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**CLINICAL RESEARCH**
*Interventional cardiology*

# Ticagrelor monotherapy in patients with chronic kidney disease undergoing percutaneous coronary intervention: TWILIGHT-CKD

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**Aims** The aim of this study was to assess the impact of chronic kidney disease (CKD) on the safety and efficacy of ticagrelor monotherapy among patients undergoing percutaneous coronary intervention (PCI).

**Methods and results** In this prespecified subanalysis 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. Chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$, was a clinical study entry criterion. Following a 3-month period of ticagrelor plus aspirin, event-free patients were randomly assigned to aspirin or placebo on top of ticagrelor for an additional 12 months. Of the 6835 patients randomized and with available eGFR at baseline, 1111 (16.3%) had CKD. Ticagrelor plus placebo reduced the primary endpoint of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding as compared with ticagrelor plus aspirin in both patients with [4.6% vs. 9.0%; hazard ratio (HR) 0.50, 95% confidence interval (CI) 0.31–0.80] and without (4.0% vs. 6.7%; HR 0.59, 95% CI 0.47–0.75; $P_{interaction} = 0.508$) CKD, but the absolute risk reduction was greater in the former group. Rates of

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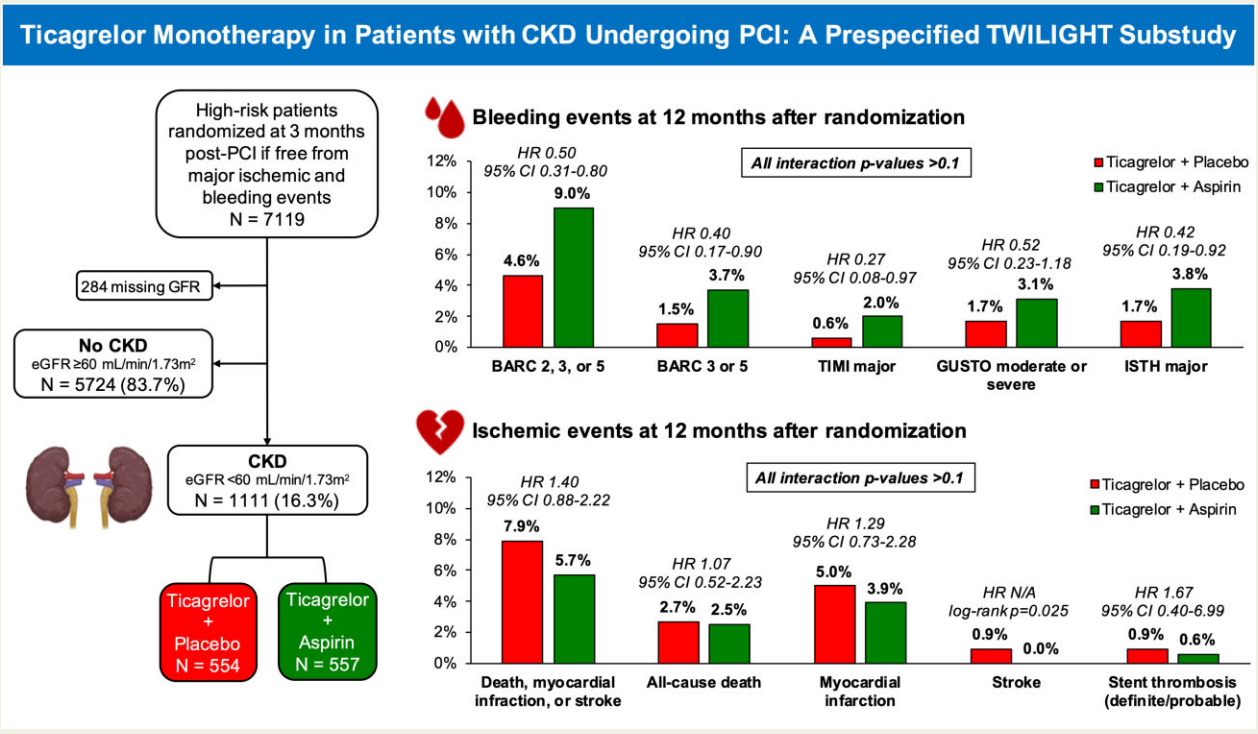
death, myocardial infarction, or stroke were not significantly different between the two randomized groups irrespective of the presence (7.9% vs. 5.7%; HR 1.40, 95% CI 0.88–2.22) or absence of (3.2% vs. 3.6%; HR 0.90, 95% CI 0.68–1.20; $P_{interaction} = 0.111$) CKD.

