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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 non-hierarchical 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.

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).

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

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WIN RATIO. The WR is a rank-based approach for assessing treatment superiority by first ranking and then pairing patients between treatment groups according to different scores, as described by Pocock et al. (17). To the purpose of the present study, 3 scores were used: 1) the propensity score built by logistic regression to match patients undergoing PCI or CABG in the first report of the DELTA registry (9); 2) the SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score; and 3) the SYNTAX score II (PCI calculator). A multiple imputation strategy was used for patients missing data required to compute their SYNTAX and SYNTAX II-PCI scores, as previously described (21). In the 3 scenarios (propensity score, SYNTAX score, and SYNTAX II score), each patient pair was evaluated to establish whether one had a death event before the other. If this was not the case (i.e., both matched patients were alive at the end of follow-up), the remaining pairs were then evaluated for the occurrence of CVA, then subsequently MI, and finally TVR (the latter in the MACCE analysis only). When pairing patients by the use of the SYNTAX and SYNTAX II scores, the treatment groups were unbalanced in number; therefore, after ranking, patients in the larger group (i.e., PCI) were randomly removed if a matching for the score was not found with the CABG counterpart. When patients in the PCI group had the same score, a random one was selected. Once the pairs were created, the number of "wins" (i.e., pairs where the CABG group had the event first) were divided by the number of "losses" (i.e., pairs where the PCI group had the event first) to provide the WR for PCI versus CABG (i.e., with a WR >1 indicating PCI as the better revascularization strategy, and values <1 indicating PCI as worse). Corresponding 95% CIs and significance tests for the WRs were calculated.

COMPETING RISK. A competing risk is an event that either hinders the observation of the event of interest or modifies the chance that this event occurs. Competing risks methods take these issues into account and, for composite endpoints, allow disentangling the contribution of an intervention on each type of event (19). In this study, the competing risk of death for combined nonfatal outcomes (MI/CVA or MI/CVA/TVR) was accounted using the Fine-Gray model, with results reported as HR and 95% CI (22).

WEIGHTED COMPOSITE ENDPOINT. The WCE computing approach extends the traditional TTE methodology by determining a weight for each of the nonfatal events (16,23). Briefly, each patient was attributed a weight of 1.0, which remained unaltered if no events occurred at follow-up. Patients with nonfatal events were considered to have their contribution to the group size reduced in weight, such that the additional weight was lost for subsequent events and the full (or residual) weight was lost for a death event. Consistent with a previous study (16), we assigned weights of 0.47 and 0.38 for CVA and MI, respectively. For TVR, a Markov decisional analytical model was designed to identify the cut off value that offsets the anticipated increase in TVR with PCI compared with CABG (24). Data from available ULMCA trials, registries, and meta-analyses were used to inform the Markov model, which finally assigned a weight of 0.25 to TVR (2–13). On the basis of the previous values, patients without events were attributed a cumulative weighting of 1, patients with CVA had 0.53 (1.00 − 0.47), patients with MI had 0.62 (1.00 − 0.38), and patients with TVR had 0.75 (1.00 − 0.25). Patient with ≥2 events during the follow-up period, if any, were attributed a cumulative weight reduced by all events.

TABLE 1 Characteristics of Different Computing Methods for Composite Clinical Outcomes

	Time-to-Event	Andersen-Gill	Win Ratio	Competing Risk	WCE
Uses first event	Yes	Yes	No	Yes	Yes
Uses all events	No	Yes	No	No	Yes
Death as most relevant	No	No	Yes	No	Yes
Uses time-to-event	Yes	Yes	No	Yes	Yes
Distribute weights	No	No	No	No	Yes

WCE = weighted composite event(s).

