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Circulation. **2010**;122:**1056–1067**
Published online before print August 30, 2010, doi:
10.1161/CIRCULATIONAHA.109.933796

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Coronary Heart Disease

Ticagrelor Versus Clopidogrel in Acute Coronary Syndromes in Relation to Renal Function

Results From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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Abstract

Background—Reduced renal function is associated with a poorer prognosis and increased bleeding risk in patients with acute coronary syndromes and may therefore alter the risk–benefit ratio with antiplatelet therapies. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor compared with clopidogrel reduced the primary composite end point of cardiovascular death, myocardial infarction, and stroke at 12 months but with similar major bleeding rates.

Methods and Results—Central laboratory serum creatinine levels were available in 15 202 (81.9%) acute coronary syndrome patients at baseline, and creatinine clearance, estimated by the Cockcroft Gault equation, was calculated. In patients with chronic kidney disease (creatinine clearance <60 mL/min; n=3237), ticagrelor versus clopidogrel significantly reduced the primary end point to 17.3% from 22.0% (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.65 to 0.90) with an absolute risk reduction greater than that of patients with normal renal function (n=11 965): 7.9% versus 8.9% (HR, 0.90; 95% CI, 0.79 to 1.02). In patients with chronic kidney disease, ticagrelor reduced total mortality (10.0% versus 14.0%; HR, 0.72; 95% CI, 0.58 to 0.89). Major bleeding rates, fatal bleedings, and non–coronary bypass–related major bleedings were not significantly different between the 2 randomized groups (15.1% versus 14.3%; HR, 1.07; 95% CI, 0.88 to 1.30; 0.34% versus 0.77%; HR, 0.48; 95% CI, 0.15 to 1.54; and 8.5% versus 7.3%; HR, 1.28; 95% CI, 0.97 to 1.68). The interactions between creatinine clearance and randomized treatment on any of the outcome variables were nonsignificant.

Conclusions—In acute coronary syndrome patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding but with numerically more non–procedure-related bleeding.

Clinical Trial Registration—URL:http://www.clinicatrials.gov. Unique identifier: NCT00391872.

Key Words:

- acute coronary syndrome
- bleeding
- clopidogrel
- mortality
- myocardial infarction
- renal function

Received December 23, 2009; accepted June 30, 2010.

Reduced renal function not only is associated with worse prognosis in patients with acute coronary syndromes (ACS) but also increases bleeding risk, which may alter the risk–benefit ratio with antiplatelet therapies. Even mild and moderate renal dysfunction increases the risk of myocardial infarction and death across the spectrum of ACS.[1,2] The mechanisms for the higher event rate are not fully understood, but accelerated atherosclerosis, oxidative stress, inflammation, and increased platelet aggregation, as well as underuse of recommended therapies such as antithrombotic agents and invasive procedures, have been proposed.[3] Furthermore, impaired renal clearance of many pharmacological agents increases the risk of overdosing in patients with reduced renal function, leading to further increased bleeding risk.

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Ticagrelor, a reversibly binding oral P2Y12 receptor antagonist, provides faster. greater, and more consistent (interpatient) P2Y12 inhibition than clopidogrel.[4] The Platelet Inhibition and Patient Outcomes (PLATO) trial demonstrated that treatment with ticagrelor instead of clopidogrel in a broad population of patients with ACS substantially reduced the risk of death from vascular causes, myocardial infarction, or stroke, and reduced cardiovascular and total mortality at 12 months without increasing the risk of major bleeding.[5]

Ticagrelor and its active metabolite, AR-C124910XX, undergo extrarenal metabolism; renal impairment has minimal effect on systemic exposure to active compounds.[6] Renal dysfunction constituted one of several risk criteria to satisfy inclusion in PLATO. Only patients with end-stage renal failure requiring dialysis could not participate. As a result, the PLATO cohort provides a varied distribution of patients according to baseline renal function. The present study investigates the main efficacy and bleeding effects of ticagrelor versus clopidogrel in relation to renal function at admission.

