Myocardial Revascularization Trials: Beyond the Printed Word

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Abstract

This article reviews the context and evidence around recent myocardial revascularization trials, which compared percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG) for the treatment of left main and multivessel coronary artery disease. We develop the rationale that some of the knowledge synthesis resulting from these trials, particularly with regards to the claimed noninferiority of PCI beyond non-diabetic patients with low anatomic complexity, may have been impacted by trial design, patient selection based on suitability towards PCI, and endpoint optimization favoring PCI over CABG. We provide recommendations that include holding a circumspect interpretation of the currently available evidence, as well as suggestions for the collaborative design and conduct of future clinical trials in this and other fields.

Over the last two decades, the question of whether percutaneous coronary intervention (PCI) is as effective a form of myocardial revascularization as coronary artery bypass grafting (CABG), for the treatment of left main (LM) and multivessel coronary artery disease (CAD), has been studied in more than a dozen, sizable randomized controlled trials (RCTs). Nowadays, cardiologists and cardiac surgeons agree that PCI is a safe and effective modality for 1) patients acutely presenting with ST-segment elevation myocardial infarction (MI); 2) patients with LM disease and low-to-intermediate anatomic complexity; and 3) selected, non-diabetic patients with multivessel CAD who have focal involvement and low anatomic complexity. At the other end of the spectrum, 1) patients who have extensive or diffuse multivessel CAD; 2) patients with LM disease and high anatomic complexity; and 3) patients with diabetes mellitus and multivessel CAD are considered likely to fare better with CABG, unless co-morbidities are significant, surgical risk is high, or the potential for long-term survival is limited. Cardiologists and cardiac surgeons also generally agree that a separate discussion should take place, after the diagnostic coronary angiography, with patients who have stable CAD and who fall outside the above criteria. During this discussion, a Heart Team recommendation, which takes into consideration not only the patient's characteristics and preferences, but also the levels of expertise at the center, should be provided to the patient, who can decide outside the constraints of an urgent setting.

There also remain areas of major controversy in the field of myocardial revascularization. From a technical perspective, interventional cardiologists and cardiac surgeons have a different view of what constitutes complete revascularization, based on either functional (i.e. PCI of vessels with an invasive fractional flow reserve of 0.80 or less)[1] or anatomic criteria (bypass of all coronary arteries with a diameter $\geq$ 1.5 mm and a luminal reduction of $\geq$ 50% in at least one angiographic view).[2] The use of PCI-based, fractional flow reserve (FFR) criteria has occasionally spread to CABG practice, without evidence that reclassification of the revascularization strategy (i.e. FFR to help determine whether medical therapy, PCI, or CABG should be recommended) or the withholding of a bypass graft during CABG because of a FFR value > 0.80 is warranted, apart from considerations around graft patency and conduit selection (i.e. whether an artery or vein graft should be used, according to competitive flow potential). Another area of controversy is whether

complete revascularization after an acute MI, which has been found to result in benefit compared to a culprit-only strategy,[3] should be undertaken with PCI or CABG; moreover, the optimal timing of revascularization for non-culprit stenoses is not known. It also remains unclear whether the results of RCTs performed in patients with stable CAD, especially with regards to anatomic complexity and the presence of diabetes, should be applied to patients who recently had an acute MI.[4] Furthermore, RCTs comparing PCI to CABG have enrolled very few patients with systolic contractile dysfunction; whether medical therapy, PCI, or CABG represents the best intervention for those patients is another topic of debate.

But above all, it is the interpretation of recent trials involving patients with LM and multivessel CAD, such as NOBLE, EXCEL, and a subsequently published patient-level meta-analysis,[5, 6, 7] that continues to fuel controversy in myocardial revascularization. These studies have suggested that PCI may be equivalent to CABG with regards to major adverse cardiovascular events (MACE; i.e. myocardial infarction, stroke, or cardiovascular death) and that, with the exception of diabetic patients with a high SYNTAX score,[7] there may be no particular subgroup of patients who benefits from CABG.[6, 7]

As no new major trial comparing PCI to CABG for LM or multivessel CAD is underway, these data are likely to represent, for many years, the latest information on this topic available to the cardiovascular community. We believe that issues related to trial design in some of the PCI versus CABG studies, including the selection of patients based on suitability towards PCI, endpoint definitions for periprocedural MI that varied between and even within trials, as well as incorrect subgroup analysis practices, could have contributed to the overoptimized design and misinterpretation of these RCTs, with a potential to affect the recommendations provided in clinical guidelines. Understanding these pitfalls, which are described in this article, may help avoid repeating them in future myocardial revascularization trials, as well as enhance the cardiovascular community's interpretation of the currently available evidence.

