S

S

Since the advent of reperfusion therapy for acute ST elevation myocardial infarction, the “open artery hypothesis” proposed that benefit is achieved from early reperfusion of the occluded coronary artery, which limits the size of infarction, reduces the degree of left ventricular dysfunction, and improves survival. After numerous studies confirmed the benefit of a patent infarct-related artery, more careful examination of the degree of reperfusion was performed using the Thrombolysis In Myocardial Infarction (TIMI) flow grading system devised in the TIMI 1 trial. When differentiating apparently normal TIMI grade 3 flow from more delayed TIMI grade 2 flow in patent arteries, greater myocardial salvage and improved survival were observed in patients who achieved TIMI grade 3 flow. There is a nearly linear correlation between higher rates of early TIMI grade 3 flow and improved survival, regardless of whether reperfusion is achieved with thrombolysis or primary percutaneous coronary intervention (PCI). The open artery hypothesis became the “open artery theory” after the results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) I trial. This trial demonstrated that a more aggressive thrombolytic regimen (using tissue plasminogen activator [t-PA]) that could improve the achievement of early TIMI grade 3 flow could also reduce mortality. Thus, an active treatment that increased TIMI grade 3 flow led to improved survival.

The importance of time to achieving reperfusion has also been emphasized by several types of studies, including observational studies of time to treatment versus mortality. Trials of prehospital thrombolysis, which saved between 30 and 120 minutes, demonstrated a 19% reduction in mortality. In GUSTO I, treatment with t-PA resulted in higher rates of TIMI grade 3 flow at 60 and 90 minutes compared with streptokinase, but by 180 minutes, rates were similar. Thus, the benefit of t-PA on improved early left ventricular function and mortality was attributed to the earlier achievement of TIMI grade 3 flow. In primary PCI, shorter door-to-balloon times were associated with lower mortality. Finally, a similar analysis in >80,000 patients treated with thrombolytic therapy showed that increases in the door-to-drug time of just 30 minutes can lead to significant increases in mortality. Thus, these various lines of evidence point to the need to shorten the time to achieving reperfusion to any extent possible, even if by just 30 minutes.

The outstanding analysis by Stone et al sheds more light on the importance of TIMI 3 flow. After combining data from >2500 patients in the 4 Primary Angioplasty in Myocardial Infarction (PAMI) trials, they compared patients who achieved TIMI grade 3 flow spontaneously on the angiogram before primary PCI, who comprised 16% of the population, with those who had TIMI 0 to 2 flow. Despite relatively similar baseline characteristics, those with spontaneous TIMI grade 3 flow had improved left ventricular function, lower rates of congestive heart failure, and lower mortality. In addition, they observed that procedural success was higher in patients with baseline TIMI 3 flow. Their observations add new data to the existing body of evidence supporting the benefits of rapid reperfusion.

This analysis thus fuels enthusiasm for the strategy of “facilitated PCI” for ST elevation myocardial infarction, in which pharmacological treatment is initiated while patients are being transported to the cardiac catheterization laboratory for primary PCI. This strategy is designed to achieve the earliest possible reperfusion, while maintaining the benefits of primary PCI (ie, complete reperfusion, relief of coronary obstruction, and prevention of arterial remodeling with primary stenting). These benefits have also translated into lower rates of death, reinfarction, and stroke (especially intracranial hemorrhage) when compared with thrombolysis. Primary PCI is especially efficacious when combined with glycoprotein IIb/IIIa inhibition.

Institutional experience, as gauged by volume of procedures, has been shown to influence mortality after primary PCI, and thus there was initial concern that the benefits of primary PCI seen in clinical trials could not be achieved in the “real world.” However, with advances in interventional cardiology, this issue has been overcome, as was demonstrated in a recent analysis from the National Registry of Myocardial Infarction, which stratified hospitals by their volume of primary PCI procedures. In this setting, there was a significantly lower mortality with primary PCI versus thrombolysis in the 75% of patients treated at the intermediate and high-volume centers and equivalent mortality at low-volume centers. However, in all volume strata, there was a significantly lower rate of nonfatal stroke with primary PCI versus thrombolysis, even at these low-volume hospitals (0.4% versus 1.1% for high versus low volume; P<0.001). Thus, in the current era, primary PCI appears to be the reperfusion strategy of choice.

How could primary PCI be enhanced? On the basis of the analysis by Stone et al and the other data listed above, reducing time to achieving reperfusion is one of the most
promising avenues. This can be accomplished by implement-
ing a critical pathway, which in one study reduced both
door-to-balloon time and mortality. 16 The National Heart
Attack Alert Program of the National Institutes of Health has,
for the last 10 years, focused attention on the problem and
proposed solutions to reduce time delays in the treatment of
acute MI (see www.nhlbi.nih.gov/about/nhaap/index.htm).8

A second means of reducing time to reperfusion is the
facilitated PCI strategy, which combines both medical and
interventional approaches. The first test of this strategy
actually occurred nearly 15 years ago using full-dose
thrombolysis followed by immediate PCI in the Thrombolysis
and Angioplasty in Myocardial Infarction (TAMI) 17 and
TIMI 2A trials.18 At that time, no benefit was seen with the
combined approach. However, interventional techniques and
adjunctive antiplatelet therapy have greatly improved since
that time; thus, many suspect that outcomes will be improved
in the current era. Indeed, a recent analysis from contempo-
rary TIMI angiographic trials of thrombolytic therapy found
that outcomes seem to be better for patients who undergo
adjunctive PCI after thrombolysis compared with those who
do not.19 This strategy of initial thrombolysis followed by PCI
was also revisited in the Plasminogen activator Angioplasty
Compatibility Trial (PACT), which found an improvement in
timely grade 3 flow with half-dose t-PA administered
before PCI (from 15% to 33%).20

