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ORIGINAL RESEARCH

On-Treatment Platelet Reactivity and Ischemic Outcomes in Patients With Diabetes Mellitus: Two-Year Results From ADAPT-DES

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BACKGROUND: Diabetes mellitus and high platelet reactivity (HPR) on clopidogrel are both associated with increased risk of ischemic events after percutaneous coronary intervention, but whether the HPR-associated risk of adverse ischemic events differs by diabetes mellitus status is unknown.

METHODS AND RESULTS: ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) was a prospective, multicenter registry of patients treated with coronary drug-eluting stents. HPR was defined as P2Y12 reaction units >208 by the VerifyNow point-of-care assay. Cox multivariable analysis was used to assess whether HPR-associated risk of major adverse cardiac events (MACE; cardiac death, myocardial infarction, or stent thrombosis) varied for patients with insulin-treated diabetes mellitus (ITDM), non–ITDM, and no diabetes mellitus. Diabetes mellitus and HPR were included in an interaction analysis. Of 8582 patients enrolled, 2429 (28.3%) had diabetes mellitus, of whom 998 (41.1%) had ITDM. Mean P2Y12 reaction units were higher in patients with diabetes mellitus versus without diabetes mellitus, and HPR was more frequent in patients with diabetes mellitus. HPR was associated with consistently increased 2-year rates of MACE in patients with and without diabetes mellitus ($P_{interaction}$=0.36). A significant interaction was present between HPR and non–insulin-treated diabetes mellitus versus ITDM for 2-year MACE (adjusted hazard ratio [HR] for non–ITDM, 2.28 [95% CI, 1.39–3.73] versus adjusted HR for ITDM, 1.02 [95% CI, 0.70–1.50]; $P_{interaction}$=0.01).

CONCLUSIONS: HPR was more common in patients with diabetes mellitus and was associated with an increased risk of MACE in both patients with and without diabetes mellitus. In patients with diabetes mellitus, a more pronounced effect of HPR on MACE was present in lower-risk non–ITDM patients than in higher-risk patients with ITDM.

REGISTRATION: URL: https://clinicaltrials.gov/ct2/show/NCT00638794; Unique identifier: NCT00638794. ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents).

Key Words: diabetes mellitus ■ drug-eluting stent ■ percutaneous coronary intervention ■ platelet reactivity

Diabetes mellitus and high platelet reactivity (HPR) on clopidogrel are both independent predictors of thrombotic events after percutaneous coronary intervention (PCI).[1–3] Studies have reported a higher prevalence of HPR in patients with diabetes mellitus, particularly those requiring insulin treatment,[4,5] but

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CLINICAL PERSPECTIVE

What Is New?

- In the prospective ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) registry, including 8582 patients undergoing percutaneous coronary artery intervention, a more pronounced effect of high platelet reactivity on major adverse cardiac events (cardiac death, myocardial infarction, or stent thrombosis) was present in lower-risk patients with non–insulin-treated diabetes mellitus than in patients with higher-risk insulin-treated diabetes mellitus.

What Are the Clinical Implications?

- Future studies should examine whether patients with non–insulin-treated diabetes mellitus, in particular, who tend to be at intermediate risk (lower than insulin-treated diabetes mellitus but higher than patients without diabetes mellitus), may benefit from platelet reactivity testing and more potent P2Y12 inhibition if high platelet reactivity on clopidogrel is found.

Nonstandard Abbreviations and Acronyms

HPR	high platelet activity
ITDM	insulin-treated diabetes mellitus
MACE	major adverse cardiac events

the extent to which HPR contributes to the increased thrombotic risk in diabetes mellitus and whether the HPR-associated thrombotic risk differs for patients with versus without diabetes mellitus is incompletely understood.[6,7] We therefore sought to examine the relationship between diabetes mellitus, HPR, and adverse ischemic events among 8582 patients undergoing PCI with contemporary drug-eluting stents in the prospective ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug Eluting Stents) registry.[3]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study design, procedures, statistical analysis, and primary results of the ADAPT-DES (NCT00638794) registry have been previously reported.[3] To summarize, 8582 consecutive patients who were successfully treated with 1 or more drug-eluting stent at 9 US and 2 German sites and who were loaded with aspirin and clopidogrel were enrolled in the study. The only exclusion criteria were unsuccessful stenting, a major complication occurring either during the procedure or before platelet testing, planned bypass surgery after stenting, or significant anemia preventing accurate measurement of platelet reactivity.

Clopidogrel was given as either (1) a dose of 600 mg at least 6 hours before platelet reactivity testing, (2) a dose of 300 mg at least 12 hours before platelet reactivity testing, or (3) a dose of 75 mg or more for at least 5 days before platelet reactivity testing. Platelet reactivity was assessed after successful PCI and after an adequate wash-in period to ensure full antiplatelet effect using the VerifyNow Aspirin, P2Y12, and IIb/IIIa assays (Accumetrics, San Diego, CA). Following PCI, aspirin was recommended indefinitely, and clopidogrel was recommended for at least 1 year. Decisions on continuation of dual antiplatelet therapy (DAPT) were at the discretion of the primary treating physicians.

Clinical follow-up was completed at 30 days, 1, and 2 years. The rate of loss to follow-up, withdrawal of consent, or refusal of contact was 2.3% at 2 years. The study was approved by the institutional review board at each participating center, and all eligible patients provided written informed consent.

End Points and Definitions

A detailed description of end point definitions has previously been reported.[3] The primary end point was definite or probable stent thrombosis according to the Academic Research Consortium criteria.[8] Death was classified as cardiac or noncardiac as specified by Academic Research Consortium criteria.[8] Myocardial infarction (MI) was defined as the presence of clinical or electrocardiographic changes consistent with MI in the setting of elevated cardiac biomarkers. Major adverse cardiac events (MACE) were defined as the composite of cardiac death, MI, or definite or probable stent thrombosis. An independent clinical events committee adjudicated all deaths, MI, and stent thrombosis events using original source documents. Clinically relevant bleeding was defined as the occurrence of any of the following: a TIMI (Thrombosis in Myocardial Infarction) major or minor bleed, a GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) bleed, an ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial bleed, or any postdischarge bleeding event requiring medical attention.

