

# Association of Risk Factors and Its Bleeding Complication for Tenecteplase Administered in Acute Myocardial Infarction (AMI)

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## INTRODUCTION

Metalyse, subgroup of Tenecteplase (TNK-tPA) is a three point mutation of alteplase. It specifically has extended half-life, increased fibrin specificity and patency. In several clinical studies, the single bolus administration of this drug has faster reperfusion, faster clots lysis and longer artery patency<sup>1,2</sup>. It is a triple-combination mutant of tissue plasminogen activator (tPA) developed to overcome some of the limitations of current thrombolytic therapy. This drug works by dissolving blood clots in patient with suspected acute myocardial infarction within six hours of first onset of the symptoms. The administration of this drug within these hours can effectively lyse clots in coronary vessels. Due to the positive evidence, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) Emergency Department has started to use TNK-tPA for ST-elevation myocardial infarction (STEMI) since the past 3 years, replacing streptokinase as the main thrombolytic drug.

There are several complications that may arise from usage of TNK-tPA. These include intracranial haemorrhage (ICH), fatal and non-fatal stroke, haematoma and mucosal bleeding. Multicenter safety study (ASSENT-1) was done on 3235 patients throughout North America and European countries showed a very low percentage of ICH which is 0.77%<sup>3</sup>. The purpose of this study is to assess the complications and safety of TNK-tPA in the multi-ethnic Malaysian population. Currently data pertaining the usage and risk of TNK-tPA use in Malaysian population is still scarce. This study can act as a platform for further multicentre extensive data collection.

## MATERIALS AND METHODS

We conducted a retrospective study on all STEMI patients who received TNK-tPA in Emergency Department UKMMC from January 2009 to December 2011. Data collection commenced after receiving approval from UKMMC'S Ethical Committee. Registration numbers of all patients that fulfilled the inclusion criteria was collected from the resuscitation log book. Patient's files of the respective hospital registration numbers were obtained from the record unit. Data was then collected from the files. Dummy tables were filled and aspects covered were adverse effects, socio-demographic factors (gender, age and ethnicity), co-morbidities (diabetes mellitus, hypertension, previous cerebrovascular accident (CVA) and

previous coronary artery disease (CAD)) and related bleeding complication. The variables were subsequently analyzed using Statistical Package for Social Sciences (SPSS) Windows Version 21.0. T test was used to analyse association between age and bleeding complication and Chi-square test was used to analyse the association between hypertension and bleeding complication. Fischer Exact test was used for the rest of variables and p value of <0.05 was described as statistically significant.

### Objective

To determine the association between demographic factors (age, gender, and ethnicity) and comorbidities (hypertension, diabetes mellitus, previous cerebrovascular accident and previous ischaemic heart disease) with complication of TNK-tPA (intracranial haemorrhage, non-haemorrhagic stroke and non-CNS bleeding complications) for acute myocardial infarction administered at department of Emergency Medicine UKMMC.

### Hypothesis

There is no association between demographic factors and comorbidities with bleeding complication of TNK-tPA. The safety profile is similar to previous international studies.

### Sample Size calculation

Formula by Kish L (1965)

$$n = \left( \frac{z}{\Delta} \right)^2 \times p (1 - p)$$

95% confidence level

z = degree of confidence value (1.96 for 95% confidence level) = 1.96

$\Delta$  = Error of margin 0.005 (0.5%)

p = expected prevalence

According to ASSENT-1 which studied on the complication of TNK-tPA, the prevalence of intracranial hemorrhage was 0.77% (sample size was 3235, and n=25)<sup>3</sup>. The confidence interval was 95%. Target sample size was 1174. This is not achievable in UKMMC since the number of patients thrombolysed with TNK-tPA was inadequate.

### Inclusion and Exclusion Criteria

Included in this study were patients that completed thrombolytic therapy with TNK-tPA for STEMI in Emergency

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Department UKMMC from January 2009 to December 2011. Excluded were patients which records were missing or transferred to another hospital.

**RESULTS**

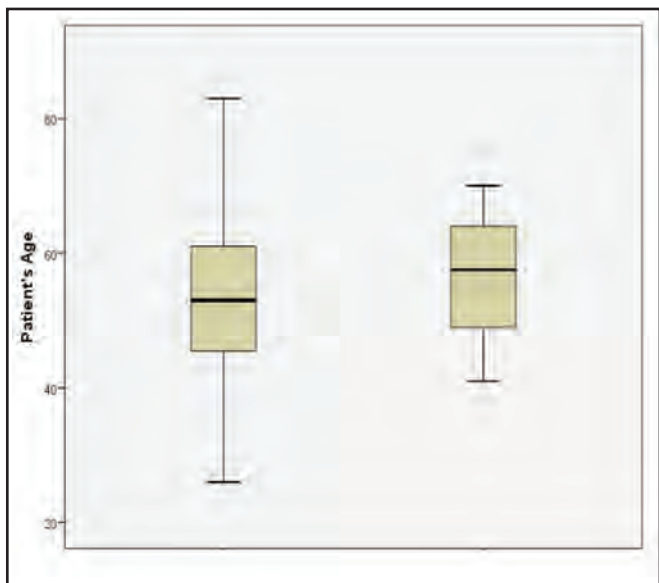
The total number of patients that fit the inclusion criteria was 100. Majority (90%) were males that aged from 26 to 83 years old. The mean age was 54 years. Ethnic group breakdown of this patients were: Malay (40%), Chinese (37%), Indian (14%) and others (9%). Overall, 12 (12%) people developed bleeding complications which includes intracranial haemorrhage (ICH), mucosal bleeding (hematuria, epistaxis and upper gastrointestinal bleed) and hematoma. The mean age of patients with complication was 56.5 while mean age without complication was 53.7 years.