STATISTICAL ANALYSIS. In the DELTA registry, the propensity score was calculated by means of a nonparsimonious multivariable logistic regression model that included age, gender, diabetes, smoking, family history of coronary artery disease, unstable angina, acute MI, chronic kidney disease, left ventricular ejection fraction, prior CABG, prior PCI, multivessel disease, and concurrent right coronary artery disease (9). Propensity score matching was performed 1:1 with a ±0.03 caliper and no replacement. A multivariable Cox proportional hazards regression model was used to obtain adjusted analyses, as previously described (9). Traditional TTE curves for propensity-matched patients were generated with the Kaplan-Meier method and compared by the log-rank test. WCE Kaplan-Meier curves were also plotted. The TTE risks of death/MI/CVA and MACCE were reported for PCI versus CABG as HRs and corresponding 95% CIs. All the analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Illinois) and R version 2.16 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The DELTA registry comprised a total of 2,775 patients with ULMCA disease (1,874 treated with PCI and 901 treated with CABG) (9). Baseline clinical characteristics of the study groups before and after propensity score matching of 602 pairs are reported in Table 2. The c-statistic of the propensity score model was 0.78, and the Hosmer-Lemeshow p value was 0.38, indicating good discrimination and calibration, respectively. At a median follow-up of 1,295 days (interquartile range: 928 to 1,713 days), in the unmatched cohort, there were 367 deaths, 108 MIs, 55 CVAs, and 334 TVRs (Table 3). In the matched cohort, there were 141 deaths, 23 MIs, 18 CVAs, and 102 TVRs, with only 4 patients experiencing a second event within the follow-up period (2 patients had MI and later had TVR, 1 patient had TVR and later had a CVA, and 1 patient had TVR and later had MI).

TIME-TO-EVENT. Using the TTE approach, there were no differences between PCI and CABG for death/MI/CVA in either unadjusted (HR: 1.11; 95% CI: 0.89 to 1.36; p = 0.38), multivariable-adjusted (HR: 1.11; 95% CI: 0.85 to 1.42; p = 0.47), or propensity score-matched (HR: 0.91; 95% CI: 0.66 to 1.26; p = 0.57) analyses. By contrast, CABG was superior to PCI with respect to MACCE in either unadjusted (HR: 1.58; 95% CI: 1.32 to 1.90; p < 0.0001), multivariable-adjusted (HR: 1.64; 95% CI: 1.33 to 2.03; p < 0.0001), or propensity score-matched (HR: 1.35; 95% CI: 1.03 to 1.76; p = 0.03) analyses, driven by a significant difference in TVR.

ANDERSEN-GILL. Applying the Andersen-Gill counting process to the outcomes of the propensity-matched cohort confirmed the results of the TTE analysis. In fact, the HRs for death/MI/CVA and MACCE were 1.01 (95% CI: 0.76 to 1.36; p = 0.93) and 1.41 (95% CI: 1.12 to 1.79; p = 0.04), respectively.

WIN RATIO. In the first scenario (propensity score, 602 pairs), the WRs for death/MI/CVA and MACCE were 1.04 (95% CI: 0.77 to 1.39; p = 0.82) and 0.75 (95% CI: 0.58 to 0.96; p = 0.025). In the second scenario (SYNTAX score, 901 pairs), the WRs for death/MI/CVA and MACCE were 0.98 (95% CI: 0.77 to 1.26; p = 0.90) and 0.79 (95% 0.64 to 0.97; p = 0.028). In the third scenario (SYNTAX II score, 901 pairs), the WRs for death/MI/CVA and MACCE were 0.94 (95% CI: 0.73 to 1.20; p = 0.611) and 0.71 (95% CI: 0.58 to 0.88; p = 0.001). Overall, all 3 scenarios—regardless of the score used for pairing—showed similar results that were consistent with the TTE analysis, suggesting CABG to represent the best strategy only when TVR was included in the composite endpoint (Figure 1).

