Ticagrelor Monotherapy in Patients with Chronic Kidney Disease Undergoing Percutaneous Coronary Intervention: TWILIGHT-CKD

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ABSTRACT

Aims: To determine the impact of chronic kidney disease (CKD) on the safety and efficacy of ticagrelor monotherapy among patients undergoing percutaneous coronary intervention (PCI).

Methods: In this pre-specified sub-analysis of the TWILIGHT trial, we evaluated the treatment effects of ticagrelor with or without aspirin according to renal function. The trial enrolled patients undergoing drug-eluting stent implantation who fulfilled at least one clinical and one angiographic high-risk criterion. CKD, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, was a clinical study entry criterion. Following a 3-month period of ticagrelor plus aspirin, event-free patients were randomly assigned to either aspirin or placebo on top of ticagrelor for an additional 12 months. The primary endpoint was Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding, while the key secondary endpoint was the composite of all-cause death, myocardial infarction, or stroke.

Results: Of the 6835 patients undergoing randomization and with available eGFR at baseline, 1145 (16.8%) had CKD. Patients with CKD were older, more often female, and had higher prevalence of cardiovascular risk factors. Ticagrelor plus placebo reduced BARC type 2, 3 or 5 bleeding as compared with ticagrelor plus aspirin in both patients with (4.4% vs. 8.9%; HR 0.48, 95% CI 0.30-0.78) and without CKD (4.0% vs. 6.7%; HR 0.60, 95% CI 0.47-0.75; $p_{interaction}$=0.44), but the absolute risk reduction was greater in the former group. Rates of death, myocardial infarction, or stroke were not statistically different between the two randomized groups irrespective of the presence (7.7% vs. 5.5%; HR 1.40, 95% CI 0.88-2.22) or absence of CKD (3.2% vs. 3.6%; HR 0.90, 95% CI 0.68-1.20; $p_{interaction}$=0.11).

Conclusion: Among CKD patients undergoing PCI, a strategy of ticagrelor monotherapy reduced the risk of bleeding without compromising ischemic protection as compared with dual antiplatelet therapy with ticagrelor plus aspirin.

Key words: chronic kidney disease; ticagrelor monotherapy; aspirin; bleeding; thrombosis; PCI

LIST OF ABBREVIATIONS

ACS: Acute Coronary Syndrome

ARC: Academic Research Consortium

BARC: Bleeding Academic Research Consortium

CKD: chronic kidney disease

DAPT: Dual Antiplatelet Therapy

HBR: High Bleeding Risk

GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries

ISTH: International Society on Thrombosis and Hemostasis

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

TIMI: Thrombolysis in Myocardial Infarction

INTRODUCTION

Impaired renal function is an established risk factor for incident and recurrent coronary events with cardiovascular disease being the leading cause of death in patients with chronic kidney disease (CKD).[1-4] The degree of CKD severity is associated with a stepwise increase in the risk of both thrombotic and bleeding complications.[5-9] The pathophysiology behind these observations is multifactorial and relates to abnormalities of both platelet function and coagulation cascade. As a result, the clinical implications of antithrombotic therapies may be different in patients with CKD as compared to the general population.[10, 11]

A combination of aspirin and $P2Y_{12}$ inhibitor, commonly referred as dual antiplatelet therapy (DAPT), is the standard of care after percutaneous coronary intervention (PCI). DAPT effectively prevent ischemic events, including stent thrombosis, but at the cost of an increase in bleeding harm.[12] Bleeding complications have been shown to negatively correlate with patient survival after PCI, thereby putting the ischemic benefits of DAPT in jeopardy.[13, 14] This risk-benefit tradeoff is further enhanced by more effective $P2Y_{12}$ inhibitors (such as prasugrel and ticagrelor), reflecting the incremental extent of platelet inhibition.[15]

Recently, a strategy of ticagrelor monotherapy after a short course of DAPT has emerged as an alternative treatment for high-risk patients undergoing PCI. In the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial, this approach was shown to significantly reduce clinically relevant bleeding without a compromise in antithrombotic efficacy.[16] Whether the clinical benefits of ticagrelor monotherapy is preserved in patients with CKD undergoing PCI is unknown. Therefore, we conducted a pre-specified analysis of the TWILIGHT to examine the safety and efficacy of ticagrelor monotherapy according to renal function.

METHODS

Trial Design and Oversight

TWILIGHT was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The trial rationale, design and principal results have been previously reported.[17] TWILIGHT was designed, coordinated, and sponsored by The Icahn School of Medicine at Mount Sinai. AstraZeneca provided an investigator-initiated grant and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data. The executive and steering committees were responsible for trial conduct, integrity of data analysis, and reporting of results. National regulatory agencies and institutional review boards or ethics committees of participating centers approved the trial protocol. An independent data safety monitoring board provided external oversight to ensure safety of trial participants.

Trial Population

Patients undergoing successful PCI with at least one drug-eluting stent required the presence of at least one clinical and one angiographic feature associated with a high risk of ischemic or bleeding events. CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73m^2, was a clinical study entry criterion; other clinical criteria included age ≥65 years, female sex, troponin positive acute coronary syndrome (ACS), atherosclerotic vascular disease (prior myocardial infarction, coronary revascularization or peripheral arterial disease) and diabetes mellitus requiring medication. Angiographic criteria included multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring 2 stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included dialysis-dependent renal

failure, in addition to presentation with an ST-elevation myocardial infarction, cardiogenic shock, prior stroke, or need for oral anticoagulation.

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily) after the index PCI. At 3 months, patients without major bleeding or ischemic events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months in adjunct to open-label ticagrelor. Patients experiencing Bleeding Academic Research Consortium (BARC) type 3b or higher bleeds or ischemic events (stroke, myocardial infarction, or coronary revascularization) between the index PCI and 3 months were not eligible for randomization. Moreover, patients were ineligible for randomization if non-adherent to ticagrelor or aspirin. Randomization was performed using a secure web-based system; an independent statistician not involved with the trial generated the allocation sequence, which was stratified by site with randomly varying block sizes of 4, 6 or 8. Follow-up occurred 1 month after randomization via telephone and in-person at 6 and 12 months after randomization. After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician followed by final telephone follow-up 3 months later.

Endpoints

The primary endpoint was the composite of BARC type 2, 3, or 5 bleeding up to 1 year after randomization. The key secondary endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke. Secondary bleeding endpoints included BARC types 3 or 5 bleeding; Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding; Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate, severe, or life-threatening bleeding; or major bleeding as defined by the International Society of Thrombosis or Hemostasis

(ISTH).[18-21] Other secondary endpoints included cardiovascular death, non-fatal MI, ischemic stroke and definite or probable stent thrombosis. MI was defined according to the third universal definition, and revascularization and stent thrombosis were classified according to the Academic Research Consortium.[22, 23] All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

Renal function assessment

Laboratory tests were performed locally at each site and collected during enrollment procedure. Renal function was assessed using the most recent value of serum creatinine preceding index PCI, up to 4 weeks before. The eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[24] The pre-specified eGFR cut-point to define CKD was <60 mL/min/1.73m^2. The Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation classification was used to further stratify patients into mild to moderate (stage 3a: eGFR 45-59 mL/min/1.73m^2) and moderate to severe CKD (stage ≥3b: eGFR <45 mL/min/1.73m^2).[25]

Statistical Analyses

Baseline characteristics and clinical outcomes were evaluated in relation to renal function. In the primary pre-specified analysis, the treatment effects of ticagrelor monotherapy versus ticagrelor plus aspirin were evaluated in patients with (eGFR <60 mL/min/1.73m^2) and without CKD (eGFR ≥60 mL/min/1.73m^2), with formal interaction testing to assess for effect modification. Clinical and procedural features are summarized by CKD status and randomized group using means (standard deviation) and frequencies for continuous and categorical variables, respectively. The cumulative incidence of both primary and secondary endpoints was estimated using the Kaplan-Meier method. Patients without a primary endpoint between randomization and

1 year 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.

