Ticagrelor in the Renal Dysfunction Subgroup: Subjugated or Substantiated?

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Chronic kidney disease (CKD) is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. The most recent data from the National Health and Nutrition Examination Survey estimated that the prevalence of CKD in the US population was 16.8% and had increased by 15.9% in comparison with that of the previous decade. These numbers are expected to rapidly increase with the aging of the population and furthermore with the epidemic of diabetes mellitus, a condition associated with a three-fold increase of the prevalence of CKD.

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CKD prevalence is twice as high in patients with cardiovascular disease, and recent registry data using the contemporary Modification of Diet in Renal Disease equation have reported a prevalence of moderate or severe CKD of 30.5% in ST elevation myocardial infarction and 42.9% in non-ST elevation myocardial infarction. This figure is much higher than what is usually reported in controlled trials where patients with CKD are often excluded, but similar to what has been observed in other registries.

Renal dysfunction is a powerful independent predictor of thrombotic and bleeding complications and, subsequently, of mortality. Worse clinical outcomes of patients with CKD are possibly explained by more frequent preexisting cardiovascular disease, more extended atherothrombosis, more serious presentation of Acute Coronary Syndrome (ACS), lower revascularization rates, and underutilization of evidence-based therapies with potential overdosing of medication which metabolism and excretion depend on renal function. This challenging group of patients represents a clearly unmet medical need.

New Oral P2Y12 Antagonists

Both prasugrel and ticagrelor, as opposed to clopidogrel, have shown that stronger P2Y12 inhibition led to significant 19% and 16% respective relative risk reduction of a similar primary end point combining cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Ticagrelor also showed a 1.1% absolute reduction of cardiovascular death, and both drugs showed a significant 0.6% absolute excess of thrombolysis in myocardial infarction (TIMI) major bleeding not related to coronary artery bypass graft (CABG) surgery (25% relative excess with prasugrel and 27% with ticagrelor). These two drugs clearly have the potential to change experts’ recommendations, physicians practices, and patients’ prognoses. They will not, however, replace clopidogrel in all patients with ACS, as the excess of bleeding makes the risk/benefit ratio questionable in some situations, particularly when translating the results from highly selected patients to real-life patients. While waiting for more information while these drugs are tested in new trials, additional analyses of the first two pivotal trials are flourishing. These landmark analyses, multivariate or risk-model analyses, subgroup analyses, and analyses of secondary or tertiary endpoints, may help identify preferential targets for these drugs, while taking into account the potential methodological flaws of such analyses. Thereby, the 21% reduction of the primary end point without any bleeding excess in the prospectively defined cohort of ST-segment elevation myocardial infarction, formed by stratification at the time of randomization or the similar optimal risk/benefit ratio in the predefined group of diabetics, now constitute preferred indications for prasugrel in stented ACS.

Ticagrelor in ACS With Renal Dysfunction

In this issue of Circulation, Dr James and colleagues elegantly present the results of a new analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial that is focused on the prespecified subgroup of patients with renal impairment (CKD stage 3 or more). Renal dysfunction was one of several risk criteria necessary for inclusion in the PLATO study, and only patients with end-stage renal failure requiring dialysis were excluded. In this subgroup analysis, 15 202 patients with ACS enrolled in the trial (81.9%) had an available measure of serum creatinine levels at baseline obtained from a central laboratory. Renal dysfunction was found in 21.3% and 16.8% of patients using the Cockcroft-Gault and the Modification of Diet in Renal Disease equation, respectively.

This work confirms that renal dysfunction, even with a definition including moderate CKD, is a powerful marker of risk in ACS, as patients with CKD have an extremely high rate of the ischemic primary end point (19.7% in patients with CKD versus 8.4% in patients without CKD) driven mostly by an impressive 12.1% all-cause death rate (compared to 3.3% in patients without CKD). As was also expected, there was an incremental bleeding risk over the different stages of renal dysfunction. Major bleeding rates were high with the PLATO...
definition (14.7% in patients with CKD versus 10.2% in patients without CKD) and were, after exclusion of CABG bleedings, still 40% higher than with the thrombolysis in myocardial infarction (TIMI) definition. When compared with patients without renal dysfunction, patients with CKD displayed a more than two-fold increase of bleeding rates with both types of definition. Altogether, these numbers show the excess of risk borne by patients with CKD on both sides, ischemic and hemorrhagic, translating into an even heavier toll paid to mortality.

Patients with CKD draw an impressive benefit from ticagrelor in this study, with a 23% relative risk reduction of the primary ischemic end point (compared with a nonsignificant 10% reduction in patients without CKD) and an even more striking 4.0% absolute and 28% relative risk reduction of all-cause mortality. These results translate into a number of patients who need to be treated to prevent 1 death of 25 CKD patients versus 200 patients without CKD. These amazing results in patients with CKD are subjugating and need a closer look.

