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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Complete Revascularization in Patients With STEMI and Multivessel Coronary Artery Disease: Is It Beneficial?

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Abstract

Purpose of review Multivessel coronary artery disease is usually present in up to 50% of patients presenting with ST-elevation myocardial infarction (STEMI). The optimal revascularization approach for non-infarct related lesions has been a topic of recent debate. Various observational studies and clinical trials have been conducted to assess the impact of multivessel revascularization. In this review, we aim to present the currently available evidence behind the different revascularization strategies.
Recent findings Early observational studies, registry-based analyses, and meta-analyses had suggested a benefit of culprit only revascularization over complete revascularization. However, in several recent randomized clinical trials, a complete revascularization approach for non-infarct-related lesions, either during the index hospitalization or as a staged approach, has been associated with improved outcomes. These findings exclude patients with cardiogenic shock and chronic total occlusions.
Summary Clinical decisions regarding the extent and timing of revascularization in STEMI patients necessitate an individualized, patient-oriented approach. Based on the evidence from recent clinical trials, complete revascularization of non-culprit lesions in STEMI should be considered.

Introduction

Acute myocardial infarction (AMI) is a common and potentially fatal presentation of cardiovascular disease. In the USA, approximately 600,000 new AMIs and 200,000 recurrent AMIs occur each year [1, 2]. Nearly 40% of the patients presenting with AMI will be found to have an ST segment elevation myocardial infarction (STEMI) [1]. Timely primary percutaneous coronary intervention (PCI) has been the preferred method of reperfusion over thrombolysis for patients with STEMI [3, 4]. Up to half of the STEMI patients have concomitant multivessel coronary artery disease (CAD) at the time of coronary angiography, with additional non-culprit lesions in other vessels [5]. Multivessel coronary disease (MVD) has been associated with worse short- and long-term outcomes. Some lesions represent stable atheromatous plaque disease, for which invasive treatment may not be beneficial. Other lesions represent unstable, vulnerable plaque with high-risk features, concerning for an increased risk for subsequent cardiovascular events.

The ideal revascularization approach to MVD in the setting of STEMI has been a topic of research and debate in the last few decades. Multiple strategies have been proposed: (1) Culprit-only revascularization (COR) with further revascularization driven by symptoms or evidence of ischemia on non-invasive imaging, (2) Complete revascularization (CR) at the time of the index culprit-lesion procedure, or (3) Complete revascularization as a staged procedure either during the same hospitalization or shortly after (within ~45 days).

Culprit only and staged revascularization

Between 2001 and 2013, several observational studies, registry-based analyses, and meta-analyses have suggested a benefit of culprit-only revascularization over complete revascularization in STEMI. In the largest registry study performed by Cavendor et al. comprised of ~32,000 patients undergoing primary PCI for STEMI, CR was associated with higher in-hospital all-cause mortality (7.9% vs 5.1%, $p < 0.01$) [6]. This was also noted in the subgroup analysis of patients presenting with STEMI and cardiogenic shock (36.5% vs 27.8%; adjusted odds ratio 1.54, 95% confidence interval 1.22 to 1.95). Iqbar et al. demonstrated similar results in their analysis of 3984 patients with MVD undergoing primary PCI between 2004 and 2011 at 8 tertiary cardiac centers in London [7]. COR strategy was associated with reduced in-hospital major adverse cardiac events (MACE) (4.6% vs 7.2%; $p = 0.010$) and mortality (7.4% vs 10.1%; $p = 0.031$) at 1 year compared to CR. Additionally, COR was an independent predictor for reduced in-hospital MACE (odds ratio, 0.49; 95% [CI], 0.32–0.75; $p < 0.001$) and survival at 1 year (hazard ratio, 0.65; 95% CI, 0.47–0.91; $p = 0.011$) in the complete cohort; and in 2821 patients in propensity-matched cohort (in-hospital MACE: odds ratio, 0.49; 95% CI, 0.32–0.76; $p = 0.002$; and 1-year survival: hazard ratio, 0.64; 95% CI, 0.45–0.90; $p = 0.010$). These findings were confirmed by inverse probability treatment weighted analyses showing COR as an independent predictor for reduced in-hospital MACE (odds ratio, 0.38; 95% CI, 0.15–0.96; $p = 0.040$) and survival at 1 year (hazard ratio, 0.44; 95% CI, 0.21–0.93; $p = 0.033$). In a meta-analysis by Lu et al. of 3 randomized controlled trials and 10 non-randomized studies, a total of 8240 patients underwent CR and 51,998 patients had COR for

