ORIGINAL RESEARCH

American Heart Association.

Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial

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Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet P2Y12 Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial, Volume: 8, Issue: 6, DOI: (10.1161/JAHA.118.011139)

Abstract

Background

There are limited data on how the combination of diabetes mellitus (DM) and chronic kidney disease (CKD) affects cardiovascular outcomes as well as response to different $P2Y_{12}$ receptor antagonists, which represented the aim of the present investigation.

Methods and Results

In this post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) trial, which randomized acute coronary syndrome patients to ticagrelor versus clopidogrel, patients (n=15 108) with available DM and CKD status were classified into 4 groups: DM+/CKD+ (n=1058), DM+/CKD− (n=2748), DM−/CKD+ (n=2160), and DM−/CKD− (n=9142). The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke at 12 months. The primary safety end point was PLATO major bleeding. DM+/CKD+ patients had a higher incidence of the primary end point compared with DM−/CKD− patients (23.3% versus 7.1%; adjusted hazard ratio 2.22; 95% CI 1.88–2.63; $P<0.001$). Patients with DM+/CKD− and DM−/CKD+ had an intermediate risk profile. The same trend was shown for the individual components of the primary end point and for major bleeding. Compared with clopidogrel, ticagrelor reduced the incidence of the primary end point consistently across subgroups (P-interaction=0.264), but with an increased absolute risk reduction in DM+/CKD+. The effects on major bleeding were also consistent across subgroups (P-interaction=0.288).

Conclusions

In acute coronary syndrome patients, a gradient of risk was observed according to the presence or absence of DM and CKD, with patients having both risk factors at the highest risk. Although the ischemic benefit of ticagrelor over clopidogrel was consistent in all subgroups, the absolute risk reduction was greatest in patients with both DM and CKD.

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Clinical Perspective

What Is New?

- Acute coronary syndrome patients with diabetes mellitus and chronic kidney disease are at markedly increased risk for long-term atherothrombotic events compared with patients without these risk factors, as well as with those with only 1 of these.
- Although the ischemic benefit of ticagrelor versus clopidogrel was consistent in all patient subgroups, the magnitude of benefit was enhanced according to the patient risk profile.

What Are the Clinical Implications?

- There is a need to define the most effective treatment options for these high-risk patients, including strategies to reduce the risk of developing chronic kidney disease in patients with diabetes mellitus.
- Similarly, in patients with established chronic kidney disease, glucose control is also critical to reduce the risk of developing diabetes mellitus.
- Clinicians should use more potent platelet-inhibiting therapy in acute coronary syndrome patients with diabetes mellitus and chronic kidney disease who are often undertreated because of high perceived risk of bleeding.

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Table 1. Baseline Characteristics by DM/CKD Status

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1058)	DM+/CKD− (n=2748)	DM−/CKD+ (n=2160)	DM−/CKD− (n=9142)	*P* Value
Demographics	Age (y), median (Q1–Q3)	72 (66–78)	61 (55–68)	74 (68–79)	59 (52–66)	<0.0001
	Age ≥75 y	429 (40.5%)	233 (8.5%)	1060 (49.1%)	604 (6.6%)	<0.0001
	Female sex	456 (43.1%)	851 (31.0%)	823 (38.1%)	2176 (23.8%)	<0.0001
	Weight (kg), median (Q1–Q3)	75 (65–84)	84 (74–95)	72 (62–80)	80 (70–90)	<0.0001
	Weight <60 kg	107 (10.1%)	120 (4.4%)	349 (16.2%)	498 (5.4%)	<0.0001
	Height (cm), median (Q1–Q3)	165 (160–172)	170 (163–175)	167 (160–173)	171 (165–177)	<0.0001
	BMI (kg/m^2), median (Q1–Q3)	26.9 (24.6–30.2)	29.3 (26.4–32.9)	25.4 (23.2–28.1)	27.4 (24.8–30.2)	<0.0001
	Waist circumference (cm), median (Q1–Q3)	99 (91–108)	103 (94–112)	95 (86–102)	97 (90–105)	<0.0001
Race, n (%)	White	922 (87.1)	2515 (91.5)	1928 (89.3)	8553 (93.6)	<0.0001
	Black	22 (2.1)	46 (1.7)	28 (1.3)	71 (0.8)	
	Asian	84 (7.9)	160 (5.8)	160 (7.4)	457 (5.0)	
	Other	30 (2.8)	27 (1.0)	44 (2.0)	61 (0.7)	
Cardiovascular risk factors, n (%)	Habitual smoker	130 (12.3)	800 (29.1)	413 (19.1)	4061 (44.4)	<0.0001
	Hypertension	925 (87.4)	2162 (78.7)	1574 (72.9)	5187 (56.7)	<0.0001
	Dyslipidemia	622 (58.8)	1629 (59.3)	916 (42.4)	3816 (41.7)	<0.0001
History, n (%)	Angina pectoris	651 (61.5)	1423 (51.8)	1137 (52.6)	3647 (39.9)	<0.0001
	Myocardial infarction	360 (34.0)	676 (24.6)	556 (25.7)	1507 (16.5)	<0.0001
	Congestive heart failure	176 (16.6)	188 (6.8)	229 (10.6)	255 (2.8)	<0.0001
	PCI	217 (20.5)	462 (16.8)	290 (13.4)	1025 (11.2)	<0.0001
	CABG	139 (13.1)	236 (8.6)	155 (7.2)	350 (3.8)	<0.0001
	TIA	48 (4.5)	75 (2.7)	81 (3.8)	191 (2.1)	<0.0001
	Nonhemorrhagic stroke	96 (9.1)	129 (4.7)	117 (5.4)	242 (2.6)	<0.0001
	Peripheral arterial disease	149 (14.1)	210 (7.6)	163 (7.5)	422 (4.6)	<0.0001
Medications on arrival, n (%)	Aspirin	1007 (95.2)	2618 (95.3)	2033 (94.1)	8756 (95.8)	0.01
	β-Blockade	842 (79.6)	2257 (82.1)	1613 (74.7)	6739 (73.7)	<0.0001
	ACE-inhibition and/or ARB	806 (76.2)	2049 (74.6)	1397 (64.7)	5361 (58.6)	<0.0001
	Statin	823 (77.8)	2230 (81.1)	1651 (76.4)	7350 (80.4)	<0.0001
	Ca-inhibitor	276 (26.1)	539 (19.6)	352 (16.3)	1054 (11.5)	<0.0001
	Diuretic	497 (47.0)	793 (28.9)	758 (35.1)	1449 (15.8)	<0.0001
	Insulin treatment before admission	282 (26.7)	572 (20.8)			0.0001
Medications index event to discharge, n (%)	GP 2b/3a inhibitor	177 (16.7)	734 (26.7)	413 (19.1)	2686 (29.4)	<0.0001
	Unfractionated heparin	524 (49.5)	1591 (57.9)	1195 (55.3)	5473 (59.9)	<0.0001

