An Observational Study Assessing Immediate Complete Versus Delayed Complete Revascularisation in Patients with Multi-Vessel Disease Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND: More than half of the patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) have multi-vessel coronary artery disease. This is associated with worse outcomes compared with single vessel disease. Whilst evidence now exists to support complete revascularisation for bystander disease the optimal timing is still debated. This study aimed to compare clinical outcomes in patients with STEMI and multi-vessel disease who underwent complete revascularisation as inpatients in comparison to patients who had staged PCI as early outpatients.

METHODS AND RESULTS: We conducted an observational cohort study consisting of 1522 patients who underwent primary PCI with multi-vessel disease from 2012 to 2019. Exclusions included patients with cardiogenic shock and previous CABG. Patients were split into 2 groups depending on whether they had complete revascularisation performed as inpatients or as staged PCI at later outpatient dates. The primary outcome of this study was major adverse cardiac events (consisting of myocardial infarction, target vessel revascularisation and all-cause mortality).

834 (54.8%) patients underwent complete inpatient revascularisation and 688 patients (45.2%) had outpatient PCI (median 43 days post discharge). Of the inpatient group, 652 patients (78.2%) underwent complete revascularisation during the index procedure whilst 182 (21.8%) patients underwent inpatient bystander PCI in a second procedure. Overall, there were no significant differences between the groups with regards to their baseline or procedural characteristics. Over the follow-up period there was no significant difference in MACE between the cohorts ($P = .62$), which persisted after multivariate adjustment (HR 1.21 [95% CI 0.72-1.96]). Furthermore, in propensity-matched analysis there was no significant difference in outcome between the groups (HR: 0.86 95% CI: 0.75-1.25).

CONCLUSIONS: Our study demonstrated that the timing of bystander PCI after STEMI did not appear to have an effect on cardiovascular outcomes. We suggest that patients with multi-vessel disease can potentially be discharged promptly and undergo early outpatient bystander PCI. This could significantly reduce length of stay in hospital.

KEYWORDS: PCI, staged PCI

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Introduction

ST-segment elevation myocardial infarction (STEMI) affects about 25% to 74% of patients presenting with acute myocardial infarction (AMI).[1,2] Approximately 50% of patients undergoing primary percutaneous coronary intervention (PCI) for STEMI have multi-vessel disease (MVD), which is associated with poorer outcomes compared with single vessel disease.[3] Although evidence now supports complete revascularisation over medical treatment, the optimal timing of the revascularisation of non-culprit lesions has not been established yet and final consensus is lacking.[4] Currently, in patients with MVD, it is possible to perform complete revascularisation at the time of treating the culprit lesion or performing a staged procedure either as an inpatient or as an outpatient. ESC guidelines currently agree that complete revascularisation should be considered however no guidance over timing is provided.[5] The COMPLETE trial is the latest randomised controlled trial, which has suggested that complete revascularisation within 45 days of the index procedure has good outcomes, however data on this is limited.[6] The aim of this prospective study is to answer the unsolved question of the timing of complete revascularisation in patients undergoing primary PCI with MVD, specifically comparing in-hospital versus staged outpatient bystander revascularisation.

Methods

Study design and patient population

The study population was derived from a registry of all patients undergoing primary PCI for STEMI between January 2012 and October 2019 at a single high volume centre. During this period, Barts Health Heart Attack Centre was the only tertiary centre for the north-east region of London, taking all STEMI patients for primary PCI in an unselected manner. This included patients in cardiogenic shock, cardiac arrest and intubated patients. The hospital covered a population of 1.6 million people and included close working with the local London ambulance services. All primary PCI patients were offered follow up at our centre. Patients admitted with out of hospital cardiac arrest, in cardiogenic shock, or those who had previous coronary artery bypass grafting (CABG), were not included in the study. Of those with MVD, those planned for medical management of bystander disease were not included.

Ethics

Data were collected as part of a national cardiac audit and all patient identifiable fields were removed prior to analysis. The local ethics committees advised that formal approval was not required.

Intervention and procedural details. Standard Primary PCI protocol included pre-loading with 300 mg aspirin, 600 mg clopidogrel or 180 mg ticagrelor and GPIIb/IIIA inhibitors (predominantly intravenous eptifibatide) unless contraindicated. Successful primary PCI result was defined as final TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 and residual stenosis <20% in the infarct-related artery at the end of the procedure.[7] Decisions regarding revascularisation of bystander disease were taken after following current protocols and ESC guidelines, and were at the discretion of the operator as there was no local guidelines.

