Complete Revascularization in Acute and Chronic Coronary Syndrome

Federica Ilardi, MD[a,b], Marco Ferrone, MD[a,c], Marisa Avvedimento, MD[a], Giuseppe Servillo, MD[d], Giuseppe Gargiulo, MD, PhD[a,*]

KEYWORDS

• Multivessel coronary artery disease (MVD) • Complete revascularization (CR)
• Incomplete revascularization (IR) • Culprit-only revascularization
• Percutaneous coronary intervention (PCI) • Coronary artery bypass graft (CABG)
• Acute coronary syndrome (ACS) • Chronic coronary syndrome (CCS)

KEY POINTS

- Multivessel coronary artery disease (MVD) is a common finding both in acute (ACS) and chronic coronary syndrome (CCS) and poses challenges to revascularization strategy.
- Complete revascularization (CR) has been based on anatomic or functional definitions, both in ACS and CCS.
- In ACS, mainly ST-segment elevation myocardial infarction, CR improves prognosis, but how define significant nonculprit lesions and when treating them still remain highly debated.
- In CCS, when myocardial revascularization (percutaneous coronary intervention or coronary artery bypass graft) is deemed beneficial, a functionally guided CR should be encouraged.
- Heart-team is essential to personalize strategies and reach balanced and optimized decision-making.

INTRODUCTION

Multivessel coronary artery disease (MVD) is a common finding both in acute (ACS) and chronic coronary syndrome (CCS) and poses challenges to revascularization strategy.

Despite the question of whether patients with MVD should undergo complete (CR) versus incomplete revascularization (IR) has been investigated in several studies, this issue still remains debated. This is attributable to conflicting results in clinical studies as well as to an evolved definition of coronary artery disease (CAD) over time, with a shift toward pursuing functional CR. Indeed, various definitions of CR exist and, to date, there is no consensus.[1,2] Although the anatomic-based definition has been the most widely used classification, in contemporary practice, a functional/physiological approach is encouraged.[3–5] Moreover, in the acute setting, the identification of nonculprit lesions (NCLs) poses relevant questions on their management. Finally, the optimal timing for

Federica Ilardi and Marco Ferrone equally contributed to this article.
[a] Department of Advanced Biomedical Sciences, Federico II University of Naples, Via S. Pansini 5, Naples 80131, Italy; [b] Mediterranea Cardiocentro, Via Orazio 2, Naples 80122, Italy; [c] Division of Invasive Cardiology, Clinica Montevergine, Via Mario Malzoni, 5, Mercogliano (Avellino) 83013, Italy; [d] Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University of Naples, Via S. Pansini 5, Naples 80131, Italy
* Corresponding author.
E-mail addresses: peppegar83@libero.it; giuseppe.gargiulo1@unina.it

Cardiol Clin 38 (2020) 491–505
https://doi.org/10.1016/j.ccl.2020.06.003

reaching CR, in particular in acute presentations, and type of revascularization strategy also remain critical issues to be fully clarified. In this review, we provide an overview of recent evidence and current indication to perform a CR in patients with ACS or CCS and MVD.

COMPLETE REVASCULARIZATION IN ACUTE CORONARY SYNDROME

The identification of NCL is frequent in both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS). Although in the latter setting there are no dedicated prospective studies on the revascularization strategy with MVD, there are relevant randomized trials for STEMI. In patients with STEMI, primary percutaneous coronary intervention (PCI) to treat the infarct related artery (IRA) or culprit lesion is essential to reduce myocardial damage and prevent reperfusion injury.[6] However, up to half of patients with STEMI show additional significant stenosis.[7,8] In this setting, the optimal management of NCL and whether to perform a CR has been a matter of discussion for years. Indeed, if on one hand most NCLs are asymptomatic or induce limited myocardial ischemia, conversely, it has been demonstrated that MVD following primary PCI associates with worse outcome than single-vessel disease.[7,8] This worse prognosis could be attributable to an increased disease burden, or a pan-coronary process of vulnerable plaque development, responsible for multiple plaque rupture even distant from the culprit lesion throughout the coronary tree.[9] One option could be a culprit-only revascularization with initial medical therapy followed by eventual further revascularization guided by recurrent symptoms. Alternatively, NCL revascularization (anatomically or functionally guided) may be performed immediately during the index procedure or as staged procedure, and the latter, in turn, could be performed during the index hospitalization or on a subsequent readmission. Thus, main open issues are as follows: (1) Is CR really beneficial? (2) If yes, how to optimally define NCLs needing revascularization? (3) Which is the optimal timing for NCL revascularization?

Clinical Evidence

Some randomized trials investigated the preferred strategy for patients with STEMI with MVD (CR vs IRA-only PCI), and also the optimal timing for CR (during index procedure or staged) (**Table 1**). In a small single-center trial, IRA-only PCI was associated with the highest risk of repeat unplanned revascularization, rehospitalization, and in-hospital death at 2.5-years compared with CR (at index PCI or staged).[10] The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial randomized 465 patients with STEMI with MVD to treatment of IRA lesion alone (n = 231) or revascularization of all obstructive (>50% angiographic stenosis) non-IRA lesions during the index procedure (n = 234).[11] Recruitment was stopped prematurely due to highly significant benefit of preventive PCI that at a mean of 23 months significantly reduced the composite of cardiac death or nonfatal myocardial infarction (MI) or refractory angina, as well as cardiac death and nonfatal MI, whereas cardiac death alone did not differ significantly. Interestingly, the benefit was evident within 6 months and maintained thereafter. Similarly, the Complete versus Lesion-only Primary PCI trial (CvLPRIT) (n = 269) showed that CR (>70% angiographic stenosis or 50% in 2 orthogonal views) during index hospitalization significantly reduced death, reinfarction, heart failure, or ischemia-driven revascularization, compared with IRA-only PCI.[12,13] There was a 40% reduction of primary endpoint after 5.6-year median follow-up, with most of the benefit occurring early. The composite of all-cause mortality and MI was also significantly lower in CR, whereas no significant difference was observed in individual components, although all were numerically lower in the CR group. Both the PRAMI and the CvLPRIT trial used the anatomic definition of significant stenosis to guide the CR, and did not evaluate the role of Fractional Flow Reserve (FFR) for MVD. Conversely, 2 randomized trials have proposed FFR to guide NCL revascularization.[14,15] The Third Danish Study of Optimal Acute Treatment of Patients with STEMI: Primary PCI in Multivessel Disease (DANAMI-3 PRIMULTI) trial (n = 627) showed a reduction in composite endpoint (all-cause mortality, reinfarction and ischemia-driven revascularization) with FFR-guided CR versus IRA-PCI only after a mean follow-up of 27 months, although this benefit was mainly driven by reduction of reintervention.[14] Notably, a recent cardiac magnetic resonance substudy on 280 patients showed that CR had no impact on left ventricle function and remodeling, nor on final infarct size, whereas a large but not significant increase of new nonculprit MI, related to periprocedural MI occurring during nonculprit intervention, was observed.[16] The Comparison Between FFR Guided Revascularization versus Conventional Strategy in Acute STEMI Patients with MVD (COMPARE-ACUTE) enrolled 885 patients who were assigned (2:1) to receive IRA-only PCI or FFR-guided CR.[15] Again, FFR-guided CR significantly reduced the composite of all-cause death, nonfatal MI, revascularization, or

