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Computing Methods for Composite Clinical Endpoints in Unprotected Left Main Coronary Artery Revascularization

A Post Hoc Analysis of the DELTA Registry

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ABSTRACT

OBJECTIVES The study sought to investigate the impact of different computing methods for composite endpoints other than time-to-event (TTE) statistics in a large, multicenter registry of unprotected left main coronary artery (ULMCA) disease.

BACKGROUND TTE statistics for composite outcome measures used in ULMCA studies consider only the first event, and all the contributory outcomes are handled as if of equal importance.

METHODS The TTE, Andersen-Gill, win ratio (WR), competing risk, and weighted composite endpoint (WCE) computing methods were applied to ULMCA patients revascularized by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) at 14 international centers.

RESULTS At a median follow-up of 1,295 days (interquartile range: 928 to 1,713 days), all analyses showed no difference in combinations of death, myocardial infarction, and cerebrovascular accident between PCI and CABG. When target vessel revascularization was incorporated in the composite endpoint, the TTE ($p = 0.03$), Andersen-Gill ($p = 0.04$), WR ($p = 0.025$), and competing risk ($p < 0.001$) computing methods showed CABG to be significantly superior to PCI in the analysis of 1,204 propensity-matched patients, whereas incorporating the clinical relevance of the component endpoints using WCE resulted in marked attenuation of the treatment effect of CABG, with loss of significance for the difference between revascularization strategies ($p = 0.10$).

CONCLUSIONS In a large study of ULMCA revascularization, incorporating the clinical relevance of the individual outcomes resulted in sensibly different findings as compared with the conventional TTE approach. In particular, using the WCE computing method, PCI and CABG were no longer significantly different with respect to the composite of death, myocardial infarction, cerebrovascular accident, or target vessel revascularization at a median of 3 years. (J Am Coll Cardiol Intv 2016;9:2280–8) © 2016 by the American College of Cardiology Foundation.

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Percutaneous coronary intervention (PCI) is broadly accepted as an alternative to coronary artery bypass grafting (CABG) when patients with unprotected left main coronary artery (ULMCA) disease present with low-to-intermediate angiographic complexity, which reflects contemporary guidelines (1) and the results of a plethora of meta-analyses (2–4), trials (5–8), and registries (9–13). Over the years, these studies have mostly investigated the comparative efficacy of PCI and CABG with respect to a primary composite endpoint mixing disparate cerebrovascular outcomes (i.e., death, myocardial infarction [MI], and cerebrovascular accident [CVA] with or without repeat revascularization).

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In both randomized and nonrandomized studies, the rationale behind merging events into a single composite measure is that of increasing the power of the comparison between study groups, which is expected to reduce the chance of untruly negative results. However, an inherent limitation of using a composite endpoint in ULMCA studies is that all the contributory outcomes are handled as if of equal importance (14). This becomes problematic when the implications of a relatively soft event (i.e., repeat revascularization) are contrasted with those of other disabling nonfatal events (i.e., MI or CVA). In addition, when composite endpoints are used, time-to-event (TTE) statistics consider only the first event, and the outcomes are typically counted in a nonhierarchical order (i.e., if repeat revascularization occurs in 1 group before death, only the first contributes to the drop of the corresponding curve for event-free survival). Finally, death may exert a competing effect on the risk of nonfatal events (15).

To address these limitations, multiple statistical approaches have been introduced that consider all events occurring at follow-up, incorporate their clinical relevance, or account for the competing risk of death (16–19). The merit of these computing methods, and their impact on the results of contemporary studies comparing PCI and CABG for ULMCA disease, have never been systematically investigated. The aim of this study was to explore the attributes of different analytical strategies for composite endpoints using DELTA (Drug Eluting stent for LefT main coronary Artery disease), 1 of the largest contemporary registries of ULMCA disease, as an example.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

CVA = cerebrovascular accident

HR = hazard ratio

MACCE = major adverse cardiac or cerebrovascular event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TTE = time-to-event

TVR = target vessel revascularization

ULMCA = unprotected left main coronary artery

WCE = weighted composite endpoint

WR = win ratio

METHODS

STUDY DESIGN AND POPULATION. The methods and definitions of the DELTA registry have been published previously (9). Briefly, DELTA included all-comers patients with ULMCA disease treated by PCI with drug-eluting stents or CABG between April 2002 and April 2006 at 14 international sites (9). The primary analysis was based on the composite of death, MI, or CVA, and a secondary analysis was based on the composite of death, MI, CVA, and target vessel revascularization (TVR), herein cumulatively referred as major adverse cardiac or cerebrovascular events (MACCE). In the present study, the death/MI/CVA and MACCE results of DELTA were used as a reference to explore the effect of applying 4 computing strategies other than the conventional TTE approach, namely: 1) Andersen-Gill; 2) win ratio (WR); 3) competing risk; and 4) weighted composite endpoint (WCE). Merits and limitations of these approaches are summarized in **Table 1**.

ANDERSEN-GILL. The Andersen-Gill counting process is an extension of the traditional Cox model in which a subject contributes to the risk set for an event as long as being under observation at the time the event occurs (20). At variance with the TTE approach, repeated events are described among all components of the primary endpoint for the overall period, assuming equal probability. To avoid too much weight for related events occurring at the same time, a 1-day blanking period was applied. The results were reported as hazard ratio (HR) and 95% confidence interval (CI).

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