Antithrombotic therapy for stable coronary artery disease: the difficult quest for the holy balance

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This editorial refers to ‘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’, by G. Magnani et al., on page 400.

From a pathophysiologic standpoint, coronary artery disease is of an atherothrombotic nature and therefore hopes to improve its prognosis rely on the treatment of both its atheromatous and thrombotic components. The way these components can be targeted, however, differs greatly in that atheroma can be targeted with medications (such as lipid-lowering agents or angiotensin-converting enzyme inhibitors) that do not carry specific safety issues, whereas antithrombotic agents have well-known adverse effects, with an increased risk of bleeding apparent as soon as they are administered and persisting for the duration of treatment. The search for more potent antithrombotic agents to more adequately prevent thrombotic complications during the course of the disease is therefore hampered by a potential increase in bleeding complications. Finding new antithrombotic agents that will truly benefit the patient has now become a quest for the holy balance between ischaemic and bleeding risks. As nature is complex, it is unlikely that this balance will be the same for every single patient, and it is therefore laudable to try and single-out specific populations where it would be the most favourable.

In this regard, Magnani et al.1 should be commended for providing a detailed analysis of the impact of ticagrelor, a potent, reversible P2Y12 inhibitor, according to renal function, using data from the PEGASUS trial, carried out in a population of stable patients 1–3 years after an acute myocardial infarction.

The choice of this specific population of interest is in no way due to chance. First, patients with renal insufficiency have a particularly high risk of coronary events, actually higher than that of most diabetic patients.2 Second, the interaction between renal failure and coagulation has long been recognised and the role of antiplatelet agents in this situation remains debated, both because of the increased bleeding risk observed in this older population and because of a potential (though not confirmed) lesser efficacy of antiplatelet agents.3,4 Third, a subgroup analysis of the Platelet Inhibition and Patient Outcomes (PLATO) trial showed a 23% risk reduction in ischaemic events with ticagrelor in patients with renal insufficiency, and a much smaller 10% reduction in patients without renal disease, although the interaction was not statistically significant.5

The PEGASUS trial used chronic kidney disease as a risk enrichment criterion, and included patients covering the whole spectrum of renal failure (except patients on dialysis). Overall, 23% of the population had an abnormal estimated glomerular filtration rate. As expected, patients with renal insufficiency were older (a 12-year difference between patients with severely altered vs. normal renal function), more often women and had more co-morbidities. After adjustment for potential confounders, they remained at increased risk of ischaemic events. The risk of bleeding was also increased, although the excess risk of thrombolysis in myocardial infarction (TIMI) major bleeding was not statistically higher after adjustment, in contrast with the observations in acute coronary syndromes.5

Relative vs. absolute risk reduction

The impact of ticagrelor did not differ according to renal function in terms of relative risk reduction of ischaemic events or relative risk increase in TIMI major and minor bleeding. In terms of absolute risks, however, and compared with placebo, ticagrelor at the 60 mg b.i.d. dose (the dose with the best benefit:risk ratio) prevented more ischaemic events at the end of 3 years in patients with altered renal function (Table 1). But it also induced more TIMI major and minor bleeding. In terms of net clinical benefit, the difference between patients with and without renal insufficiency was only 0.5

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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events/100 person-years when combining ischaemic events with major bleeding and 0.1 events/100 person-years when combining ischaemic events with both major and minor bleeding.

Importantly, for a medication with the potential to be both beneficial and harmful, ticagrelor (60 mg b.i.d. dose) resulted in a (non-significant) relative decrease in all-cause mortality of a similar extent whatever the renal function.

**How do the PEGASUS results fit with already known data on platelet inhibition and renal function?**

Previous studies have analysed the interaction between oral antiplatelet agents and clinical events according to renal function (Table 2). In patients with acute coronary syndrome (ACS), there was no significant interaction between prasugrel and renal failure for the primary efficacy endpoint in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition (TRITON) trial.

