Using real world evidence to generate cost-effectiveness analysis of fibrinolytic therapy in patients with ST-segment elevation myocardial infarction in Thailand

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Summary

Background Due to limited access to primary percutaneous coronary intervention for the management of ST-segment elevation myocardial infarction (STEMI) in low-to-middle-income countries (LMICs), fibrinolysis serves as a vital alternative reperfusion therapy. Among fibrinolytic agents, the cost-effectiveness of tenecteplase (TNK) in LMICs as compared to streptokinase (SK) for STEMI management remains unknown.

Methods Cost-effectiveness was analyzed using a hybrid model consisting of short-term analysis (30-days decision tree model) and long-term analysis (Markov model). Both health care provider and societal perspectives over a lifetime horizon with 3% discount rate were considered. Input parameters were obtained from Thailand’s national health database, a network meta-analysis and literature review. Outcome measure was an incremental cost-effectiveness ratio (ICER) determined by an incremental cost per quality-adjusted life years (QALY) gain. An ICER of less than $5,590 per QALY gain is considered cost-effective. Series of sensitivity analyses were also performed.

Findings From the societal perspective, TNK increases cost by $827 and increases QALY by 0.173. Thus, the ICER is $4,777 per QALY gained. Similarly, the ICER from health care provider perspective is $4,464 per QALY gained. In the probabilistic sensitivity analysis, using 5,590 USD per QALY as threshold, the probability of TNK being cost-effective was 83% from both perspectives. The most influential parameters were risk ratio of death for treatment with TNK compared to SK and drug cost of TNK.

Interpretation In a resource-limited country like Thailand, tenecteplase is a cost-effective fibrinolytic drug for treatment of STEMI compared to streptokinase.

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Introduction

ST-segment elevation myocardial infarction (STEMI) is a clinical syndrome resulting from myocardial ischemia in association with electrocardiographic (ECG) ST-segment changes (usually elevation) indicative of the occlusion of a major epicardial coronary artery. STEMI remains a significant health problem that contributes to
Research in context

Evidence before this study
In high-income countries, cost-effectiveness studies showed that fibrin-specific drug for treatment of ST-segment elevation myocardial infarction (STEMI) is cost-effective, nevertheless, little is known about its cost-effectiveness in the low-to-middle-income countries (LMICs) like Thailand. We searched pubmed and local Thai publications up to September 2019. To the best of our knowledge, we found only one cost-effectiveness study in LMICs setting which was conducted and published in Thai language. However, the study has several limitations such as the use of patency rate as outcome and a lack of life-time time horizon analysis.

Added value of this study
To our knowledge, this is the first cost-effectiveness analysis based on national database in LMICs setting to examine cost-effectiveness of fibrin-specific drug for treatment of STEMI. By mixing with decision tree and Markov model, both short- and long-term were evaluated in this cost-effectiveness analysis to provide the most comprehensive evidence for supporting the worthy fibrinolytic agent in treatment of patient with STEMI, especially in a resource-limited country. Our results show that tenecteplase (TNK) is a cost-effective fibrinolytic agent for the management of STEMI compared to streptokinase (SK). As a result, TNK could potentially be considered as the fibrinolytic agent of choice over SK in Thailand, despite a higher acquisition cost.

Implications of all the available evidence
We believe that our findings could facilitate evidence-informed policy decision making in Thailand and support Health Technology Assessment (HTA) development in other LMICs with similar healthcare context. In addition, this study can potentially serve as a prototype for researchers of other LMICs on how to perform HTA for national health scheme related to drug reimbursement. If more cost-effectiveness studies from LMICs become available in the future, meta-analysis of LMIC studies could be performed to broaden the understanding on the cost-effectiveness of fibrinolytic therapies in the resource-limited settings.

