Stenting in Acute STEMI Intervention

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KEYWORDS
- Stenting • Acute myocardial infarction • STEMI • Intervention

KEY POINTS
- Stenting in acute myocardial infarction (AMI) has the benefits of achieving an acute optimal angiographic result and correcting any residual dissection to decrease the incidence of restenosis and reocclusion.
- Studies have shown that percutaneous transluminal coronary angioplasty for primary treatment after AMI is superior to thrombolytic therapy with regard to the restoration of normal coronary blood flow. Coronary stenting improves the initial success rate, decreases the incidence of abrupt closure, and is associated with a reduced rate of restenosis.
- In the presence of thrombus-containing lesions, coronary stenting constitutes an effective therapeutic strategy, either after failure of initial angioplasty or electively as the primary procedure.
- All data and the current guidelines recommended by the American College of Cardiology/American Heart Association and European Society of Cardiology strongly support discouraging non–infarct-related artery percutaneous coronary intervention (PCI) procedures performed at the time of primary PCI when patients are hemodynamically stable.
- Studies, such as the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) and the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial, have demonstrated the safety of drug-eluting stents (DES) in patients with AMI as compared with bare-metal stents in stent thrombosis with the advantage of reducing target vessel revascularization. More recent studies, such as the Evaluation of Xience-V stent in Acute Myocardial Infarction (EXAMINATION) trial and subgroups of the Limus Eluted from A Durable vs ERodable Stent Coating (LEADERS) study, have shown even better results with second-generation DES in patients with AMI.

INTRODUCTION

The goals of therapy in acute myocardial infarction (AMI) are to achieve rapid and optimal restoration of flow in the infarct-related vessel and to maintain this initial result in the long term.1 Complete (Thrombolysis in Myocardial Infarction [TIMI] grade 3) patency of the infarct-related artery is a major predictor of survival and preserved left ventricular function following reperfusion therapy.2–4 Pharmacologic therapy with fibrinolytic agents is, for logistic reasons, the initial therapy of choice in most patients presenting with an AMI.1 However, there are several limitations to thrombolysis. First, the main limitation is the suboptimal restoration of TIMI grade 3 flow, which is generally not reported in more than 55% to 65% of patients within 90 minutes.2,4 Second, even within the group of patients with an open artery after fibrinolytic therapy, there is a substantial minority who has suboptimal myocardial perfusion in the territory of the infarct vessel, probably as a result of
a combination of distal embolization of thrombotic material and of microvascular spasm related to the release of potent thrombus-derived vasoactive substances. Finally, reocclusion of the infarct-related vessel occurs in roughly one-third of the patients treated by fibrinolysis in which the artery was initially patent and this proportion is not affected by either prolonged anticoagulant or antiplatelet therapy.

ADVANTAGES OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Primary or direct angioplasty is an alternative to fibrinolytic therapy. It has the advantage that normal antegrade flow can be restored acutely in a higher proportion of patients; however, the overall benefit, as for fibrinolytic therapy, depends on the delay to reperfusion. It should, therefore, only be considered as the preferred initial therapy for patients who can be rapidly admitted to an interventional center with experienced operators. In patients who are eligible for either therapy, it is clear that an initial strategy of direct angioplasty in an experienced center is associated with a better long-term outcome than an initial strategy of fibrinolytic therapy. For example, the Primary Angioplasty in Myocardial Infarction (PAMI)-1 trial evaluated a strategy of either primary angioplasty or treatment with tissue-type plasminogen activator in 395 patients. At the 2-year follow-up, patients who were randomized to primary angioplasty had significantly less recurrent ischemia (36.4% vs 48.0%) and a significantly lower rate of reintervention (27.2% vs 46.5%).

Despite the evidence that primary angioplasty was superior to fibrinolytic therapy, when both options were feasible, the relatively high rate of recurrent clinical events and of restenosis after primary angioplasty was a continuing preoccupation. The demonstration that elective stent implantation was associated with a decrease in restenosis and in clinical events in selected patients led to this strategy being applied in patients with MI, both in the acute phase and in early postinfarct angioplasty. A French trial (STENTIM-2) that randomized patients with AMI to a strategy of either systematic or provisional stenting showed that systematic stenting was associated with a significantly lower (25.3% vs 39.6%) restenosis rate. The trial was not powered to assess an effect on the clinical outcome. However, there was a trend toward a reduction in major cardiac events at 6 months in the patients who underwent systematic stenting (18.8% vs 23.3%, \( P = .14 \)) despite the crossover rate of 36.4% to stenting in the balloon group.

