ASSESSMENT OF TICAGRELOR (90 MG) AS AN ADD-ON TREATMENT FOR ADULTS WITH ACUTE CORONARY SYNDROME

Health Technology Assessment Philippines

BACKGROUND

Ticagrelor

Generic Name	Ticagrelor
Pharmacologic Category	Antiplatelet agent, Non-thienopyridine, P2Y12 Antagonist
MOA	Reversibly and noncompetitively binds the adenosine diphosphate (ADP) P2Y12 receptor on the platelet surface which prevents ADP-mediated activation of the GPIIb/IIIa receptor complex thereby reducing platelet aggregation. Due to the reversible antagonism of the P2Y12 receptor, recovery of platelet function is likely to depend on serum concentrations of ticagrelor and its active metabolite
Dosing Regimen	○ **Loading dose:** [Oral] 180 mg once as early as possible after diagnosis in combination with aspirin and a parenteral anticoagulant; followed by maintenance dose ○ **Maintenance dose:** [Oral] ■ *First 12 months after diagnosis:* 90 mg twice daily beginning ~6 to 12 hours after the initial loading dose in combination with aspirin ■ *After 12 months from diagnosis:* Reduce maintenance dose to 60 mg twice daily in combination with aspirin; in selected patients with ongoing high ischemic risk, may continue 90 mg twice daily in combination with aspirin.
Dosage Strength and Form	60 mg and 90 mg film-coated tablet
Mode of Administration	Orally (taken with or without food)

References: UpToDate 2015; MIMS Philippines

Ticagrelor

Is there a DOH-approved/ local society CPG recommending this HT?	**No**
Is the HT in the WHO EML?	**No (STATUS: Rejected)**

Applied Indication

TICAGRELOR (BRILINTA®) 90 mg Film-coated tablets
For the prevention of thrombotic events among patients with Acute Coronary Syndrome

Applied indication: Prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes ([ACS] unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting(CABG).

TICAGRELOR (BRILINTA®) 60mg Film-coated tablets
For the prevention of thrombotic events among patients with Acute Coronary Syndrome

Applied indication: Prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes ([ACS] unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting(CABG).

Both 60 and 90 mg were nominated for the prevention of thrombotic events (TE) among patients with ACS. However, after stakeholder consultation (i.e., industry and Philippine Heart Association) and literature review, HTAC decided to refine the I.

60mg was for the prevention of TE for patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event, while **90mg** was for patients with ACS or those with a **history of stroke treated with medical procedures (i.e., PCI or CABG)**

Policy Question

Should Ticagrelor (90mg) as an add-on to aspirin be financed by the government for acute coronary syndrome (ACS)*?

**(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)*

HTAC-Approved PICO (1 of 2)

P	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)
I	Ticagrelor (90mg) as an add-on to aspirin
C	Clopidogrel as an add-on to aspirin
O	*See next slide*

HTAC-approved (2 of 2)

O	**Efficacy/Effectiveness** ● Death from vascular causes, MI or stroke (CV Mortality) ● Myocardial infarction ● Stroke ● Other thrombotic events ● Target vessel failure ● MACE (major adverse cardiac events) ● QoL (CHF, Angina, and Functional Capacity) ● Stent thrombosis	**Safety** ● Major bleeding: - PLATO - TIMI ● Procedure-related bleeding*: - PLATO - TIMI - Neither PLATO nor TIMI ● Non-procedure-related bleeding** - PLATO - TIMI - Neither PLATO nor TIMI ● Fatal Bleeding/life-threatening ● All bleeding ● All-cause mortality ● Dyspnea ● Bradycardia ● GI upset ● Embolism

***Procedure-related bleeding** - puncture site bleeding, non-CABG and CABG related bleeding, coronary procedural and non-coronary procedural bleeding, perioperative bleeding, BARC type 4 bleeding: CABG-related bleeding)*
****Non-procedure-related bleeding** - non-procedure major bleeding event, CNS bleed, GI bleed*

Research Questions

C1: Responsiveness to Magnitude and Severity

RQ.1. What is the **magnitude and severity** of acute coronary syndrome as a public health problem?

C2: Clinical efficacy, effectiveness and safety

Among adult patients 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),

RQ.2.1. What is the **efficacy/effectiveness** of Ticagrelor (90 mg) as an add-on to aspirin in terms of (1) death from vascular causes, (2) myocardial infarction (MI), (3) stroke, (4) other thrombotic events, (5) target vessel failure, (6) major adverse cardiac events (MACE), and quality of life QoL (CHF, angina, and functional capacity)?

