Commentary

Completeness of revascularization in multivessel coronary artery disease

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Multivessel coronary artery disease (CAD) is frequently encountered in clinical practice among patients with both stable and unstable presentations (1). The question of whether such patients should undergo complete (CR) versus incomplete (IR) revascularization continues to be debated (1-3). This issue was originally recognized and described among patients undergoing coronary artery bypass graft (CABG) surgery, where it was observed that CR conferred both a survival and symptomatic benefit in comparison to IR (3), with CR consequently achieving the stature of a surgical mantra and accepted as a truism (4).

Despite a wealth of studies exploring whether the goal the revascularization should be CR, numerous questions exist at the present time (*Figure 1*). These dilemmas arise not only from clinical studies with conflicting results, but also because our understanding of how we define CAD has evolved over time with a shift towards pursuing functional CR, in which ischemic-causing lesions undergo coronary revascularization [CABG, percutaneous coronary intervention (PCI) or hybrid] and non-ischemic lesions are treated with optimal medical therapy (5-7).

In a single-center, prospective, observational, cohort study of consecutive patients with multivessel CAD undergoing PCI with drug-eluting stents (DES) from January 2003 through December 2013, Chang *et al.* compared outcomes in those with CR *vs.* IR (8). Using propensity-score matching, there was no significant difference in the primary outcome of all-cause mortality (8.6% *vs.* 9.0%; HR 1.03; 95% CI, 0.80–1.32, P=0.83), as well as in the secondary outcomes of stroke and repeat revascularization; whereas the risk of acute myocardial infarction (MI) on follow up was higher in those with IR *vs.* CR (HR 1.86; 95% CI, 1.08–3.19, P=0.02) (8).

We offer the following observations. First, the study by Chang *et al.* used an anatomical definition of CR, in which CR was defined as the absence of diameter stenosis ≥50% in major epicardial coronary arteries or their side branches with diameter ≥2.5 millimeters after successful stent implantation during index hospitalization irrespective of the function or viability of relevant myocardium (8). It should be emphasized that there is no guideline or expert-consensus document addressing how CR should be defined with various existing definitions as summarized in *Table 1* (1,2,9). While the anatomical-based definition has been the most widely used classification in completeness studies, reported in nearly 90% of manuscripts included in a large meta-analysis (10), in contemporary clinical practice, a functional and/or physiological approach is encouraged. According to this definition revascularization of ischemic territories, as demonstrated by either non-invasive stress testing or fractional-flow reserve, is pursued while medical management is recommended for non-flow limiting stenosis (5-7). Therefore, while the findings of the study by Chang *et al.* are informative and expand on the results seen in other observational studies of CR *vs.* IR we believe a prospective randomized clinical trial of CR *vs.* IR would have been preferable to retrospective propensity-matching. Furthermore, an ischemia-guided definition of CR that takes into account the functional status of the stenosis and the myocardium subtended by the vessel in question would have better reflected contemporary practice.

Recent data using myocardial perfusion imaging (MPI) has further elucidated on the importance of using a functional/physiological approach to define CR (11). In a small, retrospective analysis, Li *et al.* examined patients with

