EXPERT OPINION

The Excel trial and the current clinical guidelines for myocardial revascularization: What do we need to know? Keep me in the loop! Part 2.

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The 2018 ESC/EACTS clinical guidelines for myocardial revascularization have been our *"light on the pad"* since they officially appeared published in 2019. For interventional cardiologists and cardiac surgeons our highest quality standards are based upon these guidelines above. With this framework, so large a body of trials have been carried on. Excel trial is one of them into this lengthy list. The trial was initially designed in an attempt to come into the open the status of non-inferiority of the PCI compared to CABG. Unfortunately, the Excel trial has been surrounded, in a manner of saying, by many uncommon facts. All this above notwithstanding, the level of credibility of this trial has dramatically fallen far below the target levels, giving raise to the so-called "the Excel scandal". However, cutting just to the chase, what really happened? Whereas the Excel trial Investigators state out nothing wrong is happening, the crowd claims for a further transparency of open data. However, *what is truthfully necessary is to make clear if all these big-gig trials might be compared as a whole to get a true pooled effect impacting the current clinical guidelines*.

Key words: **Clinical guidelines; Coronary artery bypass grafting; Coronary artery disease; Myocardial ischemia; Myocardial revascularization; Excel trial.**

Las guías clínicas ESC / EACTS 2018 para la revascularización miocárdica han sido nuestra *"luz en el camino"* desde que aparecieron oficialmente publicadas en 2019. Para los cardiólogos intervencionistas y los cirujanos cardíacos, nuestros más altos estándares de calidad se basan en estas guías clínicas.En este contexto, se ha llevado a cabo una gran cantidad de estudios. El estudio Excel es uno de ellos en esta larga lista. El ensayo se diseñó inicialmente en un intento de probar el estado de no inferioridad del PCI en comparación con la CABG. Desafortunadamente, el estudio Excel ha estado rodeado, por así decirlo, por muchos hechos poco comunes. Al margen de todo lo anterior, el nivel de credibilidad de esta prueba ha caído dramáticamente muy por debajo de los niveles esperados, dando lugar al llamado "escándalo de Excel". Sin embargo, yendo directamente al grano, ¿qué pasó realmente? Mientras que los investigadores del Excel afirman que nada malo está sucediendo, el público clama por una mayor transparencia de los datos abiertos. No obstante, *lo que es indudablemente necesario es dejar suficientemente claro si los grandes estudios estelares pudieran ser comparados entre sí como un todo, con la finalidad de obtener un verdadero efecto grupal que impacte a las guías clínicas.*

Palabras clave: **Guías clínicas; Puentes aortocoronarios; Enfermedad coronaria; Isquemia miocárdica; Revascularización coronaria; Estudio Excel.**

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The 2018 ESC/EACTS clinical guidelines are our reference point to get the highest quality standards in cardiac surgery as well as interventional cardiology regarding myocardial revascularization [1]. Speaking specifically about the left main coronary stenosis (LMCS), the current recommendations are in accordance with the Syntax score risk-group. Hence, for low-risk group (Syntax score ≤ 22) the class of recommendation (COR) is I with level of evidence (LOE) A for both PCI (percutaneous coronary intervention) and CABG (coronary artery bypass grafting). For intermediate-risk (Syntax score 22-32), the indication is IA for CABG, whereas it is IIa A FOR PCI. And ultimately, for the high-risk group, the indication is IA for CABG, and III B for PCI. Incidentally, I have made these few remarks to call our attention

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to the other than low-risk Syntax score group (**Table 1).** How simply are these facts explained in the view of the preexisting high impact trials. Indeed, all along the years, several trials have been successfully launched. Such is the case for the Syntax [2-4], Precombat [5-6], Noble [7-8], and Excel trial [9], among countless others. In point of fact, the chapter for LMCS of the foregoing mentioned guidelines is mainly supported in all these trials above. As yet I have failed to found any trial to enable a wider scope of the indications for PCI over the specific intermediate-risk Syntax score group. Actually, the indication remains just as at the very beginning, it means as indication IIa A [1]. Therefore, no wonder the aim of the Excel trial would be to improve this COR, from IIa A towards IA, a very profitable business for industry sponsoring these trials.

