**Ticagrelor Monotherapy After PCI in Patients with Concomitant Diabetes Mellitus and Renal Disease: TWILIGHT DM-CKD**

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**Short Title:** Ticagrelor Monotherapy in DM-CKD Patients

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**ABSTRACT**

**Aims**: Chronic kidney disease (CKD) and diabetes mellitus (DM) are two established risk factors for adverse cardiovascular events in patients undergoing percutaneous coronary intervention (PCI). We aimed to evaluate the treatment effects of ticagrelor monotherapy in the very high-risk cohort of patients with concomitant CKD and DM.

**Methods and Results**: In the TWILIGHT trial, after 3 months of dual antiplatelet therapy post-PCI with ticagrelor and aspirin, patients were randomized to either aspirin or a placebo in addition to ticagrelor for an additional 12 months. Enrolled patients with available information on DM and CKD status were included in this subanalysis and were stratified by the presence or absence of either conditions. Out of 6273 patients, 3391 (54.1%) had neither CKD nor DM (DM-/CKD-), 1822 (29.0%) had DM only (DM+/CKD-), 561 (8.9%) had CKD only (DM-/CKD+), and 8.0% had both CKD and DM (DM+/CKD+). Ticagrelor plus placebo reduced the primary endpoint of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding compared with ticagrelor plus aspirin across all four groups, including DM+/CKD+ patients (4.7% vs. 8.7%; HR 0.52, 95% CI 0.25-1.07), with no evidence of heterogeneity (p-interaction=0.68). The key secondary ischemic endpoint of death, myocardial infarction, or stroke was similar between treatment arms across all groups, except for reduced risk in DM+/CKD- patients receiving ticagrelor monotherapy (p-interaction=0.03).

**Conclusions**: Irrespective of the concomitant presence of DM and CKD, ticagrelor monotherapy reduced the risk of bleeding without a significant increase in ischemic events compared with ticagrelor plus aspirin.

**Keywords:** diabetes; chronic kidney disease; ticagrelor monotherapy; aspirin; PCI

## INTRODUCTION

The prevalence of chronic kidney disease (CKD) and diabetes mellitus (DM) has globally increased over the last few decades.[1] The two conditions often co-exist as a single entity, namely diabetic kidney disease, that further increases the risk of cardiovascular complications associated with each condition alone.[2,3] This is noteworthy because diabetic kidney disease develops in approximately 40% of patients who have DM and is the leading cause of CKD worldwide.[4] In this context, antiplatelet therapy constitutes the main pillar for the prevention of ischemic events, especially among those with established coronary artery disease undergoing percutaneous coronary intervention (PCI).[5] However, patients with coexistent CKD and DM are not only exposed to an increased risk of cardiovascular events but also show a greater propensity for bleeding compared to patients with either conditions.[6-8] Therefore, the choice of antiplatelet therapy is critical in this vulnerable cohort and should be individualized. Effective antithrombotic strategies aimed at mitigating the bleeding risk without compromising the ischemic protection are of utmost importance for optimizing patient outcomes. One such strategy was tested in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, which randomized high-risk PCI patients after three months of dual antiplatelet therapy (DAPT) with the potent P2Y12 inhibitor ticagrelor to either aspirin or placebo in addition to ticagrelor. The main trial findings showed that this approach reduces the risk of clinically relevant bleeding while preserving adequate antithrombotic efficacy.[9] Nevertheless, it is unclear if the clinical benefits of early aspirin discontinuation followed by ticagrelor monotherapy post-PCI are preserved in very high-risk subsets of patients, including those with diabetic kidney disease. Research efforts are needed to address the unmet medical needs of this high-risk population. Therefore, we conducted an exploratory analysis of the

TWILIGHT trial to examine the safety and efficacy of ticagrelor monotherapy according to DM and CKD status.

## METHODS

### *Trial Design and Oversight*

We performed a post-hoc analysis of the TWILIGHT trial (NCT02270242). TWILIGHT was a randomized, placebo-controlled trial that enrolled 9006 patients in 187 sites across 11 countries, from July 2015 through July 2019. The trial rationale, study design, and main findings have been previously described.[9, 10] In brief, following successful PCI with at least one drug-eluting stent (DES) implantation, patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily) for three months. Thereafter, patients without major bleeding or ischemic events were randomized in a 1:1 double-blind fashion to aspirin or matching placebo for 12 months in addition to open-label ticagrelor.

The study was designed, coordinated, and sponsored by the Icahn School of Medicine at Mount Sinai (New York, United States of America). The trial was supported by an investigator-initiated grant from AstraZeneca, which supplied ticagrelor but had no interfering roles in the study design or execution. The trial protocol was approved by national regulatory agencies, institutional review boards, or local ethics committees. An independent data safety monitoring board provided oversight by periodically reviewing reported serious adverse events.

### *Trial Population*

The TWILIGHT trial enrolled patients with at least one clinical (i.e., age ≥65 years, female sex, troponin positive acute coronary syndrome, atherosclerotic vascular disease (prior myocardial infarction, coronary revascularization or peripheral arterial disease), DM requiring medication,

and CKD) and one angiographic (i.e., multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring two stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices) feature that confers a high risk for ischemic or bleeding events. Patients with dialysis-dependent renal failure, presentation with ST-elevation myocardial infarction, cardiogenic shock, prior stroke, or need for oral anticoagulation were excluded. As pre-specified in the trial protocol, CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73m$^2$, calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[11] To note, both CKD and DM were clinical study entry criteria.

***Outcomes***

The primary endpoint was a composite of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding up to 1 year after randomization. The key secondary endpoint was a composite of all-cause death, myocardial infarction (MI), or stroke. Other secondary endpoints included all-cause death, and MI or definite or probable stent thrombosis. MI was defined according to the third universal definition, and stent thrombosis was classified according to the Academic Research Consortium definition.[12, 13] All clinical events were adjudicated by an independent committee, blinded to the treatment assignment.

