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Evaluation of the tolerability and effectiveness of Tenecteplase in patients with ST-Segment-Elevation Myocardial Infarction in a Secondary Hospital in Malaysia: A Retrospective Case Series ☆

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ABSTRACT

Background: In Malaysia, knowledge regarding the clinical efficacy of tenecteplase (TNK), a fibrin-specific tissue-plasminogen activator, is limited.
Objectives: To evaluate the effectiveness and tolerability of TNK in patients with ST-segment-elevation myocardial infarction in a secondary referral Malaysian hospital.
Methods: This was a single-center retrospective case series based on the medical records of patients with ST-segment-elevation myocardial infarction admitted to the cardiac care unit between January 2016 and May 2019. Data regarding the mortality status and date of death were collected from the database of the National Registration Department of Malaysia.
Results: Data for 30 patients with ST-segment-elevation myocardial infarction, who received weight-adjusted doses of TNK, were analyzed. The patients' mean (SD) age was 62 (14) years, and 77% were men. The median time to treatment was 265 minutes (interquartile range = 228–660 minutes), and the clinical success rate of thrombolysis was 79%. The overall all-cause in-hospital mortality rate was 33%. The 1-year survival rates were higher in patients achieving a time to treatment ≤360 minutes ($P = 0.03$), with a trend toward greater survival in this group at 30 days. Similarly, a trend toward lower in-hospital all-cause mortality was observed in this group (21% vs 50%; $P = 0.12$). Only 1 patient (3%), who had a HAS-BLED score based on hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, old age, drug/alcohol use of 5, developed major bleeding that required blood transfusion. No cases of ischemic stroke, nonmajor bleeding, in-hospital re-infarction, or TNK-induced allergic reaction were identified.
Conclusions: We hypothesized that the mortality-related outcomes of TNK in patients with ST-segment-elevation myocardial infarction were influenced by TTT, with TTT ≤360 minutes indicating a better prognosis than TTT >360 minutes. TNK-induced bleeding-related complications were minimal in low-risk patients. Further local studies are needed to compare TNK's profile with that of streptokinase, which is a common agent currently used in clinical practice in Malaysian public hospitals. (Curr Ther Res Clin Exp. 2021; 82:XXX–XXX)

Introduction

Myocardial infarction has a high global mortality rate. According to the Department of Statistics, Malaysia, ischemic heart disease was the principal cause of death in Malaysia during 2018. Between 2007 and 2017, the total number of cases of ischemic heart

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disease increased by 54%. Since 2000, several studies on coronary artery diseases have been conducted in Malaysia.[1]

Primary percutaneous coronary intervention (PCI) remains the preferred reperfusion method in patients with ST-segment-elevation myocardial infarction (STEMI) when performed promptly by skilled operators[2]; however, this method is unfeasible in hospitals without PCI facilities. Our hospital is a secondary referral hospital, wherein patients are treated using a noninvasive approach (eg, thrombolysis); however, PCI facilities and experts are not available on site. If patients prefer PCI, they are referred to the nearest tertiary hospital, approximately 70 km away by road. Because of the limited access to hospitals and experts capable of performing PCI, most patients undergo thrombolysis at the nearest hospital.

Tenecteplase (TNK) is a genetically engineered, multiple-point mutant of the recombinant tissue-type plasminogen activator (tPA). It has a longer plasma half-life, allowing for a single intravenous bolus injection. Compared with standard tPA, it is 14-fold more fibrin-specific and 80-fold more resistant to inhibition by plasminogen activator inhibitor type 1. Thus, compared with tPA, TNK has a similar efficacy, modestly low bleeding risk, and is easily administered.[3]

Reperfusion with fibrinolytic agents reduces morbidity and mortality associated with myocardial infarction. Yew, in a work conducted in 2015 in Malaysia, suggested that TNK should be adopted as the thrombolytic agent of choice in hospitals or within the local STEMI network.[4] In addition, TNK may have another advantage of reducing door-to-needle time compared with streptokinase,[5] which could be attributed to less preparation time. In our hospital, TNK has been prescribed to patients with STEMI by medical specialists; however, TNK is almost 3 times more expensive than streptokinase (ie, approximately RM 3,400 [$820] versus RM 1,000 [$240] per vial, during 2019). Therefore, TNK use is difficult to justify in a publicly funded hospital. Thus, concerns were raised regarding the procurement flow of more TNK, especially in the public expenditure planning because medicines are provided free of charge to patients in need.