We defined HPR for this study using previously defined and widely accepted cut points (for the P2Y12 assay: P2Y12 reaction units >208; for the aspirin assay: aspirin reaction units >550). Non–insulin-treated diabetes mellitus (NITDM) included patients on oral hypoglycemic agents but without insulin; patients who stated they had diabetes mellitus but were managed with diet only or no treatment at all were classified as

Table 1. Baseline Characteristics According to Baseline Diabetes Mellitus Status

	No diabetes mellitus, n=6153	Diabetes mellitus			*P* value*	*P* value†
		All diabetes mellitus, n=2429	Insulin treated, n=998	Non–insulin treated, n=1431		
Age, y	64.0 [55.0, 71.0]	65.0 [58.0, 71.0]	65.0 [58.0, 71.0]	65.0 [58.0, 72.0]	0.0003	0.90
Race and ethnicity						
White	90.6% (5574/6153)	83.6% (2031/2429)	83.0% (828/998)	84.1% (1203/1431)	<0.0001	0.47
Non-White	9.4% (579/6153)	16.4% (398/2429)	17.0% (170/998)	15.9% (228/1431)	<0.0001	0.47
Black	4.2% (259/6153)	8.2% (198/2429)	8.7% (87/998)	7.8% (111/1431)	<0.0001	0.39
Hispanic	1.9% (114/6153)	3.3% (79/2429)	3.5% (35/998)	3.1% (44/1431)	<0.0001	0.55
Asian	0.5% (28/6153)	0.9% (23/2429)	0.5% (5/998)	1.3% (18/1431)	0.008	0.058
Native American	0.4% (22/6153)	0.8% (19/2429)	0.9% (9/998)	0.7% (10/1431)	0.01	0.58
Other	2.5% (156/6153)	3.3% (79/2429)	3.4% (34/998)	3.1% (45/1431)	0.07	0.72
Body mass index, kg/m^2	27.9 [25.2, 31.1]	30.5 [27.2, 35.0]	31.2 [27.1, 36.1]	30.1 [27.3, 34.1]	<0.0001	0.0009
History of PAD	8.5% (522/6153)	14.6% (354/2429)	18.8% (188/998)	11.6% (166/1431)	<0.0001	<0.0001
History of CHF	6.5% (403/6153)	12.2% (296/2429)	17.5% (175/998)	8.5% (121/1431)	<0.0001	<0.0001
Prior myocardial infarction	23.4% (1437/6153)	29.9% (727/2429)	32.2% (321/998)	28.4% (406/1431)	<0.0001	0.04
Prior CABG	14.5% (891/6153)	23.8% (577/2429)	27.2% (271/998)	21.4% (306/1431)	<0.0001	0.001
Prior PCI	39.8% (2451/6153)	50.5% (1227/2429)	53.9% (538/998)	48.1% (689/1431)	<0.0001	0.005
History of renal insufficiency	5.5% (336/6153)	13.3% (324/2429)	20.2% (202/998)	8.5% (122/1431)	<0.0001	<0.0001
History of dialysis	1.2% (74/6153)	2.6% (64/2429)	4.4% (44/998)	1.4% (20/1431)	<0.0001	<0.0001
Hypertension	75.1% (4621/6153)	91.1% (2212/2429)	91.4% (912/998)	90.8% (1300/1431)	<0.0001	0.65
Hyperlipidemia	70.0% (4309/6153)	85.3% (2071/2429)	86.5% (863/998)	84.4% (1208/1431)	<0.0001	0.16
Cigarette smoking	57.2% (3521/6153)	53.8% (1308/2429)	49.6% (495/998)	56.8% (813/1431)	0.005	0.0004
Current, within 1 mo	25.1% (1546/6153)	16.2% (394/2429)	14.2% (142/998)	17.6% (252/1431)	<0.0001	0.03
Former, >1 mo	32.1% (1975/6153)	37.6% (914/2429)	35.4% (353/998)	39.2% (561/1431)	<0.0001	0.055
Clinical presentation						
Stable angina	28.0% (1723/6153)	31.9% (776/2429)	32.8% (327/998)	31.4% (449/1431)	0.0003	0.47
Asymptomatic CAD	11.6% (712/6153)	14.5% (352/2429)	16.4% (164/998)	13.1% (188/1431)	0.0002	0.02
Acute coronary syndromes	53.6% (3296/6153)	46.8% (1137/2429)	46.3% (462/998)	47.2% (675/1431)	<0.0001	0.67
Unstable angina	27.3% (1680/6153)	28.4% (690/2429)	26.5% (264/998)	29.8% (426/1431)	0.30	0.07
Non-STEMI	14.8% (908/6153)	14.0% (341/2429)	16.1% (161/998)	12.6% (180/1431)	0.40	0.01
STEMI	11.5% (708/6153)	4.4% (106/2429)	3.7% (37/998)	4.8% (69/1431)	<0.0001	0.19
NYHA class II–IV	65.8% (4046/6153)	72.0% (1750/2429)	72.9% (728/998)	71.4% (1022/1431)	<0.0001	0.41
Extent of CAD						
1-vessel disease	40.4% (2484/6153)	32.9% (799/2429)	28.3% (282/998)	36.1% (517/1431)	<0.0001	<0.0001
2-vessel disease	33.2% (2044/6153)	32.6% (791/2429)	32.6% (325/998)	32.6% (466/1431)	0.56	1.00
3-vessel disease	26.4% (1625/6153)	34.5% (839/2429)	39.2% (391/998)	31.3% (448/1431)	<0.0001	<0.0001
Left main >50%	2.8% (170/6153)	3.6% (87/2429)	3.9% (39/998)	3.4% (48/1431)	0.04	0.47
LVEF <40%	28.7% (1766/6153)	33.3% (810/2429)	38.0% (379/998)	30.1% (431/1431)	<0.0001	<0.0001
Creatinine clearance	15.6% (952/6117)	18.5% (450/2426)	22.9% (228/996)	15.5% (222/1430)	0.0008	<0.0001
Hemoglobin <10 g/dL	0.4% (27/6121)	0.5% (11/2427)	0.6% (6/996)	0.3% (5/1431)	0.94	0.36
Hemoglobin <12 g/dL	7.6% (465/6121)	16.8% (407/2427)	21.7% (216/996)	13.3% (191/1431)	<0.0001	<0.0001
WBC count, K/mL	7.40 (6.10, 9.10)	7.50 (6.20, 9.10)	7.67 (6.30, 9.20)	7.40 (6.10, 9.00)	0.18	0.03
PRU	175.7±94.6	219.1±95.2	220.7±97.2	218.0±93.8	<0.0001	0.49
>208	37.2% (2259/6071)	56.8% (1350/2377)	57.4% (562/979)	56.4% (788/1398)	<0.0001	0.61

(*Continued*)

Table 1. Continued

	No diabetes mellitus, n=6153	Diabetes mellitus			*P* value*	*P* value†
		All diabetes mellitus, n=2429	Insulin treated, n=998	Non–insulin treated, n=1431		
ARU	417.7±55.1	423.1±55.6	425.2±57.3	421.6±54.5	<0.0001	0.12
≥550	5.5% (336/6118)	5.9% (142/2408)	6.9% (68/988)	5.2% (74/1420)	0.46	0.09
Dual resistance, ARU ≥550 and PRU >208	2.1% (127/6040)	3.6% (86/2361)	4.3% (42/971)	3.2% (44/1390)	<0.0001	0.14
Platelet count, $\times 10^3$/mm^3	219.0 [184.0, 260.5]	217.0 (181.0, 265.0)	216.0 (178.0, 268.0)	218.0 (183.0, 264.0)	0.39	0.94

Continuous data are expressed as median [Q1, Q3] or mean±SD. ARU indicates aspirin reaction units; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PRU, P2Y12 reaction units; STEMI, ST-segment–elevation myocardial infarction; and WBC, white blood cell.
*No diabetes mellitus vs diabetes mellitus.
†Insulin treated vs non–insulin treated.

nondiabetes mellitus. In a sensitivity analysis, patients with diabetes mellitus on diet only or no treatment were classified as NITDM.

