Viewpoint: Central adjudication of myocardial infarction in outcome-driven clinical trials – Common patterns in TRITON, RECORD, and PLATO?

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Summary
Central adjudication in randomised controlled outcome-driven trials represents a traditional approach to maintain data integrity by applying uniformed rules for assessment of clinical events. It was the purpose of this investigation to determine the patterns of myocardial infarction (MI) adjudication in the TRITON, RECORD, and PLATO trials. We were matching centrally-adjudicated MIs (CAMIs) from the official trial publication with the site-reported MI (SRMIs) count from the Food and Drug Administration's secondary analyses for the investigational compounds prasugrel (TRITON), rosiglitazone (RECORD), and ticagrelor (PLATO). CAMI numbers showed a remarkable discrepancy to SRMI's by more than a doubling of the difference: from 72 to 145 events in TRITON favoring prasugrel (from a hazard ratio [HR]=0.76, p=0.08; to a HR=0.76, p<0.001), and from 44 to 89 events in favour of ticagrelor in PLATO (from a HR=0.94, p=0.095; to a HR=0.84, p<0.001). In contrast, in the RECORD trial, the CAMI count was less than the SRMI count (from 24 to 8 events, from a HR=1.42, p=0.93; to a HR=1.14, p=0.96), in this case diminishing cardiovascular hazards in favour of rosiglitazone. In conclusion, central adjudication in the TRITON, the RECORD, and the PLATO trial turned out to have a critical impact on study outcomes. Trial publications should in the future include site-reported major efficacy and safety endpoints to preserve data integrity. The regulatory authorities should consider independent audits when there is a major disagreement between centrally adjudicated and site reported events influencing the results of a major clinical trial.

Keywords
Myocardial infarction, prasugrel, rosiglitazone, ticagrelor, clinical trials, event adjudication

Central adjudication of clinical events in randomised controlled trials is commonly used in multicentre international outcome-driven studies. Delegating such a critical mission to the central committee for final assessment of trial results counteracts a potential variability of definitions, contributes to comprehending and resolving complicated clinical scenarios, removes scientific “noise” and potential bias from the totality of evidence (1–3). However, whether or not the uniform use of central adjudication is always justified is not entirely clear. The clinical validity of event adjudication has been challenged since – as a rule of thumb – the adjudicated data usually match well with the investigator-reported event rates, but increase affiliated costs substantially (2, 4). In contrast to this general rule, recent analyses showed unexpected discrepancies between the number of site reported myocardial infarctions (SRMIs) and centrally adjudicated MIs (CAMIs) in three major trials with prasugrel (TRITON), rosiglitazone (RECORD), and ticagrelor (PLATO), respectively. Our current report wishes to set focus on these issues, including the undisputed integrity of central adjudication procedures. The summaries of the discussed trials are outlined below.

TRial to assess Improvement in Therapeutic Outcomes by optimising platelet InhibitioN with prasugrel (TRITON, TIMI-38) was a phase 3, randomised, double blind, parallel-group, multinational clinical study. On background therapy with aspirin in all patients, the trial assessed head-to-head the efficacy and safety of the thienopyridine prasugrel versus standard care with clopidogrel (5). Patients (n=13,608) with moderate to high-risk acute coronary syndromes and predefined coronary anatomy assessed by angiogram undergoing percutaneous coronary intervention (PCI) were randomised to prasugrel or clopidogrel, and followed for 6–15 months. The primary endpoint was the rate of cardiovascular death, nonfatal MI, or stroke, and was reached in 12.1% of patients treated with clopidogrel, and 9.9% of patients randomised to prasugrel (hazard ratio [HR]=0.81; confidence interval [CI]=0.73–0.90; p<0.001), indicative of a vascular outcome benefit of prasugrel over clopidogrel (5).

The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial randomised 4,474 type-2 diabetics to receive either rosiglitazone (on top of either metformin or sulfonylurea) or a metformin/sulfonylurea combination. The rate of cardiovascular hospitalisation or death from cardiovascular causes, the primary endpoint, was reached in 14.5% in both groups (HR=0.99; CI=0.85–1.16; p=0.93) over an average
of 5.5 years follow-up (6). There were no significant differences in individual rates of death, MI, or stroke. The non-significant 14% increased risk of MI in the rosiglitazone group was noteworthy, although the RECORD authors have pointed out that their trial was open-labelled, and not powered to show significant differences in the rate of MI on its own (6).

The PLATElet Inhibition and Clinical Outcomes (PLATO) trial was a phase 3, randomised, double blind, parallel-group, multinational clinical study, comparing the efficacy of ticagrelor versus standard care treatment with clopidogrel. Patients (n=18,624) with moderate to high-risk of acute coronary syndromes undergoing coronary intervention or medically managed were randomised to ticagrelor 180 mg loading dose followed by 90 mg twice daily, or clopidogrel 300–600 mg loading dose followed by 75 mg once daily, for up to 12 months (7). The primary endpoint was the time of the first event of death from vascular causes, MI, or stroke, and occurred in 11.7% of patients treated with clopidogrel, versus 9.8% of patients randomised to ticagrelor, representing a significant benefit (HR=0.84; CI=0.77–0.92; p<0.001) (7).