STEMI. CR was associated with increased short-term and long-term mortality, as well as increased risk of renal failure [8].

When complete but staged revascularization (SR) was examined, a trend toward favorable outcomes was observed. Iqbar et al. compared COR to SR and CR in their analysis of 6503 patients with STEMI and multivessel disease enrolled in the British Columbia Cardiac Registry from 2008 to 2014. COR and SR strategies were associated with decreased all-cause mortality, compared to CR at 2-year follow-up. Interestingly, SR was associated with lower all-cause mortality and repeat revascularization when compared to COR and CR signaling a benefit of a staged approach [9]. Similar findings have been demonstrated by multiple large retrospective database studies [10–14]. This notion has also been supported by several meta-analyses. In the largest meta-analysis by Vlaar et al., made up of more than 40,000 patients, SR was associated with lower short- and long-term mortality compared to COR and CR [15]. On the other hand, CR demonstrated the highest mortality rates at both short- and long-term follow-up [15]. Bainey et al. in their metanalysis demonstrated similar outcomes between COR and CR. However, when multivessel PCI was performed as SR, hospital mortality was lower. Interestingly, if multivessel PCI was performed during index catheterization, hospital mortality was increased [16].

Given these early findings, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) STEMI guidelines assigned a class III (harm) recommendation to non-culprit PCI at the time of primary PCI in stable STEMI patients [17]. Although, non-culprit PCI may be considered for patients presenting with cardiogenic shock or for those with ongoing ischemia. The European Society of Cardiology (ESC) in the 2014 ESC STEMI guidelines provided similar recommendation reserving non-culprit lesion revascularization during STEMI for patients with cardiogenic shock in the presence of multiple, critical stenoses or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption), and if there is persistent ischemia after PCI on the supposed culprit lesion (IIb) [18].

Complete revascularization

Over the past few years, multiple clinical trials have questioned the optimal revascularization approach for multivessel coronary artery disease in STEMI patients and have set the background for a shift in our understanding. In 2013, Wald et al. reported on the findings of the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) Trial [19••]. They enrolled 465 patients with acute STEMI and multi-vessel coronary artery disease (including 3 patients with left bundle-branch block) undergoing primary PCI. Patients were randomly assigned to either full revascularization with preventive PCI (234 patients) or COR (231 patients). The primary outcome was a composite of cardiac death, non-fatal MI, or refractory angina. At a mean follow-up of 23 months, the trial was terminated early due to a significantly improved primary outcome in the complete revascularization group (HR = 0.35, 95% CI: 0.21–0.58). This was driven by a reduction in the risk of repeat revascularization (6.8% vs 19.9%, $p < 0.001$), reduction in nonfatal MI (3% vs 8.7%, $p = 0.009$), and refractory angina (5.1% vs 13.0%, $p = 0.002$). In addition, there was a strong trend toward

reduced cardiac mortality (HR, 0.34; 95% CI, 0.11–1.08; $p = 0.07$). The composite of the 2 major endpoints of cardiac death and nonfatal MI was also significantly reduced (HR, 0.36; 95% CI, 0.18–0.73; $p = 0.004$).