In these terms, we have to separate the wheat from the chaff. After analyzing all these long-term trials, I have been enabled to show this extremely intricate subject. Let us now have a look inside this universe of fascinating data and facts.

The Syntax trial was first shown at 1 year-follow-up [2]. The composite primary endpoint (all-cause death, stroke, myocardial infarction) was no different between both groups, with 7.6% for PCI vs 7.5% for CABG, p=0.89. Cumulative event rates for Stroke was 2.2% for CABG, and 0.6% for PCI, p= 0.003). Cumulative event rates for repeat revascularization was 5.9% for CABG vs 13.7% for PCI, p<0.001. And finally, the composite of MACCE (major adverse cardiac and cerebrovascular events) was 12.1% for CABG vs 17.8% for PCI, p<0.001. Thus, at 1-year follow-up, while the primary composite endpoint (death, stroke and myocardial infarction showed no difference, the repeat revascularization and the MACCE were in favor of CABG. Of note, the selected group of high-risk Syntax score (≥33) exhibited a large difference for MACCE, 10.9% for CABG vs 23.4% for PCI, p<0.001 (**Fig. 1**).

Following with this same pool of patients, in the long run for 5-years [3], the cumulative event rates was more favorable for CABG compared to PCI, on a whole. For myocardial infarction (MI), it was 3.8% for CABG vs 9.7% for PCI, p<0.001; Repeat Revascularization was 13.7% for CABG vs 25.9% for PCI, p<0.001; MACCE was 26.9% for CABG vs 37.3% for PCI, p<0.001. The only item in favor of PCI was the Stroke rate of 2.4% for PCI vs 3.7% for CABG, p=0.09. It is worthwhile to highlight the trends on the graphs for the different risk groups according to the Syntax score. The cumulative event rate for MACCE in the low-risk group (≤ 22) was 28.6% for CABG vs 32.1% for PCI, p=0.43. No significant difference between groups was found. In the intermediate-risk group (22-32), both curves begin to get wider, 25.8% for CABG vs 36.0% for PCI, p=0.008. In high-risk group (≥33), 26.8% for CABG vs 44% for PCI, p<0.001. Therefore, at this point in line with all this above, the only suitable group for both treatments as indication IA is the low-risk Syntax score group [3] (**Fig. 2**).

Continuing with the Syntax trial but now at 10-years, the analysis only showed the probability of death while keeping on the dark other highly important issues such as MI, repeat revascularization and stroke. This long-term analysis emphasizes the only group that benefits by using CABG is the multivessel one [HR= 1.41 (95% CI= 1.10-1.80)] No difference was observed between diabetic or non-diabetic groups regarding the probability of death [HR= 1.10 (95% CI= 0.80-1.52)] [HR= 1.20 (95% CI= 0.09-1.51)], respectively. Of note, no difference was observed between PCI and CABG on a whole in terms of survival at 10 years [HR= 1.17 (95% CI= 0.97-1.4; p=0.092)]. LMCS group showed no important difference for both treatment modalities [HR= 0.90 (95%CI= 0.68-1.20)] [4].

Keeping our focus now on the different pools according the Syntax score in this same trial above, no difference for PCI and CABG was found out for low and intermediate score groups, [HR= 1.13 (95% CI= 0.79-1.62)] and [HR= 1.06 (95%

INDICATION	CABG		PCI	
	COR	LOE	COR	LOE
LEFT MAIN CORONARY ARTERY				
LM with LOW Syntax score (0-22)	I	A	I	A
LM with INTERMEDIATE Syntax score (22-32)	I	A	IIa	A
LM with HIGH Syntax score (≥ 33)	I	A	III	B

Table 1. Current indications for left man coronary stenosis according to 2018 ESC/EACTS clinical guidelines for myocardial revascularization. With permission and as published in García-Villarreal OA [13].

