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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

Coordinatore:

Chiar.mo Prof. Alfredo Antonio Chetta

Tutor:

Chiar.mo Prof. Diego Ardissino

Dottoranda: Giulia Magnani

Ai miei genitori

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Tu se' lo mio maestro e 'l mio autore,

tu se' solo colui da cu' io tolsi

lo bello stilo che m'ha fatto onore.

"Thou art my master, and my author thou,

Thou art alone the one from whom I took

The beautiful style that has done honour to me."

Inferno, Canto I, Dante Alighieri

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ABSTRACT

Aims: We evaluated the relationship of renal function and ischaemic and bleeding risk as well as the efficacy and safety of the P2Y12 platelet receptor inhibitor ticagrelor in stable patients with prior myocardial infarction (MI).

Methods & Results: Patients with a history of MI 1-3 years prior from the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS)-TIMI 54 were stratified based on estimated glomerular filtration rate (eGFR), with<60 ml/min/1.73m^2 prespecified for analysis of the effect of ticagrelor on the primary efficacy composite of cardiovascular death, MI, or stroke (MACE) and the primary safety endpoint of TIMI major bleeding. Of 20,898 patients, those with eGFR<60 (N=4,849, 23.2%) had a greater risk of MACE at 3 years relative to those without, which remained significant after multivariable adjustment (HR_{adj} 1.54, 95% CI 1.27–1.85, p<0.001). The relative risk reduction in MACE with ticagrelor was similar in those with eGFR<60 (ticagrelor pooled vs. placebo: HR 0.81; 95% CI 0.68–0.96) vs. ≥60 (HR 0.88; 95% CI 0.77–1.00, $p_{interaction}$=0.44). However, due to the greater absolute risk in the former group, the absolute risk reduction with ticagrelor was higher: 2.7% vs. 0.63%. Bleeding tended to occur more

frequently in patients with renal dysfunction. The absolute increase in TIMI major bleeding with ticagrelor was similar in those with and without eGFR<60 (1.19% vs. 1.43%), whereas the excess of minor bleeding tended to be more pronounced (1.93% vs. 0.69%).

Conclusion: In patients with a history of MI, patients with renal dysfunction are at increased risk of MACE and consequently experience a particularly robust absolute risk reduction with long-term treatment with ticagrelor.

INTRODUCTION

1. Renal dysfunction and ischemic outcomes.

Chronic kidney disease (CKD) is a worldwide public health problem [1,2], associated with an increased risk for cardiovascular (CV) disease [3-5], and all-cause mortality [6]. Numerous epidemiological studies have shown that patients with all stages of CKD experience higher rates of atherothrombotic disease compared to the general population [3-9]. The relationship between renal dysfunction and ischaemic risk is complex and may be caused by accelerated atherosclerosis, inflammation, oxidative stress, and a prothrombotic state [10]. As the population ages and the prevalence of conditions associated with both CV and renal dysfunction risk, such as diabetes increases, the numbers of subjects with concomitant chronic ischaemic heart disease and renal dysfunction is anticipated to grow significantly [2,11]. Nearly one third of patients with ST segment elevation myocardial infarction (MI) and more than 40% of those with a non-ST segment elevation MI have concomitant renal dysfunction [12]. The presence of renal dysfunction in patients who have a MI is associated with worse outcomes, with an inverse graded association between estimated glomerular filtration rate (eGFR) and major adverse cardiovascular events (MACE) [13].

2. Dual antiplatelet therapy in patients with previous myocardial infarction: current evidences.

Activated platelets play a central role in the pathogenesis of MI, being one of the main components of the intracoronary thrombus [14]. Therefore, antiplatelet therapy is a cornerstone for prevention of CV ischemic events [15]. Aspirin, the most commonly used antiplatelet drug, inhibits thromboxane A2 production, through cyclooxygenase (COX)-1 inhibition. Dual antiplatelet therapy (DAPT) is defined as the use of a P2Y12 receptor inhibitor (clopidogrel, ticagrelor or prasugrel) and aspirin. P2Y12 is a G_i class platelet receptor, which mediates platelet activation through adenosine diphosphate (ADP) [16] (**Figure 1**).

Aspirin reduces the risk of ischemic events both among patients who present with an acute coronary syndrome (ACS) and in secondary prevention for patients with a history of MI [15]. DAPT has been shown to reduce further the risk of ischemic events in this population [17-19] and is recommended up to 1 year after an ACS [20-23].

The first evidence of a benefit in adding a P2Y12 inhibitor to aspirin in patients with ACS came from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which showed a 20% reduction in the relative risk of MI, death and stroke in patient treated with

clopidogrel (loading dose 300 mg, followed by 75 mg daily) and aspirin compared to aspirin alone (mean duration of treatment, 9 months) [17]. Clopidogrel however, due to its pharmacokinetic and pharmacodynamic profile has several limitations, including slow onset and offset of antiplatelet effect, modest platelet inhibition, and high interindividual variability. Clopidogrel is a prodrug that requires biotransformation to an active metabolite by cytochrome P450 (CYP) enzymes whose genes are polymorphic. Patients carrying a genetic variant that diminishes the pharmacokinetic and pharmacodynamic response to clopidogrel experience a higher risk of CV ischemic events, included stent thrombosis compared to patients who are noncarriers [24]. To overcome these limitations related to clopidogrel use, more potent and faster P2Y12 inhibitors have been developed.

Prasugrel, similar to clopidogrel, needs biotransformation by cytochromes to become active. Prasugrel, however is rapidly metabolized, showing a faster onset of action, higher levels of platelet inhibition, and less interpatient variability than clopidogrel [25]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 [18], prasugrel (60 mg loading dose followed by 10

mg daily) compared with clopidogrel (300 mg loading dose and 75 mg daily) reduced by 19% the relative risk of CV death, MI, or stroke in patients with ACS (median duration of therapy 14.5 months). The benefit in the reduction of ischemic events was accompanied by a 32% increase of TIMI major bleeding, not associated with coronary artery bypass grafting (CABG), higher rates of fatal bleeding, and bleeding associated with CABG. No excess in intracranial haemorrhage was observed. Patients with a history of stroke or transient ischaemic attack had a greater risk of serious bleeding complications, including intracranial haemorrhage and a lower benefit in terms of ischemic events prevention with prasugrel than the overall trial population. Therefore the use of prasugrel is not recommended in this subgroup of patients. In elderly (>75 years) and low body weight (<60 kg) patients, the net clinical outcome with prasugrel was less favorable than in the overall trial population. On the contrary, a better net clinical benefit of prasugrel compared with the overall trial population was observed in patients with ST-segment elevation MI [26], or diabetic patients [27].

Ticagrelor, is a direct-acting P2Y12 antagonist, and unlike clopidogrel and prasugrel, does not need metabolic activation by cytochrome P450 enzymes. The drug acts rapidly, has low interindividual variability and

more potent and consistent antiplatelet effect compared to clopidogrel [28]. In the study of Platelet Inhibition and Patient Outcomes (PLATO) [19], ticagrelor (180 mg loading dose and 90 mg twice daily) compared to clopidogrel (300 mg loading and 75 mg daily) significantly reduced the primary endpoint of CV death, MI or stroke by 16%, as well as CV death alone and death from any cause at 1 year (median follow up 9 months) in 18,624 patients with ACS. This benefit was achieved without an increase of overall major bleeding.

Based on these evidences the current ACS guidelines recommend ticagrelor or prasugrel over clopidogrel and limit the duration of DAPT up to 1 year [20-23], as an artifact of the duration of the 1-year ACS trials above mentioned [17-19].

Several observations however, have suggested that more prolonged DAPT would be beneficial in patients with prior MI. Landmark analyses from the 1-year ACS trials of P2Y12 receptor antagonists showed a continued separation of the event curves over the entire year [19, 29, 30]. Similarly, we showed in landmark analyses from The Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) trial, that more intensive antiplatelet therapy, achieved by adding the PAR-1 platelet receptor inhibitor vorapaxar to standard antiplatelet

treatment, significantly reduced the risk of ischemic events over several years (median follow-up 30 months) in patients with prior MI [31], and in the population of patients with MI or peripheral artery disease, without stroke or TIA, recently approved by the Food and Drug Administration for vorapaxar use [32] (**Figure 2**). Moreover, although overall the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial did not show overall significant differences with long-term clopidogrel (medium follow up 27.6 months) for secondary prevention of ischemic events in a population including patients with multiple atherothrombotic risk factors or documented CV disease (coronary artery disease, cerebrovascular disease, or peripheral arterial disease) a significant reduction in ischemic events (CV death, MI or stroke) was observed in the subgroup of patients with prior MI [33].

Although overall these observations suggested that there is a benefit of more prolonged DAPT in patients with MI, a definitive, prospective clinical trial was required to validate this hypothesis, which was the rationale for conducting the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS)-TIMI 54 trial [34].

The PEGASUS-TIMI 54 is a randomized, double-blind, placebo-controlled multinational clinical trial designed to test two doses of ticagrelor (90 mg and 60 mg twice daily), each compared to placebo in patients with a history of spontaneous MI occurring 1 to 3 years prior to enrollment and at least one additional atherothrombosis risk factor. Ticagrelor 90 mg twice a day is the standard dose approved for ACS, while ticagrelor 60 mg twice a day was designed to achieve a lower platelet inhibition compared to 90 mg, but still greater than clopidogrel 75 mg. Both ticagrelor doses, significantly reduced the primary endpoint of CV death, MI or stroke, with a relative risk reduction of 15% with 90 mg and 16% with 60 mg (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.75-0.96; P=0.008 for 90 mg, and HR 0.84, 95% CI 0.74-0.95; P=0.004 for 60 mg) [35]. Both ticagrelor doses had highly consistent effects on all of the components of the composite endpoint, with pooled ticagrelor treatment arm hazard ratios (95% CI) vs. placebo of 0.85 (0.71-1.00) for CV death, 0.83 (0.72-0.95) for MI, and 0.78 (0.62-0.98) for stroke. The benefit of ticagrelor was consistent among major clinical subgroups, including region. The rate of the primary safety end point of TIMI major bleeding was higher with the two ticagrelor doses than with placebo (HR 2.69, 95% CI 1.96-3.70; P<0.001 for 90

mg; HR 2.32, 95% CI 1.68-3.21; P<0.001 for 60 mg), however fatal bleeding or intracranial hemorrhage did not differ significantly [35]. Thus, in terms of irreversible events of harm to the patient, a favorable benefit-risk ratio of prolonged ticagrelor is apparent. Dyspnea was more frequent with the two ticagrelor doses; the majority of the cases were of mild or moderate intensity and did not lead to cessation of therapy. The similar efficacy and numerically lower rates of adverse events with the ticagrelor 60 mg bid dose make it appear to be the more attractive long-term option [36].

The results of PEGASUS TIMI-54 are highly consistent with data both from the above-mentioned CHARISMA-MI subgroup [33], and from the recently reported subgroup of patients with MI from the DAPT trial [37]. In that subgroup, continuation of a P2Y12 receptor antagonist beyond 1 year in patients undergoing coronary stent implantation and at low risk of ischemic and bleeding events, significantly reduced the risk of CV death, MI or stroke, with a directionally consistent benefit for cardiac death and, unlike the still unexplained observation in patients without MI, no excess of non-CV death.

