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Review Article

Coronary revascularization and use of hemodynamic support in acute coronary syndromes

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ABSTRACT

Cardiogenic shock develops in up to 10% of patients with acute myocardial infarction and continues to have high mortality. Early invasive treatment is the default therapeutic approach in these patients. On the basis of the results of the CULPRIT-SHOCK trial, culprit-only revascularization during the acute phase is preferred over multivessel revascularization. Routine use of intra-aortic balloon pump (IABP) is not recommended; however, the use of mechanical circulatory support has been increasing despite limited observational data to support its use. Several studies support multivessel revascularization in patients with uncomplicated ST-segment elevation acute myocardial infarction and simple nonculprit lesions to improve subsequent clinical outcomes.

1. Introduction

Recent studies have advanced our understanding and treatment options for patients with cardiogenic shock in the setting of acute coronary syndromes (ACS), as well as coronary revascularization in ACS patients with multivessel disease.[1–7] We provide an overview of those studies and their anticipated impact on clinical practice.

2. Cardiogenic shock in ACS patients

2.1. Medical vs. invasive treatment, complete vs. infarct-related angioplasty

Cardiogenic shock is defined as a state in which ineffective cardiac output, caused by a primary cardiac disorder, results in both clinical and biochemical manifestations of inadequate tissue perfusion. Some patients with cardiogenic shock may not have hypotension; however, a commonly used definition is persistent hypotension (systolic blood pressure < 90 mmHg or mean blood pressure 30 mmHg lower than the baseline value), elevated pulmonary capillary wedge pressure (PCWP) (greater than 15 mmHg), and depressed cardiac index (less than 1.8 L/min/m^2 without support or less than 2.2 L/min/m^2 with support) accompanied by signs of hypoperfusion (such as reduced urine output, cold extremities, and confusion).[8] Cardiogenic shock develops in approximately 6-10% of patients with ST-segment elevation myocardial infarction (STEMI) and up to 3% of patients with non-ST-segment elevation myocardial infarction (NSTEMI), with >50% mortality in both settings.[9–11] Common causes of cardiogenic shock include extensive left ventricular injury, right ventricular infarction, mechanical complications, or arrhythmias.

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial randomized 302 patients with cardiogenic shock to early revascularization vs. initial medical stabilization. Compared with the medical stabilization group, patients who had early revascularization had lower mortality, both after 6 months (50.3% vs. 63.1%, respectively, RR 0.80 [95% CI 0.65–0.98], p = 0.027)[12] and after 6 years (67.2% vs. 80.4%, p = 0.028) of follow-up.[13]

Most (up to 80%) patients with cardiogenic shock in the setting of ACS have multivessel coronary artery disease.[14,15] Whether

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Table 1
Guidelines for patients with cardiogenic shock due to myocardial infarction and multivessel coronary disease

Guidelines	Recommendations	Class	Level of evidence
ACCF/AHA guidelines on STEMI (2013)[18]	In patients with cardiogenic shock due to pump failure, PCI of a severe stenosis in a large noninfarct artery might improve hemodynamic stability and should be considered during the primary procedure.	Not specified	Not specified
AHA/ACC guidelines on NSTEMI (2014)[19]	Select a revascularization strategy based on the extent of CAD, associated cardiac lesions, LV dysfunction, and prior revascularization.	I	B
ESC/EACS on myocardial revascularization (2018)[22]	In cardiogenic shock, routine revascularization of non-infarct-related arteries (non-IRA) is not recommended during primary PCI.	III	B

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; NSTEMI, Non-ST-segment elevation myocardial infarction; CAD, coronary artery disease; LV, left ventricular; ESC/EACS, European Society of Cardiology/European Association of Cardiothoracic Surgery.

culprit-only or multivessel revascularization should be performed in those patients had been controversial. Hussain et al examined 210 patients with cardiogenic shock showing that complete revascularization was independently associated with lower in-hospital mortality.[16] The 2017 European guidelines for STEMI favored complete revascularization in patients with STEMI and cardiogenic shock (class IIa, level of evidence C), while the 2013 ACCF/AHA guidelines suggested that “shock or severe heart failure is perhaps the only clinical scenario in which acute revascularization of significant stenoses in non-infarct arteries can be justified”.[17,18] Similarly, the 2014 AHA/ACC NSTEMI guidelines recommended selection of a specific revascularization strategy on the basis of the degree, severity, and extent of coronary artery disease, associated cardiac lesions, extent of left ventricular dysfunction, and history of prior revascularization (class I, level of evidence B)[19] (Table 1 and Fig. 1).