Statistical Analysis

Statistical comparisons of categorical variables were performed with the χ^2 or Fisher exact test and reported as percentages. Continuous variables were compared using the Student *t* test and are presented as mean±SD. Time to first event data were compared with log-rank test and are presented as Kaplan-Meier estimates. The adjusted association between HPR and diabetes mellitus was assessed by a multivariable Cox model including clopidogrel usage as a time-varying covariate. Covariates of interest and those historically related to adverse ischemic outcomes after PCI were included in the multivariable model: age, sex, body mass index, hypertension, hyperlipidemia, current smoker, renal insufficiency, prior coronary artery bypass grafting, prior PCI, anemia, white blood count, platelet count, aspirin reaction units, ST-segment–elevation MI or

Table 2. Procedural Characteristics According to Baseline Diabetes Mellitus Status

	No diabetes mellitus, n=6153	Diabetes mellitus			*P* value*	*P* value†
		All diabetes mellitus, n=2429	Insulin treated, n=998	Non–insulin treated, n=1431		
Vascular access						
Femoral	95.7% (5889/6153)	94.7% (2300/2429)	93.3% (931/998)	95.7% (1369/1431)	0.04	0.01
Brachial	0.2% (13/6153)	0.2% (5/2429)	0.3% (3/998)	0.1% (2/1431)	0.96	0.39
Radial	4.1% (251/6153)	5.1% (124/2429)	6.4% (64/998)	4.2% (60/1431)	0.04	0.01
No. of vessels treated per patient	1.18±0.42	1.18±0.43	1.19±0.44	1.18±0.43	0.36	0.45
Target lesion location						
Left anterior descending	46.9% (2883/6153)	43.9% (1066/2429)	45.9% (458/998)	42.5% (608/1431)	0.01	0.10
Right	37.1% (2281/6153)	37.3% (905/2429)	35.2% (351/998)	38.7% (554/1431)	0.87	0.08
Left circumflex	30.0% (1843/6153)	33.4% (811/2429)	33.5% (334/998)	33.3% (477/1431)	0.002	0.95
Left main	3.6% (224/6153)	3.9% (95/2429)	4.7% (47/998)	3.4% (48/1431)	0.55	0.09
Surgical graft	4.1% (254/6153)	7.2% (175/2429)	7.5% (75/998)	7.0% (100/1431)	<0.0001	0.62
No. of lesions treated per patient	1.50±0.78	1.53±0.80	1.53±0.79	1.54±0.81	0.06	0.70
No. of stents implanted per patient	1.71±1.01	1.74±1.03	1.76±1.04	1.73±1.02	0.15	0.56
Total stent length, mm	24.0 (18.0, 41.0)	26.0 (16.0, 43.0)	26.5 (16.0, 43.0)	24.0 (18.0, 42.0)	0.53	0.71
Any calcified lesion	30.2% (1860/6153)	32.3% (784/2429)	36.6% (365/998)	29.3% (419/1431)	0.06	0.0002
Any acute thrombosis	2.2% (133/6153)	0.6% (15/2429)	0.8% (8/998)	0.5% (7/1431)	<0.0001	0.33
Any in-stent restenosis	9.7% (597/6153)	12.2% (297/2429)	13.7% (137/998)	11.2% (160/1431)	0.0006	0.059
Any graft lesion	4.1% (254/6153)	7.2% (175/2429)	7.5% (75/998)	7.0% (100/1431)	<0.0001	0.62

Values are percent (n/N) or mean±SD.
*No diabetes mellitus vs diabetes mellitus.
†Insulin-treated diabetes mellitus vs non–insulin-treated diabetes mellitus.

Table 3. Antiplatelet Therapy According to Baseline Diabetes Mellitus Status

	No diabetes mellitus, n=6153	Diabetes mellitus			*P* value*	*P* value†
		All diabetes mellitus, n=2429	Insulin treated, n=998	Non–insulin treated, n=1431		
Aspirin						
Before hospital admission	81.1% (4991/6153)	84.4% (2050/2429)	85.6% (854/998)	83.6% (1196/1431)	0.0004	0.18
Discharge	99.3% (6103/6148)	99.1% (2405/2428)	98.7% (985/998)	99.3% (1420/1430)	0.31	0.13
1 y	87.5% (5386/6153)	86.0% (2090/2429)	85.4% (852/998)	86.5% (1238/1431)	0.06	0.42
2 y	81.0% (4986/6153)	79.1% (1922/2429)	79.0% (788/998)	79.2% (1134/1431)	0.04	0.86
Dual antiplatelet therapy						
Before hospital admission	39.1% (2408/6153)	42.4% (1029/2429)	44.0% (439/998)	41.2% (590/1431)	0.006	0.18
Discharge	99.0% (6087/6148)	98.6% (2395/2428)	98.2% (980/998)	99.0% (1415/1430)	0.14	0.11
1 y	69.6% (4281/6153)	70.0% (1700/2429)	69.5% (694/998)	70.3% (1006/1431)	0.71	0.69
2 y	42.5% (2615/6153)	47.8% (1160/2429)	47.5% (474/998)	47.9% (686/1431)	<0.0001	0.83
Clopidogrel						
Before hospital admission	41.7% (2565/6153)	45.9% (1115/2429)	47.6% (475/998)	44.7% (640/1431)	0.0004	0.16
Discharge	99.7% (6130/6148)	99.5% (2417/2428)	99.5% (993/998)	99.6% (1424/1430)	0.25	0.77
1 y	72.9% (4486/6153)	73.9% (1794/2429)	73.7% (736/998)	73.9% (1058/1431)	0.37	0.92
2 y	46.1% (2834/6153)	52.3% (1270/2429)	52.5% (524/998)	52.1% (746/1431)	<0.0001	0.86

*No diabetes mellitus vs diabetes mellitus.
†Insulin treated vs non–insulin treated.

non–ST-segment–elevation MI as clinical presentation, degree of coronary artery disease (single vessel versus multivessel), small vessel disease, target vessel location in the left anterior descending coronary artery, peripheral artery disease, and total stent length. Whether having versus not having diabetes mellitus moderated the effects of platelet reactivity on MACE risk was assessed by including interaction terms between diabetes mellitus status and HPR in the multivariable models. Whether type of diabetes mellitus treatment (insulin-treated diabetes mellitus [ITDM] versus NITDM) moderated the effects of platelet reactivity on MACE risk was assessed by including interaction terms between diabetes mellitus treatment and HPR in the multivariable models fit in the subset of patients with diabetes mellitus. Whether the effect of HPR for patients with diabetes mellitus varied over time was assessed by including interaction terms between HPR and time from PCI in 2 separate models in patients with ITDM and NITDM. All *P* values were 2-tailed, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