Two years later, similar findings were reported by the Randomized Trial of Complete versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multi-Vessel Disease trial (The CvLPRIT Trial) [20••]. CvLPRIT trial enrolled 296 STEMI patients presenting in 7 U.K. centers. Patients were randomized through an interactive voice-response program to either in-hospital CR ($n = 150$) or COR ($n = 146$). CR was performed either at the time of primary PCI or as a staged procedure before hospital discharge. Randomization was stratified by infarct location (anterior/nonanterior) and symptom onset (≤ 3 h or > 3 h). The primary endpoint was a composite of all-cause death, recurrent MI, heart failure, and ischemia-driven revascularization. At 12 months, the primary endpoint occurred in 10.0% of the CR versus 21.2% in the COR group (hazard ratio: 0.45; 95% confidence interval: 0.24 to 0.84; $p = 0.009$), which again was due to a reduction in ischemia-driven or urgent revascularization. No significant reduction in death or MI was observed; although, there was a non-significant reduction in all primary endpoint components. Importantly, no difference was reported between groups in the safety endpoints of major bleeding, contrast-induced nephropathy, or stroke. The initial benefit of CR over COR was sustained at a median follow-up time of 5.6 years [21]. However, beyond 12 months, no significant difference between major cardiac adverse event, death/myocardial infarction, and individual components of the primary endpoint was observed.

In both the PRAMI and CvLPRIT trials, the estimation of lesion severity and decision to proceed with revascularization was based on angiographic appearance without physiologic assessment of lesion severity. The DANAMI-3-PRIMULTI Trial (Complete Revascularization versus Treatment of the Culprit Lesion Only in Patients with ST segment Elevation Myocardial Infarction and Multi-Vessel Disease) and COMPARE-ACUTE trial were unique for using Factional Flow Reserve (FFR) to evaluate non-culprit lesion severity and guide revascularization. FFR was previously shown to be reliable in assessing physiological significance of non-culprit lesions in patients with multivessel AMI [22]. DANAMI-3-PRIMULTI Trial enrolled 627 patients with STEMI who had one or more clinically significant coronary stenosis, in addition to the lesion in the infarct-related artery [23••]. After successful PCI of the infarct-related artery, patients were randomly allocated to either no further invasive treatment or complete FFR-guided revascularization before discharge. The primary endpoint was a composite of all-cause mortality, non-fatal reinfarction, and ischemia-driven revascularization of lesions in non-infarct-related arteries. CR guided by FFR measurements was done at a median of 2 days after the initial PCI procedure (IQR 2–4). Primary endpoint occurred in 68 (22%) patients allocated in the COR group and in 40 (13%) patients assigned in the CR group (hazard ratio 0.56, 95% CI 0.38–0.83; $p = 0.004$). Again, the benefit of CR was driven by a reduction in ischemia-driven revascularization (HR = 0.31, 95% CI: 0.18–0.53; $p < 0.0001$), and no significant difference was observed in the other individual components of the primary endpoint. In the COMPARE-ACUTE, 885 patients with STEMI and multivessel disease who had undergone primary PCI of an infarct-related coronary artery were randomized to undergo CR guided by FFR or COR [24••]. Unlike DANAMI-3-PRIMULTI Trial, FFR

procedure was performed during primary PCI in both groups in order to limit the need for sequential catheterizations and limit costs. Additionally, in the COR group, both the patients and their cardiologist were unaware of the FFR findings in order to control for observational bias. The primary end point was a composite of death from any cause, nonfatal MI, revascularization, and cerebrovascular events at 12 months. Analogous to the prior clinical trials, CR was associated with reduced primary end point events compared to COR, mainly driven by a reduction in subsequent revascularizations.

Following the publication of the four clinical trials (PRAMI, CvLPRIT, DANAMI-3-PRIMULTI, and COMPARE-ACUTE), it was evident that there was a trend towards improved outcomes with CR and SR compared to COR. In 2015, the ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with STEMI and revised the earlier class III recommendation for multivessel revascularization published in 2013 to IIb recommendation [3••]. The updated guideline suggests that complete revascularization can be considered either at the time of primary PCI or as a subsequent staged procedure. Similarly, the 2017 European Society of Cardiology guidelines provide a class IIA recommendation for complete revascularization of STEMI patients with multivessel disease [4] (Table 1).