1. Equipoise-by-Design, from the Ground Up: *Implications at the Individual Patient, Trial, Meta-Analysis, and Guidelines Levels*

Most trials comparing PCI to CABG have not been designed and powered to individually address the potential inferiority of PCI for clinically important MACE. Furthermore, with CABG as the recognized gold standard for patients with severe LM or multivessel CAD, clinicians and investigators have been hesitant to enroll patients in myocardial revascularization trials, unless they were considered to be particularly suitable for PCI.

This issue of whether enrolled patients are typical of routine clinical practice has been raised more than a decade ago.[8] It was noted then that the trials had enrolled fewer than 5% of the total potentially eligible population, usually those with modest CAD involvement. The generalization of results from those trials, which reported no difference in survival between PCI and CABG, to the larger population of patients with severe CAD -most of whom would not have been randomized in the context of a trial- may have contributed to an explosive growth in the use of PCI.[8]

A similar situation occurred in the recent NOBLE and EXCEL trials; for instance, the EXCEL trial completed enrollment with 729 (38%) fewer subjects than originally planned.[6] Like in every myocardial revascularization trial that reported recruitment rates and the reasons for non-enrollment, the possibility of suboptimal outcomes with PCI was the predominant cause for non-enrollment, even beyond the screening phase. Similarly, in the SYNTAX trial, which aspired to represent a clinically realistic 'all-comers' trial, of the more than 1,000 patients deemed ineligible for randomization and entered into a parallel registry, the vast majority had been excluded from randomization because the complexity and severity of CAD made them unsuitable for PCI, yet still suitable for CABG.[9]

In the EXCEL trial, by the time 1,000 patients were recruited to the companion registry (who, in large part, underwent CABG), only 747 patients had been randomized into the study. Notably, EXCEL had stipulated a SYNTAX score of less than 33 for inclusion; even in those patients with less complex LM disease, the most frequent reasons for non-randomization were, firstly, that "PCI should not be performed" followed, secondly, by "the presence of any clinical condition which leads

the participating interventional cardiologist to believe that clinical equipoise is not present".[6] Less than 1/3 of patients in the EXCEL registry ultimately underwent PCI.

We believe that the repetitive practice of limiting trial enrollment to patients considered to be particularly suitable for PCI, anatomically and physiologically, amounts to a form of selection bias. Although this practice may be in the best interest of the study patients, the external validity and generalizability of myocardial revascularization trials suffers from having excluded subjects with less than optimal suitability for PCI (who may have experienced a less favorable outcome) and, nevertheless, applying the results of these RCTs to the whole population of patients with severe CAD.

Consequently, if PCI were deemed noninferior to CABG in individual myocardial revascularization trials or in the pooling of their data, would a conclusion that PCI be substituted for CABG in the real world be appropriate? Although RCTs always involve a select group of subjects, a context that emphasizes "noninferiority from the ground up", with systematic selection of patients because of suitability towards one of the two interventions, in every trial from which these data are available, may have resulted in bias at inception.

2. The Changing Definitions of Endpoints Between and Within Trials

There is an abundant literature on the use of composite primary endpoints, and their subcomponents, in trials that have compared PCI to CABG for myocardial revascularization.[10] For instance, whether a stroke 'equates' an MI or, alternatively, amounts to an MI plus a target vessel revascularization (TVR), has been a longstanding source of debate. Undoubtedly, composite primary endpoints are practical but also suboptimal.[11] Their *post hoc* splitting and pooling also can lead to methodological shortcomings,[10] as described below under Heading 3.

Individual endpoint-related questions that are relevant to recent RCTs comparing PCI to CABG include: 1) does TVR constitute a benign outcome, despite the paucity of

dedicated literature examining its late effects; and 2) should periprocedural MI, arbitrarily defined by enzyme release thresholds that vary from one trial to another, using biochemical assays that fluctuate from one laboratory to another, represent an important hypothesized clinical outcome difference between PCI and CABG?[12-15]

On these issues, the latest two trials, NOBLE and EXCEL, took opposite approaches. NOBLE, like most other trials, included TVR as part of its composite primary endpoint, while EXCEL did not.[5, 6] Furthermore, NOBLE did not consider periprocedural MI to be an important and comparable source of clinical difference, and did not include it in its composite primary endpoint. What happened in this regard, in the EXCEL trial, is noteworthy.

