Diabetes Mellitus and Non-ST Elevation Myocardial Infarction in Thai ACS Registry

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Objective: *To describe differences in in-hospital morbidity and mortality, presenting characteristics and management practices of diabetic and non-diabetic patients with non-ST elevation myocardial infarction using data from Thai ACS registry.*
Material and Method: *Thai ACS registry is a multi-center, prospective project of nationwide registration in Thailand.*
Results: *The present study consisted of 3,548 patients with non-ST elevation myocardial infarction from 17 hospitals in about a 3-year period. About 50% of the patients with diabetes were more often female, with a greater prevalence of hypertension and dyslipidemia. The diabetic group was at an increased risk for congestive heart failure (adjusted odds ratio 1.84) but not increased risk for cardiac arrhythmia, cardiac mortality, and in-hospital mortality.*
Conclusion: *There was a very high prevalence of diabetes in non-ST elevation myocardial infarction from Thai ACS registry. These patients were at increased risk for congestive heart failure as index of hospitalization but were not at increased risk for in-hospital mortality when compared with patients without diabetes.*

Keywords: *Non-ST elevation myocardial infarction, Diabetes, The Thai acute coronary syndrome registry*

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Coronary artery disease is the leading cause of morbidity and mortality in patients with diabetes mellitus[1]. Patients with diabetes who developed an acute coronary syndrome appeared to sustain worse outcomes than those without diabetes. The poor prognosis associated with diabetes after acute myocardial infarction has been observed in several studies[2-4] despite adjustment for age, sex, additional comorbidities and coronary risk factors. From the GRACE registry[5-6], in hospital mortality rates for diabetic patients with an acute coronary syndrome were almost twice as high as those for non-diabetic patients. Nearly twice as many diabetic as non-diabetic patients with an acute coronary syndrome experienced heart failure during their index hospitalization.

From Thai ACS registry, prevalence of diabetes was higher than the GRACE registry[6] and prevalence of diabetes in non-ST elevation MI group was higher than ST elevation myocardial infarction group. The purpose of the present study was to describe differences in in-hospital morbidity and mortality included total mortality and cardiac mortality, presenting characteristics and management practices of diabetic and non-diabetic patients with non-ST elevation myocardial infarction using data from the Thai ACS registry.

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Material and Method

Study design

The Thai ACS registry has recruited 17 centers including all the regions of Thailand, government and private hospitals. The enrollment of patients was performed between August 1, 2002 and October 31, 2005. Information about patients' demographic, presenting symptoms, management practices and in-hospital outcomes of patients with acute coronary syndrome were recorded. The registry classified the patients into three groups, ST elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina.

Study population

The present study included non-ST elevation myocardial infarction group of Thai ACS registry which are determined by chest pain and/or symptoms felt to be consistent with cardiac ischemia and elevated biochemical markers of myocardial necrosis either total creatine phosphokinase or creatine kinase MB fraction > 2 times upper limit of the hospital's normal range and/or positive troponin I or T results (if performed) with accompanying electro-cardiographic changes other than ST segment elevation. Diabetes is diagnosed when the patient's fasting plasma glucose is 126 mg/dL or higher by at least two times, or the patient has a history of diabetes.

Statistical analysis

Categorical data were summarized in frequencies and percentages. Continuous variables were reported as mean $\pm$ SD or median and 25^{th} and 75^{th} percentiles. Differences in baseline characteristics, presentation, treatment practices and in hospital morbidities and mortality among the comparison groups were examined using *Chi*-Square test and *t*-test for categorical and continuous variables, respectively. Mann-Whitney *U*-test was used for compared time to admission and length of stay between two groups. Significance of the difference was defined as a two-tailed p-value < 0.05. Logistic multivariable regression analysis by Stata program was used to examine differences in the risk of total death, cardiac death, congestive heart failure and cardiac arrhythmia for diabetes and other potentially confounding prognostic factors from baseline characteristics, clinical presentation, management practices and complications.

Results

The present study consisted of 3,548 patients with non-ST elevation myocardial infarction. There were 1,788 patients with diabetes mellitus, which was 50.4% of the population and 6.7% with newly diagnosed diabetes mellitus.