Given the scarcity of published evidence in the local population, there was an urgent need for a clinical study to verify the effectiveness and tolerability of TNK in patients with STEMI in Malaysia. Therefore, this study aimed to evaluate the effectiveness and tolerability of TNK in patients presenting with STEMI in our secondary referral hospital.

Materials and Methods

Patients

This study was a retrospective case series, with data collected from medical records of patients who were admitted to the cardiac care unit (CCU) of our hospital between January 2016 and May 2019. Patients were recruited based on the pharmacy tenecteplase record book at the CCU. No sample size calculations were performed; rather, we included all patients with STEMI admitted to the CCU. Data regarding the mortality status and date of death were obtained from the database of the National Registration Department of Malaysia.

The inclusion criteria were as follows: aged ≥18 years, diagnosis of STEMI, treatment with weight-adjusted doses of TNK, and admission to the CCU. In contrast, the exclusion criteria were as follows: pregnancy, diagnosis of pulmonary embolism, and incomplete medical information.

In accordance with the 1975 Declaration of Helsinki, the study was ethically approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (ethical approval No. NMRR-19-1896-47670). The need for informed consent was waived because of the retrospective nature of the study. All patients' names and other identifiers were excluded from data analyses.

Variables

The clinical data collected from medical records included the following: demographic characteristics (age, sex, and ethnicity); smoking status; medical history; body weight; dose and indication for TNK; time to treatment (TTT) and door-to-needle time (DNT); systolic blood pressure and heart rate at presentation; thrombolysis in myocardial infarction risk score; HAS-BLED score (based on hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile international normalized ratio, old age, and drug/alcohol use); the presence of nonfatal in-hospital reinfarction; in-hospital death from all causes; clinically successful thrombolysis (CST); presence of major and nonmajor bleeding; need for blood transfusion; and presence of other adverse reactions. The TTT was defined as the duration between the onset of reported symptoms and the time of thrombolytic agent administration, as recorded in the patients' medical files. CST was defined as significant relief from chest pain and 50% resolution of ST-segment elevation within 90 minutes on electrocardiography.

Statistical analysis

All data analyses were performed using the SPSS version 19 (IBM-SPSS Inc, Armonk, NY) statistical package. Data are presented as percentages for categorical variables and as means and SD, or medians and interquartile ranges for continuous variables. Intergroup differences in categorical and continuous variables were assessed using the 2-sided (unless specified) χ^2 or Fisher exact test as appropriate; normally and nonnormally distributed data were assessed using independent samples *t* test and the Mann–Whitney *U* test, respectively. Alpha or *P* values < 0.05 were considered statistically significant. Both Kaplan–Meier analysis and the log-rank test were used for the analysis of time-to-event data.

Results

Patient characteristics

Appendix 1 (in the online version) presents the total number of patients with STEMI admitted from 2016 to 2019. In total, 35 patients received TNK during the study period. Five patients were excluded from the study because of pulmonary embolism; therefore, the data of 30 patients with STEMI who received weight-adjusted doses of TNK injections in the CCU were analyzed. **Table 1** summarizes the baseline demographic characteristics, medical history, and the patients' characteristics at presentation. A comparison of the baseline characteristics between the 2 study groups (TTT ≤360 minutes and TTT >360 minutes) is presented in **Table 2**.

Mortality

We observed that the overall all-cause in-hospital mortality rate was 33%; however, patients with TTT ≤360 minutes had lower all-cause in-hospital and 30-day mortality rates than those with TTT >360 minutes (in-hospital mortality: odds ratio [OR] = 0.27; 95% CI, 0.05–1.40; 30-day mortality: OR = 0.36; 95% CI, 0.07–1.78); however, these differences were not statistically significant. **Figures 1** and **2** show the Kaplan–Meier survival curves at 30 days and 1 year. According to the log-rank test, the 1-year survival rate varied significantly between the 2 groups: the 1-year survival rate was significantly higher in patients with TTT ≤360 minutes than in those with TTT >360 minutes ($P = 0.03$); the proportions of survived patients at 1 year were 73% and 25%, respectively. Nonetheless, patients with DNT ≤180 minutes were compared with those