**Conclusion** Among CKD patients undergoing PCI, ticagrelor monotherapy reduced the risk of bleeding without a significant increase in ischaemic events as compared with ticagrelor plus aspirin.

## Graphical Abstract




**Keywords** Chronic kidney disease • Ticagrelor monotherapy • Aspirin • Bleeding • Thrombosis • PCI

# 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).[1–3] The degree of CKD severity is associated with a progressive increase in the risk of both thrombotic and bleeding complications.[4–6] The pathophysiology behind these observations is multifactorial and relates to abnormalities of both platelet function and the coagulation cascade. As a result, the clinical implications of antithrombotic therapies may be different in patients with CKD as compared to those with normal renal function.[7,8]

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). Dual antiplatelet therapy effectively prevents ischaemic events, including stent thrombosis, but at the cost of an increase in bleeding.[9] Bleeding complications have been shown to negatively correlate with patient survival after PCI, thereby putting the ischaemic benefits of DAPT in jeopardy.[10–12] This risk–benefit trade-off is further enhanced by more potent $P2Y_{12}$ inhibitors (such as prasugrel and ticagrelor), reflecting the incremental extent of platelet inhibition.[13]

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 compromising antithrombotic efficacy.[14] It is unknown whether the clinical benefits of ticagrelor monotherapy are preserved in patients with CKD undergoing PCI, who—being intrinsically characterized by high thrombotic and bleeding risks—might particularly benefit from an optimization of antithrombotic strategies. Therefore, we conducted a prespecified analysis of the TWILIGHT trial 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 from July 2015 through July 2019. The trial rationale, design, and principal results have been reported previously.[15] 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 centres approved the trial protocol. An independent data safety monitoring board provided external oversight to ensure the safety of trial participants.

## Trial population

Patients undergoing successful PCI with at least one drug-eluting stent were eligible if they had at least one clinical and one angiographic feature associated with a high risk of ischaemic or bleeding events. Chronic kidney disease, defined as an estimated glomerular filtration rate <60 mL/min/1.73 $m^2$, 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 (MI), 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 two 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, presentation with ST-elevation MI, 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 ischaemic events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for 12 months in addition to open-label ticagrelor. Patients who experienced Bleeding Academic Research Consortium (BARC) type 3b or higher bleeds or ischaemic events (stroke, MI, or coronary revascularization) between the index PCI and 3 months were not eligible for randomization. Moreover, patients were ineligible for randomization if they were 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, 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 on Thrombosis and Hemostasis (ISTH).[16–19] Other secondary endpoints included cardiovascular death, non-fatal MI, ischaemic 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.[20,21] 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 the enrolment procedure. Renal function was assessed using the most recent value of serum creatinine preceding index PCI, up to 4 weeks before. Glomerular filtration rate (eGFR) was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[22] The prespecified eGFR cut-point to define CKD was <60 mL/min/1.73 $m^2$. 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/1.73 $m^2$) or moderate to severe CKD (stage ≥3b: eGFR < 45 mL/min/1.73 $m^2$).[23]

## Statistical analyses

Baseline characteristics and clinical outcomes were evaluated in relation to renal function. In the primary prespecified analysis, the treatment effects of ticagrelor monotherapy vs. ticagrelor plus aspirin were evaluated in patients with CKD (eGFR < 60 mL/min/1.73 $m^2$) and without CKD (eGFR ≥ 60 mL/min/1.73 $m^2$), with formal interaction testing to assess for effect modification. Patients with unknown eGFR were excluded from the analysis. 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 primary and secondary endpoints was estimated using the Kaplan–Meier method. Patients without a primary endpoint between randomization and 1 year after randomization were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) 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), non-ST-segment elevation ACS indication for PCI, prior MI, diabetes mellitus, anaemia, and multivessel disease. Clinical outcomes were also evaluated according to the degree of CKD severity using eGFR as a three-level categorical variable (<45, 45–59, and ≥60 mL/min/1.73 $m^2$). In addition, cubic splines fitted with four equally spaced knots were used to plot the 1-year rate of ischaemic and bleeding events according to eGFR as a continuous variable in the overall population and in the two treatment arms, separately. For all analyses, bleeding outcomes were assessed in the intention-to-treat cohort, while ischaemic outcomes were analysed 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 (StataCorp., College Station, TX, USA).

