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ORIGINAL ARTICLE

Comparison of Investigator-Reported and Clinical Event Committee–Adjudicated Outcome Events in GLASSY

See Editorial by Dhruva

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BACKGROUND: Event adjudication by a clinical event committee (CEC) provides a standardized, independent outcome assessment. However, the added value of CEC to investigators reporting remains debated. GLASSY (GLOBAL LEADERS Adjudication Sub-Study) implemented, in a subset of the open-label, investigator-reported (IR) GLOBAL LEADERS trial, an independent adjudication process of reported and unreported potential outcome events (triggers). We describe metrics of GLASSY feasibility and efficiency, diagnostic accuracy of IR events, and their concordance with corresponding CEC-adjudicated events.

METHODS: We report the proportion of myocardial infarction, bleeding, stroke, and stent thrombosis triggers with sufficient evidence for assessment (feasibility) that were adjudicated as outcome events (efficiency), stratified by source (IR or non-IR). Using CEC-adjudicated events as criterion standard, we describe sensitivity, specificity, positive and negative predictive value, and global diagnostic accuracy of IR events. Using Gwet AC coefficient, we examine the concordance between IR- and corresponding CEC-adjudicated triggers. There was sufficient evidence for assessment for 2592 (98.3%) of 2636 triggers.

RESULTS: Overall, the adjudicated end point-to-trigger ratio was high and similar between IR- (88%) and non-IR–reported (87%) triggers. The global diagnostic accuracy and concordance between IR-reported and CEC-adjudicated outcome events was 0.70 (95% CI, 0.65–0.74) and 0.54 (95% CI, 0.45–0.62), respectively, for myocardial infarction; 0.77 (95% CI, 0.75–0.79) and 0.71 (95% CI, 0.68–0.74) for bleeding; 0.70 (95% CI, 0.62–0.79) and 0.59 (95% CI, 0.43–0.74) for stroke; 0.59 (95% CI, 0.52–0.66) and 0.39 (95% CI, 0.25–0.53) for stent thrombosis. For IR bleedings, the concordance with the CEC on type of events was generally weak.

CONCLUSIONS: Implementing CEC adjudication in a pragmatic open-label trial with IR events is feasible and efficient. Our findings of modest global diagnostic accuracy for IR events and generally weak concordance between investigators and CEC support the role for CEC adjudication in such settings.

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WHAT IS KNOWN

- GLASSY (GLOBAL LEADERS Adjudication Sub-Study) prospectively implemented, in a large sample of patients enrolled in the top 20 recruiting sites within the GLOBAL LEADERS trial (7585 of 15991; 47.5%), an independent adjudication process of reported and unreported potential outcome events, using standardized clinical event committee procedures.
- Nonfatal events reported by the investigators, such as myocardial infarction, stent thrombosis, stroke, or bleeding, especially if specific definitions are required by the protocol, are known to be suboptimal in large pragmatic trials.

WHAT THE STUDY ADDS

- Introducing independent, blinded clinical event committee–adjudication processes into a pragmatic, open-label trial appears feasible and efficient.
- The concordance between outcome events reported by the sites and those centrally adjudicated is low particularly for subtype of events. Almost 1 every 5 adjudicated outcome events was identified only via clinical event committee procedures and not reported by the investigators.
- Considering the feasibility, efficiency, and generally high discordance with investigators, the adoption of clinical event committee is highly desirable in pragmatic randomized clinical trials.