Morbidity and mortality worldwide. Mechanical reperfusion by primary percutaneous coronary intervention (primary PCI) is recommended by various guidelines as the preferred reperfusion strategy for STEMI patients who presents to PCI-capable hospitals or non-PCI hospitals with transfer time to PCI within 120 minutes. Within this timeframe, primary PCI has been shown to achieve better clinical outcomes than fibrinolytic therapy. However, access to primary PCI is limited, particularly among low- and middle-income countries (LMICs). Consequently, fibrinolytic therapy remains a crucial option in STEMI management and has been recommended in various clinical practice guidelines across the globe. Several reports indicate that tenecteplase (TNK) offers advantages over streptokinase (SK) in terms of bleeding and mortality. A recent network meta-analysis based on a systematic review of randomized controlled trials has demonstrated that tenecteplase (TNK) significantly reduced 1-month all-cause mortality and bleeding compared to streptokinase (SK). According to international and local clinical practice guidelines, TNK is the preferred fibrinolytic drug over SK based on the superior efficacy and safety. However, 98% of Thai patients still received SK as fibrinolytic therapy. This is because the reimbursement protocol mandates the use of SK as the first line agent. Due to higher acquisition price, TNK is reimbursable only in the condition of SK allergy, previous SK use in less than six months or in patients suffering from an anterior wall MI with hemodynamic instability whom access to PCI in a timely fashion is not feasible. Despite strong clinical evidence supporting the use of TNK over SK for fibrinolytic therapy in patients with STEMI, little is known about its cost-effectiveness in the resource-limited countries including Thailand. Nowadays, economic evidence has been valued as a crucial piece of information to support policy decision making process especially in those low-and middle-income countries. Thailand is an example of country that has utilized cost-effectiveness study as part of their national list of essential medicine selection process. Therefore, generating a robust cost-effective analysis is needed to facilitate an evidence-informed decision in such countries. Our study therefore aims to assess the cost-effectiveness of TNK versus SK in Thai STEMI patients in the setting where access to primary PCI is limited. We believe that our findings could facilitate evidence-informed policy decision making in Thailand and support Health Technology Assessment (HTA) development in other LMICs with similar healthcare context. In addition, this study can potentially serve as a prototype for researchers of other LMICs on how to perform HTA for national health scheme related to drug reimbursement.

Method
Our study was reported in accordance with the recommendation of Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.

Overall description
Target population were patients with STEMI who received fibrinolytic treatment in Thailand. We compared cost-effectiveness between two fibrinolytic drugs; TNK as an intervention and SK as a comparator, both on health care provider and societal perspectives.
Provider perspective included only direct medical costs e.g., drugs, procedures and hospital service. Societal perspective included both direct medical cost and direct non-medical cost e.g., cost of transportation, additional food cost (Table 1). According to Thailand’s HTA guideline, indirect cost was excluded for both perspectives to avoid double-counting.21 We used lifetime time horizon to capture long-term cost and quality of life after STEMI events. The study applied an annual discount rate of 3.0% to costs and benefits, as recommended by Thailand’s HTA guideline.21

**Description of the models**
We used a decision tree model to evaluate short-term costs and outcomes including rate of urgent PCI, major

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### Table 1 (Continued)

| Parameters | Base case | Range | Source(s) |
|------------|-----------|-------|-----------|
| **Probability for 30-day decision tree model** | | | |
| **Treatment with SK** | | | |
| Probability of receiving urgent PCI | 0.152 | 0.148-0.156 | NHSO |
| Probability of developing major bleeding in patients receiving urgent PCI | 0.085 | 0.082-0.088 | NHSO |
| Probability of developing major bleeding in patients not receiving urgent PCI | 0.064 | 0.061-0.067 | NHSO |
| Probability of death in patients with urgent PCI and with major bleeding | 0.225 | 0.220-0.230 | NHSO |
| Probability of death in patients with urgent PCI and without major bleeding | 0.063 | 0.060-0.066 | NHSO |
| Probability of death in patients without urgent PCI and with major bleeding | 0.334 | 0.328-0.340 | NHSO |
| Probability of death in patients without urgent PCI and without major bleeding | 0.155 | 0.151-0.159 | NHSO |
| **Treatment with TNK** | | | |
| Probability of receiving urgent PCI | 0.152 | 0.148-0.156 | NHSO |
| RR of developing major bleeding (TNK vs SK) | 0.86 | 0.58-1.37 | 14 |
| RR of death (TNK vs SK) | 0.89 | 0.77-1.02 | 14 |
| **Probability for Markov model** | | | |
| Annual risk of MI in the no event state | 0.019 | 0.01-0.05 | 25 |
| Annual risk of stroke in the no event state | 0.003 | 0.001-0.02 | 25 |
| Increased risk of death in the no event rate | 2 | 1-4 | 25 |
| Increased risk of death in the non-fatal MI state | 6 | 4-9 | 25 |
| Increased risk of death in the post MI state | 3 | 1-4 | 25 |
| Increased risk of death in the non-fatal stroke state | 7.43 | 5-10 | 25 |
| Increased risk of death in the post stroke state | 3 | 1-5 | 25 |
| **Cost** | | | |
| Direct medical cost | | | |
| Cost of streptokinase (per vial) | 5,400 ($189) | - | 27 |
| Cost of tenecteplase (per vial) | 22,000 ($769) | - | 27 |
| Urgent PCI with major bleeding with death | 117,818 | 89,570-146,067 | NHSO |
| Urgent PCI with major bleeding with survival | 133,338 | 115,907-150,769 | NHSO |
| Urgent PCI with no major bleeding with death | 124,959 | 107,782-142,136 | NHSO |
| Urgent PCI with no major bleeding with survival | 115,991 | 112,690-119,294 | NHSO |
| No urgent PCI with major bleeding with death | 39,637 | 34,749-44,526 | NHSO |
| No urgent PCI with major bleeding with survival | 50,493 | 35,462-65,525 | NHSO |
| No urgent PCI with no major bleeding with death | 30,585 | 28,286-32,884 | NHSO |
| No urgent PCI with no major bleeding with survival | 30,456 | 29,832-31,081 | NHSO |
| No event (per year) | 23,144 | 18,515-27,773 | 28 |

