Comparison of 2-year clinical outcomes between diabetic versus non-diabetic patients with acute myocardial infarction after 1-month stabilization

Analysis of the prospective registry of DIAMOND (Diabetic acute myocardial infarctiON Disease) in Korea: an observational registry study

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Abstract

This study assessed the 2-year clinical outcomes of patients with diabetes mellitus (DM) after acute myocardial infarction (AMI) in a cohort of the DIAMOND (Diabetic Acute Myocardial infarctiON Disease) registry. Clinical outcomes were compared between 1088 diabetic AMI patients in the DIAMOND registry after stabilization of MI and 1088 non-diabetic AMI patients from the KORMI (Korean AMI) registry after 1:1 propensity score matching using traditional cardiovascular risk factors. Stabilized patients were defined as patients who did not have any clinical events within 1 month after AMI. Primary outcomes were the 2-year rate of major adverse cardiac events (MACEs), a composite of all-cause death, recurrent MI (re-MI), and target vessel revascularization (TVR). Matched comparisons revealed that diabetic patients exhibited significantly lower left ventricular ejection fraction (LVEF) and estimated glomerular filtration rate and smaller stent size. Diabetic patients exhibited significantly higher 2-year rates of MACE (8.0% vs 3.7%), all-cause death (3.9% vs 1.4%), re-MI (2.8% vs 1.2%), and TVR (3.5% vs 1.3%) than non-diabetic patients (all $P<0.01$), and higher cumulative rates in Kaplan–Meier analyses of MACE, all-cause death, and TVR (all $P<0.05$). A multivariate Cox regression analysis revealed that chronic kidney disease, LVEF $<35\%$, and long stent were independent predictors of MACE, and large stent diameter and the use of drug-eluting stents were protective factors against MACE. The 2-year MACE rate beyond 1 month after AMI was significantly lower in diabetic patients.
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DM status in stabilized patients with AMI.
according to DM are not well evaluated in stabilized patients
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Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor, AMI = acute myocardial infarction, ARBs = angiotensin receptor
blockers, BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, CKD = chronic kidney disease, CK-MB =
creatine kinase-myocardial band fraction, CV = cardiovascular, DM = diabetes mellitus, DPP4-I = dipeptidyl peptidase 4 inhibitors,
eGFR = estimated glomerular filtration rate, GP = glycoprotein, hs-CRP = high-sensitivity C-reactive protein, LAD = left anterior
descending artery, LCX = left circumflex artery, LM = left main coronary artery, LVEF = left ventricular ejection fraction, MACE = major
adverse cardiac events, PCI = percutaneous coronary intervention, QCA = quantitative coronary angiography, RCA = right coronary
artery, reMI = recurrent myocardial infarction, ST = stent thrombosis, STEMI = ST-elevation myocardial infarction, TIMI =
 thrombolysis in myocardial infarction, TVR = target vessel revascularization.

Keywords: acute myocardial infarction, diabetes mellitus, major adverse cardiac events

1. Introduction
Diabetes mellitus (DM) is strongly associated with adverse cardiovascular (CV) events.[1] DM affects the development of
coronary artery disease (CAD) and clinical outcomes following the various manifestations of CAD. DM is a CAD risk-equivalent
because the risk of acute myocardial infarction (AMI) in DM patients with no evidence of CAD matches the risk in patients
with a previous history of AMI without DM.[2,3] Previous studies suggested that DM contributes to poor clinical outcomes after the event of AMI.[4–6] However, multiple confounding relationships between clinical factors may influence the early term events simultaneously.[7] Data on the long-term clinical outcomes according to DM are not well evaluated in stabilized patients with AMI. We compared 2-year clinical outcomes according to DM status in stabilized patients with AMI.

