CALL FOR STAKEHOLDER COMMENTS ON THE PRELIMINARY RECOMMENDATION OF THE HEALTH TECHNOLOGY ASSESSMENT (HTA) COUNCIL ON *TICAGRELOR* [90mg film-coated tablet] AS AN ADD-ON TO ASPIRIN FOR ADULTS WITH ACUTE CORONARY SYNDROME (ACS)

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As of 02 May 2025, the Health Technology Assessment (HTA) Council has completed the evidence appraisal on the assessment of **ticagrelor [90mg film-coated tablet] as an add-on to aspirin for adults with acute coronary syndrome (ACS)** for possible financing by the Department of Health (DOH) and/or the Philippine Health Insurance Corporation (PhilHealth). **The HTA Council hereby releases its preliminary recommendation on the said health technology for stakeholder feedback and comments from 02 May (Friday) to 19 May (Monday) 2025**.

The population, intervention, comparator, and outcome (PICO) set by the HTA Council for the said evaluation are shown in the table below, for your reference:

Population	Adults with acute coronary syndrome (unstable angina, non-ST-elevation myocardial infarction, ST-Elevation myocardial Infarction), including patients managed medically, and those with percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)
Intervention	Ticagrelor 90mg film-coated tablet as an add-on to aspirin
Comparator	Clopidogrel as an add-on to aspirin

Outcome	Efficacy/Effectiveness
	• Critical
	  ○ Death from vascular causes, myocardial infarction or stroke (Cardiovascular Mortality)
	  ○ Myocardial infarction
	  ○ Stroke
	  ○ Other thrombotic events
	  ○ MACE (major adverse cardiac events)
	  ○ Quality of life
	  ○ Stent thrombosis
	• Important
	  ○ Target vessel failure
	Safety
	• Critical

	○ Major bleeding: ■ PLATO* ■ TIMI** ○ Procedure-related bleeding***: ■ PLATO ■ TIMI ■ Neither PLATO nor TIMI ○ Non-procedure-related bleeding**** ■ PLATO ■ TIMI ■ Neither PLATO nor TIMI ○ Fatal/life-threatening bleeding ○ All bleeding ○ All-cause mortality ○ Dyspnea ○ Bradycardia ○ Embolism ● Important ○ Gastrointestinal upset

**Study of PLATelet Inhibition and Patient Outcomes; PLATO major life-threatening bleeding is defined as fatal bleeding, intracranial hemorrhage, intrapericardial bleeding with cardiac tamponade, bleeding resulting in hypovolemic shock or severe hypotension requiring vasopressors or surgical intervention, clinically overt bleeding with a hemoglobin decrease of >5 g/dL, or bleeding requiring transfusion of ≥4 units of whole blood or packed red blood cells (PRBCs). Other major bleeding includes significantly disabling bleeding (e.g., intraocular with permanent vision loss), a hemoglobin drop of 3 to 5 g/dL, or transfusion of 2 to 3 units of whole blood or PRBCs. Any major bleeding is defined as the occurrence of any one of these criteria.*
***Thrombolysis In Myocardial Infarction; TIMI major bleeding is defined as non-CABG-related bleeding that includes any intracranial bleeding (excluding microhemorrhages smaller than 10 mm evident only on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL, or fatal bleeding (bleeding that directly results in death within 7 days)*
****Procedure-related bleeding is defined as puncture site bleeding, non-coronary artery bypass graft surgery (CABG) and CABG-related bleeding, coronary procedural and non-coronary procedural bleeding, perioperative bleeding, or Bleeding Academic Research Consortium (BARC) type 4 bleeding, or CABG-related bleeding*
*****Non-procedure-related bleeding is defined as non-procedure major bleeding event, CNS bleed, or GI bleed*

According to the Global Burden of Disease 2021 study (Institute for Health Metrics and Evaluation, 2024), ischemic heart diseases (IHDs), which include acute coronary syndrome (ACS), have been the leading cause of mortality from 2000 to 2021. Furthermore, IHDs account for 12% of disability-adjusted life years (DALY) lost annually (Bergmark et al, 2022). In the Philippines, IHD, including ACS, has been a leading cause of death from 2014 to 2024. In addition, the study released by the Philippine Heart Association (PHA) in 2013 reported a 7.8% mortality rate among patients with ACS.

According to the 2014 PHA Clinical Practice Guidelines, the standard of care for patients with ACS is composed of the following medications: dual antiplatelet therapy (DAPT), combining low dose aspirin and a P2Y12 inhibitor, statins, beta-blockers, and either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Both aspirin and clopidogrel (a P2Y12 inhibitor) are already listed in the Philippine National Formulary (PNF). There are representative drugs under the mentioned drug classes in the PNF as well.

As a preliminary recommendation, the HTA Council does not recommend the government financing of ticagrelor [90mg film-coated tablet] as an add-on to aspirin for adults with ACS. This HTA Council preliminary recommendation draws from the following evidentiary bases:

- In terms of **clinical efficacy,** the review of evidence showed the following:
  - Ticagrelor as an add-on therapy to aspirin is **non-inferior** to clopidogrel as an add-on to aspirin in reducing the risk of cardiovascular mortality [*10 RCTs; very low certainty of evidence*], myocardial infarction [*12 RCTs; low certainty of evidence*], and other thrombotic events (i.e., arterial/venous thrombotic events) [*3 RCTs; moderate certainty of evidence*].
  - The results were **inconclusive** for stroke [*10 RCTs; low certainty of evidence*], MACE [*11 RCTs; very low certainty of evidence*], and stent thrombosis [*7 RCTs; very low certainty of evidence*].