Baseline characteristics

Patients with diabetes who had non-ST elevation myocardial infarction were the same age as patients without diabetes and 65.4% was the elderly group (age > 65). Patients with diabetes were more likely to be women, and they were more likely to have hypertension and dyslipidemia. They were less likely to be current cigarette smokers. Patients with diabetes were less likely to be presented with chest pain and more likely with cardiac dyspnea. Post cardiac arrest, shock at presentation, percentage of case refer and median time to admission were not different between the two groups (Table 1).

Management practices

Coronary angiography were performed significantly more often in the non diabetic group. Abnormal coronary angiography results were seen more often in the diabetic group. Percutaneous coronary intervention and early percutaneous coronary intervention (PCI within 7 days from onset of acute coronary syndrome) were performed less frequently in the diabetes group. Percentage of revascularization, either percutaneous coronary intervention or coronary artery bypass graft in diabetic group, was lower than in the non-diabetic group. Antiplatelet and antithrombotic used included unfractioned heparin, low molecular weight heparin, aspirin and ADP inhibitor. They were of no statistical significant difference between the two groups except antiglycoprotein IIb/IIIa, which were less often used in diabetes. Nitrate and ACE inhibitor or angiotensin receptor blocker used showed no statistical significance between the two groups but beta-blocker showed less often used and calcium blocker, statin and other lipid lowering agent were more often used in the diabetic group (Table 2).

In hospital mortality and morbidity

Patients with diabetes significantly developed heart failure Killip II, III or IV within 48 hours and included heart failure after 48 hours, but showed no significant difference to develop serious cardiac arrhythmia (heart block and/or ventricular arrhythmias). All the causes in the hospital mortality rates and mortality due to cardiac cause were not statistically significant between the two groups. Median length of stay was longer in diabetic patients. Diabetes was not an

Table 1. Baseline characteristic

Parameter	No DM (%)	DM (%)	p-value	OR (95% CI)
N	1,724	1,788		
Age (mean ± SD, yr)	67.9 ± 12.9	68.1 ± 10.1	0.605	
Age < 45	4.9	1.2	<0.001	0.23 (0.14-0.37)
Age > 65	62.1	65.4	0.04	1.16 (1.01-1.33)
Gender : female	34.7	54.9	<0.001	2.29 (2.00-2.62)
Risk				
: Hypertension	61.4	81.7	<0.001	2.80 (2.40-3.26)
: Dyslipidemia	71.7	81.4	<0.001	1.72 (1.46-2.03)
: Smoking	33.2	17.8	<0.001	0.44 (0.37-0.51)
Presentation				
: Chest pain	88.7	83.6	<0.001	0.64 (0.53-0.79)
: Cardiac dyspnea	35.6	52.0	<0.001	1.96 (1.71-2.24)
: Shock	5.9	6.3	0.667	
: Post cardiac arrest	2.3	3.1	0.167	
: Refer	32.1	30.4	0.299	
: Time to admission (hour) median (IQR)	8.1 (2.8-40.2)	9.0 (2.9-43.5)	0.18	
: Time to admission < 24 hr	63.5	62.4	0.5	

Table 2. The management practices during hospitalization

Parameter	No DM (%)	DM (%)	p-value	OR (95% CI)
N	1,724	1,788		
Coronary angiogram	46.3	41.6	0.005	
: Abnormal	94.0	97.9		
Revascularization				
: PCI	21.7	17.9	0.005	0.79 (0.67-0.93)
: Early PCI*	15.4	10.7	<0.001	0.65 (0.53-0.80)
: Elective PCI**	6.2	7.2	0.233	
: PCI or CABG	29.5	25.7	0.01	0.82 (0.71-0.96)
Medication				
: ASA	95.4	94.3	0.16	
: ADP inhibitor	59.2	58.3	0.592	
: Unfractionated heparin	20.0	22.4	0.08	
: LMWH	72.5	72.1	0.813	
: GP IIb/IIIa inhibitor	6.3	4.4	0.012	
: Beta-blocker	64.2	59.5	0.004	0.82 (0.71-0.94)
: Nitrate	86.4	87.1	0.535	
: AntiAII(ACEIorARB)	63.1	64.3	0.456	
: Calcium blocker	20.6	28.6	<0.001	1.54 (1.32-1.81)
: Statin	79.9	83.6	0.005	1.28 (1.07-1.52)

