EDITORIAL

Antithrombotic Therapy for the Prevention of Reinfarction After Reperfusion Therapy: The Price of Success

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Despite therapeutic advances, particularly in regard to the nature and delivery of acute reperfusion therapy acute ST-elevation myocardial infarction (STEMI) remains a major public health problem, resulting in approximately 330000 admissions in the US last year alone.[1] Societies in both the developed and the developing world are aging, and in conjunction with the burgeoning incidence of cardiovascular disease in the developing world and newly industrialized nations, we are in the throes of a global epidemic of cardiovascular disease (CVD) and projections for the short and medium term are alarming. The need for effective, economic, and workable STEMI treatment algorithms in a global setting thus remains as pressing as ever.

Current STEMI treatment goals focus on rapid and sustained reperfusion of the infarct related artery while minimizing treatment-related risk. The pivotal animal experiments of Reimer and Jennings which demonstrated the "wavefront phenomenon" of myocardial necrosis set the stage for 3 decades of progress based upon the correct assumption that restoration of normal antegrade flow in a culprit infarct vessel would salvage myocardium thereby preserving left ventricular systolic function and ultimately improving survival. This hypothesis was supported by the findings of GISSI-1, the first large placebo-controlled clinical trial of fibrinolytic therapy for STEMI. In this 11712 patient study, the 21-day relative risk reduction for mortality was 18% in the streptokinase group, improving to 23% in those treated in the first 3 hours.[2] Further studies have consistently confirmed that mortality reduction as a benefit of reperfusion therapy is greatest in the first 3 hours after symptom onset. This has been referred to as the golden window of opportunity or the "critical time-dependent period," with the goal of myocardial salvage.[3] After this period, the slope of the curve flattens rapidly into a relative time-independent period, with a reduction in incremental benefit per unit of time. During this period, there is a shift in emphasis from achieving reperfusion and myocardial salvage as rapidly as possible to the primary goal of opening of the infarct-related artery, and at this later phase in the evolution of STEMI, primary percutaneous coronary intervention (PPCI) is clearly superior to pharmacologic therapy in this regard. Indeed, it is generally accepted that, all things being equal, and in particular in regard to times to treatment, PPCI is superior to fibrinolytic therapy. Of course the best results from both therapeutic strategies are obtained in patients treated early. What remains somewhat controversial is the amount of acceptable delay in transferring a patient presenting to a community hospital without percutaneous coronary intervention (PCI) facilities to a PPCI center, as opposed to immediate treatment with a fibrinolytic at the admission hospital. Moreover the impact of these treatment delays is critically dependent upon the duration of symptoms prior to presentation, eg, a delay of 90 minutes in a patient presenting within an hour of symptoms is likely to be substantially greater than in a patient presenting on the flat part of the curve after 3 hours of symptoms.[3]

The benefits of earlier reperfusion provided by the prompt administration of fibrinolytic drugs in some settings must however be balanced by 2 major disadvantages. First, there is an increased risk of early recurrent reinfarction after fibrinolytic therapy for STEMI, with reinfarction being associated with significantly increased long-term mortality rates.[4] Second, the elevated risk of systemic bleeding complications due to the, non-specificity of fibrinolytic agents for the coronary circulation. Moreover, the bleeding risk increases markedly in the presence of older age, females, low body max index, and a history of hypertension. Despite these limitations and despite the shift toward PPCI as the index reperfusion strategy over the last decade, there remains a critically important role for fibrinolysis in

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the modern era. In fact, current American College of Cardiology/American Heart Association guidelines designate fibrinolytic therapy as preferred in 3 broad settings[5]: *a)* early presentation, ≤3 hours after symptom onset and any delay to invasive treatment; *b)* invasive strategy is not an option, eg, lack of access to a skilled PCI laboratory, vascular access constraints; and *c)* delay to invasive strategy, where contact–balloon time is likely to be >90 minutes. Indeed, analysis of the US National Registry of Myocardial Infarction revealed that in 2006, 27.6% of STEMI patients eligible for reperfusion received fibrinolytic therapy.[6]

Regardless of whether the primary mode of reperfusion is mechanical or fibrinolytic, pharmacologic therapy with antiplatelet agents in additional to anticoagulation is a key component of in-hospital care for STEMI, affecting both restoration and maintenance of infarct artery perfusion. In this regard, the pivotal ISIS-2 study indicated that aspirin alone was as lifesaving as streptokinase,[7] thereby establishing aspirin as a cornerstone of STEMI therapy and this provided the impetus for a 2 decade search for newer and improved anti-platelet agents. Early studies using glycoprotein IIb/IIIa inhibitors tested the hypothesis that the addition of more powerful antiplatelet inhibition to fibrinolytic therapy would offer incremental benefit. Initially, SPEED and TIMI-14 showed combination therapy to improve TIMI III flow rates in the infarct artery but at the expense of higher rates of major bleeding.[8,9] These studies were small and underpowered for mortality. However, 2 subsequent larger trials, GUSTO-V and ASSENT-3, revealed that combination therapy using a reduced dose of fibrinolytic offered no mortality advantage but significantly increased the rates of major bleeding, with such combination therapy now considered to be contraindicated.[10,11]

