Response of EXCEL leadership

On behalf of the EXCEL leadership, we hereby respond to the misleading narrative questioning the conduct of the EXCEL trial that has been reported by certain members of the cardiovascular surgical community and a recent BBC Newsnight programme. This narrative was then promulgated by EACTS by withdrawing from guidelines without so much as even asking the EXCEL study group for clarification. The following are relevant facts about the conduct of the EXCEL Study:

Summary

Choice of the procedural myocardial infarction definition
It was agreed by all involved (including surgical colleagues) that the universal definition (UD) was not suitable because of ascertainment bias, different criteria for percutaneous coronary intervention (PCI) and coronary bypass grafting (CABG) and lack of demonstrated correlation with prognosis. The protocol definition of procedural myocardial infarction (MI) that met these criteria was thus selected and agreed to by unanimous consent.

The protocol MI definition changed
This is absolutely incorrect—the principal definition of MI never changed throughout the course of the trial.
The rate of procedural MI according to universal definition has been deliberately withheld. Procedural MI according to universal definition was listed in the protocol as one of ~35 exploratory secondary endpoints. This definition is based on troponins, the collection of which was optional in EXCEL and was unfortunately infrequently performed. Thus, reporting procedural MI rates according to UD was not possible. An exploratory attempt was made to assess procedural UDMI rates using troponins in some patients and CK-MB measures in others. However, this is not scientifically sound given the different sensitivities of these assays. EXCEL has published data that the protocol definition of MI was strongly correlated with subsequent mortality within the trial, whereas smaller biomarker elevations (as included in the universal definition criteria) would not have been prognostic. And until these recent events there had been no requests from any source to prioritise reporting procedural MI according to universal definition. Thus, there was absolutely no attempt to withhold meaningful data. Nonetheless, EXCEL commits to publish a future manuscript reporting the rates and implications of MI according to numerous definitions, including the universal definition using CK-MB data.

The all-cause mortality data from EXCEL was not strongly enough emphasised
All-cause mortality was a secondary underpowered endpoint and the modest difference noted between groups was not adjusted for multiplicity and is therefore statistically uncertain. In addition, it has no biological basis given that the clinical events committee adjudicated the excess to be principally due to sepsis and cancer occurring years after randomisation. Meta-analyses of 4,394 patients from four trials of drug-eluting stents vs. CABG (including EXCEL) show there is no difference in five-year mortality between PCI and surgery for left main disease. Even longer-term data (10-year follow-up from the SYNTAX trials) shows no difference in mortality. The distinction between all-cause mortality and cardiovascular mortality (which was very similar between PCI and CABG in EXCEL) was unfortunately not mentioned in the broadcast.

The DSMC raised concerns that were not adhered to
The independent Data Safety and Monitoring Committee met frequently to review unblinded EXCEL data, each time recommending that the study continue as planned without modification.

The ESC/EAPCI/EACTS Guidelines are unsafe
Guidelines are made on summated evidence from multiple trials and data input by independent experts in the field. The existing Guidelines which EXCEL helped to inform suggest stenting may be considered as a treatment for selected patients with left main stem coronary disease.

Detailed response

1: Background
The EXCEL trial was an academically led study designed and organised by an equal number of cardiac surgeons and interventional cardiologists (as well as general cardiologists and statisticians). Several hundred academic and clinical scientists were involved in this process, as listed in the appendix of the three-year and five-year *New England Journal of Medicine* manuscripts. All decisions made during the trial were approved by all participants, including the Chair of the Surgical Committee, Professor David Taggart. EXCEL enrolled 2,905 patients between 29 September 2010 and 6 March 2014 at 126 sites in 17 countries. Abbott Vascular funded the trial, but it was led by the scientific community, with two surgical principal investigators (Joseph F Sabik and A Pieter Kappetein), and two interventional cardiology principal investigators (Patrick W Serruys and Gregg W. Stone). Two independent academic research organisations (Cardialysis in the Netherlands and the Cardiovascular Research Foundation in New York) performed all the endpoint adjudications, core laboratory data assessments, database management, biostatistical analysis, and presentation and manuscript preparation, independent of the sponsor. The sponsor was given a right to a non-binding review of publications, but at no time requested any modifications beyond typographical errors.
Certain members of the cardiovascular surgical community and a recent BBC broadcast have focused on a number of issues related to EXCEL that are addressed by this document.

