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Complete versus culprit only revascularization in ST-elevation myocardial infarction – a perspective on recent trials and recommendations

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Abstract: The presence of multivessel coronary artery disease (CAD) is strongly associated with higher 30-day mortality, reduced myocardial reperfusion success, reinfarction, and occurrence of major adverse cardiac events (MACE) at 1 year compared with single-vessel CAD. Despite higher morbidity and mortality in patients with ST-elevation myocardial infarction (STEMI) and coexistent multivessel CAD, major guidelines recommended against percutaneous coronary intervention (PCI) on non-culprit lesions at the time of primary PCI in patients with STEMI who are hemodynamically stable. The presence of multivessel CAD often poses a therapeutic dilemma for interventional cardiologists. A few larger scale randomized controlled trials (RCTs) and meta-analyses have been conducted. The conclusions regarding multivessel PCI generally trend towards lower risk of MACE, repeat revascularization, with similar risks of recurrent myocardial infarction (MI) and mortality. However, none of the RCTs were adequately powered for hard outcomes of death and MI.

Keywords: Coronary artery disease (CAD); ST-elevation myocardial infarction (STEMI); percutaneous coronary intervention (PCI); culprit lesion; multivessel CAD

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Introduction

There has been a recent decline in the incidence of ST-elevation myocardial infarction (STEMI) (1,2). However, multivessel (MV) coronary artery disease (CAD) is frequently encountered (45–60%) in patients undergoing primary percutaneous coronary intervention (PCI) for STEMI (3–6). In contrast to stable lesions in stable CAD, non-culprit lesions in patients with acute coronary syndrome (ACS) tend to have more diffuse CAD and less-calcified plaques (7,8). The plaques in ACS patients are also more vulnerable, with large amount of necrotic core (7) and thin-cap fibroatheromas, consistent with high-risk features.

This could potentially lead to development of future major adverse cardiovascular events (9). The presence of MV-CAD is strongly associated with higher 30-day mortality, reduced myocardial reperfusion success, reinfarction, and occurrence of major adverse cardiac events (MACE) at 1-year compared with single vessel CAD (4–6).

Despite higher morbidity and mortality in patients with STEMI and coexistent MV CAD, guidelines published by the American College of Cardiology/American Heart Association (ACC/AHA) in 2013 recommended against PCI on non-culprit lesions at the time of primary PCI in patients with STEMI who are hemodynamically stable (10).

The 2014 European Society of Cardiology/European Association of Cardio-Thoracic Surgery guidelines also similarly recommend systematic primary PCI of the culprit vessel and advocate for additional non-culprit vessel revascularization only in patients with cardiogenic shock, especially when the lesions are multiple, unstable, or with critical stenosis, and if persistent ischemia exists after PCI of the culprit lesion (11). However, only 25% of patients with cardiogenic shock and MV CAD receive MV PCI during STEMI (12).

The recommendations against PCI of non-culprit lesions were largely driven by results of nonrandomized observational studies with conflicting results. The rationale behind not recommending routine complete revascularization was increased in-hospital mortality, contrast-induced nephropathy (CIN), and MACEs associated with MV-PCI during the index procedure (13-17). Small randomized controlled trials (RCTs) reported potential safety and benefits of complete and staged revascularization in reducing long-term MACE (18,19). In multicenter randomized Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction (HELP-AMI) study (19), with a total of 69 patients (17 patients in culprit-only PCI group and 52 patients in multivessel PCI group), the investigators found that MVPCI at the time of index procedure was not associated with increase in in-hospital adverse events and had similar overall healthcare cost as compared to culprit-only PCI (19). In the Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis (PRAGUE-13) trial (20), the authors compared staged MV-PCI (n=106) with culprit-only PCI (n=108) in STEMI patients with MV-CAD. This study found no difference in the long term development of composite primary end-point of all-cause mortality, non-fatal MI, and stroke between the two revascularization strategies (20).

The presence of MV-CAD often poses a therapeutic dilemma for interventional cardiologists as there are multiple options in patients with MV-CAD and insufficient data regarding benefit in reducing end-point such as mortality and MI. These options are culprit artery-only primary PCI, complete revascularization (MV-PCI) at the time of index procedure, or staged revascularization (primary PCI followed by ischemia or symptom guided PCI of the non-culprit lesion within days or weeks after primary PCI). In this review, we will discuss the recently published RCTs (Table S1) designed to investigate optimal revascularization

strategy in managing STEMI patients with MV-CAD and their impact on current clinical practice and guidelines.

