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Reconsidering the Direction of Coronary Revascularization Trials

Gregg W. Stone, MD,[a] Mario Gaudino, MD, MSCE, PhD[b]

COMPOSITE OUTCOMES: HISTORICAL CONTEXT

In the 1980s, randomized trials testing fibrinolysis in myocardial infarction (MI) used mortality as the powered primary outcome, the most appropriate endpoint in an era in which in-hospital death from MI exceeded 10%. Following the positive GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) and ISIS-2 (Second International Study of Infarct Survival) trials, routine adoption of streptokinase substantially reduced mortality. Subsequent trials tested improved fibrinolytic agents and percutaneous coronary intervention (PCI). The lower mortality with fibrinolysis necessitated extremely large sample sizes to demonstrate further increases in survival (eg, 41,021 patients in the GUSTO [Global Use of Strategies to Open Occluded Coronary Arteries] trial), and PCI further improved outcomes. To increase trial efficiency, the primary outcome of MI trials shifted from mortality to a composite of major adverse cardiovascular events (MACEs), initially death or MI, and subsequently adding unplanned revascularization with or without stroke. These nonfatal outcomes shared related pathophysiologic features after reperfusion therapy, and each was significantly associated with mortality, thus justifying their pooling in a composite outcome. The same primary composite outcome was subsequently adopted in all published trials comparing PCI with coronary artery bypass surgery (CABG).

LIMITATIONS OF MACEs AS A PRIMARY ENDPOINT

We believe that the wisdom of continuing to rely on the MACE composite outcome warrants reexamination. First, the clinical relevance of each event type varies greatly and is often not consistent after PCI and CABG.[1] Second, improvement in diagnostic techniques has enabled detection of events solely on the basis of abnormal laboratory findings or imaging rather than clinical symptoms (eg, procedural MI) that are of uncertain clinical significance. Third, within each class the clinical relevance of event subtypes may vary greatly (eg, procedural vs nonprocedural MI[2] or disabling vs nondisabling stroke). Fourth, repeat revascularization represents a physician choice to reintervene rather than an independently occurring event, is thereby subject to bias, and may vary after PCI and CABG given the varying use of routine noninvasive testing and patient or physician thresholds for repeat catheterization.[3] Fifth, important consequences of revascularization procedures (eg, heart, renal, and respiratory failure; bleeding and vascular complications; arrhythmias; neuropsychological decline; time of return to work; and many others) that are arguably as important as or more important than repeat revascularization have been essentially ignored or relegated to secondary nonpowered outcomes.

The interpretation of previous revascularization trials has been highly dependent on the events (and

From [a]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; and the [b]Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, New York, USA.
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their definitions) included in the primary composite endpoint. For example, the EXCEL (Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease) and NOBLE (Nordic-Baltic-British Left Main Revascularization) trials of PCI vs CABG in left main coronary artery disease reached diametrically opposite conclusions (noninferiority of PCI vs superiority of CABG, respectively). However, the individual outcomes from these trials were more similar than different. The discordance in the primary endpoint-driven conclusions arose because EXCEL but not NOBLE included periprocedural MI, and NOBLE but not EXCEL included repeat revascularization in their primary composite outcomes.

With improving revascularization outcomes, mortality as a primary endpoint is no longer practical unless enrollment is restricted to high-risk patients (eg, left ventricular dysfunction) or follow-up is continued for a decade or more. However, selecting the optimal mix of nonfatal events to include in a composite endpoint to reduce sample size is challenging and has become controversial, especially with regard to periprocedural MI.[4] Lack of agreement on the primary composite outcome may impede participation of surgeons and interventionalists in future revascularization trials.

Moreover, all major trials to date have assessed the primary outcome by time-to-first-event analysis. Although it is easy to describe and graphically represent, limitations of this approach include the following: 1) equating the significance of all events in a composite (eg, repeat revascularization and death); 2) overweighting events that occur early during follow-up (eg, an early repeat revascularization affects the primary outcome more than a late death); 3) not accounting for repeated events; and 4) assessing nonproportional hazards during follow-up, which are common when comparing techniques with different early and late risks and benefits, such as PCI and CABG. The time is thus right to reconsider the optimal primary outcome measure and analysis methodology for coronary revascularization trials.