RQ.2.2. What is the **safety** of Ticagrelor (90 mg) as an add-on to aspirin in terms of (1) major bleeding: PLATO; TIMI, (2) procedure-related bleeding: PLATO; TIMI; neither PLATO nor TIMI, (3) non- procedure-related bleeding: PLATO; TIMI; neither PLATO nor TIMI, (4) all-cause mortality, (5) fatal Bleeding/life-threatening, (6) all bleeding, (7) dyspnea (8) bradycardia, (9) GI upset, and (9) embolism, (10) stent thrombosis ?

RQ.2.3. What are the **recommendations and guidelines** of ministries of health, HTA agencies and medical societies on the use of Ticagrelor for ACS?

IMPORTANT TERMS:

DEFINITIONS

- **Procedure-related bleeding -** includes puncture site bleeding, non-CABG and CABG related bleeding, coronary procedural and non-coronary procedural bleeding, perioperative bleeding, BARC type 4 bleeding)
- **Non-procedure-related bleeding -** covers non-procedure major bleeding event, CNS bleed, GI bleed
- **Bleeding Academic Research Consortium (BARC)-** a collaboration among academia, professional societies, and federal agencies, modeled its effort on the Academic Research Consortium, which standardized key ischemic endpoint definitions such as stent thrombosis for studies aimed at evaluating coronary stents.
- **BARC Type 4 bleeding-** includes Coronary Artery Bypass Graft–related bleeding

ACRONYMS

- **PLATO** - Study of PLATelet Inhibition and Patient Outcomes
- **TIMI** - Thrombolysis In Myocardial Infarction
- **BARC**- Bleeding Academic Research Consortium

Bleeding definitions *(AHA, 2011)*

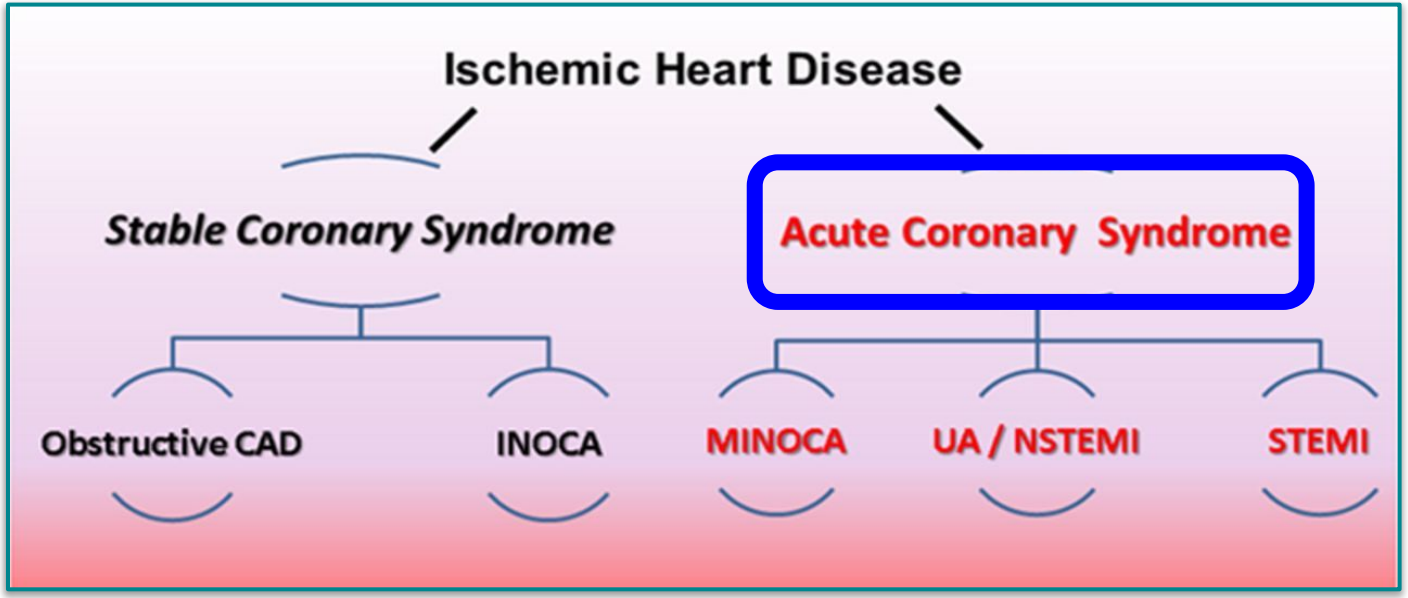
PLATO Bleeding

- Major life-threatening
  - Fatal
  - Intracranial
  - Intrapericardial with cardiac tamponade
  - Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
  - Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
  - Requiring transfusion of ≥4 U whole blood or PRBCs
- Other major
  - Significantly disabling (eg, intraocular with permanent vision loss)
  - Associated drop in hemoglobin of 3 to 5 g/dL
  - Requiring transfusion of 2 to 3 U whole blood or PRBCs
- Any major
  - Any one of the above criteria
- Minor
  - Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)
- Minimal
  - All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment

TIMI Bleeding

- Non-CABG related bleeding
  - Major
    - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
    - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
    - Fatal bleeding (bleeding that directly results in death within 7 d)
  - Minor
    - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL
  - Requiring medical attention
    - Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
    - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
    - Leading to or prolonging hospitalization
    - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
  - Minimal
    - Any overt bleeding event that does not meet the criteria above
- Bleeding in the setting of CABG
  - Fatal bleeding (bleeding that directly results in death)
  - Perioperative intracranial bleeding
  - Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
  - Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
  - Chest tube output >2 L within a 24-h period

Acute Coronary Syndrome (ACS) under the IHD umbrella



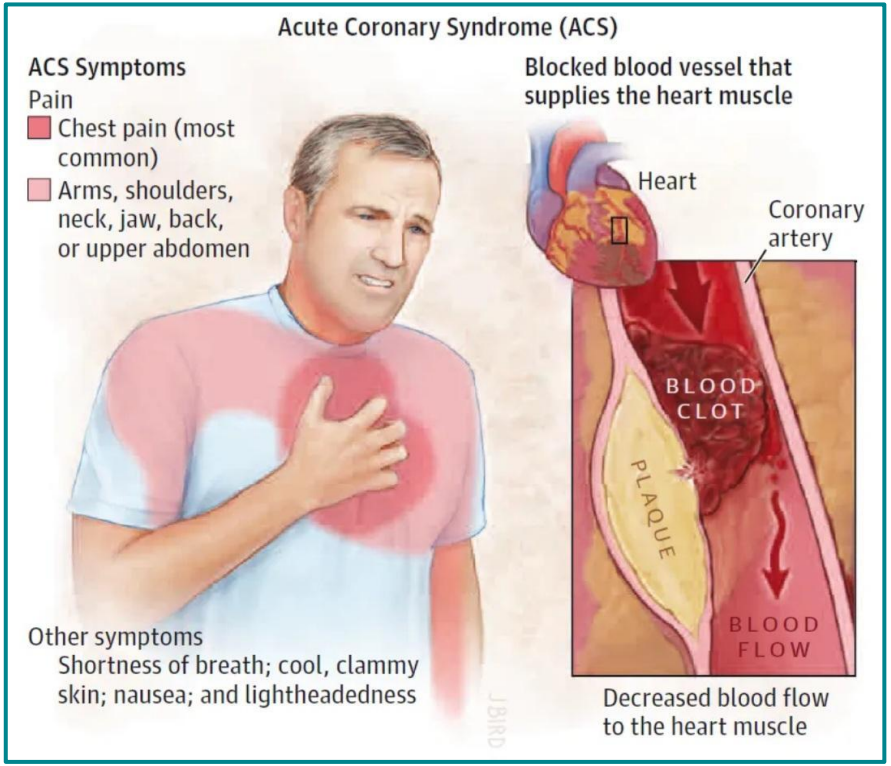
CAD- Coronary Artery Disease; INOCA- Ischemia with No Obstructive Coronary Arteries; MINOCA- Myocardial Infarction with Non-Obstructive Coronary Arteries; UA- Unstable Angina; NSTEMI- Non-ST-Elevation Myocardial Infarction; STEMI- ST-Elevation Myocardial Infarction

Image Reference: https://www.slideshare.net/slideshow/chronic-coronary-syndromepptx/261763502

Acute Coronary Syndrome or ACS *[American Heart Association]*

- Occurs when the coronary arteries get blocked due to blood clots from a ruptured plaque. This blockage prevents blood flow to the heart

- Common symptoms: chest pain or discomfort (spreads to neck, jaw, shoulders, arms, stomach or back), shortness of breath, dizziness, nausea or sweating



Types of Acute Coronary Syndrome (ACS)

ACS can be grouped into three types based on the extent of occlusion and level and cardiac injury biomarkers *(De Leon et al., 2022):*