Despite the promising findings and the update in the US and European guidelines, there were criticisms regarding (1) the lack of benefit on "hard" endpoints (mortality and recurrent MI), (2) the variability in timing of non-culprit revascularization (index procedure vs staged), and (3) the need of FFR for identification of non-culprit lesions that require complete revascularization. Additional evidence to the ongoing debate was provided by the COMPLETE trial (Complete versus Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early Percutaneous Coronary Intervention for STEMI) [25••]. The COMPLETE trial is the first trial to date, which has been adequately powered to assess whether CR strategy would lead to a meaningful reduction in the risk of cardiovascular death or new MI. In this trial, 4041 patients from 140 centers in 31 countries were randomized to either CR or COR. Patients who were randomly assigned to the complete-revascularization strategy were to have routine staged PCI of all suitable non-culprit lesions, regardless of whether there were clinical symptoms or evidence of ischemia. Investigators specified before randomization whether they intended to perform non-culprit lesion PCI during the index hospitalization or after hospital discharge (no later than 45 days after randomization). The first co-primary outcome was the composite of cardiovascular death or MI. The second co-primary outcome was the composite of cardiovascular death, MI, or ischemia-driven revascularization. At a median follow-up of 3 years, CR reduced the composite of cardiovascular death or MI (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.91; $p = 0.004$) compared to COR. This was primarily driven by a decrease in new MI (5.4% vs 7.9%; hazard ratio, 0.68; 95% CI, 0.53 to 0.86). There was no significant difference in cardiovascular mortality observed between the two groups. CR also reduced the second co-primary outcome (hazard ratio, 0.51; 95% CI, 0.43 to 0.61; $p < 0.001$). For both co-primary outcomes, the benefit of complete revascularization was consistently observed regardless of the intended timing of non-culprit lesion PCI ($p = 0.62$ and $p = 0.27$ for interaction for the first and second coprimary outcomes, respectively). Median time from randomization to non-culprit lesion PCI was 1 day (interquartile range, 1 to 3) for the patients

Table 1. Summary of major clinical trials evaluation culprit only vs complete revascularization

Trial	Year	N (complete/ culprit only)	Revascularization approach	Mean/median follow-up time	Major finding
PRAMI [19••]	2013	234/231	Primary PCI	24 months	PCI in non-infarct coronary arteries with major stenoses significantly reduces the risk of adverse cardiovascular events, as compared with PCI limited to the infarct artery.
CvLPRIT [20••]	2015	150/146	Primary PCI (67%) – staged prior to discharge (33%)	12 months	Complete revascularization is associated with an 11% absolute reduction in major adverse cardiovascular outcomes (MACE) at 12 months compared to culprit lesion-only revascularization, driven by symmetric modest reductions in each component of the primary composite outcome.
DANAMI-3-PRIMULTI [23••]	2015	314/313	Staged 2 days after primary PCI	27 months	FFR-guided complete revascularization is associated with a 9% absolute reduction in major cardiovascular adverse events (death, MI, revascularization) at 27 months.
COMPARE-ACUTE [24••]	2017	295/590	Primary PCI (83%) – staged prior to discharge (17%)	12 months	FFR-guided complete revascularization is associated with a 12.7% absolute reduction in major cardiovascular adverse events (death, MI, revascularization, stroke)
COMPLETE [25••]	2019	2016/2025	Staged: Prior to discharge (64%) – within 45 days (36%)	3 years	Complete revascularization was superior to culprit-lesion-only PCI in reducing the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization
CULPRIT-SHOCK [26]	2017	341/344	Primary PCI (91%) – staged (2.3%)	30 days	In patient with shock 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy in lower among those who initially underwent PCI of the culprit lesion only
EXPLORE [27••]	2016	150/154	Early PCI of the CTO (49.3%) – conservative (50.7%)	4 months	In CTO patients, no benefit in LVEF or LVEDV with complete revascularization