# 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, 1111 (16.3%) of whom had CKD (Supplementary material online, *Figure S1*). Of these patients, 554 patients (49.9%) were randomly assigned to ticagrelor plus

**Table 1 Baseline clinical characteristics**

| | CKD (eGFR < 60) (*n* = 1111) | | | No CKD (eGFR ≥ 60) (*n* = 5724) | | |
|---|---|---|---|---|---|---|
| | Tica + Placebo (*n* = 554) (49.9%) | Tica + Aspirin (*n* = 557) (50.1%) | *P*-value | Tica + Placebo (*n* = 2856) (49.9%) | Tica + Aspirin (*n* = 2868) (50.1%) | *P*-value |
| Age (years) | 70.1 ± 9.1 | 70.6 ± 8.7 | 0.370 | 62.1 ± 9.7 | 61.9 ± 9.9 | 0.626 |
| Female sex | 154 (27.8%) | 193 (34.6%) | 0.014 | 662 (23.2%) | 627 (21.9%) | 0.233 |
| Non-white race | 113 (20.4%) | 113 (20.3%) | 0.964 | 954 (33.4%) | 920 (32.1%) | 0.285 |
| BMI (kg/m$^2$) | 28.9 ± 5.8 | 29.3 ± 6.0 | 0.228 | 28.5 ± 5.5 | 28.4 ± 5.5 | 0.534 |
| Enrolling region | | | 0.163 | | | 0.574 |
| North America | 271 (48.9%) | 300 (53.9%) | | 1174 (41.1%) | 1156 (40.3%) | |
| Europe | 215 (38.8%) | 186 (33.4%) | | 966 (33.8%) | 1008 (35.1%) | |
| Asia | 68 (12.3%) | 71 (12.7%) | | 716 (25.1%) | 704 (24.5%) | |
| Diabetes | 251 (45.3%) | 270 (48.5%) | 0.290 | 1013 (35.5%) | 992 (34.6%) | 0.485 |
| Diabetes treated with insulin | 82 (32.7%) | 115 (42.6%) | 0.020 | 240 (23.7%) | 248 (25.0%) | 0.495 |
| Anaemia | 193 (35.2%) | 205 (37.1%) | 0.508 | 473 (16.7%) | 444 (15.6%) | 0.260 |
| Current smoker | 71 (12.8%) | 77 (13.8%) | 0.621 | 629 (22.0%) | 720 (25.1%) | 0.006 |
| Hypercholesterolaemia | 382 (69.0%) | 412 (74.0%) | 0.064 | 1697 (59.4%) | 1667 (58.1%) | 0.320 |
| Hypertension | 468 (84.5%) | 473 (84.9%) | 0.838 | 2010 (70.4%) | 2006 (70.0%) | 0.735 |
| Peripheral arterial disease | 66 (11.9%) | 69 (12.4%) | 0.809 | 172 (6.0%) | 166 (5.8%) | 0.707 |
| Previous MI | 156 (28.2%) | 162 (29.1%) | 0.733 | 820 (28.7%) | 818 (28.5%) | 0.874 |
| Previous PCI | 265 (47.8%) | 264 (47.4%) | 0.884 | 1187 (41.6%) | 1182 (41.2%) | 0.789 |
| Previous CABG | 99 (17.9%) | 86 (15.4%) | 0.277 | 255 (8.9%) | 253 (8.8%) | 0.883 |
| Multivessel CAD | 391 (70.6%) | 381 (68.4%) | 0.431 | 1779 (62.3%) | 1734 (60.5%) | 0.155 |
| Previous major bleed | 6 (1.1%) | 9 (1.6%) | 0.442 | 23 (0.8%) | 22 (0.8%) | 0.870 |
| Indication for PCI | | | 0.294 | | | 0.250 |
| Stable CAD | 244 (44.0%) | 228 (40.9%) | | 974 (34.1%) | 937 (32.7%) | |
| NSTE-ACS | 310 (56.0%) | 329 (59.1%) | | 1881 (65.9%) | 1930 (67.3%) | |

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; Tica, ticagrelor.

placebo and 557 (50.1%) to ticagrelor plus aspirin. Baseline clinical and procedural characteristics of patients with and without CKD are summarized in Supplementary material online, *Tables S1 and S2*. Baseline characteristics were balanced across treatment groups, except for a lower prevalence of female sex (27.8% vs. 34.6%; $P = 0.014$) and insulin-dependent diabetes mellitus (32.7% vs. 42.6%; $P = 0.020$) in CKD patients receiving ticagrelor plus placebo and a lower prevalence of smokers (22.0% vs. 25.1%; $P = 0.006$) in patients without CKD receiving ticagrelor plus placebo, respectively, compared with those on ticagrelor plus aspirin (*Table 1*). There were no significant differences in procedural characteristics between randomized treatment groups (*Table 2*).

