committee noted that the use of nitrates has been very steady with an increase in the use of oral spray and a decline in the use of patches.

Sympathomimetics

8.20. The Committee noted that the community use of sympathomimetic agents has declined over the last 5 years.

Vasodilators

8.21. The Committee noted the significant increase in the use of endothelin receptor antagonists (ERA). Members considered that these agents would be more accessible through the special authority structure rather than the PAH panel. It was noted that the latest evidence supported the up-front use of dual therapy in the treatment of PAH and that ambrisentan has become the preferred (ERA) agent. The Committee noted that it was challenging to formulate appropriate special authority criteria for PAH agents due to the inherent complexity of multi-agent treatment regimens and patients' clinical presentations.

Antithrombotics

8.22. The Committee noted the increase in the use of rivaroxaban and the relatively stable use of dabigatran. Members considered rivaroxaban has a favourable patient usability profile whereas dabigatran use is limited by gastrointestinal side effects with approximately 25% of patients being intolerant with these. The Committee noted that internationally apixaban is a favoured agent in this category and had a good safety profile in terms of bleeding. The Committee considered that there wasn't a pressing requirement for a reversal agent to rivaroxaban. Members reported that in their clinical experience the requirement for reversal agents was very rare.

9. Section Two: Review of Funding Applications

9.1. The Committee considered that ranolazine, which had recently been declined by Pharmac for funding, remains a good option for those patients for which a revascularisation procedure is not feasible.

9.2. The Committee considered that there is still a strong clinical need for access to ivabradine. Members noted that it is often the medication of last resort for inappropriate sinus tachycardia (IST) and considered it could be very effective. It was also noted that there had been recent interest in using ivabradine to treat post-Covid postural tachycardia syndrome (PoTS), although at this stage there is limited evidence. Members also noted that ivabradine is useful for heart failure patients who still have a high heart rate despite being on maximal beta-blocker therapy.

9.3. The Committee noted the recent PTAC consideration of Polypill with regard to an equity consideration. Members considered that a polypill would likely result in higher adherence in certain patient populations, with resulting health benefits.

10. Rivaroxaban for the prevention of major cardiovascular events

Application

10.1. The Advisory Committee reviewed the application for rivaroxaban for the first-line treatment of Peripheral Artery Disease (PAD) with or without Coronary Artery Disease (CAD).

10.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Advisory Committee **recommended** that rivaroxaban for the treatment of PAD with or without CAD be listed with a **medium priority** within the context of treatment of cardiovascular disease, subject to the following Special Authority criteria:

INITIAL APPLICATION
Applications from any relevant practitioner. Approvals valid for 12 months.
All of the following:

1. Patients must have a confirmed diagnosis of peripheral artery disease (PAD) and must have one or more of the following high-risk factors:
    - 1.1. Concomitant coronary artery disease; or
    - 1.2. Confirmed diagnosis of PAD in two or more vascular beds; or
    - 1.3. Diagnosed heart failure (left ventricular ejection fraction greater than or equal to 30% but less than 50%) ; or
    - 1.4. Diagnosed kidney disease classified by an eGFR 15-60ml/min; or
    - 1.5. Diabetes Mellitus and at least one of the following:
        - 1.5.1. age 60 years or more; or
        - 1.5.2. concomitant microalbuminuria; or
        - 1.5.3. Patient is of Māori or Pacific Island descent; and
2. Patient must be prescribed rivaroxaban 2.5 mg twice daily in combination with 100 mg aspirin once daily; and
3. Patient must not be on Dual Anti-Platelet therapy

RENEWAL:
Applications from any relevant practitioner. Approvals valid for 12 months.
The treatment remains appropriate, and the patient is benefiting from treatment.

10.4. The Advisory Committee considered the high health need for the PAD with or without CAD patient population, and the lack of currently funded effective treatment options in making this recommendation.

Discussion

Māori impact

10.5. The Committee noted that Māori experience peripheral artery disease (PAD) at a reported rate of 269 per 100,000 compared to the non-Māori population's reported rate of 438 per 100,000. The Committee noted that Māori disproportionately experience death from stroke and have higher incidences of hospitalisation from cardiovascular disease, ischemic heart disease, and lower limb amputation as a result of arterial disease. The Committee considered that the burden of PAD in the Māori population is likely greatly underdiagnosed, and significantly higher than reported.

Discussion

10.6. The Committee noted a supplier application for the use of rivaroxaban 2.5mg for the first-line treatment PAD with or without coronary artery disease (CAD). The

Committee noted that PTAC considered this application in February 2021 where it was recommended for funding with a low priority for patients with PAD with or without CAD based on robust evidence of benefit, high health need for the requested population group, manageable bleeding risk with rivaroxaban, the need to fund a reversal agent if rivaroxaban were to be funded for this patient population, concern regarding the appropriate dosing for patients in the New Zealand context, and the Māori and Pacific population in New Zealand having a higher absolute risk of major adverse cardiac events (MACE) due to the presence of comorbidities such as obesity.

