Ticagrelor

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 12. Cardiovascular medicines > 12.5. Antithrombotic medicines > 12.5.1. Anti-platelet medicines

ATC codes: B01AC24

Indication	Acute ischaemic heart disease ICD11 code: BA4Z
INN	Ticagrelor
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 60 mg ; 90 mg
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Ticagrelor
DrugBank	Ticagrelor

Expert Committee recommendation

The Expert Committee considered that reducing mortality from cardiovascular diseases was a global health priority and acknowledged that prevention and treatment of cardiovascular disease remained an area of unmet need, especially in low- and middle-income countries. The Committee noted that evidence from randomized trials, systematic reviews and network meta-analyses comparing ticagrelor with placebo and with active comparators presented in the application showed somewhat heterogeneous results, giving rise to uncertainty in the efficacy outcomes. In the PEGASUS study in patients with a history of myocardial infarction, the Committee noted that ticagrelor in combination with aspirin was superior to aspirin alone in preventing atherothrombotic events; however, no benefit was observed when ticagrelor was introduced in clinically stable patients. In the PLATO study in hospitalized patients with acute coronary syndromes, the Committee noted that the use of ticagrelor did not improve outcomes more than clopidogrel in all patient subpopulations – those with body weight lower than the sex-specific median values and participants from North America. In addition, the Committee noted that participants from Hungary and Poland made up about 20% of the trial population and provided nearly half of the data in favour of ticagrelor. When data from these participants were excluded, ticagrelor was no longer superior to clopidogrel. Finally, when myocardial infarctions were assessed only by site investigators, and not by the clinical adjudication committee, ticagrelor was no longer superior to clopidogrel. The Committee noted that in both the PEGASUS and PLATO trials, ticagrelor was associated with an increased risk of some important bleeding outcomes, such as fatal intracranial bleeding. The Committee also noted data (not presented in the application) from studies

comparing ticagrelor and clopidogrel in Asian patients with acute coronary syndromes, which indicated that ticagrelor was not superior to clopidogrel and carried a greater risk of major bleeding (27,28). The Committee noted that ticagrelor has generally been found to be cost-effective versus clopidogrel in high-income settings. However, while generics of ticagrelor are available in some countries, it remains more expensive than clopidogrel in most markets. Therefore, the Expert Committee did not recommend the inclusion of ticagrelor on the EML for the prevention of atherothrombotic events in adults with acute coronary syndromes or a history of myocardial infarction and at high risk of developing an atherothrombotic event

Background

Ticagrelor has not previously been evaluated for inclusion on the Model List. In 2015, the Expert Committee recommended the addition of clopidogrel to the EML as an antithrombotic agent for treatment of patients with acute coronary syndrome or following percutaneous coronary interventions. The Committee accepted that based on the evidence presented, dual anti-platelet therapy with clopidogrel in combination with aspirin was effective in reducing the risk of major cardiovascular events and was superior to aspirin monotherapy for patients with acute coronary syndrome or undergoing percutaneous coronary interventions. In these patient populations, the Committee considered that the benefits of dual therapy outweighed the potential harms (1).

Public health relevance

Worldwide, in 2019, ischaemic heart disease and stroke were the first and second highest causes of death, respectively, in people older than 50 years (2). The global burden of cardiovascular disease and stroke-related mortality and disability-adjusted life years (DALY) are driven by the burden in low- and middle-income countries. A report from the European Society of Cardiology, which analysed data from 56 member countries, showed that the disease burden DALY per 100 000 people due to cardiovascular disease was more than three times as high in middle-income versus high-income countries. Cardiovascular disease mortality was also higher in middle-income countries where it accounted for a greater proportion of potential years of life lost compared with high-income countries (3). All-cause mortality in low- and middle-income countries has fallen over the past three decades, but there has been no reduction in mortality from cardiovascular disease and stroke (2,4,5).