3. Dual antiplatelet therapy in patients with previous myocardial infarction and renal dysfunction: current evidences.

Patients with CKD together with a prothrombotic state and a consequently higher ischemic risk, show defective platelets function as a consequence of uremic toxins, which is responsible for a higher bleeding risk [10]. Therefore, the benefit-risk of chronic antithrombotic therapies in patients with prior MI and concomitant renal dysfunction is complex, with some studies suggesting that more intense platelets inhibition could be of less benefit [17, 38, 39], whereas others suggest benefit of similar or even greater magnitude in those with reduced renal function [18, 40, 41]. In the CURE study [17], the beneficial effect of adding clopidogrel to standard treatment, compared to placebo, was modest in term of absolute and relative risk reduction of the primary ischemic endpoints among patients with renal dysfunction compared with those with normal renal function, although without any significant interaction. In the Clopidogrel for Reduction of Events During Observation (CREDO) trial [38], clopidogrel compared to placebo reduced the primary composite end point of death, MI, and stroke in patients with normal renal function, but a trend in the opposite direction was observed in patients with stage 2 to 4 CKD. Similarly, a post hoc analysis of the CHARISMA trial

suggested that clopidogrel may even be harmful in patients with diabetic nephropathy [39]. This finding may be explained by observations that have shown in patients with CKD a higher resistance to clopidogrel, due to a decrease in its hepatic metabolization and consequent activation, through the cytochrome P450 [42]. Contrary to clopidogrel, the P2Y12 inhibitors prasugrel and ticagrelor have shown, respectively, a similar and a greater benefit in term of ischemic risk reduction in the group of patients with CKD compared to patients without or mild CKD. In the TRITON-TIMI 38 trial, the superiority of prasugrel over clopidogrel was consistent in patients with or without CKD [18]. In the PLATO trial, subjects with stage 3 to 4 CKD, derived with ticagrelor a higher absolute (4.7% versus 1.0%) and relative (23% versus 10%) reduction of the primary endpoint of CV death, MI or stroke, than clopidogrel compared with subjects with normal renal function or mild CKD. Major bleeding rates, fatal bleedings, and non-CABG related major bleedings were not significantly relatively increased with ticagrelor compared with clopidogrel in patients with stage 3 to 4 CKD [40].

If confirmed, these findings would target patients with stage 3 to 4 CKD as a preferred group for ticagrelor. We therefore evaluated in the present work, the relationship of ischaemic and bleeding risk with renal function

and whether the efficacy and safety of ticagrelor was modified by the presence of renal dysfunction in the PEGASUS TIMI-54 trial [43].

METHODS

Study Population

PEGASUS-TIMI 54 randomized patients with prior MI to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, all on a background of low-dose aspirin (**Figure 3**). The design [34] and primary results of the trial have been published [35]. In brief, the trial enrolled 21,162 patients with a spontaneous MI occurring 1 to 3 years prior to enrollment and at least one of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as a creatinine clearance less than 60 ml per minute as estimated by the Cockroft-Gault equation. Patients with end-stage renal failure requiring dialysis were excluded, but otherwise there was no restriction or dose adjustment for renal function. Patients were ineligible if there was planned use of a $P2Y_{12}$ receptor antagonist or anticoagulant therapy during the study period; if they had a bleeding disorder or a history of an ischaemic stroke or intracranial bleeding, a central nervous system tumor, or an intracranial vascular abnormality; or if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous month (**Table 1**).

Endpoints

The primary efficacy end point was the composite of CV death, MI, or stroke (MACE). The primary safety end point was TIMI major bleeding [34]. Additional safety endpoints were TIMI minor bleeding, intracranial haemorrhage (ICH) and fatal bleeding. A Clinical Events Committee blinded to treatment allocation adjudicated all efficacy and bleeding events.

Laboratory Assessments and definition of renal dysfunction

Venous blood samples were obtained at randomization, during follow up visits, and 14-28 days after the end of treatment. After centrifugation, serum was frozen at - 20°C and sent for central laboratory analysis including measurement of serum creatinine. Estimated glomerular filtration rate (eGRF) was based on the abbreviated Modification of Diet in Renal Disease Study Group equation (MDRD) [44]. In addition a sensitivity analyses assessing ischemic and bleeding risk by eGFR and the effect of treatment was also performed using the Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI) [45] formula.

Renal function was characterized two ways in evaluating the relationship with ischaemic and bleeding risk in the placebo group. First, eGFR was

examined as a continuous variable and its relationship with bleeding and MACE was evaluated using cubic splines. Second, eGFR was divided into categories consistent with Kidney Disease Outcomes Quality Initiative of the National Kidney Fundation (NFK) definition and classification of CKD [46]. Because there were few patients with eGFR <30 ml/min/1.73 m^2, patients were divided into 4 groups: ≥90, 60 - <90, 45 - <60 and <45 ml/min/1.73 m^2. In evaluating the efficacy and safety of ticagrelor compared to placebo, analyses were performed using a prespecified eGFR cut-point of 60.0 ml/min/1.73 m^2 with patients having a baseline eGFR <60 ml/min categorized as having renal dysfunction and those with eGFR ≥60 as having normal renal function.

Statistical Considerations

Baseline characteristics were summarized using medians and quartiles for continuous variables and frequencies and percentage for categorical variables. Differences were tested with the Wilcoxon rank-sum test for continuous variables and with the Pearson χ^2 test for categorical data. Cox proportional hazard models were used to assess the risk of MACE and bleeding across category of renal function and were adjusted for baseline clinical characteristics that differed significantly between

patients with and without renal dysfunction (age, sex, hypertension, current smoker, diabetes, history of percutaneous coronary intervention, CABG, multivessel coronary disease, history of more than 1 prior MI, peripheral artery disease, stroke, heart failure, type of index event). The associations between renal function and the hazard for the MACE and TIMI major bleeding were evaluated using cubic splines [47]. Analyses of the efficacy and safety of ticagrelor were not adjusted because treatment was randomized and therefore baseline characteristics and potential confounders were approximately balanced. Efficacy analyses were performed on an intention-to-treat basis with a sensitivity analysis to assess the impact of differences in drug discontinuation using an on-treatment analysis. Safety analyses included all the patients who underwent randomization and with creatinine at baseline available who received at least one dose of study drug and included all the events occurring after receipt of the first dose and within 7 days of the last dose of study drug. Adverse events were site reported and the subset of renal adverse events was predefined as a subset of adverse event preferred terms (*Supplemental Table 1*).

RESULTS

A baseline serum creatinine concentration was available in 20,898 patients (99% of the overall trial population), of whom 3,251 (15.6%), 12,798 (61.2%), 3,536 (16.9%), and 1,313 (6.3%), had an eGFR ≥90, 60 - <90, 45 - <60, and <45 ml/min/1.73 m^2, respectively (eGFR ≥60, N= 16,049, 76.8%; eGFR <60, N=4,849, 23.2%). Baseline characteristics by category of eGFR are shown in **Table 2** and stratified at <60 and ≥60 ml/min/1.73 m^2 in *Supplemental Table 2*.

Baseline Renal Function and Ischaemic Risk

There was an inverse graded relationship between category of eGFR and the risk of MACE at 3 years in the placebo arm as the eGFR dropped below 60 ml/min/1.73 m^2 (p for trend < 0.0001, **Figure 4a,** *Supplemental Table 3*) with a consistent relationship for each of the individual components (p for trend < 0.0001 for CVD and stroke, p for trend < 0.001 for MI). After adjusting for baseline clinical differences, eGFR remained an independent predictor of ischaemic risk, especially when eGFR dropped below 60 ml/min/1.73 m^2 (**Figure 4b**, *Supplemental Table 3***).** When dichotomized, patients with an eGFR below 60 ml/min/1.73 m^2 had an adjusted HR for MACE of 1.54 (95% CI 1.27 –

1.85, p < 0.001). The adjusted risk across categories of eGFR remained significant for each of the components of the primary endpoint (*Supplemental Figure 1*). The relationship between eGFR and ischemic risk was very similar when eGFR was calculated using CKD-EPI instead (correlation coefficient between eGFR calculated with MDRD and CKD-EPI 0.99, P < 0.0001) and was similar in those randomized to placebo only or all treatment arms pooled (*Supplemental Figure 2a*).

Baseline Renal Function and Bleeding Risk

There were trends across categories of lower eGFR for increased rates of TIMI major bleeding, TIMI minor bleeding, and ICH or fatal bleeding in the placebo arm (**Figure 5a,** *Supplemental Table 3*). After adjusting for baseline differences there was no longer an appreciable relationship between eGFR and TIMI major bleeding (**Figure 5b**), but there was for minor bleeding, *Supplemental Figure 3*, *Supplemental Table 3*). When dichotomizing eGFR at 60 ml/min/1.73 m^2, the adjusted HR for TIMI major bleeding for those with eGFR <60 relative to those with eGFR ≥60 was 1.19 (95% CI 0.64 – 2.24, p = 0.58) and the adjusted HR for TIMI minor bleeding was 3.02 (95% CI 1.07 – 8.48, p = 0.04). The relationship between eGFR and bleeding was similar in those randomized to placebo

only or all treatment arms pooled (*Supplemental Figure 2b*).

Efficacy of Ticagrelor in Patients with Renal Dysfunction

The relative risk reduction in MACE achieved with ticagrelor (doses pooled) was similar in patients with renal dysfunction (eGFR <60 ml/min/1.73 m^2, n = 4,849; HR, 0.81; 95% CI 0.68 – 0.96) compared with those without (eGFR ≥60 ml/min/1.73 m^2, n = 16,049; HR 0.88; 95% CI 0.77-1.00, $p_{interaction}$ = 0.44, **Figure 6**) and similar when eGFR was modeled as a continuous variable (*Supplemental Figure 4*). However, given the greater risk of MACE in patients with renal dysfunction, the respective absolute risk reduction in MACE at 3 years was 4 times higher in that group: 2.70% (95% CI 0.49 – 4.93) vs. 0.63% (95% CI -0.32 – 1.57). The pattern of efficacy was largely consistent with the individual doses and the individual components of the primary endpoint (*Supplemental Figure 5*). Results were consistent regardless of whether eGFR was calculated using MDRD or CKD-EPI (*Supplemental Table 4*). The rate of death from any cause did not differ significantly with either dose of ticagrelor as compared with placebo, regardless renal function (*Supplemental Table 5*).

Safety of Ticagrelor in Patients with Renal Dysfunction

The relative risk of TIMI major bleeding with ticagrelor was similar in those with and without renal dysfunction (ticagrelor pooled vs. placebo, eGFR <60: HR 1.98; 95% CI 1.13 – 3.46; eGFR ≥60: HR, 2.65; 95% CI 1.87 – 3.76; $p_{interaction}$ = 0.38, **Table 3**, *Supplemental Figure 6*). Likewise, the absolute risk of TIMI major bleeding with ticagrelor (pooled) was similar across eGFR category (1.19%, 95% CI 0.21 – 2.16 for those with eGFR <60 and 1.42%, 95% CI 0.92 – 1.91 for those with eGFR ≥60). The relative risk of TIMI minor bleeding was also increased consistently with ticagrelor regardless of renal function ($p_{interaction}$ = 0.98 for ticagrelor pooled); however, the absolute increase was higher in those with eGFR <60 (1.93%, 95% CI 1.05 – 2.81) compared to those with eGFR ≥60 (0.68%, 95% CI 0.42 – 0.95). The combination of ICH or fatal bleeding was not significantly increased with ticagrelor regardless of renal function. Results were consistent regardless of whether eGFR was calculated using MDRD or CKD-EPI (*Supplemental Table 4*).

Other safety events and tolerability

Renal adverse events were more frequent in patients randomized to placebo with an eGFR <60 compared to those with an eGFR ≥60 (8.53%

vs. 1.23%, HR_{adj} 7.14, 95% CI 5.00 – 10.0, $p < 0.001$). However, ticagrelor did not increase the risk of renal adverse events overall and there was no statistical heterogeneity by eGFR category ($p_{interaction} = 0.22$, *Supplemental Table 6*). Likewise, gout occurred more frequently in patients with an eGFR <60 (HR_{adj} 3.62, 95% CI 2.21 – 5.94, $p < 0.001$), but the relative risk of gout with ticagrelor was similar, if anything less pronounced in those with renal dysfunction (*Supplemental Table 6*). In patients randomized to placebo there was a non significant increase of dyspnea events in patients with an eGFR <60 compared to those with an eGFR ≥60 (7.5% vs. 6.0%, HR_{adj} 1.18, 95% CI 0.92 – 1.51, $p = 0.19$). Both ticagrelor doses increased dyspnea events, compared to placebo, regardless of renal function (*Supplemental Table 6*). In the placebo arm, premature permanent drug discontinuation was higher in those with an eGFR <60 compared those with an eGFR ≥60 (28.9% vs. 20.9%, HR_{adj} 1.27, 95% CI 1.12 – 1.43, $p < 0.001$). Similarly, rates of premature permanent drug discontinuation were higher in the ticagrelor arms in those with renal dysfunction (*Supplemental Table 6*). Because permanent drug discontinuation was higher in those with renal dysfunction, a sensitivity analysis exploring the magnitude of efficacy in patients on treatment was performed in patients stratified by eGFR. A more marked

relative risk reduction with ticagrelor was observed, particularly in those with renal dysfunction (HR 0.72, 95% CI 0.59 – 0.89, for eGFR <60; HR 0.83, 95% CI 0.72 – 0.96, for eGFR ≥60).