The main purpose of a randomized controlled trial is to obtain a valid estimate of the effect of an intervention on a study outcome. For some outcomes, such as all-cause death, no adjudication is typically necessary. However, for secondary outcomes, such as mode of death, or subtype of nonfatal events, such as the type of myocardial infarction (MI) that may be not reliably collected in the absence of standardized definitions and conventions, adjudication by an independent clinical event committee (CEC) may provide a uniform and accurate assessment of reported events, particularly for study with an open-label design. The importance of standardized adjudication may be particularly relevant to the design of pragmatic clinical trials, designed to address research questions that reflect patient care in a real-world setting. These studies may facilitate operations by optimizing efficiency and reducing costs, but they typically measure only investigator-reported (IR) outcome. An example was the GLOBAL LEADERS trial, designed by a consortium of academic investigators to investigate a new treatment paradigm in patients undergoing percutaneous coronary intervention based on early aspirin discontinuation and continuation of potent $P2Y_{12}$ inhibitor monotherapy compared with the standard of care consisting of 12-month of dual antiplatelet therapy followed by aspirin monotherapy.[1] GLOBAL LEADERS was designed as an open-label superiority trial with all study-defined outcome events (apart from Q-wave MI) being IR and not subject to formal adjudication by an independent CEC, a decision with the potential to introduce detection, reporting, or ascertainment bias.[2]

We, therefore, designed GLASSY (GLOBAL LEADERS Adjudication Sub-Study) to prospectively implement, in a sample of the GLOBAL LEADERS trial (7585 of 15991 patients; 47.5%), an independent adjudication process, using standardized CEC procedures, of reported and unreported potential outcome events.[3,4] In the evolving landscape of randomized clinical trials,[5] GLASSY provides a unique opportunity to examine key attributes of CEC processes in the context of a pragmatic randomized clinical trial designed to have only IR outcome events. We thus conducted the present analysis to describe feasibility, operational efficiency, accuracy of potential outcome events (trigger) identification and adjudication in GLASSY, concordance between IR- and CEC-adjudicated triggers, and reliability of IR outcome to estimate randomized treatment effects. Finally, we reflect on the potential advantages provided by systematic CEC processes within a pragmatic, open-label, randomized controlled trial.

METHODS

The data that support the findings of this study will be made available by the corresponding author upon reasonable request. GLASSY has been approved by the local ethics committee of all study sites or by the central ethics committee for the country depending on country-specific regulations. In all cases, they deemed that it was not necessary to obtain further informed consent from individual subjects.

Site Selection

There was no a priori attempt to select a patient population in GLASSY perfectly representative of the whole population included in the parent study as that would have required random selection of the sample ideally at the patient level or at least at the site level. This was financially unsustainable for an investigator-initiated study. A total of 7585 patients from the top 20 recruiting sites, representing 47.5% of the GLOBAL LEADERS study population of 15991 patients, were included in GLASSY. In GLOBAL LEADERS, the randomization was stratified by site. Therefore, the estimation of treatment effects in GLASSY is expected to be valid.

Trigger Definition and Strategies to Identify Outcome Events

A trigger is any potential study outcome event that undergoes evaluation by CEC. In GLASSY, triggers included all IR potential outcome events, that is, death, MI, stroke, bleeding, stent thrombosis (ST), and coronary revascularization, as well as potential outcome events (non-IR) not reported by

the investigators. We comprehensively searched for the latter using predefined case report form-based algorithms. The detailed search criteria, logics, and wording used are listed in Methods in the Data Supplement (trigger specifications). Before CEC adjudication, all possible non-IR outcome events were initially screened by a cardiologist (the study coordinator). If there was clear evidence that the non-IR–suspected event could not qualify as an outcome event based on the CRF narrative review, this was not presented to the CEC. All remaining non-IR events considered as triggers were submitted for CEC evaluation. Triggers could also be identified manually by the CEC members (X.M trigger; Methods in the Data Supplement) during event adjudication.

CEC Procedures

To conform with best adjudication practice, the CEC dataset was locked before the termination of the parent GLOBAL LEADERS study. Steps were taken to ensure the CECs were unaware of treatment assignment as described in the design paper, that is, CEC was blinded to randomization.[3] The CEC consisted of 3 independent voting members. All events were reviewed independently by 2 members. In case of disagreement, the event was reviewed by all 3 members, and if no consensus was achieved after discussion, a vote was taken. The site investigators and the CEC used identical event definitions. These definitions were presented in the protocol, at investigator meetings, and training was given at the site initiation visit for study personnel. This training specifically included (1) a detailed overview of outcome definitions, (2) criteria for outcome reporting in the CRF, and (3) remote assistance via a dedicated hotline.