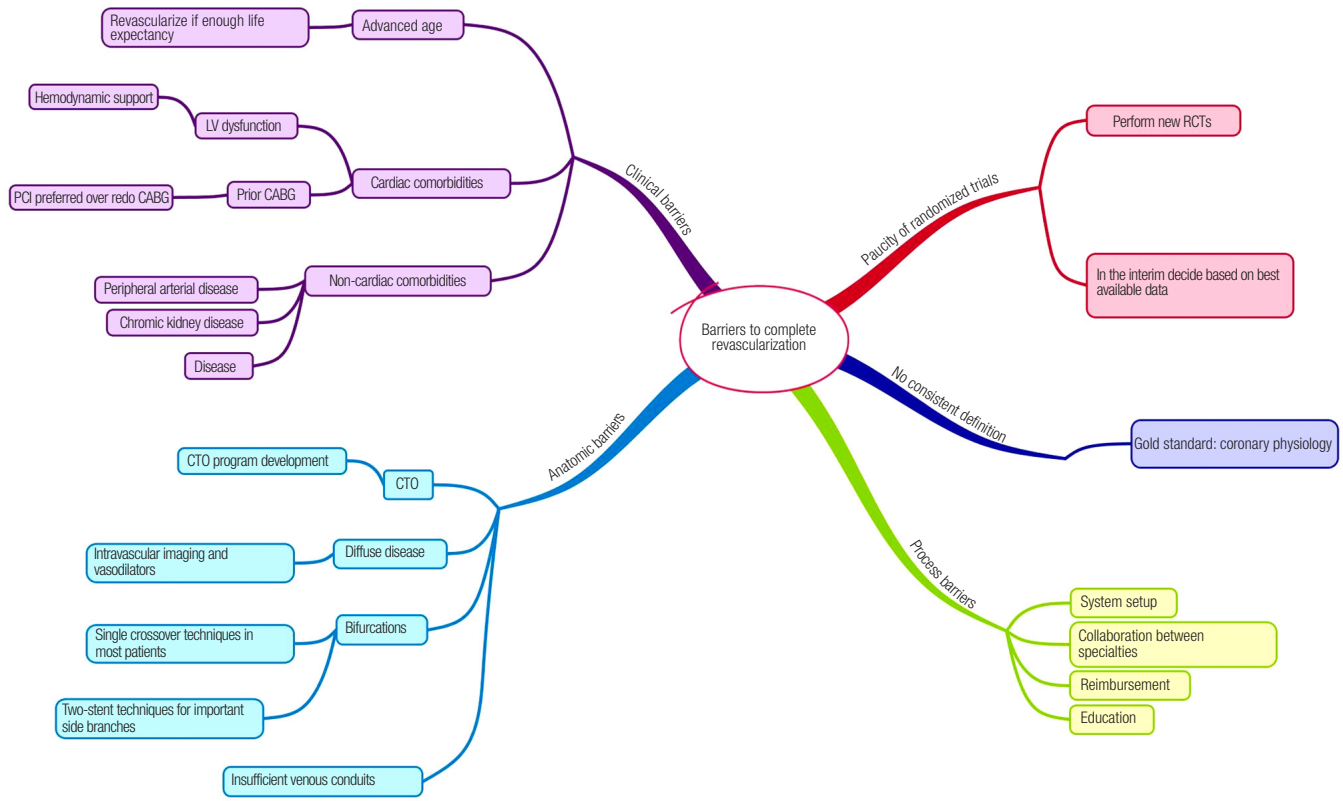

Figure 1 Barriers to achieving complete revascularization.

Table 1 Definitions of complete revascularization

Variable	Definitions
Anatomical or traditional	All diseased arterial systems with vessel size ≥1.5 (2.0–2.25 mm for PCI) with at least one significant stenosis >50% receive a graft (or stent)
Functional	All ischemic myocardial territories are grafted (or stented); areas of old infarction with no viable myocardium are not required to be reperfused
Numerical	Number of distal anastomosis ≥ number of diseased coronary segments/systems
Score-based	Scoring of stenosis in different vessels. Different weight given to different vessels according to number of myocardial segments supplied. A residual score of 0 is usually considered equivalent to CR
Physiology-based	All coronary lesions with fractional-flow reserve ≤0.75–0.80 receive a graft or stent

PCI, percutaneous coronary intervention; CR, complete revascularization.

evidence of stress-induced myocardial ischemia on SPECT MPI who had significant stenosis of the left main coronary artery and/or stenosis of at least one major coronary artery that had undergone PCI within 3 months after MPI with the purpose of evaluating the impact of IR by angiographic *vs.* functional (MPI) criteria (11). Similar to the findings by Chang *et al.*, using the anatomical/angiographic definition, Li and colleagues demonstrated that a mean follow-up of 47±21 months there was no statistical difference in the cumulative incidence of all-cause death (primary endpoint) (12% *vs.* 24%, P=0.08); with no difference observed in major adverse cardiac events (MACE) (composite of all-cause death, non-fatal MI, repeat revascularization) (20% *vs.* 30%, P=0.28). However, when using the MPI criteria,

patients with functional CR had a significantly lower cumulative incidence of both all-cause death (12% *vs.* 27%, P=0.048) and MACE (17% *vs.* 36%, P=0.025). The findings of this small, yet provocative study provide further insights into the value of using a functional/physiological-based definition.

