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Review

Completeness of Revascularization as a Determinant of Outcome: A Contemporary Review and Clinical Perspectives

Osung Kwon, MD, Duk-Woo Park, MD, PhD, and Seung-Jung Park, MD, PhD

Division of Cardiology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

ABSTRACT

It has been debated whether patients with multivessel coronary artery disease should undergo complete revascularization (CR). The benefit of CR is biologically plausible, and numerous studies and large meta-analyses suggested that CR achievement was associated with a substantial reduction of mortality and future coronary events. In patients with multivessel coronary artery disease, the aim of myocardial revascularization is to minimize residual ischemia. Therefore, CR of all significant coronary lesions has been proposed as the first priority in decision-making for myocardial revascularization between coronary artery bypass grafting and percutaneous coronary intervention (PCI). Reflecting the contemporary practice of ischemia-based revascularization, a physiological/functional approach, such as measurement of fractional flow reserve or instantaneous wave-free ratio, is considered more reasonable and should be encouraged for appropriate CR. In patients who present with acute ST-elevation myocardial infarction, current evidence suggests that an immediate or staged CR strategy

RÉSUMÉ

L'utilité d'une intervention de revascularisation complète chez les patients atteints de coronaropathie pluritronculaire est un sujet qui fait l'objet de débats. Les bienfaits de telles interventions sont plausibles sur le plan biologique. Par ailleurs, de nombreuses études et méta-analyses de grande envergure ont établi un parallèle entre la réalisation d'interventions de revascularisation complète et une réduction considérable de la mortalité et des incidents coronariens subséquents. Chez les patients atteints de coronaropathie pluritronculaire, la revascularisation myocardique vise à réduire au minimum l'ischémie résiduelle. C'est pourquoi la revascularisation complète de toutes les lésions coronariennes d'importance a été proposée comme principale priorité à prendre en compte au moment de décider laquelle des deux interventions que sont le pontage aorto-coronarien et une intervention coronarienne percutanée (ICP) sera réalisée pour revasculariser le myocarde. Reflétant la pratique actuelle en matière de revascularisation motivée par une ischémie, une

Physicians in clinical practice frequently encounter patients with multivessel coronary artery disease (CAD) in either a stable or unstable setting.[1,2] Whether such patients should undergo complete revascularization (CR) for all obstructive lesions has been questioned and one of the central theme issues of myocardial revascularization. This topic regarding extent of revascularization was initially identified and explored in patients who underwent coronary artery bypass grafting (CABG), for whom CR appeared to be associated with either survival and symptomatic benefits, compared with incomplete revascularization (IR).[3] In the subgroup analyses of the **C**oronary **A**rtery **S**urgery **S**tudy (CASS) registry, patients with multivessel CAD who received $\geq$ 3 grafts had better survival outcomes than patients who received 1 or 2 grafts.[4]

Although few randomized controlled trials (RCTs) to date have been designed to directly evaluate the extent or degree of revascularization,[5] numerous observational studies and large-scale meta-analyses have advocated CR for multivessel CAD.[1,6] Theoretically, CR might be associated with minimizing burden of residual ischemia and reduction or better tolerance of future cardiovascular events, which led to preservation or improvement of left ventricle function and survival benefits.[6] Hence, CR of all significant coronary lesions has been proposed as the first priority in decision-making for myocardial revascularization. Up until now, extensive studies have been undertaken to address the various issues regarding CR as a determinant of clinical outcomes. Herein, we summarize the cumulative clinical data and guideline recommendations about CR and discuss the clinical perspective with respect to when and how to achieve CR in "real-world" clinical practice.

Definition of CR: Angiographic and Functional Concept

Although various definitions have been proposed for the criteria of CR, there is at present no consensus.[1] In general, anatomical definition of CR is defined as the treatment of all

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Corresponding author: Dr Seung-Jung Park, Division of Cardiology, Department of Internal Medicine, Asan Medical Center, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, South Korea. Tel.: +82-2-3010-4812; fax: +82-2-475-6898.

E-mail: sjpark@amc.seoul.kr

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might be equivalent or superior to culprit-only revascularization. There is still uncertainty on when and how to perform CR in ST-elevation myocardial infarction patients; comprehensive studies dedicated to this issue are required. Hybrid coronary revascularization includes the advantages of minimally invasive bypass grafting for the left anterior descending artery and PCI for non-left anterior descending arteries and has been proposed as a viable alternative for coronary artery bypass grafting or PCI only for achieving CR. In clinical practice, the extent of revascularization and strategy for CR should be individualized, taking account of different aspects of the patients, lesions, and treating physicians. Collaboration of coronary heart teams would confer balanced decision-making and advanced therapeutic capabilities.