RCTs (Table S1)

Politi et al. (18)

Out of a total of 263 consecutive patients with STEMI and MV-CAD, 214 patients were randomly assigned to culprit-only PCI (n=81), complete revascularization during the index procedure (n=65), and staged revascularization performed approximately two months after the index procedure (n=65) (18). Patients with cardiogenic shock at presentation (systolic blood pressure ≤ 90 mmHg despite drug therapy), left main coronary disease ($\geq 50\%$ diameter stenosis), previous coronary artery bypass graft (CABG) surgery, severe valvular heart disease and unsuccessful revascularization were excluded from the study. Patients were followed for a mean duration of 2.5 ± 1.4 years (18).

The investigators found that culprit-only revascularization had a higher rate of at least one MACE (50%), compared to staged revascularization (20%) and immediate complete revascularization (23%) at a mean follow-up of 2.5 years ($P < 0.001$). The staged and immediate complete revascularization group had a 63% ($P = 0.003$) and a 60% lower risk of MACE ($P = 0.002$), respectively. This result was mainly driven by a lower incidence of in-hospital death, re-PCI, and rehospitalization. Kaplan-Meier analysis showed a worse outcome in the culprit-only revascularization group (worse survival-free of MACE, survival-free of re-PCI), but no significant difference in outcomes between the staged and immediate complete revascularization groups. There were no significant differences in CIN incidence and length of hospital stay between the 3 study groups (18). This study suffered from a small sample size and utilization of unrestricted randomization instead of block randomization leading to imbalances in the treatment arms (25). It was also unclear whether patients in the culprit-only revascularization group had any non-invasive ischemia testing within 2.5 years, which could qualify these patients for staged revascularization. This could potentially explain the higher incidence of repeat revascularization and re-hospitalization in the culprit-only revascularization group (26).

PRAMI (21)

In the Preventive Angioplasty in Acute Myocardial

Infarction (PRAMI) trial, a total of 465 patients were randomly assigned to culprit only revascularization (n=231) and complete revascularization during the index procedure (n=234) (21). Staged revascularization in the asymptomatic patients was discouraged. Once the infarct-related artery was treated, the patients were included in the trial if they had a PCI-amenable $\geq 50\%$ stenosis in one or more non-infarct-related coronary arteries. Patients who were in cardiogenic shock, unable to provide consent, had undergone previous CABG, had a non-infarct stenosis of 50% or more in the left main stem or the ostia of both the left anterior descending and circumflex arteries, or if the only non-culprit stenosis was a chronic total occlusion were excluded. Patients were followed for a mean follow-up duration of 23 months (21).

This study reported a 65% reduction in the primary endpoint in the complete revascularization group compared to the culprit-only revascularization group. Complete revascularization group also had a significantly lower risk for repeat revascularization and composite of death from cardiac causes or non-fatal MI. The Kaplan-Meier analysis showed that the risk reduction benefit was apparent within 6 months after the procedure (21). This study, however, failed to address the question whether similar benefit could be obtained when PCI was performed as a delayed procedure (staged revascularization) (27).

DANAMI-3 PRIMULTI (22)

In The Third Danish Study of Optimal Acute Treatment of Patients with STEMI: Primary PCI in Multivessel Disease (DANAMI-3 PRIMULTI), 627 patients were randomly allocated to complete revascularization (n=314) and culprit only revascularization (n=313) (22). After successful PCI of the culprit lesion, patients with an angiographic diameter stenosis of greater than 50% in one or more non-infarct related arteries were included in the trial. Patients were excluded if they were intolerant of contrast media or of relevant anticoagulant or antithrombotic drugs, unconscious or suffered from cardiogenic shock, stent thrombosis, met indication for CABG, or had an increased bleeding risk. Complete revascularization was performed in a staged manner 2 days after the index procedure during the index hospitalization, and was guided by fractional flow reserve (FFR), if appropriate. In non-culprit lesions with a greater than 50% diameter stenosis, FFR values were calculated (FFR ≤ 0.8 considered significant) (22).

One-third of patients allocated to the complete

revascularization group did not receive PCI as they had FFR values >0.80 . The investigators found that complete revascularization was associated with a 44% reduction in the incidence of the composite primary endpoint, which was largely driven by a 69% reduction of ischemia-driven revascularization of the non-infarct related arteries. There were no significant differences in the all-cause mortality and non-fatal reinfarction rates between the 2 groups. There were also no significant differences in cardiovascular death or non-fatal MI, although complete revascularization was significantly associated with a lower need for both urgent and non-urgent PCI of the lesions in the non-culprit arteries (22). This trial failed to show an impact on hard outcomes (such as death and MI due to lack of power). The optimal timing of non-infarct related artery PCI (index admission versus staged outpatient procedure) remains a debate (28,29).