The authors claim that ticagrelor does not increase major bleeding across the spectrum of renal dysfunction, which is true for PLATO-defined major bleeding. There were, however, significant 22% and 26% increases of non-CABG major bleeding in the overall population with ticagrelor using the PLATO and the thrombolysis in myocardial infarction definitions (TIMI), respectively. The bleeding excess was of similar magnitude in CKD and non-CKD subgroups.

Are these new data convincing enough to target patients with CKD as a preferred group for ticagrelor when it becomes available? For some, the answer is probably “no,” if you consider the nonsignificant probability value for interaction when defining renal insufficiency with the Cockcroft-Gault equation (see Figure), which suggests that the effect of ticagrelor remains in the same range with or without renal insufficiency. For others, the answer would be “yes,” as the drug provides to this high-risk subpopulation greater reduction of ischemic events without greater increase of bleeding when compared with patients without CKD. This is further ascertained by examining the data with the more contemporary Modification of Diet in Renal Disease equation and now a significant probability value for interaction (see Figure). Moreover, the significant 36% reduction in death in patients with CKD contrasts with the nonsignificant 9% reduction in the much larger group of patients without CKD along with a significant probability value for interaction between treatment and renal function. In this case, with the data presented, if we accept that there is a particular benefit in patients with CKD, and even a mortality benefit possibly confined to patients with CKD, it then suggests limited added value of ticagrelor over clopidogrel in the opposite subgroup (patients without CKD)–a new matter of debate.

Figure. Hazard ratio for efficacy (95% confidence interval) evaluated as the composite end point of cardiovascular death, myocardial infarction, or stroke, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Clopidogrel for Reduction of Events During Observation (CREDO), TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibiton with prasugre (TRITON) and PLATO trials according to renal function calculated with the Cockcroft-Gault equation when not specified or the Modification of Diet in Renal Disease equation when indicated so. * indicates a significant relative risk reduction with the study criteria or a significant probability value for interaction between subgroups. NA indicates not available.
P2Y12 Antagonists in Patients With CKD

The strong benefit of ticagrelor over clopidogrel in patients with CKD contrasts with the lack of effect observed with clopidogrel against placebo in similar CKD subgroups. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study,\textsuperscript{13} and the Clopidogrel for Reduction of Events During Observation (CREDO) trial,\textsuperscript{16} clopidogrel compared with placebo reduced the composite of death, myocardial infarction, and stroke in patients with normal or subnormal renal function, but the benefit of clopidogrel was not apparent in patients with mild or moderate renal dysfunction. In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial, prasugrel superiority over clopidogrel was consistent in patients with or without CKD (see Figure).

Are there any plausible explanations for the superiority observed with ticagrelor in patients with CKD? The first explanation is that choosing patients with CKD is an efficient way to select high-risk patients with high event rates, and it creates a favorable subgroup to demonstrate a benefit on hard but rare endpoints, like mortality. However, the much larger relative risk reduction observed in patients with CKD could suggest a more specific effect in these patients. Even if ticagrelor metabolism and excretion depend minimally on renal function, we could imagine a specific effect in patients with CKD. Ticagrelor-induced inhibition of adenosine reuptake by erythrocytes may potentially improve myocardial perfusion, and such an effect could possibly be more important in patients with impaired renal function.\textsuperscript{14} Dyspnea and ventricular pauses, which are considered adenosine mediated side effects of ticagrelor,\textsuperscript{17} were both more frequent in patients with CKD but with little difference between the two randomized groups. In patients without CKD, however, ticagrelor almost doubled the frequency of dyspnea (13.9\% versus 7.5\%) and led to a 51\% increase of ventricular pauses when compared to clopidogrel. This higher rate of “adenosine-like effect” in patients without CKD does not support the hypothesis of a specific effect in patients with CKD. In fact, with these data we could even conclude that the “adenosine-like effect” of ticagrelor is more important in patients without CKD.

Answers to these discrepancies to help us understand the differences in benefit of ticagrelor in patients with or without CKD remain to be found and may only reside in the benefit of intensified platelet inhibition in patients with different risk profiles. They could also be due to the play of chance as the presented data do not support a specific “adenosine like-effect” and lack physiological explanation. This creates uncertainty around plausibility along with the lack, to date, of consistency (the same results need to be reproduced in future trials) and the lack of coherence in the field (Figure), not to mention the absence of dose-response relationship, as many are missing Hill’s criteria of causation. On the other hand, absence of proof is not proof of absence, and whether there is a causal and specific effect of ticagrelor in patients with CKD just needs to be further substantiated.
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