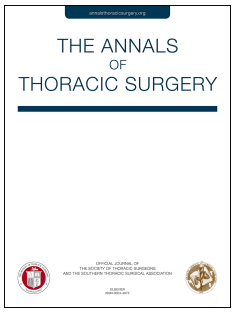
# Journal Pre-proof




Ticagrelor or aspirin after coronary artery bypass in patients with chronic kidney disease

Sigrid E. Sandner, MD, Heribert Schunkert, MD, Adnan Kastrati, MD, Milan Milojevic, MD, Andreas Böning, MD, Daniel Zimpfer, MD, Stephan Zellmer, MD, Dominik Wiedemann, MD, Günther Laufer, MD, Moritz von Scheidt, MD, for the TiCAB Investigators

PII: S0003-4975(21)00590-7

DOI: https://doi.org/10.1016/j.athoracsur.2021.03.061

Reference: ATS 35106

To appear in: *The Annals of Thoracic Surgery*

Received Date: 6 November 2020

Revised Date: 19 January 2021

Accepted Date: 22 March 2021

Please cite this article as: Sandner SE, Schunkert H, Kastrati A, Milojevic M, Böning A, Zimpfer D, Zellmer S, Wiedemann D, Laufer G, von Scheidt M, for the TiCAB Investigators, Ticagrelor or aspirin after coronary artery bypass in patients with chronic kidney disease, *The Annals of Thoracic Surgery* (2021), doi: https://doi.org/10.1016/j.athoracsur.2021.03.061.

# Ticagrelor or aspirin after coronary artery bypass in patients with chronic kidney disease

Running head: Ticagrelor or aspirin after CABG in CKD

Sigrid E. Sandner MD[a], Heribert Schunkert MD[bc], Adnan Kastrati MD[bc], Milan Milojevic MD[de], Andreas Böning MD[f], Daniel Zimpfer MD[a], Stephan Zellmer MD[bc], Dominik Wiedemann MD[a], Günther Laufer MD[a], Moritz von Scheidt MD[bc], for the TiCAB Investigators

[a]Department of Cardiac Surgery, Medical University of Vienna, Austria

[b]Deutsches Herzzentrum München, Technische Universität München, Germany

[c]German Center for Cardiovascular Research (DZHK), Munich Heart Alliance, Germany

[d]Department of Cardiothoracic Surgery, Erasmus University Medical Center, The Netherlands

[e]Department of Cardiac Surgery and Cardiovascular Research, Dedinje Cardiovascular Institute, Serbia

[f]Department of Cardiovascular Surgery, University Hospital Giessen, Germany



Word count: 4,469

Corresponding author: Sigrid E. Sandner, MD

Department of Cardiac Surgery, Medical University of Vienna

Spitalgasse 23, A-1090 Vienna, Austria

Email: sigrid.sandner@meduniwien.ac.at

Abstract

Background: The optimal antiplatelet therapy for patients with chronic kidney disease (CKD) undergoing coronary artery bypass grafting (CABG) remains unknown.

Methods: This post hoc analysis of the Ticagrelor in Coronary Artery Bypass (TiCAB) trial examined the efficacy and safety of ticagrelor versus aspirin in patients with or without CKD. Primary endpoint was the composite of cardiovascular death, stroke, myocardial infarction or revascularization (MACCE) at 1 year after CABG. Secondary endpoints included individual components of the primary endpoint, all-cause death, and major bleeding.

Results: CKD was present in 276 of 1,843 randomized patients (15.0%). Patients with CKD versus those without CKD had higher 1-year rates of MACCE (13.0% vs. 8.3%, HR 1.63, 95% CI 1.12-2.39, P=0.01) and major bleeding (5.6% vs. 3.1%, HR 1.84, 95% CI 1.03-3.28, P=0.04). The 1-year rate of MACCE was increased with ticagrelor versus aspirin in patients with CKD (18.2% vs. 8.9%, HR 2.15, 95% CI 1.08-4.30, P=0.03), but not in patients without CKD (8.5% vs. 8.1%, HR 1.05, 95% CI 0.74-1.49, P=0.79) ($P_{interaction}$=0.067). There was no difference in the 1-year rate of major bleeding with ticagrelor versus aspirin in patients with CKD (6.6% vs. 4.7%, HR 1.44, 95% CI 0.52-3.97, P=0.48) and without CKD (3.3% vs. 2.9%, HR 1.14, 95% CI 0.64-2.01, P=0.65).

