

Analysis of the Clinical Characteristics, Management, and Causes of Death in Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention from 2005 to 2014

Po-Tseng LEE,^{1*} MD, Ting-Hsing CHAO,^{1*} MD, Ya-Ling HUANG,¹ RN,
Sheng-Hsiang LIN,¹ PhD, Wei-Ming WANG,¹ MPH, Wen-Huang LEE,¹ MD,
Chen-Wei HUANG,¹ MD, Cheng-Han LEE,¹ MD, Ju-Yi CHEN,¹ MD, Chih-Chan LIN,¹ MD,
Ping-Yen LIU,¹ MD, Shih-Hung CHAN,¹ MD, Yen-Wen LIU,¹ MD, Wei-Chuan TSAI,¹ MD,
Li-Jen LIN,¹ MD, Liang-Miin TSAI,¹ MD, and Yi-Heng LI,¹ MD

SUMMARY

It is unknown whether there has been any change in the causes of death for acute ST-segment elevation myocardial infarction (STEMI) in the era of aggressive reperfusion. We analyzed the direct causes of in-hospital death in patients with STEMI treated with primary percutaneous coronary intervention (PCI) in a tertiary referral center over the past 10 years.

We retrospectively analyzed 878 STEMI patients treated with primary PCI in our hospital between January 2005 and December 2014. There were no significant changes in the age and sex of patients, but the prevalence of hypertension and smoking decreased. STEMI severity increased with more patients in Killip classification > 2. The number of out-of-hospital cardiac arrest events also increased over the 10 years. Symptom onset-to-door time did not change in the 10-year study period. The care quality was improved with shorter door-to-balloon time for primary PCI and increased use of dual antiplatelet therapy. The all-cause in-hospital mortality was 9.1%, which did not vary over the 10 years. Multivariable analysis showed that Killip classification > 2 was the most important determinant of death. Cardiogenic shock was the major cause of cardiovascular death. There was an increase in non-cardiovascular causes of death in the most recent 3 years, with infection being a major problem.

Despite improvement in care quality for STEMI, the in-hospital mortality did not decrease in this tertiary referral center over these 10 years due to increased disease severity and non-cardiovascular causes of death. (Int Heart J 2016; 57: 541-546)

Key words: Acute myocardial infarction, Coronary angioplasty, Mortality

Acute myocardial infarction is an important public health issue in Taiwan because it carries a high fatality rate and its incidence is still increasing.¹⁾ In acute ST-segment elevation myocardial infarction (STEMI), timely primary percutaneous coronary intervention (PCI) and the use of evidence-based medications significantly decrease mortality, and are strongly recommended in local²⁾ and international guidelines.^{3,4)} In Taiwan, more than 95% of STEMI patients received primary PCI as the initial reperfusion therapy, and the door-to-balloon (D2B) time has improved.^{5,6)} A previous observational study demonstrated that early primary PCI could decrease the incidence of cardiogenic shock, which is the major cause of death in STEMI.⁷⁾ It is unknown whether there has

been any temporal change in the causes of death during hospitalization for STEMI with the advent of aggressive reperfusion in recent years. Information on the specific causes of death can reveal the weak points of current treatment and enable the implementation of new strategies to improve the quality of care for STEMI patients treated with primary PCI. The major aims of the present study were to describe the 10-year secular trends in the clinical characteristics and management of STEMI patients treated with primary PCI, and to specifically analyze the causes of death in these patients in a tertiary referral center for primary PCI in Taiwan.

From the ¹ Department of Internal Medicine, Institute of Clinical Medicine and Biostatistics Consulting Center, National Cheng Kung University Hospital and College of Medicine, Tainan, Taiwan.

*These authors contributed equally to this work.

Address for correspondence: Yi-Heng Li, MD, Division of Cardiology, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng Li Road, Tainan, Taiwan. E-mail: heng@mail.ncku.edu.tw

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Table 1. Temporal Trends of Clinical Characteristics in STEMI Patients From 2005 to 2014