Table 1. (Continued)

Trial	Major adverse cardiac events	All-cause mortality	Re-infarction	Urgent revascularization
PRAMI [19••]	21/53	12/16	7/20	16/46
CvLPRIT [20••]	15/31	2/6	0/2	7/12
DANAMI-3-PRIMULTI [23••]	40/68	15/11	15/16	17/52
COMPARE-ACUTE [24••]	23/121	4/10	7/28	18/103
COMPLETE [25••]	179/339	96/106	109/160	29/160
CULPRIT-SHOCK [26]	189/158	176/149	3/4	13/74
EXPLORE [27••]	–	–	–	–

with intended timing of non-culprit lesion PCI during the index hospitalization and 23 days (interquartile range, 12.5 to 33.5) for the ones with intended timing of non-culprit lesion intervention after hospital discharge. Optical coherence tomography analysis in 93 patients from the CULPRIT trial revealed that nearly 50% had at least one obstructive non-culprit lesion containing complex vulnerable plaque [28]. Obstructive lesions more commonly harbored vulnerable plaque morphology than nonobstructive lesions. This may help explain the benefit observed with CR. Of note, patients in the COMPLETE trial had a low SYNTAX score, conferring an increased chance of successful revascularization.

A recent meta-analysis by Ahmad et al. including 10 studies with more than 7000 patients, confirmed the findings described by the clinical trials [29]. In their analysis, CR for STEMI patients was superior to COR for reduction in the risk of cardiovascular death (relative risk [RR], 0.68; 95% CI, 0.47–0.98; $p = 0.037$; $I^2 = 21.8\%$) and reduction in the risk of MI (RR, 0.65; 95% CI, 0.54–0.79; $p < 0.0001$; $I^2 = 0.0\%$). CR also significantly reduced the risk of unplanned revascularization (RR, 0.37; 95% CI, 0.28–0.51; $p < 0.0001$; $I^2 = 64.7\%$).

STEMI and cardiogenic shock

Approximately 5 to 10% of cases of AMI are complicated by cardiogenic shock (CS) [30]. CS in the setting of STEMI is associated with high mortality (40–50%) and worse outcomes [30]. Up to 80% of patients with cardiogenic shock have multivessel coronary artery disease [31]. Early revascularization, primarily with PCI, can restore blood flow to the culprit coronary artery and reduce mortality associated with CS [32, 33]. Several theoretical arguments support CR in patients with STEMI and CS as a mean to improve myocardial perfusion and function. Consideration of CR in patients with shock and STEMI has been recommended by both the 2011 ACC/AHA/SCAI [34] and 2012 ESC [35] guidelines. This recommendation was based on observational studies, as patients with cardiogenic shock were excluded from the larger clinical trials [19, 20, 23, 24]. In a prospective observational study from France, including 266 patients with STEMI and CS, CR was associated with higher 6-month survival (43.9% vs 20.4%, $p = 0.0017$) compared to COR [36••]. However, these findings were recently challenged by the randomized CULPRIT-SHOCK trial [26]. In this trial, 706 patients with MVD, AMI, and CS were randomized to one of two revascularization strategies: either PCI of the culprit lesion only with the option of staged revascularization of non-culprit lesions, or immediate multivessel PCI. The primary end point was a composite of death or severe renal failure leading to renal-replacement therapy within 30 days after randomization. Safety end points included bleeding and stroke. Staged revascularization was performed in 17.7% of the patients in the COR group, and the crossover rate was relatively low. At 30 days, primary end point events were less frequent in the COR group compared to the CR (relative risk, 0.83; 95% confidence interval [CI], 0.71 to 0.96; $p = 0.01$). This was driven by a reduced relative risk for death of 0.84 (95% CI, 0.72 to 0.98; $p = 0.03$) in the COR group as compared with the CR group. No significant difference in the relative risk for severe renal failure leading to renal-replacement therapy was observed. The time to hemodynamic stabilization, the risk of catecholamine therapy and the

duration of such therapy, the levels of troponin T and creatine kinase, and the rates of bleeding and stroke did not differ significantly between the two groups either. Based on the findings from the CULPRIT-SHOCK trial, the updated 2017 European Society of Cardiology guidelines recommend that primary PCI in patients with STEMI and shock should be restricted to culprit lesion only [4••].