Definition of Sufficient Evidence for End Point Adjudication

To examine the feasibility of GLASSY, we describe, for each of the outcome event types analyzed, the proportion of triggers with sufficient evidence for adjudication. While death was adjudicated as an outcome event in all cases, even if there was no information (unknown death), nonfatal outcome events required a minimum amount of evidence for formal assessment.[6] Evidence for CEC adjudication was deemed sufficient if included at a minimum a narrative description with pertinent medical documentation; these typically included ECG and cardiac biomarkers for MI, an angiographic report for ST, and urgent revascularization; brain imaging for stroke; and laboratory values for bleeding. In case of CRF-only narrative, the evidence was considered insufficient and the case was not adjudicated by the CEC.[3]

Statistical Analysis

For the present analysis, we focused on triggers for 4 potential outcome events: MI, bleeding, stroke, and ST, where identical definitions were used by investigators and the CEC. Urgent target vessel revascularization was only CEC-adjudicated, and its definition differed from the closest corresponding IR end point (ie, coronary revascularization). Therefore, it was analyzed for feasibility (ie, percentage of events with sufficient evidence) but not as part of the concordance analyses.

For each of the four trigger types, we report the proportion of events with sufficient evidence for adjudication and the proportion of triggers that were adjudicated as outcome events stratified by source (IR versus non-IR). Finally, we report sensitivity, specificity, positive and negative predictive values, as well as global diagnostic accuracy (95% CI) of IR outcome events using CEC-adjudicated data as the gold standard. Treatment effects for each type of event were estimated using rate ratios at 2 years with corresponding 95% CIs. The interaction between IR-reported and CEC adjudication was calculated through a generalized linear model using the link function for the binomial distribution. All analyses were performed at CTU Bern using Stata, version 16.0 (StatCorp, College Station, TX).

Concordance between IR triggers and corresponding CEC-adjudicated events was evaluated. For bleeding triggers, the most commonly reported outcome event in GLASSY, we also assessed concordance on the Bleeding Academic Research Consortium (BARC) type of event. We used a Gwet AC with exact binomial 95% CIs as a measurement of the extent of agreement beyond chance alone. The choice of the Gwet AC allows to overcome the statistical problems associated to the Cohen κ, in terms of prevalence and marginal probability. In fact, the Cohen κ is sensitive when the prevalence is not high, and the results are not consistent with the percentage of agreement, while the Gwet AC appears not to be influenced by this low prevalence. Consequently, the latter method is expected to give more robust and coherent results.[7]

Similar to what has been proposed for Cohen κ,[8] we interpreted concordance between IR and CEC outcome events as follows:

1. 0 to 0.20: none
2. 0.21 to 0.39: minimal
3. 0.40 to 0.59: weak
4. 0.60 to 0.79: moderate
5. 0.80 to 0.90: strong
6. >0.90: almost perfect

RESULTS

Overall, 2636 triggers were identified: 405 (15.4%) were for MI, 1721 (65.3%) for bleeding, 199 (7.5%) for ST, 114 (4.3%) for stroke, and 197 (7.5%) for urgent target vessel revascularization. A total of 2592 (98.3%) triggers had sufficient evidence and underwent formal adjudication. The proportion of triggers with sufficient evidence was >98% for all potential outcome events. The exception was MI (92.3%) mainly due to the absence of cardiac biomarkers (Table 1).

The overall proportion of triggers that were eventually adjudicated as outcome events was 87.9% (1726 of 1963) for those reported by the investigators (IR triggers) and 87.2% (377 of 432) for those not reported by the investigators (non-IR triggers). Among the IR triggers, ST was confirmed by the CEC only in 75.2% of cases, whereas for the other types of events, confirmation by CEC was higher. Among the non-IR trig-

Table 1. Proportion of Triggers Stratified by Type With Evidence That Was Considered Sufficient to Be Adjudicated by the Clinical Event Committee

Event type	
MI	374/405 (92.3%)
Bleeding	1712/1721 (99.5%)
Stroke	112/114 (98.2%)
ST	197/199 (99.0%)
Urgent TVR	197/197 (100%)

ST indicates stent thrombosis; and TVR, target vessel revascularization.

gers, the lowest proportion of triggers adjudicated as outcome events was observed for MI (65.1%). Overall, there were 2103 confirmed outcome events (87.8% of the total triggers), 1726 (82%) IR, and 377 (18%) CEC-identified. Most (260 of 377 or 69%) CEC-identified outcome events were bleedings (Table I in the Data Supplement).

