Facilitated Angioplasty: Neither Black Nor White

Pedro L. Sánchez and Francisco Fernández-Avilés

Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario, Valladolid, Spain.

The first thing to remember when judging ST-segment elevation acute coronary syndrome (STEACS) treatments is that the underlying mechanism is usually the rupture or erosion of an atherosclerotic plaque and consequent thrombus formation causing complete coronary artery occlusion. Although clinical consequences remain devastating, therapeutic advances in recent decades have significantly reduced mortality in acute myocardial infarction and improved long-term prognosis and quality of life.[1]

In this situation, the initial fundamental priority must be to combat arrhythmias and achieve rapid, efficient restoration of epicardial and microvascular flow. Efficient, early myocardial reperfusion at the onset of necrosis limits infarction size, reduces ventricular dysfunction and improves survival.[2] Two established strategies achieve this: drug therapy using thrombolytic agents, and mechanical intervention by primary angioplasty. Both have advantages and disadvantages. In optimal conditions, primary angioplasty appears more efficient than thrombolysis in restoring coronary flow and improving the clinical evolution of patients with STEACS.[3] However, because of inherent logistic and technical limitations angioplasty can be performed in only a small proportion of patients with infarction.[4-6] In contrast, intravenous thrombolysis reduces short-term mortality and is indicated in most patients with STEACS.[7] Moreover, bearing in mind the current availability of new, more easily administered thrombolytic agents, the efficacy and application of drug reperfusion can be expected to grow substantially in the near future.

However, the use of thrombolysis is severely limited: *a)* it entails a risk of bleeding with a 0.5%-1% incidence of cerebral hemorrhage; *b)* the clinical benefit depends greatly on early application and is substantially reduced when evolution of the infarction surpasses 6 hours[8]; *c)* there is a high incidence of partial or total failure of repermeabilization[9,10]; and *d)* 5%-25% of patients with initially successful reopening suffer reocclusion due to persistent, significant residual stenosis.[10-12]

The advantages and disadvantages of these therapies generated two distinct viewpoints on reperfusion strategies in patients with infarction, denying the existence of alternatives that lay between one option and the other. This has led researchers to question whether combining angioplasty with thrombolysis might provide a strategy as accessible as thrombolysis and as efficient, or more so, than primary angioplasty. Thus, the concept of facilitated angioplasty came into being.

DEFINITION

The correct definition of facilitated angioplasty is early percutaneous repair of the culprit artery (<12 hours) in routine (i.e. not rescue), planned (i.e. not urgent) procedures, in patients with STEACS treated initially with drug therapy to reopen the artery.[13] Thus, the most easily applied and accessible reperfusion technique to facilitate rapid recovery of arterial flow is followed by angioplasty to open the artery, if it is not already open, or eliminate residual stenosis and ensure long-term arterial permeability. However, the term facilitated angioplasty has also been used to refer to percutaneous procedures in patients with STEACS performed after administering antithrombotic agents such as glycoprotein IIb/IIIa inhibitors to

Correspondence: Dr. F. Fernández-Avilés.
Instituto de Ciencias del Corazón (ICICOR).
Hospital Clínico Universitario de Valladolid.
Avda. Ramón y Cajal, 3. 47005 Valladolid. España.
E-mail: ffaviles@uva.es

reduce risk and increase the efficiency of the procedure. This strategy should be distinguished from so-called prognostic or elective angioplasty in which systematized, percutaneous coronary procedures are performed at 12 hours post-infarction in patients initially treated with thrombolytic agents. Therefore, the distinction between facilitated and prognostic angioplasty is arbitrary and based principally on a question of time.

We believe the term pharmacomechanical reperfusion should be used whenever an antithrombotic drug regimen has been administered prior to angioplasty, and facilitated angioplasty should be reserved for systematized angioplasty in patients initially treated with thrombolysis.