In the cohort of CKD patients, adherence to ticagrelor at 1 year was similar among those randomized to ticagrelor plus placebo compared with ticagrelor plus aspirin (80.5% vs. 83.0%; $P = 0.288$). Corresponding rates of adherence to blinded study drug were 74.7% and 78.7%, respectively ($P = 0.110$). Among patients without CKD, adherence rates to ticagrelor were higher in the placebo group (88.6% vs. 86.6%; $P = 0.025$), while there were no significant differences with respect to study drug (84.7% vs. 83.0%; $P = 0.087$).

## Bleeding events

During the trial, a total of 74 (6.8%) primary endpoint events were reported in patients with CKD as compared with 302 (5.4%) in those without CKD ($P = 0.052$) (Supplementary material online, *Figure S2A*). As shown in *Figure 1*, in the CKD cohort, the primary endpoint of BARC 2, 3, or 5 bleeding occurred in 25 patients (4.6%) randomized to ticagrelor plus placebo vs. 50 patients (9.0%) randomized to ticagrelor plus aspirin (HR 0.50, 95% CI 0.31–0.80; $P = 0.004$). Treatment effects on BARC 2, 3, or 5 bleeding were consistent among patients without CKD (4.0% vs. 6.7%; HR 0.59, 95% CI 0.47–0.75; $P < 0.001$) with no evidence of heterogeneity ($P_{interaction} = 0.508$). 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 $P_{interaction} > 0.1$), but the absolute risk difference in BARC 2, 3, or 5 bleeding associated with ticagrelor monotherapy was greater in the CKD group (-4.4%, 95% CI -7.3% to -1.4%) compared with the no CKD group (-2.7%, 95% CI -3.8% to -1.5%).

## Ischaemic events

A total of 74 (6.8%) key secondary endpoint events were reported in patients with CKD as compared with 190 (3.4%) in those without CKD ($P < 0.001$) (Supplementary material online, *Figure S2B*). In the CKD cohort, the key secondary endpoint of all-cause death, MI, or stroke occurred in 43 patients (7.9%) randomized to ticagrelor plus

**Table 2 Baseline procedural characteristics**

| | CKD (eGFR < 60) (*n* = 1111) | | | No CKD (eGFR ≥ 60) (*n* = 5724) | | |
|---|---|---|---|---|---|---|
| | Tica + Placebo (*n* = 554) (49.9%) | Tica + Aspirin (*n* = 557) (50.1%) | *P*-value | Tica + Placebo (*n* = 2856) (49.9%) | Tica + Aspirin (*n* = 2868) (50.1%) | *P*-value |
| Radial artery access | 375 (67.7%) | 347 (62.3%) | 0.060 | 2124 (74.4%) | 2141 (74.7%) | 0.807 |
| Multivessel CAD | 391 (70.6%) | 381 (68.4%) | 0.431 | 1779 (62.3%) | 1734 (60.5%) | 0.155 |
| Target vessel | | | | | | |
| Left main | 34 (6.1%) | 33 (5.9%) | 0.882 | 117 (4.1%) | 148 (5.2%) | 0.055 |
| LAD | 290 (52.3%) | 283 (50.8%) | 0.608 | 1611 (56.4%) | 1652 (57.6%) | 0.362 |
| LCX | 199 (35.9%) | 183 (32.9%) | 0.282 | 906 (31.7%) | 924 (32.2%) | 0.688 |
| RCA | 193 (34.8%) | 204 (36.6%) | 0.534 | 998 (34.9%) | 991 (34.6%) | 0.757 |
| Number of vessels treated | 1.3 ± 0.5 | 1.3 ± 0.5 | 0.327 | 1.3 ± 0.5 | 1.3 ± 0.5 | 0.080 |
| Number of lesions treated | 1.5 ± 0.8 | 1.5 ± 0.7 | 0.365 | 1.5 ± 0.7 | 1.5 ± 0.8 | 0.821 |
| Lesion morphology[a] | | | | | | |
| Moderate/severe calcification | 97 (17.5%) | 111 (19.9%) | 0.301 | 374 (13.1%) | 360 (12.6%) | 0.539 |
| Bifurcation | 66 (11.9%) | 49 (8.8%) | 0.088 | 341 (11.9%) | 365 (12.7%) | 0.365 |
| Total occlusion | 25 (4.5%) | 28 (5.0%) | 0.688 | 189 (6.6%) | 184 (6.4%) | 0.757 |
| Thrombotic | 48 (8.7%) | 50 (9.0%) | 0.854 | 312 (10.9%) | 317 (11.1%) | 0.876 |
| Total stent length[b] (mm) | 39.6 ± 25.7 | 38.1 ± 22.6 | 0.310 | 40.0 ± 23.9 | 39.9 ± 24.6 | 0.787 |
| Minimum stent diameter (mm) | 2.8 ± 0.5 | 2.8 ± 0.5 | 0.764 | 2.8 ± 0.5 | 2.9 ± 0.5 | 0.320 |

CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; Tica, ticagrelor.
[a]Lesion morphology assessed by operators.
[b]Stent length calculated by operators.

placebo vs. 31 patients (5.7%) randomized to ticagrelor plus aspirin (HR 1.40, 95% CI 0.88–2.22; $P = 0.153$) for an absolute risk difference of 2.2% (95% CI -0.8 to 5.2%) (*Figure 3*). Individual rates of MI (5.0% vs. 3.9%), ischaemic stroke (0.9% vs 0.0%), and definite/probable stent thrombosis (0.9% vs. 0.6%) were numerically higher with ticagrelor plus placebo but not significantly different between treatment groups, with the exception of ischaemic stroke ($P = 0.025$) (*Figure 4*). Similar treatment effects on ischaemic events were observed in patients without CKD for the composite of all-cause death, MI, or stroke (3.2% vs. 3.6%; absolute risk difference -0.4%, 95% CI -1.3% to 0.6%; 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 material online, *Table S3 and S4*).

Of the 1111 patients with an eGFR <60 mL/min/1.73 m$^2$, 796 (71.6%) had mild-to-moderate CKD (eGFR 45–59 mL/min/1.73 m$^2$) while 315 (28.4%) had moderate-to-severe CKD (eGFR < 45 mL/min/1.73 m$^2$). There was a graded relationship between the severity of CKD and the risk of bleeding and ischaemic events (Supplementary material online, *Figure S3*), but the treatment effects of ticagrelor monotherapy on the primary and key secondary endpoints were preserved across all CKD categories (Supplementary material online, *Tables S5 and S6*).

When the estimated event rates were plotted against eGFR used as a continuous variable, the absolute risk reduction in BARC 2, 3, or 5 bleeding with ticagrelor monotherapy progressively increased with worsening renal function (Supplementary material online, *Figure S4A*). Meanwhile, the rates of death, MI, or stroke were numerically lower with ticagrelor monotherapy compared with ticagrelor plus aspirin for eGFR values >80 mL/min/1.73 m$^2$ and numerically higher below the same eGFR cut-off (Supplementary material online, *Figure S4B*).

# Discussion

The principal findings from this prespecified subgroup analysis of the TWILIGHT trial suggest that the treatment effects of ticagrelor monotherapy on bleeding and ischaemic 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 50% and 60%, respectively, among patients with 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 ischaemic events with worsening renal function (*Graphical abstract*).

Chronic kidney disease is a prevalent comorbid condition in patients undergoing PCI, an epidemiology that reflects the