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Table 1. Continued

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1058)	DM+/CKD− (n=2748)	DM−/CKD+ (n=2160)	DM−/CKD− (n=9142)	*P* Value
	Low-molecular-weight heparin	590 (55.8)	1460 (53.1)	1199 (55.5)	4734 (51.8)	0.003
	Fondaparinux	34 (3.2)	74 (2.7)	74 (3.4)	249 (2.7)	0.3
	Bivalirudin	25 (2.4)	90 (3.3)	34 (1.6)	158 (1.7)	<0.0001
Intended approach	Invasive	603 (57.0%)	1912 (69.6%)	1311 (60.7%)	6915 (75.6%)	<0.0001
	Noninvasive	455 (43.0%)	836 (30.4%)	849 (39.3%)	2227 (24.4%)	
Final ACS diagnosis	ST-elevation MI	244 (23.1%)	863 (31.4%)	638 (29.6%)	3980 (43.6%)	<0.0001
	Non-ST-elevation MI	559 (52.9%)	1259 (45.8%)	1038 (48.2%)	3622 (39.6%)	
	Unstable angina	224 (21.2%)	566 (20.6%)	427 (19.8%)	1336 (14.6%)	
	Other	29 (2.7%)	60 (2.2%)	50 (2.3%)	199 (2.2%)	
Randomized treatment	Delay from start of pain (h), median (Q1–Q3)	14.2 (6.8–21.2)	12.7 (5.7–20.4)	14.0 (5.8–21.1)	10.2 (4.3–19.0)	<0.0001
	Treatment duration (d), median (Q1–Q3)	258 (55–361)	276 (179–365)	265 (73–363)	284 (184–366)	<0.0001
Biomarkers	Creatinine (μmol/L), median (Q1–Q3)	115.0 (106.0–141.0)	80.0 (70.7–88.0)	106.0 (97.0–124.0)	80.0 (71.0–88.0)	<0.0001
	Glucose (mmol/L), median (Q1–Q3)	9.9 (7.2–13.5)	9.7 (7.2–13.2)	6.5 (5.6–7.9)	6.4 (5.6–7.7)	<0.0001
	HbA1c (mmol/mol), median (Q1–Q3)	7.5 (6.6–8.7)	7.6 (6.7–9.1)	5.9 (5.6–6.2)	5.8 (5.6–6.1)	<0.0001
	Hemoglobin (mmol/mol), median (Q1–Q3)	128.0 (116.0–140.0)	139.0 (128.0–149.0)	134.0 (123.0–145.0)	142.0 (132.0–151.0)	<0.0001
	NT-proBNP (pmol/L), median (Q1–Q3)	1734 (610.0–4071)	395.0 (146.0–953.0)	1002 (320.0–2544)	277.0 (99.0–721.0)	<0.0001
	Troponin I μg/L, median (Q1–Q3)	1.10 (0.12–6.00)	0.95 (0.11–4.30)	1.00 (0.11–5.70)	0.90 (0.12–4.70)	0.01
	Creatinine (mg/dL), median (Q1–Q3)	1.3 (1.2–1.6)	0.9 (0.8–1.0)	1.2 (1.1–1.4)	0.9 (0.8–1.0)	<0.0001
	CrCl (mL/min), median (Q1–Q3)	48.4 (38.9–55.1)	86.7 (73.2–104.5)	50.3 (42.7–55.9)	87.7 (74.5–104.0)	<0.0001

ACE indicates angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance by Cockcroft-Gault equation; DM, diabetes mellitus; GP, glycoprotein; HbA1c, hemoglobin A1c; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

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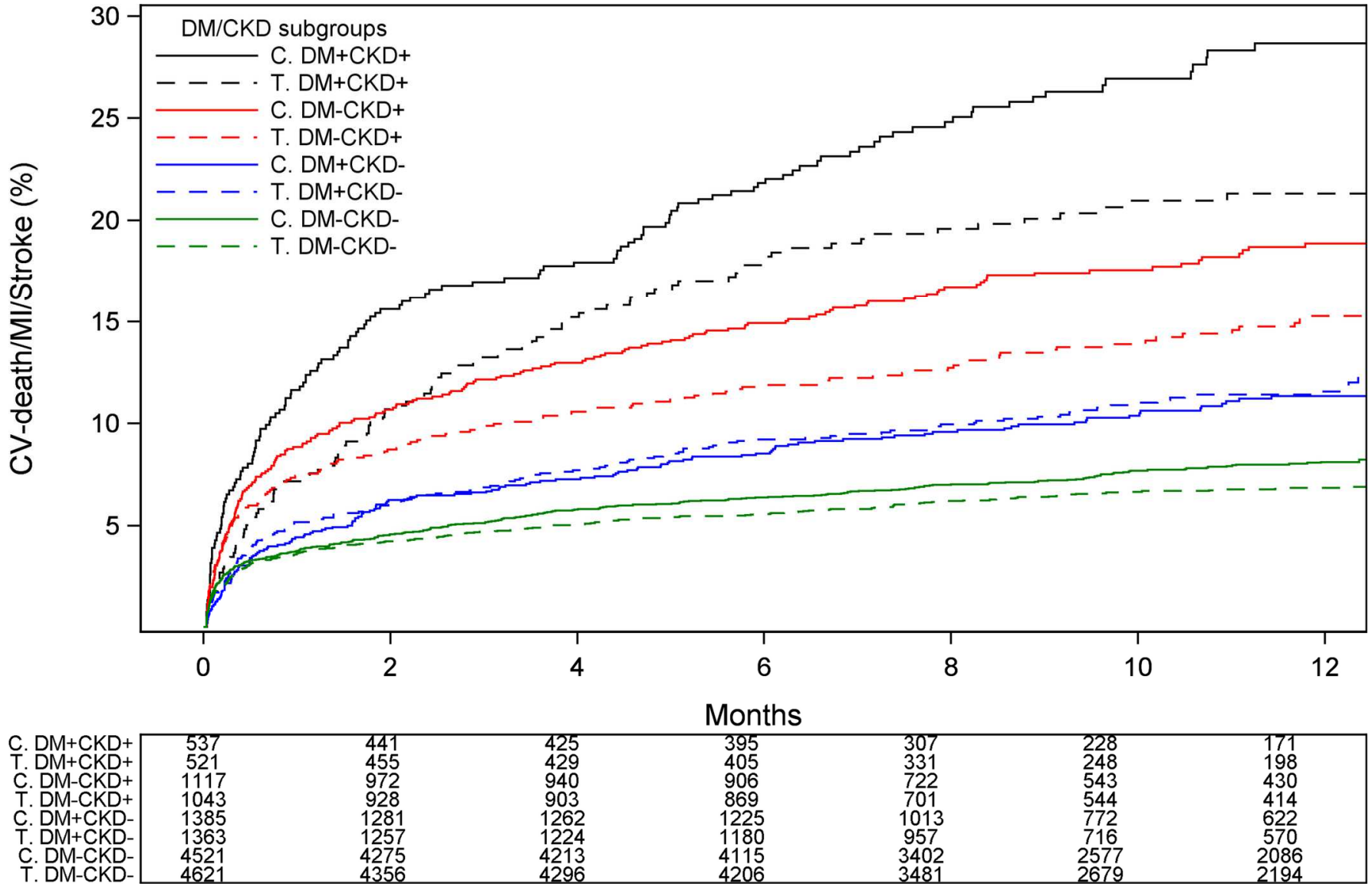

