ECRONICON OPEN ACCESS

EC CARDIOLOGY
Review Article

Patients with ST-Segment-Elevation Myocardial Infarction and Multi-Vessel Disease: Are we Ready for Complete Coronary Revascularization Yet?

Igor Kranjec*

Department of Cardiology, University Medical Centre, Ljubljana, Slovenia

***Corresponding Author:** Igor Kranjec, Department of Cardiology, University Medical Centre, Ljubljana, Slovenia.

Received: October 28, 2019; **Pubished:** November 13, 2019

Abstract

ST-segment elevation myocardial infarction (STEMI) is associated with multi-vessel coronary disease (MVD) in up to 50% of cases. The severity of MVD varies; however, the presence of three-vessel disease is one of the strongest predictors of patients' mortality. The rationale for complete revascularization is to reduce global ischemic burden and prevent further cardiovascular (CV) complications. Apart from the timely percutaneous coronary intervention (PCI) of the culprit lesion, there is still some uncertainty how to best treated non-culprit arteries. Therefore, currently available scientific data are reviewed and compared with the existing European Society of Cardiology guidelines. Randomized controlled trials have confirmed that complete revascularization reduces the risk of future CV events. Revascularization of the non-culprit arteries should follow a careful patient-tailored approach. High-risk groups of STEMI patients with MVD should be identified and non-culprit PCI carried out at the appropriate time. In stabilized patients, there is little reason not to treat tight non-culprit lesions, if proximal and easily accessible, at the index PCI. In contrast, complex non-culprit lesions such as left main or bifurcations should be revascularized separately during the index hospitalization or shortly thereafter.

Keywords: *ST-Segment-Elevation Myocardial Infarction; Vessel Disease; Coronary Revascularization*

Introduction

Timely recognition and revascularization of the culprit lesion is the primary goal of the interventional cardiologist treating patients with ST-segment elevation myocardial infarction (STEMI) [1,2]. However, these patients are often found to have multi-vessel coronary artery disease (MVD) that unfavorably affects their prognosis. For example, the number of diseased coronary arteries considerably increases mortality in STEMI patients, thereby doubling the risk of death in short- and long-term [3]. There is still some uncertainty how to best manage diseased non-culprit arteries, namely which lesions to treat and at what time. The common clinical belief is that the option of "optimal medical treatment only" is not appropriate. Consequently, when doubts regarding the significance of non-culprit lesions arise during the primary percutaneous coronary intervention (PCI), patients are usually sent for functional tests to assess inducible ischemia rather than being left on medical treatment alone [4]. Current European Society of Cardiology (ESC) guidelines are rather vague about the revascularization strategy despite the gathered scientific evidence. They recommend that 1) routine revascularization of non-culprit arteries should be considered before hospital discharge (class IIa, level A) and 2) in cardiogenic shock, routine revascularization of non-culprit arteries during the primary PCI is not recommended (class III, level B) [2].

In this review, the strategy of complete coronary revascularization (CR) on top of the primary PCI will be critically appraised. The basic dilemma remains: do we have enough evidence to change the existing ESC recommendations or is it more appropriate to identify patients' subgroups who benefit most from CR.

Importance of the multi-vessel coronary artery disease in patients with ST-segment elevation myocardial infarction

In up to 50% of cases, STEMI is associated with MVD, defined as a ≥ 50% stenosis of the vessel lumen in at least one non-culprit artery [3]. In the well-known CADILLAC trial, primary PCI was performed in 2082 patients with acute myocardial infarction (MI). One-vessel (1-VD), two-vessel (2-VD) and three-vessel disease (3-VD) were observed in 51.2%, 33.2% and 15.6%, respectively [5]. Chronic total occlusion (CTO) of the non-culprit artery was found in 10 - 15% of STEMI patients [3].

