



Review Article

New Paradigm of Complete Revascularization in Acute Coronary Syndrome with Multivessel Coronary Artery Disease: Is it Reasonable in Clinical Practice?

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ABSTRACT

Background: Coronary artery disease is the leading cause of illness and death in older adults. Around 40% to 50% of patients with ST-segment elevation myocardial infarction (STEMI) have multiple coronary artery disease. Multiple vessel coronary disease has been shown to improve cardiac outcomes and survival in patients who have undergone complete revascularization (CR) versus patients who have undergone only incomplete revascularization (ICR).

Objective: In this review, we discussed the benefit of complete revascularization in acute coronary syndrome (ACS) patients with multivessel disease and which patient can be performed aggressive revascularization to achieved CR in clinical practice.

Discussion: When coronary angiography and PCI of the source of the infarction are performed on patients with ACS, the risk of adverse cardiac death or myocardial infarction is significantly reduced. Additional research is needed to determine the efficacy of PCI in non-critical lesions. However, following procedures such as CABG or PCI, these procedures may be impossible to perform due to a variety of personal, anatomical, technical, and logistical barriers.

Conclusion: In order to make a clinical decisions, lesions need to be evaluated as well as several variables, such as patient behavior, cardiovascular health, and other factors also have to be considered. CR has been demonstrated in several studies to result in decreased rehospitalization and the need for repeated revascularization in the subsequent period in ACS patients with a low SYNTAX score and no cardiogenic shock.

1. Introduction

About half of patients with STEMI and two-thirds of patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) have additional stenosis distal to the infarct-related artery. Additional non-culprit revascularization may be possible in patients with acute coronary syndromes (ACS) and multivessel disease.¹ A worse short-term and long-term prognosis has occurred with multivessel coronary disease (MVD). Some lesions indicate a stable plaque of atherosclerosis, which may exclude invasive treatment. An unstable, fragile plaque with high-risk characteristics suggests other lesions, indicating an increased risk of further cardiovascular events.²

Cardiogenic shock exacerbates the mortality associated with acute myocardial infarction when prompt revascularization, including percutaneous coronary intervention, is performed (AMI). It remains between 40% and 60%. Additionally, patients over the age of 75 with AMI complicated by cardiogenic shock may have higher one-year mortality than their younger counterparts, regardless of age or gender.

About 34%–50% of patients with STEMI have multiple vessel coronary artery disease.³ For several decades, the ideal strategy for MVD revascularization in the setting of STEMI has been a topic of research and debate. Numerous solutions have been suggested, including the following: (a) Culprit-only revascularization (COR) with subsequent revascularization based on symptoms or non-invasive imaging proof of ischemia, (b) Complete revascularization (CR) at the time of the index culprit-lesion procedure, or (c) Complete revascularization as a staged procedure either concurrently with or shortly after the index culprit lesion procedure (within 45 days).²

While complete revascularization was not an independent predictor of mortality in the general population, it was associated with a lower risk of death in patients with chronic lung disease, a history of congestive heart failure, or who had not previously received PCI. Although this research was not intended to assess if full revascularization is superior to partial revascularization, the results indicate that when PCI is used to treat patients with coronary artery disease, achieving complete revascularization does not result in an increased risk of

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death.⁴ However, the relative benefits of full revascularization of both culprit and non-culprit vessels versus culprit-only or partial revascularization continue to be discussed around the spectrum of acute coronary syndromes treated with percutaneous coronary intervention (PCI). One obvious benefit of incomplete revascularization is that it treats ruptured or eroded plaque while preventing periprocedural complications associated with a non-culprit intervention. By contrast, as shown recently in STEMI, full revascularization may affect potential cardiac events.⁵

We discussed a new paradigm for treating ACS patients with multivessel disease in this review article. This subject has been widely discussed in recent years, and there are numerous contradictory data. We discussed which patients benefited more from complete revascularization or culprit-only revascularization.