ANTECEDENTS

Cardiac catheterization and systematized percutaneous procedures in patients with STEACS treated with thrombolytic agents have been studied and discussed since the late 80s. At that time, prior to the use of stents and glycoprotein IIb/IIIa inhibitors, or thyenopyridines, results were disappointing. In 1989 and 1991, 2 randomized studies[14,15] showed no clinical benefit in patients with STEACS and initially treated with thrombolytic agents, randomized to cardiac catheterization and cardiac procedures performed between 18 hours and 7 days after thrombolytic treatment or a conservative ischemia-guided treatment strategy. On the contrary, Barbash et al,[16] enrolled 201 patients with STEACS receiving recombinant tissue plasminogen activator and found that facilitated angioplasty at 5±2 days after fibrinolytic therapy associated with 8.2% 10-month mortality versus 3.8% (*P*=.15).[16]

These results gave rise to the clinical practice guideline recommendation that cardiac catheterization and systematized percutaneous procedures should not be performed in patients with STEACS on thrombolytic treatment regimens unless they presented episodes or signs of ischemia during follow-up.

These disappointing results can be explained in several ways. Residual post-thrombolysis stenosis normally contains unstable thrombus and mechanical manipulation of this with the balloon may cause adverse effects such as thrombotic occlusion or dissection of the vessel. The presence of thrombus also worsens restenosis, increasing neointimal hyperplasia and favoring negative remodeling. In the present era, the absence of benefits from this strategy may have been due to logistics given the delay of several days between thrombolytic treatment and cardiac catheterization.

Recently, these questions motivated 2 studies that again revealed the role of elective angioplasty (<24 hours) in the management of STEACS patients treated with thrombolysis.

The SIAM III study[17] randomized 197 patients with STEACS treated with reteplase to 2 strategies: facilitated angioplasty within 6 hours of thrombolytic treatment or elective angioplasty at 2 weeks post-thrombolysis. All patients received stent and glycoprotein IIb/IIIa inhibitor (abciximab) was administered to 9.8% of patients in the immediate stenting group and 16.0% of those in the delayed stenting group. Immediate stenting was associated with a reduction in the primary composite endpoint (death, reinfarction, unstable angina or revascularization) compared with delayed stenting (25.6% vs 50.6%; *P*=.001).

The GRACIA 1 study[18] was a randomized, multicenter clinical trial (20 centers in Spain and Portugal participated) of 500 patients with STEACS and thrombolytic treatment assigned either to coronary angiography within 24 hours of thrombolysis followed by complete revascularization with stent or surgery, or to conservative management guided by detection of spontaneous or provoked ischemia in post-infarction evaluation. The primary composite endpoint was 1-year incidence of mortality, reinfarction, stroke, and ischemia-induced revascularization. In-hospital revascularization guided by detection of spontaneous or provoked ischemia in the conservative group was not considered an event as it is standard in these patients. After enrolment, patients followed a strict management regime according to clinical practice guideline recommendations. Secondary prevention followed an exhaustive protocol in both groups. Indications for coronary angiography and revascularization in patients managed conservatively were strictly based on American Heart Association, American College of Cardiology and Spanish Society of Cardiology guidelines. In the intervention group, unfractionated heparin administration was suspended immediately after angiography. In patients randomized to intervention the use of glycoprotein IIb/IIIa inhibitors was optional but recommended in the presence of complete occlusion of the culprit lesion or lesions with angiographic signs suggesting the presence of thrombus. At 30 days, the primary endpoint was similar in both intervention and conservative groups (4.8% and 6%, respectively) with no differences in major bleeding or vascular complications. Hos-

pitalization was significantly shorter in patients randomized to intervention (7±6 vs 11±6 days; *P*=.001). At 12 months, the composite endpoint (death, infarction, or need for revascularization) was observed in 23 (9%) patients randomized to intervention compared to 51 (21%) in the conservative group (hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.28-0.70; *P*=.001). At follow-up, the incidence of death or reinfarction was 7% versus 12%, respectively (HR=0.60; 95% CI, 0.34-1.06; *P*=.07).

