GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Lessons from the trials

Culprit lesion-only versus complete revascularization in patients with STEMI: Lessons learned from PRAMI, CvLPRIT, and DANAMI-3 PRIMULTI

Ahmed Hassan[1,2], Ahmed ElGuindy[1,*], David Antoniucci[3]

[1]Aswan Heart Centre, Aswan, Egypt
[2]Department of Cardiology, Cairo University, Cairo, Egypt
[3]Careggi Hospital, Florence, Italy
*Email: ahmed_elguindy@hotmail.com

BACKGROUND

Primary percutaneous coronary intervention (PCI) is the current standard of care for ST-elevation myocardial infarction (STEMI). About 40–50% of patients presenting with STEMI have multivessel disease (MVD). Compared to patients with single vessel disease, patients with STEMI and MVD have higher mortality rates and a greater incidence of non-fatal re-infarction. The underlying mechanism for this adverse prognosis may be plaque instability in a non-infarct vessel, impaired myocardial perfusion and contractility and/or arrhythmia.[1,2,3] It has been shown that patients presenting with STEMI and coexisting chronic total occlusion (CTO) of a non-infarct artery have worse clinical outcomes – including higher mortality – compared to those with no concomitant CTO.[4] It is unclear whether the poorer prognosis of patients presenting with STEMI and MVD is attributable to residual ischemia due to untreated lesions or simply due to an increased disease burden.[5]

The concept of PCI of non-culprit lesions during index hospitalization in patients undergoing primary PCI has been debated for years. Multivessel intervention during the index primary PCI has some potential advantages. It may limit the infarct size and preserve left ventricular function, as well as prevent recurrent ischemia and infarction. On the other hand, a prolonged multivessel procedure may increase contrast use and risk of stent thrombosis in non-culprit lesions given the pro-inflammatory and pro-thrombotic state associated with STEMI.

Historical data provided conflicting evidence on the benefit of multivessel PCI in patients with STEMI. Previous meta-analyses showed that multivessel PCI compared with IRA-PCI resulted in worse outcomes in cohort studies.[6,7] Earlier non-randomized studies showed that multivessel PCI performed during the index procedure was associated with the highest mortality whereas multivessel PCI done at a later stage – either during the index admission or within one month – was associated with the lowest mortality.[8,9] Due to these uncertainties, a number of randomized trials aiming to identify the optimal management strategy of multivessel coronary artery disease in the setting of primary PCI have been conducted over the past few years.

PRAMI TRIAL

Results of the Randomized Trial of Preventive Angioplasty in Myocardial Infarction (PRAMI) were presented at the European Society of Cardiology Congress 2013. PRAMI was a multicenter, UK-based study that recruited 465 patients who underwent primary PCI. Patients were randomized to receive either infarct-related artery (IRA) only PCI (231 patients) or immediate preventive PCI of non-infarct related vessels in addition to PCI to the IRA (234 patients). Eligible patients were randomized after completion of IRA PCI.

http://dx.doi.org/10.5339/gcsp.2015.60

Submitted: 1 August 2015
Accepted: 29 September 2015

QSCIENCE.com
An Initiative of Qatar Foundation

Cite this article as: Hassan A, ElGuindy A, Antoniucci D. Culprit lesion-only versus complete revascularization in patients with STEMI: Lessons learned from PRAMI, CvLPRIT, and DANAMI-3 PRIMULTI, *Global Cardiology Science and Practice* 2015:60 http://dx.doi.org/10.5339/gcsp.2015.60

The non-infarct related vessel had to have an angiographic stenosis of 50% or more as assessed by the operator. Patients with significant left main stem disease, left main equivalent pattern of coronary artery disease, and patients with chronic total occlusions were excluded from the study. Subsequent PCI for angina was restricted to patients with refractory angina and objective evidence of ischemia. The primary outcome of the study was the composite of cardiac death, nonfatal myocardial infarction or refractory angina.

During an average follow-up of 23 months, the rate of cardiac death, nonfatal MI, or refractory angina was lower in the preventive PCI group. The reduction was statistically significant for nonfatal MI (HR 0.32, 95% CI 0.13-0.75) and refractory angina (HR 0.35, 95% CI 0.18-0.69) but not for cardiac death (HR 0.34, 95% CI 0.11-1.08). Repeat revascularization was lower with preventive PCI (HR 0.30, 95% CI 0.17-0.56) but there was no difference in non-cardiac death (HR 1.10, 95% CI 0.38-3.18).