DISCUSSION

In stable outpatients with prior MI randomized in the PEGASUS TIMI 54 trial, worsening renal function was an independent predictor of MACE. The relative risk reduction in MACE with ticagrelor was similar regardless of renal function. However, due to their higher ischaemic risk, patients with renal dysfunction, who constituted approximately one quarter of the trial population, experienced a greater absolute risk reduction in MACE when treated with ticagrelor.

Previous studies have described an inverse relationship between eGFR and ischaemic and bleeding events in patients with a recent MI [4, 9, 18]. The current study builds on these observations but now extends it to stable outpatients who were on average of 1.7 years out from their qualifying MI and who were observed for a median of 33 months. It is notable that the rate for MACE was approximately 14% at 3 years in those with renal dysfunction, which was double that for those with normal renal function, making renal dysfunction a useful clinical indicator of heightened ischaemic risk. Moreover, this risk was independent of other clinical characteristics. Bleeding risk also tended to increase with renal dysfunction. However, after multivariable adjustment, this relationship only persisted for TIMI minor bleeding. While these

findings were most pronounced for patients with an eGFR <60 (N = 4,849, 23%), it is notable that only a small proportion of patients in the trial (N=3,251, 15%) had normal renal function (ie, eGFR ≥90) and more than half (N=12,798, 60%) had slightly reduced renal function (eGFR 60 - <90). Although chronic non-end stage renal dysfunction was an enrichment criteria in the trial, the prevalence of patients with chronic kidney disease we observed is in line with previous epidemiologic observations [1, 4].

The relative risk reduction in MACE with ticagrelor tended to be slightly greater in patients with renal dysfunction (19% vs. 12%), but the difference was not statistically significant. Importantly, however, the greater rate of ischaemic events in patients with renal dysfunction translated into a greater absolute risk reduction with ticagrelor in these patients. Specifically, the absolute risk reduction in MACE with ticagrelor was 2.7%, translating into a number needed to treat of 37 to prevent one MACE event even when initiated in the stable setting. This robust risk reduction occurred in spite of higher rates of drug discontinuation, with on-treatment analyses showing an even greater magnitude of benefit.

These efficacy findings are corroborated by observations for ticagrelor in the setting of ACS, where there also tended to be a greater relative risk reduction and there was a fourfold greater absolute risk reduction in MACE in patients with renal dysfunction [9]. When integrating the findings from both data sets, patients with ACS and renal dysfunction enjoy a robust absolute risk reduction with ticagrelor which continues into the stable phase as long-term secondary prevention.

Both the relative and absolute increased risk of TIMI major bleeding with ticagrelor were similar for patients with and without renal dysfunction. However, the absolute excess of TIMI minor bleeding (hemoglobin drop between 3 and 5 g/dL) with ticagrelor was greater in those with renal dysfunction. There was no relative or absolute increase in ICH or fatal bleeding with ticagrelor overall or in those with and without renal dysfunction. Consistent with findings from other large trials with ticagrelor, there was no increase in renal adverse events with ticagrelor in the current trial. Gout was more frequent in patients with renal dysfunction and was increased with ticagrelor to a similar extent regardless of eGFR.

LIMITATIONS

There are limitations to the current study. First, although pre-specified, our observations are based on subgroups in the overall trial. Importantly, there were significant baseline differences between those with and without renal dysfunction. CKD was an enrichment factor in the PEGASUS TIMI 54 trial and non-CKD patients could have been enriched with atherothrombotic risk factors other than CKD, an observation that differs from clinical practice where patients with CKD have more comorbidities compared to patients without CKD [3]. Although when evaluating the relationship of MACE and bleeding with renal function we adjusted for these differences by multivariable analysis, some residual confounding may remain. Given that PEGASUS-TIMI 54 was a randomized trial, these differences were balanced between the two ticagrelor groups and placebo group and thus not expected to influence the treatment comparison. In addition, there were a relatively small number of patients with severe renal dysfunction and patients requiring dialysis were excluded from the trial. Our analyses were based on eGFR calculated using the MDRD equation using baseline serum creatinine. However, the PEGASUS-TIMI 54 trial enrolled a

stable population and therefore it is unlikely that there would be large fluctuations of creatinine values from baseline, as might be observed in an acute population.

CONCLUSION

In stable patients with a history of MI, renal dysfunction was independently associated with an increased risk of major adverse cardiovascular events. Although the relative risk reduction in MACE with ticagrelor was similar regardless of renal function, due to their higher ischaemic risk, patients with renal dysfunction experienced a greater absolute risk reduction in MACE when treated with ticagrelor. Our data build upon prior works providing a simple metric by which to approach the decision-making to prolong DAPT. This work will therefore help physicians to individualize patients at higher ischemic risk, that derive the greatest benefit with prolonged DAPT. These findings have important treatment implications for the large and growing proportion of patients with coronary disease and concomitant renal dysfunction.

REFERENCES

1. Ritz E, Bakris G. World Kidney Day: hypertension and chronic kidney disease. *Lancet* 2009;373:1157–58.

2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038–47.

3. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;41:47–55.

4. Manjunath G, Tighiouart H, Coresh J, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 2003;63:1121–29.

5. Mann JF, Gerstein HC, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001;134:629–36.

6. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a

predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 2003;41:1364–72.

7. O'Hare AM, Vittinghoff E, Hsia J, et al. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). *J Am Soc Nephrol* 2004;15:1046–51.

8. 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;351:1296–1305.

9. Cheung AK, Sarnak MJ, Yan G, et al. The Hemodyalysis (HEMO) Study. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int* 2000;58:353–62.

10. Capodanno D, Angiolillo DJ. Antithrombotic Therapy in Patients With Chronic Kidney Disease. *Circulation* 2012;125:2649–61.

11. Dumaine RL, Montalescot G, Steg PG, et al. REACH Registry Investigators. Renal function, atherothrombosis extent, and outcomes in high-risk patients. *Am Heart J* 2009;158:141–8.

12. Fox CS, Muntner P, Chen AY, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease: a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network registry. *Circulation* 2010;121:357–65.

13. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285–95.

14. Kapoor JR. Platelet activation and atherothrombosis. *N Engl J Med* 2008;358:1638–39.

15. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the

primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849–60.

16. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. *Nat Rev Cardiol* 2015;12:30–47.

17. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

18. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001–15.

19. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.

20. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC

Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130:2354–94.

21. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999–3054.
22. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;127:e362–425.

23. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology

(ESC), Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569–619.

24. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354–62.

25. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;116: 2923–32.

26. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;373:723–31.

27. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation* 2008;118:1626–36.

28. Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006;27:1038–47.

29. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003;107:966–72.

30. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes

undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol* 2008;51:2028–33.

31. Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet* 2012;380:1317–24.

32. Magnani G, Bonaca MP, Braunwald E, et al. Efficacy and Safety of Vorapaxar as Approved for Clinical Use in the United States. J Am Heart Assoc. 2015;4:e001505 doi: 0.1161/JAHA.114.001505.

33. Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007; 49:1982–8.

34. Bonaca MP, Bhatt DL, Braunwald E, et al. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. *Am Heart J* 2014;167:437–44.

35. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791–1800.

36. Magnani G, Bonaca MP, Sabatine MS. Editorial on PEGASUS-TIMI 54. *Eur Heart J-CVP* 2015;1:217–9.

37. Yeh RW, Kereiakes DJ, Steg PG, et al. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. *J Am Coll Cardiol* 2015;65:2211–21.

38. Best PJ, Steinhubl SR, Berger PB, et al. The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: results from the Clopidogrel

for the Reduction of Events During Observation (CREDO) trial. *Am Heart J* 2008;155: 687–93.

39. Dasgupta A, Steinhubl SR, Bhatt DL, et al. CHARISMA Investigators. Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] trial). *Am J Cardiol* 2009;103:1359–63.

40. 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;122:1056–67.

41. Montalescot G, Silvain J. Ticagrelor in the renal dysfunction subgroup: subjugated or substantiated? Circulation 2010;122:1049–52.

42. Talbert RL. Drug dosing in renal insufficiency. *J Clin Pharmacol* 1994;34:99–110.

43. 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* 2015 Oct 5. pii: ehv482. [Epub ahead of print].

44. Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clin Chem* 2007;53:766–72.

45. Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med* 2009;150:604–12.

46. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(suppl 1):S1–S266.

47. Heinzl, H., & Kaider, A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Computer methods and programs in biomedicine* 1997; 54: 201–8.

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TABLES

Table 1: Key inclusion and exclusion criteria in the PEGASUS TIMI-54 trial [34].

Key Inclusion	Key Exclusion
• **Age ≥50 years** • **Spontaneous MI 1-3 years prior** • **At least 1 of the following:** -Age ≥65 years -Diabetes requiring medication -2nd prior MI (>1 year ago) -Multivessel CAD -Chronic, non-end stage renal disfunction (CrCl <60 mL/min, Cockroft Gault equation) • **Tolerating aspirin and able to be dosed at 75-150 mg/die**	• Planned use of P2Y12 antagonist, dipyridamole, cilostazol, or anticoag • Bleeding disorder • History of ischemic stroke, ICH, CNS tumor or vascular abnormality • Recent GI bleed or major surgery • At risk for bradycardia • Dialysis or severe liver disease

MI, myocardial infarction; CAD, coronary artery disease; CrCl, creatinine clearance; ICH, intracranial hemorrhage; CNS, central nervous system; GI, gastro-intestinal.

Table 2. Baseline Characteristics by eGFR (mL/min/1.73 m^2).

	eGFR mL/min/1.73 m^2				
Characteristic	**≥90 N=3,251 n (%)**	**60 - <90 N=12,798 n (%)**	**45 - <60 N=3,536 n (%)**	**<45 N=1,313 n (%)**	**P-value**
eGFR, median (IQR)	97.7 (93.3, 105.4)	74.1 (67.5, 81.0)	54.2 (50.6, 57.4)	38.8 (33.3, 42.3)	na
Demographics					
Age – yr, median (IQR)	60 (55, 66)	65 (59, 70)	69 (64, 75)	72 (66, 78)	<0.0001
Female	478 (14.7)	2736 (21.4)	1198 (33.9)	580 (44.2)	<0.0001
BMI – Kg/m2, median (IQR)	27.7 (24.7, 31.0)	27.8 (25.2, 31.1)	27.9 (25.3, 31.3)	28.4 (25.3, 32.0)	<0.0001
Clinical Characteristics					
Hypertension	2430 (74.8)	9607 (75.1)	2973 (84.1)	1185 (90.3)	<0.0001
Hypercholesterolemia	2443 (75.2)	9908 (77.4)	2705 (76.5)	998 (76.0)	0.04
Current smoker	851 (26.2)	2125 (16.6)	400 (11.3)	122 (9.3)	<0.0001
Diabetes mellitus	1246 (38.3)	3732 (29.2)	1157 (32.7)	581 (44.3)	<0.0001
Multivessel coronary disease	2112 (65.0)	7655 (59.8)	1915 (54.2)	715 (54.5)	<0.0001
History of PCI	2800 (86.1)	10776 (84.2)	2792 (79.0)	979 (74.6)	<0.0001
History of CABG	101 (3.1)	511 (4.0)	228 (6.5)	118 (9.0)	<0.0001
History of more than 1 prior MI	505 (15.5)	2037 (15.9)	617 (17.5)	296 (22.5)	<0.0001
Peripheral artery disease	178 (5.5)	595 (4.7)	223 (6.3)	132 (10.1)	<0.0001
History of stroke	10 (0.3)	50 (0.4)	21 (0.6)	14 (1.1)	0.002
History of HF	487 (15.0)	2375 (18.6)	875 (24.8)	451 (34.4)	<0.0001
Qualifying Event					
Years from MI – median (IQR)	1.7 (1.2, 2.3)	1.7 (1.2, 2.3)	1.7 (1.3, 2.3)	1.7 (1.2, 2.4)	0.20
STEMI	1831 (56.4)	7005 (54.8)	1767 (50.0)	590 (45.1)	<0.0001
NSTEMI	1236 (38.1)	5068 (39.6)	1543 (43.7)	624 (47.7)	<0.0001
MI type unknown	181 (5.6)	713 (5.6)	221 (6.3)	95 (7.3)	<0.0001
Medications at enrollment					
Aspirin	3247 (99.9)	12779 (99.9)	3534 (99.9)	1311 (99.9)	0.60
Beta-blocker	2641 (81.2)	10525 (82.2)	2973 (84.1)	1120 (85.3)	0.0006
ACEI or ARB	2604 (80.1)	10219 (79.9)	2923 (82.7)	1070 (81.5)	0.002

eGFR, estimated glomerular filtration rate; N, total number; IQR, interquartile range; BMI, body mass index; kg, kilogram; m, meter; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HF, heart failure; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction.

