The Thrombolysis in Myocardial Infarction (TIMI) Study Group experience

Eugene Braunwald, MD, and Marc S. Sabatine, MD, MPH

The Thrombolysis in Myocardial Infarction (TIMI) study group, an academic research organization, was formed in 1984 with initial support from the National Heart, Lung, and Blood Institute. Its initial goal was to compare the effects of the then-new thrombolytic agent, recombinant tissue plasminogen activator, with streptokinase. The TIMI study group has remained active since then and has completed 50 multicenter clinical trials. The TIMI network now collaborates with more than 1000 separate sites in 45 countries on 5 continents. In addition to thrombolytic agents, TIMI has studied antithrombotic, antiplatelet, anti-ischemic, lipid lowering, and anti-inflammatory drugs. TIMI has also established robust biomarker and pharmacogenetics programs, and has devised a panel of risk assessment scores that are widely used. TIMI is currently conducting 7 large trials worldwide on novel agents designed to reduce the morbidity and mortality of a variety of cardiovascular disorders. (J Thorac Cardiovasc Surg 2012;144:762-70)

THE ORIGINS OF TIMI

Although the idea of reperfusion infarcting myocardium in the management of patients with acute myocardial infarction (MI) was developed in the early 1970s, it had its roots much earlier. In 1935, Tennant and Wiggers¹ demonstrated, in open chest anesthetized dogs, that immediately after occlusion of a major coronary artery the contraction of the myocardium perfused by the occluded vessel became severely impaired. Function recovered only if the obstruction was relieved within 23 minutes. In 1941, Blumgart, Gilligan, and Schlesinger² also studied the consequences of coronary artery occlusion and noted by both gross and microscopic examination that no infarction occurred in dogs in which reperfusion was carried out up to 20 minutes after occlusion and that with longer occlusions, the size of the infarct was proportional to the duration of the occlusion. Although these early experiments demonstrated that myocardial necrosis after coronary occlusion could be minimized and even prevented by early reperfusion, neither of these groups suggested that reperfusion was a potential therapeutic intervention in patients with an evolving infarction.

In 1969, one of us (E.B.)³ proposed that the development of cardiac pump failure could be reduced and that clinical outcome improved by limiting the quantity of myocardium that becomes necrotic after the onset of acute MI. This

hypothesis was tested again in open chest anesthetized dogs, and it was observed that the extent and severity of ischemic damage secondary to coronary occlusion could be modified.⁴ From these experiments we concluded as follows:

Of greatest interest, from the clinical point of view, is the finding that the severity and extent of myocardial ischemic injury resulting from coronary occlusion could be radically altered not only by pretreatment of the animal but also by an appropriate intervention as late as three hours after the coronary occlusion. This suggests that measures designed for reduction of myocardial oxygen demands and *improvement of coronary perfusion*, when effected promptly after a patient has been brought to a hospital, might potentially reduce the ultimate size of the infarction.*

We⁵ also observed that when coronary artery reperfusion was carried out as late as 3 hours after occlusion, there was less pathologic evidence of myocardial necrosis and improved cardiac function than when the occlusion was sustained.

When the fibrinolytic agent streptokinase was purified, investigators began to determine whether this agent administered intravenously might be beneficial in the treatment of patients with acute MI. A major step forward was taken in 1976 by Chazov, Mateeva, and Mazaev,⁶ who demonstrated, using coronary arteriography, that the *intracoronary* infusion of streptokinase lysed coronary thrombi and restored myocardial reperfusion. Subsequently, we⁷ demonstrated, using intracoronary thallium-201 myocardial perfusion scanning, that myocardial tissue actually was salvaged by the timely administration of intracoronary streptokinase.

From the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

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Address for reprints: Eugene Braunwald, MD, TIMI Study Group, 350 Longwood Ave, Boston, MA 02115 (E-mail: ebraunwald@partners.org).