2. Discussion

2.1 Culprit Only Revascularization in STEMI

Various retrospective trials and registry-based studies supported the superiority of culprit-only revascularization for ST-segment elevation myocardial infarction. Although Cavender et al. found that CR (with survival at the hospital) was associated with a significantly higher risk of mortality (7.9% vs 5.1%, $p=0.01$), Both three randomized clinical trials and eight thousand patients in total (CR, 7,498 patients; COR, 8,240) were included in the data review by Dr. Lu, along with non-randomized studies ($N = 10,999$) that additionally included 6,997 subjects undergoing CR and 7,509 subjects undergoing CABG (COR). Creativity is linked to an increased risk of death and kidney disease.⁷

When Iqbar and colleagues surveyed 3,804 patients with MVD who had PCI done at tertiary hospitals in London between 2004 and 2011, they found similar results. There was a decrease in the number of in-hospital significant incidence of major adverse cardiac events and mortality which was associated with the COR strategy at one year. Moreover, the observational results indicated a significant reductions in the chances of both MACE (OR 0.49; 95% confidence interval, 0.32–0.91; $p<0.001$) and 1-year survival (out of hospital MACE: 0.47; 95% CI, 0.32–0.91; $p=0.011$) in the entire cohort, and an expanded propensity matching group (OR 0.49; 95% CI, 0.32–0.91; OR 0.91) for MACE). This result was borne out by inverse likelihood treatments, which revealed that COR was a key independent risk factor for MACE (OR, 0.38; 95% confidence interval, 0.15–0.96; odds ratio, 0.35 to 1.44) and survival (HR, 0.33; 95% confidence interval, 0.21 to 0.45 to 0.44) over a year after an episode of AMI.)⁸

Recent results have supported the 2013 American College of Cardiology/AHA STEMI Guidelines.⁹ It has also been used to help patients with cardiogenic shock or refractory periods who do not have creatinine phosphokinase (CPK) elevations (CPI). However, the ESC also recommended non-culprit revascularization in patients who are shocked, or who have critical lesion following PCCI when other culprit causes cannot be identified, or who are not improving after PCI (IIb).¹⁰

In patients with acute myocardial infarction with cardiogenic shock, the early PCI revascularization of the culprit artery will increase the survival rate. However, a majority of cardiogenic shock patients have multivessel disorder and whether PCI should be performed in

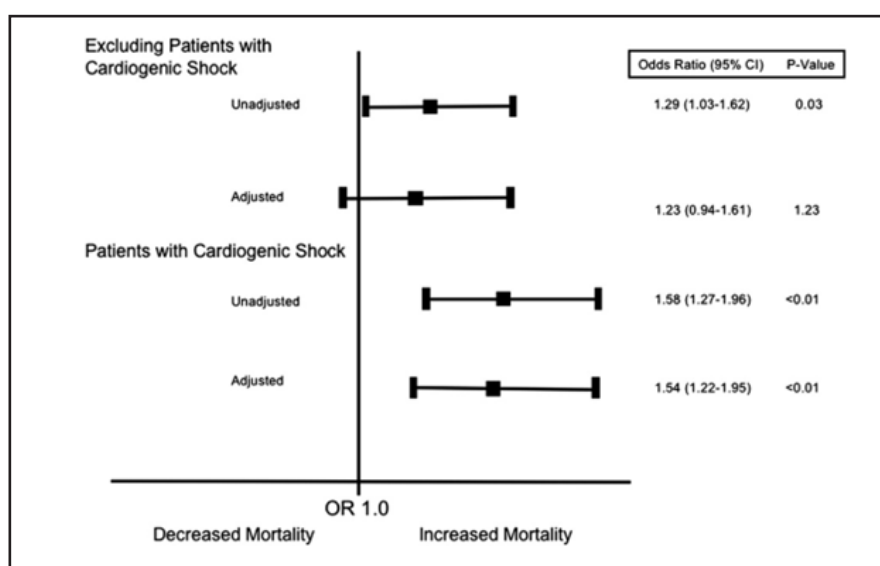


Figure 1. Odds ratios for mortality associated with multivessel PCI in a 2009 study by Cavender et al. Even after adjustment for confounding variables, patients in cardiogenic shock treated with multivessel PCI had an increased risk of death compared to patients treated with PCI of the infarct-related artery alone. Patients who were not in cardiogenic shock demonstrated a non-significant trend toward an increased risk of death.⁶

stenoses in non-culprit arteries immediately is problematic. In the CULPRIT SHOCK trial, one of two initial revascularization strategies has been randomly allocated to 706 patients suffering from a multivessel, acute myocardial infarction, and a cardiogenic shock: culprit lesion PCI alone with the option of staged revascularization of the non-culprit lesion or immediate multi-vessel PCI. In patients with a MVD and an acute cardiogenic myocardial infarction who initially suffered a PCI from the culprit lesion, the 30-day risk of having a composite death or severe renal failure requiring renal substitution was lower than for those who were immediately affected by multi-vessel PCI.¹¹