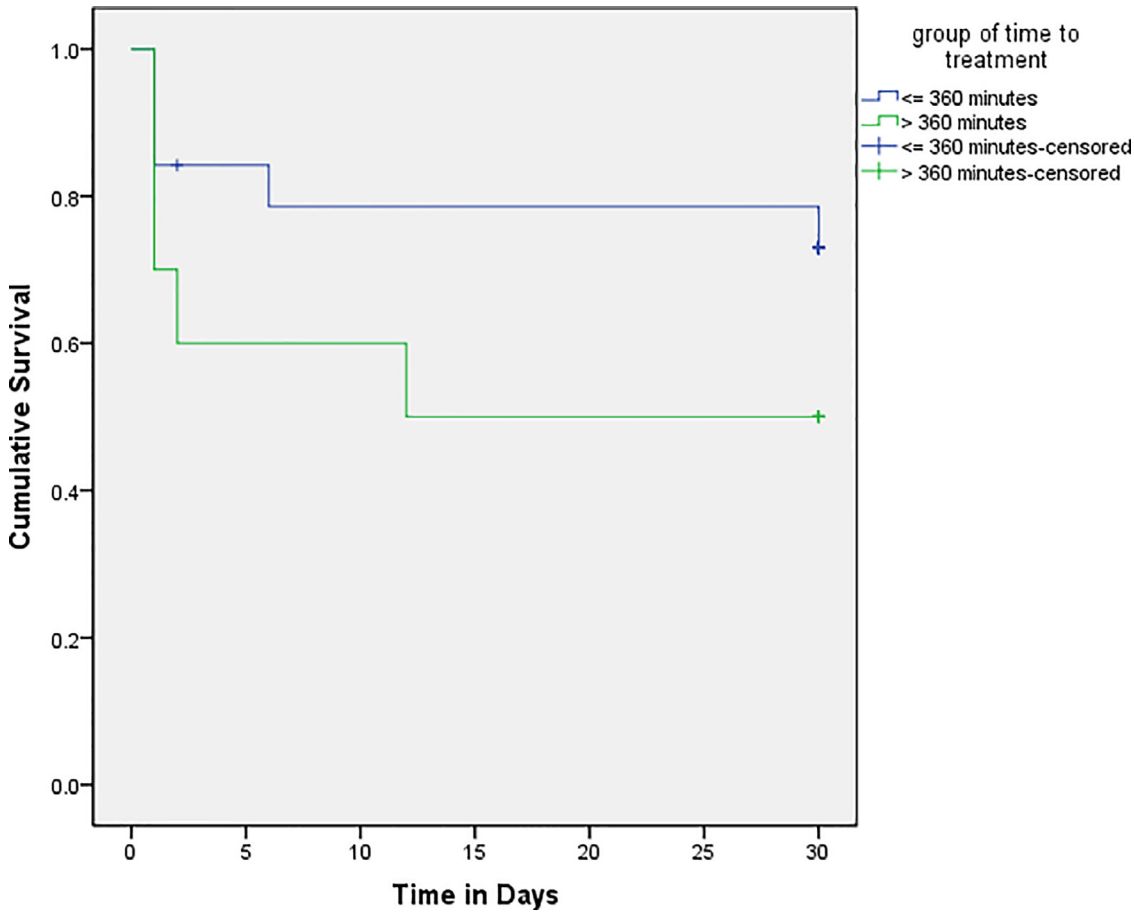

Figure 1. Kaplan–Meier survival curves for 30-day all-cause mortality. The curve for the group with time to treatment (TTT) ≤360 minutes is represented by the blue line. The curve for the group with TTT >360 minutes is represented by the green line.

with DNT >180 minutes (See Appendix 2 and 3 in the online version); the log-rank test revealed *P* values of 0.55 and 0.29 for 30-days and 1-year survival rates, respectively, between the 2 groups.

Thrombolysis success

The overall CST rate was 79%, whereas the specific CST rates in patients with TTT ≤360 minutes and TTT >360 minutes were 90% and 60%, respectively (OR = 5.67; 95% CI, 0.82–39.27). The unsuccessful thrombolysis (UT) category comprised 6 cases. The all-cause in-hospital mortality rate was 100% in patients with UT; however, it was 13% in patients with CST ($P < 0.001$). Follow-up examination of the 30-day mortality showed that patients with CST had better outcomes than those with UT ($P < 0.001$).

Adverse events

There was only 1 case (3%) of major bleeding that required blood transfusion with HAS-BLED score of 5. The HAS-BLED scores for other patients were <5 (ie, ≤4; score that occurs most often is 2 [11 times]). No events of ischemic stroke, nonmajor bleeding, in-hospital reinfarction, and allergic reaction were reported; however, arrhythmias after thrombolysis were reported in 2 patients (7%).

