BMJ Open

Rationale and Design of the GLOBAL LEADERS Adjudication Sub-StudY – GLASSY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026053
Article Type:	Protocol
Date Submitted by the Author:	19-Aug-2018
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Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

Rationale and Design of the GLOBAL LEADERS Adjudication Sub-StudY – GLASSY

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Abstract (274 of 300 words)

Introduction: The GLOBAL LEADERS is an open-label, pragmatic and superiority randomized controlled trial designed to challenge the current treatment paradigm of dual antiplatelet therapy (DAPT) for 12 months followed by aspirin monotherapy among patients undergoing percutaneous coronary intervention (PCI). By design, all study endpoints are investigator-reported (IR) and not subject to formal adjudication by an independent Clinical Event Committee (CEC), which may introduce detection, reporting, or ascertainment bias.

Methods and Analysis: We designed the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) to prospectively implement, in a large sample of patients enrolled within the GLOBAL LEADERS trial (7,601 of 15,991, 47.5%), an independent adjudication process of reported and unreported potential endpoints, using standardized CEC procedures, in order to assess whether 23-month ticagrelor monotherapy (90 mg BID) after 1-month DAPT is non-inferior to a standard regimen of DAPT for 12 months followed by aspirin monotherapy for the primary efficacy endpoint of death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization, and superior for the primary safety endpoint of type 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria.

This study will comprehensively assess the comparative safety and efficacy of the two tested antithrombotic strategies on CEC-adjudicated ischemic and bleeding endpoints and will provide insights into the role of a standardized CEC adjudication process on the interpretation of study findings by quantifying the level of concordance between IR-reported and CEC-adjudicated events.

Ethics and Dissemination: GLASSY is designed to complement the interpretation of the results of the GLOBAL LEADERS trial on a CEC-adjudicated broad range of non-fatal ischemic and bleeding endpoints, and, ultimately, test the value of standardized CEC processes within a pragmatic study design.

Clinical trial registration information: NCT01813435. Accessed at https://www.clinicaltrials.gov/ on March, 6th 2018.

Strengths and limitations of this study

- GLASSY is a comprehensive, rigorous, and standardized assessment of several non-fatal endpoints in a representative sample of the GLOBAL LEADERS trial performed according to best practices of adjudication.
- An intrinsic limitation is that GLOBAL LEADERS has been designed as an IR-only study. Therefore, systematic identification of study endpoints is limited by the eCRF and relies on source documentation provided by the site, which reduces the ability to identify all possible potential endpoints.
- For feasibility, GLASSY will be conducted in a sample rather than the entire parent study, which may bias the study toward the null hypothesis of no difference between IR- and CEC-adjudicated endpoint by selecting best enrolling sites. While this bias is possible, the relatively large study sample (≈ 50% of the parent study) makes this possibility unlikely.

Rationale

The prolonged combination of aspirin and a $P2Y_{12}$ receptor inhibitor, typically for 12 months, represents the established antiplatelet therapy in patients with or without acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting stent implantation.[1] Clopidogrel, an inconsistent $P2Y_{12}$ receptor inhibitor [2] with considerable variability in inter-patient response, [3] proved inferior to stronger and more consistent $P2Y_{12}$ inhibitors, such as ticagrelor, in preventing ischemic and thrombotic cardiovascular events among patients with ACS.[4] With the introduction and widespread adoption in clinical practice of more potent $P2Y_{12}$ inhibitors, it has been hypothesized that the addition of aspirin may yield little additional inhibition of platelet aggregation and marginal incremental clinical benefit compared with a strategy based on potent $P2Y_{12}$ receptor inhibitor-monotherapy.[5,6] This led to the hypothesis that ticagrelor monotherapy may have similar efficacy compared with the combination of aspirin and ticagrelor and be better tolerated.

The GLOBAL LEADERS trial was designed to challenge the current treatment paradigm consisting of 12-month dual antiplatelet therapy (DAPT; clopidogrel+aspirin among patients with stable CAD; ticagrelor+aspirin among patients with ACS) followed by aspirin monotherapy in patients undergoing PCI based on the superiority for the composite endpoint of all-cause death or Q-wave myocardial infarction (MI) assessed at 2 years.[7] It is an open-label, randomized comparison testing an innovative antithrombotic regimen of 23-month ticagrelor 90 mg twice daily monotherapy after 1-month DAPT (ticagrelor 90 mg twice daily plus low-dose aspirin) against conventional 12-month DAPT in all-comer patients undergoing PCI with bivalirudin-supported, biolimus-eluting stent implantation. The GLOBAL LEADERS is a pragmatic clinical trial and, by design, all study endpoints are investigator-reported (IR) and therefore not adjudicated by an independent Clinical Event Committee (CEC). Only new Q-wave MI will be identified by independent core lab assessment and validated by a physician blinded to treatment allocation. All other endpoints, including specific causes of mortality, non-Q wave MI, stroke, stent thrombosis, and bleeding will be analyzed as reported by the local investigators.

Although the use of IR endpoints in a phase III randomized trial is a simple and less expensive alternative, their sole use has potential to introduce detection, reporting, or ascertainment bias, especially in the absence of blinding to randomized treatment (i.e. in an open-label design as in the case of the GLOBAL LEADERS trial). This might challenge the interpretation of the GLOBAL LEADERS study results, especially as it relates to the effect of the randomly allocated treatment on non-fatal clinical endpoints. Moreover, the design of GLOBAL LEADERS also raises important questions regarding bleeding adverse events that may differ between groups.

We, therefore, designed the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) with the aim to prospectively implement, in a representative sample of patients enrolled within the GLOBAL LEADERS trial, an independent adjudication process of reported as well as unreported potential endpoints, leveraging on standardized CEC procedures. This GLASSY substudy is powered to test whether 23-month ticagrelor monotherapy after a short course of DAPT for 1 month is non-inferior to conventional 12-month DAPT followed by aspirin monotherapy with respect to CEC-adjudicated

death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization (TVR) and superior in preventing CEC-adjudicated major bleeding. Furthermore, GLASSY will evaluate the implications of the CEC adjudication process for the interpretation of study results by quantifying the level of concordance between IR-reported and CEC-adjudicated events and will define the role of CEC adjudication process for the assessment of the efficacy and safety of the randomized antithrombotic strategies on a broader set of fatal and non-fatal clinical endpoints.

Design

Parent Study

The GLOBAL LEADERS study is a superiority, open-label, multicenter, randomized controlled trial in an all-comer population of patients, presenting with ACS or stable coronary artery disease, undergoing PCI with the uniform use of Biolimus A9-eluting stents (BioMatrix™ BES; Biosensors Europe SA, Morges, Switzerland) and receiving bivalirudin at the time of the index procedure (**Figure 1**). A total of 15,991 patients have been randomly assigned 1:1 to ticagrelor 90 mg twice daily for 24 months plus aspirin ≤100 mg daily for 1 month (experimental arm) or standard DAPT with either ticagrelor, in case of ACS, or clopidogrel, in case of stable coronary artery disease, for 12 months plus aspirin ≤100 mg daily for 24 months (control arm). All study endpoints are investigator-reported with randomization stratified by enrolling site as well as clinical presentation. The primary endpoint of the GLOBAL LEADERS is the composite of all-cause death or new Q-wave myocardial infarction at 24 months. The presence and date of new Q wave MI will be identified by an independent ECG core laboratory and validated by a single physician blinded to treatment allocation using adverse events reported in the eCRF supplemented, if required, by additional source documents. The key safety endpoint is investigator-reported class 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) definitions. Other secondary endpoints include stroke, MI, coronary revascularization, and definite stent thrombosis. As pragmatic trial, GLOBAL LEADERS implemented a risk-based monitoring process for site-based

operational activities favoring centralized remote monitoring rather than in-person on-site monitoring. GLOBAL LEADERS terminated enrollment on November, 9th 2015.

Objectives

The primary objective of the GLASSY is to assess, in a representative subgroup of patients enrolled within the GLOBAL LEADERS study, whether 23-month ticagrelor monotherapy after a short course of DAPT (1 month) is non-inferior to conventional 12-month DAPT followed by aspirin monotherapy for the composite endpoint of CEC-adjudicated all-cause death, non-fatal MI, non-fatal stroke, or urgent TVR, and superior in preventing CEC-adjudicated major bleeding (BARC type 3 and 5) in an all-comers population undergoing PCI at 24 months (**Figure 2**). A secondary objective is to quantify the level of concordance between IR- and CEC-adjudicated endpoints.

Endpoints

GLASSY will have two independent, CEC-adjudicated, co-primary endpoints at 24 months:

1) The composite of death, non-fatal MI, non-fatal stroke, or urgent TVR (co-primary efficacy endpoint);
2) The composite of BARC type 3 or 5 bleeding (co-primary safety endpoint).

Secondary endpoints will include:

- Each component of the co-primary composite endpoints;
- Definite, probable or possible stent thrombosis according to ARC classification;
- Bleeding events according to BARC, TIMI and GUSTO classifications;
- Type of death (cardiovascular vs. non-cardiovascular and subtypes).

Clinical Event Committee Procedures

According to best adjudication practice,[8] GLASSY is being conducted according to the following features:

1. **Prospective approach to adjudication**. The CEC dataset will be locked before the termination of the parent study. Suspected events (triggers) will be assessed during the conduct of the study rather than adjudicating all cases after the study is completed and the primary results are available (i.e. retrospective adjudication). In case of updated entry of

suspected events or updated source documentation by the site after request by the CEC team of source documentation, events will be re-evaluated for adjudication.

2. **Blinding of randomized treatment allocation**. According to the PROBE methodology,[9,10] the CEC will be blinded to randomized treatment allocation. Several steps will be undertaken to ensure that the CEC personnel and physicians remain blinded.

First, any reference to treatment assignment contained in the eCRF or source documents that could lead to un-blinding of treatment assignment will be obliterated by using a black marker by the site prior to submission to the CEC physician members.

Second, the CEC coordinator and operation personnel will obliterate any reference to study drug assignment prior to distribution to the physicians if information is noted during the preparation of the event packet.

Third, if a reviewer notes the treatment assignment during the review of a particular event, the CEC coordinator is notified, and the event is sent for review by the third expert reviewer.

3. **Triggering and adjudication of investigator- as well as non-investigator reported events**.