	Period 1 (2005-2008) (n = 267)	Period 2 (2009-2011) (n = 264)	Period 3 (2012-2014) (n = 347)	P for Trend
Age (years)	62.7 ± 13.0	61.7 ± 13.3	62.8 ± 13.4	0.106
Men				
< 60 years	97 (45)	115 (53)	134 (48)	0.804
60-74 years	80 (37)	63 (29)	87 (31)	
> 75 years	38 (18)	40 (18)	60 (21)	
Women				
< 60 years	7 (13)	9 (20)	18 (27)	0.184
60-74 years	22 (42)	17 (37)	22 (33)	
> 75 years	23 (44)	20 (43)	26 (39)	
Women	52 (19)	46 (17)	66 (19)	0.922
Risk factors				
Hypertension	168 (63)	140 (53)	174 (50)	0.002*
Diabetes	98 (37)	97 (37)	122 (35)	0.680
Dyslipidemia	137 (51)	184 (70)	190 (55)	0.596
Smoking	134 (50)	134 (51)	145 (42)	0.030*
No. of risk factors < 2	79 (30)	68 (26)	129 (37)	0.010*
Medical history				
Stroke	33 (12)	24 (9)	30 (9)	0.138
PAD	2 (1)	1 (0.4)	2 (1)	0.806
PCI	17 (6)	18 (7)	42 (12)	0.010*
CABG	2 (1)	2 (1)	2 (1)	0.788
CKD	39 (15)	49 (19)	90 (26)	0.001*
Anterior MI	130 (49)	137 (52)	188 (54)	0.195
Transfer-in	65 (24)	85 (32)	120 (35)	0.008*
OHCA	1 (0.4)	11 (4.2)	30 (8.6)	< 0.001*
Killip > 2	57 (21)	64 (24)	122 (35)	< 0.001*

Data are presented as mean ± standard deviation for age and number (percentage). The temporal trends between different time periods were tested using linear-by-linear association test for categorical variables and the Jonckheere-Terpstra test for continuous variables. * indicates significant *P* values in different time periods. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

METHODS

Study population: This study was a retrospective cohort study of patients with acute STEMI who were treated with primary PCI from January 2005 to December 2014 at the National Cheng Kung University Hospital in Tainan, Taiwan. Our hospital is the only national university affiliated medical center in southern Taiwan, and covers a population of about 2.5 million in the region. The catheterization laboratory in our hospital is qualified by the Ministry of Health and Welfare as one of the major primary PCI centers in Taiwan. Diagnosis of acute STEMI requiring primary PCI depends on the presence of acute, typical cardiac ischemic symptoms within 24 hours, with ST segment elevation in 2 contiguous leads or new left bundle branch block on a 12-lead electrocardiograph. Patients with STEMI more than 24 hours after symptom onset or iatrogenic STEMI caused by any diagnostic or therapeutic coronary procedures were excluded. Primary PCI was performed using standard techniques. The interventional cardiologists in charge decided the PCI strategies and medications for each patient according to a contemporary Taiwan STEMI guideline.²⁾ The diagnosis of STEMI was further confirmed based on increased cardiac biomarkers in all patients. Clinical data including age, gender, vascular risk factors, previous disease history, and medications used during admission, were collected for each patient. Each patient was followed up until the day he or she was discharged or died during hospitalization. This study was

approved by the Institutional Review Board of our hospital (B-ER-104-195).

Causes of death: We used and modified a previously published death classification system of STEMI to analyze the direct causes of death in our patients.⁸⁾ In brief, the cause of death was classified as either a cardiovascular or a non-cardiovascular cause. Cardiovascular death was further classified as cardiac, vascular, and arrhythmic death. Cardiac death included cardiogenic shock, septal or free wall rupture, and congestive heart failure. Vascular death included cerebral infarction or hemorrhage, aortic dissection or aneurysm, abdominal or peripheral vascular causes, and pulmonary embolism. Arrhythmic death included ventricular tachycardia or fibrillation, pulseless electrical activity, bradycardia or asystole, and sudden cardiac arrest. Non-cardiovascular death included cancer, acute abdomen, sepsis with or without multi-organ failure, pneumonia, and anoxic brain damage. The cause of death was classified into one of the above mutually exclusive categories. Two cardiologists (PT Lee and YH Li) reviewed the medical records of all dead patients to define the direct cause of death independently. The medical records were reviewed by a third cardiologist (TH Chao) if there was any disagreement between the first two cardiologists' decisions. Further discussion was necessary to reach a final consensus on the causes of death if there were conflicting results between the 3 cardiologists.