In conclusion, GRACIA 1 clearly shows that routine early stenting in patients with STEACS and treated with fibrinolysis is feasible and safe, and improves clinical evolution in the following 12 months. This study also provides information on flow and myocardial perfusion parameters which are relevant to clinical evolution. Coronary angiography was performed 17±6 hours after thrombolysis in 252 patients randomized to intervention and 27% of these received glycoprotein IIb/IIIa inhibitors. Epicardial flow in the culprit artery was TIMI 3 (80%) or TIMI 2 (10%), TIMI 1 (4%), and TIMI 0 (6%). Only 30% had TIMI myocardial perfusion (TMP) 3 or TMP 2 (8%). Of note, patients with epicardial TIMI 0 or 1 flow had a worse evolution at 1-year follow-up than patients with TIMI 2 or 3 flow. In these subgroups, mortality was 20% and 2%, respectively (*P*<.001) and the combined incidence of death or reinfarction was 25% and 6% (*P*<.009). Severely affected myocardial perfusion had a similar effect. Patients with TMP 0-1 presented a 12% incidence of mortality or reinfarction at 1 year versus 1.4% in those with TMP 2-3. Interestingly, flow variables clearly improved after stenting but this did not correlate with mortality or reinfarction at follow-up. These data clearly stimulate interest in improving variables of epicardial and myocardial perfusion of isolated thrombolysis, and in the possible role of routine administration of glycoprotein IIb/IIIa inhibitors in this context.

Finally, subgroup analysis in GRACIA 1 showed that an invasive reperfusion strategy in acute myocardial infarction benefits high risk patients more, exactly like in non-ST segment elevation acute coronary syndrome. At 1 year, there was a 93% reduction in the incidence of the composite endpoint in patients with diabetes randomized to intervention compared with those treated conservatively (3.2% vs 30.3%, respectively; HR=0.07; 95% CI, 0.01-0.58; *P*=.01). Similarly, older patients in the intervention group presented a 78% reduction in the composite endpoint compared with the conservative group (8.3% vs 29.4% respectively; HR=0.22; 95% CI, 0.05-0.87; *P*=.03)[19,20].

To summarize, SIAM III and GRACIA 1 data indicate that, in the era of stents and glycoprotein IIb/IIIa inhibitors, immediate (<24 hours) elective stenting following thrombolysis is feasible and safe. Moreover, it permits rapid patient risk stratification, substantially reduces hospitalization, improves left ventricle evolution and apparently reduces the incidence of adverse coronary events at 1 year. The clinical implications of these studies are important as they suggest that for patients who cannot undergo primary angioplasty, thrombolysis followed within 24 hours by coronary angiography and adequate revascularization is the alternative.

REGIMENS USED

The definition of facilitated angioplasty supposes a systematized early percutaneous coronary intervention (<12 hours) in patients with STEACS treated initially with different drug regimens aimed at facilitating the results of the mechanical reperfusion. Regimens used in trials include prior administration of glycoprotein IIb/IIIa inhibitors, high-dose heparin and thrombolytic agents.

Facilitated Angioplasty With Glycoprotein IIb/IIIa Inhibitors

The major clinical trials investigating the use of glycoprotein IIb/IIIa inhibitors in STEACS treated with direct angioplasty and stent implantation (facilitated angioplasty) are ADMIRAL,[21] ISAR 2,[22] ACE,[23] CADILLAC,[24] TIGER-PA,[25] On-TIME,[26] Cutlip et al,[27] Zorman et al,[28] REOMOBILE,[29] and ERAMI.[30] The first 4 analyzed the benefits of treatment with abciximab versus placebo and the last 6 studied the benefits of early versus late administration of tirofiban or abciximab. In this context, glycoprotein IIb/IIIa inhibitors appear especially beneficial when administered prior to intervention, leading to improved epicardial and myocardial perfusion parameters and a tendency towards greater clinical benefit, but not so useful when administered during the procedure.

With 300 patients, ADMIRAL[21] found early administration of abciximab associated with greater pre-procedure TIMI 3 flow rate than with placebo (16.8% vs 5.4%; *P*=.01), and lower incidence of the primary endpoint (death, reinfarction, and urgent re-

vascularization) at 30 days (6% vs 14.6%) and at 6 months (7.4% vs 15.9%).