The introduction of stent implantation that allows mechanical stabilization of the unstable plaque made the initial result of angioplasty much more predictable and reduced acute complications. Furthermore, coronary stenting was proved to be effective in reducing the rates of restenosis and acute closure and in increasing the acute gain in luminal diameter in comparison with balloon angioplasty. In ST-segment elevation myocardial infarction (STEMI), the key performance criteria is to perform the intervention as early as possible because the sooner an occluded artery is opened and blood flow is restored, the less myocardium is lost and the lower the mortality. The optimization of adjuvant pharmacologic therapy, as a result of the reevaluation of the relative importance of antiplatelet and antithrombin therapy, an advance that owes much to the experience with coronary stenting, also improved outcome, in particular, by reducing bleeding complications. These two advances set the scene for a reevaluation of the role of combined fibrinolysis and percutaneous intervention.

STENTING IN AMI

For a long time, it was thought that coronary stenting was contraindicated in the setting of AMI because the implantation of a metallic device within a thrombotic environment, such as that of plaque disruption resulting in MI, would be likely to precipitate stent thrombosis with resultant vessel reocclusion. The first report of bailout stenting in AMI was published in 1991, but the first studies showing the feasibility and efficacy of stenting in patients with AMI and poor or suboptimal results after conventional coronary angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) appeared in 1996 in 4 small series of patients. At that time, stent thrombosis, with a rate that could be as high as 20% in bailout procedures, had been dramatically reduced to less than 2% by improvement in stent deployment techniques and advances in antiplatelet therapy, allowing a prompt reassessment of the role of stenting in AMI. In fact, after the encouraging results of these preliminary observational studies, stent implantation in patients with AMI grew enormously, and in 1997 the results of more than 30 observational studies in more than 2000 patients appeared. At the same time, several randomized trials comparing primary infarct-artery stenting with primary PTCA started.

Mechanisms of Benefit of Stenting in AMI

Although the efficacy of primary PTCA has been demonstrated, the benefits of a primary PTCA...
strategy are limited by the high incidence of early and late restenosis or reocclusion of the infarct vessel. As a consequence of infarct artery restenosis or reocclusion, many patients have recurrent ischemia after successful primary PTCA. Within 6 months of successful primary PTCA, restenosis or reocclusion of the infarct vessel may occur in more than 50% of patients, and the incidence of major adverse events related to recurrent ischemia, such as fatal and nonfatal reinfarction and repeat target-vessel revascularization (TVR), may be as high as 30%. With respect to early recurrent ischemia, PAMI investigators have shown that a suboptimal angiographic result after successful primary PTCA is a strong predictor of early major adverse events, whereas with respect to late recurrent ischemia, an acute optimal angiographic result, that is, the largest minimum luminal diameter achievable, is assumed to be inversely related to late restenosis or reocclusion. Thus, the postulated mechanisms of the benefit of stenting in AMI are the achievement of an acute optimal angiographic result and correction of any residual dissection to decrease the incidence of restenosis and reocclusion and of the correlated clinical events, such as fatal reinfarction, nonfatal reinfarction, and repeat TVR for recurrent ischemia. It is important to point out that most patients with recurrent ischemia after successful primary PTCA have angina or nonfatal reinfarction, whereas death as a consequence of recurrent ischemia accounts for a minority of deaths because most deaths of patients with AMI are caused by refractory cardiogenic shock despite a patent infarct artery. As a consequence, the expected benefit of stent in terms of the reduction of mortality rates is limited only to patients with a very large area at risk or severe left ventricular dysfunction. For patients not at high risk, the benefit of stenting may result only in a significant reduction of the incidence of nonfatal reinfarction and mainly of repeat TVR for recurrent angina. Obviously, repeat TVR is a soft end point as compared with death. Nevertheless, this soft end point has important clinical and economic implications when considering the quality of life of patients, the longer hospital stay in the acute phase, the need for readmission for late recurrence, and the adjunctive costs of a repeat revascularization procedure.