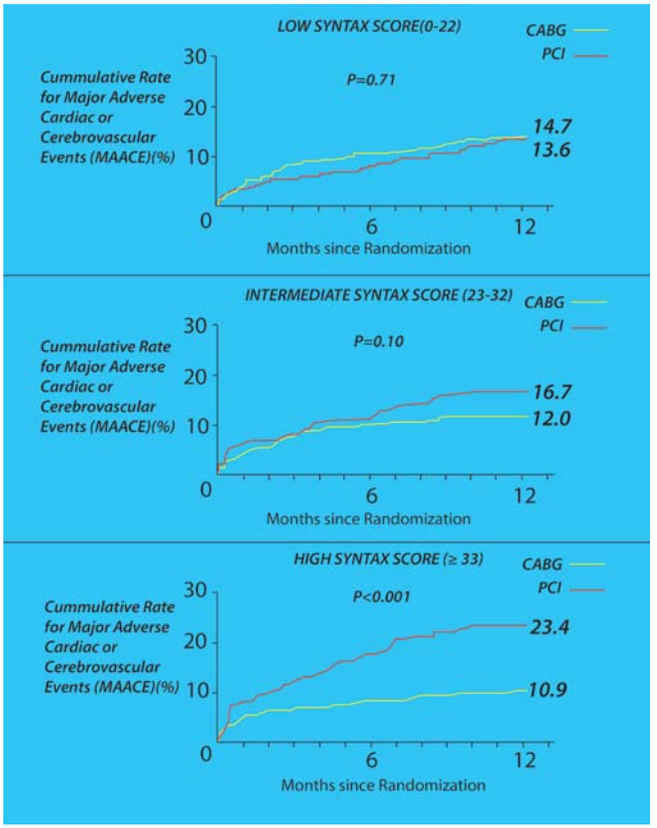

Figure 1. Cummulative rate for major adverse cardiac and cerebrovascular events (MACCE), in the Syntax trial for 1-year, according to Syntax score risk group. Adapted from Serryus PW, et al. [2].
CABG= Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

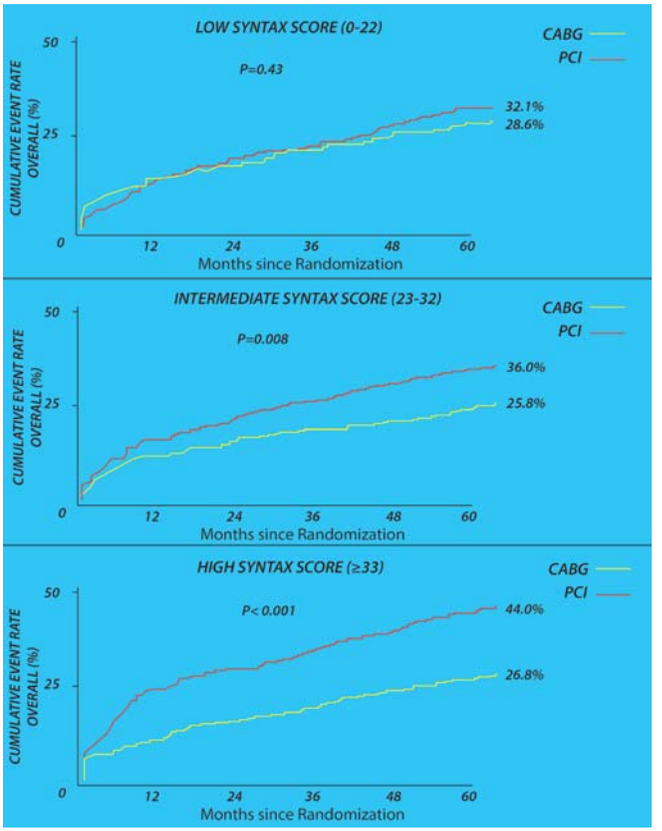

Figure 2. Cummulative rate for major adverse cardiac and cerebrovascular events (MACCE), in the Syntax trial for 5-years, according to Syntax score risk group. Adapted from Mohr FW, et al. [3].
CABG= Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

CI= 0.77-1.47)], respectively. However, for high score group, a discrete difference in favor or the CABG over PCI was evident as less probability of death in a long run of 10 years [[HR= 1.41 (95% CI= 1.05-1.89)] [4] (**Fig. 3**).

