# Implications of Diabetes Mellitus in Patients with STEMI: Data from Thai ACS Registry

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***Background:*** *Data exist on the community-based perspective on the relation of diabetes mellitus (DM) and acute ST elevation myocardial infarction (STEMI) worldwide but no data is available in Thailand.*
***Material and Method:*** *The Thai Acute Coronary Syndrome Registry (TACSR) is an observational study of patients hospitalized with ACS at 17 hospitals in different regions of Thailand. The present sub-study sample consisted of 3,725 patients with STEMI in a 3-year period.*
***Results:*** *Nearly 40% (37.15%) of them had DM who were older, predominantly women, with a greater prevalence of co-morbidities and fewer current smokers. Patients with DM who developed STEMI were at increased risk for heart failure, arrhythmia, bleeding and death. These differences remained after adjustment for potential confounding prognostic factors.*
***Conclusion:*** *A considerable proportion of patients with STEMI have DM. This proportion is higher than any other studies published. Diabetic patients who developed STEMI are also at increased risk for adverse outcomes including, heart failure, arrhythmia, bleeding and death compared to patients without DM.*

***Keywords:*** *Acute ST elevation myocardial infarction, Diabetes Mellitus, The Thai Acute Coronary Syndrome Registry*

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DM is not only a problem of glucose metabolism but also a cardiovascular disease[1]. Over the past three decades in the United States, patients with DM have not enjoyed the same decline in cardiovascular mortality as their non-diabetic counterparts[2]. Up to one quarter of the patients with myocardial infarction have DM and this figure is expected to increase. Importantly, diabetic patients may present with atypical symptoms and heart failure is a common complication[3]. Diabetic patients also represent a high-risk group for developing and surviving acute myocardial infarction[4]. Primary angioplasty was similarly successful in diabetics and non-diabetics and appeared to be more effective than thrombolytic therapy among DM with acute myocardial infarction[5]. There are indications that patients with diabetics do not receive the same extensive treatment as non-diabetics, presumably due to fear of treatment complications. Furthermore, treatment with ACE inhibitors and beta-blockers seem to be even more effective than in non-diabetic patients and the risk of complications is negligible[6,7]. Not only the impact of DM itself increasing in cardiovascular disease severity, but also the magnitude of this problem tends to be getting more and more due to increasing DM prevalence in Thailand[8] comparing with worldwide[9]. These would expect to be a heap load on the Thai health care system whose cardiovascular disease is one of the leading causes of death[10].

The purpose of the present study was to examine presentation, treatment practice and in-hospital

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outcome of DM who had STEMI admitted over a 3-year period from August 2002 to October 2005 in the Thai Acute Coronary Syndrome Registry (TACSR).

## Material and Method

Seventeen hospitals in different regions of Thailand recruited patients for the TACSR, which is a large observational study of patients hospitalized with an ACS. A series of workshops were organized to standardize and control the quality of the data and conduction of the present study. Information about patients' demographic characteristics, presenting symptoms, medical history, time between symptom onset and admission and clinical including electrocardiographic features were recorded in a standard case record form.

In TACSR, the consecutive patients were enrolled prospectively between August 1, 2002 and October 31, 2005. The inclusion criteria were the admitted patients with the discharge diagnosis of acute coronary syndrome. The index ACS symptoms, e.g. chest pain or angina equivalents, had to occur within 14 days before enrollment and accompanied by electrocardiographic ST segment deviations or T wave. At discharge, the patients were classified into one of the following categories: acute ST-segment - elevation myocardial infarction (STEMI), non-STEMI, or unstable angina. Re-admitted patients because of another ACS were excluded. In this sub-study, the authors studied only patients enrolled in TACSR who had STEMI.