démarche physiologique et fonctionnelle faisant notamment appel à la mesure de la réserve coronaire fractionnaire (FFR) ou à l'iFR (*Instantaneous Wave-Free Ratio*) est considérée comme plus valable et doit être encouragée pour pratiquer une revascularisation complète appropriée. Pour ce qui est des patients atteints d'un infarctus du myocarde avec élévation du segment ST, les données probantes actuelles portent à croire qu'une stratégie de revascularisation complète immédiate ou réalisée en plusieurs temps pourrait être équivalente, voire supérieure à une revascularisation visant uniquement les lésions significatives sur le plan fonctionnel. L'incertitude plane toujours à propos du moment propice et de la méthode pour réaliser une revascularisation complète chez ces patients. Il faudra effectuer des études approfondies sur cette question. Une intervention de revascularisation hybride comporte les avantages du pontage aorto-coronarien, une intervention très peu invasive pour l'artère interventriculaire antérieure et ceux de l'ICP pour d'autres artères hormis l'artère interventriculaire antérieure. Elle a en outre été proposée comme solution de rechange viable au pontage aorto-coronarien ou à l'ICP utilisés seuls pour réaliser une revascularisation complète. En pratique clinique, l'étendue de la revascularisation et la stratégie de revascularisation complète choisie doivent être dictées par la situation de chaque patient en tenant compte des différents facteurs qui lui sont propres, de ses lésions et des médecins traitants. La collaboration d'équipes spécialisées en médecine coronarienne serait un atout dans la prise de décisions objectives et ferait bénéficier les patients de compétences thérapeutiques de pointe.

vessels $\geq$ 1.5 mm in diameter with $\geq$ 50% stenosis. In contrast, functional CR is defined as the treatment of all lesions regarded as functionally relevant, determined using invasive and noninvasive methods, along with myocardial viability in the dependent territory. The **F**ractional Flow Reserve vs **A**ngiography for **M**ultivessel **E**valuation (FAME) trial clearly showed the clinical benefits of the fractional flow reserve (FFR)-guided revascularization strategy for multivessel CAD.[7] Although the anatomy-based definition has been the most widely used in previous studies and clinical practice, an optimal definition of myocardial revascularization should consider vessel size, the angiographic and functional/physiologic severity of the lesion, and the viability of the myocardium.

Current evidence suggests that a functional/physiological approach better reflects contemporary practice. In a recent study, the clinical performance of an FFR-guided **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery (SYNTAX) score (so-called, the functional SYNTAX score) was compared with that of the classic SYNTAX score for predicting clinical outcomes in patients with multivessel CAD who underwent percutaneous coronary intervention (PCI).[8] When SYNTAX score was recalculated by incorporating only ischemia-producing lesions, determined using FFR, the number of higher-risk patients has substantially decreased by 32%. The functional SYNTAX score showed a better predictive accuracy for major adverse cardiac events (MACE) than the SYNTAX score.[8] Further evidence for FFR-guided functional CR was provided by a study that assessed whether residual angiographic disease, determined using the residual SYNTAX score and SYNTAX revascularization index, had prognostic relevance of FFR-guided functional CR.[9] This study showed that residual angiographic lesions that were not functionally significant did not predict poorer outcomes, supporting the functional CR concept rather than angiographic CR alone. A recent study using myocardial perfusion imaging further showed the importance of a functional/physiological approach, revealing a statistically significant difference in adverse cardiac events between patients who underwent CR and IR, determined using myocardial perfusion imaging criteria, but not angiography criteria.[10] Taken together, these findings emphasize that a physiology-based CR approach might be more reasonable and should be pursued whenever feasible in patients with multivessel CAD.

CR vs IR in Stable CAD

Benefits of CR

The **C**linical **O**utcomes **U**tilizing **R**evascularization and **A**ggressive Dru**g** **E**valuation (COURAGE) nuclear substudy provided information on the role of revascularization in patients with multivessel CAD.[11] A $\geq$ 5% reduction in ischemia was associated with significantly lower rates of death and myocardial infarction (MI). This level of ischemia reduction was achieved more frequently in patients who received PCI than in those who received medication alone, indicating that a CR strategy might have resulted in a greater proportion of patients who achieved a significant reduction of residual ischemia. A landmark meta-analysis by Garcia et al. involving 89,883 patients clearly showed the clinical benefits of CR, irrespective of the CR definition.[6] CR was associated with significant reductions in mortality (risk ratio [RR], 0.71; $P < 0.001$), MI (RR, 0.78; $P = 0.001$), and repeat revascularization procedures (RR, 0.74; $P < 0.001$). Another meta-analysis also showed the further evidence of the association of CR with clinical benefits.[12] On

the basis of such cumulative evidence, it is reasonable to consider CR a goal of revascularization therapy in patients with stable multivessel CAD. The ongoing **I**nternational **S**tudy of **C**omparative **H**ealth **E**ffectiveness With **M**edical and **I**nvasive **A**pproaches (ISCHEMIA; NCT01471522) trial is planned to compare the routine invasive approach in addition to medical therapy and medical therapy alone as the initial treatment for management of patients with stable ischemic heart disease, and moderate to severe ischemia on stress testing. The results of the ISCHEMIA trial might provide more insight into the clinical value of the prognostic relevance of CR for patients with stable ischemic heart disease.

