ORIGINAL RESEARCH

Impact of Diabetes Mellitus on Antithrombotic Management Patterns and Long-Term Clinical Outcomes in Patients With Acute Coronary Syndrome: Insights From the EPICOR Asia Study

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BACKGROUND: Long-term use of antiplatelet agents after acute coronary syndrome in diabetic patients is not well known. Here, we describe antiplatelet use and outcomes in such patients enrolled in the EPICOR Asia (Long-Term Follow-up of Antithrombotic Management Patterns in Acute Coronary Syndrome Patients in Asia) registry.

METHODS AND RESULTS: EPICOR Asia is a prospective, observational study of 12 922 patients with acute coronary syndrome surviving to discharge, from 8 countries/regions in Asia. The present analysis included 3162 patients with diabetes mellitus (DM) and 9602 patients without DM. The impact of DM on use of antiplatelet agents and events (composite of death, myocardial infarction, and stroke, with or without any revascularization; individual components, and bleeding) was evaluated. Significant baseline differences were seen between patients with DM and patients without DM for age, sex, body mass index, cardiovascular history, angiographic findings, and use of percutaneous coronary intervention. At discharge, ≈90% of patients in each group received dual antiplatelet therapy. At 2-year follow-up, more patients with DM tended to still receive dual antiplatelet therapy (60% versus 56%). DM was associated with increased risk from ischemic but not major bleeding events. Independent predictors of the composite end point of death, myocardial infarction, and stroke in patients with DM were age ≥65 years and use of diuretics at discharge.

CONCLUSIONS: Antiplatelet agent use is broadly comparable in patients with DM and patients without DM, although patients with DM are more likely to be on dual antiplatelet therapy at 2 years. Patients with DM are at increased risk of ischemic events, suggesting an unmet need for improved antithrombotic treatment.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01361386.

Key Words: acute coronary syndrome ■ antiplatelet agents ■ diabetes mellitus

According to the International Diabetes Federation, in 2015, there were ≈415 million patients worldwide aged 20 to 79 with diabetes mellitus (DM), along with a further 193 million undiagnosed cases.[1]

Type 2 DM accounts for up to 90% of all cases, and the prevalence is increasing globally.[1] About half of all deaths in patients with DM are due to cardiovascular disease,[1] the majority resulting from thrombotic

CLINICAL PERSPECTIVE

What Is New?

- Among patients surviving an acute coronary syndrome, ≈90% of both patients with diabetes mellitus (DM) and patients without DM were discharged on dual antiplatelet therapy, but somewhat more patients with DM than patients without DM were on dual antiplatelet therapy at 2 years after discharge (60% versus 56%).
- Although DM was associated with increased risk of ischemic events during follow-up, there was minimal impact on risk of major bleeding.
- Multivariable analysis showed that independent predictors of the composite end point of death, myocardial infarction, and stroke in patients with DM were older age (≥65 years) and use of diuretics at discharge.

What Are the Clinical Implications?

- Despite a higher rate of dual antiplatelet therapy use in patients with DM than patients without DM at 2 years after an acute coronary syndrome, patients with DM were at increased risk of ischemic but not bleeding events, suggesting an unmet need for improved antithrombotic treatment.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
DM	diabetes mellitus
EPICOR	Long-Term Follow-up of Antithrombotic Management Patterns in Acute Coronary Syndrome Patients
PoCE	patient-oriented composite end point

events.[2] In addition, patients with DM have a 2- to 4-fold higher risk of recurrent atherothrombotic events and vascular complications than those without DM.[2] Along with oxidative stress, inflammation, and endothelial dysfunction, platelet hyperactivity plays a major role in the progression of thrombotic and cardiovascular events, and type 2 DM is characterized by altered platelet metabolism with increased platelet reactivity and aggregation, which contribute to atherothrombotic complications.[2,3] Furthermore, DM is associated with an impaired response to the antiplatelet drug clopidogrel, leading to high on-treatment platelet reactivity and increased cardiovascular risk.[4,5] The use of effective antiplatelet agents could reduce thrombotic complications by inhibiting adenosine diphosphate–induced platelet reactivity.[6]

As DM is directly related to both early and late mortality in patients with acute coronary syndrome (ACS),[7] the appropriate management of DM can effectively reduce overall mortality and improve quality of life of patients with ACS.[8] While it is recommended that patients with DM receive antiplatelet agents after ACS,[9,10] the long-term efficacy and safety of antiplatelet agents in this setting is not well known.

The large-scale prospective EPICOR Asia (Long-Term Follow-up of Antithrombotic Management Patterns in Acute Coronary Syndrome Patients in Asia) study (NCT01361386)[11] enrolled patients surviving an ACS, and provided important information regarding clinical management as well as antithrombotic management patterns for patients with ACS in Asia. We analyzed the EPICOR Asia database to compare antithrombotic management patterns and outcomes in patients with ACS, both with and without DM, including overall and propensity score-matched cohorts.

METHODS

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Study Protocol

The EPICOR Asia study has been previously described in detail[11] and, in summary, was a prospective, observational study of 12 922 patients with ACS surviving to discharge with 2-year follow-up, from 219 centers in 8 countries in Asia. All enrolled patients signed written informed consent forms at discharge. The study was conducted in accordance with the ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable legislation on noninterventional studies in participating countries and regions. The study protocol was approved by the applicable ethics committees for all participating study sites.

Patients

Patient eligibility has also been thoroughly described previously.[11] In summary, consecutive patients ≥18 years of age were considered for enrollment if they were hospitalized within 48 hours of symptom onset of the index cardiovascular event and had a discharge diagnosis of ST-segment–elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina.

Principal exclusion criteria included an ACS event secondary to or as a complication of other diseases, such as surgery, trauma, or gastrointestinal bleeding, or after percutaneous coronary intervention, or noncardiac comorbid conditions with limited short-term life expectancy or that might result in protocol noncompliance.

Treatment

All patients in EPICOR Asia underwent routine clinical assessment and received standard antiplatelet therapy. Their detailed medication regimen, which included choice of antiplatelet drugs, their combinations, dosing, timing, and continuation of use during hospitalization and after discharge, was determined by the treating cardiologist; patients did not receive any experimental intervention or treatment. Follow-up interviews were prespecified at 6 weeks and 3 months after the index event and every 3 months thereafter for 2 years in all patients.

End Points

The primary end point was defined as the CV composite[12] of all-cause death, myocardial infarction (MI), and ischemic stroke. Secondary efficacy end points were the patient-oriented composite end point (PoCE) of all-cause death, MI, stroke, and revascularization. Safety end points were bleeding, including major and minor bleeding. MI was defined in accordance with the third universal definition proposed in 2013,[13,14] and stroke as focal or partial loss of neurologic function caused by either an ischemic or hemorrhagic event. Major bleeding was defined as life-threatening intracranial, hemodynamic compromised bleeding; bleeding requiring transfusion; or a fall in hemoglobin >5 g/dL,[15] while minor bleeding was defined as bleeding that did not meet the above criteria.

Statistical Analysis

For baseline characteristics, categorical variables were summarized as frequencies and percentages and continuous variables as means (SD). Baseline characteristics between patients with DM and patients without DM were compared using the chi-square test and t-test for categorical and continuous variables, respectively.

To reduce imbalances in patient characteristics and confounding factors, patients with DM were matched 1:1 with a non-DM control based on the patient's propensity score using nearest available neighbor matching with no replacement. Here, caliper width was derived as 0.2×(SD of logit of propensity score). The propensity score for DM (probability of having DM) was estimated by multivariable logistic regression including age, sex, body mass index (≤25, >25), history of smoking, medical history (hypertension, dyslipidemia, prior MI, prior percutaneous coronary intervention, prior stroke/transient ischemic attack, peripheral artery disease, heart failure), renal insufficiency (estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2), index event diagnosis, chronic anemia, and major bleeding within 6 months before index event. Standardized differences were calculated for the propensity score–matched populations.

Time to first cardiovascular event was analyzed on the basis of a univariate Cox proportional hazards model including DM status (DM or non-DM) using the overall (full) cohort and a propensity score–matched patient cohort to estimate unadjusted and adjusted hazard ratio (HR), respectively, along with its 95% CI and P value. Kaplan–Meier plots for each end point were made for the overall and matched patient cohorts.