The EXCEL trial was published in December 2016.[6] We observed previously that the noninferiority result in EXCEL was enabled by the definition of periprocedural MI,[16] which changed during the course of the trial. The final definition, used for the trial's primary endpoint, was developed near the end of its recruitment phase by a committee from the Society for Cardiovascular Angiography and Interventions (SCAI), as an "identical definition of myocardial infarction for both PCI and CABG to minimize ascertainment bias and (…) that is clinically relevant".[6, 13] However, the SCAI periprocedural MI definition was not aligned with both the Second and Third Universal Definition of MI (Table 2), is the only definition to include an exclusively biochemical (i.e. without ancillary clinical criterion) threshold around PCI and CABG, favored the use of CK-MB over cTn, and ultimately proved entirely different from the recently published Fourth Universal Definition of MI.[17]

The results of trials comparing PCI versus CABG that have periprocedural MI as a part of their composite primary endpoint are very sensitive to its definition, as this crucially affects the quantification of outcomes. In a study by Cho and colleagues examining this issue, the differential incidence of periprocedural MI, according to various definitions, was evaluated amongst 7,697 patients who received PCI (n = 4,514) or CABG (n = 3,183) between 2003 and 2013, and for whom serial measurements of creatine kinase-MB were available.[12] Based on which MI definition was used, wide discrepancies were observed in the rates of periprocedural MI after

PCI and CABG (18.7% vs. 2.9% by the Second Universal; 3.2% vs. 1.9% by the Third Universal; and 5.5% vs. 18.3% by the SCAI definition) (Figure 1).

Hence a change in the definition of periprocedural MI, from the original EXCEL trial protocol contemporary with the Second Universal Definition, to the SCAI definition used for the analyses, affected the composite primary endpoint and the noninferiority result of the EXCEL study (Figure 2). Without this modification, it is plausible that the composite primary endpoint of MACE, which included periprocedural MI in the first 30 days, would have changed in favor of CABG, as evidenced by the 30 days to 3 years landmark analysis found in Table S9 of the *Supplementary Appendix* to the New England Journal of Medicine paper.[6] Notably, non-fatal outcomes were 'reset' at 30 days post-procedure for this landmark analysis, so that patients were 'eligible' to suffer another incidence of MI from 30-days onwards. Nonetheless, only 3 patients in the CABG group who had a periprocedural MI experienced another non-fatal MI, and subsequent MIs were much less frequent in the CABG group than in the PCI group. Although higher myocardial enzyme release at CABG might relate to less complete revascularization, because of higher baseline risk and a diminished potential for late survival (through confounding by indication),[18] it does not appear that the "excess periprocedural MIs" in the CABG group of the EXCEL trial were causally linked with repeat non-fatal MI, clinically evident loss of graft patency, or significant myocardium at risk.

In addition to the major variability between studies described above, the results of biochemical assays used for myocardial enzyme release also differ widely from one laboratory to another, resulting in important within-study differences. The fourth UDMI indicated that "*one cannot presume that values from one cTn assay are equivalent to those of another. These differences are amplified when multiples of the values are used. This could affect results, especially in trials that compare strategies such as PCI and CABG.*"[17] Taken together, there is no robust, consensual, mechanistic, or scientific evidence as to which exact biochemical cut-off value should be used to define periprocedural MI around PCI or CABG. We consequently recommend that periprocedural MI defined by enzyme release thresholds not be used as a component of the primary endpoint in trials comparing PCI and CABG, due to its arbitrary and variable nature between studies, in addition to its relative imprecision within studies.

Regarding the endpoint of stroke, no excess signal was observed in the CABG groups of NOBLE and EXCEL. This is encouraging news for patients with LM or multivessel CAD worldwide, since the incidence of perioperative stroke after CABG appears to have been significantly reduced, as also corroborated by recent population data.[19] Previously, the increased incidence of stroke around CABG noted in the SYNTAX and FREEDOM trials could have resulted from 1) misguided pharmacological strategies, such as prematurely stopping dual-antiplatelet therapy in acute coronary syndrome patients prior to CABG;[20] 2) the low utilization of in-situ arterial grafts; 3) major geographic variations;[21] and 4) the low utilization of no touch aortic techniques.[22]

Lastly, randomized and observational data indicate that guideline-directed medical therapy (GDMT) has been underutilized in CABG patients, including those enrolled in PCI versus CABG trials, despite strong evidence that GDMT markedly improves outcomes.[23, 24] With the notable exception of the EXCEL trial where important efforts were accomplished to this effect, CABG patients have received markedly inferior GDMT in nearly every RCT that compared PCI to CABG, which inherently may have led to suboptimal clinical outcomes in the CABG group.[25]