In ADAPT-DES, 2429 out of 8582 patients (28.3%) had diabetes mellitus, of whom 998 (41.1%) had ITDM. Compared with subjects without diabetes mellitus, those with diabetes mellitus were more likely to have other cardiovascular risk factors (Table 1) and more extensive coronary artery disease (Table 2). Medication use from admission through 2 years of follow-up is shown in Table 3 and Table S1. Patients with diabetes mellitus were more likely to continue DAPT up to 2 years (Table 3). Patients with diabetes mellitus had significantly higher mean P2Y12 reaction units than patients without diabetes mellitus (219.1±95.2 versus 175.7±94.6, $P<0.0001$; Table 1), and the frequency of HPR was higher in patients with diabetes mellitus compared with those without diabetes mellitus (56.8% [1350/2377] versus 37.2% [2259/6071], $P<0.0001$; Table 1). Among patients with diabetes mellitus, the mean P2Y12 reaction unit levels and incidence of HPR were similar in patients with ITDM and NITDM (Table 1).

Clinical Outcomes

Patients with diabetes mellitus had a significantly higher unadjusted risk for MACE as well as other adverse clinical outcomes at 2 years compared with those without diabetes mellitus (Table S2). The impact of HPR on clinical outcomes in patients with and without diabetes mellitus is shown in Table 4 and Figures 1 and 2. HPR was associated with higher unadjusted and adjusted 2-year risks of MACE for patients with and without diabetes mellitus without significant interaction between diabetes mellitus status and HPR (Table 4,

Table 4. Adjusted Association Between High Platelet Reactivity on Clopidogrel and the Risk of Adverse Events at 2-Year Follow-Up According to Diabetes Mellitus Status

	No diabetes mellitus	Diabetes mellitus	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	$P_{interaction}$
Major adverse cardiac events	1.21 (0.96–1.52)	1.44 (1.07–1.93)	0.36
Death	1.30 (0.96–1.75)	1.14 (0.79–1.66)	0.61
Cardiac death	1.11 (0.73–1.69)	1.33 (0.80–2.21)	0.59
Myocardial infarction	1.21 (0.93–1.59)	1.54 (1.09–2.19)	0.28
Stent thrombosis	1.42 (0.97–2.08)	1.47 (0.92–2.36)	0.91
Myocardial infarction or stent thrombosis	1.21 (0.96–1.54)	1.50 (1.11–2.04)	0.27
Ischemia-driven target vessel revascularization	1.13 (0.94–1.36)	1.06 (0.83–1.35)	0.68
Clinically relevant bleeding	0.84 (0.70–1.02)	0.83 (0.64–1.09)	0.94

The multivariable model also included age, sex, body mass index, hypertension, hyperlipidemia, current smoker, renal insufficiency, previous coronary artery bypass grafting, previous percutaneous coronary intervention, anemia, white blood counts, platelet counts, aspirin reaction units, ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction as clinical presentation, degree of coronary artery disease (single vessel vs multivessel), small vessel disease, target vessel location in the left anterior descending coronary artery, peripheral artery disease, and total stent length. HR indicates hazard ratio.

Figure 2).Among patients with diabetes mellitus, those with ITDM had higher rates of MACE compared with those with NITDM (Table S2). These results were similar when classifying patients with diabetes mellitus on diet only or no treatment as NITDM rather than nondiabetes mellitus (Tables S3 and S4). A significant interaction between insulin treatment (ITDM versus NITDM) and HPR on the risk of 2-year MACE, death, and stent thrombosis was noted such that the effect of HPR on these outcomes was stronger in NITDM than in ITDM (Table 5, Figures 1 and 3). No such interactions were significant for the outcomes of MI or bleeding. When lower-risk patients with diabetes mellitus treated with diet only or no treatment were included in the NITDM group, the interaction between HPR and diabetes mellitus type (ITDM versus NITDM) versus 2-year MACE was borderline ($P_{interaction}$=0.09), but significant interactions were present for the risks of death and ischemia-driven target vessel revascularization (Table S5). The adjusted effects of HPR on outcomes of patients with ITDM versus NITDM did not vary significantly over time during the 2-year follow-up duration either in the primary analysis (Table S6) or when patients with diabetes mellitus on diet only or no treatment were classified as NITDM (Table S7).

DISCUSSION

The main findings of this study of 8582 all-comer patients undergoing successful PCI with drug-eluting stents are as follows: (1) Mean P2Y12 reaction units

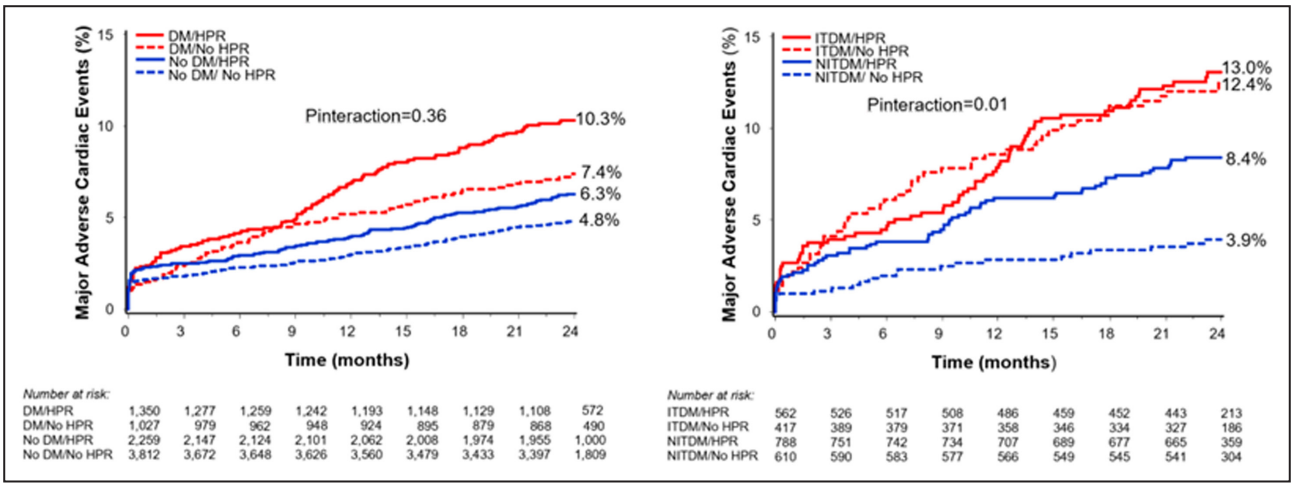

Figure 1. Major adverse cardiac events during 2-year follow-up after primary percutaneous coronary intervention according to platelet reactivity on clopidogrel and diabetes mellitus status.
DM indicates diabetes mellitus; HPR, high platelet reactivity; ITDM, insulin-treated diabetes mellitus; and NITDM, non–insulin-treated diabetes mellitus.