Another potential benefit of stenting independent of myocardial salvage is related to the early and late open artery hypotheses. By reducing the incidence of early and late reocclusion, stenting may prevent or reduce left ventricular remodeling and long-term mortality rates, as being ventricular remodeling a major determinant of survival.

APPARENT PARADOX OF PRIMARY INFARCT ARTERY STENTING AND DETERIORATION OF FLOW

After a TIMI grade 3 flow is restored by mechanical recanalization with the use of the coronary wire or, more frequently, the PTCA balloon, a deterioration of TIMI flow may occur after stent placement. The phenomenon of angiographic no-reflow (TIMI 0–1) or slow flow (TIMI 2) after primary infarct artery stenting is not frequent and is similar to that occurring in other clinical settings associated with thrombus-containing lesions or with the use of athereectomy devices that may microembolize with vessel debris and capillary plugging. Thus, primary infarct artery stenting, no-reflow or slow reflow respond to intracoronary calcium antagonists or adenosine in most cases and this suggests that microvascular spasm is the mechanism of microvascular dysfunction. Persistent flow impairment after calcium antagonist treatment suggests microembolization or microvascular reperfusion injury. In the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial, only 1 (1.3%) patient out of 75 randomly assigned to stenting had persistent slow flow despite intracoronary calcium antagonist treatment. In the Stent PAMI trial, 8 (2.6%) patients out of 350 assigned to stenting with TIMI grade 3 flow after predilatation PTCA had slow flow (7 patients) or no-reflow (1 patient).

High-pressure stent expansion is likely to be the mediator of microvascular dysfunction and degradation of angiographic TIMI flow. It is important to point out that microvascular dysfunction related to stent placement should not be confused with no perfusion despite removal of any coronary obstruction. The latter may also be associated with an angiographic slow flow with TIMI grade 3 flow and is likely to be the expression of reperfusion injury unrelated to stent placement.

DRUG-ELUTING STENTS OR BARE-METAL STENT FOR AMI: AN ISSUE OF SAFETY?

Coronary-artery stenting is commonly performed to treat MI. Acute coronary syndromes and MI (in contrast to stable angina) are the only clinical presentations in which percutaneous coronary intervention (PCI) has been shown to reduce the rate of death to a rate lower than that achieved with medical therapy alone. Despite the important role of stenting in patients with MI and, in particular, in those who have MI with STEMI, there has been little information regarding the long-term efficacy or safety of drug-eluting stents (DES) among these patients. There have been
several specific concerns about using DES (thrombogenic material) in AMI (prothrombotic state), particularly after studies and case reports relating DES thrombosis occurring in patients having suffered from acute coronary syndrome.

For instance, McFadden and colleagues reported that most late stent thrombosis occurred when a DES was placed in patients with acute coronary syndrome. Observational studies have shown that this risk continues at a constant rate up to at least years after stenting. Finn and colleagues demonstrated in their laboratory that delayed healing (ie, lack of complete endothelialization) is the primary pathologic substrate underlying these events and that greater than 50% of stent struts in humans are not covered by the endothelium up to 24 months after DES placement (Fig. 1).

Moreover, the preliminary results of the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) displayed a 3-fold higher mortality rate in the group treated with DES (sirolimus-eluting stent [SES]) compared with the group treated with bare-metal stent (BMS). Based on these data, a cautionary approach has been promulgated to refrain from the systematic use of DES in the setting of STEMI until the publication of the two first large randomized controlled trials, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) and Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION), which are summarized next.

The TYPHOON trial was a single-blind multicenter prospectively randomized trial to compare SES with BMS in primary PCI for AMI with ST-segment elevation. The trial included 712 patients at 48 medical centers. The primary end point was target-vessel failure at 1 year after the procedure, defined as target vessel–related death, recurrent MI, or TVR. A follow-up angiographic substudy was performed at 8 months among 174 patients from selected centers. In this study, the rate of the primary end point was significantly lower in the SES group than in the BMS group (7.3% vs...
14.3%, \( P = .004 \). This reduction was driven by a decrease in the rate of TVR (5.6% and 13.4%, respectively; \( P = .001 \)). There was no significant difference between the two groups in the rate of death (2.3% and 2.2%, respectively; \( P = 1.00 \)), reinfarction (1.1% and 1.4%, respectively; \( P = 1.00 \)), or stent thrombosis (3.4% and 3.6%, respectively; \( P = 1.00 \)).