By one year, the cumulative incidence of death for patients with 1-VD, 2-VD and 3-VD was 3.2%, 4.4% and 7.8%, respectively ($p = 0.003$). By multivariable analysis, the presence of 3-VD was the strongest predictor of one-year death (hazard risk 2.60, $p = 0.009$) [5].

Obstructive coronary lesions and complete coronary revascularization

Atherosclerotic lesions in humans typically form over the course of years to decades. Lesions that reduce the luminal diameter by more than 50%, when compared with adjacent segments judged to be normal, are considered to be flow limiting when myocardial oxygen rises [6]. Indeed, since the development of coronary artery bypass grafting (CABG) in 1968, the presence of a 50% diameter stenosis has been used as a threshold for revascularization. At the present time, however, ≥70% stenosis on visual estimation is reported to be a standard criterion used in coronary angiography to establish the presence of obstructive coronary artery disease (CAD) [7]. Yet, studies in man suggest that even quantitative analysis cannot predict the physiologic significance of individual coronary lesions. Fractional flow reserve (FFR) is a technique used in coronary catheterization to measure pressure differences across a coronary artery narrowing to determine the likelihood that the stenosis is related to myocardial ischemia [8]. Evidence of ischemia in the form of an FFR of ≤0.80 is usually considered diagnostic [9].

Guidelines have warned against treating multiple diseased arteries in the acute STEMI setting, particularly when the secondary sites are not clearly causing ongoing hemodynamic instability. This caution is based on concern that treating the non-culprit lesions could potentially jeopardize healthy heart muscle when the recovering areas of the injured myocardium are at their weakest [10]. However, during STEMI there is no healthy vessel, even in cases in which thrombosis is absent. It is possible that non-obstructive lesions associated with an FFR > 0.80 may still contain morphologic features consistent with unstable plaques, which confer an increased risk of recurrent events [11].

The rationale for CR in patients with STEMI and MVD is to reduce global ischemic burden and prevent further cardiovascular (CV) events [3]. Currently, patients are defined as having CR if revascularization was achieved in every significantly diseased (i.e. diameter stenosis ≥70%) epicardial coronary artery including major branches with diameter > 2.0 mm [9,12], or in moderately diseased vessels (i.e. diameter stenosis 50 - 69%) with FFR ≤ 0.80 [9]. Alternatively, incomplete revascularization (IR) is indicated by the residual SYNTAX score > 8 [13]. The prognostic impact of IR after PCI has been inconsistent between studies, partly because the universal definition of IR is not available. There is no doubt that extensive IR is likely to be hazardous and associated with considerable residual angina burden, myocardium at risk and adverse CV events [11]. In the BleeMACS registry, that enrolled 4520 MI patients, CR reduced one-year mortality (5.3% vs. 13.8% in IR, $p < 0.001$) and reinfarction (4.9% vs 17.4% in IR, $p < 0.001$) [14]. In STEMI patients, the risk for adverse events, in particular death or reinfarction, is higher in the first days and weeks and then decreases after the first month. Achieving CR as soon as possible may help reduce the risk for death and MI when this risk is higher [15]. Nevertheless, data from the large meta-analysis based almost entirely on registries suggest that a strategy of staged CR may improve outcome compared with both CR performed during the index procedure or culprit-only strategy [16].

Culprit-only vs. complete coronary revascularization: randomized controlled trials and observation studies

Randomized controlled trials and observation studies are both needed to provide a scientific basis for clinical decisions. The researchers and clinicians must be familiar with strength and weaknesses of both methods. A randomized trial is truly experimental with random allocation of the participants to exposure. The patient material is homogeneous and well defined, treatment and outcome measurements

are well controlled. Correctly performed, the randomized trial has a high internal validity. Major limitations include restrictive inclusion and exclusion criteria leading to highly selected population, insufficient power to define effects in subgroups and failure to compare new therapies with the best existing therapies. Even a well conducted and internally valid trial may therefore not be externally valid (i.e. generalizable) [17].