STEMI was defined as new or presumed new ST segment elevation $\geq$ 1mm in at least 2 standard leads or $\geq$ 2mm in at least 2 contaguous, pre-cordial leads, or presumed new left bundle branch block on the presenting electrocardiogram. They had to have $\geq$ 1 of the following criteria: persistent angina pectoris for > 20 minutes, or elevation in cardiac enzymes at least 1/3 of the following: CK-MB (or CK) $\geq$ 2 times of upper normal limit, Troponin T $\geq$ 0.1ng/ml or Troponin I $\geq$ 0.1 or 2.0 ng/ml depend on each laboratory.

DM was diagnosed when the patients had a history of diabetes controlled by diet and/or antidiabetic medications, or a fasting plasma glucose was 126 mg/dl or higher for at least twice. Hypertension was documented by history of hypertension diagnosed and treated with medications, diet and/or exercise, or blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions. Dyslipidemia was diagnosed if 1: the patient was previously diagnosed and/or treated with lipid lowering agents. 2: total cholesterol > 200 mg/dl or LDL cholesterol $\geq$130 mg/dl or HDL cholesterol < 40 mg/dl. Smoking was defined as a non-smoker if the patients never smoked or quit smoking equal or more than 2 years, ex-smoker when the patient quit smoking less than 2 years, current smoker if the patients still habitually smoked. History of stroke was documented if previously diagnosed by physicians and/or had a history of neurological function loss caused by an ischemic event with residual symptoms at least 24 hours after onset. Family history was positive if the patients had any direct relatives (parents, siblings and children) who had angina or myocardial infarction or sudden death without obvious cause at age less than 55 years (men) or less than 65 years (female).

Bleeding complication was defined as a major bleeding, including intracranial hemorrhage, from any site requiring blood transfusion, or decreasing hemoglobin $\geq$ 5 gm%. Congestive heart failure (or Killip class II) was defined as bibasilar rales in $\leq$ 50% of lung fields or presence of an S3 gallop. Killip class III was defined as bibasilar rales in $\geq$ 50% of lung fields. Cardiogenic shock (Killip class IV) was defined as symptomatic hypoperfusion with systolic blood pressure < 90 mmHg.

### *Data analysis*

The baseline characteristics for nominal variables are expressed in number and percentage. The continuous variables are expressed as mean $\pm$ SD or median. Differences in demographic information, medical history and clinical characteristics among the comparison groups were determined using Chi-square for discrete variables and T-test or Mann-Whitney U test for categorical variables. A p-value of less than 0.05 is considered statistically significant.

Hospital case-mortality rates as well as heart failure, stroke, arrhythmia and bleeding complications in diabetic and non-diabetic patients were calculated in a standard manner. Logistic multivariable regression analysis was carried out to examine differences in the risk of death and the development of hospital complications between patients with and without DM while controlling for potentially confounding prognostic factors. These factors included age, sex, dyslipidemia, smoking and presence of hypertension. Because this observational study was nonrandomized, the authors did not control for the use of coronary interventional procedures or medical therapies in the presented multivariable-adjusted regression models.

## Results

Among the 3,826 patients with STEMI in Thai

ACS Registry, there were 3,725 patients with known DM status and 37.15% of these had a history or newly diagnosis of DM, were older and more likely to be women (Table 1). Around 60% in both DM and non-DM with STEMI presented within 12 hours, and no difference was found in each period of the time to admission even with the group presented beyond 12 hours. Most patients presented with typical chest pain and this presentation was significantly found more in non-diabetic patients (Table 1). The other presented symptoms, including dyspnea and cardiogenic shock, were found more in diabetic patients. The patients with DM were more likely to have additional comorbidities and coronary risk factors, including hypertension and dyslipidemia but less likely to be current cigarette smokers.

The number of diabetic and non-diabetic patients with STEMI received primary percutaneous coronary intervention, or emergency CABG were comparable. However, a significantly smaller number of DM received thrombolytic therapy. The incidence of STEMI patients who did not get any mode of emergency reperfusion therapy was 45.8%, which had a trend to have more in the DM group. In-hospital medications used in both groups were quite similar; however, diabetic patients with STEMI were less likely to be treated with beta-blockers and aspirin and were more likely to receive angiotensin 2 receptor blocker (ARB) and non-statin lipid lowering drugs during the index hospitalization (Table 2).

