Reteplase versus alteplase or streptokinase for patients with ST-segment elevation myocardial infarction (STEMI): a systematic review and network meta-analysis (Health Technology Assessment Report)

EVIDENCE AND JUDGMENTS

[Basis for HTAC Preliminary Recommendation]

DOST

I. CONTEXT

I. A. CONTEXT OF THE ASSESSMENT

Nominated Intervention	Reteplase
Proponent/Nominator	PhilHealth
Date of Submission	October 2022 (Under the Cycle 1 of General Track Topics)

I. B. POLICY QUESTION and RESEARCH QUESTION

Policy Question	Should reteplase for adult patients with ST-segment elevation myocardial infarction (STEMI) against alternative fibrinolytics (alteplase or streptokinase) be included in the Philippine National Formulary for government financing? *Note: Streptokinase is listed in the PNF for the same indication; Alteplase is listed in the PNF for a different indication (i.e. acute ischemic stroke)*
Research Questions	
C1: Responsiveness to Magnitude and Severity	**RQ1.** What is the magnitude and severity of ST-segment elevation myocardial infarction (STEMI)?
C2: Clinical efficacy, effectiveness and safety	**RQ2.1.** Among patients with STEMI, what is the effectiveness profile (e.g., cardiovascular morbidity, stroke, length of hospital/ICU stay) of reteplase versus alternative fibrinolytics (alteplase or streptokinase)? **RQ.2.2.** Among patients with STEMI, what is the safety profile of reteplase in terms of bleeding and other adverse effects compared to alternative fibrinolytics (alteplase or streptokinase)? **RQ2.3.** What are the current recommendations from country guidelines on the use of reteplase and its comparators (e.g., alteplase or streptokinase) in the treatment of STEMI?

I. C. PICO Table

Population	Adult patients with STEMI	
Intervention	Reteplase (+/- background therapy)	
Comparator	Alteplase (+/- background therapy) Streptokinase (+/- background therapy)	
Outcome	**<u>Outcomes</u>:** (1) Effectiveness ○ Cardiovascular morbidity ○ Stroke ○ Length of hospital/ICU stay* (2) Safety ○ Bleeding ○ Other adverse events **Red font* = *No evidence found*	**<u>Importance</u>:** Critical Critical Critical Critical Critical

<u>Background therapy</u> refers to parenteral anticoagulants (PAC) such as (unfractionated heparin, low-molecular-weight heparin, anti Xa inhibitors, and direct thrombin inhibitors)

II. SUMMARY OF RECOMMENDATIONS PER CRITERIA

DOST

II. SUMMARY OF JUDGMENTS PER CRITERION

Research Questions	Direction of Judgment
RQ1. What is the magnitude and severity of ST-segment elevation myocardial infarction (STEMI)?	Significant burden
RQ2.1. Among patients with STEMI, what is the effectiveness profile (e.g., cardiovascular morbidity, stroke, length of hospital/ICU stay) of reteplase versus alternative fibrinolytics (alteplase or streptokinase)?	vs streptokinase - Inconclusive vs alteplase - Inconclusive
RQ.2.2. Among patients with STEMI, what is the safety profile of reteplase in terms of bleeding and other adverse effects compared to alternative fibrinolytics (alteplase or streptokinase)?	vs streptokinase - Increased risk for hemorrhagic stroke vs alteplase - Inconclusive
RQ2.3. What are the current recommendations from country guidelines on the use of reteplase and its comparators (e.g., alteplase or streptokinase) in the treatment of STEMI?	Not listed in the WHO EML 10 MOH/Societies recommend fibrinolytic agents which includes reteplase 4 MOH/Societies have no recommendations for STEMI

III. BACKGROUND

DOST

III. A. DESCRIPTION OF STEMI

- Myocardial infarction (MI) occurs when there is an occlusion in the **coronary arteries**, impeding the transport of oxygen in the **myocardium** (Rathore et al. 2018).
- MI can be classified based on several parameters, such as clinical manifestations, expression of cardiac biomarkers, electrocardiographic (ECG) findings, and pathological presentations (Thygesen et al., 2018). The most known types are ST-segment elevation MI (STEMI) and non-ST segment elevation (NSTEMI).
    - STEMI occurs when there is a complete thrombus occlusion, evaluated as an ST elevation and elevated cardiac troponin
    - NSTEMI happens when there is partial occlusion in the artery, detected as no ST elevation with elevated troponin (Sweiss et al., 2022).