***Statistical Analyses***

We stratified patients into four groups based on the presence (+) or absence (-) of CKD and DM. We excluded patients with unknown eGFR or DM status. Baseline clinical and procedural characteristics are described using frequencies and means (standard deviation) for categorical and continuous variables, respectively. The cumulative incidence of the primary and secondary endpoints was determined using the Kaplan-Meier method. Patients who did not experience the

primary bleeding endpoint between randomization and 12-month follow-up were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox proportional hazards models.

Bleeding and ischemic outcomes were compared across study groups with a log-rank test for trend where DM-/CKD- was considered as the lowest risk group, followed by DM+/CKD-, DM-/CKD+, and lastly DM+/CKD+. A multivariable Cox model that included the following clinically relevant variables was used for risk adjustment: age (years), gender, body mass index ($kg/m^2$), enrolling region, smoking status, anemia, prior PCI, prior coronary artery bypass, multivessel disease and indication for PCI.

Treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin were evaluated in each CKD/DM group, with formal interaction testing to assess for treatment effect modification.

For all analyses, bleeding outcomes were assessed in the intention-to-treat cohort, while ischemic outcomes were analyzed using the per-protocol cohort. A two-sided p-value of $<0.05$ was considered statistically significant. All analyses were performed using Stata version 16.0 (College Station, Texas).

## RESULTS

### *Patient Characteristics*

Of the 7119 patients undergoing randomization at 3 months after PCI, 846 were excluded for country-specific regulatory reasons (n=587) or for missing information on renal function (n=259). Out of 6273 patients included in this analysis, 3391 (54.1%) had neither CKD nor DM (DM-/CKD-), 1822 (29.0%) had DM but not CKD (DM+/CKD-), 561 (8.9%) had CKD but not DM (DM-/CKD+), and 499 (8.0%) had both DM and CKD (DM+/CKD+) (**Supplementary**

**Figure 1**). Baseline clinical and procedural characteristics are presented in **Tables 1** and **2**, respectively. Patients with DM+/CKD+ were more frequently treated with insulin as compared with DM+/CKD- and they had a higher prevalence of comorbidities such as anemia, hypercholesterolemia, peripheral artery disease, previous revascularization as compared with the other groups. Moreover, these patients had more extensive coronary disease represented by multivessel involvement and higher degree of calcification. Baseline clinical and procedural characteristics were well-balanced across randomized treatment groups (**Supplementary Tables 1** and **2**).

Adherence to ticagrelor at one year was highest in DM-/CKD- (86.9%) and lowest in DM+/CKD+ (78.7%) ($p<0.001$). A similar pattern was observed for adherence to the blinded study drug, though with numerically lower rates across the four groups as compared with open-label ticagrelor (**Supplementary Figure 2**).

***Outcomes according to DM and CKD status***

At 1 year after randomization, the incidence of BARC 2, 3, or 5 bleeding was significantly higher among CKD patients, irrespective of DM status (DM+/CKD+ 6.8%, DM-/CKD+ 7.0%, DM+/CKD- 5.2%, and DM-/CKD- 5.1%; p-trend=0.036; **Figure 1A**). Moreover, there was a stepwise increase in the rates of BARC 3 or 5 bleeding with DM+/CKD+ being at highest risk and DM-/CKD- being at lowest risk (DM+/CKD+ 3.1%, DM-/CKD+ 2.2%, DM+/CKD- 1.7%, and DM-/CKD- 1.0%; p-trend<0.001; **Figure 2B**).

The incidence of all-cause death, MI, or stroke was two- to three-fold higher among DM+/CKD+ patients compared with the other groups (DM+/CKD+ 9.2%, DM-/CKD+ 4.4%, DM+/CKD- 4.5%, and DM-/CKD- 2.9%; p-trend<0.001; **Figure 2A**). Coronary thrombotic events, including

MI or definite/probable ST, were also more frequent in the DM+/CKD+ group (DM+/CKD+ 6.4%, DM-/CKD+ 2.4%, DM+/CKD- 3.2%, and DM-/CKD- 2.3%; p-trend=0.001; **Figure 2B**) After adjustment, bleeding risk in DM+/CKD+ patients was partly attenuated (adjusted HR for BARC 2, 3 or 5: 0.97, 95% CI 0.65-1.44; p-trend=0.948, for BARC 3 or 5: 1.83, 95% CI 0.94-3.54; p-trend=0.076) while ischemic risk remained significantly elevated (adjusted HR for death, MI, or stroke: 2.78, 95% CI 1.88-4.10; p-trend<0.001; for MI or ST 2.51, 95% CI 1.58-4.00; p-trend<0.001 **Table 3**).

***Outcomes according to treatment group***

Ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced the risk of BARC 2, 3, or 5 bleeding consistently across all study groups including DM+/CKD+ patients (4.7% vs. 8.7%; HR 0.52, 95% CI 0.25-1.07), with no evidence of heterogeneity (p-interaction=0.68). Similar treatment effects of ticagrelor monotherapy were observed for major BARC 3 or 5 bleeding (p-interaction=0.17), with DM+/CKD+ patients showing the greatest absolute risk reduction (0.9% vs. 5.1%; HR 0.16, 95% CI 0.04-0.72). The key secondary ischemic endpoint of death, MI, or stroke was not significantly different between treatment arms across study groups, except for a reduced risk in DM+/CKD- patients receiving ticagrelor monotherapy (3.3% vs. 5.7%; HR 0.58, 95% CI 0.37-0.92; p-interaction=0.033). Similar treatment effects between the experimental and control arms were observed across the four groups with respect to secondary endpoints of all-cause death and the composite of MI or stent thrombosis (**Figure 3**).

## DISCUSSION

The main findings of this post hoc analysis of the TWILIGHT trial focused on patients with DM and CKD undergoing PCI are that the concomitant presence of these two conditions was

associated with a significant increase in the risk of clinically relevant BARC 2, 3, or 5 and BARC 3 or 5 bleeding as well as ischemic events, including death, MI, or stroke. Notably, this increased risk among DM+/CKD+ patients persisted after multivariable adjustment, especially when considering major bleeding and ischemic events. Ticagrelor monotherapy, compared with ticagrelor plus aspirin, reduced bleeding complications without a tradeoff in ischemic events, irrespective of CKD and DM status.