Multivariable Cox proportional hazards regression analysis, including medications at discharge, was performed in patients with DM to determine predictors of ischemic events (days to death, MI, stroke, and revascularization) and bleeding events (days to any bleeding and major bleeding) among DM patients. The proportional hazards assumption was initially assessed by inspection of the Kaplan–Meier curves for the 2 groups and confirmed by testing of the correlation between the Schoenfeld residuals from the fitted model with time (all P=NS). Variable selection was done by stepwise procedure with the P value cutoffs for selection at $P<0.01$ and retention at $P<0.20$. Results based on the final model are presented as HR with 95% CI and P value.

RESULTS

Study Patients and Baseline Characteristics

The EPICOR Asia study recruited 13 005 patients between June 2011 and May 2012. Of these, 83 were excluded: 19 did not survive to discharge and 64 were excluded due to critical data quality issues.[11] Thus, 12 922 patients met the inclusion/exclusion criteria, of whom 12 764 had known diabetic status (DM, n=3162; non-DM, n=9602) and were included in the unmatched analysis. In addition, a propensity score–matched non-DM control was identified for 3079 patients with DM (83 patients unmatched). Demographic and baseline characteristics were generally well balanced between patients with DM and patients without DM (Table 1 and Table S1). Notably, patients with DM tended to be older than patients without DM in the full cohort (61.2 versus 59.5 years;

Table 1. Baseline Characteristics of Patients With and Without DM

| Parameters | Patients With DM | | Patients Without DM | | |
	N	n (%)/Mean (SD)	N	n (%)/Mean (SD)	P Value
Age, y, mean (SD)	3162	62.1 (10.7)	9602	59.5 (11.8)	<0.0001
Age group, y					<0.0001
≤55		883 (27.9)		3529 (36.8)	
56 to 64		958 (30.3)		2807 (29.2)	
65 to 74		894 (28.3)		2192 (22.8)	
≥75		427 (13.5)		1074 (11.2)	
Male	3162	2210 (69.9)	9602	7527 (78.4)	<0.0001
BMI, kg/m^2, mean (SD)	2866	25.2 (3.5)	8853	24.5 (3.6)	<0.0001
BMI group, kg/m^2					<0.0001
≤25		1496 (52.2)		5304 (59.9)	
>25		1370 (47.8)		3549 (40.1)	
Place of residence					<0.0001
Rural	3162	1034 (32.7)	9602	3633 (37.8)	
Metropolitan		2128 (67.3)		5969 (62.2)	
Insurance type	3162		9602		
Government		2121 (67.1)		6811 (71.0)	<0.0001
Private		322 (10.2)		995 (10.4)	0.77
Employer provided		46 (1.5)		166 (1.7)	0.30
Other		117 (3.7)		368 (3.8)	0.74
None		609 (19.3)		1447 (15.1)	<0.0001
Hospital type	3162		9602		<0.0001
Reg/comm/rural		181 (5.7)		546 (5.7)	
Non–university general		736 (23.3)		2403 (25.0)	
University general		1607 (50.8)		5383 (56.1)	
Other		638 (20.2)		1270 (13.2)	
Medical history					
Hypertension	3156	2227 (70.6)	9595	4545 (47.4)	<0.0001
Hypercholesterolemia	3007	792 (26.3)	9384	1381 (14.7)	<0.0001
Current smoker	2933	802 (27.3)	8999	3516 (39.1)	<0.0001
Prior MI	3057	447 (14.6)	9380	765 (8.2)	<0.0001
Prior PCI	3063	340 (11.1)	9410	625 (6.6)	<0.0001
TIA/stroke	3056	196 (6.4)	9396	368 (3.9)	<0.0001
PVD	3047	42 (1.4)	9384	58 (0.6)	<0.0001
Chronic anemia	3074	50 (1.6)	9405	54 (0.6)	<0.0001
Major bleeding	3097	19 (0.6)	9491	33 (0.4)	<0.05
In-hospital events					
Myocardial infarction	3124	142 (4.6)	9529	244 (2.6)	<0.0001
Stroke	3135	6 (0.2)	9541	18 (0.2)	0.98
Heart failure	3133	207 (6.6)	9529	448 (4.7)	<0.0001
Severe arrhythmias	3110	140 (4.5)	9516	431 (4.5)	0.95
TVR	3162	2042 (64.6)	9602	6701 (69.8)	<0.0001
Bleeding					
Major	3162	14 (0.4)	9602	49 (0.5)	0.64
Minor	3162	46 (1.5)	9602	164 (1.7)	<0.0001
Clinical presentation	3162		9602		
STEMI		1439 (45.5)		5089 (53.0)	<0.0001

(Continued)

Table 1. Continued

Parameters	Patients With DM		Patients Without DM		
	N	n (%)/Mean (SD)	N	n (%)/Mean (SD)	P Value
NSTEMI		770 (24.4)		1770 (18.4)	
Unstable angina		953 (30.1)		2743 (28.6)	
Renal function, eGFR, mL/min per 1.73 m², mean (SD)	3162	88.1 (35.8)	9602	95.1 (34.7)	<0.0001
Renal function group, eGFR, mL/min per 1.73 m²					<0.0001
<30		127 (4.0)		103 (1.1)	
30–59		509 (16.1)		934 (9.7)	
60–89		1123 (35.5)		3480 (36.2)	
≥90		1403 (44.4)		5085 (53.0)	
Laboratory tests					
Hemoglobin, g/dL, mean (SD)	3018	13.2 (2.0)	9172	13.7 (1.9)	<0.0001
Peak Cr, mg/dL, mean (SD)	2790	1.2 (0.9)	8686	1.0 (0.6)	<0.0001
Positive cardiac markers	3103	2207 (71.1)	9458	6851 (72.4)	0.16
Medications at discharge					
Beta-blocker	3145	2220 (70.6)	9581	6552 (68.4)	<0.05
Calcium channel blocker	3122	475 (15.2)	9560	1060 (11.1)	<0.0001
ACEi/ARB	3144	2046 (65.1)	9578	5880 (61.4)	<0.001
Any LLT	3162	2835 (89.7)	9602	8727 (90.9)	<0.05
Atorvastatin		1678 (53.1)		4858 (50.6)	<0.001
Fluvastatin		45 (1.4)		144 (1.5)	
Pravastatin		23 (0.7)		85 (0.9)	
Rosuvastatin		635 (20.1)		2185 (22.8)	
Simvastatin		379 (12.0)		1298 (13.5)	
Multiple statins		20 (0.6)		47 (0.5)	
Other LLT only		55 (1.7)		110 (1.2)	
Diuretic	3128	624 (20.0)	9564	1055 (11.0)	<0.0001
Nitrate	2971	280 (9.4)	9036	712 (7.9)	<0.01
Any PPI	3162	1168 (36.9)	9602	3333 (34.7)	<0.05

Results are unadjusted. P values from chi-square test or t-test as appropriate. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; Cr, creatinine; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LLT, lipid-lowering therapy; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PVD, peripheral vascular disease; Reg/comm/rural, regional/community/rural; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack; and TVR, target vessel revascularization.

P<0.0001), with fewer patients in the ≤55 years age group (27.9% versus 36.8%); in the matched cohort, however, age was well balanced between patients with DM and patients without DM. Patients with DM also had a higher mean body mass index (25.2 versus 24.5 kg/m²; P<0.0001). Renal insufficiency was significantly more common in patients with DM than patients without DM in the full cohort (P<0.0001), but the difference disappeared in the matched cohort. Patients with DM were less likely to receive government-provided insurance (67.1% versus 70.9%; P<0.0001) and more likely to have no insurance (19.3% versus 15.1%; P<0.0001), and most patients were treated at a university general hospital, irrespective of DM status (DM, 50.8%; non-DM, 56.1%), with only 5.7% of patients treated in regional,

community, or rural hospitals and with similar results in the matched cohort.