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
MI	= myocardial infarction
NSTEMI	= non-ST-elevation myocardial infarction
PCI	= percutaneous coronary intervention
STEMI	= ST-elevation myocardial infarction
TMPG	= TIMI Myocardial Perfusion Grade
tPA	= tissue plasminogen activator

By the middle 1980s, it was appreciated that for fibrinolytic therapy to be of practical benefit, the drug had to be administered intravenously rather than by the intracoronary route. Relatively few hospitals around the world had catheterization laboratories, and even in those with such facilities it often took hours to assemble the catheterization team, take the patient to the laboratory, and infuse the lytic agent directly into the occluded coronary artery. Also, a more powerful and fibrin-specific lytic agent, produced by recombinant techniques, tissue plasminogen activator (tPA), had been developed. In 1984, the US National Heart, Lung, and Blood Institute established the Thrombolysis in Myocardial Infarction (TIMI) Trial Study Group, a confederation of experienced investigators and well-staffed and equipped coronary care units. One of the authors (E.B.) was asked to chair this group and did so until 2011, when the other (M.S.S.) assumed this role. TIMI has been privileged to have a number of talented senior investigators, including Drs Elliott M. Antman, Christopher P. Cannon, C. Michael Gibson, Robert P. Giugliano, David A. Morrow, Deepak L. Bhatt.

Since its inception, the principal goal of the TIMI Study Group has been to conduct high-quality clinical trials that enhance the care of patients with cardiovascular disease and its risk factors. TIMI has been involved in 57 major studies, which include a wide array of phase I to phase IV trials and registries. These have ranged in size from less than 30 to more than 26,000 subjects. Trials have been conducted in 45 countries and at more than 1000 separate sites. The genesis of a new clinical trial typically involves one of two pathways. In some instances, TIMI identifies an unmet need or unanswered question in cardiovascular therapeutics that we believe can be addressed by studying an existing medication for a new indication. In other cases, a pharmaceutical or biotechnology company will approach us with a drug at preclinical or early-stage clinical development and seek our counsel as to the potential benefit of the drug and how it might best be studied. Inasmuch as our time is our most precious

commodity, we carefully vet any potential new trial, benefiting from the collective experience and wisdom of both our investigators and operational staff.

Although the initial TIMI trials focused on fibrinolytic agents, we have also studied antithrombotic, antiplatelet, anti-ischemic, lipid-lowering, and anti-inflammatory agents as well as percutaneous coronary intervention (PCI). Although the first trials involved patients with ST-elevation myocardial infarction (STEMI), we have extended our observations to other types of acute coronary syndrome (ACS), as well as to patients with chronic coronary artery disease, hyperlipidemia, and to the cardiovascular outcomes in patients with diabetes mellitus. In addition, the TIMI Study Group has used its growing database of clinical findings, biomarkers, and genotypes to enhance the understanding of coronary artery disease. An equally important goal has been to train the next generation of clinical investigators. Many of our postdoctoral fellows have assumed important faculty positions at TIMI and elsewhere.

ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)

The effects of the then-new intravenously administered tPA were compared with streptokinase on coronary and clinical outcome in the TIMI group's first trial.⁸ We observed successful reperfusion of occluded coronary arteries in 62% of patients who received tPA and 31% in those who received streptokinase. Patients with a patent artery had a lower mortality at 1 year than did those who did not, leading to what we have termed the "early open artery hypothesis" (Figure 1).

By the middle 1980s, percutaneous transluminal coronary angioplasty had become widely used in the management of severe angina pectoris in patients with stable coronary artery disease, and it was suggested that it might also be useful after fibrinolytic therapy in patients with STEMI. Therefore, in the TIMI 2 trial we compared the clinical outcome in patients who received tPA with either a "late invasive strategy" consisting of coronary arteriography 18 to 48 hours after the onset of symptoms, followed by coronary revascularization if the anatomy was appropriate, or a "conservative strategy," in which coronary arteriography and revascularization were carried out *only* if recurrent ischemia occurred or a positive electrocardiographic exercise stress test was present before hospital discharge. We⁹ anticipated that the invasive strategy would lead to improved clinical outcomes, but we observed, in fact, that the incidence of death and recurrent MI was similar in the 2 groups. What we learned from the TIMI 2 trial was that with the catheter-based revascularization techniques of that era (which did not include its performance on an emergency basis or stent implantation), a *routine* invasive strategy was not necessary so long as it was readily available for post-MI patients with