Table 1
Overview of randomized clinical trials in patients with acute STEMI with MVD comparing complete revascularization with culprit-only PCI

Characteristics	Politi et al.	PRAMI	DANAMI-3-PRIMULTI	CvLPRIT	Compare-Acute	COMPLETE
Inclusion period	2003–2007	2008–2013	2011–2014	2011–2013	2011–2015	2013–2017
Trial registration	None	ISRCTN73028481	NCT01960933	ISRCTN70913605	NCT01399736	NCT01740479
Multicenter	No	Yes	Yes	Yes	Yes	Yes
Population	214	465	627	296	885	4041
Mean age	65	62	63	65	61	62
Lesion criteria	>70% stenosis	≥50% stenosis	>50%	≥70% or >50% in 2 orthogonal views	≥50% + FFR ≤0.80	≥70% or FFR ≤0.80
FFR measurement of NCL	No	No	Yes	No	Yes	Yes
Timing complete revascularization	2 CR groups randomized to index procedure vs staged revascularization	Index procedure	Index hospitalization	Index procedure or index hospitalization	Index procedure	Index hospitalization or after hospital discharge (no later than 45 d)
Median time from randomization to 2nd procedure (d)	0 (index procedure, n = 65) or 56.8 (staged, n = 65)	0 (index procedure)	2	<2	0 (index procedure)	1 (during admission, n = 1285) or 23 (after discharge, n = 596)
Primary endpoint	CV or all-death, in-hospital death, MI, rehospitalization for ACS, RR	CV death, MI, refractory angina	All-death, MI, RR or non-IRA	Death, reinfarction, HF, any RR	Death from any cause, MI, revascularization, cerebrovascular events	1) CV death or new MI; 2) CV death, new non-fatal MI or ischemia-driven revascularization
Blinded adjudication of clinical events	No	Yes	Yes	Yes	Yes	Yes
FUP, mo	30	23	27	12 (primary) and 66	12	36

(*continued on next page*)

Table 1
(*continued*)

Characteristics	Politi et al.	PRAMI	DANAMI-3-PRIMULTI	CvLPRIT	Compare-Acute	COMPLETE
Main results	20% in CR staged, 23.1% in CR index vs 50% in IR (staged HR: 0.37; 95% CI: 0.19–0.69; *P* = .002; index HR: 0.41; 95% CI: 0.22–0.74; *P* = .003)	9% in CR vs 23% in IR (HR: 0.35; 95% CI: 0.21–0.58; *P*<.001)	13% in CR vs 22% in IR (HR: 0.56, 95% CI: 0.38–0.83; *P* = .004)	At 1y: 10% in CR vs 21.2% in IR (HR: 0.45; 95% CI: 0.24–0.84; *P* = .009); At 5.6 y: 24% in CR vs 37.7% in IR (HR: 0.57; 95% CI: 0.37–0.87; *P* = .008)	7.8% in CR vs 20.5% in IR (HR: 0.35; 95% CI: 0.22–0.55; *P*<.001)	7.8% in CR vs 10.5% in IR (HR: 0.74; 95% CI: 0.60–0.91; *P* = .004)

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CR, complete revascularization; CV, cardiovascular; FFR, fractional flow reserve; FUP, follow-up; HF, heart failure; HR, hazard ratio; IR, incomplete revascularization; IRA, infarct-related artery; MACE, major adverse cardiac event; MI, myocardial infarction; MVD, multivessel coronary artery disease; NCL, nonculprit lesion; PCI, percutaneous coronary intervention; RR, repeat revascularization; STEMI, ST-segment elevation myocardial infarction.

cerebrovascular events at 12 months, mainly driven by lower reinterventions. Importantly, FFR-guided revascularizations were performed in 83.6% of cases during the index procedure and elective revascularizations of non-IRA performed within 45 days after primary PCI for clinical evaluations were not counted, as events in the group receiving IRA-only PCI (occurred in 10% of this group).

The most recent Complete versus Culprit-Only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) trial was the first powered for hard outcomes (composite of death or MI and the composite of cardiovascular death, MI, or revascularization).[17] A total of 4041 patients who had NCL with at least 70% stenosis or FFR $\leq$0.80 were randomly assigned (1:1) to CR or IRA-only PCI. At a median of 3 years, cardiovascular death or new MI was lower in CR, mainly driven by lower MI. The decision to perform preventive revascularization during the index hospitalization or after discharge (within 45 days after randomization) was specified by investigator before randomization. Interestingly, the benefit of CR was independent of timing of NCL-PCI (Pinteraction = 0.62) and a landmark analysis demonstrated that CR benefit of cardiovascular death or new MI emerged mostly over the long-term, with continued divergence of Kaplan–Meier curves for several years.[18] In an optical coherence tomography substudy, NCLs were in large proportion characterized by thin-cap fibroatheroma, thus, contributing to explain the benefit associated with multivessel revascularization.