Conclusions: In patients with CKD and CABG, those who received ticagrelor had a higher incidence of MACCE but a similar incidence of major bleeding compared to those who received aspirin.

Chronic kidney disease (CKD) is associated with increased risk of cardiovascular disease and subsequent cardiovascular events [1]. Optimal antiplatelet therapy remains controversial in these patients as potential benefits with more potent antithrombotic therapies are offset by increased bleeding risk [2]. Ticagrelor, on a background of aspirin, resulted in a greater risk reduction for the ischemic primary endpoint versus clopidogrel in acute coronary syndrome patients with CKD [3,4] and versus placebo in stable coronary artery disease patients with CKD [5], albeit with an excess in major [4] and minor [5], or non-procedure-related [3] bleeding events. Therefore, there is a need to further clarify benefits and risks of antithrombotic approaches that do not include aspirin.

The effect of ticagrelor in patients undergoing coronary artery bypass grafting (CABG) has been studied in few trials with conflicting results [6,8]. However, none have reported outcomes in patients with CKD. The Ticagrelor in Coronary Artery Bypass (TiCAB) trial compared the effect of ticagrelor monotherapy with aspirin on clinical events within the first year after CABG [8]. The presence of moderate to severe CKD was not an exclusion criterion in the trial. This post hoc analysis of the TiCAB trial aimed to examine the efficacy and safety of ticagrelor monotherapy compared with aspirin after CABG in patients with or without CKD.

## Patients and Methods

### Data source

The design and primary results of the TiCAB trial (NCT01755520) have been published [8,9]. In brief, TiCAB was a multi-center, double-blinded, placebo-controlled randomized trial that enrolled patients with stable coronary artery disease or acute coronary syndrome undergoing CABG for three-vessel disease and/or left main stenosis, or two-vessel disease with impaired left ventricular function. Patients requiring dialysis were excluded from participation. Randomized patients received either aspirin 100 mg and placebo ticagrelor or placebo aspirin and ticagrelor 90 mg within the first 24 hours after CABG. Maintenance doses consisted of aspirin 100 mg once daily or ticagrelor 90 mg twice daily. There was no dose adjustment for impaired renal function. Under the initial TiCAB protocol 245 patients also received study medication at days -5 to -3 before CABG surgery [8]. Patients were not tested for aspirin sensitivity. Primary endpoint was the composite of cardiovascular death, myocardial

to a modified intention-to treat principle. All statistical analyses were performed with the use of R v3.5.1 software.

## Results

### Patients

Of 1,859 patients undergoing CABG in the TiCAB trial 1,843 (99.1%) had serum creatinine levels available at baseline. CKD was present in 276 patients (15.0%) (Figure 1). The distribution of baseline eGFR is illustrated in Supplemental Figure 1. Baseline patient characteristics by renal function and randomized treatment are presented in Table 1 and procedural characteristics are presented in Table 2. Within the groups baseline and procedural characteristics of patients receiving either ticagrelor or aspirin were balanced as treatment was randomized. Baseline and procedural characteristics of patients stratified by the presence or absence of CKD are presented in Supplemental Table 1 and Supplemental Table 2.

### Efficacy and Bleeding Outcomes in Relation to Baseline Renal Function

The 1-year rate of MACCE was increased in patients with CKD compared to those without CKD (13.0% vs. 8.3%; HR, 1.63; 95% CI, 1.12 to 2.39; P=0.01) (Figure 2A). The HR for all-cause death associated with CKD was 2.98 (95% CI, 1.60 to 5.54; P=0.0006) (Supplemental Table 3). Patients with CKD compared to those without CKD had higher rates of major bleeding (5.6% vs. 3.1%; HR, 1.84; 95% CI, 1.03 to 3.28; P=0.04) (Figure 2B). When modeled as a continuous variable, progressively lower eGFR was associated with a greater 1-year risk of MACCE (HR per 30 mL/min/1.73 $m^2$ decrease: 1.19; 95% CI: 1.02 to 1.39) (Figure 3A) and major bleeding (HR per 30 mL/min/1.73 $m^2$ decrease: 1.21; 95% CI: 0.95 to 1.54) (Figure 3B).