Table 1 (Continued)
bleeding and death in 30 days. While Markov model was used to evaluate long-term cost-effectiveness. A 30-day decision tree began with patients diagnosed with STEMI who received fibrinolytic therapy (Figure 1). They might receive either SK or TNK. After receiving fibrinolysis, they might receive urgent PCI which was defined as a PCI performed in the same admission episode of STEMI. Patients would further have a possibility of developing major bleeding which was defined as bleeding requiring blood transfusion and intracranial hemorrhage based on Bleeding Academic Research Consortium (BARC) definition type 3.22 At the end of 30 days, patients would either be alive or dead. All surviving patients after 30 days following STEMI were subsequently analyzed in Markov model. We assumed that there was no remaining treatment effect after 30 days. Therefore, both SK and TNK arms had the same transition probabilities in the Markov model. Every surviving patient became in the “no event” health state and could have a health state change every 1-year cycle length between one of the six health states (no event, non-fatal MI, non-fatal stroke, post MI, post stroke and death) (Figure 2). The model started with patients at the age of 60 years old (mean age of surviving patients after 30 days from the database) and ran until patients reaching the age of 100 years or 40 cycles. The model structures were reviewed and validated by a health economic expert (NQ) for health-economic aspect and cardiologists for clinical aspect (PV and PS).

### Input parameters

**National database.** We retrieved inpatient and outpatient data from National Health Security Office (NHSO) database during October 2012—September 2019. This database includes completed patients’ data who had Universal Health Coverage health insurance which cover approximately 75% of Thai people. The database includes unique encrypted identification number, sex, age, diagnosis codes, procedure codes and cost for both outpatient and inpatient data. Every governmental hospital in Thailand has to transfer every patient’s data to NHSO. Diagnostic, procedure codes and costs were rechecked by NHSO before reimbursement (e.g., recheck medication prescription or duplicated data). The death status was obtained from the Bureau of Registration Administration, Department of Provincial Administration of Thailand.

**Probabilities.** International Statistical Classification of Diseases and Related Health Problems (ICD) codes were used to identify diagnoses and procedures. Details

| Parameters                      | Base case | Range          | Source(s) |
|---------------------------------|-----------|----------------|-----------|
| Non-fatal MI (per year)          | 140,259   | 112,206-168,311| 28        |
|                                 | ($4,901)  | ($3,921-$5,881)|           |
| Post MI (per year)               | 15,054    | 12,043-18,065  | 28        |
|                                 | ($526)    | ($421-$631)    |           |
| Non-fatal stroke (per year)      | 69,428    | 55,541-83,313  | 28        |
|                                 | ($2,426)  | ($1,941-$2,911)|           |
| Post stroke (per year)           | 10,999    | 8,799-13,199   | 28        |
|                                 | ($384)    | ($307-$461)    |           |
| Direct non-medical cost          |           |                |           |
| Transport                        | 145 ($)   | 122-168 ($)    | 29        |
| Food                            | 73 ($)    | 59-88 ($)      | 29        |
| No event (per year)              | 1,762 ($) | -              | 29        |
| Non-fatal MI (per year)          | 3,074 ($) | -              | 29,46     |
| Post MI (per year)               | 1,762 ($) | -              | 29        |
| Non-fatal stroke (per year)      | 3,074 ($) | -              | 29,47     |
| Post stroke (per year)           | 1,762 ($) | -              | 29        |
| Utility                          |           |                |           |
| Non-fatal MI                     | 0.67      | 0.60-0.74      | 32        |
| Non-fatal stroke                 | 0.33      | 0.26-0.40      | 32        |
| Post MI                          | 0.82      | 0.77-0.87      | 32        |
| Post stroke                      | 0.52      | 0.45-0.59      | 32        |