2.2 Complete Revascularization in STEMI

There is considerable debate about the optimal treatment strategy for patients with STEMI, cardiogenic shock, who exhibit multivessel disease on initial coronary angiography. There is disagreement about whether to revascularize the culprit only or the whole vessel during the index revascularization, and the appropriate approach needs to be re-addressed. Cardiogenic shock, which occurs in the presence of prompt revascularization, including percutaneous coronary intervention, exacerbates the mortality associated with AMI. It remains between 40% and 60%. Additionally, in terms of age and gender, patients over the age of 75 with AMI complicated by

cardiogenic shock can have higher one-year mortality than their younger counterparts. About 34%–50% of patients with STEMI have coronary artery disease involving multiple vessels.¹³

In several clinical trials published in recent years, there have been doubts as to the optimal revascularization strategy for STEMI patients with multivessel heart disease, which lays the foundations for a change in our understanding of the paradigm. In 2013, the PRAMI trial findings were presented in a paper by Wald et al. In the case of STEMI and MVD, 465 patients received primary PCI. Patients have been randomly assigned to undergo either complete PCI with 234 patients or COR with 231 patients. The main result was a combination of cardiac death, non-fatal myocardial infarction, and angina. After a median follow-up of 23 months, the analysis was completed early due to a significantly improved primary CR performance. It was the result of a reduction in the likelihood of repeated revascularization (6.8% versus 19.9%), nonfatal MI (3.5% versus 8.7%), and refractive angina (5.1 percent vs 13.0 percent). In addition, the trend to decrease heart mortality with a hazard ratio of 0.34 has also been important. Furthermore, the average of all major cardiac death endpoints and non-fatal MI decreased significantly with a risk of 0.36.¹⁴

After around two years, the Randomized Trial of Complete vs. Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI or Multi-Vessel Disease (The CvLPRIT Trial). That was conducted at seven hospitals in the U.K. hospitals and enrolled a total of 296 STEMI patients. Complete revascularization was done either concurrently with primary PCI or in stages prior to hospital discharge stratification was used in order to stratify by time of onset and location of infarction. Survival rate of any cause mortality, chronic MI, heart failure, and MI related procedure of revascularization were the primary measures of the study's efficacy. The primary outcome occurred in 10% of the CR population, compared to 21.2% of the COR group (hazard ratio: 0.24; CI: 0.13-0.44; $p = 0.009$), which was later concluded to be due to less angina events and more effective treatment of ischemia-mediated vessels and the risk of which is significantly lowered. Although there was no evidence of any real change in mortality or myocardial infarction, the study found a substantial. It should be noted that there was no significant difference in the severity of any bleeding, contrast-induced nephropathy, or stroke between groups.¹⁵

