Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients With Acute Coronary Syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)

BACKGROUND: Patients who experience an acute coronary syndrome are at heightened risk of recurrent ischemic events, including stroke. Ezetimibe improved cardiovascular outcomes when added to statin therapy in patients stabilized after acute coronary syndrome. We investigated the efficacy of the addition of ezetimibe to simvastatin for the prevention of stroke and other adverse cardiovascular events in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), with a focus on patients with a stroke before randomization.

METHODS: Patients who experienced acute coronary syndrome were randomized to a placebo/simvastatin or ezetimibe/simvastatin regimen and followed for a median of 6 years. Treatment efficacy was assessed for the entire population and by subgroups for the first and total (first and subsequent) events for the end points of stroke of any etiology, stroke subtypes, and the primary trial end point at 7 years.

RESULTS: Of 18 144 patients, 641 (3.5%) experienced at least 1 stroke; most were ischemic (527, 82%). Independent predictors of stroke included prior stroke, older age, atrial fibrillation, congestive heart failure, diabetes mellitus, myocardial infarction, and renal dysfunction. There was a nonsignificant reduction in the first event of stroke of any etiology (4.2% versus 4.8%; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.73–1.00; *P*=0.052) with ezetimibe/simvastatin versus placebo/simvastatin, driven by a significant 21% reduction in ischemic stroke (3.4% versus 4.1%; HR, 0.79; 95% CI, 0.67–0.94; *P*=0.008) and a nonsignificant increase in hemorrhagic stroke (0.8% versus 0.6%; HR, 1.38; 95% CI, 0.93–2.04; *P*=0.11). Evaluating total events, including the first and all recurrent strokes, ezetimibe/simvastatin reduced stroke of any etiology (HR, 0.83; 95% CI, 0.70–0.98; *P*=0.029) and ischemic stroke (HR, 0.76; 95% CI, 0.63–0.91; *P*=0.003). Patients who had experienced a stroke prior to randomization were at a higher risk of recurrence and demonstrated an absolute risk reduction of 8.6% for stroke of any etiology (10.2% versus 18.8%; number needed to treat=12; HR, 0.60; 95% CI, 0.38–0.95; *P*=0.030) and 7.6% for ischemic stroke (8.7% versus 16.3%; number needed to treat=13; HR, 0.52; 95% CI, 0.31–0.86; *P*=0.011) with ezetimibe added to simvastatin therapy.

CONCLUSIONS: The addition of ezetimibe to simvastatin in patients stabilized after acute coronary syndrome reduces the frequency of ischemic stroke, with a particularly large effect seen in patients with a prior stroke.

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Erin A. Bohula, MD, DPhil
Stephen D. Wiviott, MD
Robert P. Giugliano, MD, SM
Michael A. Blazing, MD
Jeong-Gun Park, PhD
Sabina A. Murphy, MPH
Jennifer A. White, MS
Francois Mach, MD
Frans Van de Werf, MD, PhD
Anthony J. Dalby, MD, DPhil, MB, ChB
Harvey D. White, DSc
Andrew M. Tershakovec, MD, MPH
Christopher P. Cannon, MD
Eugene Braunwald, MD

Correspondence to: Erin A. Bohula, MD, DPhil, Cardiovascular Division, Brigham and Women's Hospital, 350 Longwood Ave, 1st Fl, Boston, MA 02115. E-mail ebohula@partners.org

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Clinical Perspective

What Is New?

- We investigated the efficacy of the addition of ezetimibe to simvastatin for prevention of stroke, with a focus on patients with a history of stroke before randomization.
- The addition of ezetimibe to simvastatin reduces the frequency of ischemic stroke (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.67–0.94) with a particularly large effect seen in patients with a prior stroke (HR, 0.52; 95% CI, 0.31–0.86) compared with patients without a prior stroke (HR, 0.84; 95% CI, 0.70–1.01; *P* interaction=0.078).
- Hemorrhagic strokes were rare (0.6–0.8%/y); a nonsignificant increase in hemorrhagic stroke was observed with the addition of ezetimibe.

What Are the Clinical Implications?

- It is reasonable to consider the addition of ezetimibe, a generic lipid-lowering therapy with an acceptable safety profile, to a moderate- to high-intensity statin regimen for the prevention of ischemic stroke in patients with established ischemic heart disease with or without a prior stroke.