As it so happened, these initial optimistic interpretations of the published trial results were clouded by the Food and Drug Administration (FDA)’s Secondary Reviews for the TRITON (8), RECORD (9), and PLATO (10) trials. These independent data analyses revealed a major disagreement between CAMIs (5–7), and SRMIs (8–10). These differences and their impact on the overall trial results are summarised in Table 1.

The data in Table 1 indicate that there are disagreements between site-reported and centrally adjudicated MIs in these three major outcome-driven trials, which can potentially have impact on trial interpretation. Central adjudicating committees were primarily pre-planned for all three trials, and were not created per a Food and Drug Administration (FDA) suggestion due to unclear regulatory decision with regard to prasugrel and ticagrelor arm is 0.0000000000002. This will happen by

### Table 1: Differences in MI reporting and their impact on trial results.

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>MI-E/MI-C***</th>
<th>MI difference</th>
<th>HR</th>
<th>TRIAL p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-CAMI’s* [5]</td>
<td>475±620</td>
<td>145</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TRITON-SRMI’s** [8]</td>
<td>226±298</td>
<td>72</td>
<td>0.76</td>
<td>NS (0.08)</td>
</tr>
<tr>
<td>RECORD-CAMI’s [6]</td>
<td>64±56</td>
<td>8</td>
<td>1.14</td>
<td>NS (0.93)</td>
</tr>
<tr>
<td>RECORD-SRMI’s [9]</td>
<td>83±59</td>
<td>24</td>
<td>1.42</td>
<td>NS (0.96)</td>
</tr>
<tr>
<td>PLATO-CAMI’s [7]</td>
<td>504±593</td>
<td>89</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLATO-SRMI’s [10]</td>
<td>504±548</td>
<td>44</td>
<td>0.92</td>
<td>NS (0.095)</td>
</tr>
</tbody>
</table>

* CAMIs, centrally adjudicated MIs; ** SRMIs, site reported MIs; *** MIs in experimental versus control groups; E, experimental agent; HR, hazard ratio; NS, not significant.

Albeit adjudication committees are indisputably composed of some of the finest and most honorable cardiology experts in the world of science, it is difficult to deny that the results of adjudication – at least in these three examples – in fact formally favoured the study sponsors. This may lead to the bewildering thought that central adjudication – meant to assure quality control of outcome data – has actually contributed to failures of referred events, missed endpoints, and miscounting of “silent” MIs (9).

### Table 1 for de-
chance in 1 of > 5,000,000,000,000 trials (one in five trillion). This finding does not necessarily mean bias from the independent and experienced trial adjudicators, but rather indicates that the PLATO sponsor may have sent only cases from the clopidogrel arm for central adjudication, eliminating questionable ticagrelor CRFs.

Obviously, the discussed problem is not limited to the TRITON, RECORD, and PLATO trials. There may be other trials, like RE-LY (11) with the MI count controversy, although the detailed numbers and careful analyses in the frame of regulatory approval are lacking.

We are not proposing to defy central adjudication. If appropriately used, it represents an important tool, since that data delivered by study sites often are questionable. There were no discrepancies in death counts in all three discussed trials, although mortality numbers in PLATO completely mismatch non-fatal event rates. We sincerely hope that this paper will generate a continuation of a healthy debate (12–14) as an “illustrative case example” to emphasise the points on appropriate central adjudication procedures in modern clinical trials.

Taken together, central adjudication in the TRITON, RECORD, and PLATO trials turned out to provide a critical advantage to study outcome, which – intriguingly – in all three cases favoured the study sponsor. Importantly, different adjudication techniques have been applied in the three discussed studies. In fact, late change of MI definition, resulted in doubling the prasugrel advantage from 72 to 145 MIs in TRITON differs from realistic MI rates, but doubling the difference from site reported 44 MIs to 89 adjudicated MIs favouring ticagrelor in PLATO, both in turn differed from the “unnoticed” 16 MIs in RECORD. As a proposed improvement of clinical trial methodology quality and balanced presentation, trial publications ought to include site-reported major efficacy and safety endpoints, thus contributing to transparency and data integrity. The regulatory authorities should continue to demand independent audits when there is a major discrepancy between centrally adjudicated and site reported events influencing the overall results of a major clinical trial.

Acknowledgement
We wish to thank Dr. Morten Wang Fagerland (Oslo University, Norway) for expert advice on statistics.

Conflicts of interest
VLS is listed as an inventor, and received compensation for the U.S. Patent Application P-17232 “Method for treating vascular diseases with prasugrel” assigned to Lilly; and “Treating Cardiac Arrhythmias, heart failure, peripheral artery disease and stroke with CYCLOPENTYL-TRIAZOLO-PYRIMIDINE or derivative thereof” (USN 61/253,829) assigned to HeartDrug™ Research. He received funding for research studies with prasugrel, and clopidogrel, and consultant fees from the clopidogrel and ticagrelor manufacturers. DA has no disclosures.

This Viewpoint Article reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

References