Response by Prof David Taggart (in red) to the EXCEL investigators (in black), 11-page 3500 word document

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 program. 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:

DT Response 1: This opening statement is disingenuous. Criticism of the conduct of the EXCEL trial on the BBC Newsnight program was **ALSO** based on interviews with a very renowned interventional cardiologist (Professor Rod Stables) and statistician (Professor Nick Freemantle). The same concerns have now been expressed by Dr John Mandrola: https://www.medscape.com/viewarticle/922528 The letter is signed by 11 of the 36 EXCEL authors 'For the EXCEL trial leadership'. While this clearly includes the 4 PIs can the authors confirm if their response was also approved by the approximate 25 remaining authors of the final NEJM manuscript?
It is also interesting to note that, while the 3-year data were analyzed using a non-inferiority approach, with superiority testing performed only in case that non-inferiority was met (as it is generally accepted for PCI vs CABG trials) the 5-year results, in contrast, were analyzed using a superiority approach. The analytic approach for the 5-year analysis was not specified in the protocol, but the rationale for this change is unclear, as the intervention tested and the rationale for a non-inferiority design were the same and the length of the follow-up was only two years longer than in the 3-year analysis. If the EXCEL data are interpreted using the original trial design of non-inferiority with the original prespecified margin of 4.2%, the 5-year primary outcome results (difference of 2.8 %; 95% CI, −0.9 to 6.5) do not reject the null hypothesis of PCI being inferior to CABG.
Finally, I was privileged and honored to be the Chairman of the Surgical Committee of this very important trial and along with my surgical and cardiology colleagues was very committed to the EXCEL trial; indeed, the Oxford unit recruited the second largest number of patients worldwide (n=100). However, I believed, and still do, that the final interpretation of the actual data in the NEJM manuscript did not appropriately reflect its clinical reality, and especially with regards to mortality, and would therefore have potential to do real harm to patients. Consequently, I withdrew my name from the final manuscript.

Summary

- **Choice of the procedural MI 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 PCI and CABG and lack of demonstrated correlation with prognosis. The protocol definition of procedural MI that met these criteria was thus selected and agreed to by unanimous consent.

DT Response 2: It was indeed agreed by all investigators that because of a legitimate concern over ascertainment bias a new, previously untried and untested definition of MI (SCAI) would be used **IN ADDITION** to the UD. The importance of the UD was a 'safety check' to allow comparison the two definitions of MI, both within the EXCEL trial but equally importantly with other trials. The trial protocol (ie the 'rulebook'), published in the NEJM, clearly stipulated that both definitions of MI would be reported. At no time was there any agreement that the protocol specified UD would not be published and that is why I considered -and still do- that only presenting one side of the MI story (SCAI), (that was subsequently shown to be highly unfavourable to CABG), and omitting the UD definition of MI changed, in effect, the definition of MI. If it had been decided at some point not to present the UD, why was the protocol not updated accordingly?

- **The protocol MI definition changed.**
  This is absolutely incorrect – the principal definition of MI never changed throughout the course of the trial.
  Please see DT Response 2 above. By only presenting the new untried, untested definition of MI, (that was subsequently shown to be highly unfavourable to CABG) and omitting the protocol specified and widely accepted UD, the definition of MI was, in effect, a change.

- **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 Universal Definition was not possible.
  (**DT Response 3**: **THIS IS FACTUALLY COMPLETELY INCORRECT**. **The UD [**Thygesen et al UDMI. Circ 2007**] specifically states 'If troponin assays are not available the best alternative is CKMB'.** And although I have never seen and have no access to the database I understand that CKMB data was available for most patients and that that data was leaked to the BBC. It should be noted that the only definition of UD at the time the EXCEL protocol was that published (v4: 22nd July 2011; and re-produced as a supplement in the NEJM) was in Circulation in 2007 [1]. There is no mention of the III UDMI anywhere in the protocol as this new definition was not actually published until 2012.
  The EXCEL protocol also specifically states that the UD will be applied to all MIs (periprocedural, spontaneous, Q-wave and non Q-wave including large and small MIs**).** If CKMB data was available (and it must have been as it was leaked to the BBC, but never presented to the investigators) and the protocol was committed to publishing this data, why did this not happen?. This raises two vital questions: (i) did the investigators actually examine this data and decide to suppress it? (ii) how would such data have impacted on interpretation of the primary composite end-point? Would it have changed interpretation of the outcome both at 3 years and at 5 years? **Failure to present this data was the very same concern raised in the BBC Newsnight program by the statistician (Prof Freemantle) and Interventional Cardiologist (Prof Stables) regarding the potential of this protocol specified data to have changed the result of the trial**).