More patients without DM than patients with DM underwent any cardiac catheterization (82.7% versus 80.1%; P<0.001), and the rate of multivessel disease at the index event was higher in the DM than in the non-DM group (51.0% versus 44.3%; P<0.0001), with a greater percentage of patients with DM having 3 target vessels (40.5% versus 29.9%), and more than 2 stents implanted (16.8% versus 13.0%), with similar findings in the matched cohort (Table 2 and Table S2). Following discharge, there were no significant differences between the groups in terms of cardiovascular interventions in the unmatched or matched cohorts. In-hospital MI was more frequently reported in patients with DM than patients without DM (4.6% versus 2.6%;

Table 2. Angiographic and PCI Results in Patients With and Without DM

Parameters	Patients With DM		Patients Without DM		P Value
	N	n (%)	N	n (%)	
Cardiac catheterization during the index hospitalization	3119	2498 (80.1)	9513	7868 (82.7)	<0.001
Multivessel disease	3162	1612 (51.0)	9602	4256 (44.3)	<0.0001
PCI	3080	2013 (65.4)	9457	6638 (70.2)	<0.0001
Emergency PCI	3080	937 (30.4)	9457	3281 (34.7)	<0.0001
Target vessel	2146		7685		<0.05
Arterial bypass graft		1 (0)		2 (0)	
LAD		1361 (56.3)		4510 (58.7)	
LCX		355 (14.7)		939 (12.2)	
Left main		54 (2.2)		188 (2.5)	
RCA		642 (26.6)		2041 (26.6)	
Vein bypass graft(s)		3 (0.1)		5 (0.1)	
Number of target vessels	2256		7175		<0.0001
1		668 (29.6)		2941 (41.0)	
2		675 (29.9)		2086 (29.1)	
3		913 (40.5)		2148 (29.9)	
Any stent	3080	1971 (64.0)	9457	6505 (68.8)	<0.0001
Number of stents	1971		6506		<0.0001
1		1076 (54.6)		4010 (61.6	
2		564 (28.6)		1651 (25.4)	
>2		331 (16.8)		845 (13.0)	
Postdischarge interventions					
Cardiac catheterization	3162	262 (8.3)	9602	779 (8.1)	0.76
Angiography	3162	146 (4.6)	9602	460 (4.8)	0.69
Balloon PCI	3162	32 (1.0)	9602	86 (0.9)	0.55
Any stent	3162	140 (4.4)	9602	387 (4.0)	0.33
Bare metal stent	3162	14 (0.4)	9602	44 (0.5)	0.91
Drug-eluting stent	3162	126 (4.0)	9602	346 (3.6)	0.32

Results are unadjusted. P values from chi-square test or t-test as appropriate. DM indicates diabetes mellitus; LAD, left anterior descending; LCX, left circumflex; PCI, percutaneous coronary intervention; and RCA, right coronary artery.

$P<0.0001$), and patients with DM were more often prescribed diuretics at discharge (20.0% versus 11.0%; $P<0.0001$) (Table 1). Similar findings were observed in the matched cohort (Table S1). Notably, in-hospital hemoglobin level was measured less frequently in the DM group.

Antithrombotic Medication

No statistically significant difference was evident between patients with DM and patients without DM in terms of prehospital chronic treatment with aspirin or $P2Y_{12}$ inhibitors (Table 3 and Table S3). In-hospital antithrombotic treatment was also similar in the 2 groups, with the exception that patients with DM were less likely to receive aspirin or clopidogrel loading doses. Use of antiplatelet agents at discharge was also broadly comparable in each group. Most patients received dual antiplatelet therapy (DAPT)

at discharge, with somewhat lower use in patients with DM than patients without DM (88.3% versus 90.0%), although the difference disappeared in the matched cohort (88.3% versus 89.8%). At 2-year follow-up, however, patients with DM showed a modestly greater use of DAPT (60.0% versus 57.0%) and were also more likely to be receiving a $P2Y_{12}$ inhibitor (66.4% versus 62.3%). The unmatched cohort showed similar results.

Death and Ischemic Events

Overall, DM was an independent predictor of events on univariate analysis of the propensity score–matched and –unmatched cohorts (Table 4 and Table S4, respectively). The primary end point (all-cause death, MI, or stroke) occurred significantly more often in the DM group than in the non-DM group in the matched cohort (11.8% versus 8.5%; HR [95% CI], 1.41 [1.20–1.64];

Table 3. Antithrombotic Therapy in Propensity Score–Matched Patients With and Without DM

Parameters	Patients With DM		Patients Without DM		Standardized Difference
	N	n (%)	N	n (%)	
In-hospital treatment					
Aspirin	3079	2861 (92.9)	3079	2867 (93.1)	−0.0076
Loading	3079	1140 (37.0)	3079	1195 (38.8)	−0.0368
Any P2Y$_{12}$ inhibitor	3079	2875 (93.4)	3079	2849 (92.5)	0.0330
Clopidogrel	3079	2811 (91.3)	3079	2794 (90.7)	0.0193
Loading	3079	1387 (45.1)	3079	1464 (47.6)	−0.0502
Ticagrelor	3079	2 (0.1)	3079	3 (0.1)	−0.0114
Prasugrel	3079	87 (2.8)	3079	71 (2.3)	0.0329
Ticlopidine	3079	10 (0.3)	3079	9 (0.3)	0.0059
Cilostazol	3079	81 (2.6)	3079	55 (1.8)	0.0575
LMW heparin	3079	1657 (53.8)	3079	1717 (55.8)	−0.0392
Fondaparinux	3079	310 (10.1)	3079	318 (10.3)	−0.0086
GPIIb/IIIa inhibitor	3079	502 (16.3)	3079	512 (16.6)	−0.0088
Warfarin/NOAC	3079	22 (0.7)	3079	23 (0.8)	−0.0038
Thrombolytics	3079	176 (5.7)	3079	178 (5.8)	−0.0028
At discharge					
Aspirin	3036	2895 (95.4)	3052	2934 (96.1)	−0.0385
Any P2Y$_{12}$ inhibitor	3033	2866 (94.5)	3050	2873 (94.2)	0.0129
Aspirin alone	3036	162 (5.3)	3052	167 (5.5)	−0.0060
P2Y$_{12}$ inhibitor alone	3033	122 (4.0)	3050	92 (3.0)	0.0546
DAPT	3079	2720 (88.3)	3079	2765 (89.8)	−0.0469
Cilostazol	3033	78 (2.6)	3050	55 (1.8)	0.0526
Warfarin/NOAC	3079	30 (1.0)	3079	33 (1.1)	−0.0097
At 2 y					
Aspirin	2432	2166 (89.1)	2481	2183 (88.0)	0.0337
Any P2Y$_{12}$ inhibitor	2430	1613 (66.4)	2481	1546 (62.3)	0.0849
Aspirin alone	2432	699 (28.7)	2482	767 (30.9)	−0.0472
P2Y$_{12}$ inhibitor alone	2430	148 (6.1)	2481	125 (5.0)	0.0459
DAPT	2432	1460 (60.0)	2481	1413 (57.0)	0.0625
Cilostazol	2430	28 (1.2)	2480	27 (1.1)	0.0060
Warfarin/NOAC	2437	19 (0.8)	2488	19 (0.8)	0.0018

DAPT indicates dual antiplatelet therapy; DM, diabetes mellitus; GP, glycoprotein; LMW, low-molecular-weight; and NOAC, novel oral anticoagulant.

$P<0.0001$), as did all components including all-cause death (7.0% versus 5.6%; HR [95% CI], 1.26 [1.03–1.53]; $P<0.05$); MI (4.4% versus 2.8%; HR [95% CI], 1.59 [1.21–2.08]; $P<0.001$), and stroke (1.9% versus 1.2%; HR [95% CI], 1.56 [1.04–2.36]; $P<0.05$), and the differences were somewhat more marked in the unmatched cohort (Table 4 and Table S4). The incidence of PoCE was also significantly higher in patients with DM as compared with patients without DM (21.2% versus 18.2%; HR [95% CI], 1.18 [1.06–1.32]; $P<0.01$), with similar results in the unmatched cohort. However, while the rate of revascularization alone was higher in patients with DM in the full cohort (12.0% versus 10.6%; HR [95% CI], 1.17 [1.04–1.31]; $P=0.01$) (Table S4), it was similar in the 2 matched groups (11.8% versus 11.5%;

HR [95% CI]; 1.04 [0.90–1.20]; $P=0.62$) (Table 4). Time-to-event curves comparing cardiovascular events, PoCE, and mortality between patients with DM and patients without DM are shown in the Figure—Panels A through C and Figure S1A through S1C, respectively.