Benefits

The application presented summaries of recent systematic reviews, network meta-analyses, and primary research articles on the clinical effects of ticagrelor in comparison with other agents. Ticagrelor versus active comparators The PLATO study was a randomized, multicentre, double-blind study that compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) versus clopidogrel (300–600 mg loading dose, 75 mg daily thereafter) on the prevention of cardiovascular events in patients admitted to hospital with an acute coronary syndrome (18 624 participants) (6). After 12 months of treatment, ticagrelor was associated with significantly lower rates of death from vascular causes, myocardial infarction or stroke compared with clopidogrel (9.8% versus 11.7%, $P < 0.001$). Patients treated with ticagrelor had significantly lower rates of myocardial infarction (5.8% versus 6.9%, $P = 0.005$) and death from vascular causes (4.0% versus 5.1%, $P = 0.001$), but not stroke alone compared with patients treated with clopidogrel. The rate of death from any cause was also lower with ticagrelor than clopidogrel (4.5% versus 5.9%, $P < 0.001$). No significant increase was seen in the risk of major or fatal bleeding, although there was an increase in non-coronary-artery bypass graft-related major bleeding with ticagrelor versus clopidogrel (4.5% versus 3.8%, $P = 0.03$). A substudy of PLATO (10 285 participants) analysed the effects of CYP2C19 and ABCB1 genotypes, which are known to influence the effects of clopidogrel, on outcomes with ticagrelor versus clopidogrel. Cardiovascular death occurred less often with ticagrelor than clopidogrel, irrespective of CYP2C19 or ABCB1 genotype (7). The reduced risk of cardiovascular death with ticagrelor, regardless of genotype, suggests that the use of ticagrelor may be started for patients without the need for recommended genetic testing and may be a potential option for patients who are resistant or unresponsive to clopidogrel. The PLATELET substudy of the PLATO trial compared antiplatelet effects of ticagrelor versus clopidogrel in patients with acute coronary syndrome (69 participants, 28 days maintenance treatment with ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily) (8). Ticagrelor produced significantly lower platelet

reaction units with both the loading dose at 4 hours and the maintenance doses (both trough and peak), demonstrating a greater platelet inhibitor effect with ticagrelor than clopidogrel in patients with acute coronary syndrome both in the first hours of treatment and during maintenance. A meta-analysis of 10 randomized studies (56 385 participants) evaluated the safety and efficacy of ticagrelor versus clopidogrel in patients with acute coronary syndrome (9). Analysis of pooled data from eight studies indicated no significant differences in the risk of bleeding (odds ratio (OR) OR 1.07, 95% confidence interval (CI) 0.91 to 1.26), or rate of myocardial infarction (OR 0.87, 95% CI 0.72 to 1.05) between treatments. Analysis of pooled data from seven studies also indicated no significant differences in the risk of stroke between treatments (OR 0.93, 95% CI 0.64 to 1.34). A network meta-analysis of 12 randomized trials (52 816 participants) compared the efficacy and safety of prasugrel, ticagrelor and clopidogrel in acute coronary syndrome (10). Ticagrelor was associated with significantly lower cardiovascular mortality (hazard ratio (HR) 0.82, 95% CI 0.72 to 0.92) and all-cause mortality (HR 0.83, 95% CI 0.75 to 0.92) compared than clopidogrel. No significant differences were observed between ticagrelor and clopidogrel for non-cardiovascular mortality or reduction in myocardial infarction events. Seven studies provided data for the outcome of definite or probable stent thrombosis events. Both ticagrelor (HR 0.72, 95% CI 0.58 to 0.90) and prasugrel (HR 0.50, 95% CI 0.38 to 0.64) were associated with a significantly lower risk of stent thrombosis compared with clopidogrel. Prasugrel was associated with a significantly lower risk of stent thrombosis than ticagrelor (HR 0.68, 95% CI 0.50 to 0.93). A retrospective observational study using data from a Chinese nationwide database assessed clinical characteristics of patients with ST-segment elevation myocardial infarction with in-hospital cardiac arrest, as well as predictors and treatments associated with the risk of in-hospital cardiac arrest (11). Patients presenting with ST-segment elevation myocardial infarction within 24 hours after symptom onset were stratified according to in-hospital cardiac arrest or no in-hospital cardiac arrest during index hospitalization. Of the 40 670 patients with ST-segment elevation myocardial infarction, 2.2% experienced in-hospital cardiac arrest, which in turn was responsible for more than half of inpatient deaths. However, primary percutaneous coronary intervention (adjusted HR 0.82, 95% CI 0.71 to 0.95), β-blockers (adjusted HR 0.63, 95% CI 0.47 to 0.86) and ticagrelor (adjusted HR 0.57, 95% CI 0.42 to 0.76) treatments were associated with a reduced risk of in-hospital cardiac arrest (11). A systematic review of seven trials (511 participants) compared the efficacy of ticagrelor versus clopidogrel in improving endothelial function in patients with coronary artery disease (12). Compared with clopidogrel, ticagrelor resulted in a significantly higher elevation of progenitor cells CD34+KDR+ and CD34+133+, with a significantly lower rate of endothelial cell apoptosis. In addition, ticagrelor was superior to clopidogrel with regard to nitric oxide, radical oxygen species and soluble P-selectin levels. Overall, ticagrelor appeared to lead to greater improved endothelial cell function compared with clopidogrel. A network meta-analysis of nine randomized trials (91 115 participants) evaluated comparative efficacy and safety of antiplatelet and anticoagulant therapy in patients with chronic coronary syndromes after percutaneous coronary intervention (13). Compared with aspirin alone, the addition of prasugrel or ticagrelor to aspirin was associated with a lower risk of myocardial infarction (prasugrel: OR 0.48, 95% CI 0.38 to 0.62; ticagrelor: OR 0.81–0.84, 95% CI 0.69 to 0.98), but was associated with an increased risk of major bleeding (prasugrel: OR 1.79, 95% CI 1.34 to 2.39; ticagrelor: OR 2.08–2.38, 95% CI 1.56 to 3.28). Significant differences between antithrombotic treatments for the primary outcome of major adverse cardiovascular event were not observed. A systematic review and meta-analysis of 24 randomized trials (48 759 participants) assessed antithrombotic therapy for symptomatic peripheral arterial disease (14). For the primary endpoint of reducing major adverse cardiovascular events, clopidogrel (relative risk (RR) 0.78, 95% CI 0.66 to 0.93), ticagrelor (RR 0.79, 95% CI 0.65 to 0.97), aspirin plus ticagrelor (RR 0.79, 95% CI 0.64 to 0.97) and aspirin plus low-dose rivaroxaban (RR 0.84, 95% CI 0.76 to 0.93) were more effective than aspirin alone, and equally effective as each another. A systematic review and meta-analysis of 22 studies (35 004 participants) evaluated the efficacy and safety of ticagrelor compared with clopidogrel in patients with general acute coronary syndrome and a group of patients with diabetes mellitus (15). The primary endpoint was a composite endpoint of any myocardial infarction, cardiovascular death or stroke. Five studies (33 258 participants) provided data for the composite endpoint and found that compared with clopidogrel, ticagrelor was associated with a lower incidence of the composite endpoint among patients with general acute coronary syndrome (OR 0.83, 95% CI 0.77 to 0.90). Eight studies (33 282 participants) provided data for the secondary endpoint of incidence of myocardial infarction. The incidence of myocardial infarction was significantly lower in the ticagrelor

