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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

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

Methods and results Patients with a history of MI 1–3 years prior from PEGASUS-TIMI 54 were stratified based on estimated glomerular filtration rate (eGFR), with <60 mL/min/1.73 m^2 pre-specified for analysis of the effect of ticagrelor on the primary efficacy composite of cardiovascular death, MI, or stroke (major adverse cardiovascular events, MACE) and the primary safety endpoint of TIMI major bleeding. Of 20 898 patients, those with eGFR <60 ($N = 4849$, 23.2%) had a greater risk of MACE at 3 years relative to those without, which remained significant after multivariable adjustment (hazard ratio, HR_{adj} 1.54, 95% confidence interval, 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.

Keywords Ticagrelor • Myocardial infarction • Secondary prevention • Renal dysfunction

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Introduction

Nearly one-third of patients with ST segment elevation myocardial infarction (MI) and >40% of those with a non-ST segment elevation MI have concomitant renal dysfunction.[1] As the population ages and the prevalence of conditions associated with both cardiovascular (CV) risk and risk of renal dysfunction, such as diabetes, increases, the population with concomitant chronic ischaemic heart disease and renal dysfunction is anticipated to grow significantly.[2,3] The presence of renal dysfunction in patients who have an MI is associated with worse outcomes, with an inverse, graded association between estimated glomerular filtration rate (eGFR) and major adverse cardiovascular events (MACE).[4] The relationship between renal dysfunction and ischaemic risk is complex and may be caused by accelerated atherosclerosis, inflammation, oxidative stress, and a prothrombotic state.[5] In addition, renal function is a powerful integrator of several CV risk factors including age, hypertension, and diabetes. The impact of concomitant renal dysfunction in patients with prior MI is further complicated by its relationship with bleeding risk. Platelet dysfunction caused by defective activation, adhesion, and aggregation, compounded by an increased risk of overdosing with some antithrombotic drugs, results in an association between worsening renal function and bleeding.[6]

The benefit–risk of chronic antithrombotic therapies in patients with prior MI and concomitant renal dysfunction is therefore complex, with some studies suggesting that more intense platelets inhibition could be of less benefit,[7,8] whereas others suggest benefit of similar or even greater magnitude with those with reduced renal function.[9–11] Ticagrelor is a reversibly binding oral $P2Y_{12}$ receptor antagonist that provides more potent and less variable $P2Y_{12}$ inhibition compared with clopidogrel. Ticagrelor was shown to substantially reduce cardiovascular death, MI, or stroke (MACE) compared with clopidogrel in patients with acute coronary syndrome (ACS), with a consistent relative risk reduction in patients with and without renal dysfunction, but with an absolute risk reduction greater for patients with renal dysfunction.[9] In the PEGASUS-TIMI 54 trial, ticagrelor reduced MACE in stable outpatients with prior MI.[12] This reduction in ischaemic events was accompanied by an increase in Thrombolysis in Myocardial Infarction (TIMI) major bleeding. We therefore evaluated 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.

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. The design[13] and primary results of the trial have been published.[12] In brief, the trial enrolled 21 162 patients with a spontaneous MI occurring 1–3 years prior to enrolment 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 <60 mL/min 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 tumour, or an intracranial vascular abnormality; or if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous month.

Endpoints

The primary efficacy endpoint was the composite of CV death, MI, or stroke (MACE). The primary safety endpoint was TIMI major bleeding.[13] 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. Adverse events were site reported and the subset of renal adverse events was predefined as a subset of adverse event preferred terms (see Supplementary material online, *Table S1*).

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 was based on the abbreviated Modification of Diet in Renal Disease Study Group equation (MDRD).[14] In addition, a sensitivity analysis assessing ischaemic and bleeding risk by eGFR and the effect of treatment was also performed using the Chronic Kidney Disease EPIdemiology collaboration (CKD-EPI)[15] 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 relationships with MACE and bleeding were evaluated using cubic splines. Second, eGFR was divided into categories consistent with Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation definition and classification of CKD.[16] Because there were few patients with eGFR <30 mL/min/1.73 m^2, patients were divided into four groups: ≥90, 60 to <90, 45 to <60, and <45 mL/min/1.73 m^2. In evaluating the efficacy and safety of ticagrelor compared with placebo, analyses were performed using a pre-specified eGFR cutpoint 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 >1 prior MI, peripheral artery disease, stroke, heart failure, and type of index event). The associations between renal function and the hazard for the MACE and TIMI major bleeding were evaluated using cubic splines.[17] 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.