More recently, 2 landmark trials revealed that the addition of clopidogrel, a platelet ADP receptor antagonist from the thienopyridine family, offered incremental, important clinical benefit after STEMI. The CLARITY-TIMI 28 study enrolled 3491 patients under the age of 75 with STEMI, mainly from the US and Western Europe.[12] Patients were treated with a fibrinolytic agent and aspirin and were randomized to receive a 300 mg loading dose of clopidogrel and 75 mg daily thereafter, or placebo. Patients underwent coronary angiography 2-8 days after enrollment, with subsequent PCI being performed in more than half. The primary endpoint (occluded infarct artery, death or recurrent myocardial infarction before angiography) occurred in 15% of the clopidogrel treatment group compared with 21.7% of those receiving placebo, a highly significant treatment advantage. Moreover, at 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization by 20%. The study was not powered to detect a survival change, and indeed none was seen out to 30 days (cardiovascular death 4.4% in clopidogrel group vs 4.5% placebo, *P*=ns). However, improvement was noted in all pre-defined angiographic endpoints, which have previously been associated with long-term survival. Remarkably, treatment with clopidogrel was not associated with a higher rate of bleeding (30 day major bleed 1.9% vs 1.7% placebo, *P*=.8), although the trial population was relatively young, with a likely low baseline bleeding risk.

In contrast to CLARITY, the COMMIT study was much larger, comprising of 45 852 patients, and was performed exclusively in China, without an upper age limit, and with a much longer time from symptom onset to presentation (mean, 10 hours).[13] Only half of patients received fibrinolytic therapy on presentation and clopidogrel was administered as 75 mg daily, without a loading dose. Less than 5% of patients subsequently underwent angiography. Clopidogrel treatment was associated with a significant reduction in the odds of the composite of death, myocardial infarction or stroke, and perhaps most importantly, mortality alone. Two additional observations from COMMIT are worthy of note. First, the benefit of clopidogrel without a loading dose became apparent as early as day one, suggesting either that minor degrees of platelet inhibition may be effective in the setting of acute coronary thrombus or that benefit was seen in a subset of highly responsive patients. Second, there was no statistical increase in the rate of major bleeding with clopidogrel, with the study having both no upper age limit and sufficient power to detect a safety concern

Adjuvant anticoagulant therapy may provide further benefit. Those tested include unfractionated heparin, low molecular heparins, indirect factor Xa inhibitors and direct thrombin inhibitors. It is important to recognize that in addition to this range of treatment agents, one must also consider the range of treatment strategies (dose, route, duration etc), meaning that a bewildering array of options are available. The ExTRACT-TIMI 25 study compared unfractionated heparin (bolus and 48 hour infusion) with the low molecular weight heparin enoxaparin (intravenous bolus and subcutaneous administration till discharge, with dose modifications for age and renal function), with enoxaparin being associated with a 17% reduction in death or MI at the expense of a 0.7% absolute increase in major bleeding.[14] While there was no excess of intracranial bleeding overall, the ASSENT-3 PLUS evaluation of 1600 pre-hospital STEMI patients did reveal an excess

of intracranial hemorrhage with enoxaparin in the subgroup patients older than 75 years.[15] Thus, while the benefits of low molecular weight heparin as adjunctive therapy seem proved, caution is still warranted in those with a higher bleeding risk such as the elderly and those with impaired renal function. The OASIS-6 trial was a large-scale trial with a complex design that evaluated the factor Xa inhibitor fondaparinux in a STEMI population.[16] The primary endpoint of death and myocardial infarction was reduced by fondaparinux administered subcutaneously compared with placebo. However, there was no significant difference when intravenous fondaparinux was compared with unfractionated heparin. In fact, in patients undergoing PPCI in this subgroup there was a higher incidence of catheter and coronary thrombosis, necessitating a protocol modification advising additional heparin.

In contrast to their use as adjuvant pharmacological agents in PPCI, direct thrombin inhibitors have been associated with higher rates of bleeding in conjunction with fibrinolytics without any mortality advantage compared with unfractionated heparin.[17,18]

While the proven benefit for fibrinolytic agents and thienopyridines in the setting of clinical trials have led to class I (level of evidence A) recommendations for their use in STEMI, what can we learn from a real-world experience? In this regard, the GRACE project, a multinational registry of patients hospitalized with acute coronary syndromes (including STEMI) in 106 hospitals located in 14 countries, offers a unique opportunity to evaluate these drugs in a broad, unselected population.[19] In this issue of *Revista Española de Cardiología*, López-Sendón et al[20] describe their study of 14 259 registry patients who suffered a STEMI within a 6.5 year period leading up to December 2005. The study focused on in-hospital death and major bleeding as endpoints in patients treated with or without fibrinolytic agents and thienopyridines. The central finding was that thienopyridine usage, with or without fibrinolytics, was independently associated with both in-hospital survival and increased rates of major bleeding.