Diagnostic Accuracy of IR Events

The diagnostic accuracy of IR events by event type is reported in Figure 1, Table 2, and Table II in the Data Supplement. In general, the specificity and negative predictive values were low to very low for all event types, resulting in a global diagnostic accuracy measured by percentage agreement (95% CIs) that was 0.70 (0.65–0.74) for MI, 0.77 (0.75–0.79) for bleeding, 0.70 (0.62–0.79) for stroke, and 0.59 (0.52–0.66) for ST.

Trigger-Level Concordance Analysis and Treatment Effect Estimation

The trigger-level concordance analysis by type of event is presented in Figure 2. It was 0.53 (95% CI, 0.44–0.62) for MI, 0.70 (95% CI, 0.67–0.74) for bleeding, 0.58 (95% CI, 0.434–0.738) for stroke, and 0.38 (95% CI, 0.24–0.52) for ST. Within IR bleedings, the concordance between investigators and CEC on BARC classification (type 1–5) was generally weak (Table 3).

The estimation of treatment effect by event type is presented in Figure 3. In general, the direction between IR- and CEC-adjudicated outcome events of the treatment effects did not differ, with point estimates favoring the experimental strategy for MI and ST without any significant interaction.

DISCUSSION

In the present study, we observed that (1) a systematic CEC adjudication process within a pragmatic RCT is feasible, as measured by the proportion of potential events that could be assessed for adjudication; (2) the proportion of confirmed outcome events is high and similar between triggers reported and unreported by the investigators; (3) the global diagnostic accuracy of IR events is suboptimal, mostly due to a low specificity/negative predictive values as compared with CEC-adjudicated outcome events; (4) the event-level concordance between IR and CEC-adjudicated events is

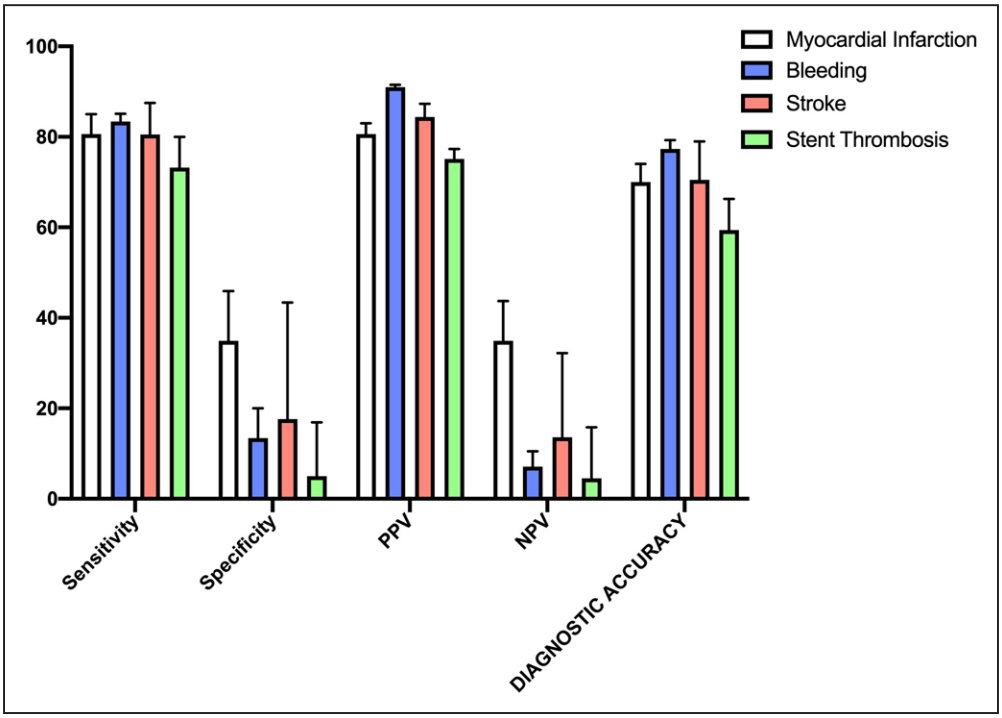

Figure 1. Diagnostic logic metrics of investigator-reported events.
NPV indicates negative predictive value; and PPV, positive predictive value.