The ISAR study[22] randomized 401 patients undergoing primary angioplasty to standard dose heparin or low-dose heparin and abciximab. Administration of abciximab reduced the incidence of the primary composite endpoint (death, reinfarction, and revascularization) at 30 days (5% vs 10.5%). At 1 year, benefits in the abciximab group led to a non-significant, absolute reduction of 5.7%.

Similar results were found in ACE,[23] which randomized 400 patients with STEACS undergoing primary angioplasty with stent implantation to treatment with and without abciximab. At 1 month, the incidence of the primary composite endpoint (death, reinfarction, revascularization, or stroke) was significantly lower among patients treated with abciximab (4.5% vs 10.5%). However, as in ISAR 2, mid-term benefits (6 months) were less obvious with a tendency towards lower mortality (4.5% vs 8%) and a significantly lower incidence of reinfarction (1% vs 5.5%).

The CADILLAC study[24] randomized 2082 patients with STEACS to 4 groups: balloon angioplasty, balloon angioplasty and abciximab, angioplasty with stent implantation, and angioplasty with stent implantation and abciximab. All patients received antiplatelet treatment with clopidogrel or ticlopidine. Angioplasty with stent implantation associated with reduced need for new revascularization due to ischemia. However, the results from CADILLAC differ from those of ADMIRAL, ISAR 2, and ACE. The reduction observed in the incidence of the primary composite endpoint (death, reinfarction, revascularization, and stroke) in the abciximab group compared with the placebo group (4.6% vs 7.0%) was principally due to an increased percentage of adverse events in patients treated with balloon angioplasty (8.5%) with no difference in patients treated with stent with or without abciximab (5.7% vs 4.6%). The only benefit observed in patients who received abciximab was a reduction in the incidence of sub-acute thrombosis (0.4% vs 1.5%).

At 1 month, abciximab was associated with a 46% reduction of the composite endpoint of death, reinfarction and revascularization, a 34% reduction in death and reinfarction and a non-significant 26% reduction in death alone.[31] The contradictory results of CADILLAC might be due to baseline differences between the studies. The CADILLAC study did not include high risk patients (patients in cardiogenic shock), not all patients presented with ST segment elevation and the incidence of adverse coronary events was consequently lower than in other studies. Moreover, all CADILLAC patients were treated with thiopyridines prior to angioplasty, whereas in other studies using thiopyridine this was administered following the intervention. Pretreatment with thiopyridines might diminish the potentially beneficial effect of abciximab.

In patients with STEACS treated with primary angioplasty, glycoprotein IIb/IIIa inhibitors seem especially useful when administered prior to the procedure. In this context, abciximab has not been the only glycoprotein IIb/IIIa inhibitor evaluated: there has also been research into tirofiban. The benefit of early administration[32] of these 2 drugs has been studied in a meta-analysis of 6 studies[25-30] which found they improve epicardial and myocardial perfusion parameters and produce greater clinical benefit.

Combined administration of glycoprotein IIb/IIIa inhibitors and fibrinolytic agents when used to facilitate mechanical revascularization is further developed below when we discuss thrombolytic agents.

Facilitated Angioplasty With High-Dose Heparin

Early administration of high-dose heparin prior to primary angioplasty was evaluated in the HEAP trial[33] which randomized 584 patients with STEACS to high-dose (300 units per kg) or low-dose heparin prior to intervention. No differences were found in incidence of adverse coronary events and, on the contrary, high-dose heparin patients presented more bleeding complications (10% vs 6%).

