

## Comparison of 1-Year Clinical Outcomes Between Ticagrelor Versus Clopidogrel in Type 2 Diabetes Patients After Implantation of Small Diameter Stents

### ABSTRACT

**Background:** Type 2 diabetes mellitus (T2DM) patients with small-diameter stents (SDS), that are equal to or less than 2.5 mm in diameter, face increased risks of restenosis and complications. This study aimed to evaluate the 1-year follow-up to assess the rate of major adverse cardiac events (MACE) and bleeding risk between ticagrelor and clopidogrel in T2DM patients after SDS implantation.

**Methods:** The study was a single-center, prospective controlled registry trial, which included 332 T2DM patients who underwent percutaneous coronary intervention with SDS implantation. Follow-up was conducted for 1 year.

**Results:** Following propensity score matching, the 1-year analysis revealed no significant difference in the risk of the composite MACE between clopidogrel and ticagrelor groups ( $P = .295$ ). Male gender, history of ischemic heart disease, ejection fraction (EF), coronary lesion type, and chronic kidney disease (CKD) were identified as potential predictors for the composite endpoint. In a sub-analysis of CKD patients, the 12-month rates of composites of cardiac death (CD), myocardial infarction (MI), stroke, and target vessel revascularization (TVR) were lower in the ticagrelor group than in the clopidogrel group ( $P = .024$ ). However, the ticagrelor group was associated with a higher rate of bleeding compared to the clopidogrel group (20% vs. 9%) ( $P = .041$ ).

**Conclusion:** Our study demonstrated that ticagrelor did not show improvement in the composite of CD, MI, stroke, TVR, or the risk of bleeding events defined by the BARC criteria in patients with T2DM and SDS compared with clopidogrel emphasizing the importance of individualized treatment decisions based on patient characteristics. However, the results may not be representative of the entire population.

**Keywords:** Clopidogrelpercutaneous coronary intervention, small diameter stents, ticagrelor type 2 diabetes mellitus

### INTRODUCTION

Previous studies have indicated that factors such as diabetes duration, HbA1c levels, and type of antihyperglycemic treatment can impact cardiovascular events in patients with type 2 diabetes mellitus (T2DM).<sup>1,2</sup> Aspirin use is recommended in recent guidelines for cardiovascular secondary prevention in order to lower cardiovascular events in individuals with T2DM.<sup>3-5</sup>

The CHARISMA study and other cohort trials suggested that DAPT (Dual antiplatelets therapy) would offer protection above and beyond what aspirin offers.<sup>6-8</sup> The use of potent P2Y<sub>12</sub> receptor inhibitors is recommended for treatment and secondary prevention,<sup>9,10</sup> such as prasugrel<sup>11</sup> and ticagrelor,<sup>8,12</sup> for patients with diabetes mellitus (DM) and coronary artery syndromes due to their greater reduction in mortality and ischemic event recurrences, albeit at the cost of more bleeding. Both ticagrelor and prasugrel can safely be used in patients with T2DM following coronary intervention since they did not show any significant differences in poor clinical outcomes or bleeding events.<sup>13</sup> While ticagrelor provides similar or greater inhibition of ADP-induced platelet reactivity compared to prasugrel, the 2 agents

### ORIGINAL INVESTIGATION

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did not show a significant difference in inhibiting non-ADP-induced platelet reactivity.<sup>14</sup>

Extra consideration needs to be given to diabetic patients after small diameter stents implantations, which accounts for 30%-70% of patients undergoing percutaneous coronary intervention (PCI)<sup>15</sup> due to increased risk of restenosis and the requirement for revascularization and potential procedure-related complications.<sup>16</sup> Small caliber vessel lesions tend to be very complicated, involving multiple vessels, distal locations, and type C lesion characteristics. The limited margin of error in stent expansion and sizing associated with small lumen size is a challenge to current therapeutic approaches. The aim of this study was to compare clinical outcomes between clopidogrel and ticagrelor in type 2 diabetic patients after implantation of small diameter stents at 1 year.

### Study Population

Proactive, open-label, controlled registry trial in a single center. During the period of October 2021-November 2023, we included and monitored 332 patients with a history of coronary artery disease and type 2 diabetes who were admitted to our hospital and were older than 18 but younger than 70 years. Our enrolled patients underwent PCI with implantation of small-diameter stents (SDS), that are equal to or less than 2.5 mm in diameter. Diabetes was defined as individuals with fasting blood glucose  $\geq 126$  mg/dL (7.0 mmol/L) or random blood glucose  $\geq 200$  mg/dL (11.1 mmol/L) or patients with a known history of ongoing hypoglycemic therapy. Pregnancy, any antiplatelet medication contraindications,<sup>17</sup> the requirement for oral anticoagulation therapy, the concurrent use of strong cytochrome P450 3A inducers or inhibitors, the combination of chronic infections, malignant tumors, end-stage liver diseases, and life expectancy less than a year were the main exclusion criteria. The supplementary material provides information on the study's inclusion and exclusion criteria.