Data collection. Data was prospectively entered into a clinical database at the time of the procedure, with PCI data entered in accordance to the British Cardiovascular Intervention Society (BCIS) standards. Data collected included patient characteristics: age; prior Myocardial infarction (MI), prior PCI cardiovascular risk factors including hypertension, diabetes mellitus, hypercholesterolaemia and smoking status. In addition, procedure related data was collected: culprit vessel, number of diseased vessels; use of diagnostic devices such as IVUS (Intravascular Ultrasound), OCT (Optical Coherence Tomography) or pressure wire, use of post-dilatation and use of GPIIb/IIIa inhibitor.

Endpoints. The primary clinical outcome was major adverse cardiac events (MACE). MACE events were defined as a composite of all-cause mortality, recurrent myocardial infarction and target vessel revascularisation. Mortality data were obtained from the Office for National Statistics. Other outcomes recorded included rates of restenosis (clinically relevant) and stent thrombosis.

Statistical analysis. All data and outcomes were compared between the in-patient and out-patient complete revascularisation groups. Normally distributed variables were expressed as mean ± SD and non-normally distributed variables as median and IQR, categorical variables were summarised using absolute values (percentage). We compared the 2 main groups using student's t tests method for continuous data (age, number of overnight stays), Mann-Whitney U test for non-normally distributed continuous variables and Fisher's method for categorical parameter (sex, risk factors, treated vessels, drugs). We used the Kaplan-Meier graph to detect differences in major adverse cardiac events between the complete revascularisation as inpatient (CR IP) and complete revascularisation as outpatient (CR OP) cohort and age-adjusted Cox with multivariate adjustment. A two-sided $P < .05$ was considered statistically significant. A propensity score analysis was carried out using a non-parsimonious logistic regression model comparing CR IP versus CR OP. This model included multiple variables including gender, diabetes, age, hypercholestrolaemia, hypertension, previous MI, previous PCI, chronic renal failure, procedural success, pre-procedure TIMI flow and GP IIb/IIIA use. We carried out a nearest neighbour 1:1 matching algorithm using callipers of 0.2 standard deviations of the logit of the propensity score after ranking propensity score in an ascending order.[8-11] Each CR IP versus CR OP patient was used in at most 1 matched pair. This resulted in a matched sample with similar distribution of baseline characteristics between 2 groups.[8-11] Cox proportional hazard model was used based on the matched samples to determine the association of CR on mortality over follow-up. STATA version 14 and Graph Pad Prism 7 were used for all analyses.[8-11]

Results

Between 2012 and 2019, 4287 patients were admitted with STEMI. Of these, 2600 (60.6%) had multi-vessel disease of which 1522 patients underwent planned complete revascularisation either as IP or OP. 834 (54.8%) underwent CR IP (complete revascularisation as inpatient) and 688 (45.2%) patients had CR OP (complete revascularisation as outpatient). Of the CR IP group, 652 patients (78.2%) (CR subgroup) underwent complete revascularisation during the index procedure whilst 182 (21.8%) (IP subgroup) underwent this in a second separate procedure within the same hospital admission. (Figure 1)

Baseline and procedural characteristics

Clinical and procedural characteristics are shown in Table 1. Overall, there were similar baseline characteristics between IP and OP groups aside from higher rates of peripheral vascular disease in the OP group.