Statistical analysis: We divided the 10-year study period into period 1 (2005 – 2008), period 2 (2009 – 2011), and period 3

Table II. Temporal Trends of Treatment and Outcome in STEMI Patients From 2005 to 2014

	Period 1 (2005-2008) (n = 267)	Period 2 (2009-2011) (n = 264)	Period 3 (2012-2014) (n = 347)	P for Trend
Primary PCI				
Onset-to-door time	123 (70-248)	140 (73-263)	136 (71-281)	0.799
D2B time	142 (118-190)	82 (64-110)	69 (55-89)	< 0.001*
D2B time < 90 minutes	13 (7)	158 (60)	252 (77)	< 0.001*
Thrombectomy	29 (11)	136 (52)	199 (57)	< 0.001*
DES	40 (15)	30 (11)	78 (22)	< 0.001*
LM intervention	1 (0.4)	2 (1)	10 (3)	< 0.001*
Medication				
Aspirin	222 (93)	236 (99)	306 (99)	< 0.001*
Plavix	236 (99)	235 (99)	290 (94)	0.001*
Ticagrelor	0 (0)	0 (0)	16 (5)	< 0.001*
DAPT	220 (92)	235 (99)	304 (98)	< 0.001*
Beta-blocker	137 (57)	120 (50)	187 (61)	0.365
ACEI or ARB	165 (69)	169 (71)	222 (72)	0.480
Statin	110 (46)	150 (63)	226 (73)	< 0.001*
Mechanical support				
IABP	36 (13)	11 (4)	29 (8)	0.045*
ECMO	5 (2)	3 (1)	10 (9)	0.336
Outcome				
Transfer for OP	7 (3)	5 (2)	4 (1)	0.176
Hospital days	9.8 ± 9.2	8.0 ± 9.2	8.1 ± 9.5	< 0.001*
Mortality	23 (9)	21 (8)	36 (10)	0.421
Mortality in Killip > 2	18 (32)	19 (30)	31 (25)	0.491

Data are presented as median (interquartile range) for onset-to-door time and D2B time (min), mean ± standard deviation for hospital days and number (percentage). The temporal trends between different time periods were tested using linear-by-linear association test for categorical variables and the Jonckheere-Terpstra test for continuous variables. * indicates significant *P* values in different time periods. ACEI indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; D2B, door-to-balloon; DES, drug-eluting stent; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LM, left main artery; OP, operation; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

(2012 – 2014) to observe the temporal trend changes. Continuous variables are expressed as the mean ± standard deviation (SD). Median with interquartile range was used for symptom onset-to-door time and D2B time. Categorical variables are expressed as numbers and percentages. The temporal trends between different time periods were tested using linear-by-linear association tests for binary and Jonckheere-Terpstra tests for continuous variables. Multivariable analyses of predictors of in-hospital mortality were performed using backward stepwise multiple logistic regression analysis. Variables for which *P* was < 0.1 in univariable analysis were entered into multivariable analysis. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated. For comparisons of the clinical characteristics between patients who died from cardiovascular and non-cardiovascular causes, the chi-square test for categorical variables and unpaired Student's *t* test for continuous variables were used. Significance was set at *P* < 0.05 (2-tailed). SAS statistical package (version 9.2 for Windows; SAS Institute, Cary, NC, USA) was used for all analyses.

RESULTS

Patient characteristics: In all, 878 patients (mean age 62.5 years, 81% men) who were treated with primary PCI for acute STEMI during the study period were included in this study. Table I shows the baseline clinical characteristics of the patients. There were no significant changes in age and gender

over the 10 years. The overall percentage of women was about 19%, and this did not vary over time. There was a slight increase in the proportion of younger women (< 60 years old) from 13% to 27% within the 10 years. Regarding vascular risk factors, the prevalence of hypertension (63% to 50%; percent change, -12.8 [95% CI, -20.6 to -5]) and smoking (50% to 42%; percentage change -8.4 [95% CI, -16.3 to -0.5]) decreased. The percentage of patients with no or only one major risk factor increased from 30% to 37%. In medical disease history, the number of patients with previous PCI (6% to 12%, percentage change 5.7 [95% CI, 1.2 to 10.3]) and chronic kidney disease (15% to 26%, percentage change, 11.3 [95% CI, 5.1 to 17.6]) increased in the 10 years. Among the patients, 270 (31%) were transferred from family physicians or non-PCI-capable hospitals. The percentage of patients transferred increased from 24% to 35% (percentage change 10.2 [95% CI, 3.1 to 17.4]). The percentage of patients with out-of-hospital cardiac arrest (OHCA) and Killip classification > 2 also increased significantly over the 10 years.

