Is Complete Revascularisation Mandated for all Patients with Multivessel Coronary Artery Disease?

Carlo De Innocentiis, Marco Zimarino and Raffaele De Caterina

Institute of Cardiology and Centre of Excellence on Ageing, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy

Abstract

In multivessel coronary artery disease (MVCAD), myocardial revascularisation can be achieved by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), with complete revascularisation on all diseased coronary segments or with incomplete revascularisation on selectively targeted lesions. Complete revascularisation confers a long-term prognostic benefit, but is associated with a higher rate of periprocedural events compared with incomplete revascularisation. In most patients with MVCAD, the main advantage of CABG over PCI is conferred by the achievement of more extensive revascularisation. According to current international guidelines, PCI is generally preferred in single-vessel disease, low-risk MVCAD or isolated left main disease; whereas CABG is usually recommended in patients with complex two-vessel disease, most patients with three-vessel disease and/or non-isolated left main disease. In patients with MVCAD, the choice on revascularisation modality should depend on a multifactorial evaluation, taking into account not only coronary anatomy, the ischaemic burden, myocardial function, age and the presence of comorbidities, but also the adequacy of myocardial revascularisation.

Keywords

Coronary artery bypass grafting, multivessel coronary artery disease, percutaneous coronary intervention, myocardial revascularization

Disclosure: The authors have no conflicts of interest to declare.

Received: 6 July 2017 **Accepted:** 7 September 2017 **Citation:** *Interventional Cardiology Review* 2018;13(1):45–50. DOI: 10.15420/icr.2017.23.1

Correspondence: Marco Zimarino, Institute of Cardiology, "G. d'Annunzio" University of Chieti-Pescara, C/O Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy. E: m.zimarino@unich.it

Multivessel coronary artery disease (MVCAD) is defined by the presence of $\geq 50\%$ diameter stenosis of two or more epicardial coronary arteries. The presence of MVCAD indicates poorer prognosis and a significantly higher mortality than single-vessel disease. In MVCAD, revascularisation can be achieved by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).^{1,2} A comprehensive definition of the adequacy of myocardial revascularisation should take into account the size of the vessel, the angiographic and functional severity of the lesion, and the viability of the myocardial territory.³ Accordingly, anatomic and functional complete revascularisation (CR) are not always synonymous. Generally, the anatomic CR is defined by treatment of all $\geq 50\%$ stenosis in vessels of ≥ 1.5 mm diameter, whereas functional CR is defined by treatment of all lesions assessed as functionally relevant (with both invasive or non-invasive methods) in the presence of myocardial viability in the dependent territory, see *Table 1*.³

At present, only a few trials have been specifically designed to directly evaluate the adequacy of revascularisation. Current literature, mostly relying on meta-analyses of non-randomised observational studies,^{4,5} lists the adequacy of revascularisation among factors that should guide the choice of treatment strategy. In most patients with MVCAD, the main advantage of CABG over PCI seems to be conferred by the achievement of more extensive revascularisation. Most of the difference in terms of the benefit of CABG over PCI seems to derive from patients who undergo incomplete revascularisation (IR). As documented in a recent patient-level analysis, long-term mortality was similar between patients undergoing CR with either PCI or CABG, whereas it was significantly higher with IR after PCI than CABG.⁶

Although much less invasive than traditional CABG, PCI yields lower rates of CR in patients with multiple coronary lesions.⁷ IR can occasionally be implemented in addition to CABG in order to reduce complications, mainly when minimally invasive or off-pump surgery is attempted.⁸

The advantages of CR have emerged from long-term follow-up studies showing a direct relationship between the number of coronary segments treated and the reduction in cardiovascular events. IR reduces potential periprocedural complications, especially in high-risk patients; however, this comes at the price of a noticeable risk of future adverse cardiovascular events.³

Complete vs Incomplete Revascularisation in ST-elevation Myocardial Infarction

Available guidelines for myocardial revascularisation clearly state that the infarct-related artery (IRA) should be systematically treated during the initial intervention in patients presenting with ST-elevation MI (STEMI).^{1,2} Nevertheless, up to 50% of these patients have MVCAD, with angiographic documentation of significant stenosis affecting a non-IRA. The presence of MVCAD in this context identifies a subgroup of patients with more than double the risk of death at 30 days than individuals in whom the IRA is the only diseased vessel.⁹

