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Thrombolysis In Myocardial Infarction (TIMI) Study Group

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

ABSTRACT

In 1984, the National Heart, Lung, and Blood Institute (NHLBI) decided to study the efficacy and safety of the treatment of acute myocardial infarction with an emerging therapy, coronary thrombolysis, and thus the TIMI (Thrombolysis In Myocardial Infarction) Study Group was born. Following completion of 3 clinical trials of thrombolytic therapy supported by the NHLBI, TIMI became an academic research organization headquartered at Brigham and Women's Hospital and subsequently branched out to study a wide range of patients, including those with stable coronary, cerebrovascular, and peripheral arterial disease; dyslipidemia; heart failure; atrial fibrillation; diabetes; and obesity. TIMI also began to study a wide range of interventions including thrombolytic, antithrombotic, lipid-modifying, anti-inflammatory, heart failure, glucose-lowering, and weight loss agents. TIMI, now in its 37th year, has completed >70 trials. This review describes the origins of the TIMI Study Group, summarizes several of its completed trials and the major lessons learned from them, and discusses ongoing trials and future directions. (J Am Coll Cardiol 2021;77:2822–45) © 2021 by the American College of Cardiology Foundation.

ORIGINS OF TIMI AND THE FIRST TRIALS

THE ORIGINS. In the 1950s, it was generally agreed that myocardial ischemia was caused by an imbalance between myocardial O_2 supply and demand. Chronic stable angina was secondary to transient imbalance, often precipitated by increased O_2 demand in the presence of coronary arterial narrowing produced by atherosclerotic plaques. Acute myocardial infarction (MI) characterized by electrocardiographic ST-segment elevation (STEMI) was thought to be a consequence of sudden thrombotic occlusion of a major coronary artery, as described by Herrick (1). The risks of developing cardiogenic shock and mortality were high in patients with STEMI who developed large infarcts (2).

In 1955, one of the authors (E.B.) served as a post-doctoral fellow in the Laboratory of Cardiovascular Physiology of the National Heart Institute (now the National Heart, Lung, and Blood Institute [NHLBI]) headed by Dr. Stanley J. Sarnoff. We studied determinants of myocardial O_2 consumption (3) and of the closely related coronary blood flow (4) in open-chest, anesthetized dogs. From 1961 to 1968, this work was continued in Eugene Braunwald's laboratory at the NHLBI (5). Eight determinants of myocardial O_2 consumption were defined but only 3 (myocardial tension development, myocardial contractility—as reflected in the velocity of contraction, and heart rate) accounted for >90% of the heart's total energy expenditure (5).

The clinical observation that in some patients, MI had a "stuttering" onset over the course of hours or even days, suggested that acute myocardial necrosis in STEMI was not necessarily a discrete event but that a finite interval between the onset of severe ischemia

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From the TIMI (Thrombolysis In Myocardial Infarction) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, and Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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HIGHLIGHTS

- Randomized controlled trials can provide the highest level of evidence for new therapies.
- The TIMI Study Group has been conducting practice-changing CV outcomes trials for >35 years.
- Clinical risk scores, biomarkers, and genetics have facilitated implementation of personalized medicine.
- Continued exploration of new therapeutics should enable further reductions in CV morbidity and mortality.

and the development of transmural myocardial necrosis might exist. This led to the hypothesis that appropriate interventions designed to restore the balance between myocardial O_2 supply and demand during this interval would limit the ultimate size of the infarction. This hypothesis was tested in a series of experiments in open-chest, anesthetized dogs in a study published in 1971 (6). In that study, we concluded: "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 3 h after the coronary occlusion. This suggests that measures designed for reduction of myocardial oxygen consumption 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*."

In 1971, it was not possible to test this hypothesis clinically because no techniques for rapid revascularization of a thrombotically occluded coronary artery were available. However, in 1975, Evgeny Chazov, a leading Soviet cardiologist, demonstrated that intracoronary infusion of streptokinase (SK) lysed the thrombus in a freshly occluded right coronary artery and restored blood flow to the ischemic myocardium (7). After confirmation of this important finding by Rentrop et al. (8) in Göttingen, Germany, a number of cardiac centers in North America and Europe initiated programs of intracoronary thrombolysis.

Three advances increased the likelihood that early reperfusion could play an important role in the treatment of acute STEMI. In 1977, Reimer et al. (9) observed a "wavefront of ischemic cell death following coronary occlusion from endocardium to epicardium" in conscious dogs. They showed a direct relationship between the duration of coronary occlusion and the size of the MI. The second advance was the demonstration by one of the authors (E.B.) that in STEMI patients reperfusion by intracoronary thrombolytic therapy, carried out shortly after the onset of ischemic pain, prevented the necrosis of ischemic myocardium and could be expected to reduce MI size. This was demonstrated by the uptake of thallium-201 by the "salvaged" myocardium (10). Next it became necessary to overcome the logistic challenge of bringing patients to the hospital immediately after the onset of chest pain and then to the catheterization laboratory where a team would be available to infuse a thrombolytic agent into an occluded coronary artery. This was managed by administering much larger doses of SK intravenously than had been employed in the intracoronary route. The first GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) trial (11) and then the ISIS-2 (Second International Study of Infarct Survival) trial (12), 2 of the first STEMI megatrials, showed a significant reduction in mortality using high-dose intravenous SK.

In 1984, prior to the completion of GISSI and ISIS-2, discussion of the emerging field with the leadership of the NHLBI led, after some gentle prodding, to the institute issuing a contract to establish a multicenter clinical trial group, which we named the Thrombolysis In Myocardial Infarction Study Group and shortened to TIMI. In a preliminary investigation using intravenous SK in STEMI patients with arteriographically totally occluded coronary arteries, we observed that only 11 of the 34 patients (32%) exhibited patency following high-dose intravenous SK (13). Clearly, a more potent thrombolytic agent was necessary. This was followed by the next important advance, the development of recombinant tissue plasminogen activator (tPA), a naturally occurring protein that catalyzes the conversion of plasminogen into the active serine protease plasmin that was more fibrin-specific and efficacious in opening thrombotically occluded coronary arteries than SK was (14,15).

THE FIRST 3 TIMI TRIALS. The investigators in the 13 institutions participating in the TIMI trial included academic cardiologists with a variety of skills,

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ASCVD = arteriosclerotic cardiovascular disease

CV = cardiovascular

FXI = factor XI

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

MI = myocardial infarction

NHLBI = National Heart, Lung, and Blood Institute

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PCSK9 = proprotein convertase subtilisin/kexin type 9

SGLT2 = sodium-glucose co-transporter 2

SK = streptokinase

STEMI = ST-segment elevation myocardial infarction

tPA = tissue plasminogen activator

UFH = unfractionated heparin

including clinical trial design, cardiac imaging, blood coagulation, statistics, and cardiac pathology, who had previously conducted translational research. The Data Coordinating Center was the Maryland Medical Research Institute led by Genell Knatterud, a distinguished and experienced biostatistician; several core laboratories were also established.

TIMI 1. The first TIMI trial (only later referred to as TIMI 1), was a triple-blinded, double-dummy study that compared intravenous tPA and SK in achieving successful reperfusion of initially angiographically occluded coronary arteries. This primary endpoint was achieved in 62% of tPA-treated patients compared with 31% of SK-treated patients (16) (**Figure 1A**). The trial was stopped early after 316 patients had been randomized on advice of the Data Safety Monitoring Board because of these highly significant, decisive results. It was also observed that there was an association between TIMI flow grade following thrombolytic therapy and survival at 1 year (**Figure 1B**) (17). Also, there was greater recovery of left ventricular function with earlier reperfusion (18). These observations and those in the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial (19) supported what was referred to as the open artery concept (20). An important contribution of the TIMI trial was defining TIMI flow grade on coronary arteriography, which has been widely used (Supplemental Tables 1 to 3).

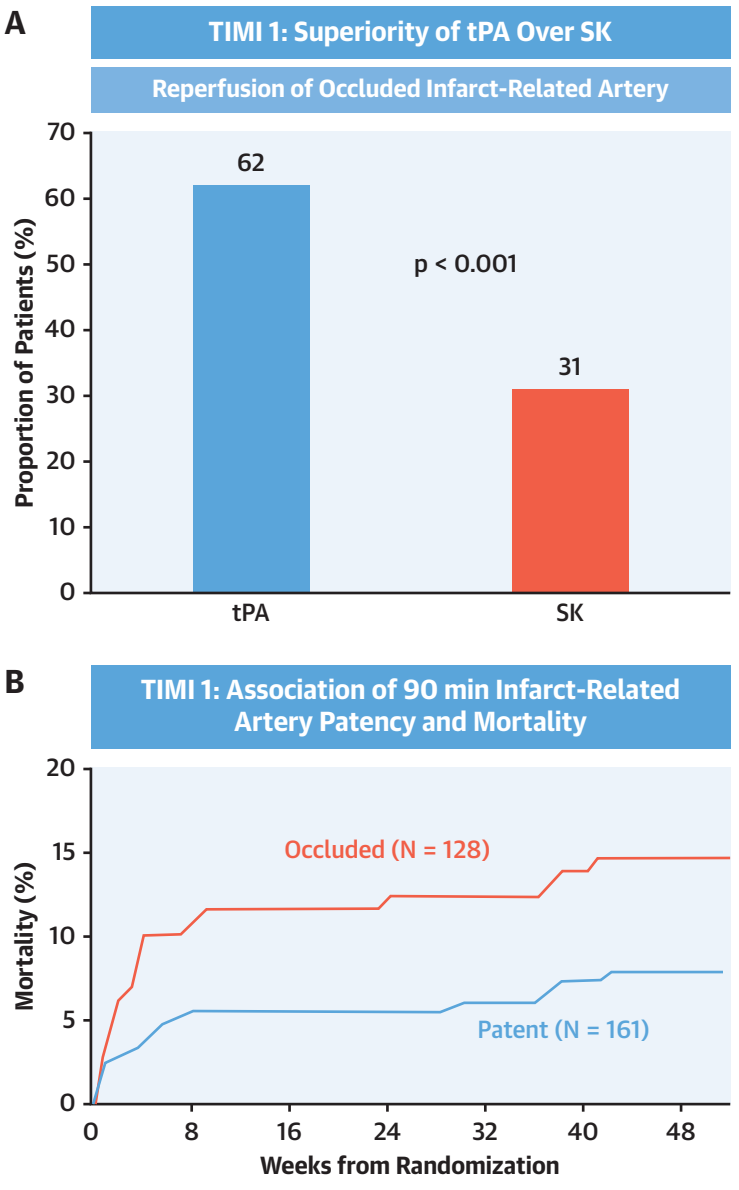
TIMI 2. The goal of the TIMI 2 trial was to study the effects of an invasive strategy following thrombolysis (21). All 3,262 patients with STEMI in the TIMI 2 trial received the "winner" of the first trial (tPA) supplemented by unfractionated heparin (UFH). The patients were randomized to an invasive or a conservative strategy. In the former, coronary arteriography was carried out 18 to 48 h after thrombolysis, followed by percutaneous transluminal coronary balloon angioplasty when feasible. In the conservative arm, coronary arteriography and percutaneous transluminal coronary balloon angioplasty were performed only if ischemia recurred or if a pre-hospital discharge electrocardiogram stress test was positive for ischemia. The primary endpoint, reinfarction or death within 42 days, did not differ significantly between the 2 arms (21). Mortality varied directly with the time interval between the onset of MI and the time to treatment (22).