Facilitated Angioplasty With Thrombolytic Agents

The first study to examine the concept of facilitated angioplasty in the modern era was published in 1999. The Plasminogen-Activator Angioplasty Compatibility Trial (PACT)[34] included 606 patients, half of whom received a half-dose of the thrombolytic agent (50 mg alteplase) to achieve permeabilization of the artery prior to angioplasty, and half received a placebo. Afterwards, although not immediately, coronary angiography and angioplasty were performed if the artery did not have completely normal flow (TIMI 3). Thrombolytic treatment was complemented if the artery had TIMI 3 flow. Stents were implanted in 26% of patients and abciximab was administered to 5%. Pa-

tients in the facilitated group (receiving plasminogen activator) had a higher rate of arterial permeability (TIMI 2 and 3 flow) at coronary angiography than in the control group (61% vs 34%; *P*<.001). Angiography was performed 3 hours after the onset of an acute myocardial infarction. After the procedure, 77% and 79% of patients had TIMI 3 flow. Significantly, PACT found that patients with normal flow at coronary angiography had better clinical evolution and ventricular function in the follow-up. Mortality and reinfarction rates at 30 days were similar and, what is more important, incidence of major bleeding complications was also similar (12.6% in the group treated with thrombolytic agents vs. 13.5% in the primary angioplasty group).

The SPEED study (a pilot study of GUSTO 4)[35] reevaluated the role of early intervention in patients treated with glycoprotein IIb/IIIa inhibitors (abciximab) and thrombolytic agents (reteplase). In 61% of patients (323) early interventions (at 60-90 minutes) were performed and their evolution was compared with 162 patients who neither underwent catheterization nor revascularization. Characteristics of the 2 groups were similar and 78% of those assigned to early intervention received one or more stents. Incidence of death, reinfarction or need for urgent revascularization at 30 days was lower in patients treated invasively (16% vs 6%, *P*=.001) with similar bleeding rates. Patients treated with the combination of abciximab and half-dose reteplase had the highest pre-intervention rate of TIMI flow 3 when compared with those receiving abciximab or reteplase (47% vs 24% and 40%, respectively; *P*=.05).

In PRAGUE 1,[36] the incidence of death, infarction or stroke at 30 days was 23% in patients treated with streptokinase and 15% in patients undergoing combined therapy (streptokinase in the original hospital and angioplasty in the reference hospital). The percentage was even lower (8%) in patients undergoing primary angioplasty.

Facilitated angioplasty was researched by Spain's GRACIA group (a research group analyzing acute ischemic cardiopathy). The GRACIA 1 report, which defined the strategy of pharmacomechanical therapy within prognostic or elective angioplasty, has been further developed in GRACIA 2. The objective of GRACIA 2[37] was to compare the efficacy of primary angioplasty with stent and abciximab, with facilitated reperfusion following thrombolytic treatment. At randomization, 212 patients were assigned to the following groups: *a)* percutaneous transluminal coronary angioplasty (PTCA) with culprit artery stenting and protection with abciximab in the first 3 hours, or *b)* thrombolysis with tenecteplase (complete dose adjusted to weight) and 30 mg intravenous enoxaparin, followed within 3-12 hours by adequate revascularization (culprit and non-culprit arteries if functionally important territory is at risk) by PTCA-stent or surgery. The major evaluation criteria were estimation of left ventricular function and myocardial perfusion. The incidence of events at 6 weeks and 6 months was also compared. Among patients treated with primary angioplasty, 83% received abciximab in comparison with 23% of facilitated strategy patients. Left ventricular function parameters did not differ between the 2 groups. However, pre-intervention myocardial perfusion (TMPG 3: 56% vs 16%; *P*<.001) and post-intervention myocardial perfusion (TMPG 3: 49% vs 26%) were greater in patients treated with facilitated angioplasty. No significant differences were found in bleeding complications (10.3% in the facilitated angioplasty group vs 6.7% in the primary angioplasty group) nor in incidence of adverse cardiovascular episodes (9% in the facilitated angioplasty group vs 14% in the primary angioplasty group) in the 2 groups. Results of GRACIA 2 suggest that a strategy of reperfusion with thrombolysis with tenecteplase followed by immediate revascularization (3-12 hours) is as efficient and safe as performing primary angioplasty in optimal conditions (stent and glycoprotein IIb/IIIa inhibitors).