Exploratory analyses were performed to examine the effects of ticagrelor monotherapy in the following clinically relevant subgroups within the CKD cohort: age (≥65 vs. <65 years), sex (male vs. female), body mass index (above vs. below median), ACS indication for PCI, prior MI, diabetes mellitus, anemia, multivessel disease. Clinical outcomes were also evaluated according to the degree of CKD severity using eGFR as a 3-level categorial variable (<45, 45-59, and ≥60 mL/min/1.73m^2). In addition, cubic splines fitted with 4 equally spaced knots were used to plot the 1-year rate of ischemic and bleeding events according to eGFR as a continuous variable in the overall population and in the two treatment arms, separately. 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

Baseline serum creatinine levels were not available in 284 (4.0%) of the 7119 randomized patients. Therefore, the final cohort for the present analysis comprised 6835 patients, 1145 (16.8%) of whom had CKD as defined by eGFR <60 mL/min/1.73m^2 (**Supplementary Figure 1**). Of these, 573 patients (50.0%) were randomly assigned to ticagrelor plus placebo and 572 (50.0%) to ticagrelor plus aspirin. CKD patients were older, more frequently female, and had higher prevalence of cardiovascular risk factors and prior myocardial revascularization than

those without CKD. Conversely, ACS as indication for index PCI was less common in patients with CKD (**Supplementary Table 1**). Baseline characteristics were balanced across treatment groups, except for a lower prevalence of female sex (27.4% vs. 34.2%; p=0.01) and insulin-dependent diabetes mellitus (32.4% vs. 41.4%; p=0.03) in CKD patients receiving ticagrelor plus placebo, and a lower prevalence of smokers (22.1% vs. 25.2%; p=0.006) in patients without CKD receiving ticagrelor plus placebo, respectively compared with those on ticagrelor plus aspirin (**Table 1**). With regard to procedural variables, CKD patients were less likely to undergo PCI via radial access, and had more often multivessel disease and moderate to severe coronary calcifications than patients with normal renal function (**Supplementary Table 2**). There were no significant differences in procedural characteristics between randomized treatment groups (**Table 2**).

In the cohort of CKD patients, adherence to ticagrelor at one year was similar among those randomized to ticagrelor plus placebo compared with ticagrelor plus aspirin (81.1% vs. 83.1%; p=0.384). Corresponding rates of adherence to blinded study drug were 75.5% and 78.9%, respectively (p=0.158). Among patients without CKD, adherence rates to ticagrelor were higher in the placebo group (88.5% vs. 86.6%; p=0.032), while there were no significant differences with respect to study drug (84.6% vs. 83.0%; p=0.104).

Bleeding events

During the trial a total of 75 (6.7%) primary endpoint events were reported in patients with CKD as compared with 301 (5.4%) in those without CKD (p=0.073) (**Supplementary Figure 2A**). As shown in **Figure 1**, in the CKD cohort, the primary endpoint of BARC 2, 3, or 5 bleeding occurred in 25 patients (4.4%) randomized to ticagrelor plus placebo versus 50 patients (8.9%) randomized to ticagrelor plus aspirin (HR, 0.48; 95% CI, 0.30 - 0.78; p=0.003).

Treatment effects on BARC 2, 3, or 5 bleeding were consistent among patients without CKD (4.0% vs. 6.7%; HR, 0.60; 95% CI 0.47 - 0.75; p<0.001) with no evidence of heterogeneity ($p_{interaction}$=0.438). Ticagrelor plus placebo resulted in lower bleeding rates also with respect to more severe (BARC 3 or 5) bleeding events and across different bleeding scales, including TIMI, GUSTO and ISTH (**Figure 2**). There was no significant interaction between CKD and treatment arm for any of the bleeding endpoints (all $p_{interaction}$>0.1), although the absolute risk reduction associated with ticagrelor monotherapy was greater in the CKD group.

Ischemic events

A total of 74 (6.6%) key secondary endpoint events were reported in patients with CKD as compared with 190 (3.4%) in those without CKD (p<0.001) (**Supplementary Figure 2B**). In the CKD cohort, the key secondary endpoint of all-cause death, MI, or stroke occurred in 43 patients (7.7%) randomized to ticagrelor plus placebo versus 31 patients (5.5%) randomized to ticagrelor plus aspirin (HR, 1.40; 95% CI, 0.88 - 2.22; p=0.157) (**Figure 3**). Individual rates of MI (4.8% vs. 3.8%), ischemic stroke (0.9% vs 0.0%) and definite/probable stent thrombosis (0.9% vs. 0.5%) were numerically higher with ticagrelor plus placebo but not significantly different between treatment groups, with the exception of ischemic stroke (p=0.025) (**Figure 4**). Similar treatment effects on ischemic events were observed in patients without CKD for the composite of all-cause death, MI, or stroke (3.2% vs. 3.6%; HR, 0.90; 95% CI, 0.68 - 1.20; p=0.477) and other secondary endpoints, with no significant interaction between CKD status and treatment arm (all $p_{interaction}$>0.1).

Exploratory analyses

Ticagrelor monotherapy reduced the risk of BARC 2, 3, or 5 bleeding without any increase in death, MI or stroke across different subgroups of CKD patients, with no evidence of

effect modification driven by the presence of additional risk features (**Supplementary Table 3 and 4**).

Of the 1145 patients with an eGFR <60 mL/min/1.73m^2, 812 (70.9%) had mild to moderate CKD (eGFR 45-59 mL/min/1.73m^2) while 329 (29.1%) had moderate to severe CKD (eGFR <45 mL/min/1.73m^2). The risk of bleeding and ischemic events was proportional to the degree of CKD severity (**Supplementary Figure 3**), but the treatment effects of ticagrelor monotherapy on the primary and key secondary endpoints were preserved across all CKD categories (**Supplementary Tables 5 and 6**).

With eGFR used as a continuous variable and plotted against the estimated event rates, the absolute risk reduction in BARC 2, 3, or 5 bleeding with ticagrelor monotherapy progressively increased with worsening renal function (**Supplementary Figure 4A**). Meanwhile, the rates of death, MI, or stroke were numerically lower with ticagrelor monotherapy compared with ticagrelor plus aspirin for eGFR values above 75 mL/min/1.73m^2, and numerically higher below the same eGFR cutoff (**Supplementary Figure 4B**).

DISCUSSION

The principal findings from this pre-specified subgroup analysis of the TWILIGHT trial suggest that the treatment effects of ticagrelor monotherapy on bleeding and ischemic outcomes observed in the overall trial are preserved irrespective of CKD. Of note, withdrawing aspirin after 3 months of DAPT with ticagrelor reduced clinically relevant BARC 2, 3, or 5 bleeding and major BARC 3 or 5 bleeding by more than 50% in patients with CKD, and to a lesser extent in patients without CKD. This translated into an absolute reduction in bleeding risk more pronounced in patients with CKD than in those without CKD. Furthermore, ticagrelor monotherapy, as compared with ticagrelor plus aspirin, was not associated with significant differences in the composite outcome of all-cause death, MI, or stroke, despite a numerical increase in the rates of ischemic events with worsening renal function.

CKD is a prevalent comorbid condition in patients undergoing PCI, an epidemiology that reflects the progressive aging of the general population as well as the broadening indications to PCI to higher risk cohorts. The increased hemorrhagic and thrombotic risk profile of patients with CKD has been extensively characterized, with clinical studies demonstrating a gradient in the rates of adverse events that parallels the degree of renal dysfunction.[5-9] Several homeostatic modifications, including impaired platelet-vessel interaction, platelet aggregation and secretion abnormalities, and a pro-coagulant state with higher levels of fibrinogen and tissue factor and reduced anti-thrombin activity have been implicated in these clinical manifestations.[26-28] Accelerated atherosclerosis, systemic inflammation and oxidative stress are other key contributors to the enhanced cardiovascular risk in presence of CKD.[29-31] Additional pharmacological issues relating to altered pharmacodynamic response, drug accumulation and modified drug interactions further compound the management of these patients.[10, 11]

In the early era of DAPT, subgroup analyses from randomized trials suggested that the benefits of adjunctive therapy with clopidogrel over aspirin alone were attenuated in patients with renal dysfunction.[32, 33] Similar findings were reported in those with diabetic nephropathy randomized to monotherapy with clopidogrel instead of aspirin for secondary cardiovascular prevention.[34] This apparent lack of benefit was partly attributed to the higher levels of platelet reactivity observed in patients with CKD during treatment clopidogrel, thus providing a rationale for the use of alternative antithrombotic regimens in this cohort.[35, 36]

Compared with clopidogrel, potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) have demonstrated a significant benefit in terms of ischemic protection among ACS patients, including those with eGFR <60 mL/min/1.73m^2.[37, 38] In the PLATO trial, the absolute and relative risk reduction for the primary endpoint of death, MI, or stroke associated with ticagrelor was enhanced in patients with CKD, although significant interaction with renal function was only achieved in a sensitivity analysis with the MDRD (Modification of Diet in Renal Disease) equation.[39] Yet, the incremental antithrombic efficacy of ticagrelor over clopidogrel was evaluated on a background aspirin therapy, and this treatment combination also generated a remarkable increase in severe bleeding, which is known to negatively affect survival just as thrombotic events.[40-42]

The idea that withdrawing aspirin after a short course of DAPT could reduce bleeding without compromising antithrombotic efficacy upon continuation of ticagrelor alone recently started to emerge. This approach was also supported by pharmacodynamic data showing a marginal antiplatelet effect of aspirin when added to potent $P2Y_{12}$ inhibitors.[43, 44] Hence, a number of PCI trials have investigated the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy after a DAPT course as short as 1 to 3 months.[45-48] In GLOBAL LEADERS, which randomized

nearly 16,000 all-comer patients to ticagrelor monotherapy after 1-month DAPT versus standard of care, the prevalence of CKD was 13.7%.[49] The trial results showed no significant differences in the primary endpoint of cause mortality or new Q-wave MI and BARC 3 or 5 bleeding at 2 years between the experimental and the control strategy, irrespective of renal function.[49] While these findings must be interpreted in the context of an overall negative trial, exploratory analyses using eGFR as a continuous variable suggested a differential treatment effect on BARC type 3 or 5 bleeding consistent with that reported in the present analysis. Compared to GLOBAL LEADERS, however, the TWILIGHT trial enrolled patients enriched with clinical and angiographic features of high risk for bleeding or ischemia. CKD, an established risk factor for both these types of events, represented a clinical study entry criterion. Most of the available risk scores developed in PCI cohorts identify CKD as a qualifying condition to define patients as high bleeding risk.[50-52] Building on this prior evidence, our results support the relevance of CKD when evaluating the bleeding-related benefits of an aspirin withdrawal strategy. The absolute and relative bleeding risk reduction that we observed largely outweigh that reported in other trials evaluating a similar treatment regimen and underscore the importance of implementing bleeding-avoidance strategies in such vulnerable cohorts.