FIGURE 1. The TIMI 1 trial enrolled 290 patients with acute myocardial infarction and randomized them to tissue plasminogen activator (tPA) or streptokinase (SK). A, Patients treated with tPA (peach bars) had improved reperfusion and vessel patency at 90 minutes. (Data from the TIMI Study Group.⁸) B, Regardless of treatment arm, a patent infarct-related artery at 90 minutes was associated with improved long-term survival. [From Dalen J, Gore JM, Braunwald E, Borer J, Goldberg RJ, Passamani ER, et al. Six- and twelve-month follow-up of the Phase I Thrombolysis in Myocardial Infarction (TIMI) trial. *Am J Cardiol.* 1988;62:179-85.]

spontaneous or induced ischemia. Initially, the conservative approach after fibrinolytic therapy was widely adopted around the world and in rural areas of North America, whereas the invasive approach was used where patients had rapid access to expert percutaneous transluminal coronary angioplasty. At present, urgent primary PCI is used whenever possible.

In the TIMI 2 trial, we also compared early intravenous metoprolol followed by oral administration of this beta-blocker with oral beta-blocker begun on day 6. Early intravenous beta-blockade was associated with statistically significant reductions in reinfarction and in recurrent ischemia.¹⁰

Four later TIMI trials have examined the effects of adjunctive therapy in STEMI patients.

1. Early Retavase–Thrombolysis in Myocardial Infarction (ER-TIMI 19): By 2000, the critical importance of minimizing the time from the onset of symptoms to the administration of a fibrinolytic or initiating other reperfusion therapy was widely appreciated. Worldwide efforts were undertaken to develop strategies to reduce this time interval. The TIMI 19 trial, led by Dr David A. Morrow, showed that administration of a lytic agent in the ambulance could reduce by one half the time interval from ambulance arrival at the patient to starting a fibrinolytic in the emergency department.¹¹ Lytic administration in the ambulance is now rarely applied in North America because of the widespread use of primary PCI and the lack of trained personnel to administer fibrinolytics in the ambulance. However, this approach is widely used in the remainder of the world. Also, radiotelemetry of the electrocardiogram from the ambulance to the receiving hospital, as performed in the TIMI 19 trial, shortens the ultimate “door to balloon time,” which has become an important measure of the efficiency of hospital systems in managing patients with STEMI.
2. Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction Study 25 (ExTRACT-TIMI 25): Unfractionated heparin had been the antithrombotic

FIGURE 2. Kaplan-Meier curves showing the superiority of enoxaparin (ENOX) over unfractionated heparin (UFH) in the primary (A) and main secondary (B) end points of the ExTRACT-TIMI 25 trial.¹² RR, Relative risk; RRR, relative risk reduction. (From Antman et al.¹²)

FIGURE 3. Death from cardiovascular causes in placebo and rivaroxaban (2.5 mg twice daily) treated patients after acute coronary syndrome in ATLAS-2-TIMI 51.⁴ *HR*, Hazard ratio; *BID*, twice a day; *NNT*, number needed to treat; *mITT*, modified intention to treat; *ITT*, intention to treat. (From Mega et al.¹⁴)

FIGURE 4. TACTICS-TIMI 18 randomized 2220 patients with unstable angina or non-ST elevation myocardial infarction to an early invasive strategy (*INV*) or conservative (*CONS*) strategy. *MI*, Myocardial infarction; *ACS*, acute coronary syndrome; *OR*, odds ratio; *CI*, confidence interval. (From Cannon et al.¹⁶)

drug used almost universally since the earliest days of fibrinolytic therapy to prevent reocclusion after successful lysis. This trial, led by Dr Elliott M. Antman, randomized 20,506 patients with STEMI receiving fibrinolytic therapy to the low molecular weight heparin enoxaparin for the entire period of hospitalization (median, 7 days) or unfractionated heparin for 48 hours. At 30 days' follow-up, enoxaparin significantly reduced the risk of death or MI (the primary end point) by 17% and reduced the risk of death, MI, or urgent revascularization by 19% (Figure 2).¹²

3. Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28): Early in the first decade of this century, increasing attention was directed to the important role of platelets in precipitating acute coronary events. This trial, led by one of the present authors (M.S.S.) and Dr Christopher P. Cannon, enrolled patients with STEMI receiving fibrinolytic therapy and aspirin and randomized them to adjunctive clopidogrel or placebo. The addition of clopidogrel significantly improved infarct-related artery patency and reduced the odds of adverse cardiovascular events.¹³
4. Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51 (ATLAS-2-TIMI 51): The contemporary treatment of STEMI includes urgent coronary arteriography followed immediately by stenting if the anatomy is suitable. Stent thrombosis is largely prevented by the administration of aspirin and clopidogrel (or other P2Y₁₂ platelet receptor blockers). The ATLAS-2-TIMI 51 trial randomized 15,526 patients with an ACS, one half of whom had STEMI (and other forms of ACS),

to placebo or 1 of 2 doses of the factor Xa inhibitor, rivaroxaban, begun an average of 4.7 days after the onset of ACS (Figure 3). The very low dose (2.5 mg bid) resulted in a 34% reduction in cardiovascular death (and a 33% reduction in all-cause death) after treatment for an average of 2 years.¹⁴ The 5-mg bid dose did not have this salutary effect. These findings open the door to adding a very low dose of an anticoagulant to dual antiplatelet therapy in ACS.

NON-ST-ELEVATION ACS (NSTEMI-ACS)

Given the enormous and growing prevalence of NSTEMI-ACS, that is, unstable angina and non-STEMI, the TIMI Study Group has focused increasingly on this syndrome. The addition of intravenous tPA to standard therapy in the TIMI 3 trial did *not* improve outcome in this condition,¹⁵ an important negative trial inasmuch as many of these patients were receiving fibrinolytic therapy at the time. In the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy (TACTICS-TIMI 18) trial, led by Dr Christopher P. Cannon, an invasive strategy consisting of coronary arteriography followed by revascularization if the anatomy was suitable, was compared with a more conservative strategy in which catheterization was carried out only if the patient experienced recurrent ischemia or exhibited a positive stress test.¹⁶ We observed a significant 22% reduction in the odds of the primary end point of death, MI, or rehospitalization in patients randomized to the invasive strategy at 6 months (Figure 4).

We also compared the low molecular weight heparin enoxaparin with unfractionated heparin in 3910 patients with NSTEMI-ACS in the TIMI 11 trial,¹⁷ which was led by Dr Elliott M. Antman. As in the EXTRACT-TIMI 25 trial, enoxaparin significantly reduced the risk of death, MI, or

FIGURE 5. TRITON-TIMI 38 randomized 13,608 patients with acute coronary syndrome undergoing percutaneous coronary intervention to prasugrel or clopidogrel. HR, Hazard ratio; CV, cardiovascular; MI, myocardial infarction; CABG, coronary artery bypass graft; NNT, number needed to treat; NNH, number needed to harm; TIMI, Thrombolysis in Myocardial Infarction. (From Wiviott et al.¹⁸)

urgent revascularization at 8 and 14 days. On the basis of this and other trials, low molecular weight heparin is now widely used around the world in patients with NSTEMI-ACS.