These results add to the body of evidence evaluating the impact of diabetic kidney disease on the outcomes of patients undergoing PCI.[3, 14, 15] Diabetic kidney disease is the leading cause of CKD worldwide, and the increasing prevalence of patients with this condition underscores the clinical relevance of our study.[4, 16] The DM+/CKD+ population represents about 5-8% of patients undergoing PCI, a prevalence that was confirmed by the results of our study.[2, 3] The TWILIGHT trial selected patients at high risk of ischemic and bleeding events because of clinical (such as CKD and DM) and angiographic characteristics, and can thus be seen as more representative of real-world practice compared with other lower risk trial cohorts.[17] Despite these high-risk study inclusion criteria, when using DM-/CKD- cohort as a control group, DM+/CKD+ patients experienced a three-fold increased risk of major bleeding and ischemic outcomes.

Both DM and CKD impair platelet-vessel interaction, cause platelet aggregation, and induce a pro-coagulant state with higher levels of fibrinogen and tissue factor.[18,19, 20] Therefore, choosing the best antithrombotic strategy in this population is critical; CKD can lead to drug accumulation and drug-drug interactions,[7, 21] whereas DM reduces enteric-coated aspirin absorption.[22] Furthermore, both diabetic and CKD patients have higher levels of platelet reactivity with clopidogrel, which raises concerns on its safety among those with diabetic kidney disease.[23 24]

To address the above concerns, potent $P2Y_{12}$ inhibitors such as ticagrelor were studied and demonstrated increased ischemic protection compared with clopidogrel among ACS patients with concomitant CKD and DM.[2] However, the ischemic benefit was evaluated on a background combination therapy with aspirin with an inherent risk of bleeding. Moreover, it is unclear whether the observed reductions in ischemic events attributed to ticagrelor reflect the incremental effects of P2Y12 inhibition alone or in combination with aspirin. In a post-hoc analysis of the GLOBAL LEADERS trial on patients with both CKD and DM, 1-month DAPT followed by ticagrelor monotherapy, compared with 12-month DAPT, reduced major cardiac and net adverse clinical events by 26% and 25%, respectively.[3] Although promising, these findings derived from a trial which failed to meet its primary endpoint, and these two outcomes were not prespecified nor adjudicated. In the current analysis, ticagrelor monotherapy after 3-month DAPT was associated with a 48% relative risk reduction in BARC 2, 3, or 5 bleeding among high-risk patients with both DM and CKD, which increased to 84% for BARC 3 or 5 bleeding. Most importantly, this bleeding benefit was achieved without a significant increase in ischemic events as compared with ticagrelor plus aspirin, although the wide confidence intervals do not conclusively rule out a potential for harm. The only exception was a reduction in the risk of the key secondary ischemic endpoint among DM+/CKD- patients receiving ticagrelor monotherapy (p-interaction=0.033). While this observation seems difficult to explain and could be due to a play of chance related to multiple testing, the effects of early aspirin withdrawal in DM patients with and without CKD deserve to be further investigate in dedicated and larger studies. Altogether, these findings reassure on both the safety and efficacy of ticagrelor monotherapy after PCI in patients with concomitant DM and CKD, making this an appealing strategy for this high-risk population.

The present study should be interpreted in light of some important limitations. First, it is a post-hoc analysis; as such, it should be considered exploratory and hypothesis-generating. Second, patients were not randomized according to the presence of DM or CKD. Therefore, we cannot exclude the presence of residual confounders between treatment arms. Third, we did not control for multiplicity, thereby increasing the risk of type 1 error. In addition, the relatively small sample size of the patients with both DM and CKD increases the risk of a type 2 error. Finally, the present findings cannot be extrapolated to patients that were not randomized either because of exclusion criteria at the enrollment (e.g., ST-elevation myocardial infarction) or because they had an adverse event or were not compliant to DAPT within the first three months after PCI.

In conclusion, we demonstrated that PCI patients with concomitant DM and CKD represent a vulnerable cohort with an incidence of both major bleeding and ischemic events nearly three times higher than in those with neither condition. Early aspirin discontinuation after 3-month DAPT followed by potent P2Y12 inhibitor monotherapy with ticagrelor might effectively balance ischemic and bleeding risks in this challenging population. Further evaluation in prospective and adequately powered trials is warranted.

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## FIGURES

**Figure 1. Incidence of bleeding at 1 year after randomization.** Kaplan-Meier curves for (A) BARC 2, 3, or 5 and (B) BARC 3 or 5 bleeding in the four study groups (DM-/CKD-, DM+/CKD-, DM-/CKD+, and DM+/CKD+). BARC: Bleeding Academic Research Consortium; CI: confidence interval; HR: hazard ratio.

