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The Dilemma of Complete Coronary Revascularization

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Abstract

Despite 20 years of investigation the Completeness of Revascularization in patients with multivessel coronary artery disease (CAD) remains an unanswered question. The lack of universal definition and the multiplicity of confounding variables that in general favor patients who receive a complete revascularization (CR) are the reason of studies' conflicting results.

The CR is achieved more commonly with coronary artery by-pass (CABG) than with percutaneous coronary intervention (PCI). In this regard, the possibility of achieving CR is one of variable that should be factored when deciding the optimal strategy of revascularization between PCI and CABG in patients with multivessel coronary artery disease. However clinical features, such as patient's age, life expectancy, symptoms at presentation, comorbidities and left ventricular function may increase the morbidity or mortality risk of CABG intervention and a "reasonable" incomplete revascularization (IR) achieved with PCI may be a better choice in particular clinical subset.

The CR is a desirable objective, but it is not mandatory and sometimes a reasonable IR offers comparable results. In this respect, we should consider IR as part of a spectrum in the completeness of revascularization.

In patients with multivessel coronary artery disease (CAD) a complete revascularization (CR) is a worthwhile objective of any coronary revascularization strategy either of coronary artery bypass graft (CABG) or of percutaneous coronary intervention (PCI). Nonetheless, in practice, the severity of the coronary artery disease as well as the patient's clinical conditions often preclude CR resulting in a high frequency of incomplete revascularization (IR) in patients with multivessel disease. In the BARI trial a CR was obtained in 29% of the 2.047 patients with multivessel coronary disease undergoing to PCI¹. This trial was conducted at the end of 1990, the progress innovations in PCI improve the role of PCI in multivessel disease treatment and in the CR. Indeed in the Syntax trial a CR was obtained in 57% of patients with multivessel disease treated with PCI and in 64% of patients with multivessel disease treated with CABG². Despite the long-held belief of greater myocardial protection of CR, observational studies have yielded conflicting results³⁻⁵ and no large multicenter randomized clinical trial has ever tested whether CR is superior to IR. One possible reason for these conflicting reports is the lack of a universal definition for CR. Indeed different criteria have been used to define the completeness of revascularization in trials and studies. According to anatomical criteria the treatment of all stenotic vessels, irrespective of size and territory supplied,

is considered a CR. A functional classification considers a CR if all ischemic myocardial territories are treated; areas of old infarction with no viable myocardium are excluded to be reperfused⁶. Recently to reduce the confounding variables, classifications of myocardial revascularization based on anatomic and functional criteria have been proposed. These classifications have also introduced the concept of reasonable IR, underlying the importance of residual burden of myocardium at risk (Table 1)^{7,8}. Despite all these proposed classifications an agreement on a universal definition of CR has not yet reached. Beyond the lack of standardized definition of CR, the multiple reasons underlying the decision not to perform CR in an individual patient and the differences in baseline features are major confounding variables, which could bias the data in favor of CR by selecting the healthier patient for CR rather than IR. Multivariate analyses adjust for differences in baseline variables but cannot eliminate the bias introduced when one group of patients is sicker than the other. In a recent meta-analysis of 83.695 patients with multivessel coronary artery disease CR was associated with a reduced risk of death (RR: 0.73; 95% CI 0.66-0.8), myocardial infarction (RR: 0.74; 95% CI 0.64-0.85), and repeat revascularization (RR: 0.77; 95% CI 0.66-0.88) compared to IR, with such results being consistent across both CABG and PCI subgroups. The clinical benefit of CR were obtained with current state-of-the-art revascularization techniques, indeed the relative risk reduction myocardial infarction obtained with CR were stronger in recent studies⁹. In a meta-analysis of 89.883 patients enrolled in randomized clinical trials and observational studies, the mortality benefit associated with CR was consistent across studies irrespective of revascularization modality (CABG: RR: 0.70, 95% CI: 0.61 to 0.80; p < 0.001; and PCI: RR: 0.72, 95% CI: 0.64 to 0.81; p < 0.001) and definition of CR (anatomic definition: RR: 0.73, 95% CI: 0.67 to 0.79; p < 0.001; and no anatomic definition: RR: 0.57, 95% CI: 0.36 to 0.89;