In principle and to start in, we must not assume that all of the shown conclusions are automatically reliable for any patient with LMCS. As already stated by Freemantel and others, the number of patients with isolated LMCS with no additional distal lesion is small and with no enough statistical power to reflect the reality. Only 92 patients are summarized under these characteristics in the Syntax study. Out of them, 42/357 (12%) underwent PCI. Thus, it is more than evident that the sample is fairly small to get strong conclusions [10].

Let us now turn on the PRECOMBAT study. This is a trial designed to demonstrate PCI non-inferiority with respect to CABG in a selected group for LMCS. In this analysis at 5 years follow-up, for death from any cause [CABG= 7.9% vs PCI= 5.7%, p=0.32), MI [CABG= 1.7% vs PCI= 2.0%, p=0.76], stroke [CABG= 0.7% vs PCI= 0.7%, p=0.99] there was no statistically significant difference. For ischemia-driven revascularization, a fancier way to refer repeat revascularization, CABG had a clear difference over PCI [CABG= 5.5% vs PCI= 11.4%, p=0.012]. With this framework, the bottom line of this study was PCI is non-inferior than CABG, for the composite primary endpoint at 5 years [5-6].

Turning for a brief space to the NOBLE trial, shall we say then that this study was designed to show non-inferiority of the PCI compared to CABG with patients with LMCS. The limit of the margin of non-inferiority was established as a HR not higher than 1.35 for the primary endpoint, a composite for death for any cause, stroke, repeat revascularization and MI. At first sight, the study failed to prove the non-inferiority of the PCI to CABG at 5-years follow-up [HR= 1.58 (95% CI= 1.24-2.1, p= 0.0002)]. At the same time, we can make some interesting remarks in the same trial. At 5 years, all-cause mortality was similar for both groups [CABG= 8.7% vs PCI= 9.4%, HR= 1.08 (95% CI= 0.74-1.59, p=0.68)]. Special emphasis should be given on the issue about non-periprocedural infarction in this trial. As expected, a comparative advantage was found in favor of CABG [CABG= 2.7% vs PCI= 7.6%, HR= 2.99 (95% CI= 1.66-5.39, p=0.0002)]. For repeat revascularization, [CABG= 10.2% vs PCI= 17.1%, HR= 1.73 (95% CI= 1.25-2.40, p=0.0009)] in favor of the CABG as well. For stroke, [CABG= 2.2% vs PCI= 3.8%, HR= 1.75 (95% CI= 0.86-3.55, p=0.1109)] with no important difference for both