III. B. DESCRIPTION OF RETEPLASE

- Reteplase as a fibrin-specific fibrinolytic agent for MI patients is particularly effective, achieving higher Thrombolysis in Myocardial Infarction (TIMI) II-III patency rates compared to currently available options in the Philippines like streptokinase and alteplase.
    - **Dose:** 10 units lyophilized powder for IV injection
    - **Dosing regimen:** 10 units given in 2 minutes and an additional 10 units administered 30 minutes after the first injection
    - **MOA:** Modified (single-chain deletion mutant) non-glycosylated recombinant form of tissue plasminogen activator (tPA). Compared to unmodified tPA, reteplase exhibits an extended half-life of minutes, reduced fibrin specificity, and penetration ability into blood clots
- According to the 2014 Philippine Heart Association (PHA) CPG for the Diagnosis and Management of Patients with Coronary Heart Disease, for STEMI patients, immediate administration of reperfusion therapy, such as percutaneous coronary intervention (PCI) or **fibrinolysis** is required.

Note:
Fibrin-specific agents *are those that cause fibrinolysis while having no significant lytic action experimentally when exposed to fibrinogen in the presence of plasminogen.*
Non–fibrin-specific agents *are those that are indiscriminate in their ability to cause both fibrinolysis and fibrinogenolysis.*

III. C. DESCRIPTION OF COMPARATORS

- **Streptokinase** *(non-fibrin specific fibrinolytic agent)*
  - Dose: 1,500,000 IU powder, vial (IV infusion)
  - Dosing regimen: By IV infusion, 1.5 million units over 1 hour; may administer second dose if re-occlusion occurs within 5 days of initial dose.
  - MOA: promotes thrombolysis by activating the conversion of plasminogen to plasmin, the enzyme that degrades fibrin, fibrinogen, and other procoagulant proteins. It decreases blood and plasma viscosity and erythrocyte aggregation tendency, thus increasing perfusion of collateral blood vessels.

- **Alteplase** *(fibrin-specific fibrinolytic agent)*
  - Dose: 50 mg powder (IV infusion)
  - Dosing regimen:
    - Accelerated (90 minute-infusion)
      - <65kg: 15mg as IV bolus, immediately followed by 0.75 mg/kg (max 50 mg) via infusion over 30 mins, then 0.5mg/kg (max:35mg) via infusion over 60 minutes
      - >65kg: 15mg as IV bolus, immediately followed by 50 mg via infusion over 30 mins then 35 mg via infusion over 60 mins (max total dose 100 mg)
    - Non-accelerated (3-hour infusion)
      - < 65 kg: 1.25 mg/kg administered over 3 hours
      - >65kg: 100 mg administered as 60 mg in the first hour (6-10 mg administered as a bolus), 20 mg over the second hour, and 20 mg over the third hour
  - MOA: glycoprotein that binds to fibrin in a thrombus which causes activation and the eventual induction of conversion of plasminogen to plasmin, thereby causing fibrin clot dissolution

2014 PHA Clinical Practice Guidelines for the Diagnosis and Management of Patients with Coronary Heart Disease

- Reperfusion therapy **IS RECOMMENDED** to all eligible patients with STEMI with symptom onset within the prior 12 hours.
- It **IS STRONGLY RECOMMENDED** to undergo immediate thrombolysis (unless contraindicated), with a door-to-needle time of less than 60 minutes as a goal.
- In the absence of contraindications and when percutaneous coronary intervention (PCI) is not available, fibrinolytic therapy **MAY BE RECOMMENDED** for patients with STEMI if there is clinical and/or ECG evidence of ongoing chest pain within 12 to 24 hours of symptom onset and presence of multiple ST segment deviations in several leads or hemodynamic instability.
- Fibrinolysis **IS RECOMMENDED** to people with acute STEMI presenting within 12 hours of onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given.

