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ORIGINAL INVESTIGATIONS

Atherothrombotic Risk Stratification and Ezetimibe for Secondary Prevention

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ABSTRACT

BACKGROUND Ezetimibe improves cardiovascular (CV) outcomes in patients stabilized after acute coronary syndrome (ACS) when added to statin therapy. After ACS, patients vary considerably in their risk for recurrent CV events.

OBJECTIVES This study tested the hypothesis that atherothrombotic risk stratification may be useful to identify post-ACS patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy.

METHODS The TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2°P) is a simple 9-point risk stratification tool, previously developed in a large population with atherothrombosis to predict CV death, myocardial infarction (MI), and ischemic stroke (CV death/MI/ischemic cerebrovascular accident [iCVA]). The current study applied this tool prospectively to 17,717 post-ACS patients randomized either to ezetimibe and simvastatin or to placebo and simvastatin in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Treatment efficacy was assessed by baseline risk for CV death/MI/iCVA, the IMPROVE-IT composite endpoints (CE), and individual component endpoints at 7 years.

RESULTS All 9 clinical variables in the TRS 2°P were independent risk indicators for CV death/MI/iCVA ($p < 0.001$). The integer-based scheme showed a strong graded relationship with the rate of CV death/MI/iCVA, the trial CE, and the individual components (p trend <0.0001 for each). High-risk patients (n = 4,393; 25%), defined by ≥3 risk indicators, had a 6.3% (95% confidence interval: 2.9% to 9.7%) absolute risk reduction in CV death/MI/iCVA at 7 years with ezetimibe/simvastatin, thus translating to a number-needed-to-treat of 16. Intermediate-risk patients (2 risk indicators; n = 5,292; 30%) had a 2.2% (95% confidence interval: −0.3% to 4.6%) absolute risk reduction. Low-risk patients (0 to 1 risk indicators; n = 8,032; 45%) did not appear to derive benefit from the addition of ezetimibe (p interaction = 0.010). Similar findings were observed for the IMPROVE-IT primary CE.

CONCLUSIONS Atherothrombotic risk stratification using the TRS 2°P identifies high-risk patients who derive greatest benefit from the addition of ezetimibe to statin therapy for secondary prevention after ACS. (Improved Reduction of Outcomes: Vytorin Efficacy International Trial [IMPROVE-IT]; NCT00202878) (J Am Coll Cardiol 2017;69:911–21) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

2°P = secondary prevention

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CV = cardiovascular

IHD = ischemic heart disease

MI = myocardial infarction

TRS 2°P = Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention

The addition of ezetimibe to simvastatin significantly reduced recurrent cardiovascular (CV) events in patients whose conditions were stabilized after acute coronary syndrome (ACS) in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (1). Patients with established coronary artery disease have a range of residual risk for recurrent CV events following ACS and may also have a differential response to intensive secondary preventive therapy (2,3).

Risk stratification tools are well validated and guideline recommended for use in ACS to assist with short-term prognostication and short-term therapeutic decision making (e.g., early invasive strategy) (4–9). However, there are fewer tools available to assist with decisions on long-term response to treatment in patients in the stable phase of ischemic heart disease (IHD), such as patients whose conditions are stabilized after ACS or who have established IHD without known previous myocardial infarction (MI) (10,11).

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We recently developed a simple 9-point risk stratification tool to predict recurrent CV events in a large population of stable patients with previous MI from the TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events-Thrombolysis In Myocardial Infarction 50) trial (11–13). The TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2°P) incorporates the following readily available clinical characteristics: older age, diabetes, hypertension, smoking, peripheral artery disease, previous stroke, previous coronary artery bypass graft (CABG), history of heart failure, and renal dysfunction (**Central Illustration**). In addition to predicting long-term outcomes, the TRS 2°P identified high-risk patients who experienced the greatest absolute benefit from intensive secondary preventive therapy with vorapaxar, an antiplatelet agent that inhibits thrombin-mediated activation of platelets through the protease activated receptor (PAR)-1 (11).

In the present analysis, we tested the hypothesis that the TRS 2°P would effectively identify a post-ACS population of patients at higher risk for recurrent CV events who have the greatest potential for benefit from the addition of ezetimibe to statin therapy in the IMPROVE-IT trial.

METHODS

STUDY POPULATION AND PROCEDURES. IMPROVE-IT was a multinational, double-blind, placebo-controlled trial of 18,144 patients stabilized after ACS and randomized in a 1:1 ratio to treatment with either simvastatin (40 mg daily) in addition to placebo or simvastatin (40 mg daily) in addition to ezetimibe (10 mg daily) (1). Patients at least 50 years of age were eligible if they had been hospitalized within the preceding 10 days for ACS, including MI with or without ST-segment elevation or high-risk unstable angina. Patients receiving long-term prescription lipid-lowering therapy were required to have a low-density lipoprotein cholesterol (LDL-C) level of 50 to 100 mg/dl; otherwise, LDL-C levels were required to be 50 to 125 mg/dl. Exclusion criteria included baseline ezetimibe use in combination with a statin, creatinine clearance of <30 ml/min, statin therapy with a potency >40 mg simvastatin, hemodynamic instability, or revascularization by CABG for the index event. The