**Figure 1A. Incidence of BARC 2, 3, or 5 bleeding at 1 year after randomization**

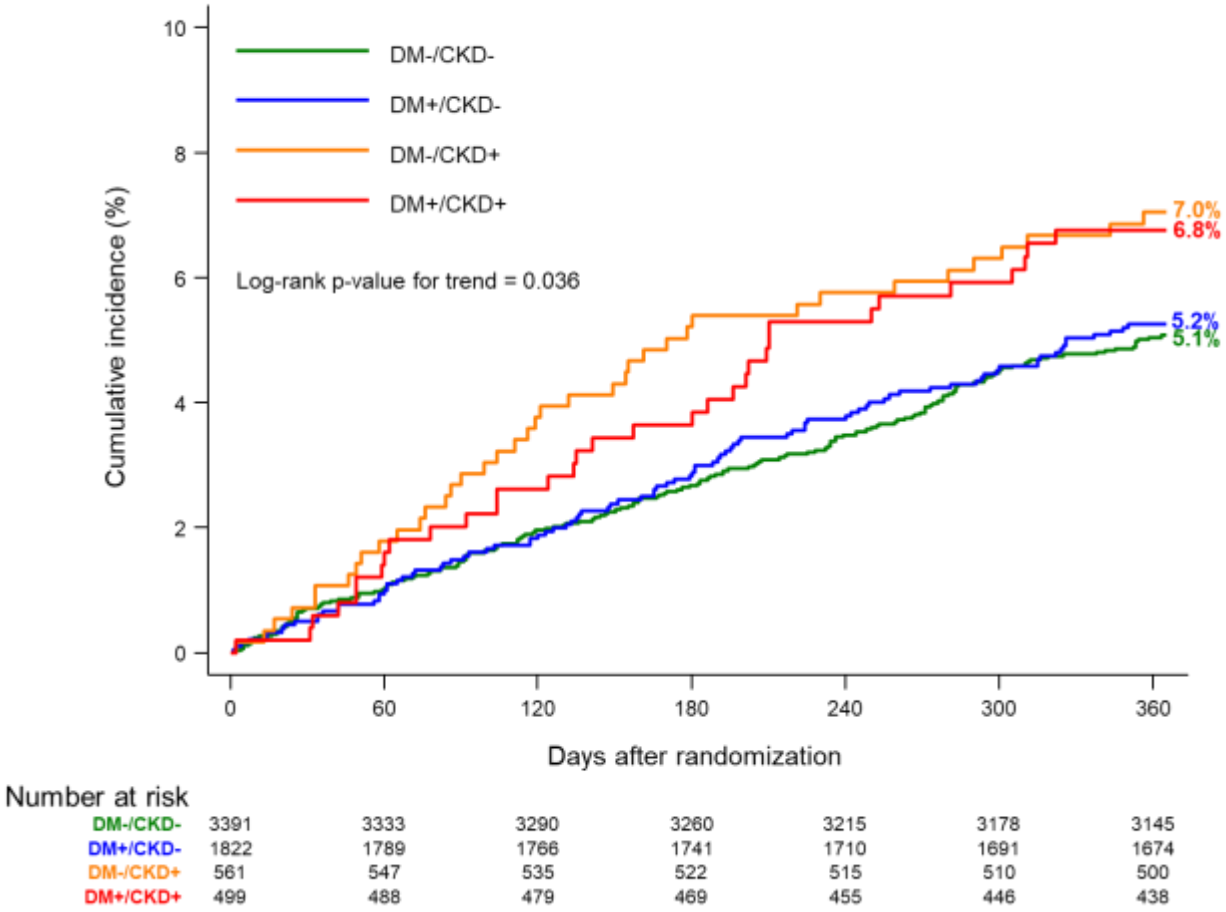
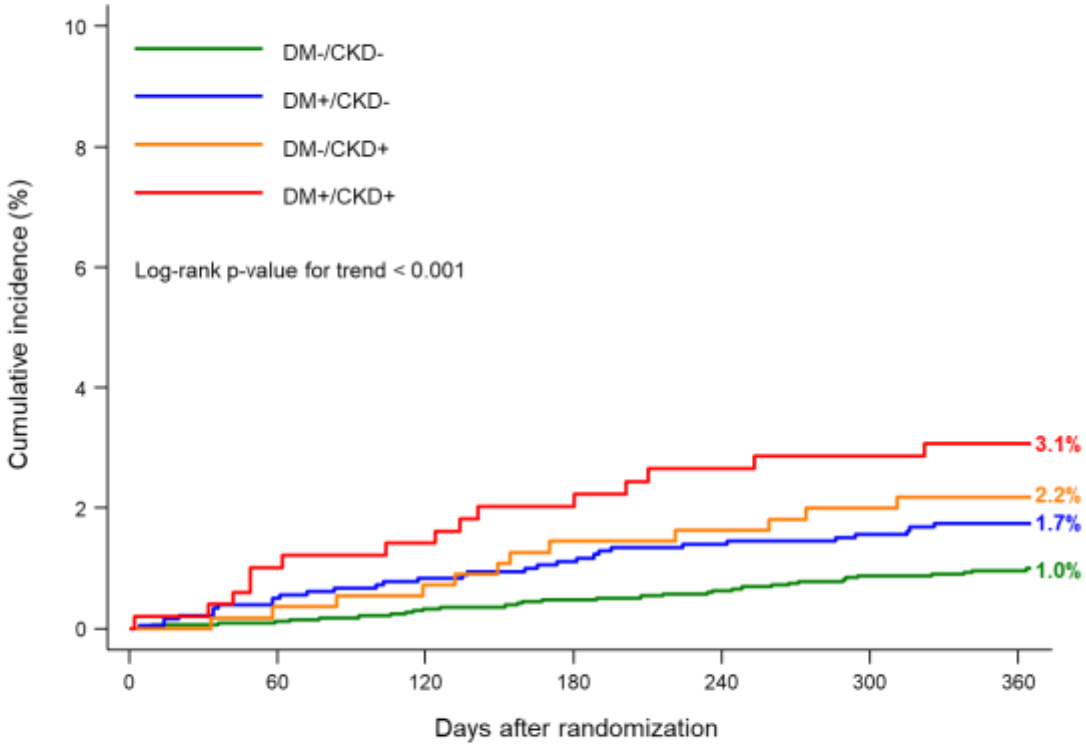


**Figure 1B. Incidence of BARC 3 or 5 bleeding at 1 year after randomization**




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| DM-/CKD- | 3391 | 3362 | 3344 | 3333 | 3310 | 3298 | 3281 |
| DM+/CKD- | 1822 | 1797 | 1783 | 1770 | 1750 | 1741 | 1733 |
| DM-/CKD+ | 561 | 555 | 552 | 543 | 537 | 533 | 526 |
| DM+/CKD+ | 499 | 490 | 485 | 477 | 467 | 460 | 454 |

**Figure 2. Incidence of ischemic events at 1 year after randomization.** Kaplan-Meier curves for (A) death, MI, or stroke and (B) MI or ST (definite/probable) in the four study groups (DM-/CKD-, DM+/CKD-, DM-/CKD+, and DM+/CKD+). CI: confidence interval; HR: hazard ratio; MI: myocardial infarction.