Bleeding Events

The incidence of predefined major bleeding was not significantly different between the full DM and non-DM groups (0.3% versus 0.3%; HR [95% CI], 1.00 [0.49–2.04]) (Table S4), nor in the matched cohort (Table 4). The incidence of minor and overall bleeding was higher in patients with DM in the full cohort (6.5% versus 5.6%; HR [95% CI], 1.19 [1.02–1.40];

Table 4. HR for Clinical Events in Propensity Score-Matched Patients With and Without DM

Parameter	Patients With DM		Patients Without DM		HR (95% CI*)	P Value*
	N	n (%)	N	n (%)		
Composite end point (death, MI, and stroke)	3079	362 (11.8)	3079	263 (8.5)	1.41 (1.20–1.64)	<0.0001
All-cause death	3079	215 (7.0)	3079	173 (5.6)	1.26 (1.03–1.53)	<0.05
MI	3079	136 (4.4)	3079	87 (2.8)	1.59 (1.21–2.08)	<0.001
Stroke	3079	57 (1.9)	3079	37 (1.2)	1.56 (1.04–2.36)	<0.05
Any revascularization	3079	364 (11.8)	3079	354 (11.5)	1.04 (0.90–1.20)	0.61
PoCE	3079	652 (21.2)	3079	560 (18.2)	1.18 (1.06–1.32)	<0.01
Bleeding	3079	202 (6.6)	3079	184 (6.0)	1.11 (0.91–1.36)	0.30
Major	3079	9 (0.3)	3079	13 (0.4)	0.70 (0.30–1.64)	0.41
Minor	3079	197 (6.4)	3079	177 (5.7)	1.13 (0.92–1.38)	0.24

DM indicates diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; and PoCE, patient-oriented composite end point.

*From univariate Cox proportional hazards model with robust standard error for the parameter estimates.

$P<0.05$; and 6.7% versus 5.9%; HR [95% CI], 1.18 [1.01–1.38]; $P<0.05$), but the difference disappeared in the matched cohort. Time-to-event curves comparing bleeding between patients with DM and patients without DM are shown in the Figure—Panel D and Figure S1D.

Predictors of Events in Patients With DM

Covariates simultaneously adjusted for in the multivariable regression were age, sex, medical history, chronic DM therapy, place of residence (rural or metropolitan), country, eGFR, index diagnosis, discharge medications, and invasive cardiac catheterization. Multivariable regression showed that the independent predictors of increased cardiovascular events (composite of death, MI, and stroke) in patients with DM were age ≥65 years and use of diuretics at discharge (Table 5). Lower rates of cardiovascular events were associated with in-hospital cardiac catheterization, residency in India or Hong Kong/Singapore/South Korea versus China, eGFR ≥30 mL/min per 1.73 m², and index diagnosis of unstable angina (versus STEMI).

Predictors of the individual end point of death were age ≥65 years and use of diuretics or aldosterone inhibitors at discharge (Table 5). Lower rates of death were predicted by cardiac catheterization, eGFR ≥30, and chronic oral DM therapy. Increased risk of MI was predicted by a diagnosis of NSTEMI (versus STEMI) and history of MI. Conversely, a diagnosis of unstable angina decreased the risk of death, along with cardiac catheterization, and residency in India versus China. The only independent predictor of stroke was female sex, whereas residency in India versus China was again associated with reduced risk.

Higher rates of PoCE were associated with use of a diuretic at discharge and index diagnosis of NSTEMI

(versus STEMI), whereas in-hospital cardiac catheterization, eGFR ≥60 mL/min per 1.73 m², index diagnosis of unstable angina (versus STEMI), and residency in India were associated with of a lower rate of PoCE (Table S5). Predictors of the individual end point of revascularization were NSTEMI, use of H₂-receptor antagonists or omeprazole at discharge, and residency in metropolitan areas, whereas residency in India lowered the event rate.

For any bleeding events, chronic anemia was a predictor of increased risk, whereas residency in any country/region versus China lowered the risk (Table 5). Use of an aldosterone inhibitor or nonsteroidal anti-inflammatory drugs at discharge were predictive of major bleeding (Table S5).

DISCUSSION

The EPICOR Asia study confirms that patients with DM treated for ACS are at increased risk of ischemic events and mortality, and that treatment with antiplatelet agents for up to 2 years after discharge is not associated with a significant increase in major bleeding complications. This is consistent with several clinical trials, despite there being a preponderance of White patients in those studies and a broad multiethnic population in our own study.[16–18] Furthermore, and again in accordance with previous trials and reviews,[19] the present study shows that while clinical outcomes are improved with antiplatelet therapy in patients with ACS, patients with DM experience relatively high rates of ischemic events during follow-up. Several reasons may account for this. First, patients with DM experience multiple metabolic abnormalities, such as insulin resistance and hyperglycemia. Such comorbidities could contribute to a prothrombotic state and possibly increase procoagulant activity and
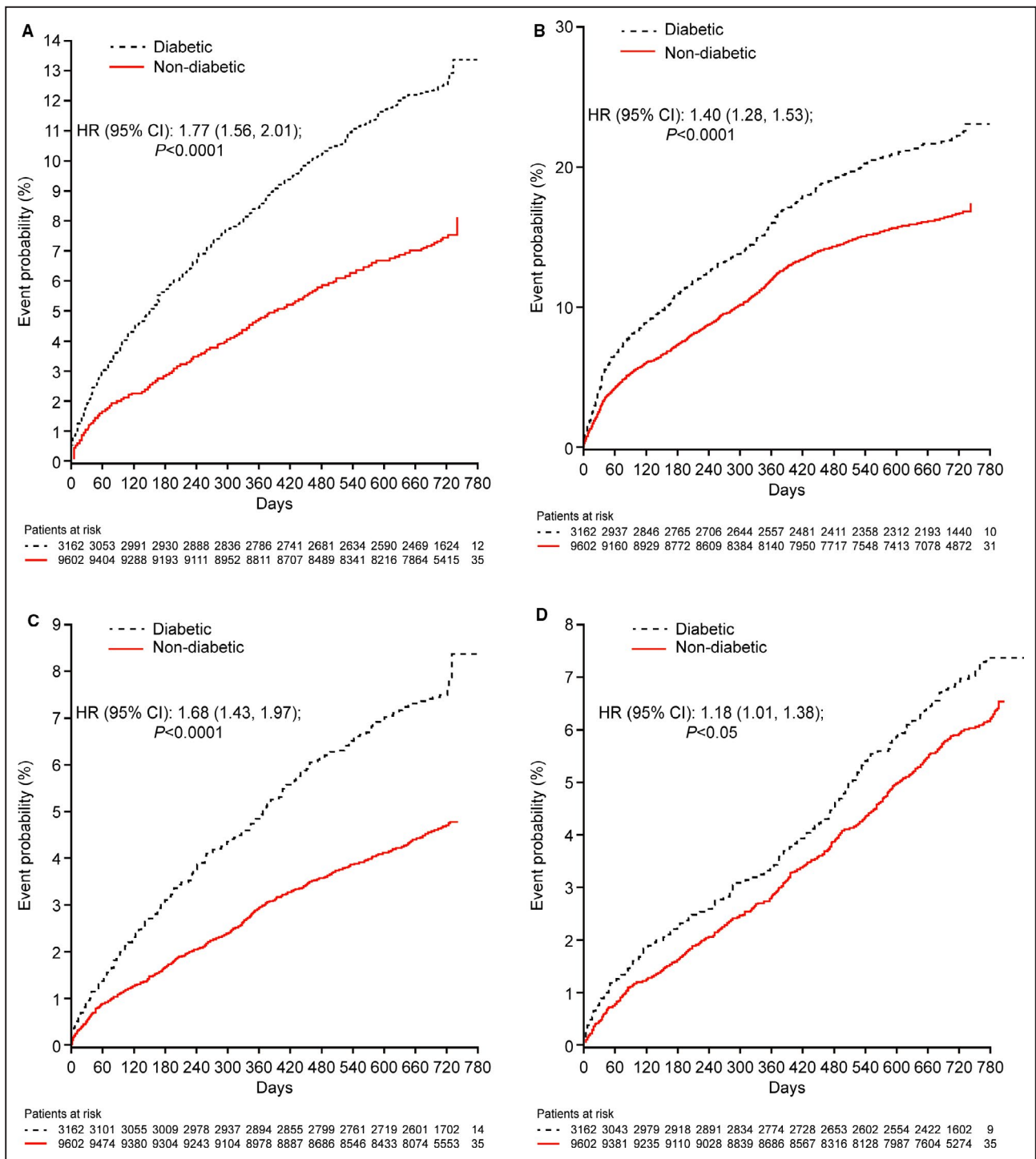
Figure 1.   Kaplan–Meier risk curves of (A) composite end point, (B) patient-oriented composite end point, (C) death, and (D) bleeding, through 2 years in patients with and without DM, for unmatched cohort.
Composite end point: composite of all-cause death, myocardial infarction (MI), and ischemic stroke. Patient-oriented composite end point: composite of all-cause death, MI, stroke, and revascularization. DM indicates diabetes mellitus; HR, hazard ratio.