group than in the clopidogrel and prasugrel groups (OR 0.81, 95% CI 0.74 to 0.89). No significant differences were seen between the ticagrelor group and the clopidogrel and prasugrel groups for incidence of cardiovascular death or stroke. A single-centre retrospective cohort study evaluated the effectiveness and safety of ticagrelor versus clopidogrel as dual antiplatelet therapy with aspirin in 908 Chinese patients aged ≥ 75 years with coronary artery disease after percutaneous coronary intervention for up to 12 months (16). Ticagrelor was associated with a lower incidence of major adverse cardiovascular events compared with clopidogrel (OR 0.49, 95% CI 0.36 to 0.68). There was no difference in the risk of bleeding between the two groups. Ticagrelor versus placebo The PEGASUS-TIMI-54 study was a randomized, double-blind, multicentre study to assess the prevention of atherothrombotic events with ticagrelor given at two doses (either 90 mg twice daily or 60 mg twice daily) versus placebo in patients with a history of myocardial infarction within 1–3 years and additional risk factors for atherothrombosis (21 162 participants) (17). All participants also received low dose aspirin (75–150 mg). The primary efficacy endpoint was the composite of cardiovascular death, myocardial infarction or stroke. Both ticagrelor doses were associated with significant reductions in the composite endpoint compared with placebo (90 mg: HR 0.85, 95% CI 0.75 to 0.96; 60 mg: HR 0.84, 95% CI 0.74 to 0.95). No evidence of benefit was seen (no reduction in the primary composite endpoint, but an increase in major bleeding) when ticagrelor 60 mg twice daily was introduced in clinically stable patients more than 2 years after the myocardial infarction, or more than 1 year after stopping previous treatment with adenosine diphosphate receptor inhibitor.