In what became characteristic of subsequent TIMI trials, the TIMI 2 investigators used the trial platform for 3 substudies. The first, using a 2 × 2 design, was designed to test the timing of commencing beta blockade in patients with STEMI receiving thrombolytic therapy. Under the leadership of Robert R. Roberts, we compared intravenous beta blockade begun immediately after thrombolysis and then continued with oral beta blockade begun after 6 days. While the immediate intravenous administration did not alter mortality, it was associated with significant reductions in reinfarction and recurrent ischemic chest pain (23). These findings were consistent with our observation in canine studies (24), the ISIS 1 (First International Study of Infarct Survival) trial (25), and other studies (26).

The other 2 substudies were designed to risk stratify patients. A clinical risk score based on 8 characteristics at baseline was developed. The number of these risk factors present prior to thrombolysis correlated with mortality at 6 weeks (27). A different approach to risk stratification came from a collaboration with a Norwegian colleague, Christian Hall. Hall et al. (28) studied a relatively new biomarker at the time, the N-terminal proatrial natriuretic factor, a forerunner of N-terminal pro-B-type natriuretic peptide (NT-proBNP), obtained during the first 12 h after the onset of chest pain. Plasma levels of this biomarker in patients who died during the first year following entry into the trial were significantly higher compared with a control group of matched survivors (28). These initial forays into clinical and biochemical risk stratification in the early 1990s foreshadowed TIMI's work in personalized medicine for the next quarter of a century (see Personalized Medicine).

TIMI 3. The goal of the TIMI 3 trial, supported by an NHLBI R01 grant, was to compare the early effects of tPA versus placebo and the clinical efficacy of an early invasive versus conservative strategy in a 2 × 2 factorial design in 1,473 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). To our surprise, despite the presence of coronary arterial thrombi in the majority of patients—albeit without total occlusion—tPA did not reduce a composite ischemic endpoint, but it was associated with an increase in intracranial hemorrhage (29). As a consequence of TIMI 3 and ISIS 2, which simultaneously published similar results in this population (12), thrombolytic therapy has been contraindicated in these patients. The invasive arm showed a numerical, but not statistically significant, benefit in the primary endpoint of death, MI, or a failed stress test at 6 weeks, but did reduce the rate of death, MI, or rehospitalization. Subsequently, with further improvement in revascularization techniques, particularly the development of stents, and in antithrombotic therapy, an early invasive approach is now widely employed.

FIGURE 1 Key Results of TIMI 1



TIMI (Thrombolysis In Myocardial Infarction) 1 randomized 316 patients with ST-segment elevation myocardial infarction to 1 of 2 thrombolytics, either tissue plasminogen activator (tPA) or streptokinase (SK). Proportion of patients with reperfusion of their occluded infarct-related artery are shown by treatment arm **(A)** and 1-year mortality with a patent versus occluded infarct-related artery at 90 min **(B)** (16,17).

Following completion of the first 3 trials sponsored and supported by the NHLBI, TIMI became a not-for-profit academic research organization, operating as a section of the Division of Cardiovascular Medicine of Brigham and Women's Hospital. All TIMI investigators are full-time members of the faculty of Harvard Medical School.

OTHER MAJOR COMPLETED TIMI TRIALS

TIMI 11 AND 25: LOW MOLECULAR HEPARIN. UFH has been administered routinely in patients with acute coronary syndromes (ACS), but had the disadvantage of requiring continuous intravenous infusion. A number of low–molecular-weight heparins,

which can be administered subcutaneously once or twice daily, were developed in the late 1990s. Two trials led by Elliott M. Antman compared the low–molecular-weight heparin enoxaparin to UFH. In TIMI 11B, carried out in 3,910 patients with NSTE-ACS, enoxaparin significantly reduced the risk of death, MI, or need for urgent revascularization at both 8 and 14 days (30).

The goal of the EXTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment)-TIMI 25 study was to compare the efficacy and safety of enoxaparin throughout the index hospitalization with UFH administered for at least 48 h in 20,506 patients with STEMI scheduled to undergo thrombolysis. At 30 days' follow-up, enoxaparin had significantly reduced the relative risk of death or MI by 17% and the relative risk of death, MI, or urgent revascularization by 19% (31).

TACTICS–TIMI 18. The TACTICS (Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy)-TIMI 18 study, led by Christopher P. Cannon, returned to a comparison between invasive and conservative strategies that had been studied previously in patients with NSTE-ACS in TIMI 3B (29,32,33). TACTICS-TIMI 18 randomized 2,220 such patients to an early invasive strategy (routine cardiac catheterization within 48 h followed by revascularization if feasible) or to a conservative strategy, both on a background of receiving upstream glycoprotein IIb/IIIa inhibition with tirofiban. The invasive strategy significantly reduced the odds of death, MI, or rehospitalization with ACS by 22% (**Figure 2A**) (32). Moreover, David A. Morrow showed that this benefit was limited to the high-risk patients, defined by an elevated cardiac troponin at randomization, whereas no benefit was observed in patients whose troponin was not elevated (**Figure 2B**) (34). Meta-analyses of the trials in this field subsequently validated this conclusion (35), and an early invasive approach in high-risk patients is recommended in practice guidelines (36).

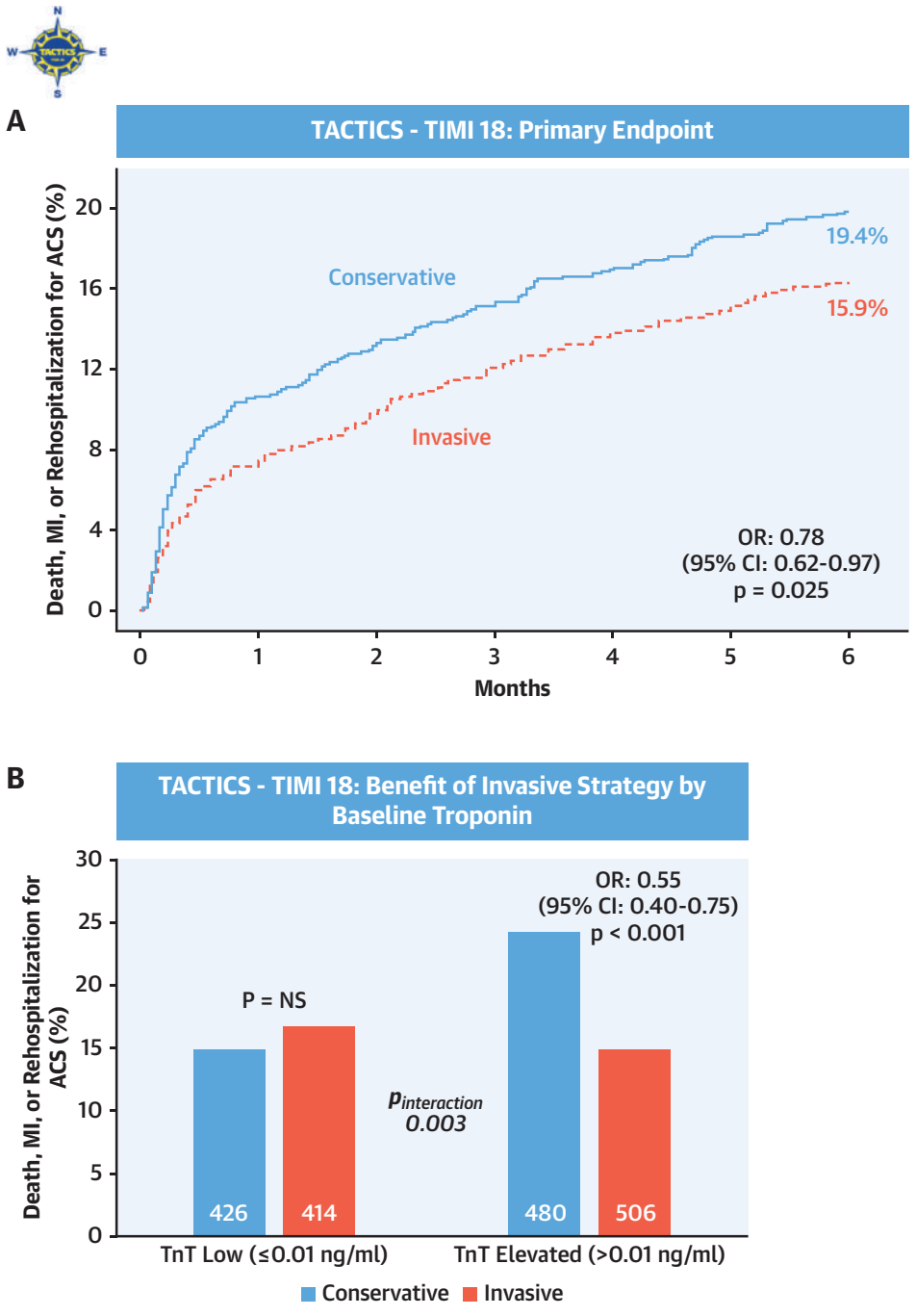
PROVE IT–TIMI 22. The goal of the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy)-TIMI 22 trial, led by Christopher P. Cannon, was to compare the efficacy of high-intensity statin therapy (atorvastatin 80 mg/day) with moderate statin therapy (pravastatin 40 mg/day) in 4,162 patients who recently experienced an ACS. On-treatment, low-density lipoprotein cholesterol (LDL-C) levels in patients randomized to atorvastatin was 62 mg/dl and in those to pravastatin it was 95 mg/dl. Intensive statin therapy reduced the risk of the composite of death, MI, or urgent revascularization by 25% and of a broader endpoint by 16% (**Figure 3A**) (37). Atorvastatin significantly reduced the relative risk of death, MI, or urgent revascularization by 33% as early as 30 days after randomization.

At the start of the PROVE IT-TIMI 22 trial, the LDL-C goals for patients with established coronary artery disease was <100 mg/dl in both American and European practice guidelines. The observed superiority of intense lipid lowering led to a reduction of this goal to <70 mg/dl on both continents and was widely adopted elsewhere (38,39). Moreover, patients who achieved low levels of both LDL-C (<70 mg/dl) and high-sensitivity C-reactive protein (hsCRP) (<2 mg/l) by 30 days had very low event rates (**Figure 3B**) (40). These data supported the importance of targeting inflammation in patients with atherosclerosis, a concept that has now been borne out in a clinical trial led by Paul M Ridker (41).

CLARITY–TIMI 28. Following the publication on the benefits of clopidogrel in patients with non-STEMI (42), one of the authors of this paper (M.S.S.) along with Christopher P. Cannon designed and led the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)-TIMI 28 study to assess the efficacy and safety of adding clopidogrel in 3,491 patients with STEMI receiving a standard thrombolytic regimen that included aspirin. The addition of clopidogrel significantly increased infarct-related artery patency by 36% and significantly reduced the odds of major cardiovascular (CV) events by 20% at 30 days (43). Patients who had been pre-treated with clopidogrel showed a significant relative reduction of 46% in the risk of cardiac events after percutaneous coronary intervention (44). The addition of clopidogrel increased bleeding numerically but not statistically; there was no increase in intracranial bleeding. Based on these and other data, dual antiplatelet therapy in patients with STEMI undergoing thrombolytic therapy became recommended in the practice guidelines (45).

