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The Excel Controversy, Lesson of the Year: Science, Data and Media

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Introduction

Traditionally, Coronary Artery Bypass Grafting (CABG) has been considered the primary therapy for isolated or multivessel coronary artery disease with left main stenosis (LMCAD). However, when the three-year outcomes of the Excel trial were published [1] and more recently followed by the five years, the 3 years results changed the European guidelines. The European Association for Cardio-Thoracic Surgery (EACTS) guidelines for coronary revascularisation 2018 has incorporated conclusions from the 3 years outcomes as well as other published evidence [2-5]. They recommend that in patients with LMCAD, and low or intermediate SYNTAX scores, both CABG and PCI offer a similar prognosis at 3-year. They recommended that the heart team should consider both options for treating patients with LMSCAD in those with ACS and SIHD [2,6,7]. These findings have influenced clinical practice over the last few years. The EXCEL was a prospective international trial, which randomised patients with unprotected LMCAD, (low to intermediate SYNTAX scores) to PCI with everolimus-eluting stents or CABG between September 2010 and March 2014 [8,9]. The EXCEL composite primary endpoint was the first occurrence of all-cause of death, stroke, or MI at three years. The trial review committee or ethics committee at each collaborating centre approved the study. All Patients singed written, informed consent. The trial was sponsored and funded by Abbott Vascular (Santa Clara, California USA) [10].

All in, this well-conducted trial with many world reputable

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centres involved was well-received [11], until the EXCEL investigators disclosed the 5-year results at the TCT 2019 meeting in San Francisco, CA, and published simultaneously in the NEJM on the 28th of September, 2019 [12]. They revealed the study's primary endpoint (death, stroke, or MI)—was 22.0% in the PCI and 19.2% in the CABG-treated patients (P = 0.13) so they established that there was no significant difference between revascularisation with PCI or CABG in patients with LMCAD (low and intermediate syntax score). While putting less emphasis what they have reported that death from any cause significantly favoured CABG surgery at 5 years (9.9% vs 13.0% with PCI; odds ratio 1.38, 95% confidence interval 1.03–1.85) and is accelerating in favour of surgery because the curves for survival continue to diverge over time.

Prof. Taggart later took a fair shot at the EXCEL trial and its investigators in the latest European Association meeting for Cardio-Thoracic Surgery (EACTS) 2019. He claimed that their suppositions contradicted the data in the published paper [12] and that he would endeavour to "amend" their interpretation of the results. They need predominantly addressing the absence of emphasis on the higher risk of death with PCI. However, he failed and consequently withdrew his name from the paper. Sadly, the public and media got involved in the debate, when the BBC Newsnight aired a program titled; "Surgeons withdraw support for heart disease advice" on the 9th of December 2019. Investigators Deborah Cohen and Ed Brown had seen unpublished data which showed that under the universal definition of MI patients in the trial who had received stents, had 80% more heart attacks than those who had open-heart surgery, and were 38% more likely to die. Consequently, this resulted in a very provocative and emotionally charged acquisition. EACTS formally withdrawn their support for the current treatment recommendations for left main coronary artery disease following the investigative report by BBC *Newsnight*.

The Excel lead academics told Newsnight that this was "false data". But the journalist claimed to have spoken to experts. These experts believe the data was credible, and that you can always find a physician who would have a different judgment.

The question is, should we ignore, Prof. Taggart's alleged remarks that one-third of studies' authors accepted fees from Abbott Vascular, and 40% received payments from the stent manufacturers which imply bias. However, we should ignore the politics, even the explicit contribution of the industry to the trial and the association of both Chief Medical Officer (CMO) of Abbott Vascular, and CMO of Medtronic as primary authors of the study. Despite having been declared as a conflict of interest in the trial protocol, the published papers still shed a shadow of a doubt on the perception of impartiality.

The real issues here are scientific debate and data analysis. We are talking of a difference of 38% in mortality between PCI and CABG at five years. So, what is the learning we should take from this?

