APPLICATION

FOR

THE INCLUSION OF TICAGRELOR

AS

A TREATMENT

FOR

THE PREVENTION OF ATHEROTHROMBOTIC EVENTS IN ADULT PATIENTS WITH ACUTE CORONARY SYNDROMES (ACS) OR A HISTORY OF MYOCARDIAL INFARCTION (MI) AND A HIGH RISK OF DEVELOPING AN ATHEROTHROMBOTIC EVENT

ON

THE WHO MODEL LIST OF ESSENTIAL MEDICINES 2023

Submitted by

AstraZeneca PLC

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Section 1: Summary Statement of the Proposal for Inclusion

This application advocates updating Section 12.5 of the WHO Model List of Essential Medicines (WHO EML) for adults. It focuses on expanding the core list of Section 12.5.1 to include ticagrelor as a treatment for:

- The prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) *or* a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event

Cardiovascular-related disease (CVD)-related death (particularly attributed to stroke and ischaemic heart disease) is recognised by the WHO as an area of high unmet need. Reducing CVD-related mortality is one of their priorities, alongside reducing mortality related to other non-communicable diseases [1]. Moreover, global CVD-related mortality is largely driven by the impact of CVD in low- and middle-income countries (LMICs) [2, 3].

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct-acting, selective and reversibly binding P2Y12 receptor antagonist that prevents ADP-mediated P2Y12-dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the P2Y12 receptor, ticagrelor prevents ADP-induced signal transduction.

Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as MI, stroke, or death [4].

Ticagrelor is co-administered with acetylsalicylic acid (ASA), and is indicated for the prevention of atherothrombotic events in adult patients with ACS or a history of MI and a high risk of developing an atherothrombotic event [4].

Ticagrelor is recommended by numerous international guidelines [5-12], and has also been shown to be as or more cost-effective than clopidogrel in LMICs for ACS [8, 13-15].

Although clopidogrel was added to the WHO Essential Medicines List (EML) in 2015 [16], some patients are deemed to be resistant to clopidogrel, thus affecting their response to the drug [17-20]. Additionally, there has been no reduction in CVD- and stroke-related mortality over the past three decades, including the period between 2015 and 2019, during which time clopidogrel was included in the WHO EML.

A 2018 analysis of data from the PURE study found that only ~5% of patients in LMIC with CHD have access to ≥ 3 drugs; ~80% don't have access to any drugs [21]. In the PURE study, 5650 participants had a prior CHD event and 2292 had experienced a prior stroke. Despite this, few individuals with CVD were still taking antiplatelet drugs, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs), or statins. The analysis noted fewest patients received no drugs in high-income countries (11.2%), compared with 45.1% in upper middle-income countries, 69.3% in lower middle-income countries, and 80.2% in low-income countries [21]. Furthermore, a fifth of European Society of Cardiology (ESC) country members do not have access to ticagrelor [3, 22]. Taken together, these observations suggest that people living with CVD, particularly in LMICs, need wider access to more CVD therapies including antiplatelet drugs such as ticagrelor.

This application describes the burden of CVD in LMICs and provides evidence of the superior efficacy of ticagrelor over clopidogrel to support a case for adding ticagrelor to the WHO EML – which might ultimately help to reduce the burden of CVD in LMICs.

Section 2: Relevant WHO Technical Department and Focal Point

No consultation has taken place.

Section 3: Names of Organizations Supporting the Argument

Egyptian Society of Cardiology**,** 9 el saraya St, Ad Doqi, Giza District, Giza Governorate 3753421, Egypt.

Prof. Fred Bukachi, Director, Africa Research Universities Alliance, Centre of Excellence for Non-Communicable Diseases

Section 4: International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical Code

ATC code	INN
B01AC24	Ticagrelor

Section 5: Dose Forms and Strengths Proposed for Inclusion for Adults

Acute coronary syndromes
Film-coated tablet: single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

History of MI
Film coated tablet: 60 mg twice daily

Section 6: Listing Request

Listing is requested for the addition of ticagrelor to the list of Antithrombotic Medicines (Section 12.5), specifically Anti-Platelet Medicines (Section 12.5.1) which currently include ASA and clopidogrel.

Ticagrelor is indicated the prevention of atherothrombotic events in adult patients with ACS, or a history of MI and a high risk of developing an atherothrombotic event.

Section 7: Treatment Details

Ticagrelor is a member of the chemical class CPTP, which is an oral, direct acting, selective and reversibly binding P2Y12 receptor antagonist that prevents ADP-mediated P2Y12 dependent platelet activation and aggregation [4]. Ticagrelor does not prevent ADP binding but when bound to the

P2Y12 receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI or stroke. Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1) [4].

Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood *in vitro*) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated [4].

Pharmacodynamic effects [4]

Onset of action

In patients with stable coronary artery disease (CAD) on ASA, ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean inhibition of platelet aggregation (IPA) for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 89% by 2-4 hours post dose and maintained between 2-8 hours. 90% of patients had final extent IPA>70% by 2 hours post dose.

Offset of action

If a coronary artery by-pass grafting (CABG) procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

Switching data

Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect.

Clinical efficacy and safety [4]

The clinical evidence for the efficacy and safety of ticagrelor is derived from two phase 3 trials:

- The PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of ticagrelor to clopidogrel, both given in combination with ASA and other standard therapy.
- The PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] study, a comparison of ticagrelor combined with ASA to ASA therapy alone.

<u>PLATO study (Acute Coronary Syndromes)</u>

The PLATO study included 18,624 patients who presented within 24 hours of onset of symptoms of unstable angina (UA), non-ST elevation MI (NSTEMI) or ST elevation MI (STEMI), and were initially managed medically, or with percutaneous coronary intervention (PCI), or with CABG.