The PASSION trial\(^ {36} \) randomly assigned 619 patients presenting with an AMI with ST-segment elevation to receive either a paclitaxel-eluting stent (PES) or BMS. The primary end point was a composite of death from cardiac causes, recurrent MI, or target-lesion revascularization at 1 year and did not reach the significance level. There was, however, a trend toward a lower rate of serious adverse events in the PES group than in the BMS group (8.8% vs 12.8%; adjusted relative risk, 0.63; 95% confidence interval, 0.37–1.07; \( P = .09 \)). A nonsignificant trend was also detected in favor of the PES group, as compared with the BMS group, in the rate of death from cardiac causes or recurrent MI (5.5% vs 7.2%, \( P = .40 \)) and in the rate of target-lesion revascularization (5.3% vs 7.8%, \( P = .23 \)). The incidence of stent thrombosis during 1 year of follow-up was the same in both groups (1.0%). The TYPHOON and PASSION trials ultimately attest to the safety and efficacy profile of these stents containing zotarolimus, a low-profile cobalt alloy stent, and a biocompatible phosphorylcholine polymer. The Endeavor stent has been shown to decrease the need for repeat revascularization compared with BMSs, but there were no differences in the incidence of death or MI between these 2 stent types.\(^ {50–52} \) Although new DESs are increasingly used for the treatment of patients with STEMI, there have been few direct comparisons of outcomes among the currently approved DESs in these patients.\(^ {53} \) The major findings of a study conducted by Lee CW and colleagues\(^ {54} \) comparing the efficacy and safety of ZESs, SESs, and PESs in patients with STEMI are as follows: (1) There was no difference in the overall rate of major cardiac events at 12 months among the ZES, SES, and PES groups. (2) There was a nonsignificant trend in favor of ZESs in the rate of stent thrombosis. (3) SESs were associated with lower late loss and restenosis rates compared with ZESs or PESs. (4) The rate of ischemia-driven TVR was the same among the 3 DESs.\(^ {54} \) The results of this study\(^ {54} \) are, thus, in agreement with those of previous studies comparing different types of DESs in stable

### Table 1

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<th>Study Design</th>
<th>No. of Centers Involved</th>
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coronary artery disease, which found that late loss was significantly higher after ZES compared with SES implantation but that, below a certain threshold level, this difference did not translate to an increase in the repeat revascularization rate.50–52

SESs and PESs have been found to decrease the risk of restenosis compared with BMS. Although SESs and PESs are effective, SESs were found to have a somewhat greater benefit in the restenosis rate. In the setting of STEMI, SES implantation resulted in a lower angiographic restenosis rate at 6 months compared with PES implantation, although there were no differences in major adverse cardiac event rates between the 2 stents. The ZES, a new type of DES based on a different type of biostable polymer, may improve arterial healing with less inflammation.55,56 Several studies have shown that ZESs provide a consistent and sustained decrease in the need for repeat procedures compared with BMSs and maintain an excellent safety profile.50–52

The Limus Eluted from A Durable vs ERodable Stent Coating (LEADERS)57 trial is a prospective randomized noninferiority trial comparing the biolimus-eluting stent (BES) with the biodegradable polymer versus the SES with durable polymer. In the subgroup analysis of this trial that included patients with STEMI, there was a significant reduction of MACE with BESs compared with SESs (9.6% vs 20.7%, P = .01). Furthermore, the very late stent thrombosis (VLST) was rare (BES 0.2% vs SES 0.9%, P = .43). There were no VLST events in patients with BESs between the 2- and 3-year clinical follow-up.

THE EVALUATION OF XIENCE-V STENT IN ACUTE MYOCARDIAL INFARCTION TRIAL: THE RESULTS

A lower rate of stent thrombosis was found with a second-generation DES than with the BMS.58 The second-generation DES Xience-V performs well in patients having primary PCI for STEMI and has a better safety profile than that of BMSs, according to results of the Evaluation of Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial.

The study was a randomized controlled trial with an all-comers design to evaluate the Xience-V stent in the complex setting of STEMI and to provide data that may be applicable to the real-world population.