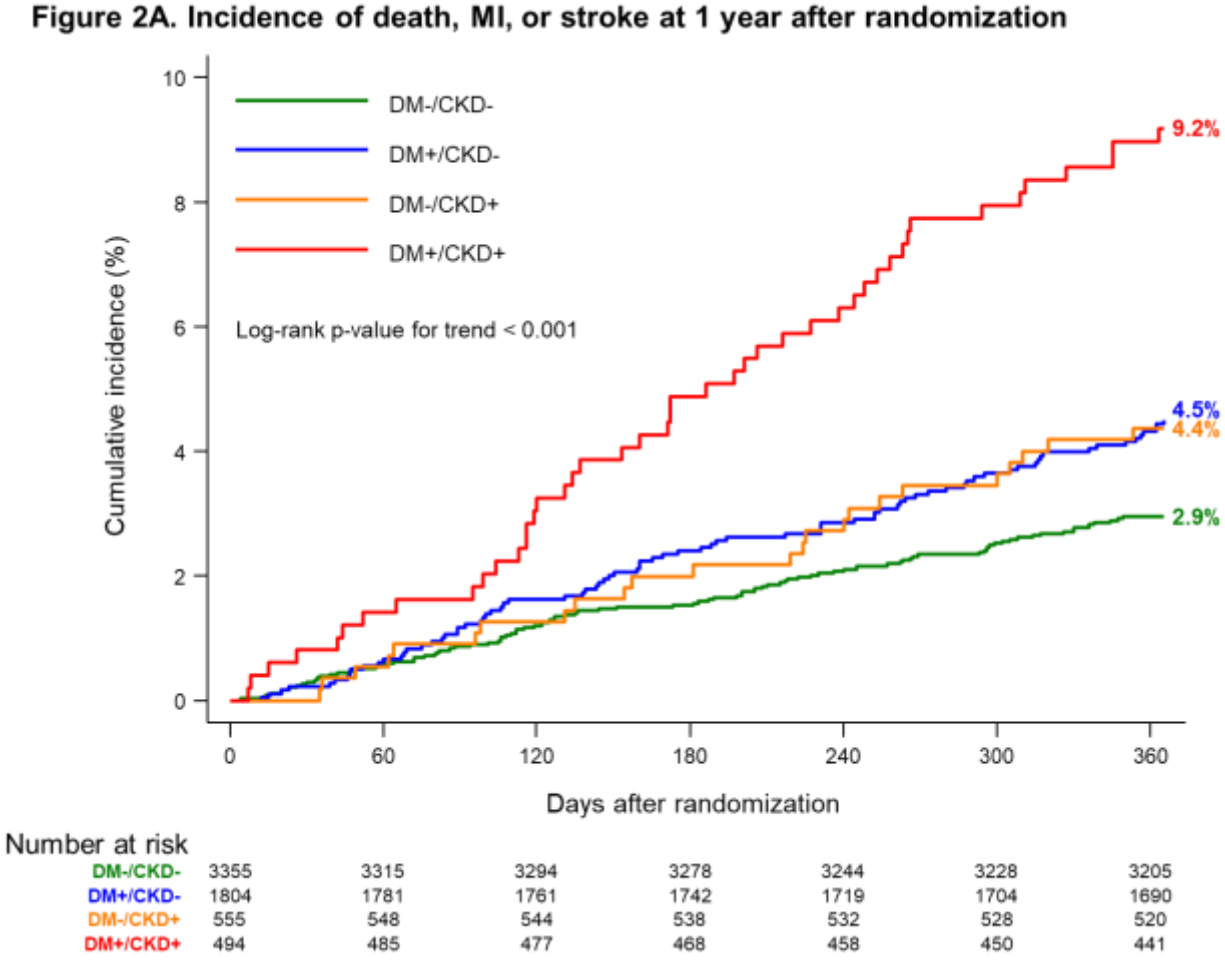
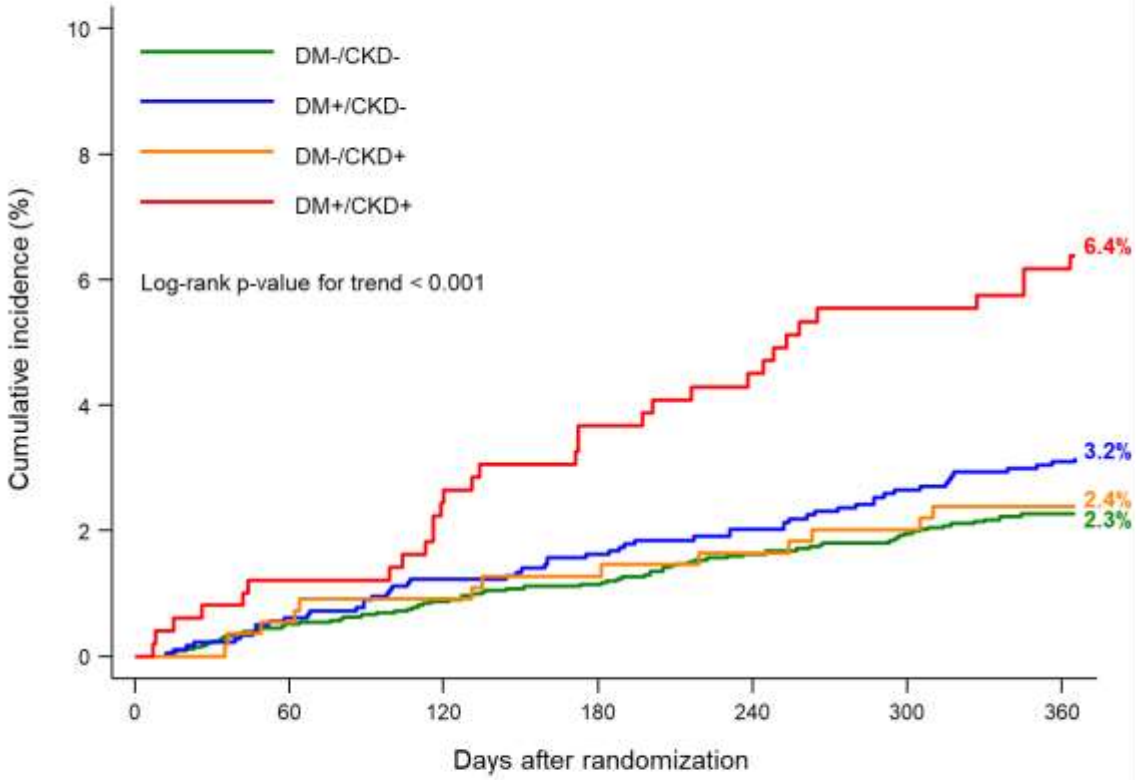