Table 2. Comparison of IR With CEC-Adjudicated MI, Bleeding

	CEC adjudicated (criterion standard)		Total events
IR-MI	Yes	No	
Yes	232	56	288
No	56	30	86
Total	288	86	374
IR-bleeding	Yes	No	
Yes	1303	129	1432
No	260	20	280
TOT	1563	149	1712
IR-stroke	Yes	No	
Yes	76	14	90
No	19	3	22
TOT	95	17	112
IR-ST	Yes	No	
Yes	115	38	153
No	42	2	44
TOT	157	40	197

CEC indicates clinical event committee; IR, investigator reported; MI, myocardial infarction; and ST, stent thrombosis.

generally weak, particularly for ST, and it is weak for the type of bleeding events.

These findings may have relevant implications to inform the design of future pragmatic RCTs, especially considering that GLASSY was the first of its kind investigation that assessed the added value of CEC adjudication processes within a pragmatic RCT that was originally designed not to rely on CEC-adjudicated outcome events.

Feasibility, Efficiency, and Impact on Event Rate of CEC Processes

While all-cause death is always included as an end point irrespective of the ascertainment of a presumed cause, nonfatal outcome events require a minimum amount of evidence to be confirmed. For this reason, in GLASSY, we distinguished between events that do not meet the end point definition due to the lack of the required data elements (unknown events) from those that were adjudicated as negative (NO events) as a measure of study feasibility. We observed that, with the exception of MI, the vast majority of triggers (>98%) could be assessed for adjudication, indicating excellent feasibility. The lack of cardiac biomarkers was the primary reason for not being able to adjudicate a potential MI event, but overall, this affected <8% of potential MIs indicating that, even for this end point, the proportion of unknown events (and the corresponding uncertainty around its estimate) was modest.[9]

We also observed that the proportion of triggers that were confirmed as events (end point-to-trigger ratio) was high and similar between triggers reported and

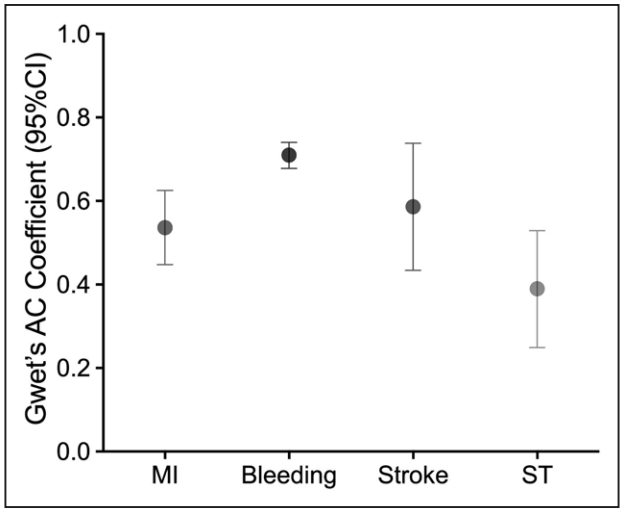

Figure 2. GLASSY (GLOBAL LEADERS Adjudication Sub-Study) agreement rate for myocardial infarction (MI), bleeding, stroke, and stent thrombosis (ST) between investigators and the clinical event committee.
The intensity of the color of the point estimate and corresponding 95% CI of the error bars is proportional to the value of point estimate.

unreported by the investigators indicating that a CRF-based strategy validated by a dedicated cardiologist is efficient in identifying triggers with high likelihood of being later confirmed as outcome events.