All IR-events (death, MI, stroke, bleeding, coronary revascularization, and stent thrombosis) will be adjudicated by the CEC through dedicated CRFs (online Appendix). We will also use comprehensive search strategies for potential cardiovascular events that are not reported by the investigator via eCRF dedicated queries. Indeed, it may happen that patients without IR-events or triggers may have experienced an event qualifying for the endpoints of the GLASSY study. [10]

It is possible that the request of source documentation may trigger endpoint reporting (and bias the study toward the null hypothesis). To quantify this, IR endpoints entered after CEC requested source documentation will be monitored and reported.

4. **Independent voting processes** by CEC members with at least 3 CEC members (see Appendix A) with knowledge of the geographic variations of care represented in the trial.

Each event will be reviewed independently by at least two CEC physicians. In case of disagreement, the event will be reviewed by a Committee of at least 3 reviewers with independent vote.

5. **Independence from parent study**.

To maximize the scientific integrity of GLASSY, CEC personnel will operate independently from the data management group of the parent study, including no cross talk on trigger logic specifications, query processes for source documentation, and most importantly event reporting and adjudication results.

6. **Quantification of sufficient evidence for adjudication of non-fatal triggers** (NO versus UNKNOWN events).

Finally, we will quantify the minimum amount of evidence required for the assessment of non-fatal endpoints. In a randomized trial, a pre-requisite to assess whether a suspected non-fatal endpoint has occurred or not is the availability of sufficient evidence for such an assessment, including relevant source documents, tests, and/or laboratory exams. While this is commonly performed for fatal events (death is adjudicated as “unknown” in case of no or insufficient description of death circumstances), it is not generally mandatory for non-fatal events.

In GLASSY, for each non-fatal trigger examined an assessment will be performed as to whether enough information is available for formal adjudication. This will allow distinguishing triggers that did not meet the endpoint definition (i.e. no event with sufficient documentation present) from triggers for which this is unknown due to insufficient documentation. For each type of non-fatal endpoint, the proportion of events with insufficient evidence will indirectly estimate a) the feasibility of GLASSY b) the quality of endpoint reported by sites and c) the uncertainty of the evidence related to the studied outcome.

Sufficient evidence for CEC adjudication includes at a minimum a narrative description with at least one pertinent medical documentation, including ECG/biomarkers for MI; angiographic report for stent thrombosis and urgent revascularization; brain imaging for stroke; and labs and other appropriate testing for bleeding. In case of CRF-

only narrative, the evidence will be considered insufficient and the case will not undergo CEC adjudication.

7. Quality control of the adjudication process

To ensure the highest reproducibility, a random sample of ≈ 5% of adjudicated events will be re-reviewed by the complete CEC committee (ie 3 member) who are blinded to the initial results.

A major disagreement will be considered if there was a disagreement on whether an event had occurred or not while a minor disagreement is any discordance on the remaining adjudicated fields. Major disagreement will be reported as part of the final study report and will be used to identify the presence of systematic problems in the adjudication process.

CEC Operations

Within the selected study patients, all IR-events as well as additional potential events (triggers) identified through a systematic analysis of the eCRF form will be considered for CEC adjudication. Non-IR triggers will be assessed after all the relevant source documentation has been requested to and provided by the participating sites and will be identified using a comprehensive search strategy that consider key words logically related to the event. In general, key words with a clear relationship to the endpoint of interest (e.g. for MI: unstable angina or ischemic heart disease) will trigger a formal CEC review, whereas keywords with a potential relationship (e.g. for MI: asystole, cardiac tamponade, hypertensive crisis) will trigger a review by a physician (independent from the CEC members) (**Appendix**). In the latter case, the event will undergo formal CEC review only if the reviewing physician will suspect an event. To limit possible reporting bias toward the null hypothesis (i.e. querying for source documentation may stimulate a site to report previously unreported endpoints), only patients who have successfully completed the follow-up, data entry, and all query processes for the parent study will be deemed eligible for the GLASSY study. For sites whose first language is not English, a mother tongue MD will be involved for source documentation translation.

The first approval for GLASSY occurred on April 18 2017 and the first adjudication has been performed on September,6, 2017..

Statistical analyses and sample size considerations

The co-primary efficacy endpoint will be firstly tested as non-inferiority followed by a superiority testing only if non-inferiority criteria will be met. The co-primary safety endpoint will be tested with a superiority hypothesis only. Alpha error will be evenly split (2.5% each) between the two co-primary endpoints. Based on best available data at the time of study design, the expected rate of the co-primary efficacy composite endpoint of death, non-fatal MI, non-fatal stroke, or urgent TVR is 11% at 24 months in the control group. The expected rate of co-primary safety endpoint of type 3 or 5 BARC bleeding is 5% at 24 months in the control group. For the co-primary efficacy endpoint non-inferiority will be declared if the upper limit of the 95% confidence interval for the experimental (i.e. ticagrelor monotherapy) versus conventional arm at 24 months is less than 1.22 on a risk ratio scale, corresponding to 2.2% absolute risk difference. A total of 3,340 patients per group (6,680 patients) will yield 85% power to detect non-inferiority with a one-sided type I error (alpha) of 2.5%. The risk ratio will be calculated using the Mantel-Cox log-rank method.

If non-inferiority will be met, 3,593 patients per group (7,186 patients) will provide 80% power to assess the superiority for the co-primary efficacy endpoint at 24 months, assuming 20% relative risk reduction in the experimental arm and a two-sided alpha of 2.5%. A total of 7,186 patients will provide more than 80% power to detect a relative risk reduction of 33% in the experimental arm at 2 years with respect to co-primary safety endpoint of BARC 3 or 5 bleeding, setting the two-sided alpha error at 2.5%. For each trigger, the CEC-adjudicated events will be used if the evidence is sufficient and the IR endpoint if the evidence is not sufficient (ie “best available” data).

Representativeness of the selected study cohort

There is no a priori attempt to select a patient population in GLASSY that could be entirely representative of the whole population included in the parent study. This would require random selection of the sample at the patient level or at least at the site

level which, although ideally desirable, would be financially unsustainable for an investigator-initiated study.

Importantly, in GLOBAL LEADERS the randomization was stratified by site. This means that GLASSY is a randomized substudy of the parent study and therefore the estimation of treatment effects are expected to be valid.

Baseline characteristics, quality indicators and risk profile of GLOBAL LEADERS patients according to GLASSY inclusion are presented in Table 1 and 2, with no significant interactions on any of the variables considered.

The estimated minimum sample size was 7,186. Therefore, to minimize the number of participating sites, only those with the highest recruitment rate based on the final number of included subjects were included. Accordingly, the top 19 recruiting sites would have provided an overall of 7,365 patients. These 19 top ranking recruitment sites were invited in Q1 2017 and all agreed to participate.

Local and, where deemed necessary, central institutional review approval was sought for all 19 participating sites in the form of either a protocol addendum or site-specific amendment. In Q1 2018, due to delays in getting study approved for the Bulgarian site ranked at 19th position, the invitation to participate was extended to an additional site that was ranked at 20th position. This would allow reaching a final population of 7,601 patients.

Evaluation of the concordance between IR- and CEC-adjudicated endpoints

Concordance between IR- and CEC-adjudicated endpoints will be assessed in events with sufficient evidence only. We will use the Cohen's kappa with exact binomial 95 percent confidence intervals as a measurement of the extent of agreement beyond chance alone. Cohen originally suggested the Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. However, Cohen's suggested interpretation was critiqued as too lenient for health-related studies because it implies that a score as low as 0.41 might be acceptable. Therefore, we will interpret concordance between IR- and CEC-endpoints as follows:[11]

0–0.20 None

0.21–0.39	Minimal
0.40–0.59	Weak
0.60–0.79	Moderate
0.80–0.90	Strong
Above 0.90	Almost Perfect

Patient and Public Involvement

In GLASSY, the research question was developed to compliment the investigator-assessment. While no specific patient reported outcome has been considered, the extensive characterization of several non-fatal endpoints is expected to provide a thorough assessment of intervention on patient experience. GLASSY results will be disseminated to patients mainly via the local investigators. We especially take here the opportunity to thank all patients and families who volunteered to help others.

Study organization

The European Cardiovascular Research Institute (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will act as Sponsor of this substudy. The leadership of the GLASSY is composed of the chair (Prof. Stephan Windecker) and principal investigator (Prof. Marco Valgimigli), in conjunction with the CEC members. Along with the executive committee of the parent study and one representative for each included GLASSY site they will form the publication committee.

Discussion

CECs are intended to enhance the scientific validity of a clinical trial through systematic, independent, and standardized identification, processing, and adjudication of suspected events. There are multiple lines of evidence indicating that central and independent adjudication of events may affect the results of a randomized trial by identifying clinically relevant unreported events, [12-14] by minimizing variability and heterogeneity inherently present when several different clinicians and data managers apply definitions of endpoints which are complex and sometimes not well known, [15] with implications on the interpretation of the effect of a randomized intervention. [16] Finally,

there has been an increasing regulatory emphasis on the requirement of an independent CEC. [17,18,19]

An analysis of the randomized PURSUIT trial documented that site investigator and CEC assessments of whether a MI had occurred disagreed in 983 (20%) of the 5,005 patients with suspected MI, mostly reflecting site misclassification of post-enrolment MIs (as enrolment MIs) or underreported periprocedural MIs with a higher mortality associated with CEC-identified MIs as compared with patients with no MI. [12] Similarly in *post-hoc* analysis of two large randomized studies testing antithrombotic therapies in patients with coronary artery disease, CEC procedures identified more events (both ischemia and bleeding) as compared to site investigators. [13,14] Moreover, independent adjudication of ischemic and bleeding endpoints may provide important mechanistic information that may deepen understanding of the primary endpoint result of the study by better characterizing components of such endpoints including, but not limited to cause of death, sub-type of MI according to standardized definitions, [20] and bleeding location.

Also standardized adjudication processes provide the basis for consistency and reproducibility. In large validation effort of all-comer stent trials, a harmonization process provided a high level of concordance for event adjudication and improved accuracy for final event reporting. [15]

Finally, the presence of a CEC has been not only strongly advocated by regulatory authorities, [17] but also requested in some instances for concern of bias in open label studies. [18] Notably, regulatory authorities have been recently involved directly in endpoint definition along with investigators, pharmaceutical and CV device manufacturers, and other stakeholders. [19]

GLASSY is a first of its kind scientific study designed to implement CEC processes in the context of a large phase III pragmatic trial intended to collect only investigator-reported endpoints. As such, it may provide unique information on how the adoption of CEC processes may affect study results. Some design features of a RCT, including blinding of randomized treatment and independent endpoint adjudication, may be complex, costly, and challenging to implement in a pragmatic trial thus limiting study feasibility. On the other hand, these characteristics are important to enhance the scientific validity and quality of the evidence generated by minimizing detection and/or reporting

bias. GLASSY may indirectly allow to assess whether such bias(es) are present in GLOBAL LEADERS by quantifying the concordance (or lack thereof) between IR- and CEC-adjudicated endpoints. In other words, to test the value of CECs. This could have relevant implications not only for the interpretation of the GLOBAL LEADERS results but also to inform the design of similar studies in the future.