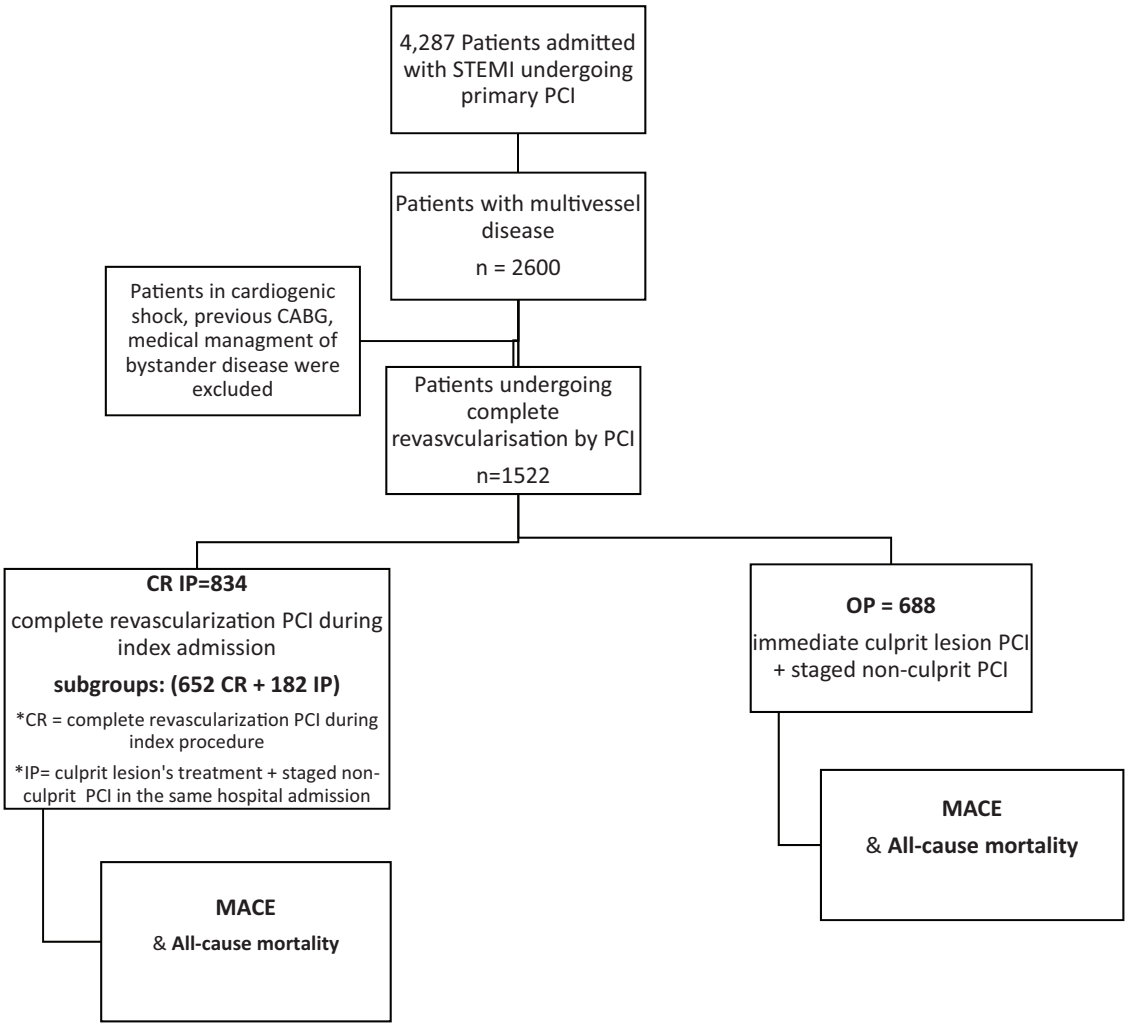

Figure 1. Study flow chart

Table 1. Baseline and angiographic data.

	CR IP N = 834 (54.8%)	OP 688 (45.2%)	*P* VALUE
Age	59.97 (SD 12.35)	59.14 (SD 11.65)	.4965
Sex (male)	679 (81.38%)	621 (90.27%)	.0187
SMOKING STATUS			
Never	342 (41.00%)	291 (42.36%)	.8385
Ex	192 (23.02%)	162 (23.61%)	.9056
current	297 (35.64%)	234 (34.02%)	.7533
Diabetes	224 (26.81%)	177 (25.69%)	.8209
Hypertension	381 (45.74%)	330 (47.91%)	.6877
Hypercholesterolemia	387 (46.37%)	291 (42.36%)	.4798
History of peripheral vascular disease	11 (1.26%)	33 (4.86%)	.0410
History of renal disease	21 (2.52%)	9 (1.38%)	.7313
History of cerebrovascular disease	16 (1.87%)	14 (2.08%)	1

(Continued)

Table 1. (Continued)

	CR IP N = 834 (54.8%)	OP 688 (45.2%)	*P* VALUE
LM stenosis pre-op (>75%)	11 (1.26%)	5 (0.69%)	1
LAD prox. stenosis pre-op (>75%)	210 (25.20%)	162 (23.61%)	.2293
LAD other stenosis pre-op (>75%)	153 (18.29%)	115 (16.66%)	.4100
RCA stenosis pre-op (>75%)	426 (51.10%)	396 (57.63%)	.2269
CX stenosis pre-op (>75%)	279 (33.43%)	196 (28.47%)	.3320
TIMI flow in IRA pre-op (0)	497 (59.59%)	492 (71.52%)	.1657
Aspirin	758 (90.85%)	602 (87.50%)	.3188
Ticagrelor	434 (46.06%)	306 (44.45%)	.6258
Clopidogrel	450 (53.94%)	382 (55.55%)	.7630
Warfarin	5 (0.63%)	5 (0.69%)	1