Methods

The PLATO trial enrolled 18 624 patients between October 2006 and July 2008. Details about the study design, patients, outcome definitions, and results have been published.[5,7] Patients were included if they were hospitalized for potential ST-segment elevation or non–ST-segment elevation ACS, with onset during the previous 24 hours. For non–ST-segment elevation ACS, at least 2 of the following 3 criteria were required: ST-segment depression or transient elevation ≥1 mm in 2 or more contiguous leads, positive biomarker indicating myocardial necrosis, or 1 additional risk indicator: age >60 years, previous myocardial infarction or coronary artery bypass graft (CABG), carotid artery disease, previous ischemic stroke, transient ischemic attack, carotid stenosis or cerebral revascularization, diabetes mellitus, peripheral artery disease, or chronic kidney disease (CKD) (creatinine clearance [CrCl] <60 mL/min estimated by Cockcroft-Gault equation). For ST-segment elevation ACS, inclusion required a planned primary percutaneous coronary intervention. The most important exclusion criteria were fibrinolytic therapy within 24 hours, need for oral anticoagulation therapy, need for dialysis, and clinically important anemia or thrombocytopenia.

Patients were randomly assigned to ticagrelor or clopidogrel before any percutaneous coronary intervention procedure was performed. Ticagrelor was given in a loading dose of 180 mg followed by 90 mg twice daily. Patients randomized to clopidogrel who had not received clopidogrel for at least 5 days before randomization received a 300-mg loading dose of clopidogrel study drug followed by 75 mg daily. Others continued a maintenance dose of 75 mg daily as clopidogrel study drug. All patients received acetylsalicylic acid unless intolerant. A daily dose of 75 to 100 mg was recommended, but doses up to 325 mg daily were allowed for 6 months after stent placement. The median duration of study treatment was 9.1 months.

The primary efficacy variable was time to first occurrence of any event from the composite of death from vascular causes, myocardial infarction, and stroke. Secondary efficacy variables included the individual end points of myocardial infarction, cardiovascular death, stroke, and all-cause mortality. The primary safety variable was the time to first occurrence of any PLATO-defined major bleeding.

Laboratory Assessments

Venous blood samples were obtained via a direct venous puncture at randomization. After centrifugation, serum was frozen at −20°C in aliquots and sent for central laboratory analysis of creatinine concentration. CrCl was calculated with the Cockcroft-Gault equation[8]: CrCl=[(140−age in y)×weight in kg]/(0.814×SCr in μmol/L)×0.85 if female (mL/min), and the Modification of Diet in Renal Disease (MDRD) formula: CrCl=30 849×(SCr in μmol/L)−1.154×(age in y) −0.203×0.742 if female (mL/min), where SCr is serum creatinine. All CrCl results were adjusted to a body surface area of 1.73 m^2. Repeated measurement of serum creatinine was made at 12 months and 1 month after the end of treatment.

Statistics

Categorical baseline variables by CrCl level were presented as frequencies and percentages with differences evaluated by the Fisher exact test. For continuous variables, medians and 25th to 75th percentiles are shown, and comparisons were evaluated with the Wilcoxon test.

The shape of the association between continuous CrCl and the hazard ratio (HR) for the end points of interest was evaluated using restricted cubic splines. Transformations were applied to subsequent models when required. The association of CrCl with different end points was estimated with a Cox model and is presented as HRs for a 5-mL/min decrease in CrCl. To illustrate the relationships by treatment, plots of 1-year predicted survival from a Cox proportional-hazards model with CrCl, treatment, and their interaction as the independent variables were generated. Additionally, patients were grouped according to deciles of CrCl, and the 1-year Kaplan-Meier rates of the outcome of interest were estimated for each group and treatment and included as separate points.

Analyses of primary and secondary efficacy and safety events were performed in patient groups based on the cut point of CrCl of 60 mL/min, the cut point defining CKD classes 3 and 4.[9] Kaplan-Meier estimates were estimated and plotted for treatment and 2 subgroups. Cox proportional-hazards models were used to estimate the treatment effect in patients with and without CKD. The interaction between CKD as a continuous variable and treatment was assessed by adding an interaction term to a model including CrCl and treatment. Adjusted HRs for the treatment effect were derived using Cox regression models overall and in the renal function subgroups. Candidate variables were prespecified and included potential confounders of treatment-end-point association (age, sex, prior myocardial infarction, congestive heart failure, diabetes mellitus, hypertension, smoking status, body mass index, previous percutaneous coronary intervention or CABG, type of ACS, N-terminal prohormone brain natriuretic peptide, and hemoglobin). The final Cox models used for adjustment were selected by the use of a backward selection algorithm using a significance level of 0.05 to remove variables from the model. The proportional-hazard assumption was assessed, extending the Cox model with a time-dependent variable formed as the product of the time to the event and the treatment variable and testing the statistical significance of its associated coefficient. Ventricular pauses are presented as frequencies and percentages, and the association between ventricular pause and treatment is described with odds ratios. A logistic regression model was used to test for the interaction between CKD and treatment. All statistical analyses were performed with SAS software package (version 9.2, SAS Institute, Cary, NC).