### Study Design

The study compared clinical outcomes between clopidogrel and ticagrelor in type 2 diabetic patients after implantation of SDS at 1 year. The choice of clopidogrel or ticagrelor,

emergent or early invasive treatment strategies, stent type, pre-dilatation or post-dilatation, use of post-procedural glycoprotein IIb/IIIa inhibitors, and antithrombotic medication were established in accordance with the Patient's clinical status and according to the clinical decision of operators under relevant guidelines and recommendations. A procedure was deemed successful if the target vessel had no residual stenosis following stenting, had a final TIMI flow grade of 3, and no major side branch occlusion or flow-limiting dissection following the procedure. Two groups of patients were identified: group 1 underwent DAPT with clopidogrel, and group 2 underwent DAPT with ticagrelor. The recommended loading and maintenance doses of aspirin, ticagrelor, and clopidogrel were given.<sup>10,18</sup> Guideline-directed medical therapy for other medical treatments was encouraged (e.g., optimal pharmacologic treatment for heart failure, control of hypertension or diabetes mellitus, and prescription of high-intensity statin). Every patient had a P2Y12 inhibitor for a year in addition to oral aspirin at a dose of 100 mg once daily for the duration of the study.

### Artificial Intelligence Disclosure

We disclose that we did not use artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of this submitted work.

### Follow-Up and Endpoints

Data have been collected about the patients' pre-existing conditions, medical background, risk factors, clinical diagnosis, medications used both upon admission and after discharge, results of in-hospital lab tests, and coronary procedures. Following PCI, each participant's general health condition, current medication, and end point-related events were recorded. This was done at follow-up appointments at the outpatient clinic or, if that was not feasible, over the phone at baseline and then again at 3, 6, 9, and 12 months.

The primary endpoint of the study was the occurrence of major adverse cardiovascular events (MACE) at 1 year, including composite (cardiac death, MI, stroke, and target vessel revascularization [TVR]), cardiac death, non-fatal MI, stroke, or TVR. As a secondary endpoint, the incidence of stent thrombosis, non-TVR, and bleeding (Bleeding Academic Research Consortium [BARC] 2, 3, or 5) was also examined. The fourth universal definition of MI was used to define it.<sup>19</sup> Angiographic restenosis was defined as a percent diameter stenosis of 50% inside and just adjacent to the proximal and distal end of the stent. Target vessel revascularization was defined as repeat angioplasty or coronary bypass surgery performed because of restenosis for the target lesion or any segment of the artery containing the target lesion during follow-up. Death was classified as cardiac in origin unless clear non-cardiac causes could be identified.<sup>20,21</sup> Bleeding complications were defined based on the criteria of the BARC definition.<sup>22</sup> Only events associated with the vessel with  $\leq 2.5$  mm were included.

### Statistical Analysis

Continuous variables were expressed as mean  $\pm$  SD or median and interquartile range, and categorical variables are

## HIGHLIGHTS

- Small caliber vessel lesions tend to be very complicated, involving multiple vessels, distal locations, and limited margin of error in stent expansion, which is a challenge to current therapeutic approaches.
- Up to 16% of diabetic patients have an increased risk of restenosis and the requirement for revascularization and potential procedure-related complications.
- Ticagrelor has significant benefits compared to clopidogrel in reducing total death, stent thrombosis, and preventing cardiovascular events according to the PLATO (PLATElet inhibition and patient Outcomes) study but this effect was not well studied in type 2 diabetic patients with small diameter stents.

represented by n (%). To check for normal distribution, either the Kolmogorov–Smirnov test was used. As appropriate, independent *t*-test or the Mann–Whitney *U* test, Pearson chi-square, or Fisher exact tests between the 2 groups were used after evaluation of normal distribution to compare the differences between the clopidogrel group and ticagrelor group. In order to reduce study selection bias, propensity score matching (PSM) was performed with a caliber width of 0.2 of the SD. The baseline characteristics, procedural variables, and outcomes of the clopidogrel and ticagrelor groups were compared once more, controlling for adjustments with PSM. Using multiple binary logistic regression models, the independent risk variables were identified. In the multiple model, only variables that had a *P*-value < .05 in the univariate analysis were included. Cox proportional hazards regression analysis was used to explore the correlation between the different antiplatelet strategies and clinical endpoints. A *P*-value < .05 was considered statistically significant. All the statistical analyses were performed using SPSS (Statistical Package for Social Science, SPSS Inc, Chicago, IL, USA) for Windows, Version 27.0.

## RESULTS

The study included 332 patients, of whom 197 patients were on clopidogrel and 135 on ticagrelor, as shown in the patient recruitment pathway in Figure 1. Males made up around 68% of the subjects. Following matching, patients in the ticagrelor group had greater rates of obesity, ischemic heart disease, hypertension, hyperlipidemia, and chronic kidney disease (CKD) compared to the clopidogrel group; however, the effect was only statistically significant for hyperlipidemia. Differences in baseline characteristics, medical history, and medications between both groups before and after propensity score matching are shown in Table 1.