Results

A baseline serum creatinine concentration was available in 20 898 patients (99% of the overall trial population), of whom 3251 (15.6%), 12 798 (61.2%), 3536 (16.9%), and 1313 (6.3%), had an eGFR ≥90, 60 to <90, 45 to <60, and <45 mL/min/1.73 m^2, respectively (eGFR ≥60, *N* = 16 049, 76.8%; eGFR <60, *N* = 4849, 23.2%). Baseline characteristics by category of eGFR are shown in *Table 1* and stratified at <60 and ≥60 mL/min/1.73 m^2 in Supplementary material online, *Table S2*. Lower eGFR was associated with older age, female sex, and CV risk factors including hypertension and diabetes, and CV disease including a history of multiple prior MIs, peripheral artery disease, and heart failure.

Baseline renal function and ischaemic risk

There was an inverse, graded relationship between category of eGFR and the risk of MACE through 3 years in the placebo arm as the eGFR dropped <60 mL/min/1.73 m^2 (*P* for trend <0.0001, *Figure 1A*, see Supplementary material online, *Table S3*) with a consistent relationship for each of the individual components (*P* for trend ≤0.001 for CV death, for MI, and for stroke, see Supplementary material online, *Figure S1A*). After adjusting for baseline clinical differences, eGFR remained an independent predictor of ischaemic risk, especially when eGFR dropped <60 mL/min/1.73 m^2 (*Figure 1B*, see Supplementary material online, *Table S3*). When dichotomized, patients with an eGFR <60 mL/min/1.73 m^2 had an adjusted hazard ratio (HR) for MACE of 1.54 (95% confidence interval, 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 (see Supplementary material online, *Figure S1B*).

Table 1 Baseline characteristics by estimated glomerular filtration rate (mL/min/1.73 m^2)

Characteristic	eGFR (mL/min/1.73 m^2)				
	≥90, *N* = 3251, *n* (%)	60 to <90, *N* = 12 798, *n* (%)	45 to <60, *N* = 3536, *n* (%)	<45, *N* = 1313, *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)	n.a.
Demographics					
Age (years), 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/m^2), 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
Hypercholesterolaemia	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)	10 776 (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 >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 enrolment					
Aspirin	3247 (99.9)	12 779 (99.9)	3534 (99.9)	1311 (99.9)	0.60
β-Blocker	2641 (81.2)	10 525 (82.2)	2973 (84.1)	1120 (85.3)	0.0006
ACEI or ARB	2604 (80.1)	10 219 (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; 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.