Inasmuch as platelets play an important role in the pathogenesis of ACS, the combination of 2 antiplatelet agents, aspirin and the second-generation thienopyridine, clopidogrel, have become central in the treatment of this condition. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, led by Dr Antman and Dr Stephen D. Wiviott,

FIGURE 6. In TRITON-TIMI 38, subjects randomized to prasugrel had a significant 52% reduction in the risk of stent thrombosis compared with clopidogrel. This benefit was seen for both drug-eluting and bare-metal stents. ARC, Academic Research Consortium; PCI, percutaneous coronary intervention; HR, hazard ratio; NNT, number needed to treat. (Modified from Wiviott et al.¹⁹)

a third-generation thienopyridine, prasugrel, more powerful than clopidogrel, was compared with clopidogrel in 13,608 patients with ACS undergoing PCI.¹⁸ Prasugrel significantly reduced the risk of the primary end point, that is, death, MI, or stroke, by 19% (Figure 5) and stent thrombosis by 52%¹⁹ (Figure 6). However, prasugrel significantly increased the risk of major bleeding and, in patients with prior stroke and transient ischemic attack, intracranial bleeding. Patients with diabetes mellitus exhibited a particular benefit with prasugrel compared with clopidogrel *without* a significant increase in major bleeding.²⁰

We compared ranolazine, a piperazine novel anti-ischemic drug, with placebo on 6560 patients in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, led by Dr David A. Morrow.²¹ Although ranolazine did not significantly reduce the risk of the composite end point of cardiovascular death, MI, or recurrent ischemia, it significantly reduced the risk of recurrent ischemia, supporting its use as an anti-ischemic drug. Furthermore, ranolazine had a favorable safety profile and significantly reduced the incidence of ventricular tachycardia as recorded on a Holter monitor by 37%²² and proved also to be a moderately effective antidiabetic agent.²³

CHRONIC ATHEROSCLEROTIC DISEASE

Although aspirin is strongly indicated in patients after MI, it is not clear whether platelet inhibition through

FIGURE 7. Comparison of intensive and standard lipid-lowering therapy with statins after an acute coronary syndrome. After acute coronary syndrome, intensive lipid-lowering therapy with a high-potency statin significantly reduced the risk of adverse outcomes as compared with moderate-potency statin therapy. MI, Myocardial infarction; RR, relative risk. (From Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, et al. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes. Results from the PROVE IT–TIMI 22 trial. *J Am Coll Cardiol.* 2005;46:1405-10. Published with permission of the American College of Cardiology Foundation.)

another mechanism is beneficial. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherosclerotic Ischemic Events–Thrombolysis in Myocardial Infarction 50 (TRA 2P–TIMI 50) trial, led by Dr David A. Morrow, we compared vorapaxar, a potent protease-activated receptor-1 platelet receptor inhibitor that blocks the platelet thrombin receptor, with placebo in 26,449 patients with stable atherosclerosis. Overall, there was a significant reduction in the primary end point of cardiovascular death, MI, or stroke that appeared to be most robust in patients with prior MI. In contrast, there was little or no benefit and an excess of intracranial bleeding in stroke patients.²⁴

CHOLESTEROL LOWERING

TIMI has been involved in studying the effects of lowering cholesterol. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial in patients after ACS, led by Dr Christopher P. Cannon, studied the effects of what was at the time (2001) considered to be extreme lowering of low-density lipoprotein cholesterol.²⁵ In this trial, 4162 post-ACS patients were randomized to *intensive* statin therapy (atorvastatin 80 mg daily) or *standard* statin therapy (pravastatin 40 mg daily). Intensive lipid lowering to a mean of 62 mg/dL significantly reduced the risk of death, MI, or urgent revascularization by 24% when compared with standard therapy, which reduced low-density lipoprotein cholesterol to 95 mg/dL. This benefit of more intensive lipid lowering with atorvastatin appeared within the first month of starting therapy²⁶ (Figure 7). This trial remains one of our favorites for several reasons: the trial demonstrated an unequivocal benefit; the findings were incorporated into practice guidelines and easily implemented by clinicians; a wealth of secondary clinical, biomarker, and genetic analyses have emanated from the trial database;

FIGURE 8. The TIMI Risk Score for unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) is a simple prognostication scheme that categorizes a patient’s risk of death and ischemic events. CAD, Coronary artery disease; D/M/I/UR, death, myocardial infarction, urgent revascularization; ASA, aspirin; TIMI, Thrombolysis in Myocardial Infarction. (From Antman et al.²⁷)

FIGURE 9. TRS, TIMI Risk Score for ST-elevation myocardial infarction. SBP, Systolic blood pressure; DM, diabetes mellitus; HTN, hypertension; LBBB, left bundle branch block; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction. (From Morrow et al.²⁸)

and, like any good experiment, the data have generated new hypotheses to test in terms of further cholesterol reduction (see “Ongoing TIMI Trials”) and the role of inflammation in cardiovascular disease.