Treatment and outcome: Table II shows the temporal trends of treatment and outcome of STEMI patients in these 10 years. There was no change in symptom onset-to-door time in the 10-year study period, but the primary PCI quality improved significantly. The D2B time decreased; the percentage of patients with D2B time < 90 minutes, the use of drug-eluting stents, and the use of manual thrombectomy all increased. The use of evidence-based medications, including dual antiplatelet therapy (DAPT) and statins increased significantly. Beta-blockers

and angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB) were underused without a significant improvement over the 10 years. The length of hospital stay was shortened in the 10 years from a mean of 9.8 to 8.1 days (percentage change -1.7 [95% CI, -3.2 to -0.2]). The overall crude in-hospital mortality rate was 9.1% in this cohort. This did not vary over time in the 10 years. In patients with Killip classification > 2, the crude in-hospital mortality rate was 28%. The independent predictors of in-hospital mortality were female sex, Killip classification > 2, and left ventricular ejection fraction < 0.5 (Supplemental Table I).

Causes of death: Overall, 80 patients died during hospitalization in this all-comer STEMI cohort. Agreement in the analysis of causes of death between the first 2 cardiologists was 78%. The other 22% cases needed the opinion of the third cardiologist. Supplemental Table II shows the temporal trends in causes of death of STEMI patients in the 10 years. Causes of death were cardiovascular in 79% and non-cardiovascular in 21% of the cases. In cardiovascular causes ($n = 63$), cardiogenic shock (60%) was the major cause of in-hospital mortality, followed by arrhythmic death (27%) and other vascular causes (13%), including aortic dissection, rupture aortic aneurysm, severe stroke, and bowel arterial occlusion. There was no change in the trend for cardiovascular causes of death in these 10 years (Supplemental Table II). In non-cardiovascular causes ($n = 17$), sepsis (65%) was the major cause of death in this group. The other non-cardiovascular causes of death included acute abdomen, pneumonia, multiple organ failure, anoxic brain damage, and cancer. There was a significant increase in non-cardiovascular causes of death. About 1/3 of our patients died from non-cardiovascular causes during hospitalization in the most recent 3 years. The contribution of OHCA to in-hospital mortality also increased from 4% to 31% in the past 10 years (Supplemental Table II). Patients who died from non-cardiovascular causes had longer admissions (Supplemental Table III).

DISCUSSION

The major findings of this study were: 1) The quality of primary PCI improved in recent years but evidence-based medications for STEMI were still underused; 2) Cardiogenic shock was the major cause of death, but there was a significant increase in non-cardiovascular causes of death after STEMI in the most recent 3 years; and 3) Out-of-hospital cardiac arrest contributed significantly to the in-hospital mortality of STEMI.

Through a campaign initiated by the Taiwan Society of Cardiology and the Ministry of Health and Welfare of the Taiwan Government, primary PCI has become the major reperfusion therapy for STEMI in Taiwan in recent years. The Taiwan Government started to evaluate the capability of primary PCI in all hospitals from 2009. In August 2015, there were 34 qualified high-grade primary PCI-capable hospitals throughout the country that could perform primary PCI 24 hours a day and 7 days a week, and achieve a D2B time < 90 minutes for at least 75% of the STEMI patients they treat.⁹⁾ Our hospital is one of those referral high-grade primary PCI-capable hospitals in southern Taiwan. After the campaign initiation and PCI network establishment, more STEMI patients were referred to our hospital for primary PCI in recent years. There are some other catheterization laboratories in this region that can perform PCI

in stable cases and during the daytime. The progressive increase in STEMI cases with Killip classification > 2 or OHCA observed in this study cohort was due to the increase in the more severe STEMI cases referred to our hospital for further management. The D2B time of primary PCI improved progressively over the 10 years, but the use of drug-eluting stents was still not high in our patients. Recent studies have shown that newer generation drug-eluting stents have less stent thrombosis and target lesion revascularization compared to bare metal stents in primary PCI for STEMI.^{10,11)} Drug-eluting stents are not completely reimbursed by national health insurance in Taiwan. Patient economic burden may explain the low penetration rate of drug-eluting stents in our study cohort. Except antiplatelet therapy, other evidence-based medications for STEMI were underused in our patients. Reports from the United States showed that more than 80 to 90% of patients with acute myocardial infarction were treated with beta-blockers, statins, and ACE/ARBs at discharge.^{12,13)} Suboptimal use of these medications is common in Asia, especially beta-blockers. In Asia, cardiologists are probably more concerned about the treatment side effects of beta-blockers, such as patient functional capacity, bradycardia, and coronary spasm, resulting in the lower prescription rate.^{14,15)}