Table 1: Input parameters.

Costs are presented as Thai Baht ($), year 2019 value.

\* Use the same rate as SK treatment.
\* Use two vial if body weight ≥ 80 kg and age < 75 years.

**SK,** streptokinase; **TNK,** tenecteplase; **PCI,** percutaneous coronary intervention; **RR,** risk ratio; **MI,** myocardial infarction; **NHSO,** National Health Security Office.

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on diagnosis and procedure codes are available in Supplementary Appendix 3. For short-term analysis, probabilities of events in SK arm were based on the national database. A total of 395,635 acute coronary syndrome hospital admissions including 132,972 (33.6%) index STEMI patients was identified in the database. Of these patients, 25,907 (19.5%) received fibrinolytic treatment. Details for baseline characteristics of the patients are available in the Supplementary Appendix 4. The mean (± standard deviation) age of the patients was 61.6 ± 12.6 years old. The proportion of patients receiving urgent PCI was 15.2%. Major bleeding rate was 8.5% in
PCI arm and 6.4% in no PCI arm. The major bleeding rate post SK treatment in the database was slightly lower than the rate from GUSTO-I study (11.8%), probably from under ICD coding. Probability of death was calculated using death status. Overall mortality rate for STEMI patients received fibrinolytic was 15.9%. Mortality rates were 7.7% in PCI arm and 16.6% in no PCI arm. Further details are available in the Supplementary Appendix 5.

Because of limited reimbursement policy of TNK, its use is limited and the majority (98%) of patients received SK for fibrinolytic therapy. In addition, since TNK was mostly used in the central areas of Thailand which could affect urgent PCI rate and mortality rate, significant selection bias would occur if the data from the national database was used in the analysis. Therefore, we used different methods to acquire probabilities of events in TNK arm. The probability of receiving urgent PCI in TNK arm was assumed to be equal to SK given the lack of urgent PCI rate reported in studies in network meta-analysis. Other probabilities of events in TNK arm were calculated using risk ratio of events of TNK compared to SK derived from a network meta-analysis comparing fibrinolytic drugs in patients with STEMI. All input parameters and sources of information used in the model were shown in Table 1.

Costs. Direct medical costs were comprised of fibrinolytic drug and other management costs. The reference prices of SK and TNK were obtained from the announcement of national drug cost year 2020 from the Drug and Medical Supply Information Center, Ministry of Public Health, Thailand. TNK dose was adjusted based on body weight and age (Supplementary Appendix 1). For 30-day decision tree, direct medical costs of each probability of events in SK treatment arm were directly obtained from the NHSSO database. We then excluded SK drug cost from total direct medical cost and added TNK drug cost to acquire total direct medical costs for each probability in TNK treatment arm. In long-term Markov model, annual costs of each health state were taken from literature review (Table 1).

The currency used was Thai Baht (THB). The costs were converted to 2019 value using the medical care consumer price index. For inter-currency comparisons, money values in THB were converted into United States dollar ($) using exchange rate of $1 equal 28.62 THB.

Utility. There is no direct utility study for cardiovascular disease in Thailand. Therefore, utility values for each health state were derived from results of a time tradeoff study (Table 1).

Analytical method
Base-case analysis. We analyzed costs and quality-adjusted life years (QALYs) over lifetime horizon and presented in mean values. Estimated incremental cost-effectiveness ratio (ICER) was calculated using mean costs and QALYs. According to Thai HTA recommendation, an ICER of 160,000 THB [5,590 USD]/QALY is the threshold considered to be ‘cost-effective’.