C. DM+CKD+	537	441	425	395	307	228	171
T. DM+CKD+	521	455	429	405	331	248	198
C. DM-CKD+	1117	972	940	906	722	543	430
T. DM-CKD+	1043	928	903	869	701	544	414
C. DM+CKD-	1385	1281	1262	1225	1013	772	622
T. DM+CKD-	1363	1257	1224	1180	957	716	570
C. DM-CKD-	4521	4275	4213	4115	3402	2577	2086
T. DM-CKD-	4621	4356	4296	4206	3481	2679	2194

Figure 1. Kaplan–Meier event rate curves for the cumulative incidence of the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

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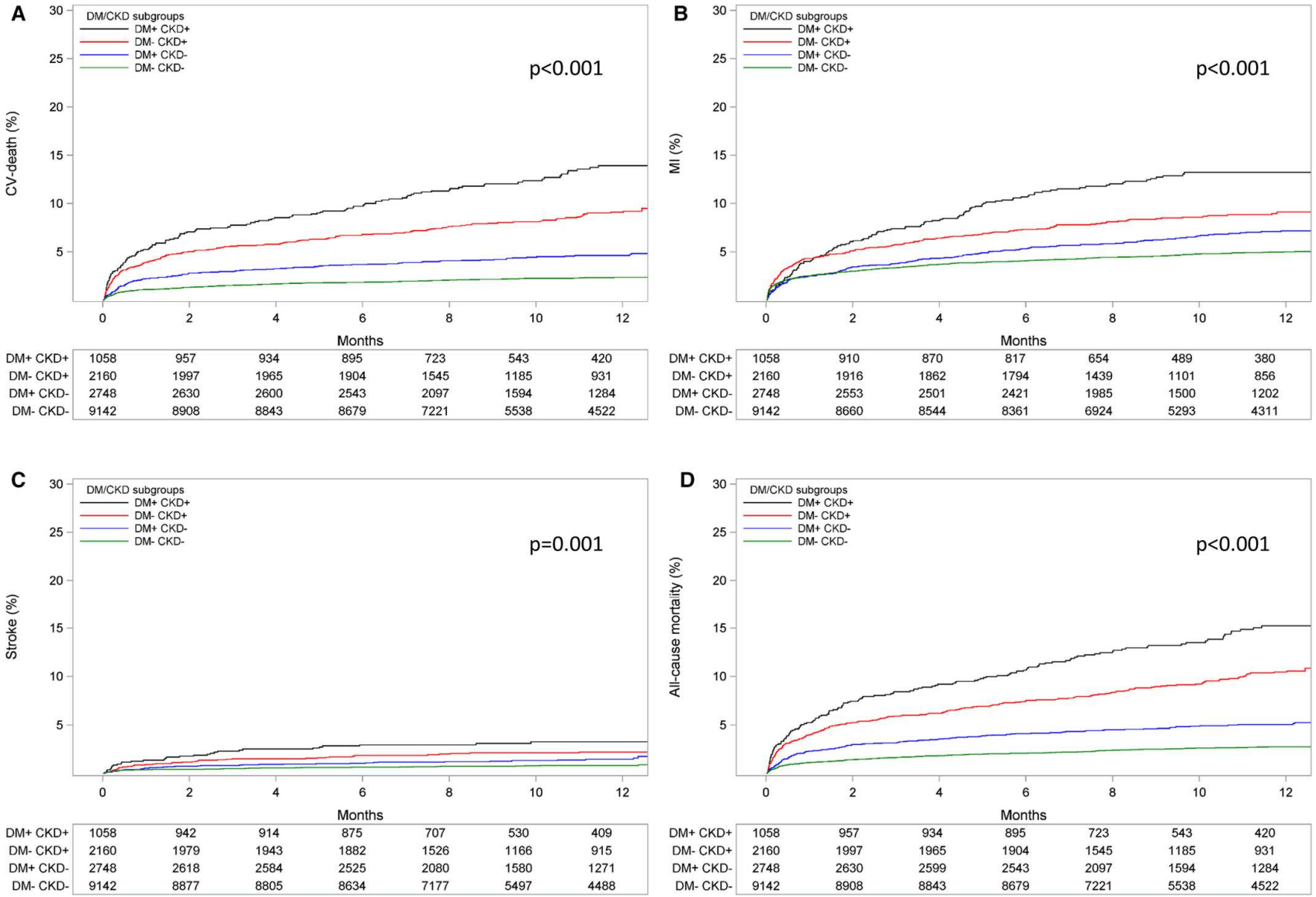