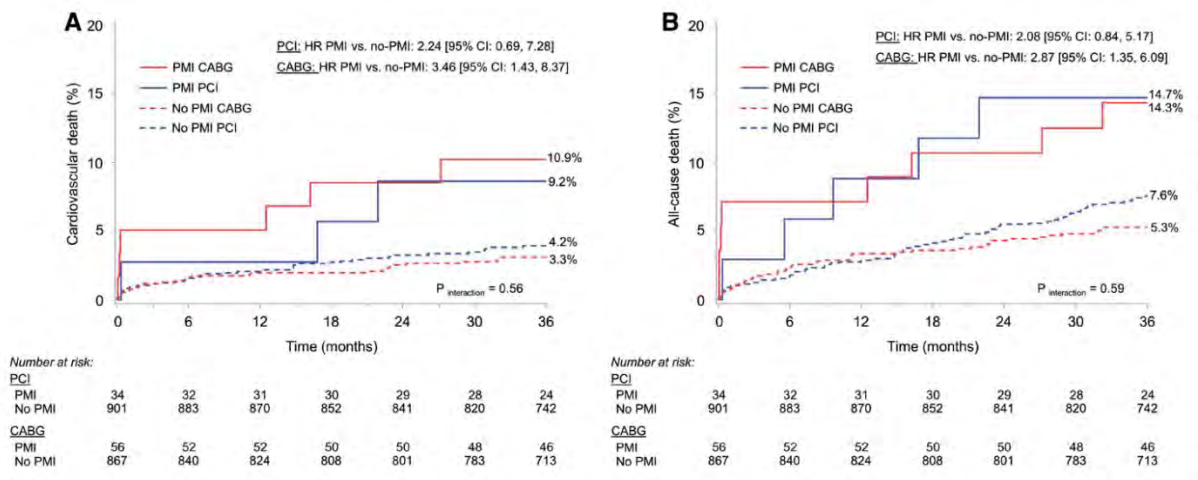
2: Choice of the procedural MI definition
For the composite primary endpoint of death, MI or stroke, there was unanimity that we wanted a procedural MI definition that 1) had been proven to correlate with adverse prognosis; 2) eliminated ascertainment bias between the PCI and CABG arms; and 3) had identical biomarker elevation thresholds for MI after CABG and PCI.
By ascertainment bias we are referring to the fact that post-procedural 12-lead ECGs are less available post-CABG than after PCI given bandages, etc.; that assessment of post-procedural chest pain is problematic after CABG because of intubation, incisional chest pain and analgesia use; and that post-CABG angiography and imaging are almost never performed. All investigators agreed that eliminating ascertainment bias was a priority if the MI rates were to be fairly compared between CABG and PCI.
We performed an extensive literature review at the time, which was presented to and discussed by the entire leadership. The vast majority of the evidence at that time demonstrated that: 1) only large biomarker increases correlated prognostically with subsequent mortality; 2) similar biomarker increases portended a similar adverse prognosis after both procedures; 3) and that only large CK-MB

biomarker elevations had been shown to be prognostic—there was very little data supporting the utility of post procedure troponin elevations.
The protocol MI definition was thus agreed on after consensus agreement of the entire leadership, including the Chair of the Surgical Committee, who agreed in particular that eliminating ascertainment bias was critical.

Note:

- A similar definition for periprocedural MI after PCI and CABG had previously been used in the SYNTAX trial and was never questioned.
- The protocol definition of procedural MI that was agreed upon was determined before the SCAI definition was created and differs from the SCAI definition.

Indeed, EXCEL has published that the protocol definition (based largely on a post-procedural CK-MB elevation to ≥10x the upper reference limit [URL]) was proven to be the correct definition in that it was shown to be independently related to subsequent cardiovascular and all-cause mortality in the EXCEL trial, with similar hazard after PCI and CABG (Ben-Yehuda O et al. *EHJ* 2019; 40: 1930–41). Figure 3 in this publication is shown here:



Note that the Chairman of the Surgical Committee was an author on this paper.