Patients who experience an acute coronary syndrome (ACS) are at a heightened risk of recurrent atherothrombotic events.[1,2] These events are not limited to the coronary vascular bed but also include ischemic strokes, one of the most feared cardiovascular events because of the risk of long-term disability.[3] Lipid-lowering therapy with statins has been shown to result in a 22% reduction in major vascular events per 1 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C), including a 21% relative risk reduction in ischemic stroke per 1 mmol/L reduction in LDL-C.[4] In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), the addition of the nonstatin lipid-lowering agent ezetimibe to a background of statin therapy with simvastatin in the long-term treatment of patients stabilized after ACS led to a significant reduction in cardiovascular events.[5,6]

In the present analysis, we evaluated the incidence and predictors of stroke after stabilization from ACS in IMPROVE-IT. We investigated the efficacy of the addition of ezetimibe to simvastatin for prevention of first and subsequent stroke and other cardiovascular events, with a particular focus on patients with a history of prior stroke. We hypothesized that the high-risk subgroup with a prior stroke would derive large absolute benefits for prevention of ischemic stroke and other atherothrombotic events with the addition of ezetimibe to statin therapy.

METHODS

Study Population and Procedures

IMPROVE-IT was a multinational, double-blind, placebo-controlled trial of 18 144 patients stabilized after ACS randomized in a 1:1 ratio to treatment with either ezetimibe (10 mg daily) plus simvastatin (40 mg daily) or placebo plus simvastatin (40 mg daily) as previously described.[5,7] Patients ≥50 years of age were eligible if hospitalized within the preceding 10 days for ACS, including myocardial infarction (MI) with or without ST elevation or high-risk unstable angina. Patients on long-term prescription lipid-lowering therapy were required to have an LDL-C level between 50 and 100 mg/dL; for all other patients, LDL-C levels were required to be between 50 and 125 mg/dL. Exclusion criteria included baseline ezetimibe use in combination with a statin, stroke or transient ischemic attack ≤24 hours of screening or randomization, statin therapy of a potency >40 mg simvastatin, hemodynamic instability, or revascularization by coronary artery bypass for the index event. Patients who had LDL-C levels >79 mg/dL on 2 consecutive measurements ≥2 months apart after randomization had the simvastatin dose increased to 80 mg daily. On release of the US Food and Drug Administration guidance in June 2011, no further uptitrations to simvastatin 80 mg were allowed, and any patient on simvastatin 80 mg for <1 year had their dose decreased to 40 mg daily. The ethics committee at each participating center approved the protocol. Written informed consent was obtained from all patients.

End Points

The IMPROVE-IT prespecified primary efficacy end point was a composite of cardiovascular death, major coronary event (nonfatal MI, documented unstable angina requiring hospital admission, or coronary revascularization occurring ≥30 days after randomization), or nonfatal stroke.[5,7] A stroke end point was defined as the new onset of focal neurological symptoms lasting >24 hours or resulting in death and classified as a stroke by the treating physician. Stroke events were further classified as nonhemorrhagic (ie, ischemic), hemorrhagic, or uncertain. All elements of these end points have been described previously and were adjudicated according to established definitions by a clinical events committee unaware of the treatment allocation.[7,8]

Statistical Analysis

Time to first event efficacy analyses were performed by intention-to-treat using Cox proportional hazards modeling with randomized treatment (placebo/simvastatin versus ezetimibe/simvastatin) and randomization stratification factors (participation in the EARLY-ACS study (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-segment Elevation Acute Coronary Syndrome), use of lipid-lowering therapy in the 4 weeks preceding the index ACS event, and type of ACS [non-ST elevation-ACS versus ST elevation MI]) as covariates. IMPROVE-IT was powered for the primary end point and not for individual components of the primary end point. All event rates are 7-year Kaplan-Meier (KM) estimates except where otherwise specified. The 95% confidence intervals (CIs) for the absolute risk reductions (ARR) were calculated based on the assumption

that the KM estimates for each treatment arm and the ARR (ie, difference in KM estimates) between treatments for each end point follow a normal distribution. Because the 2 KM estimates are from independent groups, the variance of ARR was calculated from the variances of the KM estimates for the 2 treatment arms, which allowed calculation of the 95% CIs for ARR. The subgroup of patients with a history of stroke was defined by a prior clinical diagnosis, as assessed by the investigator. We evaluated for a heterogeneous treatment effect of placebo/simvastatin versus ezetimibe/simvastatin using Cox proportional hazards regression modeling, including a treatment-by-subgroup interaction term.