p=0.014)¹⁰. However, most of the 35 studies included in this meta-analysis were observational or post-hoc analyses and in the only randomized study similar MACE rates were found between CR and IR in multivessel coronary artery disease treated with percutaneous coronary interventions¹⁰. This meta-analysis has also confirmed that the CR was achieved more commonly with CABG than with PCI, in particular CR was obtain in 75% of patients undergoing multivessel CABG and 44% of patients undergoing multivessel PCI¹⁰. Indeed in patients with complex multivessel coronary artery disease, sometimes CABG provides a higher rate of CR compared to PCI². In this regard, the possibility of achieving CR is one of variable that should be factored when deciding the optimal strategy of revascularization between PCI and CABG in patients with multivessel coronary artery disease. However clinical features, such as patient's age, life expectancy, symptoms at presentation, comorbidities and left ventricular function may increase the morbidity or mortality risk of CABG intervention. Although the off-pump beating heart revascularization technique can be a good choice for CABG of high-risk patients with a multivessel coronary artery disease, because of reducing myocardial injury¹¹, a reasonable IR achieved with PCI may be a better choice in particular clinical subset.

Complete Revascularization in Acute Coronary Syndrome

One-half of patients with ST elevation myocardial infarction (STEMI) have multivessel disease. A metaanalysis has demonstrated no superiority of CR in clinical outcomes. However a subanalysis about the timing of multivessel PCI (index procedure or staged procedure) has showed a survival benefit when a staged procedure was performed either in-hospital or after the initial hospitalization¹². In a metaanalysis of the 5 randomized clinical trials immediate or staged CR has resulted in significant reduction in repeat revascularization with no firm evidence for the reduction

Table 1. Definitions of Complete Revascularization

Revascularization	Definition	Reference
Complete anatomic revascularization	Treatment of all coronary segments >1.5 mm in diameter with ≥50% diameter stenosis.	Zimarino M <i>Eur Heart J</i> 2005
Incomplete anatomic but functionally adequate Revascularization	Treatment of all coronary segments with ≥50% diameter stenosis supplying viable myocardium.	
Incomplete functional Revascularization	Inability to treat all coronary segments with ≥50% diameter stenosis supplying viable myocardium.	
Complete anatomical revascularization	Treatment of all coronary artery segments >1.5 mm in diameter and ≥50% diameter stenosis regardless of their functional significance.	Gössl M <i>Circ Cardiovasc Interv</i> 2012
Incomplete anatomical but functionally adequate revascularization (Reasonable IR)	Treatment of coronary segments with ≥50% diameter stenosis and an FFR ≤0.8, or ≥70% diameter stenosis without FFR supplying viable myocardium.	
Incomplete anatomical and functional revascularization	The inability to treat all coronary segments that have a ≥50% to 70% diameter stenosis and an FFR ≤0.8 or >70% without FFR that supply a significant degree of viable myocardium.	