Pragmatic clinical trials are fundamental to complement earlier phase studies designed to explore the efficacy of a given intervention. In addition, recent registry based randomized trials have been appraised owing to their ability to address clinically relevant questions, in large representative patient populations at limited cost. Pragmatism, an established concept in clinical research, aims at enhancing generalizability rather than internal validity of a study result and promote clinical or policy decision-making by providing evidence for the adoption of a given intervention into real-world clinical practice. [21-23] 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. [24] Importantly, the role of independent endpoint adjudication in this context is a quality rather than a pragmatic issue. If the quality and consistency of endpoint ascertainment can be improved by adjudication without affecting routine patient care, CECs are highly desirable. [25]

A typical strength of CEC processes is to provide standardization around secondary outcomes or subtype of events, such as characterization of the modality of death, the location of a bleeding or the type of MI according to the Universal Classification, that may be not reliably collected in the absence of standardized definitions and conventions. These data however, are important to fully characterize the efficacy and safety of a antithrombotic treatment intervention, such as that studied in the GLOBAL LEDERS study. According to best adjudication practice, GLASSY will collect and analyze extensive outcome data, beyond the occurrence of the event itself, that were not considered in GLOBAL LEADERS CRF. Additionally, for each non-fatal suspected endpoint we will assess if the documentation provided by the site was sufficient to understand whether the endpoint has occurred or not that may allow indirectly estimating the quality of endpoint reporting by the site.

Limitations

An intrinsic limitation of GLASSY is that GLOBAL LEADERS has been designed as an IR-only study. Therefore, systematic identification of study endpoints is limited by the eCRF and relies on source documentation provided by the site, which reduces the ability to identify all possible potential endpoints.

In addition, GLASSY, for logistical reasons, will be conducted in a representative sample rather than the entire parent study. Although a random sample would have been ideal in this setting, this was neither feasible or financially sustainable. The practical reason to focus enrollment for GLASSY to top enrolling center may bias the study toward the null hypothesis of no difference between IR- and CEC-adjudicated endpoint by selecting best enrolling sites. While this bias is possible, the relatively large study sample (≈ 50% of the parent study) makes this possibility unlikely.

Conclusions

GLASSY will assess the scientific implications of CEC adjudication processes within a large RCT designed to collect only IR-reported events, to extend the assessment of the effectiveness and safety of the randomized intervention tested in GLOBAL LEADERS to a broad range of non-fatal ischemic and bleeding endpoints, and ultimately test the value of standardized CEC processess within a pragmatic study design.

Contributor ship, Competing Interest and Funding

MV, SW, SL, AF, EMcF designed the study. MV, SL, AF, RP, EMcF drafted the manuscripts. All other authors contributed to data management and provided substantial critical revision.

SL reports personal fees for advisory board participation from AstraZeneca, Chiesi, The Medicine Company. Dr Valgimigli reports grants from The Medicines Company, grants from Terumo, during the study; grants from AstraZeneca, and personal fees from Terumo, St Jude Vascular, and Abbott Vascular, outside the submitted work.

The study is independently financed by resources of a professorship grant at the University of Bern, Switzerland. No extramural funding was used to support this

manuscript. The authors are solely responsible for the drafting and editing of the paper and its final contents.

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Tables

Table 1. Baseline characteristics of GLOBAL LEADERS patients according to GLASSY inclusion

	GLASSY (20 sites) N = 7585	NO GLASSY (110 sites) N = 8383	p Value
Age (years)	n = 7585, 64.9 ± 10.3	n = 8383, 64.2 ± 10.3	0,41
Female	n = 7585, 1799 (23.7%)	n = 8383, 1915 (22.8%)	0,33
Hypertension	n = 7565, 5492 (72.6%)	n = 8349, 6223 (74.5%)	0,70
Diabetes mellitus	n = 7584, 1822 (24.0%)	n = 8373, 2216 (26.5%)	0,47
Renal failure (<60 eGFR)	n = 7567, 1005 (13.3%)	n = 8316, 1166 (14.0%)	0,83
Peripheral vascular disease	n = 7550, 553 (7.3%)	n = 8272, 452 (5.5%)	0,030
Current smoker	n = 7585, 2186 (28.8%)	n = 8383, 1983 (23.7%)	0,007
Previous myocardial infarction	n = 7575, 1762 (23.3%)	n = 8347, 1948 (23.3%)	0,91
Previous percutaneous coronary intervention	n = 7581, 2522 (33.3%)	n = 8373, 2699 (32.2%)	0,53
Previous coronary artery bypass grafting	n = 7581, 443 (5.8%)	n = 8374, 500 (6.0%)	0,62
Stable CAD	n = 7585, 3745 (49.4%)	n = 8383, 4736 (56.5%)	0,048
Multivessel treatment	n = 7585, 1098	n = 8383, 1248	0,65

	(14.5%)	(14.9%)	
Previous major bleeding or predisposition to bleeding	n = 7572, 48 (0.6%)	n = 8375, 50 (0.6%)	0,78

Mixed-models p-values, accounting for a random effect of hospital identifier.

Table 2. Quality indicators and risk profile of GLOBAL LEADERS patients according to GLASSY inclusion

	GLASSY	NO GLASSY	p-value	interaction p-value
Nr of patients	N = 7585	N = 8383		
All-cause mortality or New Q-wave MI or equivalent LBBB at 2 years	n = 7585, 328 (4.3%)	n = 8383, 325 (3.9%)	0,16	0,77
All-cause mortality at 2 years	n = 7585, 247 (3.3%)	n = 8383, 230 (2.7%)	0,06	0,34
New Q-wave MI or equivalent LBBB at 2 years	n = 7585, 89 (1.2%)	n = 8383, 97 (1.2%)	0,93	0,34
BARC 3 or 5 Bleeding at 2 years	n = 7585, 168 (2.2%)	n = 8383, 164 (2.0%)	0,26	0,90

BARC 1 Bleeding at 2 years	n = 7585, 657 (8.7%)	n = 8383, 662 (7.9%)	0,08	0,59
Primary endpoint complete?	n = 7585,	n = 8383,	<0.001	0,75
complete	7152 (94.3%)	7683 (91.6%)		
vital status unknown	0 (0.0%)	8 (0.1%)		
patient died post-2yrs & ECG information unavailable	11 (0.1%)	16 (0.2%)		
patient alive & ECG information unavailable	422 (5.6%)	676 (8.1%)		
Nr of sites	N = 20 sites	N = 110 sites		
Nr of protocol deviations/10 patients	n = 20, 0.4 (0.1 to 0.8)	n = 110, 0.6 (0.2 to 1.3)	0,14	
Statin at discharge	n = 7547, 6954 (92.1%)	n = 8324, 7747 (93.1%)	0,78	
Heart failure or left ventricular ejection fraction ≤ 40% treated and ACE or ARB at discharge	n = 251, 207 (82.5%)	n = 284, 232 (81.7%)	0,51	
Heart failure or left ventricular ejection fraction ≤ 40% treated and betablockers at discharge	n = 157, 130 (82.8%)	n = 221, 181 (81.9%)	0,88	

GLASSY includes 20 sites, NO GLASSY includes 110 sites, total nr of sites was 130.

p-values from Mantel-Cox logrank test, interaction p-value testing whether the GLASSY vs non-GLASSY sites modify the comparison Experimental treatment strategy vs Reference treatment strategy for the clinical outcomes. Protocol deviations compared with Mann-Whitney U-test.

Protocol deviations included: inclusion/exclusion criteria, informed consent procedure, randomization procedure, study procedures, safety reporting.

Figures

Figure 1. GLOBAL LEADERS Design.

Figure 2. GLASSY Design

APPENDIX

Clinical Events Committee

CEC project leader: Anna Franzone.

Clinical Events Committee Composition

Chair: Eugene Mc Fadden, Co-chair: Sergio Leonardi, Member: Raffaele Piccolo.

Endpoints Definitions

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification as well as according to the TIMI and the GUSTO classification as follows:

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.

Type 2: Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria:

Requiring non-surgical, medical intervention by a health care professional

Leading to hospitalization of increased level of care

Prompting evaluation

Type 3a:

- Overt bleeding plus haemoglobin drop of 3 to <5** g/dL (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus haemoglobin drop ≥5** g/dL (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)

Subcategories: confirmed by autopsy or imaging or LP

Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period*
- Chest tube output ≥ 2 L within a 24 hour period

Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious

Type 5b

- Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL haemoglobin). † Cell saver products will not be counted.

TIMI Bleeding Criteria

Non-CABG related bleeding

- Major
  - Any intracranial bleeding (excluding microhaemorrhages < 10mm evident only on gradient-echo MRI)
  - Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5g/dL
  - Fatal bleeding (bleeding that directly results in death within 7 days
- Minor
  - Clinically overt (including imaging), resulting in haemoglobin drop of 3 to < 5g/dL
- Other non-major or minor
  - Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG

- Fatal bleeding (bleeding that directly results in death)
- Perioperative intracranial bleeding
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
- Chest tube output >2 L within a 24-h period

GUSTO Bleeding Criteria

Severe or life-threatening

- Intracerebral haemorrhage
- Resulting in substantial hemodynamic compromise requiring treatment

Moderate

- Requiring blood transfusion but not resulting in hemodynamic compromise

Mild

- Bleeding that does not meet above criteria

DEATH

All deaths will be categorized as cardiovascular, non-cardiovascular or undetermined based on the definitions below.

Cardiovascular death

Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death (immediate) due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other
cardiovascular causes.

Death due to Acute Myocardial Infarction:

- Death by any mechanism (arrhythmia, heart failure, mechanical complication, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure

(CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e. chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

Sudden Cardiac Death:

- Death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:
  - Death witnessed and occurring without new or worsening symptoms.
  - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.

Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).Death after unsuccessful resuscitation from cardiac arrest.

o Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac aetiology.

o Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations: A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

Death due to Heart Failure or Cardiogenic Shock:

• Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI (see section ***). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:-

o Cool, clammy skin or

o Oliguria (urine output < 30 mL/hour) or

o Altered sensorium or

o Cardiac index < 2.2 L/min/m²

o Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke refers to death after a stroke that is either a direct consequence of the

stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Death due to Cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes: Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death:

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected

- Non-Malignant Causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug drug
- interaction)

- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal haematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.