10.7. The Committee noted that PTAC recommended that advice be sought from the Cardiovascular Advisory Committee regarding identification of high-risk population groups, and appropriate Special Authority criteria.

10.8. The Committee noted that that PAD and CAD are clinical presentations of atherosclerosis, which is a progressive condition affecting the large and medium-sized arteries. The Committee noted that PAD and CAD develop in different vascular beds but can frequently coexist in patients with multi-vessel disease. The Committee also noted that the main risk factors for atherosclerosis include age, smoking, a family history of heart disease, unhealthy diet, and lack of physical activity. The Committee noted that PAD mainly affects the lower extremities and sometimes the carotid arteries, and can include asymptomatic and symptomatic disease, the latter including intermittent claudication, chronic limb ischemia, and acute limb ischemia, which can lead to gangrene and amputation. The Committee noted that the unstable plaques in atherosclerotic disease can rupture and trigger acute atherothrombotic events because of embolus formation, such as myocardial infarction, stroke, cardiovascular death, and acute limb ischemia.

10.9. The Committee noted that PAD is broadly defined as a progressive stenosis or occlusion of any of the arteries except the coronary and intracranial arteries, and that patients with PAD are more than six times more likely to have a heart attack or stroke, and 13 times more likely to have lower limb amputation. The Committee noted that CAD is caused by atherosclerosis of the coronary arteries, which leads to a restriction of blood flow to the heart and can be categorised into acute coronary syndrome or chronic CAD. Acute coronary syndrome refers to a range of conditions associated with a sudden, reduced blood flow to the heart and includes unstable angina and acute myocardial infarction, and chronic CAD includes patients with stable angina and patients who have survived acute coronary syndrome events and have ‘restabilised’, although these patients remain at risk of recurrent major adverse cardiovascular events (MACE, which includes myocardial infarction, stroke and cardiovascular death).

10.10. The Committee also noted that Māori experience PAD at a reported rate of 269 per 100,000 compared to the non-Māori population’s reported rate of 438 per 100,000. The Committee noted that Māori disproportionately experience death from stroke and have higher incidences of hospitalisation from cardiovascular disease, ischemic heart disease, and lower limb amputation as a result of PAD. The Committee considered that the burden of PAD in the Māori population is likely greatly underdiagnosed, and significantly higher than reported, as Māori patients experience a higher prevalence of CAD and exposure to its associated risk factors. The Committee considered that there is an increased carer and financial burden on the whānau and families of patients with complications from PAD/CAD and MACE, especially in cases like stroke where patients may not be able to work or perform day to day tasks.

10.11. The Committee considered that non-surgical treatment for peripheral vascular disease is limited to statins, aspirin, and smoking cessation, and that there is an unmet need for treatment options for this patient population. The Committee noted that for both PAD and CAD patient populations, there remains a high incidence of patients having recurrent events on currently available treatments.

10.12. The Committee noted the pivotal phase III COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS) trial which gives the primary evidence for the health benefits of rivaroxaban for the prevention of cardiovascular events (Connolly et al. Lancet. 2018;391:205-18). The Committee noted that patients with stable CAD and/or PAD (N=27395) were randomised to receive rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg alone twice daily, or aspirin 100 mg alone once daily. The Committee noted that participants in COMPASS were either 65 years of age or older or were under the age of 65 with documented atherosclerosis in two vascular beds or at least two additional risk factors. The Committee noted that the primary outcomes of COMPASS were composite incidence of cardiovascular related death or myocardial infarction, and that the primary safety outcome was incidence of major bleeding.

10.13. The Committee noted that in the COMPASS trial, CAD was defined as previous myocardial infarction within the last 20 years, symptoms or history of stable or unstable angina with confirmed multivessel CAD >50% in at least two coronary arteries (or in one coronary territory if at least one other territory has been revascularized), multivessel percutaneous coronary intervention, multivessel coronary artery bypass grafting (CABG). The Committee also noted that PAD was defined as previous peripheral vascular surgery or peripheral angioplasty intervention, previous amputation for arterial vascular disease, history of intermittent claudication and either an ankle-brachial index <0.9 or a significant peripheral artery stenosis ≥50% documented on imaging, or asymptomatic carotid artery stenosis≥50% / previous carotid revascularisation.

10.14. The Committee noted that the mean body mass index (BMI) of participants in the COMPASS trial was lower than the expected mean BMI of New Zealand patients, and also noted that most patients participating in the trial were already well managed in terms of treatment and secondary prevention. The Committee noted that 90% of participants in the COMPASS trial had CAD, while only 27% had PAD.

10.15. The Committee noted that rivaroxaban in combination with aspirin was clinically and statistically superior to aspirin alone in reducing cardiovascular death, stroke, and myocardial infarction (hazard ratio (HR) 0.76; 95% CI 0.66 to 0.86; P<0.001). The Committee also noted that rivaroxaban in combination with aspirin has a significant benefit in terms of stroke incidence compared to aspirin alone (HR 0.58; 95% CI 0.44 to 0.76; P<0.001).