It is also noteworthy that, in TWILIGHT, the reduction in bleeding risk was not counterbalanced by a tradeoff in antithrombotic efficacy with ticagrelor monotherapy. Nonetheless, there was a numerical increase in ischemic events among CKD patients on ticagrelor monotherapy, which was also confirmed by visual assessment of eGFR used as a continuous variable and plotted against the ischemic event rates. Furthermore, aspirin may serve an important platelet inhibitory role in the prothrombotic milieu of CKD, although this hypothesis remains unproven. Hence, while these data seem to reassure on both the safety and

efficacy of ticagrelor monotherapy after PCI among CKD patients, the limited sample size of our subgroup analysis warrants prospective confirmation from adequately powered studies.

Study limitations

Randomization was not stratified by CKD status, and residual confounders between treatment groups may exist. Furthermore, type II error cannot be excluded in the context of an underpowered subgroup analysis. Hence, our findings must be considered hypothesis-generating and dedicated prospective research is needed to assess the optimal treatment combination in high-risk CKD patients undergoing PCI. Moreover, the TWILIGHT trial excluded subjects with dialysis-dependent renal failure as well as those undergoing primary PCI for ST-segment elevation ACS. Therefore, the safety and efficacy of ticagrelor monotherapy observed in our study cannot be generalized to patient cohorts that would not otherwise be eligible for enrollment in the TWILIGHT trial.

CONCLUSIONS

Among high-risk patients undergoing PCI, a strategy of withdrawing aspirin and continuing ticagrelor alone after 3 months of DAPT significantly reduced clinically relevant as well as major bleeding without increasing ischemic events as compared with ticagrelor plus aspirin, irrespective of renal function. However, owing to their worse risk profile, patients with CKD experienced a greater absolute risk reduction in bleeding events, but also a marginal increase in the rates of ischemic events with ticagrelor monotherapy. Future research should explore the safety and efficacy of this treatment strategy across all kidney function categories.

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FIGURE LEGENDS

Figure 1. Rates of BARC 2, 3, or 5 bleeding at 1 year after randomization. Kaplan-Meier curves for Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding with ticagrelor plus placebo versus ticagrelor plus aspirin in patients with and without CKD (eGFR<60 mL/min/1.73m^2) in the intention to treat cohort. CI: confidence interval; HR: hazard ratio.

Figure 2. Risk of bleeding events at 1 year after randomization. Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the bleeding endpoints in relation to CKD (eGFR<60 mL/min/1.73m^2). 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, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis. *Bleeding outcomes were performed in the intention-to-treat cohort. †Interaction between randomized treatment assignment and CKD.

Figure 3. Rates of death, MI, or stroke at 1 year after randomization. Kaplan-Meier curves for all-cause death, myocardial infarction, or stroke with ticagrelor plus placebo versus ticagrelor plus aspirin in patients with and without CKD (eGFR<60 mL/min/1.73m^2) in in the per protocol cohort. CI: confidence interval; HR: hazard ratio.

Figure 4. Risk of ischemic events at 1 year after randomization. Forest plots showing the effect of ticagrelor plus placebo versus ticagrelor plus aspirin on the ischemic endpoints in relation to CKD status (eGFR<60 mL/min/1.73m^2). 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. In the CKD cohort, the stroke rate was

0.9% (5 events) in patients randomized to ticagrelor plus placebo versus 0% (no events) in those randomized to ticagrelor plus aspirin (log-rang p value=0.025, hazard ratio not applicable); analogous stroke rate in patients without CKD were 0.4% (11 events) versus 0.3% (8 events), (log-rang p value=0.480; HR, 1.38; 95% CI 0.55 - 3.43). CV: cardiovascular, MI: myocardial infarction, ST: stent thrombosis. ^Ischemic outcomes were performed in the per-protocol cohort. †Interaction between randomized treatment assignment and CKD.

TABLES

Table 1. Baseline clinical characteristics

	CKD (eGFR < 60) (N=1145)			No CKD (eGFR ≥ 60) (N=5690)		
	Tica+Placebo N=572	Tica+Aspirin N=573	p-value	Tica+Placebo N=2838	Tica+Aspirin N=2852	p-value
Age, years	71.5±9.1	71.9±8.9	0.440	63.3±9.9	63.2±10.1	0.667
Female sex	157 (27.4%)	196 (34.2%)	0.013	659 (23.2%)	624 (21.9%)	0.226
Nonwhite race	118 (20.6%)	118 (20.6%)	0.988	949 (33.4%)	915 (32.1%)	0.276
BMI, kg/m^2	28.9±5.8	29.5±6.5	0.114	28.5±5.5	28.4±5.4	0.399
Enrolling region			0.216			0.594
North America	284 (49.7%)	307 (53.6%)		1161 (40.9%)	1149 (40.3%)	
Europe	218 (38.1%)	190 (33.2%)		963 (33.9%)	1004 (35.2%)	
Asia	70 (12.2%)	76 (13.3%)		714 (25.2%)	699 (24.5%)	
Diabetes	256 (44.8%)	278 (48.5%)	0.202	1008 (35.5%)	984 (34.5%)	0.422
Diabetes treated with insulin	83 (32.4%)	115 (41.4%)	0.033	239 (23.7%)	248 (25.2%)	0.438
Anemia	198 (35.1%)	207 (36.4%)	0.639	468 (16.6%)	442 (15.6%)	0.306
Current smoker	73 (12.8%)	79 (13.8%)	0.609	627 (22.1%)	718 (25.2%)	0.006
Hypercholesterolemia	391 (68.4%)	422 (73.6%)	0.049	1688 (59.5%)	1657 (58.1%)	0.291
Hypertension	481 (84.1%)	487 (85.0%)	0.673	1997 (70.4%)	1992 (69.9%)	0.683
Peripheral arterial disease	68 (11.9%)	69 (12.0%)	0.936	170 (6.0%)	166 (5.8%)	0.786
Previous MI	160 (28.0%)	168 (29.3%)	0.614	816 (28.8%)	812 (28.5%)	0.814
Previous PCI	272 (47.6%)	274 (47.8%)	0.928	1180 (41.6%)	1172 (41.1%)	0.711
Previous CABG	100 (17.5%)	89 (15.5%)	0.374	254 (9.0%)	250 (8.8%)	0.804
Previous major bleed	6 (1.0%)	9 (1.6%)	0.438	23 (0.8%)	22 (0.8%)	0.868
Indication for PCI			0.245			0.277
Stable CAD	251 (43.9%)	232 (40.5%)		967 (34.1%)	933 (32.7%)	
ACS	321 (56.1%)	341 (59.5%)		1870 (65.9%)	1918 (67.3%)	

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, Tica: ticagrelor, 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

	CKD (eGFR < 60) (N=1145)			No CKD (eGFR ≥ 60) (N=5690)		
	Tica+Placebo N=572	Tica+Aspirin N=573	p-value	Tica+Placebo N=2838	Tica+Aspirin N=2852	p-value
Radial artery access	387 (67.7%)	359 (62.7%)	0.076	2112 (74.4%)	2129 (74.6%)	0.842
Multivessel CAD	406 (71.0%)	392 (68.4%)	0.345	1764 (62.2%)	1723 (60.4%)	0.177
Target vessel						
Left Main	34 (5.9%)	35 (6.1%)	0.907	117 (4.1%)	146 (5.1%)	0.073
LAD	299 (52.3%)	296 (51.7%)	0.835	1602 (56.4%)	1639 (57.5%)	0.437
LCX	205 (35.8%)	186 (32.5%)	0.228	900 (31.7%)	921 (32.3%)	0.639
RCA	202 (35.3%)	209 (36.5%)	0.682	989 (34.8%)	986 (34.6%)	0.827
Number of vessels treated	1.3±0.5	1.3±0.5	0.385	1.3±0.5	1.3±0.5	0.085
Number of lesions treated	1.5±0.8	1.5±0.7	0.294	1.5±0.7	1.5±0.8	0.766
Lesion morphology[†]						
Moderate/severe calcification	98 (17.1%)	113 (19.7%)	0.259	373 (13.1%)	358 (12.6%)	0.506
Bifurcation	67 (11.7%)	50 (8.7%)	0.095	340 (12.0%)	364 (12.8%)	0.370
Total occlusion	26 (4.5%)	28 (4.9%)	0.785	188 (6.6%)	184 (6.5%)	0.792
Thrombotic	49 (8.6%)	51 (8.9%)	0.841	311 (11.0%)	316 (11.1%)	0.884
Total stent length, mm[‡]	39.5±25.5	38.1±23.0	0.341	40.0±23.9	39.9±24.5	0.770
Minimum stent diameter, mm	2.8±0.5	2.8±0.5	0.680	2.8±0.5	2.9±0.5	0.346