The aforementioned question was definitely answered in the Culprit Lesion-Only PCI Versus Multivessel Percutaneous Coronary Intervention in Cardiogenic Shock (CULPRIT-SHOCK) trial. In this multicenter, randomized controlled trial, 706 patients with either STEMI or NSTEMI were randomized to culprit vessel-only percutaneous coronary intervention (PCI) with possible staged revascularization later versus immediate multivessel PCI. The incidence of the composite primary endpoint of death or renal-replacement therapy at 30 days was lower in patients who underwent culprit lesion-only PCI (45.9% vs. 55.4%, RR 0.83 [95% CI 0.71-0.96], p = 0.01). All-cause mortality occurred in 149 (43.3%) patients in the culprit lesion-only PCI group and in 176 (51.6%) in the multivessel PCI (RR 0.84 [95% CI 0.72-0.98], p = 0.03) with a trend for a lower need for renal replacement therapy (11.6% vs. 16.4%, respectively, RR 0.71 [95% CI 0.49-1.03], p = 0.07).[2] Chronic total occlusions (CTOs) are often present in patients with ACS and have been associated with worse outcomes[20,21] In the CULPRIT-SHOCK trial, at least one CTO was present in 24% of patients in the multivessel PCI group and in 22.4% of patients in the culprit-only PCI group. In patients with at least one CTO, complete revascularization was achieved in 81%. The subgroup analysis for the primary endpoint at 30 days showed better outcomes with culprit-only PCI (relative risk 0.67 [95% CI 0.46-0.97]) than with multivessel PCI.

On the basis of the CULPRIT-SHOCK trial, the 2018 European Society of Cardiology/European Association of Cardiothoracic