10.16. The Committee noted that there was a higher incidence of major bleeding events with rivaroxaban in combination with aspirin, compared to aspirin alone (HR 1.70; 95% CI 1.40 to 2.05; P<0.001), but noted that there was no difference between the treatment groups for intracranial bleeding. The Committee noted that the bleeding events were primarily manageable gastrointestinal events. The Committee noted that the net clinical benefit of rivaroxaban in combination with aspirin compared to aspirin alone still favoured the combination treatment regardless of the increase in bleeding events (HR 0.80; 95% CI 0.70 to 0.91; P<0.001).

10.17. The Committee noted a COMPASS sub-study in which the absolute benefit of rivaroxaban in combination with aspirin was demonstrated to be greater in the sub-

set of patients with PAD as opposed to CAD alone (Anand et al. Lancet. 2018;391:219-29) and was sustained in patients with two or more vascular beds involved (Anand et al. J Am Coll Cardiol. 2019;73:3271-80), those with renal dysfunction (Fox et al. J Am Coll Cardiol. 2019;73:2243-50), heart failure (Branch et al. Circulation. 2019;140:529-37), those with diabetes mellitus (Bhatt et al. Circulation. 2020;141:1841-54), and regardless of BMI (Guzik et al. J Am Coll Cardiol. 2021;77:511-25).

10.18. The Committee also noted that an additional study on the safety of proton pump inhibitors was conducted with patients from the COMPASS trial who received pantoprazole 40 mg once daily or placebo to determine if pantoprazole compared with placebo reduces the risk of upper gastrointestinal (GI) bleeding, ulceration, obstruction, or perforation in those participating in the trial (Vanassche et al. Eur J Prev Cardiol. 2020;27:296-307). The Committee noted that addition of pantoprazole did not affect the occurrence of upper GI events in the rivaroxaban with aspirin arm but did significantly reduce upper GI events in the aspirin alone arm (HR 0.58; 95% CI 0.35 to 0.96).

10.19. The Committee considered that the COMPASS trial was well designed, and that the strength and quality of the evidence was high. The Committee considered that, as there are currently limited options for the treatment of PAD, rivaroxaban in combination with aspirin provides clinical benefit in terms of reducing ischaemia and amputation. The Committee considered that there were clinically beneficial endpoints.

10.20. The Committee noted the randomised, double-blind, placebo-controlled VOYAGER trial (Bonaca et al. N Engl J Med. 2020;382:1994-2004) investigating the effects of rivaroxaban 2.5 mg twice daily in combination with aspirin once daily versus aspirin alone in those with PAD following arterial revascularisation. The Committee noted that the primary outcome was a composite of acute limb ischemia, major amputation, myocardial infarction, ischaemic stroke, and cardiovascular death. The Committee noted that the primary efficacy outcome occurred in 508 patients in the rivaroxaban group and in 584 in the placebo group; the Kaplan-Meier estimates of the incidence at 3 years were 17.3% and 19.9%, respectively (hazard ratio, 0.85, 95% CI, 0.76 to 0.96; P = 0.009). The Committee also noted that major bleeding occurred in 62 patients in the rivaroxaban group and in 44 patients in the placebo group (2.65% and 1.87%; hazard ratio, 1.43; 95% CI, 0.97 to 2.10; P = 0.07).

10.21. The Committee noted that the only currently funded therapy for the prevention of PAD and CAD is aspirin alone, and that there have been a number of trials investigating other agents such as aspirin in combination with clopidogrel or ticagrelor. The Committee noted that these other agents have demonstrated limited benefit after one year, and with limited to no mortality benefit (Palmerini et al. Circ Cardiovasc Interv. 2019;12:e007541; Bonaca et al. N Engl J Med. 2015;372:1791-900). The Committee also noted that warfarin has been shown to improve recurrent ischaemia outcomes but increases the risk of bleeding.

10.22. The Committee noted that there have been various studies published with the aim to identify those at higher risk within the COMPASS trial cohort:

10.23. Vanassche et al. Eur J Prev Cardiol. 2020;27:296-307: reported that rivaroxaban reduced cardiovascular event rates independently of the number of established CVD risk factors (poor control of blood pressure, cholesterol, smoking status), with similar relative risk reductions reported across groups of patients with differing numbers of risk factors. The Committee noted that the largest absolute benefit (in terms of

'numbers needed to treat') was reported in patients with the highest number of risk factors.