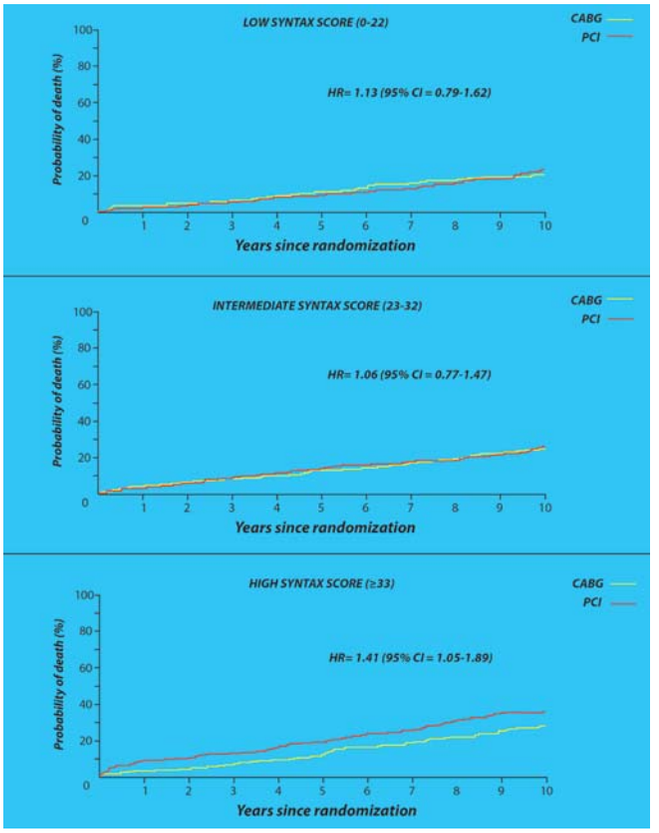

Figure 3. Probability of death, in the Syntax trial for 10-years, according to Syntax score risk group. Adapted from Thuijs DJFM, et al. [4].
CABG= Coronary artery bypass grafting; HR= Hazard ratio; PCI= Percutaneous coronary intervention.

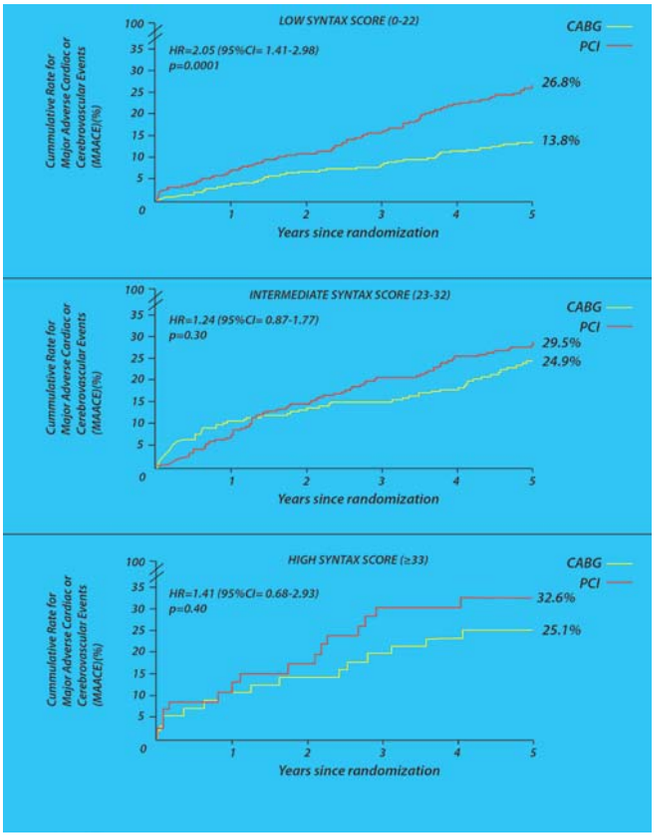

Figure 4. Cummulative rate for major adverse cardiac and cerebrovascular events (MACCE), in the NOBLE trial for 5-years, according to Syntax score risk group. Adapted from Holm NR, et al. [8].
CABG= Coronary artery bypass grafting; HR= Hazard ratio; PCI= Percutaneous coronary intervention.

groups [7-8].

Nevertheless, at last but not least for this trial above, what is really striking is the sub-analysis for groups according the Syntax score with regard MACCE (major adverse cardiac and cerebrovascular events) at 5-years follow-up. For high-score group, a clear advantage for the CABG was demonstrated [CABG= 25.1% vs PCI= 32.6%, HR= 1.41 (95% CI= 0.68-2.93, p=0.40)]. For intermediate-risk group, [CABG= 24.9% vs PCI= 29.5%, HR= 1.24 (95% CI= 0.87-1.77, p=0.30)] no important difference for both groups. And finally, a special consideration must be highlighted on the low-risk group, [CABG= 13.8% vs PCI= 26.8%, HR= 2.05 (95% CI= 1.41-2.98, p=0.0001)] in greater advantage for CABG over PCI [8] (**Fig. 4**). In point of fact, this last finding is of paramount importance because is in frank opposition to what the current guidelines indicates for the low-risk Syntax score group as IA indication [1].