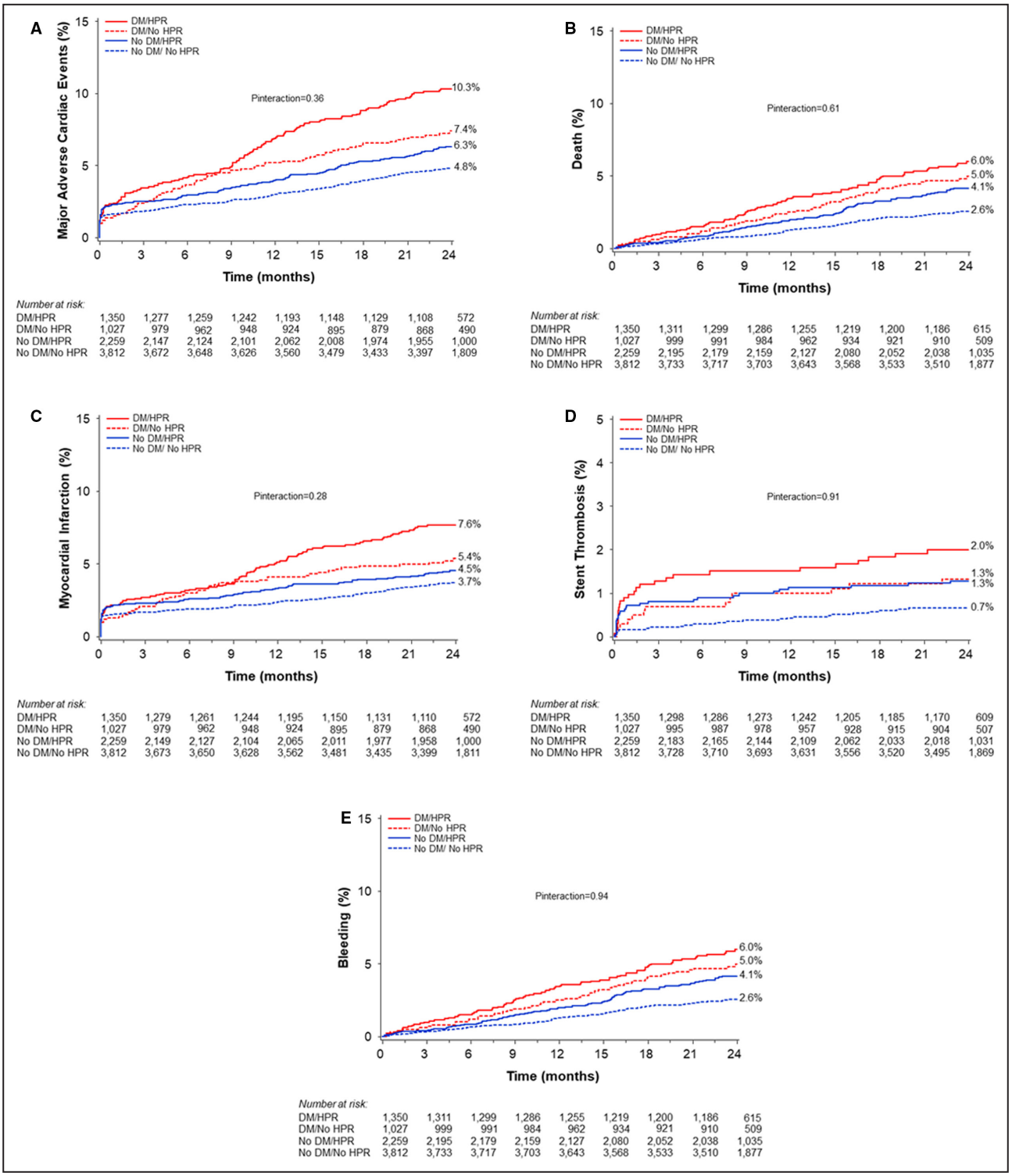

Figure 2. Kaplan-Meier time to first rates in patients with vs without diabetes mellitus according to platelet reactivity on clopidogrel.

A, Major adverse cardiac events. **B**, Death. **C**, Myocardial infarction. **D**, Stent thrombosis. **E**, Clinically relevant bleeding. DM indicates diabetes mellitus; and HPR, high platelet reactivity.

were higher and HPR was more frequent in patients with compared with those without diabetes mellitus. (2) Diabetes mellitus and HPR were both independently associated with increased 2-year MACE risk. (3) The association between HPR and the 2-year risk of MACE was similar for patients with and without diabetes

Table 5. Adjusted Association Between High Platelet Reactivity on Clopidogrel and the Risk of Adverse Events At 2-Year Follow-Up Among Patients With Diabetes Mellitus According to Insulin Treatment Status

	Non–insulin-treated diabetes mellitus	Insulin-treated diabetes mellitus	
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	$P_{interaction}$
Major adverse cardiac events	2.28 (1.39–3.73)	1.02 (0.70–1.50)	0.01
Death	2.28 (1.19–4.36)	0.75 (0.46–1.22)	0.007
Cardiac death	3.08 (1.22–7.76)	0.80 (0.41–1.55)	0.02
Myocardial infarction	2.15 (1.22–3.80)	1.18 (0.75–1.85)	0.10
Stent thrombosis	2.75 (1.23–6.15)	0.97 (0.52–1.81)	0.04
Ischemia-driven target vessel revascularization	1.24 (0.87–1.75)	0.92 (0.66–1.28)	0.22
Clinically relevant bleeding	1.09 (0.75–1.59)	0.67 (0.45–0.99)	0.08

The multivariable model also included age, sex, body mass index, hypertension, hyperlipidemia, current smoker, renal insufficiency, prior coronary artery bypass grafting, prior percutaneous coronary intervention, anemia, white blood count, platelet count, aspirin reaction units, ST-segment–elevation myocardial infarction or non–ST-segment–elevation myocardial infarction as clinical presentation, degree of coronary artery disease single vessel vs multivessel, small vessel disease, target vessel location in the left anterior descending coronary artery, peripheral arterial disease, and total stent length. HR indicates hazard ratio.

mellitus. (4) Among patients with diabetes mellitus, however, a more pronounced effect of HPR on MACE was present in lower-risk patients with NITDM than in higher-risk patients with ITDM .

The higher 2-year rate of ischemic events in patients with versus without diabetes mellitus in the present large-scale all-comers PCI study, with the highest risk among patients with ITDM, is consistent with previous observations.[4,9,10] The increased risk of ischemic events in patients with HPR and the higher prevalence of HPR among patients with diabetes mellitus in our study are also consistent with prior reports.[4,9,10] The present study is novel, however, in demonstrating a stronger effect of HPR on the risk of ischemic outcomes in lower-risk patients with NITDM compared with higher-risk patients with ITDM, a finding that has not previously been reported.