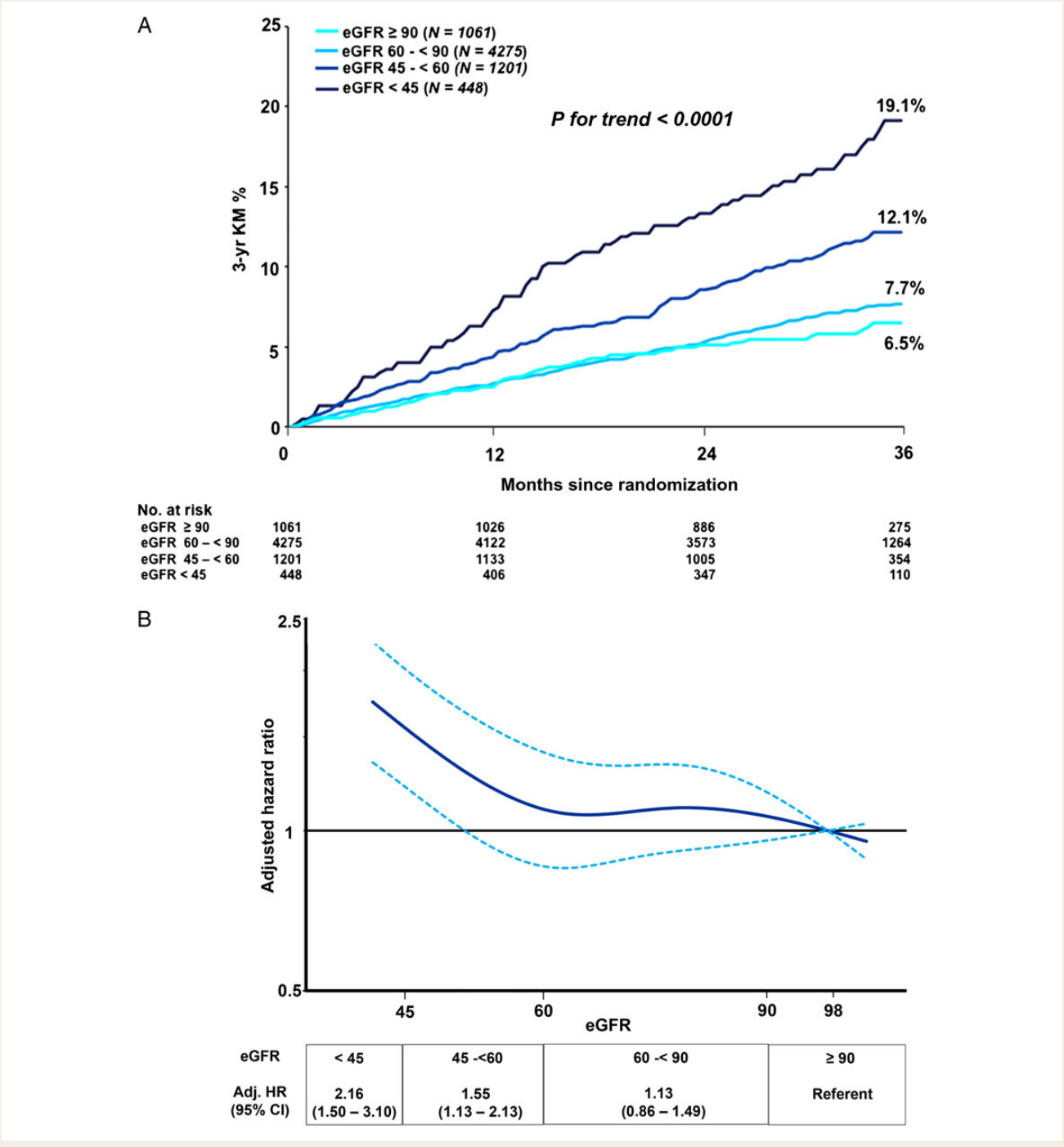

Figure 1 KM curves for the primary endpoint of cardiovascular death, myocardial infarction, or stroke by eGFR (mL/min/1.73 m^2) (*A*) and multivariable-adjusted spline curves for the HR of the primary endpoint vs. estimated glomerular filtration rate modeled as a continuous variable (*B*). Placebo group only. Patients stratified into four groups (eGFR $\geq$ 90 mL/min/1.73 m^2, 60 to $<$90 mL/min/1.73 m^2, 45 to $<$60 mL/min/1.73 m^2, and $<$45 mL/min/1.73 m^2). In *B*, the dotted lines represent the 95% pointwise confidence band. The reference value 98 is the median eGFR in the $\geq$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 one prior MI, peripheral artery disease, stroke, heart failure, and type of index event). eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan-Meier; *N*, total number; Adj., adjusted; HR, hazard ratio; CI, confidence interval.

The relationship between eGFR and ischaemic 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 (see Supplementary material online, *Figure S2*).