Malignant Causes

Death results directly from the cancer;

OR

Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy);

OR

Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently should be further classified (worsening prior malignancy; new malignancy).

Undetermined cause of death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (ie a a fatal bleeding occurred) or not.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of peri-procedural MI after PCI, which will be defined according to the SCAI definition. 34,35
For secondary analyses, PCI-related MI according to the Third Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:34:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB.
- Development of new Q waves in the ECG

Evidence of new loss of viable myocardium or new regional wall motion abnormality

- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a target or non-target vessel or lesion in most cases.

Type 2 MI

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

The distinction between type 1 and type 2 MI will be based by consensus on the preponderance of clinical evidence. The diagnosis of type 2 MI requires a predisposing

condition as well as an acute Trigger of supply/demand imbalance, including acute anemia, respiratory failure, hypotension, sustained hypertension (with or without left ventricular hypertrophy), prolonged tachy- and brady-arrhythmias, coronary embolism, coronary artery spasm. If the evidence is conflicting or unclear, the MI will be classified as type 1.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (NOT USED for primary analysis; see definition below)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

In addition, at least one of the following is required:

- symptoms suggestive of myocardial ischaemia
- new ischaemic ECG changes
- angiographic findings consistent with a procedural complication
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

Type 4b MI

Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI

Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline

cTn values (≤URL).

In addition, at least one of the following is required:

- o new pathological Q waves or new LBBB
- o angiographic documented new graft or new native coronary artery occlusion
- o imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

2. Periprocedural MI after PCI (within 48 hours after PCI)

Periprocedural MI is defined based on the SCAI definitions as follows:

1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. .

2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

STENT THROMBOSIS

Stent Thrombosis is defined by the Academic Research Consortium as follows:

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
- Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
- Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days.

- Irrespective of the time after the index procedure, any myocardial infarction (MI) which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by
central nervous system (CNS) vascular injury as a result of hemorrhage or infarction. CNS includes brain, spinal cord and retina.
Classification:
Ischemic Stroke
Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as ”Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or in absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Note, Haemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischaemic stroke
Cerebral Haemorrhage
Hemorrhages in the CNS are classified as stroke if they are non-traumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The

diagnoses included in this section are intracerebral hemorrhage (intra-parenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and non-aneurysmal).

Stroke caused by intracerebral haemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid haemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma. Haemorrhages may be further classified according to location (example, supratentorial, subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

URGENT TARGET VESSEL REVASCULARIZATION

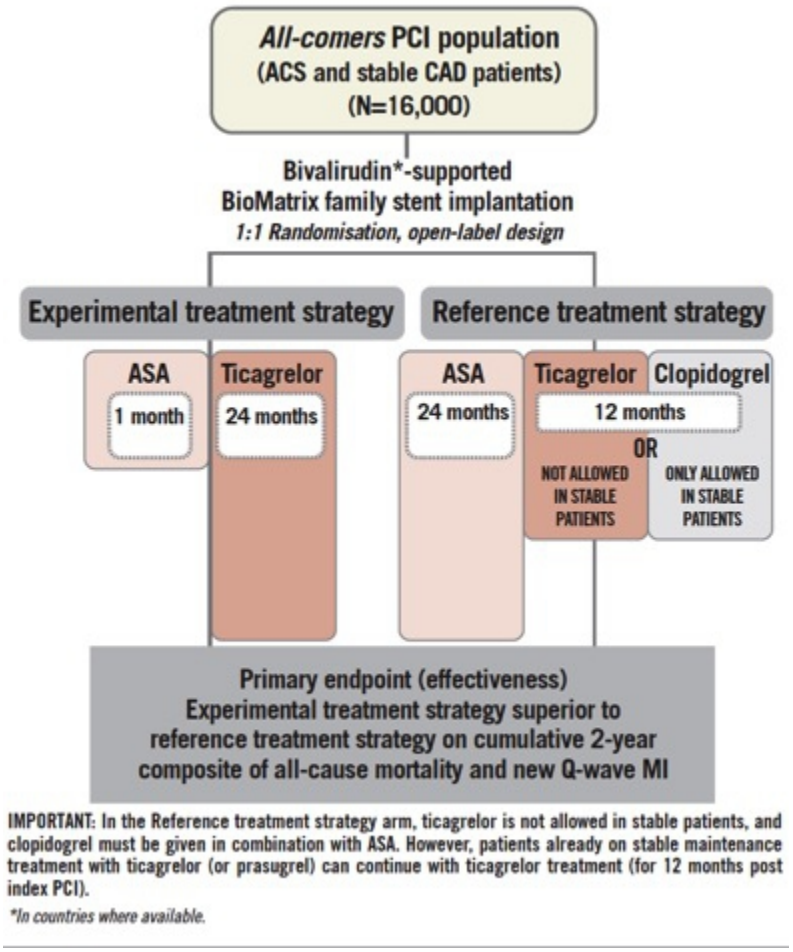
A urgent target vessel revascularization (TVR) is a urgent coronary revascularization in a target coronary vessel (ie a vessel treated during the index PCI). Urgent coronary revascularization is defined as follows:

One or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST segment changes (a new ST segment shift > 0.05 mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary oedema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischemia and not be identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide

wire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered a urgent coronary revascularization endpoint.

GLASSY participating sites

Country	*Site*	*PI*
Belgium	JESSAZIEKENHUIS	Edouard Benit
Germany	Kerckhoff Heart Center	Christoph Liebetrau
Belgium	Imelda Ziekenhuis	Luc Janssens
Italy	Policlinico San Matteo	Maurizio Ferrario
Switzerland	Uni. Hospital Bern	Stephan Windecker
Poland	PAKS Chrzanów	Zurakowski Aleksander
Netherlands	Erasmus MC R'dam	Robert Jan van Geuns
Italy	Ospedaliera S. Maria	Marcello Dominici
Austria	Wilhelminenspital	Kurt Huber
Netherlands	OLVG A'dam	Ton Slagboom
Poland	PAKS Dabrowa	Paweł Buszman
Italy	Ospedale S. Donato	Leonardo Bolognese
Italy	Azienda Ospedaliero di Ferrara	Carlo Tumscitz
Poland	JP2 Krakov	Krzysztof Żmudka
Belgium	CHU de Charleroi	Adel Aminian
Belgium	ZOL St.Jan	Mathias Vrolix
Bulgaria	City Clinic Sofia	Ivo Petrov
UK	Royal Blackburn	Scot Garg
Germany	Rhein Ruhr Center	Christoph Naber
Poland	PAKS Kozle	Janusz Prokopczuk



GLOBAL LEADERS design

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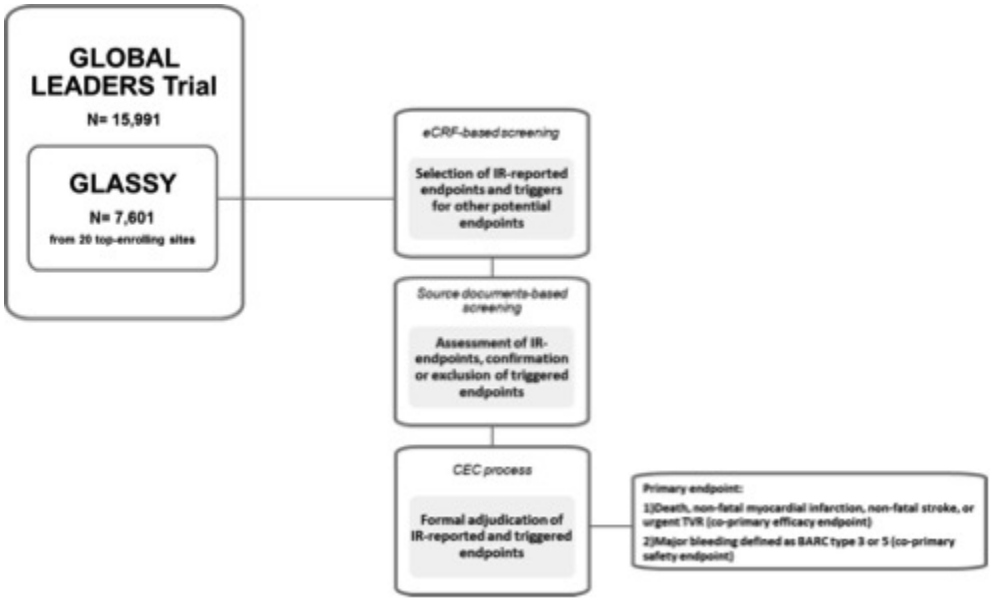

GLASSY Design

41x25mm (300 x 300 DPI)

BMJ Open

Rationale and Design of a Prospective Sub-StudY of Clinical Endpoint Adjudication Processes Within an Investigator-Reported Randomized Controlled Trial in Patients with Coronary Artery Disease: The GLOBAL LEADERS Adjudication Sub-StudY – GLASSY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026053.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Nov-2018

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

Rationale and Design of a Prospective Sub-StudY of Clinical Endpoint Adjudication Processes Within an Investigator-Reported Randomized Controlled Trial in Patients with Coronary Artery Disease: The GLOBAL LEADERS Adjudication Sub-StudY – GLASSY

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Abstract (299 of 300 words)

Introduction: The GLOBAL LEADERS is an open-label, pragmatic and superiority randomized controlled trial designed to challenge the current treatment paradigm of dual antiplatelet therapy (DAPT) for 12 months followed by aspirin monotherapy among patients undergoing percutaneous coronary intervention (PCI). By design, all study endpoints are investigator-reported (IR) and not subject to formal adjudication by an independent Clinical Event Committee (CEC), which may introduce detection, reporting, or ascertainment bias.

Methods and Analysis: We designed the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) to prospectively implement, in a large sample of patients enrolled within the GLOBAL LEADERS trial (7,601 of 15,991, 47.5%), an independent adjudication process of reported and unreported potential endpoints, using standardized CEC procedures, in order to assess whether 23-month ticagrelor monotherapy (90 mg BID) after 1-month DAPT is non-inferior to a standard regimen of DAPT for 12 months followed by aspirin monotherapy for the primary efficacy endpoint of death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization, and superior for the primary safety endpoint of type 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria.