Sensitivity analysis. Sensitivity analysis strategies were used to deal with uncertainty of variable values. First, one-way sensitivity analysis was computed to evaluate results by alter one variable at a time. Second, we executed probabilistic sensitivity analysis to evaluate uncertainty of parameters by simultaneously varying every
input parameters’ values over their respective feasible ranges. A beta distribution was chosen for probability and utility parameters. A log-normal distribution was used for risk ratio parameters. A gamma distribution was assigned for all cost parameters. Simulations were performed for one-thousand times. Results were demonstrated as a cost-effectiveness acceptability curve which shows the relationship between the willingness to pay for a unit of outcome and the probability of favoring each strategy.34 Third, if TNK were not cost-effective, we planned to perform a cost threshold analysis to determine the price of TNK that would meet cost-effectiveness in Thailand.

Role of the funding source
There is no funding source for this study.

Results

Base-case analysis
From societal perspective, the average lifetime cost was $12,373 (354,108 THB) for TNK treatment and $11,546 (330,445 THB) for SK treatment. From health care provider perspective, the average lifetime cost was $11,333 (324,340 THB) for TNK treatment and $10,525 (301,239 THB) for SK treatment. From both perspectives, QALYs were 8.82 and 8.65 for TNK and SK treatment, respectively (Table 2). TNK was more cost effective than SK in both societal and provider perspectives. From societal perspective, TNK increases cost by $827 (23,663 THB) and increases QALY by 0.173. Thus, the ICER is $4,777 (136,719 THB) per QALY gained. Similarly, the ICER from health care provider perspective is $4,664 (133,471 THB) per QALY gained (Table 2).

Sensitivity analyses
One-way sensitivity analyses showed that the most influential parameters were risk ratio of death for treatment with TNK compared to SK and cost of TNK. (Figure 3). TNK would not be cost-effective (more costly but less effective) if we use upper value of risk ratio of death for treatment with TNK compared to SK (from 0.89 to 1.02). In the probabilistic sensitivity analysis, at a 5,590 USD (160,000 THB) per QALY threshold, the probability of TNK being cost-effective was 83% from both health care provider and societal perspective (Figure 4 and 5).

Discussion
Despite increasing incidence of STEMI and established mortality benefit of primary PCI for STEMI treatment, many LMICs still have challenges to deliver primary PCI to their patients in a timely fashion and with broad geographical coverage.8,9,19 Fibrinolytic therapy therefore remains the vital alternative treatment in this setting. Fibrin-specific drugs (e.g. TNK) are preferred over non-fibrin-specific drugs (e.g. SK) for fibrinolytic therapy due to rich evidences of superior efficacy and safety, therefore recommended in various international guidelines for both high-income countries and LMICs including Thailand.3,4,11 In high-income countries, cost-effectiveness studies showed that fibrin-specific drug is cost-effective and therefore routinely used in these countries.35,36 To the best of our knowledge, we found only one cost-effectiveness study in LMICs setting which was conducted and published in Thai language.37 However, the study has several limitations such as the use of patency rate as outcome and a lack of life-time horizon analysis. As a result, there is a clear need for a study with more robust methodology that meets both national and international standard for health technology assessment to help guide a health policy decision.

In addition to the methodological aspect, input parameters used to perform cost-effectiveness analysis is also crucial, especially when the outcomes could potentially be affected by the health system delivery.39 Disparity on the developmental stages of the health system among high-income countries versus LMIC can potentially lead to differences in drug performance.39,40 As a result, a cost

| Variable | Societal perspective | Health care provider perspective |
|----------|----------------------|---------------------------------|
|          | TNK                  | SK                              |
|          | Costs                | Costs                           |
|          | 354,108 ($12,373)    | 330,445 ($11,546)               |
| QALYs    | 8.82                 | 8.65                            |
| Incremental cost | 23,663 ($827)      | Incremental QALYs | 23,101 ($808) |
| Incremental QALYs | 0.173               | ICER                            |
| ICER     | 136,719 ($4,777)    | 133,471 ($4,664)               |
|          | (cost-effective)     | (cost-effective)                |

Table 2: Base case analysis.
Costs are presented as Thai Baht ($). ICER are presented as Thai Baht/QALY ($/QALY).
TNK, tenecteplase. SK, streptokinase. QALYs, quality-adjusted life years. ICER, incremental cost-effectiveness ratio.
effectiveness analysis may be more applicable to a health system if the local data are used as input parameters.\(^4^1\) Real-world evidence has been recognized for its strength in answering the actual questions based on real-world data and widely encouraged in informing treatment reimbursement decision-making.\(^4^2\) Various countries worldwide including those in Asia have used real-world evidence to support their national health policy.\(^4^3\) With data retrieved from the national database covering 75% of the whole population, evidence generated from this study is therefore highly applicable to the context of policy decision making in Thailand.