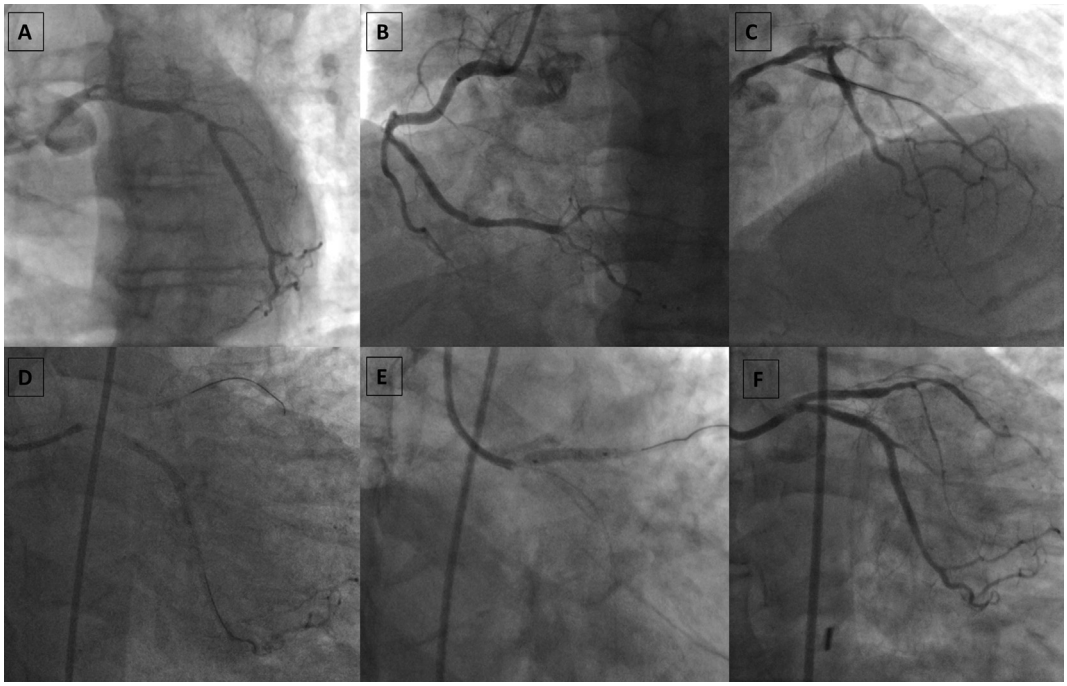

Fig. 1. Panel A: A patient with cardiogenic shock caused by non-ST-segment elevation myocardial infarction underwent emergent coronary angiography, which demonstrated complete obstruction of the left anterior descending artery (LAD) and an ulcerated lesion causing 90% obstruction, proximally, in the circumflex artery (CX). **Panel B:** A lesion was present in the distal right coronary artery (RCA) causing 70% obstruction. **Panel C:** After the inflation of a 2.5 mm balloon in the proximal LAD, severe diffuse disease in mid-LAD was revealed. **Panel D:** Because of the proximal location of the LAD and CX lesions, it was decided to proceed with percutaneous coronary intervention (PCI) to the CX in addition to the LAD. Two drug-eluting stents (DES) were implanted in the proximal CX. **Panel E:** One DES was implanted in the proximal LAD. **Panel F:** The final result showed that TIMI flow-3 was restored in both vessels. PCI of the RCA was not performed.

Surgery provided a class III (level of evidence B) recommendation for the routine revascularization of non-infarct-related arteries (non-IRA) during primary PCI in patients with STEMI and NSTEMI complicated by cardiogenic shock.[22]

2.2. Mechanical circulatory support devices in cardiogenic shock

Intra-aortic balloon pump (IABP) has been the most commonly used short-term mechanical circulatory support device because it is easy to use, inexpensive, and readily available. IABP use declined after the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial. IABP-SHOCK II was the first randomized controlled trial that evaluated the use of the IABP in patients with acute MI complicated by cardiogenic shock and showed similar 30-day (39.7% vs. 41.3%, RR 0.96 [95% CI 0.79-1.17], p = 0.69) and 12-month (52% vs. 51%, RR 1.01 [95% CI 0.86-1.18], p = 0.91) mortality. The trial was criticized, however, because of the relatively small number of patients enrolled (n = 600) and the lower than anticipated mortality (40%) that reduced the power of the study. Moreover, 10% of patients crossed over from the control group to the IABP group.[1] A recent meta-analysis of seven trials that included a total of 790 patients demonstrated no difference in 30-day mortality with vs. without IABP in patients with acute MI and cardiogenic shock.[23] Given the IABP-SHOCK II trial results, the 2018 European guidelines on myocardial revascularization recommend against the routine use of IABP in patients with cardiogenic shock due to ACS (class III, level of evidence B)[18,22] (Table 2); however, the IABP can remain useful particularly in patients in early stages of shock.

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is often used in patients with cardiac arrest and cardiogenic shock. A meta-analysis of 4 studies that included 235 patients with cardiogenic shock after acute MI showed that VA ECMO was associated with improved 30-day survival as compared with IABP (risk difference 33%, [95% CI 14–52%], p = 0.0008, NNT 3). When VA ECMO was compared with Impella or Tandem Heart, 30-day survival was similar (risk difference −3% [95% CI −21 to 14%], p = 0.70).[24]

Seyfarth et al performed a prospective, randomized study comparing Impella LP 2.5 with IABP in 25 patients with cardiogenic shock caused by acute MI. After 30 minutes of support, the cardiac index was significantly higher in the Impella group than in the IABP group; however, the overall 30-day mortality was similar in the two groups.[25] In another prospective, randomized trial that included 42 patients, Burkhoff et al tested whether or not TandemHeart provided superior hemodynamic support compared with IABP in patients with cardiogenic shock (due to MI in 70%). TandemHeart improved the hemodynamic parameters but did not improve 30-day survival.[26] A recent meta-analysis of 148 patients from four randomized trials that investigated the efficacy and safety of TandemHeart and Impella vs. IABP demonstrated that LVADs significantly increased mean arterial blood pressure and decreased arterial lactate and PCWC at the cost of a high rate of bleeding from vascular access sites compared with IABP.[27] The Impella versus IABP Reduces mortality in STEMI patients treated with primary PCI in the Severe cardiogenic SHOCK (IMPRESS) trial randomized 48 patients with STEMI and cardiogenic shock to either Impella CP or IABP. The all-cause mortality at 30 days and 6 months was similar in the two groups (46% vs. 50%, p = 0.92 and 50% vs. 50%, p = 0.92%), while Impella CP was associated with more major bleeding events (8 vs. 2 patients).[28]