As in DT Response 1 (above) the same concerns have been raised by Dr John Mandrola, a highly respected cardiologist and totally independent of the EXCEL trial, who has actually recommended that the NEJM should withdraw the manuscript, at least temporarily, until this issue is resolved. 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. (**DT Response** 4: This is specious as the UD [1] specifically states 'If troponin assays are not available the best alternative is CKMB' and that data was available and leaked to the BBC, but never presented to the investigators.) 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 (**DT Response 5**: this still fails to address the missing, protocol specified, UD CKMB data). And until these recent events there had been no requests from any source to prioritize reporting procedural MI according to Universal Definition. (**DT Response 6**: It was the publication of a review in Circulation in 2018 [Ruel et al,Dec18] that showed how much the new SCAI definition of MI inflated procedural MI in the CABG group (five-fold) and reduced it in the PCI group (threefold) that it became critical to publish both SCAI and UD data to genuinely understand how the new, untried, untested SCAI definition of procedural MI was driving the composite end point). Thus, there was absolutely no attempt to withhold meaningful data (**DT Response 7**: this appears illogical. CKMB data, acceptable by the UD definition [1], was available, leaked to the BBC, and should have been published as stipulated in the protocol). 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. (**DT Response 8**: Again, this appears illogical. CKMB data, acceptable by the UD definition [1], was available, leaked to the BBC, and should have been published as stipulated in the protocol)

- **The all-cause mortality data from EXCEL was not strongly enough emphasized.**
  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. (**DT Response 9**: First, this is a rather simplistic viewpoint because all-cause mortality does and must trump everything else. For most clinicians death cannot just be dismissed as just 'one of around 35 exploratory secondary endpoints'. Second, and again in my opinion, the difference in death rates was not 'modest' but both clinically and conventionally statistically significant (OR: 1.38 (95% CI 1.03-1.85). Clinically, as an HR it means that for every 100 deaths in the CABG group there would be 135 in the PCI group. Death is unquestionably the most important clinical outcome for patients and their relatives (and should also be for their doctors) and should be given greatest prominence. Furthermore, it was additionally troublesome that there was an accelerating divergence in death at 5 years and especially considering that these were relatively young patients (mean age 66 years) with low or moderate disease. And, indeed, the initial NEJM review stated '*The finding of a higher mortality rate in one group than another in a clinical trial (unless the difference is clearly trivial) should receive central emphasis in the report of the results, and we would generally consider it important to include such information in the concluding statement in the final paragraph.'* It is still inexplicable to me why this did not happen in the final version of the manuscript)

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 randomization. (**DT Response 10**: I disagree, first, because there is a clear biologic basis for the EXCEL results as many patients had multi-vessel disease where there is a well-documented clear survival advantage for CABG, independent of the presence of left main disease. Second, and as stated in the initial NEJM review,: *'The result of a higher mortality rate in the PCI group, in particular, is addressed in the Discussion in terms that seek to vigorously dismiss the finding as a potential concern. It is emphasized that the differential is mostly accounted for by non-cardiac deaths, although the determination of cause of death is well known to be subject to error and, in an open-label trial, possibly bias'*. It is still inexplicable to me why this did not happen in the final version of the manuscript*)*
Meta-analyses of 4,394 patients from 4 trials of drug-eluting stents vs. CABG (including EXCEL) show there is no difference in 5-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. (**DT Response 11**: This is all important data for discussion but cannot be used to dismiss the mortality data of the EXCEL trial- the largest and most definitive trial of LM disease. As explained above, while mortality is the only hard indisputable fact adjudication of cause of death is notoriously unreliable and open to bias.).

