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VIEWPOINT
Clinical trials

Beyond the classic major cardiovascular event outcome for cardiovascular trials

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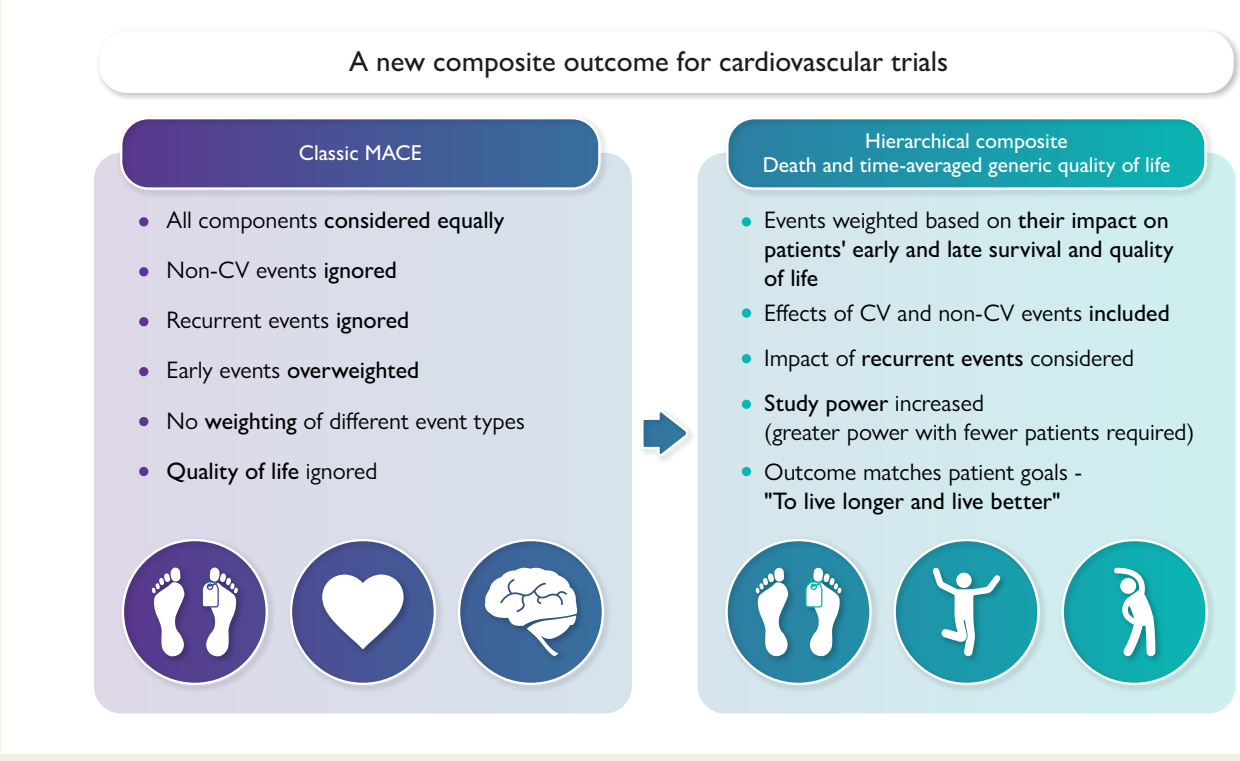
Graphical Abstract



Comparison of the classic MACE outcome and the new composite outcome for cardiovascular trials. CV, cardiovascular; MACE, major adverse cardiovascular event. Images from: Flaticon.com.

Since its introduction over 30 years ago, many cardiovascular trials have used a composite of major adverse cardiovascular events (MACE) as the primary outcome measure. After more than three decades, we believe that a continued use of MACE for this purpose warrants re-evaluation.