Despite the lack of data demonstrating survival benefit with mechanical circulatory support, in the United States, use of IABP has been decreasing and use of VA ECMO, Impella, and TandemHeart has been increasing.[29–31]

The 2013 ACCF/AHA STEMI guidelines recommend the use of LVADs as an alternative to IABP for patients with refractory cardiogenic shock (class IIb, level of evidence C).[18] Because of the lack of strong data, the European revascularization guidelines do not provide recommendations for the use of LVADs in patients with MI complicated by cardiogenic shock (Table 2).

3. Multivessel disease in acute coronary syndromes

3.1. Multivessel disease in NSTEMI

Approximately 40-80% of NSTEMI patients have multivessel disease, and up to 40% of patients have more than one culprit lesion.[32] Culprit lesion(s) determination and the optimal revascularization strategy remain controversial.[33–37] The Impact of Different Treatment in Multivessel Non-ST-Elevation Myocardial Infarction Patients: One Stage Versus Multistaged Percutaneous Coronary Intervention (SMILE) trial randomized 584 patients with multivessel disease and NSTEMI to complete 1-stage coronary revascularization vs. multi-stage revascularization. The complete 1-stage coronary revascularization group had lower incidence of the composite endpoint of cardiac death, death, reinfarction, rehospitalization for unstable angina, repeat coronary revascularization (target vessel revascularization), and stroke at 1 year (13.63% vs. 23.19%, HR: 0.549 [95% CI 0.363-0.828], p = 0.004), driven by lower incidence of target vessel revascularization.[38] The 2014 AHA/ACC NSTEMI guidelines suggest that a strategy of multivessel PCI, in contrast to culprit lesion-only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTEMI (class IIb, level of evidence C).[19] The 2018 ESC/EACTS guidelines on myocardial revascularization state that revascularization strategy should be based on the clinical status, comorbidities, and disease severity according to the principles for stable coronary artery disease (class I, level of evidence B)[22] (Table 3).

3.2. Multivessel disease in STEMI

Approximately 50% of STEMI patients have multivessel coronary artery disease, which is associated with lower rates of successful myocardial reperfusion and high rate of major adverse cardiac evets

Table 2
Guidelines for the use of mechanical circulatory support devices in patients with myocardial infarction complicated by cardiogenic shock

Guidelines	Recommendations	Class	Level of evidence
ACCF/AHA guidelines on STEMI (2013)[18]	The use of intra-aortic balloon pump (IABP) counterpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.	IIa	B
ACCF/AHA guidelines on STEMI (2013)[18]	Alternative LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock.	IIb	C
ESC/EACS on myocardial revascularization (2018)[22]	Routine use of IABP in patients with cardiogenic shock due to ACS is not recommended.	III	B

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; STEMI, ST-segment elevation myocardial infarction; LV, left ventricular; ESC/EACS, European Society of Cardiology/European Association of Cardiothoracic Surgery; ACS, acute coronary syndrome.

Table 3
Guidelines for patients with NSTEMI and multivessel coronary artery disease without cardiogenic shock

Guidelines	Recommendations	Class	Level of evidence
AHA/ACC guidelines on NSTEMI (2014)[19]	A strategy of multivessel PCI, in contrast to culprit lesion-only PCI, may be reasonable in patients undergoing coronary revascularization as part of treatment for NSTE-ACS.	IIb	B
ESC/EACS on myocardial revascularization (2018)[22]	It is recommended to base the revascularization strategy (ad hoc culprit lesion PCI/multivessel PCI/CABG) on the clinical status and comorbidities, as well as the disease severity [i.e., the distribution and angiographic lesion characteristics (e.g., SYNTAX score)], according to the principles for SCAD.	I	B

AHA/ACC, American Heart Association/American College of Cardiology; NSTEMI, Non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; NSTE-ACS, Non-ST-segment elevation acute coronary syndrome; ESC/EACS, European Society of Cardiology/European Association of Cardiothoracic Surgery; CABG, coronary artery bypass surgery; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; SCAD, stable coronary artery disease.