Discussion

This study evaluated the effectiveness and tolerability of TNK in patients presenting with STEMI in clinical practice at a secondary hospital in Malaysia. We observed that the mortality-related outcomes of TNK in patients with STEMI were influenced by early treatment, and treatment within 6 hours of symptom onset provided a better prognosis. DNT <3 hours provided a better prognosis according to the graph (see **Appendix 3** in the online version); however, this difference was not statistically significant. In addition, bleeding-related complications caused by TNK were minimal when administered in low-risk patients.

Nonetheless, a patient's survival is highly dependent on the success or failure of thrombolysis. The thrombolytic treatment failure was associated with high mortality. Our sample included a high proportion of patients with a history of myocardial infarction, hypertension, and diabetes mellitus.

Generally, in public hospitals in Malaysia, TNK is only administered after obtaining permission from a medical specialist or cardiologist. It is mainly administered as a second-line treatment after patients have received streptokinase as the default lytic or first-line treatment or in cases of allergy to streptokinase (streptokinase or TNK is administered for each incident; once administered, it is unlikely that the same drug would be repeated).[6] In this study, the mean age of the patients was similar to that reported in the 10th Report of the National Cardiovascular Database (NCVD) in 2015 (age = 57.6 years)[7] and the Indian Registry for TNK (age = 55.4 years).[8] Male individuals and the Malay race represented the majority of the study population. Similarly, male individuals and Malay patients comprised approximately 79% and 56%, respectively, of the STEMI population in the 2015 NCVD report. Therefore, our sample was not different from the general population of STEMI patients.

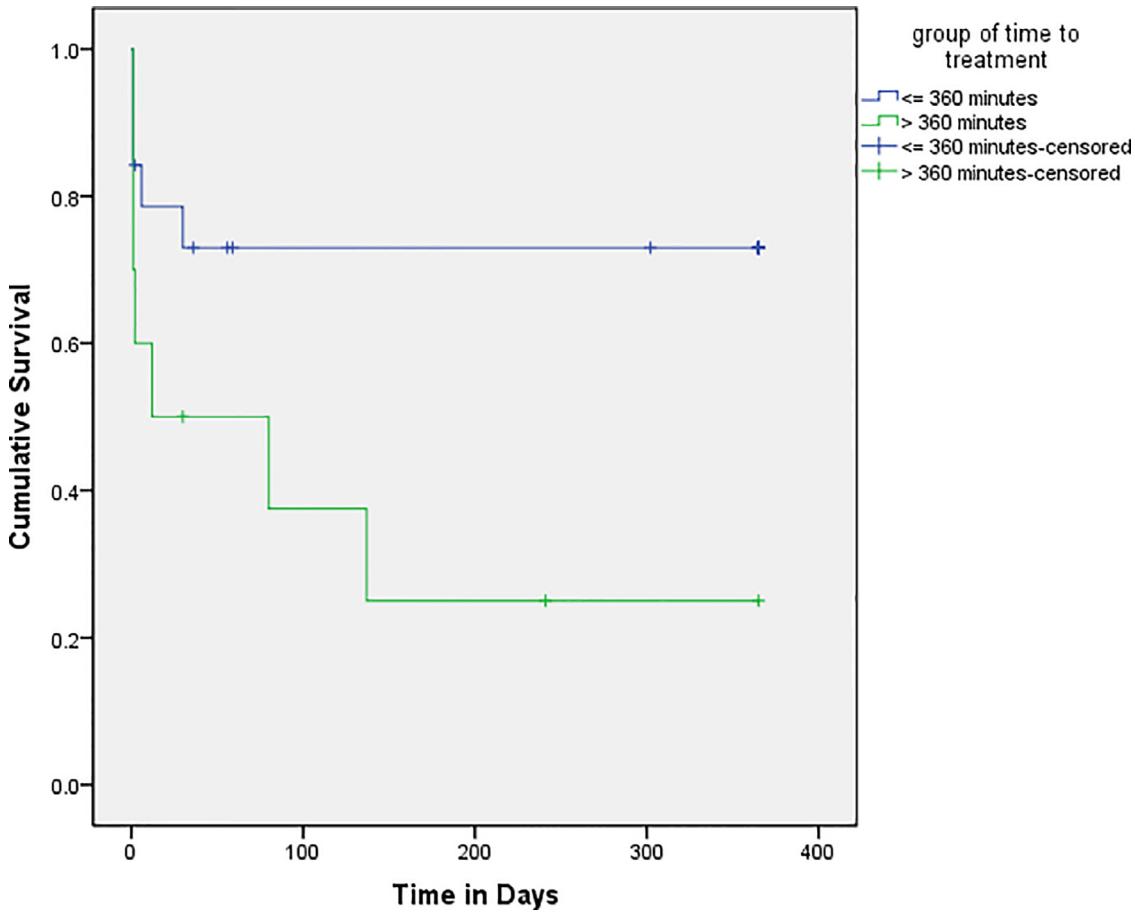

Figure 2. Kaplan–Meier survival curves for 1-year all-cause mortality. The curve for the group with time to treatment (TTT) ≤360 minutes is represented by the blue line. The curve for the group with TTT >360 minutes is represented by the green line.