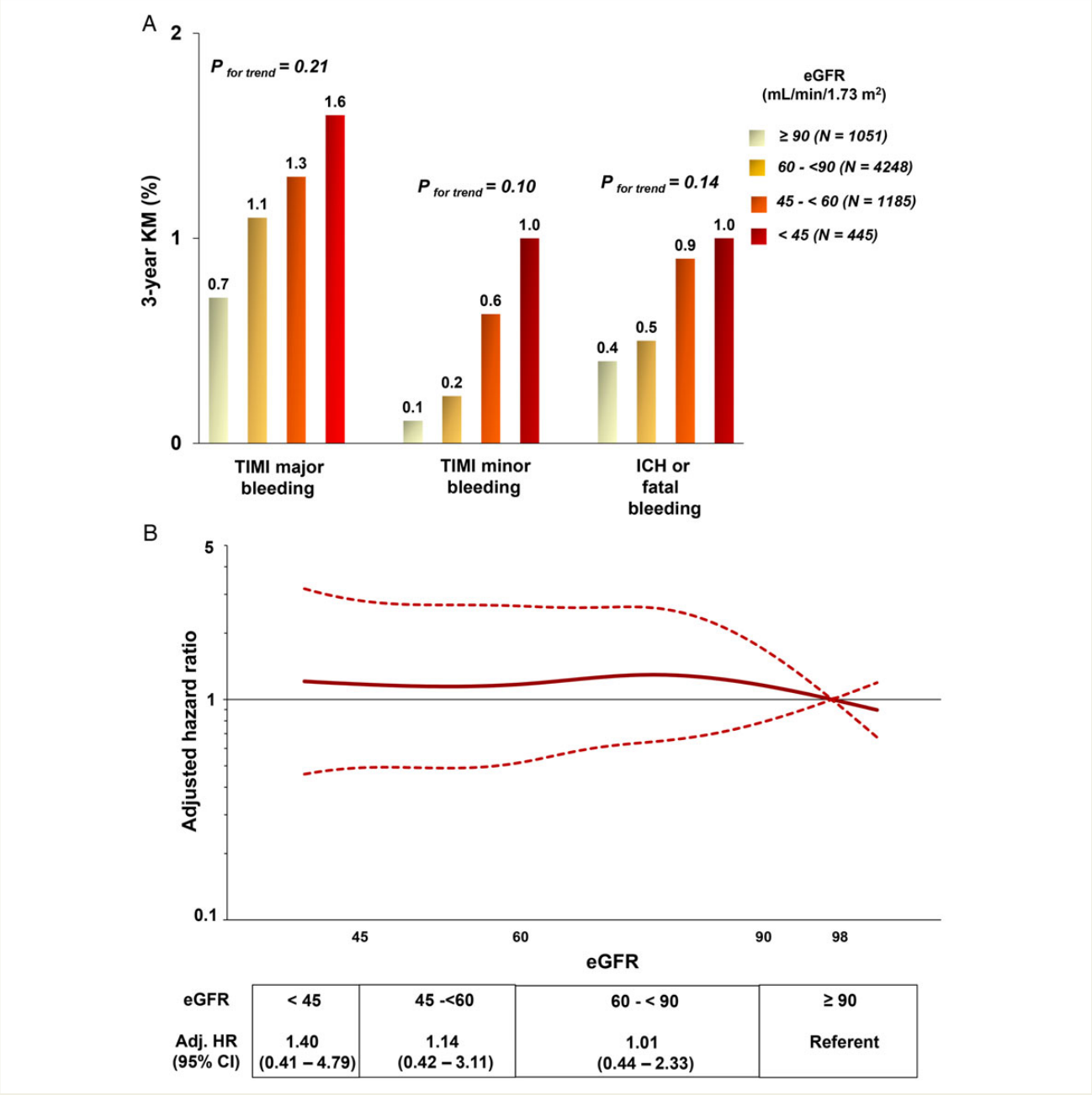

Figure 2 Bleeding risk by estimated glomerular filtration rate (mL/min/1.73 m^2) (*A*) and multivariable-adjusted spline curves for the HR of the main efficacy endpoint vs. estimated glomerular filtration rate modeled as a continuous variable (*B*). Placebo group only. Patients stratified into four groups (eGFR ≥90 mL/min/1.73 m^2, 60 to <90 mL/min/1.73 m^2, 45 to <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 one prior MI, peripheral artery disease, stroke, heart failure, and type of index event). eGFR, estimated glomerular filtration rate; yr, year; KM, Kaplan-Meier; *N*, total number; Adj., adjusted; HR, hazard ratio; CI, confidence interval; ICH, intracranial haemorrhage; 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.

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 2A*, see Supplementary material online, *Table S3*). After adjusting for baseline differences, there was no longer an appreciable relationship between eGFR and TIMI major bleeding (*Figure 2B*), but there was for minor bleeding, Supplementary material online, *Figure S3* and *Table S3*). 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 (see Supplementary material online, *Figure S2*).

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, $n = 4849$; 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 3*) and similar when eGFR was modeled as a continuous variable (see Supplementary material online, *Figure S4*). However, given the greater risk of MACE in patients with renal dysfunction, the respective absolute risk reduction in MACE at 3 years was four 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 (see Supplementary material online, *Figure S5*). Results were consistent regardless of whether eGFR was calculated using MDRD or CKD-EPI (see Supplementary material online, *Table S4*). The rate of death from any cause did not differ significantly with either dose of ticagrelor when compared with placebo, regardless renal function (see Supplementary material online, *Table S5*).

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 2*, see Supplementary material online, *Figure S6*). 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 with 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 (see Supplementary material online, *Table S4*).