This study will comprehensively assess the comparative safety and efficacy of the two tested antithrombotic strategies on CEC-adjudicated ischemic and bleeding endpoints and will provide insights into the role of a standardized CEC adjudication process on the interpretation of study findings by quantifying the level of concordance between IR-reported and CEC-adjudicated events.

Ethics and Dissemination: GLASSY has been approved by local ethics committee of all study sites and/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. The study has been registered on ClinicalTrials.Gov NCT01813435, a website that will be also used for reporting of study results and dissemination.

Strengths and limitations of this study

- GLASSY is a comprehensive, rigorous, and standardized assessment of several non-fatal endpoints as well as death (including type, mechanism, and relationship to bleeding) in a representative sample of the GLOBAL LEADERS trial performed according to best practices of adjudication.
- An intrinsic limitation is that GLOBAL LEADERS has been designed as an IR-only study. Therefore, systematic identification of study endpoints is limited by the eCRF and relies on source documentation provided by the site, which reduces the ability to identify all possible potential endpoints.
- For feasibility, GLASSY will be conducted in a sample rather than the entire parent study, which may bias the study toward the null hypothesis of no difference between IR- and CEC-adjudicated endpoint by selecting best enrolling sites. While this bias is possible, the relatively large study sample (≈ 50% of the parent study) makes this possibility unlikely.

Rationale

The prolonged combination of aspirin and a $P2Y_{12}$ receptor inhibitor, typically for 12 months, represents the established antiplatelet therapy in patients with or without acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting stent implantation.[1] Clopidogrel, an inconsistent $P2Y_{12}$ receptor inhibitor [2] with considerable variability in inter-patient response, [3] proved inferior to stronger and more consistent $P2Y_{12}$ inhibitors, such as ticagrelor, in preventing ischemic and thrombotic cardiovascular events among patients with ACS.[4] With the introduction and widespread adoption in clinical practice of more potent $P2Y_{12}$ inhibitors, it has been hypothesized that the addition of aspirin may yield little additional inhibition of platelet aggregation and marginal incremental clinical benefit compared with a strategy based on potent $P2Y_{12}$ receptor inhibitor-monotherapy.[5,6] This led to the hypothesis that ticagrelor monotherapy may have similar efficacy compared with the combination of aspirin and ticagrelor and be better tolerated.

The GLOBAL LEADERS trial was designed to challenge the current treatment paradigm consisting of 12-month dual antiplatelet therapy (DAPT; clopidogrel+aspirin among patients with stable CAD; ticagrelor+aspirin among patients with ACS) followed by aspirin monotherapy in patients undergoing PCI based on the superiority for the composite endpoint of all-cause death or Q-wave myocardial infarction (MI) assessed at 2 years.[7] It is an open-label, randomized comparison testing an innovative antithrombotic regimen of 23-month ticagrelor 90 mg twice daily monotherapy after 1-month DAPT (ticagrelor 90 mg twice daily plus low-dose aspirin) against conventional 12-month DAPT in all-comer patients undergoing PCI with bivalirudin-supported, biolimus-eluting stent implantation. The GLOBAL LEADERS is a pragmatic clinical trial and, by design, all study endpoints are investigator-reported (IR) and therefore not adjudicated by an independent Clinical Event Committee (CEC). Only new Q-wave MI will be identified by independent core lab assessment and validated by a physician blinded to treatment allocation. All other endpoints, including specific causes of mortality, non-Q wave MI, stroke, stent thrombosis, and bleeding will be analyzed as reported by the local investigators.

Although the use of IR endpoints in a phase III randomized trial is a simple and less expensive alternative, their sole use has potential to introduce detection, reporting, or ascertainment bias, especially in the absence of blinding to randomized treatment (i.e. in an open-label design as in the case of the GLOBAL LEADERS trial). This might challenge the interpretation of the GLOBAL LEADERS study results, especially as it relates to the effect of the randomly allocated treatment on non-fatal clinical endpoints. Moreover, the design of GLOBAL LEADERS also raises important questions regarding bleeding adverse events that may differ between groups.

We, therefore, designed the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) with the aim to prospectively implement, in a representative sample of patients enrolled within the GLOBAL LEADERS trial, an independent adjudication process of reported as well as unreported potential endpoints, leveraging on standardized CEC procedures. This GLASSY substudy is powered to test whether 23-month ticagrelor monotherapy after a short course of DAPT for 1 month is non-inferior to conventional 12-month DAPT followed by aspirin monotherapy with respect to CEC-adjudicated

death, non-fatal myocardial infarction, non-fatal stroke, or urgent target-vessel revascularization (TVR) and superior in preventing CEC-adjudicated major bleeding. Furthermore, GLASSY will evaluate the implications of the CEC adjudication process for the interpretation of study results by quantifying the level of concordance between IR-reported and CEC-adjudicated events and will define the role of CEC adjudication process for the assessment of the efficacy and safety of the randomized antithrombotic strategies on a broader set of fatal and non-fatal clinical endpoints.

Design

Parent Study

The GLOBAL LEADERS study is a superiority, open-label, multicenter, randomized controlled trial in an all-comer population of patients, presenting with ACS or stable coronary artery disease, undergoing PCI with the uniform use of Biolimus A9-eluting stents (BioMatrix™ BES; Biosensors Europe SA, Morges, Switzerland) and receiving bivalirudin at the time of the index procedure (**Figure 1**). A total of 15,991 patients have been randomly assigned 1:1 to ticagrelor 90 mg twice daily for 24 months plus aspirin ≤100 mg daily for 1 month (experimental arm) or standard DAPT with either ticagrelor, in case of ACS, or clopidogrel, in case of stable coronary artery disease, for 12 months plus aspirin ≤100 mg daily for 24 months (control arm). All study endpoints are investigator-reported with randomization stratified by enrolling site as well as clinical presentation. The primary endpoint of the GLOBAL LEADERS is the composite of all-cause death or new Q-wave myocardial infarction at 24 months. The presence and date of new Q wave MI will be identified by an independent ECG core laboratory and validated by a single physician blinded to treatment allocation using adverse events reported in the eCRF supplemented, if required, by additional source documents. The key safety endpoint is investigator-reported class 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) definitions. Other secondary endpoints include stroke, MI, coronary revascularization, and definite stent thrombosis. As pragmatic trial, GLOBAL LEADERS implemented a risk-based monitoring process for site-based

operational activities favoring centralized remote monitoring rather than in-person on-site monitoring. GLOBAL LEADERS terminated enrollment on November, 9th 2015.

Objectives

The primary objective of the GLASSY is to assess, in a representative subgroup of patients enrolled within the GLOBAL LEADERS study, whether 23-month ticagrelor monotherapy after a short course of DAPT (1 month) is non-inferior to conventional 12-month DAPT followed by aspirin monotherapy for the composite endpoint of CEC-adjudicated all-cause death, non-fatal MI, non-fatal stroke, or urgent TVR, and superior in preventing CEC-adjudicated major bleeding (BARC type 3 and 5) in an all-comers population undergoing PCI at 24 months (**Figure 2**). A secondary objective is to quantify the level of concordance between IR- and CEC-adjudicated endpoints.

Endpoints

GLASSY will have two independent, CEC-adjudicated, co-primary endpoints at 24 months:

1) The composite of death, non-fatal MI, non-fatal stroke, or urgent TVR (co-primary efficacy endpoint);
2) The composite of BARC type 3 or 5 bleeding (co-primary safety endpoint).

Secondary endpoints will include:

- Each component of the co-primary composite endpoints;
- Definite, probable or possible stent thrombosis according to ARC classification;
- Bleeding events according to BARC (primary safety endpoint) as well as the alternative TIMI and GUSTO classifications;
- Type of death (cardiovascular vs. non-cardiovascular and subtypes).

Clinical Event Committee Procedures

According to best adjudication practice,[8] GLASSY is being conducted according to the following features:

1. **Prospective approach to adjudication**. The CEC dataset will be locked before the termination of the parent study. Suspected events (triggers) will be assessed during the conduct of the study rather than adjudicating all cases after the study is completed and the

primary results are available (i.e. retrospective adjudication). In case of updated entry of suspected events or updated source documentation by the site after request by the CEC team of source documentation, events will be re-evaluated for adjudication.

2. **Blinding of randomized treatment allocation**. According to the PROBE methodology,[9,10] the CEC will be blinded to randomized treatment allocation. Several steps will be undertaken to ensure that the CEC personnel and physicians remain blinded.

First, any reference to treatment assignment contained in the eCRF or source documents that could lead to un-blinding of treatment assignment will be obliterated by using a black marker by the site prior to submission to the CEC physician members.

Second, the CEC coordinator and operation personnel will obliterate any reference to study drug assignment prior to distribution to the physicians if information is noted during the preparation of the event packet.

Third, if a reviewer notes the treatment assignment during the review of a particular event, the CEC coordinator is notified, and the event is sent for review by the third expert reviewer.

3. **Triggering and adjudication of investigator- as well as non-investigator reported events**.

All IR-events (death, MI, stroke, bleeding, coronary revascularization, and stent thrombosis) will be adjudicated by the CEC through dedicated CRFs (online Appendix). We will also use comprehensive search strategies for potential cardiovascular events that are not reported by the investigator via eCRF dedicated queries. Indeed, it may happen that patients without IR-events or triggers may have experienced an event qualifying for the endpoints of the GLASSY study. [10]

It is possible that the request of source documentation may trigger endpoint reporting (and bias the study toward the null hypothesis). To quantify this, IR endpoints entered after CEC requested source documentation will be monitored and reported.

4. **Independent voting processes** by CEC members with at least 3 CEC members (see Appendix A) with knowledge of the geographic variations of care represented in the trial. Each event will be reviewed independently by at least two CEC physicians. In case of disagreement, the event will be reviewed by a Committee of at least 3 reviewers with independent vote.

5. **Independence from parent study**.

To maximize the scientific integrity of GLASSY, CEC personnel will operate independently from the data management group of the parent study, including no cross talk on trigger logic specifications, query processes for source documentation, and most importantly event reporting and adjudication results.

6. **Quantification of sufficient evidence for adjudication of non-fatal triggers** (NO versus UNKNOWN events).

Finally, we will quantify the minimum amount of evidence required for the assessment of non-fatal endpoints. In a randomized trial, a pre-requisite to assess whether a suspected non-fatal endpoint has occurred or not is the availability of sufficient evidence for such an assessment, including relevant source documents, tests, and/or laboratory exams. While this is commonly performed for fatal events (death is adjudicated as "unknown" in case of no or insufficient description of death circumstances), it is not generally mandatory for non-fatal events.