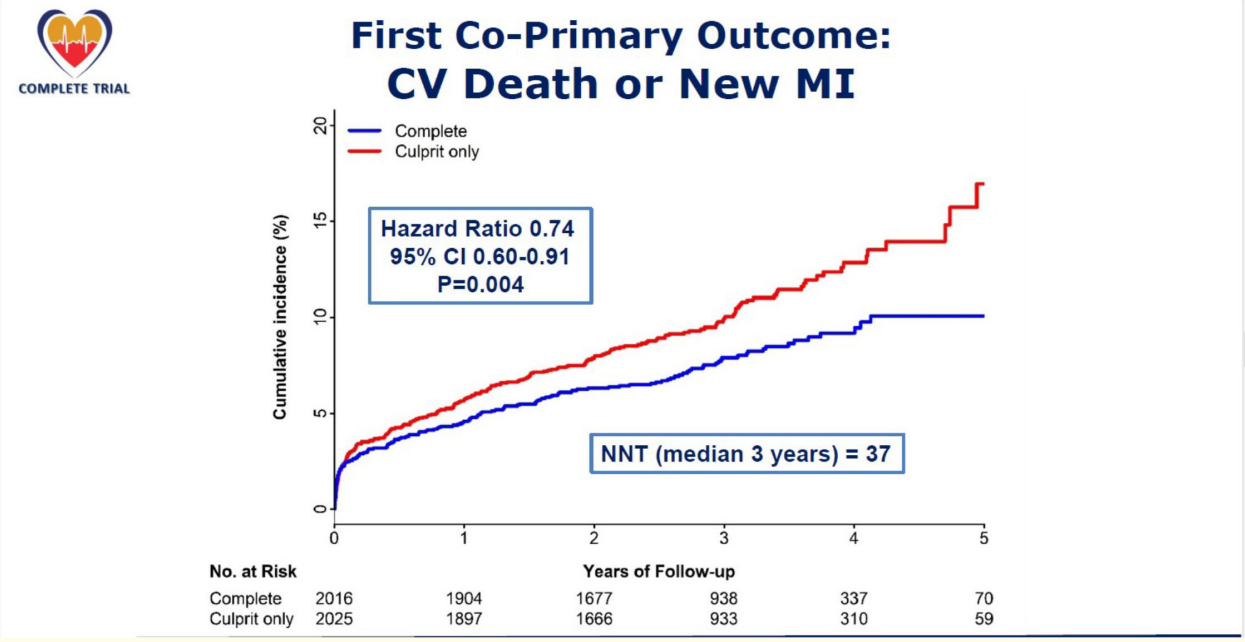
From the year 2009 to 2017, we found six randomized controlled trials that had altogether included 2.832 patients with STEMI and concomitant MVD [18-23]. The exclusion criteria were advanced age, shock, renal insufficiency, limited life expectancy, significant left main coronary artery stenosis, previous or planned CABG and in one trial CTO of the con-culprit artery [19]. Primary endpoint used to be some combination of major adverse events (all-cause or CV death, recurrent MI, refractory angina, CVA, ischemia-driven revascularization and CABG). A sufficient sample size was usually chosen to give the trial 80% power to detect approximately 20% lower risk of primary endpoint in tested population. Follow-up period ranged from 12 months to a mean of 3.9 years. In all the trials, CR strategy as compared with culprit-only strategy consistently reduced the occurrence of the primary endpoint (hazard risk 0.35 to 0.56; $p < 0.001$ to $p = 0.008$). This finding was mainly supported by a reduction in subsequent revascularization. PRAMI trial also reported that preventive PCI of the non-culprit lesions reduced the risk of CV death (hazard risk 0.35) and non-fatal MI (hazard risk 0.32), though the study was not empowered for secondary endpoints or single components [19].