Abnormal CAG: ≥ 50% stenosis in coronary vessel
* Early PCI: PCI within 7 days from onset, ** Elective PCI: PCI > 7 days after onset

independent risk factor of in-hospital mortality. This is the same as other baseline risk factors such as gender, hypertension, dyslipidemia and smoking but not age group older than sixty-five years compared with younger than forty-five years. Other independent predictors for an increased risk of in-hospital mortality in non-ST elevation MI in present study were shock, post arrest at presentation, congestive heart failure during

Table 3. In-hospital outcome

Parameter	No DM (%)	DM (%)	p-value	OR (95% CI)
Number of patients	1,724	1,788		
Death	11.9	13.8	0.089	1.19 (0.97-1.45)
Cardiac death	8.1	8.7	0.479	
Congestive heart failure	45.8	66.1	0.001	2.31 (2.02-2.64)
Killip II in 48 hour	24.3	36.5	0.001	1.79 (1.54-2.08)
Killip III, IV in 48 hour	18.4	26.5	0.001	1.59 (1.36-1.87)
Cardiac arrhythmia	10.3	10.6	0.771	
Length of stay (days): median (IQR)	7.4 (4.3-12.8)	8.9 (5.1-16.1)	<0.110	
In hospital stroke	1.7	2.4	0.130	
In hospital bleeding	5.3	6.5	0.112	

Congestive heart failure = heart failure at index of hospitalization (Killip II-IV within 48 hour or heart failure after 48 hour)
Cardiac arrhythmias = heart block and/or ventricular arrhythmia

Table 4. Logistic multivariate regression analysis for the predictor of mortality/morbidity in non-ST elevation acute coronary syndrome

Predictor	OR (95% CI) Total death	OR (95% CI) Cardiac death	OR (95% CI) Heart failure	OR (95% CI) Car.arrhythmia*
DM			1.84 (1.56-2.19)	
Age group	1.34 (1.18-1.51)	1.19 (1.03-1.37)	1.24 (1.14-1.34)	
Refer	0.77 (0.61-0.96)			
Chest pain				0.70 (0.52-0.94)
Shock	4.00 (2.79-5.72)	4.79 (3.24-7.09)	1.75 (1.16-2.64)	1.89 (1.33-2.69)
Post arrest	2.62 (1.57-4.39)	2.24 (1.31-3.84)		7.35 (4.71-11.47)
Car.dyspnea**			15.00 (12.3-18.2)	
ASA	0.56 (0.37-0.84)			
Nitrate	0.66 (0.49-0.90)			0.68 (0.50-0.91)
Calcium blocker			0.74 (0.61-0.92)	
Beta-blocker	0.62 (0.48-0.81)		0.42 (0.34-0.51)	0.45 (0.35-0.58)
Statin	0.53 (0.41-0.71)	0.48 (0.34-0.65)		0.71 (0.54-0.93)
Anti A-II	0.61 (0.48-0.78)	0.72 (0.53-0.97)	1.26 (1.04-1.51)	
Heart failure	2.84 (2.11-3.82)	3.25 (2.27-4.67)		1.68 (1.29-2.19)
Arrhythmia	9.32 (7.0-12.4)	15.90 (11.7-21.8)	1.71 (1.26-2.33)	
PCI	0.46 (0.31-0.68)	0.41 (0.25-0.66)	0.59 (0.47-0.74)	1.56 (1.16-2.09)
In hospital stroke	3.56 (2.00-6.33)		2.16 (1.13-4.10)	
In hospital bleeding	2.56 (1.75-3.74)	1.75 (1.08-2.86)		

* Car.arrhythmia: cardiac arrhythmia, **Car.dyspnea: cardiac dyspnea

admission, cardiac arrhythmia, in-hospital stoke, and in-hospital bleeding (Table 3). But referral case, percutaneous coronary intervention, beta-blocker, aspirin, nitrate, anti angiotensin II, which included ACE inhibitor and angiotensin receptor blocker and statin were decreased risk of in-hospital mortality. Age more than 75 years, shock, post arrest at presentation, heart failure during admission, cardiac arrhythmia and in-hospital bleeding were also independent predictors for cardiac death. Percutaneous coronary intervention, statin, and anti angiotensin II showed decreased risk of cardiac mortality. Diabetes was an independent predictor for congestive heart failure but was not an independent risk factor for cardiac arrhythmias (Table 4).