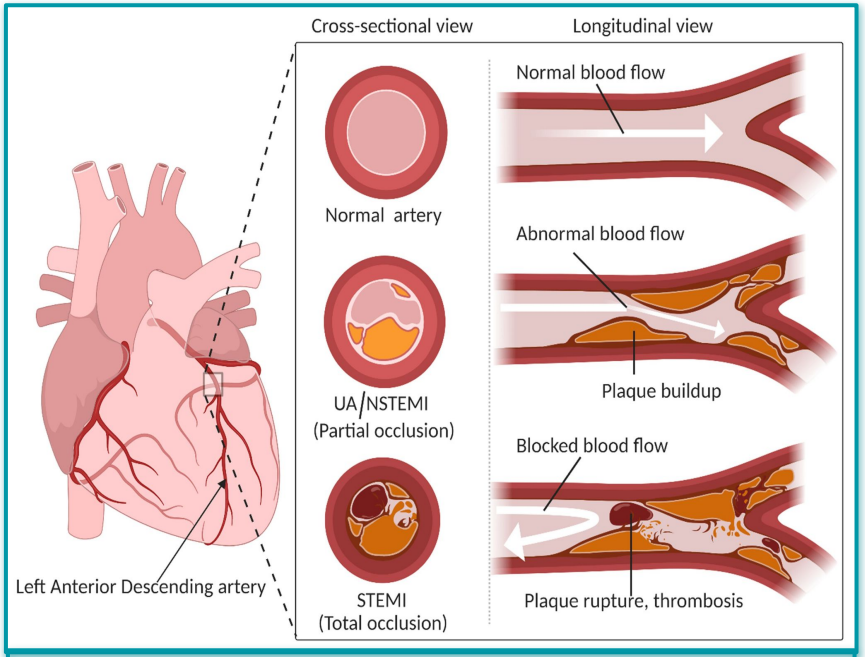


Photo from Surendran et al, 2021

1) Unstable Angina (UA) and 2) Non-ST Elevated Myocardial Infarction (NSTEMI)

-occur when the ruptured plaque *partially occludes* the vasculatures, which leads to non-transmural subendocardial ischemia (Daga et al., 2011; Radwan et al., 2019).

- UA if no elevation in troponins, with or without electrocardiogram changes indicative of ischemia (eg, ST-segment depression or transient elevation or new T-wave inversion).
- NSTEMI if with elevation in troponins is present. *(UptoDate, 2024)*

3) ST Elevated Myocardial Infarction (STEMI)

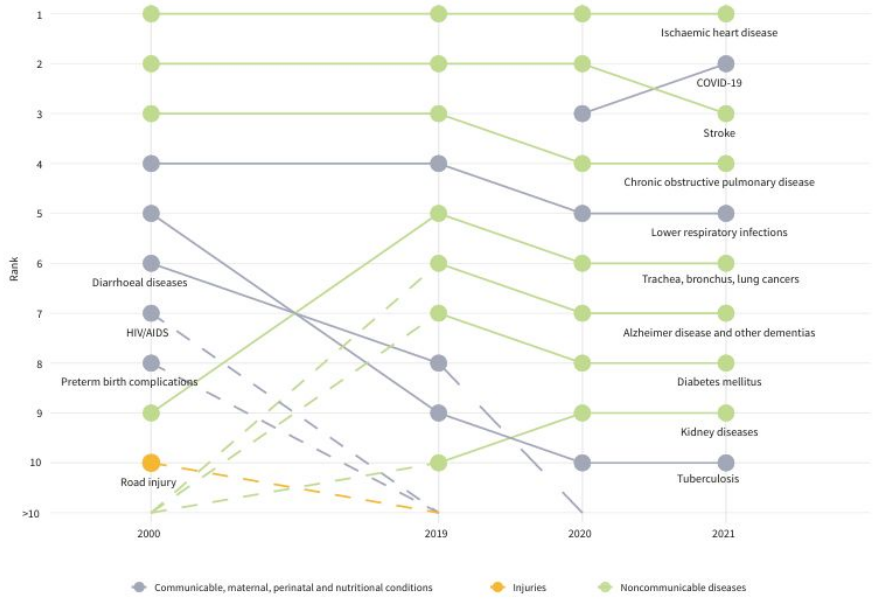
complete vessel occlusion due to acute thrombus formation secondary to a ruptured plaque *(Kotecha and Rakhit 2016)*.

CI: DISEASE MAGNITUDE AND SEVERITY

C1 Responsiveness to Magnitude and Severity

Global Causes of Death

Figure 1.7 Top 10 causes of death globally in 2000, 2019, 2020 and 2021



ACS, with an ICD-10 code of I24.9, is classified under ischemic heart diseases (IHD), which was the leading cause of death globally from 2000, 2019, 2020, and 2021

WHO World Health Statistics 2024
Chart based on data from **Global Burden of Disease 2021**

C1 Responsiveness to Magnitude and Severity (Global data)

