The contemporary management of patients with ST-segment elevation myocardial infarction (STEMI) involves a series of timely decisions, including the primary reperfusion strategy and a triage and transfer strategy for patients presenting to a facility not capable of percutaneous coronary intervention (PCI). Even for PCI-eligible patients presenting to a PCI-capable hospital, there are a myriad of choices. To start, what is the optimal thienopyridine? Which parenteral anticoagulant should be used? Is a glycoprotein IIb/IIIa inhibitor needed? Then, add the questions of dosing; timing and duration of drug administration; and patient-specific factors, such as age, bleeding risk, or prior stroke. Once a culprit lesion is identified, should thrombectomy be performed? Is a drug-eluting stent (DES) or bare-metal stent best for the patient and lesion, and if a DES, which specific type? Although we have information on several of the possible combinations, we cannot extrapolate to all possible options.

The number of decisions increases when a patient with STEMI presents to a non-PCI-capable hospital. Although primary PCI is recognized as the preferred reperfusion strategy, geographical or logistical considerations may limit this option. Numerous studies tested the combination of fibrinolysis with or without glycoprotein IIb/IIIa inhibition immediately followed by PCI or facilitated PCI as a means to early and sustained reperfusion of the infarct artery. Compared to primary PCI, the facilitated approach results in higher mortality; nonfatal reinfarction; bleeding; and stroke, including hemorrhagic stroke. The caveat is that if primary PCI is not an option, and fibrinolytic therapy is part of the primary reperfusion strategy, a strategy of routine or adjunctive PCI is superior to rescue or selective ischemia-guided PCI with respect to adverse events. This approach is now referred to as a pharmacoinvasive strategy in lieu of the terms facilitative or rescue.

Patients treated with a pharmacoinvasive strategy require anticoagulant and antiplatelet therapy before PCI. As is the case with primary PCI, there are a number of acceptable antithrombotic therapy and stent combinations, but few have been tested prospectively. In this issue of *Circulation: Cardiovascular Interventions*, Sanchez et al report the first randomized trial of the paclitaxel-eluting stent (PES) and the small-molecule glycoprotein IIb/IIIa receptor antagonist tirofiban for postfibrinolysis PCI in the Role of Tirofiban and the Paclitaxel Eluting Stent in Postfibrinolysis Angioplasty (GRACIA-3) trial. In this multicenter, open-label trial, 436 patients with STEMI treated with tenecteplase, enoxaparin, and aspirin were randomized using a 2×2 factorial design to an antiplatelet strategy (tirofiban or no tirofiban) and a stent strategy (PES or a comparable-platform bare-metal stent). The trial was carried out in 20 Spanish hospitals, and 34% of patients were initially admitted to 1 of the 7 non-PCI-capable hospitals, with a median transportation time to a PCI hospital of 61 minutes. No assessment of reperfusion in response to fibrinolysis was made, and tirofiban was started 2 hours after fibrinolysis and continued for 24 hours. The median time from symptom onset to fibrinolysis was 2.92 hours and from fibrinolysis to angiography, 5.16 hours; times were similar among the 4 treatment groups. A clopidogrel-loading dose of 300 mg was given immediately after stenting, and the duration of dual antiplatelet therapy was 1 year.

The study was well executed, with a high percentage of patients receiving assigned treatment, a low crossover rate of tirofiban use of 1%, and near complete clinical and 86% angiographic follow-up at 1 year. The main findings of the trial were negative in that there was no benefit of tirofiban on epicardial and myocardial perfusion as assessed by the angiography, and there was no difference in angiographic binary restenosis in PES compared to bare-metal stent (rates, 10.1% versus 11.3%; *P*=0.89). The study was not powered for clinical outcomes, but several are notable. In the stent stratum, all measured clinical outcomes in the PES and bare-metal stent groups were similar, including stent thrombosis, myocardial infarction, and ischemia-driven revascularization; however, there was a higher rate of death in the PES patients (9.7% versus 6.9%; *P*=0.39). In the antiplatelet stratum, cardiovascular outcomes did not differ according to treatment assignment; however, patients randomized to tirofiban were significantly more likely to have any bleeding (major and minor) and the quadruple end point of death, myocardial infarction, revascularization, and major bleeding. Disturbing trends also were noted in major (6.1% versus 2.7%; *P*=0.15) and intracranial bleeding (3.3% versus 0.9%; *P*=0.3.
higher bleeding rates were observed, including intracranial bleeding. Even with this delay and in the absence of clopidogrel, tirofiban administration was delayed 2 hours to allow for elimination of tenecteplase and reduce the risk of bleeding.7 Tirofiban administration was delayed 2 hours to allow for elimination of tenecteplase and reduce the risk of bleeding. Therefore, in a trial designed to test therapeutic options in patients treated with a routine pharmacoinvasive strategy, the timing of PCI in GRACIA-3 appears to be optimal.