The rate of complications including procedure-related stroke, bleeding requiring transfusion or surgery, and contrast-induced nephropathy requiring dialysis, was similar in the two groups ($p = 0.84$). Procedure time, fluoroscopy dose, and contrast volume were higher in the preventive-PCI group.[10]

CvLPRIT TRIAL

Complete versus Lesion-only Primary PCI trial was an open-label, multicenter, randomized UK study. Patients presenting for primary PCI within 12 hours of symptom onset in whom angiography demonstrated multivessel coronary disease were randomized to receive IRA-only (n = 146) or complete revascularization (n = 150). Multivessel disease at angiography was defined as at least one lesion in a non-IRA deemed angiographically significant (≥70% luminal diameter narrowing in single projection). The non-IRA should be a major epicardial coronary artery or branch that is larger than 2mm and suitable for stent implantation.

Exclusion criteria included any contra-indication to primary PCI, contra-indication to multivessel PCI according to operator judgment, previous Q-wave myocardial infarction, cardiogenic shock, ventricular septal defect, moderate/severe mitral regurgitation, known severe chronic kidney disease, and previous coronary artery bypass grafting.

Complete revascularization was performed either at the time of primary PCI, or before hospital discharge. The primary end point was a composite of all-cause death, recurrent myocardial infarction, heart failure, and ischemia-driven revascularization within 12 months. The secondary endpoints were safety endpoints of: confirmed ischemic stroke, intracranial hemorrhage, major non-intracranial bleeding, and repair of vascular complications.

The primary endpoint of this trial was presented as time to first event. Major adverse cardiovascular events (MACE) were significantly lower in the complete revascularization arm (10.0%) than the IRA-only arm (21.2%; hazard ratio: 0.45; 95% confidence interval: 0.24 to 0.84; $p = 0.009$). The difference between the two groups was seen early (p = 0.055 at 30 days). There was a trend toward lower rates of the individual components of the primary end point and cardiovascular mortality in the complete revascularization arm. The incidence of procedure-related stroke, major bleeding or contrast-induced nephropathy was similar in both arms. Procedure time and contrast volume were significantly higher in the complete revascularization group compared to the IRA-only PCI group.[11]

DANAMI-3 PRIMULTI TRIAL

DANAMI-3 PRIMULTI trial is part of the DANAMI-3 trial program. The program encompasses three randomized trials investigating the effect of deferred stenting (DANAMI-3 DEFER), ischemic post-conditioning (DANAMI POSTCON), and complete revascularization (DANAMI-3 PRIMULTU). DANAMI-3 PRIMULTI was an open-label, randomized controlled trial that was conducted at two university hospitals in Denmark. It recruited 627 patients presenting with STEMI who had one or more clinically significant coronary stenoses in addition to the lesion in of the infarct-related artery. After completion of PCI to the IRA, patients were randomized to receive either no further invasive treatment (n = 313) or complete FFR-guided revascularization before discharge (n = 314). PCI was performed to non-IRA lesions in large vessels (diameter >2mm) with FFR values of 0.80 or lower in addition to vessels with visually estimated stenoses greater than 90%.

Exclusion criteria included intolerance to contrast media or to relevant anticoagulant or antithrombotic drugs, unconsciousness or cardiogenic shock, stent thrombosis, indication for coronary-artery bypass grafting, or increased bleeding risk. The primary endpoint was a composite of

all-cause mortality, re-infarction, or ischemia-driven (subjective or objective) revascularization of lesions in non-infarct related arteries. Key secondary endpoints were components of the primary endpoint: occurrence of cardiac death, and urgent and non-urgent PCI of lesions of non-infarct-related arteries.

Complete revascularization guided by FFR measurements was done at a median time of 2 days after the initial PCI procedure. The results of the trial were recently published in *The Lancet*.[12] The primary endpoint occurred in 68 (22%) patients allocated to no further invasive treatment and in 40 (13%) patients assigned to complete revascularization (hazard ratio 0.56, 95% CI 0.38–0.83; p = 0.004). This was driven by a lower rate of repeat revascularization (69% reduction in the need for repeat revascularizations) in the complete revascularization arm. There were no differences between the groups with regard to nonfatal MI or mortality. The need for both urgent and non-urgent PCI of lesions in non-infarct-related arteries was significantly lower in the complete revascularization group. There was no significant difference in procedure related complications between the two groups.[12]

DISCUSSION

In real world clinical practice, there are different interventional strategies that have been used for managing hemodynamically stable patients with STEMI and MVD during the index hospitalization. The first is PCI to IRA and no other diseased vessels are targeted, regardless of their significance; the second is PCI to IRA then staged PCI to other significant lesions before discharge; the last and least utilized strategy is immediate complete revascularization during the index procedure.