In previous studies of patients with diabetes mellitus treated with DAPT,[11–13] poor glycemic control has been associated with higher platelet reactivity, leading to speculation that patients with diabetes mellitus (especially ITDM) may require intensified antiplatelet strategies. However, previous randomized trials such as PLATO (Platelet Inhibition and Patient Outcomes), TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis In Myocardial Infarction), and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction) have not shown a greater relative clinical benefit from intensified DAPT with ticagrelor or prasugrel compared with clopidogrel in patients with diabetes mellitus, nor were differences apparent in the relative benefits from more potent DAPT among diabetics with or without insulin treatment.[6,7,14] The less pronounced association between HPR and clinical outcomes for patients with ITDM, as observed in the present study, may partly explain why higher-risk patients with ITDM have not particularly benefitted from intensified DAPT despite having a considerably higher prevalence of HPR. Our data suggest that the mechanisms underlying the increased risk of late events in patients with ITDM may be less platelet dependent than in patients with NITDM. In addition, although the present study did not address detailed disease mechanisms, patients on insulin treatment have longer exposure to hyperglycemia, insulin resistance, endothelial dysfunction, impaired fibrinolysis, and hypercoagulability, all of which contribute to a complex prothrombotic disease state in which the relative contribution of HPR to the overall thrombotic risk may be less prominent.[15,16]

Platelet reactivity, as measured by the VerifyNow assay, has also been reported to be more variable over time in patients with ITDM compared with NITDM or no diabetes mellitus.[17] Post-PCI HPR could therefore be less representative of longer-term platelet reactivity in patients with ITDM; however, we did not detect a time-dependent association between HPR and MACE risk in patients with ITDM.

Limitations

First, although we controlled for several important covariates in multivariable analysis, we cannot exclude an effect of residual and unmeasured confounders on our results. Second, newer non–platelet targeted therapies for diabetes mellitus have been introduced since the performance of this study. In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, the factor Xa inhibitor (rivaroxaban), which has been shown to improve endothelial function in mouse models, reduced

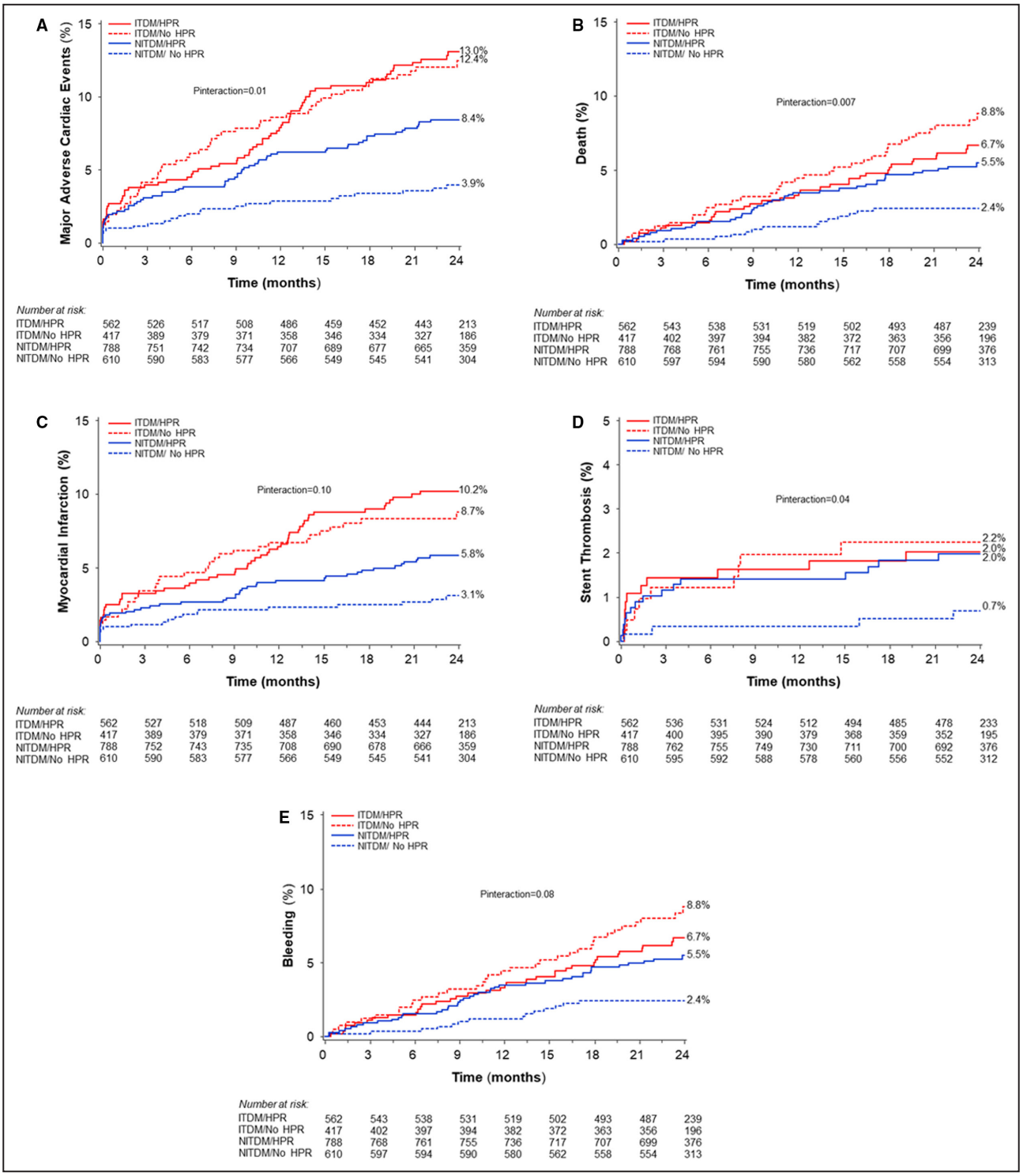

Figure 3. Kaplan-Meier time to first rates in patients with insulin-treated diabetes mellitus vs non–insulin-treated diabetes mellitus according to platelet reactivity on clopidogrel.
A, Major adverse cardiac events. **B**, Death. **C**, Myocardial infarction. **D**, Stent thrombosis. **E**, Clinically relevant bleeding. HPR indicates high platelet reactivity; ITDM, insulin-treated diabetes mellitus; and NITDM, non–insulin-treated diabetes mellitus.

cardiovascular events in patients with diabetes mellitus when coupled with low-dose aspirin.[18] The Fourier trial demonstrated improved cardiovascular outcomes in patients with diabetes mellitus on statin therapy who received the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab.[19] Cardiovascular event rates in patients with diabetes mellitus have decreased with SGLT2 (sodium-glucose cotransporter

2) inhibitors and GLP-1 (glucagon-like peptide-1) agonists.[20] Although we would not expect these agents to modify the relative outcomes between HPR and cardiovascular events in patients with versus without diabetes mellitus, their impact on reclassifying patients as NITDM versus ITDM and their effect on the relationship between HPR and insulin versus noninsulin treatment observed in the present study in patients with diabetes mellitus is uncertain. Third, testing for platelet reactivity was only conducted at a single time point.[17] Although the effect of post-PCI HPR on MACE risk in patients with ITDM was consistent over the course of the study, serial platelet reactivity evaluation may have provided further insight into the association between ITDM, platelet reactivity, and MACE risk. Fourth, diabetes mellitus status was only assessed at baseline and may have changed during follow-up, an effect not accounted for in our analysis.[21] Finally, the decision to continue or discontinue clopidogrel after the first year was made at the discretion of the patient's physician and possibly influenced by the patient, a bias that might have affected event rates.