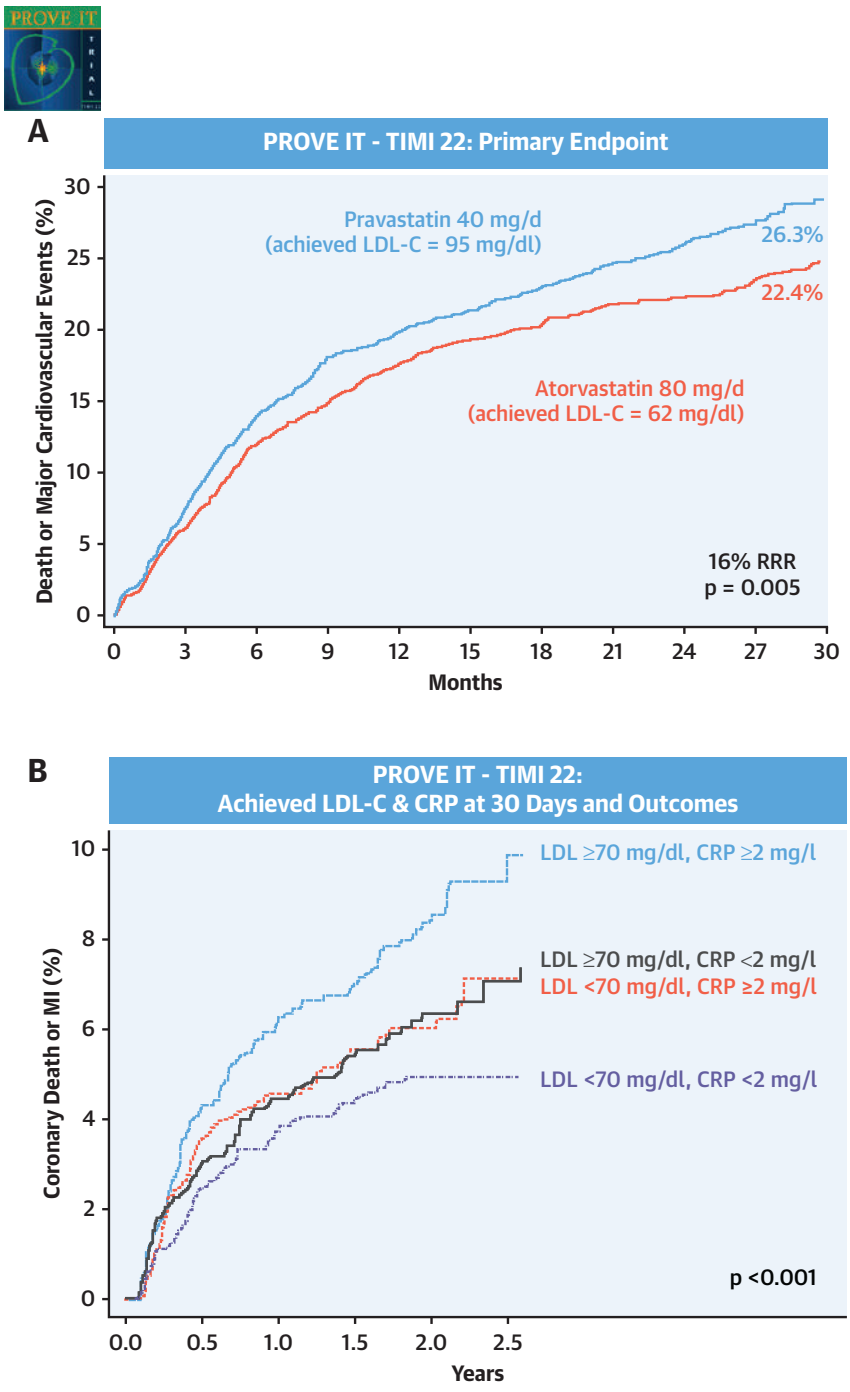
TRITON–TIMI 38. The goal of the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel)-TIMI 38 study, led by Stephen D. Wiviott and Elliott M. Antman, was to compare clopidogrel with prasugrel, a more potent $P2Y_{12}$ inhibitor (46), in 13,608 patients with ACS undergoing percutaneous coronary intervention. Prasugrel significantly reduced the incidence of death, MI, or stroke by 19% (**Figure 4A**) (47). Patients randomized to prasugrel also had a reduction of 52% in the risk of stent thrombosis compared to clopidogrel (**Figure 4B**) (48). Although the overall

FIGURE 2 Key Results of TACTICS-TIMI 18



TACTICS (Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy)–TIMI (Thrombolysis In Myocardial Infarction) 18 randomized 2,220 patients with non-ST-segment elevation acute coronary syndrome (ACS) to either an invasive strategy (routine cardiac catheterization within 48 h) or a conservative strategy (selective angiography in patients with recurrent ischemia or a high-risk stress test finding). Cumulative incidence curves are shown for death, myocardial infarction (MI) or rehospitalization for ACS by treatment arm **(A)** and benefit of an invasive versus conservative strategy by cardiac troponin T (TnT) level at presentation **(B)** (32,34).
CI = confidence interval; OR = odds ratio.

FIGURE 3 Key Results of PROVE IT-TIMI 22



PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy)-TIMI 22 randomized 4,162 patients with ACS to either intensive lipid-lowering with atorvastatin 80 mg/day versus moderate lipid-lowering with pravastatin 40 mg/day. Cumulative incidence curves are shown for death, MI, unstable angina requiring rehospitalization, revascularization, or stroke by treatment arm **(A)** and for death or MI stratified by achieved low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hsCRP) at 30 days **(B)** (37,40). RRR = relative risk reduction; other abbreviations as in Figures 1 and 2.

bleeding rates were low with both $P2Y_{12}$ inhibitors, prasugrel significantly increased the risk of serious bleeding. Based on these data, both US and European practice guidelines now recommend prasugrel over clopidogrel in appropriate patients (36,49).

IMPROVE-IT–TIMI 40. The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)-TIMI 40, led by Christopher P. Cannon, in collaboration with colleagues at the Duke Clinical Research Institute, was conducted to assess the efficacy and safety of adding ezetimibe, a drug that inhibits the intestinal absorption of cholesterol, to a statin. The trial randomized 18,144 patients who were post-ACS to simvastatin 40 mg and ezetimibe 10 mg or simvastatin 40 mg and placebo. The addition of ezetimibe to simvastatin reduced LDL-C levels to an average of 54 mg/dl and significantly reduced the risk of CV death, MI, stroke, unstable angina, or urgent revascularization (50). Patients who achieved both pre-specified lipid (LDL-C <70 mg/dl) and inflammation (hsCRP <2 mg/l) targets had very low event rates (51). Effectiveness of ezetimibe was particularly high in patients at higher risk, including the elderly, patients with type 2 diabetes, polyvascular disease, and prior stroke (52). Patients tolerated extremely low levels of LDL-C <30 μg/dl quite well. No adverse effects of ezetimibe were noted.

ENGAGE AF–TIMI 48. The goal of the ENGAGE AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation)-TIMI 48 trial, co-led by Robert P. Giugliano, Christian T. Ruff, and Elliott M. Antman, was to compare the efficacy and safety of edoxaban, an oral direct factor Xa inhibitor, with warfarin in 21,105 patients with atrial fibrillation (53). Compared with warfarin, both the higher-dose (60 mg daily) and lower-dose (30 mg) edoxaban regimens: 1) significantly reduced major bleeding (by 20% to 50%), intracranial hemorrhage (by 50% to 70%), and CV mortality (by ~10%); 2) were noninferior in preventing stroke and/or systemic embolic events; and 3) achieved superior net clinical outcomes. A reduction in intracranial hemorrhage and mortality with a non-vitamin K oral anticoagulant versus warfarin has now been consistently seen, whereas the effect on major bleeding depends on the particular drug (54). Non-vitamin K oral anticoagulants are now recommended over warfarin in most patients with atrial fibrillation (55).

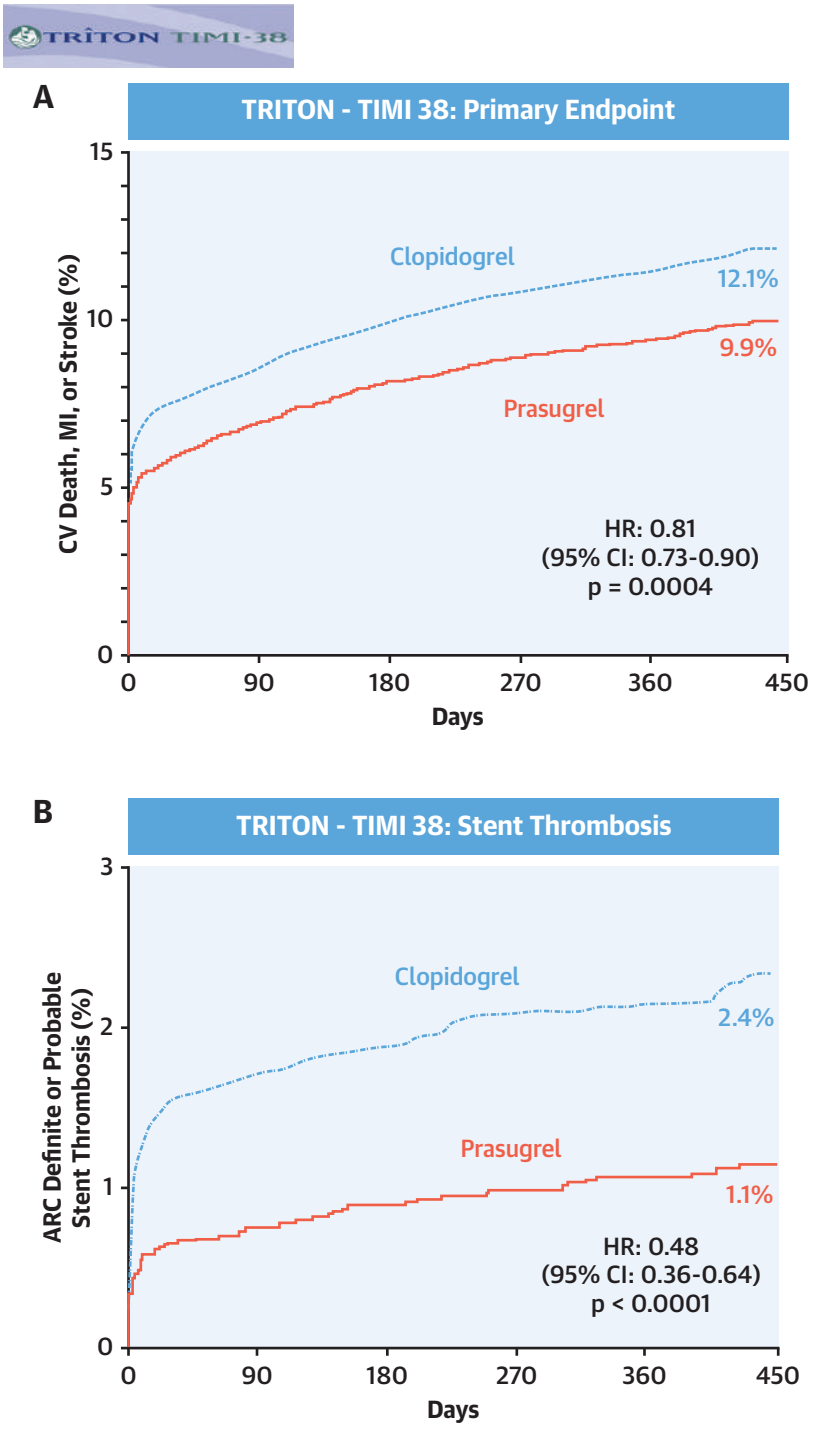
Particular strengths of this trial included extensive pharmacokinetic and pharmacodynamic data to support the clinical findings (56). One common theme across the secondary analyses is the preservation of efficacy with a reduction in bleeding with edoxaban compared with warfarin in higher risk patients, such as those who are elderly, frail, and have multiple comorbidities.