### Efficacy Outcomes in Relation to Baseline Renal Function and Randomized Treatment

The risk of MACCE increased with decreasing eGFR at baseline in the ticagrelor (HR per 30 mL/min/1.73 $m^2$ decrease: 1.40; 95% CI: 1.13 to 1.72) and aspirin (HR per 30 mL/min/1.73 $m^2$ decrease: 1.00; 95% CI: 0.81 to 1.24) groups (Figure 3A). At 1 year there was a significant difference

in the rate of the primary endpoint with ticagrelor versus aspirin in patients with CKD (18.2% vs. 8.9%; HR, 2.15; 95% CI, 1.08 to 4.30; P=0.03) but not in those without CKD (8.5% vs. 8.1%; HR, 1.05; 95% CI, 0.74 to 1.49; P=0.79) (Figure 4). There was no significant treatment by renal function interaction for the primary endpoint ($P_{interaction}$=0.067) (Figure 5). The majority of primary endpoint events (71%) occurred within 30 days after randomization. A landmark analysis showed that the estimate of the treatment effect of ticagrelor versus aspirin from randomization to 30 days (HR, 2.14; 95% CI, 0.94 to 4.89) was comparable to that from >30 days to 1 year (HR, 2.18; 95% CI, 0.62 to 7.74). The 1-year rates of the secondary efficacy endpoints were numerically higher but not significantly elevated with ticagrelor versus aspirin in patients with and without CKD (Figure 5).

Bleeding Outcomes in Relation to Baseline Renal Function and Randomized Treatment

The risk of major bleeding increased with decreasing eGFR at baseline similarly in the ticagrelor (HR per 30 mL/min/1.73 $m^2$ decrease: 1.24; 95% CI: 0.9 to 1.71) and aspirin (HR per 30 mL/min/1.73 $m^2$ decrease: 1.18; 95% CI: 0.81 to 1.70) groups (Figure 3B). At 1 year the rate of major bleeding was higher but did not differ significantly with ticagrelor versus aspirin in patients with CKD (6.6% vs. 4.7%; HR, 1.44; 95% CI, 0.52 to 3.97; P=0.48) and in those without CKD (3.3% vs 2.9%; HR, 1.14; 95% CI, 0.64 to 2.01; P=0.65) ($P_{interaction}$=0.69) (Figure 5, Figure 6).

Comment

This post hoc analysis of the TiCAB trial examined the efficacy and safety of ticagrelor monotherapy compared with aspirin for secondary prevention of ischemic events after CABG in patients with or without CKD. The presence of CKD was associated with an increased risk of cardiovascular death, stroke, non-fatal myocardial infarction, or revascularization (MACCE), all-cause death and bleeding at 1 year after CABG irrespective of antiplatelet therapy. Ticagrelor compared with aspirin was associated with an increased risk of MACCE at 1 year after CABG in patients with CKD but not in those without CKD, although the interaction between renal function and antiplatelet therapy was not significant. The effects of ticagrelor and aspirin on major bleeding were similar among patients with or without CKD.

There is a growing interest in the impact of CKD as its prevalence in patients requiring myocardial revascularization is increasing [13]. This study confirms that CKD is a powerful marker of risk in patients presenting for CABG, as patients with CKD had a significantly higher rate of the composite primary endpoint of MACCE, and a nearly three-fold increase in the risk of death. As expected, when compared with patients without CKD, patients with CKD displayed a nearly two-fold increase in major bleeding rates. These findings are consistent with recently published subgroup analyses from three landmark revascularization trials in three-vessel and left main disease (SYNTAX, FREEDOM, and EXCEL) that reported substantially higher rates of composite outcomes of hard clinical endpoints [14-16], all-cause death [14-16], and hemorrhagic adverse events [16] in patients with CKD.