TABLE 2 Baseline Characteristics of the Propensity-Matched Groups

	All (N = 1,204)	PCI (n = 602)	CABG (n = 602)	p Value
Male	797 (66.2)	406 (67.4)	391 (65.0)	0.36
Age, yrs	66.5 ± 11.0	66.3 ± 11.5	66.8 ± 10.5	0.41
Family history of CAD	327 (27.2)	162 (26.9)	162 (27.4)	0.85
Hypertension	808 (67.1)	398 (66.1)	398 (68.1)	0.46
Dyslipidemia	757 (62.9)	363 (60.3)	363 (65.6)	0.07
Smoker	512 (42.5)	253 (42.0)	253 (43.0)	0.73
Diabetes	374 (31.1)	184 (30.6)	184 (31.6)	0.71
CKD	62 (5.1)	30 (5.0)	32 (5.3)	0.79
Clinical presentation				
Unstable angina	532 (44.2)	532 (44.7)	532 (43.7)	0.73
Acute MI	178 (14.8)	178 (15.3)	178 (14.3)	0.63
Previous CABG	47 (3.9)	47 (4.3)	47 (3.5)	0.46
Previous PCI	198 (16.4)	198 (16.1)	198 (16.8)	0.76
LVEF, %	53.2 ± 11.3	53.2 ± 11.3	53.2 ± 11.4	0.96
EuroSCORE, n	5.0 ± 3.2	5.0 ± 3.6	5.1 ± 2.9	0.60
Multivessel disease	1,127 (93.6)	564 (93.7)	563 (93.5)	0.91
RCA disease	841 (69.9)	427 (70.9)	414 (68.8)	0.41
Distal lesion location	777 (64.5)	387 (64.5)	390 (64.8)	0.92

Values are n (%) or mean ± SD.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

COMPETING RISK. After accounting for the competing risk of death, the HRs for combined nonfatal events were 0.85 (95% CI: 0.46 to 1.58; p = 0.61) with respect to MI/CVA and 1.89 (95% CI: 1.33 to 2.68; p < 0.001) with respect to MI/CVA/TVR.

WEIGHTED COMPOSITE ENDPOINTS. Kaplan-Meier curves using the TTE approach and modified

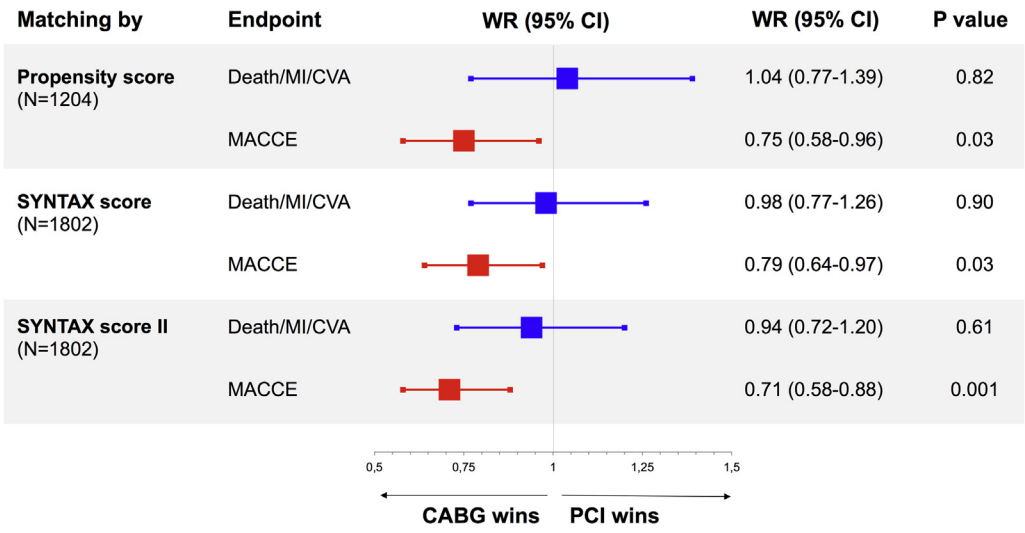
TABLE 3 Clinical Events in the Unmatched Cohorts

	PCI (n = 1,874)	CABG (n = 901)
In-hospital events		
Cardiac death	33 (1.7)	20 (2.2)
Noncardiac death	8 (0.5)	9 (1.0)
MI	88 (4.7)	213 (23.6)
CVA	4 (0.2)	12 (1.3)
TVR	15 (0.8)	3 (0.3)
MACCE	148 (7.9)	257 (28.4)
Events at follow-up		
Cardiac death	140 (7.5)	61 (6.8)
Noncardiac death	124 (6.6)	42 (4.6)
MI	75 (3.7)	33 (4.0)
CVA	30 (1.6)	25 (2.9)
TVR	290 (15.5)	44 (5.2)
MACCE	659 (34.9)	205 (23.5)

Values are n (%).