Discussion

The presented study found that 50% of non-ST elevation myocardial infarction was diabetes, while approximately one quarter of patients with ACS had diabetes from GRACE registry. Almost all diabetic patients (93.3%) were diagnosed before admission. Diabetic patients in the present study were more often female, more likely to have hypertension and dyslipidemia, less likely to be a smoker. This was the same as the GRACE registry. Chest pain as presentation was less often in diabetes, while cardiogenic dyspnea at presentation was more frequent. Shock and post cardiac arrest were not different. Congestive heart failure, within 48 hours and either Killip II, III and IV were found more often in the diabetic group. Diabetic patients received less invasive strategy such as less coronary angiogram or less percutaneous coronary intervention especially early PCI. The GRACE registry showed that the frequency of cardiac catheterization performed in diabetes was similar to non-diabetes but less PCI was performed in the non-STEMI group. In the presented study, less beta blocker and more calcium blocker were used in diabetes. This was the same as the GRACE registry. Nitrates and ACE inhibitor or ARB used were not different between both groups and were different from the GRACE registry. The percentage of diabetic patients treated with nitrate and ACE inhibitor were greater than that for non-diabetic patients. From the GRACE registry, diabetes was an independent risk for death in overall acute coronary syndrome patients, STEMI and unstable angina patients, but not in non-STEMI patients, which was the same as the presented study.

Several studies have shown that diabetic patients have a high mortality rate after acute myocardial infarction[2,4-12]. From these studies, diabetes was an independent predictor for mortality, both in short-term and long-term follow-up. Recently, from CRUSADE database[9], they found that the in hospital mortality rate was increased in diabetic patients with non-ST elevation acute coronary syndrome (5.8% vs. 4.3%) and patients with highest risk of mortality included diabetic patients are treated less commonly with guideline-recommended acute medications and invasive cardiac procedures. This is the same as the presented study. The beta-blocker use and percutaneous revascularizton rate were less in diabetic patients. In the presented study, diabetic patients had more comorbidity, more morbidity especially congestive heart failure and received less revascularization. Therefore, in-hospital mortality should have been higher in the diabetic group, however, surprisingly, the result of the present study showed no difference in total mortality and cardiac mortality between diabetic and non-diabetic group. There were some possible reasons to explain these findings. The first, mortality in non-ST elevation MI patients in the non-diabetic group was so high. The second, because of the strong independent predictor for in-hospital and cardiac mortality included shock, post arrest at presentation and cardiac arrhythmia. The third, diabetes itself was not an independent predictor for in-hospital mortality from multivariate analysis, while congestive heart failure was independent predictor. The fourth, a study by J Sala et al in REGICOR investigator[13], found that hyperglycemia that was under poor control during admission would be an independent predictor of short-term mortality of myocardial infarction patients, regardless of diagnosis of diabetes. So if diabetic patients in the presented study had good glycemic control during admission, the importance of diabetes to affect the outcome may be decreased. However, the authors didn't have the data to see if the diabetic patients had control or not.

Mortality in non-ST elevation MI patients either diabetic group or non-diabetic group from Thai ACS registry was higher than the literature. This could be from higher prevalence of congestive heart failure. However, diabetes was an independent predictor for increased risk of congestive heart failure during admission. The authors could not explain what mechanism played a role because the authors did not have data about renal function, diabetic nephropathy, history of previous myocardial infarction or congestive heart failure, and LV function. Prevalence of congestive heart failure in type 2 diabetic patients was higher from the literature[14]. From the GRACE registry[6], diabetes was an increased risk of congestive heart failure and renal failure. They have invoked the role of diabetic cardiomyopathy as a potential causative factor in the development of heart failure in patients with diabetes and acute coronary syndrome.