Therefore, COMPLETE, the largest trial on the topic, confirmed that CR in patients with STEMI is associated with a significant reduction of the need for repeated revascularization and recurrence of MI. It remained, however, unclear if the lack of benefit in terms of cardiovascular and all-cause mortality was related to unpowered sample size, or to patient characteristics. Indeed, patients were relatively young and with a low mean SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) score, that could not reflect the clinical setting, often characterized by sicker patients with more diffuse and complex CAD.

All individual trials were underpowered for cardiovascular mortality. A recent meta-analysis included all of them with 6528 patients with STEMI with MVD (3139 CR vs 3389 culprit-only) demonstrating that CR significantly reduced cardiovascular mortality, as well as recurrent MI and repeated revascularization (**Fig. 1**).[19] Notably, CR was not associated with a significant increase of acute kidney injury (AKI), suggesting no

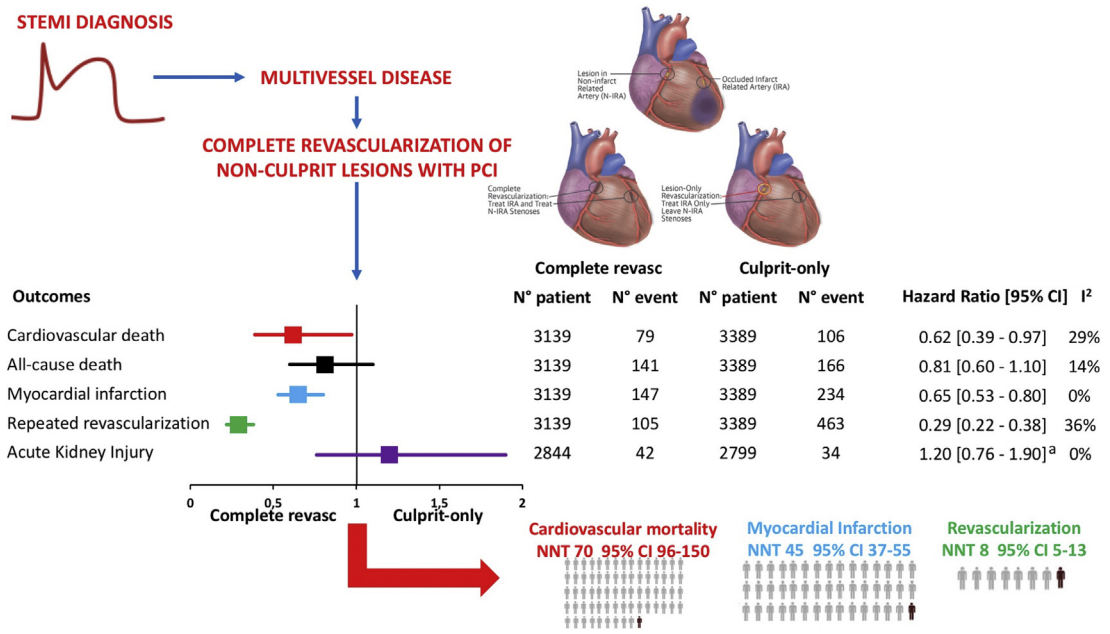

Fig. 1. Impact of complete revascularization on clinical outcomes in patients with STEMI. Summary results of a meta-analysis of 6 trials comparing CR versus culprit-only. CI, confidence interval; NNT, number needed to treat. [a] Risk ratio [95% CI]. (*Data from* Pavasini R, Biscaglia S, Barbato E et al. Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2019.)

complications for this strategy; however, this outcome should be interpreted with caution considering that it was available in a limited number of patients and affected by heterogeneous definitions used. There was no benefit on all-cause mortality, likely related to low-risk population, or to length of follow-up. Conversely, a significant reduction in both all-cause mortality and MI was demonstrated in a previous meta-analysis in which the greater benefit was observed in CR performed during index PCI, suggesting that also timing of NCL treatment could affect prognosis.[20]

Data on patients with NSTE-ACS with MVD derive mainly form retrospective studies. In contrast with STEMI, in this setting to identify the culprit lesion is often difficult. Despite limited, some data indicate that CR might improve prognosis even in NSTE-ACS,[21–23] and a randomized trial showed that CR performed in a single procedure seems better than multistage PCI.[24] However, the long-term benefit of CR has to be balanced with the periprocedural risk of pursuing CR, mainly in those patients with complex coronary anatomy or chronic total occlusion (CTO).[25]

Practical Considerations and Future Perspectives

According to European Society of Cardiology (ESC) guidelines for STEMI, revascularization of NCL should be completed before hospital discharge (class IIa, level A).[6] Latest evidence will be incorporated in future recommendations and could change clinical practice. However, the decision whether to perform CR or not, and when/how, should take into account several factors, and data supporting benefits of CR should be interpreted with caution and in light of relevant considerations:

- COMPLETE showed small benefit in terms of cardiovascular mortality that instead was greater in older and smaller trials.
- There was huge variation in trial design, mainly on NCL evaluation (angio vs functional) and when CR was achieved (index vs staged PCI during same or subsequent hospitalization). In COMPLETE, treatment of NCL was mainly based on visual estimation, but nearly 60% of lesions had at least 80% stenosis, thus not requiring FFR. Therefore, beyond those lesions angiographically significant, FFR or instantaneous wave-free ratio (iwFR) may still be important in diagnosing intermediate lesions (50%–69%), and whether CR of such intermediate lesions further reduces the hard endpoints of death or MI at long-term remains unclear. Contrarily, some concerns on the value of functional assessment in the early phase of STEMI are related to concomitant microvascular dysfunction.[26]
- Different antiplatelet regimens may have influenced the findings described among studies conducted in different time periods. In a recent subanalysis of the TRITON-TIMI38 trial a more potent therapy with prasugrel reduced nonculprit MI compared with clopidogrel.[27] This supports that CR in patients with ACS should be attempted to prevent future events, but it could also be speculated that CR might influence the decision-making on the intensity of the antiplatelet therapy (ie, a more potent P2Y12 inhibitor should be always prioritized in patients with ACS, and deescalation to clopidogrel should not be considered in patients not receiving CR).
- Risks related to CR (including AKI and periprocedural MI) may have been underestimated and should never be forgotten because they can negatively impact on prognosis. Some concerns are related to perform CR during the index PCI; indeed, not rarely, an initial thrombotic burden, a nonoptimal IRA reperfusion result, or a significant coronary spasm that would cause inaccurate stent size, can occur and represent potential challenges to CR. Also the potential risk of AKI that may occur in some patients during primary PCI should be taken into account and could induce to decide for a staged approach. On the other hand, an advantage of CR during the index hospitalization is to avoid that patients after discharge do not return to complete procedure.
- Clinical factors always should be considered (patient's age and comorbidities, like chronic kidney disease), to avoid futile complex procedures in frail and old patients. Overall, patients participating in trials are generally less sick than those in the real world, and extending the results to patients with a greater risk of complications may not be safe. Yet, trials had specific exclusions criteria and were not designed to address the specific setting of cardiogenic shock in which MVD is frequent and associated with higher mortality. Guidelines recommended CR of all angiographic significant lesions during the index procedure (class IIa, level C),[6] but the recent CULPRIT shock trial, the largest randomized controlled trial in cardiogenic shock complicating MI (62% STEMI), showed that IRA-only PCI significantly reduced death or renal-replacement therapy at 30 days, and the difference was mainly driven by significantly

lower all-cause mortality. At 1-year, however, mortality did not differ significantly, suggesting that the benefit of culprit-only PCI was confined to the early period during which death in patients with cardiogenic shock mainly occurs.[28] Therefore, a subsequent document stated that in patients with cardiogenic shock complicating MI, primary PCI should be restricted to the IRA, whereas multivessel PCI should be limited to cases in which IRA is difficult to identify or incorrectly defined initially or when multiple culprit lesions are identified.[29]

In patients with NSTE-ACS, given the paucity of data, guidelines suggest to tailor CR to age, general patient condition and comorbidities, and to select a CR during a single procedure or with staged procedures based on clinical presentation, comorbidities, complexity of coronary anatomy, ventricular function, and revascularization modality.[30,31]

Available evidence supports NCL revascularization in patients with STEMI; however, the optimal tool(s) to guide NCL revascularization (which NCL to revascularize?) and the optimal timing for this (NCL assessment and revascularization) remain unsolved. Ongoing randomized trials will provide important insights in the future and are summarized in **Table 2**.

COMPLETE REVASCULARIZATION IN CHRONIC CORONARY SYNDROME

CAD is a chronic and frequently progressive disease that can present long, stable periods but can also become unstable at any time. Because of its dynamic nature, CAD can have different clinical presentations, including ACS or CCS. The latter group includes several clinical scenarios sharing the risk, although variable, of future cardiovascular events (mortality or MI).[32] Together with appropriate lifestyle modifications and optimal medical therapy (OMT), successful myocardial revascularization is crucial to reduce such risk.[30,32] OMT is essential to reduce symptoms, limit atherosclerosis progression, and prevent atherothrombotic events in patients with CCS, but on top of it (without supplanting it), myocardial revascularization (PCI or CABG) is fundamental for 2 main reasons: symptom relief and/or prognosis improvement. Huge evidence has shown that when compared with OMT alone, revascularization is effective in relieving angina, reducing the need for antianginal drugs, and improving exercise capacity and quality of life, as well as reducing the risk of major acute cardiovascular events, including MI and cardiovascular death.[30,32] A practical approach to the indication to revascularization in patients with CCS according to ESC guidelines is summarized in **Fig. 2**.

Selecting PCI or CABG remains a matter of ongoing discussion, but this is beyond our scope and is detailed elsewhere.[30,32–36] However, CR is key for both strategies; indeed, the benefit of CABG versus PCI has been attributed, in part, to greater degree of CR, and relevant evidence has demonstrated worse prognosis with IR compared with CR, either with PCI or CABG.[37–41]

Clinical Evidence

Most data evaluating the impact of CR is based on anatomic definition derived from studies comparing long-term outcomes of PCI versus CABG in MVD patients. In 2 pivotal trials, CR was more frequently reached with CABG, and the benefit of CR over IR was significant in patients with PCI but not in those with CABG.[42–44] Notably, they included PCI using bare-metal stents (BMS) or first-generation drug-eluting stents (DES, paclitaxel-eluting stent). More contemporary data on PCI with new-generation DES, specifically everolimus-eluting stents, showed that among 15,046 patients with MVD, CR was obtained in 30% and significantly reduced cardiovascular events including death compared with IR, and most relevant predictors of IR were the number of vessels diseased and the presence of a CTO.[39] Yet, data from 6539 patients demonstrated that surgical IR had negative impact on long-term survival, and this was strongly associated with age (higher mortality in <60 years but not in older patients).[45] A large meta-analysis on 89,883 patients comparing CR versus IR in MVD confirmed that CR was more often achieved with CABG than PCI and was associated with significantly better long-term mortality, MI, and repeat revascularization.[37] Remarkably, CR benefit was present in both PCI and CABG, and was independent of study design and definition. Similarly, in a pooled analysis of 3 trials including 3212 patients, CR rate was 61.7% (57.2% with PCI and 66.8% with CABG) and CR-PCI was associated with similar survival to CR-CABG at a median of 4.9 years.[46] Moreover, PCI resulting in IR had a higher risk of all-cause death and the composite of death/MI/stroke than CR-CABG. Importantly, these findings were consistent in subgroup analysis of MVD, high SYNTAX score (>32), and diabetes.

Overall, much evidence supports that CR improves outcomes, irrespective of whether achieved through PCI or CABG.