**Figure 2B. Incidence of MI or ST (def/prob) at 1 year after randomization**




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| DM-/CKD- | 3355 | 3317 | 3297 | 3282 | 3248 | 3233 | 3211 |
| DM+/CKD- | 1804 | 1781 | 1762 | 1746 | 1724 | 1709 | 1696 |
| DM-/CKD+ | 555 | 548 | 545 | 539 | 533 | 529 | 521 |
| DM+/CKD+ | 494 | 485 | 477 | 469 | 459 | 451 | 443 |

**Figure 3. Effects of ticagrelor monotherapy of bleeding and ischemic events.** Forest plots showing the effects of ticagrelor plus placebo versus ticagrelor plus aspirin on the bleeding and ischemic endpoints according to DM and CKD status. Event rates at one year were estimated using the Kaplan-Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) with interaction p-values generated using Cox regression. BARC: Bleeding Academic Research Consortium. Bleeding outcomes were performed in the intention-to-treat cohort, while the ischemic outcomes were performed in the per-protocol cohort. *Interaction between randomized treatment assignment and CKD/DM status.

# Figure 3. Effects of ticagrelor monotherapy of bleeding and ischemic events

| | No. of patients | Tica+Placebo no. of events (%) | Tica+Aspirin no. of events (%) | HR (95% CI) | Interaction P-value* |
|---|---|---|---|---|---|
| **Bleeding outcomes** | | | | | |
| BARC 2, 3, or 5 | | | | | |
| DM-/CKD- | 3391 | 59 (3.6%) | 111 (6.6%) | 0.53 (0.39 - 0.73) | |
| DM+/CKD- | 1822 | 40 (4.4%) | 54 (6.1%) | 0.72 (0.48 - 1.08) | 0.680 |
| DM-/CKD+ | 561 | 14 (4.9%) | 25 (9.3%) | 0.51 (0.27 - 0.99) | |
| DM+/CKD+ | 499 | 11 (4.7%) | 22 (8.7%) | 0.52 (0.25 - 1.07) | |
| BARC 3 or 5 | | | | | |
| DM-/CKD- | 3391 | 13 (0.8%) | 20 (1.2%) | 0.66 (0.33 - 1.33) | |
| DM+/CKD- | 1822 | 9 (1.0%) | 22 (2.5%) | 0.40 (0.18 - 0.86) | 0.170 |
| DM-/CKD+ | 561 | 6 (2.1%) | 6 (2.2%) | 0.94 (0.30 - 2.91) | |
| DM+/CKD+ | 499 | 2 (0.9%) | 13 (5.1%) | 0.16 (0.04 - 0.72) | |
| **Ischemic outcomes** | | | | | |
| Death, MI, or stroke | | | | | |
| DM-/CKD- | 3355 | 55 (3.3%) | 43 (2.6%) | 1.30 (0.87 - 1.94) | |
| DM+/CKD- | 1804 | 30 (3.3%) | 50 (5.7%) | 0.58 (0.37 - 0.92) | 0.033 |
| DM-/CKD+ | 555 | 14 (5.0%) | 10 (3.8%) | 1.34 (0.59 - 3.01) | |
| DM+/CKD+ | 494 | 25 (10.5%) | 20 (7.9%) | 1.34 (0.74 - 2.40) | |
| All-cause death | | | | | |
| DM-/CKD- | 3355 | 10 (0.6%) | 13 (0.8%) | 0.78 (0.34 - 1.78) | |
| DM+/CKD- | 1804 | 8 (0.9%) | 16 (1.8%) | 0.49 (0.21 - 1.14) | 0.556 |
| DM-/CKD+ | 555 | 6 (2.1%) | 5 (1.8%) | 1.15 (0.35 - 3.76) | |
| DM+/CKD+ | 494 | 9 (3.8%) | 9 (3.5%) | 1.06 (0.42 - 2.68) | |
| MI or ST (definite/probable) | | | | | |
| DM-/CKD- | 3355 | 42 (2.5%) | 33 (2.0%) | 1.29 (0.82 - 2.04) | |
| DM+/CKD- | 1804 | 23 (2.6%) | 33 (3.8%) | 0.68 (0.40 - 1.16) | 0.270 |
| DM-/CKD+ | 555 | 8 (2.8%) | 5 (1.9%) | 1.52 (0.50 - 4.65) | |
| DM+/CKD+ | 494 | 16 (6.8%) | 15 (6.0%) | 1.14 (0.56 - 2.30) | |