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, 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

Figure 1

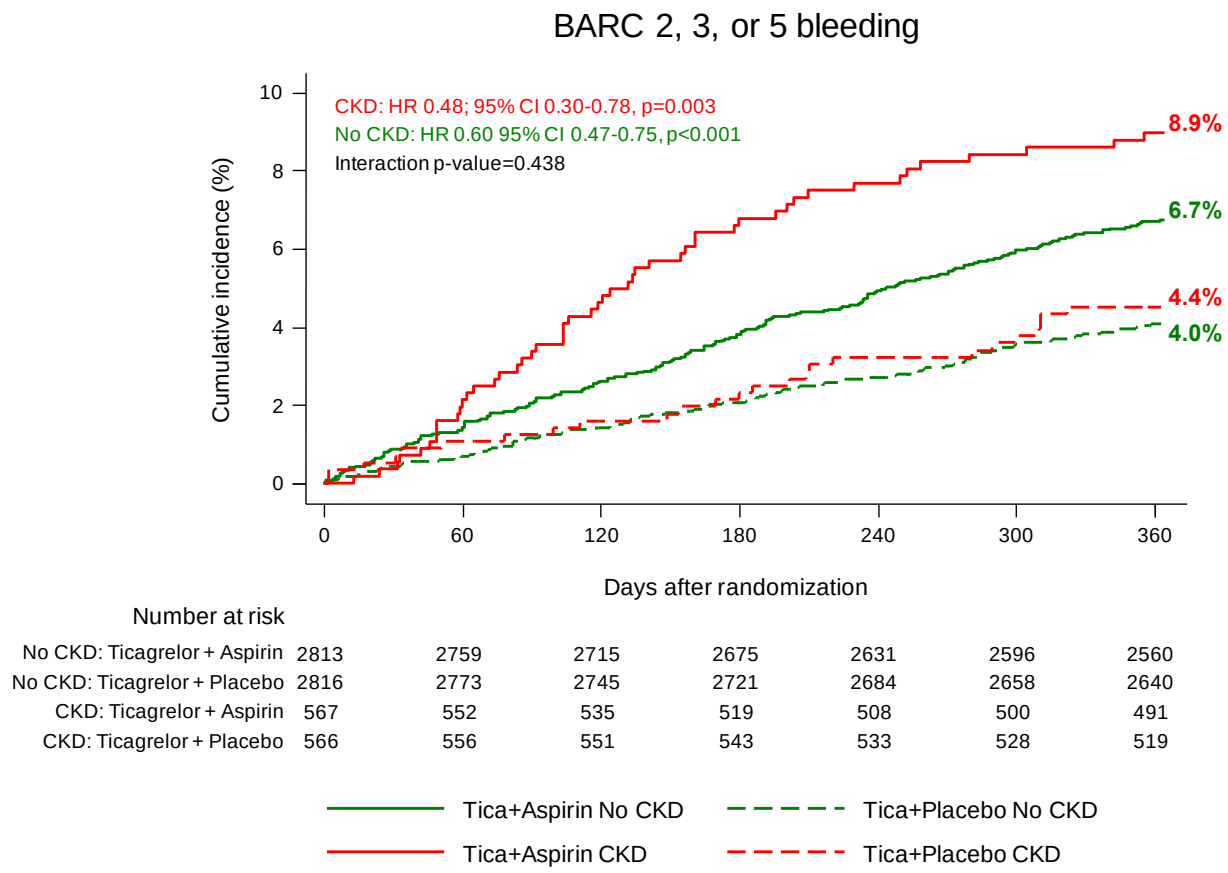

BARC 2, 3, or 5 bleeding
CKD: HR 0.48; 95% CI 0.30-0.78, p=0.003
No CKD: HR 0.60 95% CI 0.47-0.75, p<0.001
Interaction p-value=0.438
8.9%
6.7%
4.4%
4.0%
Cumulative incidence (%)
0
2
4
6
8
10
0
60
120
180
240
300
360
Days after randomization
Number at risk
No CKD: Ticagrelor + Aspirin 2813 2759 2715 2675 2631 2596 2560
No CKD: Ticagrelor + Placebo 2816 2773 2745 2721 2684 2658 2640
CKD: Ticagrelor + Aspirin 567 552 535 519 508 500 491
CKD: Ticagrelor + Placebo 566 556 551 543 533 528 519
Tica+Aspirin No CKD
Tica+Placebo No CKD
Tica+Aspirin CKD
Tica+Placebo CKD

Figure 2

	No. of patients	Tica+Placebo no. of events (%)	Tica+Aspirin no. of events (%)	HR (95% CI)	Interaction P-value**
BARC 2, 3, or 5					
No CKD	5690	113 (4.0%)	188 (6.7%)	0.60 (0.47 - 0.75)	0.438
CKD	1145	25 (4.4%)	50 (8.9%)	0.48 (0.30 - 0.78)	
BARC 3, or 5					
No CKD	5690	26 (0.9%)	46 (1.6%)	0.57 (0.35 - 0.92)	0.388
CKD	1145	8 (1.4%)	21 (3.7%)	0.37 (0.17 - 0.85)	
TIMI major					
No CKD	5690	14 (0.5%)	23 (0.8%)	0.61 (0.32 - 1.19)	0.263
CKD	1145	3 (0.5%)	11 (2.0%)	0.27 (0.08 - 0.97)	
GUSTO moderate or severe					
No CKD	5690	17 (0.6%)	31 (1.1%)	0.55 (0.31 - 1.00)	0.825
CKD	1145	9 (1.6%)	18 (3.2%)	0.49 (0.22 - 1.10)	
ISTH major					
No CKD	5690	29 (1.0%)	48 (1.7%)	0.61 (0.38 - 0.96)	0.369
CKD	1145	9 (1.6%)	22 (3.9%)	0.40 (0.19 - 0.87)	