IV. C1: RESPONSIVENESS TO DISEASE MAGNITUDE AND SEVERITY

DOST

C1. Responsiveness to Magnitude and Severity

RQ.1. What is the magnitude and severity of STEMI?

Myocardial infarction (MI) is the leading cause of disability and mortality worldwide. It is responsible for over 7.4 million (15%) global deaths each year, contributing the highest proportion in CVD-associated deaths worldwide (WHO, 2015). In 2021, 17.8% of total deaths in the Philippines were caused by ischemic heart diseases (PSA, 2022). From 2011 to 2015, 37.1% of acute coronary syndrome (ACS) patients enrolled in the Philippine Heart Association ACS Registry were diagnosed with STEMI, while 48.1% were diagnosed with NSTEMI. Among patients <40 years old, 53.5% and 36.4% were diagnosed with STEMI and NSTEMI, respectively (Lerios et al., 2017).

Patients who were not promptly treated for MI (STEMI and NSTEMI) experienced significant late complications including the development of cardiogenic shock due to papillary muscle rupture, cardiac tamponade resulting from left ventricle rupture, and the formation of a cardiac aneurysm with associated thrombus. These conditions required mitral-valve replacement and repair of the rupture, and treatment for the clot (Chamuleau et al., 2005).

GLOBAL DATA

Leading causes, 2021	Age-standardized death rate (per 100,000), 2021
1 Ischemic heart disease	108.7 (99.8 to 115.6)
2 COVID-19	94.0 (89.2 to 100.0)
3 Stroke	87.4 (79.5 to 94.4)
4 COPD*	45.2 (40.7 to 49.8)
5 Other pandemic-related...**	32.3 (24.8 to 43.3)
6 Neonatal disorders	29.6 (25.3 to 34.4)
7 Lower respiratory infections	28.7 (26.0 to 31.1)
8 Alzheimer's disease	25.2 (6.4 to 65.6)
9 Lung cancer	23.5 (21.2 to 25.9)
10 Diabetes	19.6 (18.2 to 20.8)

IHD, which includes STEMI, is the leading cause of mortality globally in 2021.

Leading causes, 2021	Number of DALYs (millions), 2021
1 COVID-19	212.0 (198.0 to 234.5)
2 Ischemic heart disease	188.3 (176.7 to 198.3)
3 Neonatal disorders	186.3 (162.3 to 214.9)
4 Stroke	160.4 (148.0 to 171.7)
5 Lower respiratory infections	82.5 (72.9 to 93.2)
6 COPD*	79.8 (74.0 to 86.0)
7 Diabetes	78.9 (66.8 to 94.5)
8 Other COVID outcomes**	77.4 (59.7 to 101.9)
9 Low back pain	70.2 (50.2 to 94.1)
10 Road injuries	65.1 (60.7 to 69.8)
11 Diarrheal diseases	59.3 (47.4 to 73.2)

IHD, which includes STEMI, is the 2nd leading cause of disease burden globally in 2021.