It should be noted that left anterior descending coronary artery was the culprit vessel in 79 (23.7%) vs. 54 (16.2%) patients in the clopidogrel and ticagrelor groups, respectively. In the study, anterior wall MI accounted for 50.5% of

all ST-segment myocardial infarction (STEMI) cases, with clopidogrel patients having higher rates of STEMI. The presentations and procedural outcomes among the clopidogrel and ticagrelor groups were comparable in Table 2. Second-generation Drug eluting stent, everolimus-eluting coronary stent, Xience (Abbott Vascular, Santa Clara, CA, USA) or Synergy (Boston Scientific), and zotarolimus eluting coronary stents: Resolute Onyx and Onyx Frontier (Medtronic, Santa Rosa, CA, USA) were used. Prior to stenting, nearly all patients (97.3%) underwent predilation balloon angioplasty. With respect to ischemic events, there was no significant interaction in the total trial group based on insulin treatment or baseline HbA1c levels. No cardiovascular death, myocardial infarction, or ischemic stroke were recorded in either group during the 30-day treatment period.

### Analysis of Risk Factors of Outcomes

Logistic regression analysis of clinical characteristics, medical history, medications, laboratory biomarkers, and coronary angiography outcomes showed that male gender, history of ischemic heart disease, EF, coronary lesion type and presence of CKD were found to be potential predictors for the composite of CD, MI, stroke, TVR endpoint (Table 3).

### Clinical Outcomes and Survival Analysis

Univariate and multiple Cox proportional hazards regression were used to identify the factors affecting the survival outcome of primary and secondary endpoints, including the predictors from logistic regression analysis (Table 4). The 12-month analysis showed a higher incidence of composite of CD, MI, stroke, and TVR in clopidogrel group (21.6% vs. 15.5%) than in the ticagrelor group. However, based on the Cox survival regression analysis, the results showed no significant difference in the primary endpoint between the 2 groups in the crude analysis (HR = 1.25, 95% CI: 0.70-2.22, *P* = .437) and in the propensity score matched analysis (HR = 1.39, 95% CI: 0.751-2.573, *P* = .295) (Figure 2). Compared with the patients who received clopidogrel, those who received ticagrelor had lower incidences of cardiac death after 12 months follow-up.

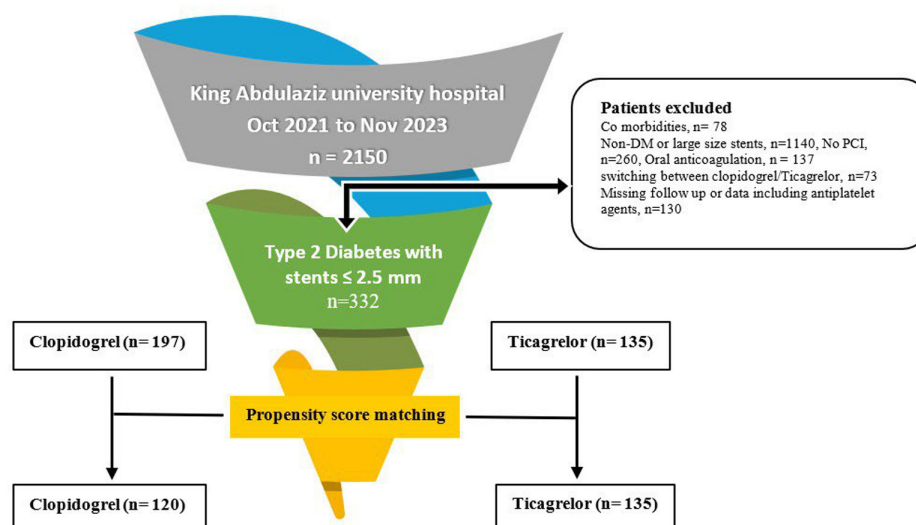


Figure 1. Study flow chart.