Overall incidence of cerebrovascular accident was not increased but the major clinical outcomes including, heart failure, arrhythmia, bleeding and in-hospital mortality were increased significantly in STEMI with diabetic patients. The cause of arrhythmia that increased significantly in the diabetic group was atrioventricular block while no difference was found in ventricular arrhythmia. The increased mortality in patients with DM was mainly caused by cardiac problems, which leads by pumping failure and then arrhythmia. Mortality in STEMI with diabetic patients was 1.6 times higher than that in non-DM. Not only cardiac causes of death but also non-cardiac death were significantly higher in the diabetic group (Table 3).

The authors also examined the differences in the risk of DM to the development of the authors' principal study outcomes for acute ST elevation myocardial infarction while controlling for the potential

**Table 1.** Baseline characteristic of patients with STEMI in TACSR

| | ST elevation MI (n = 3725) | | p-value |
|---|---|---|---|
| | Diabetic (n = 1384) | Non-diabetic (n = 2341) | |
| Age ≥ 65 yr | 48.1% | 42.4% | 0.001 |
| Age, median (yr) | 64.37 | 61.25 | <0.001 |
| Female (%) | 41.8 | 25.9 | <0.001 |
| Time to admission, hr (%) | | | |
| ≤ 3 hr | 31.9 | 31.6 | 0.329 |
| 3.01-6 hr | 16.7 | 16.6 | |
| 6.01-12 hr | 12.8 | 12.4 | |
| >12 hr | 38.5 | 39.3 | |
| Presentation (%) | | | |
| Overall chest pain | 89.3 | 93.1 | <0.001 |
| Chest pain (typical) | 80.2 | 83.1 | 0.039 |
| Chest pain (atypical) | 9.7 | 10.2 | 0.66 |
| Cardiogenic dyspnea | 31.5 | 19.9 | <0.001 |
| Shock | 18.4 | 14.1 | <0.001 |
| Post cardiac arrest | 7.2 | 6.8 | 0.62 |
| Risk factor (%) | | | |
| Hypertension | 65.9 | 42.8 | <0.001 |
| Family history | 9.7 | 10.2 | 0.876 |
| Smoking | 31.7 | 49 | <0.001 |
| Dyslipidemia | 79.7 | 68.4 | <0.001 |

**Table 2.** Mode of reperfusion and in-hospital medications of STEMI by diabetic status in TACSR

| | ST elevation MI | | p-value |
|---|---|---|---|
| | Diabetic (%) (n = 1384) | Non-diabetic (%) (n = 2341) | |
| Mode of reperfusion | | | |
| Thrombolysis | 28 | 32 | 0.012 |
| Primary angioplasty | 22.7 | 22.2 | 0.714 |
| Angioplasty | 44.9 | 46.3 | 0.435 |
| Emergency CABG | 2.7 | 2.3 | 0.432 |
| CABG | 6.5 | 5.8 | 0.362 |
| No emergency reperfusion | 47.6 | 44.4 | 0.056 |
| In-hospital medications | | | |
| Aspirin | 94.2 | 96.2 | 0.005 |
| ADP inhibitor | 60.8 | 61.2 | 0.84 |
| GP IIbIIIa inhibitor | 19.3 | 19.7 | 0.766 |
| ACE inhibitor | 58.6 | 61.3 | 0.109 |
| ARB | 7.2 | 4.3 | <0.001 |
| Beta-Blockers | 55.6 | 61.1 | 0.001 |
| $Ca^{++}$ blocker | 10.9 | 10 | 0.399 |
| Nitrates | 78.4 | 76.5 | 0.174 |
| Statins | 77.2 | 79.2 | 0.151 |
| Other Lipid lowering drugs | 3.8 | 2.1 | 0.003 |