Results

Patients and Outcome in Relation to Renal Function

The 15 202 patients (81.9%) with serum creatinine levels available at baseline had a median calculated CrCl of 80.3 mL/min (25th to 75th percentile, 63 to 99 mL/min). Patients with missing values were not different from those with available creatinine levels regarding baseline characteristics and outcome except for a higher major bleeding rate (12.7% versus 11.1%; P=0.02). Patients with CKD, defined as a baseline CrCl <60 mL/min, constituted 21% of those with baseline creatinine measurements and had more high-risk characteristics compared with

patients with normal renal function (Table 1⇓) but to a high degree received medical therapy according to published guidelines. The treatment groups were balanced with respect to key demographic factors for the CKD subgroup.

Table 1. Baseline Characteristics by 60–mL/min CrCl Level

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Table 1. Continued

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Baseline calculated CrCl strongly predicted ischemic and bleeding end points. The relationship between the log hazard of all end points and CrCl was linear for values of CrCl <100 mL/min and constant above that value except for stroke and major bleeding, for which the relationship was linear regardless of CrCl level. There was a significant relative increase ($P<0.001$) in the risk of the primary composite outcome by 12%, total mortality by 19%, myocardial infarction by 8%, stroke by 11%, and major bleeding by 4% for every decrease in CrCl of 5 mL/min per 1.73 m^2 body surface area (Table 2). In fact, patients with CKD had an incidence of the primary composite end point that was more than twice as high, an almost 4–times higher mortality and 1.5–times higher rate of major bleedings compared with patients with normal renal function (Tables 2 and 3⇓). After adjustment for other significant clinical and laboratory predictors of outcome in multivariable analyses, CKD was significantly associated with higher incidences of the primary composite outcome, of mortality, and of major bleeding.

Table 2. Outcome in Relation to Renal Function Measured by Calculated CrCl

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Table 3. Outcome of Ticagrelor– and Clopidogrel–Treated Patients With CKD Versus Normal Renal Function Using Cockcroft–Gault Estimation

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Ischemic Outcome in Relation to Renal Function and the Randomized Treatments

Figure 1 displays the primary composite end point (Figure 1A) and total mortality (Figure 1B) plotted against deciles of CrCl for the ticagrelor and clopidogrel groups. The numeric absolute (and relative) risk reductions of the primary composite end point and total mortality by ticagrelor versus clopidogrel were 4.7% (23%) and 4.0% (28%) in patients with CKD and 1% (10%) and 0.5% (11%) in patients with normal renal function (Table 3 and Figure 2). The number needed to treat to prevent an additional event in patients with CKD was 21 (95% confidence interval [CI], 13 to 56) for the primary composite event and 25 (95% CI, 16 to 63) for total mortality. The smaller cohort of 214 patients with calculated CrCl <30 mL/min showed similar results for the primary composite end point, 28.9% per 12 months (27 patients) for ticagrelor versus 39.0% (39 patients) for clopidogrel (HR, 0.77; 95% CI, 0.49 to 1.30) and for mortality, 23.4% (21 patients) versus 29.6%, (29 patients) (HR, 0.77; 95% CI, 0.47 to 1.44). In fact, ticagrelor reduced the primary composite end point and total mortality versus clopidogrel consistently, regardless of CrCl cutoff value for CKD, with progressively decreasing point estimates of the HR with decreasing cutoffs values of CrCl from 100 to 30 mL/min (Figure 3). The interaction term between randomized treatment and CrCl entered as a continuous variable was not significant for any of the evaluated outcome events (Table 3). The proportional–hazard assumption was valid for most models in the overall population and all subgroups defined by CrCl. The results were unaffected by multivariable adjustments for significant predictors of outcome. The adjusted HR for the primary end point in patients with CKD was 0.78 (95% CI, 0.66 to 0.93) and in patients with normal renal function was 0.93 (95% CI, 0.81 to 1.06;

P for interaction=0.16). For mortality, the corresponding numbers were 0.71 (95% CI, 0.57 to 0.90) and 0.93 (95% CI, 0.75 to 1.15; *P* for interaction=0.14).