TIMI RISK SCORES

The TIMI Study Group has used its large database to establish clinical scores for risk stratification. The TIMI Risk Score for NSTEMI-ACS is a simple 7-point scale that categorizes a patient’s risk of death and ischemic events and provides a basis for therapeutic decision making²⁷ (Figure 8). This score was derived in TIMI 11B and was subsequently validated in several trials. The TIMI Risk Score for STEMI consists of a 14-point scale based on the history, physical examination, and presentation²⁸ (Figure 9). The TIMI Risk Index is a simple index and is based on a combination of age, heart rate, and systolic arterial pressure at presentation, characteristics that are easily assessed by nonphysicians in patients with STEMI. Every 5-point increase is associated with a 43% increase in 30-day mortality. The index was derived from the Intravenous NPA for the Treatment of Infarcting Myocardium Early–Thrombolysis in Myocardial Infarction 17 (InTIME 2–TIMI 17) trial and validated in TIMI 9 and 25 as well as in the National Registry of Myocardial Infarction.²⁹

The TIMI Coronary Flow Grade, established in the TIMI 1 trial, was designed to assess epicardial perfusion at angiography.⁸ It is scored from 0 to 3, with TIMI Flow Grade 0 representing a total occlusion and TIMI Flow Grade 3 representing normal epicardial perfusion. The TIMI Flow Grade is a powerful predictor of clinical outcome (Figure 10); its value has been confirmed in many trials and it is now universally used. The number of cineangiographic frames required for contrast medium to reach a standardized distal landmark after injection into a proximal

FIGURE 10. TIMI Flow Grade is scored from 0 to 3. It is a powerful predictor of outcome. Here shown are the findings from the TIMI 1 trial. *TIMI*, Thrombolysis in Myocardial Infarction. [Data from Flyngenring BP, Sheehan FH, Kennedy JW, Dodge HT, Braunwald E. Does arterial patency 90 minutes following thrombolytic therapy predict 42 day survival? *J Am Coll Cardiol*. 1991;17(Suppl A):275A.]

coronary artery, termed the TIMI Frame Count, was established by Dr C. Michael Gibson to enhance reproducibility of the angiographic assessment of coronary blood flow. The risk of adverse clinical outcomes rises proportionately with an increased frame count.³⁰

The TIMI Myocardial Perfusion Grade (TMPG), also developed by Dr Gibson, assesses microvascular perfusion of the portion of the left ventricle in the area of distribution of the culprit artery.³¹ It is scored from 0 to 3 with TMPG 0 representing no apparent tissue-level perfusion and TMPG 3 indicating normal perfusion. It too has been found to be an independent predictor of clinical outcome.

BIOMARKERS

The TIMI Group has had a strong interest in biomarkers because of their ability to improve risk stratification. This effort is led by Dr David A. Morrow. In the TIMI 3 trial in patients with NSTEMI,³² patients with a serum troponin greater than 9 ng/mL had a 7.5-fold higher risk of death than patients with a troponin less than 0.4 ng/mL. In TACTICS-TIMI 18, patients with an elevated troponin at baseline appeared to derive a greater treatment benefit with an early invasive strategy, as compared with patients without a troponin elevation.³³

In Orbofiban in Patients with Unstable Coronary Syndromes—Thrombolysis in Myocardial Infarction 16 (OPUS-TIMI 16), elevated levels of B-type natriuretic peptide were associated with an increased risk of death, an observation that was confirmed in the Aggrastat to Zocor-TIMI 21 (A to Z-TIMI 21) trial.³⁴