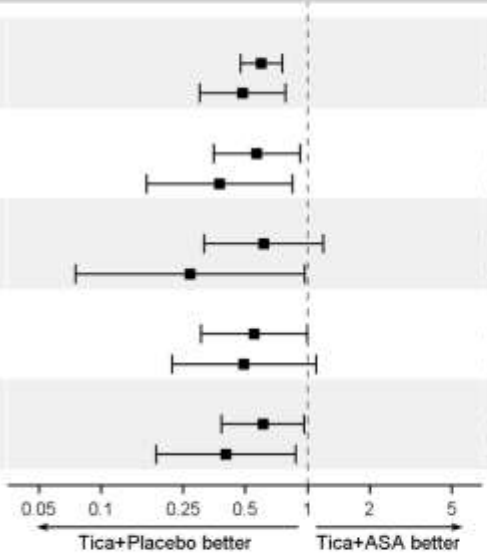


Figure 3

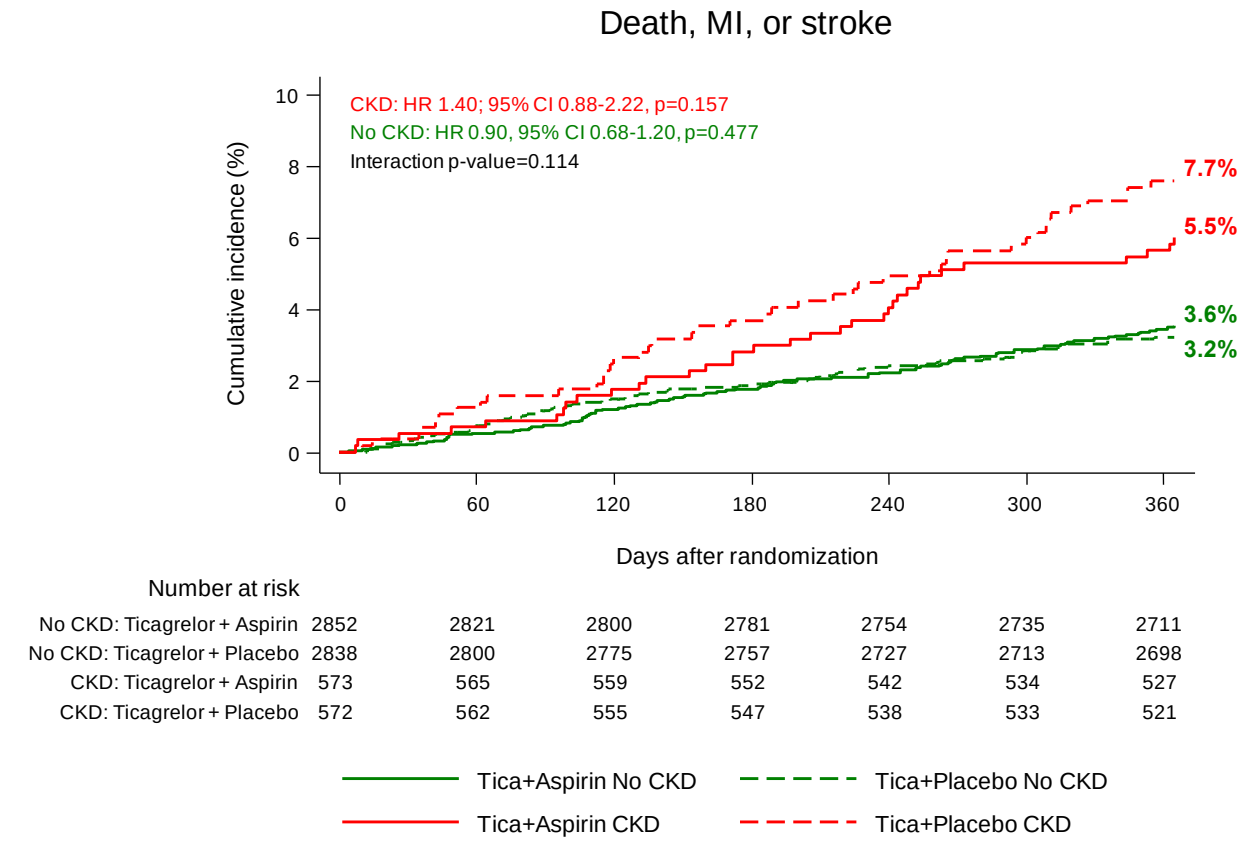
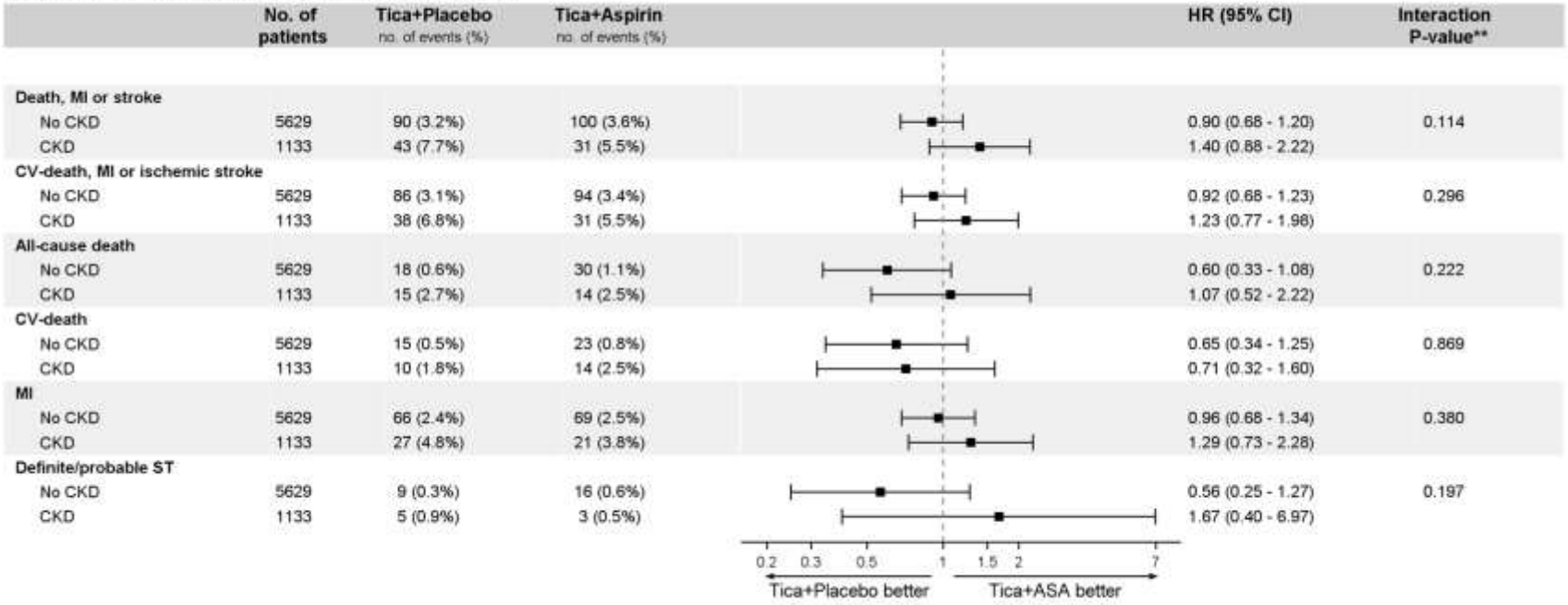

Death, MI, or stroke
CKD: HR 1.40; 95% CI 0.88-2.22, p=0.157
No CKD: HR 0.90, 95% CI 0.68-1.20, p=0.477
Interaction p-value=0.114
Cumulative incidence (%)
10
8
6
4
2
0
7.7%
5.5%
3.6%
3.2%
0
60
120
180
240
300
360
Days after randomization
Number at risk
No CKD: Ticagrelor + Aspirin 2852 2821 2800 2781 2754 2735 2711
No CKD: Ticagrelor + Placebo 2838 2800 2775 2757 2727 2713 2698
CKD: Ticagrelor + Aspirin 573 565 559 552 542 534 527
CKD: Ticagrelor + Placebo 572 562 555 547 538 533 521
Tica+Aspirin No CKD
Tica+Placebo No CKD
Tica+Aspirin CKD
Tica+Placebo CKD

Figure 4


No. of patients
Tica+Placebo no. of events (%)
Tica+Aspirin no. of events (%)
HR (95% CI)
Interaction P-value**
Death, MI or stroke
No CKD 5629 90 (3.2%) 100 (3.6%) 0.90 (0.68 - 1.20) 0.114
CKD 1133 43 (7.7%) 31 (5.5%) 1.40 (0.88 - 2.22)
CV-death, MI or ischemic stroke
No CKD 5629 86 (3.1%) 94 (3.4%) 0.92 (0.68 - 1.23) 0.296
CKD 1133 38 (6.8%) 31 (5.5%) 1.23 (0.77 - 1.98)
All-cause death
No CKD 5629 18 (0.6%) 30 (1.1%) 0.60 (0.33 - 1.08) 0.222
CKD 1133 15 (2.7%) 14 (2.5%) 1.07 (0.52 - 2.22)
CV-death
No CKD 5629 15 (0.5%) 23 (0.8%) 0.65 (0.34 - 1.25) 0.869
CKD 1133 10 (1.8%) 14 (2.5%) 0.71 (0.32 - 1.60)
MI
No CKD 5629 66 (2.4%) 69 (2.5%) 0.96 (0.68 - 1.34) 0.380
CKD 1133 27 (4.8%) 21 (3.8%) 1.29 (0.73 - 2.28)
Definite/probable ST
No CKD 5629 9 (0.3%) 16 (0.6%) 0.56 (0.25 - 1.27) 0.197
CKD 1133 5 (0.9%) 3 (0.5%) 1.67 (0.40 - 6.97)
0.2 0.3 0.5 1 1.5 2 7
Tica+Placebo better
Tica+ASA better

SUPPLMENETARY MATERIAL

Ticagrelor Monotherapy in Patients with Chronic Kidney Disease Undergoing Percutaneous Coronary Intervention: TWILIGHT-CKD

Table of contents

Supplementary Table 1. Baseline clinical characteristics according to renal function

	CKD (eGFR < 60) N=1145, 16.8%	No CKD (eGFR ≥ 60) N=5690, 83.2%	p-value
Age, years	71.7±9.0	63.2±10.0	<.001
Female sex	353 (30.8%)	1283 (22.5%)	<.001
Nonwhite race	236 (20.6%)	1864 (32.8%)	<.001
BMI, kg/m^2	29.2±6.1	28.5±5.5	<.001
Enrolling region			<.001
North America	591 (51.6%)	2310 (40.6%)	
Europe	408 (35.6%)	1967 (34.6%)	
Asia	146 (12.8%)	1413 (24.8%)	
Diabetes	534 (46.6%)	1992 (35.0%)	<.001
Diabetes treated with insulin	198 (37.1%)	487 (24.4%)	<.001
Anemia	405 (35.8%)	910 (16.1%)	<.001
Current smoker	152 (13.3%)	1345 (23.6%)	<.001
Hypercholesterolemia	813 (71.0%)	3345 (58.8%)	<.001
Hypertension	968 (84.5%)	3989 (70.1%)	<.001
Peripheral arterial disease	137 (12.0%)	336 (5.9%)	<.001
Previous MI	328 (28.6%)	1628 (28.6%)	0.981
Previous PCI	546 (47.7%)	2352 (41.3%)	<.001
Previous CABG	189 (16.5%)	504 (8.9%)	<.001
Previous major bleed	15 (1.3%)	45 (0.8%)	0.086
Indication for PCI			<.001
Stable CAD	483 (42.2%)	1900 (33.4%)	
ACS	662 (57.8%)	3788 (66.6%)	