Notably, almost 1 in 5 of the outcome events included in GLASSY (377 of 2103 events; 18% of the total) were not reported by the investigators with 2 of 3 of these unreported event being bleedings. These data indicate that the potential underreporting of outcome events by investigator only could be substantial and this difference that may have implications not only for the accuracy of the event rate estimates but also for the accurate assessment of treatment effect.

Diagnostic Accuracy of IR Events and Concordance Between Investigators and the CEC

Using CEC-adjudicated outcome events as criterion standard, we observed that the diagnostic accuracy of the IR events analyzed was between 59% and 77%. These suboptimal values were mostly related to low true negative end point rates and corresponding negative predictive values, indicating that there is generally low confidence on the absence of confirmed outcome events when these are not reported by the investigators.

The trigger-level concordance analysis between IR and corresponding CEC-adjudicated events was moderate for bleeding, weak for MI and stroke, and minimal for ST. The lack of concordance on bleeding and ST has been already observed,[10] may have potential implications for the accurate assessment of treatment effects, and may be related to several factors including the complexity of the event definitions (and the relative

Table 3. Agreement Rate on BARC Type of Investigator-Reported Bleedings

Total	Percentage confirmed by CEC	Agreement rate
BARC 1 (n=778)	75% (n=586)	Weak (0.41)
BARC 2 (n=459)	76% (n=301)	None (0.10)
BARC 3 (n=163)	72% (n=118)	Weak (0.43)
BARC 4 (n=6)	33% (n=2)	None (0.16)
BARC 5 (n=26)	65% (n=17)	Moderate (0.60)

BARC indicates Bleeding Academic Research Consortium; and CEC, clinical event committee.

novelty of some classification used such as the BARC) and the medical qualifications of the study staff entering the data in the CRF. Notably, as GLASSY was conducted in the top recruiting sites of GLOBAL LEADERS, it is possible that the concordance between CEC and investigators in smaller sites may be even lower.

Finally, we observed that the concordance between IR and CEC bleeding according to the BARC classification, with the exception of fatal bleeding events, was extremely poor. This may have major implications for the use of composite outcome events. Major bleeding events, usually defined as BARC type 3 or 5, sometimes also including BARC type 2 bleeding,[11] are the most common safety end point in cardiovascular RCTs testing antithrombotic strategies. The lack of concordance between investigators and CEC indicates that adjudication should be always considered when bleeding is included as safety outcome events.

Potential Implications for Pragmatic Clinical Trial Design

Pragmatism—an established concept in clinical research—aims at enhancing generalizability rather than internal validity of a study result and promotes clinical or policy decision-making by providing evidence for the use of an intervention into real-world clinical practice.[12–14]

Therefore, pragmatic clinical trials are intended to determine the effectiveness of an intervention in broad populations representative of the disease of interest with minimal exclusion criteria while explanatory clinical trials are designed to determine its efficacy under ideal conditions, usually in a highly selected population. These pragmatic trials are thus essential to complement earlier phase studies designed to explore the efficacy of a given intervention.

To quantify the pragmatism of a clinical trial, tools have been proposed to examine whether key dimensions of a study, such as eligibility, recruitment, and primary outcome, are directly related and relevant to usual care.[15] Importantly, the role of independent end point adjudication in this context is a quality rather than a pragmatic issue. If the quality and consistency of end point ascertainment can be improved by adjudication without affecting routine patient care, CECs are highly desirable.[16]

In pragmatic studies, such as the GLOBAL LEADERS, the use of IR outcome has been advocated, mostly for operational efficiency and cost minimization. A pragmatic trial of management strategies in patients with chronic obstructive pulmonary disease in clinical practice used data from an established electronic health record system for both effectiveness and safety monitoring with no formal adjudication.[17] The study documented a reduction of the primary outcome of moderate or severe exacerbations in the interventional group by 8.4% ([95% CI, 1.1–15.2] *P*=0.02) but with an unexpected ≈50% increase in total mortality, with a limited possibility of further analyses[18] lacking standardization