**Table 1. Baseline Clinical and Medical Characteristics Between Clopidogrel and Ticagrelor Group**

Variables	All Patients			P	Propensity-Matched Patients		
	Total (n = 332)	Clopidogrel (n = 197)	Ticagrelor (n = 135)		Clopidogrel (n = 120)	Ticagrelor (n = 135)	P
Age, years	55 (48.0-62.0)	54.3 ± 9.1	54.3 ± 9.4	.482	55.44 ± 8.5	54.3 ± 9.4	.955
BMI, kg/m <sup>2</sup>	23.9 (22.3-25.8)	23.7 ± 4.1	24.1 ± 7.2	.542	23.1 ± 4.7	24.1 ± 7.2	.614
Females, n (%)	106 (31.9%)	65 (33.0%)	41 (30.4%)	.614	39 (32.5%)	41 (30.4%)	.714
Males, n (%)	226 (68.1%)	132 (67.0%)	94 (69.6%)		81 (67.5%)	94 (69.6%)	
Medical history							
Current smoker, n (%)	84 (25.3%)	52 (26.4%)	32 (23.7%)	.576	31 (25.8%)	32 (23.7%)	.694
X-smoker, n (%)	29 (8.7%)	15 (7.6%)	14 (10.4%)	.853	11 (9.2%)	14 (10.4%)	.747
Previous MI, n (%)	20 (6%)	13 (6.6%)	7 (5.2%)	.595	8 (6.7%)	7 (5.2%)	.616
Ischemic heart disease, n (%)	110 (33.1%)	57 (28.9%)	53 (39.3%)	.065	42 (35.0%)	53 (39.3%)	.483
Peripheral vascular disease, n (%)	3 (0.9%)	1 (0.5%)	2 (1.5%)	.357	1 (0.8%)	2 (1.5%)	.632
Ischemic stroke, n (%)	5 (1.5%)	3 (1.5%)	2 (1.5%)	.976	2 (1.7%)	2 (1.5%)	.905
Previous PCI, n (%)	76 (22.9%)	45 (22.8%)	31 (23.0%)	.999	32 (26.7%)	31 (23.0%)	.494
Previous CABG, n (%)	10 (3.0%)	7 (3.6%)	3 (2.2%)	.596	5 (4.2%)	3 (2.2%)	.374
Hypertension, n (%)	209 (62.9%)	119 (60.4%)	90 (66.7%)	.386	78 (65.0%)	90 (66.7%)	.779
Hyperlipdemia, n (%)	49 (14.8%)	23 (11.7%)	26 (19.3%)	.056	11 (9.2%)	26 (19.3%)	.022*
CKD, n (%)	77 (23.2%)	52 (26.3%)	25 (18.5%)	.095	19 (15.8%)	25 (18.5%)	.494
Previous cancer, n (%)	2 (0.6%)	1 (0.5%)	1 (0.7%)	.787	1 (0.8%)	1 (0.7%)	.933
Medications							
ACEI, n (%)	29 (8.7%)	15 (7.6%)	14 (10.4%)	.382	8 (6.7%)	14 (10.4%)	.293
ARB, n (%)	188 (56.6%)	104 (52.7%)	84 (62.2%)	.343	90 (75%)	84 (62.2%)	.494
Statins, n (%)	37 (11.1%)	21 (10.7%)	16 (11.9%)	.735	13 (10.8%)	16 (11.9%)	.798
Beta blockers, n (%)	198 (59.6%)	97 (49.2%)	101 (74.8%)	.502	67 (55.5%)	101 (74.8%)	.357
Proton pump inhibitors, n (%)	192 (57.8%)	91 (46.1%)	101 (74.8%)	.202	72 (60%)	101 (74.8%)	.521
Calcium channel blockers, n (%)	67 (20.1%)	42 (21.3%)	25 (18.5%)	.332	31 (25.8%)	25 (18.5%)	.611
Diuretics, n (%)	148 (44.5%)	76 (38.5%)	72 (53.3%)	.622	58 (48.3%)	72 (53.3%)	.774
Insulin, n (%)	213 (64.1%)	118 (59.8%)	95 (70.3%)	.554	72 (60.0%)	95 (70.3%)	.324
hypoglycemic agents, n (%)	167 (50.3%)	116 (58.8%)	51 (37.7%)	.078	69 (57.5%)	51 (37.7%)	.224
Baseline laboratory findings							
Hemoglobin, g/dL	14.3 (12.7-15.6)	13.8 ± 2.5	14.3 ± 2.3	.550	14.2 ± 2.2	14.3 ± 2.3	.573
Leukocyte, 10 <sup>9</sup> /L	9.3 (7.5-11.9)	10.3 ± 3.8	9.4 ± 3.5	.020*	10.0 ± 3.5	9.4 ± 3.5	.182
Platelets, 10 <sup>9</sup> /L	106 (214.0-299.7)	268 ± 102	266 ± 111	.844	266 ± 116	266 ± 111	.998
Glycosylated hemoglobin, %	6.5 (5.7-8.8)	7.4 ± 2.2	7.2 ± 2.1	.572	6.8 ± 2.0	7.2 ± 2.1	.101
eGFR, mL/min	78.3 (61.2-90.7)	75 ± 23.3	79 ± 20.6	.908	74.9 ± 22.6	79 ± 20.6	.123
Total cholesterol, mmol/L	4.1 (3.4-5.3)	4.3 ± 1.3	4.2 ± 1.3	.452	4.2 ± 1.3	4.2 ± 1.3	.442
Triglyceride, mmol/L	1.4 (1.0-2.1)	1.75 ± 1.00	1.74 ± 1.05	.908	1.7 ± 1.05	1.74 ± 1.05	.744
LDL, mmol/L	3.0 (2.2-3.9)	4.3 ± 1.4 b	3.0 ± 1.1	.377	3.0 ± 1.2	3.0 ± 1.1	.864

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention.