Clinical efficacy

On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of CV death, MI or stroke, with the difference driven by CV death and MI. Patients received a 300 mg loading dose of clopidogrel (600 mg possible if having PCI) or 180 mg of ticagrelor.

The result appeared early (absolute risk reduction [ARR] 0.6% and relative risk reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12-month period, yielding ARR

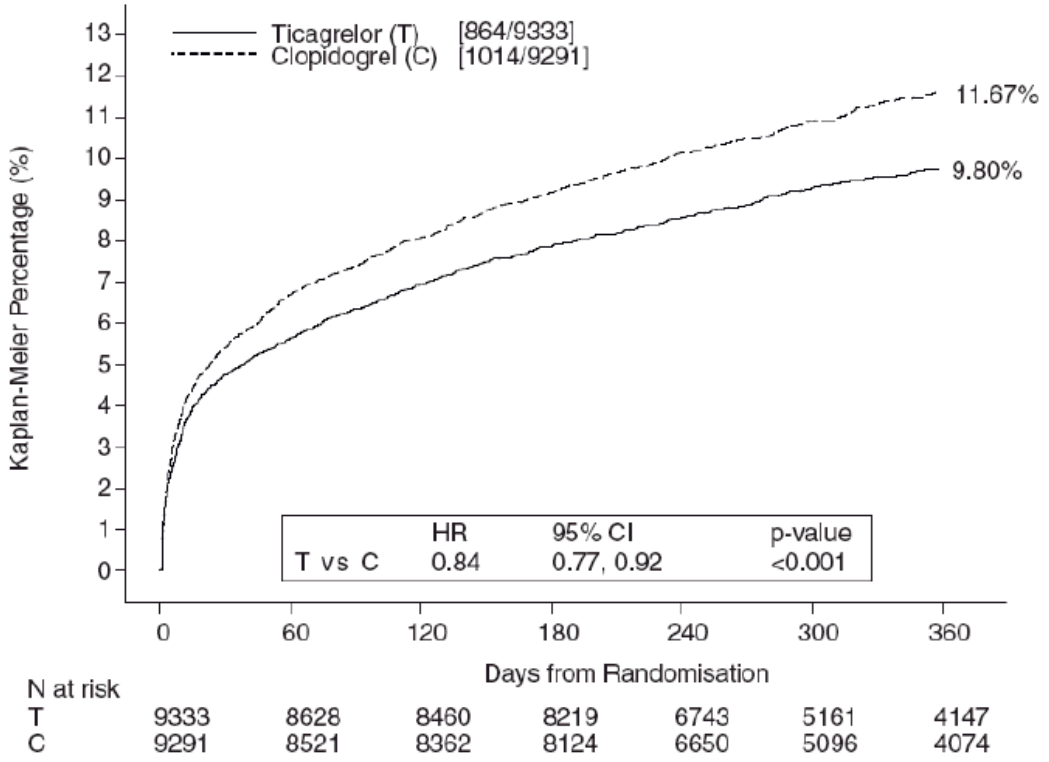
1.9% per year with RRR of 16%. This suggests it is appropriate to treat patients with ticagrelor 90 mg twice daily for 12 months. Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will prevent 1 CV death.

The treatment effect of ticagrelor over clopidogrel appears consistent across many subgroups, including weight; sex; medical history of diabetes mellitus, transient ischaemic attack or non-haemorrhagic stroke, or revascularisation; concomitant therapies including heparins, GpIIb/IIIa inhibitors and proton pump inhibitors; final index event diagnosis (STEMI, NSTEMI or UA); and treatment pathway intended at randomisation (invasive or medical).

A weakly significant treatment interaction was observed with region whereby the hazard ratio (HR) for the primary endpoint favours ticagrelor in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). Exploratory analyses suggest a possible association with ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Chronic daily ASA doses to accompany ticagrelor should be 75-150 mg.

The figure below shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint.

Figure 1: Analysis of primary clinical composite endpoint of CV death, MI and stroke (PLATO)



Ticagrelor reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population. Thus, ticagrelor 90 mg twice daily together with low-dose ASA can be used in patients with ACS (unstable angina, non-ST elevation MI [NSTEMI] or ST elevation MI [STEMI]); including patients managed medically, and those who are managed with PCI or CABG.

PLATO genetic substudy

CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient CYP2C19 or ABCB1 genotype. Similar to the overall PLATO study, total PLATO Major bleeding did not differ between ticagrelor and clopidogrel, regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele [4].

Combined efficacy and safety composite
A combined efficacy and safety composite (CV death, MI, stroke or PLATO-defined 'Total Major' bleeding) indicates that the benefit in efficacy of ticagrelor compared to clopidogrel is not offset by the major bleeding events (ARR 1.4%, RRR 8%, HR 0.92; p=0.0257) over 12 months after ACS.

Clinical safety

Holter substudy:
To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6%, respectively, after 1 month. The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of CHF (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history). This imbalance did not occur at one month: 2.0% versus 2.1% for ticagrelor patients with and without CHF history, respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients [4].

PEGASUS study (History of MI)

The PEGASUS TIMI-54 study was a 21,162 patient, event-driven, randomised, double-blind, placebo-controlled, parallel group, international multicentre study to assess the prevention of atherothrombotic events with ticagrelor given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose ASA (75-150 mg), compared to ASA therapy alone in patients with history of MI and additional risk factors for atherothrombosis. Patients were eligible to participate if they were aged 50 years or over, with a history of MI (1 to 3 years prior to randomisation) and had at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD or chronic non-end-stage renal dysfunction [4].

Patients were ineligible if there was planned use of a P2Y12 receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; if they had a bleeding disorder or a history of an ischaemic stroke or intracranial bleeding, a central nervous system tumour or an intracranial vascular abnormality; if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days [4].