The efficacy of prasugrel, however, was slightly less in patients with impaired renal function; the impact on bleeding was not reported. Similar observations were made in the Thrombin Receptor Antagonist for Clinical Event Reduction (TRACER) trial, which randomised ACS patients to vorapaxar or placebo. In stable patients in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, dual antiplatelet therapy with clopidogrel was associated with a slightly higher risk of ischaemic events in symptomatic patients with diabetic nephropathy defined by clinical history, while the risk was slightly decreased in diabetic patients without nephropathy, and more so in non-diabetic patients. The Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) severe bleeding was not significantly higher, whether the patients had diabetic nephropathy or not. In the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA2P) trial, which included patients from 2 weeks to 1 year after acute myocardial infarction, or when they had a history of stroke or peripheral artery disease, vorapaxar on top of single or dual antiplatelet therapy had a similar efficacy whatever the renal function; severe bleeding was increased with vorapaxar to the same extent in patients with or without renal dysfunction.

**Overall, what does the present analysis bring . . . and not**

The study confirms that patients with chronic renal failure are at increased cardiovascular risk, although even the best statistical techniques are unlikely to fully adjust for the major imbalances related to

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### Table 1

<table>
<thead>
<tr>
<th>Ischaemic events</th>
<th>Net benefit (ischaemic events + major bleeding)</th>
<th>Net benefit (ischaemic events + major and minor bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 60 $ ml/min/1.73 m²</td>
<td>2.60</td>
<td>1.08</td>
</tr>
<tr>
<td>$≥ 60 $ ml/min/1.73 m²</td>
<td>0.64</td>
<td>−0.46</td>
</tr>
<tr>
<td>Absolute additional gain at 3 years for patients with vs. without renal failure</td>
<td>2.04</td>
<td>1.54</td>
</tr>
</tbody>
</table>

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### Table 2

<table>
<thead>
<tr>
<th>Stable disease</th>
<th>CHARISMA* (clopidogrel)</th>
<th>TRA2P (vorapaxar)</th>
<th>PEGASUS (ticagrelor, 60 mg b.i.d.)</th>
<th>PEGASUS (ticagrelor, 90 mg b.i.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 60 $ ml/min/1.73 m²</td>
<td>1.14 (0.83–1.57)</td>
<td>0.89 (0.75–1.04)</td>
<td>0.82 (0.66–1.01)</td>
<td>0.83 (0.67–1.02)</td>
</tr>
<tr>
<td>$≥ 60 $ ml/min/1.73 m²</td>
<td>0.88 (0.77–1.10)</td>
<td>0.84 (0.76–0.93)</td>
<td>0.87 (0.75–1.00)</td>
<td>0.87 (0.75–1.00)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute coronary syndromes</th>
<th>TRITON** (prasugrel)</th>
<th>TRACER (vorapaxar)</th>
<th>PLATO (ticagrelor, 90 mg b.i.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 60 $ ml/min/1.73 m²</td>
<td>0.86 (0.66–1.25)</td>
<td>0.97 (0.80–1.17)</td>
<td>0.77 (0.65–0.90)</td>
</tr>
<tr>
<td>$≥ 60 $ ml/min/1.73 m²</td>
<td>0.80 (0.72–0.91)</td>
<td>0.94 (0.85–1.03)</td>
<td>0.90 (0.79–1.02)</td>
</tr>
</tbody>
</table>

*Figures for hazard ratios and 95% confidence intervals derived from Dasgupta et al.*8 (Figure 3). Comparison of patients with diabetic nephropathy vs. non-diabetics. Diabetic nephropathy defined from clinical criteria (creatinine clearance not available in the trial). CHARISMA did not include only coronary artery disease patients.

**Figures for 95% confidence intervals derived from Wiviott et al.*6 (Figure 2).
the huge difference in age according to renal dysfunction. It also confirms that there is no interaction between ticagrelor and renal function for the prevention of ischemic events, as the observed difference in hazard ratio according to renal function in PEGASUS is much smaller than what had been found in PLATO. Finally, it provides additional evidence of the lack of interaction between renal function and the effects of P2Y12 inhibitors and other antiplatelet agents such as vorapaxar.

However, the study does not answer the clinician’s question as to who are the patients with stable coronary artery disease likely to benefit most from prolonged dual antiplatelet therapy. If, from a public health standpoint, absolute risk reduction is the most important factor, from a physician’s standpoint, what should count most is the way a treatment reduces risk for his/her individual patient (i.e. relative risk reduction). In this regard, the data reported here are unlikely to change physicians’ approach to their patients.

The quest for the holy balance between benefit and risk for antithrombotic agents in patients with coronary artery disease has not yet ended.

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References