How simply are all these facts explained when the same parameters to measure the criteria are considered for each and every study. When the primary endpoint is defined as a composite of the same individual issues, and each issue measured with the same parameters, the results can be in all likelihood anticipated. I have made all these remarks to call attention to the subject of the MI definition in the Excel trial. The Excel trial [9] can be considered as a part of the four "A-listers" trials to study LMCS and supported the chapter about the LMCS in the current guidelines for myocardial revascularization [1]. At first, the Excel trial was designed, like all other three of them, to investigate the non-inferiority of the PCI regarding the CABG for the LMCS, with special focus on the low and intermediate Syntax score group. However, I would like to begin by expressing the main concern in respect thereof. Properly speaking, it is a well-designed trial. Nevertheless, the primary endpoint composite (death from any-cause, stroke, periprocedural MI) is sensibly different to the other trials [2-8]. The key point making the wide difference, in term of concepts, is double; namely, the universal definition for MI (UDMI) was supplanted by the SCAI definition, and the inclusion of the peri-procedural MI as a part of the events to register. I state this because it has been erroneously assumed that an independent analysis of data should be done by any external committee. However, let us now to analyze in depth step by step what is really happening with this trial to give it our best shot in order to understand in a better way the final outcome expressing as a composite primary endpoint. Firstly, whether or not the term was changed once the trial was run-

	cardiac biomarker	PCI	CABG
2nd UDMI	cardiac troponin	3x	5x
3rd UDMI	cardiac troponin	> 5× and ischemia, electrocardiographic changes, angiographic findings, or new RWMA	idem
SCAI	CK-MB	Any of: CK-MB ≥10×; CK-MB ≥5× ULN and new Q waves or LBBB;cTn ≥70× ULN;cTn ≥35× ULN and evidence of new Q waves or LBBB	idem
4th UDMI	cardiac troponin	> 5× and new Q waves, angiographic findings, or new RWMA	> 10× and new Q waves, angiographic findings, or new RWMA

Table 2. Several definitions for Myocardial Infarction.
CABG= Coronary artery bypass grafting; LBBB= Left bundle branch block; UDMI= Universal definition for myocardial infarction; PCI= Percutaneous coronary intervention; SCAI= Society for Cardiovascular Angiography and Interventions. RWMA= Regional wall motion abnormality; cTn= Cardiac troponin. Adapted from Ruel M, et al [11].

ning out or on the way, this is not a matter of our business and it is far beyond our knowledge. This is running completely out of our hands and this is not the scope of this writing. Secondly, in accordance with the definition for MI utilized for this study, a big difference can be noted from the Excel trial with regard to the other trials. As already stated above, SCAI definition was used [9]. Certainly, several definitions for MI have been proposed. This last utterance is of paramount importance. Several MI definitions are summarized in **Table 2** [11]. The main difference is by using the SCAI definition instead of the 2nd or 3rd UDMI. This SACI definition uses MB-CK as biochemical marker primary choice 10X or 5X with additional clinical and/or paraclinical findings. The other UDMI use troponine as biochemical marker first choice. The second difference is by including the periprocedural MI as a part of the primary endpoint, which is defined as taking place within the procedure and extended up to the first 72 postprocedural hours. It is worthwhile to highlight the wide difference among the trials when considering the composite primary endpoint, specifically speaking about MI period. Whilst other than Excel trials include the non-periprocedural MI as a part of the composite primary endpoint, the Excel is the only one including the periprocedural MI. This fact calls highly our attention because the periprocedural MI is most likely to occur in CABG than PCI. Therefore, the comparison among all the four trials for the primary endpoint becomes almost impossible in terms of fairness or non-bias.

The other main difference between Excel and the other trials in the composite primary endpoint is the exclusion of repeat revascularization rate. All death from any-cause, stroke and MI are used by all of them (Syntax, Precombat, Noble and Excel), while repeat revascularization was excluded from the Excel [9]. Thus, even when some meta-analyses comparing these four main trials have been carried on, a high degree of suspicion must remain. We need to separate the wheat from the chaff, avoiding comparing apples with oranges.