Source: IHME GBD 2021 Study

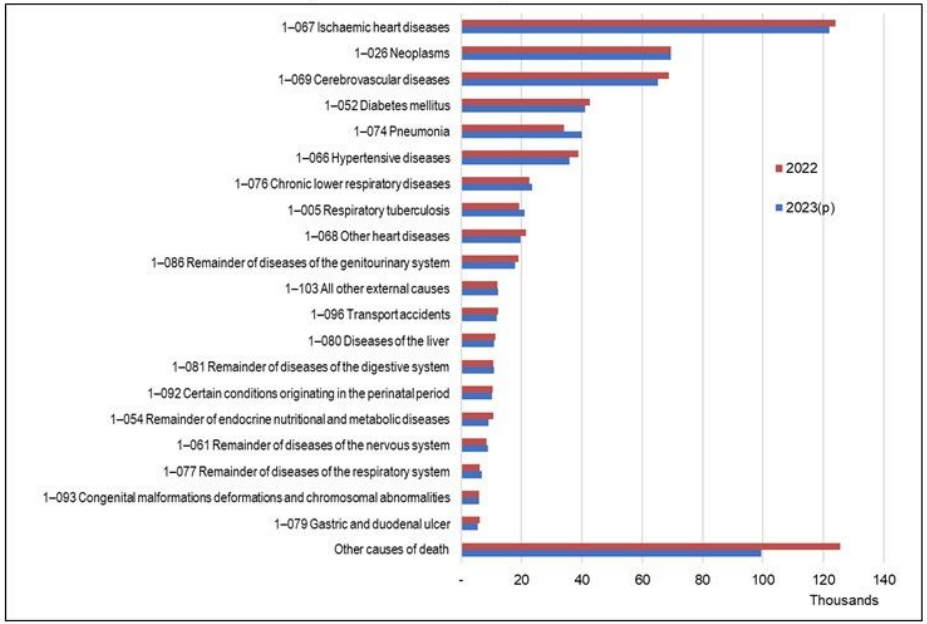
DOST

LOCAL DATA

IHD, which includes STEMI, was the leading cause of mortality in the country in 2022 and 2023.

Among patients with acute coronary syndrome (ACS) from 2011 to 2015, 37.1% were diagnosed with STEMI. Among patients who are younger than 40 years, 53.5% were diagnosed with STEMI, while 36.1% were diagnosed with STEMI among those who are 40 years or older.

Figure 1. All Causes of Mortality (Top 20), Philippines: January to December, 2022 and 2023



Source: PSA (2024)

Table 3. Management of ACS patients for 2011-2015.

Parameters	All (N=3346)	<40 (n=129)	≥40 (n=3217)	p-value
Working Diagnosis (n, %)				0.0001*
STEMI	1243 (37.1%)	69 (53.5%)	1174 (36.4%)	
NSTEMI	1611 (48.1%)	47 (36.4%)	1564 (48.6%)	
Unstable Angina	492 (14.7%)	13 (10.1%)	479 (14.9%)	

Source: Lerios et al. (2017)

V. C2: EFFICACY, EFFECTIVENESS, AND SAFETY

DOST

V. C2: Efficacy, Effectiveness, and Safety

RQ2.1. Among patients with STEMI, what is the effectiveness profile (e.g., cardiovascular morbidity, stroke, length of hospital/ICU stay) of reteplase versus alternative fibrinolytics (alteplase or streptokinase)?

Reteplase + parenteral anticoagulants (PAC) was compared to streptokinase + PAC (k=1), non-accelerated alteplase + PAC (k=1), and accelerated alteplase + PAC (k=2) in terms of the risk of all-cause mortality within 30 to 35 days, recurrent infarction, and total stroke. Additionally, cardiogenic shock is reported for reteplase + PAC vs accelerated alteplase + PAC.

Reteplase + PAC vs Streptokinase + PAC showed **inconclusive results for all-cause mortality, recurrent infarction, and total stroke.**

- All-cause mortality within 30 to 35 days: RR 0.95, 95%CI 0.81 to 1.11; *moderate certainty of evidence*
- Recurrent infarction: RR 0.92, 95%CI 0.74 to 1.15; *moderate certainty of evidence*
- Total stroke: RR 1.24, 95%CI 0.76 to 1.99; *moderate certainty of evidence*

Length of hospital/ICU stay is not included as an outcome in the study.