PEGASUS–TIMI 54. Trials of $P2Y_{12}$ inhibition in patients presenting with ACS have typically been approximately 1 year in length, largely for historical and logistical rather than for biological reasons. The goal of the PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin)-TIMI 54 study, led by one of the authors (M.S.S.), was to assess the clinical efficacy and safety of prolonged $P2Y_{12}$ inhibition with ticagrelor, comparing both the ACS dosage of 90 mg twice a day and a lower dosage of 60 mg twice a day versus placebo, in 21,162 patients with a prior MI 1 to 3 years earlier. Both doses significantly reduced the risk of CV death, MI, or stroke (**Figure 5**) (57). Although ticagrelor increased the risk of bleeding, neither fatal nor intracranial bleeding was increased.

Patients within 2 years of their MI or within 1 year after stopping previous $P2Y_{12}$ inhibition were at higher risk for ischemic events and had a more pronounced clinical benefit, including a reduction in all-cause mortality (58). A history of spontaneous bleeding requiring hospitalization and the presence of anemia were independent predictors of bleeding. In the 81% of patients without either of those risk factors, the absolute excess in bleeding with ticagrelor was one-third of what it was in patients with at least 1 of those risk factors, and ticagrelor reduced all-cause mortality (59). Long-term use of $P2Y_{12}$ inhibition post MI has been incorporated into both US and European practice guidelines (49,60).

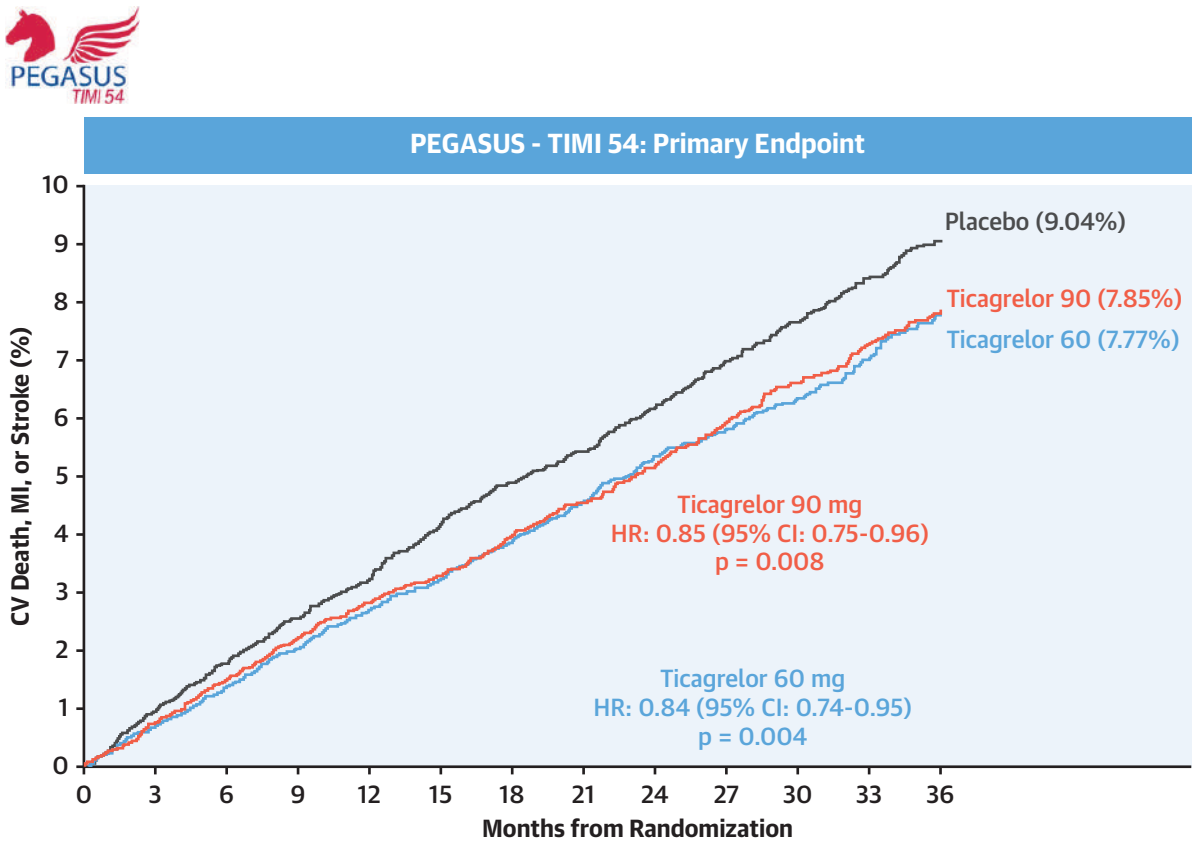
DECLARE–TIMI 58. The goal of DECLARE (Dapagliflozin Effect on Cardiovascular Events)-TIMI 58, led by Stephen D. Wiviott and, from the Hadassah Medical Organization, Itamar Raz, was to assess the clinical safety and efficacy of dapagliflozin, a member of the sodium-glucose co-transporter 2 (SGLT2) inhibitor class, in 17,160 patients who had or were at risk for arteriosclerotic cardiovascular disease (ASCVD). These drugs lower glycosylated hemoglobin by increasing urinary glucose excretion. Importantly, though, they also have multiple additional effects including decreasing body weight, blood pressure, interstitial fluid volume, and intraglomerular hydrostatic pressure, as well as raising the hematocrit (61,62). Dapagliflozin significantly reduced the risk of CV death or hospitalization for heart failure (HF) (**Figure 6**) (63). Although it did not decrease the risk of CV death, MI, or stroke overall, it did so in patients with prior MI, with the benefit driven by a reduction

FIGURE 4 Key Results of TRITON-TIMI 38



TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel)-TIMI 38 randomized 13,608 patients with ACS and planned percutaneous coronary intervention to 1 of 2 $P2Y_{12}$ platelet inhibitors, either prasugrel or clopidogrel. Cumulative incidence curves are shown by treatment arm for cardiovascular (CV) death, MI, or stroke **(A)** and stent thrombosis **(B)** (47,48). ARC = Academic Research Consortium; HR = hazard ratio; other abbreviations as in Figures 1 and 2.

FIGURE 5 Key Results of PEGASUS-TIMI 54

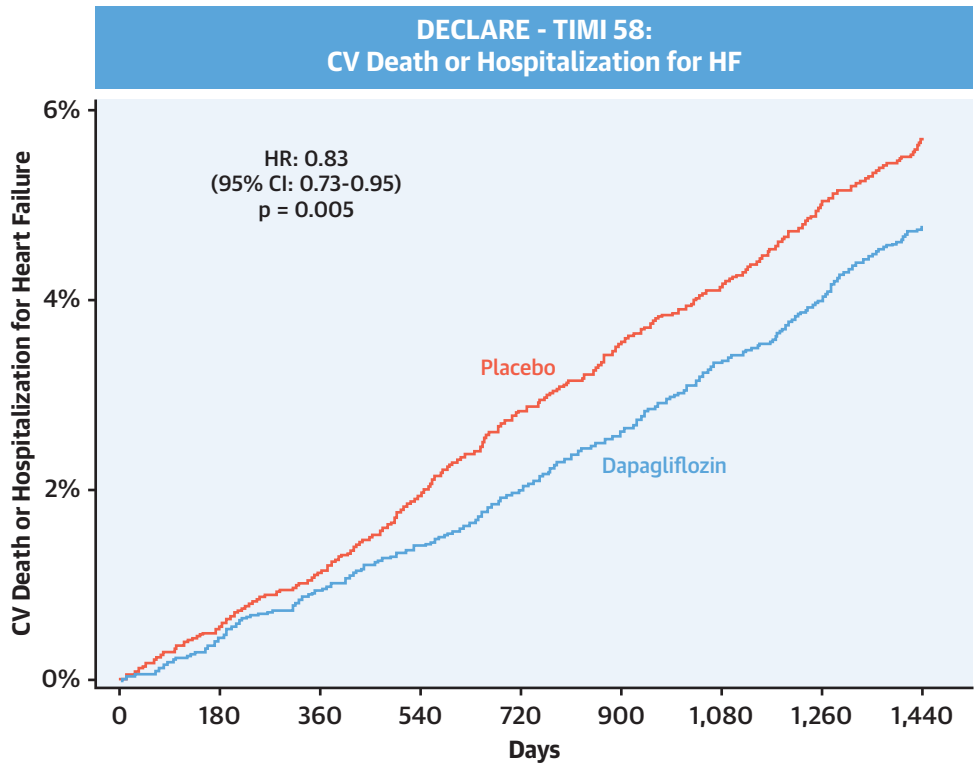


PEGASUS (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin)-TIMI 54 randomized 21,162 patients with an MI 1 to 3 years earlier to either the $P2Y_{12}$ platelet inhibitor ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, or placebo, all on a background of low-dose aspirin. Cumulative incidence curves for CV death, MI, or stroke by treatment arm (57). Abbreviations as in Figures 1, 2, and 4.

in recurrent MI (64). The reduction in CV death or hospitalization for HF was most pronounced in patients with a history of heart failure with reduced ejection fraction (HFrEF) (65), an observation later supported by the robust reduction in CV death or worsening HF seen in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure Trial), a dedicated trial of dapagliflozin in stable patients with HFrEF, with or without diabetes (66). We also observed a near halving in the risk of progression of kidney disease (67), a finding later supported by robust reductions in progression of kidney disease and all-cause mortality in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) study, a dedicated trial of dapagliflozin in patients with chronic kidney disease, with or without diabetes (68). These data and analogous data for other members of the SGLT2 inhibitor class have led to major changes in US and European diabetes practice guidelines, which now recognize CV risk reduction as the major guiding principle for treatment selection (69,70).