Figure 2. Kaplan–Meier event rate curves for the cumulative incidence of (A) cardiovascular (CV) death, (B) myocardial infarction (MI), (C) stroke, and (D) all-cause mortality stratified by DM/CKD status. P value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

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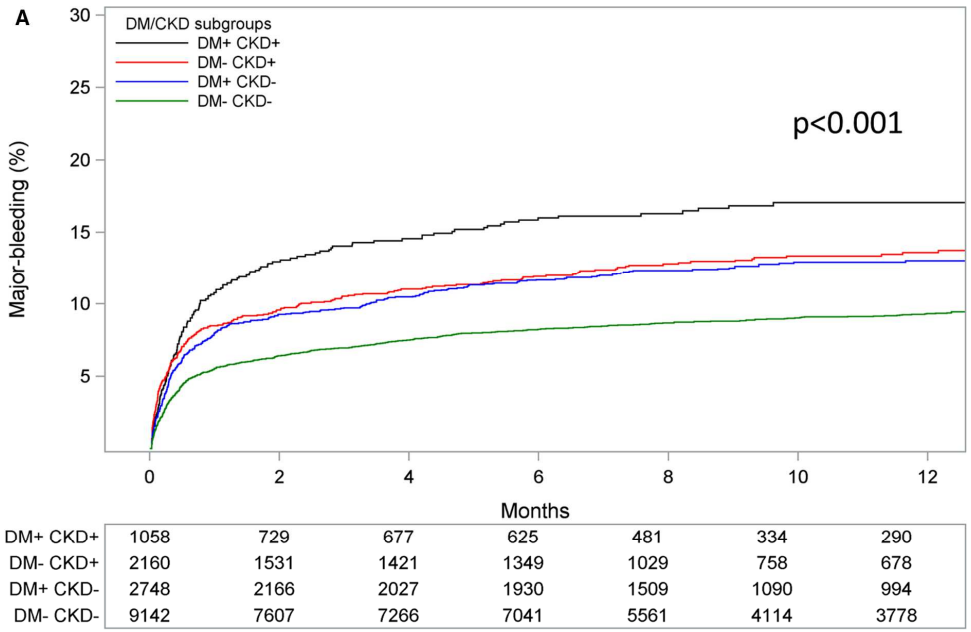
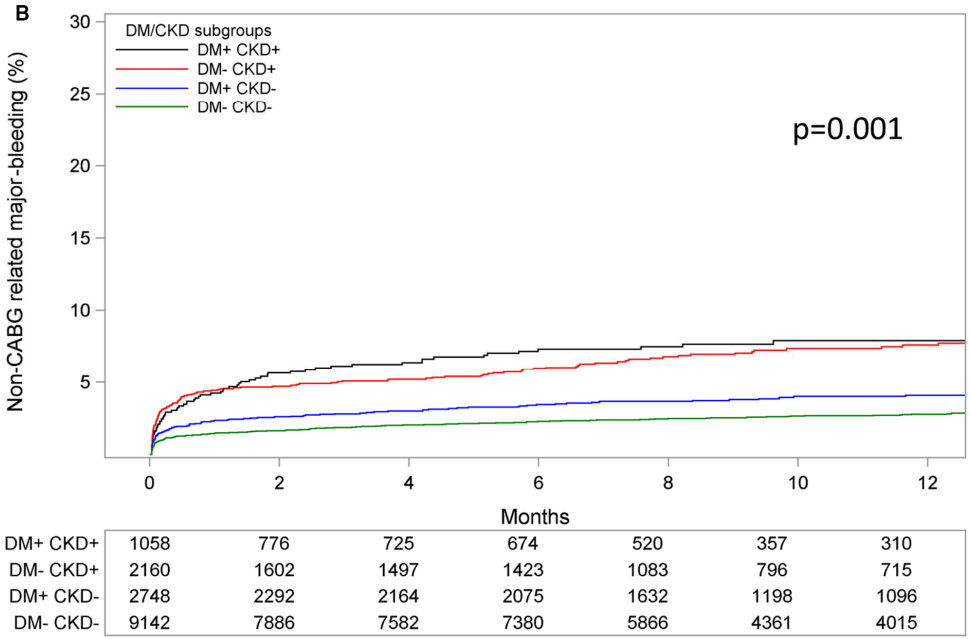


DM+ CKD+	1058	729	677	625	481	334	290
DM- CKD+	2160	1531	1421	1349	1029	758	678
DM+ CKD-	2748	2166	2027	1930	1509	1090	994
DM- CKD-	9142	7607	7266	7041	5561	4114	3778



DM+ CKD+	1058	776	725	674	520	357	310
DM- CKD+	2160	1602	1497	1423	1083	796	715
DM+ CKD-	2748	2292	2164	2075	1632	1198	1096
DM- CKD-	9142	7886	7582	7380	5866	4361	4015

Figure 3. Kaplan–Meier event rate curves for the cumulative incidence of (A) major bleeding, and (B) non-CABG-related major bleeding stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. Bleeding is defined according to PLATO criteria. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention, or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; PLATO, Platelet Inhibition and Patient Outcomes.