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

V. C2: Efficacy, Effectiveness, and Safety

RQ2.1. Among patients with STEMI, what is the effectiveness profile (e.g., cardiovascular morbidity, stroke, length of hospital/ICU stay) of reteplase versus alternative fibrinolytics (alteplase or streptokinase)?

Reteplase + PAC vs non-accelerated alteplase + PAC showed **inconclusive results for all-cause mortality, recurrent infarction, and total stroke.**

- All-cause mortality within 30 to 35 days: RR 0.50, 95%CI 0.13 to 1.96; *low certainty of evidence*
- Recurrent infarction: RR 0.57, 95%CI 0.17 to 1.91; *low certainty of evidence*
- Total stroke: RR 0.08, 95%CI 0.004 to 1.35*; low certainty of evidence*

Length of hospital/ICU stay is not included as an outcome in the study.

Reteplase + PAC vs accelerated alteplase + PAC showed **inconclusive results for all-cause mortality, recurrent infarction, total stroke and cardiogenic shock.**

- All-cause mortality within 30 to 35 days: pooled RR 1.02, 95%CI 0.90 to 1.15; *low certainty of evidence*
- Recurrent infarction: pooled RR 1.00, 95%CI 0.85 to 1.17; *low certainty of evidence*
- Total stroke: pooled RR 0.90, 95%CI 0.70 to 1.16; *low certainty of evidence*
- Cardiogenic shock: RR 1.04, 95%CI 0.89 to 1.22; *low certainty of evidence*

Length of hospital/ICU stay is not included as an outcome in the study.

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

V. C2: Efficacy, Effectiveness, and Safety

RQ2.2. Among patients with STEMI, what is the safety profile of reteplase in terms of bleeding and other adverse effects compared to alternative fibrinolytics (alteplase or streptokinase)?

Reteplase + PAC was compared to streptokinase + PAC (k=1), non-accelerated alteplase + PAC (k=1), and accelerated alteplase + PAC (k=2) in terms of the risk of major bleeding, hemorrhagic stroke, and severe/serious allergic reaction.

Reteplase + PAC vs. Streptokinase + PAC:

- **Inconclusive evidence** for major bleeding: RR 0.98, 95%CI 0.78 to 1.23; *moderate certainty of evidence*
- **Increased risk** for hemorrhagic stroke: RR 2.09, 95%CI 1.02 to 4.28; *moderate certainty of evidence*
- **Decreased risk** for severe/serious allergic reaction: RR 0.20, 95%CI 0.06 to 0.69; *high certainty of evidence*

Reteplase + PAC vs. Non-accelerated alteplase + PAC showed **inconclusive results** for major bleeding and hemorrhagic stroke:

- Major bleeding: RR 0.86, 95%CI 0.29 to 2.49; *low certainty of evidence*
- Hemorrhagic stroke: RR 0.11, 95%CI 0.01 to 2.05; *low certainty of evidence*

Reteplase + PAC vs. Accelerated alteplase + PAC showed **inconclusive results** for major bleeding, hemorrhagic stroke, and severe/serious allergic reaction:

- Major bleeding: pooled RR 0.81, 95%CI 0.59 to 1.10; low certainty of evidence
- Hemorrhagic stroke: pooled RR 1.01, 95%CI 0.71 to 1.43; *low certainty of evidence*
- Severe/serious allergic reaction: RR 0.81, 95%CI 0.19 to 3.39; *low certainty of evidence*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

V. C2. B. Methodology

- **Search Strategy:**
  - **Databases**: EBSCO CINAHL, MEDLINE, clinicaltrials.gov, Latin American and Caribbean Health Sciences Database (Lilacs), Scopus, and Scientific Electronic Library Online (SciELO)
  - From inception until September 2023
  - (reteplase AND (alteplase OR streptokinase)) AND (“myocardial infarc*” OR reinfarction OR “heart attack” OR “cardiovascular stroke” OR STEMI).
- **Results**
  - 1 SR-NMA detected: Jinatongthai et al., 2017 (last search date: Feb. 28, 2017)
  - No primary studies detected after Feb. 28, 2017
  - 4 primary studies were retrieved from Jinatongthai et al (2017) for direct comparisons
- **Final Methodology:** De novo systematic review