The PCI strategies available in patients with STEMI and MVCAD include: IRA-only primary PCI with medical management of non-culprit lesions in the absence of spontaneous angina or myocardial ischaemia on stress testing; MVCAD PCI at the time of primary PCI

Table 1: Revascularisation Strategies

Revascularization Strategy	Definition
Complete anatomic revascularisation	Treatment of all coronary segments >1.5 mm with a $\geq 50\%$ DS supplying viable ischemic myocardium
Functionally-adequate revascularisation	
Lesion-specific	Treatment of all coronary segments >1.5 mm with a FFR <0.80
Myocardial specific	Treatment of all coronary segments >1.5 mm with a $\geq 50\%$ DS supplying viable ischemic myocardium
Incomplete revascularisation	When it is not possible or suitable to treat all coronary segments with significant disease (either $\geq 50\%$ DS or FFR <0.80) supplying viable myocardium

DS = diameter stenosis; FFR = fractional flow reserve. Adapted from Zimarino et al., 2013.³

(ad hoc procedure); and primary PCI of the IRA followed by staged PCI of non-IRAs later during the index hospitalisation or soon after hospital discharge.^{1,2,10}

Previous clinical practice guidelines recommended against PCI of non-culprit artery stenoses at the time of primary PCI in haemodynamically-stable patients with STEMI; however, there is now growing evidence that a strategy of multivessel PCI – either at the time of primary PCI or as a planned, staged procedure – may be beneficial and safe in selected patients with STEMI.^{1,10} A network meta-analysis has suggested that multivessel staged PCI may be associated with a better outcome than multivessel primary PCI,¹¹ but such data are still insufficient to inform a recommendation with regard to the optimal timing of non-culprit vessel PCI.^{12–14} In fact, a more recent meta-analysis showed that CR at the index procedure or as a staged procedure – whether during hospitalisation or after discharge – was associated with a reduction in the risk of adverse events, although the effect was mostly due to a reduction in the risk of urgent revascularisation. There was no difference between various strategies in the risk of all-cause mortality and spontaneous reinfarction at a median of 25 months.¹⁵ The best revascularisation strategy of the non-culprit lesions is not, therefore, well established.¹⁶

Apart from the potential overestimation of the severity of non-IRA due to heightened vascular tone,¹⁷ major concerns when attempting CR in a STEMI derive from: the prolongation of the primary PCI procedure, which will increase the volume of contrast medium used with its inherent risk of contrast-induced nephropathy;¹⁸ the risk of jeopardising viable myocardium during revascularisation of a non-IRA; and the higher risk of stent thrombosis by operating in the highly thrombogenic peri-infarction milieu. More extensive acute revascularisation in patients with STEMI may be safer in the current era due to advances in stent technology and antiplatelet therapy, mainly in higher risk subgroups.¹⁹ This might reduce the duration of hospitalisation, resource utilisation and costs.

Available studies have excluded subjects with concurrent chronic total occlusion (CTO) lesions. This condition is a further independent predictor of both early and late survival.²⁰ It is usually found in 10–15 % of patients with STEMI. The Percutaneous Intervention for Concurrent

Chronic Total Occlusions in Patients With STEMI (EXPLORE) trial recently showed that additional CTO-PCI within 1 week after primary PCI for STEMI is feasible and safe, but does not infer a benefit in terms of left ventricular function or volumes.²¹

The main points of criticism of published studies are that no ischaemia testing nor guideline-based treatments (staged PCI) were performed in the control group, leaving potentially critical lesions untreated.^{12–14} This criticism can be partially overcome thanks to the MULTIVessel Immediate Versus STaged Revascularization in Acute Myocardial Infarction (MULTISTARS AMI) trial (NCT03135275), which is currently randomising individuals to immediate or staged CR. This study intends to include approximately 1,200 patients. It has a primary composite endpoint of all-cause death, non-fatal MI and unplanned ischaemia-driven coronary revascularisation. The on-going Complete vs Culprit-only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) trial (NCT01740479) is randomising patients with STEMI to CR strategy with staged PCI of all suitable non-culprit lesions or culprit lesion-only revascularisation. The estimated enrolment is 3,900 individuals and the primary endpoint is the composite of cardiovascular death or new MI. The study should be completed in December 2018.