Diagnostics; and has received institutional grant support from Abbott Laboratories, Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Merck, Novartis, and Roche Diagnostics. Dr. Giugliano has received institutional grant support from Merck during the conduct of the study; has received institutional grant support from Amgen; and has received honoraria for consulting and continuing medical education from Amgen, Merck, Daiichi-Sankyo, Pfizer, CVS Caremark, Regeneron, and Sanofi. Dr. Blazing has received institutional grant support from Merck during the conduct of the study; and has received consulting fees from Merck, Sanofi, Amgen, Novartis, AstraZeneca, and Pfizer. Ms. Murphy has received modest consulting fees from Merck. Dr. Pedersen has received grant support from Amgen; has received consulting fees from Merck; is on the speakers bureau of Amgen, Merck, and Sanofi; and has received consulting fees from Merck, Sanofi, AstraZeneca, and Boehringer Ingelheim. Dr. Brady has received research fees from Merck; and has received consulting fees from Bayer, AstraZeneca, Servier, and Merck. Dr. Mitchel is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., and is able to hold stock or stock options in the company. Dr. Cannon has received grant support from Amgen, Arisaph, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Janssen, Merck, and Takeda; and has received consulting fees from Alnylam, Amgen, Arisaph, AstraZeneca, Boehringer Ingelheim, Boehringer Ingelheim/Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Kowa, Merck, Takeda, Lipimedix, Pfizer, Regeneron, and Sanofi. Dr. Braunwald has received institutional grant support from Merck during the conduct of the study; has received consulting fees from Daiichi-Sankyo, Sanofi, The Medicines Company, Menarini International, Bayer, Merck, and Theravance; and has received lecture fees from Medscape. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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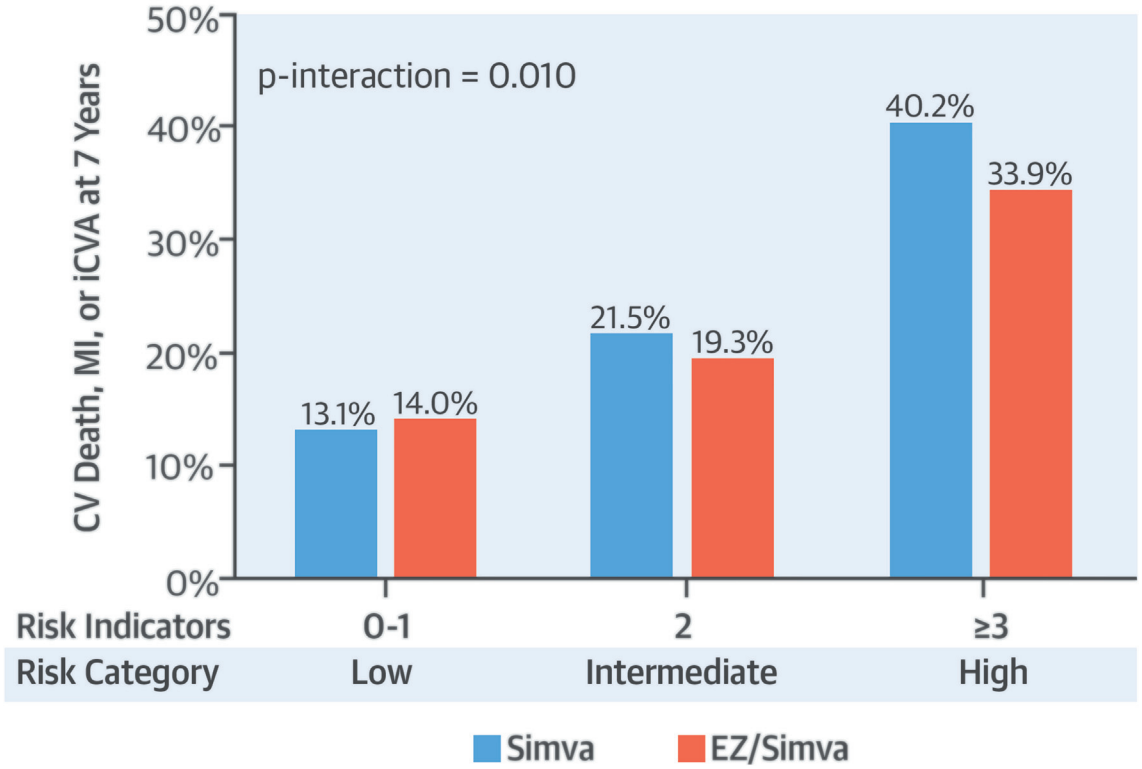
CENTRAL ILLUSTRATION **TRS 2°P**

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	**9**



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In patients stabilized after acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the TRS 2°P, a simple risk stratification tool using 9 readily available clinical characteristics, identified a strong gradient of risk for cardiovascular death, MI, or ischemic stroke and an increasingly favorable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile. CABG = coronary artery bypass graft; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; EZ = ezetimibe; HTN = hypertension; iCVA = ischemic cerebrovascular accident; MI = myocardial infarction; PAD = peripheral artery disease; Simva = simvastatin; TRS 2°P = TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention.

analyzed population included patients with complete baseline data for all 9 risk indicators (n = 17,717; 98%). The ethics committee at each participating center approved the protocol. Written informed consent was obtained from all patients.