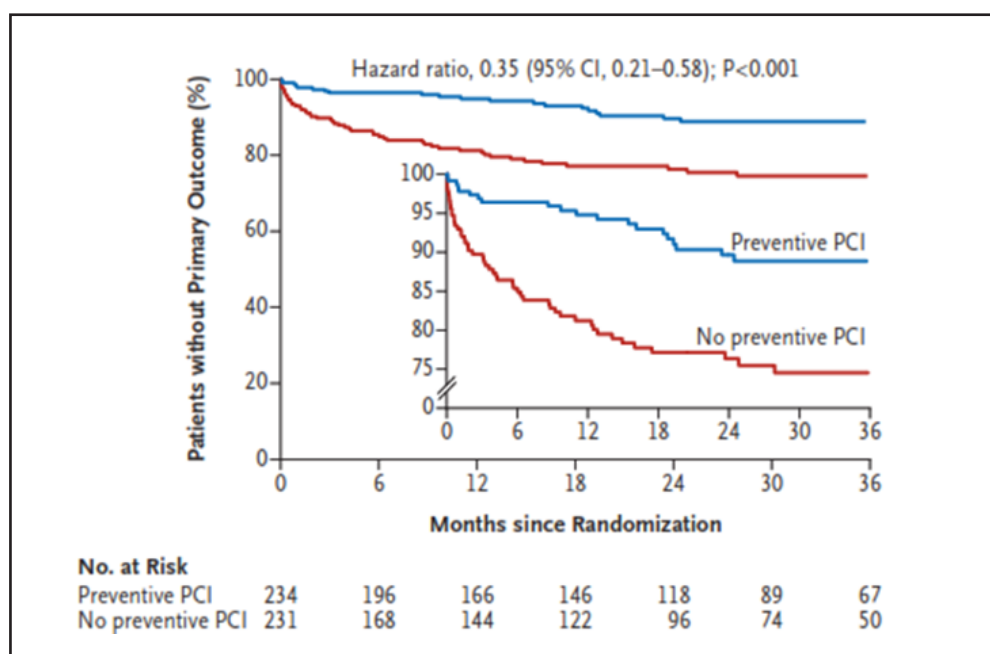


Figure 2. Primary Outcome from PAMI study. The primary result was a cardiac death composite, non-fatal myocardial infarction, or angina refractory. All patients in the study were randomized immediately before infarction-artery PCI.¹⁴

Physiologic severity of lesion was not considered in the PRAMI and CvLPRIT trials. The DANAMI-3PRIMULTI Trial and COMPASS trials were revolutionary in their use of the fractional flow reserve (FFR). There is evidence to show that the FFR is an effective way to evaluate non-culprit lesion in patients with multiple-vessel AMI.¹⁶ Study that analyzed 627 STEMI patients were included in the DANAMI-3-PRIMULTI Trial who had at least one other significant coronary artery lesion. Patients were divided into two groups: those in whom PCI plus FFR revascularization prior to discharge and those in whom no further care was indicated. The research objectives included evaluating the association between primary out-come measures of reinfarction, nonfatal infarction, and revascularization of non culprit related arteries. Complete revascularization led by FFR measurements was performed a median of two days after initial PCI procedure. Primary endpoint was achieved in 68 (22%) patients assigned to the COR group and 40 (13%) patients assigned to the CR group with hazard

ratio 0.56. According to the current findings, again CR had beneficial effect due to its impact on ischemia-induced revascularization (CI: 0.18-0.53; HR: $p < 0.001$).¹⁷

The COMPARE-ACUTE study target-guided PCI to those who used FFR or COR in 885 patients with multivessel disease who received primary PCI of a vessel-related target. Unlike the DANAMI-3-PRIMULTI Trial, both groups underwent the FFR procedure during primary PCI to avoid the need for sequential catheterizations and to save money. The design of the study did not enable the patients and their cardiologists to know the relative frequency of positive and negative FFR outcomes to be compared, eliminating the possibility of confounding biases. By the year mark, the primary endpoint was catastrophic MI, nonfatal MI, and cerebrovascular event. CR as found in earlier trials to be mainly due to a decline in subsequent revascularizations.¹⁸

From the outcomes of four clinical trials, it was decided that CR and COR had better results on average (PRAMI, CvLPRIT, COMPARE, and DANAMI-3-PRIMULTI). The American College of Cardiology, American Heart Association, and SCAI upgrade their approach to primary percutaneous coronary intervention in 2013 from class III to class IIb in the following year. According to the revised guidelines, complete revascularization may be considered either as part of the primary percutaneous coronary intervention or in a subsequent staged procedure. According to these recommendations, multivessel procedures should be applied to all patients with STEMI in 2017 ESC guideline.²⁰

2.3 Complete Revascularization in NSTEMACS

Bailey et al. showed that complete revascularization occurs regularly and is associated with improved clinical results, through a detailed prospective angiography-based registry of ACS patients undergoing PCI. A 10% (risk-myocardium) residual angiographical risks score was correlated with a decreased death risk from any new cause or MI within five years. In addition, after complete revascularization, this study showed a drop in total mortality. Incomplete revascularization, on the contrary, has increased the adverse effects proportionally to the amount of myocardium affected. The full renewal was correlated with a decrease of 22 percent in the composite of death or recurrent MI over the long-term following adjustment for confusing variables. Comparable death and MI reductions have also been found alone. The benefits of complete revascularization are also almost definitely related to the treatment of non-cultural lesions as a preventive step to reduce long-term risk.²¹