2. Methods
2.1. Study design and population
The DIabetic Acute Myocardial infarctiON Disease (DIAMOND) is a prospective, multicenter, observational study for the identification of clinical outcomes after an AMI event in type 2 DM patients in the Korean population. A total of 1192
consecutive DM patients presenting with ST-elevation myocardial
infarction (STEMI) or non-STEMI (NSTEMI) were enrolled
at 22 tertiary or university hospitals in Korea between April 2010
and June 2012. The following inclusion criteria were used: age ≥45 years; documented STEMI or NSTEMI as elevated cardiac
troponin-I or T levels (exceeding upper normal limit) or creatine
 kinase-myocardial band fraction (CK-MB) levels (exceeding 3
times the upper limit of normal); angiographically
≥50% coronary luminal stenosis with or without intracoronary
filling defect or haziness suggesting coronary thrombus, or
coronary spasm-induced AMI without significant stenosis
(≥50% narrowing of the coronary luminal diameter measured
by coronary quantitative angiography (QCA)); and documented
type 2 DM; and AMI patients were stabilized (i.e., did not have
any clinical events within 1 month after the initial presentation of
AMI). Sixty-seven patients who died during hospital admission
or were lost to follow-up within 1 month after discharge were
excluded from the present study. This study finally included 1125
diabetic patients with AMI from the DIAMOND registry.

Chronic kidney disease (CKD) was defined as an estimated
glomerular filtration rate <60 mL/min/1.73 m^2. Body mass index
(BMI) was calculated as weight (kg) divided by height (m^2).
Multivessel disease was defined as having other lesions with
≥50% stenosis in the noninfarct-related coronary artery.
Transthoracic echocardiography assessed the left ventricular
ejection fraction (LVEF) using the modified Simpson’s biplanar
method. Angiographic findings were collected when angiography
was performed at any time during the follow-up period. All data
were collected using an electronic case report form. DM patients
with AMI in the DIAMOND study were matched 1:1 with 3178
non-DM patients with AMI in the Korea AMI (KORMI) registry
to compare clinical outcomes according to DM status in
stabilized AMI patients. KORMI was a prospective, multicenter,
national registry from February 2008. The Institutional Review
Board/Ethical Committees at each clinical site approved the study
protocol, and written informed consent was obtained from all
patients.

2.2. Study outcomes
The primary outcome in this study was rate of major adverse cardiac events (MACEs) including all-cause death, recurrent
myocardial infarction (re-MI), and target vessel revascularization
(TVR). The secondary outcomes were the rates of the individual
components of the primary outcome and definite or probable
stent thrombosis (ST) using the Academic Research Consortium
criteria definition.[8] All death was considered cardiac unless
there was a clear noncardiac cause. Re-MI was defined as the
occurrence of characteristics of MI 28 days after the initial
presentation of AMI,[9] TVR was defined as any repeat
percutaneous or surgical revascularization of any segment of the
target vessel.[8]

2.3. Statistical analysis
Continuous variables are expressed as the mean ± standard
deviceation and compared using Student t test. Categorical
variables are presented as absolute counts and percentages and
compared using the χ^2 test or Fisher exact tests, where
appropriate. Statistical analyses were of an explorative and
descriptive nature, and the study was primarily used for
hypothesis generation. All issues concerning patient validity,
data consistency checks, and permissible data modifications are
described in detail in the Data Management Plan, and all
statistical items, including calculated variables and proposed
table format and content, were detailed in the Statistical Analysis
Plan (SAP), which was finalized before the study database lock.
All analyses were performed on the total study population (i.e.,
pooled analysis). Propensity score analysis was used to
compensate for the single-arm, nonrandomized characteristics
of this study. The pre-specified clinical variables were age, gender, and coronary risk factors, including hypertension, hyperlipidemia, and smoking. Kaplan–Meier analysis was used to calculate the cumulative incidences of primary and secondary clinical outcomes according to DM status. Comparisons between groups were performed using the log-rank test. A logistic regression model was used to identify independent determinants for the primary outcome. Variables with P < 0.05 in the univariate analysis were entered into multivariate logistic regression analysis. Analyses were performed using SPSS statistical software, version 20.0 (SPSS, Inc., Chicago, IL). A P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline patient characteristics