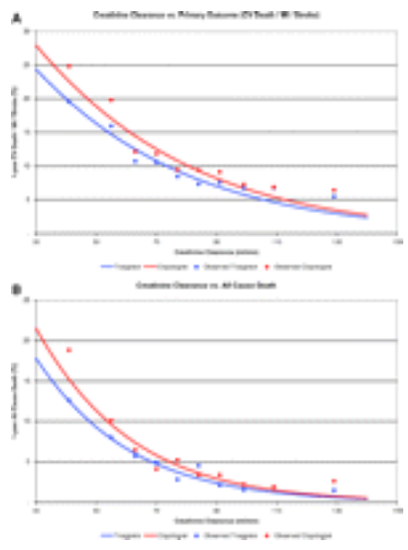

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Figure 1. Deciles of baseline levels of CrCl by treatment are on the horizontal axis. A, Kaplan–Meier estimate of the yearly event rate for the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke on the vertical axis. B, Total mortality on the vertical axis. Each plot includes smoothed estimates of the relationships.

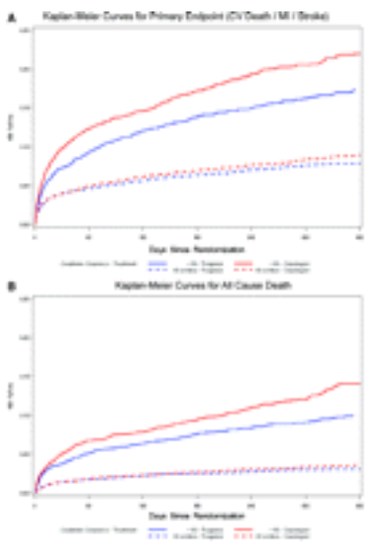

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Figure 2. Kaplan–Meier (KM) event rate curves of (A) the primary composite of cardiovascular death, myocardial infarction, and stroke and (B) total mortality in the ticagrelor (blue lines) and clopidogrel (red lines) groups stratified by renal function. Patients with CKD (solid lines) and normal renal function (dotted lines) were determined by calculated CrCl at baseline.

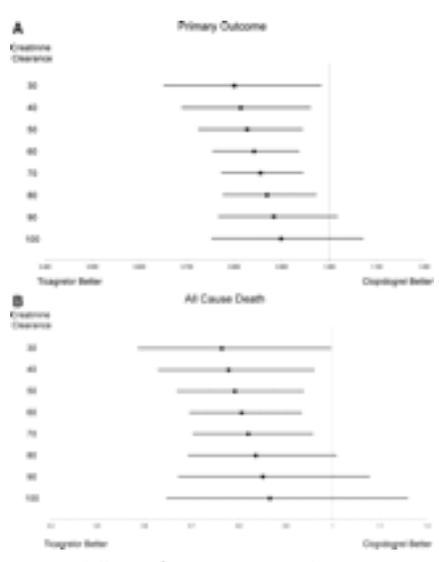

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Figure 3. HRs with 95% CIs for (A) the primary composite end point of cardiovascular death, myocardial infarction, and stroke and (B) total mortality for ticagrelor vs clopidogrel at different cut points of CrCl.

A smaller group, defined as those with CKD, was identified with the MDRD equation (n=2562). The numeric absolute (and relative) risk reduction of the primary composite end point by ticagrelor versus clopidogrel was 6.0% (29%) in patients with CKD and 1.1% (10%) in patients with normal renal function (*P* for interaction=0.03; Table 4). For all-cause mortality, the corresponding numbers were 5.3% (36%) and 0.5% (9%) (*P* for interaction=0.02). After multivariable adjustment, the interaction term for the primary end point did not remain significant.