Findings from our study demonstrated that tenecteplase is a cost-effective fibrinolytic drug for treatment of
STEMI compared to streptokinase, in the local context as an LMIC where willingness to pay threshold is much less than those of high-income countries. TNK is found to be cost-effective in both societal and provider perspectives, which is an encouraging finding. In addition to clinical superiority of TNK over SK in terms of reduced mortality and less bleeding, another important aspect of TNK is the ease of administration. TNK is required to be administered only as a single intravenous administration which is much more convenient than SK which required intravenous administration over 30-60 minutes. Since transportation of a STEMI patient to a PCI-capable hospital is a common scenario, ease of administration is a practical and relevant advantage of TNK over SK, especially for pre-hospital setting. Considering both clinical and economic benefits, TNK should be considered as the fibrinolytic agent of choice for patients with STEMI in a middle-income country like Thailand.

The primary strength of our study comes from comprehensiveness and validity of the patients’ data. ICD codes and costs were rechecked by NHSO before reimbursement (e.g., recheck medication prescription or duplicated data). Mortality rate was especially accurate as this was based on national vital statistics of Thailand. Data from NHSO represented majority of Thai population with a large number of patients. The results are robust and potentially have direct impact on national health policy and could change routine clinical practice for substantial number of patients.

There are some limitations in our study. First, we did not have real world data of the use of TNK as SK is used mostly in this population. Real world data would give more accurate estimate of benefit of Tenecteplase which might have changed the result of cost-effectiveness analysis, however we used the most justifiable available data from a network meta-analysis. Second, input parameters used for long-term analysis were derived from literatures review. Nonetheless, one-way sensitivity analysis showed that the key parameters were in the short-term part rather than long-term part. Third, we have not performed budget impact analysis which could help decision making of substitution of TNK for SK.

We believe that benefit from this study is not limited to one country but can potentially be extended to other LMICs with similar health care systems. In addition, other LMICs might use the concept of incorporating national database and economic models as a prototype to evaluate cost-effectiveness in their countries. If more cost-effectiveness studies from LMICs become available in the future, meta-analysis of LMIC studies could be performed to broaden the understanding on the cost-effectiveness of fibrinolytic therapies in the resource-limited settings.

**Conclusion**

In a resource-limited setting like Thailand, TNK is a cost-effective fibrinolytic agent for the management of STEMI compared to SK, for both societal and provider perspectives. Sensitivity analyses suggested that changes in the risk ratio of death for treatment with TNK and the acquisition cost of TNK are the most influential factors affecting the cost-effectiveness balance. As a result, TNK could potentially be considered as the fibrinolytic agent of choice over SK in Thailand, despite a higher acquisition cost.
Contributors
NC, PV and PS conceptualized the original idea for the study. PJ, KT and NP made the data curation. PJ and KT do the data analysis and investigation. NC provided methodology. PV was the project administrator and supervisor. PS and NC provided resources and supervision. PD validated the results. SN provided visualization. KT and NC wrote the first draft of the manuscript. KT, NC, PD, SN and LML revised the manuscript. All authors approved the final manuscript as submitted.

Data sharing statement
Data will not be available for others as the data custodians have not given permission.

Declaration of interests
The authors declare no conflict of interests.