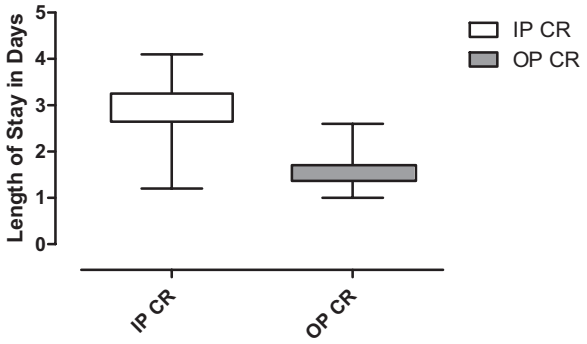

Figure 2. Box and Whisker plot of the Length of Stay between inpatient complete revascularisation (IP CP) and outpatient complete revascularisation (OP CR). There was significant difference between the 2 groups $P = .04$.

Procedural characteristics

Right radial artery access (RRA) was used in 83.9% of cases, with the remaining cases performed from the femoral approach. The average number of lesions attempted in each procedure was 1.74 (SD 0.66). GPIIb/IIIa inhibitors (eptifibatide or abciximab) were used in 63.5% of patients, (39.7% of CR IP group and 69.4%) of the OP group. No difference between the 2 groups in terms of the treatment of chronic total occlusions (CTO), use of intravascular imaging (Intravascular ultrasound (IVUS), optical coherence tomography (OCT)) or rates of successful procedures were seen. There were no differences in the rates of poor LV function (EF <35%) between the groups before or after the procedure.

Post-procedural

In terms of length of stay (LoS), the median LoS in the IP CR group was 3.2 days (IQR 1.2-4.1). The median LoS in the OP CR group was 1.4 (IQR 1-2.6) (Figure 2). The median time for OP PCI was 43 days (IQR 25-76). Eight patients (1.2%) waiting OP PCI presented prior to their planned procedures for unscheduled urgent revascularisation however none were associated were ACS admissions (all troponin negative). No difference in procedural complications including no differences in pre-procedure or post-procedure creatinine (83 ± 20.1 vs 92 ± 22.4, $P = .768$) or eGFR (67.2 ± 19.1 vs 68.9 ± 16.3, $P = .844$) in CR IP group compared with the OP group.

There were no differences in bleeding rates between the 2 groups. BARC ⩾2 (5.4% vs 6.2%, $P = .362$), TIMI major 2.3% vs 3.5%, $P = .642$), TIMI minor 4.3% vs 5.7%, *P*-0.711), TIMI minimal (7.3% vs 9.2%, *P*-0.287).

Long-term follow-up

The primary clinical outcome of MACE was measured at a median of 2.4 years (Interquartile range: 1.3-3.6 years). Kaplan-Meier analysis demonstrates no difference between the cumulative incidence of MACE between CR IP and the OP groups (13.3 IP vs 12.9% OP, $P = .62$) over the follow-up period (Figure 3). No difference was seen in any of the individual MACE components including death (6.3% in the CR IP vs 5.9% in the OP group, *P*-value .34), MI (2.8% in the CR IP vs 2.5% in the OP group, *P*-value .76), and unscheduled revascularisation (4.2% in the CR IP vs 4.5% in the OP group, *P*-value .56).

Multivariate analysis

No difference in age-adjusted Cox analysis was seen between the IP and OP groups (HR 1.42 [95% CI 0.85-1.94]), which persisted after adjustment for potential confounding variables (HR 1.21 [95% CI 0.72-1.96]). This was the same after adjustment of year of study (HR 1.16 [95% CI 0.75-1.85]) and location of bystander disease (HR 1.08 [95% CI 0.50-2.15]) (proximal LAD vs non-proximal LAD).