Other studies (TIMI 14,[38] INTRO-AMI,[39] INTEGRITI[40]) have also shown that combining potent platelet inhibitors and low-dose thrombolytic agents improves arterial flow at 60 minutes with respect to isolated thrombolysis. With this strategy, 60% of culprit arteries in patients with STE-ACS reached TIMI 3 flow at 60 min. These data suggest that combined therapy of drug reperfusion (fibrinolytic agents and glycoprotein IIb/IIIa inhibitors) followed by immediate coronary angiography and intervention would be at least as efficient as primary angioplasty.

Facilitated angioplasty was evaluated in BRAVE,[41] which randomized 253 patients to abciximab or abciximab and half-dose reteplase followed by angioplasty with stent. The principal objective of the study was to estimate infarction size by scintigraphy and results indicated no difference (11.5% in abciximab only patients vs 13.0%). Incidence of adverse cardiovascular events (death, reinfarction or acute

stroke) was 1.6% in abciximab patients and 3.2% in the combined drug therapy group (*P*=.66).

FUTURE OF FACILITATED ANGIOPLASTY

Percutaneous revascularization with stent has notably increased the efficiency of mechanical treatments of reperfusion and revascularization in ST segment elevation acute myocardial infarction both when performed directly (primary angioplasty) and when performed after routine administration of a drug treatment aimed at reopening the culprit artery (facilitated angioplasty). However, unresolved problems remain: research into the efficiency and safety of drug-eluting stents in this context is insufficient; the value of treatments to combat the assumed microembolic component of microvascular dysfunction inherent to reperfusion of the myocardium with severe ischemia is unclear; and the real role of glycoprotein IIb/IIIa inhibitors in these treatments is unknown.

The safety and efficiency of potent platelet inhibitors together with low doses of thrombolytic agents will again be evaluated in 3 studies (CADILLAC II, ASSENT 4, and FINESSE) that randomize 2700 patients with STEACS to primary angioplasty in 60-120 min with abciximab or abciximab with reteplase followed by angioplasty. Analysis of their results will show whether facilitated angioplasty is more efficient than primary angioplasty with abciximab alone.

The GRACIA 3 study formulated the hypothesis that paclitaxel-covered stents are safe and reduce need for revascularization. It also tested the hypothesis that administering IIb/IIIa receptor antagonists, before angioplasty but late enough to avoid the bleeding complications that occur when they are administered with fibrinolytic agents, might be a safe way of optimizing epicardial and microvascular reperfusion of the evolving infarction. The study uses an open, multicenter, randomized clinical trial design and has already enrolled 436 patients with STEACS treated with thrombolytic agents, randomized to 4 strategies of treatment: *a)* paclitaxel-covered stents with tirofiban; *b)* paclitaxel-covered stents without tirofiban; *c)* conventional stents with tirofiban; and *d)* conventional stents without tirofiban. The primary objective of this study is to evaluate the efficiency of taxol-covered stents compared with conventional stents in ST segment elevation acute myocardial infarction and the effect of tirofiban administered before percutaneous revascularization but 120 minutes after fibrinolysis, on epicardial and myocardial perfusion, before and after mechanical revascularization. Efficiency will be evaluated in terms of reestenosis at 12 months and improvement of epicardial and myocardial perfusion parameters.

In conclusion, there can be no doubt that facilitated angioplasty modifies the current scenario of reperfusion in STEACS. The real but not always ideal strategy of reperfusion should be based on the following cardinal points: efficiency, time, applicability and cost. Bearing in mind that facilitated angioplasty can perfectly well be implemented in the current healthcare infrastructure in Spain, in the future it may constitute the strategy of choice in reperfusion of STEACS in this country. Facilitated angioplasty with thrombolytic agents has a role beyond the competitive dualism with which early reperfusion of victims with acute myocardial infarction has been viewed to date. It is a symbiosis aimed at combining the advantages of drug therapy (easy to apply, universally available) and mechanical therapy (efficient). Neither black nor white, but just the opposite.