V. C2.C. Tabulation of Evidence

	Wilcox et al (1995) N= 6,010	Smalling et al (1995) N=308	Bode et al (1996) N= 324	GUSTO III Trial (1997) N= 15,059
Population	Adult patients with STEMI			
Intervention	**Reteplase + PAC** n= 3,004	**Reteplase + PAC** n=154	**Reteplase + PAC** n=169	**Reteplase + PAC** n=4,921
Comparator	Streptokinase + PAC n=3,006	Non-accelerated alteplase + PAC n=154	accelerated alteplase + PAC n=155	Accelerated alteplase + PAC n=10,138
Outcome	• All-cause mortality • Recurrent infarction • Total stroke • Major bleeding • Hemorrhagic stroke • Severe allergy	• All-cause mortality • Recurrent infarction • Total stroke • Major bleeding	• All-cause mortality • Recurrent infarction • Total stroke • Major bleeding • Hemorrhagic stroke	• All-cause mortality • Recurrent infarction • Total stroke • Cardiogenic shock • Major bleeding • Hemorrhagic stroke • Severe allergy
Study Design	RCT, double-blinded	RCT, open-label	RCT, open-label	RCT, open-label

V. C2.C. Tabulation of Available Evidence

Green = available evidence	Wilcox et al (1995)	Smalling et al (1995)	Bode et al (1996)	GUSTO III (1997)
	vs. streptokinase + PAC	*vs. non-acc alteplase + PAC*	*vs. acc alteplase + PAC*	*vs. acc alteplase + PAC*
Efficacy				
All-cause mortality	✔	✔	✔	✔
Recurrent infarction	✔	✔	✔	✔
Stroke	✔	✔	✔	✔
Cardiogenic shock				✔
Length of hospital/ICU stay				
Safety				
Major bleeding	✔	✔	✔	✔
Hemorrhagic stroke	✔	✔	✔	✔
Severe allergy	✔			✔

V. C2.D. Tabulation of Results: Efficacy

Efficacy Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
All-cause mortality		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**0.95** (0.81 to 1.11) *MODERATE*
Reteplase + PAC vs Non-accelerated alteplase + PAC	1 (N= 308)	**0.50** (0.13 to 1.96) *LOW*
Reteplase + PAC vs Accelerated alteplase + PAC	2 (N=15,383)	**POOLED RR (HTAD Computation):** **1.02** (0.90 to 1.15) *LOW* EAG extracted estimates: Study 1 (n=324) **0.49** (0.20 to 1.20) *LOW* *Study 2 (n=15,059)* **1.03** (0.92 to 1.16) *MODERATE*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2.D. Tabulation of Results: Efficacy

Efficacy Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
Recurrent infarction		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**0.92** (0.74 to 1.15) MODERATE
Reteplase + PAC vs Non-accelerated alteplase + PAC	1 (N=308)	**0.57** (0.17 to 1.91) *LOW*
Reteplase + PAC vs Accelerated alteplase + PAC	2 (N=15,383)	**POOLED RR (HTAD Computation):** **1.00** (0.85 to 1.17) *LOW* *EAG extracted estimates:* *Study 1 (n=324)* **1.05** (0.38 to 2.73) *LOW* *Study 2 (n=15,059)* **1.00** (0.85 to 1.17) *LOW*
Cardiogenic shock		
Reteplase + PAC vs Accelerated alteplase + PAC	1 (N= 15, 059)	**1.04** (0.89 to 1.22) *MODERATE*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2.D. Tabulation of Results: Efficacy