In GLASSY, we will report all non-fatal endpoints but for each non-fatal trigger examined an assessment will be performed as to whether enough information is available for formal adjudication. This will allow distinguishing triggers that did not meet the endpoint definition (i.e. no event with sufficient documentation present) from triggers for which this is unknown due to insufficient documentation. For each type of non-fatal endpoint, the proportion of events with insufficient evidence will indirectly estimate a) the feasibility of GLASSY b) the quality of endpoint reported by sites and c) the uncertainty of the evidence related to the studied outcome.

Sufficient evidence for CEC adjudication includes at a minimum a narrative description with at least one pertinent medical documentation, including ECG/biomarkers

for MI; angiographic report for stent thrombosis and urgent revascularization; brain imaging for stroke; and labs and other appropriate testing for bleeding. In case of CRF-only narrative, the evidence will be considered insufficient and the case will not undergo CEC adjudication.

7. Quality control of the adjudication process

To ensure the highest reproducibility, a random sample of ≈ 5% of adjudicated events will be re-reviewed by the complete CEC committee (ie 3 member) who are blinded to the initial results.

A major disagreement will be considered if there was a disagreement on whether an event had occurred or not while a minor disagreement is any discordance on the remaining adjudicated fields. Major disagreement will be reported as part of the final study report and will be used to identify the presence of systematic problems in the adjudication process.

CEC Operations

Within the selected study patients, all IR-events as well as additional potential events (triggers) identified through a systematic analysis of the eCRF form will be considered for CEC adjudication. Non-IR triggers will be assessed after all the relevant source documentation has been requested to and provided by the participating sites and will be identified using a comprehensive search strategy that consider key words logically related to the event. In general, key words with a clear relationship to the endpoint of interest (e.g. for MI: unstable angina or ischemic heart disease) will trigger a formal CEC review, whereas keywords with a potential relationship (e.g. for MI: asystole, cardiac tamponade, hypertensive crisis) will trigger a review by a physician (independent from the CEC members) (**Appendix**). In the latter case, the event will undergo formal CEC review only if the reviewing physician will suspect an event. To limit possible reporting bias toward the null hypothesis (i.e. querying for source documentation may stimulate a site to report previously unreported endpoints), only patients who have successfully completed the follow-up, data entry, and all query processes for the parent study will be

deemed eligible for the GLASSY study. For sites whose first language is not English, a mother tongue MD will be involved for source documentation translation.

The first approval for GLASSY occurred on April 18 2017 and the first adjudication has been performed on September,6, 2017.

Statistical analyses and sample size considerations

The co-primary efficacy endpoint will be firstly tested as non-inferiority followed by a superiority testing only if non-inferiority criteria will be met. As the experimental treatment is simpler than the control treatment, it may be useful in patients with low drug adherence and/or who become intolerant to aspirin. For this reason GLASSY adopted a non-inferiority design for one of the two co- primary endpoints. The co-primary safety endpoint will be tested with a superiority hypothesis only. Alpha error will be evenly split (2.5% each) between the two co-primary endpoints. Based on best available data at the time of study design, the expected rate of the co-primary efficacy composite endpoint of death, non-fatal MI, non-fatal stroke, or urgent TVR is 11% at 24 months in the control group. The expected rate of co-primary safety endpoint of type 3 or 5 BARC bleeding is 5% at 24 months in the control group. For the co-primary efficacy endpoint non-inferiority will be declared if the upper limit of the 95% confidence interval for the experimental (i.e. ticagrelor monotherapy) versus conventional arm at 24 months is less than 1.22 on a risk ratio scale, corresponding to 2.2% absolute risk difference. A total of 3,340 patients per group (6,680 patients) will yield 85% power to detect non-inferiority with a one-sided type I error (alpha) of 2.5%. The risk ratio will be calculated using the Mantel-Cox log-rank method.

If non-inferiority will be met, 3,593 patients per group (7,186 patients) will provide 80% power to assess the superiority for the co-primary efficacy endpoint at 24 months, assuming 20% relative risk reduction in the experimental arm and a two-sided alpha of 2.5%. A total of 7,186 patients will provide more than 80% power to detect a relative risk reduction of 33% in the experimental arm at 2 years with respect to co-primary safety endpoint of BARC 3 or 5 bleeding, setting the two-sided alpha error at 2.5%. For each trigger, the CEC-adjudicated events will be used if the evidence is sufficient and the IR endpoint if the evidence is not sufficient (ie “best available” data).

Representativeness of the selected study cohort

There is no a priori attempt to select a patient population in GLASSY that could be entirely representative of the whole population included in the parent study. This would require random selection of the sample at the patient level or at least at the site level which, although ideally desirable, would be financially unsustainable for an investigator-initiated study.

Importantly, in GLOBAL LEADERS the randomization was stratified by site. This means that GLASSY is a randomized substudy of the parent study and therefore the estimation of treatment effects are expected to be valid.

Baseline characteristics, quality indicators and risk profile of GLOBAL LEADERS patients according to GLASSY inclusion are presented in Table 1 and 2, with no significant interactions on any of the variables considered.

The estimated minimum sample size was 7,186. Therefore, to minimize the number of participating sites, only those with the highest recruitment rate based on the final number of included subjects were included. Accordingly, the top 19 recruiting sites would have provided an overall of 7,365 patients. These 19 top ranking recruitment sites were invited in Q1 2017 and all agreed to participate.

Local and, where deemed necessary, central institutional review approval was sought for all 19 participating sites in the form of either a protocol addendum or site-specific amendment. In Q1 2018, due to delays in getting study approved for the Bulgarian site ranked at 19th position, the invitation to participate was extended to an additional site that was ranked at 20th position. This would allow reaching a final population of 7,601 patients.

Evaluation of the concordance between IR- and CEC-adjudicated endpoints

Concordance between IR- and CEC-adjudicated endpoints will be assessed in events with sufficient evidence only. We will use the Cohen's kappa with exact binomial 95 percent confidence intervals as a measurement of the extent of agreement beyond chance alone. Cohen originally suggested the Kappa result be interpreted as follows: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair,

0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. However, Cohen's suggested interpretation was critiqued as too lenient for health-related studies because it implies that a score as low as 0.41 might be acceptable. Therefore, we will interpret concordance between IR- and CEC-endpoints as follows:[11]

0–0.20	None
0.21–0.39	Minimal
0.40–0.59	Weak
0.60–0.79	Moderate
0.80–0.90	Strong
Above 0.90	Almost Perfect

Ethics and Dissemination

GLASSY has been approved by local ethics committee of all study sites. A complete list is attached in the appendix. All patients enrolled signed a dedicated informed consent, in addition to that of the parent study explaining that their outcome data will be subjected to an independent review. The study has been registered on *ClinicalTrials.Gov* registration number:NCT01813435 (protocol version 1), a website that will be also used for reporting of study results and dissemination.

Patient and Public Involvement

In GLASSY, the research question was developed to compliment the investigator-assessment. While patients were not directly involved in the design or conception of the study and no specific patient reported outcome has been considered, the extensive characterization of several non-fatal endpoints is expected to provide a thorough assessment of intervention on patient experience. GLASSY results will be disseminated to patients mainly via the local investigators. We especially take here the opportunity to thank all patients and families who volunteered to help others.

Study organization

The European Cardiovascular Research Institute (ECRI-Trials B.V., PO Box 2125, 3000 CC Rotterdam, The Netherlands) will act as Sponsor of this substudy. The

leadership of the GLASSY is composed of the chair (Prof. Stephan Windecker) and principal investigator (Prof. Marco Valgimigli), in conjunction with the CEC members. Along with the executive committee of the parent study and one representative for each included GLASSY site they will form the publication committee.

Discussion

CECs are intended to enhance the scientific validity of a clinical trial through systematic, independent, and standardized identification, processing, and adjudication of suspected events. There are multiple lines of evidence indicating that central and independent adjudication of events may affect the results of a randomized trial by identifying clinically relevant unreported events, [12-14] by minimizing variability and heterogeneity inherently present when several different clinicians and data managers apply definitions of endpoints which are complex and sometimes not well known, [15] with implications on the interpretation of the effect of a randomized intervention. [16] Finally, there has been an increasing regulatory emphasis on the requirement of an independent CEC. [17,18,19]

An analysis of the randomized PURSUIT trial documented that site investigator and CEC assessments of whether a MI had occurred disagreed in 983 (20%) of the 5,005 patients with suspected MI, mostly reflecting site misclassification of post-enrolment MIs (as enrolment MIs) or underreported periprocedural MIs with a higher mortality associated with CEC-identified MIs as compared with patients with no MI. [12] Similarly in *post-hoc* analysis of two large randomized studies testing antithrombotic therapies in patients with coronary artery disease, CEC procedures identified more events (both ischemia and bleeding) as compared to site investigators. [13,14] Moreover, independent adjudication of ischemic and bleeding endpoints may provide important mechanistic information that may deepen understanding of the primary endpoint result of the study by better characterizing components of such endpoints including, but not limited to cause of death, sub-type of MI according to standardized definitions, [20] and bleeding location.

Also standardized adjudication processes provide the basis for consistency and reproducibility. In large validation effort of all-comer stent trials, a harmonization

process provided a high level of concordance for event adjudication and improved accuracy for final event reporting. [15]

Finally, the presence of a CEC has been not only strongly advocated by regulatory authorities, [17] but also requested in some instances for concern of bias in open label studies. [18] Notably, regulatory authorities have been recently involved directly in endpoint definition along with investigators, pharmaceutical and CV device manufacturers, and other stakeholders. [19]

GLASSY is a first of its kind scientific study designed to implement CEC processes in the context of a large phase III pragmatic trial intended to collect only investigator-reported endpoints. As such, it may provide unique information on how the adoption of CEC processes may affect study results. Some design features of a RCT, including blinding of randomized treatment and independent endpoint adjudication, may be complex, costly, and challenging to implement in a pragmatic trial thus limiting study feasibility. On the other hand, these characteristics are important to enhance the scientific validity and quality of the evidence generated by minimizing detection and/or reporting bias. GLASSY may indirectly allow to assess whether such bias(es) are present in GLOBAL LEADERS by quantifying the concordance (or lack thereof) between IR- and CEC-adjudicated endpoints. In other words, to test the value of CECs. This could have relevant implications not only for the interpretation of the GLOBAL LEADERS results but also to inform the design of similar studies in the future.