3. Short-Term Follow-Up, Subgroup Analyses, and the Pooling of Subcomponents from Composite Endpoints: "*Not Observing a Difference" Is Not the Same as "Showing No Difference"*

Clinical trials, whether positive, neutral or negative, generate data for meta-analyses. Although patient data and studies brought together into a meta-analysis virtually always differ in their baseline, enrollment, and in some of their therapeutic characteristics, other issues also can arise. For instance, the pooling of data from RCTs conducted in relatively young patients with short follow-up, and the performance of subgroup analyses using individual subcomponents of composite endpoints (such as all-cause mortality), can lead to underpowered or methodologically incorrect analyses, even with an apparently sizable number of patients at inception.[10, 26]

Patients in their early sixties with few health issues and with good left ventricular function, who represent the typical population randomized in trials comparing PCI and CABG, may enjoy on average two decades of additional life expectancy, according to US lifetables. Death should not frequently occur in such study patients, who have a low incidence of co-morbidities, are treated for their LM or multivessel CAD, and receive GDMT with close follow-up. Consequently, a numerically increased hazard for death over a follow-up window of less than 4 years, in patients who are in their early sixties (subdefined by the presence of diabetes, or by SYNTAX score), may not reach statistical significance.[7] However, over the patients' average potential lifespan of ~20 additional years, a numerically increased hazard can harbor profoundly negative impacts on late survival. In such patients, short- and medium-term mortality data should therefore be considered premature for the purpose of making comparisons between PCI and CABG.

Methodologically, both *a priori* prespecification and a *p*-value of less than 0.05 on the test for interaction (after accounting for repeat testing) are required, in order to provide convincing evidence for the validity of subgroup analyses from RCTs or in meta-analyses.[27] The recent meta-analysis by Head and colleagues, which concluded that "…the mortality benefit of CABG over PCI was seen only in patients with multivessel disease and diabetes", did so without providing evidence of multiple testing-adjusted, positive interaction tests.[7] Furthermore, the subgroup analyses were markedly underpowered, with the width of the confidence interval for the LM subgroup including not only the point of no difference, but also the beneficial survival effects of CABG estimated in all patients as well as in the multivessel CAD subgroup. Interpreting these data as 'showing no difference' between modalities in the LM subgroup represents incorrect subgroup analysis practices, and introduces the risk of potentially being generalized, affecting not only the interpretation of study results but, more importantly, future patient outcomes.

Lastly, pooling individual components of composite endpoints across patient subgroups also incorporates heterogeneity between trials, which cannot be accounted for in a *post hoc* manner. Should the conclusions of FREEDOM,[28] a trial exclusively performed in diabetic patients that found increased mortality with PCI irrespective of SYNTAX score, be invalidated by the pooling of scattered diabetic patients from smaller trials, followed over shorter periods of time?[7] As per the

discussion under Heading 1, above, the question arises again as to *who are the diabetic patients in the smaller, non-dedicated trials*…. those carefully identified as likely to respond well to PCI? Overall, we must remember that the *failure to observe a difference* between groups is not the same as *showing no difference*.

4. Quality of Life, Quantity of Life, and the Possible Impact of Target Vessel Revascularization

In 2017, it was reported that patients randomized to the PCI group in the EXCEL trial had 1-year quality of life (QOL) and freedom from angina that were equivalent to patients in the CABG group.[29] This was in contrast with prior observations from the SYNTAX and FREEDOM trials, where QOL scores were significantly better with CABG than with PCI, one year after revascularization.[30, 31]

In the EXCEL trial, nearly twice as many ischemia-driven revascularization events were noted in the PCI group (P<0.001). In this regard, any patient with known LM CAD who has persistent or recurrent angina is unlikely to be left untreated, and even more so in the context of a research study, due to the well-known life-threatening consequences. Whether these revascularization events become positively or negatively perceived by the patient may depend in part on the research team, as these encounters constitute an additional opportunity for the team to interact with the patient. Attentive team dynamics around revascularization episodes, which were significantly more common with PCI, might have helped level a perception of different QOL and overall functioning between PCI and CABG patients.[32]

More importantly, we believe that *quality of life* equivalence should only be claimed once *quantity of life* equivalence has been well established. The slopes of the MACE curves at 3 years in the EXCEL trial suggest that the PCI group could become significantly worse than the CABG group at years 4 and 5. Similarly, this trial's landmark analysis (from 30 days to 3 years post revascularization) shows significantly more events, and a numerical increase in the incidence of death, in the PCI group. Previous trials such as FREEDOM have indicated that differences in all-

cause mortality may take 2 to 3 years to develop between PCI and CABG patient groups (Figure 3). Although the EXCEL authors report that excess deaths in the PCI arm were noncardiovascular in etiology, they rightly recognize that adjudication processes can be subject to ascertainment and misclassification biases.[6]