Total revascularization, irrespective of the type of ACS presentation, was correlated with better clinical results within five years. There are no randomized trials to support complete revascularization of multivessel PCI-patients with NSTEMACS. In an ACUTY research (ACUTY) study, a rise in the probability of mortality, MI, or unplanned revascularization and the trend towards increased death was correlated with incomplete revascularization. The multivessel PCI was associated with a decrease in death or recurring MI or revascularization over 2-year median follow-up in a small retrospective study conducted in 1240 NSTEMACS patients.²²

The advantage of using FFR to guide PCI in dysfunctional angina/NSTEMI population is comparable with the stable angina population, as seen for the first time in a FAME report. The use of FFR, including NSTEMI's culprit lesion, was subsequently demonstrated to be feasible and secure in a randomized controlled trial setting.²³ The expected time frame of non-culprit lesion PCI was fixed for randomization in the COMPLETE trial. Prior to the randomization, investigators had to find out, whether during the index hospitalization or after discharge (within 45 days) they needed to perform PCI for non-culprit lesions whether the patient was allocated to a whole population of revascularization. This study found that complete revascularization is clearly advantageous, irrespective of whether the lesion was not the culprit. PCI was performed immediately or several weeks later following index hospitalization.⁵

2.4 Complete Revascularization in Specific Population

Chronic kidney disease (CKD) is rising in prevalence among

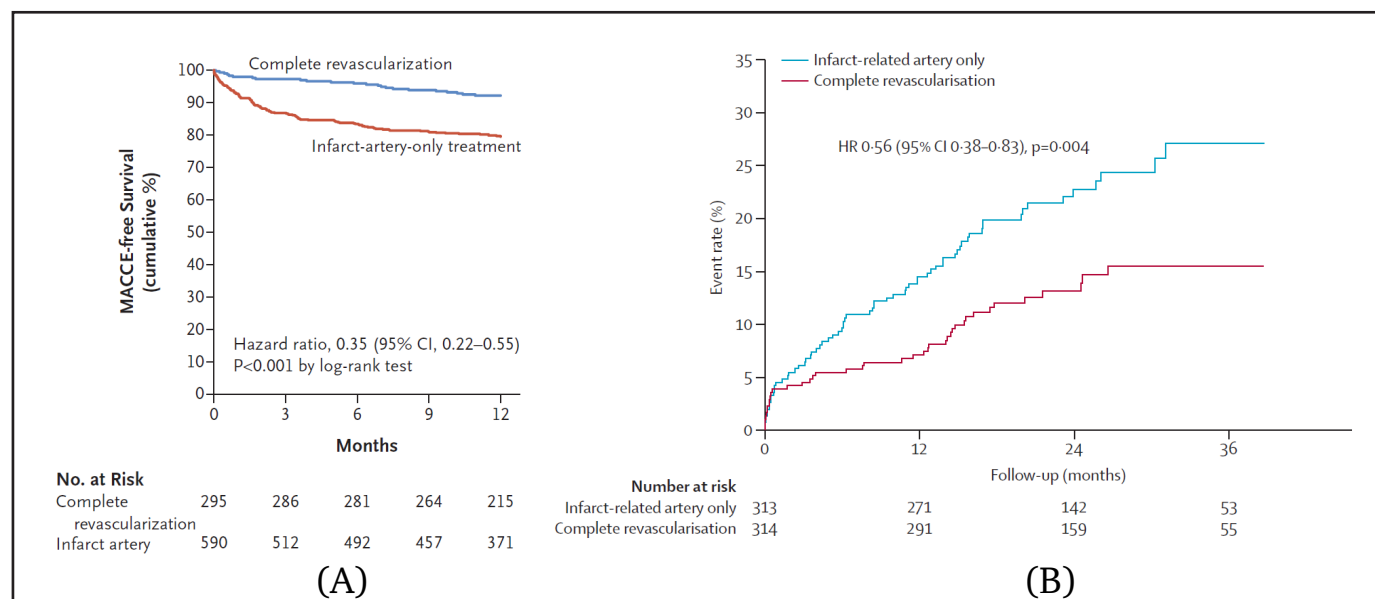


Figure 3. Result of trial that showed benefit of CR in STEMI with guidance of FFR. (A) COMPLETE-ACUTE trial showed CR significantly improved survival than COR in first year¹⁸ (B) DANAMI-3 PRIMULTI trial showed reduced event rate in patient that performed complete revascularization.¹⁷