Table 2
Overview of ongoing randomized clinical trials on NCL management in STEMI and/or ACS as reported on clinicaltrials.gov

	FULL REVASC	iMODERN	FLOWER-MI	Safe STEMI for Seniors	FRAME-AMI	MULTISTARS AMI	BIOVASC	FIRE
Trial registration	NCT02862119	NCT03298659	NCT02943954	NCT02939976	NCT02715518	NCT03135275	NCT03621501	NCT03772743
Official title	Ffr-gUidance for compLete Non-cuLprit REVASCularization - a Registry-based Randomized Clinical Trial	Instantaneous Wave-free Ratio Guided Multi-vessel revascularizatiOn During Percutaneous Coronary intervEntion for Acute myocaRdial iNfarction	FLOW Evaluation to Guide Revascularization in Multi-vessel ST-elevation Myocardial Infarction	Study of Access Site for Enhancing PCI in STEMI for Seniors	Comparison of Clinical Outcomes Between FFR-guided Strategy and Angiography-guided Strategy in Treatment of Non-Infarction Related Artery Stenosis in Patients With Acute MI	MULTivessel Immediate vs STAged RevaScularization in Acute MI	Percutaneous Complete Revascularization Strategies Using Sirolimus Eluting Biodegradable Polymer Coated Stents in Patients Presenting With ACS and MVD	Functional vs Culprit-only Revascularization in Elderly Patients With MI and MVD
Estimated N	4052	1146	1170	875	1292	700	1525	1385
Type of patients	STEMI	STEMI	STEMI	STEMI	STEMI	STEMI	STEMI and NSTE-ACS	Elderly (>74y) STEMI and NSTEMI
Study start date	Aug 2016	Dec 2017	Dec 2016	Aug 2017	Aug 2016	Jan 2017	Jun 2018	Jul 2019
Estimated primary completion date	Jun 2021	Jan 2021	Dec 2019	Oct 2022	June 2020	Jun 2020	Dec 2020	Dec 2021

Intervention	FFR-guided PCI of NCL(s) during index hospital admission	iFR-guided revascularization of NCL with >50% diameter stenosis and iFR $\leq$0.89 during index procedure or index hospitalization	Angiography-guided PCI of NCL	iFR-guided revascularization of NCL	Angiography-guided PCI of NCL during index procedure or index hospitalization	Staged CR PCI (new hospitalization after 19–45 d, to complete the coronary revascularization)	Staged CR PCI (within 6 wk after index procedure)	Functionally-guided CR PCI
Alternative intervention	Initial conservative management of NCL	Adenosine stress perfusion CMR scan within 6 wk after STEMI, with revascularization of NCL associated with perfusion defects	FFR-guided PCI of NCL	Initial conservative management of NCL	FFR-guided PCI of NCL during index procedure or index hospitalization	Immediate CR PCI	Immediate CR PCI	Initial conservative management of NCL
Primary endpoint	all-cause mortality and MI during follow-up of minimum 1y	All-cause death, recurrent MI and hospitalization for heart failure at 1y	death, MI and unplanned hospitalization leading to urgent revascularization at 1y	cardiac death, infarct artery target-vessel MI, or ischemia-driven index IRA revascularization at 1y	Any death and any MI at 2 y	all-cause death, non-fatal MI, unplanned ischemia-driven revascularization, hospitalization for heart failure, and stroke at 1y	all-cause mortality, nonfatal type 1 MI, any unplanned revascularization, and cerebrovascular events at 1y	all-cause death, any MI, any stroke, any coronary revascularization at 1y

Abbreviations: ACS, acute coronary syndrome; CMR, cardiac magnetic resonance; CR, complete revascularization; FFR, fractional flow reserve; FUP, follow-up; HF, heart failure; iFR, instantaneous-wave free ratio; IRA, infarct-related artery; MI, myocardial infarction; NCL, nonculprit lesion; NSTE-ACS, non–ST-segment elevation ACS; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

Data from NIH. National Library of Medicine. Clinicaltrials.gov.

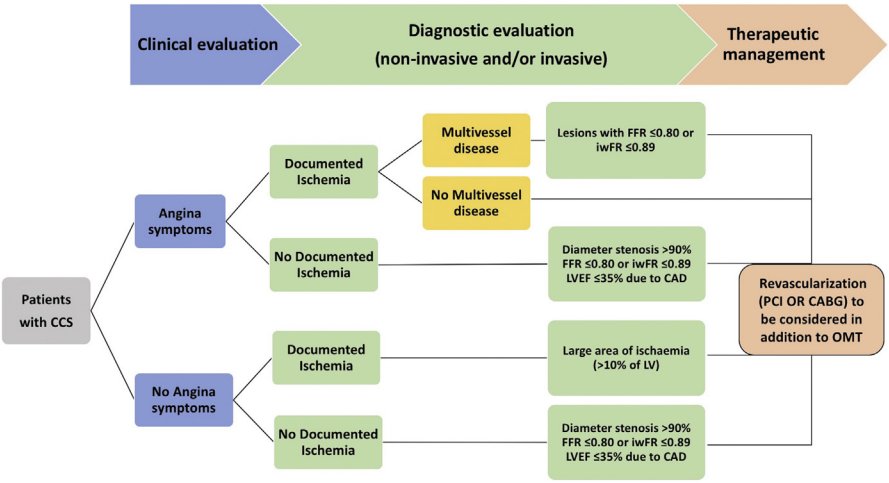

Fig. 2. Algorithm for patients undergoing invasive coronary angiography. CAD, coronary artery disease; FFR, fractional flow reserve; iwFR, instantaneous wave-free ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy. (*Data from* Knuuti J, Wijns W, Saraste A et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-477.)

Since IR has been considered a surrogate marker of greater burden on anatomic coronary complexity and associated with worse outcome,[21] the residual SYNTAX score after PCI has been proposed as an objective measure of residual stenosis and indicator of clinical outcome.[47] In the PCI group of SYNTAX, a residual SYNTAX score greater than 8 was associated with increased long-term mortality and death/MI/stroke, whereas a residual SYNTAX $\leq$8 was associated with long-term mortality comparable with CR-PCI. This finding introduced the concept of "reasonable IR," which implies that an acceptable burden of obstructive CAD postrevascularization is associated with similar outcomes than CR.