A subgroup analysis of the PLATO trial demonstrated an impressive benefit of ticagrelor over clopidogrel (as part of dual antiplatelet therapy [DAPT] with aspirin) in acute coronary syndrome patients with CKD for the composite primary endpoint of death from vascular causes, myocardial infarction, or stroke, and all-cause death [3]. However, a recent subgroup analysis of the GLOBAL LEADERS trial [17] comparing the experimental strategy of 1-month ticagrelor plus aspirin DAPT followed by 23-month ticagrelor monotherapy with the control arm of 12-month DAPT followed by 12-month aspirin showed no differential treatment effects with regard to all-cause death or new Q-wave myocardial infarction after percutaneous coronary intervention in patients with CKD [18]. In this post hoc analysis of the TiCAB trial we found that patients with CKD had a significantly higher rate of MACCE with ticagrelor when compared to aspirin (18.2% versus 8.9%). In fact, the rate of MACCE in patients with CKD randomized to aspirin was similar to the rate of MACCE in patients without CKD irrespective of randomized treatment (ticagrelor 8.5%, aspirin 8.1%). The nonsignificant probability value for interaction suggests that there is no differential effect of ticagrelor in patients with or without CKD; however, this test does not address significance testing at an alpha level of 0.05 in the presence of underpowered tests and the potentially low prevalence of real between-group differences. It may therefore have limited ability to inform individual treatment decision-making because of the high probability of false-negative results in the presence of an inadequate sample size [19]. In addition, our finding that patients with CKD randomized to ticagrelor had numerically higher, albeit nonsignificant, rates of individual secondary efficacy endpoints than those randomized to

aspirin, may support routine use of aspirin in secondary prevention after CABG in patients with CKD and careful evaluation of preference for ticagrelor over other P2Y12 inhibitors in those resistant to aspirin.

A possible explanation for the differences seen in the effect of ticagrelor in the TiCAB trial and other trials of ticagrelor is an efficacy disparity between ticagrelor on a background of aspirin as DAPT versus ticagrelor monotherapy. The PLATO trial reported a reduction in all-cause and cardiovascular death for ticagrelor over clopidogrel DAPT irrespective of renal function in patients undergoing CABG [6]. However, this effect on mortality has not been observed with ticagrelor monotherapy in patients undergoing percutaneous coronary intervention [17,20] or in CABG patients [7,8]. Furthermore, the majority of patients in TiCAB presented with stable coronary artery disease (>65% in the CKD group), whereas PLATO included acute coronary syndrome patients who due to their higher ischemic risk are more likely to experience a benefit on hard endpoints such as mortality. Of note, the TiCAB trial showed opposing trends with secondary endpoints, suggesting that ticagrelor and aspirin may have diverse efficacy in preventing specific outcomes such as myocardial infarction or stroke.

Ticagrelor may add to the risk of adverse outcomes in patients with CKD undergoing CABG by directly adversely affecting renal function. In the PLATO trial a larger increase in the mean serum creatinine concentration from baseline to 12 months was observed in patients randomized to ticagrelor that resolved with ticagrelor discontinuation [3]. The underlying mechanisms are unclear, but it has been suggested that ticagrelor can alter renal hemodynamics by decreasing vascular tone in the afferent arteriole thereby lowering the glomerular filtration pressure [21].

Ticagrelor did not significantly increase major bleeding versus aspirin across the spectrum of renal function. Importantly, randomized trials investigating ticagrelor monotherapy have shown favorable bleeding outcomes compared with DAPT. Among high-risk patients who underwent percutaneous coronary intervention and completed 3 months of DAPT in the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial, ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor DAPT [22]. Similarly, in the GLOBAL LEADERS Adjudication Sub-Study (GLASSY) [20] the results at 2 years showed identical rates of Bleeding Academic Research Consortium Type 3 or 5 bleeding in the

experimental and control groups. However, these trials have not yet analyzed effects of ticagrelor monotherapy on bleeding outcomes in patients with CKD.