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References
1 Kushner FG, Bates ER. Chapter 10 - ST-segment elevation myocardial infarction. In: Antman EM, Sabatine MS, eds. Cardiovascular Therapeutics: a Companion to Braunwald (Fourth Edition). Philadelphia: W.B. Saunders; 2017:78–213.
2 Choudhury T, West NE, El-Omar M. ST elevation myocardial infarction. In: Antman EM, Sabatine MS, eds. Cardiovascular Therapeutics: a Companion to Braunwald (Fourth Edition). Philadelphia: W.B. Saunders; 2017:78–213.
3 Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(4):277–282.
4 Ilbaze B, James S, Aggewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(4):277–282.
5 O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78–e140.
6 Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation. 2003;108(15):1809–1814.
7 Keeley EC, Boura JA, Grines CI. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet North Am Ed. 2001;359(9313):11–20.
8 Pinto DS, Kirtane AJ, Nallamothu BK, et al. Hospital delays in reperfusion for ST-elevation myocardial infarction: implications when selecting a reperfusion strategy. Circulation. 2006;114(19):2019–2025.
9 Ramakrishnan S, Mishra S, Chakraborty R, Chandra KS, Mardikar HM. The report on the Indian coronary intervention data for the year 2011—National Interventional Council. Indian Heart J. 2013;65(5):518–521.
10 Rossello X, Hsu Y, Pocock S, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. Int J Cardiol. 2017;245:27–34.
11 Sriramachota S, Boonyaratavej S, Kankanavist R, et al. Thai Registry in Acute Coronary Syndrome (TRACS)—an extension of Thai Acute Coronary Syndrome registry (TACS) group. lower-in-hospital but still high mortality at one year. J Med Assoc Thai. 2012;95(4):508–518.
12 Thai Acute Coronary Syndromes Guidelines 2020. Bangkok: The Heart Association of Thailand under the Royal Patronage of H.M. The King. 2020.
13 Chau H, Choi K. Efficacy and Safety of Tenecteplase versus Streptokinase in Treating ST-Elevation Myocardial Infarction Patients in Hong Kong: a four-year retrospective review in Queen Elizabeth Hospital. Hong Kong J Emerg Med. 2012;20(6):339–343.
14 Yazdi AHKEZ A, Pouya SA, Pakrou M, Ghaznavi MA, Mikhailand A, Rouzitalab M. Fibrinolytic therapy with streptokinase vs tenecteplase for patients with ST-elevation MI not amenable to primary PCI. Iran Heart J. 2017;18(1):7.
15 Jintatongthi P. Kongwatcharapong P, Foo CY, et al. Comparative efficacy and safety of reperfusion therapy with fibrinolytic agents in patients with ST-segment elevation myocardial infarction: a systematic review and network meta-analysis. Lancet North Am Ed. 2017;390(10096):747–759.
16 Thai ACS. Ministry of Public Health. registry. Thailand. 2019,. http://www.ncvd.org/Default.aspx. Accessed 10 October 2020.
17 Thailand National List of Essential Medicines (NLEM). National Drug Policy Committee. 2020. http://nidi.fda.moph.go.th/Drug_national. Accessed 10 October 2020.
18 Guha S, Sethi R, Ray S, et al. Cardiological society of India: position statement for the management of ST-elevation myocardial infarction in India. Indian Heart J. 2017;69(Suppl 1):S61–S97.
19 Li J, Li X, Ross JS, et al. Fibrinolytic therapy in hospitals without percutaneous coronary intervention capabilities in China from 2001 to 2011: China PEACE-registry AMI study. Eur Heart J Acute Cardiovasc Care. 2017;6(1):232–243.
20 Limwattanon C, Jaratpatthararoj J, Thungthong J, Limwattananon F. Kikkhuandee A. Access to reperfusion therapy and mortality outcomes in patients with ST-segment elevation myocardial infarction under universal health coverage in Thailand. BMC Cardiovasc Diol. 2020;20(1):121.
21 Chaikledkaew U, Kittrongsiri K. Guidelines for health technology assessment in Thailand (second edition)—the development process. J Med Assoc Thai. 2014;97(Suppl 5):S4–S9.
22 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2765–2747.
23 Survey on Health and Welfare. National Statistical Office, Ministry of Digital Economy and Society, 2019, http://statinfo.moe.go.th/stati creport/page/sector/th/05.aspx. Accessed 20 September 2020.
24 Berkowitz SD, Granger CB, Pieper KS, et al. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. Circulation. 2010;121(23):2765–2747.
25 Mehra A, Rao SV. Bhattacharyya A. Guidelines for health technology assessment in Thailand (second edition)—the development process. J Med Assoc Thai. 2014;97(Suppl 5):S4–S9.
26 Mehra A, Rao SV. Bhattacharyya A. Guidelines for health technology assessment in Thailand (second edition)—the development process. J Med Assoc Thai. 2014;97(Suppl 5):S4–S9.
27 Life tables by country. Thailand: World Health Organization. April, 2018. https://apps.who.int/gho/data/databox/61640. Accessed 1 November 2020.
28 Announcement of national drug cost year 2020. Drug and Medical Supply Information Center Ministry of Public Health; 2020. http://dnmisc.moph.go.th/index/dataservice/97/0. Accessed 20 September 2020.
29 Kongpakwattana K, Ademi Z, Chaiyasothi T, et al. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J. 2015;36(1):220–228.
30 Bureau of Trade and Economic Indices. Thailand: Ministry of Commerce; 2020. http://www.price.moc.go.th/price/cpi/index_new_e. aspx. Accessed 20 September 2020.
31 Foreign Exchange Rates. Bank of Thailand; 2021. https://www.bot.or.th/english/statistics/financialmarkets/exchangerate/ | lazyload/Application/ExchangeRate/ExchangeRate.aspx. Accessed 20 February 2021.