Clinical efficacy

Both 60 mg twice daily and 90 mg twice daily regimens of ticagrelor in combination with ASA were superior to ASA alone in the prevention of atherothrombotic events (composite endpoint: CV death, MI, and stroke), with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% ARR for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg. Although the efficacy profiles of 90 mg and 60 mg were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to risk of the bleeding and dyspnoea. Therefore, only Brilique 60 mg twice daily co-administered with ASA is recommended for the prevention atherothrombotic events (CV death, MI, and stroke) in patients with a history of MI and a high risk of developing an atherothrombotic event.

Relative to ASA alone, ticagrelor 60 mg twice daily significantly reduced the primary composite endpoint of CV death, MI, and stroke. Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR and stroke 25% RRR). The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

There was no evidence of benefit (no reduction in the primary composite endpoint of CV death, MI, and stroke, but an increase in major bleeding) when ticagrelor 60 mg twice daily was introduced in clinically stable patients >2 years from the MI, or more than one year after stopping previous ADP receptor inhibitor treatment.

Clinical safety

The rate of discontinuations with ticagrelor 60 mg due to bleeding and dyspnoea was higher in patients >75 years (42%) than in younger patients (range: 23-31%), with a difference versus placebo higher than 10% (42% vs. 29%) in patients >75 years.

Guidelines Recommendations on the Use of Ticagrelor

International guidelines support the use of ticagrelor for patients with CVD. Selected American College of Cardiology/American Heart Association guidelines indicate that it is reasonable to use ticagrelor in preference to clopidogrel for P2Y12 treatment (including maintenance P2Y12 treatment) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) who undergo an early invasive or ischemia-guided strategy [5]. Further, in patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischaemic events, including stent thrombosis [9].

Canadian Association of International Cardiology/Canadian Cardiology Society guidelines indicate that dual anti-platelet therapy (DAPT) with ASA 81 mg daily with either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily over clopidogrel 75 mg once daily for 1 year is recommended in patients with ACS (ST segment elevation MI [STEMI] or non-ST-elevation MI [NSTEMI]) who receive PCI [10].

The ESC has stated that recommendations for antithrombotic treatment in patients with NSTE-ACS, undergoing PCI, include ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg loading dose, 90 mg twice daily), prasugrel in P2Y12 receptor inhibitor-naïve patients proceeding to PCI (60 mg loading dose, 10 mg/d as standard dose, 5 mg/d for patients aged ≥ 75 years or with a body weight <60 kg), or clopidogrel (30–600 mg loading dose, 75 mg daily dose),

only when prasugrel or ticagrelor are not available, cannot be tolerated or are contraindicated [6]. Further, recommendations on periprocedural and post-procedural antithrombotic therapy in patients with STEMI undergoing PCI includes the use of a potent P2Y12 inhibitor (ticagrelor or prasugrel) or clopidogrel if these are not available or are contraindicated, is recommended before (or at the latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding [7]. For maintenance antithrombotic treatment after STEMI, DAPT in the form of ASA plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contradictions such as excessive risk of bleeding.

Select ECS/EACTS guidelines suggest that in patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of ASA is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications [12]. In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established. Lastly, in patients with MI and high ischaemic risk who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg twice daily for longer than 12 months on top of ASA may be preferred over clopidogrel or prasugrel. In patients with NTSE-ACS undergoing PCI antithrombotic treatment may include prasugrel in P2Y12-naïve patients who proceed to PCI (60 mg loading dose and 10 mg daily dose); ticagrelor irrespective of the pretreatment and revascularization strategy (180 mg loading dose, 90 mg twice daily); clopidogrel (600 mg loading dose and 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated [11]. Recommendations for antithrombotic therapy in patients with STEMI undergoing PCI include a potent P2Y12 inhibitor (prasugrel or ticagrelor) or clopidogrel if these are not available or are contraindicated, is recommended before (or at the latest time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.

Section 8: Information Regarding the Public Health Relevance

The Global CVD and stroke related mortality and disability-adjusted life years (DALY)-burden are driven by the burden in LMICs. Specifically, a report from the ESC Atlas analysed CVD disease statistics across 56 member countries, placing emphasis on international inequalities in disease burden and healthcare delivery together with estimates of progress towards meeting 2025 WHO non-communicable disease targets [3]. Report findings showed that there were associated inequalities in disease burden DALY per 100,000 people due to CVD over three times as high in middle-income versus high income countries. CVD 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].

Figure 3: Age-standardized prevalence of ischaemic heart disease, stroke and DALY due to cardiovascular diseases in inhabitants of ESC countries [23]

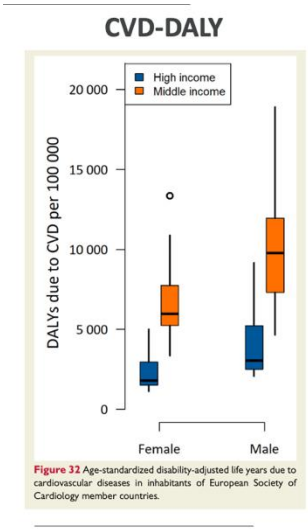


Figure 32 Age-standardized disability-adjusted life years due to cardiovascular diseases in inhabitants of European Society of Cardiology member countries.

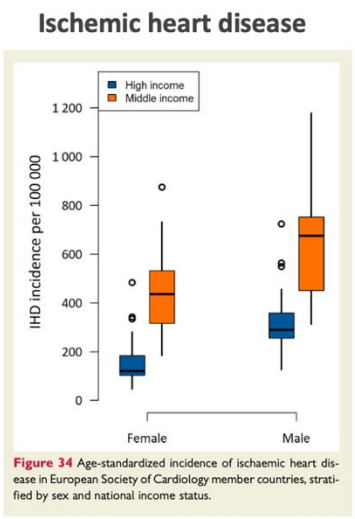


Figure 34 Age-standardized incidence of ischaemic heart disease in European Society of Cardiology member countries, stratified by sex and national income status.