Treatment strategy: comparative outcomes of PCI vs CABG and impact of CR

In daily practice, physicians face the decision of choosing the revascularization modality of PCI or CABG. Although CABG has been, for a long time, recommended as the first choice of revascularization strategy for multivessel CAD, PCI is currently the most common form of revascularization, because of its less invasive nature and marked advancement of outcomes.[13]

Table 1 shows a summary of the major RCTs that compared PCI with CABG in patients with multivessel CAD. Because of the better clinical outcomes of second-generation or newer-generation drug-eluting stents (DES) compared with bare-metal stents or first-generation DES, it is important to mention that the major trials conducted shown in Table 1 exclusively compared PCI using bare-metal stents or first-generation of DES. As a first landmark RCT using DES, the SYNTAX trial showed that CABG was associated with a significant reduction of major adverse cardiac and cerebrovascular events (MACCE) compared with PCI with DES, mainly because of the higher rate of repeat revascularization in the PCI group.[14] The **B**ypass Surgery and **E**verolimus-Eluting **S**tent Implantation in the **T**reatment of Patients With Multivessel Coronary Artery Disease (BEST) trial also showed better outcomes of CABG.[15] Several studies have also compared PCI with CABG in diabetic populations. The **C**oronary **A**rtery **R**evascularization in **Dia**betes (CARDia) and **F**uture **Re**vascularization **E**valuation in Patients With **Di**abetes Mellitus: **O**ptimal Management of **M**ultivessel Disease (FREEDOM) trials similarly showed that CABG was superior to PCI.[16,17]

Several meta-analyses also showed consistent findings. A recent meta-analysis of 5 RCTs reported that PCI with DES was associated with a 154% increased relative risk of repeat revascularization, late mortality (increased by 51%), and MI (increased by 102%) whereas CABG was hampered by a 29% increase risk of stroke.[18] Focusing on diabetic subjects, a meta-analysis of 14 studies including more than 5000 diabetic patients with multivessel CAD showed that the early mortality rate was lower in the PCI with DES than in the CABG group and periprocedural stroke rates were lower in the PCI group, but those were comparable in the 2 groups at the end of 1 year.[19] During a follow-up of 3-5 years, the rate of adverse events was much higher in the PCI than in the CABG group. Recently, a pooled analysis of 11 RCTs with 11,518 patients was conducted including patients with multivessel or left main CAD who did not present with acute MI.[20] The study showed that the 5-year all-cause mortality rate was significantly higher in patients who underwent PCI than those who underwent CABG (hazard ratio [HR], 1.28; 95% CI, 1.09-1.49; $P = 0.0019$), including in patients with diabetes (HR, 1.48; 95% CI, 1.19-1.84; $P = 0.0004$), but not without diabetes (HR, 1.08; 95% CI, 0.86-1.36; $P = 0.49$), indicating that CABG provided significant benefits to patients with complex mulltivessel disease and diabetes.

An interesting point has emerged from meta-analyses that have compared the outcomes of CR and IR in merged analyses. The previous report by Garcia et al. showed that IR was associated with increased rates of mortality and repeated revascularization, independent of the mode of treatment.[6] A patient-level pooled analysis of the 3 RCTs showed that compared with patients who underwent CABG with CR, those who underwent PCI with IR had a higher risk for all-cause death and the composite of death, MI, or stroke. However, PCI resulting in CR was associated with a long-term survival rate similar to CABG resulting in CR.[21] Furthermore, several major RCTs in which CABG was superior to PCI showed significantly higher rates of CR achievement of CABG than PCI (Table 1). It might be argued that the main advantages of CABG over PCI in most patients with multivessel CAD seem to be conferred by the achievement of more extensive revascularization and if CR is achieved using PCI like CABG, the overall outcomes could be comparable. Therefore, the ability to achieve CR should enter into the decision algorithm for choice of revascularization strategy. Accordingly, the 2011-2012 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines indicated that the completeness of revascularization is one of the clinical factors that influence the choice of revascularization.[22,23] The recent 2018 European Society of Cardiology (ESC) guidelines also suggested that completeness of revascularization should be prioritized, when considering CABG vs PCI (class IIa).[24]

Specific consideration: chronic total occlusion

Coronary chronic total occlusion (CTO) is observed in approximately 15%-30% of patients referred for cardiac catheterization and 75% of patients with CTOs have multivessel disease.[25] Observational studies or small-sized RCTs showed that CTO revascularization is associated with improvement of angina symptoms, quality of life, exercise capacity, and left ventricular function as well as reduction of the risk for ventricular arrhythmias.[26-28] Despite the high prevalence and potential benefits of CTO revascularization, there remains uncertainty regarding which CTO is indicated for revascularization and which revascularization modality is undertaken because of the scarcity of RCTs.

Large observational studies explored the clinical outcomes of the CTO revascularization strategy. Jang et al. reported that revascularization (PCI or CABG) coupled with medical therapy significantly decreased the long-term risk of cardiac death, all-cause death, and MACE compared with medical therapy alone.[29] A study of the Italian registry showed that CTO PCI significantly improved the survival and decreased MACCE occurrence at 1 year follow-up in comparison with medical treatment and/or CABG.[30] However, the major limitations of both registry studies are the higher risk profile of

Table 1. Summary of clinical trials comparing PCI and CABG in patients with multivessel CAD and effect of CR

