



Editorial

New-generation drug-eluting stents for unselected patients with left main coronary artery disease: Crossing a second Rubicon?

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ARTICLE INFO

Article history:

Received 7 January 2019

Accepted 10 January 2019

Available online 15 January 2019

1. Introduction

Left main coronary artery disease (LMCAD) has major prognostic implications due to the large amount of myocardium at risk and remains a major therapeutic challenge [1,2]. Just a decade ago percutaneous coronary interventions (PCI) still had a Class III indication for patients with LMCAD eligible for coronary artery bypass grafting (CABG) [1]. Major medical advances including the advent of new generation drug-eluting stents (DES) have completely revolutionized the field and, in particular, the choice of revascularization strategies in this unique setting [3–7]. Accordingly, recent European clinical practice guidelines on coronary revascularization gave a similar recommendation (IA) for PCI and CABG for patients with LMCAD with low anatomic complexity [2]. These contemporary guidelines still consider that CABG remains superior to PCI (IA vs IIIB) in patients with LMCAD and very high anatomical complexity (Syntax score >32) [2]. Two recent major randomized trials have fuelled the controversy providing apparently conflicting data [8,9]. The NOBLE trial suggested that CABG remains the therapy of choice for eligible patients with LMCAD [8]. However, the largest EXCEL trial demonstrated that in patients with LMCAD and low-to-moderate anatomic complexity treatment with everolimus-DES was not inferior to CABG regarding the combined clinical outcome measure of death, stroke and myocardial infarction (MI) at 3 years [9]. Importantly, and in contradistinction to previous trials, in EXCEL PCI was also non-inferior to CABG when ischemia driven revascularization was included in the composite endpoint [9].

However, how the results of these controlled clinical trials may be best translated into every day clinical practice still remains unclear.

2. Current study

In this issue of the *Journal* Tanaka et al. [10] report an interesting retrospective study comparing the clinical outcomes of PCI with new-generation DES in the all-comer, international, multicenter DELTA-2 registry with the historical CABG cohort enrolled in the DELTA-1 registry, focussing in assessing the influence of main EXCEL inclusion/exclusion enrolment criteria on the clinical results. Propensity score models were implemented to better compare the effect of these revascularization strategies. Out of 3986 patients included in the DELTA-2 PCI registry, 2418 were EXCEL candidates and 1568 were not. The occurrence of the primary endpoint (a composite of death, MI or stroke) at late follow-up (median 501 days) was 2.5-fold higher among non-EXCEL compared with EXCEL candidates (15.4% vs. 6.9%, $p < 0.001$). Alternatively, among 901 patients enrolled in the historical DELTA-1 CABG cohort, 471 were EXCEL candidates and 430 were not. When comparing the DELTA-2 PCI with the historical DELTA-1 CABG cohort, the occurrence of the primary endpoint was lower in the PCI group among EXCEL candidates (6.9% vs. 10.7%) while no significant difference was observed among non-EXCEL candidates (15.4% vs. 12.5%), resulting in a significant statistical interaction [10].

This study suggests that, in a real-world population, PCI can be selected more favourably as an alternative to CABG in patients fulfilling the enrolment criteria of the EXCEL trial [10]. These results are of potential major clinical relevance. However, some issues should be discussed.

First, in the DELTA-2 cohort patients were treated with PCI during an entire decade. During this period, major advances in clinical management ensued. This problem is even more pronounced for the DELTA-1 CABG historical registry. Therefore, the results of these studies may differ from those currently obtained in contemporary clinical practice.

Second, the retrospective study design and the use of a historical CABG cohort explain why some relevant data, needed to assess inclusion/exclusion criteria of the EXCEL trial, were not available. The main 3 characteristics used to differentiate EXCEL from non-EXCEL candidates were a Syntax score <33, absence of acute MI and absence of prior CABG. However, in 1105 out of 3986 patients the Syntax score was not available. However, in a sensitive analysis these investigators were able to demonstrate consistent findings when this subset of patients with missing data was excluded.

DOI of original article: <https://doi.org/10.1016/j.ijcard.2018.12.003>.

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<https://doi.org/10.1016/j.ijcard.2019.01.040>

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Table 1
Relevant variables for “Elective” unprotected LMCAD stenting in patients eligible for CABG.

Clinical characteristics
Age
Diabetes
Left ventricular function
STS score (better than EuroSCORE II)
Anatomic features
Completeness of revascularization
Distal bifurcation involvement
LAD and LCX ostial disease
LCX size, Dominance (RCA vs. LCX)
Syntax score
Specific adverse features of additional lesions in major vessels ^a
Number of lesions
Lesion length
Chronic total occlusion
Major bifurcation
Severe calcification

LMCAD = left main coronary artery disease. LAD = left anterior descending coronary artery. LCX = left circumflex coronary artery. RCA = right coronary artery (*updated from reference [1]*).

^a Vessels suitable for coronary artery bypass grafting (CABG).

Third, as expected, there was a large heterogeneity of non-EXCEL candidates that, in this real-world population, included emergent patients, some presenting with acute MI or cardiogenic shock. This helps to explain the poorer results obtained in this subgroup. However, as CABG remains rarely indicated for unstable patients requiring urgent revascularization the results of this analysis should not be interpreted to suggest that PCI should not be offered to these complex patients with LMCAD. Likewise, non-EXCEL candidates had more adverse clinical and anatomic characteristics. Therefore, it is highly likely that other unmeasured confounders (impossible to adjust for with propensity score analyses) were also more unfavourable in this cohort.

Fourth, site-determined Syntax scores were used instead of central core-laboratory analyses. This remains a methodological limitation considering the potential inter-centre variability in the assessment of this score. However, this strategy was also used in the main EXCEL trial [7] where, interestingly enough, one-fourth of randomized patients eventually proved to have a Syntax score >32 when analyzed at the core laboratory.

Finally, the duration of follow-up was <2 years. In fact, scrutinizing the survival curves of this study it becomes clear that most events after CABG occurred very early but afterwards the curves run flat. Alternatively, in the PCI arm events progressively accrue overtime and the graphic trend suggests that survival curves might converge at long-term follow-up. Therefore, a longer follow-up is required to confirm the superiority of PCI over CABG in LMCAD patients with low-to-moderate complexity.

3. Final remarks

A decade ago we suggested that DES had crossed the Rubicon and were more than ready for primetime in patients with LMCAD [1]. At that time, we asked for a change in the existing revascularization guidelines [1]. Currently, the value of PCI for patients with LMCAD is well established [2]. Equipose, defined as sufficient uncertainty regarding the potential benefits of “competing” therapeutic strategies, currently exists for patients with low to intermediate complexity. However, the real challenge remains to identify the best revascularization strategy for each individual patient according to baseline clinical and anatomic characteristics (Table 1). As emphasized by recent guidelines [2] careful discussion in the “Heart Team” remains of paramount importance in this regard. The results of this combined analysis of the DELTA registries [7] provide additional insights on patient characterization to inform the decision-making process required to identify the optimal revascularization strategy in these challenging patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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