Pragmatic clinical trials are fundamental to complement earlier phase studies designed to explore the efficacy of a given intervention. In addition, recent registry based randomized trials have been appraised owing to their ability to address clinically relevant questions, in large representative patient populations at limited cost. Pragmatism, an established concept in clinical research, aims at enhancing generalizability rather than internal validity of a study result and promote clinical or policy decision-making by providing evidence for the adoption of a given intervention into real-world clinical practice. [21-23] 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. [24] Importantly, the role of independent endpoint adjudication in this context is a quality rather than a pragmatic

issue. If the quality and consistency of endpoint ascertainment can be improved by adjudication without affecting routine patient care, CECs are highly desirable. [25]

A typical strength of CEC processes is to provide standardization around secondary outcomes or subtype of events, such as characterization of the modality of death, the location of a bleeding or the type of MI according to the Universal Classification, that may be not reliably collected in the absence of standardized definitions and conventions. These data however, are important to fully characterize the efficacy and safety of a antithrombotic treatment intervention, such as that studied in the GLOBAL LEDERS study. According to best adjudication practice, GLASSY will collect and analyze extensive outcome data, beyond the occurrence of the event itself, that were not considered in GLOBAL LEADERS CRF. Additionally, for each non-fatal suspected endpoint we will assess if the documentation provided by the site was sufficient to understand whether the endpoint has occurred or not that may allow indirectly estimating the quality of endpoint reporting by the site.

Limitations

An intrinsic limitation of GLASSY is that GLOBAL LEADERS has been designed as an IR-only study. Therefore, systematic identification of study endpoints is limited by the eCRF and relies on source documentation provided by the site, which reduces the ability to identify all possible potential endpoints.

In addition, GLASSY, for logistical reasons, will be conducted in a representative sample rather than the entire parent study. Although a random sample would have been ideal in this setting, this was neither feasible or financially sustainable. The practical reason to focus enrollment for GLASSY to top enrolling center may bias the study toward the null hypothesis of no difference between IR- and CEC-adjudicated endpoint by selecting best enrolling sites. While this bias is possible, the relatively large study sample (≈ 50% of the parent study) makes this possibility unlikely.

Conclusions

GLASSY will assess the scientific implications of CEC adjudication processes within a large RCT designed to collect only IR-reported events, to extend the assessment of the effectiveness and safety of the randomized intervention tested in GLOBAL LEADERS to a broad range of non-fatal ischemic and bleeding endpoints, and ultimately test the value of standardized CEC processess within a pragmatic study design.

Contributor ship

Marco Valgimigli, Stephan Windecker, Sergio Leonardi, Anna Franzone, Eugene McFadden: study design, manuscript drafting, data interpretation and critical revision.

Eugene McFadden, Sergio Leonardi, Anna Franzone, Raffaele Piccolo: Clinical Event Committee operations and adjudications.

Anna Franzone: data management

Dierik Heg, Peter Juni: statistical analysis, data interpretation and critical revision.

Pascal Vranckx, Patrick W. Serruys, Edouard Benit, Christoph Liebetrau, Luc Janssens, Maurizio Ferrario, Aleksander Zurakowski, Robert Jan van Geuns, Marcello Dominici, Kurt Huber, Ton Slagboom, Paweł Buszman, Leonardo Bolognese, Carlo Tumscitz, Krzysztof Bryniarski, Adel Aminian, Mathias Vrolix, Ivo Petrov, Scot Garg, Christoph Naber, Janusz Prokopczuk, Christian Hamm, Gabriel Steg: data acquisition, interpretation and critical revision

Competing Interest

SL reports personal fees for advisory board participation from AstraZeneca, Chiesi, The Medicine Company. Dr Valgimigli reports grants from The Medicines Company, grants from Terumo, during the study; grants from AstraZeneca, and personal fees from Terumo, St Jude Vascular, and Abbott Vascular, outside the submitted work.

Funding

The study is independently financed by resources of a professorship grant at the University of Bern, Switzerland. No extramural funding was used to support this

manuscript. The authors are solely responsible for the drafting and editing of the paper and its final contents.

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Tables

Table 1. Baseline characteristics of GLOBAL LEADERS patients according to GLASSY inclusion

	GLASSY (20 sites) N = 7585	NO GLASSY (110 sites) N = 8383	p Value
Age (years)	n = 7585, 64.9 ± 10.3	n = 8383, 64.2 ± 10.3	0,41
Female	n = 7585, 1799 (23.7%)	n = 8383, 1915 (22.8%)	0,33
Hypertension	n = 7565, 5492 (72.6%)	n = 8349, 6223 (74.5%)	0,70
Diabetes mellitus	n = 7584, 1822 (24.0%)	n = 8373, 2216 (26.5%)	0,47
Renal failure (<60 eGFR)	n = 7567, 1005 (13.3%)	n = 8316, 1166 (14.0%)	0,83
Peripheral vascular disease	n = 7550, 553 (7.3%)	n = 8272, 452 (5.5%)	0,030
Current smoker	n = 7585, 2186 (28.8%)	n = 8383, 1983 (23.7%)	0,007
Previous myocardial infarction	n = 7575, 1762 (23.3%)	n = 8347, 1948 (23.3%)	0,91
Previous percutaneous coronary intervention	n = 7581, 2522 (33.3%)	n = 8373, 2699 (32.2%)	0,53
Previous coronary artery bypass grafting	n = 7581, 443 (5.8%)	n = 8374, 500 (6.0%)	0,62
Stable CAD	n = 7585, 3745 (49.4%)	n = 8383, 4736 (56.5%)	0,048
Multivessel treatment	n = 7585, 1098	n = 8383, 1248	0,65

	(14.5%)	(14.9%)	
Previous major bleeding or predisposition to bleeding	n = 7572, 48 (0.6%)	n = 8375, 50 (0.6%)	0,78

Mixed-models p-values, accounting for a random effect of hospital identifier.

Table 2. Quality indicators and risk profile of GLOBAL LEADERS patients according to GLASSY inclusion

	GLASSY	NO GLASSY	p-value	interaction p-value
Nr of patients	N = 7585	N = 8383		
All-cause mortality or New Q-wave MI or equivalent LBBB at 2 years	n = 7585, 328 (4.3%)	n = 8383, 325 (3.9%)	0,16	0,77
All-cause mortality at 2 years	n = 7585, 247 (3.3%)	n = 8383, 230 (2.7%)	0,06	0,34
New Q-wave MI or equivalent LBBB at 2 years	n = 7585, 89 (1.2%)	n = 8383, 97 (1.2%)	0,93	0,34
BARC 3 or 5 Bleeding at 2 years	n = 7585, 168 (2.2%)	n = 8383, 164 (2.0%)	0,26	0,90

BARC 1 Bleeding at 2 years	n = 7585, 657 (8.7%)	n = 8383, 662 (7.9%)	0,08	0,59
Primary endpoint complete?	n = 7585,	n = 8383,	<0.001	0,75
complete	7152 (94.3%)	7683 (91.6%)		
vital status unknown	0 (0.0%)	8 (0.1%)		
patient died post-2yrs & ECG information unavailable	11 (0.1%)	16 (0.2%)		
patient alive & ECG information unavailable	422 (5.6%)	676 (8.1%)		
Nr of sites	N = 20 sites	N = 110 sites		
Nr of protocol deviations/10 patients	n = 20, 0.4 (0.1 to 0.8)	n = 110, 0.6 (0.2 to 1.3)	0,14	
Statin at discharge	n = 7547, 6954 (92.1%)	n = 8324, 7747 (93.1%)	0,78	
Heart failure or left ventricular ejection fraction ≤ 40% treated and ACE or ARB at discharge	n = 251, 207 (82.5%)	n = 284, 232 (81.7%)	0,51	
Heart failure or left ventricular ejection fraction ≤ 40% treated and betablockers at discharge	n = 157, 130 (82.8%)	n = 221, 181 (81.9%)	0,88	

GLASSY includes 20 sites, NO GLASSY includes 110 sites, total nr of sites was 130.

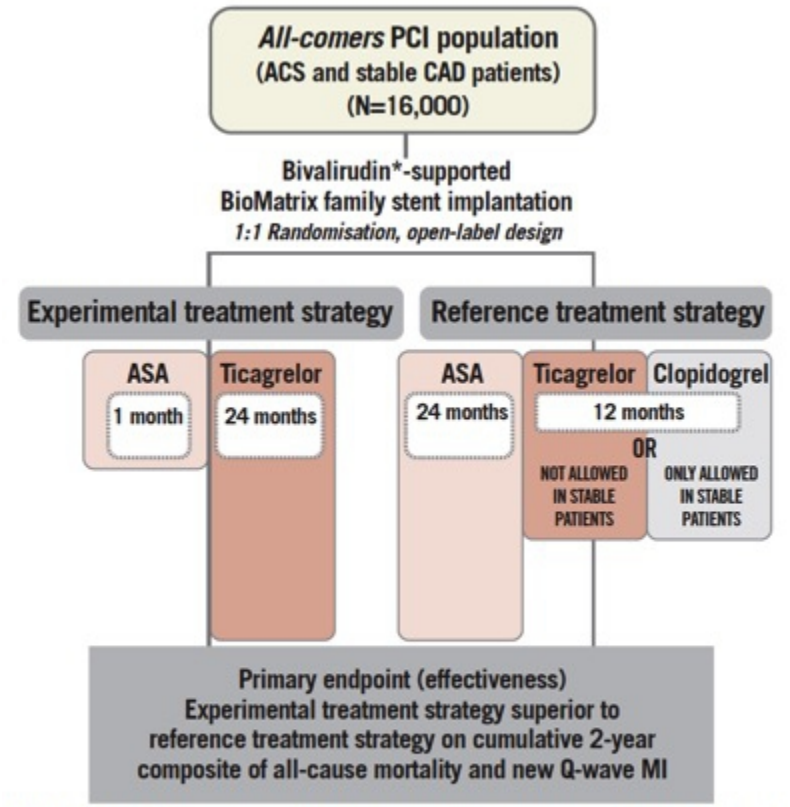
p-values from Mantel-Cox logrank test, interaction p-value testing whether the GLASSY vs non-GLASSY sites modify the comparison Experimental treatment strategy vs Reference treatment strategy for the clinical outcomes. Protocol deviations compared with Mann-Whitney U-test.

Protocol deviations included: inclusion/exclusion criteria, informed consent procedure, randomization procedure, study procedures, safety reporting.