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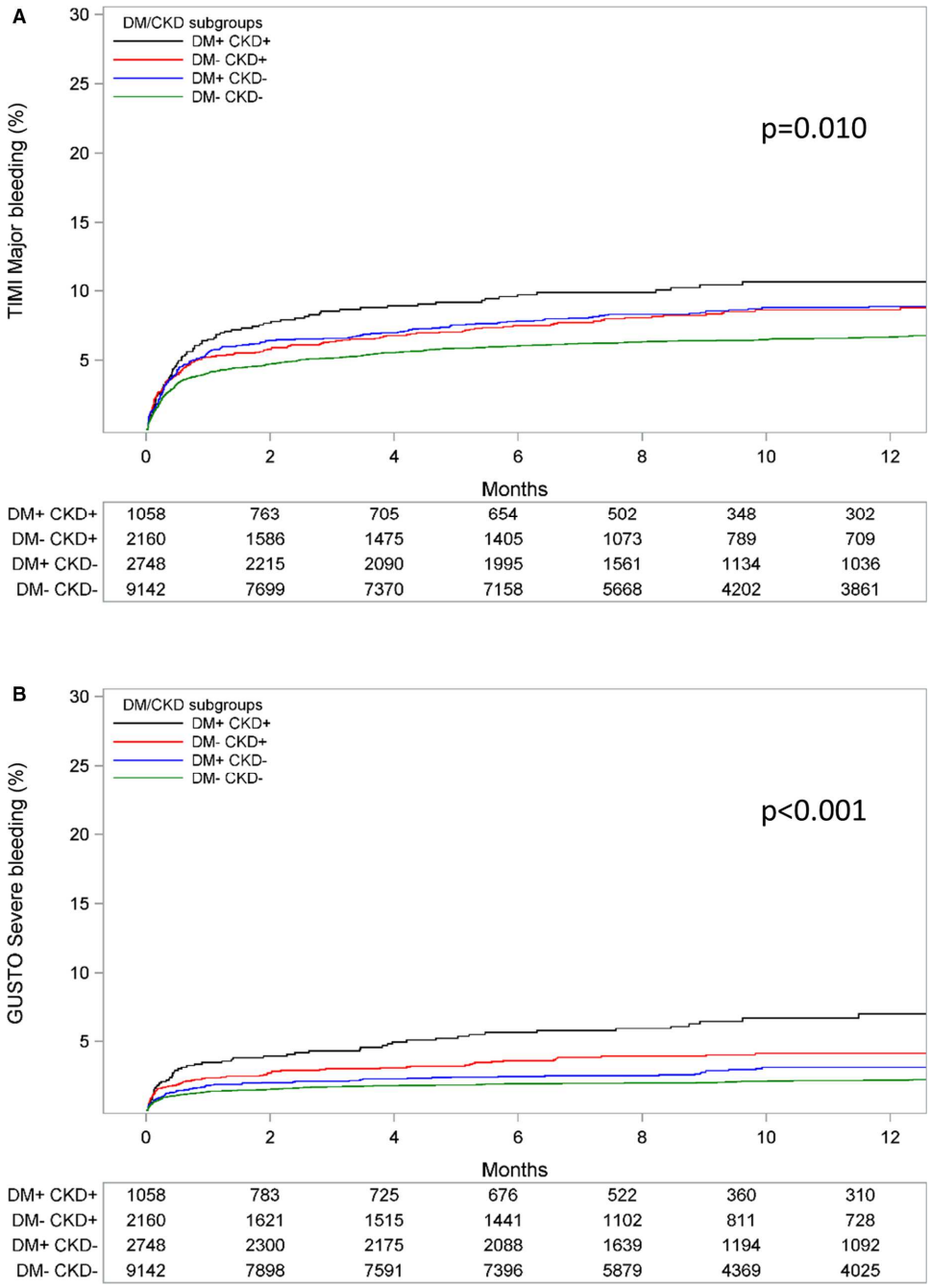

Figure 4. Kaplan–Meier event rate curves for the cumulative incidence of major/severe bleeding according to (A) TIMI, and (B) GUSTO criteria stratified by DM/CKD status. *P* value represents the overall comparison among groups according to DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus; GUSTO, Global Use of Strategies to Open Occluded Arteries; TIMI, thrombolysis in myocardial infarction.

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Table 2. Ischemic and Bleeding Outcomes According to DM/CKD Subgroup, With Poor Glycemic Control Defined by HbA1c and CKD Defined by the Creatinine-Cystatin C CKD-EPI Equation

DM/CKD Subgroup	No. of Events	No. of Patients	Event Rate (%)*	HR (95% CI)†	*P* Value‡
Cardiovascular death/MI/stroke					
DM−/CKD−	392	1264	6.9		<0.0001
DM+/CKD−	580	5726	10.1	1.33 (1.16–1.52)	
DM−/CKD+	123	734	16.8	1.72 (1.39–2.13)	
DM+/CKD+	263	1264	20.8	2.09 (1.76–2.49)	
Cardiovascular death					
DM−/CKD−	121	5673	2.1		<0.0001
DM+/CKD−	215	5726	3.8	1.54 (1.23–1.94)	
DM−/CKD+	65	734	8.9	2.50 (1.81–3.44)	
DM+/CKD+	155	1264	12.3	3.44 (2.64–4.48)	
MI					
DM−/CKD−	258	5673	4.5		<0.0001
DM+/CKD−	357	5726	6.2	1.24 (1.05–1.47)	
DM−/CKD+	69	734	9.4	1.60 (1.21–2.12)	
DM+/CKD+	130	1264	10.3	1.66 (1.32–2.10)	
All-cause death					
DM−/CKD−	145	5673	2.6		<0.0001
DM+/CKD−	238	5726	4.2	1.45 (1.17–1.79)	
DM−/CKD+	72	734	9.8	2.21 (1.63–2.99)	
DM+/CKD+	174	1264	13.8	3.19 (2.49–4.08)	
Stroke					
DM−/CKD−	46	5673	0.8		0.1679
DM+/CKD−	74	5726	1.3	1.43 (0.98–2.08)	
DM−/CKD+	11	734	1.5	1.15 (0.58–2.29)	
DM+/CKD+	27	1264	2.1	1.67 (0.99–2.81)	
Major bleeding					
DM−/CKD−	484	5673	8.5		0.0039
DM+/CKD−	629	5726	11.0	1.26 (1.11–1.42)	
DM−/CKD+	86	734	11.7	1.14 (0.90–1.45)	
DM+/CKD+	148	1264	11.7	1.14 (0.94–1.39)	

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Non-CABG-related major bleeding					
DM−/CKD−	161	5673	2.8		0.0070
DM+/CKD−	180	5726	3.1	1.00 (0.81–1.25)	
DM−/CKD+	44	734	6.0	1.34 (0.94–1.91)	
DM+/CKD+	88	1264	7.0	1.55 (1.16–2.07)	
CABG-related major bleeding					
DM−/CKD−	367	5628	6.5		0.1678
DM+/CKD−	366	5673	6.5	1.02 (0.88–1.18)	
DM−/CKD+	44	727	6.1	0.96 (0.69–1.32)	
DM+/CKD+	96	1250	7.7	1.29 (1.01–1.65)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS define and randomized treatment. BMI indicates body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*The crude event rate, (no. events/no. of subjects)× 100%.