Limitation of study

Because the presented study was a sub-analysis of the main Thai ACS registry, no information was available about diabetes such as duration of diabetes or adequacy of control and type of treatment whether insulin or oral hypoglycemic agent. This may effect the different prognosis from previous studies[6,7]. Criteria for newly Diagnosis, the authors did not use OGTT as part of the diagnosis. Therefore, the diagnosis of diabetes was from the medical record. The authors did not have data about the result of glycemic control in

hospital, which may affect short-term mortality in myocardial infarction patients. The present study showed that congestive heart failure as index of hospitalization was very high, at about 66% of diabetic patients with acute non-ST elevation MI. This would overlap between presentation and complication but no available information about the history of previous MI, previous congestive heart failure, baseline LV function, initial creatinine level, and detail of abnormal coronary angiography was available. This may effect congestive heart failure and mortality. The presented study showed only the hospital-mortality, cardiac death, non-cardiac death and cause of cardiac death. There is no data of long-term follow up available, thus the authors think it may affect the OASIS registry[10]. In any case, what the authors have learned from the study is the very high prevalence of diabetes in non-ST elevation myocardial infarction and diabetes was an increased risk of congestive heart failure. In-hospital mortality in diabetic patients was so high but surprisingly, diabetes was not an increased risk of in-hospital mortality as shown in the literature.

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โรคกล้ามเนื้อหัวใจตายเฉียบพลันชนิด non-ST elevation ในผู้ป่วยเบาหวาน: ข้อมูลจากโครงการทะเบียนผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแห่งประเทศไทย

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วัตถุประสงค์: *เพื่อศึกษาความแตกต่างระหว่างอัตราการเสียชีวิต,ภาวะแทรกซ้อน,อาการนำและวิธีการรักษาของโรคกล้ามเนื้อหัวใจตายเฉียบพลันชนิด non-ST elevation ในกลุ่มผู้ป่วยเบาหวานเทียบกับกลุ่มที่ไม่เป็นเบาหวาน โดยใช้ข้อมูลจากโครงการทะเบียนผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแห่งประเทศไทย*

วัสดุและวิธีการ: *โครงการทะเบียนผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแห่งประเทศไทย เป็นการศึกษาแบบสหสถาบันโดยการเก็บข้อมูลร่วมกันจาก 17 สถาบันทั่วทุกภาคของประเทศ ทั้งโรงเรียนแพทย์, โรงพยาบาลของรัฐและโรงพยาบาลเอกชน*

ผลการศึกษา: *มีผู้ป่วยที่เป็นโรคกล้ามเนื้อหัวใจตายเฉียบพลันชนิด non-ST elevation ในการศึกษาจำนวน 3,548 ราย ในระยะเวลา 3 ปี 3 เดือนที่เก็บข้อมูล ประมาณ 50% ของผู้ป่วยเป็นเบาหวาน ซึ่งในกลุ่มที่เป็นเบาหวานมักเป็นเพศหญิงและมีความชุกของการเป็นโรคความดันโลหิตสูงและไขมันในเลือดสูงมากกว่ากลุ่มที่ไม่เป็นเบาหวาน กลุ่มที่เป็นเบาหวานมีความเสี่ยงต่อการเกิดภาวะหัวใจล้มเหลวสูงกว่ากลุ่มที่ไม่เป็นเบาหวานอย่างมีนัยสำคัญ แต่ไม่มีผลต่อการเกิด ภาวะหัวใจเต้นผิดจังหวะ, อัตราการเสียชีวิตจากโรคหัวใจและอัตราการเสียชีวิตโดยรวม เมื่อเทียบกับกลุ่มที่ไม่เป็นเบาหวาน*

สรุป: *การศึกษานี้แสดงข้อมูลของผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันชนิด non-ST elevation ในประเทศไทย ซึ่งพบอุบัติการณ์ของโรคเบาหวานสูงมากเมื่อเทียบกับข้อมูลจากต่างประเทศ และผู้ป่วยกลุ่มนี้มีความเสี่ยงสูงที่จะเกิดภาวะหัวใจล้มเหลวระหว่างอยู่ในโรงพยาบาล แต่ไม่ได้มีผลต่ออัตราการเสียชีวิตเมื่อเทียบกับกลุ่มที่ไม่เป็นเบาหวาน*