Although the fractional flow reserve (FFR) is infrequently evaluated in non-IRA in the setting of primary PCI, it may be helpful to assess the haemodynamic significance of potential target lesions. In this context, the FFR-guidance for complete Non-culprit Revascularization (FULL REVAS) study (NCT02862119) is currently randomising STEMI patients with MVCAD to a conservative strategy of IRA-only primary PCI or to FFR-guided ad hoc or staged revascularisation. This study will enrol an estimated 4,052 patients. The primary outcome is the combined endpoint of all-cause mortality and MI. It is anticipated that all of the data will be collected by October 2019.

In summary, based on current evidence, patients with STEMI and MVCAD should receive CR if admitted with cardiogenic shock or with persistent ischaemia after treatment of the culprit lesion. In haemodynamically-stable patients, multivessel PCI is a valuable option, either at the time of primary PCI or as a planned staged procedure during the same hospitalisation.

Complete vs Incomplete Revascularisation in Non-ST-Elevation Acute Coronary Syndromes

Non-ST-elevation acute coronary syndrome (NSTEMI) is the most frequent phenotype of acute coronary syndromes. Patients presenting with NSTEMI are a very heterogeneous group with a highly variable prognosis. In patients with NSTEMI, the optimal timing and treatment strategy in the presence of MVCAD is still unclear.^{1,22,23}

In NSTEMI, the identification of the culprit lesion can be more problematic than in STEMI, as ECG is a poor predictor of IRA and ST-depression usually does not precisely localise in the myocardial territory with evolving ischaemia. Thus, the identification of the culprit lesion is usually achieved by a combination of factors including angiographic characteristics and information from an imaging technique.

MVCAD is present in approximately 50 % of patients with NSTEMI. In such cases, the revascularisation strategy is more complex and the choice has to be made between multivessel PCI, culprit-lesion-

only PCI occasionally followed by a staged PCI, CABG or a hybrid revascularisation.¹ Immediate CR during the index procedure can be more safely performed in MVCAD than with STEMI. Multivessel stenting is potentially associated with greater contrast load and periprocedural myocardial infarction,²⁴ as well as with a higher risk of both later restenosis and stent thrombosis.²⁵ Multivessel PCI, in contrast, has been repeatedly associated with lower death and MI at mid-term follow up.^{26–28} A functional assessment of lesion severity and myocardial viability is likely to be crucial to limit intervention to coronary segments expected to provide myocardial benefit from revascularisation, thus maximising the benefit and reducing risks. The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trial has shown that FFR “re-categorises” patients otherwise classified as MVCAD by angiography, and that the treatment of lesions with a FFR <0.80 reduces long-term adverse events in comparison to the allegedly unnecessary deployment of stents in all lesions judged as severe only on the basis of angiography.²⁹ As for the assessment of an “acceptable” angiography-based IR, Genereaux et al. proposed the residual SYNTAX (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) score, documenting a significant increased risk of 1-year death or MI for a value >8.³⁰

In order to define the optimal timing of CR, the Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients (SMILE) trial randomised patients to immediate CR or to culprit-only revascularisation, followed by revascularisation of the remaining lesions during the index hospitalisation. Lower rates of major adverse cardiovascular and cerebrovascular events in the ad hoc group were documented at a 1-year follow up.³¹ However, the difference was essentially driven by the higher rate of target vessel revascularisation in the multistage group.

In some cases hybrid coronary revascularisation, combining minimally-invasive CABG to the left anterior descending (LAD) coronary artery and PCI of non-LAD arteries might offer potential advantages beyond CABG or PCI alone.³² Guidelines are inconclusive about the most appropriate timing of treatment in patients presenting with NSTEMI-ACS and MVCAD at present.^{22,23}

Concerning treatment strategy, in current guidelines CABG is recommended over PCI in patients with a baseline SYNTAX score >22, with left main or three-vessel coronary artery disease involving the proximal LAD. Ad hoc multivessel PCI, although extensively performed in low-risk patients (see Figure 1), is associated with increased risk of periprocedural damage and contrast-induced nephropathy. In patients with a SYNTAX score ≤22, a staged PCI aimed at treating all significant coronary segments supplying viable myocardium after an initial PCI directed only to the culprit lesion might be the strategy of choice as it reduces the procedural risk, dilutes the amount of contrast medium over time and allows the functional evaluation of “presumed non-culprit” lesion-related myocardial territories, as well as reducing patients’ symptoms.^{1,22,23}

