

Cardiovascular Diagnosis and Therapy (CDT) Editorial: the Minimalist Immediate Mechanical Intervention study

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Comment on: Belle L, Motreff P, Mangin L, *et al.* Comparison of Immediate With Delayed Stenting Using the Minimalist Immediate Mechanical Intervention Approach in Acute ST-Segment-Elevation Myocardial Infarction: The MIMI Study. *Circ Cardiovasc Interv* 2016;9:e003388.

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Primary percutaneous coronary intervention (PCI) has become the standard of care in patients presenting with ST Elevation Myocardial Infarction (STEMI) (1). However, since stent implantation may cause intra-procedural thrombotic complications (IPTEs), including distal embolization of thrombus leading to microvascular obstruction (MVO) and no-reflow (2,3) some clinicians have questioned whether immediate stent implantation is mandated in all patients, or instead, whether stent implantation could be deferred for a limited period to enable the beneficial effects of restored blood flow and medical therapy. With this in mind, a number of clinical investigations of deferred stenting (DS) strategies have been assessed (4-16). This was the focus of the Minimalist Immediate Mechanical Intervention (MIMI) trial (14).

One of the main concerns for a cardiologist who is undertaking primary PCI in a patient with an acute STEMI is the potential to cause harm. Whilst treatment to reperfuse the culprit artery is the immediate priority, subsequent manoeuvres, including stent implantation and high pressure balloon optimisation of the stent may aggravate reperfusion injury by various mechanisms including endothelial swelling, capillary obstruction, vasospasm, inflammatory response and IPTEs resulting as no-reflow which has been defined as an acute reduction in myocardial blood flow despite a patent epicardial coronary artery (17). Slow flow or no reflow can enhance myocardial injury and is associated with poor clinical outcomes (18). Slow or no-

reflow affects 10% of all STEMI patients and as many as two thirds of patients at high risk (19). Elderly patients with delayed presentations and those with completely occluded culprit arteries or heavy thrombus burden are particularly vulnerable (20).

Immediate stent implantation may cause distal embolization of clot and resultant microvascular thrombosis and MVO. These are associated with a larger infarct size and an adverse prognosis (21). The hypothesis underpinning a DS approach is the potential to reduce coronary thrombus burden after initial stabilization of infarct related lesion and preserve microvascular function, therefore reducing the likelihood of slow and no reflow and MVO (14-16).

The Deferred Stenting Versus Immediate Stenting to Prevent No or Slow Reflow in Acute ST-Segment Elevation Myocardial Infarction (DEFER-STEMI) was a single centre proof of concept trial comparing immediate and deferral of stent implantation for 4-16 hours in patients at risk of slow or no reflow (15). Compared with patients treated with best standard care, patients randomized to a deferred stent strategy experienced slow flow or no reflow and intra-procedural thrombotic events less often. They also had higher TIMI flow at the end of the procedure and a higher myocardial salvage index at 6 months. Moreover about 4% of patients in deferred strategy had minimal disease at the time of second procedure and did not require stent implantation. Subsequently, the findings of the DEFER-STEMI trial were not substantiated in a larger open label,

multi-centre clinical trial in Denmark. The Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI-3-DEFER) trial randomized 1,215 patients to immediate or delayed PCI at 48 hours (16). Routine DS implantation did not reduce the incidence of death, myocardial infarction, or repeat revascularization when compared with immediate stent implantation. Deferred stent implantation was associated with a slightly higher left ventricular ejection fraction as revealed by transthoracic echocardiography at 12 months (54.8% vs. 53.5%; $P=0.0431$). This finding, which is directionally different to the main clinical results, could be viewed as hypothesis generating. Moreover 85 (14%) patients did not get stents implanted as compared to 9 (1%) in immediate group.

In a recent issue of *Circulation Cardiovascular Interventions* the MIMI investigators reported their experience in a randomised trial of immediate stenting versus DS in 160 patients ($n=140$ randomised in 16 hospitals) presenting within 12 hours of STEMI (14). They tested the hypothesis that DS improves myocardial perfusion compared to immediate stenting in the setting of primary PCI for acute STEMI. Patients in the DS group underwent a second angiogram 36 (range, 29–46 hours) later. Cardiac MRI was used to assess MVO and LV function and volumes at a median of 5 days later. There was a trend towards lower MVO in the immediate stenting group compared with deferred stent group and other measures of reperfusion injury e.g., ST-segment resolution, as well as TIMI flow grades, infarct size, and LV ejection fraction were similar between the randomized groups. No difference was apparent in the rate of major cardiovascular and cerebral events. All patients in immediate stenting group received stents while no stents were required in 4 (6%) patients in the deferred stent group. The deferred stent group had a higher rate of nonculprit artery angioplasty. No cases of coronary re-occlusion occurred in the deferred group. We appreciate the efforts put in by the authors but a number of important points merit further consideration. Firstly, there were important differences between the two groups. Patients randomized to immediate stenting were younger, mostly active smoker and had less incidence of hypertension. Secondly, there is a possibility of selection bias, as the results of 63% of the eligible patients who were not included in the trial remain unreported. The majority of the participating hospitals (approximately 14 centres) enrolled <10 patients during an 18-month enrolment period, implying a selected population was enrolled.

