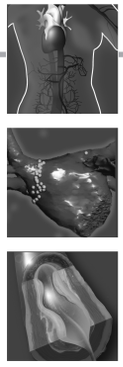

Drug-eluting stents and glycoprotein IIbIIIa inhibitors in the pharmacoinvasive management of ST elevation MI

Evaluation of: Sanchez, P, Gimeno F, Ancillo P *et al.*: Role of the paclitaxel-eluting stent and tirofiban in patients with ST elevation myocardial infarction undergoing postfibrinolysis angioplasty (GRACIA 3 Trial). *Circ. Cardiovasc. Interv.* 3, 297–307 (2010). In ST elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention (PCI)-capable hospitals, a pharmacoinvasive strategy utilizing fibrinolysis with early but not immediate angiography is a reasonable reperfusion strategy. The optimal antiplatelet regimen and stent type has not been defined in this clinical setting. The article by Sanchez *et al*. reported a 2 × 2 factorial design trial of 436 ST segment elevation myocardial infarction patients treated with full-dose tenecteplase and adjunctive PCI, comparing outcomes in patients randomized to the glycoprotein IIbIIIa inhibitor tirofiban versus placebo 2 h after fibrinolysis and the paclitaxel drug-eluting stent versus the bare-metal stent. The median time between fibrinolysis and PCI was 5.16 h. Tirofiban did not improve measures of epicardial or myocardial perfusion and resulted in a significant increase in bleeding that negatively impacted on 1-year mortality. In the stent stratum, the paclitaxel drug-eluting stent resulted in less neointimal hyperplasia but this did not translate into lower rates of restenosis. Until further studies are completed, patients treated with fibrinolysis should receive antiplatelet therapy with aspirin and clopidogrel, without routine use of glycoprotein IIbIIIa inhibitors, and drug-eluting stents should be used at the discretion of the interventional cardiologist.

KEYWORDS: bare-metal stent ■ drug-eluting stent ■ fibrinolysis ■ glycoprotein IIbIIIa inhibitor ■ ST elevation myocardial infarction ■ STEMI

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This article reviews the recent paper by Sanchez *et al.* that examined the use of the glycoprotein IIbIIIa inhibitor tirofiban and the paclitaxel drug-eluting stent (PES) in ST elevation myocardial infarction (STEMI) patients treated with fibrinolyis [1]. Primary percutaneous coronary intervention (PCI) has emerged as the preferred strategy for the management of patients with acute STEMI [2]. In settings without access to primary PCI, the default reperfusion strategy is fibrinolytic therapy. To capitalize on the advantages of the widespread availability and timely access to fibrinolysis and the reduction in reinfarction and long-term vessel patency that results from PCI, the two treatments are often combined. Immediate angiography and intervention following successful fibrinolysis, previously termed 'facilitated PCI', has fallen into disfavor owing to high rates of bleeding, stroke and mortality compared with primary PCI [3]. However, a number of studies have demonstrated that in patients treated with fibrinolytic therapy, a strategy utilizing routine adjunctive or early-elective angioplasty is superior to a strategy of selective ischemia-guided PCI, particularly in high-risk patients [4–7]. The optimal timing of PCI in this setting appears to be between 2 and 24 h. The term 'pharmacoinvasive strategy' is preferred for this strategy of planned angiography with or without PCI following fibrinolyis, in lieu of the terms 'facilitated' or 'rescue' PCI [2].

Within the pharmacoinvasive strategy, the optimal dosing and timing of antiplatelet agents has not been well defined. This is particularly true of glycoprotein IIbIIIa inhibitors, as the role of these agents in STEMI in the era of dual antiplatelet therapy is uncertain [8,9]. Furthermore, the safety and efficacy of drug-eluting stents (DESs) in the post-fibrinolysis milieu have not been examined. The GRACIA-3 trial is one of the few clinical trials to help guide decisions among treatment options in patients treated with fibrinolysis and planned PCI.