Complete vs Incomplete Revascularisation in Stable Coronary Artery Disease

Stable coronary artery disease (SCAD) is generally characterised by episodes of reversible myocardial demand/supply mismatch related to ischaemia. Episodes are usually inducible by exercise, emotion or other stress but may also occur spontaneously. SCAD also includes

Figure 1: An 87-year-old Patient with Previous Stroke Admitted for Non-ST-elevation Acute Coronary Syndrome

(A, B) Coronary angiography documented a left main bifurcation critical lesion (black arrows) and (C) severe lesions in mid right coronary artery (white arrow), which was distally occluded (*). (D, E) The risk of cardiac surgery was considered unacceptable so the patient underwent provisional drug-eluting stenting (E, dotted lines) on the left main with final kissing balloon, while the right coronary artery was left untreated. After the procedure, creatinine clearance remained within normal limits. LAD = left anterior descending; LCx = left circumflex; LM = left main; RCA = right coronary artery.

the stabilised, often asymptomatic, phases following an acute coronary syndrome.^{1,33,34}

Guideline-directed optimal medical therapy (OMT) is recommended for all patients with SCAD because of the reduced risk of death and MI and the improvement of symptoms; however, 50 % of medically-treated patients have persistent symptoms within 1 year.³⁴ The principal goal of revascularisation here is the relief of ischaemia to improve quality of life and exercise capacity, to reduce the amount of antianginal drugs, and ultimately to improve prognosis over and above the beneficial effects of medical treatment. Most recent international guidelines recommend myocardial revascularisation for patients with SCAD in the presence of flow-limiting lesions and limiting symptoms if individuals are unresponsive to medical treatment. There is substantial evidence supporting the association between the extent of myocardial ischaemia and the risk of cardiovascular events, as well as the direct relationship between the burden of ischaemia and the severity of prognosis.^{1,33,34}

The most valuable source of data on an adequately-sized population of patients who have undergone either CABG or PCI is the randomised SYNTAX trial.³⁵ This trial compared drug-eluting stent-PCI with CABG in patients with stable MVCAD.⁷ Patients were treated with the intention of achieving anatomic CR of all vessels ≥1.5 mm in diameter with stenosis ≥50 %. No functional evaluation was available. Individuals with less extensive MVCAD, as documented by a low (<22) SYNTAX score, had similar 1- and 3-year major adverse cardiac or cerebrovascular event rates after PCI and CABG. A higher 3-year risk of major adverse cardiac or cerebrovascular events has been documented after PCI compared to CABG for patients with intermediate (23–32) and high (>32) scores.³⁶

Robust data now recommend functional evaluation of reversible myocardial ischaemia prior to elective revascularisation. It is now well documented that revascularisation of lesions that are not producing significant ischaemia confers a cost in terms of adverse outcomes.³⁷ Here, OMT is a better alternative. Conversely, patients with moderate-to-severe

Figure 2: A 67-year-old Patient with Diabetes Admitted for Recurrent Chest Pain and had a Positive Exercise Test

Echocardiogram showed a normal ventricular function with a mild-to-moderate mitral regurgitation. Coronary angiography showed: (A) critical stenosis (arrowhead) of the right coronary artery (RCA); and (B) severe lesions of both the mid left anterior descending (LAD) (arrows) and the left circumflex (LCx) (*) artery. The SYNTAX score was <22. The patient underwent fractional flow reserve assessment on non-culprit lesions. Fractional flow reserve on the LAD artery was 0.75 and on the left LCx was 0.93. (C, D) Percutaneous coronary intervention with a drug-eluting stent was performed on both RCA and LAD (dotted lines), while the LCx lesion was left untreated. The patient was discharged on dual antiplatelet and statin therapy. LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery.

symptoms and/or extensive ischaemia should be strongly considered for revascularisation therapy. Despite this recommendation, the majority of patients with SCAD undergoing elective PCI have no preceding documentation of myocardial ischaemia.³⁸⁻⁴⁰

In this setting, accurate non-invasive (multidetector CT, stress echocardiography, perfusion scintigraphy, stress-MRI and/or PET-CT) or invasive (FFR, intravascular ultrasound, optical coherence tomography scan) identification of the lesions deemed responsible for ischaemia might improve outcomes in patients undergoing revascularisation. The availability and extensive validation of the FFR now offer a surrogate for ischemia and thereby represent an alternative to non-invasive stress imaging (see Figure 2).