CvLPRIT (23)

The Complete versus Lesion-only Primary PCI (CvLPRIT) trial randomized 296 STEMI patients and MVCAD to culprit-only (n=146) and complete (n=150) revascularization (23). Exclusion criteria were an age <18 years, clear indication for, or contraindication to, MV primary PCI according to operator judgement, prior MI, patients with prior CABG, cardiogenic shock, ventricular septal rupture or moderate/severe mitral regurgitation, chronic kidney disease, suspected or confirmed thrombosis of a previously stented artery, and when the only significant non-infarct-related lesion is a chronic total occlusion (23).

Complete revascularization was done either during the index procedure or the index hospitalization (staged revascularization). The primary endpoint of this study was MACE, which was a composite of all-cause mortality, recurrent MI, heart failure, and ischemic-driven revascularization by PCI or CABG within 12 months. This study reported a 55% reduction of MACE in the patients undergoing complete revascularization compared to the culprit-only revascularization. The occurrence of individual components of the primary endpoint was insignificantly lower in the complete revascularization group. Sixty-four percent of patients underwent complete revascularization during the index procedure, while the others had a staged revascularization. Patients receiving complete revascularization during the index procedure had a trend towards a reduced prevalence of MACE compared to staged revascularization. There were no differences in the

occurrence of adverse events, such as stroke, major bleeding (all non-CABG related), or CIN between the infarct-related revascularization and complete revascularization groups (23). The study was not powered to assess the individual components of the primary composite endpoint (30). The study did not include intravascular ultrasound or FFR for the non-infarct-related lesion characterization anatomically or physiologically, respectively.

Compare-Acute Trial (24)

The Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With MVD (COMPARE-ACUTE) Trial enrolled 885 STEMI patients with non-infarct-related coronary stenosis of 50% or more (24). Patients were randomly assigned in a ratio of 1:2 to FFR-guided complete revascularization (n=295) and culprit-only revascularization (n=590). Exclusion criteria were left main CAD, chronic total occlusion, severe stenosis with a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 2 or less in the non-infarct-related coronary artery, a suboptimal result or complication after treatment of infarct-related artery, severe valve dysfunction, and Killip class III or IV. Complete revascularization was performed in lesions with FFR ≤ 0.80 , preferably within 72 hours (complete PCI was performed during index procedure in 83.4 % patients). Primary end-point of the study was the composite of all-cause mortality, non-fatal MI, any revascularization, and cerebrovascular events (MACCE) at 12 months (24).

As the FFR measurement was performed in both groups, this study showed that approximately half of the patients had one or more non-infarct-related artery lesions with an FFR of 0.80 or less. The investigators found that complete revascularization group had significantly lower rate of MACCE compared to culprit-only revascularization group which seems to be driven mainly by the decreased need for revascularization. The other components of primary end-point (all-cause mortality, MI, and cerebrovascular event) did not differ statistically between both groups (24).

Although this study showed that FFR-guided revascularization could be safely performed in acute setting of STEMI and cost-effective, it is questionable whether the result of trial can also be applied to much sicker patient populations. In addition, there is a potential bias as the angiographic result of culprit-only revascularization group was made known to patients and cardiologist, which could contribute to higher subsequent revascularization among

that group (31).

Meta-analyses

Spencer *et al.* (32) in their systematic review, which included five RCTs [RCT by Politi *et al.* (18), HELP-AMI (19), PRAMI (21), DANAMI-3 PRIMULTI (22), and CvLPRIT (23)] enrolling 1,606 patients, concluded that complete revascularization was associated with significant reduction in the risk of repeat revascularization, non-fatal MI, cardiovascular mortality compared to culprit-only revascularization. However, the investigators did not find any difference in the total mortality between the two groups (32). A separate meta-analysis which recruited nine RCTs with total 2,176 patients, agreed that complete revascularization strategy was overall better in lowering risk of MACE, repeat revascularization, cardiovascular mortality, but found no difference in mortality or recurrent MI. The investigators also compared the three revascularization strategies (culprit-only, complete revascularization at index procedure, and complete revascularization as staged procedure) and showed that complete revascularization during index procedure seemed to be more superior than two other strategies (33). However, more recent meta-analysis, conducted by Fan *et al.* (34), concluded the opposite: complete revascularization as staged procedure deemed better than immediate complete revascularization or culprit-only revascularization in reducing all-cause mortality (34).