\*Significant value, data expressed in median and interquartile range, mean and SD or n and % which is percentage from total population in the group.

**Table 2. Baseline Presentations and Procedural Characteristics Between Clopidogrel and Ticagrelor Group**

Variables	All Patients			P	Propensity-Matched Patients		
	Total (n = 332)	Clopidogrel (n = 197)	Ticagrelor (n = 135)		Clopidogrel (n = 120)	Ticagrelor (n = 135)	P
Systolic BP	128.92 ± 18.9	129.07 ± 19.6	128.71 ± 19.7	.709	130.47 ± 19.4	128.71 ± 19.7	.454
LVEF	43.59 ± 12.3	43.32 ± 12.2	43.00 ± 12.00	.424	44.58 ± 12.6	43.00 ± 12.00	.714
Vasopressor use after PCI	36 (10.8%)	25 (7.5%)	11 (3.3%)	.414	13 (10.8%)	11 (3.3%)	.760
Presentations							
STEMI	89 (26.8%)	76 (38.6%)	13 (9.6%)	.001*	27 (22.5%)	13 (9.6%)	.015*
NSTEMI	131 (39.5%)	71 (36%)	60 (44.4%)		53 (44.2%)	60 (44.4%)	
UA	68 (20.5%)	27 (13.7%)	41 (30.4%)		22 (18.3%)	41 (30.4%)	
CCS	44 (13.3%)	23 (11.7%)	21 (15.6%)		18 (15.0%)	21 (15.6%)	
Lesion type				.200			.456
Type A	94 (28.3%)	54 (27.4%)	40 (29.6%)		36 (30.0%)	40 (29.6%)	
Type B	103 (31.0%)	64 (32.5%)	39 (28.9%)		41 (34.2%)	39 (28.9%)	
Type C	76 (22.9%)	45 (22.8%)	31 (23.0%)		21 (17.5%)	31 (23.0%)	
Total thrombotic	35 (10.5%)	24 (12.2%)	11 (8.1%)		13 (10.8%)	11 (8.1%)	
CTO	21 (6.3%)	10 (5.0%)	11 (8.1%)		9 (7.5%)	11 (8.1%)	
ISR	3 (0.9%)	0	3 (2.2%)		0	3 (2.2%)	
Number of vessels affected				.118			.228
Single vessel	178 (53.6%)	111 (56.3%)	67 (49.6%)		63 (52.5%)	67 (49.6%)	
Two vessels	95 (28.6%)	58 (29.4%)	37 (27.4%)		40 (33.3%)	37 (27.4%)	
≥3 vessels	59 (17.8%)	28 (14.2%)	31 (22.9%)		17 (14.1%)	31 (22.9%)	
Stent location				.169			.564
Ostial	28 (8.4%)	12 (6.0%)	16 (11.9%)		8 (6.7%)	16 (11.9%)	
Proximal	110 (33.1%)	63 (32.0%)	47 (34.8%)		44 (36.7%)	47 (34.8%)	
Proximal to mid	45 (13.5%)	27 (13.7%)	18 (13.3%)		13 (10.8%)	18 (13.3%)	
Mid	79 (23.7%)	55 (27.9%)	24 (17.8%)		28 (23.3%)	24 (17.8%)	
Mid to distal	15 (4.5%)	10 (5.1%)	5 (3.7%)		7 (5.8%)	5 (3.7%)	
Distal	55 (16.5%)	30 (15.2%)	25 (18.5%)		20 (16.7%)	25 (18.5%)	
Stent size	2.44 ± 0.13	2.45 ± 0.11	2.42 ± 0.15	.045*	2.45 ± 0.12	2.42 ± 0.15	.177
Stent length	23.42 ± 8.4	23.17 ± 8.2	23.70 ± 8.8	.519	22.4 ± 7.91	23.70 ± 8.8	.221
Glycogen 2b3a inhibitor	52 (15.7)	37 (18.8%)	15 (11.1%)	.059	14 (11.7%)	15 (11.1%)	.889
Everolimus stent	128 (38.6%)	81 (41.1%)	116 (58.9%)	.247	41 (34.2%)	116 (58.9%)	.913
Zotarolimus stent	204 (61.4)	47 (34.8%)	88 (65.2%)		79 (65.8%)	88 (65.2%)	

BP, blood pressure; CCS, chronic coronary syndrome; CTO, chronic total occlusion; ISR, in stent restenosis; LVEF, left ventricular ejection fraction; NSTEMI, Non-ST-segment myocardial infarction; SBP, systolic blood pressure; STEMI, ST-segment myocardial infarction; UA, unstable angina.

\*Significant value, data expressed in mean and SD or n and % which is percentage from total population in the group.

For the secondary endpoints, the total number of bleeding events defined by BARC 2, 3, or 5 did not reach significant statistical difference in crude analysis (HR = 1.315, 95% CI: 0.588-2.941,  $P = .505$ ) and in propensity score matched analysis (HR = 1.095, 95% CI: 0.478-2.511,  $P = .829$ ) (Figure 3).