Table 3. Safety endpoints at 3 years by eGFR (mL/min/1.73 m^2).

Endpoint	eGFR	Ticagrelor Pooled	Ticagrelor 90	Ticagrelor 60	Placebo	Ticagrelor Pooled vs. Placebo		Ticagrelor 90 vs. Placebo		Ticagrelor 60 vs. Placebo	
		% 3-yr KM				HR (95% CI)	P-int	HR (95% CI)	P-int	HR (95% CI)	P-int
Bleeding											
TIMI major	**≥ 60**	2.41	2.74	2.09	0.99	2.65 (1.87 - 3.76)	0.38	3.05 (2.10 - 4.43)	0.11	2.29 (1.56 - 3.36)	0.998
	< 60	2.53	2.13	2.94	1.34	1.98 (1.13 - 3.46)		1.69 (0.89 - 3.19)		2.29 (1.25 - 4.19)	
TIMI minor	**≥ 60**	0.89	0.95	0.84	0.21	4.05 (2.02 - 8.12)	0.98	4.51 (2.17- 9.37)	0.95	3.63 (1.73 - 7.62)	0.997
	< 60	2.62	2.65	2.59	0.69	4.00 (1.90 - 8.40)		4.36 (2.00 - 9.51)		3.62 (1.62 - 8.05)	
ICH or Fatal	**≥ 60**	0.64	0.65	0.62	0.52	1.38 (0.81 - 2.86)	0.27	1.50 (0.72 - 2.51)	0.15	1.28 (0.70 - 2.35)	0.65
	< 60	0.79	0.60	0.98	0.95	0.82 (0.38 - 2.78)		0.64 (0.24 - 2.74)		1.00 (0.42 - 2.43)	

eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan Maier; HR, hazard ratio; CI, confidence interval; TIMI, Thrombolysis in Myocardial Infarction; ICH, intracranial haemorrhage

Figure Legends

Figure 1: Platelet pathways and commonly used oral antiplatelet treatments. Disruption of the endothelium exposes adhesive proteins of the subendothelial matrix (collagen and von Willebrand factor [vWF]) that interact with platelet-receptor glycoproteins (GP). Intracellular signalling pathways result in the release of robust platelet activators such as ADP, adrenaline, serotonin, thrombin, and thromboxane A2. These agonists bind to G-protein-coupled receptors and further potentiate the process. Ultimately, GP IIb/IIIa binds to fibrinogen and results in platelet aggregation. 5-HT2A=serotonin receptor 2A. COX-1=cyclooxygenase-1. PAR=protease-activated receptor. TP-R=thromboxane prostanoid receptor. TXS=thromboxane A2 synthase. G=G-protein. Dotted arrows show movement of molecules. Adapted from Franchi and Angiolillo, [16] by permission of Nature Reviews Cardiology.

Figure 2: Landmark analysis of CV death MI and stroke during the first 360 days after randomization (left) and from 360 days to the end of the study (right) in the FDA approved population (patients with previous MI or peripheral artery disease, without stroke or TIA) for vorapaxar use. CI indicates confidence interval; HR, hazard ratio. Magnani G, Bonaca MP, Braunwald E, et al. JAHA 2015 [32].

Figure 3: PEGASUS TIMI-54 trial design. MI = Myocardial Infarction , FU = Follow Up, IQR = Interquartile Range, yr = year, mos = months. Bonaca MP, Bhatt DL, Braunwald E, et al. Am Heart J 2014;167:437-44 [34].

Figure 4: KM curves for the primary endpoint of cardiovascular death, myocardial infarction or stroke by eGFR (mL/min/1.73 m^2) (Panel A) and multivariable adjusted spline curves for the HR of the primary endpoint vs. eGFR modeled as a continuous variable (Panel B). Placebo group only. Patients stratified into 4 groups (eGFR ≥90 ml/min/1.73 m^2, 60 - <90 ml/min/1.73 m^2, 45 - <60 ml/min/1.73 m^2, <45 ml/min/1.73 m^2). In Panel B the dotted lines represent the 95% pointwise confidence band. The reference value 98 is the median eGFR in the ≥90 group from the overall population. Cox proportional hazard models adjusted for baseline clinical characteristics that differed significantly between patients with and without renal dysfunction (age, sex, hypertension, current smoker, diabetes, history of percutaneous coronary intervention, CABG, multivessel coronary disease, history of more than 1 prior MI, peripheral artery disease, stroke, heart failure, type of index event). eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan Maier; N, total number; Adj., adjusted; HR, hazard ratio; CI, confidence interval. By permission of Eur Heart J. 2015 [42].

Figure 5: Bleeding risk by eGFR (mL/min/1.73 m^2) (Panel A) and multivariable adjusted spline curves for the HR of the main safety endpoint vs. eGFR modeled

as a continuous variable (Panel B). Placebo group only. Patients stratified into 4 groups (eGFR ≥ 90 ml/min/1.73 m^2, 60 - <90 ml/min/1.73 m^2, 45 - <60 ml/min/1.73 m^2, and <45 ml/min/1.73 m^2). Cox proportional hazard models adjusted for baseline characteristics that differed significantly between patients with and without renal dysfunction (age, sex, hypertension, current smoker, diabetes, history of percutaneous coronary intervention, CABG, multivessel coronary disease, history of more than 1 prior MI, peripheral artery disease, stroke, heart failure, type of index event). eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan Maier; N, total number; Adj., adjusted; HR, hazard ratio; CI, confidence interval; ICH, intracranial hemorrhage; TIMI, Thrombolysis in Myocardial Infarction. The dotted lines represent the 95% pointwise confidence band. The reference value 98 is the median eGFR in the ≥90 group from overall population.

Figure 6: Kaplan-Meier estimated occurrence of CV death, MI, or stroke by eGFR. Kaplan–Meier rates of primary endpoints through 3 years, according to study group and by an eGFR cut-point of 60 ml/min/1.73 m^2. P for interaction = 0.44. eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan Maier; HR, hazard ratio; CI, confidence interval; ARR, absolute risk reduction.

Figure 1: Platelet pathways and commonly used oral antiplatelet treatments. Adapted from Franchi and Angiolillo, [16] by permission of Nature Reviews Cardiology.

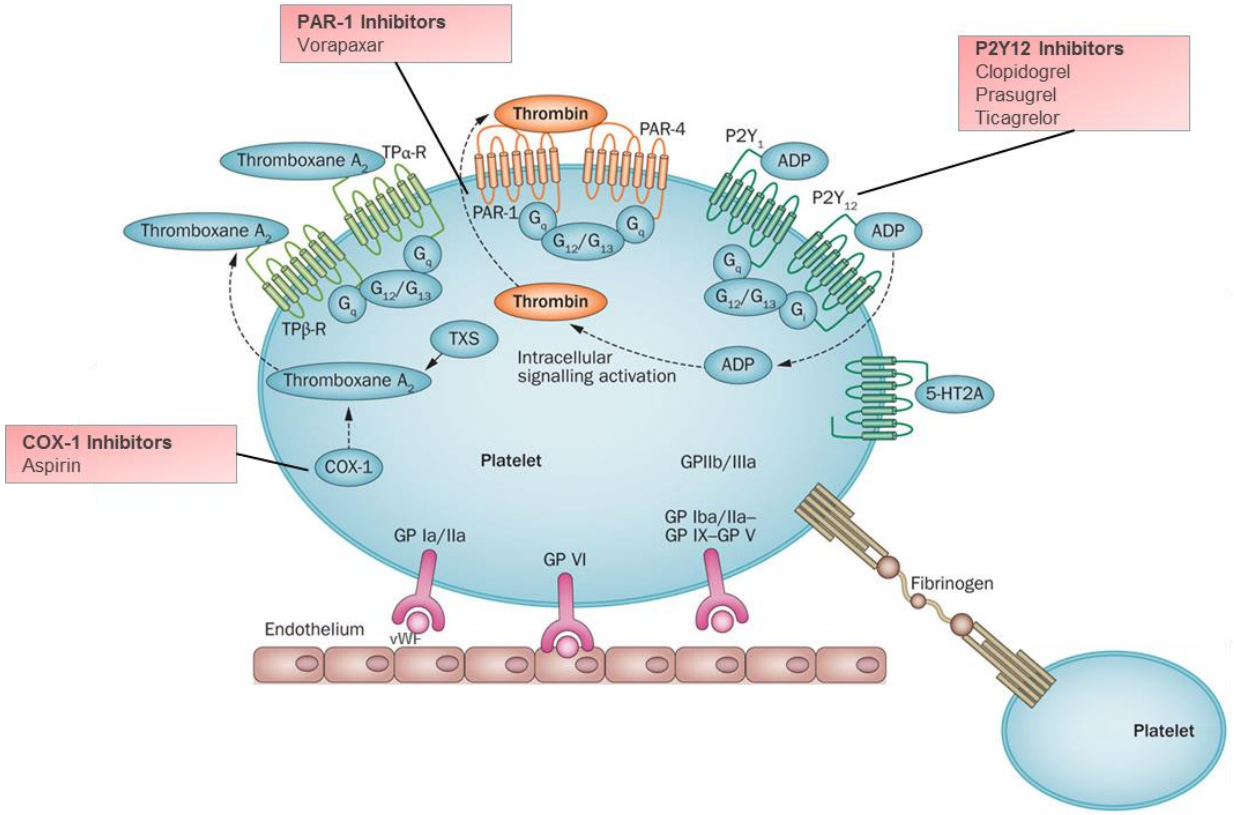


Figure 2: Early and late efficacy of vorapaxar for cardiovascular death, myocardial infarction and stroke prevention in patients with previous myocardial infarction or peripheral artery disease, without stroke or TIA. Magnani G, Bonaca MP, Braunwald E, et al. JAHA 2015 [32].