Methods

GRACIA-3 is a prospective, multicenter, randomized placebo-controlled trial involving STEMI patients treated with a pharmacoinvasive reperfusion strategy. Between October 2004 and

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August 2006, 436 patients at 20 Spanish hospitals presenting with STEMI treated with aspirin, full-dose tenecteplase and enoxaparin were randomized in a 2 × 2 design to the small-molecule glycoprotein IIbIIIa inhibitor tirofiban versus placebo, initiated 2 h after fibrinolytic administration before PCI and continued for 24 h and a bare-metal stent (BMS) versus a PES. This randomization resulted in four groups of patients: BMS without tirofiban, BMS with tirofiban, PES without tirofiban and PES with tirofiban. The rationale for the timing of tirofiban was to avoid concomitant use of the potent intravenous platelet inhibitor during the expected 2-h pharmacodynamic duration of tenecteplase activity in an attempt to limit bleeding complications. Patients underwent fibrinolysis at a median time of approximately 3 h after symptom onset and, by protocol, catheterization within 3–12 h of tenecteplase administration. Approximately a third of patients were initially admitted to a hospital without PCI capabilities and the median transport time was 61 min in this group of patients. Predilatation was performed on the infarct-related artery in cases of a stenosis greater than 50% or if the thrombolysis in myocardial infarction (TIMI) flow grade was less than 3; otherwise, direct stenting was performed. Stenting of nonculprit lesions was also performed when a large amount of myocardium was supplied by a greater than 2.75-mm vessel with over 90% stenosis. Clopidogrel was administered with a 300-mg loading dose following successful PCI and was continued for 12 months.

The prespecified primary outcome was the PES versus BMS was binary restenosis rate, measured by quantitative coronary angiography, at 12 months. The prespecified primary outcome to assess tirofiban versus placebo was the angiographic perfusion score, an angiographic assessment of epicardial and myocardial flow pre- and post-PCI. Prespecified secondary end points included clinical safety and efficacy in the overall patient cohort and predefined subgroups, rates of stent thrombosis using the academic research consortium criteria and 12-month quantitative coronary angiography analysis of late lumen loss assessed by a core laboratory.

Results

The baseline characteristics of the study populations were similar between the four groups and comparable with previous trials of primary angioplasty and fibrinolysis. There were no important differences in time to presentation, time to fibrinolysis or angiography, or concomitant treatment regimens among the four treatment groups, in hospital or post-discharge. The median time between fibrinolysis and PCI was 5.16 h. The study was well executed, demonstrating 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 12 months.

The primary end points of the study were negative in that there was no benefit of tirofiban on epicardial and myocardial perfusion, and there was no difference in angiographic binary restenosis in PES compared with BMS patients at 12 months (10.1 vs 11.3%; p = 0.89) . The secondary end point of late lumen loss favored PES, suggesting less intimal hyperplasia compared with BMS (0.04 ± 0.055 mm versus 0.27 ± 0.057 mm; p = 0.003). Although the study was not powered for clinical outcomes, a number of interesting observations could be made. In the stent stratum, all measured clinical outcomes in the PES and BMS groups demonstrated no difference, including stent thrombosis, myocardial infarction and ischemia-driven revascularization; however, there was a numerically but not statistically higher rate of death among the PES patients (9.7 vs 6.9%; p = 0.39). In the antiplatelet stratum, cardiovascular clinical outcomes were not different between treatment groups; however, patients randomized to tirofiban were significantly more likely to have any bleeding (major and minor) and the quadruple end point of death, MI, revascularization and major bleeding. Concerning signals were observed in major (6.1 vs 2.7%; p = 0.15) and intracranial (3.3 vs 0.9%; p = 0.10) bleeding with tirofiban. Of note, patients experiencing bleeding, even classified as minor, had significantly higher mortality rates at 1 year (22.1 vs 2.7%; p < 0.001).

Discussion

The GRACIA-3 trial is an important study helping to elucidate the optimal antiplatelet and stent regimens in the treatment of STEMI, utilizing a pharmacoinvasive strategy. The rationale for the use of tirofiban following thrombolytic administration is justified by evidence demonstrating increased platelet activation and aggregation following thrombolytic therapy, which glycoprotein IIbIIIa antagonists have been demonstrated to overcome [10,11]. Platelet inhibition after fibrinolysis and with PCI reduces recurrent ischemia and stent thrombosis. However, the risk is increased bleeding and this is related to the degree of

platelet inhibition [12]. The pharmacotherapy protocol in the trial was designed to minimize bleeding risk. The administration of tirofiban was delayed after tenecteplase, the clopidogrel loading dose was not given until after stenting and an appropriately conservative dosing regimen was utilized for enoxaparin [2]. Despite these precautions, patients in the tirofiban groups had higher rates of any bleeding and a concerning trend of higher rates of major and intracranial bleeding, even with the study's limited power for clinical events. Furthermore, the presence of any bleeding was predictive of 1-year mortality (22.1 vs 2.7%; $p < 0.001$). The expense of harm was not counterbalanced by any benefit in efficacy.