Although the anatomy-based definition of CR has been the most widely used in previous studies and practice, optimized decision-making on myocardial revascularization should also account for vessel size, angiographic and functional/physiologic severity of lesions, and myocardial viability. In the past decade, functional-based definition of CR has reached great clinical relevance and attention. Functional CR is accomplished when all lesions causing resting or stress-induced ischemia are treated by either PCI or CABG.

A pivotal trial investigating the impact of functionally guided decision in CCS was the Clinical Outcomes Utilizing Revascularization and AGgressive drug Evaluation (COURAGE) study in which PCI (with BMS) plus OMT had apparently similar all-cause death and MI than OMT alone in 2287 patients with significant coronary lesions and evidence of myocardial ischemia, after a median of 4.6 years. This inevitably led to the conclusion that OMT is as effective as PCI in CCS.[48] However, a nuclear imaging substudy, despite underpowered for prognosis, provided insights into the importance of functional evaluation, indeed, reduction of $\geq$5% of myocardial ischemia was associated with significantly lower rates of death and MI, and this level of ischemia reduction was achieved more frequently with PCI, suggesting that CR might have developed a larger proportion of patients reaching a significant reduction of residual ischemia.[49] As an alternative to noninvasive stress-imaging, FFR provides a validated and recommended method for ischemia detection. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study, FFR-guided PCI in patients with MVD (cutoff FFR 0.80) was associated with a significant reduction of death, nonfatal MI, or repeat revascularization at 1 year,[50] and mortality plus MI at 2 years.[51] Furthermore, it was cost-saving and cost-effective, being associated with lower use of stents and contrast medium, compared with angiographically guided PCI.[52] In FAME-2, FFR-guided PCI of functional relevant lesions was superior to OMT in preventing urgent revascularization.[5] These results were confirmed at 3 and 5 years with a significant reduction of major adverse cardiac events (MACE), including death, MI, and urgent revascularization.[53,54] These important findings led to propose an FFR-guided SYNTAX score (so-called, "functional SYNTAX score") in patients with PCI with MVD. It showed a better predictive accuracy for MACE than classic

SYNTAX score and also led to decrease by 32% the number of higher-risk patients.[55] Further evidence supporting the functional CR concept rather than angiographic CR alone derived by FAME analysis showed that residual angiographic lesions not functionally significant did not predict poorer outcomes.[56]

A special setting of patients with CCS with MVD is characterized by those with CTO. CTO influences CR and can have an impact on the decision between PCI or CABG. Despite limited evidence from large trials, data from registries and small trials show encouraging results in favor of CTO revascularization (probably due to optimal CR), that improves angina symptoms, quality of life, exercise capacity, and left ventricular function; reduces the risk of ventricular arrhythmias; and improves clinical outcomes.[57]

Recent studies have questioned revascularization value in CCS and generated huge debate. The Objective Randomized Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) was the first trial to investigate the influence of PCI in a sham-controlled fashion on angina symptoms and exercise time.[58] Despite all included patients had anatomically and/or functionally significant stenosis, PCI failed to improve exercise times or chest pain frequency. However, this was a small study (n = 200) with relevant limitations that should be interpreted with caution when considering daily practice.[59] The recent International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial represents an important additional piece of evidence (**Fig. 3**, **Box 1**). ISCHEMIA questioned whether in stable patients with at least moderate ischemia on a stress test, there is a benefit to adding cardiac catheterization and, if feasible, revascularization to OMT.[60] The primary endpoint did not differ at 4 years between conservative and invasive strategy.

Practical Considerations and Future Perspectives

Large evidence and practice guidelines support the role of the heart team to consider myocardial revascularization, whether with PCI or CABG, in patients with CCS with symptoms and/or documented ischemia and MVD, based on a functional/physiologic approach (see **Fig. 2**). Therefore, reflecting contemporary practice of ischemia-based revascularization, a physiologic/functional approach (FFR or iwFR) is considered

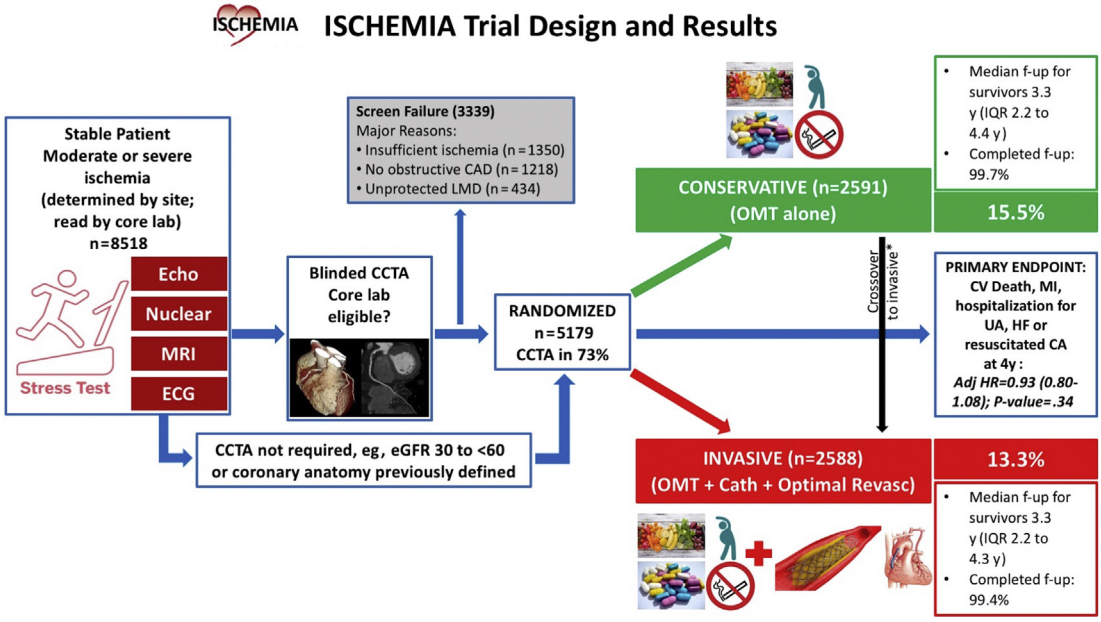

Fig. 3. Design and main results of the ISCHEMIA trial. CCTA, coronary computed tomography angiography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; f-up, follow-up; HF, heart failure; HR, hazard ratio; IQR, interquartile range. *At 4 years, indications for cath in CON: 25.8% cumulative incidence 28%): suspected/confirmed event 13.8%; OMT failure 3.9%; nonadherence 8.1%, and revascularization in CON: 16% (cumulative incidence 23%). CA, cardiac arrest; CAD, coronary artery disease; Cath, cathererization; CV, cardiovascular; LMD, left main disease; MI, myocardial infarction; MRI, magnetic resonance imaging; OMT, optimal medical therapy; UA, unstable angina.