Recently, the long awaited "Complete versus Culprit-only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) trial" has been published in the New England Journal of Medicine [9]. In this large trial, 4041 patients with STEMI and MVD, who had undergone successful culprit artery PCI, were randomized to complete revascularization or culprit-only PCI. Patients with planned revascularization of non-culprit lesions, scheduled CABG, associated co-morbidities reducing life expectancy to less than five years, any factor precluding five-year follow-up, or prior CABG were excluded from the trial. The first co-primary outcome was the composite of CV death or MI and the second co-primary outcome was the aggregate of CV death, MI or ischemia-driven revascularization. A sample of 4000 patients was expected to give the trial 80% and 89% power, respectively, to detect a 22% hazard risk reduction, assuming an event rate of 5% per year in the culprit-only PCI group. At a median follow-up of three years, the complete revascularization as compared with the culprit-only PCI reduced the first co-primary outcome by 26% ($p = 0.004$, NNT = 37) and the second co-primary outcome by 49% ($p < 0.001$, NNT = 13) (Figure 1). The benefit of complete revascularization was similar in those undergoing non-culprit lesion PCI during index hospitalization or several weeks after hospital discharge. Moreover, there were no significant complication related to the extensive PCI such as bleeding, stent thrombosis, or contrast-associated kidney injury.

Although generally providing a lower evidence-level than randomized trials, observational studies can make an important contribution to the evidence base when the study outcomes are clinically important and the populations involved are representative. Non-randomized prospective registries document the treatment and outcomes for consecutive patients in clinical practice. Therefore, data are gained from a 'real-world' selection of patients, many of whom would be excluded from randomized trials, in a variety of clinical settings. If higher-risk patients are not adequately represented in randomized, registries have an important role in validating trial findings in groups that are excluded or under-represented. However, it is important that the potential confounding associated with the analysis of non-randomized populations is considered. Standardized methodologies are crucial to the quality of registry data and facilitate comparisons between the findings of different registries [24].

Observation studies based on large registries are particularly interesting when focusing on hard endpoints, such as all-cause and CV mortality. The effect of CR on all-cause deaths in patients with STEMI and MVD was tested in three large studies [14,25,26]; the beneficial effect of CR, however, remained elusive. The long-term results seemed encouraging initially. Dimitriou-Leen., *et al*. reported mortality 12% in CR group vs. 24% in IR group ($p < 0.001$) during a median follow-up of 6.7 years [25]. Furthermore, Quadri., *et al*. reported one-year mortality 5.3% in CR group vs. 13.8% in IR group ($p < 0.001$) [14]. Finally, Iqbal., *et al*. reported three-year mortality 10.8% in CR group vs. 13.1% in IR group ($p = 0.047$) [26]. However, multivariable adjusted analyses indicated that CR was not independently associated with mortality confirming unforeseen confounding factors.