CVA = cerebrovascular accident; MACCE = major adverse cardiac or cerebrovascular event(s); TVR = target vessel revascularization; other abbreviations as in Table 2.

FIGURE 1 Win Ratio Estimates Based on Different Matching Criteria



Graphical representation of win ratio (WR) estimates and corresponding 95% confidence intervals (CIs) in patients from the DELTA (Drug Eluting stent for LefT main coronary Artery disease) registry for the comparison of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), based on different matching criteria. The results were confirmative of the corresponding traditional time-to-event analyses and did not appear to rely on the method chosen for matching (i.e., propensity score, SYNTAX [Synergy between PCI with Taxus and Cardiac Surgery] score, SYNTAX score II). CVA = cerebrovascular accident; MACCE = major adverse cardiac or cerebrovascular event(s); MI = myocardial infarction.

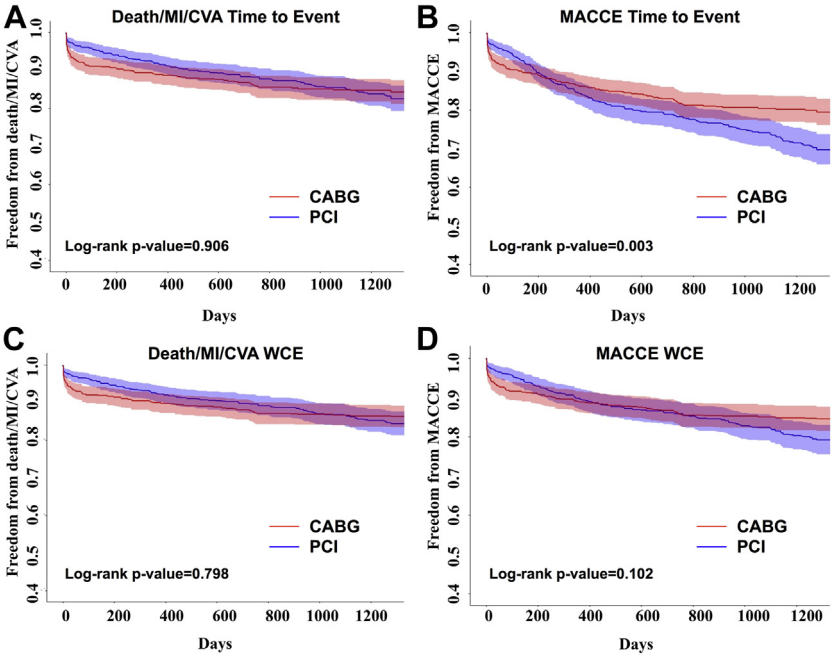
Kaplan-Meier curves using WCEs are shown for PCI and CABG groups of patients matched by propensity score in Figure 2. Table 4 reports corresponding 1-, 2-, and 3-year Kaplan-Meier estimates of PCI and CABG as reflected by the TTE and WCE analyses, as well as the absolute risk differences between PCI and CABG, and within PCI or CABG by using different computing methods. The profile of the TTE and WCE curves for death/MI/CVA was comparable (Figure 2), with the outcomes of PCI and CABG diverging during the first 100 days and the difference attenuating over time until the curves reached substantial overlap at the end of the follow-up period. Inclusion of TVR in the composite MACCE endpoint resulted in CABG being superior to PCI in the TTE analysis, with a progressive separation of the curves starting at 9 months ($p = 0.003$) (Figure 2). By contrast, this difference was markedly attenuated and no longer significantly different ($p = 0.10$) when the WCE computing method was used (Table 4). This finding was consistent in a sensitivity analysis where the weight given to TVR was 0.30 rather than 0.25 ($p = 0.08$).