To fully understand the implications of the GRACIA-3 trial on glycoprotein IIbIIIa inhibitor use as part of a routine pharmacoinvasive strategy, it is helpful to review the details of the antithrombin and antiplatelet therapy. The enoxaparin dose used in this study differed according to age and tirofiban assignment. All patients aged ≥75 years and those randomized to tirofiban received 0.75 mg/kg subcutaneous enoxaparin only, whereas the no-tirofiban patients aged <75 years received an enoxaparin IV bolus of 30 mg followed by a subcutaneous dose of 1 mg/kg. Only 1 dose of enoxaparin was administered if PCI was successfully performed within 8 hours of randomization. Would the outcomes have differed if an alternative antithrombin regimen, such as unfractionated heparin, was used? On the basis of the conservative enoxaparin dosing in this trial and the outcomes of patients treated with fibrinolytic therapy for STEMI who underwent subsequent PCI in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction 25 trial, unfractionated heparin would not be expected to affect ischemic end points or decrease the unfavorable bleeding with adjunctive tirofiban in this setting.

What about the type, timing, and dosing of glycoprotein IIbIIIa inhibitor in GRACIA-3? Experimentally, thrombolytic therapy for STEMI results in platelet activation and aggregation, and glycoprotein IIbIIIa antagonists can overcome this effect. Tirofiban administration was delayed 2 hours to allow for elimination of tenecteplase and reduce the risk of bleeding. Even with this delay and in the absence of clopidogrel, higher bleeding rates were observed, including intracranial bleeding; therefore, earlier administration should not be tested. Tirofiban was dosed as a 25 μg/kg IV bolus and 0.15 μg/kg per minute infusion, similar to primary PCI trials. Although there are no data comparing the small-molecule glycoprotein IIbIIIa inhibitors to abciximab in patients receiving full-dose fibrinolytic therapy, the expected outcomes can be extrapolated from primary PCI trials where the 2 therapies are equivalent.

A major shortcoming of the GRACIA-3 trial is that patients were not treated with clopidogrel at the time of fibrinolytic therapy, which is now considered standard of care based on the PCI-Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 trial.4,10 In patients receiving fibrinolytics for STEMI, pretreatment with clopidogrel rather than given at the time of PCI significantly reduces cardiovascular death, myocardial infarction, and stroke without excess in the rates of bleeding. A more contemporary trial design would have included a 300-mg loading dose of clopidogrel at the time of fibrinolytics (for patients aged <75 years) in addition to randomization to tirofiban. With clopidogrel pretreatment, however, the potential benefits of glycoprotein IIbIIIa inhibitors would be less,11,12 and bleeding risk potentially exaggerated. Thus, on the basis of the GRACIA-3 trial, a routine strategy of adjunctive glycoprotein IIbIIIa inhibitor use with full-dose fibrinolytics in patients intended for a pharmacoinvasive strategy is not recommended. In addition, higher doses of clopidogrel or prasugrel should not be used in this setting until safety has been examined in clinical trials.

With respect to PCI techniques, the infarct-related artery was predilated if the thrombolysis in myocardial infarction flow grade was <3 or the stenosis was >50%; otherwise, direct stenting was performed. Thrombectomy, which has benefits in primary PCI, was not examined in this trial.13,14 In addition, nonculprit PCI, which is not routinely recommended, was performed in 31% of patients, and how this affected outcomes is unclear. Conclusions about the optimal stent type to use in patients treated with a pharmacoinvasive strategy cannot be made from this trial due to the small sample size and use of only the PES. In patients treated with primary PCI despite inconsistent efficacy of DES, a meta-analysis suggests that target vessel revascularization rates are reduced with DES (PES and sirolimus-eluting stents) without compromising safety.15 Therefore, until further data on DES outcomes in patients undergoing fibrinolytic therapy are available, selective use of DES in patients at high risk for restenosis due to patient or lesion characteristics and that can comply with prolonged dual antiplatelet therapy is recommended.

In summary, although the GRACIA-3 trial cannot determine the optimal postfibrinolytic pharmacological approach or stent choice, several important conclusions can be drawn. There is no benefit and clear harm with the routine use of tirofiban and, by extension, any glycoprotein IIbIIIa inhibitor in patients treated with full-dose fibrinolytics and a pharmacoinvasive approach. Whether selected high-risk patients who have no response to fibrinolytic therapy have a net clinical benefit from glycoprotein IIbIIIa inhibitors is unclear and should be tested in the context of a clinical trial or otherwise discouraged. Finally, the influence of the postfibrinolytic milieu on the effectiveness and safety of DES requires further study. As interventionalists, we move quickly in performing PCI in patients with STEMI, but we are wading slowly through the complex array of medical and device options to identify the best combination of therapies.

Disclosures

None.

References


$P=0.10$ with tirofiban. In addition, patients experiencing bleeding, even classified as minor, had significantly higher mortality rates at 1 year.
Pharmacoinvasive Strategy for ST-Segment Elevation Myocardial Infarction: Wading Through the Treatment Options

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