FOURIER-TIMI 59. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an important regulator of the LDL receptor, helping to chaperone it to its destruction in the lysosome rather than permitting it to be recirculated back to the surface of the hepatocyte (71). Evolocumab is a monoclonal antibody against PCSK9 that Giugliano et al. (72) showed reduces circulating levels of LDL-C by ~60%. The goal of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, led by one of the authors (M.S.S.), Robert P. Giugliano, and an international executive committee,

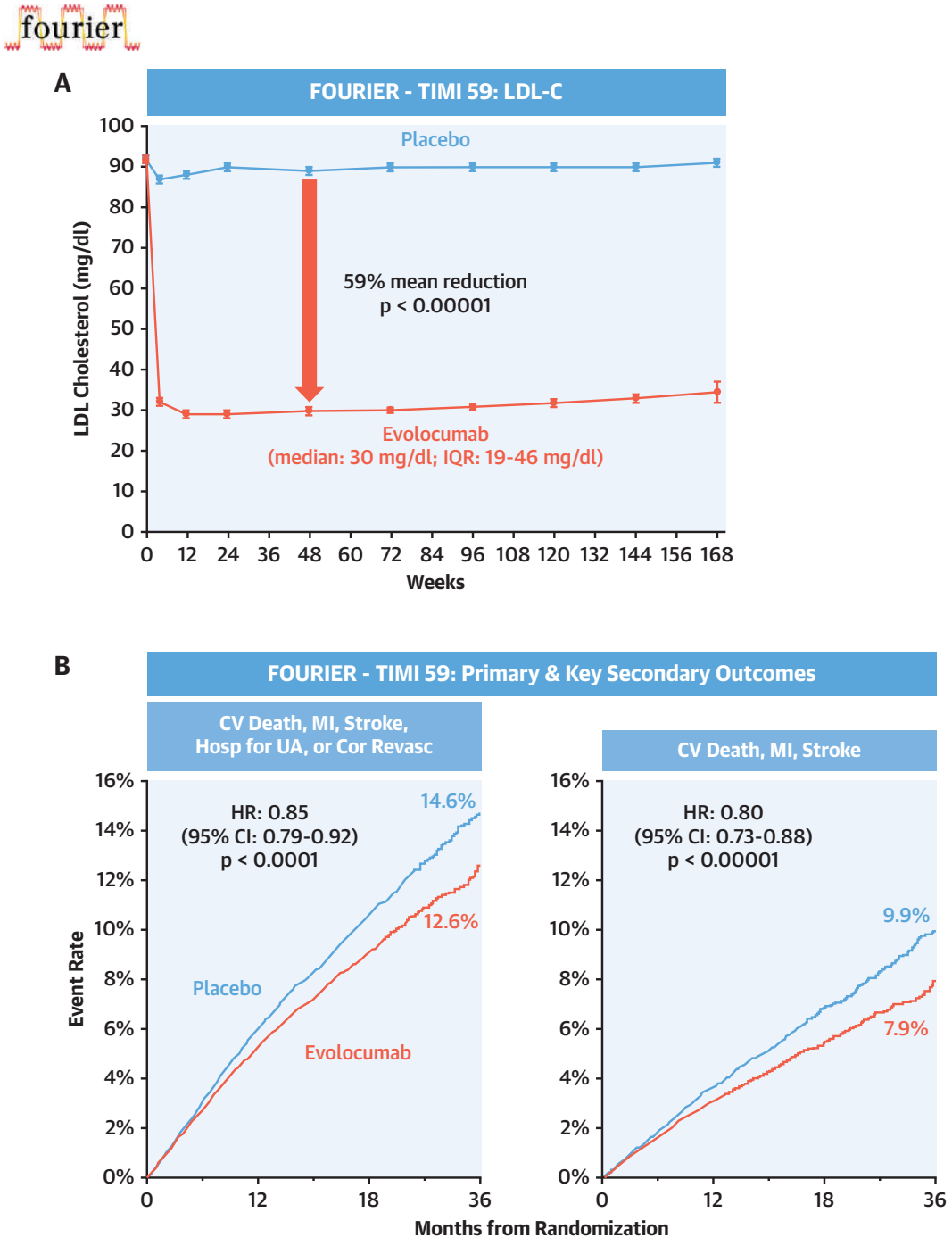
FIGURE 6 Key Results of DECLARE-TIMI 58



DECLARE (Dapagliflozin Effect on Cardiovascular Events)–TIMI 58 randomized 17,160 patients with type 2 diabetes mellitus and either established arteriosclerotic CV disease or multiple risk factors to either the sodium-glucose co-transporter 2 inhibitor dapagliflozin or placebo. Cumulative incidence curves for CV death or hospitalization for heart failure (HF) by treatment arm (63). Abbreviations as in **Figures 1, 2, and 4**.

was to assess the clinical efficacy and safety of adding evolocumab to statin therapy in 27,564 patients with a history of major ASCVD (prior MI, stroke, or peripheral arterial disease). The median achieved LDL-C in the evolocumab arm was 30 mg/dl, the lowest level recorded to date in a major CV outcomes trial (**Figure 7A**). After a relatively brief follow-up of only 2.2 years, FOURIER was the first trial to show that a PCSK9 inhibitor significantly reduced the risk of major vascular events with no major side effects (**Figure 7B**) (73,74). Of note, evolocumab was just as efficacious and safe in the >2,000 patients enrolled with a baseline LDL-C <70 mg/dl, indicating that treatment thresholds for the addition of nonstatin therapy of 70 mg/dl need to be lowered (75). Indeed, in analyses examining the association between achieved LDL-C at 4 weeks and subsequent CV risk, a monotonic, nearly linear relationship was observed, with risk continuing to be lower as LDL-C levels went below 15 mg/dl, with no inflection point (76). Reassuringly, there was no safety signal in patients who achieved extremely low levels of LDL-C. Data from FOURIER and subsequent PCSK9 inhibitor trials have led to a change in U.S. and European cholesterol management guidelines, which now include PCSK9 inhibition in the treatment algorithms and, in the European guidelines, now embrace lower LDL-C targets of <55 mg/dl in very high-risk patients and <40 mg/dl in patients with a second vascular event on optimized statin therapy (77,78).

FIGURE 7 Key Results of FOURIER-TIMI 59



FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)-TIMI 59 randomized 27,564 patients with prior MI, stroke, or peripheral arterial disease on optimized statin therapy to either evolocumab, a PCSCK9 inhibitor monoclonal antibody, or placebo. Achieved LDL-C **(A)** and cumulative incidence curves for the primary composite endpoint of CV death, MI, stroke, hospitalization (Hosp) for unstable angina (UA), or coronary revascularization (Cor Revasc) and for the key secondary composite endpoint of CV death, MI, or stroke **(B)** are shown by treatment arm (73). IQR = interquartile range; other abbreviations as in Figures 1, 2, 3, and 4.

PIONEER HF–TIMI 62. PIONEER HF (Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode)-TIMI 62, conducted as a collaboration between the TIMI Study Group and members of Duke Clinical Research Institute, was designed to test the efficacy and safety of angiotensin-neprilysin inhibition (sacubitril and valsartan) in 881 patients with HFrEF hospitalized for acute decompensated HF. The primary efficacy outcome was the reduction in the NT-proBNP, which was significantly greater in the angiotensin-neprilysin inhibitor group (79). The drug was well tolerated and was associated with a significant 44% reduction of early rehospitalization for HF.

COMBINED TRIAL ANALYSES. The combined TIMI trials have enrolled approximately 400,000 patients, and we are approaching 1,000,000 person-years of follow-up, providing a rich database for analyses (**Central Illustration**, panel A). All of our analyses are performed by our biostatistical team led by Sabina A. Murphy. We have compared and contrasted different TIMI trials examining similar interventions in similar patient populations, but tested in different eras with different background therapies (33,80). We have also combined data across multiple TIMI trials to provide insights that individual trials could not, such as detailed investigations of the nuances of specific CV outcomes and examinations of the associations of important clinical characteristics such as sex and diabetes on CV outcomes (81–83).

TRIAL EXECUTION. The successes of TIMI trials depend not only on the careful contemplation of the designs, but also on the meticulous execution of the protocols. TIMI trials are typically global in nature and we utilize a carefully curated database of >4,000 sites in >50 countries in order to match the right sites to the right trials. The work has been greatly facilitated by our large and experienced team of project managers under the leadership first of Carolyn H. McCabe and now M. Polly Fish. Our clinical events committee, chaired by Stephen D. Wiviott and directed by Cheryl Lowe, adjudicates the clinical events in our TIMI trials, providing confidence in the outcomes and supporting the regulatory approval of new drugs. The TIMI Safety Desk, first chaired by Marc P. Bonaca and now by Michelle L. O'Donoghue, facilitates the timely, accurate, and complete reporting of safety events and events of special interest throughout the course of TIMI trials. The TIMI Hotline, managed by Robert P. Giugliano, provides medical support for our trials 24 h/day and 7 days/week.

PERSONALIZED MEDICINE

An additional objective that spans all of our trials is helping to advance personalized medicine. The overall goals are 2-fold. The first is to predict more accurately a patient's risk of adverse CV outcomes. The second goal, which leverages our randomized controlled trials, is to identify patients who derive greater (or lesser) benefit from specific interventions. We have approached these goals in several complementary ways.

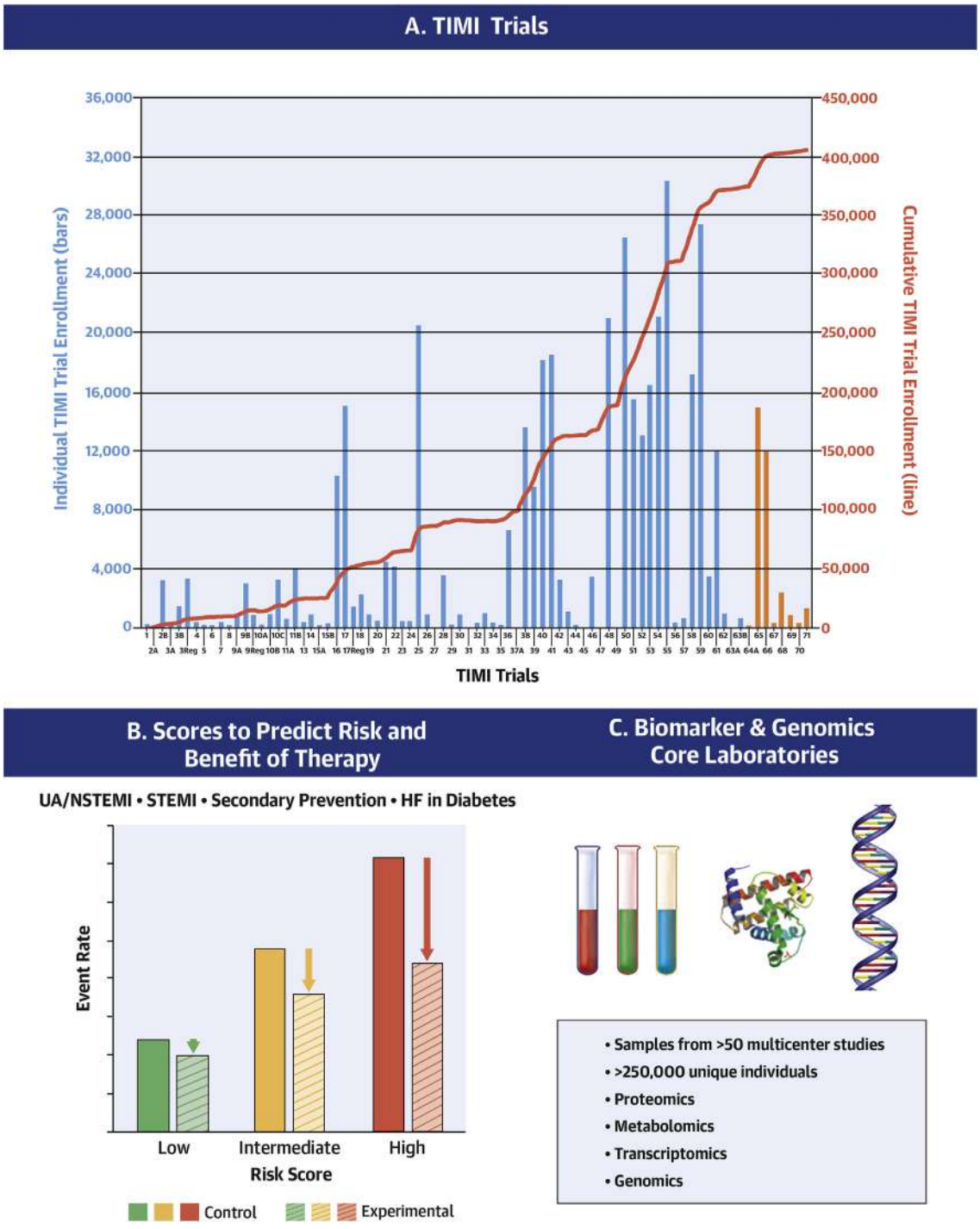
CLINICAL RISK SCORES. Our first efforts were with clinical risk scores (**Central Illustration**, panel B). The TIMI Risk Score for UA/NSTEMI was developed by Elliott M. Antman using data from TIMI 11B and combines 7 readily ascertainable clinical factors into a simple point-score system (**Figure 8A,** Supplemental Tables 4 and 5) (84). The score has been validated to predict accurately the risk of death or recurrent ischemic events and to provide a basis for therapeutic decision making by identifying patients who have a greater benefit from more aggressive antithrombotic therapy and an invasive strategy (**Figure 8B**) (32,84), and thus has been incorporated into practice guidelines (36).