Conclusions

Based on the above considerations pertaining to trials that compare PCI versus CABG for the treatment of LM and multivessel CAD, we recommend the following:

- Public funding should be made available and used to design, oversee and execute myocardial revascularization trials;
- Methods papers of RCTs should be published early on, and ideally prior to trials having made significant strides in patient enrollment. Although updates on www.clinicaltrials.gov are practical, they also should highlight the first approved version of each protocol, including original target recruitment numbers and endpoint definitions;
- Rather than designing and pooling data from trials with short follow-up duration, only trials with 5 or more years of follow-up should be considered in order to comparatively evaluate outcomes after myocardial revascularization;
- A common set of definitions for outcomes and complications, such as the VARC-2 criteria in the transcatheter aortic valve implantation literature, should serve as a common basis for designing and reporting the outcomes of myocardial revascularization trials. Such a process would include balanced authorship representation, a predefined and accountable review committee, wide stakeholder acceptance, and co-leadership from the key specialities;
- Outcomes of an arbitrary nature and that are prone to considerable variability between and within trials, such as myocardial enzyme release assay thresholds, should not be used as a component of the primary endpoint in trials comparing PCI and CABG;
- Revascularization guidelines should not be changed on the basis of the EXCEL trial and the recent meta-analysis by Head and colleagues, until meaningful follow-ups are completed and analyzed, employing primary endpoint components that are not arbitrarily defined or subject to modification

during the course of the trial, as well as using adequately powered, methodologically justified noninferiority boundaries and subgroup analyses;

- If myocardial revascularization trials have primarily randomized patients likely to do as well with PCI as with CABG, with most of the screened patients not having been randomized and having majoritarily undergone CABG instead, then the conclusions of these trials, and the guidelines stemming from them, should not be applied to the entire population of patients with severe CAD;
- The development of guidelines should follow the methodology suggested by the Institute of Medicine,[33] with an independent epidemiology/statistician group appraising the evidence and detecting statistical flaws, as well as a separate group made of physicians writing the recommendations, based on the synthesised evidence and its independent critical analysis;[34]
- Data from myocardial revascularization RCTs should better focus on the characteristics of LM lesions, to ascertain who are the patients with LM CAD that may fare as well with PCI as with CABG;
- Until more evidence is available, with the exception of ostial or midshaft isolated LM, or LM associated with 1-vessel disease, all decisions for stable multivessel, LM with 2- or 3-vessel, or LM with bifurcation CAD should be discussed with the patient after review and recommendation by a Heart Team, which includes a cardiac surgeon;
- Patients undergoing CABG should be offered the best and latest in terms of adjunctive GDMT, not only within the context of myocardial revascularization trials, but also -and more importantly- because they represent such a large population of patients with severe CAD, who can crucially benefit from GMDT;
- Cardiologists and cardiac surgeons must work together, in true collaborative fashion and with balanced leadership opportunities, to advance the optimal clinical care and research aimed at improving the current and future status of patients with severe CAD.

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Table 1. Areas of General Acceptance and Ongoing Controversy in Myocardial Revascularization for Left Main and Multivessel Coronary Artery Disease

Topics with General Acceptance

ST-segment elevation MI	PCI of culprit lesion is preferred
LM CAD with low-to-intermediate anatomic complexity	Both PCI and CABG are acceptable
Non-diabetic patients with focal multivessel CAD and low anatomic complexity	Both PCI and CABG are acceptable
Diffuse multivessel CAD	CABG is preferred
Diabetes mellitus and multivessel CAD	CABG is preferred
Stable CAD outside of the above contexts	Heart Team recommendation conveyed to the patient at a time and setting separate from the coronary angiography

Topics with Ongoing Controversy

Complete revascularization	Functional: FFR-based beneficial in PCI. Is there a role for FFR in CABG (i.e. treatment reclassification; grafting strategy)? Anatomic: appears beneficial in CABG (despite possibility of confounding by indication).[18] Should it be artery-based or territory-based?
ST-segment elevation MI	Should completion of revascularization be performed with CABG?
Heart failure with reduced ejection fraction in the presence of LM or multivessel CAD	In non-diabetic patients, is there a role for PCI, particularly if complete revascularization can be achieved?[35, 36]
LM CAD of high anatomic complexity **Multivessel CAD of moderate-to-high anatomic complexity** **LM or multivessel CAD in diabetic patients**	Should PCI be utilized in patients who are good surgical candidates?