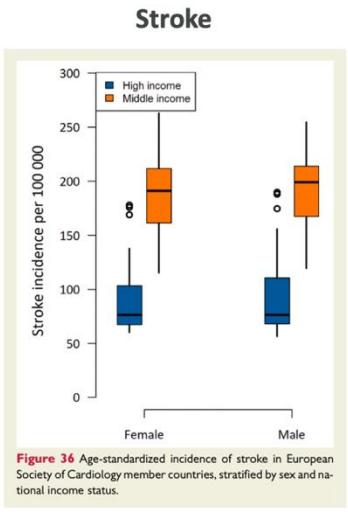
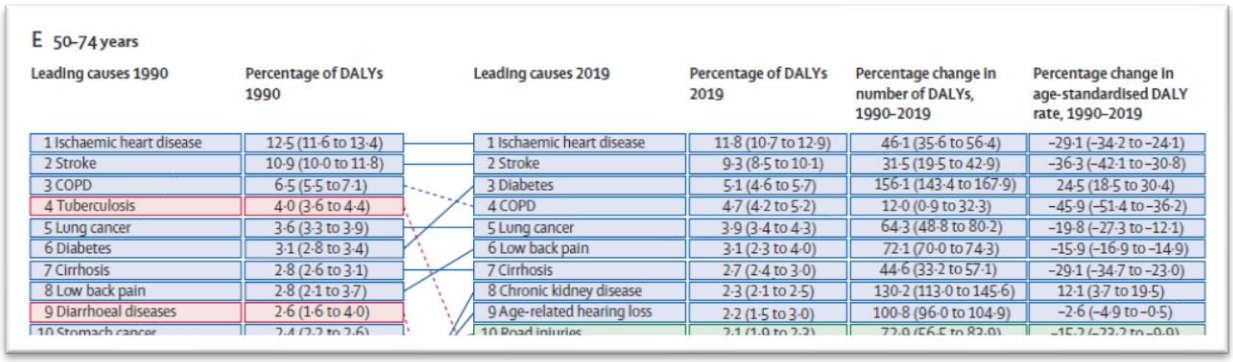


Figure 36 Age-standardized incidence of stroke in European Society of Cardiology member countries, stratified by sex and national income status.

In 2019 (4 years after the introduction of clopidogrel to the WHO Essential Medicines List), ischaemic heart disease (IHD) and stroke were the 1st and 2nd highest causes of mortality worldwide in the over 50s [16, 24].

Figure 3: Leading Level 3 causes of global DALYs and percentage of total DALYs (1990 and 2019), and percentage change in number of DALYs and age-standardised DALY rates from 1990 to 2019 for both sexes combined for age 50-74 years



E 50–74 years

Leading causes 1990	Percentage of DALYs 1990	Leading causes 2019	Percentage of DALYs 2019	Percentage change in number of DALYs, 1990–2019	Percentage change in age-standardised DALY rate, 1990–2019
1 Ischaemic heart disease	12·5 (11·6 to 13·4)	1 Ischaemic heart disease	11·8 (10·7 to 12·9)	46·1 (35·6 to 56·4)	−29·1 (−34·2 to −24·1)
2 Stroke	10·9 (10·0 to 11·8)	2 Stroke	9·3 (8·5 to 10·1)	31·5 (19·5 to 42·9)	−36·3 (−42·1 to −30·8)
3 COPD	6·5 (5·5 to 7·1)	3 Diabetes	5·1 (4·6 to 5·7)	156·1 (143·4 to 167·9)	24·5 (18·5 to 30·4)
4 Tuberculosis	4·0 (3·6 to 4·4)	4 COPD	4·7 (4·2 to 5·2)	12·0 (0·9 to 32·3)	−45·9 (−51·4 to −36·2)
5 Lung cancer	3·6 (3·3 to 3·9)	5 Lung cancer	3·9 (3·4 to 4·3)	64·3 (48·8 to 80·2)	−19·8 (−27·3 to −12·1)
6 Diabetes	3·1 (2·8 to 3·4)	6 Low back pain	3·1 (2·3 to 4·0)	72·1 (70·0 to 74·3)	−15·9 (−16·9 to −14·9)
7 Cirrhosis	2·8 (2·6 to 3·1)	7 Cirrhosis	2·7 (2·4 to 3·0)	44·6 (33·2 to 57·1)	−29·1 (−34·7 to −23·0)
8 Low back pain	2·8 (2·1 to 3·7)	8 Chronic kidney disease	2·3 (2·1 to 2·5)	130·2 (113·0 to 145·6)	12·1 (3·7 to 19·5)
9 Diarrhoeal diseases	2·6 (1·6 to 4·0)	9 Age-related hearing loss	2·2 (1·5 to 3·0)	100·8 (96·0 to 104·9)	−2·6 (−4·9 to −0·5)
10 Stomach cancer	2·4 (2·2 to 2·6)	10 Road injuries	2·1 (1·9 to 2·3)	72·9 (56·5 to 82·9)	−15·2 (−22·2 to −9·9)

Additionally, all-cause mortality in LMIC has reduced over the past three decades, but there has been no reduction in CVD and stroke-related mortality [24-26].