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, Tica: ticagrelor, BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: acute coronary syndrome

Supplementary Table 2. Baseline procedural characteristics according to renal function

	CKD (eGFR < 60) N=1145, 16.8%	No CKD (eGFR ≥ 60) N=5690, 83.2%	p-value
Radial artery access	746 (65.2%)	4241 (74.5%)	<.001
Multivessel CAD	798 (69.7%)	3487 (61.3%)	<.001
Target vessel			
Left Main	69 (6.0%)	263 (4.6%)	0.044
LAD	595 (52.0%)	3241 (57.0%)	0.002
LCX	391 (34.1%)	1821 (32.0%)	0.157
RCA	411 (35.9%)	1975 (34.7%)	0.443
Number of vessels treated	1.3±0.5	1.3±0.5	0.918
Number of lesions treated	1.5±0.7	1.5±0.7	0.570
Lesion morphology†			
Moderate/severe calcification	211 (18.4%)	731 (12.8%)	<.001
Bifurcation	117 (10.2%)	704 (12.4%)	0.041
Total occlusion	54 (4.7%)	372 (6.5%)	0.020
Thrombotic	100 (8.7%)	627 (11.0%)	0.022
Total stent length, mm‡	38.8±24.3	40.0±24.2	0.141
Minimum stent diameter, mm	2.8±0.5	2.9±0.5	0.438

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, 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

Supplementary Table 3. Subgroup analyses for BARC 2, 3, or 5 bleeding in the CKD cohort

Subgroups	No. of patients	Ticagrelor +Placebo	Ticagrelor +Aspirin	HR (95% CI)	Interaction p-value
		no. of patients (%)			
Age (years)					
<65	224	3 (2.5%)	3 (3.0%)	0.84 (0.17 - 4.17)	0.491
≥65	921	22 (5.0%)	47 (10.2%)	0.47 (0.28 - 0.78)	
Sex					
Male	792	14 (3.5%)	31 (8.3%)	0.40 (0.21 - 0.75)	0.262
Female	353	11 (7.1%)	19 (10.0%)	0.69 (0.33 - 1.46)	
BMI (kg/m^2)					
Below median	572	13 (4.5%)	23 (8.4%)	0.51 (0.26 - 1.01)	0.821
Above median	573	12 (4.4%)	27 (9.3%)	0.46 (0.23 - 0.91)	
Indication for PCI					
Stable	483	14 (5.7%)	20 (8.8%)	0.64 (0.32 - 1.26)	0.278
ACS	662	11 (3.5%)	30 (9.0%)	0.37 (0.19 - 0.74)	
Prior MI					
No	817	19 (4.7%)	36 (9.0%)	0.50 (0.29 - 0.88)	0.773
Yes	328	6 (3.8%)	14 (8.6%)	0.43 (0.16 - 1.12)	
Diabetes Mellitus					
No	611	14 (4.5%)	27 (9.3%)	0.47 (0.25 - 0.89)	0.890
Yes	534	11 (4.4%)	23 (8.4%)	0.50 (0.24 - 1.03)	
Anemia					
No	727	10 (2.8%)	26 (7.4%)	0.36 (0.18 - 0.75)	0.256
Yes	405	15 (7.8%)	24 (11.7%)	0.64 (0.34 - 1.22)	
Multivessel CAD					
No	347	7 (4.3%)	15 (8.4%)	0.50 (0.20 - 1.22)	0.935
Yes	798	18 (4.5%)	35 (9.1%)	0.48 (0.27 - 0.84)	

Supplementary Table 4. Subgroup analyses for death, myocardial infarction, or stroke in the CKD cohort

Subgroups	No. of patients	Ticagrelor +Placebo	Ticagrelor +Aspirin	HR (95% CI)	Interaction p-value
		no. of patients (%)			
Age (years)					
<65	224	11 (9.2%)	6 (5.9%)	1.59 (0.59 - 4.29)	0.765
≥65	909	32 (7.2%)	25 (5.5%)	1.34 (0.79 - 2.26)	
Sex					
Male	785	32 (7.9%)	20 (5.4%)	1.47 (0.84 - 2.57)	0.736
Female	348	11 (7.1%)	11 (5.8%)	1.24 (0.54 - 2.86)	
BMI (kg/m^2)					
Below median	566	21 (7.2%)	14 (5.1%)	1.43 (0.73 - 2.81)	0.934
Above median	567	22 (8.1%)	17 (5.9%)	1.37 (0.73 - 2.59)	
Indication for PCI					
Stable	478	15 (6.1%)	9 (4.0%)	1.52 (0.66 - 3.47)	0.848
ACS	655	28 (8.9%)	22 (6.5%)	1.38 (0.79 - 2.41)	
Prior MI					
No	808	26 (6.4%)	17 (4.3%)	1.53 (0.83 - 2.81)	0.680
Yes	325	17 (10.7%)	14 (8.6%)	1.25 (0.62 - 2.54)	
Diabetes Mellitus					
No	605	16 (5.2%)	10 (3.5%)	1.51 (0.68 - 3.32)	0.881
Yes	528	27 (10.7%)	21 (7.7%)	1.40 (0.79 - 2.47)	
Anemia					
No	719	24 (6.6%)	20 (5.7%)	1.17 (0.65 - 2.11)	0.330
Yes	401	19 (9.9%)	11 (5.4%)	1.87 (0.89 - 3.94)	
Multivessel CAD					
No	345	8 (4.9%)	9 (5.1%)	0.96 (0.37 - 2.48)	0.381
Yes	788	35 (8.8%)	22 (5.8%)	1.56 (0.91 - 2.65)	

Supplementary Table 5. Risk of ischemic events by degree of CKD

Bleeding outcomes*	Severe CKD (eGFR < 45) (N=333)			Moderate CKD (eGFR 45 - 59) (N=812)			No CKD (eGFR ≥ 60) (N=5690)			Interaction p-value†
	Tica+ placebo (N=153)	Tica+ Aspirin (N=180)	Hazard ratio (95% CI)	Tica+ placebo (N=419)	Tica+ Aspirin (N=393)	Hazard ratio (95% CI)	Tica+ placebo (N=2838)	Tica+ Aspirin (N=2852)	Hazard ratio (95% CI)	
	no. of events (%)			no. of events (%)			no. of events (%)			
BARC 2, 3 or 5	9 (6.1%)	18 (10.2%)	0.57 (0.26 - 1.27)	16 (3.9%)	32 (8.3%)	0.45 (0.25 - 0.83)	113 (4.0%)	188 (6.7%)	0.60 (0.47 - 0.75)	0.691
BARC 3 or 5	3 (2.0%)	8 (4.5%)	0.44 (0.12 - 1.65)	5 (1.2%)	13 (3.4%)	0.35 (0.13 - 0.99)	26 (0.9%)	46 (1.6%)	0.57 (0.35 - 0.92)	0.684
TIMI major	0 (0.0%)	5 (2.8%)	NA	3 (0.7%)	6 (1.6%)	0.46 (0.12 - 1.84)	14 (0.5%)	23 (0.8%)	0.61 (0.32 - 1.19)	0.141
GUSTO moderate or severe	3 (2.0%)	7 (4.0%)	0.50 (0.13 - 1.93)	6 (1.5%)	11 (2.9%)	0.50 (0.19 - 1.36)	17 (0.6%)	31 (1.1%)	0.55 (0.31 - 1.00)	0.983
ISTH major	3 (2.0%)	8 (4.5%)	0.44 (0.12 - 1.65)	6 (1.5%)	14 (3.6%)	0.39 (0.15 - 1.02)	29 (1.0%)	48 (1.7%)	0.61 (0.38 - 0.96)	0.673

CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, Tica: ticagrelor, CI: confidence interval, BARC: Bleeding Academic Research Consortium, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis

*Bleeding outcomes were performed in the intention-to-treat cohort

†Interaction between randomized treatment assignment and CKD subgroups

The percentages mentioned above represent K-M rates at 12 months after randomization