Negative binomial regression analysis, a type of modified Poisson model, was performed to compare the total number of strokes (first and subsequent strokes) and the primary trial end point events (first and subsequent) in patients treated with ezetimibe/simvastatin and placebo/simvastatin, as previously described.[6] For the total events analysis, the first end point refers to the first event after randomization. A subsequent or recurrent event is 1 that occurred after randomization, after the first event. The negative binomial model included an exposure variable for duration of follow-up because this could vary by subject. Incidence risk ratio (RR) and corresponding 95% CIs are reported from the negative binomial regression model.

Independent predictors of stroke were identified by consistency of forward, backward, and stepwise model selection using 14 candidate baseline variables selected based on a significance level of $P<0.05$ on univariate analysis: randomized treatment, older age, sex, diabetes mellitus, smoking, hypertension, congestive heart failure, peripheral artery disease, prior MI, prior stroke, aspirin use, renal dysfunction, and elevated high-sensitivity C-reactive protein. With the exception of the estimated glomerular filtration rate (measured), all other candidate variables (eg, hypertension, diabetes mellitus) were defined by a prior clinical diagnosis as assessed by the investigator. All reported P values are 2-sided. $P<0.05$ signified nominal statistical significance with no adjustment for multiple comparisons. All analyses were conducted using Stata/IC, version 13.1 (StataCorp LP) or SAS, version 9.4 (SAS Institute).

RESULTS

Study Population

Of the 18 144 patients after ACS randomly assigned to placebo/simvastatin (N=9077) or ezetimibe/simvastatin (N=9067), 641 (3.5%) experienced at least 1 stroke during a median follow-up of 6 years. The majority of the first strokes were ischemic (527, 82%), with a smaller number of hemorrhagic strokes (100, 16%) and strokes of unknown type (14, 2%); 95 (15%) of the strokes were fatal. The baseline characteristics of patients who did and did not experience a stroke during follow-up are shown in Table 1 and were similar between treatment groups. LDL-C values were similar between the 2 groups at the time of randomization. With the exception of small differences in sex and race, the baseline

Table 1. Baseline Characteristics in Those With Stroke of Any Etiology Versus No Stroke During Follow-Up

Variable	No Stroke (N=17 503)	Any Stroke (N=641)	*P* Value
Demographics			
Age (median, IQR), y	63 (57, 71)	69 (61, 76)	<0.001
Age ≥75, y	15	28	<0.001
Female	24	28	0.039
White	84	85	0.28
BMI (median, IQR), kg/m^2	28 (25, 31)	27 (25, 31)	0.12
Coexisting conditions			
Diabetes mellitus	27	35	<0.001
Current smoking	33	28	0.003
Hypertension	61	70	<0.001
Heart failure	4.2	8.6	<0.001
Peripheral artery disease	5.4	9.2	<0.001
Prior MI (before index ACS)	21	29	<0.001
Prior CABG (before index ACS)	9.2	12.9	0.001
Prior stroke	3.5	12.0	<0.001
Atrial fibrillation	5.0	12.3	<0.001
CHA_2DS_2-VASc score (median, IQR)	3 (2, 4)	4 (2, 5)	<0.001
Score 1–3	70	47	<0.001
Score 4–9	30	53	
Before index ACS event			
Medications			
Lipid-lowering agent	35	44	<0.001
Statin	34	42	<0.001
Aspirin	42	51	<0.001
At index ACS event			
Type of event			
STEMI	29	28	0.51
NSTEMI	47	48	0.84
Unstable angina	24	25	0.64
Labs at the index ACS event			
Total cholesterol (median, IQR), mg/dL	163 (144, 181)	160 (139, 179)	0.009
LDL-C (median, IQR), mg/dL	95 (79, 110)	92 (74, 108)	0.005
HDL-C (median, IQR), mg/dL	40 (33, 49)	41 (34, 50)	0.16
Triglycerides (median, IQR), mg/dL	120 (85, 172)	116 (80, 171)	0.12
At randomization			
Time from ACS to randomization (median, IQR)	5.0 (3.0, 8.0)	5.0 (3.0, 8.0)	0.35
Medications			
Aspirin	97	95	0.005

(*Continued*)