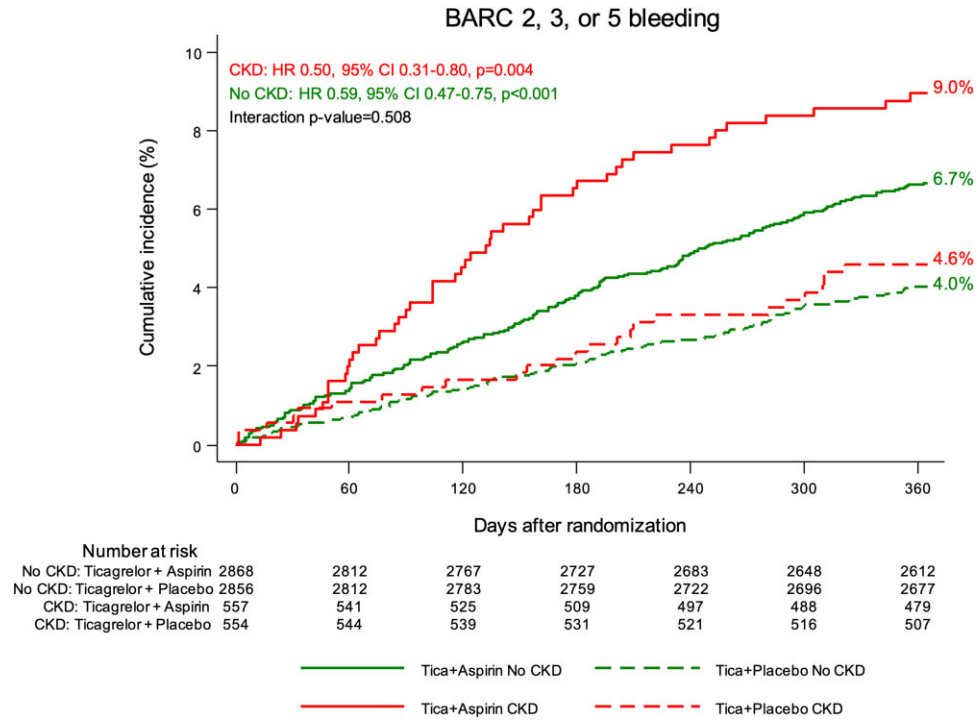



**Figure 1** Rates of BARC 2, 3, or 5 bleeding at 1 year after randomization. Kaplan–Meier curves for BARC 2, 3, or 5 bleeding with ticagrelor plus placebo vs. ticagrelor plus aspirin in patients with and without CKD (estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$) in the intention-to-treat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

| | 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 | 5724 | 113 (4.0%) | 189 (6.7%) | 0.59 (0.47 - 0.75) | 0.508 |
| CKD | 1111 | 25 (4.6%) | 49 (9.0%) | 0.50 (0.31 - 0.80) | |
| **BARC 3, or 5** | | | | | |
| No CKD | 5724 | 26 (0.9%) | 47 (1.7%) | 0.56 (0.34 - 0.90) | 0.481 |
| CKD | 1111 | 8 (1.5%) | 20 (3.7%) | 0.40 (0.17 - 0.90) | |
| **TIMI major** | | | | | |
| No CKD | 5724 | 14 (0.5%) | 23 (0.8%) | 0.61 (0.32 - 1.19) | 0.266 |
| CKD | 1111 | 3 (0.6%) | 11 (2.0%) | 0.27 (0.08 - 0.97) | |
| **GUSTO moderate or severe** | | | | | |
| No CKD | 5724 | 17 (0.6%) | 32 (1.1%) | 0.53 (0.30 - 0.96) | 0.972 |
| CKD | 1111 | 9 (1.7%) | 17 (3.1%) | 0.52 (0.23 - 1.18) | |
| **ISTH major** | | | | | |
| No CKD | 5724 | 29 (1.0%) | 49 (1.7%) | 0.59 (0.38 - 0.94) | 0.461 |
| CKD | 1111 | 9 (1.7%) | 21 (3.8%) | 0.42 (0.19 - 0.92) | |

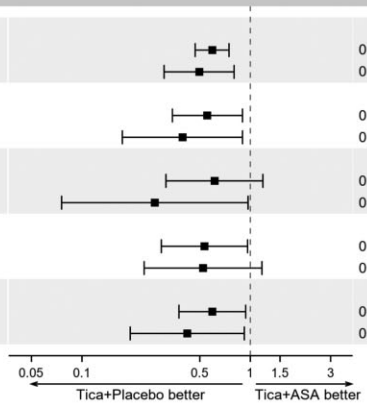



**Figure 2** Risk of bleeding events at 1 year after randomization. Forest plots showing the effect of ticagrelor plus placebo vs. ticagrelor plus aspirin on the bleeding endpoints in relation to CKD (estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$). Event rates at 1 year were estimated using the Kaplan–Meier method. Hazard ratios and 95% confidence intervals with interaction *P*-values generated using Cox regression. ASA, aspirin; BARC, Bleeding Academic Research Consortium; CI, confidence interval; CKD, chronic kidney disease; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; Tica, ticagrelor; TIMI, Thrombolysis in Myocardial Infarction.