PCI candidates, owing to the aging population and the growing burden of comorbidities such as diabetes mellitus. Additionally, since patients with chronic kidney disease have more severe and complex coronary lesions than patients with retained renal function, CKD has been identified as a significant indicator of adverse cardiovascular events following PCI. A trial was conducted to determine the therapeutic utility of angiographic full revascularization with contemporary stents in a population of patients with chronic kidney disease by using the Grand Drug-Eluting Stent registry in Korea. The findings demonstrate that angiographic complete revascularization resulted in improved clinical outcomes in patients with chronic kidney disease (CKD) and

outcomes. This finding was consistent with a sub-study of the SYNTAX trial, which demonstrated that a residual SYNTAX score of less than 8 was associated with comparable 5-year mortality following full revascularization. However, a residual SYNTAX score of 3 was a fair degree of revascularization in patients with chronic kidney disease. While we were unable to determine a definitive degree of appropriate incomplete revascularization using registry data, our findings indicate that we should treat residual disease more carefully in patients with CKD and that efforts to achieve complete revascularization are more critical in patients with CKD than in patients with preserved renal function.²⁵

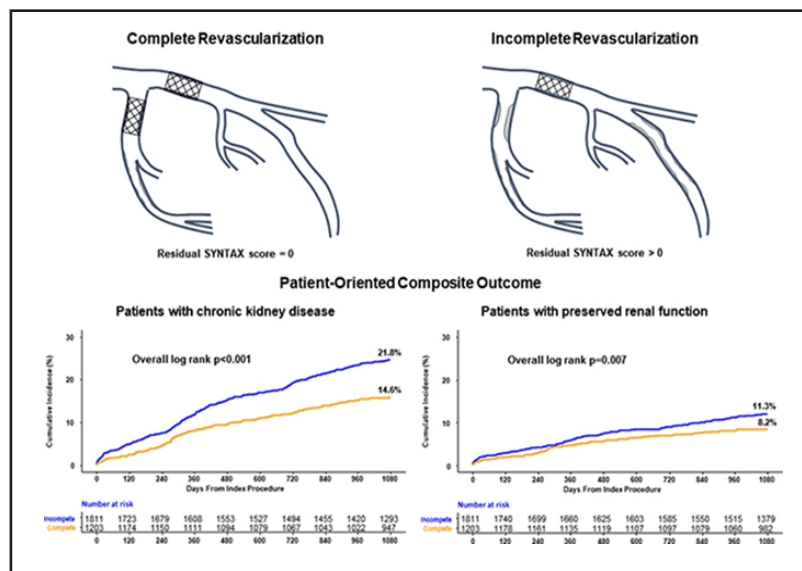


Figure 4. Cumulative incidence of clinical outcomes after complete and incomplete revascularization in patient with CKD.²⁴

Around 40% of patients with a one permanent chronic occlusion (CTO) also have diabetes melitus (DM). In exchange, DM is associated with an increased CTO risk. Although successful CTO renewal in patients with diabetes tends to be associated with better clinical outcomes, there is no evidence that this high-risk population has an appropriate choice of care. Coronary artery graft bypass (CABG) is the recommended form of revascularisation in multi-vessel patients with diabetes mellitus (DM). In addition to single medicamentosa treatment, the effective PCI of CTO is associated with lower long-term mortality rates. The CABG group experiences complete revascularization more frequently than the PCI group (62 percent vs. 32 percent). Multivariable research found that the rates of all-cause CABG and cardiac mortality in relation to PCI were correlated with substantially lower. The effective PCI CTO procedure has been correlated with an all-cause mortality trend.²⁶

2.5 Cost Benefit of Complete Revascularization

The leading cause of death and major worldwide burden in Indonesia is cardiovascular disease, with more than 150 000 deaths per year, and annual costs in the United Kingdom of over £15 billion.²⁷ The cost of a PCI procedure was RM11 471 (US\$ 3186) to RM14 465 (USD 4018) in Malaysia, and over half the total cost of PCI consumables. As shown in this cross-sectional study, alternative procurement practices for PCI consumables could lead to cost savings. Economic analysis can be performed with a costing approach adapted to the context of the country for countries with limited access to data.²⁸