3: Assessment and reporting of the universal definition of procedural MI
The original and third UDMIs were active during enrolment of EXCEL. These definitions did not meet the leadership criteria for having been shown to be prognostically important, and to be free from ascertainment bias. The following is the third UDMI for post-PCI assessment (type (4a) and post-CABG assessment (type 5) (Table 2 from Thygesen K *et al. Circulation* 2012; 126: 2020–35).

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

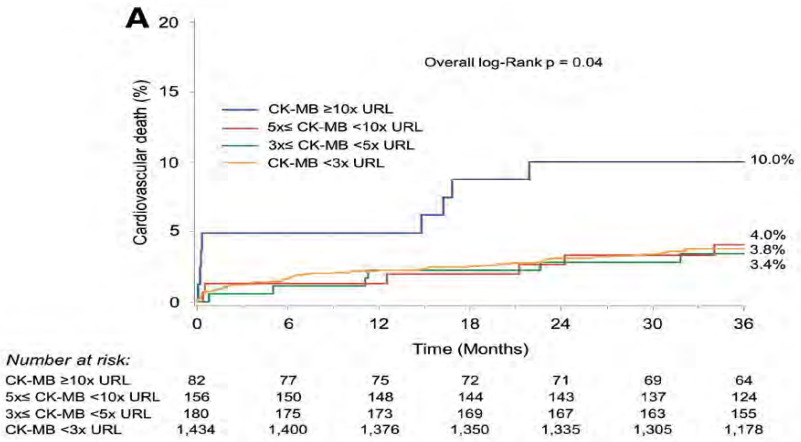
Note these definitions 1) are based on troponins as the biomarker; 2) have different biomarker thresholds for procedural MI criteria after PCI and CABG; and 3) require additional supporting data such as ECG or imaging findings. Furthermore, the UDMI authors themselves noted in the publications that their procedural MI biomarker thresholds for both the original and 3rd UDMI procedural definitions were chosen by "arbitrary" convention. Given this, and for the reasons stated above we rejected these definitions for the protocol procedural MI definition. The published EXCEL protocol is very clear on this, stating "Thus, in the present study only CK-MB elevations will be used for determination of periprocedural MI…"

There was consideration to undertake an exploratory sub-study in adjudicating procedural MI by the UD type 4a and 5 MI criteria to determine its frequency and prognostic impact in comparison to the protocol definition of procedural MI. In this regard, while the sites were <u>required</u> to draw baseline and serial CKMB values for the primary definition, they were asked <u>if possible</u> to also draw troponins at the same times for this purpose. This was described as <u>optional</u> in the protocol, but we were hopeful that sufficient troponin data would be available such that the CEC could adjudicate the UDMI type 4a and 5 rates in enough patients for a valid comparison.

Unfortunately, given cost considerations at the sites, troponin values were collected in a minority of patients in whom PCI and CABG were performed. The CEC was thus unable to properly and accurately adjudicate and report type 4a and 5 MI according to the UDMI.

An exploratory attempt was made to assess UDMI rates using troponins in some patients and CK-MB measures in others (the latter having been collected with high compliance). However, this is not scientifically sound given the different sensitivities of these assays. Moreover, these data were never cleaned and finalised. Any data leaked to the BBC purporting to show UDMI rates are not accurate. We asked the BBC to send us this data so we could verify it, but they refused.

Importantly, additional MIs added by the UDMI would not have been prognostically related to subsequent mortality. In the Ben-Yehuda manuscript, we reported prognosis as a function of CK-MB elevation. Only CK-MB ≥10x URL was associated with subsequent death (from Figure 4):



In multivariable analysis, only large biomarker elevations were independently predictive of mortality. CKMB 5-10x URL elevations were not correlated with death, even if additional criteria were present such as ECG changes or imaging evidence of infarction (Table 5 in the manuscript):

Table 5 Multivariable predictors of 3-year cardiovascular death

PMI definition	Adjusted hazard ratio (95% CI)	*P*-value
CK-MB ≥10× URL	2.94 (1.31–6.59)	0.01
CK-MB ≥5 to <10× URL with additional protocol criteria for periprocedural MI[a]	1.44 (0.20–10.60)	0.72
CK-MB ≥5 to <10× URL without additional protocol criteria for periprocedural MI[a]	0.89 (0.32–2.50)	0.82