Other safety events and tolerability

In the placebo arm, renal adverse events were more frequent in patients with an eGFR <60 compared with 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 ($P_{interaction} = 0.22$, see Supplementary material online, *Table S6*). Likewise, gout occurred more frequently in patients with an eGFR

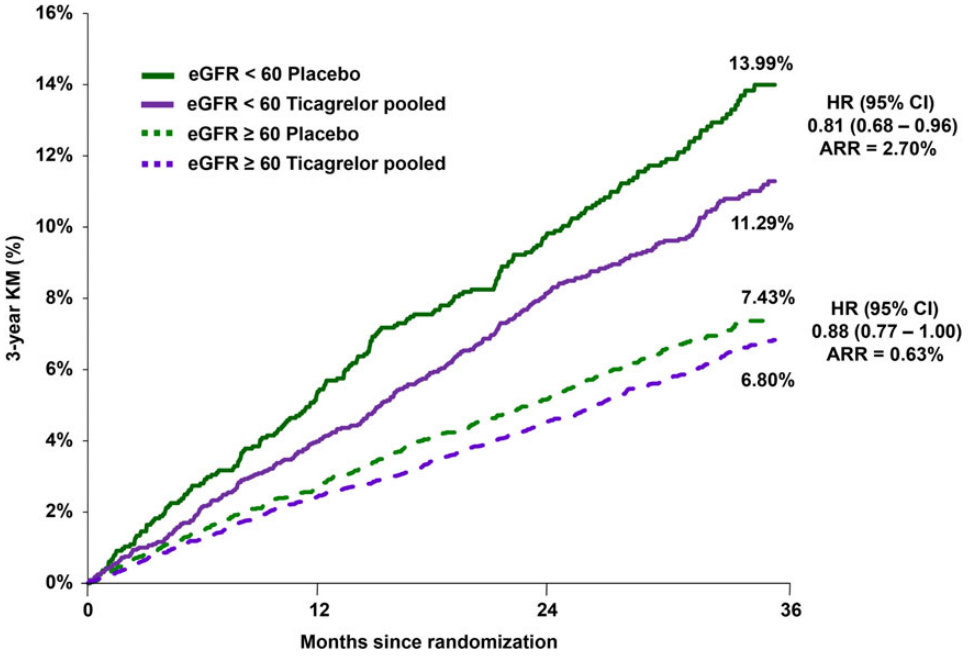

Figure 3 Kaplan–Meier estimated occurrence of CV death, MI, or stroke by estimated gloemrular filtration rate. Kaplan–Meier rates of primary endpoints through 3 years, according to the study group and by an eGFR cut-point of 60 mL/min/1.73 m^2. *P* for interaction = 0.44. eGFR, estimated glomerular filtration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

Table 2 Safety endpoints at 3 years by estimated glomerular filtration rate (mL/min/1.73 m^2)

Endpoint	eGFR	% 3-year KM				Ticagrelor pooled vs. placebo HR (95% CI)	*P*-int	Ticagrelor 90 vs. placebo HR (95% CI)	*P*-int	Ticagrelor 60 vs. placebo HR (95% CI)	*P*-int
		Ticagrelor pooled	Ticagrelor 90	Ticagrelor 60	Placebo						
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; KM, Kaplan–Maier; HR, hazard ratio; CI, confidence interval; TIMI, thrombolysis in myocardial infarction; ICH, intracranial haemorrhage.

<60 (HR_{adj} 3.62, 95% CI 2.21–5.94, $P < 0.001$), but the relative risk of gout with ticagrelor was, if anything, less pronounced in those with renal dysfunction (see Supplementary material online, *Table S6*). In patients randomized to placebo, there was a non-significant increase of dyspnoea events in patients with an eGFR <60 compared with 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 dyspnoea events, compared with placebo, regardless of renal function (see Supplementary material online, *Table S6*). 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 (see Supplementary material online, *Table S6*). 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, worse 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 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 ~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 ($N = 4849$, 23%), it is notable that only a small proportion of patients in the trial ($N = 3251$, 15%) had normal renal function (i.e. eGFR ≥90) and more than half ($N = 12\,798$, 60%) had slightly reduced renal function (eGFR 60 to <90). Although chronic non-end-stage renal dysfunction was an enrichment criteria in the trial, the prevalence of patients with CKD 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 datasets, 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 (haemoglobin 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 prespecified, 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 with 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 MACE. 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. These findings have important treatment implications for the large and growing proportion of patients with coronary disease and concomitant renal dysfunction.

Authors' contributions

G.M., E.B., M.S.S., and M.P.B.: conceived and designed the research; PEGASUS-TIMI 54 Investigators: acquired the data; J.K. and K.I.: performed statistical analysis; G.M. and M.P.B.: drafted the manuscript; All authors made critical revision of the manuscript for key intellectual content M.S.S. and E.B.: handled funding and supervision.

Supplementary material

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

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