Box 1
Eligibility criteria of the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial

Clinical and Stress Test Eligibility Criteria

Inclusion criteria

Age ≥21 years

Moderate or severe ischemia[a]:

- Nuclear ≥10% left ventricular ischemia (summed difference score ≥7)
- Echo ≥3 segments stress-induced moderate or severe hypokinesis, or akinesis
- Cardiac Magnetic Resonance:
  - Perfusion: ≥12% myocardium ischemic, and/or
  - Wall motion: ≥3/16 segments with stress-induced severe hypokinesis or akinesis

Exercise Tolerance Testing (ETT) >1.5 mm ST depression in greater than 2 leads or >2 mm ST depression in single lead at less than 7 METS, with angina

Major exclusion criteria

New York Heart Association Class III-IV heart failure

Unacceptable angina despite medical therapy

Left ventricular ejection fraction <35%

Acute coronary syndrome within 2 months

Percutaneous coronary intervention or coronary artery bypass grafting within 1 year

Estimated glomerular filtration rate less than 30 mL/min or on dialysis (ISCHEMIA chronic kidney disease study)

Coronary Computed Tomography Angiography Eligibility Criteria

Inclusion criteria

≥50% stenosis in a major epicardial vessel (stress imaging participants)

≥70% stenosis in a proximal or mid vessel (ETT participants)

Major exclusion criteria

≥50% stenosis in unprotected left main

[a] Ischemia eligibility determined by sites. All stress tests interpreted at core laboratories.

more reasonable and should be encouraged for appropriate CR.

In past years the so-called "hybrid" revascularization approach in patients with MVD has emerged as alternative to PCI or CABG alone with the aim to achieve CR by reducing the risks of a conventional CABG. Hybrid CR is characterized by the graft of internal mammary artery to the left anterior descending coronary artery through a small thoracotomy and then PCI with DES to other diseased vessels. Promising data support this approach, although potential limitations are also present (technically demanding, bleeding risks related to dual antiplatelet therapy in the immediate postoperative setting). Current ESC guidelines state that hybrid procedures may be considered in specific patient subsets at experienced centers (class IIb, level B).[30] Future studies will offer new insights (NCT03089398).

Despite small and inconclusive, ORBITA highlights that patients with CCS should be carefully evaluated before PCI. Yet, ISCHEMIA results overcome the previous COURAGE limitations (eg, PCI with new-generation DES, revascularization including both PCI and CABG) and reinforce the concept that probably not all patients with CCS with demonstrated ischemia/lesions should undergo revascularization. While waiting for its results be digested by the scientific community and incorporated into guidelines, some considerations can be made:

- Coronary computed tomography angiography reinforced its role in screening patients with suspected CAD, confirming the extent of disease and excluding left main disease.
- OMT and lifestyle changes are essential to all patients.
- Results cannot be extended to all patients with CCS (main exclusion criteria were ACS within 2 months, highly symptomatic patients, left main stenosis, and heart failure or left ventricular ejection fraction <35%).
- In people with chest pain symptoms, revascularization improved symptoms better than conservative strategy and the more symptomatic the patient was, the more symptoms improved after revascularization.
- Procedural MI was increased with an invasive strategy, but spontaneous MI was reduced.
- There were very low rates of procedure-related stroke and death, and all-cause death was low in both groups.
- During follow-up, a not negligible proportion of conservative patients required invasive management.
- Data on CR are not yet available.

SUMMARY

In patients with MVD, CR is the most biologically plausible approach irrespective of definition (anatomic or functional) or type (PCI or CABG) or clinical setting (ACS or CCS). It aims at minimizing residual ischemia, relieving symptoms and reducing the risk of future cardiovascular events. Large evidence supports CR benefits in ACS, predominantly STEMI, except cardiogenic shock, although the optimal tool to evaluate NCL and timing for achieving it remain to be clarified. In CCS, when revascularization is deemed appropriate, a functional CR should be attempted. Therefore, the heart-team plays a crucial role in the individualization of therapies aimed at selecting the ideal strategy for each patient to optimize decision-making. Ongoing studies will further inform our current knowledge.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Sandoval Y, Brilakis ES, Canoniero M, et al. Complete versus incomplete coronary revascularization of patients with multivessel coronary artery disease. Curr Treat Options Cardiovasc Med 2015;17:366.
2. Ong AT, Serruys PW. Complete revascularization: coronary artery bypass graft surgery versus percutaneous coronary intervention. Circulation 2006; 114:249–55.
3. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;55:2816–21.
4. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49: 2105–11.
5. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367: 991–1001.
6. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–77.
7. Sorajja P, Gersh BJ, Cox DA, et al. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Eur Heart J 2007;28:1709–16.
8. Park DW, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. JAMA 2014;312: 2019–27.
9. Asakura M, Ueda Y, Yamaguchi O, et al. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: an angioscopic study. J Am Coll Cardiol 2001; 37:1284–8.
10. Politi L, Sgura F, Rossi R, et al. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. Heart 2010;96:662–7.
11. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med 2013;369:1115–23.
12. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2015;65:963–72.
13. Gershlick AH, Banning AS, Parker E, et al. Long-term follow-up of complete versus lesion-only revascularization in STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol 2019;74:3083–94.
14. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. Lancet 2015;386:665–71.
15. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional flow reserve-guided multivessel angioplasty in myocardial infarction. N Engl J Med 2017;376: 1234–44.
16. Kyhl K, Ahtarovski KA, Nepper-Christensen L, et al. Complete revascularization versus culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease: a DANAMI-3-PRIMULTI Cardiac Magnetic Resonance Substudy. JACC Cardiovasc Interv 2019;12:721–30.
17. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med 2019;381:1411–21.
18. Wood DA, Cairns JA, Wang J, et al. Timing of staged nonculprit artery revascularization in patients with ST-segment elevation myocardial infarction: COMPLETE trial. J Am Coll Cardiol 2019;74: 2713–23.
19. Pavasini R, Biscaglia S, Barbato E, et al. Complete revascularization reduces cardiovascular death in patients with ST-segment elevation myocardial infarction and multivessel disease: systematic