Further supporting the use of functionally-guided CR, the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) sub-study assessed whether the presence of residual angiographic disease using the residual SYNTAX score (RSS) and SYNTAX revascularization index (SRI) had prognostic significance after achieving functionally CR with FFR guidance and demonstrated that residual angiographic lesions that are not functionally significant do not predict a worse outcome (12).

Second, it has long-been recognized in studies examining CR *vs.* IR that observational studies have yielded conflicting results and large multicenter randomized clinical trials, while preferable from a methodological standpoint, are lacking (10). Ijsselmuiden *et al.* randomized 219 patients with multivessel disease to CR or culprit-only revascularization and found no benefit of CR during a follow-up of 4.6±1.2 years (13). There are 3 published RCTs showing benefit of CR in patients with ST-segment elevation acute myocardial infarction (STEMI) (14-16) and a large ongoing RCT (*COMPLETE*) trial (NCT01740479) expected to have results in 2018. Two large meta-analyses have been performed and both have favored CR over IR (10,17). Our group performed the largest meta-analysis (assessing both CABG and PCI) of CR in 35 studies including 89,883 patients, and demonstrated that relative to IR, CR was associated with a 30% reduction in long-term mortality, 22% reduction in MI, and a 26% reduction in repeat coronary revascularization; with the mortality benefit being consistent across studies irrespective of revascularization modality (CABG: RR 0.70; 95% CI, 0.61–0.80, P<0.001; and PCI: RR 0.72; 95% CI, 0.62–0.81, P<0.001) and the definition of CR (anatomic definition: RR 0.73; 95% CI, 0.67–0.79, P<0.001; and non-anatomic definition: RR 0.57; 95% CI, 0.36–0.89, P=0.014) (10). Similarly, Aggarwal *et al.* performed a large meta-analysis (nine studies, including 37,116 patients) focused exclusively on PCI during the stent era and demonstrated that compared to IR, patients undergoing CR had a 18% reduction in mortality, 33% reduction in non-fatal MI and 30% reduction subsequent CABG, with no difference in the incidence of repeat PCI (17).

Similarly, and in contrast to the findings by Chang *et al.*, a recent large study of 23,342 patients assessing the long-term outcome of IR after PCI in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (18), in which IR was defined as any non-treated significant (at least 60%) stenosis in a coronary artery supplying over 10% of the myocardium, demonstrated that IR was associated with an adjusted hazard ratio (HR) of 2.12 (95% CI, 1.98–2.28, P<0.000) for the composite end-point of death, MI, or repeat revascularization at 1-year.

In summary, the study by Chang *et al.* adds to the existing literature of observational studies with conflicting results between IR and CR. Despite the existing differences observed among various observational studies, large meta-analyses studies have suggested a significant benefit of CR over IR. Many of the previously existing barriers to achieving CR, such as the presence of chronic total occlusion (CTO) have been surpassed in contemporary registries using the hybrid approach now reporting procedural success in over 90% of cases (19). Until we have more definitive data from *COMPLETE*, the best available evidence in 2016 suggests that CR using a physiology-based definition should be pursued whenever feasible in symptomatic patients with multivessel disease.

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Footnote

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Comment on: Chang M, Ahn JM, Kim N, *et al.* Complete

versus incomplete revascularization in patients with multivessel coronary artery disease treated with drug-eluting stents. Am Heart J 2016;179:157-65.

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