Table 2. The Complete Revascularization (CR) in particular clinical subsets

Clinical Subsets	Definition of CR	Recommendations
Stable coronary artery disease		
Diabetes	Metanalyses of randomized and observational studies with different definition of CR	The CR is associated to reduction in mortality, myocardial infarction and re-percutaneous coronary intervention ⁹ .
Coronary Chronic Total Occlusion (CTO)	Anatomic definition	The benefit of a successful CTO PCI in terms of mortality reduction is more evident in patients with multivessel disease and at least 1 CTO compared to patients with an isolated CTO ^{18,19} .
Ischemic Heart Failure (HF)	Anatomic definition	The CR is an independent factor improving 12-month survival. In patients with ischemic HF the restoration of perfusion in regions of hibernated myocardium may improve contractility and minimize adverse ventricular remodeling, with a much more prominent effect relative to patients with preserved ejection fraction ²³ .
Acute Coronary Syndrome		
ST segment elevation myocardial infarction	Metanalyses of randomized and observational studies with different definition of CR	A routine revascularization of non-infarct related artery lesions should be considered before hospital discharge (<i>Class IIa Level A, ESC/EACST Guideline</i>). The optimal timing of revascularization (immediate vs. staged) has not been adequately investigated and no recommendation in favor of immediate vs. staged multivessel PCI can be formulated ¹¹ .
Cardiogenic shock in myocardial infarction	Anatomical definition for immediate revascularization and Anatomical/ Functional definition for staged revascularization	The acute revascularization of the IRA is a proven effective therapy for multivessel STEMI complicated by cardiogenic shock, whereas the benefit of routine CR during the index PCI procedure has not been formally demonstrated ^{14,15} .

in death or myocardial infarction when compared with culprit-only revascularization¹³ (Table 2). To resolve the dilemma between CR or IR in multivessel STEMI patients, a randomized trial Complete Versus Culprit-Only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) is in progress.

Multivessel disease is commonly observed in patients with STEMI complicated by cardiogenic shock and it adversely affects clinical outcomes, including mortality¹⁴. Nevertheless, the recommendation for non-infarct related artery (IRA) PCI is yet controversial. Recently the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial have demonstrated that the 30-day risk of death was lower among those who initially underwent only IRA PCI than among those who underwent immediate multivessel PCI¹⁵. Contrarily, data from Korea Acute Myocardial Infarction-National Institutes of Health (KAMIR-NIH) registry have showed that multivessel PCI was associated with a significantly lower risk of all-cause death compared to only IRA PCI in multivessel STEMI patients complicated by cardiogenic shock¹⁶. Differences in timing of myocardial revascularization can explained the discrepancy between these data. CULPRIT-SHOCK has only investigated immediate multivessel PCI, whereas in KAMIR-NIH registry 60.4% of enrolled patients have received an immediate multivessel PCI, with the remainder undergoing staged PCI before discharge. The staged PCI strategy has introduced selection bias, patient survived to initial presentation of cardiogenic shock long enough to undergo a second procedure. Moreover, an attempt to

revascularize chronic total occlusions during the index procedure was mandated in CULPRIT-SHOCK, increasing procedure duration and contrast use. Unfortunately, data on the presence and attempted revascularization of chronic total occlusions, which has been shown to predict worse outcome in STEMI complicated by cardiogenic shock¹⁷, is not available in the KAMIR-NIH registry. Therefore the acute revascularization of the IRA is a proven effective therapy for multivessel STEMI complicated by cardiogenic shock, whereas the clinical benefit of a routine immediate CR strategy is debated (Table 2).

Complete Revascularization in Stable Coronary Artery Disease

Patients with diabetes have an accelerated atherothrombosis with an early onset of atherosclerosis, and more diffuse and extensively coronary disease compared with patients without diabetes. Indeed among patients undergoing multivessel revascularization, both with CABG or PCI, 25% have diabetes. According to European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Guidelines on myocardial revascularization¹⁸ in diabetics patients with stable multivessel coronary disease and an acceptable surgical risk, CABG is the revascularization modality of choice (Class of recommendation I, Level of Evidence A); however, PCI can be considered as a treatment alternative among diabetic patients with multivessel disease and low SYNTAX score (≤ 22) (Class of recommendation IIa, Level of Evidence B). Nonetheless PCI is commonly performed in diabetic patients with intermediate ad high Syntax score. A

meta-analysis of 28 studies has demonstrated the benefit of CR, performed with a State-of-the-Art PCI Techniques, in terms of reduction in mortality, myocardial infarction and re-PCI, in patients with diabetes⁹ (Table 2).