Benefits of revascularization of lesions in non-infarct-related arteries should be balanced against the potential risks of the additional procedure. In contrast to the randomized studies addressed in this report, earlier non-randomized observational studies showed higher mortality with a complete revascularization strategy in STEMI patients with multivessel disease. However, this observation might be due to the sicker cohort of STEMI patients enrolled in these studies with outcomes simply reflecting the burden of disease rather than the effect of a particular treatment strategy. In addition, the observational nature of these studies makes the reported associations susceptible to confounding, and a treatment-effect relationship cannot be determined reliably.

While the three randomized studies addressed in this report add extremely valuable information on the safety and potential benefits of complete revascularization in patients with STEMI and multivessel disease, they suffered from some key limitations. Importantly, all three trials were not sufficiently powered to detect differences in hard clinical end-points – namely death and myocardial infarction (MI). PRAMI trial intended to enroll 600 patients, however the trial was stopped prematurely after an interim analysis showed the advantage of preventive PCI. This might have resulted in falsely exaggerating the benefit seen with complete revascularization. In addition, the decision to perform PCI to non-IRA lesions was based on angiographic judgment of the severity of stenosis in both PRAMI and CvLPRIT trials. Diffuse coronary spasm is frequently present in the acute phase of STEMI, and many of the apparently significant lesions during the acute phase of MI may not require PCI in follow up.[13] This may have led to intervention in a number of insignificant lesions.

DANAMI-3 PRIMULTI trial showed that staged FFR-guided complete revascularization seems to result in the best clinical outcome for patients with STEMI and multivessel disease which is in agreement with PRAMI and CvLPRIT and some previous observational studies.[8,9] This trial utilized a more physiological assessment of stenosis severity. However, the disturbances in microvascular function in the setting of STEMI might alter the FFR values. Older studies showed that microvascular dysfunction might persist up to 3 months in remote, non-infarcted territories after an acute MI,[14,15] which raises a concern about the accuracy of FFR measurements in this setting. However, these concerns have largely been refuted in more recent studies where FFR assessment of non-IRA lesions has proven to be reliable in the setting of STEMI.[16]

Uncertainty remains whether the strategy of immediate complete revascularization utilized in PRAMI is superior to a staged PCI strategy. A previous meta-analysis suggested that staged multivessel PCI was superior to multivessel PCI during the index procedure.[9]

On the basis of these findings, the ACC/AHA/SCAI recently released a joint focused update on primary percutaneous coronary intervention PCI for patients with STEMI where the prior Class III recommendation designated to multivessel primary PCI in hemodynamically stable patients with STEMI, has been modified to a Class IIb recommendation. While this update does not endorse a routine multivessel PCI strategy to patients with STEMI and multivessel disease, it reflects the current

understanding that this is a safe and potentially beneficial approach to consider in select cases based upon an individualized risk-benefit estimate that takes into account the clinical scenario, lesion severity and/or complexity, risk of contrast nephropathy and overall burden of residual ischemia. The writing committee acknowledges that there is insufficient data at this stage to recommend whether multivessel PCI should be performed at the time of the primary procedure or as a staged procedure during the index hospitalization.[17]

What have we learned?

There is growing evidence that complete revascularization during the index admission in patients with STEMI and multivessel disease reduces the risk of future events, essentially repeat PCI. The trials highlighted in this report were not designed to detect difference in mortality and did not address the best time to perform PCI to a non-IRA. There is pressing need for larger randomized studies to verify the impact of multivessel PCI on harder clinical endpoints, define the optimal timing of non-IRA revascularization, and determine the value of functional assessment of non-IRA lesions.