Table 1 presents baseline clinical characteristics of the 1125 AMI patients with DM and 3178 AMI patients without DM. The mean duration of DM was 10.9 ± 8.3 years in the present study. DM patients compared with non-DM patients in unmatched populations were significantly older with higher BMI, high-sensitivity C-reactive protein (hs-CRP) levels, and incidences of hypertension, hyperlipidemia, history of previous MI, LVEF < 35%, and CKD and lower CK-MB and troponin-I peak levels, incidence of smoking, and STEMI. Similar distributions of
medication use, including glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins, were observed. Hs-CRP level and the incidence of history of previous MI, LVEF <35%, and CKD remained significantly higher in DM patients than non-DM patients after 1:1 propensity score matching (Fig. 1).

3.2. Angiographic characteristics

Table 1 presents baseline clinical characteristics of the 1125 AMI patients with DM and 3178 AMI patients without DM. The mean duration of DM was 10.9±8.5 years in the present study. DM patients compared with non-DM patients in unmatched populations were significantly older with higher BMI, high-sensitivity C-reactive protein (hs-CRP) levels, and incidences of hypertension, hyperlipidemia, history of previous MI, LVEF <35%, and CKD and lower CK-MB and troponin-I peak levels, incidence of smoking, and STEMI. Similar distributions of medication use, including glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins, were observed. Hs-CRP level and the incidence of history of previous MI, LVEF <35%, and CKD remained significantly higher in DM patients than non-DM patients after 1:1 propensity score matching (Fig. 1).

3.3. Two-year clinical outcomes

3.3.1. Initial populations. The rate of MACE (8.2% vs 4.2%), all-cause death (3.9 vs 1.7), re-MI (2.8% vs 1.3%), and ST (0.9 vs 0.2) was significantly higher in DM than non-DM patients with AMI (all *P* < 0.05). The rates of cardiac and noncardiac death were 2.5% and 1.4% in DM patients, respectively, and 0.9% and 0.8% in non-DM patients, respectively (Table 3).

3.3.2. Propensity score matched populations. The rates of MACE (8.0% vs 3.7%; *P* < 0.01), all-cause death (3.9 vs 1.4; *P* < 0.001), re-MI (2.8% vs 1.2%; *P* < 0.01), and TVR (3.5% vs 1.3%; *P* < 0.01) were also significantly higher in DM than non-DM patients with AMI, respectively. However, the rate of ST (0.9% vs 0.5%, *P* = 0.20) was comparable (Table 3). Kaplan–Meier survival analysis revealed that the cumulative incidences of MACE, all-cause death, and TVR were significantly higher in DM patients than non-DM patients (all *P* < 0.05). However, the cumulative incidences of re-MI and ST were not significantly different between DM and non-DM patients (Fig. 2, A–E).

3.4. Independent determinants for MACE in initial populations

Univariate logistic regression analysis revealed that age ≥60 years [odds ratio, 1.90 (95% confidence interval, 1.41–2.56)], previous MI [1.97 (1.09–3.55)], hyperlipidemia [1.41 (1.01–1.95)], hypertension [1.65 (1.26–2.17)], CKD [2.49 (1.87–3.30)], Killip III–IV [1.83 (1.25–2.68)], LVEF <35% [2.43 (1.59–3.72)], DM [2.01 (1.53–2.64)], multivessel disease [1.36 (1.03–1.79)], stent diameter [0.59 (0.41–0.85)], stent length [1.02 (1.01–1.04)], and DES use [0.51 (0.34–0.75)] were significantly associated with 2-year MACE (all *P* < 0.05).

Multivariate logistic regression analysis revealed that CKD [1.46 (1.01–2.12)], LVEF <35% [1.98 (1.17–3.34)], stent diameter [0.64 (0.43–0.96)], stent length [1.02 (1.01–1.04)], and DES use [0.44 (0.29–0.68)] were independent predictors for MACE in initial populations.
2-year MACE (all $P < 0.05$). However, DM was not independently associated with 2-year MACE after adjusting for confounding risk factors $[1.40 (0.99–1.99); P = 0.06]$ (Fig. 3) (Supplementary file: Table S1, http://links.lww.com/MD/B31).