Table 2. Definitions of Periprocedural Myocardial Infarction used in Myocardial Revascularization Trials

	Panel composition	Cardiac biomarker	Time after procedure	PCI definition	CABG definition
UDMI* [15]	44 task force members / authors 14 reviewers	cTn preferred; if not available, CK-MB	≤ 72 hours	3 x 99th percentile URL	5 x 99th percentile URL and new Q waves or LBBB, angiographic findings, or new RWMA
Third UDMI [14]	52 task force members / authors 26 reviewers	cTn preferred; if not available, CK-MB	≤ 48 hours	> 5 x 99th percentile URL and ischemia, ECG changes, angiographic findings, or new RWMA	> 10 x 99th percentile URL, and new Q waves or LBBB, angiographic findings, or RWMA
SCAI [13]	10 authors Reviewers not listed	CK-MB preferred	≤ 48 hours	*Any of:* CK-MB: ≥10 × ULN CK-MB: ≥5 × ULN and new Q waves or LBBB cTn: ≥70 × ULN cTn: ≥35 × ULN and evidence of new Q waves or LBBB	*Any of:* CK-MB: ≥10 × ULN CK-MB: ≥5 × ULN and new Q waves or LBBB cTn: ≥70 × ULN cTn: ≥35 × ULN and evidence of new Q waves or LBBB
ARC-2 [37]	18 authors Reviewers not listed	cTn preferred	≤ 48 hours	> 35 x URL and new Q waves, angiographic findings, or new RWMA	> 35 x URL and new Q waves, angiographic findings, or new RWMA
Fourth UDMI [17]	39 task force members / authors 40 reviewers	cTn preferred; if not available, CK-MB	≤ 48 hours	> 5 x 99th percentile URL and new Q waves, angiographic findings, or new RWMA	> 10 x 99th percentile URL and new Q waves, angiographic findings, or new RWMA

ARC, Academic Research Consortium; CK-MB, creatine kinase MB isoform; cTn, cardiac troponin T or I; LBBB, left bundle branch block; RWMA, regional wall motion abnormality; SCAI, Society for Cardiovascular Angiography and Interventions; UDMI, Universal Definition of Myocardial Infarction; ULN, upper limit of normal; URL, upper reference limit.

* UDMI has also been called the 'Second' Universal Definition of Myocardial Infarction. The prior MI definition had not been termed 'First' or 'Universal', but rather a 'Consensus Document' of the *Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction*.[38]