ENDPOINTS. The efficacy endpoint of primary interest for atherothrombotic risk stratification was a composite of CV death, MI, or ischemic stroke (11). The IMPROVE-IT pre-specified primary efficacy endpoint was a composite of CV death, a major coronary event (nonfatal MI, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke. The 3 pre-specified secondary efficacy endpoints for IMPROVE-IT were as follows: a composite of all-cause death, a major coronary event, or nonfatal stroke; a composite of coronary heart disease-induced death, nonfatal MI, or urgent coronary revascularization 30 days or more after randomization; and a composite of CV death, nonfatal MI, hospitalization for unstable angina, all revascularization procedures 30 days or more after randomization, or nonfatal stroke. All elements of these endpoints have been described previously and were adjudicated according to established definitions by a clinical events committee blinded to the treatment allocation (1).

STATISTICAL ANALYSIS. Each patient was assessed for the presence of any of the 9 previously described risk indicators at baseline: age ≥75 years, diabetes mellitus, hypertension, peripheral artery disease, previous stroke, previous CABG, history of heart failure, active smoking, and renal dysfunction (defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 using the Modification of Diet in Renal Disease equation) (11). All variables, with the exception of age and renal dysfunction, were determined on the basis of clinical history. As described, each atherothrombotic risk indicator was weighted evenly to define total risk for each patient as the arithmetic sum of risk indicators (11). Simple risk categories were defined to parallel the annualized risk of CV death, MI, or ischemic stroke observed in the derivation population from patients in TRA 2°P who were randomized to placebo, thus translating to a low-risk (<2%/year) category with 0 to 1 risk indicators, an intermediate-risk (2% to 5%/yr) category with 2 risk indicators, and a high-risk (>5%/year) category with ≥3 risk indicators.

The calibration of the model for prediction of CV death, MI, or ischemic stroke was assessed using the goodness-of-fit chi-square statistic with 5 degrees of freedom that compared annualized event rates in the placebo-treated population from TRA 2°P and the control (placebo and simvastatin) group from IMPROVE-IT (14). The discriminatory capacity of the risk indicators was assessed by the area under the receiver-operating characteristic curve (c-statistic) as a measure of model performance (15,16).

All efficacy analyses were performed by intention-to-treat using Cox proportional hazards modeling with randomized treatment (placebo and simvastatin vs. ezetimibe and simvastatin) and randomization stratification factors (participation in the EARLY-ACS [Early Glycoprotein IIb/IIIa Inhibition in Non-ST-segment Elevation Acute Coronary Syndrome] study, use of lipid-lowering therapy in the 4 weeks preceding the index ACS event, and type of ACS [non-ST-segment elevation ACS vs. ST-segment elevation MI]) as covariates. All presented event rates are 7-year Kaplan-Meier estimates except where otherwise specified. We assessed for a heterogeneous treatment effect of ezetimibe and simvastatin versus placebo and simvastatin by using Cox proportional hazards regression modeling including a treatment-by-risk category interaction term. Confidence intervals (CIs) for absolute risk reduction estimates were calculated. All reported p values are 2-sided; $p < 0.05$ was considered to signify nominal statistical significance with no adjustment for multiple comparisons. All analyses were conducted using Stata/IC version 13.1 (StataCorp, LLC, College Station, Texas) or SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

STUDY POPULATION. The baseline characteristics of the 17,717 patients with complete baseline clinical data are summarized in **Table 1**. The median age of patients was 63 years, and 24% of participants were women. The most prevalent of the 9 atherothrombotic risk indicators were hypertension, active smoking, diabetes, and renal dysfunction (**Table 1**). Baseline characteristics were well matched between the placebo and simvastatin treatment group (n = 8,869) and the ezetimibe and simvastatin treatment group (n = 8,848) ($p > 0.05$ for all variables in **Table 1**). The median follow-up was 6.0 years (quartiles: 4.3; 7.1 years).

APPLICATION OF THE TIMI RISK SCORE FOR SECONDARY PREVENTION. Each of the 9 clinical variables in the TRS 2°P were independent predictors of CV death, MI, or ischemic stroke in the control (placebo and simvastatin) treatment group ($p < 0.001$ for each) (Online Table 1). The mean number of risk indicators for each patient was 1.8 ± 1.2 in both treatment arms.