A second pharmacological approach that has been tested is
glycoprotein IIb/IIIa inhibition. In 4 trials, including TIMI
14,21 an improvement to ~30% to 35% TIMI grade 3 flow
(and ~50% patency) has been achieved with the administra-
tion of IIb/IIIa inhibitors in the Emergency Department
before PCI. The advantage of this approach is that it will
enhance reperfusion before PCI, with very low rates of
intracranial hemorrhage (<0.1%). The other advantage of
using IIb/IIIa inhibition is that it has been shown to improve
TIMI myocardial perfusion grade 3, which is an important
determinant of mortality, even among patients with TIMI
grade 3 (epicardial) flow.22,23

Stone et al12 also suggest that early reperfusion could be
facilitated by early initiation of another class of antiplatelet
agents, thienopyridines. Patients in the 2 PAMI stent trials, in
which these drugs were administered in the emergency
department, had higher baseline rates of TIMI grade 3 flow
(20.7% versus 11.3% in the PAMI 1 and 2 trials, which did
not administer ticlopidine before PCI). However, as the
authors note, these data should be interpreted cautiously
because these rates were also assessed at different core
laboratories, which might explain some of the difference.
Indeed, it should be noted that the definition of TIMI grade 3
flow in these trials is actually different than the real definition
from the TIMI 1 trial. The PAMI definition of TIMI 3 flow,
“complete filling of the distal vessel by the third cardiac
cycle,” when compared with the original definition, which is
based on flow compared with the non-infarct-related artery,2
actually overestimates the number of patients who are
deemed to have TIMI 3 flow by ~10%.24 Nonetheless, the
data from Stone et al12 are consistent with the early (eg,
within 2 hours) reduction in clinical events seen with clopi-
dogrel in the Clopidogrel in Unstable Angina to prevent

Recurrent Events (CURE) trial. Further study of this class of
agents on early reperfusion for ST elevation myocardial
infarction is warranted.

Finally, the use of combination therapy with half-dose
thrombolytic therapy plus IIb/IIIa inhibition has been seen as
the strategy with the highest potential for improving early
reperfusion. TIMI 14 showed that substantial improvements
in both early reperfusion and in myocardial perfusion can be
achieved with this combination therapy.21,22 The GUSTO V
trial found no difference in early mortality but a significant
reduction in death or MI with the combination versus
thrombolytic therapy alone (7.4% versus 8.8%; P = 0.001).25
Analysis of patients who underwent facilitated PCI in this
trial may shed further light on this important new strategy.

Thus, the body of observational evidence, as now ex-
panded by Stone et al12 reinforces the central goal of
achieving TIMI 3 flow (both epicardial grade 3 flow and
myocardial perfusion grade 3) as early as possible in ST
elevation myocardial infarction. It is thus time for prospective
trials of the various strategies of facilitating PCI as a means
of improving outcomes. Pending these trials, we should focus
our efforts on reducing time delays in initiating reperfusion
therapy, both for thrombolysis and primary PCI. It is hoped
that with a multimodality approach to reperfusion therapy,
using time reductions and pharmacological and interventional
strategies to maximize rates of early TIMI 3 flow, survival
and overall clinical outcomes after ST elevation myocardial
infarction will be further improved.

References

1. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction
of left ventricular dysfunction, and improved survival: should the

2. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI)

ventricular function and early cardiac events as a function of time to

4. Cannon CP, Braunwald E. Time to reperfusion: the critical modulator in
thrombolysis and primary angioplasty. J Thromb Thrombolysis. 1996;3:
117–125.


6. The GUSTO Investigators. An international randomized trial comparing
four thrombolytic strategies for acute myocardial infarction. N Engl J

7. The GUSTO Angiographic Investigators. The comparative effects of
tissue plasminogen activator, streptokinase, or both on coronary artery
patency, ventricular function and survival after acute myocardial

8. National Heart Attack Alert Program Coordinating Committee, 60
Minutes to Treatment Working Group. Emergency department: rapid
identification and treatment of patients with acute myocardial infarction.

9. The European Myocardial Infarction Project Group. Prehospital
thrombolytic therapy in patients with suspected acute myocardial

10. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-
onset-to-balloon time and door-to-balloon time with mortality in patients
undergoing angioplasty for acute myocardial infarction. JAMA. 2000;283:
2941–2947.

11. Cannon CP, Gibson CM, Lambrew CT, et al, for the NRMI 2 and 3
Investigators. Longer thrombolysis door-to-needle times are associated
with increased mortality in acute myocardial infarction: an analysis of
85,899 patients in the National Registry of Myocardial Infarction 2 + 3.


**Key Words:** Editorials ▪ angioplasty ▪ catheterization ▪ myocardial infarction ▪ platelet aggregation inhibitors ▪ stents ▪ thrombolysis
Importance of TIMI 3 Flow
Christopher P. Cannon

Circulation. 2001;104:624-626
doi: 10.1161/01.CIR.104.6.624

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/6/624

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/