Sub analysis of CKD patients, the 12-month rates of the composite of CD, MI, stroke, and TVR were lower in the ticagrelor group than in the clopidogrel group in propensity-matched patients (HR = 1.41, 95% CI: 0.619-3.558,  $P = .024$ ). However, ticagrelor group was associated with a higher rate of bleeding than clopidogrel group (20% vs. 9%) (HR = 1.190, 95% CI:

0.580-4.059,  $P = 0.041$ ). In ACS patients, the overall incidences of ischemic (HR = 1.300, 95% CI: 0.692-2.444,  $P = .414$ ) and bleeding (HR = 1.282, 95% CI: 0.553-2.973,  $P = .562$ ) events during the 12-month follow-up period did not differ between treatment groups.

## DISCUSSION

Patients with DM have a higher incidence of cardiovascular events compared with nondiabetic patients, as a result of increased adhesion, chronic proinflammatory and prothrombotic environments that promote platelet activation.<sup>23,24</sup> In managing a certain subset of diabetic patients



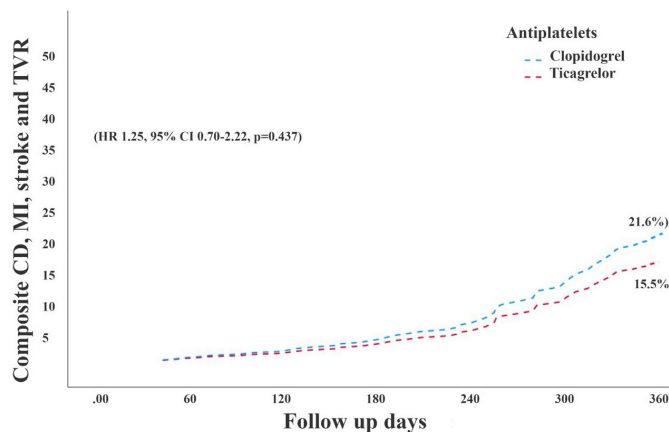
**Table 3. Logistic Regression Analysis of Risk Factors and Predictors of Composite Cardiac Death, MI, stroke, and TVR in Studied Population**

Prognostic factors	OR	95% CI	P
Age	0.979	0.935-1.026	.378
Male gender	2.704	1.237-5.912	.013*
Current smoking	1.268	0.515-3.121	.606
Ischemic heart disease	0.470	0.203-1.087	.048*
Presence of ACS on admission	0.792	0.297-2.109	.640
Hypertension	.995	0.412-2.404	.991
CKD	1.305	0.687-4.058	.019*
Previous stroke	1.220	0.664-4.719	.837
Stent length >15 mm	1.011	0.966-1.057	.643
EF % in-hospital	1.007	0.975-1.139	.049*
Lesion type			
Type A lesion	1.604	0.705-1.996	.033*
Type B lesion	1.881	0.747-3.130	.062
Type C lesion	1.552	0.614-2.763	.031*
Total thrombotic occlusion	1.353	0.627-4.691	.430
CTO	1.531	0.438-2.969	.048*
Stents location inside the vessel			
Ostial stents location	0.674	0.108-4.222	.674
Proximal stents location	1.332	0.391-4.538	.647
Proximal to mid stents location	1.261	0.290-5.491	.757
Mid stents location inside the vessel	2.151	0.608-7.606	.235
Mid to distal stents location	2.496	.427-14.610	.310
LDL	0.678	.458-1.004	.052

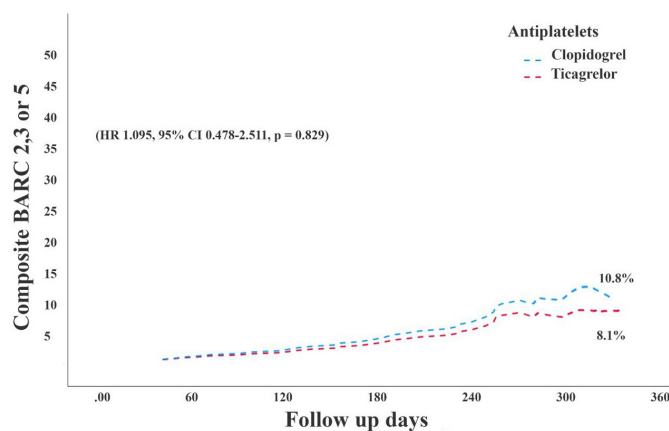
\*Significant values. ACS, Acute coronary syndrome; CKD, chronic kidney disease; CTO, chronic total occlusion; EF, ejection fraction; OR, odds ratio; LDL, low density lipoprotein.

with atherosclerotic small diameter vessels, it is necessary to optimize the antiplatelet strategy and further pay attention to the anatomical and technical complexities. Consideration should be given to the distal location, calcifications, vessel tortuosity, malposition, stent under-expansion, and difficulty in achieving adequate preparation prior to stenting small diameter vessels, which might lead to uncertain outcomes.<sup>25-28</sup>