Figures

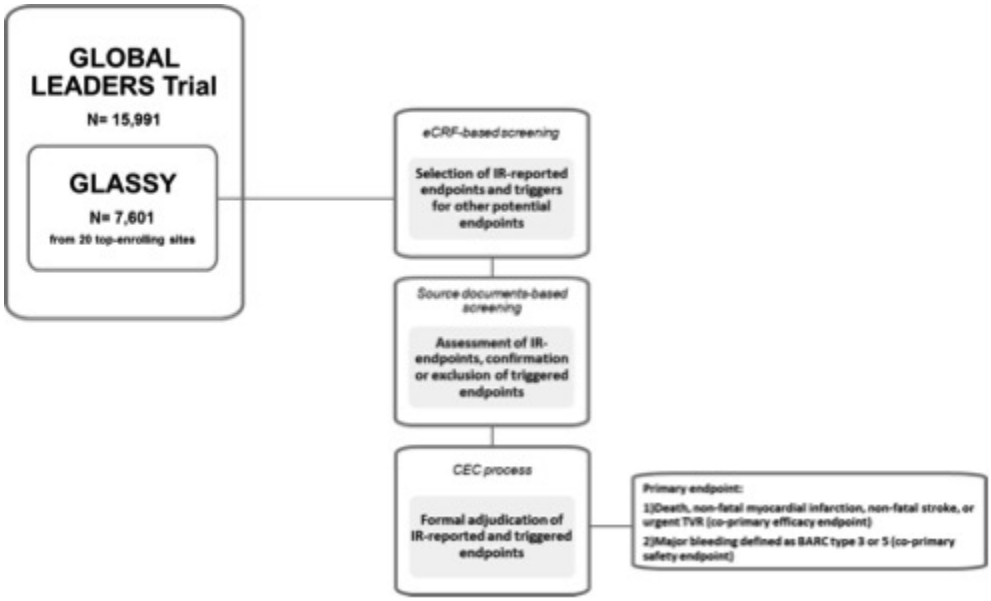
Figure 1. GLOBAL LEADERS Design.

Figure 2. GLASSY Design



GLOBAL LEADERS design

33x40mm (300 x 300 DPI)



GLASSY Design

41x25mm (300 x 300 DPI)

APPENDIX

Clinical Events Committee

CEC project leader: Anna Franzone.

Clinical Events Committee Composition

Chair: Eugene Mc Fadden, Co-chair: Sergio Leonardi, Member: Raffaele Piccolo.

Endpoints Definitions

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification as well as according to the TIMI and the GUSTO classification as follows:

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.

Type 2: Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria:

Requiring non-surgical, medical intervention by a health care professional

Leading to hospitalization of increased level of care

Prompting evaluation

Type 3a:

- Overt bleeding plus haemoglobin drop of 3 to <5** g/dL (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus haemoglobin drop ≥5** g/dL (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)

Subcategories: confirmed by autopsy or imaging or LP

Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period*
- Chest tube output ≥ 2 L within a 24 hour period

Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious

Type 5b

- Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL haemoglobin). † Cell saver products will not be counted.

TIMI Bleeding Criteria

Non-CABG related bleeding

- Major
  - Any intracranial bleeding (excluding microhaemorrhages < 10mm evident only on gradient-echo MRI)

- Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5g/dL
- Fatal bleeding (bleeding that directly results in death within 7 days

• Minor

- Clinically overt (including imaging), resulting in haemoglobin drop of 3 to < 5g/dL

• Other non-major or minor

- Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG

• Fatal bleeding (bleeding that directly results in death)

• Perioperative intracranial bleeding

• Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding

• Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.

• Chest tube output >2 L within a 24-h period

GUSTO Bleeding Criteria

Severe or life-threatening

- Intracerebral haemorrhage
- Resulting in substantial hemodynamic compromise requiring treatment

Moderate

- Requiring blood transfusion but not resulting in hemodynamic compromise

Mild

- Bleeding that does not meet above criteria

DEATH

All deaths will be categorized as cardiovascular, non-cardiovascular or undetermined based on the definitions below.

Cardiovascular death

Cardiovascular Death is defined as death resulting from an acute myocardial infarction,

sudden cardiac death, death due to heart failure, death due to stroke, death (immediate) due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other
cardiovascular causes.

Death due to Acute Myocardial Infarction:

- Death by any mechanism (arrhythmia, heart failure, mechanical complication, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e. chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

Sudden Cardiac Death:

- Death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:
  - Death witnessed and occurring without new or worsening symptoms.

o Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.

Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).Death after unsuccessful resuscitation from cardiac arrest.

o Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac aetiology.

o Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations: A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

Death due to Heart Failure or Cardiogenic Shock:

• Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI (see section ***). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:-

o Cool, clammy skin or

o Oliguria (urine output < 30 mL/hour) or

o Altered sensorium or

o Cardiac index < 2.2 L/min/m²

o Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke refers to death after a stroke that is either a direct consequence of the
stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Death due to Cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes: Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death:

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected

- Non-Malignant Causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide

- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug drug
- interaction)
- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal haematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.

Malignant Causes

Death results directly from the cancer;

OR

Death results from a complication of the cancer (e.g. infection, complication of surgery /

chemotherapy / radiotherapy);

OR

Death results from withdrawal of other therapies because of concerns relating to the poor

prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which

developed subsequently should be further classified (worsening prior malignancy; new

malignancy).

Undetermined cause of death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (ie a a fatal bleeding occurred) or not.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of peri-procedural MI after PCI, which will be defined according to the SCAI definition. 34,35

For secondary analyses, PCI-related MI according to the Third Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:34:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB.
- Development of new Q waves in the ECG

Evidence of new loss of viable myocardium or new regional wall motion abnormality

- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a target or non-target vessel or lesion in most cases.

Type 2 MI

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

The distinction between type 1 and type 2 MI will be based by consensus on the preponderance of clinical evidence. The diagnosis of type 2 MI requires a predisposing condition as well as an acute Trigger of supply/demand imbalance, including acute anemia, respiratory failure, hypotension, sustained hypertension (with or without left ventricular hypertrophy), prolonged tachy- and brady-arrhythmias, coronary embolism, coronary artery spasm. If the evidence is conflicting or unclear, the MI will be classified as type 1.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (NOT USED for primary analysis; see definition below)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

In addition, at least one of the following is required:

- symptoms suggestive of myocardial ischaemia
- new ischaemic ECG changes
- angiographic findings consistent with a procedural complication
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

Type 4b MI

Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI
Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin
values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline
cTn values (≤URL).

In addition, at least one of the following is required:
o new pathological Q waves or new LBBB
o angiographic documented new graft or new native coronary artery occlusion
o imaging evidence of new loss of viable myocardium or new regional wall motion
abnormality.

2. Periprocedural MI after PCI (within 48 hours after PCI)
Periprocedural MI is defined based on the SCAI definitions as follows:
1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. .
2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

STENT THROMBOSIS

Stent Thrombosis is defined by the Academic Research Consortium as follows:

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
- Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
- Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days.

- Irrespective of the time after the index procedure, any myocardial infarction (MI) which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by
central nervous system (CNS) vascular injury as a result of hemorrhage or infarction. CNS includes brain, spinal cord and retina.
Classification:
Ischemic Stroke
Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as ”Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or in absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Note, Haemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischaemic stroke
Cerebral Haemorrhage
Hemorrhages in the CNS are classified as stroke if they are non-traumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral hemorrhage (intra-parenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and non-aneurysmal).
Stroke caused by intracerebral haemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid haemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Haemorrhages may be further classified according to location (example, supratentorial,
subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be
classified as one of the above.

URGENT TARGET VESSEL REVASCULARIZATION

A urgent target vessel revascularization (TVR) is a urgent coronary revascularization in a target coronary vessel (ie a vessel treated during the index PCI). Urgent coronary revascularization is defined as follows:

One or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST segment changes (a new ST segment shift > 0.05 mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary oedema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischemia and not be identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide wire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered a urgent coronary revascularization endpoint.

Approval Details of GLASSY Ethics Committee

Country	Sites	Central Ethic Committee	Protocol Number	Approval Date
Austria	4301	Ethikkommision der Stadt Wien	13-064-0413	03-Jul-2017
Belgium	3204-3202-3205-3203	Comité d'Etique LS.P.P.C OM 008	A17/31_23/08	27-Sep-2017
Germany	4902-4903	Ethikkommission des Fachbereichs Medizin-Bfarm	78/13 4038963	21-Jun-2017 15-Aug-2017
Netherlands	3101-3104	Medisch Etische Toetsings Commissie Erasmus MC	NL-43637.678.13	31-May-2017
Italy	3902-3905-3909-3903	Comitato Etico Area Pavia AIFA	20170018252 88004	03-Jul-2017 30-Jul-2018
UK	4404	North-West Liverpool Central Research Ethics Committee	13/NW/0283	26-Jun-2017
Switzerland	4106	Kantonale Ethikkommision Bern	039/13	18-Apr-2017
Poland	4802-4805-4801-4807	PRZEWODNICZACY Komisji Bioetycznej	2013/07/18/02	7-may-2018
Bulgaria	9901	MECTHA ETHYJA KOMHCHR	109-3-010	7-May-2018

GLASSY participating sites

Country	*Site*	*PI*
Belgium	JESSAZIEKENHUIS	Edouard Benit
Germany	Kerckhoff Heart Center	Christoph Liebetrau
Belgium	Imelda Ziekenhuis	Luc Janssens
Italy	Policlinico San Matteo	Maurizio Ferrario
Switzerland	Uni. Hospital Bern	Stephan Windecker
Poland	PAKS Chrzanów	Zurakowski Aleksander
Netherlands	Erasmus MC R'dam	Robert Jan van Geuns
Italy	Ospedaliera S. Maria	Marcello Dominici
Austria	Wilhelminenspital	Kurt Huber
Netherlands	OLVG A'dam	Ton Slagboom
Poland	PAKS Dabrowa	Paweł Buszman
Italy	Ospedale S. Donato	Leonardo Bolognese
Italy	Azienda Ospedaliero di Ferrara	Carlo Tumscitz
Poland	JP2 Krakov	Krzysztof Żmudka
Belgium	CHU de Charleroi	Adel Aminian
Belgium	ZOL St.Jan	Mathias Vrolix
Bulgaria	City Clinic Sofia	Ivo Petrov
UK	Royal Blackburn	Scot Garg
Germany	Rhein Ruhr Center	Christoph Naber
Poland	PAKS Kozle	Janusz Prokopczuk

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N.A.
Protocol version	3	Date and version identifier	3, 13
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	N.A.
Objectives	7	Specific objectives or hypotheses	7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N.A.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N.A.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N.A.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N.A.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N.A.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7-11

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13-14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N.A.

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N.A.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.