STEMI and chronic total occlusion

Approximately 10% of STEMI patients have a chronic total occlusion (CTO) in a non-infarct-related artery (IRA). Their presence has been previously demonstrated to be an independent predictor of early and late mortality [27••]. Additionally, patients with STEMI and a non-IRA CTO are significantly less likely to achieve post-procedural TIMI 3 flow, more often have absence of myocardial blush, and less frequently achieve complete ST segment resolution [27••]. The EXPLORE trial (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) evaluated whether patients with STEMI and concurrent CTO in a non–IRA benefit from additional PCI of CTO shortly after primary PCI [37]. Three hundred and four patients with acute STEMI and concurrent CTO were enrolled to COR or early PCI of the CTO. Primary outcomes were left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) on cardiac magnetic resonance imaging after 4 months. The investigator-reported procedural success rate in the CTO PCI arm of the trial was 77%, and the adjudicated success rate was 73%. At 4 months, mean LVEF and mean LVEDV did not differ significantly between the 2 groups. A subgroup analysis of patients with CTO located in the left anterior descending coronary artery who were randomized to the CTO PCI strategy revealed significantly higher LVEF compared with patients randomized to the no–CTO PCI strategy. Further studies are needed to examine whether routine revascularization of non-IRA CTO lesions in STEMI patients, particularly in the left anterior descending coronary artery, will lead to improved clinical outcomes.

Conclusion

In the last few decades, optimal revascularization strategy for MVD in patients with STEMI has changed. The process of reaching a therapeutic decision often necessitates individualized and patient-centered approach based on lesion characteristics, hemodynamic parameters, as well as other comorbidities. CR should be considered in STEMI patients with low SYNTAX score and without CS. This can be achieved either during the index hospitalization or as a staged procedure within 45 days from discharge. On the other hand, patients with CS or non-IRA CTO are likely to benefit from a COR approach. FFR-guided revascularization can be used with decisions regarding which non-culprit lesions should be treated; although, in several clinical trials, angiographic guidance alone was used. Given the body of evidence, both ACC/AHA and ESC have updated their STEMI guidelines. The European guidelines from 2017 now suggest a IIa recommendation (level of evidence, A) and state that "routine revascularization of non-infarct-related artery lesions should be considered in STEMI patients with multivessel disease before hospital discharge" [4••]. The

ACC/AHA guidelines from 2015 give a class IIb recommendation (level of evidence, B-R) and state that "PCI of a non-infarct 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 procedure" [3••]. Future US guidelines will likely support a stronger recommendation for non-infarct artery PCI in STEMI, given the evidence from the COMPLETE trial [25••].

Compliance with Ethical Standards

Conflict of interest
Konstantinos V. Voudris declares that he has no conflict of interest. Dmitriy N. Feldman declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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PRAMI trial – first clinical trial to show improved primary outcome in the complete revascularization group.

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CvLPRIT trial – confirmed the PRAMI trial findings. Improved outcomes were the result of a reduction in ischemia driven or urgent revascularization.

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DANAMI-3-PRIMULTI trial– included the use of Factional Flow Reserve (FFR) to evaluate non-culprit lesion severity and guide revascularization.

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COMPARE-ACUTE trial - FFR procedure was performed during primary PCI in both groups in order to limit the need for sequential catheterizations and limit costs.

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COMPLETE trial - largest trial, adequately powered to assess whether CR strategy would lead to a meaningful reduction in

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EXPLORE trial – Worse outcomes with complete revascularization in CTO patients.

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CULPRIT-SHOCK trial – Complete revascularization in shock patients associated with worse outcomes.

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