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EDITORIAL

Defining the need for cardiovascular event definitions

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Introduction

There has been a transformation in clinical care and outcomes for patients with cardiovascular disease in recent times. This has largely been enabled by the robust evaluation of the safety and efficacy of new pharmaceutical agents and health technologies in randomized clinical trials (RCT). Integral to this progress is the judicious and *a priori* selection and definition of key cardiovascular outcome measures against which an intervention is assessed and evaluated.[1]

Definitions determine results

Alongside testing the efficacy or effectiveness of an intervention, the choice of primary outcome measures and their definitions can determine the result of an RCT. Outcome measures are typically cardiovascular events in cardiovascular trials, and a positive trial can influence guideline recommendations and clinical practice. For example, in the 'Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)' trial, peri-procedural myocardial infarction (MI) was part of the major adverse cardiac or cerebrovascular events (MACE), a composite of primary outcome measures. Peri-procedural MI was defined as either a rise in creatinine kinase myocardial band to greater than 10 times the upper reference limit or greater than five times the upper reference limit with accompanying features such as electrocardiographic changes and angiographic or imaging features of ischaemia.[2] At 3 years, percutaneous coronary intervention (PCI) was non-inferior (margin 4.2 percentage points) to coronary artery bypass graft (CABG) surgery [hazard ratio for MACE 0.93, 95% confidence interval (95% CI) 0.67–1.28, $P = 0.64$]. This finding contributed to the European Society of Cardiology guidelines for revascularization in patients with left main disease that were considered at low to intermediate risk of peri-operative mortality according to their SYNTAX score.[3] Subsequent *post hoc* analyses found that the rate of peri-procedural MI occurring within 48 h after each intervention arm varied significantly according to the definition used. Rates of peri-procedural MI were 2.7% for patients allocated to PCI and 2.4% for CABG surgery ($P = 0.76$) using the more stringent SYNTAX definition, compared with 5.7 and 16.5% ($P < 0.001$) with a subsequent change in direction of effect using SCAI or EXCEL definitions.[4] In SYNTAX, the definition of procedural MI required evidence of elevated cardiac biomarkers and electrocardiographic changes, whereas in SCAI and EXCEL, the definition could be based on cardiac biomarkers alone. The use of internationally agreed, standardized definitions may reduce unnecessary uncertainty following the publication of a study.

Clarity in composite outcome measures

The use of composite outcome measures is increasingly frequent in RCTs.[5] When the incidence of individual components of the composite is expected to be low, a combination provides financial and logistical efficiency to detect a minimally clinically important and statistically significant difference between randomized arms (as well as reducing the probability of a type 2 error). Composite outcome measures may therefore allow RCTs that would not otherwise be feasible, and so have an important role in cardiovascular research.[1] However, this approach has limitations: composites can lead to a loss of clarity over the mechanism of the effect, make comparability between trials more challenging, and clinical interpretation less straightforward.

Both the use of composites and the number of components that constitute a composite in cardiovascular outcome trials have increased over time.[5] Increasing the number of components in a composite will also lead to a higher event rate. Notably, there is wide heterogeneity in the component selection of composites, even when investigating similar interventions for the same disease process.[6] This can make it challenging to interpret the conclusions of a study, especially when 'soft' outcomes with high event rates (such as hospitalization) are grouped together with 'hard' outcomes with fewer events (such as mortality).[7] Some 'softer' outcome measures can also be less relevant and more subjective than others. For example, the recent Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial reported a primary composite of cardiovascular death and worsening heart failure, which was defined as either an urgent outpatient visit or an unplanned hospitalization for heart failure.[8] Urgency of outpatient visits is subjective and difficult to define.

A recent cross-sectional study of composites illustrated that as many as half of all composites for primary outcome measures incorporated a 'soft' outcome. Additionally, 'soft' outcome measures such as revascularization are more likely to determine the results of an overall composite outcome whereas 'hard' outcome, measures

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were shown to contribute the least.[7] A recent example of this was the Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure (DAPA-MI) RCT. The primary composite contained seven components, including all-cause mortality, heart failure hospitalization, non-fatal MI, atrial fibrillation/flutter, the New York Heart Association classification from the last visit, type 2 diabetes mellitus, and a 5% reduction in body weight. The overall positive results of the trial were driven by cardiometabolic outcomes rather than death or non-fatal MI.[9] These results can be misinterpreted, and comparisons of similar RCTs with similar interventions yet different components of a composite are less easily made, although meta-analyses may be possible.