While ticagrelor offers quicker and more favorable antiplatelet results, clopidogrel is the antithrombotic adjunct to aspirin that is most frequently administered.<sup>29,30</sup> In fact, head-to-head assessments have shown that ticagrelor provides better advantages than clopidogrel in the treatment of acute coronary syndrome.<sup>8</sup> Furthermore, ticagrelor may be favorable in diabetes mellitus, where platelet turnover rates are high.<sup>9</sup> One possible explanation for the advantages of ticagrelor over clopidogrel in people with type 2 diabetes mellitus is impaired clopidogrel metabolism resulting in less



**Figure 2. Twelve-month cumulative incidence of cardiac death, MI, stroke, and TVR.**



**Figure 3. Twelve-month cumulative incidence of bleeding BARC 2, 3, and 5.**

exposure to the active clopidogrel metabolite.<sup>31</sup> Notably, no differences in clopidogrel- or ticagrelor-mediated platelet inhibition were found when comparing patients with or without insulin therapy. The antiplatelet impact of ticagrelor, however, is more potent than clopidogrel after the loading dose and during the maintenance phase of therapy.<sup>32</sup>

Our study compared clinical outcomes between the clopidogrel and ticagrelor groups in patients with diabetes after stenting with small diameter stents. The rates of MACEs, bleeding, and net adverse clinical events did not significantly differ between individuals treated with ticagrelor or clopidogrel during a 12-month follow-up. These outcomes were comparable to those of earlier research projects including individuals with diabetes. According to research by Ahn et al, prasugrel/ticagrelor (n = 1000) significantly increased the number of major bleeding events compared to clopidogrel treatment (n = 2985) but did not improve the composite of cardiac mortality, recurrent MI, or stroke in MI patients with diabetes having PCI.<sup>33</sup> In addition, Goto et al<sup>34</sup> and Park et al<sup>35</sup> discovered a minor rise in the number of major bleeding incidents in the ticagrelor treatment group. However, among Asian patients, there was no appreciable difference in the risk of ischemia between the ticagrelor and clopidogrel groups.<sup>33-35</sup> It should be noted that part of this study

**Table 4. Primary and Secondary Endpoints Between Clopidogrel and Ticagrelor Groups After Propensity Matching**

Variables	All Patients				Propensity-Matched Patients			
	C (n = 197)	T (n = 135)	HR (95% CI)	P	C (n = 120)	T (n = 135)	HR (95% CI)	P
Primary endpoints								
Composite 1 year of CD, MI, stroke, TVR	40 (20.3%)	21 (15.5%)	1.256 (0.707-2.229)	.437	26 (21.6%)	21 (15.5%)	1.390 (0.751-2.573)	.295
CD	9 (4.6%)	3 (2.2%)	1.88 (0.450-3.915)	.385	5 (4.2%)	3 (2.2%)	1.44 (.677-3.495)	.136
MI	7 (3.6%)	4 (3.0%)	1.38 (0.473-2.970)	.422	5 (4.2%)	4 (3.0%)	1.20 (0.492-2.362)	.382
Stroke	4 (2.0%)	3 (2.2%)	0.74 (0.124-1.495)	.750	2 (1.7%)	3 (2.2%)	0.69 (0.095-1.127)	.722
TVR	20 (10.2%)	11 (8.1%)	0.86 (0.962-1.905)	.717	14 (11.7%)	11 (8.1%)	0.90 (0.389-2.081)	.806
Secondary endpoints								
Stent thrombosis	5 (2.5%)	3 (2.2%)	0.75 (0.126-4.524)	.757	2 (1.7%)	3 (2.2%)	0.93 (0.149-5.824)	<b>.564</b>
Non-TVR	16 (8.1%)	10 (7.4%)	0.99 (0.421-2.340)	.986	11 (9.2%)	10 (7.4%)	0.87 (0.336-2.252)	.775
Composite BARC 2, 3, or 5	15 (7.6%)	11 (8.1%)	1.31 (0.588-2.941)	.505	13 (10.8%)	11 (8.1%)	1.09 (0.478-2.511)	.829
<b>Sub analysis of CKD matched patients ≥ stage 2</b>	<b>C (n = 33)</b>	<b>T (n = 25)</b>						
Composite 1 year of CD, MI, stroke, TVR	9 (27.3%)	4 (16.0%)	1.41 (0.619-3.558)	.024				
Composite BARC 2, 3, or 5	3 (9%)	5 (20%)	1.19 (0.580-4.059)	.041				
<b>Sub analysis of ACS matched patients</b>	<b>C (n = 114)</b>	<b>T (n = 114)</b>						
Composite 1 year of CD, MI, stroke, TVR	22 (19.2%)	17 (14.9%)	1.30 (0.692-2.444)	.414				
Composite BARC 2, 3, or 5	10 (8.8%)	12 (10.5%)	1.28 (0.553-2.973)	.562				

\*Significant values.