Numerous other meta-analyses have been conducted and published since the RCTs (Table 1). They have discordant results, which was largely driven by the inclusion of different variety of trials to conduct the meta-analyses and by the fact that none of the RCTs were adequately powered for the hard outcomes of death and MI. Overall, MV-PCI seems to be associated with lower risk of MACE, repeat revascularization, but with a similar risks of recurrent MI and mortality compared to culprit-only revascularization (32-44).

Timing of revascularization

Timing of revascularization remains an area of intense controversy and debate. Wang *et al.* (43) performed a subgroup analysis in their meta-analysis, comparing outcomes in complete revascularization at the time of the index procedure (immediate complete revascularization) and staged revascularization with culprit-only revascularization. Immediate complete revascularization had a significantly lower incidence of MACE, all-cause death and/or MI, non-

Table 1 Meta-analyses of complete vs. culprit only revascularization

First author, year published	Studies included	Culprit-only revascularization (N)	Complete revascularization (N)	Results
Bangalore (35), 2015	5 RCTs	519	646	Lower risk of MACE, mortality, repeat revascularization in complete revascularization group. Non-fatal MI was similar
El-Hayek GE (36), 2015	4 RCTs	478	566	Lower all-cause mortality, CV mortality, recurrent MI, repeat revascularization in complete revascularization group
Kowalewski M (37), 2015	7 RCTs	666	637	Lower risk of MACE, recurrent MI, repeat revascularization in complete revascularization group. All-cause mortality, CV mortality were similar
Bitti JA (38), 2015	4 RCTs, 14 observational studies	40, 180	7,588	Similar mortality risk
Spencer FA (32), 2015	5 RCTs	775	793	Lower risk of repeat revascularization, recurrent non-fatal MI, CV mortality in complete revascularization group. Total mortality was similar
Bajaj NS (39), 2015	8 RCTs	919	1,054	Lower risk of MACE, revascularization, repeat PCI in complete revascularization group. All-cause mortality, reinfarction were similar
Tarantini G (40), 2016	13 prospective; 19 retrospective studies	42, 112	Immediate complete: 8,138; staged: 3,898	Lower short and long term mortality in staged revascularization compared to culprit-only and immediate complete revascularization
Villablanca PA (41), 2016	7 RCTs	940	1,066	Lower risk of MACE, CV mortality, repeat revascularization in complete revascularization group. All-cause mortality and MI were similar
Shah R (33), 2016	9 RCTs	940	1,236	Lower risk of MACE, revascularization, CV mortality in complete revascularization group. MI and all-cause mortality were similar
Bainey KR (42), 2016	7 RCTs	939	1,065	Similar risk of death and MI
Wang CH (43), 2017	8 RCTs	980	1,080	Lower risk of MACE and repeat revascularization in complete revascularization group. Mortality and MI are similar
Fan ZG (34), 2017	9 RCTs	789	975	Lower risk of MACE, long-term mortality, reinfarction, and repeat revascularization in complete revascularization group
Li Z (44), 2017	4 RCTs 6 non-RCTs	–	Immediate complete: 347; staged: 562	Lower risk of mortality and MACE with staged PCI. No difference in MI and revascularization

RCT, randomized controlled trial; MACE, major adverse cardiac events; MI, myocardial infarction; CV, percutaneous coronary intervention.

fatal MI, and repeat revascularization when compared to the culprit-only revascularization. Staged revascularization reduced only the incidence of MACE. This showed that immediate complete revascularization might be more superior compared to staged revascularization. This finding seems to be opposite of what was found in other meta-analyses (40,44) and the few observational studies (45,46).

Kornowski *et al.* (45) performed a post-hoc analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. This was a RCT originally designed to compare bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor and paclitaxel-eluting stents versus bare-metal stents in patients undergoing primary PCI for STEMI. A total of 668 STEMI patients were identified to have undergone MV-PCI in the original trial. Two hundred and seventy-five patients underwent MV-PCI during the index procedure, whereas 393 patients underwent staged revascularization (6–50 days after primary PCI). This study showed that MV-PCI during index procedure was associated with an increased all-cause mortality [hazard ratio (HR) 4.1, 95% CI: 1.93–8.86, $P < 0.0001$] and cardiovascular mortality (HR 3.41, 95% CI: 1.35–7.27, $P = 0.005$) compared to the staged MV-PCI (45). Similarly, a meta-analysis by Tarantini *et al.* (40) revealed that staged revascularization was associated with short- and long-term survival compared with both immediate complete revascularization and culprit-only revascularization. In separate meta-analysis by Li *et al.* (44) which compared staged revascularization and immediate complete revascularization head-to-head, the former seemed to be a better strategy.