Study	Design and inclusion criteria	Primary outcomes and follow-up	Results	Comment	CR vs IR subgroup findings
ARTS[55]	1:1 PCI vs CABG (n = 1205); stable or unstable angina or silent ischemia	Composite of death, MI, stroke, and repeat revascularization at 1 year	26.2% PCI vs 12.2% CABG ($P < 0.001$)	PCI with BMS; no significant differences in the rates of death, MI, or stroke at 1 year	CR achievement 70.5% PCI vs 84.1% CABG ($P < 0.001$)[56]; 1-year primary outcome (IR vs CR) 30.6% vs 23.4% in PCI ($P < 0.05$); 12.2% vs 10.1% in CABG (P = NS)
SoS[57]	1:1 PCI vs CABG (n = 988); symptomatic angina	Repeat revascularization at a median of 2 years	21% PCI vs 6% CABG (HR, 3.85; $P < 0.001$)	PCI with BMS; death or Q-wave MI (HR, 0.95; $P = 0.80$)	CR achievement 54% PCI vs 86% CABG
MASS II[58]	1:1:1 Medication vs PCI vs CABG (n = 611); documented ischemia with stress testing or typical stable angina	Death, MI, stroke, or repeat revascularization at 1 year	Event numbers: 29 with medication vs 50 with PCI vs 13 with CABG ($P < 0.001$)	PCI with BMS	CR achievement; 41% PCI vs 74% CABG ($P < 0.001$)
SYNTAX[14]	1:1 PCI vs CABG (n = 1800, including 1095 with multivessel disease); stable/unstable angina or being asymptomatic with positive evidence of myocardial ischemia	Composite of death, MI, stroke, and repeat revascularization at 1 year	17.8% PCI vs 12.4% CABG ($P = 0.002$)	PCI with PES; stroke: 0.6% PCI vs 2.2% CABG ($P = 0.003$); repeat revascularization: 13.5% PCI vs 5.9% CABG ($P < 0.001$)	CR achievement 56.7% PCI vs 63.2% CABG ($P = 0.005$); 5-year outcome (IR vs CR)[59] 42.6% vs 32.7% in PCI ($P = 0.01$); 26.9% vs 22.2% in CABG ($P = 0.17$)
CARDia[16]	1:1 PCI vs CABG (n = 510, all diabetes); either multivessel CAD or complex single-vessel disease	Composite of death, MI, and stroke at 1 year	13.0% PCI vs 10.5% CABG (HR, 1.25; $P = 0.039$)	PCI with BMS (31%) or first-generation SES (69%)	CR achievement 88% PCI vs 90% CABG among patients with 3-vessel disease
FREEDOM[17]	1:1 PCI vs CABG (n = 1900, all diabetes); multivessel CAD; symptoms of angina, and/or objective evidence of ischemia	Composite of death, nonfatal MI, or nonfatal stroke at a median of 3.8 years	26.6% PCI vs 18.7% CABG ($P = 0.005$)	PCI with first-generation DES; CABG significantly reduced rates of death and MI, but had a higher rate of stroke	No comparative data on CR vs IR in this study
VA CARDS[60]	1:1 PCI vs CABG (n = 790, but 198 enrolled, all diabetes); either multivessel CAD or isolated proximal LAD disease	Composite of death or nonfatal MI at a mean of 2 years	31% PCI vs 53% CABG (HR, 0.89; 95% CI, 0.47-1.71)	PCI with 1% BMS, 55% first-generation DES, 20% second-generation DES, and 16% mixed	No comparative data on CR vs IR in this study
BEST[15]	1:1 PCI vs CABG (n = 1775, but 880 enrolled); symptoms of angina and/or objective evidence of ischemia	Composite of death, MI, or TVR at 2 years	11.0% PCI vs 7.9% CABG (absolute risk difference, 3.1% points; $P = 0.32$ for noninferiority)	PCI with EES; at a median of 4.6 years of follow-up, 15.3% PCI vs 10.6% CABG (HR, 1.47; $P = 0.04$)	CR achievement 50.9% PCI vs 71.5% CABG ($P < 0.001$)

ARTS, **A**rterial **R**evascularization **T**herapies **S**tudy; BEST, **B**ypass Surgery and **E**verolimus-Eluting **S**tent Implantation in the **T**reatment of Patients With Multivessel Coronary Artery Disease; BMS, bare-metal stent; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CARDia, **C**oronary **A**rtery **R**evascularization in **Dia**betes; CI, confidence interval; CR, complete revascularization; DES, drug-eluting stent; EES, everolimus-eluting stent; FREEDOM, **F**uture **Re**vascularization **E**valuation in Patients With **D**iabetes Mellitus: **O**ptimal Management of **M**ultivessel Disease; HR, hazard ratio; IR, incomplete revisualization; LAD, left anterior descending; MASS II, **M**edicine, **A**ngioplasty, or **S**urgery **S**tudy II; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; SoS, **S**tent **o**r **S**urgery; SYNTAX, **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery; TVR, target vessel revascularization; VA CARDS, **VA C**oronary **A**rtery **R**evascularization in **D**iabete**s**.

the medical treatment groups, and selection and ascertainment biases because of the observational nature. A meta-analysis that compared the long-term outcomes of successful vs failed CTO PCI with 25 studies showed that successful CTO PCI was associated with a lower risk of death, stroke, and CABG.[31] Of note, comparison of successful vs failed CTO PCIs has an inherent drawback because patients in whom CTO PCI fails have more complex angiographic characteristics and more comorbidities, which are associated with adverse outcomes. To date, no large RCT adequately evaluating the long-term prognostic benefits of CTO revascularization is available. Thus, CTO revascularization would be indicated on the basis of expected improvement of symptoms, functional status, and ischemia reduction.