Model adjusted for age, sex, hypertension, diabetes mellitus, chronic obstructive lung disease, left ventricular ejection fraction, SYNTAX score, baseline biomarker elevation, and treatment (PCI vs. CABG).
PMI, periprocedural myocardial infarction; URL, upper reference limit.
[a]New pathological Q waves in at least two contiguous leads or new persistent non-rate related left bundle branch block, or angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

The ~7:1 relationship between the magnitude of troponin elevations to CK-MB means smaller troponin elevations would not have been associated with death. And as stated, the Chairman of the Surgical Committee was a co-author on the Ben-Yehuda manuscript and fully agreed with its findings, including understanding that we could not report the type 4a and 5 UDMI definitions because of lack of troponin data.

Indeed, until the recent accusations, not a single person had requested the UDMI procedural MI rates, nor raised their absence as an issue.

We have published >30 manuscripts to date from EXCEL, and plan on 100 or more papers before we're finished. Our goal is to be completely transparent with all the data from this landmark study which may prove to be of utility for physicians caring for patients with left main coronary artery disease. There certainly has never been an attempt to "withhold" any data from the academic community. Just the opposite—our study group is renowned for supporting presentations and publications of secondary hypothesis generating analyses from our major studies, whatever they show.

Two comprehensive manuscripts on the implications of MI after left main revascularization in EXCEL will be prepared. The first will examine the prognostic impact of spontaneous (non-procedural) MI relative to procedural MI, and the second examining the relative rates and prognostic impact of

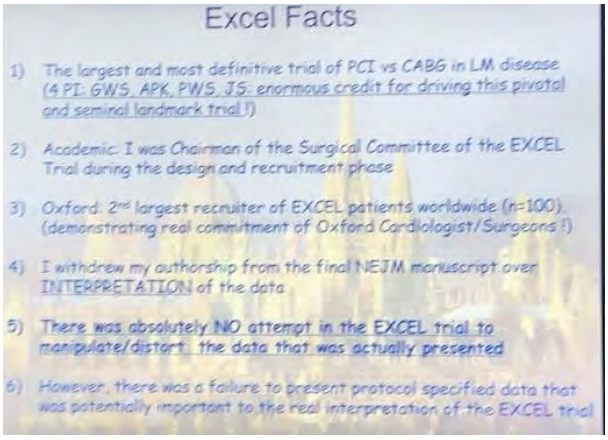
procedural MI using the UDMI type 4a and 5 criteria (using CK-MB in all patients), the procedural MI definition, and other definitions if possible such as the SCAI and ARC-2 definitions.

4: The protocol MI definition changed

It was claimed publically by Professor Taggart at the 33rd EACTS annual meeting on 5 October 2019 shortly after the five-year EXCEL publication that "What happened in EXCEL was a disgrace that halfway through the trial the definition of myocardial infarction was changed." And that "The only reason there was a difference in these results is that there was a change in the biochemical definition of myocardial infarction." He has stated this multiple times since. This is absolutely false – the protocol definition of MI NEVER changed as can be seen from the first and last versions of the protocol on the *NEJM* website. However, Professor Taggart has now withdrawn this fiction: at the recent International Coronary Congress in New York City on 6 December 2019, Professor Taggart stated that he no longer claims that the MI definition changed.

5: The EXCEL trial data was manipulated.

Professor Taggart claimed at the same EACTS meeting "So I believe the data was manipulated using a changed definition of myocardial infarction to try to prove for the composite endpoint that there was no difference." These statements were widely repeated on social media and in other press coverage. He has now withdrawn his charge of data manipulation. He stated this strongly and on two occasions during his talk on December 6, 2019 where he showed the following slide (note #5 that he wrote in bold and underlined text):



Prior to this document, this retraction was known only by those attending the course.

Note that Professor Taggart's point #6 refers to the procedural definition of UDMI, that as described above was not presented because of lack of troponin data, and regardless wouldn't have changed the conclusions of the trial as these MIs (excluding those with CKMB elevation ≥10x ULN) would not have been prognostic. He was of course aware of all of this, as an author of the EXCEL MI manuscript in *EHJ*.