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Table 1. Continued

Variable	No Stroke (N=17 503)	Any Stroke (N=641)	*P* Value
Thienopyridine	87	83	0.012
β Blocker	87	86	0.53
ACEi/ARB	75	81	0.002
Labs at randomization			
Total cholesterol (median, IQR), mg/dL	149 (130, 168)	147 (130, 168)	0.37
LDL-C (median, IQR), mg/dL	80 (65, 96)	80 (63, 96)	0.45
HDL-C (median, IQR), mg/dL	39 (34, 47)	41 (34, 48)	0.066
Triglycerides (median, IQR), mg/dL	127 (98, 168)	122 (95, 162)	0.036
hs-CRP (median, IQR), mg/L	9.5 (3.9, 26.4)	12.4 (4.3, 32.0)	0.005
eGFR (median, IQR), mL/min/1.73m^2	74 (64, 84)	70 (58, 82)	<0.001
eGFR <60 mL/min/1.73m^2	20	29	<0.001

ACS indicates 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 MDRD; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention. Baseline characteristics were well matched (*P*>0.05) by randomization in patients allocated to placebo/simvastatin and ezetimibe/simvastatin. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. Number denotes proportion (%) unless otherwise specified.

characteristics of patients who had an ischemic versus hemorrhagic stroke were similar, including similar rates of aspirin and thienopyridine usage at randomization and simvastatin uptitration to 80 mg during the trial (Table I in the online-only Data Supplement).

Independent Predictors of Stroke

A history of prior stroke was the most potent independent predictor of recurrent stroke of any etiology, with a >3-fold increased risk in patients with a prior stroke compared with those without a prior stroke (7-year KM rate of 18.8% versus 4.3%; HR, 3.06; 95% CI, 2.40–3.92; *P*<0.001; Figure 1). Other independent predictors of stroke were ≥75 years of age, atrial fibrillation, diabetes mellitus, prior MI, renal dysfunction, and heart failure. The independent predictors of ischemic stroke were the same with the exception of heart failure; treatment with ezetimibe/simvastatin was protective for ischemic stroke (HR, 0.81; 95% CI, 0.68–0.96; *P*=0.015; Figure 1). Only a history of atrial fibrillation, heart failure, and hypertension independently predicted hemorrhagic stroke during follow-up (Figure 1).

Efficacy and Safety of Ezetimibe for Stroke Prevention

In the overall population, a nonsignificant reduction occurred in the first event of stroke of any type with the addition of ezetimibe to simvastatin compared with simvastatin monotherapy with rates of 4.2% versus 4.8%, respectively (HR, 0.86; 95% CI, 0.73–1.00; *P*=0.052; Figure 2A and Table 2). Ischemic stroke as a first event was significantly reduced by 21% with ezetimibe/simvastatin compared with placebo/simvastatin (7-year KM rate of 3.4% versus 4.1%; HR, 0.79; 95% CI, 0.67–0.94; *P*=0.008; Figure 2B and Table 2). Hemorrhagic strokes were rare (n=102). However, a nonsignificant but greater number of hemorrhagic strokes occurred with ezetimibe/simvastatin versus placebo/simvastatin (KM rates of 0.8% versus 0.6%; HR, 1.38; 95% CI, 0.93–2.04; *P*=0.11; Figure 2B and Table 2).