The TIMI Risk Score for Secondary Prevention (TRA2°P) was developed by Erin A. Bohula and David A. Morrow using data from the TRA2°P (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis)-TIMI 50 (85). Using 10 clinical variables, this score has been validated to predict the risk of major adverse CV events in patients with atherosclerotic CV disease (**Figure 9A,** Supplemental Table 6). Likewise, it also helps identify patients who derive greater clinical benefit from a variety of secondary prevention therapies, including antithrombotic and LDL-C lowering therapies (**Figure 9B**), and has been incorporated into practice guidelines (77,86).

Most recently, David D. Berg has developed the TIMI risk score for hospitalization for HF in diabetes (Supplemental Table 7) using data from the SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus)-TIMI 53 trial (87). Using 5 clinical variables, this score has been validated to predict accurately the risk of hospitalization for HF in patients with diabetes and to identify patients who, by virtue of their higher baseline risk, derive greater absolute reductions in the risk of hospitalization for HF with SGLT2 inhibitor therapy in DECLARE-TIMI 58.

BIOMARKERS. The TIMI Biomarker Core Laboratory, led by David A. Morrow for the past 2 decades, has

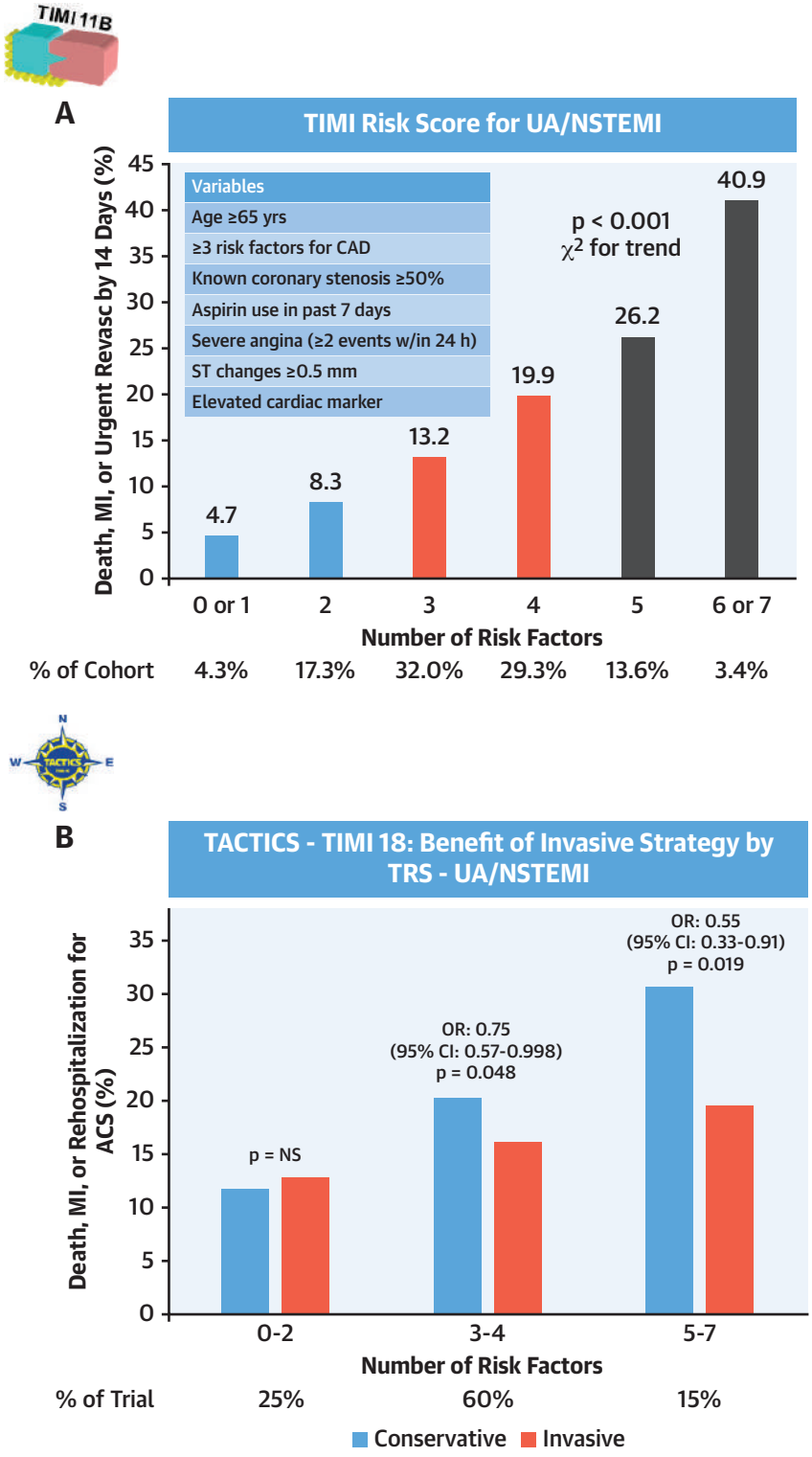
CENTRAL ILLUSTRATION **Key Aspects of the Thrombolysis In Myocardial Infarction Study Group**



Sabatine, M.S. and Braunwald, E. J Am Coll Cardiol. 2021;77(22):2822–45.

(A) Enrollment in TIMI (Thrombolysis In Myocardial Infarction) trials is shown with **bars** for individual trials (**blue** for completed, **orange** for ongoing) and **red line** indicating cumulative enrollment. **(B)** The concept of scores to predict risk (relative height of **solid bars** of different colors) and benefit of experimental therapy versus control (relative height of paired **solid** and **striped bars**) is depicted. **(C)** The number of samples and types of analyses done by the TIMI Biomarker and Genomics Core Laboratories are noted. HF = heart failure; NSTEMI = non-ST-segment myocardial infarction; UA = unstable angina.

FIGURE 8 TIMI Risk Score for UA/NSTEMI



Application of the TIMI Risk Score for UA/NSTEMI to predict the risk of death, MI, or need for urgent revascularization in TIMI 11B **(A)** and the benefit of an invasive versus conservative strategy in TACTICS–TIMI 18 at varying levels of risk **(B)** are shown (32,84). CAD = coronary artery disease; NS = not significant; OR = odds ratio; other abbreviations as in Figures 1, 2, and 7.

enabled the integration of protein biomarkers into personalized medicine (**Central Illustration**, panel C). The TIMI Biobank has blood samples and clinical data from >250,000 patients. Using these banked samples, we have demonstrated the prognostic value of what have now become well-accepted CV biomarkers. For example, an important substudy of TIMI 3 led by Elliott M. Antman demonstrated in 1996 that cardiac troponin measured in patients with NSTE-ACS was strongly predictive of mortality at 6 weeks (**Figure 10**) (88). David A. Morrow then showed that even so-called minor elevations of cardiac troponin, in patients with a clinical presentation suggestive of ACS, portend high clinical risk (34). Subsequently, we have demonstrated the prognostic value of even very low levels of elevated cardiac troponin in patients with stable ischemic heart disease using newer, high-sensitivity assays (89,90). As noted, we have also demonstrated the importance of achieving a low level of hsCRP and the prognostic value of natriuretic peptides (40,91).

Moreover, leveraging our randomized clinical trials, we have shown that levels of certain biomarkers can help identify patients who derive greater benefit from specific therapeutic interventions. As noted, in TACTICS-TIMI 18, the benefit of an early invasive strategy was confined to patients with an elevated cardiac troponin (34). In DECLARE-TIMI 58, the reduction in the risk of CV death or hospitalization for HF with dapagliflozin was confined to patients in the top half of NT-proBNP levels (92). In ENGAGE AF-TIMI 48, integration of biomarkers with a few clinical variables outperformed traditional clinical risk scores for stratification of stroke and bleeding (93).

We have used multimarker approaches to further refine risk prediction and identify subsets of patients who derive greater benefit from CV interventions. For example, in the OPUS (Orbofiban in Patients With Unstable Coronary Syndromes)-TIMI 16 and in TACTICS-TIMI 18 trials, we demonstrated the enhanced value of a multimarker approach to risk stratification that categorized patients based on the number of elevated CV biomarkers (cardiac troponin, BNP, and hsCRP) at presentation (**Figure 11**) (94). In the IMPROVE-IT study, we demonstrated that using 4 CV biomarkers (cardiac troponin, hsCRP, NT-proBNP, and growth differentiation factor 15) not only aided in prognosis, but also helped define a gradient of benefit from more intensive LDL-C lowering (95).