The overall all-cause mortality was 9.1% in this unselected all-comers study, and this did not vary over time. This mortality rate is lower than that of Taiwan whole country data, 12.3% in 2008,¹⁾ and is similar to the mortality rate reported in other high-grade primary PCI-capable hospitals in Taiwan.^{16,17)} It is also comparable to the data reported from Japan and other countries.^{18,19)} A recent multicenter registry in Japan suggested the combination of CKD and anemia on admission confers significant effects on in-hospital mortality.²⁰⁾ The mortality rate due to cardiovascular causes was 7.5% in our study. This did not vary over the 10 years. Cardiogenic shock and malignant arrhythmias were still the major direct causes of death. Increased severity of STEMI with more patients having Killip > 2 in recent years was the major reason that prevented a decrease of in-hospital mortality in our hospital. Another study also demonstrated that the presence of chronic total occlusion in a non-infarct-related coronary artery in AMI patients presenting as cardiogenic shock at arrival may predict an even higher 30-day mortality rate.²¹⁾ As a major center for primary PCI in the region, more patients were transferred to our hospital for primary PCI, especially the critical cases with high Killip classification (Table I). The other reason may be due to the long symptom onset-to-door time which did not change over the 10-year period. In STEMI treatment, this delay increased the total ischemia time which is an even more important predictor than D2B time of impaired myocardial reperfusion and mortality.^{22,23)} Public education of early hospital contact to minimize symptom onset-to-door time should be another important task to improve STEMI care in Taiwan. We also noted that more patients resuscitated from OHCA were sent in for primary PCI, which contributed significantly to the increased in-hospital mortality. Primary PCI improves clinical outcomes in STEMI patients with OHCA²⁴⁾ and is recommended by the current guideline.²⁵⁾ Resuscitated OHCA patients with STEMI have a higher risk of cardiogenic shock and in-hospital mortality even after undergoing primary PCI.²⁶⁾ Longer delay in the start of cardiopulmonary resuscitation (CPR) in OHCA is an important predictor of in-hospital mortality. Increasing the by-

stander CPR rate, which is still low in Taiwan, plays a critical role in improving survival in these patients.²⁷⁾ Non-cardiovascular causes of death increased to 34% in the most recent 3 years in our STEMI patients treated with primary PCI. Infection was the major cause. In a long-term mortality analysis after PCI between 1991 and 2008, there was a decline in cardiac deaths and an increase in non-cardiac deaths during follow up. The most common causes of non-cardiac death were cancer and chronic diseases.^{28,29)} A short-term study showed that, in patients who died within 30 days of PCI, 42% of deaths were due to non-cardiac causes, and infection was the most common reason.³⁰⁾ The rising rate of non-cardiac mortality was most likely related to the increased prevalence of non-cardiovascular comorbidities, such as chronic kidney disease in our study. These comorbidities make patients more susceptible to infection during admission. The aging society in Taiwan is also a probable cause of increasing non-cardiac cause of death. In a PCI registry study, older patients had a higher risk of non-cardiac mortality from the second years after the initial procedure and the age was a strong risk factor of 5-year non-cardiac mortality but not cardiac mortality.³¹⁾ Although guideline-recommended cardiac therapies are important for STEMI management, other comprehensive strategies must be developed to reduce mortality of STEMI in clinical real-world settings in Taiwan.

The major limitation of the current study was that the number of subjects was relatively small, as this was a single center study. The data from a national cohort in Taiwan is needed. However, since our hospital is the major referral center for primary PCI in the region, the study results at least may reflect the 10-year trend of STEMI treatment and outcome in southern Taiwan. Our results were also consistent with observations from other countries. The strength of our study was the accuracy in determining causes of death. Previous studies on cause of death usually retrieved data from the registration system or death certificate. Potential errors in determining the exact cause of death may have occurred with these methods. We performed a detailed chart review by cardiologists of all cases with in-hospital mortality to avoid possible mistakes.

Conclusions: The in-hospital mortality of STEMI treated with primary PCI remained stable over the 10 years in this tertiary referral center, despite increased cases of Killip classification > 2 and OHCA. There was an increase in non-cardiovascular causes of death in the most recent 3 years. In addition to improving the quality of primary PCI and increasing the use of evidence-based medications, other comprehensive measures should be developed to further reduce STEMI mortality in Taiwan.

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SUPPLEMENTAL FILES

Supplemental Table I, II, III
Please find supplemental files;
https://www.jstage.jst.go.jp/article/ihj/57/5/57_15-454/_article/supplement