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Editorial

Is it time to change how we think about incomplete coronary revascularization?

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ABSTRACT

The optimal degree of revascularization for patients with chronic multivessel coronary artery disease remains an unsolved issue. Intuitively, complete revascularization decreases cardiovascular events and improves outcomes compared to incomplete procedures, but in recent years the concept of incomplete revascularization moved from a sub-optimal or a defective treatment towards the most appropriate revascularization technique in some categories of patients. A reasonable level of incomplete anatomic revascularization has been shown to be safe and achievable with both percutaneous (PCI) and surgical procedures (CABG), despite with different long-term outcomes. What are the mechanisms underlying the clinical benefits of an incomplete revascularization and what are the factors explaining the discrepancy in the long-term clinical outcomes between the two modes of revascularization PCI and CABG? The biological consequences of coronary reperfusion might provide valuable hints in this context and at the same time cast new light on the way we think about incomplete revascularization.

Is it time to change how we think about incomplete coronary revascularization (ICR)? Current evidences [1] and general practice dictates that in patients with chronic coronary artery disease (CAD), multivessel lesions require a full revascularization. Complete coronary revascularization (CCR) is considered a requirement in percutaneous coronary interventions (PCI) and implied when a patient is referred for coronary artery bypass grafting surgery (CABG). Indeed, inability to completely revascularize during the CABG procedure may be considered an indication for the completion of revascularization by follow on PCI. A recent metaanalysis promotes the *status quo* i.e. that most favourable outcomes are associated with complete revascularization [1], but what of the patient who is not fully revascularized? Comorbidities and anatomical variables often conspire against the accomplishment of a full revascularization and real life registry trials indicate an ICR rate as much as 40% [2–4].

The evidence for complete revascularization of patients is compelling, as testified by several reports [4,5]. Indeed, ICR has been identified as an independent risk predictor of adverse events (hazard ratio of 1.67 with $P = 0.01$) [4] and Milojevic associated ICR with increased risk of death or cardiac adverse events, proportionally to the level of incompleteness of the revascularization [5].

However, a body of evidence is now emerging which suggests that complete revascularization may not be the only overriding tenet. In patients with comorbidities reduction of the procedural risk may be a preferred strategy, and a groundswell of literature supports ICR as an acceptable method of revascularization. In the context of PCI, Generaux et al. have developed the Syntax Revascularization Index (SRI) to quantify the level of complete (or incomplete) revascularization. The SRI is calculated by comparing the baseline SYNTAX score (bSS) [6] to the residual SYNTAX score (rSS) [2,3] and represents the proportion of coronary artery disease treated. This index aimed to objectify the level of revascularization and was shown to have a strong association with 1-year mortality [7]. SRI was associated also to all adverse ischemic events and was identified as one of the independent predictors of 5-year all-cause mortality [7]. Interestingly, these Authors identified a threshold of SRI ≥ 80% at which long-term mortality is not affected by the incompleteness of revascularization [7]. Even more importantly, the achievement of an SRI ≥ 80% substantially improved the prognosis among

Abbreviations: bSS, baseline SYNTAX score; CABG, coronary artery bypass grafting surgery; CAD, coronary artery disease; CCR, complete coronary revascularization; CST, catestatin; CTO, chronic total occlusion; FFR, fractional flow reserve; ICR, incomplete coronary revascularization; LAD, left anterior descending artery; LIMA, left internal mammary artery; MI, myocardial infarction; PCI, percutaneous coronary interventions; rSS, residual SYNTAX score; SRI, Syntax Revascularization Index.

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Table 1
Summary of the main evidences supporting incomplete myocardial revascularization and its differences between PCI and CABG.

Reference	Study type	Patients	Treatment	Follow up	Main findings
Vander Salm et al., 2002 [9]	RCT subanalysis	1507	1507 CABG	7 years	• No differences in cardiac-related mortality or MACCEs for traditional or functional CMR as compared with IMR. • More than one graft to a non-LAD system was associated with higher risk of death and myocardial infarction (RR 1.37)
Van den Brand et al., 2002 [15]	RCT	1205	600 PCI 605 CABG	1 year	• Among PCI: IMR had higher rate of MACCEs compared to CMR (+7.2%) and greater repeated revascularization with CABG. • Among CABG: IMR and CMR had similar incidence of MACCEs (87.8% vs 89.9%).
Rastan et al., 2009 [10]	Cohort	8806	8806 CABG	3–5 years	• Complex coronary artery disease was associated to IMR. • Hospital mortality was not related to IMR.
Head et al., 2012 [4]	Cohort	1766	896 PCI 870 CABG	3 years	• IMR predicted MACCEs (HR 1.55) only among patients who underwent PCI, not in CABG. • Among PCI: CMR had lower rate of MACCEs (−9.7%), with no differences in death and MI. IMR was related to chronic total occlusion (OR 2.46) and the number of diseased vessels (OR 1.58). • Among CABG: no differences between CMR and IMR in terms of MACCEs. IMR was related to unstable angina (OR 1.42), small coronary arteries (OR 1.87) and the number of diseased vessels (OR 1.70).
Genereux et al., 2015 [7]	Cohort	2618	2618 PCI	1 year	• "Reasonable IMR" was achieved in patients with Syntax Revascularization Index ≥ 80%; this level of IMR produced no survival differences when compared to CMR.
Milojevic et al., 2016 [5]	RCT	1800	903 PCI 897 CABG	5 years	• IMR predicted all-cause mortality (HR 1.37) and cardiac related mortality (HR 1.67) in the overall population. Subsequent analysis revealed significant differences depending on revascularization strategy. • Among PCI: IMR predicted all-cause mortality (HR 1.73) and cardiac related mortality (HR 1.83). • Among CABG: IMR did not increase the risk of death of MACCEs

