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). 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
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 details. Similarly, the significant MI risk in rosiglitazone-treated patients, revealed by the RECORD FDA review (9), was initially diminished to be solely a trend when applying central adjudication (6). Importantly, central adjudication in these trials dominated the regulatory decision with regard to prasugrel and ticagrelor approval, since the FDA, for the final approval, – justly or not – put more value into adjudicated, rather than site-reported event count. One might ponder the question whether the lack of significant end-point efficacy based on SRMIs might have altered the regulatory approval process for both agents. Conversely, since the FDA reviewers were emphasising the controversy of MI adjudication in the RECORD trial (9), prescribing physicians became aware of affiliated rosiglitazone risks.

Second, central adjudicating committees applied three different strategies in MI reporting. This fact, by itself, is not surprising given the development in definition of MI over time. In TRITON, the MI definition has been switched to a more liberal one towards the trial end (8), raising the MI rate to an unprecedented 9.5% in the clopidogrel arm (5). These “extra” MIs were equally adjudicated to both arms, keeping the HR unchanged at 0.76. However, this change in procedure doubled the MI difference from 72 as reported by the TRITON investigators to 145 events (TRITON-CAMI’s* [5] 475/620 145 0.76 <0.001, Table 1). In PLATO, on the other hand, the MI definition was not changed, and the MI rate in both arms appears in line with what can be expected in the studied populations. However, similar to TRITON, the site-reported difference of 44 events was doubled to 89 counts by adjudicating extra 45 MIs exclusively to the clopidogrel arm. In other words: there was no impact of central adjudication in the ticagrelor PLATO arm when all vascular deaths, strokes, and all 504 MIs reported by sites were adjudicated. Finally, in the RECORD trial, the discrepancies between site reported and adjudicated events have been attributed to failures of referred events, missed endpoints, and miscounting of “silent” MIs (9).

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 what may be perceived as a problematic influence.

The statistical probability aspect can be further highlighted when scrutinising the PLATO computation: The proportion of SRMI in the ticagrelor arm was 504 out of 9,333 patients = 5.40%; while in the clopidogrel arm it was 548 MIs out of 9,291 patients = 5.90%. Thus, the event is (5.90–5.40)/5.40 = 9.26% more likely to occur in the clopidogrel arm. Of note, we do not consider time to event, only whether an event has occurred or not; that approximation will not make a noticeable difference on the calculations. Let us suppose that a blinded adjudication committee finds an undiagnosed MI; the probability that a single event belongs to the clopidogrel arm is 52.2% with the assumption that the CAMIs have the same distribution as the SRMIs. Since the committee has found 45 undiagnosed MIs, the probability that all of them belong to the clopidogrel arm is 0.000000000000002. This will happen by

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>MI-E/MI-C***</th>
<th>MI difference</th>
<th>HR</th>
<th>TRIAL p-value</th>
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<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>
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<tr>
<td>RECORD-CAMI’s [6]</td>
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<td>8</td>
<td>1.14</td>
<td>NS (0.93)</td>
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<tr>
<td>RECORD-SRMI’s [9]</td>
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<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.
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 “illuminating 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.

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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.

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