6: The mortality data from EXCEL was not strongly enough emphasised

The major complaint of Professor Taggart, and the principal reason for his withdrawing from the 5-year publication, was that he believed a stronger emphasis of the nominal observed difference in all-cause mortality between PCI and CABG was warranted. It is essential to make clear the EXCEL trial was not

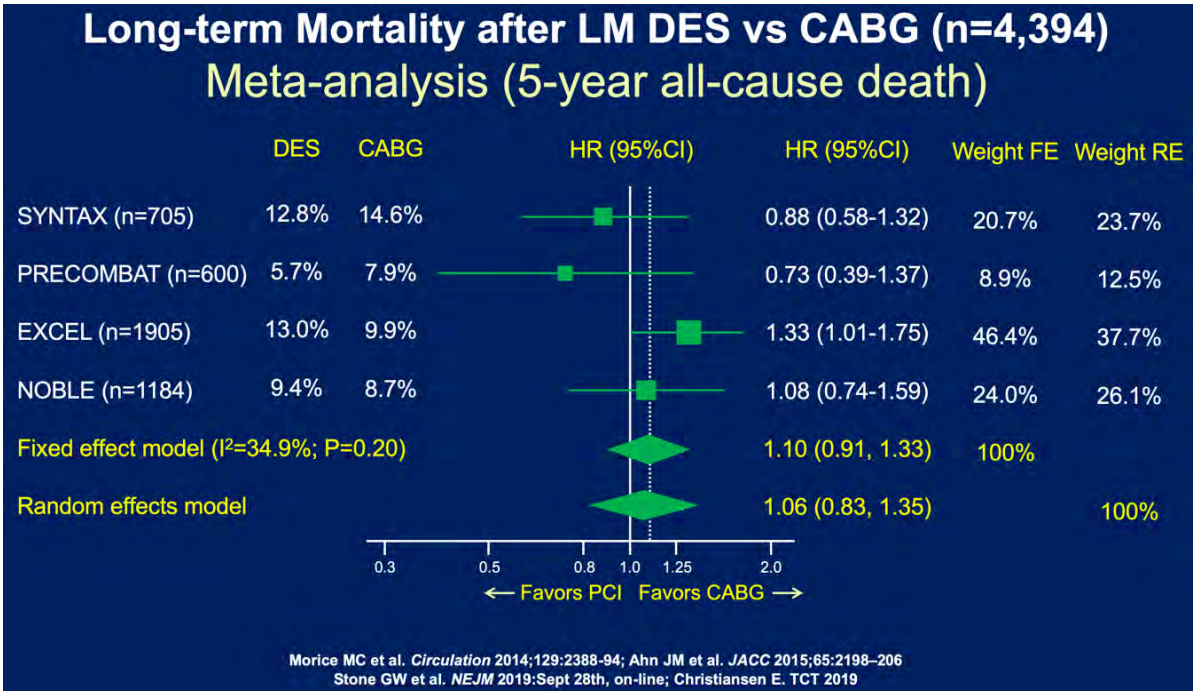
powered for all-cause mortality; it was powered to examine the relative rates in the composite endpoint of death, stroke or MI, which the entire trial leadership (including Professor Taggart) agreed was the major basis on which the therapies would be compared. This endpoint, which showed no significant differences between PCI and CABG at 5 years, was thus appropriately given the most emphasis in the 5-year NEJM manuscript. Nonetheless, the overall mortality results were described and discussed in the 5-year NEJM paper in the Abstract, Results, Discussion, Tables 1 and 2, Figure 3 and in multiple places in the Supplemental Appendix. Clearly no attempt was made to conceal these data.

We carefully considered the appropriate scientific interpretation of the all-cause mortality endpoint. All-cause mortality was an under-powered secondary endpoint – one of ~35 such secondary endpoints reported. All such endpoints are considered exploratory and hypothesis generating. The difference in all-cause mortality noted was statistically borderline (difference [95% CI] = 3.1% [0.2%, 6.1%]), which if corrected for multiplicity by Bonferroni or any other technique wouldn't have approached statistical significance.