EFFICIENCY OF EVENT USE. The distribution and use of events according to the TTE, Andersen-Gill, WR, competing risk, and WCE methods are reported in Table 5. The Andersen-Gill and WCE methods included all events, whereas the TTE, WR, and competing risk methods used fewer than all collected events.

DISCUSSION

TVR has been for years the driving force of the observed superiority of CABG over PCI in ULMCA studies (25). However, the true impact of repeat revascularization on patient well-being and quality-adjusted life-years has been questioned (26), and some interventional cardiologists argue that the reduction in revascularization with CABG does not outweigh the increased recovery time of cardiac surgery, and the higher risk of perioperative CVA (14). In the DELTA registry, there was evidence of substantial equipoise between PCI and CABG for death/MI/CVA, but not for MACCE (9). This is in line with the results of several meta-analyses (2-4), randomized clinical trials (5-8), and observational studies (9-13). On this background, we sought to explore whether applying alternative methods for assessing clinical outcomes within composite endpoints may depotentiate the confounding effect of TVR, and provide insights on potentially

FIGURE 2 Event-Survival Curves in the Propensity-Matched Cohorts



Survival curves with 95% CIs in PCI and CABG patients from the DELTA (Drug Eluting stent for LefT main coronary Artery disease) registry, matched by propensity score (602 pairs). Time-to-event freedom from **(A)** death/MI/CVA and **(B)** MACCE. WCE curves for **(C)** death/MI/CVA and **(D)** MACCE. WCE = weighted composite endpoint; other abbreviations as in Figure 1.

different interpretations to the results of contemporary ULMCA studies.

In our analysis, the use of a computing method that describes repeated events among all components of the primary endpoint (i.e., Andersen-Gill), prioritizes all follow-up events (i.e., WR), or accounts for the potential of death to obscure subsequent nonfatal outcomes (i.e., competing risk) determined no significant deviation from what was obtained by computing only the first event regardless of its fatality rate (i.e., TTE). By contrast, incorporating the clinical relevance of the individual outcomes (i.e., WCE) resulted in PCI and CABG being nonsignificantly different at a median of 3 years with respect to the composite endpoint of MACCE, which comes at variance with the propensity-matched TTE analysis of PCI and CABG in DELTA. Overall, these findings imply that the sizeable impact of TVR on MACCE in ULMCA studies may be corrected or attenuated by using an alternative computing approach that accounts for all events occurring at follow-up and incorporates their clinical relevance.

To the best of our knowledge, this is the first study to apply additional methods other than TTE for assessing clinical outcomes in the context of a study of PCI or CABG for ULMCA disease. The Andersen-Gill computing method was introduced in 1982, and is regarded as a meaningful approach to account for repeated events within the follow-up period (20). Indeed, a patient undergoing ULMCA revascularization may experience from repeated events during the subsequent years (i.e., multiple TVRs), but this was unlikely to happen in the propensity-matched cohort of the DELTA registry, where the number of repeated events was low, and the potential for events that may be under-reported or insufficiently captured by the extent of follow-up available cannot be entirely ruled out (9). These considerations may contribute to explain why in our study, the results of the Anderson-Gill analysis substantially replicated those of the TTE analysis, regardless of whether TVR was incorporated or not in the composite endpoint. In a population with multiple recurrent events, the results of the Andersen-Gill method could have been different. Also notably, the Andersen-Gill method assumes equal probabilities for first and subsequent events, which may be an unlikely assumption in a general population, although this issue has been likely minimal in this study due to the few number of repeated events. Alternative models have been

TABLE 4 Kaplan-Meier Estimates of Survival Free From Death/MI/CVA and MACCE Based on the TTE and WCE Computing Methods

	TTE		WCE		Δ	Δ	Δ	Δ
	PCI (A)	CABG (B)	PCI (A′)	CABG (B′)	PCI (A′-A)	CABG (B′-B)	TTE (B-A)	WCE (B′-A′)
Death/MI/CVA								
1 year	91.8%	88.9%	92.5%	89.9%	+0.7%	+1.0%	-2.9%	-2.6%
2 years	88.1%	86.4%	89.6%	87.9%	+1.5%	+1.5%	-1.7%	-1.7%
3 years	85.4%	84.9%	86.9%	86.7%	+1.5%	+1.8%	-0.5%	-0.2%
MACCE								
1 year	84.1%	86.0%	89.5%	88.8%	+5.4%	+1.8%	+1.9%	-0.7%
2 years	78.4%	82.4%	85.8%	86.4%	+7.4%	+4.0%	+4.0%	+0.6%
3 years	74.0%	80.3%	82.3%	84.9%	+8.3%	+4.5%	+6.3%	+2.6%