In patients with coronary total occlusions the IR is sometimes be justified when there is no viable myocardium to be preserved. Although some studies on CR are unable to identify when this is the case, the benefit of a successful CTO PCI in terms of mortality reduction is likely to be of a marginal importance in patients with an isolated CTO, whereas it is more evident in patients with multivessel disease and at least 1 CTO^{19,20} (Table 2).

Two-thirds of all systolic heart failure (HF) cases are related to CAD and its treatment represents a significant challenge. After the STICH trial, CABG in HF has become the recommended form of revascularization²¹. Nonetheless, only a minor percentage of patients actually undergo this procedure. PCI has been shown to exceed the number of CABG in this population, even despite the lack of compelling data from contemporary randomized studies^{22,23}. Despite the fact that revascularization has been shown to improve prognosis, data on revascularization strategy in ischemic HF population are still insufficient. The COMMIT-HF results have identified the CR by PCI in ischemic HF patients with multi-vessel CAD as an independent factor improving 12-month survival. In patients with ischemic HF the restoration of perfusion in regions of hibernated myocardium may improve contractility and minimize adverse ventricular remodeling, with a much more prominent effect relative to patients with preserved ejection fraction²⁴ (Table 2).

The Complexity of Multivessel Coronary Artery Disease and the Degree of Incomplete Revascularization

In the evaluation of the clinical impact of CR the complexity of the coronary disease should be also considered. The ARTS-II registry has investigated the relationship between the survival, the completeness of revascularization and the complexity of coronary anatomy. In particular, in patients with IR treated with PCI stratified according to SYNTAX score tertiles a significantly lower 5-year MACE-free survival was revealed in the higher SYNTAX tertile compared to the low (HR=0.56, 0.32 to 0.96, log-rank p= 0.04) and intermediate (HR=0.50, 0.28 to 0.91, log-rank p=0.02) tertiles, whereas survival between the low and intermediate SYNTAX tertiles was not significantly different (HR=1.13, 0.60 to 2.13, log-rank p=0.71)²⁵. Therefore the clinical impact of IR is worse in more complex coronary anatomy.

The degree of IR is another important aspect in the relationship between the extensity of revascularization and the clinical outcomes. Recently many studies have

investigated the clinical impact of the proportion of coronary artery disease burden treated by revascularization and different indexes are proposed to quantify the degree of IR. The Residual Syntax Score (rSS) after PCI has provided an independent prognostic utility as a quantitative measure of IR. Specifically, rSS > 8.0 after PCI in patients with moderate and high-risk acute coronary syndrome is associated with a poor 30-day and 1-year prognosis²⁶. Furthermore in STEMI patients the rSS adds important prognostic information over GRACE score, being an independent predictor of MACE and all-cause mortality at 2.4 years follow-up²⁷. The Syntax Revascularization Index (SRI) is a useful tool in assessing the degree of revascularization after PCI and a SRI \geq 70% represents a “reasonable” goal for patients with complex CAD²⁸. The Functional Syntax score, considering only ischemia-producing lesions (FFR \leq 0.80), has been able to discriminate risk for adverse events in 497 FAME patients²⁹.

Conclusions

In conclusion many studies that support an approach of CR versus IR are inconclusive because of the multiplicity of confounding variables that in general favor patients who were completely revascularized. Although CR is a desirable goal, it is not mandatory and the concept of reasonable IR appears to offer comparable results. In this respect, we should consider IR as part of a spectrum in the completeness of revascularization.

Disclosures

Dr. Aurigemma discloses to have been involved in advisory board activities by Biotronic or having received speaker's fees from Abbott and Abiomed. Dr. Burzotta discloses to have been involved in advisory board meetings or having received speaker's fees from Medtronic, St Jude Medical, Abiomed, Biotronic. Dr. Trani discloses to have been involved in advisory board meetings or having received speaker's fees from St Jude Medical, Abiomed, Biotronic.

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