32 Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities. BMC Health Serv Res. 2015;15(1):173.

33 Thavorncharoensap M, Teerawattananon Y, Natanant S, Kulpeng W, Yothisamut J, Werayingyong P. Estimating the willingness to pay for a quality-adjusted life year in Thailand: does the context of health gain matter? Clinicoecon Outcomes Res. 2013;5:29–36.

34 Walker D, Fox-Rushby JA. Allowing for uncertainty in economic evaluations: qualitative sensitivity analysis. Health Policy Plan. 2001;16(4):435–442.

35 Kalish SC, Gurwitz JH, Krumholz HM, Avorn J. A cost-effectiveness model of thrombolytic therapy for acute myocardial infarction. J Gen Intern Med. 1995;10(6):121–130.

36 Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med. 1995;332(21):1418–1424.

37 Srisubat A, Saengtong B, Ronpant P, Tangweerapornpong S, Hengnussamee K, Potnari S. Cost-effectiveness analysis of tissue plasminogen activator (tPA) compared with streptokinase (SK) in treating ST-elevated myocardial infarction (STEMI). Bull Dept Med Serv. 2014;39:173–183.

38 Bowrin K, Briere JB, Levy P, Millier A, Clay E, Toumi M. Cost-effectiveness analyses using real-world data: an overview of the literature. J Med Econ. 2010;13(6):545–555.

39 Mitsuntisuk P, Nathisuwan S, Junapanichjaroen A, et al. Real-world comparative effectiveness and safety of non-Vitamin K antagonist oral anticoagulants vs. warfarin in a developing country. Clin Pharmacol Ther. 2021;109(3):1282–1292.

40 Noviyani R, Youngkong S, Nathisuwan S, et al. Economic evaluation of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) for stroke prevention in patients with atrial fibrillation: a systematic review and meta-analysis. BMJ Evid Based Med. 2021.

41 Liu ZK, Xiong X, Lee T, Wu J, Yuan J, Jiang B. Big data and real-world data based cost-effectiveness studies and decision-making models: a systematic review and analysis. Front Pharmacol. 2021;2.

42 The REAL World Data In Asia for HEalth Technology Assessment in Reimbursement (REALISE) working group. Use of Real-World Data and Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia. 2020. https://iper.nus.edu.sg/wp-content/uploads/2020/12/REALISE-Full-guidance_updated-2020101.pdf. Accessed 15 September 2021.

43 Justo N, Espinoza MA, Ratto B, et al. Real-world evidence in healthcare decision making: global trends and case studies from Latin America. Value Health. 2019;22(6):739–749.

44 Lou J, Kc S, Toh KY, et al. Real-world data for health technology assessment for reimbursement decisions in Asia: current landscape and a way forward. Int J Technol Assess Health Care. 2020;36(5):474–480.

45 Facey RM, Rannanheimo P, Batchelor L, Borchardt L, de Cock J. Real-world evidence to support Payer/HTA decisions about highly innovative technologies in the EU-actions for stakeholders. Int J Technol Assess Health Care. 2020;1–10.

46 Moleerergpoom W, Kanjanavanit R, Jintapakorn W, Sritara P. Costs of payment in Thai acute coronary syndrome patients. J Med Assoc Thai. 2007;90(Suppl 1):21–31.

47 Sribundit N, Riewpaiboon A, Chaisiddikaw U, Stewart J, Tantritissak T, Hanschaipookkul S. Cost of acute care for ischemic stroke in Thailand. Southeast Asian J Trop Med Public Health. 2017;48(3):628–640.