TABLE 1 Baseline Characteristics

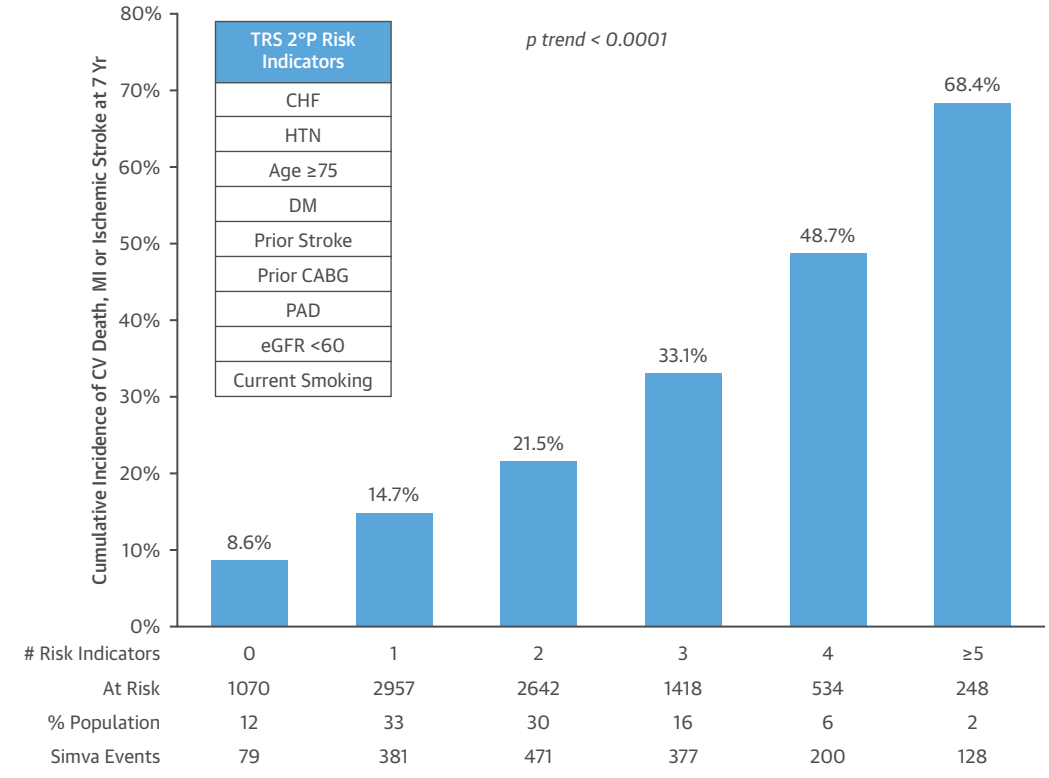
	Overall (n = 17,717)	Low (0-1) (n = 8,032; 45%)	Intermediate (2) (n = 5,292; 30%)	High (≥3) (n = 4,393; 25%)
Demographics				
Age, yrs	63 (57-71)	61 (55-67)	63 (57-71)	70 (62-78)
Age ≥75 yrs*	15.0	3.8	15.0	37.0
Female	24.0	19.0	25.0	33.0
Caucasian	84.0	86.0	83.0	82.0
BMI, kg/m^2	28 (25-31)	27 (25-30)	28 (25-31)	28 (25-32)
Coexisting conditions				
Diabetes*	27.0	5.2	33.0	60.0
Current smoking*	33.0	27.0	40.0	36.0
Hypertension*	61.0	31.0	81.0	93.0
Heart failure*	4.3	0.2	1.9	15.0
Peripheral artery disease*	5.5	0.5	3.0	18.0
Previous MI (before index ACS)	21.0	14.0†	21.0	34.0
Previous PCI (before index ACS)	20.0	14.0	21.0	29.0
Previous CABG (before index ACS)*	9.3	1.4	6.7	27.0
Previous stroke*	3.7	0.3	2.5	12.0
Before index ACS event				
Medications				
Lipid-lowering agent	35.0	24.0	37.0	55.0
Statin	34.0	23.0	36.0	53.0
Aspirin	42.0	29.0	46.0	62.0
At index ACS event				
Type of event				
MI with ST-segment elevation	29.0	36.0	28.0	17.0
MI without ST-segment elevation‡	47.0	47.0	47.0	48.0
Unstable angina	24.0	17.0	26.0	35.0
Pre-randomization PCI	70.0	76.0	69.0	61.0†
Total cholesterol, mg/dl	163 (144-181)	167 (150-184)	162 (143-180)	155 (137-174)
LDL-C, mg/dl	95 (79-110)	100 (85-113)	94 (78-109)	87 (73-101)
Non-HDL-C, mg/dl	120 (103-138)	124 (107-140)	120 (102-138)	113 (97-132)
At randomization				
Time from ACS to randomization	5.0 (3.0-8.0)	5.0 (3.0-7.0)	5.0 (3.0-8.0)	5.0 (3.0- 8.0)
Medications				
Aspirin	97.0	98.0	97.0	95.0
Thienopyridine	87.0	90.0	86.0	82.0†
Beta-blocker‡	87.0	87.0	88.0	86.0
ACEI/ARB	76.0	69.0	80.0	83.0
Laboratory findings				
hs-CRP, mg/l	9.6 (3.9-26.5)	9.1 (3.7-25.1)	9.9 (4.1-27.5)	10.3 (4.1-27.9)
eGFR, ml/min/1.73 m^2	74 (63-84)	78 (70-89)	74 (64-86)	60 (52-76)
eGFR <60 ml/min/1.73 m^2*	20.0	3.9	18.0	52.0

Values are median (interquartile range) or %. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. *Indicates TIMI (Thrombolysis In Myocardial Infarction) risk score for secondary prevention risk indicator variables. †Baseline characteristics were well matched ($p > 0.05$) by randomization in patients allocated to simvastatin and ezetimibe/simvastatin, with the exception of clinically minimal differences in previous MI (simvastatin 13% vs. ezetimibe/simvastatin 15%) in low-risk patients and pre-randomization PCI (simvastatin 31% vs. ezetimibe/simvastatin 28%), PCI for the index event (simvastatin 59% vs. ezetimibe/simvastatin 62%), and thienopyridine use (simvastatin 80% and ezetimibe/simvastatin 83%) in high-risk patients. ‡p for trend < 0.05 for all variables for comparison across risk groups, with the exception of the rate of MI without ST-segment elevation ($p = 0.20$) and beta-blocker use ($p = 0.20$).