In summary, although a question remains whether CTO lesions are an independent determinant of prognosis, the presence of CTO could be an important factor for the heart team to take into consideration in the shared decision for management of patients with multivessel CAD. The decision should be made using a comprehensive evaluation of all the aspects of patients including the severity of the symptoms, extent of ischemia and viability, the patient's suitability for procedures, and the operators' experience.

CR vs IR in Patients With ST-Elevation MI

Benefits of CR

Approximately 50% of patients with ST-elevation MI (STEMI) have concomitant obstructive CAD in nonculprit vessels.[2] The presence of concomitant multivessel CAD in patients with STEMI was significantly associated with a higher risk of mortality.[2] Thus, the treatment strategy of nonculprit lesions during STEMI has been the subject of intense debate. In the clinical viewpoint, early revascularization of nonculprit lesions has advantages for reduction of residual ischemic burden and prevention of future coronary events. This also might reduce the duration of hospitalization, resource utilization, and costs. However, this strategy also has disadvantages; it might pose risks such as procedural complications, longer procedure times, higher contrast volume, and stent thrombosis in the highly thrombogenic periinfarction milieu. PCI options for patients with STEMI and multivessel CAD can be stratified into 3 strategies: (1) culprit-only revascularization (COR), consisting of culprit artery-only primary PCI; (2) CR, consisting of multivessel PCI at the time of primary PCI; and (3) staged revascularization (SR), consisting of culprit artery-only primary PCI followed by staged PCI of nonculprit arteries, either during the same hospitalization or shortly afterward.[32]

Previous guidelines recommended against PCI of non-infarct-related arteries (IRAs) stenoses at the time of primary PCI in hemodynamically stable patients with STEMI.[33] However, although PCI in patients with STEMI has become safer within the past few years because of advances in PCI technology and concomitant medical therapy, several RCTs have investigated the efficacy and safety of multivessel PCI (Table 2). The **Pr**eventive **A**ngioplasty in Acute **MI** (PRAMI) trial showed that, compared with COR-PCI, preventive PCI in non-IRAs was associated with a 65% reduction of the primary composite outcome during a mean follow-up of 23 months.[34] The **C**omplete **v**s **L**esion Only **Pr**imary PC**I** **T**rial (CvLPRIT) trial showed that in-hospital CR significantly lowered the 12-month rate of the primary composite end point compared with COR.[35] Similarly, recent large RCTs such as the Third **Dan**ish Study of Optimal **A**cute Treatment of Patients With STE**MI**: **Pri**mary PCI in **Multi**vessel Disease (DANAMI3-PRIMULTI) and **Compa**rison Between FFR Guided **Re**vascularization Versus Conventional Strategy in **Acute** STEMI Patients With MVD (COMPARE-ACUTE) trials showed that FFR-guided CR significantly reduced the risk of future events compared with no further PCI after primary PCI.[36,37] Despite the heterogeneity of trial designs and target populations, overall findings of previous RCTs have shown the superiority of CR, either during the index procedure or as a staged procedure. A recent meta-analysis showed that CR at the index procedure or a staged procedure had advantages, including a reduction in the risk of adverse events, albeit mostly because of a reduction in the risk of revascularization.[38] On the basis of such evidence, the 2015 ACCF/AHA guidelines changed the recommendations for multivessel PCI (either immediate or staged PCI) from a class III to a class IIb recommendation.[32] Similarly, the 2017-2018 ESC STEMI guidelines now provide a class IIa recommendation favouring routine revascularization of non-IRA lesions before hospital discharge.[24,39]

In contrast, the recent **Culprit** Lesion Only PCI versus Multivessel PCI in Cardiogenic **Shock** (CULPRIT-SHOCK) trial determined the clinical effect of non-IRA revascularization in STEMI patients complicated with cardiogenic shock at presentation, who were mostly excluded from previous trials.[40] In this trial, the primary end point of death or renal replacement therapy at 30 days was significantly lower in the COR group than in in the multivessel PCI group. At 1-year follow-up, mortality did not differ significantly between the 2 groups, despite a nonsignificant trend favouring the COR approach (RR, 0.88; 95% CI, 0.76-1.01).[41] On the basis of these findings, the recent 2017-2018 ESC STEMI guidelines recommend against revascularization of non-IRA lesions during PCI in patients with cardiogenic shock (class III, level of evidence B), in contrast to recommendations in hemodynamically stable patients who present with STEMI.[24]

The role of functional guidance for non-IRA lesions in the STEMI setting was recently evaluated. In the DANAMI3-PRIMULTI and COMPARE-ACUTE trials, up to 50% of the lesions with $>$ 50% stenosis were not hemodynamically significant, determined using FFR measurements. In this context, the **F**FR-G**ui**dance for Comp**l**ete Non-Cu**l**prit **Revasc**ularization (FULL REVASC; NCT02862119) trial, which randomized STEMI patients with multivessel CAD to IRA-only primary PCI or to FFR-guided ad hoc or SR, would provide evidence about the effect of FFR on outcomes in patients with acute MI.

Optimal timing of CR in STEMI: index or staged procedure?