1A



1B

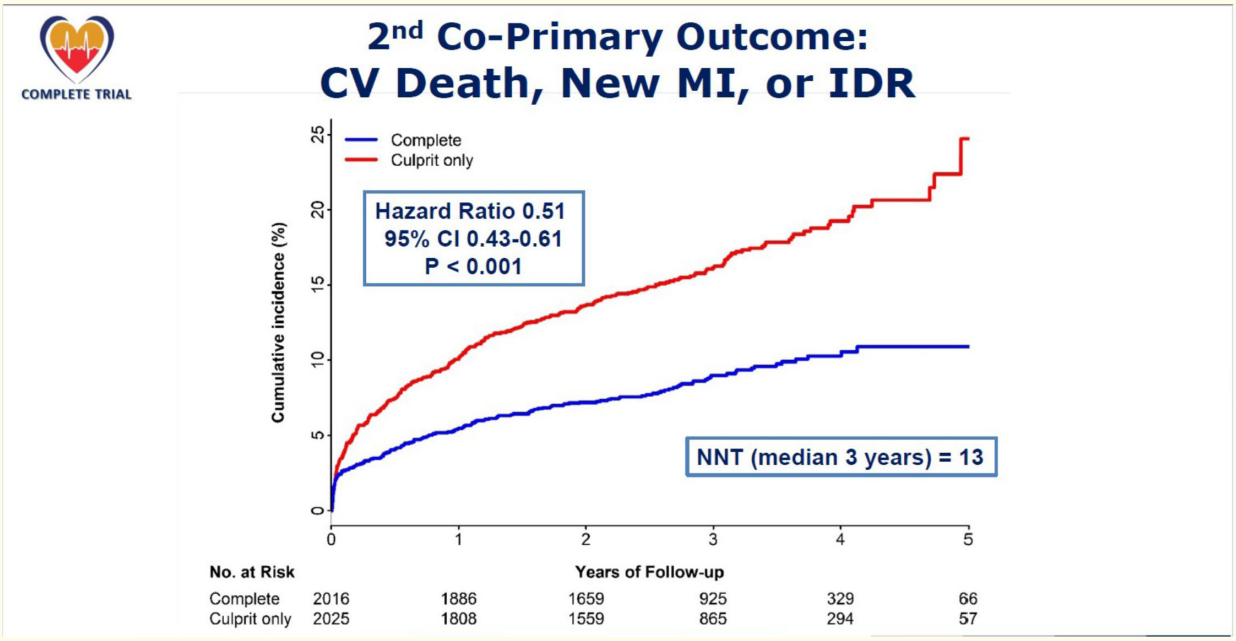


Figure 1: *Cumulative incidence of the first and secondary co-primary outcomes. Panels A and B show Kaplan-Meier estimates of the cumulative incidence of the first co-primary outcome (cardiovascular death or new myocardial infarction) and the second co-primary outcome (cardiovascular death, new myocardial infarction, or ischemia-driven revascularization), respectively. Source [9].*

When to revascularize non-culprit arteries

According to accumulated scientific data, CR improves outcomes in patients with STEMI and MVD. However, timing of the non-culprit artery PCI has remained uncertain. ESC guidelines state that routine revascularization of non-culprit lesions should be considered before hospital discharge (Class IIa, Level of recommendation A), while in cardiogenic shock non-culprit artery PCI is discouraged (Class III, Level of recommendation B). In randomized controlled trials, timing of non-culprit artery PCI has only been addressed in post-hoc analyses. Apparently, CR should be performed during the index hospitalization or shortly thereafter (9,18). Similarly, staged PCI of the non-culprit diseased artery seems to be the best option as claimed by registry observations [12,26]. Most of the meta-analyses also favor staged non-culprit PCI (16,27,28). Pasceri., *et al*. [15] identified 11 trials studying the revascularization in STEMI and MVD including 3561 patients. Surprisingly, meta-regression showed that performing CR at the time of primary PCI was associated with better outcomes ($p = 0.016$), whereas the five trials performing only staged revascularization did not show any significant benefit in either total mortality (RR: 1.02; 95% CI: 0.65 to 1.62; $p = 0.87$) or MI (RR: 1.04; 95% CI: 0.48 to 1.68; $p = 0.86$).

Safety of percutaneous coronary interventions on non-culprit diseased arteries

CR attempts can improve outcomes compared with a culprit-only strategy in patients being treated with primary PCI who have MVD presenting with STEMI. However, there is concern that non-culprit PCI may cause additional MI. Early recurrent MI cannot be reliably ascertained in trails evaluating CR when performed during the same sitting as the primary PCI [29]. However, contrast-enhanced cardiovascular magnetic resonance data have confirmed that non-culprit PCI is associated with additional MI. Those type 4a MI are, fortunately, relatively infrequent and generally small [30]. Furthermore, data from recent COMPLETE trial have shown that non-culprit PCI do not increase the risk of major bleeding, stroke, contrast-associated acute kidne injury, or stent thrombosis [9].