### 4. Discussion

The primary findings of this propensity score matching study is that stabilized AMI patients with DM have a higher incidence of comorbidities, such as CKD and systolic heart failure with LVEF $<35\%$, and cumulative incidence of 2-year MACE than non-DM patients. The latter comorbidities, but not DM, were independent predictors of MACE. These results suggest that the higher incidence of comorbidities in DM patients is strongly associated with worse clinical outcomes in stabilized patients with AMI.

Diabetics exhibit multiple concomitant metabolic abnormalities, including hypertension, obesity, and hyperlipidaemia.$^{[10,14]}$ The present study performed propensity score matching between DM and non-DM patients to minimize the confounding metabolic impact on adverse clinical outcomes after an AMI event. Notably, the incidence of CKD and LVEF $<35\%$ was significantly higher in DM patients than non-DM patients after matching CV risk factors. Several previous studies reported that the presence of mild to moderate renal impairment after AMI increased the rate of adverse clinical outcomes.$^{[12–14]}$ Recently, Anavekar et al.$^{[15]}$ emphasized that even mild renal impairment should be considered a potent and independent risk factor for CV complications in patients with AMI. The longstanding history of DM in DIAMOND registry participants suggests that the higher incidence of CKD in DM patients in the present study is associated with diabetic nephropathy.$^{[16]}$ A previous large cohort study identified that reduced LV function was significantly associated with increased 1-month and 1-year mortality risk in patients with AMI.$^{[17]}$ Ehl et al.$^{[17]}$ reported that DM patients exhibited a lower LVEF than non-DM patients regardless of CAD extent and suggested that this difference was associated with worse CV mortality in DM patients. The present study found that the incidence of LVEF $<35\%$ was significantly higher in DM patients despite the absence of significant differences in the incidence of multivessel disease and type B2/C lesions between the propensity-matched populations. Therefore, the higher comorbidity of CKD and LVEF $<35\%$ in DM patients may contribute to the increased risk for the development of MACE during the 2-year follow-up in this study.

The incidences of multivessel and small vessel disease are significantly higher in DM patients than non-DM patients because of the greater burden of atherosclerosis associated with diabetes.$^{[18]}$ This association may translate into the need to implant a greater number of longer and smaller sized stents in DM patients, which was observed in the initial populations in the present study. DES use for the treatment of AMI was more frequently observed in DM patients than non-DM patients in the present study, which may reflect operator preference driven by the more favorable profile for DES in the prevention of restenosis and repeat revascularization.$^{[19–24]}$

Previous studies investigating the impact of DM on clinical outcomes yielded inconsistent results, which likely reflects differences in clinical diagnosis.$^{[22–24]}$ and data on clinical outcomes after DES implantation according to AMI status in patients with AMI are limited. Syed et al.$^{[23]}$ reported that a 1-year composite of death, Q-wave MI, and TLR were not different between AMI patients with and without DM who underwent first-generation DES implantation after adjustment for baseline comorbidities. The cumulative incidence of 2-year MACE was significantly higher in DM patients than non-DM patients in the present study, but DM was not an independent predictor for the event of MACE. The higher use of DES in DM patients may explain the result that DM did not independently predict 2-year MACE in the present study because DES use was independently associated with a decreased risk for 2-year MACE in patients with AMI.