Nonetheless, any apparent difference in overall mortality deserves careful consideration, which we provided, consuming a substantial proportion of the Discussion in the 5-year NEJM manuscript. When a low frequency under-powered secondary endpoint becomes positive (especially when not adjusted for multiplicity), one should ask if it is biologically plausible, and consistent with other data.

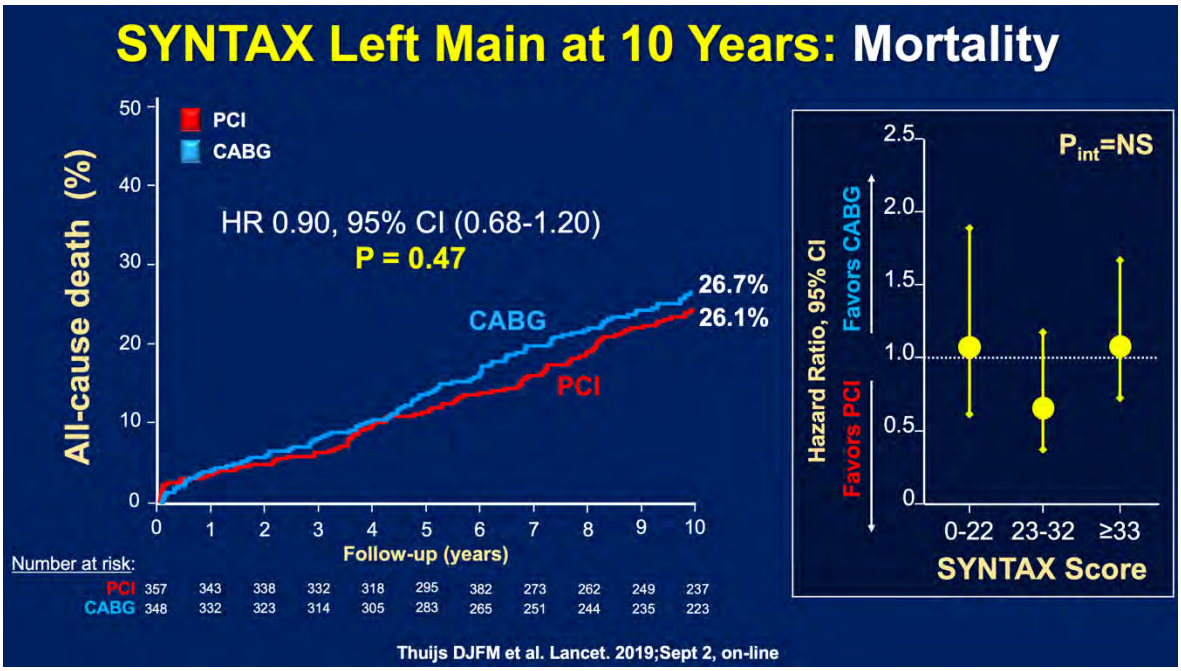
In this case the excess mortality was adjudicated by an independent and neutral Clinical Events Committee, who after detailed review of source documents determined that the difference was largely due to non-cardiovascular causes, especially cancer and infections, occurring several years after the index procedure. Lacking a biologic mechanism for these findings (it is unlikely that CABG is protective from late malignancies or sepsis), these occurrences are likely to be due to chance. In addition, if CABG would reduce death compared to PCI, it would likely do so through reduced MI. In this regard both the five-year rates of cardiovascular death and total MI were similar and non-significant after PCI and CABG in EXCEL.

Considering all available data from all studies is also essential in attempting to interpret under-powered secondary endpoints such as all-cause mortality. Four drug-eluting stent (DES) vs. CABG trials have been performed in 4,394 patients with left main disease in which 5-year follow-up is available (including EXCEL). With 4,394 patients, this analysis has much greater power to examine whether the all-cause mortality observation in EXCEL was typical or was an outlier (as suggested by the similar rates of cardiovascular mortality). The most recent and comprehensive meta-analysis from these data is as follows:



Thus, there clearly is no significant difference in five-year all-cause mortality between CABG and PCI. To emphasise the results from only one trial to suit a particular bias is non-scientific and disingenuous.