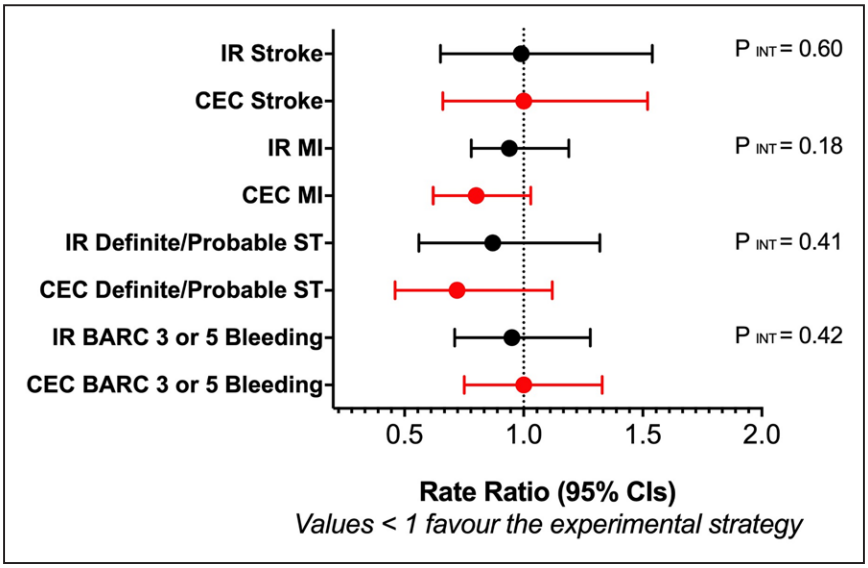

Figure 3. Estimates of randomized treatment effect on outcome event components in GLASSY (GLOBAL LEADERS Adjudication Sub-Study).
BARC indicates Bleeding Academic Research Consortium; CEC, clinical event committee; IR, investigator reported; MI, myocardial infarction; and ST, stent thrombosis.

on the attribution of mode of death. Guimaraes et al[19] compared the 1-year cumulative event rates when events were identified by medical claims as compared with physician adjudication. The accuracy of bill-identified events using physician adjudication as the criterion standard was also assessed. They found that event rates at 1 year were lower for MI, stroke, and bleeding when medical claims were used to identify events than when adjudicated by physicians. They concluded that medical claims diagnoses were only modestly accurate in identifying MI and stroke admissions and also had limited accuracy for bleeding events and suggested that an alternative approach may be needed to ensure good safety surveillance in cardiovascular studies.

Registry-based randomized trials, one of the most innovative pragmatic clinical trials, are emerging as a potentially disruptive approach owing to their ability to address clinically relevant questions in large representative patient populations at limited cost. These studies, arguably one of the best example of pragmatic clinical trials, are now promoted as paradigm for collection of structured clinical data in Sweden.[20] Recent Swedish guidelines on these studies not only promoted the use of CEC as optimal practice for end point reporting but also identified pathways for continuous reporting of source documentation to facilitate prompt adjudication of study data.[20]

Limitations

By GLOBAL LEADERS design (ie, IR-only study), the systematic identification of potential outcome events in GLASSY is limited by the eCRF and relies on source documentation provided by the site, including cardiac biomarkers to adjudicate MI, which reduces the ability to identify all possible potential outcome events. Also, the present study was designed after the initiation of the parent trial but before the completion of 2-year follow-up. Therefore, part of the source documentation was collected after the patients had completed the study follow-up. Finally, to be financially sustainable, GLASSY was conducted in the subgroup of the highest enrolling sites rather than the entire parent study. This may bias the study toward the null hypothesis of no difference between IR- and CEC-adjudicated end points although the relatively large study sample (≈50% of the parent study) makes this possibility less likely.

Conclusions

Systematic implementation of CEC adjudication processes within a pragmatic randomized controlled trial is feasible and efficient. Considering the modest global diagnostic accuracy of events reported by the investigators and the generally weak concordance of investigators with CEC, CEC adjudication should be routinely implemented to provide a standardized and independent assessment of the effects of new treatments.

ARTICLE INFORMATION

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Supplemental Material

Methods
Tables I and II

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