        - No evidence found for *target vessel failure* and *quality of life* outcomes.

- In terms of **clinical safety**, the review of evidence showed the following:
    - Ticagrelor as an add-on to aspirin is **non-inferior** to clopidogrel as an add-on to aspirin in terms of all-cause mortality (*12 RCTs; very low certainty of evidence*).
    - Ticagrelor as an add-on to aspirin **increases the risk** of major bleeding (PLATO definition) [*7 RCTs; very low certainty of evidence*], procedure-related bleeding (PLATO definition) [*4 RCTs; very low certainty of evidence*], all bleeding [*6 RCTs; moderate certainty of evidence*], and dyspnea [*7 RCTs; moderate certainty of evidence*] as compared to clopidogrel as an add-on to aspirin.
    - The results were **inconclusive** for major bleeding (TIMI definition) [*6 RCTs; low certainty of evidence*], procedure-related bleeding (TIMI definition) [*2 RCTs; very low certainty of evidence*], procedure-related bleeding (neither TIMI nor PLATO definition) [*3 RCTs; low certainty of evidence*], non-procedure-related bleeding (PLATO definition) [*1 RCT; low certainty of evidence*], fatal/life-threatening bleeding [*5 RCTs; very low certainty of evidence*], bradycardia [*3 RCTs; moderate certainty of evidence*], and gastrointestinal upset [*3 RCTs; moderate certainty of evidence*].
    - No evidence was found for *embolism*.

- Upon review of recommendations and guidelines:
    - The WHO, in 2023, did not recommend the inclusion of ticagrelor to the Essential Medicines List (EML) for the prevention of atherothrombotic events in adults with ACS, or a history of myocardial infarction, and at high risk of developing an atherothrombotic event. The rationale for its non-recommendation includes the associated increased risk of some important bleeding outcomes (i.e., fatal intracranial bleeding) and uncertainty in efficacy outcomes. Further, ticagrelor was also not superior to clopidogrel and carried a greater risk of major bleeding in Asian patients. Despite its cost-effectiveness versus clopidogrel in high-income settings, it remains to be more expensive than clopidogrel in most markets.
    - Among the 12 Ministries of Health (MoH) scoped, four recommended the use of ticagrelor (90mg) + aspirin for the treatment of ACS. Specifically, these include two high-income countries (UK and Singapore), one upper-middle-income country (Malaysia), and one lower-middle-income country (Vietnam). The rest of the MoHs scoped (i.e., US, Europe, Canada, China, Thailand, India, Nepal, and Philippines) did not have a recommendation on the use of ticagrelor as an add-on to aspirin for patients with ACS.
    - Among 12 HTA agencies reviewed, two high-income countries (UK and Singapore) recommended ticagrelor (90 mg) + aspirin for ACS treatment. The HTA agency from Canada did not recommend the government financing of ticagrelor because of limited evidence on the superiority of ticagrelor compared with clopidogrel in the North American patient population, thus failing to justify its higher cost compared to clopidogrel. The remaining HTA agencies reviewed (i.e., US, Europe, China, Malaysia, Thailand, Vietnam, India, Nepal, Philippines) did not issue a recommendation on the use of ticagrelor as an add-on to aspirin for patients with ACS.
    - Medical societies from three high-income countries (US, Canada, Europe) and two upper-middle-income countries (Malaysia, Thailand) supported the use of ticagrelor as an add-on to aspirin for patients with ACS. Additionally, the Asia Pacific Society of Cardiology, composed of medical societies from 24 countries in the Asia Pacific region, also recommended this treatment. The remaining international medical societies scoped (i.e., UK, China) did not have a recommendation on the use of ticagrelor as an add-on to aspirin for patients with ACS.
    - Despite recommendations from some countries, the WHO and most MoHs/HTA agencies from lower-middle-income countries similar to the Philippines did not have recommendations on the use of ticagrelor as an add-on to aspirin for patients with ACS.

In conclusion, ticagrelor [90mg film-coated tablet] as an add-on to aspirin demonstrates **non-inferior clinical efficacy but inferior safety** compared to clopidogrel as an add-on to aspirin, rated with moderate to very low certainty of evidence across key outcomes. There is also no supporting guidance for its use from WHO and other countries with healthcare settings similar to the Philippines. As such, the HTA Council does not recommend its government financing.

For the supporting evidence reviewed and discussed by the HTA Council in coming up with this preliminary recommendation, please refer to: https://tinyurl.com/PrelimRecommTicagrelorACS. All comments, inputs, and/or appeals on the above preliminary recommendation may be submitted until **16 May 2025 (Friday)**, for the consideration of the HTA Council, through email at hta@dost.gov.ph. Please use the prescribed form for appeals indicated in the official HTA Philippines website [https://hta.dost.gov.ph/appeals-2/]. **Appeals not following the prescribed format, and those submitted beyond the deadline shall not be entertained**.

Should you have any questions or concerns regarding the preliminary recommendation, please do not hesitate to contact us through the same email address or *via telephone call at (02) 8837 2071 loc. 4100*.

Thank you very much and best regards.

On behalf of the HTA Philippines:

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