Among 12 patients that developed complications, 2(2%) patients developed intracranial haemorrhage (ICH). One patient who developed complications died due to extensive ICH with hypertensive emergency. Average age of patients with ICH was 61.5 years (60 and 63 years each) and both had history of diabetes, hypertension and previous coronary artery disease (CAD). The patient with ICH and survived had a thalamic, internal capsule and intraparenchymal bleed. Other 9 patients (9%) developed mucosal bleed (5 patients developed hematuria, 3 developed hematemesis and epistaxis. 1 not mentioned). 2 patients developed hematoma after insertion of intra-arterial cannulation. Among this 2 patients, one patient developed hematuria. 1 patient developed hematemesis (which also developed hematuria). No other complications (non-haemorrhagic stroke and allergic reaction) were recorded after administration of TNK-tPA. All mucosal bleed and hematoma resolved prior to discharge from hospital. 5 out of 12 (42%) patients that developed adverse effects failed thrombolysis and had to proceed to facilitated / rescue percutaneous coronary intervention (PCI). Other 88 (88%) patients did not develop adverse effects from TNK-tPA. Out of the 88 patients, 43 patients (48.9%) had to proceed to facilitated / rescue PCI and 6 (6.8%) patients did Coronary Artery Bypass Grafting at a later date. Total number of failed thrombolysis warranted for PCI or CABG was 54.

**DISCUSSION**

Fisher’s Exact Test showed no association between comorbidities (diabetes, hypertension, hyperlipidemia, previous CVA and previous CAD) to complications of TNK-tPA ( $p>0.05$ ). It also shows that there is no race (Malay, Chinese and Indian) significance to bleeding complications. To determine the clinical significant of the bleeding complications for the TNK-tPA administered in STEMI, logistic regression was used. The risk factors included in this study are diabetes mellitus, hypertension and previous coronary artery disease (CAD). As of the first risk factor, t-test showed no significant association between age and bleeding complication ( $p=0.427$ ). However mean age of patients with complication is higher (56.5 years vs. 53.7 years)(figure 1).

There were 57 hypertensive patients who in this study and 14% of them developed bleeding complications compared to



**Fig. 1 :** The association of the patient's median age with bleeding complications of the tenecteplase (median age = 54).

12% of the whole sample. However no significant association between hypertension and bleeding complications was seen. ( $p=0.504$ ). A study conducted by R.P. Giugliano et al, among 93 hypertensive patients who received the TNK-tPA in STEMI, approximately about 52.7% of this patients developed haemorrhagic events<sup>4</sup>. The study showed significance between hypertension and bleeding complication. ( $p=0.012$ ). However the study did not include bleeding complications due to iatrogenic case (intra-atrial cannulation, urinary catheter insertion).

Our data shown among 40 diabetic patients who received the TNK-tPA, approximately about 15% of them developed bleeding complications. The significant value of the diabetic patients that developed bleeding complications and none was  $p=0.535$ . This show there was no association between the diabetes mellitus and bleeding complications of the TNK-tPA in STEMI. Our results correlate with the study done by and Van der Werff<sup>5</sup>.

In our study, there was 14 patients had previous history of ischaemic heart disease who received the TNK-tPA. Among these patients, 28.6% developed bleeding complications. The  $p=0.062$  which shown there is no significant in association between the history of previous CAD with the bleeding complication of the TNK-tPA. However the correlation is the highest compared to other risk factors.

There were 9 patients in our study had previous history of CVA with 22.2% of them developed bleeding complications. The p value was 0.294. Thus there was no significant in association between of previous cerebral vascular accidents and bleeding complication of TNK-tPA administered in acute myocardial infarction. This was also due to the incidence of ICH was only 2 and only 1(50%) had history of previous CVA. All of the patients were not contraindicated for thrombolysis (last CVA more than 6 months). The single patient that died

from complications of TNK-tPA administration had a previous history of CVA (more than 6 months) and uncontrolled hypertension. His blood pressure on arrival was 200/100 mmHg and reduced to 160/90 mmHg with intravenous glyceryl trinitrate prior to the administration of TNK-tPA. Patients with acute myocardial infarction and a history of hypertension or elevated blood pressure on admission have a greater risk of intracranial hemorrhage after thrombolysis<sup>6</sup>. In this study 2% of patients developed ICH which was higher than recorded in ASSENT-1 trials which was 0.77%<sup>3</sup>. Further multicentre study to provide adequate sample size is necessary to validate these results.

Bleeding complications due to iatrogenic triggers occur in a number of patients. Out of 5 patients who developed hematuria, 2 patients had a urinary catheter inserted. One patient developed hematoma secondary to insertion of intra-arterial cannulation. One patient developed epistaxis due to a minor fall.

Our limitation in this study was retrospective data collection. Medical records provide incomplete and inconsistent data. Furthermore the number of patient's thrombolysed with TNK-tPA is still minimal due to small number of cases, cost and the availability of primary PCI during office hours.

#### CONCLUSION

Based on results, all four factors were not significant for association between patient's age, Diabetes Mellitus, Hypertension and Previous CAD with bleeding complication

for TNK-tPA in treatment of acute myocardial infarction. TNK-tPA safety currently is comparable to previous study. Physicians should be more alert in following guidelines to minimize iatrogenic cause of complications. Decision to thrombolysed must be carefully weighed against risk, especially in patients who had previous CVA and uncontrolled hypertension. This study could be a platform for further multicentre studies concerning safety and risk of TNK-tPA use in our population throughout the country.

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