Iqbal *et al.* (46) performed an observational study which compared the 3 revascularization strategies (immediate complete revascularization, staged revascularization, and culprit-only revascularization) in 6,503 STEMI patients with MV-CAD. The primary outcome was all-cause mortality and repeat revascularization at 2 years. The investigators found that staged revascularization was associated with a lower mortality at 1 year and 2 years when compared with either immediate complete revascularization or culprit-only revascularization. This study also showed lower repeat revascularization rates at 30 days, 1 year, and 2 years when compared with culprit-only revascularization. The authors concluded that staged PCI of the non-culprit vessel (if indicated) may yield better results, and MV-PCI at time of index procedure may be considered in patients with non-culprit LAD disease (46).

Of the RCTs discussed in detail above, Politi *et al.* (18) was the only trial that included both staged and immediate

complete revascularization and analyzed them separately. PRAMI (21) was the only trial that specifically compared MV-PCI at time of index procedure to culprit-only revascularization. DANAMI-3 PRIMULTI (22) compared only staged revascularization to culprit-only revascularization. CvLPRIT (23) and Compare-Acute Trial (24) combined both immediate and staged revascularization (mentioned as complete revascularization) at time of data analysis. The variability on how the trials were conducted leads to uncertainty and confusion on when and how complete revascularization should be performed. This warrants a larger scale RCT to confirm the present findings, as well as to determine the impact of such intervention on hard endpoints such as mortality or MI.

A large, ongoing, Complete *vs.* Culprit-only Revascularization to Treat Multivessel Disease After Primary PCI for STEMI (COMPLETE) trial (ClinicalTrials.gov. Identifier: NCT01740479) was designed to enroll 3,900 STEMI patients with MV-CAD randomly assigning them to receive either staged revascularization or culprit-only revascularization, on top of optimal medical therapy (including low dose aspirin and ticagrelor). This trial was started in December, 2012, and is estimated to be completed in December, 2018. The primary outcome of this study is a composite of cardiovascular death or new MI over a follow-up of approximately 4 years. The secondary outcome is a composite of cardiovascular death, new MI, ischemia-driven revascularization or hospitalization for unstable angina or heart failure. The results of this trial are expected to provide a better understanding of whether staged revascularization is better than culprit-only revascularization in STEMI patients with MV-CAD undergoing primary PCI.

2015 ACC/AHA focused update and 2016 ACC/AHA appropriate use criteria

The publication of larger scale RCTs has prompted ACC/AHA to change the recommendation for complete revascularization to class IIb in the recent 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Intervention for Patients with ST-Elevation Myocardial Infarction (47). These guidelines specifically mention that PCI of a non-infarct artery may be considered in selected patients with STEMI and MV-CAD who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure (47).

The 2016 Appropriate Use Criteria for Coronary Revascularization in Patients with ACS also addressed the

issue on how to treat MV-CAD in STEMI patients (48). Multivessel revascularization at the time of the index procedure with PCI or CABG was deemed appropriate in patient with cardiogenic shock persisting after PCI of the presumed culprit artery. Whereas revascularization of non-culprit artery during initial hospitalization (as staged procedure) was considered appropriate in MV-CAD patients with spontaneous or easily provoked symptoms of myocardial ischemia, asymptomatic patients with findings of ischemia on non-invasive testing, and asymptomatic patients with an intermediate (50–70%) stenosis and a FFR ≤ 0.8 (48).