Harms

The application presented the special warnings and precautions for use for ticagrelor as described in the summary of product characteristics issued by the European Medicines Agency (18). Selected safety findings from clinical trials are described below. Risk of bleeding In the PLATO trial of ticagrelor versus clopidogrel, no significant differences were seen in the rates of major bleeding between treatment arms as defined in the trial (HR 1.04, 95% CI 0.95 to 1.13), major bleeding defined according to the Thrombolysis in Myocardial Infarction criteria (HR 1.03, 95% CI 0.93 to 1.15), fatal or life-threatening bleeding (HR 1.03, 95% CI 0.90 to 1.16), or major bleeding related to coronary artery bypass graft surgery (HR 0.95, 95% CI 0.85 to 1.06) or bleeding requiring transfusion of red cells (OR 1.00, 95% CI 091 to 1.11). Ticagrelor was associated with significantly higher rates of major bleeding not related to coronary artery bypass graft surgery according to the study criteria (HR 1.19, 95% CI 1.02 to 1.38) and the Thrombolysis in Myocardial Infarction criteria (HR 1.25, 95% CI 1.03 to 1.53). Ticagrelor was also associated with significantly more episodes of intracranial bleeding (HR 1.87, 95% CI 0.98 to 3.58), including fatal intracranial bleeding. There were fewer episodes of non-intracranial fatal bleeding in the ticagrelor group (6). In the PEGASUS-TIMI-54 placebo-controlled study of ticagrelor in patients with a history of myocardial infarction, ticagrelor 60 mg (the only dose approved for use in this patient population) was associated with significantly higher rates of bleeding, including major (HR 2.32, 95% CI 1.68 to 3.21) and minor (HR 3.31, 95% CI 1.94 to 5.63) bleeding as defined by Thrombolysis in Myocardial Infarction criteria, bleeding requiring transfusion (HR 3.08, 95% CI 2.12 to 4.48) and bleeding leading to treatment discontinuation (HR 4.40, 95% CI 3.48 to 5.57) compared with placebo. A non-significant increase in fatal bleeding or non-fatal intracranial haemorrhage was observed with ticagrelor 60 mg treatment (HR 1.20, 95% CI 0.73 to 1.97) compared with placebo (17). Dyspnoea In the PLATO study, any dyspnoea was reported significantly more frequently in the ticagrelor arm than the clopidogrel arm (HR 1.84, 95% CI 1.68 to 2.02). Dyspnoea leading to treatment discontinuation was also more frequent in patients treated with ticagrelor (HR 6.12, 95% CI 3.41 to 11.01) (6). In the PEGASUS trial, dyspnoea was reported significantly more frequently in patients taking ticagrelor 60 mg compared with aspirin alone (HR 2.81, 95% CI 2.50 to 3.17) and more frequently led to treatment discontinuation (HR 6.06, 95% CI 4.50 to 8.15) (17). Uric acid elevations In the PLATO trial, serum uric acid increased to more than the upper limit of normal in 22% of patients receiving ticagrelor compared with 13% of patients receiving clopidogrel. The corresponding numbers in PEGASUS were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively. Mean serum uric acid increased about 15% with ticagrelor compared with about 7.5% with clopidogrel. After treatment was stopped, uric acid decreased to about 7% in patients on ticagrelor but no decrease was observed for clopidogrel. In PEGASUS, a reversible increase in mean serum uric acid levels of 6.3% and 5.6% was found for ticagrelor 90 mg and 60 mg, respectively, compared with a 1.5% decrease in the placebo group. In PLATO, the frequency of gouty

arthritis was 0.2% for ticagrelor versus 0.1% for clopidogrel. The corresponding numbers for gout/gouty arthritis in PEGASUS were 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively (18).

Cost / cost effectiveness

The application identified and briefly summarized findings from cost–effectiveness analyses comparing ticagrelor and clopidogrel in Brazil (20), Colombia (21), Egypt (22,23), Germany (20), Singapore (24), Sweden (20), Thailand (25), United Kingdom (20) and Viet Nam (26) which determined ticagrelor to be cost-effective versus clopidogrel based on national perspectives and willingness-to-pay thresholds. The application also presented a comparison of the price per day of treatment in United States dollars for ticagrelor and clopidogrel from selected low- and middle-income countries where prices were available for both medicines (Table 21, refer TRS 1049). Prices are published list prices and do not take into account confidential discounts or rebates that may be in place.

WHO guidelines

The WHO HEARTS technical package for cardiovascular disease management in primary health care includes recommendations on interventions for the management of hypertension, diabetes and elevated lipid levels in primary care (19). Recommendations specifically for the secondary prevention of atherothrombotic events in adults with acute coronary syndromes or a history of myocardial infarction and at high risk of developing an atherothrombotic event are not currently included.

Availability

Ticagrelor has regulatory approval worldwide and remains under patent protection until 2024. Generics are available in some settings.

Other considerations

The technical team for Screening, Diagnosis and Treatment in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. The technical department did not support the inclusion of ticagrelor on the EML for the following reasons: an unfavourable cost-to-benefit ratio; very limited uptake of less costly aspirin for secondary prevention of cardiovascular disease; and preference to support uptake efforts for statins and aspirin, in line with WHO guidance in the package of essential noncommunicable diseases interventions, and HEARTS technical packages.

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