Table 4. Outcome of Ticagrelor- and Clopidogrel-Treated Patients With CKD Versus Normal Renal Function Using the MDRD Estimation

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Bleeding Outcome in Relation to Renal Function and the Randomized Treatments

Figure 4 plots PLATO-defined major bleeding rates against deciles of CrCl. Major bleeding increased with decreasing calculated CrCl at entry similarly in the ticagrelor and clopidogrel groups. The incidence of major bleeding did not differ significantly between the ticagrelor and clopidogrel groups (Table 3 and Figure 4) in patients with normal renal function or in patients with CKD. The incidence of PLATO-defined major and Thrombolysis in Myocardial Infarction (TIMI) major bleedings not related to CABG increased with lower levels of calculated CrCl at entry with numerically higher rates with ticagrelor versus clopidogrel in patients with CKD (Table 3 and Figure 5).The incidence of fatal bleeding was numerically lower and the incidence of intracranial bleeding numerically higher in the ticagrelor group versus the clopidogrel group with no significant interactions with renal function (Table 3). The adjusted HR for major bleeding in patients with CKD was 1.11 (95% CI, 0.91 to 1.37); in patients with normal renal function, the adjusted HR was 1.08 (95% CI, 0.95 to 1.22; *P* for interaction=0.78). When the MDRD equation was applied, major bleeding rates did not differ between the groups in patients with CKD (HR, 1.08; 95% CI, 0.87 to 1.34) or normal renal function (HR, 1.08; 95% CI, 0.96 to 1.20; *P* for interaction=0.98; Table 4). Among patients with CrCl under 30, 20 out of 99 (KM 23.6%) patients randomized to ticagrelor, had a major bleeding and 12 out of 115 (14.1%) randomized to clopidogrel.

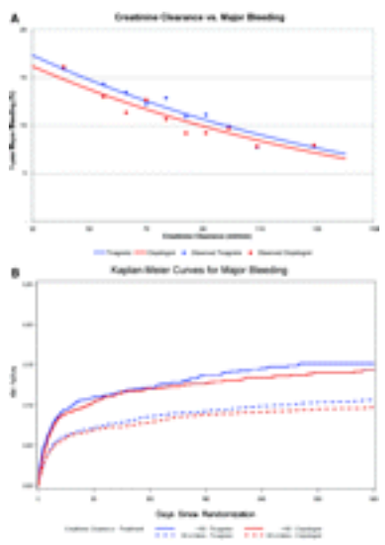

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Figure 4. Deciles of baseline levels of CrCl by treatment are on the horizontal axis. A, Kaplan–Meier (KM) estimate of the yearly event rate for PLATO major bleeding. B, Kaplan–Meier estimate of the yearly event rate for non–CABG-related TIMI major bleeding.

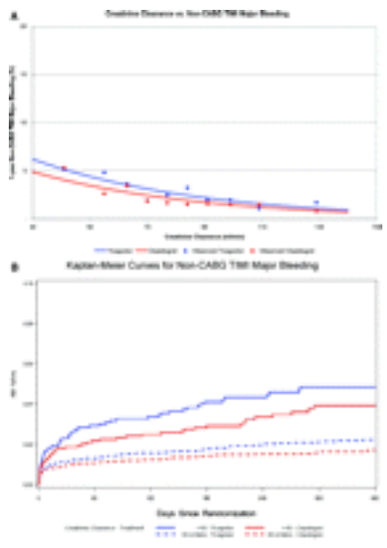

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Figure 5. Kaplan Meier event rate curves of (A) PLATO major bleeding and (B) non–CABG-related TIMI major bleeding in patients in the ticagrelor (blue lines) and clopidogrel (red lines) groups stratified by renal function. Patients with CKD(solid lines) and normal renal function (dotted lines) were determined by calculated CrCl at baseline.

Side Effects in Relation to Renal Function and the Randomized Treatments

Dyspnea occurred significantly more often with ticagrelor compared with clopidogrel in patients with CKD (5% absolute increase) and in patients with normal renal function (6.2% absolute increase; Table 3). The occurrence of ventricular pauses ≥3 seconds during the first week (Table 3) or 30 days later (not shown) did not differ significantly between the randomized groups. There was a relative increase in serum creatinine from baseline to 12 months that was higher in patients with normal renal function than in those with CKD and significantly higher in the ticagrelor compared with the clopidogrel group, but there was no difference between the treatment groups at 1 month after the end of treatment (Table 5).

Table 5. Change in Creatinine From Baseline

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Discussion

In the PLATO trial, similar to other published data sets, even a small reduction in renal function was associated with an increased risk of all evaluated ischemic and bleeding end points, including myocardial infarction and total mortality. Approximately one fourth of the study population met the general definition of CKD,[9,10] CrCl <60 mL/min, reflecting that there were no exclusion criteria for renal dysfunction in the PLATO trial except for the requirement of dialysis.[7] This patient cohort had a very high-risk clinical profile, including higher levels of N-terminal prohormone brain natriuretic peptide and lower hemoglobin, but still the proportion of patients receiving guideline-recommended pharmacological therapies was high.