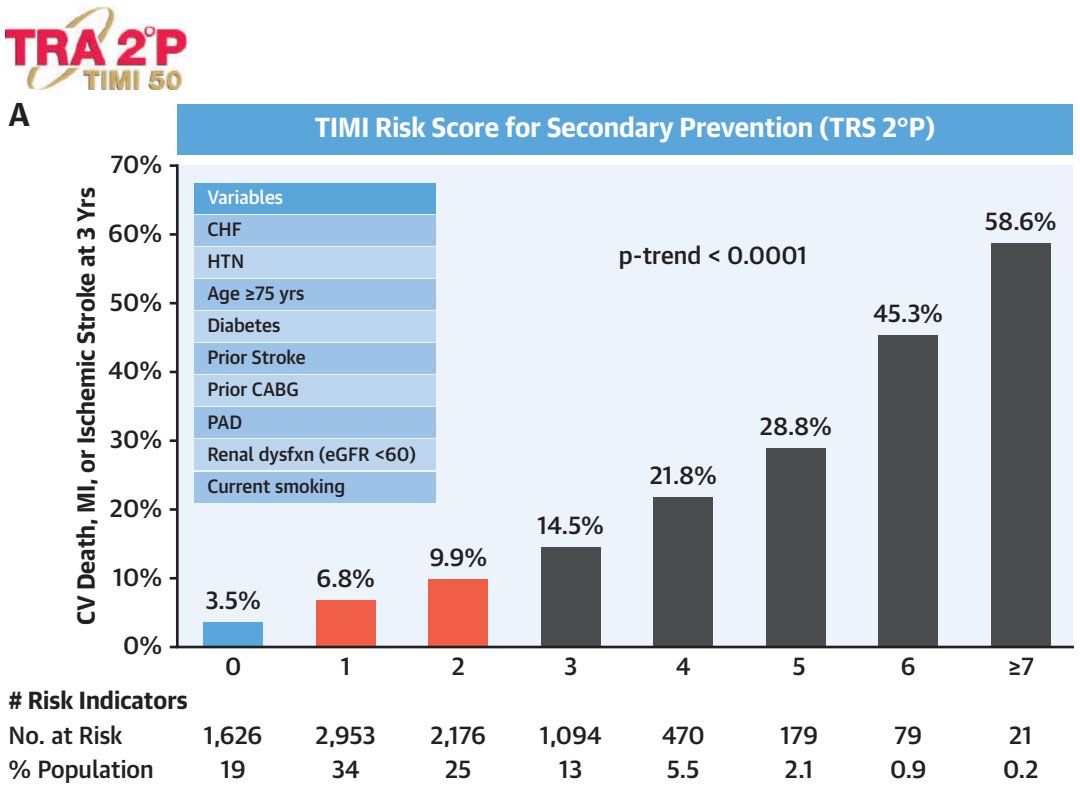
GENETICS. One of the authors (M.S.S.) founded the TIMI Genetics Core Laboratory when he joined TIMI as a research fellow. Subsequently, the laboratory was led by Jessica L. Mega and now by Christian T. Ruff. Over the years, we have gathered deoxyribonucleic acid in >200,000 patients from TIMI trials (**Central Illustration**, panel C). Our first major foray into pharmacogenetics was investigating known loss-of-function variants in the gene encoding cytochrome P450 2C19, an enzyme that plays a critical role in the biotransformation of clopidogrel into its active metabolite. Among individuals treated with clopidogrel in the TRITON-TIMI 38 trial, those who harbored such variants had, when compared with wild-type individuals, lower levels of the active metabolite of clopidogrel, less platelet inhibition, and higher rates of major adverse CV events, particularly stent thrombosis (**Figure 12**) (96). We have also demonstrated that variants in *CYP2C9* and *VKORC1*, which affect the pharmacokinetics and pharmacodynamics of warfarin, not only help define patients at risk for bleeding with warfarin, but, using the ENGAGE AF-TIMI 48 trial, identify the magnitude of bleeding risk reduction with the direct oral anticoagulant edoxaban versus warfarin (97). Lastly, we have shown that polygenic risk scores for coronary disease can not only add to risk prediction beyond clinical risk factors, but define the clinical benefit derived from LDL-C lowering therapy with statins and with PCSK9 inhibitors using data from the PROVE IT-TIMI 22 and FOURIER trials (98,99).

MAJOR TIMI LESSONS

Although we have gained many insights from all of our TIMI trials, here are what we would consider to be perhaps the 10 most important (not in ranked order) lessons learned.

1. Prompt reperfusion and achieving optimal epicardial and myocardial reperfusion in STEMI is associated with better outcomes (16,17,22).
2. An early invasive as compared with a conservative strategy reduces the risk of death or ischemic complications in NSTE-ACS, particularly for high-risk patients with an elevated cardiac troponin (32,34).
3. More potent $P2Y_{12}$ inhibition in ACS reduces the risk of ischemic events and stent thrombosis, with a modest increase in bleeding (47).
4. More intensive long-term antithrombotic therapy, either $P2Y_{12}$ or factor Xa inhibition, after an MI reduces the risk of ischemic events, with a modest increase in bleeding (57,100).
5. More intensive LDL-C lowering with high-intensity statin, ezetimibe, and a PCSK9 inhibitor each reduce the risk of major vascular events in patients with ASCVD (37,50,73).

FIGURE 9 TIMI Risk Score for Secondary Prevention



Application of the TIMI risk score for secondary prevention (TRS 2°P) to predict the risk of CV death, MI, or stroke in TRA2°P (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis)-TIMI 50 **(A)** and the benefit of ezetimibe versus placebo in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)-TIMI 40 at varying levels of risk **(B)** are shown (85,86). ARR = absolute risk reduction; CABG = coronary artery bypass graft; CHF = chronic heart failure; dysfxn = dysfunction; eGFR = estimated glomerular filtration rate; EZE = ezetimibe; HTN = hypertension; intermed = intermediate; KM = Kaplan-Meier event rate; PAD = peripheral artery disease; other abbreviations as in Figures 1, 2, and 4.

Continued on the next page

6. SGLT2 inhibition reduces the risk of HF and progression of renal disease (63).
7. Factor Xa inhibition is as effective and much safer than vitamin K antagonism in atrial fibrillation (53,54).
8. Clinical risk scores for NSTE-ACS, STEMI, stable ASCVD, and HF help refine prognosis and identify patients who are more likely to benefit from specific interventions (84,85,87,101).
9. Circulating biomarkers, most notably cardiac troponin, C-reactive protein, and the natriuretic peptides, as well as multimarker scores, are powerful predictors of CV risk and identify patients who are more likely to benefit from specific interventions (34,40,88,91,94,95).
10. Genetic variants identify patients who are at higher risk for CV events and exhibit greater response to therapeutic interventions (96-99).

FUTURE DIRECTIONS

ONGOING TIMI TRIALS. The TIMI Study Group continues to have a deep interest across a broad range of therapeutic domains. In terms of lipid-lowering therapy, we have 2 large CV trials ongoing. The first is the ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Cardiovascular Disease)/Heart Protection Study-4/TIMI 65 study (NCT03705234), which is being carried out in conjunction with the Oxford Clinical Trials Unit and is studying inclisiran, a small interfering

FIGURE 9 Continued

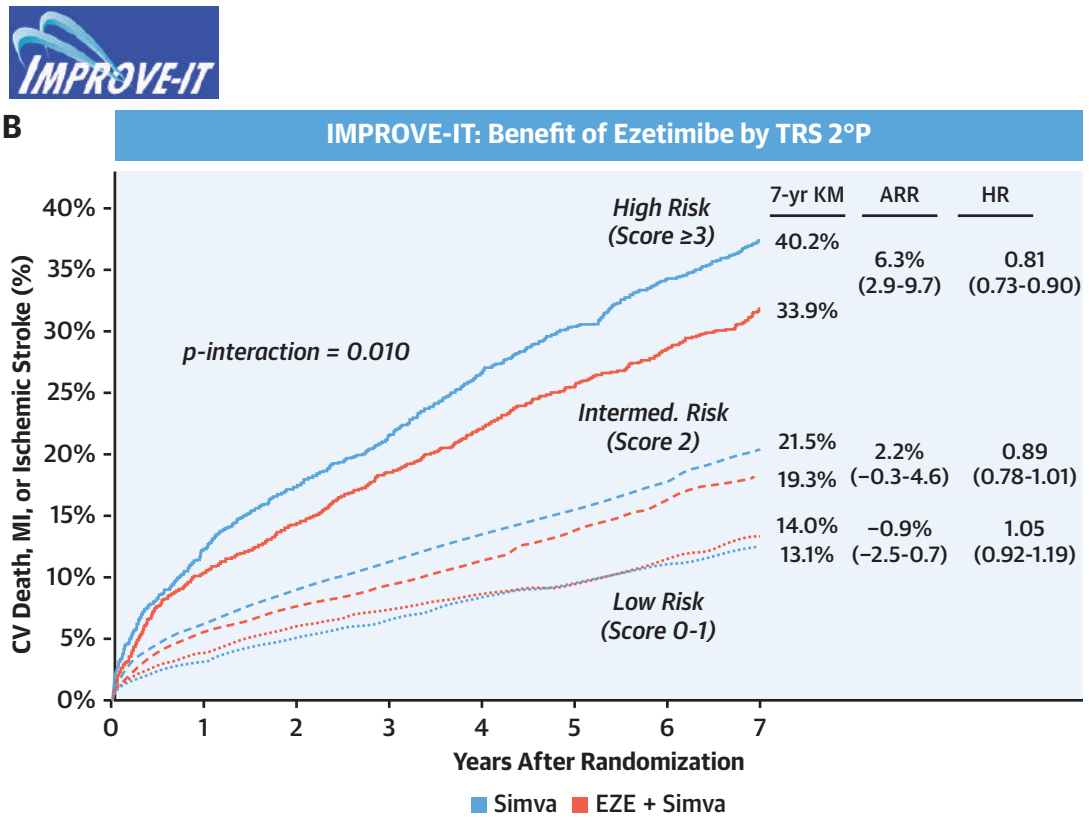
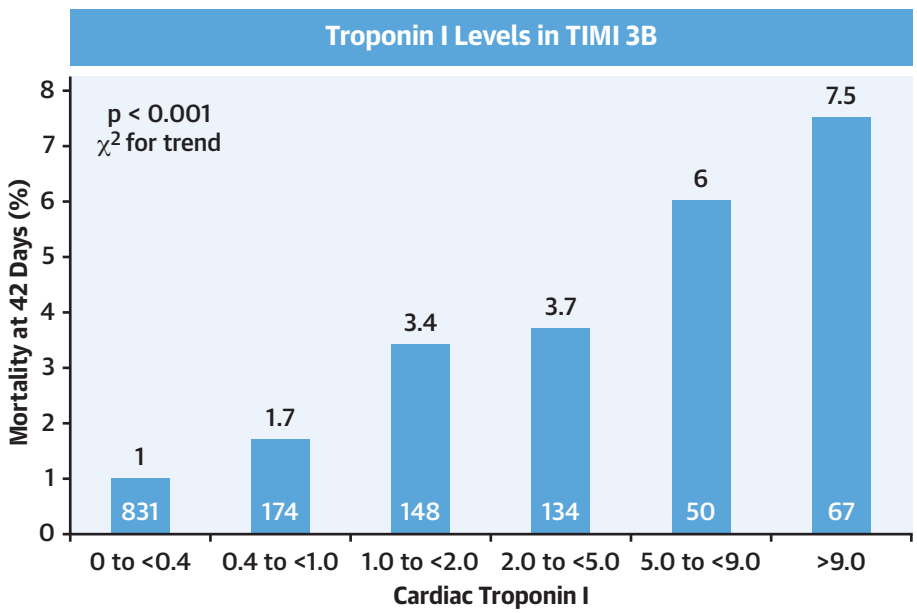
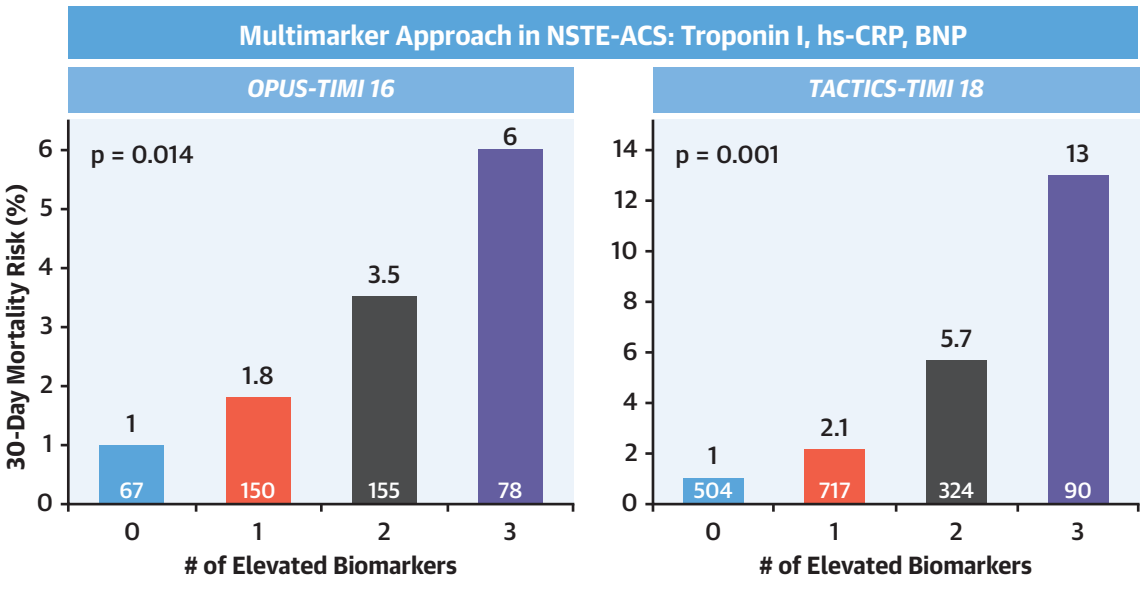


FIGURE 10 Prognostic Utility of Cardiac Troponin



Ability of cardiac troponin I to predict mortality in 1,404 patients with non-ST-segment ACS from TIMI 3B (88). Abbreviations as in Figures 1 and 2.