10.23.1. Anand et al. J Am Coll Cardiol. 2019;73:3271-80: a COMPASS follow-on study conducted to identify subsets of patients in the COMPASS trial at higher risk of recurrent vascular events. The Committee noted that patients were stratified by risk using REACH (REduction of Atherothrombosis for Continued Health) atherothrombosis risk score and CART (Classification and Regression Tree) analysis, which reported that high-risk patients using the REACH score were those with two or more vascular beds affected, history of heart failure, or renal insufficiency, and by CART analysis were those with ≥2 vascular beds affected, history of heart failure, or diabetes. The Committee noted that for patients with multi-vessel disease, i.e. PAD with CAD, the absolute risk reduction for cardiovascular events was 6.02% (HR=0.64; 95% CI 0.51 to 0.81) versus 1.36% (HR=0.80; 95% CI 0.68 to 0.93) for patients with one vascular bed affected.

10.23.2. Anand et al. Lancet. 2018;391:219-29: investigated cardiovascular death, myocardial infarction or stroke in participants with PAD; the primary peripheral artery disease outcome was major adverse limb events including major amputation. The Committee noted that the combination of rivaroxaban plus aspirin compared with aspirin alone reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (5% vs 7%; HR 0.72; 95% CI 0.57 to 0.90; p=0.0047), and major adverse limb events including major amputation (1% vs 2%; HR 0.54; 95% CI 0.35 to 0.82; p=0.0037).

10.24. The Committee noted that the COMPASS trial participants were not representative of the New Zealand Māori and Pacific patient population, as it included fewer smokers, fewer participants with chronic kidney disease, generally lower BMI patients, and lower diabetes incidence, and an over-representation of hypertension. The Committee considered, however, that any benefits from rivaroxaban in combination with aspirin would likely result in enhanced benefits for the Māori and Pacific patient population.

10.25. The Committee considered that using ankle-brachial index (ABI) as restriction criteria for access to rivaroxaban, if it were to be funded, may not be clinically appropriate, as it is only one component of the definition of PAD and is variably accessible across centres. The Committee also noted that treating those at a higher risk of adverse bleeding events comes down to individual clinical input and is regularly considered when initiating and managing patients on anticoagulant therapy. The Committee considered that there is a minimal need for haemostatic/reversal agents if rivaroxaban were to be funded for the requested indication, as higher doses of rivaroxaban have been funded in New Zealand for some time without the availability of a dedicated reversal agent.

10.26. The Committee considered that twice daily dosing is not as suitable as once daily dosing for most patients which may affect adherence to treatment over the long term.

10.27. The Committee noted that the prevalence of PAD is 0.42%, equating to approximately 21,000 patients (National Health Committee, 2013). The Committee considered that a restriction of rivaroxaban access based on identification of high-risk groups and a clear definition of underlying conditions, such as in Anand et al. (2019) would limit patient numbers to those with the highest need.

10.28. The Committee noted the PBAC (Australia) guidelines for access to funded rivaroxaban for those with CAD and PAD, considered that the criteria were specific

and detailed in their definitions of high-risk patient populations, and noted that ethnicity was included as a part of the Australian access criteria (for those with Aboriginal or Torres Straight Island descent). The Committee considered that this approach would also be appropriate in the New Zealand treatment context.

10.29. The Committee considered that the patients who would benefit most from treatment with rivaroxaban include those with widespread disease (i.e. those with both PAD and CAD), and that those with the poorest risk control had the highest benefit in the COMPASS trial.

10.30. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for rivaroxaban 2.5 mg if it were to be funded in New Zealand for the prevention of PAD with or without CAD. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with peripheral artery disease, AND
	• concomitant CAD; OR
	• a previous peripheral/carotid artery revascularisation intervention; OR
	• intermittent claudication with an ankle-brachial index less than 0.9; OR
	• asymptomatic carotid artery stenosis greater than 50%
	
	In addition to the above, the patient has one of the following risk factors:
	• Diagnosed heart failure (with ejection fraction >30% and <50%); OR
	• Diagnosed kidney disease classified by an eGFR in the range of 15-60 mL/min; OR
	• Diagnosed diabetes mellitus, in addition to one of the following:
	  ○ Age at least 60 years
	  ○ Concomitant microalbuminuria
	  ○ Māori or Pacific ethnicity

Intervention	Rivaroxaban 2.5 mg twice daily + 100 mg aspirin daily
Comparator(s)	100mg aspirin daily
Outcome(s)	Reduction in the risk of serious vascular events • Serious vascular events are defined as MACE, limb ischaemia (ALI), and vascular amputation. • A follow-on study from COMPASS reported that among a high-risk group of patients (with multi-vascular disease, a history of heart failure, or diabetes) rivaroxaban in combination with aspirin was associated with a reduced risk of the composite endpoint of MACE, ALI and vascular amputation compared to aspirin alone (HR=0.75; 95% CI 0.66 to 0.85) for patients with (Anand et al. J Am Coll Cardiol. 2019;73:3271-80).
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

11. Empagliflozin for the treatment of CHFrEF, as add-on to optimal standard CHF treatments, in patients with NYHA class II-IV and LVEF ≤40%.