Therefore, at first glance, when comparing PCI with CABG at the Excel trial, there was no difference for the primary endpoint at five years between them [CABG= 19% vs PCI= 22%, HR= 1.19 (95% CI= 0.95-1.50, p=0.13)]. Hence, PCI is non-inferior than CABG for patients with LMCS of low or intermediate anatomical complexity [9].

According to the foregoing and already explained facts, when analyzing the curves for MI along several time-intervals, some capital differences come into the open. Regardless the definition used for MI, for the 0-day to 30-day, the periprocedural MI is mostly observed in CABG than PCI [CABG= 8% vs PCI= 4.9%, HR= 0.61 (95% CI= 0.42-0.88, p=0.008)]. From 30-day to 1-year no important difference [CABG= 3.8% vs PCI= 4.1%, HR= 1.07 (95% CI= 0.68-1.70, p=0.76)]. From 1-year to 5-years, a wide difference was noted between both comparative groups in favor of the CABG [CABG= 9.7% vs PCI= 15.1%, HR= 1.61 (95% CI= 1.23-2.12, p <0.001)] [9]. However, when the item so-called ischemia-driven revascularization is included as a part of the primary endpoint, CABG is better than PCI at 5 years follow-up [CABG= 24.9% vs PCI= 31.3%, OR= 1.39 (95% CI= 1.13-1.71, p= 0.002)] [9]. Moreover, the only secondary endpoint in favor of PCI is the stroke rate [CABG= 3.7% vs PCI= 2.9%, OR= 0.79 (95% CI= 0.46-1.31)]. Death from any cause [CABG= 9.9% vs PCI= 13%, OR= 1.38 (95% CI= 1.03-1.85)], MI [CABG= 9.1% vs PCI= 10.6%, OR= 1.14 (95% CI= 0.84-1.55)], and ischemia-driven revascularization [CABG= 10% vs PCI= 16.9%, OR= 1.84 (95% CI= 1.39-2.44, p <0.001)], all of them are markedly in favor of the CABG [9].