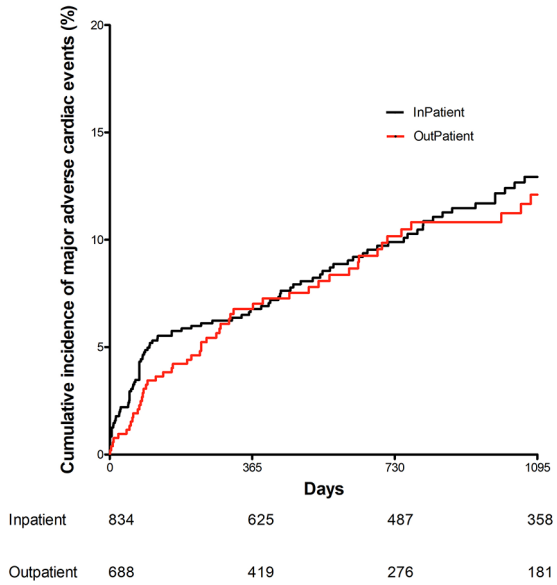

Figure 3. Kaplan Meier curves showing cumulative probability of MACE after primary PCI according to group.

Propensity matching

In order to account for confounding variables and bias further, propensity score matching was performed to adjust for differences in baseline clinical and procedural factors producing a total of 660 patients (330 in the CR IP and 330 in the CR OP group).[8-11] Following matching the baseline demographics and procedural variables were well balanced in the 2 propensity-matched cohorts (*P* values all >.05). In the propensity-matched cohorts, Cox regression analysis[8-11] revealed that there was no significant difference in outcome between the CR IP and OP groups (HR: 0.86 95% CI: 0.75-1.25).

Discussion

This prospective observational registry study, looking at clinical outcomes in STEMI patients with MVD undergoing complete revascularisation, is 1 of the largest studies specifically looking at the question of the timing of complete revascularisation. Revascularisation strategy in STEMI patients with MVD has been a trending topic in the recent years. Currently the great majority of studies confirm that complete revascularisation is preferred, with recent guidelines affirming that non-IRA PCI should be considered, however the timing of this complete revascularisation remains debatable.[12,13] There is no clear consensus regarding the choice of proceeding through a unique index procedure or performing the revascularisation in 2 procedures (culprit lesion first and bystander in a second intervention) in the same hospital stay or in 2 separated admission. This observational study, investigated complete revascularisation as inpatients compared with staged PCI as early outpatients (median 43 days). We found that during the follow-up period there was no significant difference in outcomes between CR IP and OP procedures (HR 1.40 [95% CI 0.87-1.92]), which persisted after multivariate adjustment (HR 1.21 [95% CI 0.72-1.96] and propensity-matched analysis (HR: 0.86 95% CI: 0.75-1.25).

Previous randomised studies have found a reduction in composite outcomes with non-culprit lesion PCI.[6,14,15] However, they were not powered to detect improvements in certain clinical outcomes (hard endpoints such as cardiovascular death or new myocardial infarction).[16] Although, there are meta-analyses that indicate a reduction in myocardial infarction or cardiovascular death with non-culprit lesion PCI,[17,18] until recently there was a lack of a large-scale study showing benefit on this clinically important outcome.[6] In the COMPLETE trial[6] there were a total of 4041 patients with multivessel coronary artery disease and STEMI, who assigned to complete revascularisation with additional PCI of angiographically significant non-culprit lesions, or to no further revascularisation. Stratification of randomisation was carried out by the intended timing of non-culprit lesion PCI: (ie, during or after the index hospitalisation). The study found that complete revascularisation was superior to culprit-only revascularisation, with a reduction in cardiovascular death or MI. Complete revascularisation was beneficial if performed either during or after the index hospitalisation which was accomplished without an increase in major bleeding or contrast-induced nephropathy. This suggests that complete revascularisation could be performed safely out to 43 days post index procedure rather than all procedures performed pre-discharge which to date was the direction the evidence was pointing (PRAMI/CvLPRIT).[14,15] Our data supports the concept that early outpatient staged complete revascularisation is non-inferior to complete inpatient revascularisation and in itself has advantages in terms of length of stay.

With the weight of evidence (meta-analyses)[19,20] and the COMPLETE trial supporting complete revascularisation,[6] the main outstanding question remains 'when' the complete revascularisation is performed. This study provides real world data to support the idea of in-patient or early outpatient complete revascularisation being comparable. Unique to this study is the variability in patient characteristics that are seen in a real world setting. There are patients who would benefit from complete revascularisation in a single up-front procedure (ie, Such as difficult access) compared with some patients with severe renal impairment who should have a period or recovery to ensure renal function returns to baseline before a second procedure. These patients are often not included in randomised clinical trials and therefore there is little evidence to support a pathway of managing these patients, this study suggests that it is safe and clinically reasonable to do either and whichever suits the individual patient.