TTE = time-to-event; WCE = weighted composite event(s); other abbreviations as in Tables 2 and 3.

described that take the varying nature of risk for repeated events into account (27).

The WR analysis was introduced in 2012 and so far investigated only in few clinical scenarios (16,17). This approach allows prioritizing the hardest outcomes within a composite endpoint. Interestingly, with the WR, more of the component events are potentially included and computed in the analysis, whereas TTE retains only 1 event. However, because this method prioritizes and retains events, a number of nonfatal endpoints experienced by a subject are finally excluded. This explains why the largest proportion of events that went unused by the different computing methods was observed with the WR. Being a rank-based approach, calculation of the WR requires pairing of patients between treatment groups according to a risk score. The rationale for pairing patients by propensity score in our study was that of using one of the most accepted methodologies to adjust for baseline imbalances that could have influenced the patient attribution to a treatment group rather than the other in a large registry (28,29). For exploratory purposes, the SYNTAX and SYNTAX II scores were also used to reflect the underlying risk for the outcomes of interest and investigate their individual ability and implication as a matching criterion (21,30). Interestingly, all the 3 approaches provided similar results, which highlights the ability of the SYNTAX score and SYNTAX score II to capture and possibly maximize the control of major confounding factors affecting treatment selection in ULMCA disease.

Because death was the most frequent first event in the DELTA registry, we also explored whether a competing risk of mortality exists over the composite of nonfatal outcomes (i.e., MI/CVA and MI/CVA/TVR). Obviously, if a patient dies, there is no chance to experience subsequent nonfatal outcomes at later follow-up. The results of the competing risk analysis demonstrate that this bias was unlikely to affect the results of the DELTA registry, and confirmed the major role of TVR in driving the difference between PCI and CABG.

Using WCE allows attributing a weight to each type of event within a composite endpoint, differentiating its components on the basis of their severity and clinical impact. In addition, WCE allows including in the analysis multiple events occurring over time. Capturing the second event(s) is potentially relevant, as recurrences have clear implications for both health care costs and quality of life: this may be true especially when long-term follow-up is planned and the majority of events are nonfatal. Even more importantly, the attribution of a differential weight to each event addresses the problematic interpretation of mixing hard and soft outcomes within a composite endpoint, which frequently occurs in studies of ULMCA revascularization. Notably, the WCE method is different from the Andersen-Gill approach that also considers second events, because in that case, the weights of all recurrent events are considered equal. Our hypothesis of the WCE analysis displaying different results from the TTE computing method proved to be true once tested in the DELTA registry. In fact, PCI was no longer associated with worse outcomes compared with CABG when the lower prognostic weight of TVR over death, MI and CVA was taken into account. It can be speculated that weighting the lower risk of CVA compensates the excess in TVR with PCI compared with CABG patients (2). On this background, whether the use of second-generation drug-eluting stents—poorly represented in the DELTA registry—further modifies this equation, moving the pendulum toward PCI, may warrant future investigation.

The EXCEL (Evaluation of the Xience Everolimus-Eluting Stent Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial (NCT01205776) recently compared PCI with second-generation drug-eluting stents and CABG with respect to the composite of all-cause death, MI, or stroke at 3 years (31). By contrast, the NOBLE (Nordic-Baltic-British Left Main Revascularization Study) trial (NCT01496651) compared PCI with second-generation drug-eluting stents and CABG with respect to the 5-year combined endpoint of death, stroke, MI, and new revascularization (PCI or CABG) (32). Incorporation of repeat revascularization in the primary endpoint of the NOBLE trial is one of the potential explanations for the difference in the results and conclusions of the two trials (31,32). In this context, challenging the study findings of NOBLE by using WCE is of interest.