## Limitations

This analysis of treatment groups stratified by renal function was a post hoc analysis of a randomized trial and findings should be considered observational and hypothesis-generating only. Although all analyses in the main TiCAB trial were carried out on pre-specified subgroups, the use of multiple testing could still lead to false-positive results [19]. Nevertheless, given the fact that the present analysis did not reach conventional levels of statistical significance for interaction, the findings should be interpreted in the context of the main trial, which was underpowered for the primary endpoint and did not demonstrate an effect of ticagrelor versus aspirin.

Patients requiring dialysis were excluded from participation in the TiCAB trial and the findings of this analysis may therefore not be representative of patients across the entire spectrum of CKD. Estimations of GFR were based on creatinine measurements obtained within 14 days of enrollment into the trial and may not accurately reflect renal function in the setting of acute coronary syndrome. Creatinine measurements were not consistently obtained at 1-year follow-up, precluding an analysis of deterioration of renal function from baseline to 1 year after CABG in the TiCAB population.

## Conclusions

In patients with CKD and CABG, those who received ticagrelor had a higher incidence of MACCE but a similar incidence of major bleeding compared to those who received aspirin. An adequately powered, dedicated clinical trial is needed to provide evidence for optimal antiplatelet therapy in patients with CKD after CABG.

References

1. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296-305.

2. Bonello L, Angiolillo DJ, Aradi D, et al. P2Y12-ADP Receptor Blockade in Chronic Kidney Disease Patients With Acute Coronary Syndromes. Circulation 2018;138(15):1582-96.

3. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation 2010;122(11):1056-67.

4. Edfors R, Sahlen A, Szummer K, et al. Outcomes in patients treated with ticagrelor versus clopidogrel after acute myocardial infarction stratified by renal function. Heart 2018;104(19):1575-82.

5. Magnani G, Storey RF, Steg G, et al. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights from the PEGASUS-TIMI 54 trial. Eur Heart J 2016;37(4):400-8.

6. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011;57(6):672-84.

7. Zhao Q, Zhu Y, Xu Z, et al. Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting: A Randomized Clinical Trial. JAMA 2018;319(16):1677-86.

8. Schunkert H, Boening A, von Scheidt M, et al. Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial. Eur Heart J 2019;40(29):2432-40.

9. de Waha A, Sandner S, von Scheidt M, et al. A randomized, parallel group, double-blind study of ticagrelor compared with aspirin for prevention of vascular events in patients undergoing coronary artery bypass graft operation: Rationale and design of the Ticagrelor in CABG (TiCAB) trial: An Investigator-Initiated trial. Am Heart J 2016;179:69-76.

10. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736-47.

11. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12.

12. Stevens PE, Levin A, Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group M. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158(11):825-30.

13. Sarnak MJ, Amann K, Bangalore S, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. J Am Coll Cardiol 2019;74(14):1823-38.

14. Milojevic M, Head SJ, Mack MJ, et al. The impact of chronic kidney disease on outcomes following percutaneous coronary intervention versus coronary artery bypass grafting in patients with complex coronary artery disease: five-year follow-up of the SYNTAX trial. EuroIntervention 2018;14(1):102-11.

15. Baber U, Farkouh ME, Arbel Y, et al. Comparative efficacy of coronary artery bypass surgery vs. percutaneous coronary intervention in patients with diabetes and multivessel coronary artery disease with or without chronic kidney disease. Eur Heart J 2016;37(46):3440-47.

16. Giustino G, Mehran R, Serruys PW, et al. Left Main Revascularization With PCI or CABG in Patients With Chronic Kidney Disease: EXCEL Trial. J Am Coll Cardiol 2018;72(7):754-65.

17. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940-49.

18. Tomaniak M, Chichareon P, Klimczak-Tomaniak D, et al. Impact of renal function on clinical outcomes after PCI in ACS and stable CAD patients treated with ticagrelor: a prespecified analysis of the GLOBAL LEADERS randomized clinical trial. Clin Res Cardiol 2020;109(7):930-43.