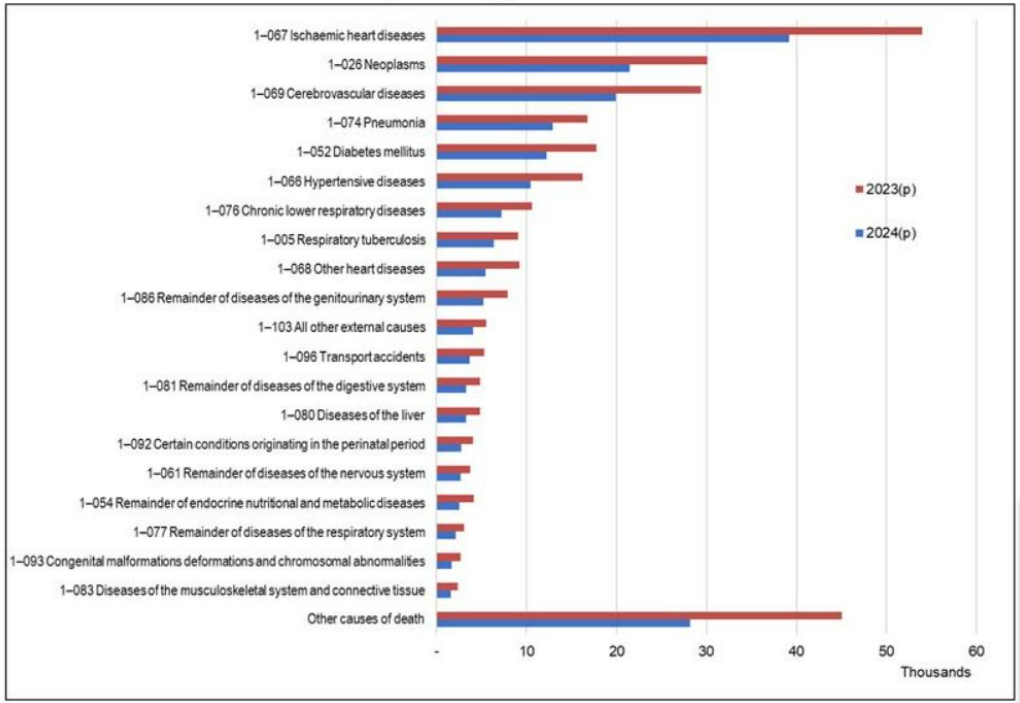
Bergmark et al, 2022

- 12% of disability-adjusted life-years (DALYs) lost annually are attributable to Ischemic heart diseases (IHD)
- The proportion of STEMI cases is decreasing in high-income countries (HIC). One of the reasons could be the declining rate of smoking in Western Europe and North America

C1 Responsiveness to Magnitude and Severity (Local data)

PSA 2024 (as of Sept 2024)

Figure 1. All Causes of Mortality (Top 20), Philippines: January to May, 2023 and 2024



2023 FHSIS report

2023 Top 10 Causes of Morbidity	2023		
	Count	Rate per 100k population	%change vs. 2022
1. Acute Respiratory Infection (ARI)	1,897,902	1,700.04	-38.39%
2. Hypertension	861,049	771.28	28.73%
3. Animal Bites	607,031	543.75	20.64%
4. Urinary Tract Infection (UTI)	392,413	351.5	12.81%
5. Pneumonia	304,912	273.12	51.10%
6. Skin Diseases	256,897	230.11	21.34%
7. Acute Lower Respiratory Tract Infection	243,236	217.88	-13.77%
8. Tuberculosis (all forms)	145,412	130.25	21.62%
9. Bronchitis	90,165	80.77	96.62%
10. Fever of Unknown Origin	86,503	77.48	-9.19%

ACS is classified under IHD, which was the leading cause of death in the Philippines in 2024. However, IHD is not included in the top causes of morbidity in the country, based on the 2023 data from FHSIS.

C1 Responsiveness to Magnitude and Severity

Philippine Heart Association - ACS Registry (2013)

Out of **1,939** patients:

49.3% diagnosed with NSTEMI	**35.6%** diagnosed with STEMI	**14.5%** diagnosed with unstable angina

53% of the patients were 61 years and above

Majority of the patients were **male** with a **median age of 60.8 years**

Common risk factors for coronary heart diseases: **hypertension** (76.1%), **diabetes** (38.6%), and **smoking history** (33.1%)

7.8% mortality rate of ACS patients enrolled in the study

C2: EFFICACY/EFFECTIVENESS AND SAFETY

C2 Efficacy/Effectiveness: Overview of Available Evidence

Efficacy/Effectiveness Outcomes	Study Design (k)	Available Evidence
Cardiovascular mortality or death from vascular causes, MI, or stroke	RCT (k=10)	• Cannon, 2007 • Gimbel, 2020 • Goto, 2015 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang and Wang, 2016 • Welsh 2019 • Wu, 2020
Myocardial infarction	RCT (k=12)	• Berwanger, 2019 • Cannon, 2007 • Gimbel, 2020 • Goto, 2015 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang, 2019 • Wang and Wang, 2016 • Welsh, 2019 • Wu, 2020
Stroke	RCT (k=10)	• Berwanger, 2019 • Cannon, 2007 • Gimbel, 2020 • Goto, 2015 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang and Wang, 2016 • Welsh, 2019 • Wu, 2020
Major adverse cardiac events (MACE)	RCT (k=11)	• Berwanger, 2019 • Cannon, 2007 • DukWoo, 2020 • Gimbel, 2020 • Goto, 2015 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang and Wang, 2016 • Welsh, 2019 • Wu, 2020