- **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. (**DT Response 12**: Although I was chairman of the surgical committee of the EXCEL trial I was never made aware of any of these concerns which should also have been discussed with the Trial Steering Committee. **This new revelation now also raises the critically important issue of what was known and when. Abbott made the decision to halt the trial early, from the initially proposed 2600 patients to 1906 patients. Was this decision influenced because the investigators and company were aware of mortality concerns raised by the DSMB? or simply co-incidental?** Did the DSMB also have access to or comment on the protocol specified UD CKMD data?).

- **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. **(DT Response 13**: I was not a member of the Guidelines Committee. However, if many of the Guideline members had financial links, direct or indirect, with stent companies then this is clearly of concern**)**

- **New Issue: Failure to Share Data**

DT Response 14: The EXCEL investigators have specifically stated in the NEJM that they would not allow data sharing. This is not only at odds with conventional recommendations and practice that data should be shared to allow pooled analysis of individual patient data but at odds with the authors' previous practice of conducting the very same analyses with data from other trials. This obviously begs the question 'Why' and what is the rationale for this very counterintuitive position from academic clinicians.

Detailed response

1. Background.

The EXCEL trial was an academically led study designed and organized 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 3-year and 5-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 2905 patients between September 29, 2010 and March 6, 2014 at 126 sites in 17 countries. Abbott Vascular funded the trial, but it was led by the scientific community, with 2 surgical principal investigators (Joseph F. Sabik and A. Pieter Kappetein), and 2 interventional cardiology principal investigators (Patrick W. Serruys and Gregg W. Stone). Two independent academic research organizations (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.

(DT response: I was honoured and privileged to be the Chairman of the Surgical Committee of this very important trial. The Oxford surgeons and cardiologists recruited the second largest number of patients worldwide (n=100) showing a very serious commitment to answering the very important question raised in the EXCEL trial)

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.

(DT: At no point does this response appear to address the same concerns raised by the statistician (Prof Freemantle) or Interventional Cardiologist (Prof Stables).

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.

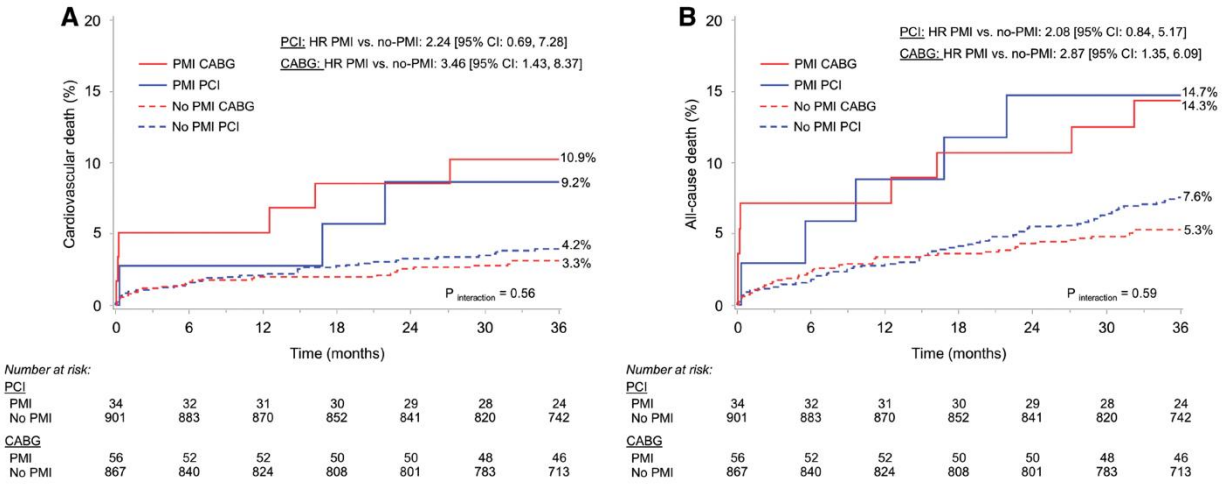
The protocol MI definition was thus agreed on after consensus agreement of the entire leadership, including the Chair of the Surgical Committee, who agreed in particular that eliminating ascertainment bias was critical.

(DT: This has been responded to, in detail, above)

Note:

- A similar definition for peri-procedural 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.