ACS = acute coronary syndrome; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary artery bypass; eGFR = estimated glomerular filtration rate by the Modification of Diet in Renal Disease study equation; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention.

The TRS 2°P showed a strong graded relationship with the rate of CV death, MI, or ischemic stroke at 7 years in the control (placebo and simvastatin) group that ranged from 8.6% for patients with 0 risk indicators to 68.4% for patients with ≥5 risk indicators (p trend <0.0001) (**Figure 1**). A similar, significant pattern of increasing event rates with an increasing number of risk indicators was observed for the pre-specified primary (Online Figure 1) and secondary IMPROVE-IT endpoints, as well as for individual

FIGURE 1 Risk Stratification of CV Death, MI, or Ischemic Stroke in the Control Arm (Placebo/Simvastatin)



The 7-year Kaplan-Meier estimates are shown. The basis of the p value is the chi-square test for trend. CABG = coronary artery bypass graft; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; MI = myocardial infarction; PAD = peripheral artery disease; Simva = simvastatin; TRS 2°P = TIMI (Thrombolysis In Myocardial Infarction) Risk Score for Secondary Prevention.

component endpoints (Figures 2A to 2C) (p trend <0.0001 for each endpoint).

The chi-square value for goodness-of-fit was 4.5 (p = 0.48) for the comparison of annualized rates of CV death, MI, or ischemic stroke in placebo-treated patients from TRA 2°P and the control arm (placebo and simvastatin) from IMPROVE-IT, thereby indicating adequate calibration of the integer-based approach (Online Figure 2). The c-statistic for the 9-component multivariable model for CV death, MI, or ischemic stroke was 0.67 (95% CI: 0.65 to 0.68) in the patients randomized to placebo and simvastatin, consistent with the derivation data set (c-statistic: 0.67; 95% CI: 0.65 to 0.69) (11).

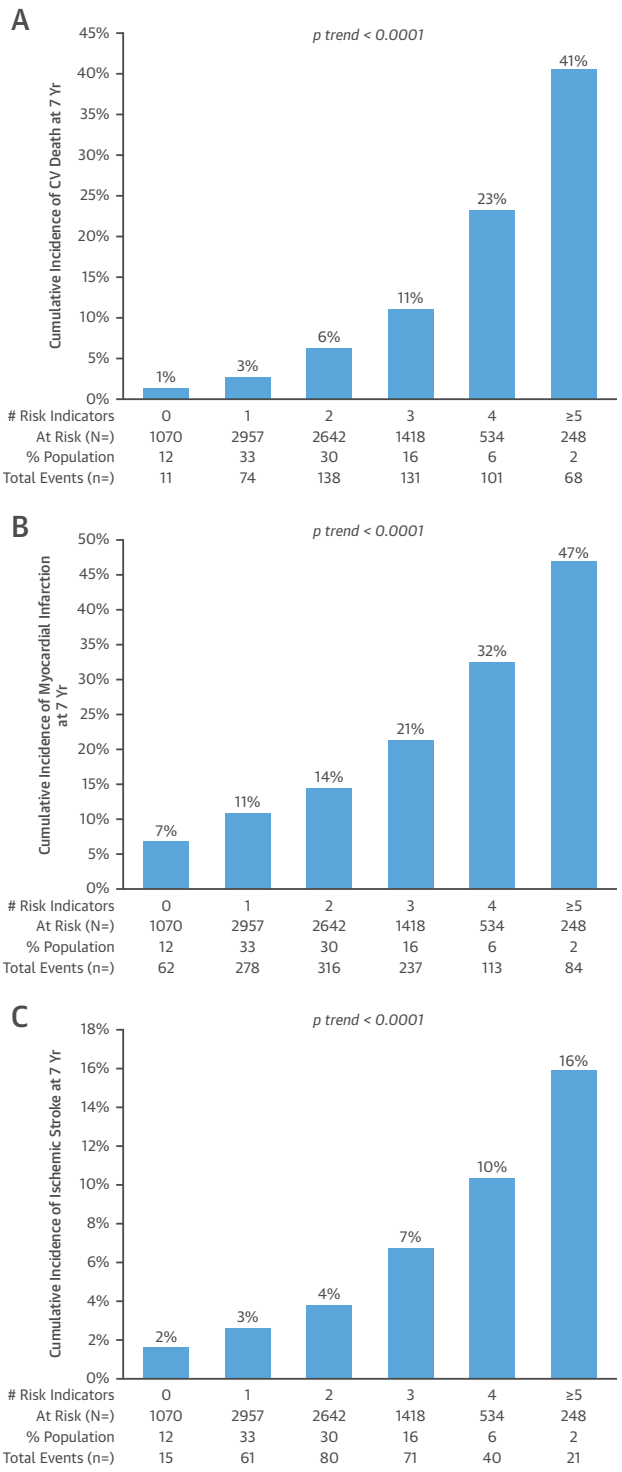
TREATMENT EFFECT OF EZETIMIBE ON RECURRENT CARDIOVASCULAR EVENTS BY ATHEROTHROMBOTIC RISK CATEGORY. Risk categories, defined as low (0 to 1 risk indicators), intermediate (2 indicators), and high (≥3 indicators), represented 45% (n = 8,032), 30% (n = 5,292), and 25% (n = 4,393) of the overall population, respectively (Table 1). The index ACS event was non-ST-segment elevation MI in 47% to 48% of patients in all risk categories, with higher rates of ST-segment elevation and lower rates of unstable angina in lower-risk patients. There was a higher rate of previous lipid-lowering therapy with increasing risk and correspondingly lower baseline LDL-C at the time of the index ACS event. Adherence to guideline-based therapies was high across all risk categories, with 95% to 98% of randomized patients receiving aspirin, 86% to 88% receiving a beta-blocker, and 82% to 90% a thienopyridine at the time of randomization, which was a median of 5.0 days after the index ACS event in all risk categories. Baseline characteristics were well matched (p > 0.05) by randomization in patients allocated to placebo in addition to simvastatin and ezetimibe in addition to simvastatin, with the exception of clinically minimal differences in previous MI (placebo and simvastatin 13% vs. ezetimibe and