The finding of increased bleeding without clinical benefit is reminiscent of facilitated angioplasty trials with concomitant half-dose thrombolytics and glycoprotein IIbIIIa inhibitors [13,14]. On the basis of the GRACIA-3 trial, it is reasonable to conclude that a routine strategy of adjunctive glycoprotein IIbIIIa inhibitor use with full-dose fibrinolytics in patients intended for a pharmacoinvasive strategy is not recommended. Dual antiplatelet therapy with aspirin and a 300 mg loading dose of clopidogrel, however, should be administered with thrombolytic therapy. Compared with aspirin alone and clopidogrel loading at the time of PCI post-lytics, the strategy of upfront dual antiplatelet therapy improves clinical outcomes without an increase in bleeding in patients less than 75 years old, and is the current standard of care [2,15].

The timing of angiography following fibrinolysis in the GRACIA 3 trial is in accordance with several other studies showing a benefit of routine over-selective ischemia-driven PCI when performed between 2 and 17 h in post-lytic patients [4–7]. Conclusions cannot be made about the other aspects of interventional techniques that were not randomized, including the frequent use of direct stenting, the lack of thrombectomy and the routine non-infarct-related artery stenting. This study is unable to define the optimal stent type, given the small sample size and use of only PES. Extrapolation of data from primary PCI trials suggests that DESs (including studies of the PESs and sirolimus-eluting stents) reduce target vessel revascularization rates compared with BMSs without compromising safety [16,17]. Importantly however, information is lacking on how DESs perform in the post-fibrinolysis milieu, and on everolimus- and zotarolimus-eluting stents in STEMI. Therefore, while we await further data regarding DES outcomes in patients undergoing fibrinolytic therapy, selective use of DESs is recommended for patients that can comply with prolonged dual antiplatelet therapy and who are at high risk for restenosis due to patient or lesion characteristics.

Future perspective

The role of glycoprotein IIbIIIa inhibitors continues to shrink in the modern era as patients are treated early with oral antiplatelet agents [8,18]. Perhaps, future data may show a benefit for

Executive summary

Background

- In the treatment of ST elevation myocardial infarction with fibrinolysis as the initial reperfusion strategy, the optimal combination of adjunctive antiplatelet therapy and stent type is uncertain in patients referred for percutaneous coronary intervention as part of a pharmacoinvasive strategy.

Methods

- This multicenter randomized, placebo-controlled trial of 436 ST elevation myocardial infarction patients treated with tenecteplase used a 2 × 2 factorial design to compare: tirofiban versus placebo, and paclitaxel drug-eluting stents versus bare-metal stents (BMSs), in patients undergoing planned adjunctive percutaneous coronary intervention within 24 h.

Results

- The study was negative with no improvement in epicardial and myocardial perfusion with tirofiban compared with the placebo, and no difference in 12-month in-segment binary restenosis between paclitaxel drug-eluting stents and BMSs (10.1 vs 11.3%; relative risk: 1.06; 95% CI: 0.74–1.52; $p = 0.89$). The combination of major and minor bleeding was found to be more frequent among patients receiving tirofiban (relative risk with tirofiban: 1.39; 95% CI: 1.13–1.71; $p = 0.009$).

Significance

- There is no observable benefit and demonstrated harm with the routine use of tirofiban, and by extension glycoprotein IIbIIIa inhibitors, as part of a pharmacoinvasive strategy for ST elevation myocardial infarction. Further investigation into the safety and efficacy of drug-eluting stents post-fibrinolysis is warranted before their routine use can be recommended.

Future perspective

- The optimal antiplatelet agent and degree of platelet inhibition in patients treated with a pharmacoinvasive strategy warrants further investigation. Drug-eluting stents have demonstrated superior long-term patency compared with BMS in most clinical settings, however, their efficacy after primary fibrinolysis still remains to be defined.

more potent oral antiplatelet therapy, such as ticagrelor, or short-acting intravenous antiplatelet agents, such as cangrelor, in the setting of primary thrombolysis for STEMI [19,20]. The unanswered question that is of paramount importance is what degree of platelet inhibition is required in patients treated with a pharmacoinvasive strategy to minimize the risk of recurrent ischemic events and simultaneously minimize adverse events, including stroke and bleeding? In addition, the role of platelet function testing to tailor antiplatelet therapy for optimal clinical outcomes remains to be determined. DESs have demonstrated superior outcomes over BMSs in most clinical and lesion subsets, with lower rates of revascularization and similar rates of death and myocardial infarction. The benefits of DESs would be expected to translate to the post-fibrinolytic setting, although confirmation will require larger randomized controlled trials.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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