CONCLUSIONS

In the present analysis from the large-scale, all-comers ADAPT-DES registry, HPR was more frequent in patients with diabetes mellitus, and both diabetes mellitus and HPR were independent predictors of increased 2-year MACE risk after successful PCI. The relative effect of HPR on the 2-year risk of MACE was consistent for patients with and without diabetes mellitus. Among patients with diabetes mellitus, the association between HPR and the 2-year risk of MACE was more pronounced among lower-risk patients with NITDM than in higher-risk patients with ITDM. On the basis of these results, future studies should examine whether non–insulin-treated patients with diabetes mellitus, in particular, who tend to be at intermediate risk (lower than insulin-treated diabetes mellitus but higher than nondiabetes mellitus) may benefit from platelet reactivity testing and more potent P2Y12 inhibition if HPR is found.

ARTICLE INFORMATION

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Supplemental Material

Table S1–S7

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SUPPLEMENTAL MATERIAL

Table S1. Medication Use from Hospital Discharge Through 2 Years According to Diabetes Status

	No diabetes (n=6153)	All diabetes (n=2429)	Insulin-treated diabetes (n=998)	Non-insulin-treated diabetes (n=1431)	p Value*	p Value†
Statin						
Pre-hospital admission	58.6% (3605/6153)	74.8% (1817/2429)	76.1% (759/998)	73.9% (1058/1431)	<0.0001	0.24
Discharge	92.5% (5690/6152)	90.6% (2201/2429)	89.9% (897/998)	91.1% (1304/1431)	0.004	0.30
1 year	87.1% (5199/5970)	84.5% (1977/2340)	83.8% (802/957)	85.0% (1175/1383)	0.002	0.45
2 years	84.4% (4816/5705)	83.0% (1816/2188)	82.4% (725/880)	83.4% (1091/1308)	0.12	0.53
Proton pump inhibitor						
Pre-hospital admission	24.0% (1475/6153)	27.5% (668/2429)	29.7% (296/998)	26.0% (372/1431)	0.0007	0.05
Discharge	25.4% (1563/6152)	24.7% (599/2429)	27.3% (272/998)	22.9% (327/1431)	0.47	0.01
1 year	22.1% (1317/5968)	24.7% (577/2339)	26.9% (257/956)	23.1% (320/1383)	0.01	0.04
2 years	21.7% (1238/5704)	24.6% (538/2188)	27.5% (242/880)	22.6% (296/1308)	0.006	0.009
ACE inhibitor or ARB						
Pre-hospital admission	50.3% (3098/6153)	73.0% (1772/2429)	76.5% (763/998)	70.5% (1009/1431)	<0.0001	0.001
Discharge	69.9% (4298/6152)	81.2% (1973/2429)	82.3% (821/998)	80.5% (1152/1431)	<0.0001	0.27
1 year	65.8% (3929/5970)	73.5% (1720/2340)	74.3% (711/957)	73.0% (1009/1383)	<0.0001	0.47
2 years	64.1% (3656/5706)	71.7% (1569/2188)	71.4% (628/880)	71.9% (941/1308)	<0.0001	0.77
Beta blockers						
Pre-hospital admission	57.4% (3534/6153)	69.5% (1688/2429)	70.5% (704/998)	68.8% (984/1431)	<0.0001	0.35
Discharge	83.2% (5121/6152)	83.3% (2024/2429)	83.3% (831/998)	83.4% (1193/1431)	0.92	0.95
1 year	78.1% (4662/5968)	79.1% (1850/2339)	81.1% (775/956)	77.7% (1075/1383)	0.33	0.051
2 years	74.8% (4270/5705)	77.1% (1688/2188)	79.0% (695/880)	75.9% (993/1308)	0.03	0.09
Calcium blockers						
Pre-hospital admission	18.5% (1139/6153)	28.6% (695/2429)	30.4% (303/998)	27.4% (392/1431)	<0.0001	0.11
Discharge	17.6% (1083/6152)	28.3% (687/2429)	29.9% (298/998)	27.2% (389/1431)	<0.0001	0.15
1 year	17.9% (1066/5968)	25.9% (605/2339)	26.7% (255/956)	25.3% (350/1383)	<0.0001	0.46
2 years	19.3% (1102/5706)	25.9% (567/2188)	26.5% (233/880)	25.5% (334/1308)	<0.0001	0.62
Diuretics						
Pre-hospital admission	28.3% (1740/6153)	45.7% (1110/2429)	51.9% (518/998)	41.4% (592/1431)	<0.0001	<0.0001
Discharge	32.1% (1977/6152)	47.7% (1159/2429)	53.3% (532/998)	43.8% (627/1431)	<0.0001	<0.0001
1 year	29.0% (1729/5968)	43.2% (1010/2339)	50.8% (486/956)	37.9% (524/1383)	<0.0001	<0.0001
2 years	28.8% (1641/5706)	42.8% (936/2187)	49.3% (434/880)	38.4% (502/1307)	<0.0001	<0.0001
Warfarin						
Pre-hospital admission	4.1% (254/6153)	5.8% (140/2429)	7.1% (71/998)	4.8% (69/1431)	0.001	0.02
Discharge	5.2% (320/6152)	6.3% (154/2429)	7.8% (78/998)	5.3% (76/1431)	0.04	0.01
1 year	5.0% (297/5968)	7.7% (181/2339)	8.9% (85/956)	6.9% (96/1383)	<0.0001	0.08
2 years	5.6% (319/5706)	9.0% (197/2187)	11.0% (97/880)	7.7% (100/1307)	<0.0001	0.007

*No diabetes versus diabetes; †insulin-treated versus non-insulin-treated diabetes. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Table S2. Unadjusted 2-Year Outcomes According to Diabetes Status

	No diabetes (n=6153)	All diabetes (n=2429)	Insulin-treated diabetes (n=998)	Non-insulin-treated diabetes (n=1431)	p Value*	p Value†
Major adverse cardiac events	5.4% (318)	9.2% (213)	13.2% (124)	6.5% (89)	<0.0001	<0.0001
Stent thrombosis	0.9% (49)	1.7% (40)	2.2% (21)	1.4% (19)	0.03	0.41
Ischemia-driven target vessel revascularization	8.6% (498)	12.9% (291)	16.7% (151)	10.3% (140)	<0.0001	<0.0001
Clinically relevant bleeding	8.6% (509)	10.1% (230)	11.4% (106)	9.1% (124)	0.054	0.08
Death	3.2% (186)	5.7% (130)	8.0% (74)	4.1% (56)	<0.0001	0.0001
Cardiovascular	1.9% (110)	3.9% (87)	5.1% (47)	3.0% (40)	<0.0001	0.01
Cardiac	1.6% (96)	3.4% (77)	4.7% (43)	2.5% (34)	<0.0001	0.006
Myocardial infarction	4.0% (237)	6.7% (154)	9.6% (90)	4.7% (64)	<0.0001	<0.0001

*No diabetes versus diabetes; †insulin-treated versus non-insulin-treated diabetes.