A number of additional findings are of interest. Over the period studied, 65% did not receive fibrinolytic therapy and 27% of received neither fibrinolysis nor a thienopyridine. Moreover, the patient subset that received neither was older, sicker, with more risk factors and more likely to be female, and exhibited the highest in-hospital mortality rate by far (15%). These findings mirror those from the US National Registry of Myocardial Infarction study of over eighty thousand patients performed in the fibrinolytic era,[21] which concluded that reperfusion strategies were underutilized in patient subsets with the highest baseline risk of mortality. Of some encouragement in the study presented here by López-Sendón et al,[20] is that this patient group, with the highest risk, also had the highest rates of in-hospital revascularization by both coronary artery bypass grafting (8.2%) and PCI (11%) when compared with patients that had been treated with a fibrinolytic, thienopyridine, or both. This contrasts somewhat with the CRUSADE registry data, which suggested the opposite in a non-ST segment elevation acute coronary syndrome population.[22] Nonetheless, only a minority of patients in any subset underwent in-hospital revascularization (certainly low by current standards) with a remarkable 53.8% of all STEMI patients, including those with the highest risk receiving neither early reperfusion nor in-hospital revascularization. The reasons are of course likely to be multifactorial but are unlikely to be explained by the incidence of absolute contraindications to reperfusion. Moreover, in this study, the group with the highest baseline risk also had the lowest usage of aspirin, beta-blockers, IIb/IIIa inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and statins. Collectively the findings underscore the need for ongoing efforts directed toward increasing the uptake of potentially lifesaving reperfusion, antiplatelet, and other pharmacologic strategies in patients who have the highest potential for gain.

It is noteworthy and encouraging that uptake of thienopyridine usage increased over the study period. In fact it is perhaps surprising that as many as 32% of patients in 1999, six years before publication of the CLARITY and COMMIT studies, received a thienopyridine (clopidogrel or ticlopidine). While the use was more frequent in patients undergoing PCI, the high proportion is more likely to be explained, as the authors suggest, by a perception of benefit in the STEMI population based upon benefit seen in other coronary syndromes. The use of thienopyridines conferred a markedly reduced risk of in-hospital mortality in this observational study (with lowest rates in those additionally receiving fibrinolysis), which persisted after adjusting for short-term risk variables and PCI (odds ratio = 0.50). Whether this represented a thienopyridine treatment effect or whether it is explained by confounding variables is unclear. Indeed, thienopyridine usage in this study was additionally associated with statin and ACE inhibitor treatment, making it difficult to implicate an independent effect of thienopyridine therapy. Nonetheless, the findings are consistent with those revealed in the large-scale randomized COMMIT study and complement those seen in randomized studies and registries of thienopyridine usage in other coronary syndromes. Moreover, these findings are also consistent with the fact that the use of evidence-based therapies is in itself a surrogate marker of improved outcomes.[23]

Another key finding reported by López-Sendón et al[20] in this issue of *Revista Española de Cardiología* is that thienopyridine usage in this patient subset of the registry was associated with higher rates of major bleeding. Moreover the bleeding rates reported were much higher than those seen in randomized studies. Almost certainly this discrepancy is explained by the presence of older and frailer people in the registry, with a higher incidence of co-morbidities, a population with a much higher baseline risk of bleeding. Although the effect of major bleeding on outcomes was not evaluated in this study, there is growing appreciation of bleeding as a competing risk factor for major adverse events and mortality. The reasons for this are complex and incompletely understood. First, as alluded to earlier, bleeding may be a marker of frailty or co-morbidity, thus being associated with deleterious endpoints in a non-causative manner.[24] Second, the site of bleeding, eg, intracranial may directly result in death or serious morbidity. Third, the hemodynamic consequences of bleeding may be directly deleterious in the setting of coronary disease and myocardial injury. Fourth, patients who bleed are far more likely to have beneficial antiplatelet and antithrombotic drugs discontinued and are less likely to have them restarted when eligible.[25] Fifth, bleeding may lead to transfusions which in themselves may confer additional risk. Irrespective of the mechanisms, bleeding is a major predictor of mortality and remains the dark side of reperfusion strategies. Important registry studies such as the one reported in this issue of the journal serve to underscore the importance of minimizing bleeding risk while maintaining reperfusion efficacy. Whether data from newer antiplatelet agents, including prasugrel, will maintain an ischemia advantage in the long term in the face of elevated bleeding risks remains to be seen.

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