Supplementary Table 6. Risk of ischemic events by degree of CKD

Ischemic outcomes[^]	Severe CKD (eGFR < 45) (N=329)			Moderate CKD (eGFR 45 - 60) (N=804)			No CKD (eGFR ≥ 60) (N=5629)			Interaction p-value[†]
	Tica+ placebo (N=152)	Tica+ Aspirin (N=177)	Hazard ratio (95% CI)	Tica+ placebo (N=414)	Tica+ Aspirin (N=390)	Hazard ratio (95% CI)	Tica+ placebo (N=2816)	Tica+ Aspirin (N=2813)	Hazard ratio (95% CI)	
	no. of events (%)			no. of events (%)			no. of events (%)			
Death, MI or stroke	13 (8.7%)	14 (7.9%)	1.11 (0.52 - 2.36)	30 (7.3%)	17 (4.4%)	1.66 (0.92 - 3.01)	90 (3.2%)	100 (3.6%)	0.90 (0.68 - 1.20)	0.180
Cardiovascular death, MI or ischemic stroke	11 (7.4%)	14 (7.9%)	0.94 (0.42 - 2.06)	27 (6.6%)	17 (4.4%)	1.49 (0.81 - 2.74)	86 (3.1%)	94 (3.4%)	0.92 (0.68 - 1.23)	0.352
All-cause death	3 (2.0%)	5 (2.8%)	0.70 (0.17 - 2.92)	12 (2.9%)	9 (2.3%)	1.26 (0.53 - 2.98)	18 (0.6%)	30 (1.1%)	0.60 (0.33 - 1.08)	0.372
Cardiovascular death	1 (0.7%)	5 (2.8%)	0.24 (0.03 - 2.03)	9 (2.2%)	9 (2.3%)	0.93 (0.37 - 2.35)	15 (0.5%)	23 (0.8%)	0.65 (0.34 - 1.25)	0.446
MI	9 (6.1%)	12 (6.8%)	0.89 (0.37 - 2.11)	18 (4.4%)	9 (2.4%)	1.87 (0.84 - 4.17)	66 (2.4%)	69 (2.5%)	0.96 (0.68 - 1.34)	0.280
Ischemic stroke	1 (0.7%)	0 (0.0%)	NA	4 (1.0%)	0 (0.0%)	NA	11 (0.4%)	8 (0.3%)	1.38 (0.55 - 3.43)	0.099
Stent thrombosis (definite/probable)	1 (0.7%)	2 (1.2%)	0.59 (0.05 - 6.53)	4 (1.0%)	1 (0.3%)	3.74 (0.42 - 33.4)	9 (0.3%)	16 (0.6%)	0.56 (0.25 - 1.27)	0.205

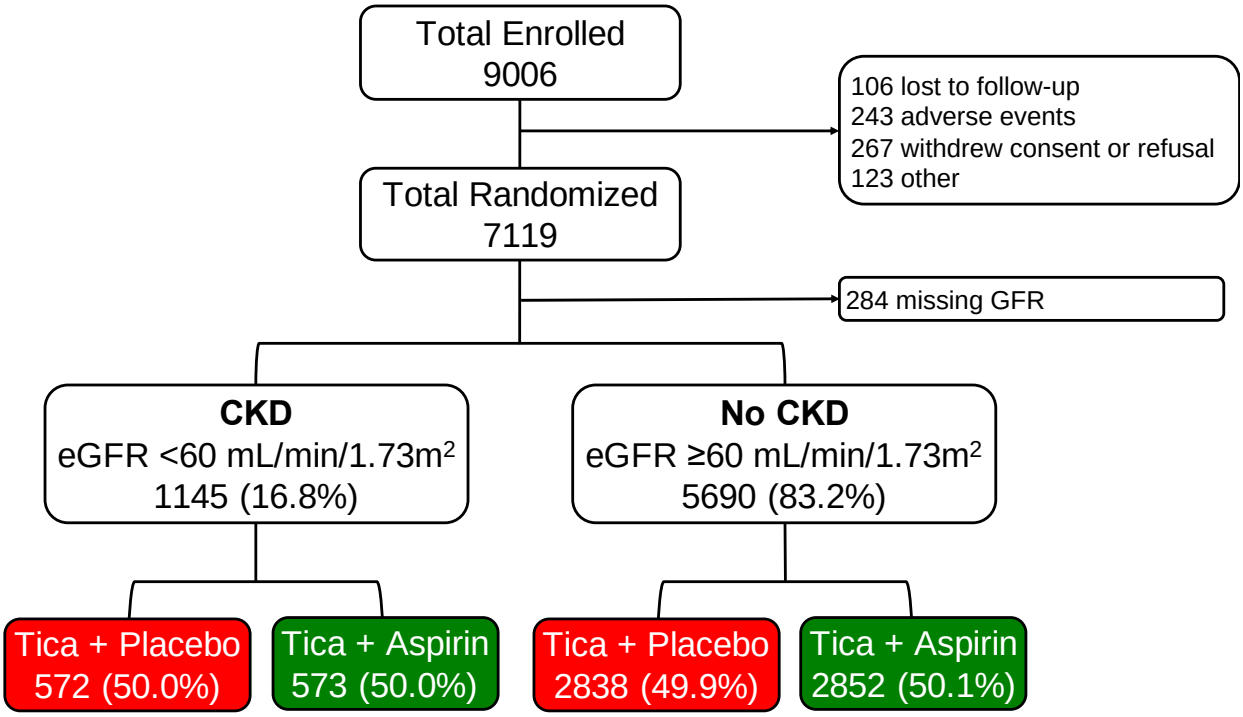
CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, Tica: ticagrelor, CI: confidence interval, MI: myocardial infarction

[^]Ischemic outcomes were performed in the per-protocol cohort

[†]Interaction between randomized treatment assignment and CKD subgroups

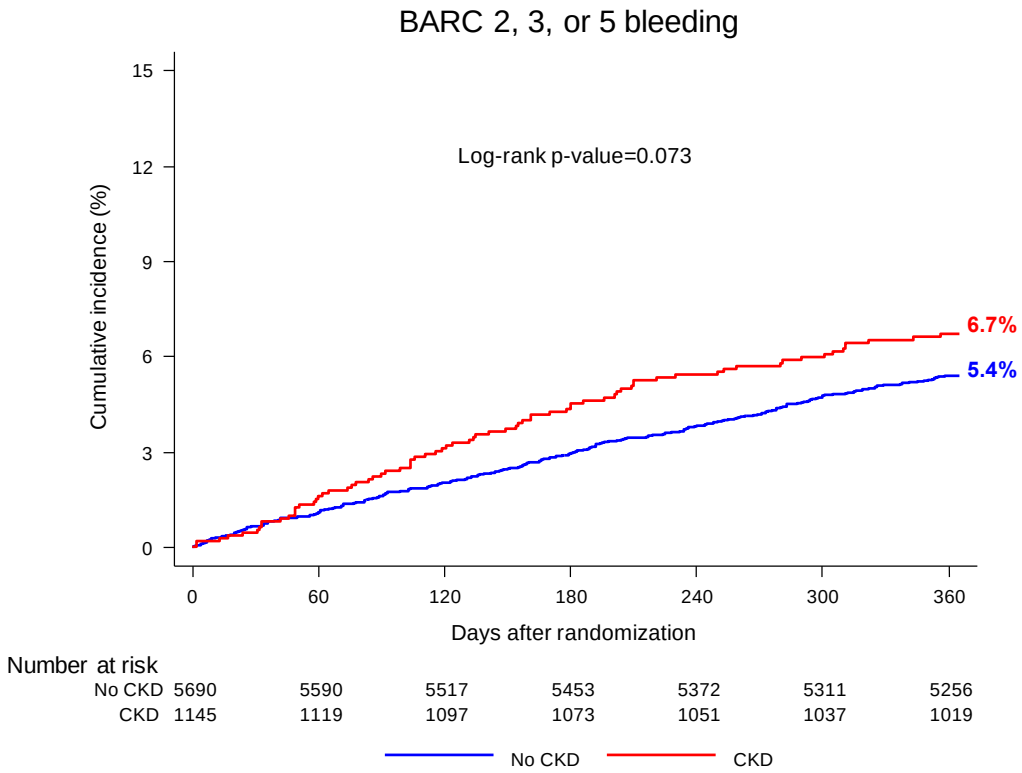
The percentages mentioned above represent K-M rates at 12 months after randomization

Supplementary Figure 1. Study population



Supplementary Figure 2. Rates of bleeding (A) and ischemic (B) events by presence of CKD