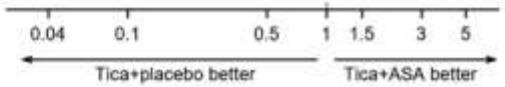


**Table 1.** Baseline clinical characteristics.

| Clinical parameters | Overall (N=6273) | DM-/CKD- N=3391 (54.1%) | DM+/CKD- N=1822 (29.0%) | DM-/CKD+ N=561 (8.9%) | DM+/CKD+ N=499 (8.0%) | P-value |
|---|---|---|---|---|---|---|
| Age, years | 64.0±10.1 | 62.9±10.0 | 61.8±9.4 | 71.9±8.6 | 69.8±8.8 | <0.001 |
| Female sex | 1479 (23.6%) | 757 (22.3%) | 389 (21.4%) | 174 (31.0%) | 159 (31.9%) | <0.001 |
| Nonwhite race | 1538 (24.5%) | 742 (21.9%) | 621 (34.1%) | 70 (12.5%) | 105 (21.0%) | <0.001 |
| BMI, $kg/m^2$ | 28.9±5.7 | 28.1±5.3 | 30.0±5.8 | 28.1±4.9 | 30.7±6.7 | <0.001 |
| Enrolling region | | | | | | <0.001 |
| North America | 2901 (46.2%) | 1460 (43.1%) | 870 (47.7%) | 284 (50.6%) | 287 (57.5%) | |
| Europe | 2375 (37.9%) | 1398 (41.2%) | 576 (31.6%) | 236 (42.1%) | 165 (33.1%) | |
| Asia | 997 (15.9%) | 533 (15.7%) | 376 (20.6%) | 41 (7.3%) | 47 (9.4%) | |
| DM treated with insulin | 627 (27.0%) | N/A | 441 (24.2%) | N/A | 186 (37.3%) | <0.001 |
| Anemia | 1195 (19.2%) | 449 (13.3%) | 369 (20.5%) | 153 (27.6%) | 224 (45.3%) | <0.001 |
| Current smoker | 1350 (21.5%) | 861 (25.4%) | 352 (19.3%) | 82 (14.6%) | 55 (11.0%) | <0.001 |
| Hypercholesterolemia | 4095 (65.3%) | 2045 (60.3%) | 1262 (69.3%) | 378 (67.4%) | 410 (82.2%) | <0.001 |
| Hypertension | 4619 (73.6%) | 2253 (66.5%) | 1462 (80.2%) | 448 (79.9%) | 456 (91.4%) | <0.001 |
| Peripheral arterial disease | 462 (7.4%) | 197 (5.8%) | 131 (7.2%) | 52 (9.3%) | 82 (16.4%) | <0.001 |
| Previous MI | 1857 (29.6%) | 1009 (29.8%) | 540 (29.6%) | 148 (26.4%) | 160 (32.1%) | 0.232 |
| Previous PCI | 2743 (43.7%) | 1386 (40.9%) | 844 (46.3%) | 259 (46.2%) | 254 (50.9%) | <0.001 |
| Previous CABG | 686 (10.9%) | 279 (8.2%) | 223 (12.2%) | 88 (15.7%) | 96 (19.2%) | <0.001 |
| Multivessel CAD | 3908 (62.3%) | 1954 (57.6%) | 1218 (66.8%) | 376 (67.0%) | 360 (72.1%) | <0.001 |
| Previous major bleed | 52 (0.8%) | 26 (0.8%) | 13 (0.7%) | 4 (0.7%) | 9 (1.8%) | 0.140 |
| Indication for PCI | | | | | | <0.001 |
| Stable CAD | 2295 (36.6%) | 1116 (32.9%) | 716 (39.3%) | 248 (44.2%) | 215 (43.1%) | |
| ACS | 3977 (63.4%) | 2274 (67.1%) | 1106 (60.7%) | 313 (55.8%) | 284 (56.9%) | |

DM: diabetes mellitus, CKD: chronic kidney disease, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome

**Table 2.** Baseline procedural characteristics.

| Procedural characteristics | Overall (N=6273) | DM-/CKD- N=3391 (54.1%) | DM+/CKD- N=1822 (29.0%) | DM-/CKD+ N=561 (8.9%) | DM+/CKD+ N=499 (8.0%) | P-value |
|---|---|---|---|---|---|---|
| Radial artery access | 4454 (71.0%) | 2518 (74.3%) | 1263 (69.3%) | 368 (65.6%) | 305 (61.1%) | <0.001 |
| Multivessel CAD | 3908 (62.3%) | 1954 (57.6%) | 1218 (66.8%) | 376 (67.0%) | 360 (72.1%) | <0.001 |
| Target vessel | | | | | | |
| Left Main | 271 (4.3%) | 145 (4.3%) | 66 (3.6%) | 30 (5.3%) | 30 (6.0%) | 0.070 |
| LAD | 3488 (55.6%) | 1925 (56.8%) | 1021 (56.0%) | 286 (51.0%) | 256 (51.3%) | 0.014 |
| LCX | 2020 (32.2%) | 1057 (31.2%) | 600 (32.9%) | 183 (32.6%) | 180 (36.1%) | 0.135 |
| RCA | 2194 (35.0%) | 1178 (34.7%) | 636 (34.9%) | 209 (37.3%) | 171 (34.3%) | 0.687 |
| Number of vessels treated | 1.3±0.5 | 1.3±0.5 | 1.3±0.5 | 1.3±0.5 | 1.3±0.5 | 0.939 |
| Number of lesions treated | 1.5±0.7 | 1.5±0.7 | 1.5±0.7 | 1.5±0.7 | 1.5±0.8 | 0.183 |
| Lesion morphology[†] | | | | | | |
| Moderate/severe calcification | 896 (14.3%) | 425 (12.5%) | 267 (14.7%) | 96 (17.1%) | 108 (21.6%) | <0.001 |
| Bifurcation | 747 (11.9%) | 422 (12.4%) | 214 (11.7%) | 61 (10.9%) | 50 (10.0%) | 0.355 |
| Total occlusion | 350 (5.6%) | 186 (5.5%) | 118 (6.5%) | 30 (5.3%) | 16 (3.2%) | 0.041 |
| Thrombotic | 702 (11.2%) | 458 (13.5%) | 148 (8.1%) | 57 (10.2%) | 39 (7.8%) | <0.001 |
| Total stent length, mm[‡] | 38.7±23.4 | 39.0±23.4 | 38.7±23.4 | 38.7±24.1 | 37.2±22.8 | 0.478 |
| Minimum stent diameter, mm | 2.8±0.5 | 2.9±0.5 | 2.8±0.5 | 2.8±0.5 | 2.8±0.5 | <0.001 |
| Complex PCI[§] | 1976 (31.5%) | 1042 (30.7%) | 566 (31.1%) | 201 (35.8%) | 167 (33.5%) | 0.076 |

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

[†]Lesion morphology assessed by operators

[‡]Stent length calculated by operators

[§]Complex PCI defined as any of the following: 3 vessels treated, ≥ 3 lesions treated, total stent length > 60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions

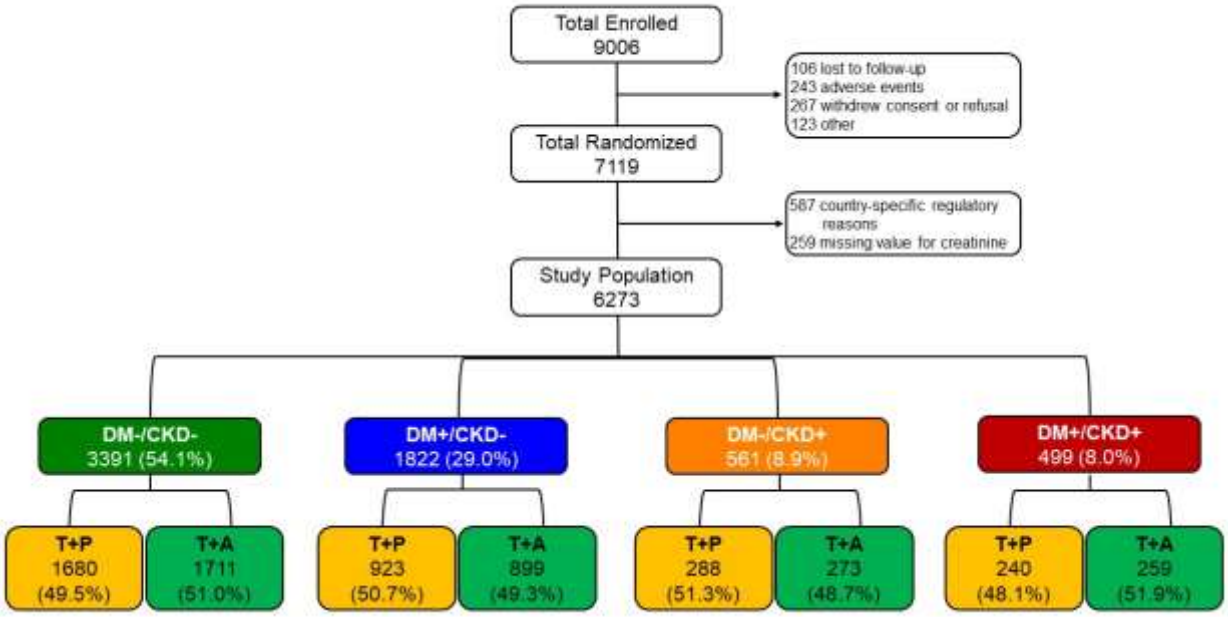
**Table 3.** Adverse events by DM and CKD status at one year randomization.

| | No. of event (%) | HR (95% CI) | p-value | Adjusted HR (95% CI) | p-value | p-value for trend |
|---|---|---|---|---|---|---|
| **Bleeding outcomes** | | | | | | |
| **BARC 2, 3, or 5** | | | | | | |
| DM-/CKD- | 170 (5.1%) | Reference | | Reference | | |
| DM+/CKD- | 94 (5.2%) | 1.04 (0.80 - 1.33) | 0.788 | 1.05 (0.81 - 1.37) | 0.697 | 0.948 |
| DM-/CKD+ | 39 (7.0%) | 1.42 (1.00 - 2.01) | 0.050 | 1.06 (0.73 - 1.52) | 0.766 | |
| DM+/CKD+ | 33 (6.8%) | 1.35 (0.93 - 1.96) | 0.114 | 0.97 (0.65 - 1.44) | 0.883 | |
| **BARC 3 or 5** | | | | | | |
| DM-/CKD- | 33 (1.0%) | Reference | | Reference | | |
| DM+/CKD- | 31 (1.7%) | 1.77 (1.08 - 2.88) | 0.023 | 1.75 (1.05 - 2.93) | 0.033 | 0.076 |
| DM-/CKD+ | 12 (2.2%) | 2.22 (1.15 - 4.30) | 0.018 | 1.35 (0.68 - 2.72) | 0.392 | |
| DM+/CKD+ | 15 (3.1%) | 3.17 (1.72 - 5.84) | <0.001 | 1.83 (0.94 - 3.54) | 0.075 | |
| **Ischemic outcomes** | | | | | | |
| **Death, MI, or stroke** | | | | | | |
| DM-/CKD- | 98 (2.9%) | Reference | | Reference | | |
| DM+/CKD- | 80 (4.5%) | 1.53 (1.14 - 2.06) | 0.005 | 1.63 (1.20 - 2.22) | 0.002 | <0.001 |
| DM-/CKD+ | 24 (4.4%) | 1.49 (0.95 - 2.33) | 0.080 | 1.31 (0.82 - 2.08) | 0.262 | |
| DM+/CKD+ | 45 (9.2%) | 3.21 (2.26 - 4.57) | <0.001 | 2.78 (1.88 - 4.10) | <.0001 | |
| **All-cause death** | | | | | | |
| DM-/CKD- | 23 (0.7%) | Reference | | Reference | | |
| DM+/CKD- | 24 (1.3%) | 1.95 (1.10 - 3.45) | 0.022 | 2.27 (1.26 - 4.09) | 0.006 | <0.001 |
| DM-/CKD+ | 11 (2.0%) | 2.90 (1.41 - 5.94) | 0.004 | 2.10 (0.98 - 4.48) | 0.055 | |
| DM+/CKD+ | 18 (3.6%) | 5.38 (2.90 - 9.97) | <0.001 | 4.27 (2.17 - 8.42) | <0.001 | |
| **MI or ST (definite/probable)** | | | | | | |
| DM-/CKD- | 75 (2.3%) | Reference | | Reference | | |
| DM+/CKD- | 56 (3.2%) | 1.40 (0.99 - 1.98) | 0.056 | 1.43 (1.00 - 2.05) | 0.051 | 0.001 |
| DM-/CKD+ | 13 (2.4%) | 1.05 (0.59 - 1.90) | 0.860 | 0.98 (0.53 - 1.81) | 0.960 | |
| DM+/CKD+ | 31 (6.4%) | 2.89 (1.90 - 4.39) | <0.001 | 2.51 (1.58 - 4.00) | <0.001 | |

DM: diabetes mellitus, CKD: chronic kidney disease, HR: hazard ratio, CI: confidence interval, BARC: Bleeding Academic Research Consortium, MI: myocardial infarction, ST: stent thrombosis.

†Model adjusted for age (years), gender, BMI (kg/m2), enrolling region, current smoker, anemia, prior PCI, prior CABG, multivessel disease, indication for PCI
The percentages above represent K-M estimates at 12 months after randomization

**Supplementary Figure 1. Study population**




**Supplementary Figure 2. Adherence rates to blinded study drug and ticagrelor at 1 year after randomization**