Although these results are confirmed in larger studies, emerging clinical studies make a cost-effectiveness assessment of overall against infarct-only revascularisation. Although there may be increased upfront costs associated with revascularization, it is important that we understand whether these costs are covered by lower future hospital admissions and less adverse events. CvLPRIT research has shown that complete revascularization during index admission has been more effective in terms of fewer major adverse cardiovascular events and an increase in QALY gain than IRA-only revascularisation in a population of STEMI patients and multivessel diseases. Since higher procedural costs are generally compensated for by lower re-admission rates, implying comparable total costs, these data show that complete revascularization is an economical way to treat STEMI and multivessel patients.²⁷

Between 2005 and 2015, a CAD epidemic costs the Government of India 237 million US dollars (USD) reported by the World Health Organization (WHO). The use of an FFR-guided approach in the treatment of SIHD patients demonstrated substantial cost savings both in private and public health in Asia-Pacific countries. The evaluation of FFR by Thomson et al. has found that 80 percent of patients have changed their management strategy. In almost one-third of patients referred for coronary PCI, only 29% of surveyed lesions were hemodynamically significant, resulting in stent avoidance. In countries where most of the patients self-support their health care, the PCI is convenient and cost-effective with almost one in three coronary angioplasty patients refusing stent and PCI.²⁸ The subsequent report from the COMPARE-ACUTE trial would examine the outcome after three years, as well as the cost of this technique. After 36 months, the primary outcome (death, myocardial infarction, revascularization, and stroke) occurred substantially less frequently in the FFR-guided complete revascularization group: 46/295 patients (15.6 percent) versus 178/590 patients (30.2 percent) (HR 0.46, 95 percent confidence interval [CI]: 0.33-0.64; p0.001). This advantage was primarily due to a decrease in revascularizations during the follow-up period (12.5 percent vs 25.2 percent; HR 0.45, 95% CI: 0.31-0.64; p0.001). Cost analysis demonstrates the utility of the FFR-guided complete revascularization approach, which can reduce costs per patient by up to 21% in the first year (8,150€ vs 10,319€) and by 22% in the second year (8,653€ vs 11,100€).¹⁹

3. Conclusion

Due to advances in the optimal treatment of STEMI, the strategy for revascularization has progressed over the years. In order to make a clinical decisions, lesions need to be evaluated as well as several variables, such as patient behavior, cardiovascular health, and other factors also have to be considered. In STEMI patients with a low SYNTAX score and no cardiogenic shock, CR should be pursued. This can be attempted either simultaneously with the admission or after the discharge of the patient from the hospital within 45 days. CS and non-IRA CTO patients respond best to a COR approach. While some clinical trials used angiographic guidance alone, FFR-guided revascularization can be used to make decisions on which non-culprit lesions to treat. In some specific conditions associated with the patient, such as chronic kidney disease (CKD) or diabetes, choosing a fair partial revascularization is still permissible if complete revascularization is not possible. The cost effectiveness of CR has been demonstrated in several

variables, such as patient behavior, cardiovascular health, and other factors also have to be considered. In STEMI patients with a low SYNTAX score and no cardiogenic shock, CR should be pursued. This can be attempted either simultaneously with the admission or after the discharge of the patient from the hospital within 45 days. CS and non-IRA CTO patients respond best to a COR approach. While some clinical trials used angiographic guidance alone, FFR-guided revascularization can be used to make decisions on which non-culprit lesions to treat. In some specific conditions associated with the patient, such as chronic kidney disease (CKD) or diabetes, choosing a fair partial revascularization is still permissible if complete revascularization is not possible. The cost effectiveness of CR has been demonstrated in several studies to result in decreased rehospitalization and the need for repeat revascularization in the subsequent period.

4. Declarations

4.1. Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3. Availability of data and materials
Data used in our study were presented in the main text.

4.4. Competing interests
Not applicable.

4.5. Funding source
Not applicable.

4.6. Authors contributions
Idea/concept: APW. Design: APW, MSR. Control/supervision: MSR. Data collection/processing: APW. Analysis/interpretation: APW, MSR. Literature review: APW. Writing the article: APW. Critical review: MS, NK, CTT. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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