In addition, it has been hypothesised that a survival benefit after CABG would emerge after longer-term follow-up. The only study with >five-year follow-up is the SYNTAX trial, which recently published their 10-year data:



Again, no overall survival benefit for CABG was present even with very long-term follow, even in patients with complex coronary artery disease (high SYNTAX scores). If anything, the point estimate favoured PCI with a trend toward lower mortality.

These considerations were addressed in the NEJM five-year EXCEL manuscript:

"Although the cause of death can sometimes be ambiguous, rates of adjudicated definite cardiovascular death were similar among patients who underwent PCI and those who underwent CABG, consistent with the similar rates of myocardial infarction at five years. The difference in all-cause mortality between the groups was driven by non-cardiovascular deaths, especially those from cancer and infection, which occurred more commonly after PCI during late follow-up. The finding of a possible excess of deaths from any cause after PCI is at odds with the similar rates of death at 5 years among patients who underwent PCI and among those who underwent CABG in the contemporary Nordic–Baltic–British Left Main Revascularization (NOBLE) trial,[3] an individual patient-data pooled analysis of six randomized trials involving 4478 patients with left main coronary artery disease, and in other meta-analyses[4,21] and with the similar mortality at 10 years after PCI and CABG among patients with left main coronary artery disease in the SYNTAX trial.[22]"

Note that there were other differences present between PCI and CABG in EXCEL, including some important findings favouring PCI such as fewer cerebrovascular events that were also not more strongly emphasized in the NEJM publication.

7: Reports from the Data Safety and Monitoring Committee

The Data Safety and Monitoring Committee (DSMC) met frequently to review un-blinded EXCEL data, each time recommending that the study continue as planned without modification. The DSMC did want to ensure that any safety concerns were communicated to the scientific community. This was regularly achieved through major presentations of the primary and secondary endpoints (including mortality) at median 3-year follow-up (the primary endpoint), complete 3-year follow-up, 4-year follow-up and 5-year follow-up. All of these slide sets are available on TCTMD.com. The 3-year principal and 5-year final results were prominently published without delay in the New England Journal of Medicine. Between these publications were dozens of other publications with 3-year and 4-year data, all containing the mortality endpoint. We are now working on numerous additional sub-studies with the five-year data.

8: The ESC/EAPCI/EACTS Guidelines are unsafe

Guidelines are made on summated evidence from multiple trials and data input by independent experts in the field. The current EU guidelines which the 3-year EXCEL data informed suggest stenting may be considered as a treatment for selected patients with left main stem coronary disease. Of note, the 2018 ESC/EAPCI/EACTS guidelines (written before the 5-year EXCEL data) provide class I, IIa or III recommendations for left main stenting according to the complexity of associated coronary artery disease and other conditions. The final 5-year EXCEL data, 10-year STYNAX data and other emerging studies and analysis will appropriately inform future revisions to these recommendations.

9: Summary

A large academic study group consisting of prominent surgeons, interventional cardiologists, general cardiologists, statisticians and 2 academic research organizations drove EXCEL, a trial that has

consumed >10 years, and which we believe sets a new standard for cooperation between the cardiac surgical and interventional cardiology subspecialties in a search for the truth to improve outcomes of patients with coronary artery disease.

Every important study raises new questions, and some of the findings will rightfully foster scientific debate—such deliberations are healthy, and we openly welcome this from all informed parties. To suggest, however, that hundreds of EXCEL investigators, including cardiologists, surgeons, statisticians and entire academic research organizations conspired to change definitions or withhold important study findings is offensive and without merit. Specifically, the surgical instigator of these concerns has now retracted several of his original grievances as being unfounded – whether his original statements were intentional mistruths or unintentional errors and exaggeration is not for us to speculate. We are equally concerned that journal editors, leaders of societies, social media followers, broadcasters and others appear to accept one-sided declarations without requesting a full accounting of the facts. Regardless of the motivations and actions of others, the EXCEL leadership will continue to exercise the highest scientific principles and ethics of our profession.

- Philippe Genereux
- Bernard J Gersh
- Anthony Gershlick
- David J Kandzari
- Arie Pieter Kappetein
- Roxana Mehran
- Marie-Claude Morice
- Stuart J Pocock
- Joseph F Sabik III
- Patrick W Serruys
- Gregg W Stone

For the EXCEL trial leadership