thrombin generation via several mechanisms, leading to atherosclerosis and thrombosis. Moreover, hyperglycemia per se could exacerbate insulin resistance and promote an altered platelet metabolic milieu, resulting in increased platelet reactivity and potentially contributing to the pathogenesis of atherothrombotic complications.

Notably, several abnormal signaling pathways, including receptor and intracellular downstream signaling, have been identified in platelets of patients with DM.[20]

On multivariable regression analysis, independent predictors of cardiovascular events during long-term follow-up in patients with DM included a number of

Table 5. Independent Predictors of Composite and Individual Ischemic End Points of Death, MI, and Stroke, and Any Bleeding Events Among Patients With DM Based on Final Multivariable Cox Proportional Hazards Model

Parameter Predictors	HR (95% CI)	P Value
Composite of death, MI and stroke		
Age, y, vs ≤55		<0.0001
56–64	1.13 (0.82–1.55)	
65–74	1.40 (1.02–1.91)	
≥75	2.29 (1.64–3.18)	
Cardiac catheterization for index event	0.44 (0.35–0.55)	<0.0001
Country/region, vs China		<0.01
Hong Kong, Singapore, South Korea	0.71 (0.48–1.06)	
India	0.60 (0.46–0.80)	
Malaysia, Thailand, Vietnam	0.91 (0.66–1.25)	
Discharge medications: diuretics	1.62 (1.30–2.02)	<0.0001
eGFR group, mL/min per 1.73 m², vs <30		<0.0001
≥30 to <60	0.66 (0.46, 0.96)	
≥60 to <90	0.48 (0.33–0.70)	
≥90	0.39 (0.27–0.58)	
Final diagnosis of index admission event, vs STEMI		<0.0001
NSTEMI	1.25 (0.99–1.58)	
UA	0.64 (0.48–0.84)	
Death		
Age, y, vs ≤55		<0.0001
56–64	1.57 (0.96–2.56)	
65–74	1.95 (1.21–3.15)	
≥75	4.35 (2.71–6.97)	
Discharge medications: aldosterone inhibitors	1.58 (1.10–2.28)	0.01
Cardiac catheterization for index event	0.40 (0.31–0.53)	<0.0001
Discharge medications: diuretics	1.74 (1.27–2.38)	<0.001
eGFR group, mL/min per 1.73 m², vs <30		<0.0001
≥30 to <60	0.66 (0.43–1.00)	
≥60 to <90	0.36 (0.23–0.56)	
≥90	0.28 (0.18–0.45)	
Chronic DM therapy: oral agent	0.69 (0.53–0.91)	<0.01
MI		
Cardiac catheterization for index event	0.26 (0.19–0.37)	<0.0001
Country/region, vs China		<0.0001
Hong Kong, Singapore, South Korea	1.08 (0.64–1.83)	
India	0.12 (0.06–0.27)	
Malaysia, Thailand, Vietnam	0.99 (0.63–1.56)	
Final diagnosis of index admission event, vs STEMI		<0.0001

(Continued)

Table 5. Continued

Parameter Predictors	HR (95% CI)	P Value
NSTEMI	1.56 (1.08–2.25)	
UA	0.34 (0.20–0.57)	
History: MI	1.79 (1.22–2.64)	<0.01
Stroke		
Country/region, vs China		<0.05
Hong Kong, Singapore, South Korea	0.44 (0.14–1.40)	
India	0.22 (0.08–0.60)	
Malaysia, Thailand, Vietnam	0.66 (0.26–1.66)	
Female	2.46 (1.48–4.06)	<0.001
Any bleeding		
Chronic anemia	5.38 (2.92–9.93)	<0.0001
Country/region, vs China		<0.0001
Hong Kong, Singapore, South Korea	0.43 (0.25–0.76)	
India	0.04 (0.01–0.13)	
Malaysia, Thailand, Vietnam	0.31 (0.16–0.59)	

Variable selection was done by stepwise procedure with the *P* value cutoffs for selection at *P*<0.01 and retention at *P*<0.20. For each outcome, the final model only included the variables shown in this table. DM indicates diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; and UA, unstable angina.

unsurprising factors, such as age ≥65 years (composite cardiovascular events and death) and index event diagnosis of NSTEMI versus STEMI (PoCE and revascularization). Similarly, predictors of lower cardiovascular event rates in patients with DM included in-hospital cardiac catheterization or eGFR ≥30 mL/min per 1.73 m². Other predictors of increased risk of events, such as use of diuretics at discharge, are more difficult to interpret; they may be indicators of patients' overall health status or may simply be attributable to chance in this nonrandomized cohort population or be artefacts of the way some data were collected. The observation that residency in countries/regions other than China was associated with lower risk of cardiovascular events may be interpreted as attributable to variability in access to healthcare facilities (either because of genuine regional variations or because of the specific centers included in the study or issues associated with cost of treatment).

Use of antiplatelet therapy is the fundamental treatment strategy for management of patients with ACS, and guidelines recommend that the majority of patients receive DAPT (aspirin plus a P2Y$_{12}$ inhibitor) for at least 12 months following an ACS event. Individual duration of DAPT, however, depends on a fundamental trade-off between ischemic risk and bleeding risk.[9,10,21,22]

The recommendation in current guidelines is usually for use of DAPT for at least 6 to 12 months, depending on the setting.[9,10,22] Our study shows that, although ACS patients with DM are at increased risk of ischemic events and mortality, the number that receive DAPT at 2-year follow-up is comparable with patients without DM. While a direct association between DAPT use and cardiovascular events cannot be inferred in this observational study, it is likely that patients with DM were sicker than patients without DM. Given that the EPICOR Asia study was performed largely before the availability of the newer oral antiplatelet agents prasugrel and ticagrelor, it is also possible that more intensive long-term antithrombotic therapy may be of benefit in patients with DM, particularly given the nonsignificant difference in major bleeding between patients with DM and patients without DM in this study. However, further large-scale, multicenter, randomized controlled trials are needed to test this hypothesis.

Notably, available guideline recommendations are invariably based on evidence from American and European trials and cannot simply be extrapolated to the Asian population because of ethnic and environmental distinctions. The EPICOR Asia study recruited eligible patients from 219 centers in 8 countries across Asia, while the present analysis mainly focused on the use of antiplatelet agents and outcomes in patients ACS with DM from the EPICOR Asia study. Accordingly, these findings may better guide ACS management in the clinical setting in Asia. A further consideration is that the use of antiplatelet agents reported in EPICOR Asia at 2-year follow-up is relatively high, which does not generally accord with routine practice. Interestingly, this is consistent with observations from the EPICOR (Europe and South America) study, where 60.3% of patients with DM and 55.5% of patients without DM remained on DAPT at 2-year follow-up.[23] The reasons for this also require further investigation.