The most striking finding with the present results is that, independently of renal function, ticagrelor compared with clopidogrel reduced ischemic end points and mortality with no significant increase in major or fatal bleedings. Patients with CKD are at a particularly high risk for ischemic and bleeding events. This high-risk group had an absolute reduction by ticagrelor versus clopidogrel of the primary composite end point of 4.7%/y compared with 1%/y in those with normal renal function. Use of the MDRD formula identified a smaller and higher-risk group of patients with CKD; in fact, the interaction terms for the primary composite end point and mortality in the randomized groups were significant. The reduction in the primary composite end point by ticagrelor among patients with CKD may have been driven more by a reduction in mortality, with an absolute reduction of 4%/y in patients with CKD compared with 0.5%/y in patients with normal renal function. This relationship may reflect the more effective reduction in ischemic events with a higher and more consistent level of platelet inhibition with ticagrelor in patients at high risk for thromboembolic events with minimal impact on excess bleedings. Alternatively, ticagrelor-induced inhibition of adenosine reuptake by erythrocytes may improve myocardial perfusion, an effect possibly more important in patients with impaired renal function.[6] Dyspnea and ventricular pauses, potential adenosine-mediated side effects of ticagrelor, occurred with low frequency and did not increase with reduced renal function. Reduced mortality with ticagrelor occurred despite the fact that patients with CKD who initiated treatment later after randomization discontinued study treatment prematurely more often, leading to a shorter duration of therapy (Table 1⇑).

The significant benefit of ticagrelor over clopidogrel in patients with CKD contrasts with lack of a benefit of clopidogrel versus placebo. In the Clopidogrel for Reduction of Events During Observation (CREDO) trial, clopidogrel versus placebo reduced the composite of death, myocardial infarction, and stroke in patients with normal renal function, but there was in fact a trend in the opposite direction with an absolute increased event rate in patients with mild or moderate renal dysfunction.[11] In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, there was also a modest absolute and relative reduction in the primary ischemic end point with clopidogrel versus placebo among patients with renal dysfunction compared with those with normal renal function, although without any significant interaction.[12]

With lower levels of CrCl, there was an increase in the incidence of major bleeding in the PLATO population, similar to findings in previously published studies.[13] Reduced renal function and other associated baseline characteristics such as female sex, low body weight, diabetes mellitus, low hematocrit, and heart failure are independent strong predictors of bleeding in ACS.[14] However, with worse renal function, despite a higher level of platelet inhibition with ticagrelor compared with clopidogrel, there was no increase in PLATO-defined major, non-CABG-related TIMI major or fatal bleeding. Consistent with the overall PLATO population, the incidence of non-CABG-related TIMI major bleeding was higher with ticagrelor than with clopidogrel, but there was no relative increase in this difference in the CKD cohort. Ticagrelor metabolism and excretion depend minimally on renal function.[6] Renally excreted antithrombotic agents such as enoxaparin, tirofiban, and eptifibatide carry an increased bleeding risk in patients with renal dysfunction and are recommended to be administered at a lower dose in such patients.[15,16] Nearly half of the patients in the PLATO CKD subgroup were >75 years of age, and among baseline characteristics, age is considered the most important contributor to increased bleeding risk in patients with reduced renal function.[17] Forty percent of the PLATO patients with CKD were women, and 15% had a body weight <60 kg. These factors may contribute to a higher pharmacodynamic effect and higher bleeding risk.[18]

Limitations

The randomization was not stratified for renal function; therefore, some imbalance between the randomized groups may exist among patients with renal dysfunction. However, this was a prespecified subgroup analysis based on prespecified cut points of renal function at admission. Creatinine levels were missing in 3422 of the patients (18%), but the population without samples did not differ from the population with creatinine levels available on most baseline characteristics and outcome measures. The Cockcroft–Gault equation may underestimate renal function in the lower range. It has still been suggested to be preferable over the MDRD, particularly in small women and the elderly with high bleeding risk.[8] Nevertheless, our results are supported and strengthened by use of the MDRD equation for estimation of renal function.