Application

11.1. The Advisory Committee reviewed the application from Boehringer Ingelheim New Zealand Limited for the use of empagliflozin (Jardiance) for the treatment of congestive heart failure (CHF) with reduced ejection fraction (HFrEF), as add-on to optimal standard CHF treatments, in patients with New York Heart Association (NYHA) class II-IV and left ventricular ejection fraction (LVEF) ≤40%.

11.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Advisory Committee **recommended** that empagliflozin for the treatment of HFrEF, as an add-on to optimal standard CHF treatments, in patients with NYHA class II-IV and LVEF ≤40% be listed with a **high priority** within the context of treatment of cardiovascular disease, subject to the following Special Authority criteria:

> **EMPAGLIFLOZIN**
> **Initial application – Empagliflozin in chronic heart failure**
> Applications from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> 1. Patient has heart failure; and
> 2. Patient is in NYHA/WHO functional class II or III or IV; and
> 3. Either:
> 3.1. Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%; or
> 3.2. An ECHO is not reasonably practical, and in the opinion of the treating practitioner the patient would benefit from treatment; and
> 4. Patient is receiving concomitant optimal standard chronic heart failure treatments

11.4. In making this recommendation, the Committee considered:

11.4.1. The high health need and severe impact of HFrEF on the patient and their family/whānau

11.4.2. The evidence that showed empagliflozin provides a health benefit in reducing hospitalisation, reducing all-cause mortality, and improving quality of life in those with HFrEF

11.4.3. The suitability benefit of empagliflozin allowing for improved adherence with heart-failure treatments

Discussion

Māori impact

11.5. The Committee considered that Māori are disproportionately impacted by HFrEF, and noted the related evidence discussed at the February 2022 PTAC meeting. The Committee considered that while there is a paucity of evidence within this population, a significant population of Māori and Pacific peoples without diabetes would benefit from empagliflozin given the health outcomes observed in these population groups. The Committee considered that Lam et al. 2018 provides the best New Zealand data,

including the proportion of Māori diagnosed with different subsets of HF (HFrEF n=103 [9%]) (Lam et al. Eur Heart J. 2018;20:1770-1180).

Background

11.6. The Committee noted that this funding application was reviewed by PTAC in February 2022 and recommended for decline. The Committee noted that, at this time, PTAC considered the evidence provided did not show empagliflozin offered clinically important additional health benefits over currently available treatments.

11.7. The Committee noted that PTAC considered the evidence was difficult to translate to the New Zealand population given that study participants in the Empire HF study were 98% Caucasian, and those in the EMPEROR-Reduced trial were 70% Caucasian with no Māori or Pacific peoples included. It was also noted that while PTAC considered the evidence associated empagliflozin with reduced hospitalisation rates, it could not exclude the likely possibility that a reduction in hospitalisation may reflect changes in clinical practice rather than being a good proxy for actual treatment benefit for a patient. The Committee noted that PTAC considered the evidence regarding the impact of empagliflozin on cardiovascular mortality in HFrEF patients was uncertain. The Committee noted that PTAC also considered that it was unclear what incremental benefit empagliflozin would have in Māori and Pacific peoples with HFrEF, given the lack of evidence available for this population group.

11.8. The Committee noted that PTAC requested advice from the Cardiovascular Advisory Committee regarding interpretation of evidence, specifically regarding the health benefit of empagliflozin in the New Zealand population. It was noted that PTAC also sought advice from the Cardiovascular Advisory Committee on whether there is a subgroup of individuals who would benefit from empagliflozin, such as Māori or Pacific peoples, including patient number estimates for these populations.

Discussion

11.9. The Committee noted that the health need of those with HFrEF had been previously discussed and established at the February 2022 PTAC meeting.

11.10. The Committee considered that those with HFrEF NYHA class II-IV present with increasingly complex co-morbidities. The Committee considered that CHF is underdiagnosed in the community and often presents in emergency settings, especially among Māori, Pacific, and rural patients due to various accessibility issues delaying diagnosis. The Committee considered that patients receive a greater benefit from heart failure medications when treatment is started earlier in disease. The Committee noted that the key challenges for the management of heart failure include titrating medications to an effective dose, maintaining long-term adherence to these medications, and managing interactions. The Committee noted that optimal treatment of HFrEF requires multiple physician visits, and patients experiencing access barriers to health services were therefore unlikely to receive adequate treatment.

11.11. The Committee noted that empagliflozin is currently funded for HFrEF by other HTA agencies such as PBAC (Australia) and NICE (England/Wales) and is currently undergoing reimbursement review by CADTH (Canada). The Committee considered that international guidelines are shifting to include empagliflozin as a standard treatment for those with HFrEF. The Committee noted that the 2018 NZ Heart Foundation Guidelines are out of date and are due to be updated to be in line with that of other jurisdictions.

11.12. The Committee noted the evidence previously considered at the February 2022 PTAC meeting reporting on the use of empagliflozin (EMPEROR-Reduced and Empire HF trials) and other SGLT2 inhibitors (DAPA-HF and CANDLE trials) in the treatment of HFrEF (Packer et al. N Engl J Med. 2020;15:1413-1424; Jensen et al. Am Heart J. 2020;228:47-56; Jensen et al. Trials. 2019;20:374); McMurray et al. N Engl J Med. 2019;21;1995-2008; Tanaka et al. Cardiovasc Diabetol. 2021;1:175; Zannad et al. Lancet. 2020;396:819-829).