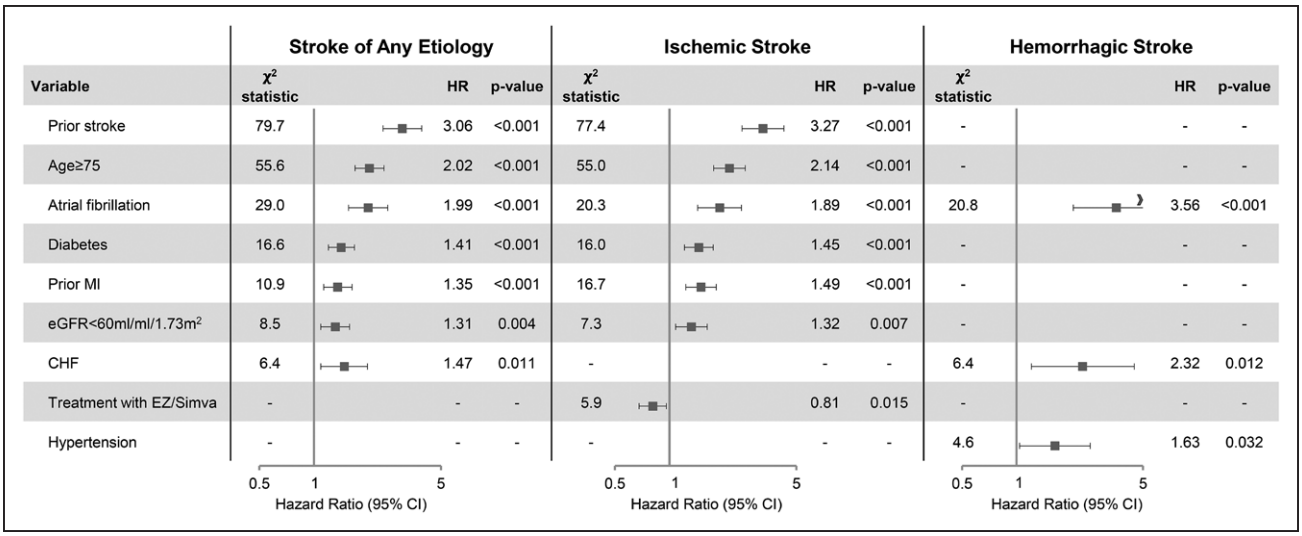

Figure 1. Independent predictors of stroke during follow-up.
Multivariable baseline predictors of stroke of any etiology, ischemic stroke, and hemorrhagic stroke are shown. CHF indicates congestive heart failure; CI, confidence interval; eGFR, estimated glomerular filtration rate; EZ, ezetimibe; HR, hazard ratio; MI, myocardial infarction; and simva, simvastatin.

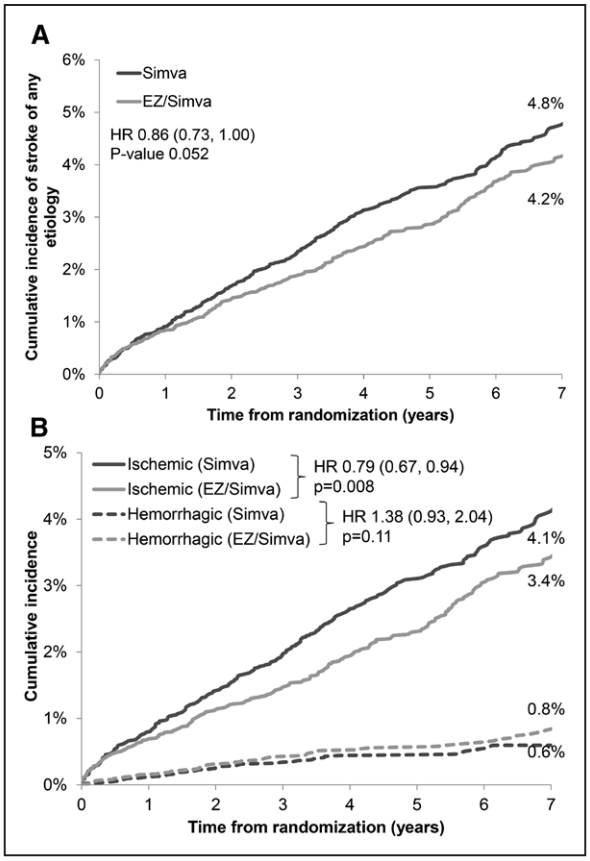

Figure 2. First occurrence of stroke in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) by randomized treatment. Kaplan-Meier curves for the first event of (**A**) stroke of any etiology and (**B**) ischemic or hemorrhagic stroke by placebo/simvastatin and ezetimibe/simvastatin. Hazard ratio (HR) and 95% confidence interval are shown. EZ indicates ezetimibe; and simva, simvastatin.

During the course of the trial, 719 strokes of any etiology occurred (Figure 3A). Of these, 641 (89%) were first events and 78 (11%) were recurrences within the trial. In addition to the 49 fewer first strokes with ezetimibe/simvastatin compared with placebo/simvastatin, 20 fewer subsequent strokes occurred, translating to a significant 17% reduction in total strokes (n=325 versus n=394; RR, 0.83; 95% CI, 0.70–0.98; *P*=0.029; Figure 3A).