C2 Efficacy/Effectiveness: Overview of Available Evidence

Efficacy/Effectiveness Outcomes	Study Design (k)	Available Evidence
Death from vascular causes, MI, or stroke (CV Mortality)	RCT (k=9)	• Gimbel, 2020 • Goto, 2015 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang and Wang, 2016 • Welsh 2019 • Wu, 2020
Major adverse cardiac events (MACE)	RCT (k=11)	• Berwanger, 2019 • Cannon, 2007 • DukWoo, 2020 • Gimbel, 2020 • Goto, 2015 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang and Wang, 2016 • Welsh, 2019 • Wu, 2020
Other thrombotic events	RCT (k=3)	• Berwanger, 2019 • Wallentin, 2009 • Wang and Wang, 2016
Target vessel failure	*No available evidence*	
QoL (CHF, Angina, and Functional Capacity)		

Risk of Bias of Included Studies

Study	Method of Randomization	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective Reporting	Other Bias	Final rating
Cannon 2007								
Welsh 2019								
Wallentin 2009								
Gimbel 2020								
Duk Woo 2020								
Wang and Wang 2016								
Goto 2015								
Wu 2020								
Park 2019								
Wang 2019								
Gu 2017								
Tang, 2016								
Berwanger, 2019								

Summary of Efficacy/Effectiveness Outcomes

Clinical decision threshold: 0.9 to 1.1

Outcome	Follow-up Period *(months)*	Study Design *(k)*	Heterogeneity *(I^2 values)*	Risk Ratio *(95% CI)*	Certainty of Evidence
Cardiovascular mortality	3,6,12	RCT (k=10)	I^2=56%	0.79 (0.56 to 1 .10)	Very Low
Myocardial infarction	3,6,12	RCT (k=12)	I^2=25%	0.85 (0.71 to 1.01)	Low
Other thrombotic events (i.e., arterial/venous thrombotic events)	12	RCT (k=3)	I^2=0%	0.66 (0.40 to 1.09)	Moderate
Stroke	3,6,12	RCT (k=10)	I^2=0%	1.06 (0.87 to 1.29)	Low
Major adverse cardiac events (MACE)	3,6,12	RCT (k=11)	I^2=76%	0.96 (0.76 to 1.20)	Very Low
Stent Thrombosis	6, 12	RCT (k=7)	I^2=67%	0.91 (0.62 to 1.34)	Very Low
Target vessel failure	*No available evidence*				
Quality of life (congestive heart failure, angina, and functional capacity)					

LEGEND

- Favors Ticagrelor
- Non-inferior
- Inconclusive
- Favors Clopidogrel

C2: EFFICACY/EFFECTIVENESS AND SAFETY

Bleeding definitions *(AHA, 2011)*

PLATO Bleeding

- Major life-threatening
  - Fatal
  - Intracranial
  - Intrapericardial with cardiac tamponade
  - Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
  - Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
  - Requiring transfusion of ≥4 U whole blood or PRBCs
- Other major
  - Significantly disabling (eg, intraocular with permanent vision loss)
  - Associated drop in hemoglobin of 3 to 5 g/dL
  - Requiring transfusion of 2 to 3 U whole blood or PRBCs
- Any major
  - Any one of the above criteria
- Minor
  - Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)
- Minimal
  - All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment

TIMI Bleeding

- Non-CABG related bleeding
  - Major
    - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
    - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
    - Fatal bleeding (bleeding that directly results in death within 7 d)
  - Minor
    - Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL
  - Requiring medical attention
    - Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
    - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
    - Leading to or prolonging hospitalization
    - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
  - Minimal
    - Any overt bleeding event that does not meet the criteria above
- Bleeding in the setting of CABG
  - Fatal bleeding (bleeding that directly results in death)
  - Perioperative intracranial bleeding
  - Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
  - Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
  - Chest tube output >2 L within a 24-h period