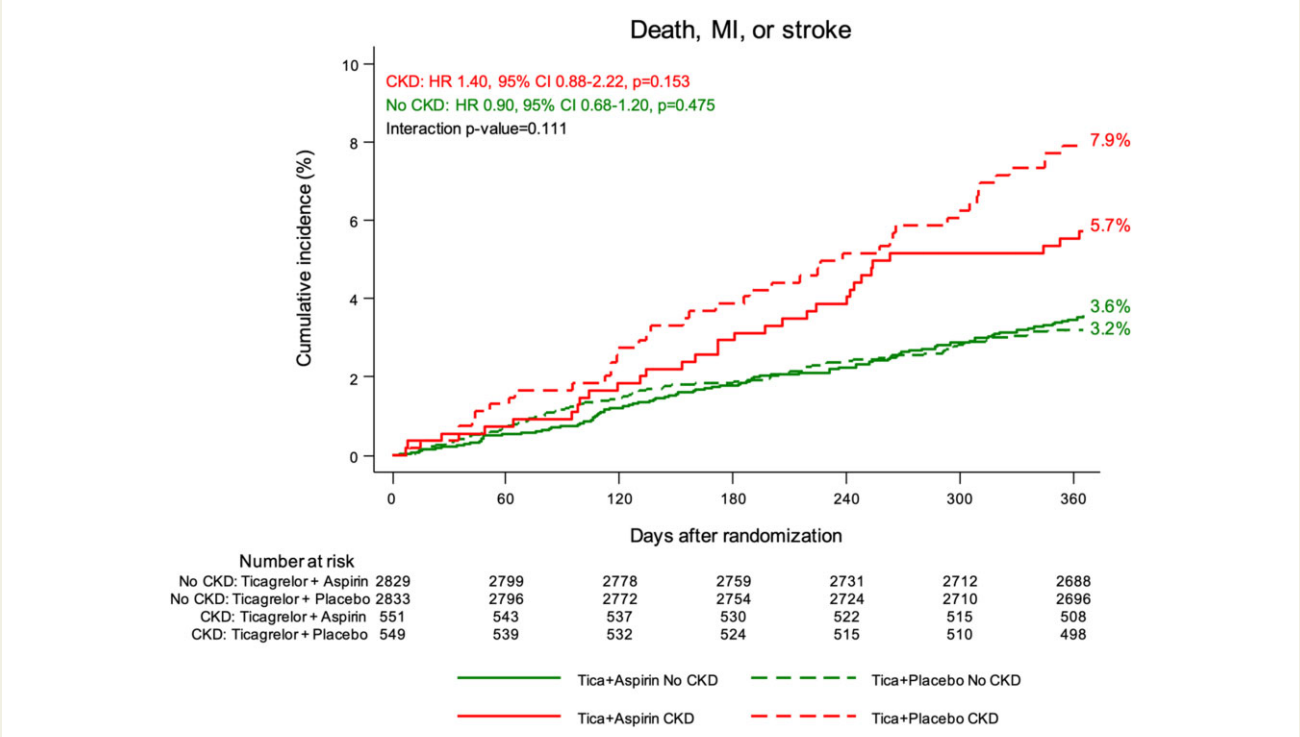



**Figure 3** Rates of death, myocardial infarction, or stroke at 1 year after randomization. Kaplan–Meier curves for all-cause death, myocardial infarction, or stroke with ticagrelor plus placebo vs. ticagrelor plus aspirin in patients with and without CKD (estimated glomerular filtration rate < 60 mL/min/1.73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

progressive ageing of the general population as well as the broadening of the indications to PCI to higher risk cohorts. The increased haemorrhagic 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.[4–6] 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.[24] Accelerated atherosclerosis, systemic inflammation, and oxidative stress are other key contributors to the enhanced cardiovascular risk associated with CKD.[25,26] Additional pharmacological issues relating to altered pharmacodynamic response, drug accumulation, and modified drug interactions further compound the management of these patients.[7,8]

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.[27,28] Similar findings were reported in those with diabetic nephropathy randomized to monotherapy with clopidogrel instead of aspirin for secondary cardiovascular prevention.[29] This apparent lack of benefit was partly attributed to the higher levels of platelet reactivity observed in patients with CKD during treatment with clopidogrel, thus providing a rationale for the use of alternative antithrombotic regimens in this cohort.[30,31]

Compared with clopidogrel, potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) have demonstrated a significant benefit in terms of ischaemic protection among ACS patients, including those with eGFR <60 mL/min/1.73 $m^2$. 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.[32] 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 to a similar extent as thrombotic events.[11,12]

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.[33] This approach was also supported by pharmacodynamic data suggesting a marginal antiplatelet effect of aspirin when added to potent $P2Y_{12}$ inhibitors.[34,35] Hence, a number of PCI trials have investigated the safety and efficacy of $P2Y_{12}$ inhibitor monotherapy after a DAPT course as short as 1–3 months.[36–39] In GLOBAL LEADERS, which randomized nearly 16 000 all-comer patients to ticagrelor monotherapy after 1-month DAPT vs. standard of care, the prevalence of CKD was 13.7%.[40] The trial results showed no significant differences in the primary endpoint of all-cause mortality or new Q-wave MI and BARC 3 or 5 bleeding at 2 years between the experimental and the