In the FAME study, patients who had been listed for multivessel PCI were randomised to angiographically- or FFR-guided stenting (using a FFR cut-off value of 0.80).⁴¹ The FFR-guided strategy was found to be both cost-saving and cost-effective.⁴² The strategy was also associated with a significant reduction in the occurrence of the composite primary clinical endpoint of death, nonfatal MI and repeat revascularisation at 1 year ($p=0.02$), as well as a significant reduction in mortality plus MI at 2 years ($p=0.02$).⁴³

A functional evaluation of lesion severity may now be obtained by non-invasive coronary imaging. The Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) trial documented that FFR can be non-invasively obtained with CT angiography and, together with CT itself, is associated with improved diagnostic accuracy and discrimination compared with CT alone for the diagnosis of haemodynamically-significant coronary artery disease.⁴⁴ Finally, cardiac magnetic resonance is increasingly being utilised in ischaemic heart disease for both the detection of lesions producing ischaemia⁴⁵ and the identification of myocardial viability.⁴⁶

The importance of functional evaluation has been well demonstrated by the results of the FAME 2 trial.⁴⁷ About 900 SCAD patients with functionally-significant stenosis ($FFR \leq 0.80$) were randomly assigned to either OMT or OMT plus FFR-guided PCI, with predominant use of drug-eluting stents (>97 %). The study was stopped prematurely by the Data Safety Monitoring Board due to the significantly lower incidence of a composite of death, MI and urgent revascularisation favouring FFR-guided PCI plus OMT (4.3 %) as compared with OMT alone (12.7 %, $p<0.001$), although the result was driven by the “soft” component of urgent revascularisation. The on-going International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (NCT01471522) should finally answer the fundamental question of whether myocardial revascularisation in addition to OMT in patients with moderate to severe ischaemia is associated with survival benefit compared with OMT alone.

Another point of criticism in achieving CR is the presence of CTO, which is frequently documented in patients with MVCAD (between 18 % and 52 % of cases).^{1,48} There is little consensus as to whether such lesions should be routinely treated by PCI.^{49,50} Potential benefits of successful PCI may include symptom relief, resolution of ischaemia and functional improvement. CTO-PCI has lower success rates than PCI of non-CTO lesions, with potentially serious complications; however, in high-volume centres with specific expertise, contemporary success rates of 80–90 % have been reported.^{51,52} In the setting of SCAD there is a clear lack of evidence, with randomised data derived from two unpublished trials. The optimal medical therapy with or without stenting for chronic coronary occlusion (Drug-Eluting Stent Implantation Versus Optimal Medical Treatment in Patients with Chronic Total Occlusion [DECISION-CTO], NCT01078051), although with some relevant limitations and despite a high technical success rate, failed to demonstrate a benefit with CTO-PCI on top of OMT. Recently released data from the Randomized Multicentre Trial to Evaluate the Utilization of Revascularization or Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusion (EuroCTO, NCT01760083) showed that CTO-PCI improved quality of life, as assessed by the standardised Seattle Angina Questionnaire, in patients undergoing CTO-PCI. This benefit was coupled with a low rate of periprocedural complications. Further studies are necessary to assess the impact of PCI-CTO on symptom improvement and prognosis, especially in selected populations such as patients with high ischaemic burden. Currently, the use of CTO-PCI to improve quality of life should be restricted to selected patients in high-volume centres with specific expertise.

Current guidelines recommend CABG over PCI in patients with three-vessel disease, non-isolated left main disease or with involvement of the proximal LAD artery plus one other major coronary artery. CABG has to be considered in patients when in-stent restenosis recurrence is located on the LAD, where several devices have evenly failed.²⁵ The benefit obtained with CABG seems to be larger with a systematic utilisation of the left internal mammary artery (IMA), an atherosclerosis-free conduit with patency rates >90 % at 10 years.⁵³ Nevertheless, the Arterial Revascularization Trial (ART) recently failed to document any 5-year benefit for patients with MVCAD who received bilateral IMA as compared with single left IMA utilisation.⁵⁴

The choice between revascularisation techniques should be based on several factors, including anatomical and clinical features.