RETHINKING THE OUTCOMES THAT MATTER MOST

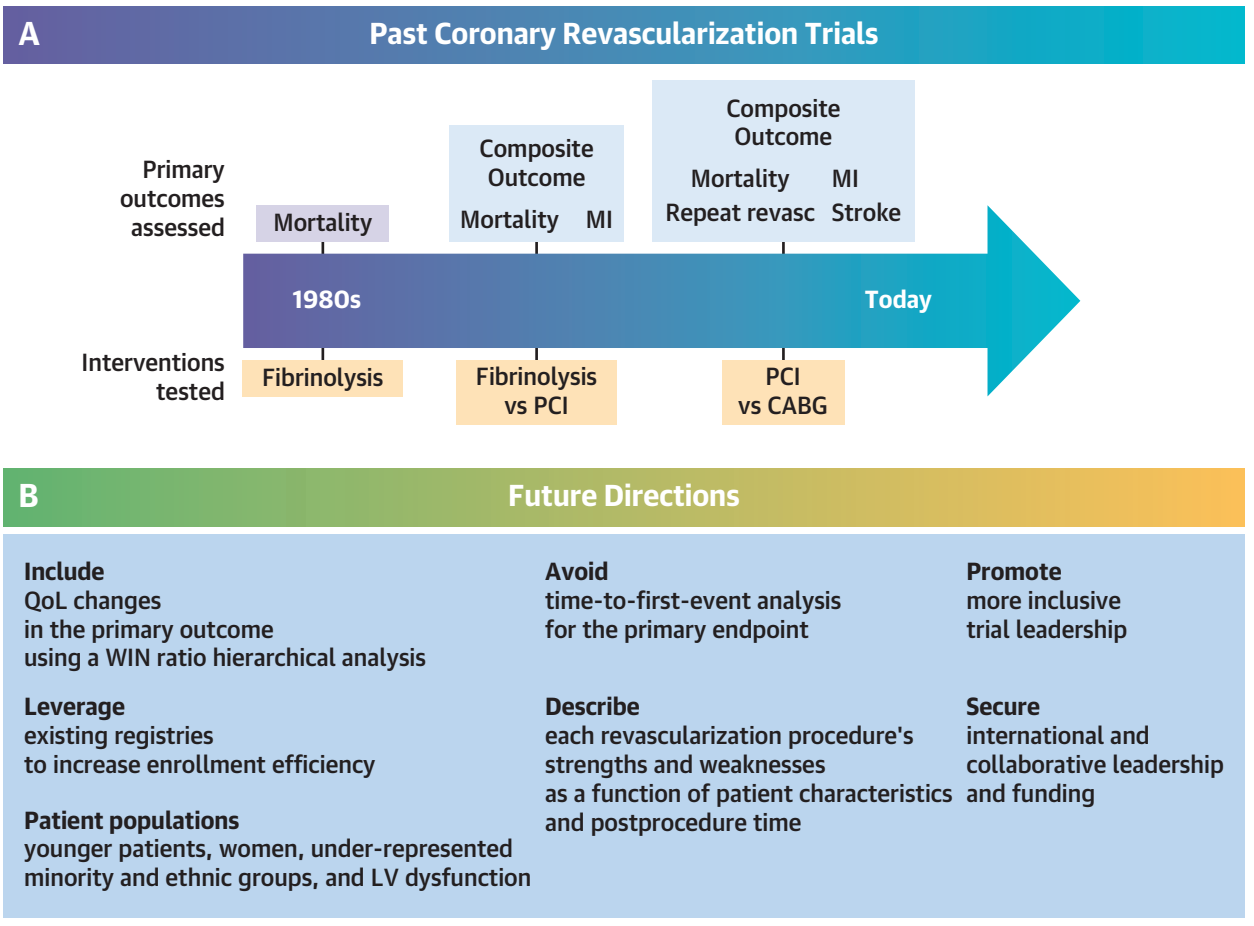
When asked about their treatment goals, patients often state that they want “to live longer and live better,” the latter embodied by quality of life (QOL). With the growing focus on patient-centered outcomes, the fundamental importance of patient QOL has been increasingly emphasized. For example, in a systematic review of studies investigating >3,700 patient or caregiver preferences and prioritized outcomes after cardiac surgery, improved QOL was the most important outcome for both groups.[5] QOL changes incorporate the net effect of all nonfatal outcomes, including discrete events such as MI and stroke (and their relative severity), the effects of new onset atrial fibrillation requiring anticoagulation, progressive kidney disease, heart failure, and angina relief, as well as the physical, cognitive, and psychosocial effects of recovering from the disease state as well as the revascularization procedure itself.

However, QOL has to date not been included in the primary outcome of revascularization trials for several reasons.[6] QOL has been considered subjective and difficult to quantify in a reproducible and unbiased manner, especially in unblinded revascularization trials. Clinical events have been preferred because of their objective nature and established associations with survival.[7] Finally, QOL has been difficult to incorporate alongside mortality and other adverse events in a composite endpoint.[8]

These limitations have been overcome by advances in trial design and methodology. Robust generic and disease-specific QOL questionnaires such as the 36-Item Short Form Survey, the Seattle Angina Questionnaire, and the Kansas City Cardiomyopathy Questionnaire have been validated to be independently associated with mortality.[6] Because most revascularization trials are necessarily unblinded, use of QOL instruments with a standardized questionnaire minimizes bias, as do QOL assessments over an extended postprocedure duration. New analytical methods such as Finkelstein-Schoenfeld and win ratio tests allow QOL to be hierarchically incorporated alongside mortality and other clinical outcomes within a composite endpoint.[8] By ranking and allowing assessment of event severity, timing, and recurrence, as well as competing risks, this method also overcomes major limitations of time-to-first-event analyses. Missing endpoint data are addressed with the win ratio by assessing pairs of patients during their shared follow-up duration. Alternatively, multiple imputation or other methods may be used to account for missing data. Prespecification of a minimum follow-up time that captures the entire effect of the tested interventions and averaging frequent QOL assessments during this period reflect the early and late harms and benefits of varying revascularization approaches and comprise a superior approach compared with assessing QOL only at a single time point.