Rationale for major adverse cardiovascular event

Randomized trials in the 1980s demonstrated that fibrinolysis reduced mortality after acute myocardial infarction (MI), and that some fibrinolytic agents were more effective than others.[1,2] However, powering these trials for improved survival alone required sample sizes of tens of thousands of patients, which was logistically and financially unsustainable, especially given the lower event rate after fibrinolysis. To improve efficiency and reduce sample size, Califf, Braunwald, and others in the early 1990s proposed to expand the primary outcome to include non-fatal MI and stroke, major cardiovascular events that are mechanistically associated with mortality, into a three-component MACE outcome.[3,4] It is important to note that (i) MACE was initially designed to measure the safety and early efficacy of the intervention; (ii) the originators of MACE suggested that the events included in

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the composite outcome should be weighted differently or tested in a hierarchical model, reflecting their relative clinical importance; and (iii) interventions that were found to be effective in reducing MACE would then be tested in mega trials with mortality as the primary outcome. From its inception, Braunwald *et al.*[4] described MACE as an 'unsatisfactory (clinical outcome) composite endpoint', with its major benefit being to afford the initial evaluation of innovative approaches in relatively small trials. Given its limitations, it was never envisioned that MACE would become the standard on which regulatory and clinical decisions were based.

Adoption and evolution of major adverse cardiovascular events

In the following years, a composite MACE endpoint was widely adopted in cardiology trials, with variations based on the specific trial focus (e.g. death or heart failure hospitalization in heart failure trials). To further increase the number of events (to enable even smaller trials), investigators often added additional outcomes of even lesser clinical importance. In a review of 140 cardiovascular trials, 63.5% added other components to MACE, with unplanned revascularization being the most common,[5] and in a review of 136 mostly cardiovascular trials that used a composite outcome, 47% included four or more components in MACE.[6] Rehospitalization, angina recurrence, and even surrogate outcomes based on imaging and biomarker parameters were added to MACE in different combinations,[6] and the focus shifted from early to longer-term outcomes.

Limitations of major adverse cardiovascular events

The inclusion of multiple events of differing clinical relevance and that may variably respond to a test therapy in the composite endpoint adds considerable heterogeneity. Moreover, as different physicians and patients rank clinical events differently, assigning meaningful weights or ranks is problematic.[7] A hierarchical or weighted approach to attributing the components of MACE was therefore never widely adopted because of a lack of interpretability and clinical consensus. In addition, outcomes that are often determined by physicians' decisions (i.e. elective revascularization, non-urgent rehospitalization) rather than unambiguous events may introduce bias, and their inclusion in the MACE outcome is strongly associated with a positive trial result.[8]

Non-fatal events that are of lesser clinical importance occur more frequently than fatal events, and their response to treatment generally drives the composite outcome, which risks masking the effect of the more clinically relevant outcomes. A challenging scenario occurs when components of MACE with differing clinical relevance move in qualitatively different directions. For example, an invasive intervention may increase the early incidence of adverse events due to procedural complications but also lead to a reduction in long-term mortality compared with a conservative therapy. In this situation, the MACE outcome is driven by the more frequent but less clinically relevant early events, and the survival benefit may be masked. As mortality is generally a late outcome and is most often preceded by non-fatal events, time-to-first-event analyses (the analytic approach most commonly used in cardiovascular trials) promotes this limitation. Interpretation is further complicated when non-proportional hazards are present. Moreover, recurrent events are ignored in time-to-first-event analyses; a single MI counts equally to the primary outcome as three MIs in the same patient.

In addition, not all events of a certain type have similar prognostic importance. For example, peri-procedural MIs are often diagnosed by clinically silent biomarker elevations, and unless very large, may be less clinically relevant than out-of-hospital spontaneous MIs.[9] Minimally symptomatic strokes requiring brain imaging for confirmation are of less impact than those resulting in hemiplegia. Many other cardiovascular outcomes of equal or greater importance are ignored in MACE (e.g. heart failure, arrhythmias, non-stroke-related thromboembolism). Finally, a critical limitation of MACE is that it includes only cardiovascular events; many cardiovascular therapies also affect other organ systems (renal, respiratory, genitourinary), and important treatment-related adverse events (e.g. bleeding, vascular complications, reoperations, early readmissions) are ignored by MACE. Furthermore, more-difficult-to-measure outcomes that may be more important to the patients than most discrete MACE endpoints are not accounted for (e.g. time to recovery, return to work, social functioning, depression, etc.).