simvastatin 15%) in low-risk patients and pre-randomization percutaneous coronary intervention (31% vs. 28%), percutaneous coronary intervention for the index event (59% vs. 62%), and thienopyridine use (80% vs. 83%) in high-risk patients.

The relative and absolute risk reductions in CV death, MI, or ischemic stroke increased significantly across risk categories with the addition of ezetimibe to simvastatin therapy (p interaction for relative risk reduction = 0.010) (**Figure 3A**, Online Table 2). Specifically, among patients in the high-risk group, the addition of ezetimibe to simvastatin demonstrated a significant 19% relative and 6.3% absolute risk reduction (7-year Kaplan-Meier rate of 40.2% for placebo and simvastatin vs. 33.9.% for ezetimibe and simvastatin) with a number-needed-to-treat of 16 to prevent 1 event by 7 years (**Figure 3A**, Online Table 2). Among patients with intermediate risk, the addition of ezetimibe to simvastatin conferred an 11% relative reduction and a 2.2% absolute risk reduction compared with simvastatin alone (7-year Kaplan-Meier rate of 21.5% for placebo and simvastatin vs. 19.3% for ezetimibe and simvastatin) (**Figure 3A**, Online Table 2). In contrast, low-risk patients demonstrated no risk reduction (7-year Kaplan-Meier rate of 13.1% for placebo and simvastatin vs. 14.0% for ezetimibe and simvastatin; hazard ratio: 1.05; 0.92 to 1.19; absolute risk reduction: −0.9%; −2.5% to 0.7%) (**Figure 3A**, Online Table 2).

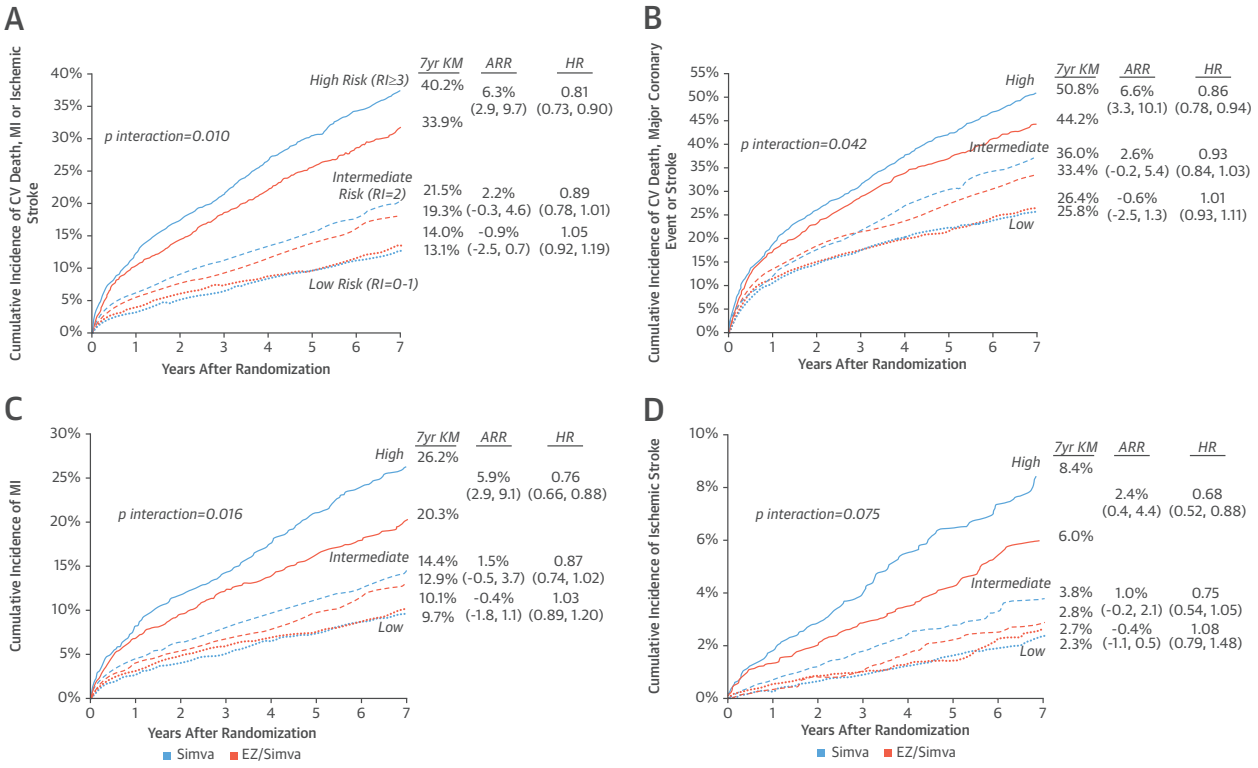
A similar pattern of increasing benefit was observed across risk categories for the IMPROVE-IT pre-specified primary and secondary trial endpoints, as well as for most of the individual, nonfatal endpoints (**Figures 3B to 3D**, Online Table 2). For example, with the addition of ezetimibe, high-risk patients had a significant 14% relative and 6.6% absolute reduction in the rate of CV death, major coronary event, or stroke, thus translating to a number-needed-to-treat of 15. Intermediate-risk patients had a 7% relative reduction and a 2.6% absolute reduction. In contrast, low-risk patients demonstrated no reduction in CV death, major coronary event, or stroke with the addition of ezetimibe (p interaction = 0.042). The observations in high-risk patients were driven by reductions in nonfatal recurrent CV events, where there was a 24% relative and 5.9% absolute reduction in MI (p interaction = 0.016) (**Figure 3C**), a 32% relative and 2.4% absolute reduction in ischemic stroke (p interaction = 0.075) (**Figure 3D**), and a 31% relative and 4.3% absolute reduction in urgent coronary revascularization (p interaction = 0.10) (Online Table 2) There were no significant reductions in CV death or all-cause mortality in