REFERENCES

[1] van der Schaaf RJ, Timmer JR, Ottervanger JP, Hoorntje JC, de Boer MJ, Suryapranata H, Zijlstra F, Dambrink JH. Long-term impact of multivessel disease on cause-specific mortality after ST elevation myocardial infarction treated with reperfusion therapy. *Heart*. 2006;92:1760–1763.
[2] Muller DW, Topol EJ, Ellis SG, Sigmon KN, Lee K, Califf RM. Multivessel coronary artery disease: A key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group. *Am Heart J*. 1991;121:1042–1049.
[3] Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, Stuckey T, Tcheng JE, Mehran R, Lansky AJ, Grines CL, Stone GW. Impact of multivessel disease on reperfusion success and clinical outcomes in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. *Eur Heart J*. 2007;28:1709–1716.
[4] Mozid AM, Mohdnazri S, Mannakkara NN, Robinson NM, Jagathesan R, Sayer JW, Aggarwal RK, Clesham GJ, Gamma RA, Tang KH, Kelly PA, Davies JR. Impact of a chronic total occlusion in a non-infarct related artery on clinical outcomes following primary percutaneous intervention in acute ST-elevation myocardial infarction. *J Invasive Cardiol*. 2014;26:13–16.
[5] Brener SJ, Mintz GS, Cristea E, Weisz G, Maehara A, McPherson JA, Marso SP, Farhat N, Botker HE, Dressler O, Xu K, Templin B, Zhang Z, Lansky AJ, de Bruyne B, Serruys PW, Stone GW. Characteristics and clinical significance of angiographically mild lesions in acute coronary syndromes. *JACC Cardiovasc Imaging*. 2012;5:86–94.
[6] Bagai A, Thavendiranathan P, Sharieff W, Al Lawati HA, Cheema AN. Non-infarct-related artery revascularization during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: A systematic review and meta-analysis. *Am Heart J*. 2013;166:684–693.e1.
[7] Rasoul S, van Ommen V, Vainer J, Ilhan M, Veenstra L, Erdem R, Ruiters LA, Theunissen R, Hoorntje JC. Multivessel revascularisation versus infarct-related artery only revascularisation during the index primary PCI in STEMI patients with multivessel disease: A meta-analysis. *Netherlands Hear J*. 2015;23:224–231.
[8] Vlaar PJ, Mahmoud KD, Holmes DR Jr, van Valkenhoef G, Hillege HL, van der Horst IC, Zijlstra F, de Smet BJ. Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: A pairwise and network meta-analysis. *J Am Coll Cardiol*. 2011;58:692–703.
[9] Bainey KR, Mehta SR, Lai T, Welsh RC. Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: A systematic review and meta-analysis. *Am Heart J*. 2014;167:1–14.e2.
[10] Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG, PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115–1123.
[11] Kelly DJ, McCann GP, Blackman D, Curzen NP, Dalby M, Greenwood JP, Fairbrother K, Shipley L, Kelion A, Heatherington S, Khan JN, Nazir S, Alahmar A, Flather M, Swanton H, Schofield P, Gunning M, Hall R, Gershlick AH. Complete versus culprit-Lesion only PRimary PCI Trial (CVLPRIT): A multicentre trial testing management strategies when multivessel disease is detected at the time of primary PCI: Rationale and design. *EuroIntervention*. 2013;8:1190–1198.
[12] Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L, DANAMI-3—PRIMULTI Investigators. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): An open-label, randomised controlled trial. *Lancet*. 2015;386:665–671.
[13] Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. Exaggeration of nonculprit stenosis severity during acute myocardial infarction: Implications for immediate multivessel revascularization. *J Am Coll Cardiol*. 2002;40:911–916.
[14] Kramer CM, Rogers WJ, Theobald TM, Power TP, Petruolo S, Reichek N. Remote noninfarcted region dysfunction soon after first anterior myocardial infarction. A magnetic resonance tagging study. *Circulation*. 1996;94:660–666.
[15] Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med*. 1994;331:222–227.

[16] Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:1274–1281.

[17] Levine GN, O'Gara PT, Bates ER, Blankenship JC, Kushner FG, Bailey SR, Bittl JA, Brindis RG, Casey DE Jr, Cercek B, Chambers CE, Chung MK, de Lemos JA, Diercks DB, Ellis SG, Fang JC, Franklin BA, Granger CB, Guyton RA, Hollenberg SM, Khot UN, Krumholz HM, Lange RA, Morrow DA, Moussa ID, Mukherjee D, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Ting HH, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for t. *J Am Coll Cardiol*. 2015; doi:10.1016/j.jacc.2015.10.005.