**Table 3.** Outcomes of STEMI by diabetic status

| | ST elevation MI | | p-value |
|---|---|---|---|
| | Diabetic (%) (n = 1384) | Non-diabetic (%) (n = 2341) | |
| Outcomes | | | |
| CHF | 54.3 | 36.9 | <0.001 |
| Arrhythmia | 32.2 | 26.6 | <0.001 |
| AV block | 39.1 | 29.6 | <0.001 |
| Ventrecular arrhythmia | 54.6 | 64.5 | 0.738 |
| CVA | 2.8 | 2.3 | 0.378 |
| Bleeding complications | 10.3 | 6.4 | <0.001 |
| Death | 21.2 | 13.0 | <0.001 |
| Cardiac death | 17.7 | 11.6 | 0.001 |
| Non-cardiac death | 57.4 | 42.6 | 0.008 |

confounding factors including age, sex, dyslipidemia, smoking and hypertension using logistic multivariable regression analysis. DM was at a significant increased risk for heart failure, bleeding, arrhythmia especially from atriventricular block, overall death and cardiac death during acute hospitalization compared with non-diabetic patients (Table 4).

## Discussion

Traditionally, it is estimated that approximately 30% of hospitalized patients with a STEMI will have DM[11], compared with a DM prevalence of approximately 40% in this registry. In accordance with previous studies[12], the present study showed that diabetic patients who had STEMI were older, more likely to be

**Table 4.** Logistic multivariable-Adjusted risk of selected hospital outcomes in DM with STEMI compared with non-DM

| Outcomes | STEMI (odds ratio for DM) | Adjusted OR* (95%CI) |
|---|---|---|
| Death | 1.793 (1.503-2.139)** | 1.823 (1.48-2.244)** |
| Cardiac death | 1.516 (1.176-1.1954)** | 1.574 (1.163-2.129)** |
| Morbidities | | |
| - CHF | 2.038 (1.78-2.332)** | 1.897 (1.634-2.204)** |
| - Arrhythmia | 1.31 (1.133-1.515)** | 1.338 (1.139-1.572)** |
| - AV block | 1.686 (1.354,2.098)** | 1.72 (1.35-2.19)** |
| - Bleeding | 1.695 (1.334-2.155)** | 1.47 (1.126-1.92)** |

* Adjusted odds by potentially confounding prognostic factors included
Adjust by age, sex, dyslipidemia, smoking, and hypertension

** Indicates significance at $p < 0.05$

women, to have hypertension and dyslipidemia but less likely to be current smokers. An explanation of increasing of these coronary artery risk factors in diabetic patients is that DM is part of the metabolic syndrome which is a collection of the risk factors including hypertension, dyslipidemia, hyperglycemia, insulin resistance, as well as abdominal obesity[13]. However, it lacked of detail in TACSR to answer whether this patient group had metabolic syndrome or not.

In this registry, even diabetic patients with STEMI presented with typical chest pain significantly less than the others, however time to admission did not differ between both groups. With regard to reperfusion treatment, the present results were similar to a number of studies[12] that the presented diabetic patients with STEMI had fewer opportunities to receive thrombolytic therapy than non-DM and had a non-significant trend toward get no emergency reperfusion at all. The pattern of receiving concomitant medications were similar in both groups except that diabetic patients with STEMI were less likely to receive beta-blocker and aspirin although a significant mortality reduction shown among diabetic patients received beta blockers[7] and aspirin. The higher prevalence of heart failure and shock starting from presentation may be an explanation why diabetic patients with STEMI were less likely to receive beta-blocker similar to previous studies[14].