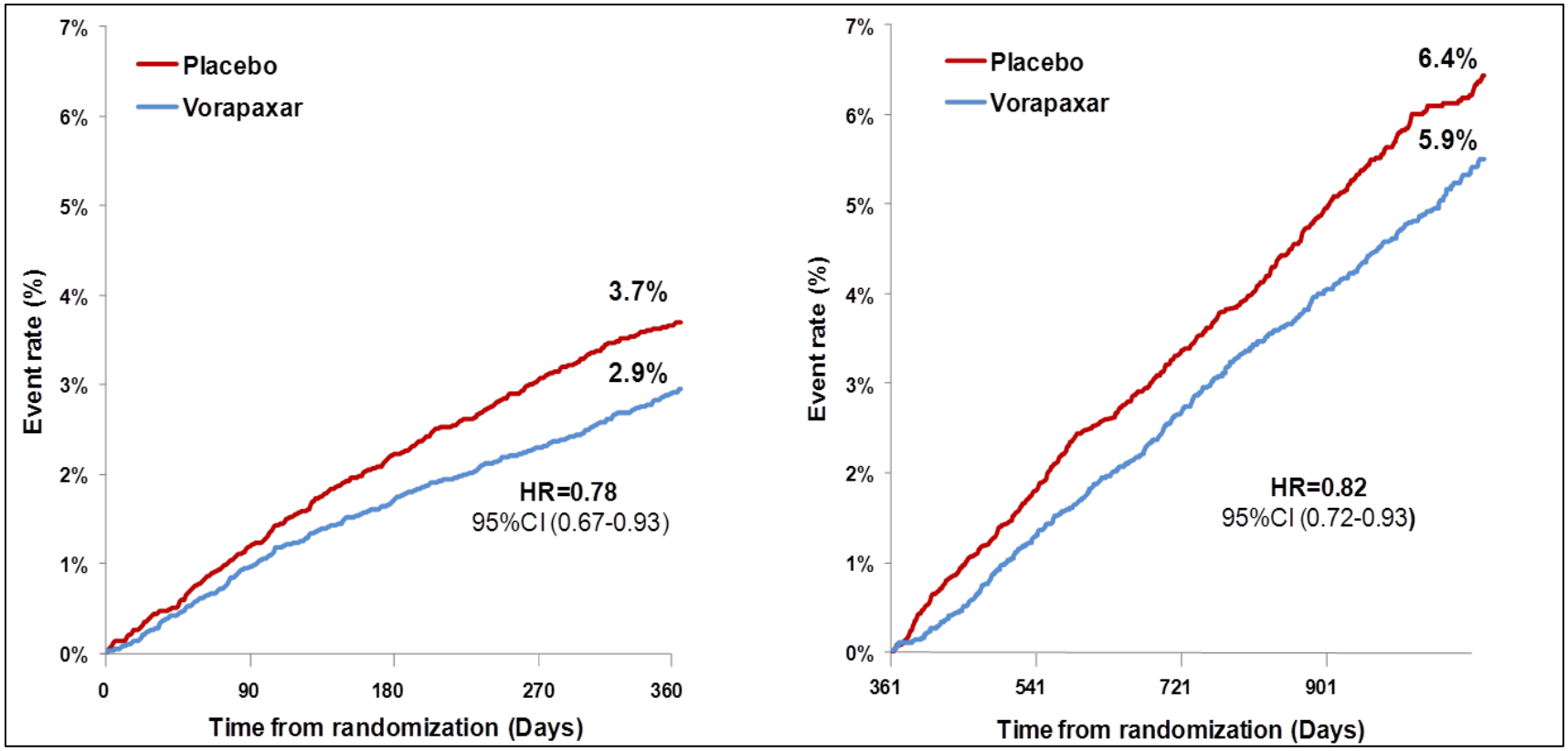


Figure 3: PEGASUS TIMI-54 trial design. Bonaca MP, Bhatt DL, Braunwald E, et al. Am Heart J 2014;167:437-44 [34].

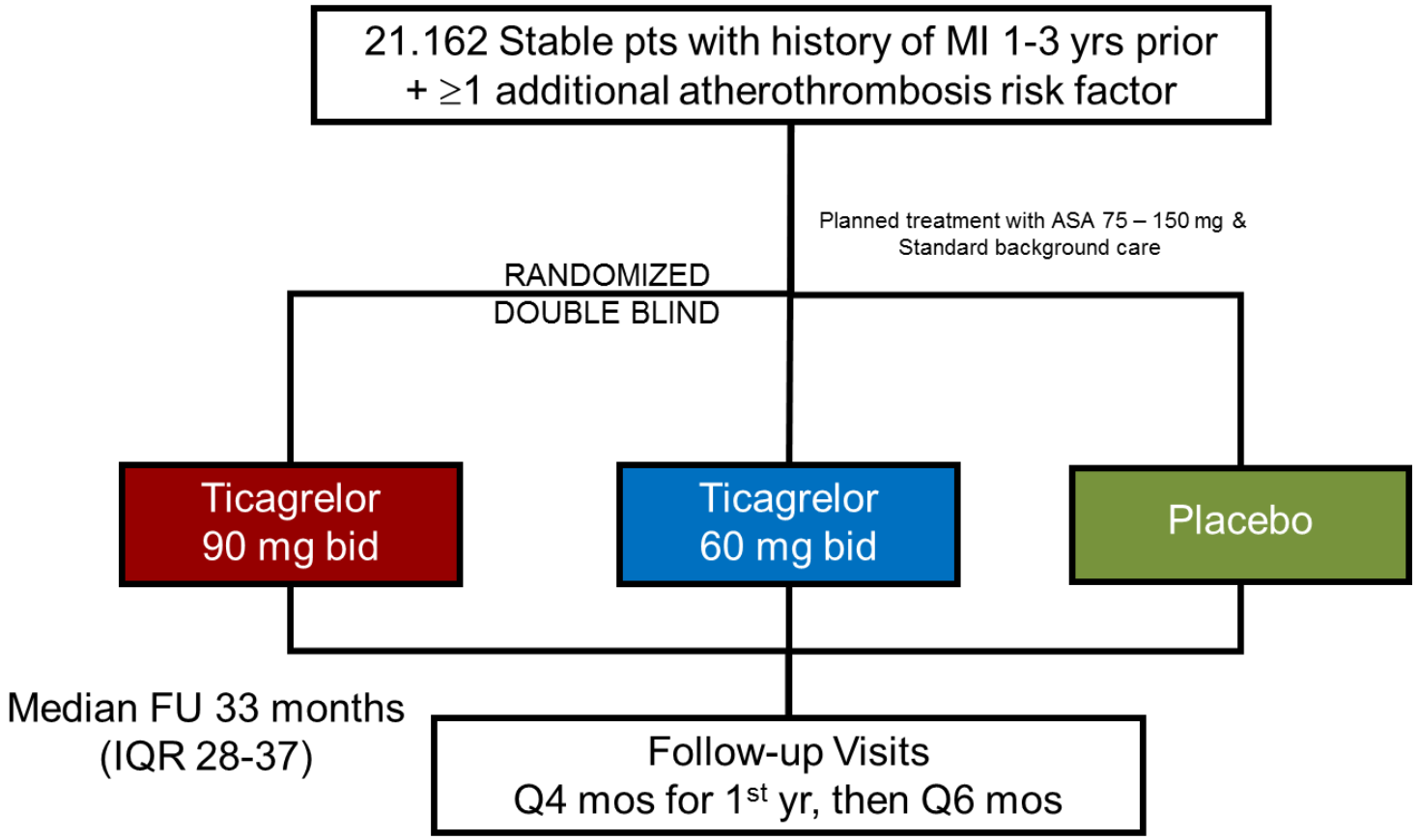
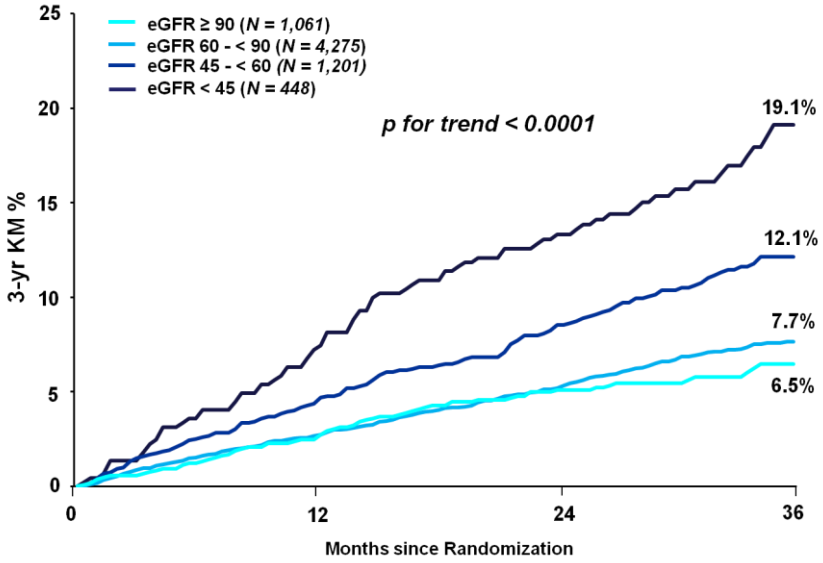


Figure 4: KM curves (Panel A) and spline curves with adjusted HR (Panel B) for the primary endpoint of cardiovascular death, myocardial infarction or stroke by eGFR (mL/min/1.73 m^2).

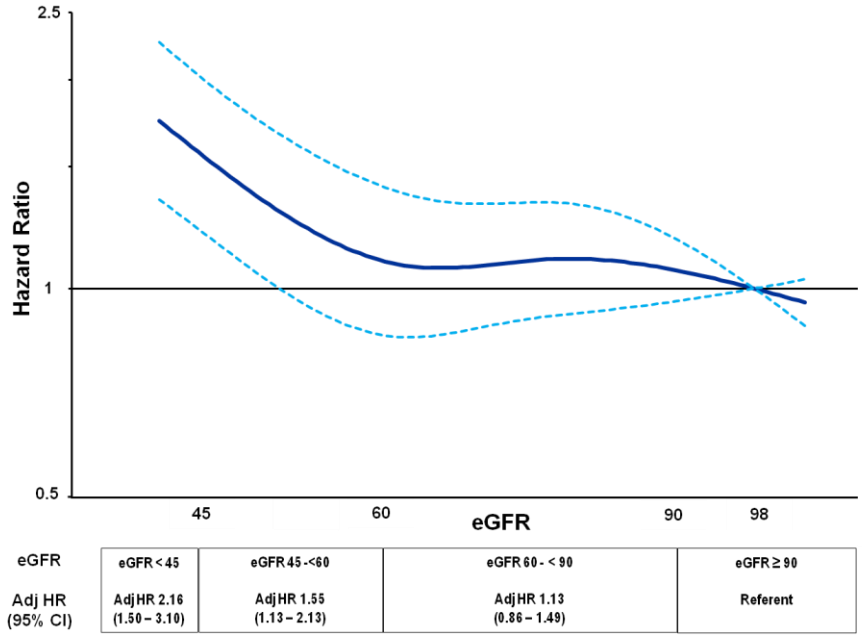
Panel A



No. at risk

eGFR ≥ 90	1061	4275	1201	448
eGFR 60 – < 90	1026	4122	1133	406
eGFR 45 – < 60	886	3573	1005	347
eGFR < 45	275	1264	354	110