(MACE) and 1-year mortality.[39,40] Prior studies have suggested that PCI of the non-IRA during the index procedure may adversely affect prognosis: Cavender et al examined 28,936 patients from the National Cardiovascular Data Registry and found that multivessel PCI during primary PCI was associated with higher in-hospital mortality rates (7.9% vs. 5.1%, p <0.01).[41] Hannah et al showed in an observational study of 3,521 patients that culprit lesion-only PCI was associated with lower in-hospital mortality than multivessel PCI during the index procedure (0.9% vs. 2.4%, p = 0.04). Staged revascularization with PCI at 60 days after primary PCI, however, reduced the one-year mortality compared with IRA-only PCI (1.3% vs. 3.3%, p = 0.04).[42] A meta-analysis that included 18 studies and 40,280 patients confirmed that staged PCI was consistently associated with lower mortality.[43] In a subanalysis of the HORIZONS-AMI trial (harmonizing outcomes with revascularization and stents in acute myocardial infarction), 688 patients who underwent PCI of culprit and nonculprit vessel were categorized into single PCI strategy vs. staged PCI: 1-year mortality (9.2% vs. 2.3%, p < 0.0001), cardiac mortality (6.2% vs. 2.0%, p = 0.005), and definite/probable stent thrombosis (5.7% vs. 2.3%, p = 0.02) were all in favor of staged PCI.[44]

Several randomized controlled trials have advanced our understanding of optimal revascularization strategies in STEMI (Table 4). Politi et al, in a study that included 263 patients, showed that IRA-only PCI was associated with a higher rate of MACE (death, reinfarction, rehospitalization for ACS, and repeat coronary revascularization) during a mean follow-up of 2.5 years compared with either staged PCI or simultaneous treatment of the non-IRA (50.0% vs. 20.0% vs. 23.1%, p<0.001).[3] The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial randomized 465 patients to IRA-only PCI (no preventive PCI) or IRA and non-IRA PCI too (preventive PCI). Patients in the preventive group had a lower rate of MACE (death from cardiac causes, nonfatal myocardial infarction, or refractory angina) than those in the no-preventive PCI group (21 vs. 53 cases, HR in the preventive PCI group, 0.35 [0.21-0.58] 95% CI, p<0.001). However, there was no statistically significant difference in cardiac mortality between the two groups (4 vs. 10 cases, HR 0.34 [0.1-1.08] 95% CI, p = 0.07).[7] In the Complete versus Lesion-only Primary PCI trial (CvLPRIT), investigators compared the outcomes of patients with STEMI who had a complete revascularization during their hospital stay (complete revascularization could be performed during the index procedure or before hospital discharge) with patients who had PCI only to the infarct-related artery. The primary endpoint (all-cause death, recurrent MI, heart failure, and ischemia-driven revascularization within 12 months) was significantly lower among patients who underwent complete revascularization (10.0% vs. 21.2%, HR 0.45 [0.24-0.84] 95% CI, p = 0.009). All-cause mortality was numerically lower in the complete revascularization group (2.7% vs. 6.9%, HR 0.38 [0.12-1.2] 95% CI, p = 0.09).[5] The Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI) evaluated the concept of complete revascularization not by using angiographic criteria (percent stenosis) for non-IRA revascularization, but by a functional test (FFR). Complete revascularization took place before hospital discharge. The rate of the primary composite endpoint of all-cause mortality, nonfatal reinfarction, and ischemia-driven

Table 4
Randomized trials comparing IRA-only PCI vs. complete revascularization in stable patients with STEMI and multivessel disease