A subgroup analysis of patients with acute coronary syndrome (ACS) in 11 Thrombolysis in Myocardial Infarction Study Group trials revealed that the mortality rate at 30 days and 1-year follow-up was significantly higher in DM than in non-DM patients.$^{[26]}$ The mortality rate between 30 days and 1 year in their study was approximately 5% in 10,613 DM patients, which is higher than the present study (3.9% at 2 years). The latter discrepancy in mortality may be secondary to the higher incidence of PCI with DES and optimal medical therapy with statins and thienopyridine in the present study. The cumulative incidence of 2-year MACE was 8.2% in DM patients with AMI in the present study. This result may be acceptable in the setting of DM patients with AMI based on contemporary PCI with optimal medical treatment compared with previous results of the event rate for a composite of adverse clinical outcomes in DM patients.$^{[27,28]}$

Coronary atherosclerosis involves a prolonged asymptomatic developmental phase, and the first manifestations often result in AMI or sudden cardiac death. The prognostic risk stratification of symptomatic or asymptomatic but at a high risk of CAD patients using noninvasive methods becomes more important with the development of noninvasive imaging modalities for CAD diagnosis.$^{[29–32]}$ Several studies emphasized the role of
physical activity and nutrition in the prevention of the progression of subclinical atherosclerosis, metabolic abnormalities, and adverse CV events in the general population. The prevalence of metabolic syndrome is rapidly increasing worldwide, and it affects approximately 31% of Korean adults. Previous studies in Korea reported that abdominal obesity was associated with CAD risk regardless of the level of physical activity, and high carbohydrate intake, which may be somewhat different in Asian than Western populations, was significantly associated with the risk of DM and low high-density lipoprotein-cholesterol (HDL-C) levels in Korea. However, the impact of physical activity and nutrition on clinical outcomes was primarily evaluated on the primary prevention of CV events in the general population. A recent meta-analysis reported the efficacy of exercise-based cardiac rehabilitation in patients with coronary heart disease, but further prospective studies of

Figure 2. Kaplan–Meier curves for the primary and secondary outcomes according to DM in the propensity score matched population. Cumulative incidence curves are shown for (A) MACE, (B) all-cause death, (C) re-MI, (D) TVR, and (E) ST.
larger sample sizes are warranted because of the paucity of data on these issues beyond strict medical treatment for the secondary prevention after major adverse CV events.

A number of studies that were performed in Western countries strongly suggested that socioeconomic inequality in mortality was a substantial public health issue.[43-47] Especially, Bucholz et al.[48] reported that life expectancy after AMI was significantly lower in patients with low socioeconomic status than in those with high socioeconomic status irrespective of race. In south Korea, a previous large cohort study reported that the contribution of the causes of death to socioeconomic inequality in life expectancy varied by age groups and differed by educational comparisons.[49] Recently, Lim et al.[50] reported that the consistent increase in the attainment of education contributed to the reduction in the population attributable fractions of lower education for mortality, although the fact that mortality inequalities have not improved. However, there is a paucity of data on the impact of socioeconomic and educational inequality on long-term MACE in patients with AMI. Further investigation to identify this issue might be necessary in South Korea.

The present study has several potential limitations. First, it compared single-arm data from 2 different registries, which inherently introduces selection bias and uneven distribution of risk factors. However, propensity score matching analysis was performed to minimize this limitation. Second, the present study focused on stabilized AMI patients, that is, without clinical events within hospital stay or 1 month after discharge, and clinical events are likely to occur during the acute stage after AMI presentation, especially for high-risk patients. Therefore, the present study may underestimate the risk of MACE in diabetic AMI patients. Third, the DIAMOND study was prospectively designed to compile clinical data sets to extend our knowledge of AMI with DM. Therefore, detailed angiographic and interventional information was not available. Fourth, the DIAMOND study did not include assessments of glucose control or adherence to antplatelet medications during the follow-up period. Therefore, the influence of these factors on long-term MACE was not evaluated. Fifth, we could not address the impact of noninvasive imaging modalities, physical activity, or nutrition on clinical outcomes in the present study. Finally, the incidence of ST was low in both groups, which rendered the study underpowered to evaluate the impact of DM on long-term safety after DES implantation.

5. Conclusion

The incidence of 2-year MACE was significantly higher in stabilized AMI patients with DM than without DM after matching traditional CV risk factors. The higher comorbidities in DM patients may contribute to worse clinical outcomes compared with non-DM patients.

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