†Subgroup DM−/CKD− is the reference category.

‡*P* value for the effect of DM/CKD subgroup.

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Table 3. Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
Cardiovascular death						0.3
DM+/CKD+	521	537	55 (13.60)	77 (19.40)	0.79 (0.55–1.11)	
DM−/CKD+	1043	1117	69 (8.33)	111 (12.80)	0.68 (0.51–0.92)	
DM+/CKD−	1363	1385	59 (5.30)	62 (5.38)	1.00 (0.70–1.44)	
DM−/CKD−	4621	4521	98 (2.51)	104 (2.71)	0.93 (0.70–1.22)	
MI						0.2
DM+/CKD+	521	537	52 (13.79)	72 (19.66)	0.76 (0.53–1.09)	
DM−/CKD+	1043	1117	77 (9.77)	100 (12.29)	0.83 (0.62–1.12)	
DM+/CKD−	1363	1385	93 (8.76)	84 (7.58)	1.13 (0.84–1.52)	
DM−/CKD−	4621	4521	195 (5.16)	233 (6.33)	0.82 (0.67–0.99)	
All-cause death						0.5
DM+/CKD+	521	537	63 (15.58)	82 (20.66)	0.85 (0.61–1.18)	
DM−/CKD+	1043	1117	80 (9.66)	125 (14.41)	0.70 (0.53–0.93)	
DM+/CKD−	1363	1385	64 (5.75)	69 (5.98)	0.98 (0.70–1.37)	
DM−/CKD−	4621	4521	112 (2.87)	123 (3.21)	0.90 (0.69–1.16)	
Stroke						0.6
DM+/CKD+	521	537	13 (3.26)	18 (4.66)	0.78 (0.38–1.59)	
DM−/CKD+	1043	1117	23 (2.81)	20 (2.33)	1.24 (0.68–2.26)	
DM+/CKD−	1363	1385	22 (1.99)	16 (1.40)	1.42 (0.75–2.71)	
DM−/CKD−	4621	4521	40 (1.03)	31 (0.81)	1.28 (0.80–2.04)	
Major bleeding						0.3
DM+/CKD+	521	537	78 (27.37)	79 (26.89)	1.02 (0.75–1.40)	
DM−/CKD+	1043	1117	129 (21.73)	125 (19.42)	1.13 (0.88–1.44)	
DM+/CKD−	1363	1385	150 (17.61)	171 (18.88)	0.91 (0.73–1.13)	
DM−/CKD−	4621	4521	420 (13.23)	355 (11.19)	1.16 (1.01–1.34)	
Non-CABG-related major bleeding						0.7
DM+/CKD+	521	537	39 (12.87)	32 (10.18)	1.32 (0.82–2.10)	
DM−/CKD+	1043	1117	75 (12.15)	62 (9.14)	1.34 (0.96–1.88)	
DM+/CKD−	1363	1385	48 (5.30)	50 (5.13)	1.03 (0.69–1.52)	
DM−/CKD−	4621	4521	129 (3.88)	97 (2.93)	1.30 (1.00–1.69)	

The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or CABG, type of acute coronary syndrome and randomized treatment. CABG indicates coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction.

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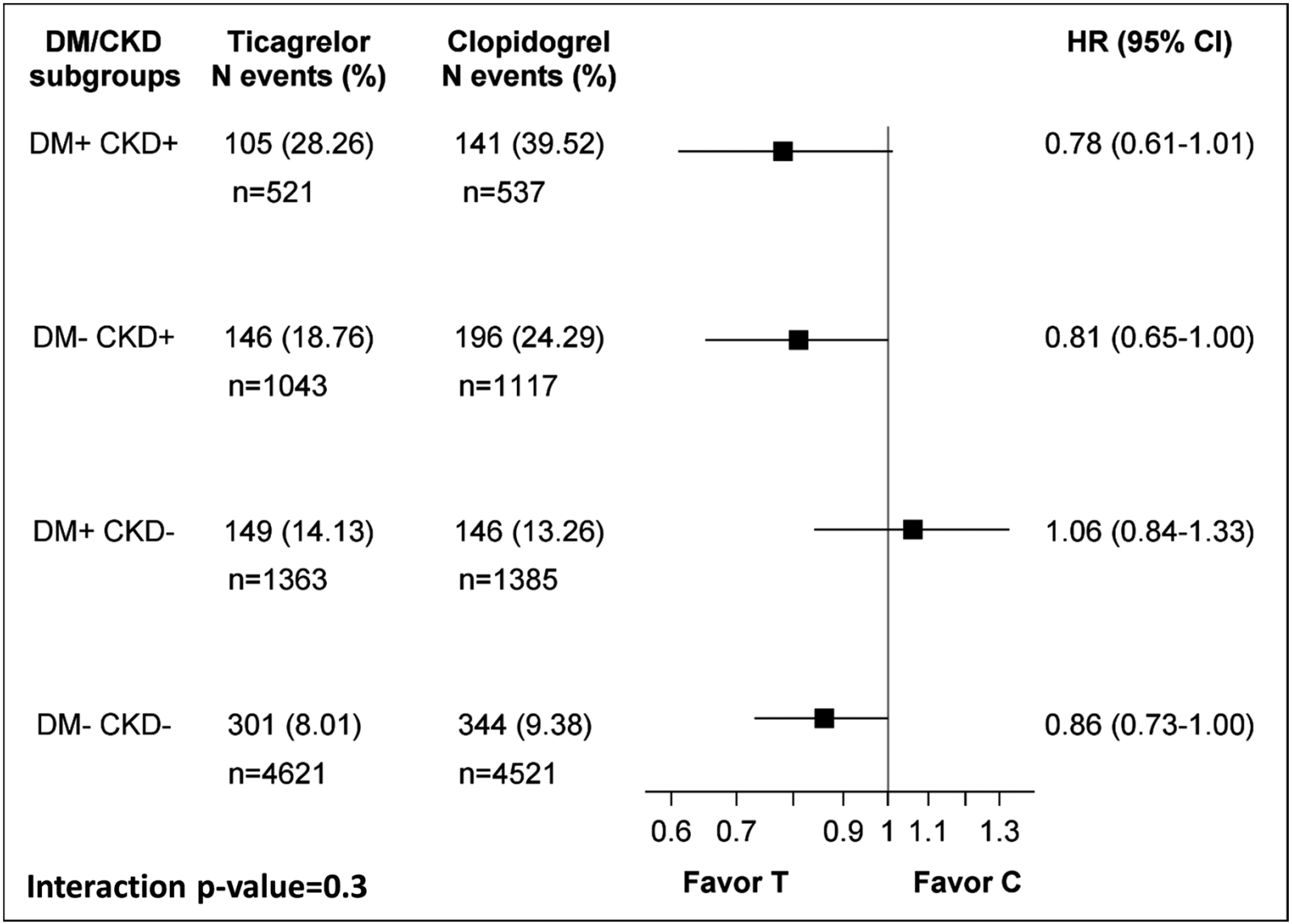