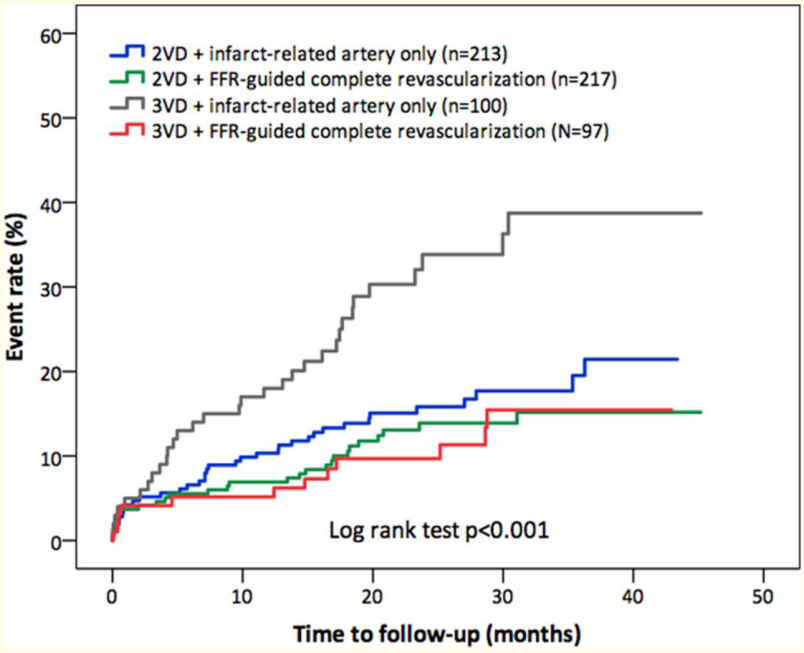
Patient-tailored revascularization

The severity of MVD varies, the location of the non-culprit diseased artery can be proximal or more distal and the CAD may involve different number of diseased vessels; these factors represent various extents of ischemic burden that may influence the benefit of CR on outcome. Therefore, the non-culprit artery PCI should usually follow a careful patient-tailored approach. In stabilized patients, there is little reason not to treat unambiguous tight non-culprit lesions, if proximal and easily accessible. In contrast, patients with complex non-culprit lesions such as lef main or complex bifurcation should be revascularized in a staged procedure [3]. The presence of untreated proximal left anterior descending artery (LAD) and right coronary artery disease appears to portend unfavorable prognosis and CR may be considered in selected patients' group with such an anatomical subset [26]. Results from the substudy of the randomized DANAMI 3-PRIMULTI trial demonstrate that the benefit from staged FFR-guided complete revascularization compared with culprit-only PCI depends on the presence of 3-VD and at least 1 non-culprit lesion with diameter stenosis ≥ 90% (Figure 2). These patients represent a high-risk population in whom FFR-guided complete revascularization should be considered, whereas it seems safe to waive revascularization in the patients who do not meet these criteria. Surprisingly, proximal versus distal location did not influence the benefit from CR. Moreover, the benefit from CR among high-risk patients appeared to be only driven by ischemia-driven revascularization. Finally, non-culprit diseased arteries should be treated according to combined angiographic and hemodynamic criteria: the lesions are deemed angiographically significant if they are associated with at least 70% stenosis of the vessel diameter on visual estimation or with 50 to 69% stenosis accompanied by a FFR measurement of ≤0.80 and should be accordingly revascularized.

Conclusion

MVD is frequently found in patients with STEMI and portends unfavorable prognosis. The rationale for CR is to reduce global ischemic burden and prevent further CV complications. Randomized controlled trials have confirmed that CR, as compared to IT, indeed reduces the risk for short- and long-term major adverse CV events. The most of the benefit appears, though, to be driven by ischemia-driven revascularization. Other hard endpoints, such as mortality reduction and MI prevention, still need to be proven in future trials. Until then, high-risk groups of STEMI patients should be identified and non-culprit revascularization carried out at the optimal time after the index event.