The potential for bias is further increased if outcome measures are not pre-specified and fully reported. The Centre for Evidence-Based Medicine Outcome Monitoring Project (COMPare) trial illustrated that overall outcome reporting in the manuscript was poor amongst publications in five reputable journals, with wide variation in the completeness of reporting pre-specified outcome measures.[10] The included journals were the New England Journal of Medicine, The Lancet, the Journal of American Medical Association, the British Medical Journal and the Annals of Internal Medicine. Furthermore, five novel outcome measures were added on average during the conduct of the study without declaration. These issues can be mitigated through consistency in the component variables and pre-specified, standardized definitions for important and widespread cardiovascular composite outcomes such as MACE.

Use of the same components of a composite, such as MACE, may also lead to divergent results when definitions of MACE differ. This is illustrated in the Nordic-Baltic-British-Left Main Revascularization Study (NOBLE) trial, which, like EXCEL, randomized patients to either PCI or CABG surgery. In the study, MACE was defined as all-cause mortality, non-procedural MI, stroke, and repeat coronary revascularization, whereas in EXCEL, MACE was defined as all-cause mortality, stroke, and procedural MI. By 5 years, MACE was reported for 28% of the PCI group and 18% of the CABG surgery group (HR 1.51, 95% CI 1.13–2.00, $P = 0.0044$).[11] In contrast to EXCEL, the authors concluded that CABG surgery was superior to PCI despite using 'the same' primary composite outcome measure. It has been proposed that MACE should not be routinely used as a cardiovascular outcome measure—and if it is used, then the accompanying definitions must be standardized.[7]

Standardization as a solution

There is an argument in favour of reporting cardiovascular events in a manner that is more informative for clinicians, regulators, and patients. The standardization of clinical variables and their definitions is central to this. Having a catalogue of key cardiovascular outcome measures underpinned by the available evidence and supported by international agreement would enable more efficient evaluation and interpretation of the safety and efficacy of drug and device development. This could allow for the construction of pre-specified composites as part of the repository (such as vascular complications) that are device-specific. General composites could be carefully constructed and defined. For example, MACE should come into the three-point (death, MI, and stroke), four-point (unstable angina in addition), or five-point (heart failure in addition) definitions that have been recommended previously.[6] An example is the Valve Academic Research Consortium (VARC) definitions and pre-specified composites for transcatheter aortic valve intervention (TAVI).[12]

A weighted meta-analysis of over 3000 patients from 16 studies from 1 year of study demonstrated its wide adoption in the TAVI research community. This illustrates a desire for standardized definitions and the potential speed of implementation.[13]

Given the rapid pace of technology, traditional outcome measures such as MI could be surpassed with the advent of new biomarkers and imaging modalities. However, updating these outcome measures would be particularly useful as part of a wider framework of key cardiovascular endpoints. Within a decade, VARC has undergone two iterations with updated definitions of MI and the implementation of new outcome measures such as valve thrombosis to accommodate the recent adoption of TAVI in younger patients.[14]

We recognize that not all cardiovascular outcome measures could be contained within a catalogue, and niche studies will require nuanced variables and definitions to address specific populations and interventions. But for studies investigating similar cardiovascular disease processes, there is an opportunity to standardize outcome measures for wider use.

Conclusion

Heterogeneity in the definitions of events in cardiovascular research may have an important impact on the results of clinical trials, which in turn influence guidelines and practice. There is an opportunity to reach consensus on the standardized variables and their definitions across the whole of cardiology for use in cardiovascular research. Internationally endorsed catalogues of definitions allow clinicians, policymakers, and patients to have confidence in research findings. The consistency and transparency of their use enable us to compare findings within similar areas of cardiology while allowing for trial-specific definitions.

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