Three independent biomarkers (troponin, C-reactive protein, and B-type natriuretic peptide) were obtained on admission in a multimarker strategy devised by Dr Marc S. Sabatine. One point was assigned for each biomarker that was abnormally elevated (troponin I > 0.1 mg/mL,

C-reactive protein > 1.5 mg/dL, and B-type natriuretic peptide > 80 pg/mL). The relative risk rose progressively with the number of elevated biomarkers.³⁵

PHARMACOGENETICS

Over the past several years, the TIMI Study Group has delved into pharmacogenetics. Efforts led by M.S.S. and Dr Jessica L. Mega demonstrated that approximately 30% of individuals harbor a loss-of-function allele in the *CYP2C19* gene that results in lower levels of the active clopidogrel metabolite, lesser degrees of platelet inhibition, and, using patients from TRITON-TIMI 38 with an ACS

FIGURE 11. Efficacy outcomes (cardiovascular [CV] death, myocardial infarction [MI], and stroke) among carriers of the *CYP2C19* reduced function allele in clopidogrel-treated patients in the TIMI 38 trial. *CI*, Confidence interval. (From Mega et al.³⁶)

and planned PCI, approximately 50% higher risk of cardiovascular death, MI, or stroke, and more than a threefold increased risk of stent thrombosis³⁶ (Figure 11).

The subsequent Escalating Clopidogrel by Involving a Genetic Strategy–Thrombolysis in Myocardial Infarction 56 (ELEVATE-TIMI 56) trial, led by Dr Mega, demonstrated that it requires tripling the daily maintenance dose of clopidogrel to achieve platelet inhibition equivalent to that seen with the standard clopidogrel maintenance dose in wild-type individuals.³⁷

ONGOING TIMI TRIALS

The TIMI Study Group is currently conducting 7 large-scale multinational, multicenter trials. Improved Reduction of Outcomes: Vytarin Efficacy International Trial–Thrombolysis in Myocardial Infarction 40 (IMPROVE IT–TIMI 40), led by Drs Cannon and Giugliano, and conducted in collaboration with the Duke Clinical Research Institute, is a randomized, double-blind trial designed to assess the possible benefit of treating more than 18,000 patients stabilized after ACS to low-density lipoprotein cholesterol goals that are even lower than those targeted in PROVE IT–TIMI 22, using a combination of simvastatin and ezetimibe.³⁸ The ENGAGE-TIMI 48 trial, led by Drs Antman and Giugliano, is comparing the novel factor Xa antagonist edoxaban with warfarin in 20,500 patients with atrial fibrillation to look at the incidence of systemic embolism, stroke and bleeding.³⁹

The Stabilization of Plaques Using Darapladib–Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial, led by Dr Cannon, is studying the effects of the lipoprotein-PLA2 antagonist darapladib in 13,500 patients after ACS.⁴⁰ The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial is studying the effects of the DPP4 inhibitor saxagliptin on cardiovascular outcomes in 16,500 patients with type 2 diabetes.⁴¹ The PEGASUS-TIMI 54 trial, led by M.S.S., is studying the effects of adding ticagrelor, a reversible P2Y₁₂ platelet receptor antagonist, to aspirin in patients 1 to 3 years after MI. The Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification–Thrombolysis in Myocardial Infarction 55 (REVEAL Hps-3–TIMI 55) trial, carried out in collaboration with the Clinical Trial Service Unit at the University of Oxford, is studying the cholesterol ester transport protein inhibitor anacetrapib in 30,000 patients with chronic coronary artery disease. This drug raises high-density lipoprotein cholesterol and reduces low-density lipoprotein cholesterol. The LDL-C Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy–Thrombolysis (LAPLACE-TIMI 57) trial, led by M.S.S., is studying the effects of a potent new inhibitor of PCSK-9 on

low-density lipoprotein cholesterol concentration in patients with hypercholesterolemia.⁴²

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