Among our main findings was that the all-cause in-hospital mortality rate was surprisingly high at 33%. However, the overall mortality rates in patients with STEMI in the hospital were 5%, 3%, 1%, and 3% in 2016, 2017, 2018, and 2019, respectively.

According to the Indian Registry, a surprisingly low in-hospital mortality rate among 15,222 patients in India was reported (ie, 1.69%),[8] whereas the corresponding rate was 10% in the 2015 NCVD report. Therefore, the in-hospital mortality rate of 33%, which was observed in our study, was comparatively higher than those reported in the 2015 NCVD report and in the Indian registry. The initial research in ASSENT-2, Assessment of the Safety and Efficacy of a New Thrombolytic reported a 30-day mortality rate of approximately 6% when TNK was administered within 6 hours of symptom onset.[9] The high mortality rate could have been accidental considering the small number of patients who were administered TNK. Another possible explanation for this high mortality rate could be the high percentage of patients with a history of myocardial infarction (adjusted in-hospital mortality: OR = 1.27; 95% CI, 1.05–1.53), diabetes mellitus (adjusted 30-days mortality OR = 1.40; 95% CI, 1.24–1.57), and antecedent hypertension (adjusted in-hospital mortality: hazard ratio = 1.33; 95% CI, 1.02–1.74) in our sample.[10–13] Notably, issues, such as delays in initiating treatment in patients, especially those administered even 6 hours after symptoms onset, resulted in higher mortality. The delays might have been attributed to patients' slow treatment-seeking responses, multiple patients requiring simultaneous treatment, and limited manpower in the emergency department at the hospital. DNT was approximately 3 hours on average. Patients with acute STEMI in high-income countries, cardiac centers, or tertiary hospitals may have better access to specialized expertise and equipment: care from cardiac specialists and other well-trained personnel, personalized treatment, and monitoring machines. Conversely, our secondary hospital faced constraints concerning the number of health care providers and services available to STEMI patients. Additional administrative work to control the medicine cost delayed the prescription process of TNK (this process included obtaining a specialist approval despite the high workload and long waiting time in the emergency department, interdepartment medicine delivery, and documentation of TNK use).

In addition, the subgroup analysis showed that if TNK was administered within 6 hours from symptom onset, the all-cause in-hospital mortality rate would be much lower than that when administered 6 hours after symptom onset (21% vs 50%); however, no statistical significance was observed, probably because of our small sample size. Thus, a shorter TTT may yield better mortality outcomes. Moreover, according to the Kaplan–Meier survival curves, the long-term survival (30-day and 1-year mortality rates) of the population that received TNK within 6 hours tended to be better than that of patients who received TNK after 6 hours. These results support the rule of time is muscle that urges practitioners to perform interventions in a timely manner.[14–16]

The effectiveness of TNK was considered optimal when administered within 6 hours, with a high CST of approximately 90%; the result is comparable with that of an Indian population (CST = 95%).[8] Notably, in patients with failed thrombolysis, there was substantial evidence of higher mortality. Consistently, failure of thrombolytic treatment was previously associated with a higher mortality rate.[17] It is unclear whether patients with failed throm-

Table 1
Overall study population's baseline demographic characteristics, medical history, and presentation characteristics (n = 30)

Characteristic	Tenecteplase (n = 30)
Demographic	
Age*, y	62 (14)
Ethnicity†	
Malay	21 (70)
Indian	7 (23)
Chinese	2 (7)
Men†	23 (77)
Bodyweight*, kg	70 (15)
Medical history†	
Smoking†	16 (53)
Diabetes mellitus†	13 (43)
Hypertension†	14 (47)
Previous MI†	13 (43)
Previous CABG	None
Presentation characteristic‡	
HR, beats/min	81 (63-103)
SBP, mm Hg	140 (106-171)
Time (symptoms onset) to treatment, min	265 (228-660)
Door-to-needle time, min	180 (83-251)
TIMI risk score†	
Low (0–4)	11 (37)
Intermediate (5–9)	17 (57)
High (10–14)	2 (7)
HAS-BLED score†,	
Low (0–1)	10 (33)
Intermediate (2)	11 (37)
High (3–5)	9 (30)
Very high (>5)	None

CABG = coronary artery bypass graft; HAS-BLED = score for major bleeding risk; HR = heart rate; MI = myocardial infarction; SBP = systolic blood pressure; TIMI = thrombolysis in myocardial infarction.
* Values are presented as mean (SD).
† Values are presented as n (%).
‡ Values are presented as median (interquartile range).