The first-generation DESs have been evaluated in randomized controlled trials in the setting of STEMI, with positive results overall. However, most of these trials lacked good generalizability to real-world circumstances because of their highly selected inclusion/exclusion criteria. Moreover, no safety and efficacy data exist for the new generation of DESs in this high-risk group of patients with STEMI. The all-comers design of the EXAMINATION trial applied wide inclusion and few exclusion criteria, “which may result in a more representative sample of the target population.”

The study was an investigator-initiated, multicenter, multinational trial involving 1498 patients with STEMI randomized to either a Xience-V stent (everolimus-eluting stent [EES]) or cobalt chromium BMS. The primary end point was a composite of all-cause death, any recurrent MI, and any repeat revascularization at the 1-year follow-up. Individual components of the primary end point and stent thrombosis were the main secondary end points. Patients included in the trial represented up to 70% of all the patients with STEMI present in the centers during the recruitment period, reflecting the real-world nature of the design.

Results presented during the Hot Line session in Paris at the European Society of Cardiology Congress 2011 included 98% of patients with 1-year follow-up data. In terms of the primary end point, there was a nonsignificant trend toward a benefit with the Xience-V stent by virtue of a lower rate of new revascularizations during follow-up as compared with the BMS.

In terms of safety, the rates of definite and definite/probable stent thrombosis at the 1-year follow-up were significantly lower with the Xience-V stent as compared with the BMS, accounting for 0.5% (definite) and 0.9% (definite or probable) at 1 year with the Xience-V stent and 1.9% and 2.6% with the BMS (both P = .01).

The use of EES in the setting of STEMI resulted in a numerically (not significantly) reduced primary end point at the expense of a trend in reduction of the repeat revascularization rate. The significant reduction observed in the definite and definite/probable stent thrombosis rates suggest an excellent safety profile of the EES in these high-risk patients presenting with STEMI. The results of this all-comer randomized trial are highly representative of the real-world population.

So in conclusion, the use of DESs in selected patients with AMI seems to be safe and, with the presence of the new generations of DESs (BES, ZESs, EES), has shown acceptable results in terms of safety and efficacy in the treatment of STEMI.

STENTS VERSUS PLAIN OLD BALLOON ANGIOPLASTY

As previously stated, PTCA for primary treatment after AMI has been demonstrated to be superior
to thrombolytic therapy with regard to the restoration of normal coronary blood flow, and is associated with lower rates of recurrent ischemia, reinfarction, stroke, and death. In a study comparing primary angioplasty with angioplasty accompanied by the implantation of the heparin-coated Palmaz-Schatz stent, Grines and colleagues have demonstrated that there is a divergence between the stent group and the angioplasty group in the rate of clinical events occurring between 1 and 6 months after intervention, finding consistent with the known time course of restenosis. As expected, they found a lower rate of restenosis in the stent group than in the angioplasty group. The rate of restenosis after emergency implantation of a stent for AMI was similar to that observed in elective cases. This finding suggests that thrombus and activated platelets already present at the time of AMI may not influence the risk of restenosis or perhaps that a reduction in platelet deposition caused by the use of the heparin-coated stent, as compared with an uncoated stent, had a positive effect on the rate of restenosis. Stenting was also known to be superior to plain old balloon angioplasty (POBA) at improving coronary flow reserve (CFR). Edep and colleagues recently showed that coronary blood flow is increased after stenting compared with POBA in the setting of AMI as measured by the TIMI frame count method. In addition, Sasao and colleagues reported that primary stenting is superior to POBA in acute anterior MI for preventing myocardial injury and restoring left ventricular function. They also speculated that primary stenting improves regional wall motion by improving the coronary vasodilator reserve. It has been shown that CFR is not commonly normalized after PTCA, although reports suggest that CFR may be normalized after stent implantation. Clearly, coronary stenting improves the initial success rate, decreases the incidence of abrupt closure, and is associated with a reduced rate of restenosis. For these reasons, coronary stenting is increasingly used to treat AMI.