Efficacy Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
Stroke		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**1.24** (0.76 to 1.99) *MODERATE*
Reteplase + PAC vs. Non-accelerated alteplase + PAC	1 (N=308)	**0.08** (0.004 to 1.35) *LOW*
Reteplase+PAC vs. accelerated alteplase + PAC	2 (N= 15,383)	**POOLED RR (HTAD Computation):** **0.90** (0.70 to 1.16) *LOW* *EAG extracted estimates:* *Study 1 (n=324)* **0.69** (0.15 to 2.94) *LOW* *Study 2 (n=15,059)* **0.91** (0.70 to 1.19) *LOW*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2.D. Tabulation of Results: Safety

Safety Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
Major Bleeding		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**0.98** (0.78 to 1.23) *MODERATE*
Reteplase + PAC vs Non-accelerated alteplase + PAC	1 (N = 308)	**0.86** (0.29 to 2.49) *LOW*
Reteplase + PAC vs Accelerated alteplase + PAC	2 (N = 15,383)	**POOLED RR (HTAD Computation):** **0.81 (0.59 to 1.10)** *LOW* *EAG extracted estimates:* *Study 1 (n=324)* **1.65** (0.56 to 4.54) *LOW* *Study 2 (n=15,059)* **0.79** (0.57 to 1.09) *LOW*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2.D. Tabulation of Results: Safety

Safety Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
Hemorrhagic Stroke		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**2.09** (1.02 to 4.28) *MODERATE*
Reteplase + PAC vs Non-accelerated alteplase + PAC	1 (N = 308)	**0.11** (0.01 to 2.05) *LOW*
Reteplase + PAC vs Accelerated alteplase + PAC	2 (N = 15,383)	**POOLED RR (HTAD Computation):** **1.01 (0.71 to 1.43)** *LOW* *EAG extracted estimates:* *Study 1 (n=324)* **0.61** (0.10 to 3.50) *LOW* *Study 2 (n=15,059)* **1.04** (0.72 to 1.49) *LOW*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2.D. Tabulation of Results: Safety

Safety Outcomes	No. of studies	Risk Ratio (95% CI) *Certainty of Evidence*
Severe allergy		
Reteplase + PAC vs. Streptokinase + PAC	1 (N = 6,010)	**0.20 (0.06 to 0.69)** *HIGH*
Reteplase + PAC vs Accelerated alteplase + PAC	1 (N= 15,059)	**0.81 (0.19 TO 3.39)** *LOW*

NOTE: While included studies reported odds ratios, risk ratios were computed by the EAG and HTA Division with the data extracted from the same studies.

VI. C2: REVIEW OF GUIDELINES

DOST

VI. C2: Review of Guidelines

RQ.2.3. What are the current recommendations from country guidelines on the use of reteplase and its comparators (e.g., alteplase or streptokinase) in the treatment of STEMI?

Based on the review of guidelines for the management of STEMI, 10 countries/organizations (India, UK, Canada, Australia, Europe, Malaysia, US, Thailand, Taiwan, and the Philippines) recommend the use of fibrinolytic agents, which include reteplase, if percutaneous coronary intervention (PCI) cannot be performed in a timely manner. There are no guidelines that recommend the use of reteplase over other fibrinolytic agents in the management of STEMI. Meanwhile, no clinical guidelines for STEMI management were found in the WHO and in 3 organizations (Vietnam MOH, Singapore's Agency for Care Effectiveness, and Singapore Heart Failure Society).

Among the 10 countries/organizations, majority recommend the use of fibrinolytic therapy only when primary PCI cannot be performed in a timely manner. Meanwhile, India recommends the combination of fibrinolytic therapy and PCI as a "pharmaco-invasive therapy".