19. Milojevic M, Nikolic A, Juni P, et al. A statistical primer on subgroup analyses. Interact Cardiovasc Thorac Surg 2020;30(6):839-45.

20. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting. J Am Coll Cardiol 2019;74(18):2223-34.

21. Serebruany VL, Tomek A, Pokov AN, et al. Clopidogrel, prasugrel, ticagrelor or vorapaxar in patients with renal impairment: do we have a winner? Expert Rev Cardiovasc Ther 2015;13(12):1333-44.

22. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;381(21):2032-42.

Table 1. Baseline patient characteristics by baseline renal function and randomized treatment

Beta-blocker
ACE inhibitor
Angiotensin-receptor blocker
Calcium channel inhibitor
Diuretic

Figure Legends

Figure 1. Study population, by presence or absence of chronic kidney disease (CKD). CABG, coronary artery bypass grafting.

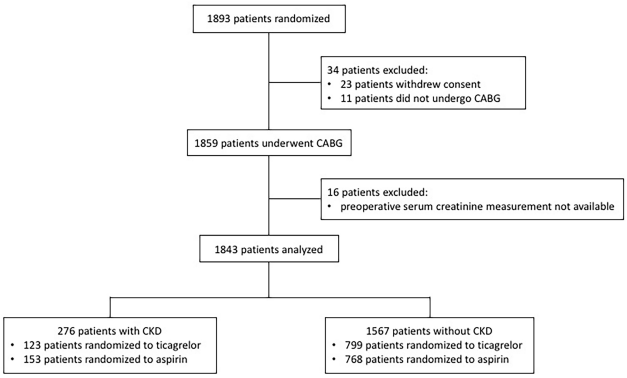
Figure 2. 1-Year outcomes in patients after coronary artery bypass grafting in patients with and without chronic kidney disease (CKD).
Kaplan-Meier event rate curves of (A) the primary endpoint; and (B) major bleeding.

Figure 3. Smooth hazard function for the risk of (A) the primary endpoint; and (B) major bleeding at 1 year after CABG according to baseline renal function. eGFR, estimated glomerular filtration rate.

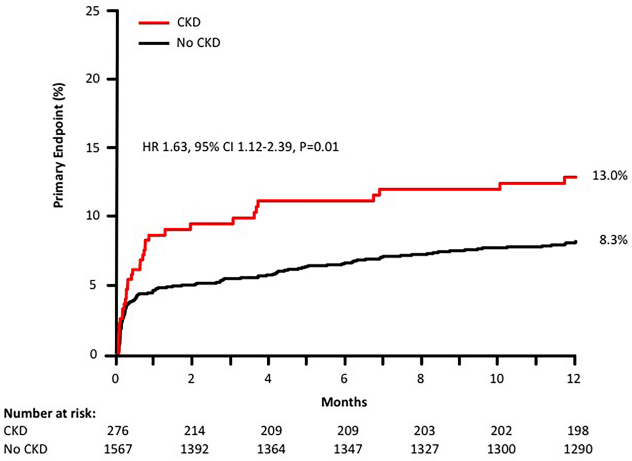
Figure 4. Kaplan-Meier event rate curves of the primary endpoint stratified by presence or absence of chronic kidney disease (CKD) in the ticagrelor and aspirin randomized treatment arms.

Figure 5. Forest plot showing associations for efficacy and safety endpoints in relation to chronic kidney disease (CKD) and randomized treatment.

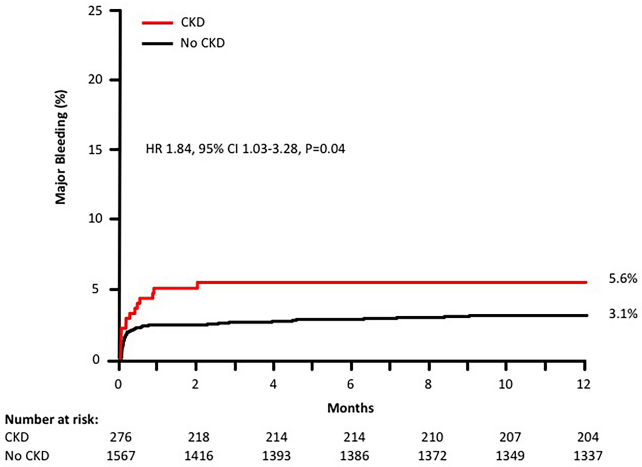
Figure 6. Kaplan-Meier event rate curves for major bleeding stratified by presence or absence of chronic kidney disease (CKD) in the ticagrelor and aspirin randomized treatment arms.