Alternative approaches

One option to address the limitations of the traditional MACE endpoint is to expand the composite to include a larger number of cardiovascular and non-cardiovascular events (i.e. atrial fibrillation, heart failure, rehospitalization, etc.). Statistical methods that account for recurrent events (i.e. Andersen–Gill model, joint frailty models, and others)[10] have been described but are not widely adopted. Moreover, these approaches do not address the issues of the varying clinical relevance of different event types and the differences in treatment effect between the MACE components.

Reporting days alive and out of hospital (DAOH) has been proposed as a more clinically meaningful outcome that reflects numerous adverse events.[6] However, hospitalizations and days spent in the hospital are determined not only by the disease process, but also by providers' decisions and logistic considerations that may introduce bias and heterogeneity. In addition, days out of hospital does not necessarily reflect patient quality of life (QOL), increasingly recognized as an important outcome metric. It has been suggested that the 'patient journey' may better be portrayed by adjusting the number of DAOH for the patients' self-reported well-being and the need for therapy escalation, a concept similar to that of quality-adjusted life-years (QALYs) frequently used in cost-effectiveness analyses.[11] The limitations of this approach as described include the arbitrary value attributed to its components, lack of precision of the 5-point ordinal well-being scoring system, and the inclusion of outcomes (hospitalization and change in therapy) that may be driven by subjective decisions.

The win ratio method[12] analyses the composite outcome based on a hierarchy of events of predefined clinical importance and compares pairs of patients from the two trial arms to determine the number of wins, ties, and losses; this method accounts for recurrent events and allows the incorporation of classic cardiovascular events with patient-reported outcomes into a single metric. While challenges with this method have been discussed,[13] the win ratio is being increasingly used in cardiovascular trials.[10]

A path forward: a hierarchical composite outcome including death and quality of life

Patients often prioritize their QOL over discrete clinical outcomes, such as MI, stroke, or rehospitalization.[14] Few trials have formally assessed patient QOL and have generally assessed it only as a secondary endpoint; QOL has infrequently been included in the primary outcome

of cardiovascular trials. This may in part be ascribed to the perception of QOL (and other patient-reported outcomes) as less objective and more prone to placebo effects and ascertainment bias in open-label trials than 'harder' cardiovascular outcomes. However, several QOL instruments such as the 12-Item Short Form Survey (SF-12), the Seattle Angina Questionnaire (SAQ), and the Kansas City Cardiomyopathy Questionnaire have been developed that afford a standardized objective assessment of patients' QOL after a range of cardiovascular interventions. Improvement in scores from these instruments have been validated to correlate with survival and freedom from hospitalization,[15] and the US Food and Drug Administration recognizes QOL as a valid endpoint for clinical trials.[16] Moreover, the use of QOL as an endpoint overcomes the challenges with selecting and weighting different cardiovascular outcomes, as each clinical event (even of the same type) affects QOL to a variable degree (which may vary in individual patients). In this regard, the use of a generic rather than a disease-specific QOL score reflects both the benefits and the harms of a treatment beyond the cardiovascular system and may be particularly appropriate in trials comparing interventions that have very different risks and benefits as well as non-cardiovascular effects (such as surgery vs. transcatheter interventions or interventional vs. conservative treatments).

Early and late (3–5 years) generic and disease-specific QOL using the SF-12, SF-36, SAQ, and other instruments has been reported in numerous prior cardiovascular trials, including ISCHEMIA, SYNTAX, FREEDOM, and EXCEL, although only at discrete time points. It is important to prespecify a prolonged duration of follow-up that captures the effect of the tested intervention on QOL in both the early peri-procedural and later time periods. Building on this concept, we believe that QOL should be assessed frequently, and its change from baseline should be time-averaged over the entire follow-up duration to reflect the entire 'patient journey' and to avoid over-emphasizing changes in QOL at any single fixed time point. The choice of a disease-specific QOL instrument must be carefully individualized for each trial to reflect the nature of the disease and the treatments being studied. This consideration does not apply to generic QOL instruments that have been validated in patients with a variety of chronic conditions and can be used to reflect overall patient well-being and health status across the total spectrum of cardiovascular disease.