Contemporary practice for primary PCI has evolved

since these trials. The majority of the patients in the DEFER-STEMI, MIMI and DANAMI-3-DEFER trials were treated with aspiration thrombectomy. The American College of Cardiology (ACC), American Heart Association (AHA) and Society for Cardiovascular Angiography and Intervention (SCAI) in the focused update on primary PCI in STEMI published in 2015 downgraded the routine use of Thrombus Aspiration in STEMI to Class III and changed to Class IIb in bailout situations following practice changing results from the TASTE (Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction) (22) and the TOTAL (Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy) (23) trials (24). The European Society of Cardiology (ESC) guidelines for the management of patients with acute STEMI are due to be updated in 2017. Moreover routine use of glycoprotein IIb/IIIa inhibitor therapy is no longer the standard of care in primary PCI, and now is recommended only as a bailout therapy and ticagrelor and prasugrel are recommended in favour of clopidogrel. A recent post hoc analysis of the Complete Versus Lesion-Only Primary PCI Trial-CMR (CvLPRIT-CMR) sub study showed prasugrel and ticagrelor are associated with smaller infarct size and lower incidence of MVO versus clopidogrel for STEMI patients (25).

How should we interpret the differences in the results of these trials? The MIMI investigators have proposed that relatively increased number of pre and post dilatation in DEFER-STEMI may explain the differences in results from their trial (15). Contrary to preliminary studies DANAMI 3-iPOST has failed to show any significant differences in revascularization reperfusion injury leading to clinical outcomes, comparing graded, gradual post conditioning by multiple balloon inflations versus standard revascularization strategy (26). Moreover the MIMI investigators also suggested that leaving the culprit lesion uncovered in the deferred group could have increased the incidence of MVO in their trial but this observation was not replicated in the larger DANAMI-3-DEFER trial, which showed no difference in the incidence of major cardiac events between immediate stenting and DS strategy (16). In our opinion, the disparity in patients' risk profile and the timing of second intervention may explain the difference in outcomes between these trials. Importantly, the DEFER-STEMI was the only trial that stratified patients with clinically evident risk factors for slow and no reflow. Our view is that it makes no sense to expose low risk patients with acute STEMI and an expectedly good prognosis, to the theoretical risk of culprit artery re-occlusion and a second invasive procedure. Although in a meta-analysis

involving 590 patients there was no adverse cardiac event in the interval between the two procedures (12). There was no documented re-occlusion in the MIMI trial. Similarly only 2 patients in DEFER-STEMI had target vessel re-occlusion and one of these can be attributed to deviation from the study protocol. Interestingly in DANAMI-3 DEFER, 11 (2%) patients in the deferred stent group had a stent implanted before the scheduled deferred procedure because of recurrent symptoms or ST-segment elevation. In our opinion a focused analysis of the primary and secondary outcomes of DANAMI-3-DEFER participants with risk factors for no-reflow would be of great interest, and potentially relevant to inform future research. Differences in the timing of the second procedure in DEFER-STEMI, DANAMI-3-DEFER and MIMI trials (median delays of 9, 48 and 36 hours respectively) may also be relevant, not least to avoid prolonging the duration of the hospital admission. Results from Immediate versus Delayed Stenting after Primary Percutaneous Reperfusion in ST Elevation Myocardial Infarction (PRIMACY) will not be available until 2017 (NCT01542385).

What lies ahead? To date, MVO and slow/no reflow phenomena in STEMI patients have no known preventive therapy. Other candidate interventions, such as intra-coronary adenosine, have recently been associated with an increase in adverse cardiac events compared with placebo treated patients (27). DANAMI-3-DEFER has provided conclusive evidence that routine deferral of stent implantation in all-comers with acute STEMI does not improve outcomes. Our view is that the potential clinical benefits of a stratified approach focused on patients with risk factors for no-reflow remains an unanswered question and a further randomised clinical trial in a selected higher-risk population of STEMI patients, with a limited time interval until the second procedure e.g., about 12 hours, seems warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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