It requires a multidisciplinary approach to decision making by the heart team.

Conclusions

The extent of myocardial revascularisation is a major determinant of survival among MVCAD patients. Based on available evidence, revascularisation with either CABG or PCI has similar benefits in terms of survival in patients with MVCAD, with a prognostic advantage for CABG in the presence of more extensive disease and in patients with diabetes.

Both PCI and CABG should always aim at functional CR. Patients with diabetes and extensive coronary disease have a reduced

risk of death and MI when they have undergone CABG, which attains CR more frequently than PCI. PCI is better suited in patients presenting with acute coronary syndrome and a suitable anatomy, where CR can be achieved through staged procedures that allow risk containment and the evaluation of both myocardial viability and lesion relevance.

The adequacy of myocardial revascularisation should be the priority when choosing between PCI and CABG in patients with MVCAD. A concerted multidisciplinary decision-making process should guide physicians, taking into account anatomy, left ventricular function, the extent of inducible ischaemia, myocardial viability, comorbidities and patients' informed choices. ■

1. Authors/Task Force Members, Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;**35**:2541–619. DOI: 10.1093/eurheartj/ehu278; PMID: 25173339.
2. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2016;**133**:1135–47. DOI: 10.1161/CIR.0000000000000336; PMID: 26490017.
3. Zimarino M, Curzen N, Cicchitti V, De Caterina R. The adequacy of myocardial revascularization in patients with multivessel coronary artery disease. *Int J Cardiol* 2013;**168**:1748–57. DOI: 10.1016/j.ijcard.2013.05.004; PMID: 23742927.
4. 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. DOI: 10.1016/j.jacc.2013.05.033; PMID: 23747787.
5. Zimarino M, Ricci F, Romanelli M, et al. Complete myocardial revascularization confers a larger clinical benefit when performed with state-of-the-art techniques in high-risk patients with multivessel coronary artery disease: a meta-analysis of randomized and observational studies. *Catheter Cardiovasc Interv* 2016;**8**:3–12. DOI: 10.1002/ccd.25923; PMID: 25846673.
6. 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. DOI: 10.1016/j.jcin.2017.04.037; PMID: 28728654.
7. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013;**381**:629–38. DOI: 10.1016/S0140-6736(13)60141-5; PMID: 23439102.
8. Zimarino M, Gallina S, Di Fulvio M, et al. Intraoperative ischemia and long-term events after minimally invasive coronary surgery. *Ann Thorac Surg* 2004;**78**:135–41. DOI: 10.1016/j.athoracsur.2003.12.030; PMID: 15223418.
9. 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. DOI: 10.1001/jama.2014.15095; PMID: 25399277.
10. Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–619. DOI: 10.1093/eurheartj/ehs215; PMID: 2292241.
11. Vlaar PJ, Mahmoud KD, Holmes DR, et al. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis. *J Am Coll Cardiol* 2011;**58**:692–703. DOI: 10.1016/j.jacc.2011.03.046; PMID: 21816304.
12. Wald DS, Morris JK, Wald NJ, et al. The PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;**369**:1115–23. DOI: 10.1056/NEJMoa1305520; PMID: 23991625.
13. Kelly DJ, McCann GP, Blackman D, et al. Complete Versus Culprit-Lesion only Primary PCI Trial (CVLPRI): a multicentre trial testing management strategies when multivessel disease is detected at the time of primary PCI: rationale and design. *EuroIntervention* 2013;**8**:1190–8. DOI: 10.4244/EIJV8I10A183; PMID: 23425543.
14. Engstrom T, Kelbaek H, Helqvist S, et al. DANAMI-3-PRIMULTI Investigators. 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. DOI: 10.1016/S0140-6736(15)60648-1; PMID: 26347918.
15. Elgendy IY, Mahmoud AN, Kumbhani DJ, et al. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2017;**10**:315–24. DOI: 10.1016/j.jcin.2016.11.047; PMID: 28231899.