Potential limitations of our proposed approach must be considered. Frequent QOL assessments during follow-up are desirable to capture changes over time; however, these study processes may increase costs and staff and patient burden. Completeness and rigor of the QOL data is critical. A robust patient engagement plan employed during the course of the study is essential. The QOL follow-up completion rates should be high if QOL is the primary endpoint of interest. Patient and QOL-assessor blinding is optimal for the interpretation of patient-reported outcomes. If the patient cannot be blinded, assessor bias and site burden may be reduced by employing a highly trained central follow-up unit blinded to randomization to remotely collect QOL data. The trial must be adequately powered to detect clinically meaningful changes in hierarchical death and QOL, and the statistical plan must pre-specify the approach to missing data, among other issues.

A traditional composite event endpoint may still prove useful when comparing treatments that are very similar (e.g. two anticoagulants or lipid-lowering therapies). However, to comprehensively assess the global net clinical impact of therapies with differing risk–benefit profiles that may have effects on numerous organ systems, a hierarchical composite outcome that includes death and time-averaged change in generic QOL offers promise to overcome the major limitations of the classic 'unsatisfactory' MACE outcome and reflects what patients desire from healthcare delivery—to 'live longer and live better'. Such an approach is being utilized in the REvascularization CHoices Among under-Represented Groups Evaluation (RECHARGE) trial (NCT 06399692 and 06399705) in which 1200 women and minority group patients with left main or multivessel coronary artery disease are being randomized to percutaneous coronary intervention vs. coronary artery bypass graft surgery. The primary endpoint is the hierarchical composite of death and time-averaged change in generic QOL at 5 years measured by the SF-12v2 questionnaire. The choice of a generic rather than disease-specific QOL instrument was based on patient feedback obtained during the planning stages of this trial; the patients said they regarded their global well-being as more important than any single event or domain metric. However, the time-averaged change in the SAQ score is a powered secondary outcome in RECHARGE. In addition, >20 cardiovascular and non-cardiovascular adverse events will be adjudicated to assess their relationship to the primary outcome. Funded by the Patient-Centered Outcomes Research Institute, RECHARGE will not only generate important data in patient groups that have been poorly represented in prior revascularization trials, but also introduces a potentially transformative pathway for assessing the totality of the risks and benefits after cardiovascular interventions in an endpoint that is most meaningful to patients and overcomes the limitations of the traditional MACE endpoint.

Declarations

Disclosure of Interest

G.W.S. has received speaker honoraria from Medtronic, Pulnovo, Abiomed, Amgen, and Boehringer Ingelheim; has served as a consultant to Abbott, Daiichi Sankyo, Ablative Solutions, CorFlow, Cardiomech, Robocath, Miracor, Vectorious, Apollo Therapeutics, Elucid Bio, Cardiac Success, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, HighLife, Elixir, Remote Cardiac Enablement, and Aria; and has equity/options from Cardiac Success, Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Valfix, and Xenter. G.W.S.'s employer, Mount Sinai Hospital, receives research grants from Shockwave, Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense Webster, Vascular Dynamics, Pulnovo, V-wave, and the Patient-Centered Outcomes Research Institute (via the Weill Cornell Medical Center). E.B. receives grants from Astra Zeneca, Daiichi Sankyo, Merck, and Novartis, textbook royalties from Elsevier, consulting fees from Amgen, Bristol Myers Squibb, Boehringer Ingelheim/Lilly, Cardurion, Edgewise, and Verve, lecture honoraria from ADA Premier India, the International Atherosclerosis Society, Inova Advanced Heart Failure Symposium, the Society of Cardiovascular Computed Tomography, and the Hypertrophic Cardiomyopathy Society, participates on advisory councils or data safety monitoring boards for Amgen, Cardurion, and Verve, and reports a leadership or fiduciary role in Broadview Ventures. M.G. receives research grants from the National Health Institute, the Patient-Centered Outcomes Research Institute, and the Canadian Institutes for Health and Research and participates in the medical advisory board of Abbott Vascular/Core Diagnostics 3rd Abbott PPMI.

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