C2 Efficacy/Effectiveness: Overview of Available Evidence

Safety Outcomes	Study Design (k)	Available Evidence
All-cause Mortality	RCT (k=12)	• Berwanger, 2019 • Cannon, 2007 • Gimbel, 2020 • Goto, 2015 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang 2019 • Wang and Wang, 2016 • Welsh 2019 • Wu, 2020
Major bleeding (PLATO)	RCT (k=7)	• Berwanger, 2019 • Gimbel, 2020 • Goto, 2015 • Park, 2019 • Wallentin, 2009 • Wang and Wang, 2016 • Wu, 2020
Major bleeding (TIMI)	RCT (k=6)	• Berwanger, 2019 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wallentin, 2009 • Wang 2019
Procedure-related Bleeding: PLATO	RCT (k=4)	• Gimbel, 2020 • Goto, 2015 • Park, 2019 • Wallentin, 2009
Procedure-related Bleeding: TIMI	RCT (k=2)	• Gimbel, 2020 • Wallentin, 2009
Procedure-related Bleeding: Neither PLATO nor TIMI	RCT (k=3)	• Berwanger, 2019 • Cannon, 2007 • Gimbel, 2020

C2 Efficacy/Effectiveness: Overview of Available Evidence

Safety Outcomes	Study Design (k)	Available Evidence
Non-procedure-related Bleeding: PLATO	RCT (k=2)	• Park, 2019 • Wallentin, 2009
Fatal/Life-threatening Bleeding	RCT (k=6)	• Berwanger, 2019 • Cannon, 2007 • Gimbel, 2020 • Park, 2019 • Wallentin, 2009 • Wang and Wang, 2016
All Bleeding	RCT (k=6)	• Cannon, 2007 • Gu, 2017 • Park, 2019 • Tang, 2016 • Wang, 2019 • Wu, 2020
Dyspnea	RCT (k=7)	• Berwanger, 2019 • Cannon, 2007 • Goto, 2015 • Gu, 2017 • Park, 2019 • Wallentin, 2009 • Wu, 2020
Bradycardia	RCT (k=3)	• Goto, 2015 • Gu, 2017 • Wallentin, 2009
GI Upset	RCT (k=3)	• Berwanger, 2019 • Cannon, 2007 • Park, 2019
Embolism	*No available evidence*	

Summary of Safety Outcomes *(1 of 2)*

Clinical decision threshold: 0.9 to 1.1

Outcome	Ff-up Period *(months)*	Study Design *(k)*	Heterogeneity *(I^2 values)*	Risk Ratio *(95% CI)*	Certainty of Evidence
All-cause mortality	3,6,12	RCT (k=12)	I^2=50%	0.79 (0.63 to 1.00)	Very Low
Major Bleeding: PLATO	12	RCT (k=7)	I^2=41%	1.17 (0.94 to 1.46)	Very Low
Procedure-related Bleeding: PLATO	12	RCT (k=4)	I^2=66%	1.32 (0.96 to 1.82)	Very Low
All Bleeding	3, 6, 12	RCT (k=6)	I^2=0%	1.45 (1.11 to 1.89)	Moderate
Dyspnea	3, 12	RCT (k=7)	I^2=0%	1.87 (1.74 to 2.01)	Moderate
Major Bleeding: TIMI	12	RCT (k=6)	I^2=11%	1.06 (0.84 to 1.34)	Low
Procedure-related Bleeding: TIMI	12	RCT (k=2)	I^2=81%	1.58 (0.56 to 4.46)	Very Low
Procedure-related Bleeding: Neither TIMI nor PLATO	12	RCT (k=3)	I^2=0%	0.76 (0.48 to 1.21)	Low

LEGEND

- Favors Ticagrelor
- Non-inferior
- Inconclusive
- Favors Clopidogrel

Summary of Safety Outcomes *(2 of 2)*

Clinical decision threshold: 0.9 to 1.1

Outcome	Ff-up Period *(months)*	Study Design *(k)*	Heterogeneity *(I^2 values)*	Risk Ratio *(95% CI)*	Certainty of Evidence
Non-procedure-related Bleeding: PLATO	12	RCT (k=1)	I^2=24%	2.00 (0.82 to 4.90)	Low
Fatal/Life-threatening Bleeding	3, 12	RCT (k=5)	I^2=59%	1.24 (0.87 to 1.77)	Very Low
Bradycardia	3, 12	RCT (k=3)	I^2=0%	1.10 (0.96 to 1.26)	Moderate
GI upset	3, 12	RCT (k=3)	I^2=0%	1.11 (0.67 to 1.84)	Moderate
Embolism	*No available evidence*				