FIGURE 11 Prognostic Utility of Combining Multiple Biomarkers



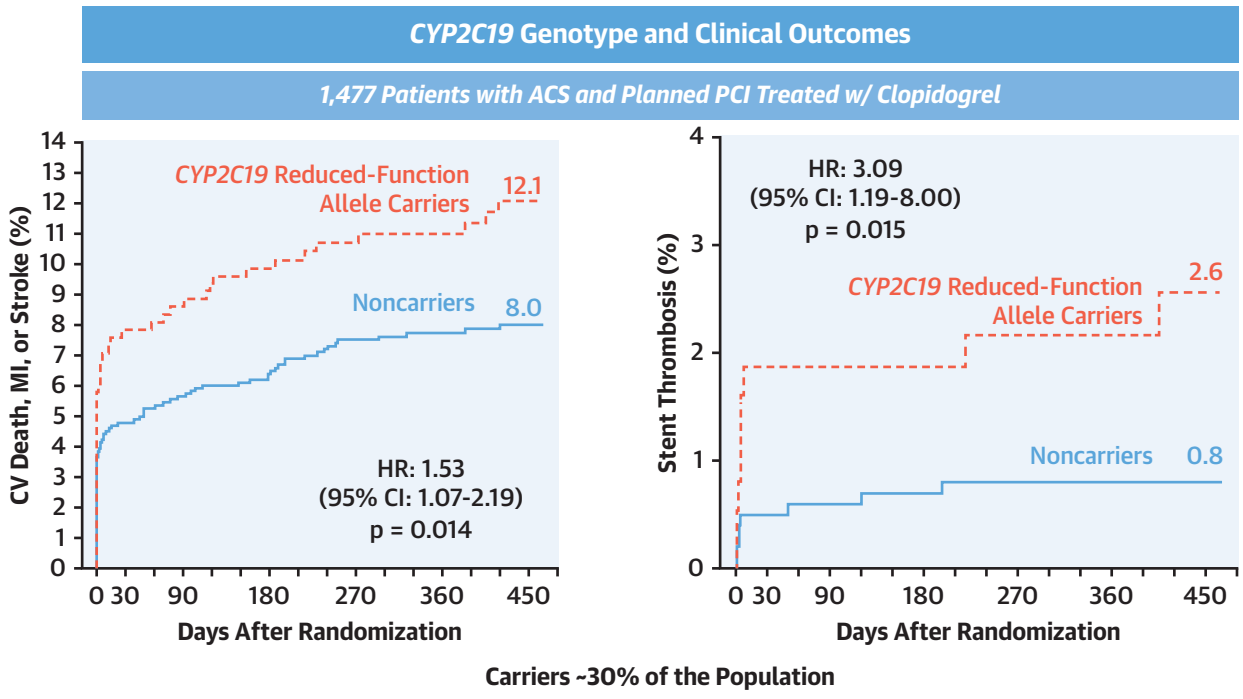
Ability of a multimarker strategy to predict mortality by categorizing patients with non–ST-segment acute coronary syndrome (NSTE-ACS) on the basis of the number of elevated cardiac biomarkers (troponin, high-sensitivity C-reactive protein [hsCRP], and B-type natriuretic peptide [BNP]) in OPUS (Orbofiban in Patients With Unstable Coronary Syndromes)–TIMI 16 (derivation) and TACTICS–TIMI 18 (validation) (94). Abbreviations as in Figures 1 and 2.

ribonucleic acid targeting PCSK9 that, with only 2 injections a year, lowers LDL-C by ~50% (102). The ORION-4 study aims to enroll approximately 15,000 patients with a history of major ASCVD (prior MI, prior stroke, or peripheral arterial disease). Patients are being randomized to inclisiran or placebo on a background of lipid-lowering therapy as tolerated, and the primary endpoint is the composite of coronary heart death, MI, stroke, or urgent coronary revascularization.

The second trial in this area, VESALIUS-CV (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke)-TIMI 66 (NCT03872401), aims to enroll approximately 12,000 patients with atherosclerosis or diabetes mellitus, but without a prior MI or stroke. Patients are being randomized to evolocumab or placebo on a background of optimized lipid-lowering therapy, and the dual primary endpoints are the composite of coronary heart death, MI, or stroke and that composite plus ischemia-driven coronary revascularization. Whereas in the FOURIER trial, we demonstrated that evolocumab reduced the risk of MI or stroke in patients with a history of MI or stroke (73), our goal in VESALIUS-CV is to demonstrate that evolocumab can reduce the risk of patients experiencing their first MI or stroke. For both of these lipid-reducing trials, the targeted median follow-up is 4 to 5 years to ensure that the full benefit of LDL-C lowering on CV risk is realized.

We are also looking at additional lipid targets beyond LDL-C. Lipoprotein(a) [Lp(a)] is a cholesterol-rich circulating lipoprotein that has an apolipoprotein B-100 that is covalently bound to apolipoprotein(a), a protein with homology to plasminogen. Epidemiological, genetic association, and Mendelian randomization studies have underscored a strong association between Lp(a) levels and risk of CV disease (103,104). No drugs are now approved for lowering levels of Lp(a). In OCEAN(a)-DOSE (Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction-DOSE)-TIMI 67 (NCT04270760), we are conducting a dose-ranging study of olpasiran, a silencing ribonucleic acid targeting Lp(a), in approximately 240 patients with atherosclerotic disease and an Lp(a) >150 nmol/l. Triglyceride-rich lipoproteins such as very low-density lipoproteins remain another important risk factor for atherosclerosis that is relatively neglected. ANGPTL3 is a secretory protein that inhibits lipoprotein lipase, a key metabolizer of very low-density lipoproteins. Individuals with loss-of-function variants in *ANGPTL3* have a lower risk of coronary disease (105). In TRANSLATE (Targeting ANGPTL3 with an Antisense Oligonucleotide in Adults with Dyslipidemia)-TIMI 70 (NCT04516291),

FIGURE 12 Impact of *CYP2C19* Genotype on Clinical Outcomes in Patients Treated with Clopidogrel



In 1,477 ACS patients treated with clopidogrel in TRITON–TIMI 38, carriers of a reduced-function allele in *CYP2C19* had higher rates of CV death, MI, or stroke and of stent thrombosis compared with wild-type patients (96). CYP2C19 = cytochrome P450 2C19; other abbreviations as in Figures 1, 2, and 4.

we are conducting a dose-ranging study of vupanorsen, an antisense oligonucleotide targeting ANGPTL3 in approximately 260 patients with non-high-density cholesterol ≥100 mg/dl and triglycerides 150 to 500 mg/dl.

We also continue to explore novel anticoagulants. Factor XI (FXI) is part of the intrinsic (contact-activation) pathway. Data suggest that FXI-mediated amplification of thrombin generation may be dispensable for physiologic hemostasis. Thus, FXI inhibitors may represent a new class of anticoagulants that may prevent pathologic thrombosis without precluding physiologic hemostasis. In AZALEA (A Multicenter, Randomized, Active-Controlled Study to Evaluate the Safety and Tolerability of Two Blinded Doses of Abelacimab Compared with Open-Label Rivaroxaban in Patients with Atrial Fibrillation)-TIMI 71, we are conducting a dose-ranging study of abelacimab, a monoclonal antibody against FXI/FXIa in approximately 1,200 patients with atrial fibrillation.

Combining our interests in diabetes mellitus and HF, in DAPA ACT HF (Dapagliflozin and Effect on Cardiovascular Events in Acute Heart Failure)-TIMI 68 (NCT04363697), we are randomizing approximately 2,400 patients with HFrEF during their hospitalization with acute decompensated HF to dapagliflozin or placebo. Patients will be followed for 2 months and the primary endpoint is CV death or worsening HF. DAPA ACT HF-TIMI 68 builds on DAPA-HF, which studied patients with HFrEF who had been stable for at least 4 weeks.

The Critical Care Cardiology Trials Network is a collaborative research network under the leadership of David A. Morrow that is drawn from national leaders in critical care cardiology and coordinated by the TIMI Study Group. Its mission is to design and execute observational studies and clinical trials that will advance the care of patients who require cardiac critical care (106). To date >15,000 patients have entered the registry.

OMICS. Moving beyond measuring and combining just several biomarkers, we are now using highly multiplexed assays to measure hundreds and soon thousands of biomarkers in a single sample (107). Furthermore, in conjunction with colleagues at the Broad Institute, we have used discovery proteomics to identify novel biomarkers (108). Likewise, for genetics, we are now doing whole exome sequencing on our deoxyribonucleic acid samples to enable us to

interrogate the genome beyond what genome-wide association studies can provide.

EDUCATION. Another key part of the mission of the TIMI Study Group is to train the next generation of clinical investigators and clinical trialists. TIMI research fellows have usually already completed their general cardiology training, typically spend 2 years at TIMI learning about clinical research, and take courses in biostatistics at the Harvard School of Public Health, which is close by. They also learn how to design and execute clinical trials and how to present and publish results. TIMI has trained approximately 50 fellows, many of whom have gone on to hold important academic positions in cardiology divisions around the world.

ACKNOWLEDGMENTS The authors thank the hundreds of thousands of patients around the world who have participated in TIMI trials. They also thank all former and current TIMI investigators, fellows, biostatisticians, and operational and administrative staff for their hard work and dedication, noting in particular the long-term contributions of our most senior current and former investigators, including Drs. Elliott M. Antman, Christopher P. Cannon, C. Michael Gibson, Robert P. Giugliano, David A. Morrow, and Stephen D. Wiviott; our Director of Biostatistics Ms. Sabina A. Murphy; and our former Director of Operations Ms. Carolyn McCabe and current Director of Operations Ms. M. Polly Fish.

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ADDRESS FOR CORRESPONDENCE: Dr. Marc Sabatine, TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, Massachusetts 02115, USA. E-mail: msabatine@bwh.harvard.edu. Twitter: @TIMIStudyGroup.

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APPENDIX For supplemental text and tables, please see the online version of this paper.