A

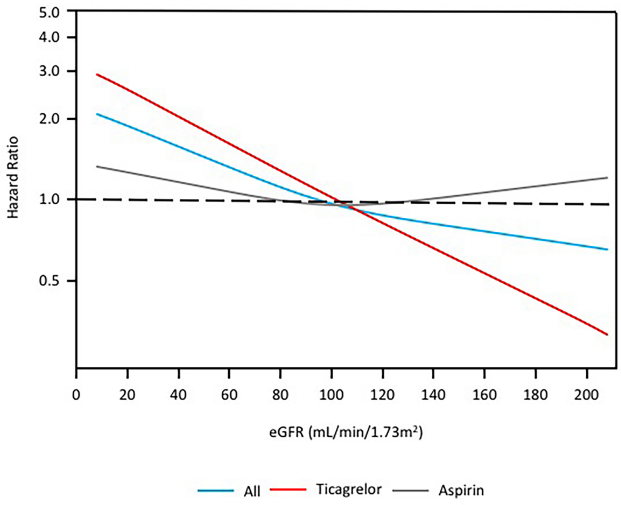


B

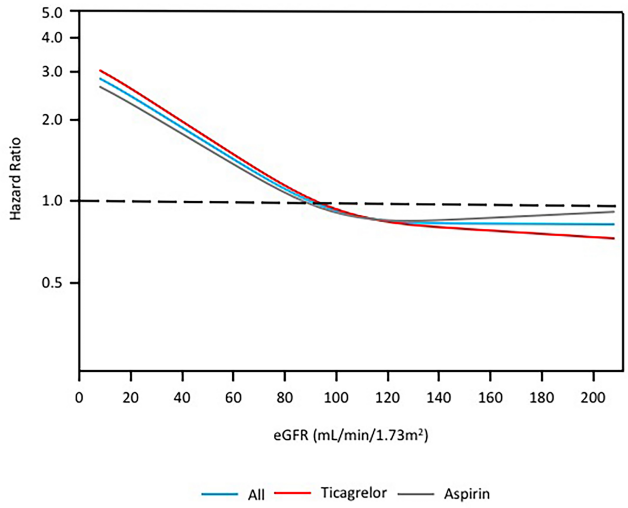


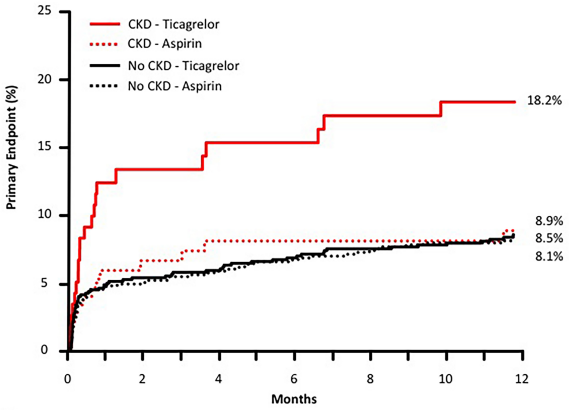

| Number at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| CKD | 276 | 218 | 214 | 214 | 210 | 207 | 204 |
| No CKD | 1567 | 1416 | 1393 | 1386 | 1372 | 1349 | 1337 |