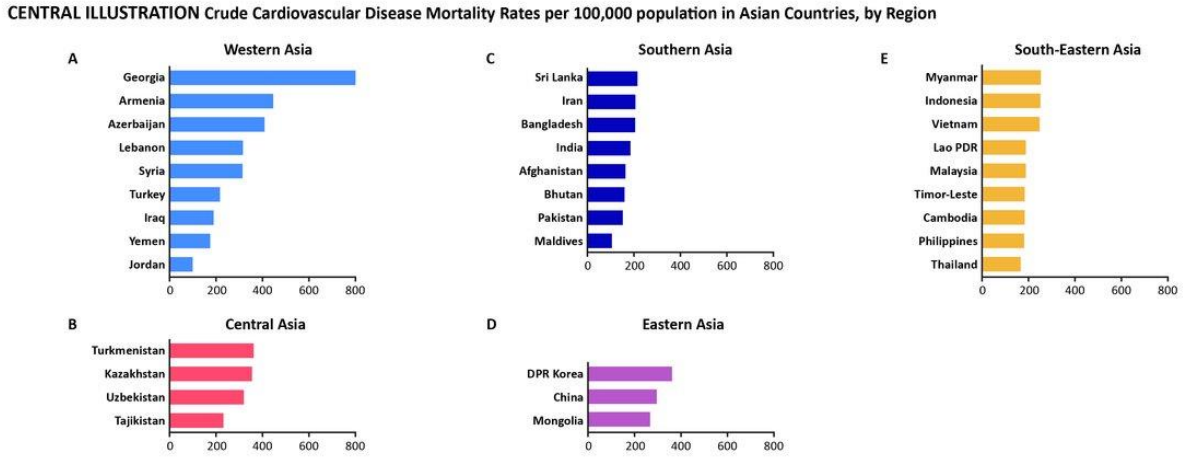
The COVID-19 pandemic has further increased the CVD-related burden, impacting LMIC countries the most. Indeed, among nations with high COVID-19 mortality, China is forecast to have the highest growth rate for CVD mortality indicating the country has less time to implement control and preventive measures to reduce the overall impact on health systems [27].

Impact of CVD in LMICs

Notably, rates of hospitalisation, mortality, probability of CVD death and stroke are substantial in datasets from LMICs, including Albania, Asia-Pacific, Iran, Kazakhstan, Pakistan, and Sub-Saharan Africa [28-33].

There is also continuously increasing CVD mortality rate, with a high proportion of premature CVD deaths in Asia. An analysis of data from four sources (the open database of the GBD (Global Burden of Disease), study in the Global Health Data Exchange of The Institute for Health Metrics and Evaluation, World Population Prospects 2019, a report by the Department of Economic and Social Affairs, Population Division of the United Nations , World Health Statistics 2020, an updated report of the World Health Organization, and an in-depth PubMed search of CVD epidemiology in Asian regions or countries), found that CVD was the leading cause of death in Asia in 2019, causing 10.8 million deaths, representing approximately 35% of the total deaths in Asia [34]. Additionally, from 1990 to 2019, the number of CVD deaths in Asia increased from 5.6 million to 10.8 million, the proportion of CVD deaths in total deaths increased from 23% to 35%, and there was a continuous increase in crude CVD mortality rates in both men and women [34]. The authors of the analysis note that "in addition to the impact of demographic changes, increasing CVD epidemics in Asia are likely the consequence of complex effects from changes in socioeconomics, living environments, lifestyles, prevalence of CVD risk factors, and capacities to prevent and treat CVD".

Figure 4: Crude cardiovascular disease mortality rates per 100,000 population in Asian countries by region [34]



Section 9: Review of Benefits: Summary of Evidence of Comparative Effectiveness

The following reviews the evidence to support this application for addition of ticagrelor to the WHO Model List of Essential Medicines.

The benefits of ticagrelor in people with CVD include:

- Effective antiplatelet activity that is irrespective of genetic background [35]
- Reduced risk of in-hospital cardiac arrest [36, 37]
- Reduction of risk for cardiovascular death, MI, or ischaemic stroke [38]

The following section summarises recent systematic reviews, network meta-analyses, and primary research articles on the clinical effects of ticagrelor in comparison to other agents.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) study was a multi-centre, double-blind, randomised study that compared ticagrelor (180 mg loading dose, 90 mg twice daily

thereafter) versus clopidogrel (300 to 600 mg loading dose, 75 mg daily thereafter) on the prevention of cardiovascular effects in patients admitted to the hospital with an acute coronary syndrome (N=18,624; NCT00391872) [39]. After 12 months of treatment, ticagrelor compared to clopidogrel had significantly reduced rates of death from vascular causes, MI, or stroke (9.8% vs 11.7%, *P*<0.001). Likewise, patients with ticagrelor treatment had significant differences in the rates of MI (5.8% vs 6.9%, *P*=0.005) and death from vascular causes (4.0% vs 5.1%, P=0.001), but not stroke alone compared to clopidogrel. The rate of death from any cause was also reduced with ticagrelor versus clopidogrel (4.5% vs 5.9%, P<0.001). There was no significant increase in the risk of major or fatal bleeding, although there was an increase in non-CABG-related major bleeding with ticagrelor versus clopidogrel (4.5% vs 3.8%, P=0.03).

A substudy of PLATO (n=10,285) analyzed 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 versus clopidogrel, irrespective of CYP2C19 or ABCB1 genotype [35]. The reduced risk of cardiovascular death with ticagrelor, regardless of genotype, suggests that the use of ticagrelor may be initiated for patients without the need for recommended genetic testing and may be a potential option for patients who are resistant or unresponsive to clopidogrel.

A meta-analysis of 10 randomised controlled studies in ACS identified similar efficacy and safety profiles for ticagrelor versus clopidogrel. No significant differences were found between patients receiving ticagrelor or clopidogrel for the risk of bleeding rate (*P*=0.43), MI (*P*=0.14), and stroke (*P*=0.70) [38].