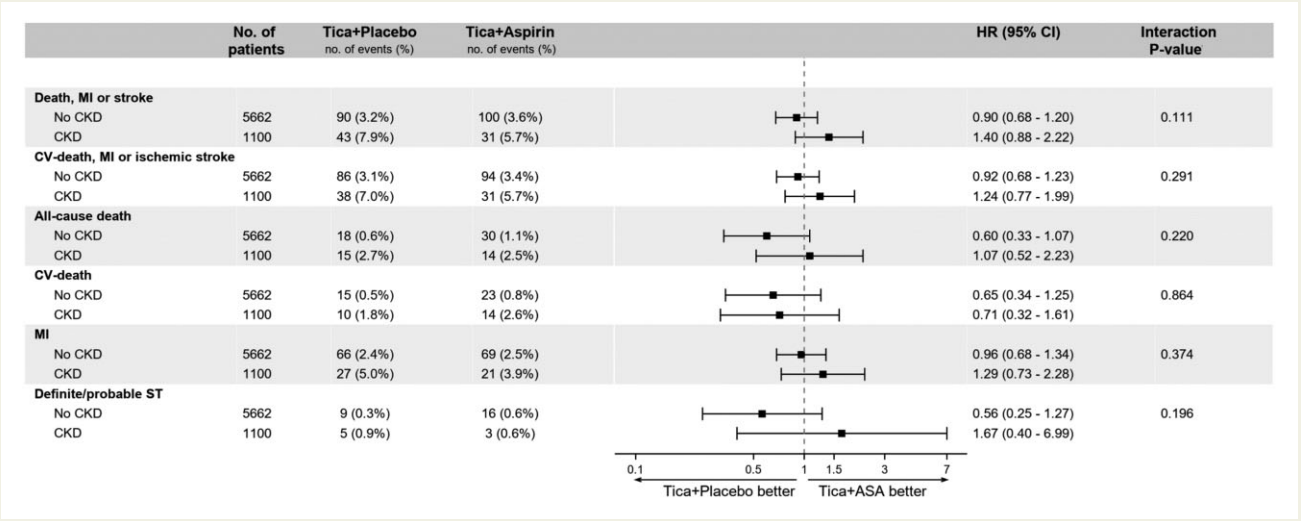



**Figure 4** Risk of ischaemic events at 1 year after randomization. Forest plots showing the effect of ticagrelor plus placebo vs. ticagrelor plus aspirin on the ischaemic endpoints in relation to CKD (estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$). Event rates at 1 year were estimated using the Kaplan–Meier method. Hazard ratios and 95% confidence intervals (CI) with interaction *P*-values generated using Cox regression. In the CKD cohort, the stroke rate was 0.9% (five events) in patients randomized to ticagrelor plus placebo vs. 0% (no events) in those randomized to ticagrelor plus aspirin (log-rank *P* = 0.025, hazard ratio not applicable); Corresponding stroke rates in patients without CKD were 0.4% (11 events) vs. 0.3% (8 events) (log-rank *P* = 0.481; hazard ratio 1.38; 95% CI 0.55–3.43). ASA, aspirin; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular, HR, hazard ratio; MI, myocardial infarction, ST, stent thrombosis, Tica, ticagrelor.

control strategy, irrespective of renal function.[40] While these findings must be interpreted in the context of an overall negative trial, exploratory analyses using eGFR as a continuous variable suggested a lower bleeding risk with ticagrelor monotherapy with decreasing eGFR, consistent with what 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 ischaemia. Chronic kidney disease, 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.[41–43] 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 reductions that we observed were larger than 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 trade-off in antithrombotic efficacy with ticagrelor monotherapy. Nonetheless, there was a numerical increase in ischaemic events among CKD patients on ticagrelor monotherapy, mainly driven by an excess in stroke rates. Such trend, although not statistically significant, was also suggested by visual assessment of the relationship between ischaemic event rates and eGFR used as a continuous variable. Whether aspirin serves an important platelet inhibitory role in the prothrombotic milieu of CKD, however, 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 enrolment 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 ischaemic 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 ischaemic events with ticagrelor monotherapy. Future research should explore the safety and efficacy of this treatment strategy across all kidney function categories.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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