Ministry of Health	HTA Agency	Societies
World Health Organization		
High Income Countries (n=6)		
Australia (Australian Commission on Safety and Quality in Health Care) **Canada** (Health Canada)	**UK** (National Institute for Health and Care Excellence [NICE]) **Singapore** (Agency for Care Effectiveness)	**US** (American College of Cardiology, American Heart Association) **Australia** (National Heart Foundation of Australia; Cardiac Society of Australia and New Zealand) **Canada** (Canadian Cardiovascular Society; Canadian Association of Interventional Cardiology) **Singapore** (Singapore Heart Failure Society) **Taiwan** (Taiwan Society of Cardiology) **Europe** (European Society of Cardiology)
Upper Middle Income Countries (n=2)		
Malaysia (Ministry of Health)		**Thailand** (Heart Association of Thailand)
Lower Middle Income Countries (n=3)		
India (Ministry of Health and Family Welfare) **Vietnam** (Ministry of Health)		**Philippines** (Philippine Heart Association)

5 Recommending Reteplase	5 Recommends fibrinolytics but did not specify Reteplase	4 No recommendation
Ministry of Health		
India (MoHFW)	**Malaysia** MOH*	**WHO** (WHO EML)**, **Vietnam** MOH
HTA Agencies		
UK (NICE)	NA	**Singapore** (ACE)
Societies		
Canada (CCS/CAIC)* **Australia** (NHF & CSANZ) **Europe** (ESC)	**US** (ACC/AHA/SCAI) **Thailand** (Heart Assoc. of Thailand) **Taiwan** (TSOC) **Philippines** (PHA)	**Singapore** (SHFS)

**Reteplase is not registered in Canada and Malaysia*
WHO EML includes alteplase (cerebral ischemic stroke) and **streptokinase (AMI)

VII. HTAC CLINICAL JUDGEMENT

DOST

VII. HTAC Clinical Judgment

	Overall Clinical Judgment [vs streptokinase]	Next Steps for Costing Analysis
Option A *[Non-inferior]*	Reteplase has **comparable efficacy and safety** vs. streptokinase for STEMI	**CMA + BIA** *CMA = Cost Minimization Analysis* *BIA = Budget Impact Analysis*
Option B *[Inferior]*	Reteplase has **inferior efficacy and safety** vs. streptokinase for STEMI	**Do not proceed to Economic Assessment**
Option C *[Not enough evidence]*	There is **limited evidence (i.e., inconclusive)** in the clinical efficacy/ effectiveness of reteplase vs streptokinase. In terms of safety, while there is decreased risk of serious allergic reaction, there is increased risk of hemorrhagic stroke compared to streptokinase. While these outcomes are both critical outcomes, we placed higher value on the outcome of hemorrhagic stroke over serious allergic reaction. There is a need for further studies to be conducted in order to provide the needed evidence that is responsive to its decision criteria based on the UHC Law.	**Do not proceed to Economic Assessment**

Key Considerations:

- Reteplase vs streptokinase
  - In terms of efficacy, there is inconclusive evidence between reteplase and streptokinase
  - The is moderate certainty evidence that reteplase increases risk of hemorrhagic stroke by 2x compared to streptokinase *(harm)*.
  - *Note:* Streptokinase is listed in the PNF for the same indication

VII. HTAC Clinical Judgment

	Overall Clinical Judgment [vs alteplase]	Next Steps for Costing Analysis
Option A *[Non-inferior]*	Reteplase has **comparable efficacy and safety** vs. alteplase for STEMI	**CMA + BIA** *CMA = Cost Minimization Analysis* *BIA = Budget Impact Analysis*
Option B *[Inferior]*	Reteplase has **inferior efficacy and safety** vs. alteplase for STEMI	**Do not proceed to Economic Assessment**
Option C *[Not enough evidence]*	There is **limited evidence (i.e., inconclusive)** in the clinical efficacy/ effectiveness and safety of reteplase vs alteplase. There is a need for further studies to be conducted in order to provide the needed evidence that is responsive to its decision criteria based on the UHC Law.	**Do not proceed to Economic Assessment**

Key Considerations:

- Reteplase vs alteplase: Inconclusive evidence on the efficacy and safety of reteplase vs alteplase (accelerated or non-accelerated)
    - *Note:* Alteplase is included in the PNF; however, it is not indicated for STEMI

Thank you!