Table S3. Unadjusted 2-Year Outcomes According to Diabetes Status*

	No diabetes (n=5799)	Insulin-treated diabetes (n=998)	Non-insulin-treated diabetes (n=1785)*	Overall p Value
Major adverse cardiac events	5.2% (289)	13.2% (124)	6.8% (118)	<0.0001
Stent thrombosis	0.9% (48)	2.2% (21)	1.3% (23)	0.0007
Ischemia-driven target vessel revascularization	8.5% (468)	16.7% (151)	10.0% (170)	<0.0001
Clinically relevant bleeding	8.7% (484)	11.4% (106)	8.8% (149)	0.04
Death	4.1% (56)	5.7% (130)	8.0% (74)	<0.0001
Cardiovascular	3.1% (170)	8.0% (74)	4.2% (72)	<0.0001
Cardiac	1.8% (98)	5.1% (47)	3.1% (52)	<0.0001
Myocardial infarction	3.9% (218)	9.6% (90)	4.9% (83)	<0.0001

*In this sensitivity analysis, the category "Non-insulin-treated diabetes" included patients with diabetes who were on oral medical treatment, diet only or no treatment.

Table S4. Adjusted Association Between High Platelet Reactivity on Clopidogrel and the Risk of Adverse Events at 2-Year Follow-up According to Diabetes Status*

	No diabetes Adjusted HR (95% CI)	Diabetes Adjusted HR (95% CI)	$p_{interaction}$
Major adverse cardiac events	1.44 (1.16-1.78)	1.02 (0.73-1.43)	0.09
Death	1.45 (1.10-1.92)	0.89 (0.58-1.38)	0.06
Cardiac death	1.37 (0.93-2.02)	0.94 (0.53-1.66)	0.27
Myocardial infarction	1.42 (1.11-1.82)	1.14 (0.77-1.69)	0.35
Stent thrombosis	1.70 (1.20-2.40)	1.01 (0.58-1.74)	0.11
Myocardial infarction or stent thrombosis	1.45 (1.17-1.80)	1.07 (0.76-1.51)	0.14
Ischemia-driven target vessel revascularization	1.17 (0.99-1.39)	0.96 (0.71-1.30)	0.26
Clinically relevant bleeding	0.87 (0.74-1.04)	0.72 (0.51-1.03)	0.35

*In this sensitivity analysis, the category "Non-insulin-treated diabetes" included patients with diabetes who were on oral medical treatment, diet only or no treatment. The multivariable model also included age, sex, body mass index, hypertension, hyperlipidemia, current smoker, renal insufficiency, previous coronary artery bypass grafting, previous percutaneous coronary intervention , anemia, white blood counts, platelet counts, aspirin reaction units, ST-elevation myocardial infarction (STEMI) or non-STEMI as clinical presentation, degree of coronary artery disease (single vessel versus multivessel), small vessel disease, target vessel location in the left anterior descending coronary artery, peripheral arterial disease, and total stent length.

Table S5. Time-Varying Effect of High Platelet Reactivity on the Risk of Major Adverse Cardiac Events in Non-Insulin Treated Diabetes (NITDM) and Insulin-Treated Diabetes (ITDM)

Time Interval	$p_{interaction}$ HPR Versus Time for NITDM	$p_{interaction}$ HPR Versus Time for ITDM
0-30 days versus 30 days - 2 years	0.75	0.73
0-1 year versus 1-2 years	0.66	0.36
0-30 days versus 30 days-1 year versus 1-2 years	0.80	0.51
Time as a continuous variable	0.57	0.44

HPR = high platelet reactivity; ITDM = insulin-treated diabetes mellitus; NITDM = non-insulin-treated diabetes mellitus.

Table S6. Adjusted Association Between High Platelet Reactivity on Clopidogrel and the Risk of Adverse Events At 2-Year Follow-up Among Patients with Diabetes* According to Insulin Treatment Status

	Non–insulin-treated diabetes mellitus Adjusted HR (95% CI)	Insulin-treated diabetes mellitus Adjusted HR (95% CI)	$p_{interaction}$
Major adverse cardiac events	1.65 (1.12-2.45)	1.04 (0.71-1.51)	0.09
Death	2.09 (1.22-3.57)	0.74 (0.46-1.21)	0.005
Cardiac death	2.41 (1.19-4.85)	0.78 (0.40-1.52)	0.02
Myocardial infarction	1.55 (0.98-2.46)	1.19 (0.76-1.86)	0.41
Stent thrombosis	2.17 (1.13-4.17)	1.00 (0.54-1.85)	0.09
Myocardial infarction or stent thrombosis	1.16 (0.85-1.58)	0.92 (0.66-1.28)	0.31
Ischemia-driven target vessel revascularization	1.11 (0.79-1.56)	0.66 (0.44-0.98)	0.049
Clinically relevant bleeding	1.65 (1.12-2.45)	1.04 (0.71-1.51)	0.09

*In this sensitivity analysis, the category “Non-insulin-treated diabetes” included patients with diabetes who were on oral medical treatment, diet only or no treatment. The multivariable model also included age, sex, body mass index, hypertension, hyperlipidemia, current smoker, renal insufficiency, previous coronary artery bypass grafting, previous percutaneous coronary intervention , anemia, white blood counts, platelet counts, aspirin reaction units, ST-elevation myocardial infarction (STEMI) or non-STEMI as clinical presentation, degree of coronary artery disease (single vessel versus multivessel), small vessel disease, target vessel location in the left anterior descending coronary artery, peripheral arterial disease, and total stent length.

Table S7. Time-Varying Effect of High Platelet Reactivity on the Risk of Major Adverse Cardiac Events in Non-Insulin Treated Diabetes (NITDM)* and Insulin-Treated Diabetes (ITDM)

Time Interval	$p_{interaction}$	
	HPR Versus Time for NITDM	HPR Versus Time for ITDM
0-30 days versus 30 days - 2 years	0.71	0.73
0-1 year versus 1-2 years	0.28	0.36
0-30 days versus 30 days-1 year versus 1-2 years	0.56	0.51
Time as a continuous variable	0.45	0.44

*In this sensitivity analysis, the category "Non-insulin-treated diabetes" included patients with diabetes who were on oral medical treatment, diet only or no treatment. HPR = high platelet reactivity; ITDM = insulin-treated diabetes mellitus; NITDM = non-insulin-treated diabetes mellitus.