FIGURE 2 Risk Stratification of Individual Endpoints in the Control Arm (Placebo/Simvastatin)



(A) Cardiovascular (CV) death endpoint. **(B)** Myocardial infarction endpoint. **(C)** Ischemic stroke endpoint. The 7-year Kaplan-Meier estimates are shown. The basis of the p value is the chi-square test for trend.

FIGURE 3 Outcomes by Risk Category and Randomized Treatment



Kaplan-Meier (KM) curves stratified by low-, intermediate-, and high-risk category and randomized treatment (placebo/simvastatin [Simva] vs. ezetimibe [EZ]/simvastatin) for the first event of the following: **(A)** cardiovascular (CV) death, myocardial infarction (MI), or ischemic stroke; **(B)** CV death, MI, unstable angina, or coronary revascularization >30 days from randomization or stroke; **(C)** MI; and **(D)** ischemic stroke. The p interaction for treatment by risk category is shown. The basis of the p value is the chi-square test for trend < 0.0001 across risk groups within treatment arms for each endpoint. Hazard ratios (HR) and absolute risk reductions (ARR) with corresponding 95% confidence intervals for ezetimibe/simvastatin versus placebo/simvastatin within risk groups are shown. RI = risk indicators.

any risk group with the addition of ezetimibe (Online Table 2).

ACHIEVED LIPID VALUES AT 1 YEAR BY ATHEROTHROMBOTIC RISK CATEGORY. The median achieved LDL-C values at 1 year were similar across risk categories by treatment (66 to 68 mg/dl for placebo and simvastatin and 48 to 51 mg/dl for ezetimibe and simvastatin) (Online Table 3), thereby resulting in a consistent 17 to 18 mg/dl reduction in LDL-C from the time of randomization with ezetimibe and simvastatin compared with placebo and simvastatin in each of the risk categories (p interaction for 1 year achieved value by risk group = 0.97). Additional achieved lipid and inflammatory parameters are described in Online Table 3.

DISCUSSION

Ezetimibe has been shown to improve CV outcomes when it is added to statin therapy in patients stabilized after ACS (1). We sought to determine whether we could identify higher-risk populations of patients who have the greatest potential for benefit from the addition of ezetimibe to statin therapy by using the TRS 2°P, a simple 9-point risk stratification tool (11). In this secondary analysis, we found that in patients who conditions were stabilized after ACS in IMPROVE-IT, the TRS 2°P identified the following: 1) a strong gradient of risk for recurrent CV events; and, importantly; 2) an increasingly favorable relative and absolute benefit from the addition of ezetimibe to simvastatin therapy with increasing risk profile.

TREATMENT BENEFIT WITH THE ADDITION OF EZETIMIBE TO STATIN THERAPY. The TRS 2°P identified differential treatment benefit for the addition of ezetimibe to simvastatin therapy when patients at higher risk for recurrent CV events experienced the greatest relative and absolute risk reductions.

Specifically, patients at highest risk, representing 25% of the population, had a 19% relative and 6.3% absolute reduction in CV death, MI, or ischemic stroke. Intermediate-risk patients, accounting for 30% of the population, had an 11% relative and 2.2% absolute reduction in recurrent CV events. Notably, patients with 0 or 1 risk indicators did not appear to derive benefit from the addition of ezetimibe to simvastatin therapy in IMPROVE-IT. These findings were consistent across the IMPROVE-IT primary and secondary endpoints and were primarily driven by reductions in the clinically important endpoints of MI, ischemic stroke, and urgent coronary revascularization. All-cause mortality and CV death rates were not reduced with the addition of ezetimibe in any risk category, a finding that is consistent with the overall trial results from IMPROVE-IT and also with trials of intensive-dose versus standard-dose statin therapy (1,17–21).