11.13. The Committee also noted the findings of a meta-analysis of several randomised-controlled trials (DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced, SOLOIST-WHF) which included 15,684 patients with heart failure with reduced (n=9199) or preserved (n=6482) ejection fraction. The Committee noted that treatment with SGLT2 inhibitors resulted in a significant reduction in the composite of CV death and heart failure hospitalisation compared to placebo (hazard ratio [HR]=0.76; 95% confidence interval [CI] 0.70 to 0.82; I2=0%; P<0.00001). It was noted that this was consistent in LVEF sub-groups (P-for-interaction=0.57) as well as in sub-groups of patients with and without diabetes mellitus at baseline (P-for-interaction=0.81) (LVEF ≤40% HR=0.74, 95% CI 0.68 to 0.81, I2=0%; LVEF >40% HR=0.78, 95% CI 0.68 to 0.89, I2=0%). The Committee noted that SGLT2 inhibitors significantly reduced the hazard of cardiovascular death (HR=0.87, 95% CI 0.79 to 0.97, I2=0%, P<0.00001) and total heart failure hospitalisation (relative risk=0.71, 95% CI 0.67 to 0.76, I2=0%, P<0.00001) (Pandey et al. ESC Heart Fail. 2022;9:942-6).

11.14. The Committee considered that the evidence demonstrated that empagliflozin provided a benefit in terms of reduced hospitalisation in those with HFrEF. The Committee considered an absolute reduction in hospitalisation represents a meaningful outcome due to the severe impact it has on those with heart failure as well as their family/whānau. The Committee considered that, while PTAC noted that hospitalisation provides an optimal setting to review medication efficacy, that it is also an indicator of poor overall clinical management of the condition and that a hospital environment is generally not conducive to patient respite and wellbeing. The Committee considered that heart failure-related hospitalisations occur in situations where patients are inadequately managed on their current medication and require admission to a coronary care unit.

11.15. The Committee considered that the trial evidence suggested that empagliflozin provided little overall benefit on reducing mortality. However, the Committee considered that the lack of a statistically significant all-cause mortality benefit in the EMPEROR trial was likely a function of underpowering with small sample sizes and short follow-up periods. The Committee also considered that these trials were conducted in relatively low-risk patients who were already receiving standard heart failure treatment in addition to empagliflozin, both features further lessening baseline event rates and thus power to detect statistically significant differences. The Committee considered had these trials been conducted in a higher-risk population, absolute reductions in all-cause mortality with empagliflozin may have been greater. The Committee noted that DAPA-HF and the meta-analyses conducted by Zannad et al. and Pandey et al. each reported a benefit in reducing all-cause death and cardiovascular death. The Committee also considered that the Empire HF study reported outcomes based on a surrogate marker (NT-proB-type natriuretic peptide [BNP]), which is a poor indicator in measuring the benefit of empagliflozin in those with HFrEF. The Committee also considered the positive impact empagliflozin has on renal function.

11.16. The Committee considered that the 10mg once-daily dose of empagliflozin provides a suitability advantage compared to currently funded treatments, for which doses may

be more frequent and multiple physician visits may be required to titrate the patient to the optimal dose. The Committee considered that these simplified dosing requirements in combination with the favourable side effect profile of empagliflozin contribute to improved adherence with treatment.

11.17. The Committee considered that, if funded access were to be widened, the number of those eligible to receive empagliflozin for HFrEF is uncertain. The Committee considered that it would be appropriate to estimate patient numbers based on the number of those currently receiving sacubitril/valsartan, with approximately two thirds of this patient population estimated to be symptomatic and therefore eligible to receive empagliflozin if funded access were to be widened.

11.18. The Committee considered that an additional subgroup of patients not currently receiving sacubitril with valsartan would also be eligible for empagliflozin and that it was reasonable to assume this group was roughly 10% of the size of the group currently receiving sacubitril with valsartan. The Committee also considered that patient number estimates would need to account for those with type 2 diabetes who are already being treated with empagliflozin, and those with severe renal impairment for which empagliflozin is contraindicated.

11.19. The Committee considered that empagliflozin would be prescribed to those who have not experienced adequate symptom control with currently funded treatment options. The Committee considered it reasonable to require patients to have trialled at least three other classes of heart failure medications before being prescribed empagliflozin.

11.20. The Committee considered that a reduction in heart failure-related hospitalisations as a result of widening access to empagliflozin was likely to significantly benefit the healthcare system, as well as alleviate some of the burden on patients and their whānau. The Committee considered that heart failure hospitalisations are very expensive, as patients often require admission to coronary care units in combination with high-intensity care.