Conclusions

In conclusion, it seems prudent to consider MV-PCI at the time of the index procedure in patients with cardiogenic shock, severe left ventricular dysfunction and hemodynamic instability. MV-PCI at the time of the index procedure can also be considered in patients with angiographically critical atherosclerotic plaques (high thrombus burden, ulcerated, TIMI flow <3 , angiographic stenosis $>95\%$) especially in the left anterior descending artery. MV-PCI at the index procedure may be considered in situations where it is difficult to determine the culprit lesion (for example coexistent left circumflex and right coronary artery critical lesions in patients with inferior wall ACS). In patients who are older, have chronic comorbid conditions such as diabetes or chronic kidney disease, a staged approach for non-culprit lesions may be preferred to prevent acute kidney injury. Timing of the staged procedure is debatable (same admission versus outpatient) and relies on the clinical scenario, ongoing symptoms and patient-physician preference after a risk-benefit discussion. Noninvasive or invasive testing (FFR) may be considered in the non-acute staged setting, as appropriate. Until more data are available, an individualized approach should be adopted after careful evaluation of the lesion severity, hemodynamics, underlying comorbidities, vascular access, physician comfort, and cardiac catheterization laboratory ancillary staff availability (day versus night).

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Footnote

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Table S1 RCTs of complete vs. culprit only revascularization

RCT	Timing of study	Study group	Total of patients	Number of patient in multivessel PCI	Number of patient in culprit-only PCI	Lesion criteria (% stenosis)	Timing for non-culprit lesion revascularization	Duration of follow up	Primary end-point	Secondary end-point	Study results
Politi <i>et al.</i> (18)	Jan 2003–Dec 2007	Culprit only revascularization vs. staged revascularization vs. complete revascularization	214	Staged: 65 patients (30.4%); complete: 65 patients (30.4%)	84 (39.2%)	>70% of two or more coronary arteries or their major branches by visual estimation	During index procedure (30.4% of patients) or staged (30.4% of patients), staged procedure done 56.8±12.9 days after the index procedure	2.5±1.4 years	Major adverse cardiac event (cardiac or non-cardiac death, inhospital death, re-infarction, re-hospitalization for ACS and repeat coronary revascularization)	–	63% lower risk of MACE in staged revascularization group, 60% lower risk of MACE in complete revascularization group compared to culprit-only revascularization group, higher risk of repeat unplanned revascularization, rehospitalization and in-hospital death in culprit-only revascularization group
PRAMI (21)	April 2008–January 2013	Culprit only revascularization vs. complete revascularization	465	234	231	>50% stenosis	During index procedure	23 months	Composite of death from cardiac causes, non-fatal MI, refractory angina	Death from non-cardiac cause, repeat revascularization procedures (PCI or CABG)	65% reduction in primary outcome, no significant difference in death (either from cardiac or non-cardiac cause)
Danami-3 PRIMULTI (22)	March 2011–Feb 2014	Culprit only revascularization vs. ffr-guided complete revascularization (staged)	627	314	313	>50% in one or more non-infarct related arteries	2 days after index procedure before discharge	27 (range 12–44) months	Composite of all-cause mortality, reinfarction, or ischemia-driven revascularizations in non-infarct related arteries	Components of the primary end-point, occurrence of cardiac death, urgent and non-urgent PCI of lesions in non-infarct related arteries	44% reduction in primary endpoint, largely driven by 69% reduction in all-cause mortality
CvLPRIT (23)	May 2011–May 2014	Complete vs. culprit-only revascularization	296	150	146	>70% diameter stenosis in one plane or >50% in 2 planes	During index procedure or index admission	12 months	MACE (all-cause mortality, recurrent MI, HF, ischemic-driven revascularization by PCI/CABG)	Cardiovascular death, individual component of the primary endpoint, and the safety endpoints of stroke, major bleeding, and CIN	55% lower risk of MACE in complete revascularization group
Compare-Acute Trial (24)	July 2011–October 2015	Culprit-only revascularization vs. ffr-guided complete revascularization	885	295	590	>50% plus history of angina or evidence of ischemia; or >70% on angiography; with FFR ≤0.80	During index hospitalization (83.4% of patients had complete PCI during index procedure)	36 months	Composite of all-cause mortality, non-fatal MI, any revascularization, and cerebrovascular events at 12 months	Primary end-point at 24 and 36 months; each components of primary end-point; composite of all-cause mortality and MI; composite of cardiac death, MI, any revascularization, stroke, and major bleeding; composite of heart failure hospitalization and unstable angina pectoris; stent thrombosis; treatment cost; bleeding at 48 hours and 12 months	65% lower risk of primary end-point, largely drive by 68% reduction in revascularization

ACS, acute coronary syndrome; RCT, randomized controlled trial; MACE, major adverse cardiac events; MI, myocardial infarction; CV, cardiovascular; PCI, percutaneous coronary intervention; HF, heart failure; CIN, contrast-induced nephropathy; CABG, coronary artery bypass grafting.