It has been known that DM is a major risk for heart failure in STEMI, as shown by the result in this TACSR. Hypertension, which occurred in two-thirds of the DM subgroup, was the most common cause of heart failure. DM increases the likelihood to develop heart failure in hypertensive patients especially in women[15]. However, after adjustment for hypertension and other potential confounding factors, DM was still a risk for heart failure. Both myocardial systolic and diastolic abnormalities can be identified in apparently healthy diabetic patients without overt cardiac dysfunction in recent studies[16]. Congestive heart failure and cardiogenic shock are more common and more severe in DM than would be expected from the size of the index infarction[17,18] and no evidence that patients with DM sustain more extensive infarctions than their non-diabetic counterparts[19]. Therefore, it is suggested that preexisting left ventricular diastolic dysfunction may be a major cause of heart failure[20] since congestive symptoms occur in diabetic patients despite a modest decrease in left ventricular ejection fraction. Subclinical diabetic cardiomyopathy, which is characterized by diastolic dysfunction[21], is likely to be an important factor in this setting.

There are other interesting findings that compensatory hyperkinesis of the non-infarct-related areas, which is found more common in the subject without DM immediately after myocardial infarction, is often blunted in the diabetic patients[22] and DM also have a reduced ability to develop collateral blood vessels in the presence of CAD[23]. The diffuse nature of coronary atherosclerosis in DM may contribute to systolic dysfunction of the non-infarcted myocardium[22] and poor collateral quality may explain the more frequent incidence of post-infarction angina and infarct extension[19,20,24]. Unfortunately, this data on left ventricular performance after STEMI, post-infarction angina and infarct extension were not provided in the TACSR, so apart from confirming DM as a risk for heart failure there was not enough data to conclude what should be the mechanism correlated DM to heart failure.

Not only DM itself is responsible for heart failure, but response to treatment in DM also somewhat differs from the others. Treatment with beta-blockers in DM seems to be even more effective than in non-diabetic patients[7]. Beta-blocker can reduce ischemia and diastolic failure but as the data showed that using beta-blocker in DM group is less than the other. In an overview of fibrinolytic trials in patients with myocardial infarction, the relative reduction in short-term mortality was slightly, but not significantly, greater in patients with DM than in non-diabetic patients (21.7% vs. 14.3%)[25]. However, diabetic patients were less likely to get this thrombolytic therapy. There also is evidence that DM is associated with impaired ST resolution and reduced myocardial blush grade after successful primary percutaneous coronary intervention[26]. All this evidence may also be responsible for heart failure prone in diabetic patients.

The causes of major bleeding complications were not clarified in this registry. Apart from a few intracranial bleeding found, it lacked detail of what the causes of bleeding were. They may be from gastrointestinal bleeding, following percutaneous or surgical coronary revascularization procedures, or a different threshold for transfusion as a result of lower baseline hemoglobin. It has been reported that more advanced age and female, who are predominant in the DM group in this registry, are prone to get the bleeding complications[27,28] mentioned above. Interestingly, DM is still a significant risk of bleeding complication even after being adjusted for age, sex, dyslipidemia, smoking, and hypertension. However, results from a previous study[29] showed that low body mass index, renal insufficiency and peripheral vascular disease also increased the risk of bleeding in STEMI patients. Most of these confounders are usually found in diabetic patients but unfortunately TACSR did not provide these data, so re-analysis in these baseline data would help to determine whether DM itself is a major risk for bleeding complication or not.

DM in the patients enrolled in this registry is not at increased risk of sudden death and ventricular arrhythmia. This is in contrast to past speculation suggesting a pro-arrhythmic effect of autonomic dysfunction in diabetic patients[30]. A potential explanation is that after a heart attack, DM in healthy men is a known risk factor for sudden death[31]. Therefore, there was a selection bias due to patients being included only if they survived their STEMI. However, it is also possible that DM is not a risk for sudden death and ventricular arrhythmia partly due to the use of glibenclamide, which appears to reduce ventricular arrhythmia[32]. The finding that arrhythmia especially atrioventricular block is strongly related to DM in STEMI is also found in most studies[17,24]. Up to now, there is no good explanation for this and we could not get enough data from TACSR for analysis about what the mechanism of this correlation is.