11.21. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for empagliflozin if it were to be funded in New Zealand for HFrEF. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with NYHA class II-IV and LVEF ≤40%.
Intervention	Empagliflozin, 10mg once daily. Taken as an adjunctive therapy in addition to standard heart failure treatments.
Comparator(s) (NZ context)	Standard heart failure treatments, which include: • Angiotensin II receptor blockers-neprilysin inhibitors • Angiotensin-converting enzyme inhibitors • Angiotensin II receptor blockers • Beta blockers • Mineralocorticoid receptor antagonists

	• Hydralazine plus nitrates • Digoxin • Diuretics
Outcome(s)	1. Reduced hospitalisations for heart failure • Zannad et al. Lancet. 2020;396:819-829 reported that SGLT2 inhibitors were associated with a decreased risk of first hospitalisation for heart failure compared to placebo (HR 0.69; 95% CI 0.62 to 0.78) 2. Reduced all-cause mortality • Zannad et al. Lancet. 2020;396:819-829 reported that SGLT2 inhibitors were associated with a decreased risk of all-cause mortality compared to placebo (HR 0.87; 95% CI 0.77 to 0.98) 3. Reduced cardiovascular mortality • Zannad et al. Lancet. 2020;396:819-829 reported that SGLT2 inhibitors were associated with a decreased risk of cardiovascular mortality compared to placebo (HR 0.86; 95% CI 0.76 to 0.98) 4. Reduced risk of adverse renal outcomes (50% or higher sustained decline in (eGFR), development of end-stage renal disease (ESRD), or renal death) • Zannad et al. Lancet. 2020;396:819-829 reported that SGLT2 inhibitors were associated with a decreased risk of the renal composite outcome, outlined above, compared to placebo (HR 0.62; 95% CI 0.43 to 0.90)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

12. Prasugrel – Patients presenting with an acute coronary syndrome (ACS) – ST elevation myocardial infarct or non-ST elevation myocardial infarct (STEMI or non-STEMI)

Application

12.1. The Advisory Committee reviewed the application from a clinician for patients with an acute coronary syndrome (ACS), ST elevation myocardial infarct or non-ST elevation myocardial infarct (STEMI or non-STEMI).

12.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

12.3. The Advisory Committee **recommended** that prasugrel for the treatment of acute coronary syndrome (ACS), ST elevation myocardial infarct or non-ST elevation myocardial infarct (STEMI or non-STEMI) be listed with a **high priority**. subject to the following Special Authority criteria:

PRASUGREL
Initial application – Acute coronary syndrome
Applications from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient has recently (within the last 60 days) been diagnosed with an ST-elevation or non-ST-elevation acute coronary syndrome; and
2. Fibrinolytic therapy has not been given in the last 24 hours and is not planned

Renewal – Acute coronary syndrome
Applications from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

1. Patient has recently (within the last 60 days) been diagnosed with an ST-elevation or non-ST-elevation acute coronary syndrome; and
2. Fibrinolytic therapy has not been given in the last 24 hours and is not planned

12.4. In making this recommendation, the Committee considered:

- The high health need and severe impact of ACS on the patient and their family/whānau;
- The high prevalence of ACS affecting Māori and Pacific peoples;
- The demonstrated non-inferiority of prasugrel over ticagrelor for the treatment of patients after ACS.
- The evidence that prasugrel provides a health benefit in reducing all-cause mortality, subsequent myocardial infarction in those with ACS; and
- The suitability benefit of once daily dosing with prasugrel over alternative post ASC treatments, which may result in improved adherence and would be likely to have a pro-equity impact

Discussion

12.5. The Advisory Committee noted that prasugrel has previously been listed on the Pharmaceutical Schedule subject to special authority criteria (for patients receiving coronary stenting and demonstrating a clopidogrel allergy/stent thrombosis while on clopidogrel) from April 2012 until it was delisted in January 2021 due to the supplier discontinuing distribution in New Zealand. The Committee noted that generic prasugrel products may be available for supply in the future.

12.6. The Committee considered that while there may not be an unmet health need in the context of post-ACS therapy with the availability of both clopidogrel and ticagrelor, it was noted that some patients may be intolerant of or contraindicated to both agents and thus have no suitable treatment options.

12.7. The Committee noted that in the last full year of listing, 83 people were dispensed prasugrel and at the time Members of the Committee considered that ticagrelor was a reasonable funded alternative.

12.8. The Committee noted that the health needs of those with ACS is severe and post event clinical management is critical to achieve favourable long-term outcomes, such as the avoidance of additional ACS and related events. The Committee noted that ACS is a significant cause of mortality, with significant inequity experienced by Māori and Pacific people who experience ACS at a younger age. The Committee noted that ACS is encompassed in the Māori health area of focus, Hauora Arotahi - Manawa Ora (Heart Health – high blood pressure and stroke), with Ischaemic Heart Disease

(IHD) responsible for 40% of deaths in Māori under the age of 65 versus 10% for non-Māori. It is estimated that the one year post-ACS presentation, the mortality rate for Māori is 2.55 times that of non-Māori / non-Pacific populations (Mazengarb et al. NZMJ 2020;133:1521).

