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

Rajiv Gulati and Bernard J. Gersh

Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota United States

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 330,000 admissions in the US last year alone. 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 11,712 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. 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. 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.

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. 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...
the modern era. In fact, current American College of Cardiology/American Heart Association guidelines designate fibrinolytic therapy as preferred in 3 broad settings: 1) early presentation, ≤3 hours after symptom onset and any delay to invasive treatment; 2) invasive strategy is not an option, eg, lack of access to a skilled PCI laboratory, vascular access constraints; and 3) 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 addition 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 al20
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. 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. 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. 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.

REFERENCES

19. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: a multinational registry of patients...