The optimal timing of CR in patients with STEMI, whether during the index procedure or staged within weeks after STEMI, remains unclear. To date, few RCTs were dedicated to compare CR and SR during primary PCI for STEMI. A recent network meta-analysis suggested that SR was associated with lower short-term and long-term mortality compared with COR

Table 2. Summary of clinical trials evaluating the timing and effect of CR in patients with STEMI

Study	Design	Primary outcomes and follow-up	Results	Comment
HELP-AMI[61]	52 CR vs 17 COR (n = 69)	Repeat revascularization at 1 year	17% CR vs 35% COR ($P = 0.247$)	PCI with heparin-coated stent
Politi et al.[62]	1:1:1 CR vs SR vs COR (n = 214)	Composite of death, reinfarction, rehospitalization for ACS, repeat revascularization for a mean of 2.5 years	23.1% CR vs 20.0% SR vs 50.0% COR ($P < 0.001$)	
Ghani et al.[63]	2:1 CR (SR within 3 weeks of primary PCI) vs COR (n = 121)	Composite of death, nonfatal MI, repeat revascularization at 3 years	35.4% CR vs 35.0% COR ($P = 0.96$)	FFR-guided
PRAMI[34]	1:1 CR (during index PCI) vs COR (n = 465)	Composite of CV death, nonfatal MI, and refractory ischemia for a mean of 23 months	9/100 CR vs 23/100 COR (HR, 0.35; $P < 0.001$)	
DANAMI3-PRIMULTI[36]	1:1 CR (SR before discharge) vs COR (n=627)	Composite of death, MI, ischemia-driven revascularization for a median 27 months	13% CR vs 22% COR (HR: 0.56, P =0.004)	FFR-guided
CvLPRIT[35]	1:1 CR (immediate or staged nonculprit PCI during index hospitalization) vs COR (n = 296)	Composite of death, MI, heart failure, and ischemia-driven revascularization at 1 year	10% CR vs 21.2% COR (HR, 0.45; $P = 0.009$)	
Zhang et al.[64]	1:1 CR (SR within 10 days after AMI) and COR (subsequent PCI only for patients with evidence of ischemia) (n = 428)	Cardiac death and MI at 24 months	8.4% CR vs 10.8% COR ($P = 0.394$)	Decreased angina and rehospitalization rates in the CR group
Hamza et al.[65]	1:1 CR (immediate or staged PCI within 72 hours) vs COR (n = 100)	Composite of death, recurrent MI, and ischemia-driven revascularization at 6 months	6% CR vs 24% COR ($P = 0.01$)	Diabetic patients; no difference of safety end points
COMPARE-ACUTE[37]	1:2 CR (mostly index PCI) vs COR (n = 885)	Composite of death, nonfatal MI, revascularization, and cerebrovascular events at 1 year	8/100 CR vs 21/100 COR (HR, 0.35; $P < 0.001$)	FFR-guided
CULPRIT-SHOCK[40]	1:1 CR vs COR (with the option of SR) (n=706)	Composite of death or renal replacement therapy at 30 days	55.4% CR vs 45.9% COR (RR, 0.83; $P = 0.01$)	Acute MI with cardiogenic shock

ACS, acute coronary syndrome; AMI, acute myocardial infarction; COMPARE-ACUTE, **Compa**rison Between FFR Guided **Re**vascularization Versus Conventional Strategy in **Acute** STEMI Patients With MVD; COR, culprit-only revascularization; CR, complete revascularization; CV, cardiovascular; CULPRIT-SHOCK, **Culprit** Lesion Only PCI Versus Multivessel PCI in Cardiogenic **Shock**; CvLPRIT, **C**omplete **vs** **L**esion Only **Pr**imary PC**I** **T**rial; DANAMI3-PRIMULTI, Third **Dan**ish Study of Optimal **A**cute Treatment of Patients With STE**MI**: **Pri**mary PCI in **Multi**vessel Disease; FFR, fractional flow reserve; HELP-AMI, **He**pacoat for Cu**lp**rit or Multivessel Stenting for **A**cute **M**yocardial Infarction; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; PRAMI, **Pr**eventive **A**ngioplasty in Acute **MI**; RR, risk ratio; SR, staged revascularization; STEMI, ST-elevation myocardial infarction.

	Stable angina	Non-STE ACS	STEMI	STEMI with cardiogenic shock
ACCF/AHA	2011-2012 CR is one of clinical factors for choice of revascularization	2014 Multivessel-PCI might be reasonable (Class IIb)	2015 Multivessel PCI (either immediate or staged PCI) (Class IIb)	Not available
ESC	2018 Prioritize completeness of revascularization, when considering CABG vs. PCI (Class II)	2015 Tailor the need for CR to age, general patient condition and comorbidities	2017-2018 Routine revascularization of non-IRA lesions before hospital discharge (Class IIa)	2017-2018 Against revascularization of non-IRA lesions (Class III)

Figure 1. Guideline recommendations for completeness of revascularization. ACCF/AHA, American College of Cardiology Foundation/American Heart Association; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CR, complete revascularization; ESC, European Society of Cardiology; IRA, infarct-related artery; PCI, percutaneous coronary intervention; STE, ST-elevation; STEMI, ST-elevation myocardial infarction.

and single-stage multivessel PCI.[42] Another network meta-analysis compared 4 treatment strategies (CR at the index procedure, SR during the hospitalization, SR after discharge, or COR).[38] Although MACE was significantly reduced by CR, there were no differences among the different CR strategies. The risks of all-cause mortality or reinfarction were similar among the 4 revascularization strategies. In contrast, a recent meta-analysis of 11 RCTs evaluated the effectiveness of early CR during the index hospitalization, delayed CR, and COR. Compared with COR, early CR was associated with significantly reduced risks of MACE, MI, and repeat revascularization, but not of all-cause mortality.[43] Because there is still uncertainty on when and how to perform CR in STEMI patients, it warrants more definite, larger trials. The **Mult**ivessel **I**mmediate Versus **Sta**ged **R**eva**s**cularization in **A**cute **M**yocardial **I**nfarction (MULTISTARS AMI; NCT03135275) trial, comparing immediate and staged CR, is currently ongoing and might provide further insight on the timing of CR.