Figure 5. Hazard ratios (HR) with 95% CI for the primary composite end point (cardiovascular death, myocardial infarction, and stroke) of ticagrelor (T) vs clopidogrel (C) stratified by DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

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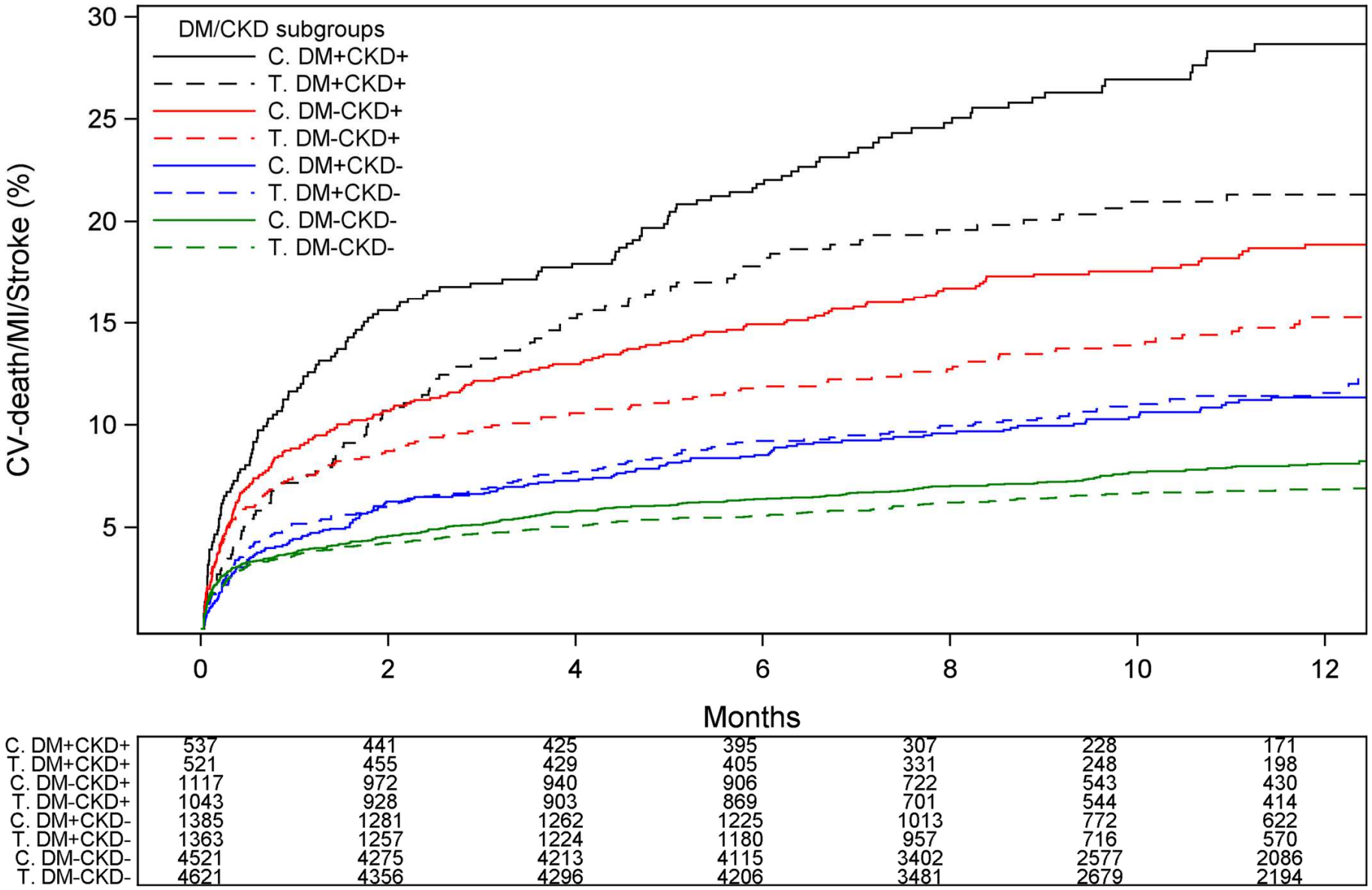

C. DM+CKD+	537	441	425	395	307	228	171
T. DM+CKD+	521	455	429	405	331	248	198
C. DM-CKD+	1117	972	940	906	722	543	430
T. DM-CKD+	1043	928	903	869	701	544	414
C. DM+CKD-	1385	1281	1262	1225	1013	772	622
T. DM+CKD-	1363	1257	1224	1180	957	716	570
C. DM-CKD-	4521	4275	4213	4115	3402	2577	2086
T. DM-CKD-	4621	4356	4296	4206	3481	2679	2194

Figure 6. Kaplan–Meier event rate curves for the cumulative incidence of the primary composite end point of cardiovascular (CV) death, myocardial infarction, and stroke stratified by treatment group and DM/CKD status. C indicates clopidogrel; CKD, chronic kidney disease; DM, diabetes mellitus; T, ticagrelor.