TABLE 5 Distribution and Weighting of MACCE by Computing Method

	All		Death		MI		CVA		TVR	
	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI	CABG
All events*	169 (Ref)	115 (Ref)	75 (Ref)	66 (Ref)	13 (Ref)	10 (Ref)	6 (Ref)	12 (Ref)	75 (Ref)	27 (Ref)
TTE	166 (98.2)	114 (99.1)	75 (100.0)	66 (100.0)	13 (100.0)	9 (90.0)	5 (83.3)	12 (100.0)	73 (97.3)	27 (100.0)
Andersen-Gil	169 (100.0)	115 (100.0)	75 (100.0)	66 (100.0)	13 (100.0)	10 (100.0)	6 (100.0)	12 (100.0)	75 (100.0)	27 (100.0)
WR†	141 (83.4)	103 (89.5)	68 (90.7)	63 (95.5)	11 (84.6)	10 (90.9)	6 (100.0)	12 (100.0)	56 (75.7)	18 (69.2)
Competing risk	166 (98.2)	114 (99.1)	75 (100.0)	66 (100.0)	13 (100.0)	9 (90.0)	5 (83.3)	12 (100.0)	73 (97.3)	27 (100.0)
WCE	169 (100.0)	115 (100.0)	75 (100.0)	66 (100.0)	13 (100.0)	10 (100.0)	6 (100.0)	12 (100.0)	75 (100.0)	27 (100.0)

Values are n (%). *In the periprocedural period (i.e., within 72 h), there were 9 deaths, 3 MIs, 0 CVAs, and 1 TVR in the PCI group and 20 deaths, 2 MIs, 2 CVAs, and 2 TVRs in the CABG group. †With the win ratio (WR), more of the component events are potentially included and computed in the analysis, whereas TTE retains only 1 event. However, because this method prioritizes and retains events, a number of nonfatal endpoints experienced by a subject are finally excluded.

TVR = target vessel revascularization; Ref = reference; other abbreviations as in Tables 2, 3, and 4.

STUDY LIMITATIONS. We acknowledge some important limitations of our study. The impact of different computing strategies for composite endpoints was tested on a propensity-matched cohort from a large registry, rather than a randomized clinical trial. However, the propensity-matched results of the DELTA registry are in line with existing literature, including randomized trials, and the impact of confounding has been minimized—although not eliminated—by a well-calibrated and discriminative model. Indeed, using randomized data would have not necessarily been a better method for investigating the WR, which requires matching being performed by a risk score rather than the play of chance. The attribution of weights for the purposes of the WCE analysis might sound arbitrary. However, for MI and CVA, we used weights attributed on the basis of a rigorous consensus (16). Because such weights have not been determined for TVR, we developed a Markov model, and based on the available literature, we found a clinically plausible value of 0.25. A sensitivity analysis in which the weight was increased at 0.30 showed consistent results. We finally acknowledge that our results apply to the cohort of patients included in the DELTA registry, but could have been different in other settings with a higher rate of recurrent events or a larger disproportion between hard and soft endpoints.

CONCLUSIONS

Repeat revascularization is the major contributing factor to explain the superiority of CABG over PCI for MACCE in studies of ULMCA disease. In this post hoc analysis of the DELTA registry, incorporating the clinical relevance of individual outcomes within MACCE resulted in a sensible deviation from the results otherwise obtained by the conventional TTE analysis, with PCI and CABG being no longer different at a median of 3 years.

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PERSPECTIVES

WHAT IS KNOWN? Time-to-event 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.

WHAT IS NEW? In ULMCA revascularization studies, weighting events is the most effective method to reduce the impact of TVR on the combined clinical endpoint, resulting in no difference between PCI and CABG at a median of 3 years.

WHAT IS NEXT? The weight of TVR should be taken into account in revascularization studies that use combined primary endpoints. The impact of computing methods for composite endpoints other than time-to-event statistics should be reappraised in populations with long-term follow-up and multiple repeated nonfatal events.

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