Table 2. Stroke Outcomes by Randomized Treatment

End Point	Simva N=9077 n (%)	EZ/Simva N=9067 n (%)	HR (95%CI)	*P* Value
Stroke of any etiology	345 (4.8)	296 (4.2)	0.86 (0.73–1.00)	0.052
Ischemic stroke	297 (4.1)	236 (3.4)	0.79 (0.67–0.94)	0.008
Hemorrhagic stroke	43 (0.6)	59 (0.8)	1.38 (0.93–2.04)	0.11
Unknown stroke	8 (0.1)	6 (0.1)	0.75 (0.26–2.17)	0.60
Ischemic/ unknown stroke	305 (4.2)	242 (3.5)	0.79 (0.67–0.94)	0.007
Fatal stroke	43 (0.6)	52 (0.7)	1.22 (0.81–1.82)	0.34

CI indicates confidence interval; EZ, ezetimibe; HR, hazard ratio; and simva, simvastatin. Event rate (%) represents 7-year Kaplan-Meier estimate.

During follow-up, 596 ischemic strokes occurred, of which 533 (89%) were first events and 63 (11%) were subsequent events. In addition to the 61 fewer first ischemic strokes with ezetimibe/simvastatin compared with placebo/simvastatin, 19 fewer subsequent strokes occurred, translating to a significant 24% reduction in total ischemic strokes (n=258 versus n=338; RR, 0.76; 95% CI, 0.63–0.91; *P*=0.003; Figure 3B). During follow-up, 109 hemorrhagic strokes occurred, including 102 (94%) first and 7 (6%) subsequent strokes. Although 16 more first hemorrhagic strokes occurred with ezetimibe/simvastatin, 3 fewer subsequent events took place with ezetimibe/simvastatin (n=2) versus placebo/simvastatin (n=5), resulting in a nonsignificant increase in the rate of hemorrhagic stroke (n=61 versus n=48; RR, 1.35; 95% CI, 0.88–2.08; *P*=0.17).

Subgroup Analyses

The relative benefit of the addition of ezetimibe to simvastatin for prevention of the first stroke during follow-up was generally consistent across all subgroups (P interaction>0.05 for each; Figure 4). Patients with a history of prior stroke were the highest risk subgroup evaluated here; these patients tended to be older, to be female, and to have a greater burden of comorbidities, such as diabetes mellitus, hypertension, renal dysfunction, and carotid arterial disease than patients without a history of stroke (Table II in the online-only Data Supplement). Patients with a history of stroke at baseline were more likely to have been treated with lipid-lowering therapy prior to the index ACS event (58% versus 35%; *P*<0.001) and had lower LDL-C levels at the time of the index ACS event (87 mg/dL versus 95 mg/dL; *P*<0.001). Despite this evidence, the achieved LDL-C values were similar at 1 year across the subgroups (50–51 mg/dL with ezetimibe/simvastatin and 67–68 mg/dL with simvastatin alone), translating to a consistent 17 mg/dL between treatment difference in LDL-C within each subgroup at 1 year (Table III in the online-only Data Supplement). The between-treatment differences achieved at 1 year for other lipid and inflammatory parameters were similar for those with and without a history of stroke (Table III in the online-only Data Supplement).

Patients with a history of prior stroke were at high risk for recurrent stroke after randomization, including ischemic and hemorrhagic forms, and they also had a greater risk of MI, death, and the primary trial end point (Table 3). In this high-risk subgroup, a nonsignificant trend (*P* interaction=0.11) occurred toward a greater reduction in stroke with the addition of ezetimibe to

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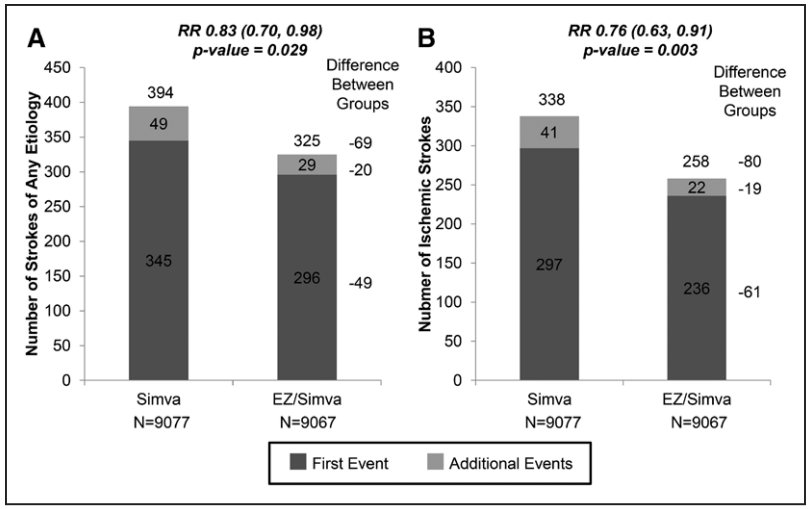