CR vs IR in Acute Coronary Syndrome Without ST Elevation

Several observational studies showed that multivessel PCI was associated with better clinical outcomes than culprit-only PCI in patients with non-ST-elevation acute coronary syndrome (ACS).[44,45] Of note, unlike in STEMI—in which the location of the culprit lesion can be identified easily—in non-STEMI, locating the lesion might be not straightforward. When it is difficult to identify the culprit lesions, CR would be recommended if technically feasible. In the 2014 ACCF/AHA guidelines for the management of patients with non-STEMI, a class IIb level was recommended, suggesting that a strategy of multivessel PCI might be reasonable.[46] The timing of CR is also unclear. The recent Impact of Different Treatment in Multivessel Non **S**T Elevation **M**yocardial **I**nfarction Patients: One Stage Versus Mu**l**tistag**e**d Percutaneous Coronary Intervention (SMILE) trial compared single-stage (n = 253) with multistage (n = 247) CR during the index hospitalization in non-STEMI patients.[47] At 1 year, the composite end point of death, reinfarction, rehospitalization for ACS, repeat revascularization, and stroke was significantly higher in patients who underwent multi-stage than single-stage CR (23% vs 13%; $P = 0.0036$). Further studies are needed to determine the optimal time of CR for non-ST-elevation ACS patients in case that PCI could be the preferred treatment modality.

In summary, Figure 1 illustrates the guideline recommendations for completeness of revascularization according to the clinical presentation.

Hybrid Coronary Revascularization

Hybrid coronary revascularization (HCR) combines minimally invasive CABG of the left anterior descending (LAD) artery with PCI of the non-LAD vessels. This approach was designed to take advantage of the long-term patency of the left internal thoracic artery-LAD graft, which exceeds 90% at 10-15 years, while avoiding the morbidity of a sternotomy and use of a cardiopulmonary bypass. HCR also has advantages over contemporary PCI with DES, being less invasive and favouring long-term patency. Thus, HCR combining the 2 modalities can provide an opportunity for CR. However, HCR also has technical difficulties and potential risks; minimally invasive, beating heart left internal thoracic artery-LAD anastomosis is technically demanding, the bleeding risks because of dual antiplatelet therapy in the immediate postoperative setting, and the risk of adverse coronary events between staged CABG and PCI.

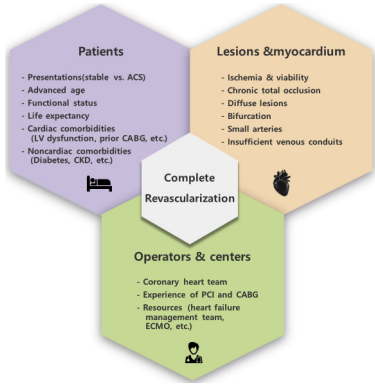

Figure 2. Decision-making for complete revascularization. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; PCI, percutaneous coronary intervention.

Table 3. Subjects requiring the randomized trials related to the completeness of revascularization

Topic	Question
PCI vs CABG in patients with LV dysfunction and multivessel CAD	Which is more effective and safer between PCI and CABG for patients with LV dysfunction and multivessel CAD?
PCI vs CABG in nondiabetic patients with multivessel CAD	Which is more effective and safer between PCI and CABG for nondiabetic patients with multivessel CAD?
PCI vs CABG achieving CR according to FFR guidance	If CR is achieved using PCI like CABG in patients with multivessel CAD defined by FFR, is PCI comparable with CABG?
FFR-guided vs angiography-guided CABG in patients with multivessel CAD	Could FFR-guided CABG show better clinical outcomes, compared with angiography-guided CABG?
Clinical outcomes of PCI vs medical treatment for CTO in patients with multivessel CAD including CTO	Does CTO PCI confer prognostic benefits such as mortality for the patients with multivessel CAD including CTO?
PCI vs CABG in patients with non-STE ACS and multivessel CAD	Which is more effective and safer between PCI and CABG for patients with multivessel CAD in the setting of non-STE ACS?
Multivessel PCI vs culprit-only PCI in patients with non-STE ACS and multivessel CAD	Is multivessel PCI associated with better clinical outcomes in patients with multivessel CAD in the setting of non-STE ACS, compared with culprit-only PCI?
Optimal time of nonculprit revascularization in patients with non-STE ACS	Which is more effective or safer between single-staged multivessel PCI and multistaged PCI in patients who present with non-STE ACS?
Clinical outcomes of HCR vs CABG or PCI	Is HCR comparable or better than conventional CABG or PCI in terms of major adverse cardiac events?

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CR, complete revascularization; CTO, chronic total occlusion; FFR, fractional flow reserve; HCR, hybrid coronary revascularization; LV, left ventricular; PCI, percutaneous coronary intervention; STE, ST-elevation.