Table 2
Baseline characteristics of study groups based on time to treatment.

Characteristic	≤360 min	>360 min	*P* value
No. of patients	19	10	
Female, %	16	40	0.15
Age, y*	63 (53-71)	61 (57-77)	0.95
DM, %	37	60	0.23
Hypertension, %	42	50	0.68
Previous MI, %	47	40	0.71
Previous CABG	None	None	None
Systolic BP, mm Hg*	142 (117-175)	131 (98-170)	0.54
HR, beats/min*	81 (58-96)	87 (64-106)	0.43
Reinfarction, %	None	None	None
Arrhythmia, %	5	10	1.00
Door-to-needle time, min*	120 (75-205)	405 (191-765)	0.02

BP = blood pressure; CABG = coronary artery bypass graft; DM = diabetes mellitus; HR = heart rate; MI = myocardial infarction.
* Values are presented as median (interquartile range).

bolysis underwent rescue PCI because there was no established cardiology network in the center. None of the patients with CST underwent elective PCI. Patients with CST and failed thrombolysis were referred to the cardiology department for early appointments 3 to 6 months after discharge from the CCU. Both time to treatment delay and inadequate care after thrombolysis may have contributed to the higher mortality rate in our study population.

In our study, electrocardiogram records and patients' symptoms were used to assess thrombolysis success instead of performing coronary angiography, which was probably attributed to the limitation of onsite clinical treatment. This is because the number of cardiologists performing coronary angiography in Malaysia (only 338 specialists are registered for a population of 32 million in 2021, less than one-third of whom are practicing in government publicly funded hospitals)[18] is insufficient compared with those in many developed countries.

The only patient who experienced major bleeding had a HAS-BLED score of 5 (high risk of bleeding). Thus, screening for bleeding risk is essential before TNK bolus injection. Notably, no episode of minor bleeding was reported in our sample. In our study, 2 (7%) patients had arrhythmias after thrombolysis. This was relatively lower than the corresponding proportion (10%) reported in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; however, it posed a significant risk for survival in the long term (ie, at 1 year).[19] Physicians should promptly recognize this occurrence and administer appropriate treatment, such as a beta-blocker, after establishing a diagnosis.

This study had several limitations. First, the sample size in this study was relatively small, despite the recruitment period of 3 years and 5 months. This raises serious concerns regarding the validity of our results. Second, the data were collected retrospectively from the medical records using invalidated methods. In addition, neither inter- nor intrarater reliability of the data was tested, and this could have predisposed the study to selection bias or produced unreliable data. Third, the New York Heart Association Functional Classification, the systolic function of the left ventricle, and the performed adjuvant treatments, such as administration of antithrombotic agents, might have influenced the clinical outcomes because these were not recorded and, thus, limited the analyses of our study.

Based on our findings, we suggest the inclusion of the STEMI pathway in the emergency department protocols for prompt electrocardiography in triage or patients with chest pain to enable accurate diagnosis, immediate activation of the specialist required to authorize TNK, and removal of barriers to TNK access for patients with prior MI treated with streptokinase. Therefore, patients can be randomized and achieve a TTT <360 minutes.

Conclusions

We hypothesized that the outcomes of TNK treatment in patients with STEMI were negatively influenced by prolonged TTT because patients with TTT ≤360 minutes had better outcomes than those with TTT >360 minutes. TNK-induced bleeding-related complications were minimal in patients with low HAS-BLED scores. Additional prospective, controlled, double-blind studies would be needed to compare the efficacy and safety profiles of TNK and streptokinase in similar Malaysian patients. However, the high mortality rate observed in TNK-treated patients compared with SK-treated patients raised serious ethical concerns regarding the justification of such a study, unless only patients in whom early administration is allowed are included.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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K.-W. Chua was responsible for conceptualization, data curation, formal analysis, methodology, validation, visualization, writ-

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2021.100641.

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