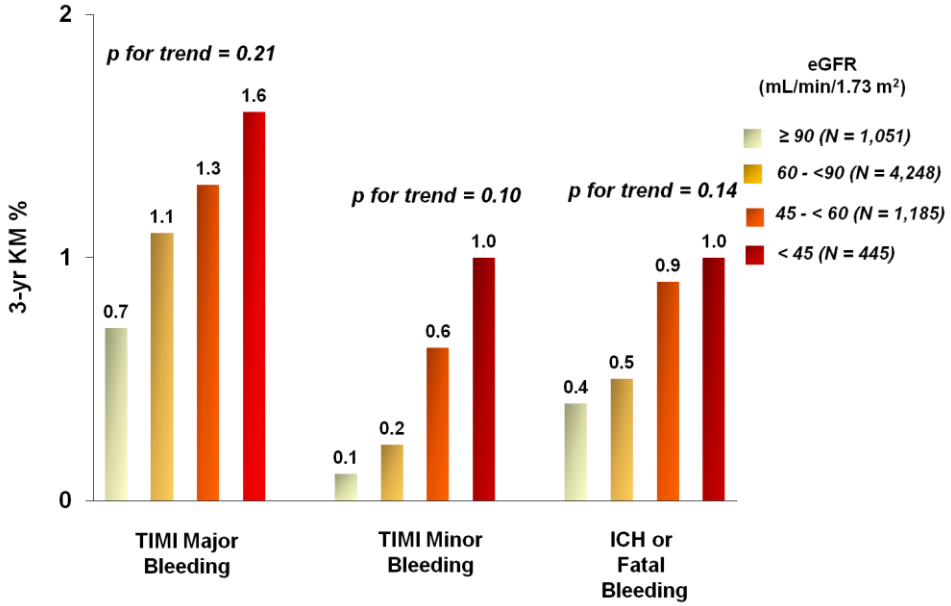
Panel B



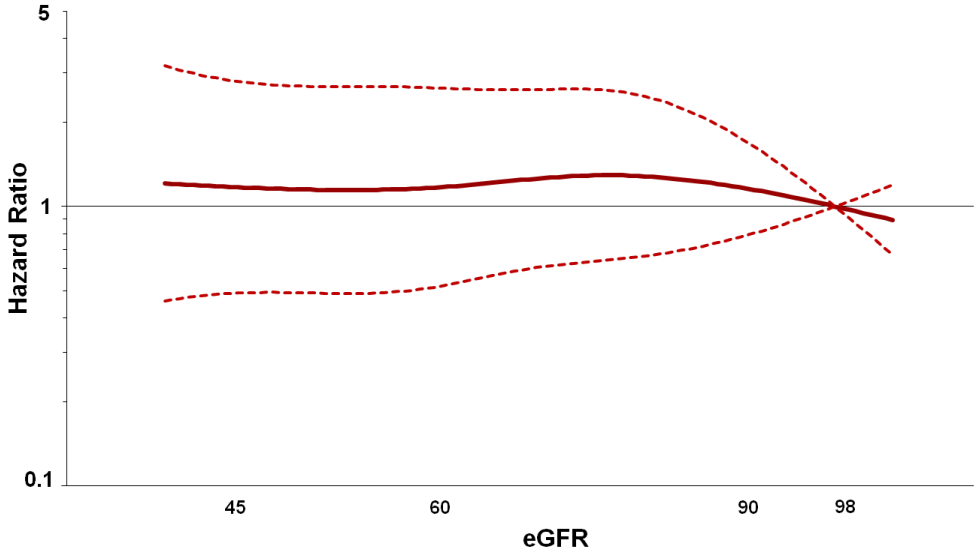
eGFR	eGFR < 45	eGFR 45 -<60	eGFR 60 - < 90	eGFR ≥ 90
Adj HR (95% CI)	Adj HR 2.16 (1.50 – 3.10)	Adj HR 1.55 (1.13 – 2.13)	Adj HR 1.13 (0.86 – 1.49)	Referent

Figure 5: Bleeding risk by eGFR (mL/min/1.73 m^2) (Panel A) and spline curve with adjusted HR for TIMI major bleeding (Panel B).

Panel A

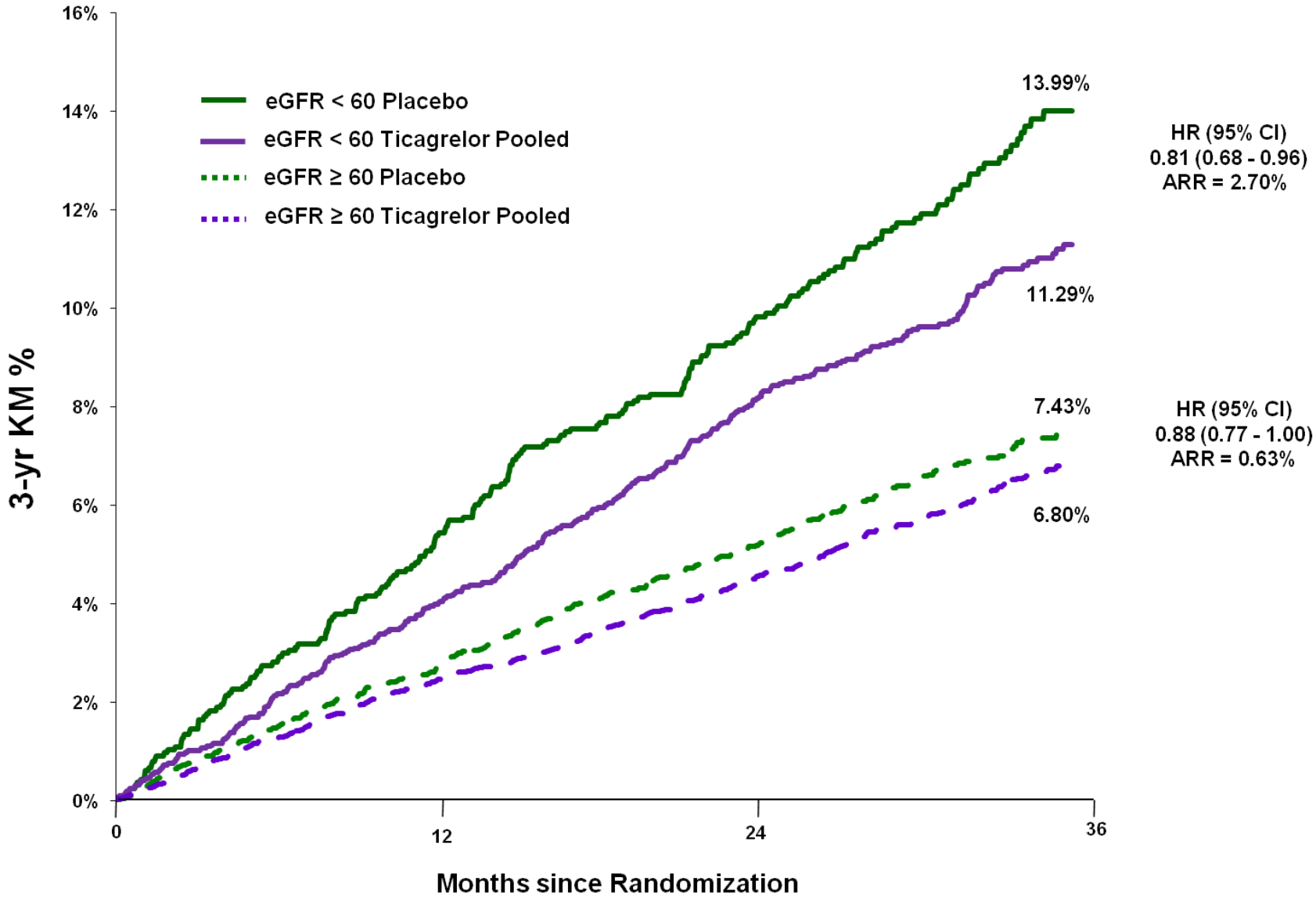


Panel B



eGFR	eGFR < 45	eGFR 45 -<60	eGFR 60 - < 90	eGFR ≥ 90
Adj HR (95% CI)	Adj HR 1.40 (0.41 – 4.79)	Adj HR 1.14 (0.42 – 3.11)	Adj HR 1.01 (0.44 – 2.33)	Referent

Figure 6: Kaplan-Meier estimated occurrence of cardiovascular death, myocardial infarction, or stroke by eGFR (mL/min/1.73 m^2).



Supplemental Appendix

Table of contents

Supplemental Table 1: List of adverse renal events collected in the electronic case report from (eCFR).

Acute prerenal failure
Azotaemia
Blood creatinine abnormal
Blood creatinine increased
Blood urea increased
Glomerular filtration rate decreased
Hypercreatininemia
Nephritis
Prerenal failure
Protein urine present
Renal failure acute
Renal impairment
Tubolointerstitial nephritis

Supplemental Table 2 Baseline Characteristics by eGFR cut at 60 mL/min/1.73 m^2.

	eGFR (mL/min/1.73 m^2)		
Characteristic	**≥60 N=16,049 n (%)**	**<60 N=4,849 n (%)**	**P-value**
eGFR, median (IQR)	77.4 (69.3, 87.4)	51.6 (44.3, 56.3)	n/a
Demographics			
Age – yr, median (IQR)	64 (58,70)	70 (64,76)	<0.0001
Female	3214 (20.0)	1778 (36.7)	<0.0001
BMI – Kg/m2, median (IQR)	27.8 (25.1,31.1)	28 (25.3,31.5)	<0.0001
Clinical Characteristics			
Hypertension	12037 (75.0)	4158 (85.8)	<0.0001
Hypercholesterolemia	12351 (77.0)	3703 (76.4)	0.38
Current smoker	2976 (18.6)	522 (10.8)	<0.0001
Diabetes mellitus	4978 (31.0)	1738 (35.8)	<0.0001
Multivessel coronary disease	9767 (60.9)	2630 (54.3)	<0.0001
History of PCI	13576 (84.6)	3771 (77.8)	<0.0001
History of CABG	612 (3.8)	346 (7.1)	<0.0001
History of more than 1 prior MI	2542 (15.8)	913 (18.8)	<0.0001
Peripheral artery disease	773 (4.8)	355 (7.3)	<0.0001
History of stroke	60 (0.4)	35 (0.7)	0.002
Qualifying Event			
Years from MI – median (IQR)	1.7 (1.2 – 2.3)	1.7 (1.3 – 2.3)	0.12
STEMI	8836 (55.1)	2357 (48.7)	<0.0001
NSTEMI	6304 (39.3)	2167 (44.8)	<0.0001
MI type unknown	894 (5.6)	316 (6.5)	<0.0001
Medications at enrollment			
Aspirin	16026 (99.9)	4845 (99.9)	0.30
Beta-blocker	13166 (82.0)	4093 (84.4)	0.0001
ACEi or ARB	12823 (79.9)	3993 (82.4)	0.0002

eGFR, estimated glomerular filtration rate; N, total number; IQR, interquartile range; BMI, body mass index; kg, kilogram; m, meter; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HF, heart failure; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; ACEi,angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Supplemental Table 3: Unadjusted and adjusted HR for efficacy and safety endpoints with lower eGFR, modeled per 10 mL/min/1.73m^2.

Endpoints	HR (95% CI)	p -value	Adjusted HR (95% CI)	p-value
Efficacy endpoints				
CVD, MI, Stroke	1.18 (1.13 – 1.24)	<0.0001	1.12 (1.06 – 1.18)	<0.0001
CVD	1.25 (1.16 – 1.35)	<0.0001	1.12 (1.03 – 1.21)	0.008
MI	1.12 (1.06 – 1.19)	0.0002	1.10 (1.03 – 1.18)	0.004
Stroke	1.32 (1.19 – 1.46)	<0.0001	1.23 (1.10 – 1.37)	0.0003
Safety endpoints				
TIMI major bleeding	1.09 (0.94 – 1.27)	0.25	1.03 (0.88 – 1.21)	0.72
TIMI minor bleeding	1.41 (1.07 – 1.85)	0.01	1.41 (1.05 – 1.90)	0.02
ICH or Fatal bleeding	1.21 (0.98 – 1.48)	0.07	1.20 (0.96 – 1.51)	0.11

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular death; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction. Cox proportional hazard models adjusted for age, sex, hypertension, current smoker, diabetes, history of percutaneous coronary intervention, CABG, multivessel coronary disease, history of more than 1 prior MI, peripheral artery disease, stroke, heart failure, type of index event.

Supplemental Table 4: Primary efficacy and safety outcomes by eGFR calculated with the CKD-EPI equation.

Endpoint	eGFR	Ticagrelor Pooled	Ticagrelor 90	Ticagrelor 60	Placebo	Ticagrelor Pooled vs. Placebo		Ticagrelor 90 vs. Placebo		Ticagrelor 60 vs. Placebo	
		% 3-yr KM				HR (95% CI)	P-int	HR (95% CI)	P-int	HR (95% CI)	P-int
CVD, MI, Stroke	≥ 60	6.73	6.71	6.74	7.48	0.87 (0.76 – 0.98)	0.67	0.87 (0.75 - 1.00)	0.74	0.87 (0.75- 1.00)	0.68
	< 60	12.11	12.18	12.04	14.69	0.82 (0.69 – 0.99)		0.83 (0.67- 1.02)		0.82 (0.66 - 1.01)	
TIMI major bleeding	≥ 60	2.34	2.69	2.01	1.00	2.54 (1.81 – 3.58)	0.69	2.96 (2.05 - 4.26)	0.18	2.16 (1.48- 3.15)	0.56
	< 60	2.86	2.28	3.44	1.35	2.22 (1.23 – 4.01)		1.77 (0.90- 3.47)		2.69 (1.43- 5.05)	

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular death; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction. eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan Maier; P-int, p for interaction.