review and meta-analysis of randomized clinical trials. Eur Heart J 2019. https://doi.org/10.1093/eurheartj/ehz896.
20. Pasceri V, Patti G, Pelliccia F, et al. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. JACC Cardiovasc Interv 2018;11:833–43.
21. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;61:282–94.
22. Shishehbor MH, Lauer MS, Singh IM, et al. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? J Am Coll Cardiol 2007;49:849–54.
23. Rathod KS, Koganti S, Jain AK, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. J Am Coll Cardiol 2018;72:1989–99.
24. Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. J Am Coll Cardiol 2016;67:264–72.
25. Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol 2010;55:2435–45.
26. van der Hoeven NW, Janssens GN, de Waard GA, et al. Temporal changes in coronary hyperemic and resting hemodynamic indices in nonculprit vessels of patients with ST-segment elevation myocardial infarction. JAMA Cardiol 2019;4(8):736–44.
27. Scirica BM, Bergmark BA, Morrow DA, et al. Nonculprit lesion myocardial infarction following percutaneous coronary intervention in patients with acute coronary syndrome. J Am Coll Cardiol 2020;75:1095–106.
28. Thiele H, Akin I, Sandri M, et al. One-year outcomes after PCI strategies in cardiogenic shock. N Engl J Med 2018;379:1699–710.
29. Ibanez B, Halvorsen S, Roffi M, et al. Integrating the results of the CULPRIT-SHOCK trial in the 2017 ESC ST-elevation myocardial infarction guidelines: viewpoint of the task force. Eur Heart J 2018;39:4239–42.
30. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165.
31. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.
32. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.
33. Capodanno D, Gargiulo G, Buccheri S, et al. Computing methods for composite clinical endpoints in unprotected left main coronary artery revascularization: a post hoc analysis of the DELTA Registry. JACC Cardiovasc Interv 2016;9:2280–8.
34. Gargiulo G, Tamburino C, Capodanno D. Five-year outcomes of percutaneous coronary intervention versus coronary artery bypass graft surgery in patients with left main coronary artery disease: an updated meta-analysis of randomized trials and adjusted observational studies. Int J Cardiol 2015;195:79–81.
35. Giacoppo D, Colleran R, Cassese S, et al. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: a systematic review and meta-analysis. JAMA Cardiol 2017;2:1079–88.
36. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939–48.
37. Garcia S, Sandoval Y, Roukoz H, et al. Outcomes after complete versus incomplete revascularization of patients with multivessel coronary artery disease: a meta-analysis of 89,883 patients enrolled in randomized clinical trials and observational studies. J Am Coll Cardiol 2013;62:1421–31.
38. Hannan EL, Racz M, Holmes DR, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. Circulation 2006;113:2406–12.
39. Bangalore S, Guo Y, Samadashvili Z, et al. Outcomes with complete versus incomplete revascularization in patients with multivessel coronary disease undergoing percutaneous coronary intervention with everolimus eluting stents. Am J Cardiol 2020;125:362–9.
40. Synnergren MJ, Ekroth R, Oden A, et al. Incomplete revascularization reduces survival benefit of coronary artery bypass grafting: role of off-pump surgery. J Thorac Cardiovasc Surg 2008;136:29–36.
41. Takagi H, Watanabe T, Mizuno Y, et al. A meta-analysis of adjusted risk estimates for survival from observational studies of complete versus incomplete revascularization in patients with multivessel disease undergoing coronary artery bypass

grafting. Interact Cardiovasc Thorac Surg 2014;18:679–82.
42. van den Brand MJ, Rensing BJ, Morel MA, et al. The effect of completeness of revascularization on event-free survival at one year in the ARTS trial. J Am Coll Cardiol 2002;39:559–64.
43. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961–72.
44. Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. Eur Heart J 2014;35:2821–30.
45. Girerd N, Magne J, Rabilloud M, et al. The impact of complete revascularization on long-term survival is strongly dependent on age. Ann Thorac Surg 2012;94:1166–72.
46. Ahn JM, Park DW, Lee CW, et al. Comparison of stenting versus bypass surgery according to the completeness of revascularization in severe coronary artery disease: patient-level pooled analysis of the SYNTAX, PRECOMBAT, and BEST Trials. JACC Cardiovasc Interv 2017;10:1415–24.
47. Farooq V, Serruys PW, Bourantas CV, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. Circulation 2013;128:141–51.
48. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
49. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
50. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
51. Pijls NH, Fearon WF, Tonino PA, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177–84.
52. Fearon WF, Bornschein B, Tonino PA, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. Circulation 2010;122:2545–50.
53. Fearon WF, Nishi T, De Bruyne B, et al. Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: three-year follow-up of the FAME 2 trial (fractional flow reserve versus angiography for multivessel evaluation). Circulation 2018;137:480–7.
54. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med 2018;379:250–9.
55. Nam CW, Mangiacapra F, Entjes R, et al. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. J Am Coll Cardiol 2011;58:1211–8.
56. Kobayashi Y, Nam CW, Tonino PA, et al. The prognostic value of residual coronary stenoses after functionally complete revascularization. J Am Coll Cardiol 2016;67:1701–11.
57. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. Eur Heart J 2018;39:2484–93.
58. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet 2018;391:31–40.
59. Schueler R, Al-Lamee R, Mahfoud F, et al. Will ORBITA change my practice? ORBITA trial: objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina. EuroIntervention 2018;14:951–4.
60. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395–407.