Conclusions

Among patients with ACS, any degree of impairment of renal function is associated with a worse prognosis and an increased bleeding risk. The present results provide clinical evidence that ticagrelor is a more effective antiplatelet agent than clopidogrel in patients with ACS, regardless of renal function, and that the benefits are larger at poor renal function and without any need for dose reduction to prevent major bleeding. The advantage of ticagrelor over clopidogrel in reducing major adverse cardiac events is accentuated in cohorts with successively increasing renal dysfunction. Given the high prevalence of renal dysfunction among patients with atherosclerotic disease and the associated elevated risk of ischemic and bleeding complications, ticagrelor provides an important opportunity to substantially improve outcome in patients with ACS and impaired renal function.

Acknowledgments

The complete list of PLATO investigators and main study committees has been published previously.[5] We acknowledge Karen Pieper, DCRI for statistical support and Ebba Bergman, UCR for editorial support.

Sources of Funding

The PLATO study was funded by AstraZeneca. Support for the analysis and interpretation of results and preparation of the manuscript was provided through funds to the Uppsala Clinical Research Center and Duke Clinical Research Institute as part of the Clinical Study Agreement.

Disclosures

Dr James has received research grants and advisory board fees from AstraZeneca and honoraria from AstraZeneca, Bristol-Myers Squibb, Schering-Plough, and Eli Lilly. Dr Budaj has received consulting fees from Sanofi-Aventis, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Glaxo Smith Kline. Dr Aylward has received research grants and advisory board and speaker fees from Boehringer Ingelheim, Sanofi-Aventis, AstraZeneca, Eli Lilly, The Medicines Co, CSL Biotherapies, Bristol-Myers Squibb, Merck, Pfizer, Schering-Plough, and Servier. Dr Cannon has received research grants from Accumetrics, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, Glaxo Smith Kline, Intekrin Therapeutics, Merck, Merck/Schering-Plough Partnership, Novartis, and Takeda; Dr Cannon reports equity ownership interest in Automedics. Dr Harrington has received consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Portola Pharmaceuticals, Schering-Plough, AstraZeneca, and Eli Lilly and grant support from Millenium Pharmaceuticals, Schering-Plough, The Medicines Co, Portola Pharmaceuticals, AstraZeneca, and Bristol-Myers Squibb. Dr Lewis has received consulting fees from Bristol-Myers Squibb and Sanofi-Aventis and grant support from Boehringer Ingelheim. Dr Keltai has received consulting fees from AstraZeneca. Dr Storey has received research grants from AstraZeneca, Dynabyte, the Eli Lilly/Daiichi Sankyo alliance, and Schering-Plough, as well as honoraria or consultant fees from AstraZeneca, Eli Lilly/Daiichi Sankyo, Novartis, Schering-Plough, Eli Lilly/Daiichi Sankyo, Teva, and The Medicines Co. Dr Wallentin has received research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Glaxo Smith Kline, and Schering-Plough, as well as honoraria or consultant fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Glaxo Smith Kline, Schering-Plough, Eli Lilly, Regado, and Athera. Drs Horrow and Buck are employees of AstraZeneca. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Among patients with acute coronary syndromes, any degree of impairment of renal function is associated with a worse prognosis but also an increased bleeding risk, which may alter the risk–benefit ratio with antiplatelet therapies. The Platelet Inhibition and Patient Outcomes (PLATO) trial investigated the effects of ticagrelor compared with clopidogrel in a broad population of patients with non–ST-segment elevation acute coronary syndromes, regardless of the intended management strategy. Patients with chronic kidney disease, defined as a baseline creatinine clearance <60 mL/min, constituted 21% of those with baseline creatinine measurements (15 202). The numeric absolute (and relative) risk reductions of the primary composite end point and total mortality by ticagrelor versus clopidogrel were 4.7% (23%) and 4.0% (28%) in patients with chronic kidney disease and 1% (10%) and 0.5% (11%) in patients with normal renal function. The incidence of major bleeding did not differ significantly between the ticagrelor and clopidogrel groups in patients with normal renal function or in patients with chronic kidney disease. Thus, ticagrelor is a more effective antiplatelet agent than clopidogrel in acute coronary syndrome patients regardless of renal function, and the benefits are larger in those with poor renal function without any need for dose reduction to prevent major bleeding. Given the high prevalence of renal dysfunction among patients with atherosclerotic disease and the associated elevated risk of ischemic and bleeding complications, ticagrelor provides an important opportunity to substantially improve outcome in patients with acute coronary syndromes and impaired renal function.

Footnotes

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Guest Editor for this article was Robert A. Vogel, MD.

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