16. Patel MR, Dehmer GJ, Hirshfeld JW, et al. American College of Cardiology Foundation/American College of Cardiology Foundation Appropriate Use Criteria Task Force; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association of Thoracic Surgery; American Heart Association; American Society of Nuclear Cardiology; Society of Cardiovascular Computed Tomography. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2012;**59**:857–81. DOI: 10.1016/j.jacc.2011.12.001; PMID: 22296741.
17. Hanratty CG, Koyama Y, Rasmussen HH, et al. Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization. *J Am Coll Cardiol* 2002;**40**:911–6. DOI: 10.1016/S0735-1097(02)02049-1; PMID: 12225715.
18. Sgura FA, Bertelli L, Monopoli D, et al. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. *Circ Cardiovasc Interv* 2010;**3**:491–8. DOI: 10.1161/CIRCINTERVENTIONS.110.955310; PMID: 20923986.
19. Patti G, De Caterina R, Abbate R, et al. Working Group on Thrombosis of the Italian Society of Cardiology. Platelet function and long-term antiplatelet therapy in women: is there a gender-specificity? A 'state-of-the-art' paper. *Eur Heart J* 2014;**35**:2213–23b. DOI: 10.1093/eurheartj/ehu279; PMID: 25024407.
20. Claessen BE, Dangas GD, Weisz G, et al. Prognostic impact of a chronic total occlusion in a non-infarct-related artery in patients with ST-segment elevation myocardial infarction: 3-year results from the HORIZONS-AMI trial. *Eur Heart J* 2012;**33**:768–75. DOI: 10.1093/eurheartj/ehs471; PMID: 22240495.
21. Henriques JP, Hoehers LP, Ramunddal T, et al. EXPLORE Trial Investigators. Percutaneous Intervention for Concurrent Chronic Total Occlusions in Patients With STEMI: The EXPLORE Trial. *J Am Coll Cardiol* 2016;**68**:1622–32. DOI: 10.1016/j.jacc.2016.07.744; PMID: 27712774.
22. Amsterdam EA, Wenger NK, Brindis RG, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**64**:e139–228. DOI: 10.1016/j.jacc.2014.09.017; PMID: 25260718.
23. Roffi M, Patrono C, Collet JP, et al. Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 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. DOI: 10.1093/eurheartj/ehv320; PMID: 26320110.
24. Zimarino M, Cicchitti V, Genovesi E, et al. Isolated troponin increase after percutaneous coronary interventions: does it have prognostic relevance? *Atherosclerosis* 2012;**221**:297–302. DOI: 10.1016/j.atherosclerosis.2011.10.010; PMID: 22062591.
25. Ajani AE, Waksman R, Zimarino M, et al. Device selection in the treatment of in-stent restenosis with and without radiation (from the Gamma Radiation Trials). *Am J Cardiol* 2002;**89**:137–44. DOI: 10.1016/S0002-9149(01)02189-0; PMID: 11792331.
26. 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. DOI: 10.1161/CIRCULATIONAHA.106.612267; PMID: 16702469.
27. Hannan EL, Wu C, Walford G, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv* 2009;**2**:17–25. DOI: 10.1016/j.jcin.2008.08.021; PMID: 19463393.
28. Shishenbor 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. DOI: 10.1016/j.jacc.2006.10.054; PMID: 17320742.
29. 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. DOI: 10.1016/j.jacc.2009.11.096; PMID: 20579537.
30. Gnreux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. *J Am Coll Cardiol* 2012;**59**:2165–74. DOI: 10.1016/j.jacc.2012.03.010; PMID: 22483327.
31. 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. DOI: 10.1016/j.jacc.2015.10.082; PMID: 26796390.
32. Puskas JD, Halkos ME, DeRose JJ, et al. Hybrid coronary revascularization for the treatment of multivessel coronary artery disease: a multicenter observational study. *J Am Coll Cardiol* 2016;**68**:356–65. DOI: 10.1016/j.jacc.2016.05.032; PMID: 27443431.
33. Fihn SD, Gardin JM, Abrams J, et al. American College of Cardiology Foundation; American heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Study for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;**60**:e44–e164. DOI: 10.1016/j.jacc.2012.07.013; PMID: 23182125.
34. Task Force Members, Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;**34**:2949–3003. DOI: 10.1093/eurheartj/ehs296; PMID: 23996286.
35. Serruys PW, Morice MC, Kappetein AP, et al. The SYNTAX Investigators. Percutaneous coronary intervention versus

- coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–72. DOI: 10.1056/NEJMoa0804626; PMID: 19228612.
36. 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. DOI: 10.1161/CIRCULATIONAHA.113.001803; PMID: 23766350.
37. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003;**107**:2900–7. DOI: 10.1161/01.CIR.0000072790.23090.41; PMID: 12771008.
38. Chan PS, Patel MR, Klein LW, et al. Appropriateness of percutaneous coronary intervention. *JAMA* 2011;**306**:53–61. DOI: 10.1001/jama.2011.916; PMID: 21730241.
39. Wijns W, Kolh P. Appropriate myocardial revascularization: a joint viewpoint from an interventional cardiologist and a cardiac surgeon. *Eur Heart J* 2009;**30**:2182–5. DOI: 10.1093/eurheartj/ehp315; PMID: 19684022.
40. Lin GA, Dudley RA, Lucas FL, et al. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008;**300**:1765–73. DOI: 10.1001/jama.300.15.1765; PMID: 18854538.
41. 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**(3):213–24. DOI: 10.1056/NEJMoa0807611; PMID: 19144937.
42. 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. DOI: 10.1161/CIRCULATIONAHA.109.925396; PMID: 21126973.
43. Pijls NH, Fearon WF, Tonino PA, et al. Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) Study Investigators. 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. DOI: 10.1016/j.jacc.2010.04.012; PMID: 20537493.
44. Min JK, Leipsic J, Pencina MJ, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;**308**:1237–45. DOI: 10.1001/2012.jama.11274; PMID: 22922562.
45. Watkins S, McGeoch R, Lyne J, et al. Validation of magnetic resonance myocardial perfusion imaging with fractional flow reserve for the detection of significant coronary heart disease. *Circulation* 2009;**120**:2207–13. DOI: 10.1161/CIRCULATIONAHA.109.872358; PMID: 19917885.
46. Kirschbaum SW, Springeling T, Boersma E, et al. Complete percutaneous revascularization for multivessel disease in patients with impaired left ventricular function: pre- and post-procedural evaluation by cardiac magnetic resonance imaging. *JACC Cardiovasc Interv* 2010;**3**:392–400. DOI: 10.1016/j.jcin.2010.01.011; PMID: 20398866.
47. 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. DOI: 10.1056/NEJMoa1205361; PMID: 22924638.
48. Jeroudi OM, Alomar ME, Michael TT, et al. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. *Catheter Cardiovasc Interv* 2014;**84**(4):637–43. DOI: 10.1002/ccd.25264; PMID: 24142769.
49. Ng AK, Shah PB, Williams DO. Percutaneous revascularization of chronic total coronary occlusion: for whom? *Circ Cardiovasc Interv* 2017;**10**:e005512. DOI: 10.1161/CIRCINTERVENTIONS.117.005512; PMID: 28615235; epub ahead of press.
50. Tamburino C, Capranzano P, Capodanno D, et al. Percutaneous recanalization of chronic total occlusions: wherein lies the body of proof? *Am Heart J* 2013;**165**:133–42. DOI: 10.1016/j.ahj.2012.10.017; PMID: 23351815.
51. Morino Y, Kimura T, Hayashi Y, et al. J-CTO Registry Investigators. In-hospital outcomes of contemporary percutaneous coronary intervention in patients with chronic total occlusion insights from the J-CTO Registry (Multicenter CTO Registry in Japan). *JACC Cardiovasc Interv* 2010;**3**:143–51. DOI: 10.1016/j.jcin.2009.10.029; PMID: 20170870.
52. Galassi AR, Tomasello SD, Reifart N, et al. In-hospital outcomes of percutaneous coronary intervention in patients with chronic total occlusion: insights from the ERCTO (European Registry of Chronic Total Occlusion) registry. *EuroIntervention* 2011;**7**(4):472–9. DOI: 10.4244/EIJV7I4A77; PMID: 21764666.
53. Cameron A, Davis KB, Green G, Schaff HV. Coronary bypass surgery with internal-thoracic-artery grafts—effects on survival over a 15-year period. *N Engl J Med* 1996;**334**:216–9. DOI: 10.1056/NEJM199601253340402; PMID: 8531997.
54. Taggart DP, Altman DG, Gray AM, et al. ART Investigators. Randomized trial of bilateral versus single internal-thoracic-artery grafts. *N Engl J Med* 2016;**375**:2540–9. DOI: 10.1056/NEJMoa1610021; PMID: 27959712.