2A



2B

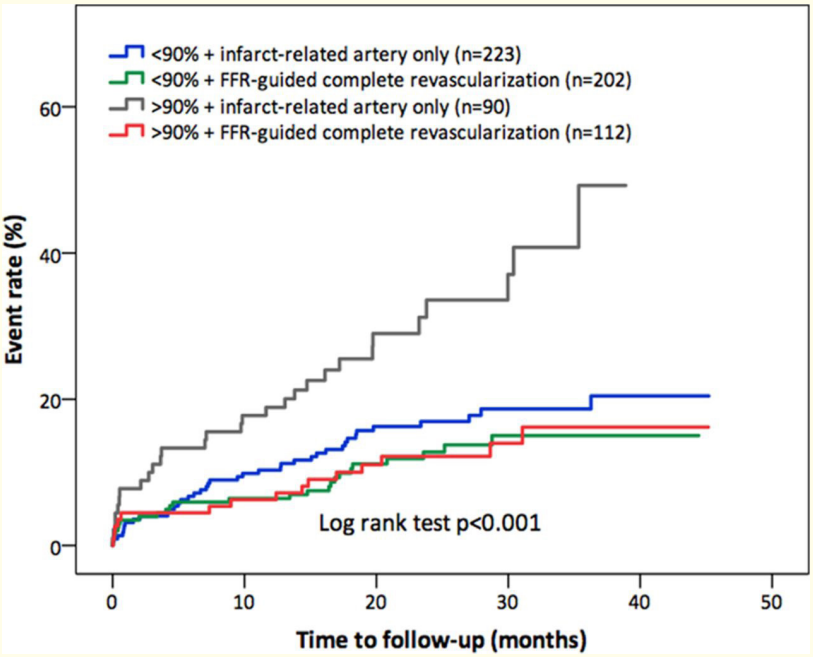


Figure 2: *A. The primary composite endpoint according to randomization and degree of vessel disease. Kaplan-Meier curves for patients with 2- or 3-vessel disease treated with percutaneous coronary intervention (PCI) of the culprit-only artery or fractional flow reserve (FFR)-guided complete revascularization. B. The primary composite endpoint according to randomization group and severity of non-culprit stenosis. Kaplan-Meier curves for patients with or without at least 1 non-culprit stenosis ≥90% treated with culprit-only PCI or FFR-guided complete revascularization. Source: [31].*

Bibliography

1. Ibanez B., *et al*. "2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation". *European Heart Journal* 39.2 (2018): 119-177.

2. Neumann FJ., *et al*. "2018 ESC/EACTS Guidelines on myocardial revascularization". *European Heart Journal* 40.2 (2019): 87-165.

3. Hasun M., *et al*. "Culprit vessel only versus complete revascularisation in patients with ST-segment elevation myocardial infarction – should we stay or stage?". *Interventional Cardiology Review* 13.3 (2018): 129-134.

4. Di Mario C., *et al*. "Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study". *International Journal of Cardiovascular Interventions* 6.3-4 (2004): 128-133.

5. Sorajja P., *et al*. "Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction". *European Heart Journal* 28.14 (2007): 1709-1716.

6. Davies MJ., *et al*. "Atherosclerosis: what is it and why does it occur?". *British Heart Journal* 69 (1993): S3-S11.

7. Rosenthal RL. "The 50% coronary stenosis". *The American Journal of Cardiology* 115.8 (2015): 1162-1165.

8. Pijls NHJ., *et al*. "Measurement of fractional flow reserve to assess the functional severity Of coronary-artery stenosis". *The New England Journal of Medicine* 334.26 (1996): 1703-1708.

9. Mehta SR., *et al*. "COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with multivessel PCI for myocardial infarction". *The New England Journal of Medicine* 381.14 (2019): 1411-1421.

10. Mauri L. "Nonculprit lesions - innocent or guilty by association". *The New England Journal of Medicine* 369.12 (2013): 1166-1167.