BARC, bleeding academic research consortium; C, clopidogrel group; CD, cardiac death; CKD, chronic kidney disease; HR, hazards ratio; MI, myocardial infarction; T, ticagrelor group; TVR, target vessel revascularization.

population is Asian and this may contribute to our results; hence, a racially differentiated antiplatelet strategy might be needed in future studies. Additionally, small diameter coronary artery intervention still has a technical challenge with uncertain outcomes.<sup>25-28</sup>

In the current study, male gender, history of ischemic heart disease, EF, coronary lesion type and presence of CKD were found to be potential predictors for the composite of CD, MI, stroke, TVR endpoint in univariate logistic regression model analysis. Further research is required on this. Without doubt, both DM and CKD are independently linked to a higher risk of cardiovascular ischemic events; moreover, these 2 conditions might compound the hazards when they co-exist.<sup>9,36</sup> The combination of DM and CKD had a 2-3 folds increase in the risk of mortality.<sup>37,38</sup> Despite the continuous improvements in stent design and preventive therapies, diabetic patients with CKD still had a 1.6-fold greater risk of repeat revascularization and 1.6-fold higher risk of BARC 3 or 5 bleeding, compared with patients without these risk factors.<sup>38</sup>

The advantage of ticagrelor was seen in a subgroup analysis of the PLATO research, with patients with CKD (eGFR of <60 mL/min) seeing a higher absolute reduction in ischemia risk than those with normal renal function; however, the associated risk of bleeding increased with CKD stage.<sup>39</sup> In our analysis, we found that 20%-25% of diabetic patients had CKD. This proportion is consistent with previous cardiovascular RCTs.<sup>8</sup> Sub analysis of CKD patients in the present study demonstrated similar results at a 12-month follow-up, as rate of composite of CD, MI, stroke, and TVR was lower in the ticagrelor group than in the clopidogrel group in propensity-matched patients (HR = 1.41, 95% CI: 0.619-3.558, *P* = .024). However, ticagrelor group was associated with a higher rate of bleeding than clopidogrel group (20% vs. 9%), (HR = 1.190, 95% CI: 0.580-4.059, *P* = .024). SWEDEHEART database sub-analysis of patients with ACS and CKD showed that patients with CKD stage 3 treated with ticagrelor had a lower mortality rate, MI, and stroke at 12 months than the clopidogrel group; however, no definite benefit was observed for patients with advanced CKD and End stage renal disease

(ESRD). Meanwhile, for patients with CKD stage 3, bleeding rates were comparable between both treatment groups; however, a tendency toward higher bleeding rates was recorded in patients with advanced CKD, including those with ESRD.<sup>40</sup> Anyhow, long-term randomized clinical trials including mortality are needed to verify this patient cohort.

### Study Limitations

There are various constraints to consider when interpreting the results of this study. First, residual confounding, a known potential source of error in registry research, is made possible by the observational study design. Secondly, the absolute risk of bleeding is lower in the registry than the risk seen in clinical trials. It is conceivable that this relates to underreporting of bleeding events in the registry. However, this should impact the absolute number of bleeds and not the relative risk with ticagrelor. Third, intravascular imaging-guided stent deployment was not used in this study in demonstrating that coronary stenting is effective in establishing and maintaining small coronary artery patency without complications. Finally, a larger number of patients would increase the study's power, resulting in more precise estimates. Further prospective multicenter trials enrolling larger patient numbers with diabetes, different risk factors, and ESRD are recommended to evaluate the outcomes in the Middle East population.

### CONCLUSION

In conclusion, our study shows that ticagrelor did not improve the composite of cardiac death, MI, stroke, target vessel revascularization, or the risk of bleeding events defined by the BARC criteria in patients with diabetes and small diameter stents compared with clopidogrel emphasizing the importance of individualized treatment decisions based on patient characteristics and preferences. However, the results may not be representative of the entire population. Further research is warranted to validate these findings and explore long-term outcomes.

**Data Availability Statement:** The data supporting the findings of this study are not publicly available due to privacy concerns but are available from the corresponding author.

**Ethics Committee Approval:** The study was approved by the Unit of Biomedical Ethics in King Abdulaziz University Hospital, Chairman of the Research Ethics Committee; Professor Hasan Alzahrani. Research Ethics Committee (REC) NCBE Registration No.: (HA-02-J-008) with Reference No. 307-21.

**Informed Consent:** Written informed consent was obtained from participants to participate in 1-year follow-up. The study was conducted in accordance with the Helsinki Declaration of 1971, as revised in 1983.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** A.S.A. and M.Q. contributed to conceptualization, methodology, and statistical analysis. R.M.A. and E.M.E. organized and collected database. G.Y.D. and H.H.M. prepared draft preparation. R.H.A., R.S.B., and A.H. contributed to supervision, review, and editing. All authors have read and agreed to the published version of the manuscript.

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