**STENTING IN THE PRESENCE OF THROMBUS**

Animal studies revealed that endothelial denudation is less in direct stenting cases compared with conventional stenting, which may mean less vascular wall trauma and thrombosis risk. In addition, Webb and colleagues reported lesser atheromatous embolic debris during intervention in saphenous vein grafts with direct stenting compared with conventional stenting, which may lead to the no reflow phenomenon. They also reported that stents reduced the dislodgement of the thrombus and embolization by entrapping friable material. In their study of direct stenting in angiographically apparent thrombus-containing lesions, Timurkayanak and colleagues have shown that TIMI flow grades after stenting are quite high, with the majority being TIMI 3 flow (93%). Trapping of the thrombus with the stent might also be an important factor in protecting the flow. The trauma caused by balloon predilation might be responsible for a greater amount of distal embolization of the thrombi and debris.

In the presence of thrombi, a stent may act as a jail for the thrombus and prevent distal propagation. However, the potential pitfalls of direct stenting should always be considered. Although stenosis severity was not reported to be an indicator of successful direct stenting, passing a stent through a severe undilated stenosis might be more traumatic. However, direct stenting may not be an appropriate approach in all lesion subsets and requires distal opacification of the vessel for accurate assessment of lesion characteristics and stent choice.

Thus, coronary stenting constitutes an effective therapeutic strategy for patients with thrombus-containing lesions, either after failure of initial angioplasty or electively as the primary procedure. Coronary stenting in this adverse anatomic setting results in a high degree of angiographic success, a low incidence of subacute thrombosis, and an acceptable restenosis rate.

**STENTING CULPRIT VERSUS NONCULPRIT IN AMI**

Current guidelines recommend that elective PCI should not be performed in a non-infarct–related artery at the time of primary PCI of the infarct-related artery in patients without hemodynamic compromise. In their study comparing culprit vessel PCI with multivessel and staged PCI for STEMI, Hannan E and colleagues found that patients with multivessel disease STEMI undergoing multivessel primary PCI at the time of the index procedure had mortality rates that were trending higher than rates for patients with culprit vessel PCI alone. Also, when outcomes for the subset of patients without hemodynamic instability, ejection fraction, less than 20%, or malignant ventricular arrhythmia were examined, patients with culprit vessel PCI alone had lower in-hospital mortality rates (0.9% vs 2.4%, \( P = .04 \)). Because the current guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) recommend culprit vessel PCI for patients without hemodynamic compromise,
Hannan and colleagues support the recommendations in their findings. Another part of this study consisted of comparing differences in mortality between patients with multivessel disease STEMI treated with culprit vessel PCI and those patients who did not undergo multivessel PCI during the index procedure but did undergo multivessel PCI within 60 days after the index procedure, either during the index admission or afterward. Conclusions from these analyses were that patients who underwent multivessel PCI within 60 days of the index procedure fared better than patients who were limited to culprit vessel PCI within 60 days. In the largest report of its kind to date, Toma and colleagues have shown that nonculprit coronary interventions, when performed concurrently with primary PCI, are associated with adverse outcomes, including excess death. All data strongly support both current guideline (ACC/AHA and the European Society of Cardiology) recommendations discouraging non-infarct-related artery PCI procedures performed at the time of primary PCI when patients are hemodynamically stable.

**ADJUNCTIVE THERAPY: ANTITHROMBOTICS AND ANTIPLATELETS**

**Oral Antiplatelet Therapy**

**Aspirin**

Aspirin reduces the frequency of ischemic complications after PCI. Although the minimum effective aspirin dosage in the setting of PCI has not been established, aspirin 325 mg given at least 2 hours, and preferably 24 hours, before PCI is recommended, after which aspirin 81 mg daily should be continued indefinitely.

**Clopidogrel**

Several investigations have explored various loading doses of clopidogrel before or during PCI. Compared with a 300-mg loading dose, doses of either 600 mg or 900 mg achieve greater degrees of platelet inhibition with fewer low responders. A meta-analysis of 7 studies that included 25,383 patients undergoing PCI demonstrated that intensified loading of clopidogrel with 600 mg reduces the rate of MACE without an increase in major bleeding compared with 300 mg. Another study suggested that a 600-mg loading dose of clopidogrel is associated with improvements in procedural angiographic end points and 1-year clinical outcomes in patients with STEMI who undergo primary PCI compared with a 300-mg dose. There is no benefit with increasing the loading dose to 900 mg compared with 600 mg. Clopidogrel 75 mg daily should be given for a minimum of 4 weeks after balloon angioplasty or BMS implantation (a minimum of 2 weeks if increased bleeding risk is present) and for at least 12 months after DES implantation (unless the risk of bleeding outweighs the anticipated benefit). Patients should be counseled on the need for and risks of DAPT before stent implantation, especially DES implantation, and alternative therapies pursued (BMS or balloon angioplasty) if they are unwilling or unable to comply with the recommended duration of DAPT.