A



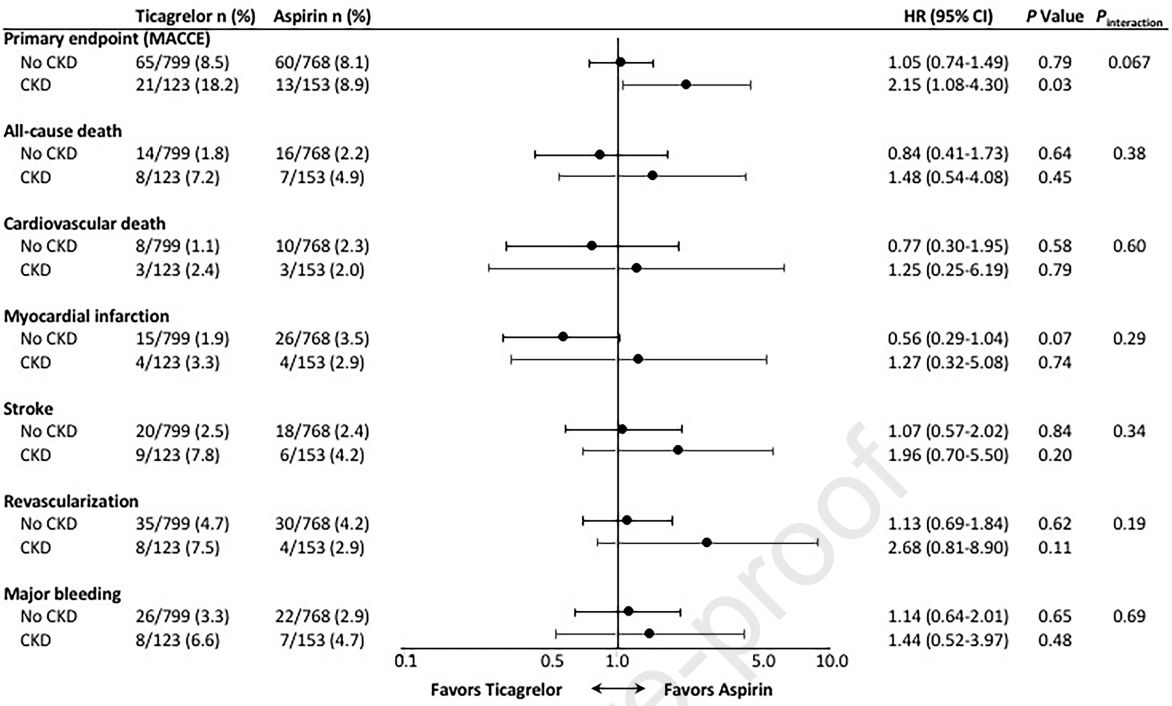
B

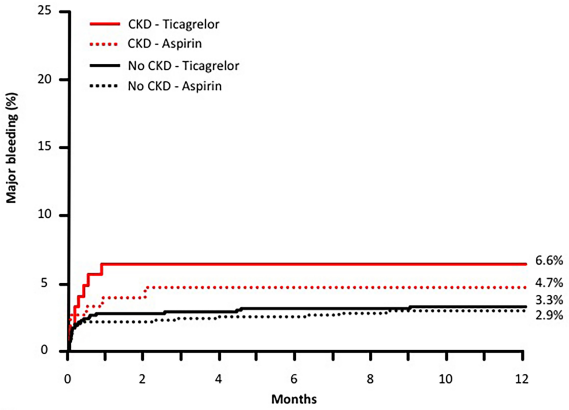





**Number at risk:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CKD - Ticagrelor | 123 | 88 | 86 | 86 | 82 | 82 | 79 |
| CKD - Aspirin | 153 | 126 | 123 | 123 | 121 | 120 | 119 |
| No CKD - Ticagrelor | 799 | 704 | 692 | 684 | 671 | 660 | 653 |
| No CKD - Aspirin | 768 | 688 | 672 | 663 | 656 | 640 | 637 |






**Number at risk:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CKD - Ticagrelor | 123 | 93 | 90 | 90 | 88 | 86 | 84 |
| CKD - Aspirin | 153 | 125 | 124 | 124 | 122 | 121 | 120 |
| No CKD - Ticagrelor | 799 | 716 | 706 | 703 | 694 | 683 | 675 |
| No CKD - Aspirin | 768 | 700 | 687 | 683 | 678 | 666 | 662 |