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Editorial

The Day When Coronary Stents Ruined Everything

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See article by Cassese et al., pages 1573–1580 of this issue.

Primary percutaneous intervention (PCI) is better than thrombolytic therapy to treat most patients with ST-segment myocardial infarction.[1-3] Still, primary PCI is far from perfect. Despite the evolution of adjunctive antithrombotic therapy, the slow-flow or no-flow phenomenon frequently occurs during primary PCI and remains associated with recurrent infarction and increased mortality.[4,5] Although manual thrombectomy has been associated with beneficial effects on coronary flow, it has failed to improve clinical outcomes in recent clinical trials.[6-8] Proponents of delayed stenting believe that a stent abruptly implanted in a thrombus-laden artery ruins everything. When a strategy of delayed stenting is attempted, flow is first restored in the infarct-related coronary artery (typically by thrombectomy or with a small-size balloon angioplasty catheter), but aggressive angioplasties and stenting are withheld until after the thrombus has melted down, in the hope of preventing distal embolization, microvascular obstruction (MVO), and ensuing myocardial damage. This strategy assumes that clot lysis by the in situ endothelial fibrinolytic system combined with an adjunctive systemic anticoagulation will reduce the thrombus burden,[9,10] stabilize the plaque,[11] and minimize the chances of no reflow after stenting. Another advantage of withholding stent implantation is to allow referral for surgical revascularization in patients with complex coronary artery disease, with no fear of acute stent thrombosis in the perioperative period.

Whether delayed stenting prevents myocardial damage remains uncertain.[4,12-14] In the present issue of the *Journal*, Cassese et al.[15] report that delayed stenting, compared with immediate stenting, improves coronary flow acutely but does not reduce longer-term myocardial damage. By pooling the study-level estimates of 4 trials (n = 797 participants), they show that delayed stenting yielded the same risk of MVO compared with immediate stenting, when measured by cardiac magnetic resonance imaging (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.76-1.14; $P = 0.51$). Notably, the current study presents the largest magnetic resonance imaging–based comparative analysis of MVO after immediate versus delayed stenting in patients with ST-segment myocardial infarction. None of these estimates were obtained from patient-level data and therefore should be interpreted with caution.[15]

Of the trials included in the meta-analysis, only the DANAMI-3–DEFER trial (Third **Dan**ish Study of Optimal **A**cute Treatment of Patients With ST-elevation **M**yocardial **I**nfarction) was powered to compare the efficacy of delayed stenting (n = 603) versus routine immediate stenting (n = 612) on hard clinical outcomes. Over a median follow-up of 42 months, 17% of participants assigned to delayed stenting compared with 18% of participants assigned to immediate stenting experienced the primary end point of all-cause death, heart failure, recurrent infarction, or any unplanned target vessel revascularization (hazard ratio, 0.99; 95% CI, 0.76-1.29; $P = 0.92$). The DANAMI-3 trial was instructive in many ways. The strategy of delayed stenting was associated with a clinically potentially meaningful yet not statistically significant reduction in all-cause death (from 9% to 7%, hazard ratio, 0.83; 95% CI, 0.56-1.20; $P = 0.37$), with no significant change in the rates of heart failure (from 5% to 4%, hazard ratio, 0.82; 95% CI, 0.47-1.40).[13,14]

The paradigm of delayed stenting is multifaceted. It remains unclear if, when, and how delayed stenting should be attempted. Important variations have been described in the execution of delayed stenting, including the time interval between the index reperfusion and stenting (ranging from 12 hours to 7 days),[16] the type of adjunctive antithrombotic therapy used (bivalirudin vs unfractionated heparin; infrequent vs mandatory use of glycoprotein IIb/IIIa inhibitors), and the thrombus burden at baseline. Using meta-regression, Cassese et al. observed that although an important proportion of participants presented with a low thrombus burden at baseline (43.3% presented with a Thrombolysis in

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Myocardial Infarction [TIMI] thrombus grade $\leq$ 3), a favourable treatment effect on slow flow or no reflow (P interaction = 0.047) and MVO (P interaction = 0.03) with delayed stenting was predominantly seen in participants with a high thrombus burden (TIMI thrombus grade > 3).

In the context of uncertain efficacy of delayed stenting, can it be reasonably attempted in selected subgroups, such as those with high thrombus burden? One additional contribution of the meta-analysis by Cassese et al. is that it quantifies the hazards associated with delayed stenting and points toward a nonsignificant increase in the risks of recurrent myocardial ischemia and of unplanned target vessel revascularization in the interval between reperfusion and stenting (RR, 2.42; 95% CI, 0.88-6.63; $P = 0.09$ and RR, 1.63; 95% CI, 1.00-2.66; $P = 0.051$, respectively). Although these trends are not statistically significant, they are large enough to suggest potential clinical importance. In the **I**mpact of Immediate Ste**n**t Implan**t**ation Versus Deferred Stent Implantati**o**n on Infarct Size and Micro**v**ascular Perfusion in P**a**tients With ST-Segmen**t** Elevat**i**on My**o**cardial Infarctio**n** (INNOVATION) study alone, the target vessel re-occluded in 7% of patients assigned to delayed stenting.[17] Of note, delayed stenting was not associated with an increased bleeding risk compared with immediate stenting, despite the prolonged systemic anti-coagulation used with the former.

The upcoming PRIMACY trial (**Prima**ry Reperfusion Se**c**ondar**y** Stenting Trial; NCT01542385) and its Bayesian patient-level pooled analysis are expected to bring additional insights into these complex questions.

Disclosures

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