A



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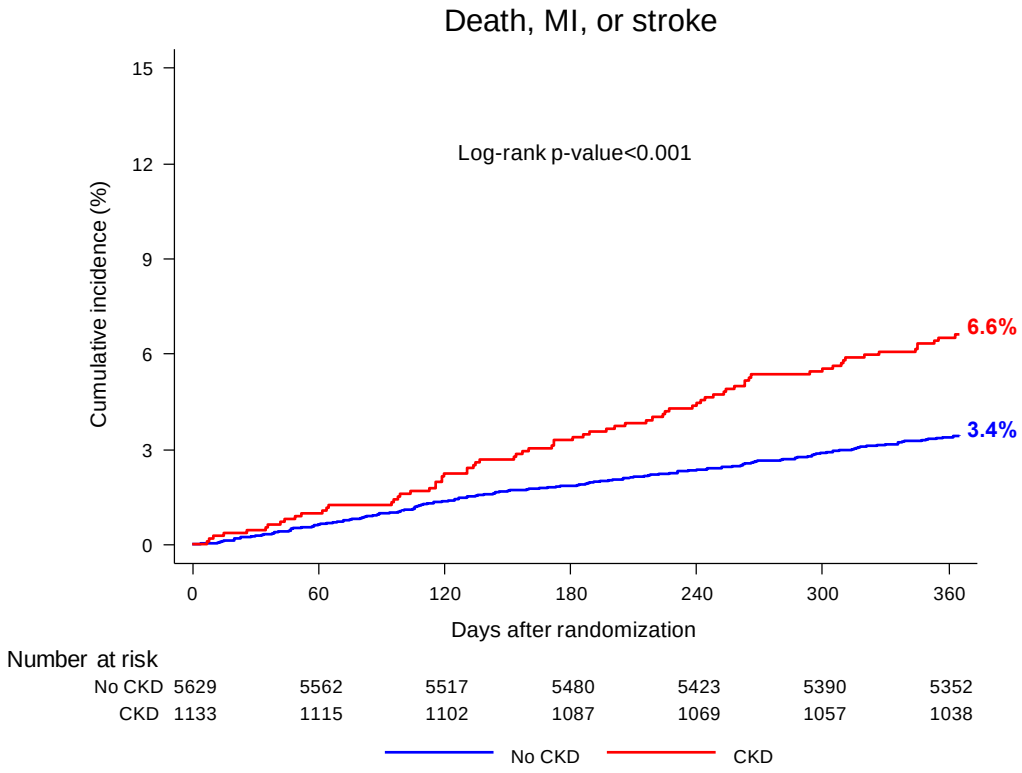
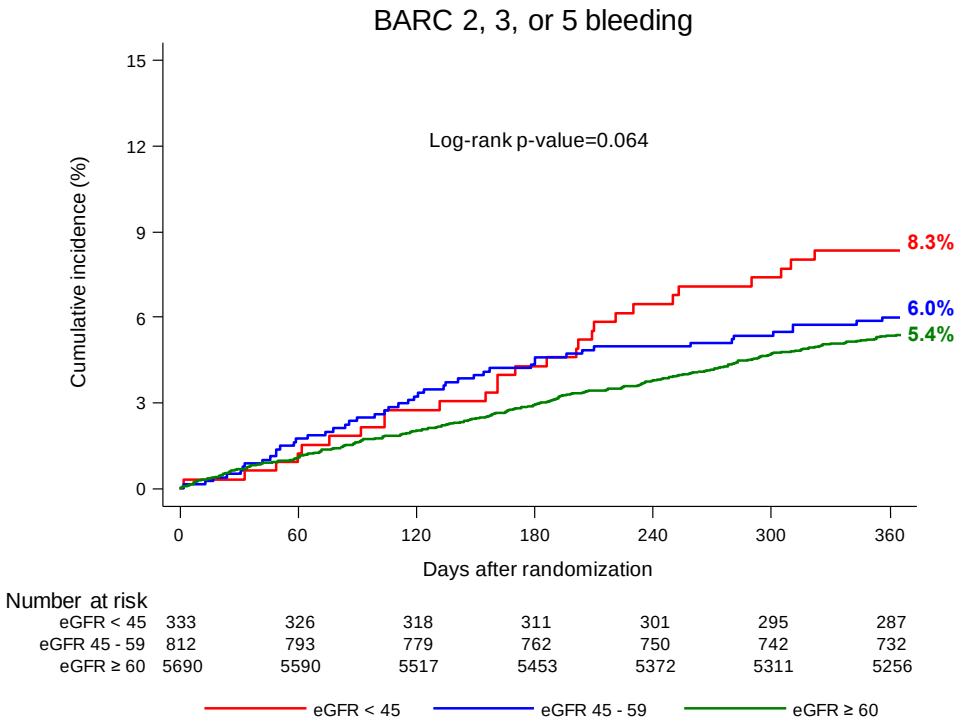


Supplementary Figure 3. Rates of bleeding (A) and ischemic (B) events by degree of CKD

A



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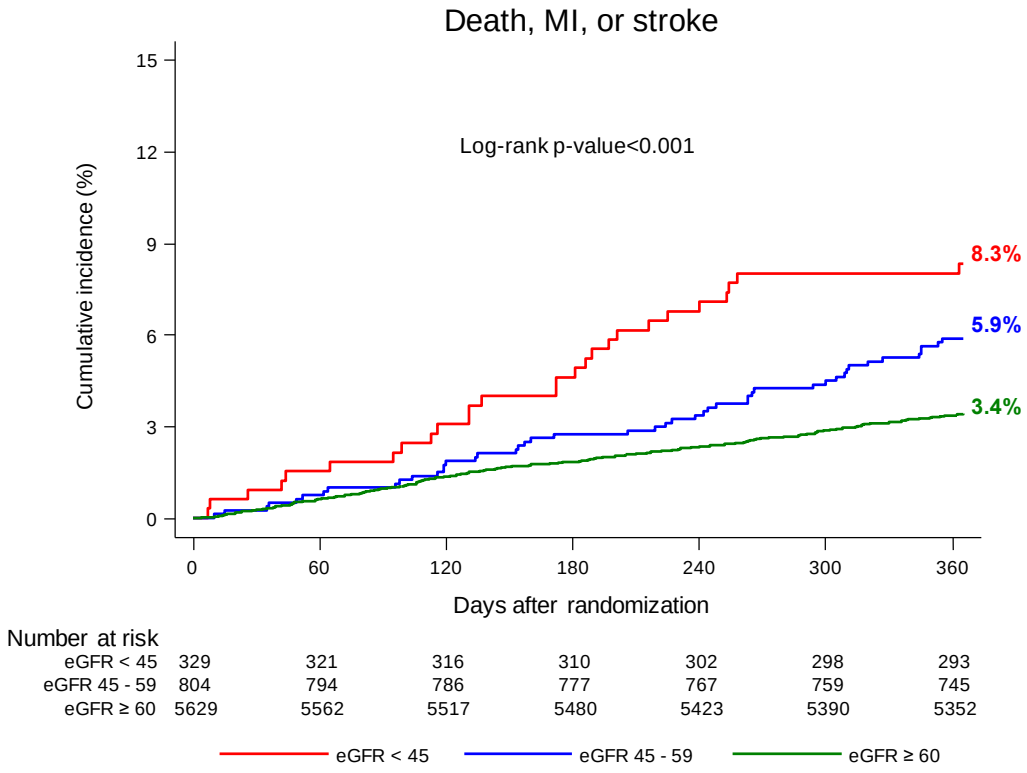
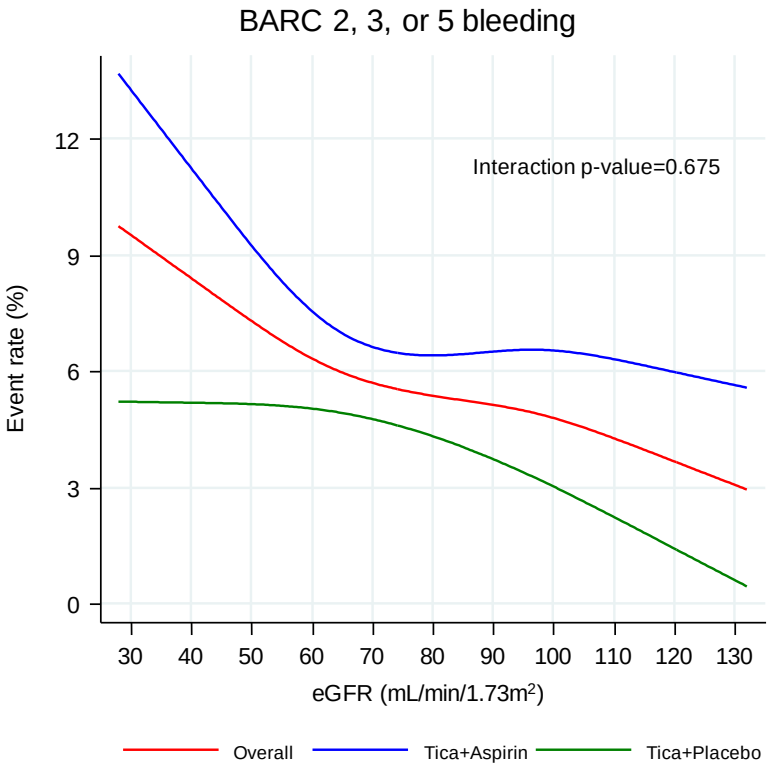


Figure 4. Cubic splines for the rates of BARC 2, 3, or 5 bleeding (A) and all-cause death, myocardial infarction, or stroke (B) at 1 year after randomization according to continuous eGFR.

A



B