In a network meta-analysis of ACS patients (N=52,816) from 12 randomised trials, ticagrelor significantly reduced cardiovascular mortality (HR, 0.82 [95% CI, 0.72–0.92) and all-cause mortality (HR, 0.83 [95% CI, 0.75–0.92]) compared to clopidogrel [40]. Also, stent thrombosis risk was significantly reduced by both ticagrelor and prasugrel versus clopidogrel (28%–50% range of reduction). The PLATlet inhibition and patient Outcomes (PLATELET) analysis, a substudy of PLATO, compared antiplatelet effects of ticagrelor versus clopidogrel in patients with ACS (N=69, 28 days maintenance treatment with ticagrelor [n=37; 90 mg twice daily] or clopidogrel [n=32; 75 mg/day]) [41]. Ticagrelor produced significantly reduced 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 ACS both in the first hours of treatment and during maintenance.

A nationwide database was used to assess clinical characteristics of STEMI patients with IHCA, as well as predictors and treatments associated with risk of IHCA. In the CCC-ACS (Improving Care for Cardiovascular Disease in Chine-Acute Coronary Syndrome) project (2014-2019), patients presenting with STEMI within 24 hours after symptom onset were stratified according to IHCA or no IHCA during index hospitalization [36]. Of the 40,670 STEMI patients, 2.2% experienced IHCA, which in turn was responsible for more than half of inpatient deaths. However, PCI (adjusted HR: 0.82; 95% CI: 0.71-0.95), β-blockers (adjusted HR: 0.63; 95% CI: 0.47-0.86), and ticagrelor (adjusted HR: 0.57; 95% CI: 0.42-0.76) treatments were associated with a reduced risk of IHCA [36].

A systematic review compared the efficacy of ticagrelor versus clopidogrel in improving endothelial function in patients with CAD (7 trials, n=511) [42]. Ticagrelor versus clopidogrel resulted in greater elevation of progenitor cells CD34+KDR+, and CD34+133+ (*P*=0.036 and *P*=0.019), with a lower rate of endothelial cell apoptosis rate (*P*<0.001). In addition, ticagrelor demonstrated superiority regarding nitric oxide, radical oxygen species, and soluble P-selectin levels (*P*=0.03, *P*=0.02, *P*=0.019)

versus clopidogrel. Altogether, ticagrelor appeared to exert improved endothelial cell function compared to patients receiving clopidogrel.

A network meta-analysis of randomised controlled trials found that compared to ASA alone, addition of prasugrel or ticagrelor to ASA resulted in lower risk of MI (OR: 0.38 (95% confidence interval 0.38–0.62); 0.810–0.84 (0.69–0.98)] and any stroke [0.56 (0.42–0.75)] [43].

A systematic review and meta-analysis assessed antithrombotic therapy for symptomatic peripheral arterial disease (24 randomised controlled trials, N=48,759) [44]. With regard to reducing MACE, clopidogrel [RR 0.78, 95% confidence interval (CI) 0.66–0.93], ticagrelor (RR 0.79, 95% CI 0.65–0.97), ASA plus ticagrelor (RR 0.79, 95% CI 0.64–0.97), and ASA plus low-dose rivaroxaban (RR 0.84, 95% CI 0.76–0.93) were more effective than ASA, and equally effective to one another [44]. Another systematic review and meta-analysis conducted with 22 studies (N=35,004) evaluated the efficacy and safety of ticagrelor compared to clopidogrel in general ACS patients [45]. Compared to clopidogrel, ticagrelor reduced the incidence of the composite endpoint of cardiovascular death [OR = 0.83, 95%CI (0.77, 0.90), P<0.00001] and the incidence of MI [OR = 0.81, 95% CI (0.74, 0.89), *P*=0.0001] [45].

A single-centre retrospective cohort study was conducted with patients with CAD receiving dual antiplatelet therapy after PCI for up to 12 months (n=908) [1]. Patients received ticagrelor plus ASA (n=264) or clopidogrel with ASA (n=644). Ticagrelor was associated with a lower incidence of MACE versus clopidogrel using the inverse probability of treatment weighting model (OR, 0-493; 95% confidence interval, 0.356-0.684). There was no difference in the risk of Bleeding Academic Research Consortium bleeding between the two groups *(P*> 0.05).

Section 10 Review of Harms and Toxicity: Summary of Evidence of Safety

Special warnings and precautions for use [4]

Bleeding risk

The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, ticagrelor should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding) or who are at increased risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment.

- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g., non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of ticagrelor dosing.

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ticagrelor with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.

Surgery
Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.

In PLATO patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery. If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery

Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months (PLATO study). In PEGASUS, patients with history of MI with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients.

Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients.

Patients at risk for bradycardic events
Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. Patients with an increased risk of bradycardic events (e.g., patients without pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) have been excluded from the main studies evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinical experience, ticagrelor should be used with caution in these patients.

In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia. However, no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g., 96% betablockers, 33% calcium channel blockers diltiazem and verapamil and 4% digoxin).

During the Holter substudy in PLATO, more patients had ventricular pauses >3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population.

Bradyarrhythmic events and AV blocks have been reported in the post-marketing setting in patients taking ticagrelor, primarily in patients with ACS, where cardiac ischemia and concomitant drugs reducing the heart rate or affecting cardiac conduction are potential confounders. The patient's clinical condition and concomitant medication should be assessed as potential causes prior to adjusting treatment.

Dyspnoea
Dyspnoea was reported in patients treated with ticagrelor. Dyspnoea is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with

asthma/chronic obstructive pulmonary disease (COPD) may have an increased absolute risk of experiencing dyspnoea with ticagrelor. Ticagrelor should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged, or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped.

Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with ticagrelor, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase
Hyperuricaemia may occur during treatment with ticagrelor. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction, or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)
In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies inpatient serum activate platelets of healthy donors in the presence of heparin. False negative results in a platelet function test (to include but may not be limited to the HIPA test) for HIT have been reported in patients administered ticagrelor. This is related to inhibition of the P2Y12-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.