Study Limitations

Although prespecified, the present research is a retrospective subgroup analysis that is based on the prospective, observational EPICOR Asia study, with inherent limitations of an observational study based on phone call follow-up with subsequent event validation from clinical records. Although this approach included 98% of the original full cohort (all patients with known DM or non-DM status) some reported clinical outcomes were low in absolute number implying underpowering of corresponding comparisons and wider CIs. Hence, some true differences between patients with DM and patients without DM, and some known risk factors, may not have been detected. While underpowering was somewhat larger for the "case-control"

evaluation, in this matched cohort confounding was reduced to facilitate appropriate interpretation of the results. In addition, the DM group was not stratified by type of DM or level of glycemic control, which might have influenced assessment of end point events. As only around 5% to 6% of patients in this study were treated in regional, community, or rural centers, it is also possible that participating sites were weighted toward relatively well-equipped centers. Finally, and as mentioned above, the study was largely carried out before the availability of the more potent oral antiplatelet agents prasugrel and ticagrelor.

Notwithstanding these limitations, our study clearly shows that the rates of all-cause death, MI, and stroke in Asian patients with DM who had an ACS were more frequent compared with those in patients without DM. There was no significant difference between the 2 groups in the rates of overall bleeding, major bleeding, and minor bleeding in the matched cohort. In summary, patients with DM are at increased risk of ischemic events, suggesting an unmet need for improved antithrombotic treatment.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of Propensity Score-Matched Patients.

Parameters	Diabetic		Nondiabetic		Standardized difference
	N	n (%)/Mean (SD)	N	n (%)/Mean (SD)	
Age, years, mean (SD)	3079	61.9 (10.6)	3079	62.4 (11.1)	–0.0463
Age group, years					
≤55		879 (28.6)		821 (26.7)	0.0692
56–64		937 (30.4)		957 (31.1)	
65–74		867 (28.2)		841 (27.3)	
≥75		396 (12.9)		460 (14.9)	
Male	3079	2171 (70.5)	3079	2165 (70.3)	0.0043
BMI, kg/m^2, mean (SD)	2792	25.1 (3.5)	2865	24.9 (3.6)	0.0766
≤25		1463 (52.4)		1518 (53.0)	–0.0117
>25		1329 (47.6)		1347 (47.0)	
Place of residence	3079		3079		
Rural		1012 (32.9)		1094 (35.5)	–0.0562
Metropolitan		2067 (67.1)		1985 (64.5)	
Insurance type	3079		3079		
Government		2055 (66.7)		2264 (73.5)	–0.1487
Private		318 (10.3)		286 (9.3)	0.0349
Employer provided		46 (1.5)		47 (1.5)	–0.0027
Other		116 (3.8)		126 (4.1)	–0.0167
None		592 (19.2)		416 (13.5)	0.1550
Hospital type	3079		3079		
Reg/comm/rural		170 (5.5)		153 (5.0)	0.2065

Non-university general		710 (23.1)		791 (25.7)	
University general		1569 (51.0)		1735 (56.4)	
Other		630 (20.5)		400 (13.0)	
Medical history					
Hypertension	3073	2146 (69.8)	3078	2165 (70.3)	−0.0110
Hypercholesterolemia	2925	739 (25.3)	2998	738 (24.6)	0.0150
Current smoker	2855	794 (27.8)	2904	755 (26.0)	0.0409
Prior PCI	2980	309 (10.4)	3009	281 (9.3)	0.0346
TIA/stroke	2973	185 (6.2)	3004	161 (5.4)	0.0370
PVD	2965	39 (1.3)	3000	31 (1.0)	0.0262
Chronic anemia	2991	34 (1.1)	3018	31 (1.0)	0.0106
Major bleeding	3014	15 (0.5)	3049	13 (0.4)	0.0105
In-hospital events					
Myocardial infarction	3043	140 (4.6)	3059	84 (2.8)	0.0987
Stroke	3053	6 (0.2)	3063	5 (0.2)	0.0079
Heart failure	3051	197 (6.5)	3058	171 (5.6)	0.0364
Severe arrhythmias	3028	139 (4.6)	3051	141 (4.6)	−0.0015
TVR	3079	2006 (65.2)	3079	2053 (66.7)	−0.0322
Bleeding					
Major	3079	14 (0.4)	3079	21 (0.7)	−0.0302
Minor	3079	46 (1.5)	3079	64 (2.1)	−0.0441
Clinical presentation	3079		3079		
STEMI		1427 (46.4)		1460 (47.4)	0.0359
NSTEMI		722 (23.5)		676 (22.0)	

Unstable angina		930 (30.2)		943 (30.6)	
Renal function, eGFR, mL/min/1.73 m^2, mean (SD)	3079	89.5 (35.0)	3079	88.6 (32.7)	0.0259
Renal function group, eGFR, mL/min/1.73 m^2					
<30		83 (2.7)		78 (2.5)	0.0162
30–59		477 (15.5)		464 (15.1)	
60–89		1118 (36.6)		1124 (36.5)	
≥90		1401 (45.5)		1413 (45.9)	
Laboratory tests					
Hemoglobin, g/dL, mean (SD)	2939	13.3 (2.0)	2937	13.5 (1.9)	–0.1108
Peak Cr, mg/dL, mean (SD)	2715	1.1 (0.8)	2788	1.1 (0.8)	0.0295
Positive cardiac markers	3020	2147 (71.1)	3034	2135 (70.4)	0.0159
Medications at discharge					
Beta-blocker	3063	2162 (70.6)	3072	2132 (69.4)	0.0258
Calcium channel blocker	3041	450 (14.8)	3068	445 (14.5)	0.0083
ACEi/ARB	3062	2000 (65.3)	3071	1956 (63.7)	0.0339
Any LLT	3079	2760 (89.6)	3079	2801 (91)	–0.0450
Atorvastatin		1644 (53.4)		1541 (50.1)	0.1379
Fluvastatin		44 (1.4)		48 (1.6)	
Pravastatin		23 90.8)		31 (1.0)	
Rosuvastatin		623 (20.2)		696 (22.6)	
Simvastatin		352 (11.4)		440 (14.3)	
Multiple statins		19 (0.6)		15 (0.5)	
Other LLT only		55 (1.8)		30 (1.0)	

Diuretic	3046	583 (19.1)	3072	393 (12.8)	0.1739
Nitrate	2894	264 (9.1)	2876	253 (8.8)	0.0114
Any PPI	3079	1132 (36.8)	3079	1081 (35.1)	0.0345

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; Cr,

creatinine; eGFR, estimated glomerular filtration rate; LLT, lipid-lowering therapy; NSTEMI, non-ST-segment

elevation myocardial infarction; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; PVD,

peripheral vascular disease; Reg/comm/rural, regional/community/rural; STEMI, ST-segment elevation

myocardial infarction; TIA, transient ischemic attack; TVR, target vessel revascularization.

Table S2. Angiographic and Percutaneous Coronary Intervention (PCI) Results in Diabetic and Nondiabetic Propensity Score-Matched Patients.

Parameters	Diabetic		Nondiabetic		Standardized difference
	N	n (%)	N	n (%)	
Catheterization during the index hospitalization	3036	2460 (81.0)	3050	2431 (79.7)	0.0333
Multivessel disease	3079	1585 (51.5)	3079	1421 (46.2)	0.1067
PCI	2997	1978 (66.0)	3034	2030 (66.9)	−0.0193
Emergency PCI	2997	919 (30.7)	3034	951 (31.3)	−0.0147
Target vessel	2381		2373		
Arterial bypass graft		1 (0)		1 (0)	0.0609
LAD		1339 (56.2)		1367 (57.6)	
LCX		346 (14.5)		299 (12.6)	
Left main		53 (2.2)		62 (2.6)	
RCA		639 (26.8)		641 (27.0)	
Vein bypass graft(s)		3 (0.1)		3 (0.1)	
Number of target vessels	2220		2233		
1		659 (29.7)		819 (36.7)	0.1608
2		669 (30.1)		658 (29.5)	
3		892 (40.2)		756 (33.9)	
Any stent	2997	1941 (64.8)	3034	1989 (65.6)	−0.0166
Number of stents	1941		1989		
1		1061 (54.7)		1195 (60.1)	0.1112
2		558 (28.8)		514 (25.8)	
>2		322 (16.6)		280 (14.1)	

Post-discharge interventions

Cardiac catheterization	3079	249 (8.1)	3079	254 (8.3	−0.0059
Angiography	3079	139 (4.5)	3079	150 (4.9)	−0.0169
Balloon PCI	3079	27 (0.9)	3079	27 (0.9)	0.0000
Any stent	3079	133 (4.3)	3079	135 (4.4)	−0.0032
Bare metal stent	3079	14 (0.5)	3079	16 (0.5)	−0.0093
Drug-eluting stent	3079	119 (3.9)	3079	121 (3.9)	−0.0034

LAD, left anterior descending; LCX, left circumflex, RCA, right coronary artery.