12.9. The Committee noted the findings of the ISAR-REACT 5 trial (Schupke et al, N Engl J Med 2019;381:1524-34), which included 4018 patients presenting with ACS who were randomised to either ticagrelor (n=2012) or prasugrel (n=2006) for a 12 month period. The Committee noted that the ISAR-REACT 5 trial was designed to show a benefit of ticagrelor over prasugrel in the treatment of patients post-ACS. The trial reported an advantage to prasugrel with regards to the composite endpoint of death any cause / myocardial infarction or stroke at one year with a hazard ratio for ticagrelor of 1.36 (95% CI 1.09 to 1.70 P<0.006). It was also noted that the hazard ratio for death any cause for ticagrelor was 1.23 (95% CI 0.91-1.69) versus prasugrel, and the hazard ratio for ticagrelor for myocardial infarction was 1.63 (95% CI 1.18-2.25).

12.10. The Committee noted the findings of the HOST_REDUCE_POLYTECH_ACS open label non-inferiority randomised controlled trial (Kim et al. Lancet 2020; 396:1079-89), which randomised 2338 patients presenting with ACS to treatment with prasugrel using either a standard dose (n=1168) of 10 mg prasugrel + 100 mg aspirin for one year versus a de-escalation dose (n=1170) of 10 mg prasugrel + 100 mg aspirin for one month then 5 mg prasugrel + 100 mg aspirin for 11 months. The trial reported on Net Adverse Clinical Events defined as a composite of all-cause death, non-fatal MI, stent thrombosis and bleeding events BARC grade 2 or higher. The Committee noted that the trial reported a hazard ratio (HR) of 0.70 (CI 0.52-0.92) in favour of the de-escalation treatment arm. The Committee noted that the advantage of the de-escalation dosing strategy was particularly noticeable with the secondary safety end point of bleeding BARC type 2 or greater, where a HR of 0.48 (CI 0.32-0.73) was observed.

12.11. The Committee considered that the trial evidence demonstrated that prasugrel was at least as effective as ticagrelor in the treatment of patient post-ACS, with the advantage of having once daily dosing, which the Committee considered may result in improved treatment adherence over the required 12-month post-ACS treatment period.

12.12. The Committee considered that the evidence tabled in the HOST_REDUCE POLYTECH_ACS trial was impressive, demonstrating non-inferior primary efficacy with a significant reduction in on-treatment bleeding. However, the Committee noted that this was an open-label trial and that it was conducted on an East Asian population (Korean), and its results may or may not be realised in a New Zealand population to the same degree.

12.13. The Committee noted that both trials used objective endpoints of death, myocardial infarction (MI) and stroke. It was observed by some Members of the Committee that the period of the trials was only 12 months; however it was noted that there was no strong evidence available to support continued post-ACS dual anti-platelet therapy (DAPT) past 12 months.

12.14. The Committee considered that most prescribers would likely favour the use of prasugrel over ticagrelor should it be made available on the Pharmaceutical Schedule.

12.15. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for prasugrel if it were to be funded in New Zealand for the treatment of acute coronary syndrome (ACS), ST elevation myocardial infarct or non-ST elevation myocardial infarct (STEMI or non-STEMI). This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with Acute Coronary Syndrome (ACS) - ST elevation myocardial infarct or non-ST myocardial infarct (STEMI or non-STEMI)
Intervention	Prasugrel loading dose 60 mg then maintenance dose 10 mg or 5 mg once daily Taken with 100 mg aspirin For a 12-month period post ACS
Comparator(s)	Optimal standard post ACS DAPT consisting of either: • Ticagrelor – loading dose 180 mg then 90 mg twice daily or • Clopidogrel – loading dose 300 mg then 75 mg once daily With aspirin 100 mg once daily. For a 12-month period post ACS
Outcome(s)	1. Composite End Point (Death/MI/Stroke) • Schupke et al , N Engl J Med 2019:381:1524-34 ticagrelor vs. prasugrel at 12 months HR 1.36; 95% CI 1.09-1.70 2. Reduced all-cause mortality • Schupke et al , N Engl J Med 2019:381:1524-34 ticagrelor vs. prasugrel at 12 months HR 1.23; 95% CI 0.91 – 1.68 3. Reduced Myocardial Infarction • Schupke et al , N Engl J Med 2019:381:1524-34 ticagrelor vs. prasugrel at 12 months HR 1.63 ; 95% CI 1.18 – 2.25 4. Reduced Stroke Risk • Schupke et al , N Engl J Med 2019:381:1524-34 ticagrelor vs. prasugrel at 12 months HR 1.17 ; 95% CI 0.63 – 2.15

Table definitions:
Population: The target population for the pharmaceutical, including any population defining characteristics (e.g., line of therapy, disease subgroup)
Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.