Supplemental Table 5: All cause of death at 3 years by eGFR (mL/min/1.73 m^2) and treatment.

Endpoint	eGFR	Ticagrelor Pooled	Ticagrelor 90	Ticagrelor 60	Placebo	Ticagrelor Pooled vs. Placebo		Ticagrelor 90 vs. Placebo		Ticagrelor 60 vs. Placebo	
		% 3-yr KM				HR (95% CI)	P-int	HR (95% CI)	P-int	HR (95% CI)	P-int
All cause death	**≥ 60**	3.91	4.29	3.55	3.79	1.01 (0.84 – 1.21)	0.51	1.12 (0.91 – 1.37)	0.19	0.90 (0.73 – 1.11)	0.83
	< 60	8.31	8.06	8.58	9.11	0.92 (0.75 – 1.13)		0.91 (0.71 – 1.15)		0.94 (0.73 – 1.19)	

eGFR, estimated glomerular filtration rate; yr, years; KM, Kaplan Maier; HR, hazard ratio; CI, confidence interval; P-int, p for interaction

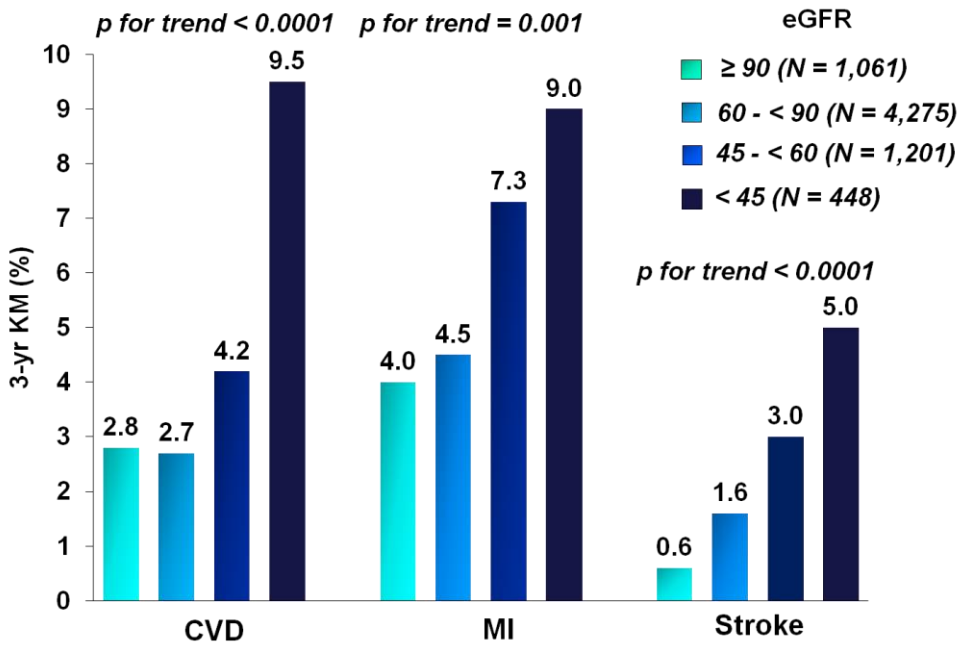
Supplemental Table 6: Renal Events, Gout, and Discontinuation rate at 3 years by eGFR (mL/min/1.73 m^2) and treatment.

Endpoint	eGFR	Ticagrelor Pooled	Ticagrelor 90	Ticagrelor 60	Placebo	Ticagrelor Pooled vs. Placebo		Ticagrelor 90 vs. Placebo		Ticagrelor 60 vs. Placebo	
		% 3-yr KM				HR (95% CI)	P-int	HR (95% CI)	P-int	HR (95% CI)	P-int
Renal event	**≥ 60**	1.65	1.60	1.69	1.23	1.44 (1.04 – 1.99)	0.22	1.43 (0.99 – 2.06)	0.28	1.46 (1.02 – 2.09)	029
	< 60	9.86	9.50	10.24	8.53	1.12 (0.88 – 1.41)		1.10 (0.84 – 1.44)		1.13 (0.87 – 1.49)	
Gout	**≥ 60**	1.61	1.68	1.55	0.89	2.00 (1.38 – 2.91)	0.11	2.10 (1.40 – 3.17)	0.21	1.90 (1.26 – 2.88)	0.10
	< 60	4.00	4.33	3.65	3.69	1.29 (0.88 – 1.89)		1.44 (0.94 – 2.19)		1.14 (0.73 – 1.79)	
Dyspnea	**≥ 60**	16.2	17.7	14.6	6.0	3.09 (2.72 – 3.51)	0.26	3.50 (3.05 – 4.00)	0.46	2.72 (2.37 – 3.13)	0.16
	< 60	21.9	23.2	20.5	7.5	3.59 (2.90 – 4.44)		3.89 (3.10 – 4.87)		3.32 (2.64 – 4.19)	
Drug Discontinuation	**≥ 60**	29.6	31.4	27.8	20.9	1.54 (1.44 – 1.66)	0.86	1.68 (1.55 – 1.82)	0.57	1.42 (1.31 – 1.54)	0.37
	< 60	39.9	40.4	39.3	28.9	1.56 (1.40 – 1.74)		1.61 (1.42 – 1.82)		1.51 (1.34 – 1.71)	

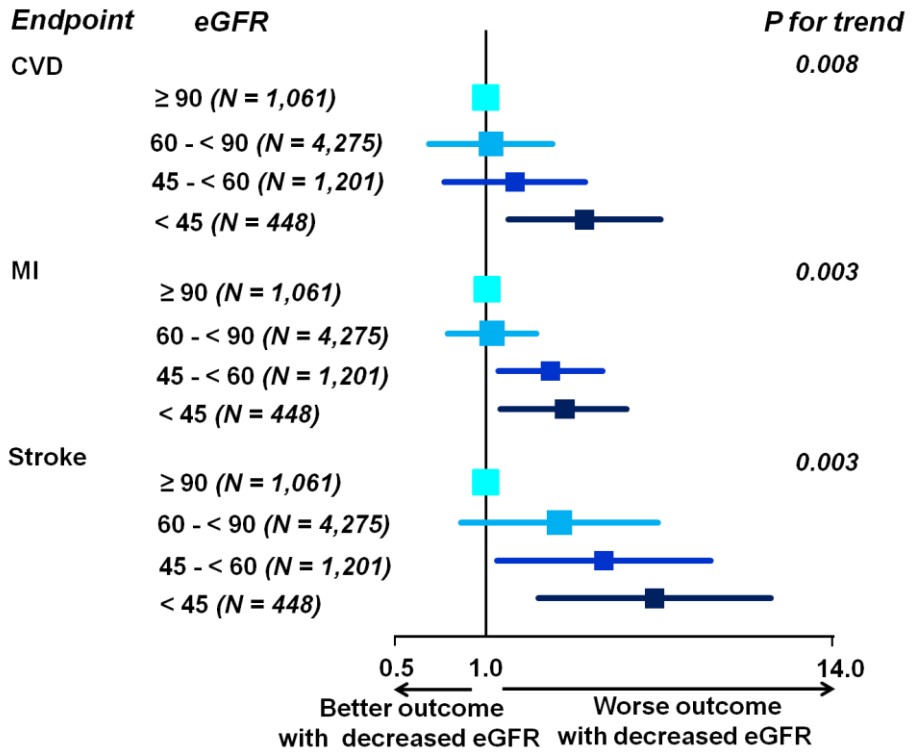
eGFR, estimated glomerular filtration rate; yr, years; KM, Kaplan Maier; HR, hazard ratio; CI, confidence interval; P-int, p for interaction

Supplemental Figure 1: KM event rates (Panel A) and adjusted HR for the individual components of the primary endpoint by eGFR (mL/min/1.73 m^2).

Panel A

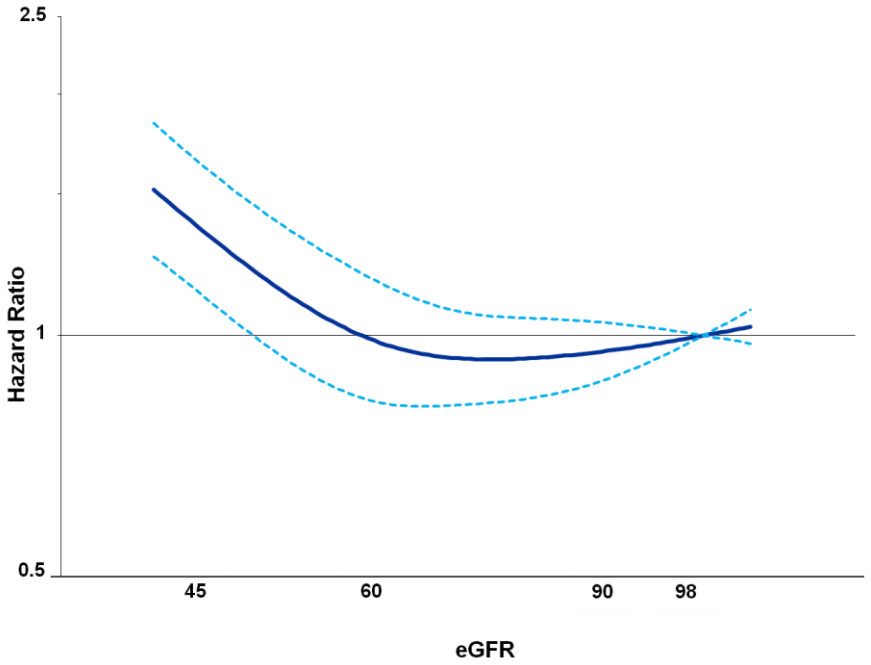


Panel B

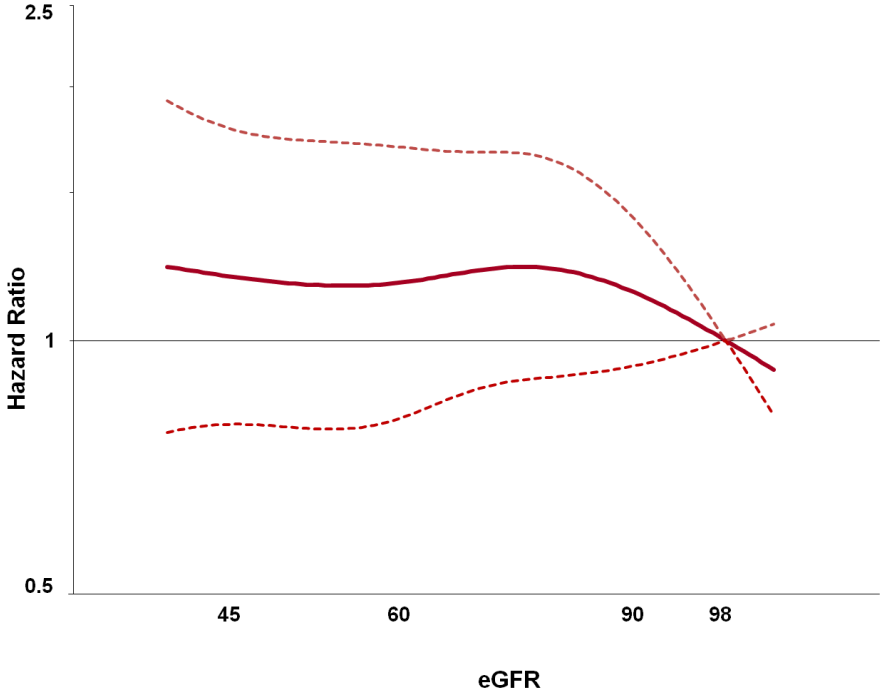


Supplemental Figure 2: Multivariable adjusted spline curves for the HR of primary endpoint (Panel A) and TIMI major bleeding (Panel B) vs. eGFR modeled as a continuous variable (all treatment arms pooled).