Table S3. Antithrombotic Therapy in Diabetic and Nondiabetic Patients (Overall Cohort).

Parameters	Diabetic		Nondiabetic		P Value
	N	n (%)	N	n (%)	
In-hospital treatment					
Aspirin	3162	2940 (93.0)	9602	8956 (93.3)	0.57
Loading	3162	1166 (36.9)	9602	3834 (39.9)	**<0.01**
Any P2Y$_{12}$ inhibitor	3162	2951 (93.3)	9602	8973 (93.5)	0.81
Clopidogrel	3162	2886 (91.3)	9602	8744 (91.1)	0.72
Loading	3162	1416 (44.8)	9602	4650 (48.4)	**<0.001**
Ticagrelor	3162	2 (0.1)	9602	6 (0.1)	0.99
Prasugrel	3162	88 (2.8)	9602	306 (3.2)	0.26
Ticlopidine	3162	11 (0.4)	9602	23 (0.2)	0.31
Cilostazol	3162	83 (2.6)	9602	166 (1.7)	**<0.01**
LMW heparin	3162	1705 (53.9)	9602	5393 (56.2)	**<0.05**
Fondaparinux	3162	317 (10.0)	9602	1027 (10.7)	0.29
GP IIb/IIIa inhibitor	3162	505 (16.0)	9602	1851 (19.3)	**<0.0001**
Warfarin/NOAC	3162	22 (0.7)	9602	55 (0.6)	0.44
Thrombolytics	3162	180 (5.7)	9602	670 (7.0)	**0.01**
At discharge					
Aspirin	3116	2972 (95.4)	9506	9123 (96.0)	0.15
Any P2Y$_{12}$ inhibitor	3113	2941 (94.5)	9501	8996 (94.7)	0.65
Aspirin alone	3116	167 (5.4)	9506	480 (5.1)	0.50
P2Y$_{12}$ inhibitor alone	3113	125 (4.0)	9501	306 (3.2)	**<0.05**

DAPT	3162	2792 (88.3)	9602	8638 (90.0)	**<0.01**
Cilostazol	3113	79 (2.5)	9501	173 (1.8)	**0.01**
Warfarin/NOAC	3162	30 (1.0)	9602	104 (1.1)	0.52
At 2 years					
Aspirin	2485	2216 (89.2)	7805	6865 (88.0)	0.10
Any $P2Y_{12}$ inhibitor	2483	1650 (66.5)	7802	4816 (61.7)	**<0.0001**
Aspirin alone	2485	713 (28.7)	7806	2472 (31.7)	**<0.01**
$P2Y_{12}$ inhibitor alone	2483	150 (6.0)	7802	397 (5.1)	0.07
DAPT	2485	1495 (60.2)	7805	4378 (56.1)	**<0.001**
Cilostazol	2483	28 (1.1)	7801	96 (1.2)	0.68
Warfarin/NOAC	2490	20 (0.8)	7827	78 (1.0)	0.39

DAPT, dual antiplatelet therapy; GP, glycoprotein; LMW, low molecular weight; NOAC, novel oral anticoagulant.

Results are unadjusted. *P* values from chi-square test or t-test as appropriate.

Table S4. Hazard Ratio (HR) for Clinical Events in Diabetic Versus Nondiabetic

Patients (Overall Cohort).

Parameter	Diabetic		Nondiabetic		HR (95% CI*)	*P* Value
	N	n (%)	N	n (%)		
Composite endpoint (death, MI, and stroke)	3162	390 (12.3)	9602	690 (7.2)	1.77 (1.56, 2.01)	**<0.0001**
All-cause death	3162	236 (7.5)	9602	435 (4.5)	1.68 (1.43, 1.97)	**<0.0001**
MI	3162	146 (4.6)	9602	223 (2.3)	2.04 (1.66, 2.51)	**<0.0001**
Stroke	3162	61 (1.9)	9602	103 (1.1)	1.84 (1.34, 2.53)	**<0.001**
Any revascularization	3162	380 (12.0)	9602	1018 (10.6)	1.17 (1.04, 1.31)	**0.01**
PoCE	3162	689 (21.8)	9602	1556 (16.2)	1.40 (1.28, 1.53)	**<0.0001**
Bleeding	3162	213 (6.7)	9602	562 (5.9)	1.18 (1.01, 1.38)	**<0.05**
Major	3162	10 (0.3)	9602	31 (0.3)	1.00 (0.49, 2.04)	>0.99

Results are unadjusted. *From univariate Cox proportional hazards model.

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; PoCE,

patient-oriented composite endpoint.

Table S5. Independent Predictors of Patient-oriented Composite Endpoint (All-cause Death, Myocardial Infarction (MI), Stroke, and Revascularization), Revascularization, and Major Bleeding Events among Diabetes Mellitus Patients Based on Final Multivariable Cox Proportional Hazards Model*

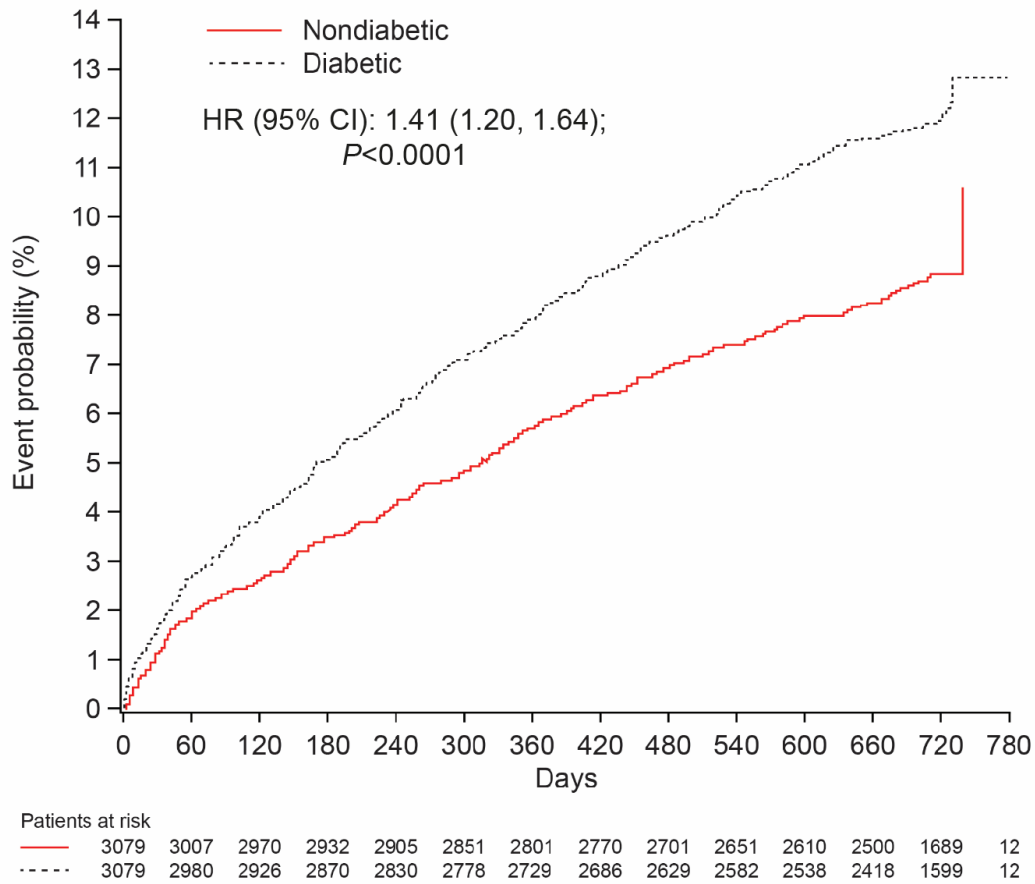| Parameter Predictors	HR (95% CI)	Overall *P* Value
PoCE (all-cause death, MI, stroke and revascularization)		
Cardiac catheterization for index event	0.65 (0.54, 0.77)	**<0.0001**
Country/region, versus China		**<0.0001**
Hong Kong, Singapore, South Korea	1.11 (0.86, 1.42)	
India	0.38 (0.30, 0.48)	
Malaysia, Thailand, Vietnam	1.17 (0.92, 1.47)	
Discharge medications: diuretics	1.47 (1.24, 1.76)	**<0.0001**
eGFR group, ml/min/1.73 m^2, versus <30		**0.0001**
≥30–<60	0.80 (0.58, 1.11)	
≥60–<90	0.67 (0.49, 0.92)	
≥90	0.54 (0.39, 0.74)	
Final diagnosis of index admission event, versus STEMI		**<0.0001**
NSTEMI	1.37 (1.14, 1.64)	
UA	0.80 (0.66, 0.97)	
Revascularization		
Country/region, versus China		**<0.0001**
Hong Kong, Singapore, South Korea	1.34 (0.99, 1.80)	