DT: This has been responded to, in detail, above

3. Assessment and reporting of the Universal Definition of procedural MI

The original and third UDMIs were active during enrollment 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 3rd UDMI for post-PCI assessment (type (4a) and post-CABG assessment (type 5) (Table 2 from Thygesen K et al. Circulation. 2012;126:2020-2035).

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.

(DT: The III UDMI was never discussed or appear anywhere in the protocol as it was not described until 2012)

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,…"

(**DT: This has been responded to, in detail, above**)

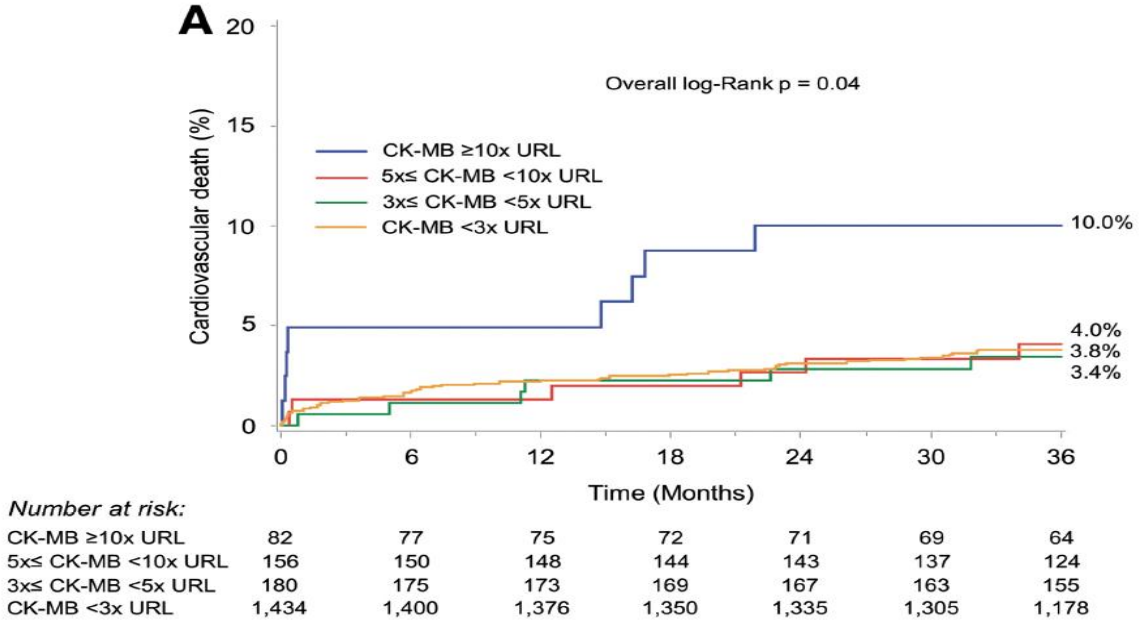
There was consideration to undertake an exploratory sub-study in adjudicating procedural MI by the UD type 4a and 5 MI criteria to determine its frequency and prognostic impact in comparison to the protocol definition of procedural MI. In this regard, while the sites were required to draw baseline and serial CKMB values for the primary definition, (**DT: This has been responded to, in detail, above**) they were asked if possible to also draw troponins at the same times for this purpose. This was described as optional 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.

(**DT: This has been responded to, in detail, above**)

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 finalized. 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 $\geq$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.

(**DT Response 6 (above)**: It was the publication of a review in Circulation in 2018 [2] that showed how much the new SCAI definition of MI inflated procedural MI in the CABG group (five-fold) and reduced

it in the PCI group (threefold) that it became critical to publish both SCAI and UD data to genuinely understand how the new, untried, untested SCAI definition of procedural MI was driving the composite end point).

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.

(**DT: This has been responded to, in detail, above**)

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.