REFERENCES

1. Arós F, Loma-Osorio A, Bosch X, González Aracil J, López Bescós L, Marrugat J, et al. Manejo del infarto de miocardio en España (1995-1999). Datos del registro de infartos de la Sección de Cardiopatía Isquémica y Unidades Coronarias (RISCI) de la Sociedad Española de Cardiología. Rev Esp Cardiol. 2001;54: 1033-40.
2. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction and improved survival: should the paradigm be expanded? Circulation. 1989;79:441-4.
3. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003:361: 13-20.
4. Hasdai D, Behar S, Vallentin L, Danchin N, Gitt AK, Boersma E, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survery of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J. 2002;23:1190-201.
5. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J; GRACE Investigators. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet. 2002;359:373-7.
6. Gibson CM. NRMI and current treatment patterns for ST-elevation myocardial infarction. Am Heart J. 2004;148:S29-33.
7. Yusuf S, Collins R, Peto R, Furberg C, Stampfer MJ, Goldhaber SZ, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side-effects from 33 randomized controlled trials. Eur Heart J. 1985;6:556-85.
8. Boersma E, Mass ACP, Deckers JW, Simoons ML. Early throm-

bolytic treatment in acute myocardial infarction. Reappraisal of the golden hour. Lancet. 1996;348:771-5.
9. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673-82.
10. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. N Engl J Med. 1993;329:1615-22.
11. Ohnam EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, et al. Consequences of reocclusion after succesful reperfusion therapy in acute myocardial infarction: the TAMI Study Group. Circulation. 1990;82:781-91.
12. Granger CB, White HD, Bates ER, Ohman EM, Califf RM. A pooled analysis of coronary arterial patency and left ventricular function after intravenous thrombolysis for acute myocardial infarction. Am J Cardiol. 1994:74:1220-8.
13. Keeley EC, Cigarroa JE. Facilitated primary percutaneous transluminal coronary angioplasty for acute ST segment elevation myocardial infarction: rationale for reuniting pharmacologic and mechanical revascularization strategies. Cardiol Rev. 2003;11:13-20.
14. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group. BMJ. 1991;302:555-60.
15. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. The TIMI Study Group. N Engl J Med. 1989;320:618-27.
16. Barbash GI, Roth A, Hod H, Modan M, Miller HI, Rath S, et al. Randomized controlled trial of late in-hospital angiography and angioplasty versus conservative management after treatment with recombinant tissue-type plasminogen activator in acute myocardial infarction. Am J Cardiol. 1990;66:538-45.
17. Scheller B, Hennen B, Hammer B, Walle J, Hofer C, Hilpert V, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. J Am Coll Cardiol. 2003;42:634-41.
18. Fernández-Avilés F, Alonso JJ, Castro-Beiras A, Vázquez N, Blanco J, Alonso-Briales J, et al; GRACIA (Grupo de Análisis de la Cardiopatía Isquémica Aguda) Group. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA 1): a randomised controlled trial. Lancet. 2004;364:1045-53.
19. Sánchez PL, Alonso JJ, Castro-Beiras A, Vázquez N, Blanco J, Alonso J, et al, Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA). Resultados del estudio GRACIA 1 (comparación en el IAM entre revascularización en las 24 horas tras trombólisis y el tratamiento conservador) en la población anciana. Rev Esp Cardiol. 2004;57 Supl 2:120.
20. Alonso JJ, Sánchez PL, Castro A, López J, Calvo I, Martínez L, et al. Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA). Resultados del estudio GRACIA 1 (comparación en el IAM entre revascularización en las 24 horas tras trombólisis y el tratamiento conservador) en la población diabética. Rev Esp Cardiol. 2004;57 Supl 2:135.
21. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med. 2001;344:1895-903.
22. Neumann FJ, Kastrati A, Schmitt C, Blasini R, Hadamitzky M, Mehilli J, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. J Am Coll Cardiol. 2000;35:915-21.