RCT: randomized controlled trial; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; IMR: incomplete myocardial revascularization; CMR: complete myocardial revascularization; MACCEs: major adverse cardiac events; RR: relative risk; HR: hazard ratio; OR: odds ratio.

patients with a bSS > 32, with a 50% absolute reduction in 5-year mortality and a similarly low 5-year mortality rate when compared to patients who were fully revascularized [7].

The extent of ICR has been investigated also in cardiac surgery trials and the concept of "reasonable incomplete surgical revascularization" was initially proposed by Dauerman in 2011 [8].The Bypass Angioplasty Revascularization Investigation trial (BARI) supported the hypothesis that grafting more than one target other than left anterior descending artery (LAD) did not confer any long-term advantage and was associated with an increased mortality risk [9]. Rastan et al. in a large cohort study indicated that in the presence of left internal mammary artery (LIMA) to LAD graft, reasonable ICR of the circumflex or right coronary artery territory did not adversely affect early or long-term survival in patients with multivessel CAD [10]. This is consistent with the work by our group demonstrating the superiority of off-pump ICR using LIMA to the LAD over optimal medical treatment in very-high risk patients [11].

As comprehensively summarized by Zimarino and colleagues, recent PCI and CABG trials suggest that ICR may be an acceptable option in certain circumstances on the basis of the long-term satisfactory outcomes [12].

It could be argued that this is an effect of maximal medical therapy, which is administered to virtually all patients following any kind of revascularization procedure. Medical therapy is known to deliver a survival benefit similar to more invasive strategies in low-risk CAD such as single vessel coronary artery disease and therefore may provide protection from adverse cardiac events that could originate from small ungrafted territories [13]. However, the benefits deriving from an incomplete revascularization seem notably more evident in CABG than PCI patients, which would equally undergo to optimized medical therapy after the procedure. Moreover, it has been demonstrated that the differences in short-term clinical outcomes are related to the reduced risk of adverse peri-procedural events [12,14]. Results from the Arterial Revascularization Therapies Study (ARTS), showed that patients with incomplete percutaneous revascularization had a significantly lower event-free survival (69%) than patients receiving complete revascularization with stent-PCI (77%; P = 0.05), however CABG incomplete revascularization produced only a marginally lower event-free survival rate in comparison to those with complete revascularization (88% vs 90%) [15]. Analyzing data from the SYNTAX Trial, it appears that ICR in PCI patients, but not in the CABG cohort, is a predictor of adverse outcomes [4], and Milojevic et al. showed that ICR in the CABG arm of the study did not increase the risk of death or cardiac adverse events, while an opposite trend was observed in the PCI group [5].

Therefore, from a careful review of the literature it appears that the achievement of a reasonable level of anatomic revascularization, compared with absolute CCR, in some categories of patients allows for satisfactory clinical results, but there is a discrepancy in the long-term clinical outcomes of ICR between PCI and CABG. In brief, cardiac surgery produces better results in case of ICR, as compared with PCI and CCR seems mandatory in percutaneous procedures to achieve similar results (Table 1).

In the real-life surgical scenario decision-making on which target to graft is often driven by the subjective evaluation of the surgeon of the calibre of the vessel and of the additional intraoperative risk to obtain a complete revascularization of targets which were originally considered adequate (>1.5 mm) on the basis of the angiogram. During surgery a vessel is not grafted if it is small and has a poor runoff as assessed by the surgeon while looking and feeling the vessels. For example, if after a LIMA-to-LAD graft, a short diagonal branch serving a limited area close to the LAD is felt very calcified and small in calibre, it might be considered ungraftable and left non-bypassed by the surgeon in light of the vicinity with the grafted LAD and the potential ancillary circulation and perfusion overlap given by the LIMA graft. Indeed, if ungraftable, the extra cross-clamp time, tissue dissection and risk of bleeding will increase the procedural risk for a graft that will not remain patent.

Conversely, the interventionist finds difficult anatomy (as bi or trifurcation), severe calcification or inability to cross the lesion because of chronic total occlusion (CTO) as the main reasons for failing to achieve a CCR. CTO has been claimed as one of the major causes of ICR in the PCI group in the SYNTAX trial [3]. Failure to revascularize a chronically occluded vessel with a reasonable calibre distal to the stenosis, normally left untreated by the cardiologist, has a different clinical consequence and prognostic value than a small, calcified vessel, with a poor run-off or serving small-sized territory, normally left ungrafted by the surgeon. While CTO is challenging for the interventionist if the vessel has a large runoff distal to the lesion it can nearly always be grafted during surgery. Unfortunately, surgical revascularization is still mainly driven by an "anatomy-based strategy" [16,17] and fractional flow reserve (FFR) guided revascularization is not routinely used. Therefore, it is