It could be expected that there would be a greater absolute treatment benefit for an effective therapy in a higher-risk population; however, the observed gradient in relative risk reduction in the 3 risk groups despite similar reductions in LDL-C merits further consideration. It is possible that subjects at high risk, reflecting greater atherosclerotic burden, are more likely to benefit from the same degree of lipid lowering than are lower-risk patients. The observation of a graded relative benefit with lipid-lowering therapy across risk groups warrants investigation in other datasets and with other statin and nonstatin agents to understand the underlying mechanism more clearly.

The 2016 American College Cardiology Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering recommended consideration of the addition of ezetimibe in patients with atherosclerotic cardiovascular disease and comorbidities, including recent ACS, with on-treatment LDL-C levels ≥70 mg/dl (22). However, our findings support a strategy for identifying patients who may benefit from add-on lipid-lowering therapy with ezetimibe after considering overall patient risk in addition to achieved LDL-C. For example, in patients with well-controlled LDL-C (e.g., <70 mg/dl), one could consider adding ezetimibe to statin therapy in those with intermediate or high risk as determined by the TRS 2°P to target an LDL-C of 50 mg/dl or less.

RISK STRATIFICATION IN THE STABLE PHASE OF ISCHEMIC HEART DISEASE. Risk stratification tools are well validated for use in ACS to assist with short-term prognostication and short-term management decisions (e.g., early invasive strategy) (4–9). However, there continues to be a need for similar tools in patients in the stable phase of IHD (e.g., stabilized after ACS), particularly in light of the increasing number of effective, evidence-based therapies and potentially counterbalancing concerns regarding compliance, patients' preferences, and possible side effects. It is in this context that risk stratification offers clinicians a practical strategy to identify those patients with the greatest potential for benefit from intensive secondary preventive therapy.

To this end, we previously showed that the TRS 2°P effectively identified a 5-fold gradient in the risk of recurrent major CV events across low-, medium-, and high-risk categories in patients in stable condition who have established IHD and previous MI (11). Similar to the findings described here, application of this simple categorization of baseline atherothrombotic risk distinguished a pattern of differential treatment benefit with vorapaxar, an inhibitor of thrombin-mediated platelet activation, where the absolute net clinical benefit increased across increasing risk category.

In this analysis, the TRS 2°P identified differential risk for long-term recurrent CV events in IMPROVE-IT, an early post-ACS population of patients, with a 3- to 4-fold gradient for MI or ischemic stroke and a 7-fold gradient for CV death across low-, medium-, and high-risk categories over 7 years. Despite the pragmatic approach to risk stratification, the TRS 2°P demonstrated reasonable discrimination and good calibration for long-term outcomes in post-ACS patients. Moreover, our findings demonstrate a practical approach to personalizing secondary preventive therapy on the basis of patients' risk.

STUDY LIMITATIONS. The TRS 2°P was designed to be a simple tool, using readily available clinical data. There are other previously identified risk indicators (e.g., abnormal imaging and angiography) and other yet to be identified parameters (e.g., biochemical or genetic characteristics) that may provide additional refinement for stratification. However, the ability of this simple scoring system to identify differential treatment benefit for different classes of secondary preventive therapy supports its clinical utility. Our data are derived from a population of patients who met specific trial inclusion criteria and agreed to participate in a clinical trial, and this may influence generalizability to the general population. For example, low-risk patients, as defined by the TRS criteria with higher baseline LDL-C than those who

were enrolled in IMPROVE-IT (>100 mg/dl during statin therapy or >125 mg/dl in the absence of lipid-lowering therapy), may derive benefit from the addition of ezetimibe to statin therapy. Furthermore, the generalizability of this approach to other lipid-lowering therapy, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, will need to be evaluated. Finally, the IMPROVE-IT trial evaluated a strategy of the addition of ezetimibe to a moderate- to high-intensity statin (simvastatin 40 to 80 mg) versus moderate- to high-intensity statin alone to achieve on-treatment LDL-C levels of 48 to 51 mg/dl and 66 to 68 mg/dl, respectively. The additive, proportionate reduction in LDL-C when ezetimibe was combined with a statin in this study was similar to that seen in other studies regardless of the background dose (or type) of statin (23,24). Therefore, although it is not possible specifically to address the CV benefit of the addition of ezetimibe to a high-intensity statin (e.g., atorvastatin 80 mg daily) because it was not studied in IMPROVE-IT, it could be hypothesized that the magnitude of benefit for the addition of ezetimibe would be more related to the baseline LDL-C (and therefore the absolute reduction in LDL-C on the basis of a consistent, proportionate reduction in LDL-C with ezetimibe on top of statin therapy), than to the intensity of statin dosing (1,25).

CONCLUSIONS

Atherothrombotic risk stratification using the TRS 2°P may help clinicians with therapeutic decisions regarding the addition of ezetimibe to statin therapy for secondary prevention after ACS.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Atherothrombotic risk stratification using the TRS 2°P, which incorporates 9 readily available clinical characteristics, identifies high-risk patients who derive the greatest benefit from the addition of ezetimibe to statin therapy for long-term secondary prevention after ACS.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify patients at risk who gain benefit from addition of ezetimibe to statin therapy for primary prevention, before the development of an ischemic event.

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APPENDIX For supplemental tables and figures, please see the online version of this article.