11. Genereux P., *et al*. "Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention". *Journal of the American College of Cardiology* 59.24 (2012): 2165-2174.

12. Hannan EL., *et al*. "Association of coronary vessel characteristics with outcome in patients with percutaneous coronary interventions with incomplete revascularization". *JAMA Cardiology* 3.2 (2018): 123-130.

13. Cardi T., *et al*. "Prognostic Value of Incomplete Revascularization after Percutaneous Coronary Intervention Following Acute Coronary Syndrome". *Clinical Medicine* 8.6 (2019): E810.

14. Quadri G., *et al*. "Complete or incomplete coronary revascularisation in patients with myocardial infarction and multivessel disease: a propensity score analysis from the "real-life" BleeMACS (Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome) registry". *EuroIntervention* 13.4 (2017): 407-414.

15. Pasceri V., *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: Cardiovascular Interventions* 11.9 (2018): 833-843.

16. Bainey KR., *et al*. "Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis". *American Heart Journal* 167.1 (2014): 1-14.

17. Granger CB., *et al*. "Clinical trials and registries in cardiovascular disease: competitive or complementary?". *European Heart Journal* 31.5 (2010); 520-521.

18. Politi L., *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* 96.9 (2010): 662-667.

19. Wald DS., "Randomized trial of preventive angioplasty in myocardial infarction". *The New England Journal of Medicine* 369.12 (2013): 115-123.

20. Engstrøm T., *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* 386.9994 (2015): 665-671.

21. Gershlick AH., *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". *Journal of the American College of Cardiology* 65.10 (2015): 963-972.

22. Elias J., *et al*. "EXPLORE investigators. Long-term impact of chronic total occlusion recanalisation in patients with ST-elevation myocardial infarction". *Heart* 104.17 (2018):1432-1438.

23. Smits PC., *et al.* "Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction". *The New England Journal of Medicine* 376.13 (2017): 1234-1244.

24. Gitt AK., *et al*. "The role of cardiac registries in evidence-based medicine". *European Heart Journal* 31.5 (2010): 525-529.

25. Dimitriu-Leen AC., *et al*. "Prognosis of complete versus incomplete revascularisation of patients with STEMI with multivessel coronary artery disease: an observational study". *Open Heart* 4.1 (2017): e000541.

26. Iqbal MB., *et al*. "The prognostic significance of incomplete revascularization and untreated coronary anatomy following percutaneous coronary intervention: An analysis of 6,755 patients with multivessel disease". *Catheterization and Cardiovascular Interventions* 91.7 (2018): 1229-1239.

27. Vlaar PJ., *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". *Journal of the American College of Cardiology* 58.7 (2011): 692-703.

28. Tarantini G., *et al*. "Survival after varying revascularization strategies in patients with st-segment elevation myocardial infarction and multivessel coronary artery disease: a pairwise and network meta-analysis". *JACC: Cardiovascular Interventions* 9.17 (2016): 1765-1776.

29. Wood DA., *et al*. "Multivessel Revascularization and ST-Segment–Elevation Myocardial Infarction. Do We Have the Complete Answer?". *Circulation: Cardiovascular Interventions* 10.4 (2017): e005215.

30. McCann GP., *et al*. "Complete Versus Lesion-Only Primary PCI: The Randomized Cardiovascular MR CvLPRIT Substudy". *Journal of the American College of Cardiology* 66.24 (2015): 2713-2724.

31. Lonborg J., *et al*. "For the DANAMI 3-PRIMULTI Investigators. Fractional Flow Reserve–Guided Complete Revascularization Improves the Prognosis in Patients With ST-Segment–Elevation Myocardial Infarction and Severe Nonculprit Disease A DANAMI 3-PRIMULTI Substudy (Primary PCI in Patients With ST-Elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization". *Circulation: Cardiovascular Interventions* 10.4 (2017): e004460.

Volume 6 Issue 12 December 2019