In the light of the foregoing, it makes us wonder what

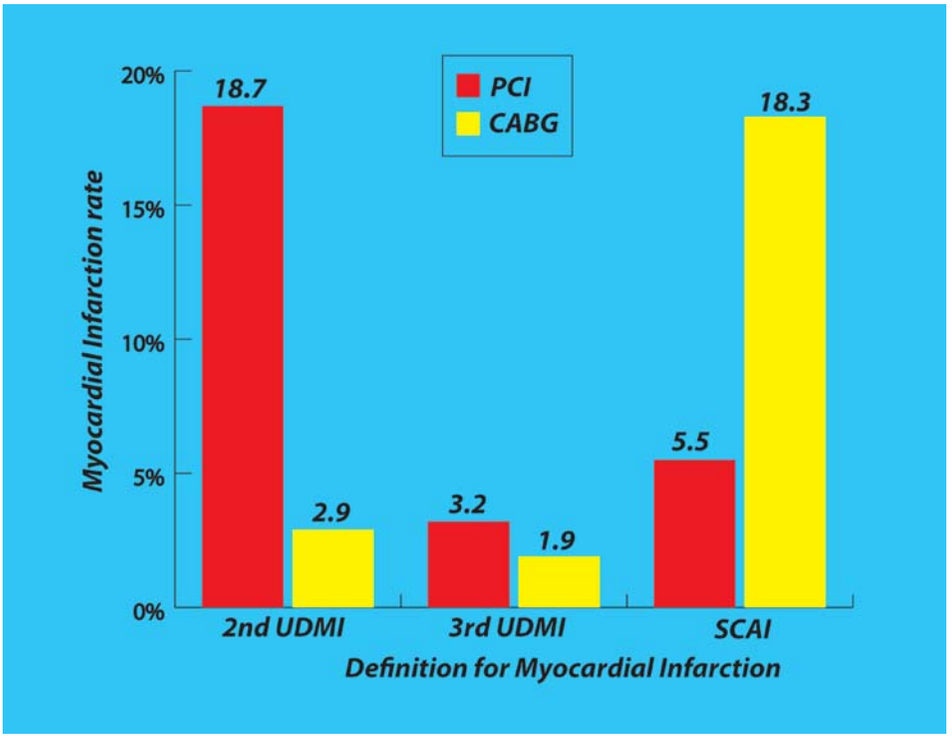

Figure 5. Different alternative graphics comparing CABG and PCI by using several myocardial infarction definitions, according to data coming from the Excel trial.
CABG= Coronary artery bypass grafting; UDMI= Universal definition for myocardial infarction; PCI= Percutaneous coronary intervention; SCAI= Society for Cardiovascular Angiography and Interventions. Adapted from Ruel M, et al [11].

might have happened if the 2nd or even 3rd UDMI used in the Excel trial instead of the SCAI definition. Ruel et al. [11] have make a general draw of the hypothetical scenario. By using the 2nd UDMI (CABG= 2.9% vs PCI= 18.7%) we would get a clear advantage for CABG. Now, regarding by using the 3rd UDMI (CABG= 1.9% vs PCI= 3.2%) a more suitable balance can be noted, but still remaining in lightly favor of CABG. Contrariwise, by using SCAI definition, shall we note (CABG= 8.3% vs PCI= 5.5%) enormous difference in favor of PCI. As a conclusion, with no modification in MI definition it would be in all likelihood in favor of the CABG when analyzing the MAACE as a primary endpoint [11] (**Fig. 5**).

And more to the point, when dividing the non-periprocedural from the periprocedural MI, the following data can be obtained; for non-periprocedural MI [OR= 1.96 (95% CI= 1.25-3.06)], CABG in clear advantage over PCI; for periprocedural MI [OR= 0.63 (95% CI= 0.41-0.96)], markedly divergent and in stark contrast with the later. But the truth of the matter goes slightly deeper. If we calculate as an alternate analysis the composite primary endpoint (death from any-cause, stroke, including just the non-periprocedural MI) [OR= 1.44 (95% CI= 1.14-1.82)], the final outcome as a primary endpoint would be in favor of CABG. In other words, PCI would be inferior to CABG at 5-year follow-up. Now, the original composite primary endpoint (death from any-cause, stroke, including the periprocedural MI) shows the following data: OR= 1.19 (95% CI= 0.95-1.50), in an evident advantage for PCI. Therefore, we are driven to conclude that the key point is how to define the composite primary endpoint.

Putting in a nutshell, as far as the extreme intricate of the matter allow us to understand, the most important issue is how and to what extent all these results may affect the already accepted clinical guidelines [1]. LMCS chapter is chiefly based upon the four "A-listers" big-gig trials; viz, Syntax [2-4], Precombat [5,6], Noble [7,8], and Excel [9]. According to the guidelines, the current indications for LMCS revascularization are summarized in Table 1. No matter about the high-score group; CABG is IA indication, whilst PCI is IIIB; intermediate-risk group, CABG still remains (IA indication) as preferable over PCI (IIa B). For low-risk group, indication IA is the same for both CABG as well as PCI. Hitherto, extremely contrasting data have been obtained for the low and intermediate-risk groups from the aforementioned main trials [2-9]. Despite the foregoing data, this standpoint has been ably maintained by many. Albeit optionally, I can feel assured that a new revision of the already existing data coming from trials will be extremely urged on. At the same time, all this has ended up with the withdrawal of the support to the current clinical guidelines for myocardial revascularization regarding the chapter for LMCS from EACTS [12].

To sum up, I gave herein a brief sketch about the most recent scenery on LMCS and the current clinical guidelines. We therefore must not fall into the error of ignoring all the ins and outs surrounding any trial before making any final conclusion. We are in no state for such declarations of bias. We do not need another specialized data analysis. However, what is truthfully necessary is to make clear if all these big-gig trials might be compared as a whole to get a true pooled effect. I have been tossing and turning all nights while trying to solve this big trouble we are getting at. As far as I can understand, the only way to find a solution is to be equal in definitions. The truth must always be black and white. It can make or break the final outcome from any trial.

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