LEGEND

- Favors Ticagrelor
- Non-inferior
- Inconclusive
- Favors Clopidogrel

Review of Guidelines *(N=33)*

Agency	Recommended	No recommendation	Not Recommended
World Health Organization			**WHO**
Ministry of Health ***(N=12)***	**n = 4** **UK[b], Singapore** **Malaysia[a], Vietnam[a]**	**n = 8** **US, Europe, Canada, China, Thailand, India, Nepal, Philippines**	
HTA Agency ***(N=12)***	**n = 2** **UK[b], Singapore**	**n = 9** **US, Europe, China, Malaysia, Thailand, Vietnam, India, Nepal, Philippines**	**n=1** **Canada**
Medical Society ***(N=8)***	**n = 6** **US[a], Canada[a], Europe[a], Malaysia[a], Thailand[a,b], Asia Pacific Society of Cardiology[a]***	**n = 2** **UK, China**	

LEGEND
High income Countries
Upper-Middle income countries
Low income countries
a - recommended among others (clopidogrel, prasugrel, P2Y12 in general)
b - not specific to 90 mg ticagrelor

Note: ***Majority of the countries that recommend ticagrelor are from upper-middle to high income countries***

*Asia Pacific Society of Cardiology: Australia, New Zealand, Hong Kong, Japan, Mongolia, South Korea, Taiwan, Papua New Guinea, Brunei, Cambodia, Indonesia, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam, Bangladesh, India, Iran, Nepal, Pakistan, Sri Lanka, and UAE

WHO EML, 2023

World Health Organization

Ticagrelor

- *Was associated with an **increased risk** of some important bleeding outcomes such as **fatal intracranial bleeding based on the PEGASUS* and PLATO** trials***
- ***Uncertainty in efficacy outcomes** across RCTs, SRs , and NMA comparing ticagrelor and ticagrelor (due to heterogeneous results)*
- ***Was not superior to clopidogrel** and carried a **greater risk of major bleeding in Asian patients***
- ***Was cost-effective versus clopidogrel in high-income settings, but remains to be more expensive than clopidogrel in most markets***

EML status history	Application rejected in 2023 (TRS 1049)

The Expert Committee **did not recommend the inclusion of ticagrelor on the EML for the prevention of atherothrombotic events in adults with ACS or a history of MI and at high risk of developing an atherothrombotic event.**

*PLATO trial: comparison of ticagrelor to clopidogrel, both given in combination with ASA and other standard therapy.
**PEGASUS TIMI-54 study, a comparison of ticagrelor combined with ASA to ASA therapy alone.

OVERALL CLINICAL JUDGMENT

Summary of Efficacy/Effectiveness Outcomes

Clinical decision threshold: 0.9 to 1.1

Outcome	Risk Ratio *(95% CI)*	Certainty of Evidence
Cardiovascular mortality	0.79 (0.56 to 1 .10)	Very Low
Myocardial infarction	0.85 (0.71 to 1.01)	Low
Other thrombotic events (i.e., arterial/venous thrombotic events)	0.66 (0.40 to 1.09)	Moderate
Stroke	1.06 (0.87 to 1.29)	Low
Major adverse cardiac events (MACE)	0.96 (0.76 to 1.20)	Very Low
Stent Thrombosis	0.91 (0.62 to 1.34)	Very Low
Target vessel failure	*No available evidence*	
Quality of life (congestive heart failure, angina, and functional capacity)		

LEGEND
Favors Ticagrelor
Non-inferior
Inconclusive
Favors Clopidogrel

Summary of Safety Outcomes

Outcome	Risk Ratio *(95% CI)*	Certainty of Evidence
All-cause mortality	0.79 (0.63 to 1.00)	Very Low
Major Bleeding: PLATO	1.17 (0.94 to 1.46)	Very Low
Procedure-related Bleeding: PLATO	1.32 (0.96 to 1.82)	Very Low
All Bleeding	1.45 (1.11 to 1.89)	Moderate
Dyspnea	1.87 (1.74 to 2.01)	Moderate
Major Bleeding: TIMI	1.06 (0.84 to 1.34)	Low
Procedure-related Bleeding: TIMI	1.58 (0.56 to 4.46)	Very Low
Procedure-related Bleeding: Neither TIMI nor PLATO	0.76 (0.48 to 1.21)	Low

Outcome	Risk Ratio *(95% CI)*	Certainty of Evidence
Non-procedure-related Bleeding: PLATO	2.00 (0.82 to 4.90)	Low
Fatal/Life-threatening Bleeding	1.24 (0.87 to 1.77)	Very Low
Bradycardia	1.10 (0.96 to 1.26)	Moderate
GI upset	1.11 (0.67 to 1.84)	Moderate
Embolism	*No available evidence*	

LEGEND	
Favors Ticagrelor	Inconclusive
Non-inferior	Favors Clopidogrel

OVERALL CLINICAL JUDGMENT

Ticagrelor [90mg film-coated tablet] as an add-on to aspirin has **non-inferior efficacy BUT inferior safety** vs. clopidogrel as an add-on to aspirin

THANK YOU!