(**DT: This has been responded to, in detail, above**)

4. The protocol MI definition changed

It was claimed publically by Professor Taggart at the 33rd EACTS annual meeting on October 5th, 2019 shortly after the 5-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.
(**DT: This has been responded to, in detail, above**)

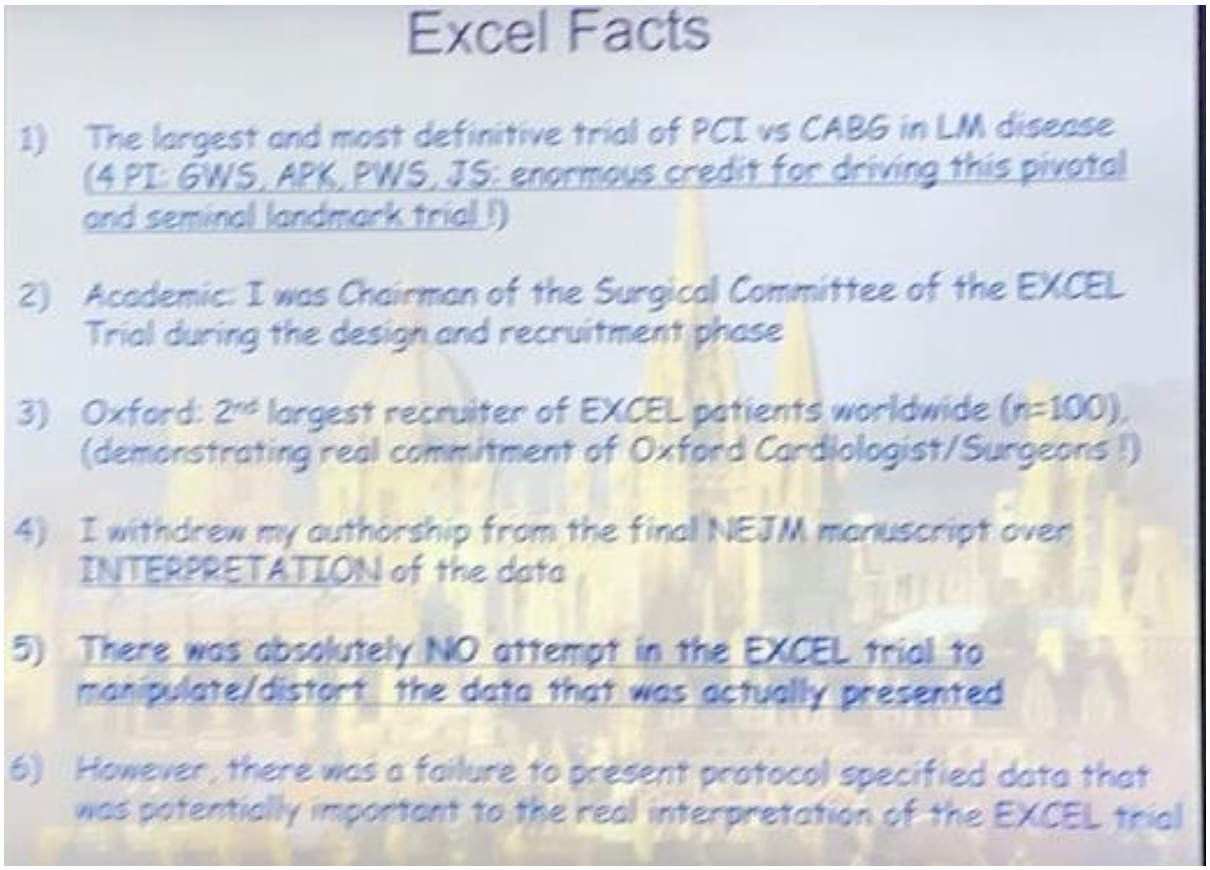
However, Professor Taggart has now withdrawn this fiction: at the recent International Coronary Congress in New York City on December 6, 2019, Professor Taggart stated that he no longer claims that the MI definition changed.

(**DT: This has been responded to, in detail, above**)

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):

DT response: Although I am not on social media I was informed repeatedly that I was being accused of claiming that the data presented in the EXCEL manuscript had been manipulated. My slide was to clarify that I had NEVER said that. But what I said and maintain is that the failure to present the protocol specified UD and only the new untried, untested SCAI definition of MI was a major failing and especially following the publication in Circulation [2]. The same issue of failure to present available data has also been severely criticized by interventional cardiologists (Professor Rod Stables on BBC Newsight, Dr John Mandrola in his podcast), and statistitians (Prof Nick Freemantle on Newsnight).



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, (DT: This is factually incorrect. The 1st line of paragraph 2 on p 2638 of UD states 'If troponin assays are not available the best alternative is

CKMB' So if we had that data, and were committed to publishing it according to the protocol, why did we not do so ?) 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 emphasized.