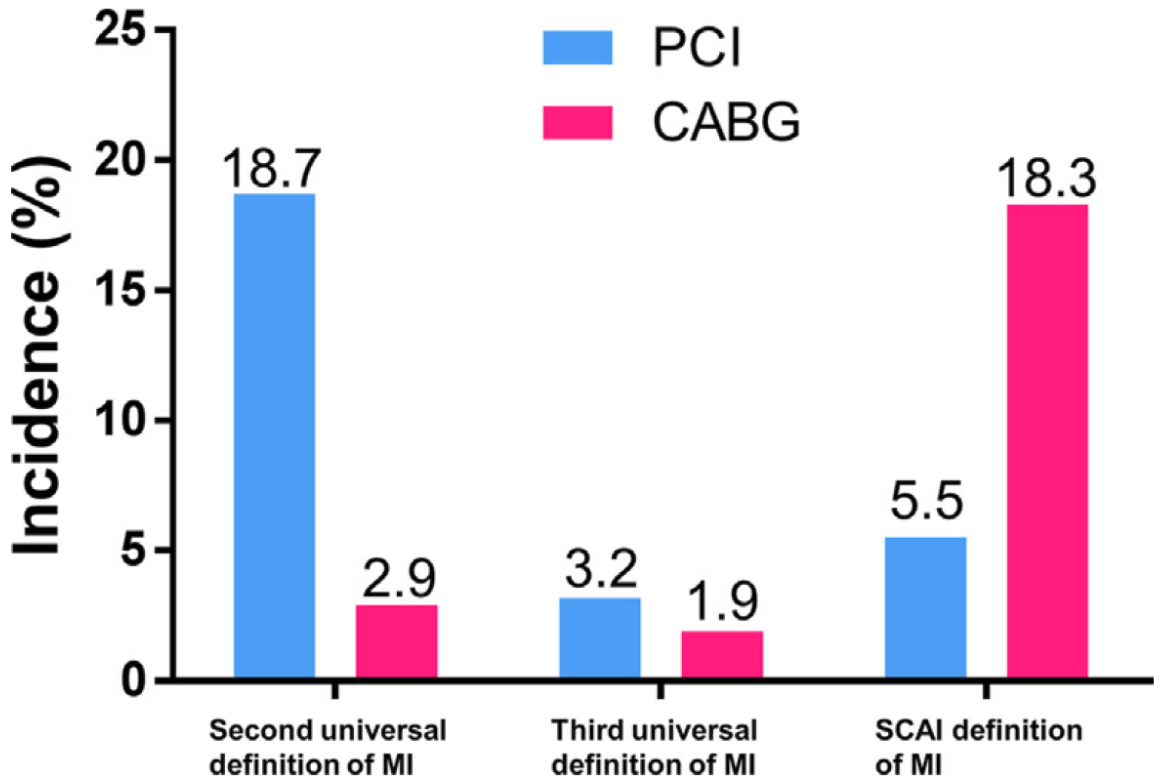

Figure 1. Rates of periprocedural MI according to various definitions, in 7,697 patients who received PCI (n = 4,514) or CABG (n = 3,183) between 2003 and 2013, and for whom serial measurements of creatine kinase-MB were available. (From Cho and colleagues[12])