In patients who have developed HIT, the benefit-risk of continued treatment with ticagrelor should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.

Other
Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended.

Premature discontinuation
Premature discontinuation with any antiplatelet therapy, including Brilique, could result in an increased risk of cardiovascular (CV) death, MI, or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

Description of Selected Adverse Events

Bleeding findings in PLATO
Overall outcome of bleeding rates in the PLATO study are shown in the Table below.

Table 1: Analysis of overall bleeding events, Kaplan-Meier estimates at 12 months (PLATO)

	Ticagrelor 90 mg twice daily N=9235	Clopidogrel N=9186	*p*-value*
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084
Non-Procedural PLATO Major + Minor	5.9	4.3	<0.0001
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

Bleeding category definitions:
Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/L decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor Bleed: Requires medical intervention to stop or treat bleeding.
TIMI Major Bleed: Clinically apparent with >50 g/L decrease in haemoglobin or intracranial haemorrhage.
TIMI Minor Bleed: Clinically apparent with 30-50 g/L decrease in haemoglobin.
*p-value calculated from Cox proportional hazards model with treatment group as the only explanatory variable.

Ticagrelor and clopidogrel did not differ in rates of PLATO Major Fatal/Life-threatening bleeding, PLATO total Major bleeding, TIMI Major bleeding, or TIMI Minor bleeding (Table 2). However, more PLATO combined Major + Minor bleeding occurred with ticagrelor compared with clopidogrel. Few patients in PLATO had fatal bleeds: 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel.

Age, sex, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO Major bleeding. Thus, no particular group was identified at risk for any subset of bleeding.

CABG-related bleeding:
In PLATO, 42% of the 1584 patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery had a PLATO Major Fatal/Life-threatening bleeding with no difference between treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group.

Non-CABG related bleeding and non-procedural related bleeding:
Ticagrelor and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedure related bleeds, more bleeding occurred with ticagrelor than with clopidogrel. Discontinuation of treatment due to nonprocedural bleeding was more common for ticagrelor (2.9%) than for clopidogrel (1.2%; p<0.001).

Intracranial bleeding*:*

There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.

Bleeding findings in PEGASUS
Overall outcome of bleeding events in the PEGASUS study are shown in the Table below.

Table 2: Analysis of overall bleeding events, Kaplan-Meier estimates at 36 months (PEGASUS)

	Ticagrelor 60 mg twice daily + ASA N=6958		ASA alone N=6996	
Safety Endpoints	**KM%**	**Hazard Ratio (95% CI)**	**KM%**	***p*-value**
TIMI-defined bleeding categories				
TIMI Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other TIMI Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
TIMI Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001
PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

Bleeding category definitions:
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of 15%.
Fatal: A bleeding event that directly led to death within 7 days.
ICH: Intracranial haemorrhage.
Other TIMI Major: Non-fatal non-ICH TIMI Major bleeding.
TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.
TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalisation, OR prompting evaluation.
PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin or ≥4 red cell units transfused.
PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
PLATO Minor: Requires medical intervention to stop or treat bleeding.

In PEGASUS, TIMI Major bleeding for ticagrelor 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of TIMI Major bleeding with ticagrelor 60 mg was primarily due to a higher frequency of Other TIMI Major bleedings driven by events in the gastrointestinal SOC.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor and PLATO Major and PLATO Major or Minor bleeding categories. Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were of less severity (classified as TIMI Requiring medical attention), e.g., epistaxis, bruising and haematomas.

The bleeding profile of ticagrelor 60 mg was consistent across multiple pre-defined subgroups (e.g., by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy and medical history) for TIMI Major, TIMI Major or Minor and PLATO Major bleeding events.

Intracranial bleeding:
Spontaneous ICHs were reported in similar rates for ticagrelor 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedural ICHs showed a minor increase with ticagrelor 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with ticagrelor 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was low in both treatment groups given the significant comorbidity and CV risk factors of the population under study.

Dyspnoea
Dyspnoea, a sensation of breathlessness, is reported by patients treated with ticagrelor. In PLATO, dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal and nocturnal dyspnoea), when combined, was reported by 13.8% of patients treated with ticagrelor and by 7.8% of patients treated with clopidogrel. In 2.2% of patients taking ticagrelor and by 0.6% taking clopidogrel investigators considered the dyspnoea causally related to treatment in the PLATO study and few were serious (0.14% ticagrelor; 0.02% clopidogrel). Most reported symptoms of dyspnoea were mild to moderate in intensity, and most were reported as a single episode early after starting treatment.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel). In absolute terms, this risk was higher than in the overall PLATO population. Ticagrelor should be used with caution in patients with history of asthma and/or COPD.

About 30% of episodes resolved within 7 days. PLATO included patients with baseline congestive heart failure, COPD or asthma; these patients, and the elderly, were more likely to report dyspnoea. For ticagrelor, 0.9% of patients discontinued study drug because of dyspnoea compared with 0.1% taking clopidogrel. The higher incidence of dyspnoea with ticagrelor is not associated with new or worsening heart or lung disease. Ticagrelor does not affect tests of pulmonary function.

In PEGASUS, dyspnoea was reported in 14.2% of patients taking ticagrelor 60 mg twice daily and in 5.5% of patients taking ASA alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity. Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, COPD, or asthma at baseline.

Investigations
Uric acid elevations: In PLATO, serum uric acid increased to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. The corresponding numbers in PEGASUS were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, 60 mg and placebo, respectively. Mean serum uric acid increased approximately 15% with ticagrelor compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on ticagrelor but with no decrease 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 to a 1.5% decrease in the placebo group. In PLATO, the frequency of gouty arthritis was 0.2% for ticagrelor vs. 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, 60 mg and placebo, respectively.