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.

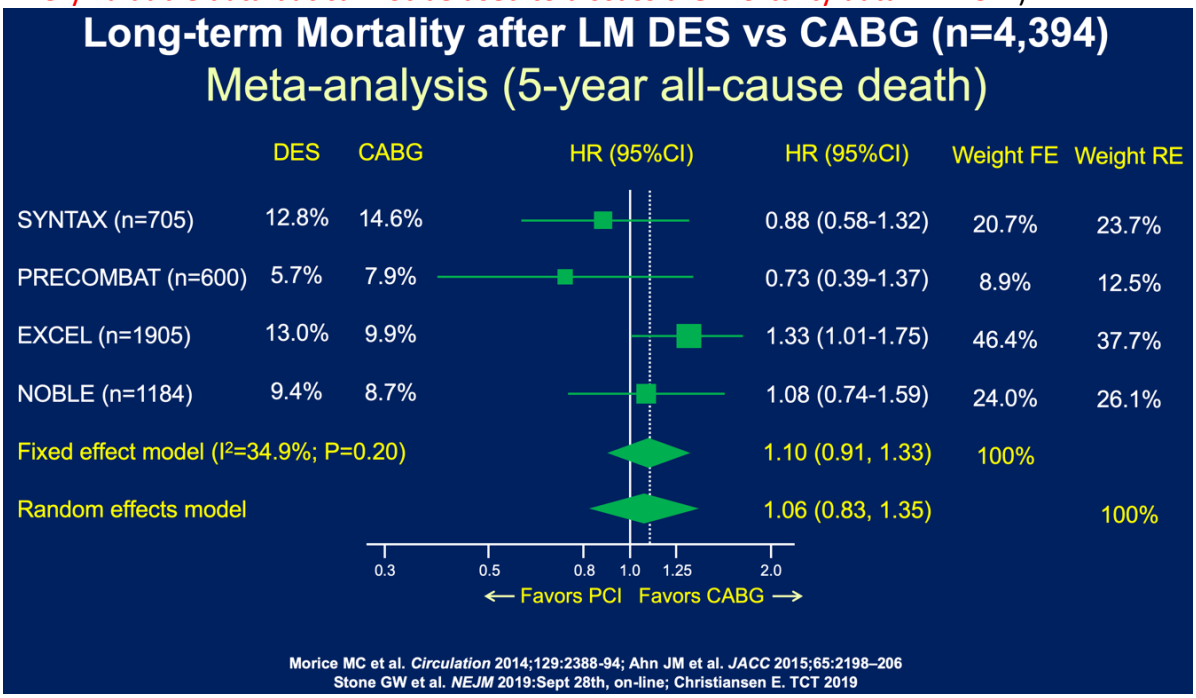
(DT : I never alleged that morality issue was concealed but rather as explained in **DT Response 9**: First, this is a rather simplistic viewpoint because all-cause mortality does and must trump everything else. For most clinicians death cannot just be dismissed as just 'one of around 35 exploratory secondary endpoints'. Second, and again in my opinion, the difference in death rates was not 'modest' but both clinically and conventionally statistically significant (OR: 1.38 (95% CI 1.03-1.85). Clinically, as an HR it means that for every 100 deaths in the CABG group there would be 135 in the PCI group. Death is unquestionably the most important clinical outcome for patients and their relatives (and should also be for their doctors) and should be given greatest prominence. Furthermore, it was additionally troublesome that there was an accelerating divergence in death at 5 years and especially considering that these were relatively young patients (mean age 66 years) with low or moderate disease. And, indeed, the initial NEJM review stated '*The finding of a higher mortality rate in one group than another in a clinical trial (unless the difference is clearly trivial) should receive central emphasis in the report of the results, and we would generally consider it important to include such information in the concluding statement in the final paragraph.'* It is still
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 5-year rates of cardiovascular death and total MI were similar and non-significant after PCI and CABG in EXCEL.