Death from any cause significantly favoured CABG surgery at 5 years (9.9% vs 13.0% with PCI; odds ratio 1.38, 95% confidence interval 1.03–1.85) and is accelerating in favour of surgery because the curves for survival continue to diverge over time this was underplayed in the first NEJM paper and corrected recently in the newly published paper [12,13].

Firstly, the sharing and disclosing of raw data, even if it is negative [14], is the duty of all scientists. Harlan M Krumholz, Editor-in-Chief of NEJM Journal Watch (Cardiology) remarked, "The sharing of results is the responsibility of all scientists – and is our ethical obligation to the participants". Clearly that there are difficulties in the diagnostic accuracy of acute MI hence the multiple definition and multiple markers [15]. If the endpoint is essential, why wasn't the marker troponin used for MI diagnosis? [16], troponin has established itself around the world as a more sensitive and accurate marker for MI diagnosis. Shortcuts to save money or effort, diminishes the certainty of the findings and creates further difficulties.

With many investigators involved in a big experiment, you might have picked a bizarre patient population that maybe by chance has indicated one-time high drug effectiveness. Or you might have just gotten a peculiar statistical concurrence. It does not matter how an experiment or trial got garbled, "negative results" can be beneficial-sometimes even more valuable than positive results.

It is well known that a vast number of major clinical trials never see the light of day, especially if they are negative. In the latest study by Tatsioni et al. they found that 67 of the 500 randomised trials (registered with ClinicalTrials.gov) did not publish for a median of 9 years following their completion. With a staggering excess of 87,883 patients in the trials [14]. No reasons have been forthcoming.

Errors are the gateways to innovation. 'Good science' involves making mistakes, and we have to be open and honest about our scientific slip-ups, and understand how mistakes can help to model and shape science - keeping silent about them jeopardies others, who unwittingly may repeat them. Pursuing and recording scientific mistakes for all to gain knowledge, is an essential part of the western scientific philosophy and has served us well over the years.

All the positive and negative data, which feeds back into the information ecosystem, enable this information to flourish and survive and remain healthy.

The collective intelligence of the medical and scientific community as they interrogate and question the data must also be included in the body of knowledge (letters to the editor).

Secondly, a composite endpoint is an outcome measure, which is an amalgamation of multiple clinical parameters. These composite endpoints can be primary or secondary.

The benefits of composite endpoints are self-explanatory; it does improve statistical efficiency and precision. The smaller the trial, the lower the cost and the earlier it would be completed since there is less need to wait for a significant number of rare events [17]. When a study has an infrequent endpoint, it's common to use a composite endpoint. We should only use composite endpoints when each parameter in the composite is significant and related both to the trial rationale and to the patient. Each endpoint should be analysed independently (Excel investigator should release this information) to estimate if the clinical trial has significant results for all elements of the composite or just some [18,19]. Excel composite endpoints dilute fatal and severe outcomes (death and MI needed an intervention) with non-serious ones (enzyme raise and temporary TIAs), so with the confirmation bias added to the mix we have now serious controversy

The main risk to a trial with composite endpoints is the potential for bias. Therefore, a careful analysis of the data is man-

datory to avoid inherent bias due to the possibility of competing values between endpoints. It is prudent to avoid mixing fatal events with less serious ones like enzyme raise as in Excel [20].

Thirdly, truth always shines at the end, and we would never forget the Autism story and the MMR vaccine. Scientists make advancements by repeating each other's experiments —reproducing them to see if they can get the identical outcome. More frequently than not, they can't. Failure is a good thing; this is how new approaches and new ideas come to light.

Conclusion

Today's medicine is directed by trade and technology, and the majority of research is funded (if not entirely) by commerce. Therefore we editors, readers, and authors are obliged to learn how to read between the lines of published papers. At the same time, as professionals and scientists, we are being scrutinised by the media who have the use of extensive technological capabilities and resources for investigations. It is a commendable that NEJM have recently published the correction [13] which is a step in the right direction. Being watched requires us to be vigilant, a bit of a 'Hawk' always on guard. In our quest for progress to aid industry in developing new technologies, we must not unconsciously sell our integrity as we are the entrusted last guardian for the patient and their families.

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