**Prasugrel**

When prasugrel was compared with clopidogrel in patients with ACS in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (TRITON–TIMI 38), prasugrel was associated with a significant 2.2% reduction in absolute risk and a 19.0% reduction in relative risk in the composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke, and a significant increase in the rate of TIMI major hemorrhage (1.8% vs 2.4%). Prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke. Patients weighing less than 60 kg have an increased risk of bleeding on the 10-mg daily maintenance dosage. The package insert suggests that consideration should be given to lowering the maintenance dosage to 5 mg daily, although the effectiveness and safety of the 5-mg dosage has not been studied. Prasugrel is not recommended for patients older than 75 years because of the increased risk of fatal and intracranial bleeding and lack of benefit, except in patients with diabetes or a history of prior MI. Prasugrel should not be started in patients likely to undergo urgent coronary artery bypass graft. Prasugrel has not been studied in elective PCI and, thus, no recommendation can be made regarding its use in this clinical setting.

**Ticagrelor**

Ticagrelor reversibly binds the P2Y12 receptor. Unlike clopidogrel or prasugrel, ticagrelor is not a thienopyridine. It also does not require metabolic conversion to an active metabolite. Compared with clopidogrel in patients with ACS in the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was associated with a significant 1.9% reduction in absolute risk and a 16.0% reduction in relative risk in the primary composite end point of vascular death, nonfatal MI, or nonfatal stroke. Ticagrelor was associated with higher rates of transient dyspnea and bradycardia compared with clopidogrel, although only a small percentage of patients discontinued the study drug because of...
dyspnea. Based on post hoc analysis of the PLATO study, specifically the results in the US patient cohort, a black box warning states that maintenance doses of aspirin more than 100 mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, ticagrelor should be used with aspirin 75 mg to 100 mg per day.

Given the twice-daily dosing and reversible nature of the drug, patient compliance may be a particularly important issue to consider and emphasize. Ticagrelor has not been studied in elective PCI or in patients who received fibrinolytic therapy, thus, no recommendations about its use in these clinical settings can be made.

**Antiplatelet Therapy**

In the era before DAPT, trials of adequately dosed glycoprotein (GP) IIb/IIIa inhibitors in patients undergoing balloon angioplasty and coronary stent implantation demonstrated a reduction in the incidence of composite ischemic events with GP IIb/IIIa treatment, primarily through a reduction of enzymatically defined MI. In some trials, the use of GP IIb/IIIa inhibitors is associated with some increased bleeding risk, and trials of these agents have generally excluded patients at high risk of bleeding (eg, coagulopathy). Thus, recommendations about the use of GP IIb/IIIa inhibitors are best construed as applying to those patients not at a high risk of bleeding complications. Abciximab, double-bolus epifibatide (180 mcg/kg bolus followed 10 minutes later by a second 180 mcg/kg bolus), and high-bolus dose tirofiban (25 mcg/kg) all result in a high degree of platelet inhibition, and have been demonstrated to reduce ischemic complications in patients undergoing PCI.

Ticagrelor has not been studied in elective PCI or in patients who received fibrinolytic therapy, thus, no recommendations about its use in these clinical settings can be made.