India	0.19 (0.11, 0.30)	
Malaysia, Thailand, Vietnam	1.34 (0.98, 1.85)	
Final diagnosis of index admission event, versus STEMI		**<0.001**
NSTEMI	1.49 (1.17, 1.89)	
UA	0.88 (0.68, 1.13)	
Discharge medications: H_2-receptor antagonist	1.78 (1.24, 2.55)	**<0.01**
Discharge medications: omeprazole	1.90 (1.41, 2.55)	**<0.0001**
Place of residence: metropolitan	1.65 (1.27, 2.13)	**0.0001**
Major bleeding		
Discharge medications: aldosterone inhibitors	5.95 (1.67, 21.18)	**<0.01**
Discharge medications: NSAIDs	14.92 (3.15, 70.61)	**<0.001**

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NSAIDs, nonsteroidal

anti-inflammatory drugs; NSTEMI, non-ST-segment elevation myocardial infarction; PoCE, patient-oriented

composite endpoint; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.
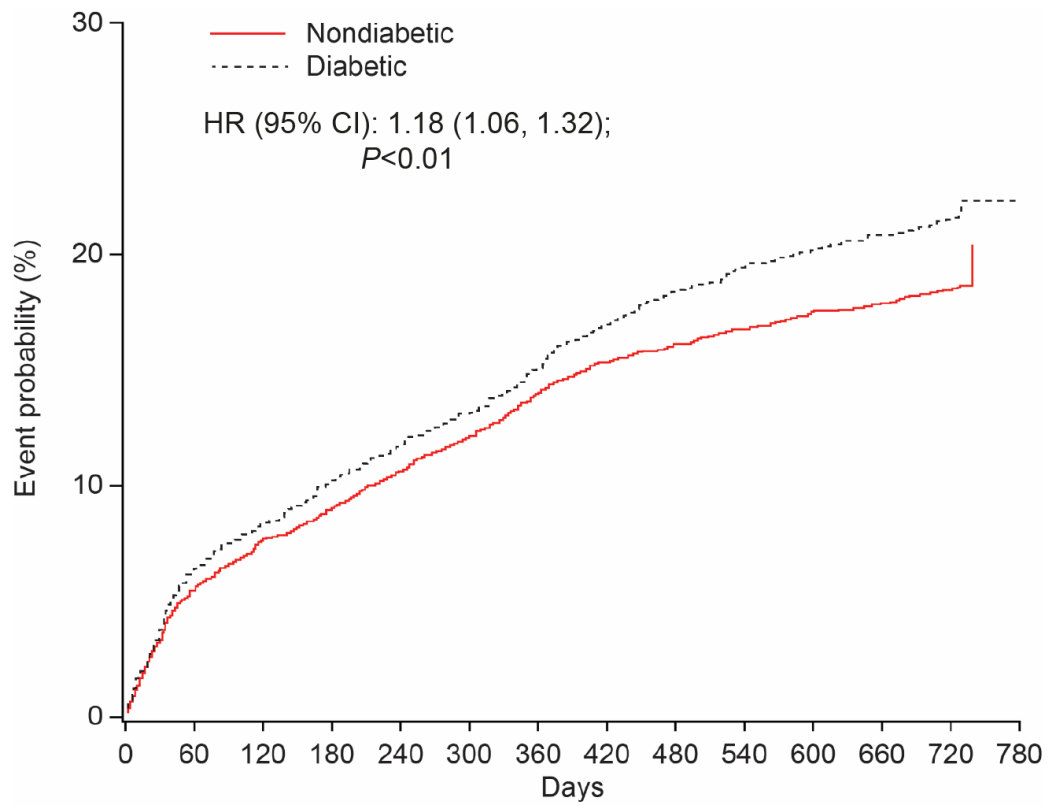

Variable selection was done by step-wise procedure with the *P* value cut-offs for selection at *P*<0.01 and

retention at *P*<0.20. For each outcome, the final model only included the variables shown in this table.

Figure S1. Kaplan–Meier risk curves of (A) composite endpoint, (B) patient-oriented composite endpoint, (C) death, and (D) bleeding, through 2 years in diabetic and nondiabetic patients, for propensity score-matched cohort.
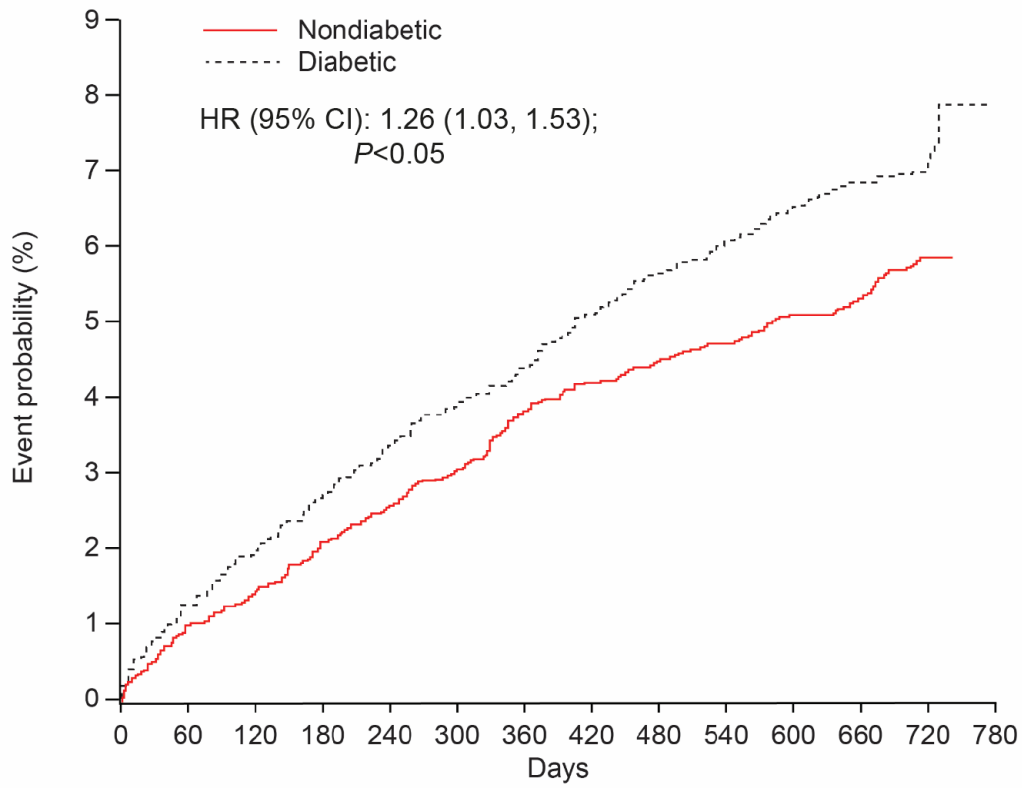
A

B

C

D

Cardiovascular events: composite of all-cause death, myocardial infarction (MI) and ischemic stroke.

Patient-oriented composite endpoint: composite of all-cause death, MI, stroke, and revascularization.

CI, confidence interval; HR, hazard ratio.