23. Antoniucci D, Rodriguez A, Hempel A, Valenti R, Migliorini A, Vigo F, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. J Am Coll Cardiol. 2003;42:1879-85.
24. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med. 2002; 346:957-66.
25. Lee DP, Herity NA, Hiatt BL, Fearon WF, Rezaee M, Carter AJ, et al. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. Circulation. 2003;107:1497-501.
26. van't Hof AWJ, Ernst N, deBoer MJ, de Winter R, Boersma E, Bunt T, et al. Facilitation of primary coronary angioplasty by early start of a glycoprotein 2b/3a inhibitor: results of the Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME) trial. Eur Heart J. 2004;25:837-46.
27. Cutlip DE, Ricciardi MJ, Frederick SL, Fearon WF, Rezaee M, Carter AJ, et al. Effect of tirofiban before primary angioplasty on initial coronary flow and early ST-segment resolution in patients with acute myocardial infarction. Am J Cardiol. 2003;92:977-80.
28. Zorman S, Zorman D, Noc M. Effects of abciximab pretreatment in patients with acute myocardial infarction undergoing primary angioplasty. Am J Cardiol. 2002;90:533-6.
29. Arntz HR, Schroder JF, Pels K, Schwimmbeck P, Witzenbichler B, Schultheiss HP, et al. Prehospital versus periprocedural administration of abciximab in STEMI: early and late results from the randomised REOMOBILE-study [abstract]. Eur Heart J. 2003;24 Suppl:268.
30. Mesquita Gabriel H, Oliveira J, Canas da Silva P, Marques da Costa J, Correia da Cunha JA, França C, et al. Early administration of abciximab bolus in the emergency room improves microperfusion after primary percutaneous coronary intervention, as assessed by TIMI frame count: results of the ERAMI trial [asbtract]. Eur Heart J. 2003;24 Suppl:543.
31. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. J Am Coll Cardiol. 2003;42:1886-9.
32. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. JAMA. 2004; 292:362-6.
33. Liem A, Zijlstra F, Ottervanger JP, Hoorntje JC, Suryapranata H, De Boer MJ, et al. High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the Heparin in Early Patency (HEAP) randomized trial. J Am Coll Cardiol. 2000;35: 600-4.
34. Ross AM, Coyne KS, Reiner JS, Greenhouse SW, Fink C, Frey A, et al. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. PACT investigators. Plasminogen-activator Angioplasty Compatibility Trial. J Am Coll Cardiol. 1999;34:1954-62.
35. Herrmann HC, Moliterno DJ, Ohman EM, Stebbins AL, Bode C, Betriu A, et al. Facilitation or early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction. Results from the SPEED (GUSTO 4 Pilot) Trial. J Am Coll Cardiol. 2000;36:1489-96.
36. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. Eur Heart J. 2000;21:823-31.
37. Fernández-Avilés F, Alonso JJ, Castro Beiras A, Goicolea J, Blanco J, Alonso J, et al. Primary optimal PCI versus facilitated intervention (Tenecteplase plus stenting) in patients with ST elevated acute myocardial infarction: the GRACIA 2 randomized trial [abstract]. Circulation. 2003;108 Suppl:2149.
38. Antman EM, Giugliano RP, Gibson CM, McCabe CH, Cousse-

ment P, Kleiman NS, et al. Abciximab facilitates the rate and extent of thrombolysis: result of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 investigators. Circulation 1999;99:2720-32.
39. Brener SJ, Zeymer U, Adgey AA, Vrobel TR, Ellis SG, Neuhaus KL, et al. Eptifibatide and low-dose tissue plasminogen activator in acute myocardial infarction: the integrilin and low-dose thrombolysis in acute myocardial infarction (INTRO AMI) trial. J Am Coll Cardiol. 2002;39:377-86.
40. Giugliano RP, Roe MT, Harrington RA, Gibson CM, Zeymer U, van de Werf F, et al. Combination reperfusion therapy with eptifibatide and reduced-dose tenecteplase for ST-elevation myocardial infarction: results of the integrilin and tenecteplase in acute myocardial infarction (INTEGRITI) phase II angiographic trial. J Am Coll Cardiol. 2003;16:1251-60.
41. Kastrati A, Mehilli J, Schlotterbeck K, Dotzer F, Dirschinger J, Schmitt C, et al. Bavarian Reperfusion Alternatives Evaluation (BRAVE) Study Investigators. Early administration of reteplase plus abciximab vs abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized controlled trial. JAMA. 2004;291:947-54.