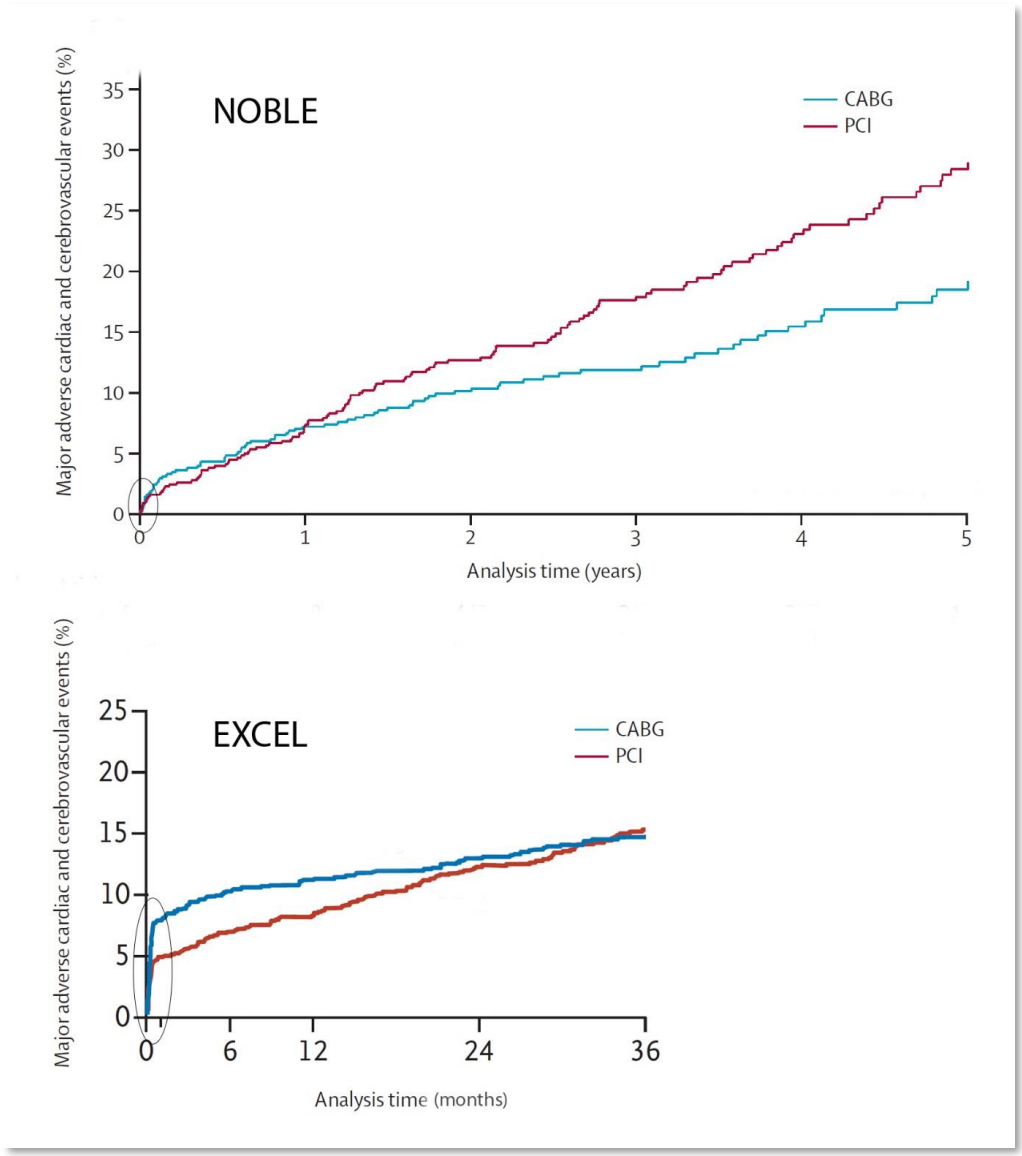

Figure 2. Rates of the primary endpoint event of death, myocardial infarction, or stroke, in the Nordic-Baltic-British left main revascularization (NOBLE) trial[5] and in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of left main revascularization (EXCEL) trial,[6] at 5 and 3 years of follow-up, respectively. (Figure modified and scaled from references [5] and [6], and adapted from reference [16])

A new periprocedural MI definition was used in EXCEL and the two studies differed in their inclusion of periprocedural MI in the composite primary endpoint, resulting in early outcome differences (circles) in EXCEL but not in NOBLE. Outside of the periprocedural period, the slopes of event rates within the PCI and CABG groups across both studies appear remarkably similar. NOBLE reported that PCI was inferior to CABG at 5 years, while EXCEL indicated that PCI was noninferior to CABG at 3 years.

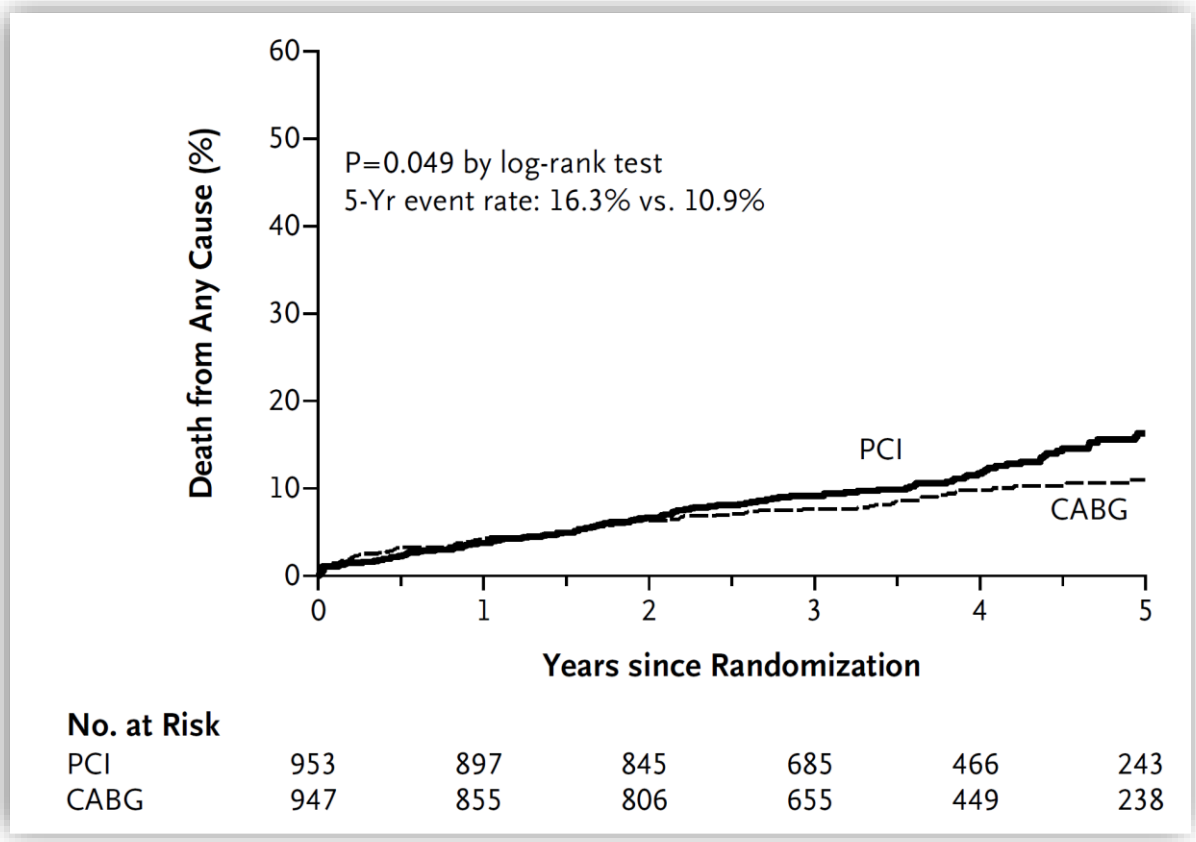

Figure 3. Incidence of death from any cause in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial (adapted from reference [28])