Strengths and limitations of this study

This study consists of 1 of the largest cohorts based within a large metropolitan city with a diverse ethnic and social make up and includes patients with a number of co-morbidities, this strength means it is therefore representative of the broad range

of patients encountered in daily clinical practice. Whilst inclusion of such patients may result in some baseline differences between the groups, differences were mitigated by use of multivariate analyses and propensity analyses. The multivariate analyses is also reassuring as it confirms that well-recognised predictors of mortality were associated with adverse outcome in our data set. However, our study has limitations including those of a registry and with all the potential bias and unmeasured confounding associated with non-randomised analyses. Importantly these results are applicable to patients undergoing planned complete revascularisation and the timing between IP and OP, patients with bystander disease managed medically or those with previous CABG or in cardiogenic shock were not included with the results not generalisable to those groups.

Conclusion

This study demonstrated that the timing of bystander PCI after STEMI did not seem to have an effect on cardiovascular outcomes. These results suggest that patients with multi-vessel disease could be promptly discharged and have early outpatient PCI for bystander disease, which could significantly reduce hospital length of stay.

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REFERENCES

1. Mandelzweig L, Battler A, Boyko V, et al. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur Heart J*. 2006;27:2285-2293.
2. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165.
3. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med*. 2000;343:915-922.
4. Lu DY, Zhong M, Feldman DN. Complete versus culprit-only revascularization in STEMI: a contemporary review. *Curr Treat Options Cardiovasc Med*. 2018;20:41.
5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119-177.
6. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381:1411-1421.
7. Rathod KS, Koganti S, Jain AK, et al. Complete versus culprit-only lesion intervention in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2018;72:1989-1999.
8. Rathod KS, Koganti S, Jain AK, et al. Complete versus culprit only revascularisation in patients with cardiogenic shock complicating acute myocardial infarction: incidence and outcomes from The London Heart Attack Group. *Cardiovasc Revasc Med*. 2020;21:350-358.
9. Jones DA, Rathod KS, Pavlidis AN, et al. Outcomes after chronic total occlusion percutaneous coronary interventions: an observational study of 5496 patients from the Pan-London CTO Cohort. *Coron Artery Dis*. 2018;29:557-563.
10. Rathod KS, Koganti S, Iqbal MB, et al. Contemporary trends in cardiogenic shock: incidence, intra-aortic balloon pump utilisation and outcomes from the London Heart Attack Group. *Eur Heart J Acute Cardiovasc Care*. 2018;7:16-27.
11. Jones DA, Rathod KS, Gallagher S, et al. Manual thrombus aspiration is not associated with reduced mortality in patients treated with primary percutaneous coronary intervention: an observational study of 10,929 patients with ST-segment elevation myocardial infarction from the London Heart Attack Group. *JACC Cardiovasc Interv*. 2015;8:575-584.
12. Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS, Rao SV. Prevalence, predictors, and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol*. 2009;104:507-513.
13. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541-2619.
14. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115-1123.
15. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol*. 2015;65:963-972.
16. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol*. 2013;62:1563-1570.
17. Elgendy IY, Mahmoud AN, Kumbhani DJ, Bhatt DL, Bavry AA. Complete or culprit-only revascularization for patients with multivessel coronary artery disease undergoing percutaneous coronary intervention: a pairwise and network meta-analysis of randomized trials. *JACC Cardiovasc Interv*. 2017;10:315-324.
18. Pasceri V, Patti G, Pelliccia F, et al. Complete revascularization during primary percutaneous coronary intervention reduces death and myocardial infarction in patients with multivessel disease: meta-analysis and meta-regression of randomized trials. *JACC Cardiovasc Interv*. 2018;11:833-843.
19. Bainey KR, Engstrøm T, Smits PC, et al. Complete vs culprit-lesion-only revascularization for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *JAMA Cardiol*. 2020;e201251.
20. Gupta K, Chopra L, Salame A, et al. Complete versus culprit-vessel only revascularization in STEMI: an updated meta-analysis of randomized control trials. *Int J Cardiol Heart Vasc*. 2020;27:100481.