Diabetic patients here contained many high risk characters for STEMI such as older, age, predominant female, more heart failure and cardiogenic shock together with being less likely to receive proven benefit treatment, like thrombolysis, aspirin, beta blocker and they had more complications including, heart failure, arrhythmia and bleeding. All of these unsurprisingly could explain why they have got higher mortality in DM. Other studies also reported that the increase in in-hospital mortality among patients with DM with acute myocardial infarction is due predominantly to an increase in the incidence of congestive heart failure[19,20,24] when the authors adjusted all these confounders; however, DM remains an independent predictor for death after STEMI similar to previous studies[33]. Apart from heart failure, the increase in incidence of re-infarction, infarct extension and recurrent ischemia have also been reported[18,20,24] in correlation with DM in STEMI patients. These major outcomes have not been explored in this registry, but it would help determining how strong DM impacts onto STEMI patients.

## Conclusion

The results of this registry suggest that patients with acute ST-elevation myocardial infarction in Thailand present with a unique feature in the greater incidence of DM compared to anywhere else. Diabetic patients who survive a STEMI is in a high-risk group where heart failure is a common occurrence, warranting early detection and vigorous management.

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## *ความเกี่ยวพันของเบาหวานในโรคกล้ามเนื้อหัวใจตายเฉียบพลัน: ข้อมูลจากโครงการลงทะเบียนผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแห่งประเทศไทย*

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***ภูมิหลัง:*** *มีการศึกษาในชุมชนต่าง ๆ ทั่วโลกเกี่ยวกับความสัมพันธ์ระหว่าง โรคเบาหวานและกล้ามเนื้อหัวใจตายเฉียบพลัน แต่อย่างไรก็ตามข้อมูลเหล่านี้ในประเทศไทยยังมีน้อยมาก*

***วัสดุและวิธีการ:*** *โครงการลงทะเบียนผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันของประเทศไทย เป็นการศึกษารวบรวมลงทะเบียนผู้ป่วยกลุ่มอาการหลอดเลือดหัวใจเฉียบพลันที่นอนรักษาในโรงพยาบาลทั้ง 17 แห่งในภูมิภาคต่าง ๆ ของไทย*

***ผลการศึกษา:*** *มีผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลัน อยู่ 3,725 คนในช่วง 3 ปีของการศึกษา โดยเกือบ 40% ของผู้ป่วยกลุ่มนี้ พบมีเบาหวานร่วมด้วย โดยจะมีอายุมากกว่า, มักเป็นผู้หญิง, มีความดันเลือดสูง, ไขมันในเลือดสูง แต่มักไม่สูบบุหรี่ ผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันที่มีเบาหวานร่วมด้วย มีอัตราเสี่ยงสูงต่อภาวะหัวใจวาย, หัวใจเต้นผิดจังหวะ, ภาวะแทรกซ้อนมีเลือดออกและการเสียชีวิต ซึ่งอัตราเสี่ยงนี้ยังคงสูงอยู่ แม้ว่าจะปรับค่าด้วยปัจจัยร่วมต่าง ๆ*

***สรุป:*** *มีผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลันจำนวนมากเป็นเบาหวาน ซึ่งสัดส่วนที่เป็นนี้จะสูงกว่าในการศึกษาอื่น ๆ และเบาหวานยังพบเป็นอัตราเสี่ยงในผู้ป่วยกล้ามเนื้อหัวใจตายเฉียบพลัน ต่อผลแทรกซ้อนซึ่งรวมถึงหัวใจวาย, หัวใจเต้นผิดจังหวะ, เลือดออก และเสียชีวิต เมื่อเปรียบเทียบกับกลุ่มที่ไม่เป็นเบาหวาน*