Currently, several prospective studies and meta-analyses have assessed outcomes of HCR. The **P**rospective Randomized Pil**o**t Study Eva**l**uating the Safety and Efficacy of Hybrid Revascularization in **M**ulti**v**essel Coronary Artery **D**ise**a**se (POLMIDES) trial randomized 200 patients with multivessel CAD to receive HCR or conventional CABG.[48] At 12 months, the rates of death, MI, major bleeding, and repeat revascularization were similar in the 2 groups. Moreover, at 5 years, there were no differences in the rates of all-cause mortality and MACCE.[49] A meta-analysis involving 2245 patients from 1 RCT and 7 observational studies, showed that compared with the CABG group, patients in the HCR group had similar risks of all-cause mortality, MI, stroke, and repeat revascularization.[50] The need for postoperative blood transfusion and hospital stay was significantly lower in the HCR group. To compare HCR with PCI, a multicentre observational study reported the propensity score-adjusted risks for MACCE (death, stroke, MI, or repeat revascularization) were similar at 12 months.[51]

With growing data supporting HCR, the major guidelines document the role of HCR. The 2012 ACCF/AHA guidelines proposed HCR as a reasonable approach for patients who might encounter limitations undergoing traditional CABG (ie, a heavily calcified proximal aorta, poor target vessels for CABG, lack of conduits, or an unfavourable LAD artery for PCI; class IIa).[22] Furthermore, HCR might be an alternative to multivessel PCI or CABG for improving the overall risk-benefit ratio (class IIb). The 2018 ESC guidelines suggest HCR for specific situations such as redo revascularization when the lack of a conduit limits a conventional surgical approach (class IIb).[24]

However, still, in clinical practice, there is the controversy with the HCR strategy for replacing conventional CABG. Although saphenous vein graft occlusion occurs at a higher rate compared with stent thrombosis, the clinical effect of the latter is greater, with a negative effect on short-term to long-term mortality.[52] A recent patient-level combined analysis of RCTs showed a lower rate of MACE and a higher rate of patency of radial arterial grafts to non-LAD territories compared with the use of saphenous vein grafts.[53] This finding supports the use of multiple arterial grafts for conventional CABG rather than HCR. In addition, pooled results of the 2 propensity-matched cohort studies that compared HCR vs CABG showed similar long-term mortality, but increased revascularization rate in patients who undergo HCR.[54]

In summary, the HCR approach might be effective and safe for select patients, making it a valuable option for achieving CR in patients with multivessel CAD. The further development of HCR can be invoked by not only the active collaboration of the coronary heart team but validated results from well designed RCTs. The ongoing **H**ybrid **C**oronary **R**evascularization (HCR; NCT03089398) trial, comparing HCR with multivessel PCI for patients with proximal LAD or left main coronary disease, might provide further compelling evidence of the role of HCR.

Decision-Making for Achieving CR

Although the CR approach is the gold standard for patients requiring coronary revascularization, it is not mandatory for everyone in all situations. CR should be performed when the anticipated benefits outweigh the potential risks. Decisions on the extent of revascularization should depend on the clinical characteristics of each individual patient. Factors associated with the patients, lesions, and physicians should be considered when determining revascularization strategy (Fig. 2).

Patients' overall medical condition and concomitant comorbidities are the first and foremost factors to be considered. CR might have limited benefits and greater risks in patients of advanced age, those with short-term life expectancy, or those with considerable comorbidities. Left ventricular dysfunction and decompensated hemodynamics might be associated with an increased risk of revascularization as well as more dramatic benefits of treatment. The complexity of coronary lesions and subtended myocardium is one of the keys to determine the extent of myocardial revascularization. Low-risk lesions supplying a large viable myocardial territory should generally be revascularized,

whereas complex high-risk lesions supplying a small myocardial territory might indicate conservative management. When it has been decided that the patient will undergo revascularization, all efforts must be made to achieve maximal revascularization, hence, well collaborated coronary heart teams are crucial to provide the best results. Furthermore, advanced heart failure management teams are of importance to maximize patient safety and provide good clinical outcomes, even in patients who experience complications. In summary, there are no simple answers to the question about when and how to achieve CR. This decision is individualized for each patient and should be made by the patient and the heart team on the basis of careful assessment of clinical and lesional data.

Conclusions

In patients with multivessel CAD, CR of all significant coronary lesions is biologically plausible and provides substantial clinical benefits and therefore should be considered the first priority of myocardial revascularization. Certainly, the method and timing of CR are dependent primarily on clinical presentation (ie, stable angina or MI). In clinical practice, the extent of revascularization and strategy of CR should be customized to each individual, on the basis of factors associated with patients, lesions, and physicians. In addition, because the definition of CR has been varied, caution is required in interpretation of the literature and its application to clinical practice. Reflecting contemporary practice, the functional/physiological assessment such as FFR measurement should be pursued for adequate CR achievement. Collaboration of the coronary heart team is essential for balanced decision-making and advanced therapeutic capabilities, including HCR. Finally, several ongoing trials as previously mentioned and proposed RCTs shown in Table 3 might provide valuable insight and compelling evidence for the optimal CR approach.

Disclosures

The authors have no conflicts of interest to disclose.

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