Perhaps more importantly, the principal objective of previous revascularization trials—to demonstrate superiority (or noninferiority) of PCI or CABG—has dictated the choice of the primary outcome, sample size, and follow-up duration. This approach made

FIGURE 1 Transitioning to the Next Generation of Coronary Revascularization Trials



(A) Primary outcomes and interventions tested in the past coronary revascularization trials. **(B)** Recommendations for the design and performance of new-generation coronary revascularization trials. CABG = coronary artery bypass grafting; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; QoL = quality of life; Revasc = revascularization.

sense for new therapies such as fibrinolysis that were expected to have a large influence on mortality, thereby effecting major change in the standard of care. In contrast, after >20 large-scale randomized trials, both PCI and CABG have stood the test of time and represent complementary approaches that are essential to treat patients across the spectrum of coronary artery disease. However, the safety and effectiveness profiles of CABG and PCI vary according to patient comorbidities, coronary anatomy, and time after the procedure. For many patients who, in the opinion of both a cardiac surgeon and an interventional cardiologist, can safely undergo reasonably complete revascularization, the absolute differences in mortality will be small and unlikely to affect patient preferences.[9] However, a substantial proportion of patients can be treated only by CABG (usually because of extensive and complex anatomical disease) or PCI (usually because of comorbidities or frailty).[10] Both PCI and CABG are mature techniques, and neither will be abandoned on the basis of the results of any new trial.

A NOVEL PRIMARY COMPOSITE OUTCOME

We believe that future revascularization trials for most patient cohorts should abandon the use of the classic composite MACE endpoint. New trials should be designed to report holistic outcomes not limited to the cardiovascular system and assess the patient's life journey; thus, QOL should be a major component of the primary endpoint and serves to account for most

nonfatal outcomes. For example, the powered primary outcome may consist of the hierarchy of all-cause death, time-averaged change in generic QOL, and time-averaged change in disease-specific QOL. Discrete (nonpowered) adverse clinical events (eg, stroke and MI) should be reported in parallel, and the oversimplification of relying solely on time-to-first-event analysis should be abandoned, thereby enabling description of each revascularization procedure's strengths and weaknesses as a function of patient characteristics and time postprocedure. Bayesian approaches could also be adopted. Leveraging registries to increase recruitment efficiency into a randomized structure should be encouraged. Enrollment should be collaborative, with a central steering committee including all stakeholders, ideally with combined government and industry funding. Trial leadership should include interventionalists, surgeons, clinical cardiologists, and trialists or statisticians, as well as patients. In this regard, dedicated trials are encouraged to assess revascularization outcomes specifically in young patients, in women, in patients with left ventricular dysfunction, and in underserved racial and ethnic groups that have been poorly represented in earlier studies. Regarding the latter, involvement of patient advocacy groups and community organizers can foster enrollment of patients who have historically either not been approached or have been reticent to participate in medical research. Incorporating these principles, a large-scale trial of PCI vs CABG restricted to enrolling women and racial and ethnic groups that have been underrepresented in previous revascularization studies, with a primary hierarchical endpoint of death and QOL, has been submitted for funding.

CONCLUSIONS

The classic academic exercise of comparing revascularization modalities in an elusive search for a clear "winner" has failed. Both PCI and CABG are here to stay, and future comparative research should empower each patient (assisted by their physician) with the knowledge to choose the right procedure for them. Coronary revascularization trials need to enable accurately informed treatment decisions on the basis of each patient's clinical status as well as their preferences and goals. A Copernican shift from providing the average treatment effect in the average patient (an artificial construct with limited clinical utility for the individual patient) to reporting precise outcome estimates in specific patient groups is warranted. Large randomized trials will permit risk scores to be developed for this purpose, aided by artificial intelligence. As summarized in **Figures 1A and 1B**, a new generation of coronary revascularization trials designed around the paradigm shift of "living longer and living better," performed efficiently and analyzed with contemporary methodology, should provide patients, their families, and physicians with the key information necessary to inform the choice of revascularization most likely to achieve each individual patient's life objectives.

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ADDRESS FOR CORRESPONDENCE: Dr Gregg W. Stone, The Mount Sinai Hospital, 1 Gustave L. Levy Place, New York, New York 10029, USA. E-mail: gregg.stone@mountsinai.org. Twitter: @GreggWStone.

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