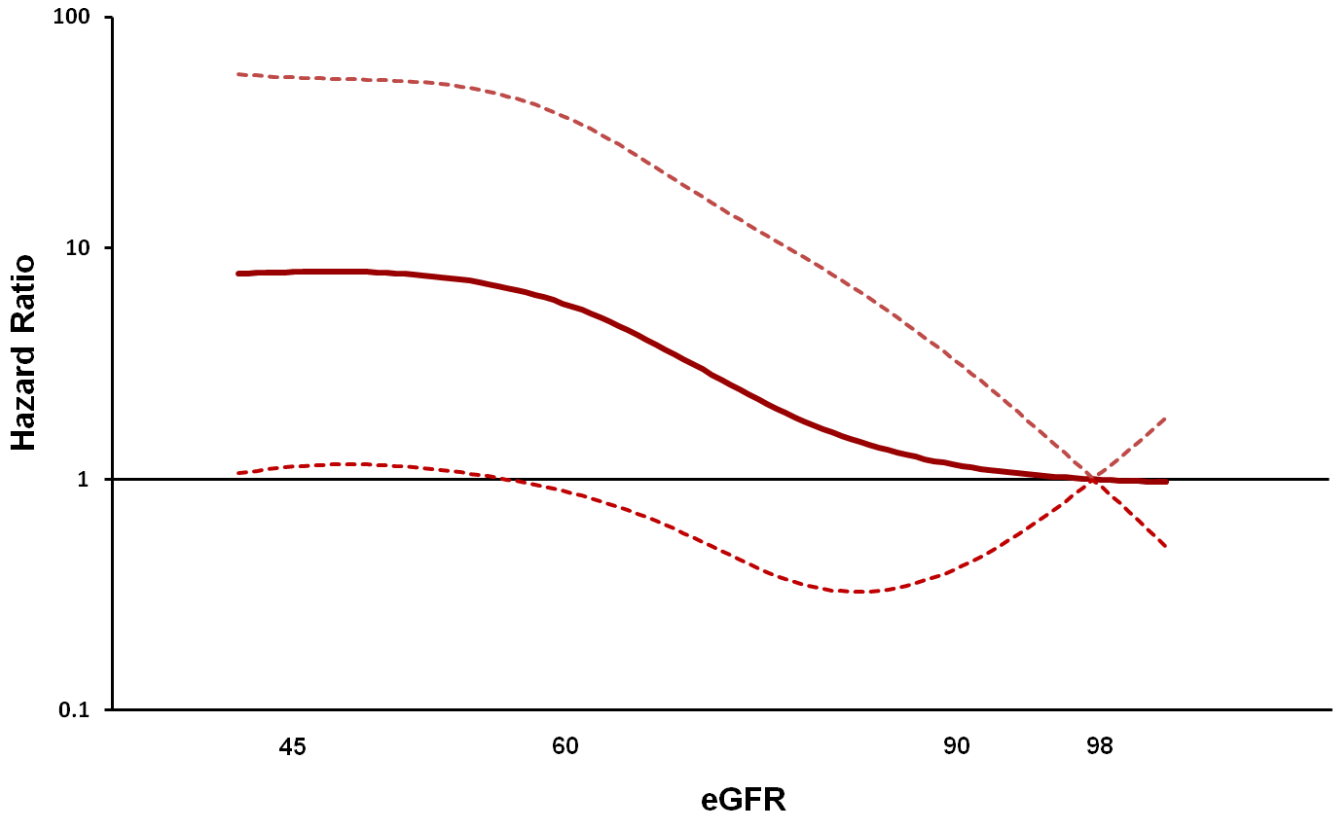
Panel A



Panel B

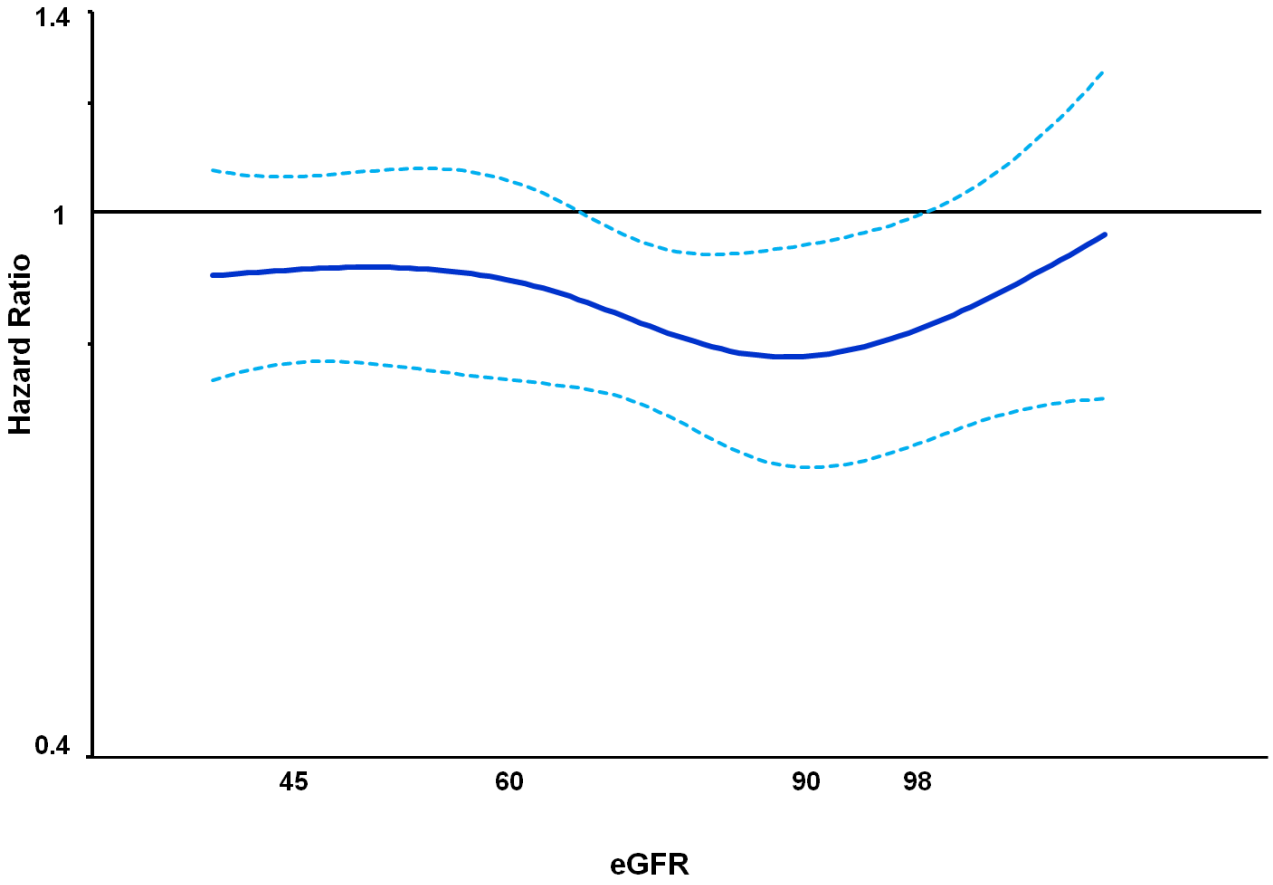


Supplemental Figure 3: Multivariable adjusted spline curves for the HR of TIMI minor bleeding vs. eGFR modeled as a continuous variable (placebo group only).

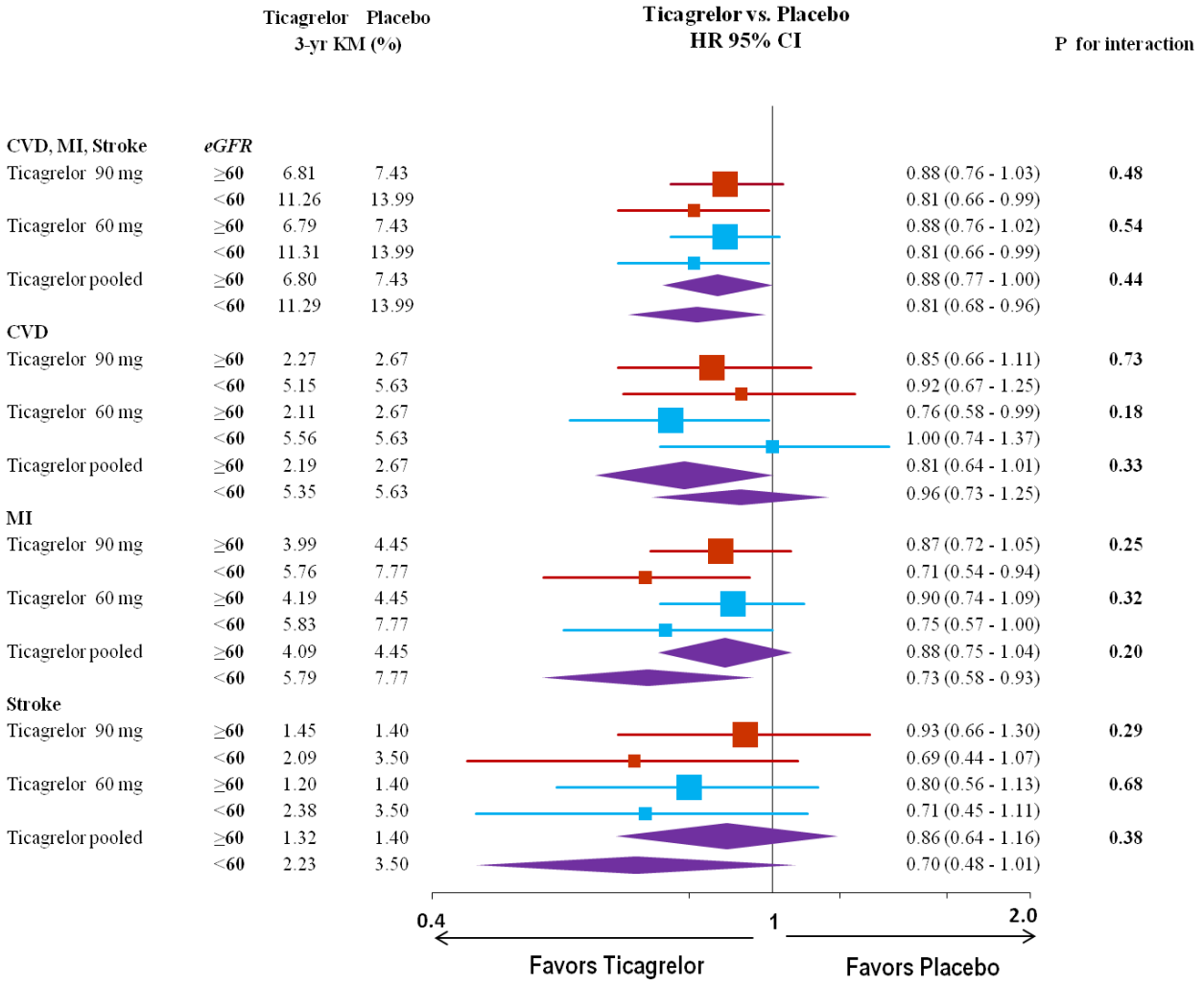


eGFR	eGFR < 45	eGFR 45 -<60	eGFR 60 - < 90	eGFR ≥ 90
Adj .HR (95% CI)	Adj HR 5.05 (0.41 – 62.77)	Adj HR 5.66 (0.63 – 50.46)	Adj HR 1.99 (0.24 – 16.22)	Referent

Supplemental Figure 4: Multivariable adjusted spline curve for the HR (tiacgrelor pooled vs. placebo) of the primary endpoint vs. eGFR modeled as a continuous variable.



Supplemental Figure 5: Hazard ratios and rates of the primary endpoint and individual components for each dose of ticagrelor and for the two doses pooled by eGFR (mL/min/1.73 m^2).



Supplemental Figure 6: Kaplan-Meier estimated occurrence of TIMI major bleeding by eGFR.