Study	Number of patients	Primary composite endpoint	Results
Politi et al (2010)[3]	263	Cardiac or noncardiac death, in-hospital death, re-infarction, re-hospitalization for acute coronary syndrome, and repeat coronary revascularization at 2.5 years mean follow-up.	50% COR vs. 20% SR vs. 23.1% CR group, p<0.001.
PRAMI (2013)[7]	465	Death from cardiac causes, nonfatal myocardial infarction, or refractory angina at 23 months mean follow-up.	9% in preventive PCI group vs. 23% in non-preventive PCI group, p<0.001.
CvLPRIT (2015)[5]	296	All-cause death, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization within 12 months.	10.0% in the complete revascularization group vs. 21.2%, p<0.009, in the IRA-only revascularization group.
PRAGUE-13 (2015)[46]	214	All-cause mortality, nonfatal myocardial infarction, and stroke at 38 months median follow-up.	16.0% in complete revascularization group vs. 13.9% in culprit lesion-only PCI group, HR = 1.35; 95% CI, 0.66-2.74.
DANAMI-3-PRIMULTI (2015)[4]	627	All-cause mortality, non-fatal reinfarction, and ischemia-driven revascularization of lesions in non-infarct-related arteries when the last enrolled patient had been followed up for 1 year.	13% in patients who had complete revascularization vs. 22% in patients who had PCI of the IRA only, p< 0.004.
Compare-Acute (2017)[6]	885	Death from any cause, nonfatal myocardial infarction, revascularization, and cerebrovascular events at 12 months.	8% in IRA-only PCI group vs. 21% in complete revascularization group, p<0.001.

IRA, infarct-related artery; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction, COR, culprit vessel angioplasty-only; SR, staged revascularization, CR, simultaneous treatment of non-infarct-related artery, HR, hazard ratio; CI, confidence interval.

Table 5
Guidelines for patients with STEMI and multivessel coronary artery disease without cardiogenic shock

Guidelines	Recommendations	Class	Level of evidence
The 2015 ACC/AHA/SCAI focused update on primary PCI for patients with STEMI[45]	PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure.	IIb	B-R
ESC/EACS on myocardial revascularization (2018)[22]	Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.	IIa	A

ACC/AHA/SCAI, American College of Cardiology/American Heart Association/Society Cardiovascular Angiography Interventions; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; ESC/EACS, European Society of Cardiology/European Association of Cardiothoracic Surgery; non-IRA, non-infarct-related artery.

revascularization of lnon-IRA lesions assessed when the last enrolled patient had been followed up for 1 year was significantly lower in the complete FFR-guided revascularization group (13% vs. 22%, HR 0.56, [0.38–0.83] 95% CI, p = 0.004), driven by fewer repeat revascularizations.[4] In the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease study (Compare-Acute), the most current and largest randomized controlled trial in this area to date, investigators evaluated the outcomes of FFR-guided complete revascularization in patients with STEMI. The primary composite endpoint of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months occurred in 8% of patients who had FFR-guided complete revascularization and in 21% of patients who underwent IRA only PCI (HR 0.35, [0.22 to 0.55] 95% CI, p<0.001).[6]

Interpretation of the above study findings should consider differences in study design: in two studies (PRAMI and Compare-Acute) non-IRA PCI took place during the index procedure, in one (DANAMI3–PRIMULTI) during admission, in one (CvLPRIT) either during index procedure or during hospital stay, while in the study by Politi et al, patients were randomized to three different groups (IRA PCI only, staged PCI, or repeat coronary revascularization). Furthermore, two trials (DANAMI-3–PRIMULTI and Compare-Acute) used FFR for guiding complete revascularization instead of only using angiography.

In conclusion, current data favor complete revascularization before hospital discharge; however, the optimal timing (during the index procedure or later during the same hospitalization) and whether revascularization should be guided by functional assessment remain unclear. Importantly, none of the previously mentioned studies showed lower mortality with non-IRA PCI. The 2015 ACC/AHA/SCAI focused update on primary PCI for patients with STEMI recommends non-IRA PCI in selected hemodynamically stable patients either during primary PCI or as a planned staged procedure (class IIb, level of evidence B-R).[45] The 2018 European guidelines on myocardial revascularization suggest that “routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge” (class IIa, level of evidence A)[22] (Table 5).

4. Conclusion

Patients with cardiogenic shock in the setting of ACS should undergo culprit-only coronary revascularization. Use of mechanical circulatory support in such patients is increasing despite lack of randomized controlled trials supporting their safety and efficacy in this setting. Multivessel revascularization during index admission is reasonable and supported by several randomized controlled trials particularly when guided by FFR, although it does not reduce mortality. The optimal timing for achieving complete revascularization and the optimal strategy for evaluating the nonculprit lesions are still being debated.

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