Section 11: Summary of Available Data on Comparative Cost and Cost-effectiveness

There is little information on the cost effectiveness of ticagrelor vs clopidogrel in LMICs. However, it appears that the few cost-effectiveness assessments in LMICs have found ticagrelor to be cost-effective vs clopidogrel. These assessments are summarised below. *Please note that for each study below, the summary includes direct excerpts from the cited reference.*

Colombia

For example, a cost-effectiveness analysis from the Colombian health system compared ticagrelor and clopidogrel for the treatment of patients with ACS using a Markov model, in which patients could remain stable without experiencing new cardiovascular events, suffer from a new event, or die [4]. Transition probabilities were extracted from the PLATO trial. The additional cost per quality-adjusted life-year gained with ticagrelor was COP $28,411,503, and the probability of ticagrelor being cost-effective was 75% [4].

Thailand

In Thailand, using a Markov model and data from PLATO, a base-case analysis found that incremental cost-effectiveness ratio (ICER) with ticagrelor was 292,504 ($9,476) and 60,055 ($1,946) THB ($)/QALY compared with generic and branded clopidogrel [17]. The probability of ticagrelor being cost-effective was above 99% at a threshold of 160,000 THB/QALY compared with branded clopidogrel.

Singapore

A Singapore healthcare perspective also found ticagrelor to have a >99% probability of being cost-effective, with a lifetime QALY gain of 0.13, primarily driven by lower mortality, as compared to clopidogrel [46].

Egypt

From an Egyptian perspective, one analysis also used a Markov model and PLATO efficacy data to assess cost-effectiveness of ticagrelor plus ASA versus clopidogrel plus ASA, and found that ticagrelor was the most cost-effective when used as dual antiplatelet therapy [14]. During the life-time horizon, total costs, QALY gained for ticagrelor plus ASA was 9.5 QALY versus 9.3 QALY with clopidogrel and ASA. Another Egypt analysis used a Markov model and PLATO-STEMI substudy

analysis to show that over 25 years, ticagrelor provides an incremental health gain of 16.87 QALY versus clopidogrel, at an incremental cost of 243,499 EGP resulting in an ICER of 14,433 EGP/QALY [13].

Brazil

A cost effectiveness model was used to estimate long-term costs and outcomes for patients scheduled for non-invasive management. Healthcare costs, event rates and health related quality of life under treatment with either ticagrelor or clopidogrel over 12 months were estimated from the PLATO study, from perspectives of Swedish, UK, German, and Brazilian public healthcare systems. Ticagrelor was associated with lifetime QALY gains of 0.17 (Sweden), 0.16 (UK), 0.17 (Germany), and 0.13 (Brazil) compared with clopidogrel, with increased healthcare costs of €467, €551, €739 and €574. The cost per QALY gained with ticagrelor was €2747, €3395, €4419 and €4471 from a Swedish, UK, German and Brazilian public healthcare system perspective, respectively, suggesting that treatment of patients with ACS scheduled for 12 months' non-invasive management with ticagrelor is associated with a cost per QALY gained below conventional threshold values of cost effectiveness compared with clopidogrel.[8]

Vietnam

Lastly, a study investigated the long-term cost-effectiveness, from a Vietnamese healthcare payers' perspective, of ticagrelor vs clopidogrel in ACS patients. Using a two-part cost-effectiveness model to estimate long-term costs and QALY, the study authors found that ticagrelor was associated with an incremental cost of USD 216.49 and a QALY gain of 0.11, resulting in a cost per QALY gained of USD 2009.96. The authors therefore concluded that "ticagrelor can be considered a cost-effective treatment for ACS compared with clopidogrel from a Vietnamese healthcare payers' perspective".[15]

Average published prices for ticagrelor and clopidogrel in LMICs.

Table 3: Average published price per day of treatment (US$†) for ticagrelor and clopidogrel in LMIC where prices are published for both medicines

	BANGLADESH	EGYPT	INDIA	INDONESIA	MOROCCO	NICARAGUA	TUNISIA	UKRAINE	VIETNAM
Ticagrelor*	0.05	0.56	0.72	2.79	2.05	3.18	1.83	2.00	1.33
Clopidogrel**	0.10	0.16	0.10	0.97	0.45	1.26	0.44	0.06	0.32

*Average price of the 90 mg strength. ** Average price of the 75 mg strength. † Converted using Oanda Rate 15/12/22. Source: Navlin (https://data.navlin.com/alspc/#!/). Note: Prices are published list prices and do not take into account confidential discounts/rebates therefore it is likely there could be significant variation at confidential net price level. The definition of list price varies by country, for example the inclusion/exclusion of wholesaler/pharmacy mark-ups and tax.

Section 12: Summary of Regulatory Status and Market Availability

Table 4. Regulatory Approval Status for Ticagrelor (Brilinta) in Selected Jurisdictions

Ticagrelor (Brilinta) Formulation and Dose	**US**	**EMA**	**Japan**	**Australia**	**Canada**
Film-Coated Tablets,	Yes	Yes	Yes	No	Yes

60 mg					
Film-Coated Tablets, 90 mg	Yes	Yes*	Yes	Yes	Yes
Orodispersible Tablets, 90 mg	No	Yes	No	Yes	No

*Not authorised through EMA's centralised procedure, as predates establishment of this pathway, but approved in many EU countries nationally. Withdrawn post-approval in the UK.

Section 13: Availability of Pharmacopeial Standards

A monograph for ticagrelor tablets is available in the European Pharmacopeia (Ph. Eur.). Reference standards for ticagrelor tablets are available from the European Directorate for the Quality of Medicines and Healthcare (EDQM).

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