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Table 4. Bleeding Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status According to TIMI and GUSTO Criteria

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
TIMI major bleeding						0.049
DM+/CKD+	521	537	48 (16.16)	48 (15.71)	1.02 (0.68–1.52)	
DM−/CKD+	1043	1117	78 (12.67)	81 (12.13)	1.05 (0.77–1.43)	
DM+/CKD−	1363	1385	93 (10.58)	124 (13.32)	0.77 (0.59–1.01)	
DM−/CKD−	4621	4521	308 (9.56)	252 (7.82)	1.21 (1.02–1.42)	
TIMI non-CABG-related major bleeding						0.219
DM+/CKD+	521	537	24 (7.84)	15 (4.71)	1.69 (0.89–3.23)	
DM−/CKD+	1043	1117	38 (6.01)	36 (5.22)	1.16 (0.74–1.83)	
DM+/CKD−	1363	1385	27 (2.95)	34 (3.47)	0.84 (0.51–1.40)	
DM−/CKD−	4621	4521	88 (2.63)	57 (1.71)	1.51 (1.08–2.11)	
GUSTO severe bleeding						0.882
DM+/CKD+	521	537	25 (8.12)	34 (10.88)	0.77 (0.46–1.28)	
DM−/CKD+	1043	1117	36 (5.72)	39 (5.70)	0.99 (0.63–1.56)	
DM+/CKD−	1363	1385	33 (3.63)	40 (4.09)	0.88 (0.55–1.39)	
DM−/CKD−	4621	4521	89 (2.67)	92 (2.78)	0.95 (0.71–1.27)	
GUSTO non-CABG-related severe bleeding						0.545
DM+/CKD+	521	537	20 (6.44)	19 (5.98)	1.08 (0.58–2.03)	
DM−/CKD+	1043	1117	25 (3.93)	25 (3.61)	1.06 (0.61–1.85)	
DM+/CKD−	1363	1385	17 (1.85)	25 (2.54)	0.74 (0.40–1.36)	
DM−/CKD−	4621	4521	54 (1.61)	41 (1.23)	1.28 (0.85–1.91)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS, and randomized treatment. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DM, diabetes mellitus; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

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Table 5. Outcomes of Ticagrelor Versus Clopidogrel According to DM/CKD Status, With Poor Glycemic Control Defined by HbA1c and CKD Defined by the Creatinine-Cystatin C CKD-EPI Equation

DM/CKD Subgroup	Ticagrelor Patients (N)	Clopidogrel Patients (N)	Ticagrelor Event Rate, N (%)	Clopidogrel Event Rate, N (%)	HR (95% CI)	*P* Value Interaction
Cardiovascular death/MI/stroke						0.265
DM+/CKD+	633	631	105 (22.66)	158 (36.57)	0.68 (0.53–0.88)	
DM−/CKD+	344	390	49 (19.68)	74 (27.22)	0.77 (0.54–1.11)	
DM+/CKD−	2841	2886	267 (11.79)	313 (13.64)	0.87 (0.74–1.03)	
DM−/CKD−	2877	2797	191 (8.31)	201 (8.99)	0.92 (0.76–1.13)	
Cardiovascular death						0.257
DM+/CKD+	633	631	57 (11.52)	98 (20.70)	0.63 (0.45–0.87)	
DM−/CKD+	344	390	25 (9.42)	40 (13.63)	0.74 (0.45–1.23)	
DM+/CKD−	2841	2886	103 (4.34)	112 (4.62)	0.96 (0.73–1.25)	
DM−/CKD−	2877	2797	57 (2.39)	64 (2.75)	0.87 (0.61–1.24)	
MI						0.734
DM+/CKD+	633	631	53 (11.28)	77 (17.53)	0.71 (0.50–1.00)	
DM−/CKD+	344	390	29 (11.57)	40 (14.61)	0.84 (0.52–1.36)	
DM+/CKD−	2841	2886	165 (7.24)	192 (8.31)	0.87 (0.71–1.08)	
DM−/CKD−	2877	2797	124 (5.36)	134 (5.97)	0.89 (0.70–1.14)	
All-cause death						0.481
DM+/CKD+	633	631	68 (13.75)	106 (22.39)	0.70 (0.51–0.95)	
DM−/CKD+	344	390	28 (10.55)	44 (14.99)	0.74 (0.46–1.20)	
DM+/CKD−	2841	2886	113 (4.76)	125 (5.15)	0.94 (0.73–1.21)	
DM−/CKD−	2877	2797	64 (2.68)	81 (3.48)	0.77 (0.56–1.07)	
Stroke						0.293
DM+/CKD+	633	631	15 (3.08)	12 (2.57)	1.33 (0.62–2.85)	
DM−/CKD+	344	390	5 (1.90)	6 (2.06)	0.95 (0.29–3.12)	
DM+/CKD−	2841	2886	33 (1.40)	41 (1.70)	0.82 (0.52–1.30)	
DM−/CKD−	2877	2797	29 (1.22)	17 (0.73)	1.67 (0.92–3.05)	

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Major bleeding						0.143
DM+/CKD+	633	631	74 (20.61)	74 (20.51)	1.03 (0.75–1.42)	
DM−/CKD+	344	390	43 (23.41)	43 (19.59)	1.12 (0.74–1.71)	
DM+/CKD−	2841	2886	307 (16.44)	322 (16.72)	0.97 (0.83–1.14)	
DM−/CKD−	2877	2797	272 (14.15)	212 (10.97)	1.28 (1.07–1.54)	
Non-CABG-related major bleeding						0.782
DM+/CKD+	633	631	48 (12.89)	40 (10.69)	1.29 (0.84–1.96)	
DM−/CKD+	344	390	23 (12.06)	21 (9.15)	1.36 (0.75–2.45)	
DM+/CKD−	2841	2886	93 (4.71)	87 (4.23)	1.12 (0.84–1.50)	
DM−/CKD−	2877	2797	95 (4.71)	66 (3.29)	1.39 (1.02–1.91)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS, and randomized treatment. ACS indicates acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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ORIGINAL RESEARCH

Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial

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Conclusions

In conclusion, the results of the present analysis showed that ACS patients with DM and CKD are at markedly increased risk for long-term atherothrombotic events compared with patients without these risk factors, as well as with those with only 1 of these. Although the ischemic benefit of ticagrelor versus clopidogrel was consistent in all patient subgroups, the magnitude of benefit was enhanced according to the patient risk profile. Although patients with DM and CKD are at increased risk of bleeding, there were no signals of increased risk of major bleeding events with ticagrelor. Overall, these data underscore the need for using more potent platelet-inhibiting therapy in ACS patients with DM and CKD who are often undertreated because of high perceived risk of bleeding.

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