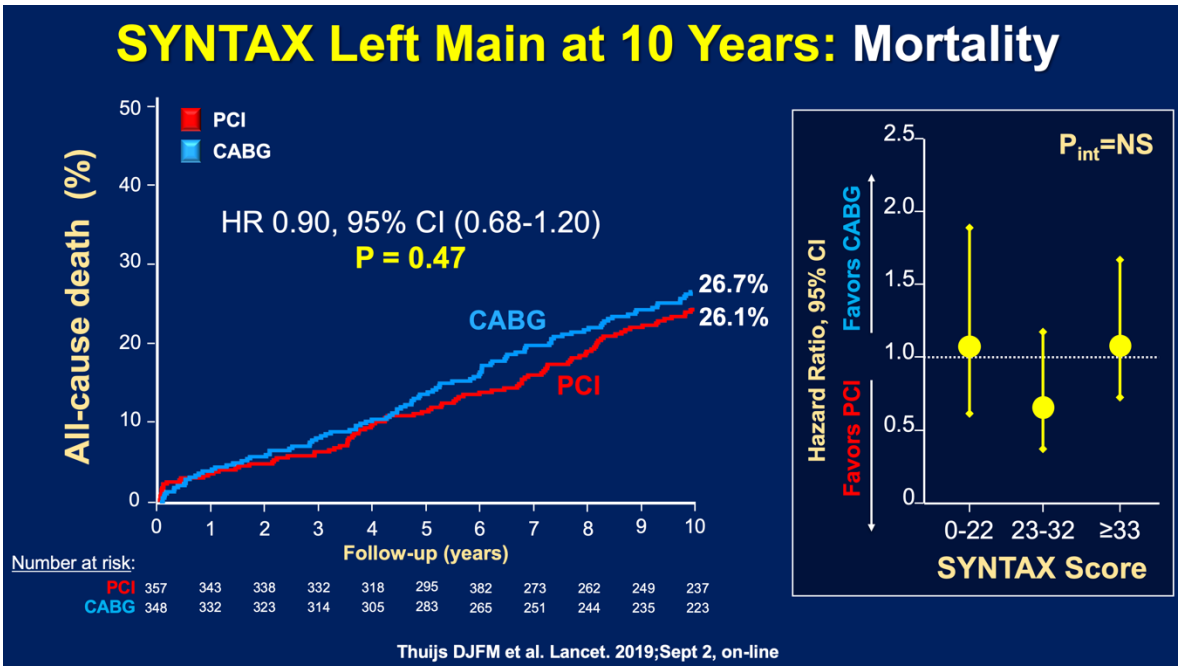
Considering all available data from all studies is also essential in attempting to interpret under-powered secondary endpoints such as all-cause mortality. Four drug-eluting stent (DES) vs. CABG trials have been performed in 4,394 patients with left main disease in which 5-year follow-up is available (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:

(DT: All very valuable data but cannot be used to discuss the mortality data in EXCEL)



Thus, there clearly is no significant difference in 5-year all-cause mortality between CABG and PCI. To emphasize the results from only one trial to suit a particular bias is non-scientific and disingenuous.

In addition, it has been hypothesized that a survival benefit after CABG would emerge after longer-term follow-up. The only study with >5-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 favored PCI with a trend toward lower mortality.

These considerations were addressed in the NEJM 5-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 5 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.

(DT response: As stated in the initial NEJM review: *'The result of a higher mortality rate in the PCI group, in particular, is addressed in the Discussion in terms that seek to vigorously dismiss the finding as a potential concern. It is emphasized that the differential is mostly accounted for by non-cardiac deaths, although the determination of cause of death is well known to be subject to error and, in an open-label trial, possibly bias.)*

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 favoring 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 5-year data.

(**DT Response 12**: Although I was chairman of the surgical committee of the EXCEL trial I was never made aware of any of these concerns which should also have been discussed with the Trial Steering Committee. **This new revelation now also raises the critically important issue of what was known and when. Abbott made the decision to halt the trial early, from the initially proposed 2600 patients to 1906 patients. Was this decision influenced because the investigators and company were aware of mortality concerns raised by the DSMB? or simply co-incidental?** Did the DSMB also have access to or comment on the protocol specified UD CKMD 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 (DT response: this is completely factually incorrect. As repeatedly explained in my detailed responses, my profound concerns remain the same and, in my opinion, the very long rebuttal response by the EXCEL investigators does not adequately respond to the core issues) – 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.

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