**REFERENCES**


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<th>Location in article</th>
<th>Query / Remark: Click on the Q link to find the query’s location in text</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Please approve the short title to be used in the running head at the top of each right-hand page.</td>
</tr>
<tr>
<td>Q2</td>
<td>This is how your name will appear on the contributor’s list. Please add your academic title and any other necessary titles and professional affiliations, verify the information, and OK AHMED MAGDY, MD, FACC, FSCAI, National Heart Institute, Cairo, Egypt HISHAM SELIM, MD, National Heart Institute, Cairo, Egypt MONA YOUSSEF, MD, National Heart Institute, Cairo, Egypt</td>
</tr>
<tr>
<td>Q3</td>
<td>Are author names and order of authors OK as set?</td>
</tr>
<tr>
<td>Q4</td>
<td>The following synopsis was created from the “Key Points” section of your article because a separate abstract was not provided. Please confirm OK or submit a replacement (also less than 100 words). Please note that the synopsis will appear in PubMed: “Stenting in acute myocardial infarction (AMI) has the benefits of achieving acute optimal angiographic results and correcting residual dissection to decrease the incidence of restenosis and reocclusion. Studies have shown that percutaneous transluminal coronary angioplasty for primary treatment after AMI is superior to thrombolytic therapy regarding the restoration of normal coronary blood flow. Coronary stenting improves initial success rates, decreases the incidence of abrupt closure, and is associated with a reduced rate of restenosis. In the presence of thrombus-containing lesions, coronary stenting constitutes an effective therapeutic strategy, either after failure of initial angioplasty or electively as the primary procedure.”</td>
</tr>
<tr>
<td>Q5</td>
<td>Please verify the affiliation addresses and provide the missing information (department name, street name and zip code).</td>
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<tr>
<td>Q6</td>
<td>Are keywords OK as set?</td>
</tr>
<tr>
<td>Q7</td>
<td>Please verify the titles for “EXAMINATION” and “LEADERS” in the “Key Points” section.</td>
</tr>
<tr>
<td>Q8</td>
<td>As per editorial remarks “per Dr. Mehta, Throughout the manuscript, most of the studies emphasize the beneficial use of DES. Maybe you should mention SESAMI 3 year follow up, as well as the 1 year follow</td>
</tr>
</tbody>
</table>
up results, showing BMS benefits in MACE and TLR. Also consider mentioning T SEARCH and RESEARCH data over late stent thrombosis with SES vs BMS, to balance data."

Q9 Please check the article throughout to be sure that edits have preserved your intent.

Q10 Is the hierarchy of the heading levels OK as set?

Q11 Please spell out “STENTIM-2” at first mention.

Q12 Please clarify the sentence beginning “By reducing the…”

Q13 Reference citations were not in sequential order. Hence, Refs. 23–118 have been renumbered both in text and in reference list. Please verify.

Q14 Originally Refs. 25, 100–102, 106, 107 were not cited in the text. Hence they have been combined with the citation of previous Refs. 24, 99, 105 respectively. Please verify.

Q15 Please verify the trial name for “Stent PAMI trial” and clarify whether it is the same as the “PAMI-1” trial.

Q16 Please clarify the number of years in the sentence beginning “Observational studies have…”

Q17 Please provide the manufacturer names/locations for “Cypher and Taxus” at first mention, if applicable.

Q18 Please provide manufacturer name/location for “Endeavor” at first mention, if applicable.

Q19 Please verify the term “biostable” in the sentence beginning “The ZES…”

Q20 Please spell out “MACE” at first mention.

Q21 Please verify the full trial name for “EXAMINATION.”

Q22 As per Clinics style, citation is not allowed in section headings. Hence the citation of Ref. 58 has been moved to the end of the first sentence of the paragraph “Lower rate of stent…” Please verify.

Q23 Please verify the name “Xience-V” and provide the manufacturer name/location, if applicable.

Q24 Please provide the complete reference citation for the direct quote in the sentence beginning “The all-comers…”

Q25 Please verify the name “Palmaz-Schatz” and provide the manufacturer name/location, if applicable.

Q26 Please clarify what “less than 20%” refers to in the sentence beginning “Also, when…”

Q27 There is a discrepancy in the author name between the reference list (Smith et al) and the text (Hannan et al) of Ref. 75. Please clarify.

Q28 Please verify all doses throughout the article.

Q29 Please spell out “DAPT” at first mention.

Q30 Please spell out “ACS” at first mention.

Q31 Please spell out “RCT” at first mention (clinical or controlled?).

Q32 Refs. 28 and 37 were identical, the latter has been removed from the reference list and subsequent references have been renumbered. Please verify.

Q33 Please provide the complete accessed date for Ref. 58.

Q34 Please verify the title of Ref. 67.

Q35 Please provide URL for Ref. 86.

Q36 Please provide the manufacturer name/location for “Taxus” in Fig. 1 legend, if applicable.

Q37 Please spell out “TVF” in Table 1.
As per editorial remarks; Dear Authors, about whether or not table and Fig was borrowed. Will submit permission if applicable.

Please check this box if you have no corrections to make to the PDF file

Thank you for your assistance.