Figure 3. Total stroke events in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) by randomized treatment. Counts of first and additional events of (**A**) stroke of any etiology and (**B**) ischemic stroke with randomized treatment. Risk ratio (RR) and 95% confidence intervals for total events are shown. EZ indicates ezetimibe; and simva, simvastatin.

simvastatin (HR, 0.60; 95% CI, 0.38–0.95) compared with patients without a history of prior stroke (HR, 0.90; 95% CI, 0.76–1.06; Table 3). This translated into a large ARR of 8.6% (95% CI, 2.1–15.1%, *P*=0.010; number needed to treat=12) for stroke of any etiology (KM rates of 18.8% for placebo/simvastatin versus 10.2% for ezetimibe/simvastatin; Figure 5) in patients with a history of stroke before randomization. This benefit of ezetimibe for stroke prevention was observed within the first 6 months after ACS (Figure 5) in those with a history of prior stroke. Large absolute risk reductions were also observed with ezetimibe in this subgroup for ischemic stroke at 7.6% (95% CI, 1.6–13.6%; *P*=0.013; number needed to treat=13; KM rates of 8.7% versus 16.3%; HR, 0.52; 95% CI, 0.31–0.86; Table 3).

Efficacy for Total Events in the Subgroup With and Without a History of Stroke at Baseline

Compared with patients without a history of prior stroke, greater relative reductions occurred in total stroke (RR, 0.54; 95% CI, 0.33–0.90; *P*=0.019 versus RR, 0.88; 95% CI, 0.74–1.05; *P*=0.16; *P* interaction<0.001) and total ischemic stroke (RR, 0.45; 95% CI, 0.26–0.80; *P*=0.006 versus RR, 0.82; 95% CI, 0.68–1.00; *P*=0.045; *P* interaction<0.001) in patients with a prior stroke (Figure IA and B in the online-only Data Supplement). Total primary end point events were similarly reduced with the addition of ezetimibe in patients with a prior stroke (*P* interaction=0.89; Figure IC in the online-only Data Supplement).

DISCUSSION

Ezetimibe has been shown to reduce recurrent cardiovascular events when added to moderate- to high-intensity statin therapy (simvastatin 40–80 mg) in patients stabilized after ACS.[5] In the present analysis, we sought to investigate the treatment benefit for first and subsequent events of stroke with the addition of ezetimibe to background statin in the overall study population as well as in patients with a history of stroke. We observed a significant reduction in both first and total (first and subsequent) ischemic strokes, with a nonsignificant increase in hemorrhagic stroke in patients in whom ezetimibe was added to background statin therapy. Taken together, this translated into a nonsignificant reduction in the first occurrence of any stroke and a significant reduction in total (first and subsequent) strokes in patients in whom ezetimibe was added to background statin therapy. The relative benefit for stroke was consistent across the subgroups evaluated. We did observe a nonsignificant trend (*P* interaction=0.11) toward a greater relative benefit with a large 8.6% ARR (number needed to treat=12) in patients with a history of prior stroke at baseline with the addition of ezetimibe compared with patients without a history of prior stroke at baseline.

Prevention of Ischemic Stroke

In this analysis, we observed a significant 21% relative reduction in ischemic stroke when ezetimibe was added to simvastatin in patients stabilized after ACS. The magnitude of benefit from the simvastatin-ezetimibe combination is similar to that seen in statin trials when adjusted for the degree of LDL-C lowering. With a between-group difference in LDL-C of 17 mg/dL, the relative reduction in ischemic stroke per millimole of LDL-C reduction with ezetimibe in IMPROVE-IT was 25% compared with a 21% reduction seen with statin monotherapy in the CTT meta-analysis.[4] The consistency of these findings support the benefit of LDL-C lowering on stroke prevention through a nonstatin mechanism. Because not all lipid-lowering agents have demonstrated similar improvements in cardiovascular outcomes, it has been proposed that the specific mechanism of LDL-C lowering—namely,

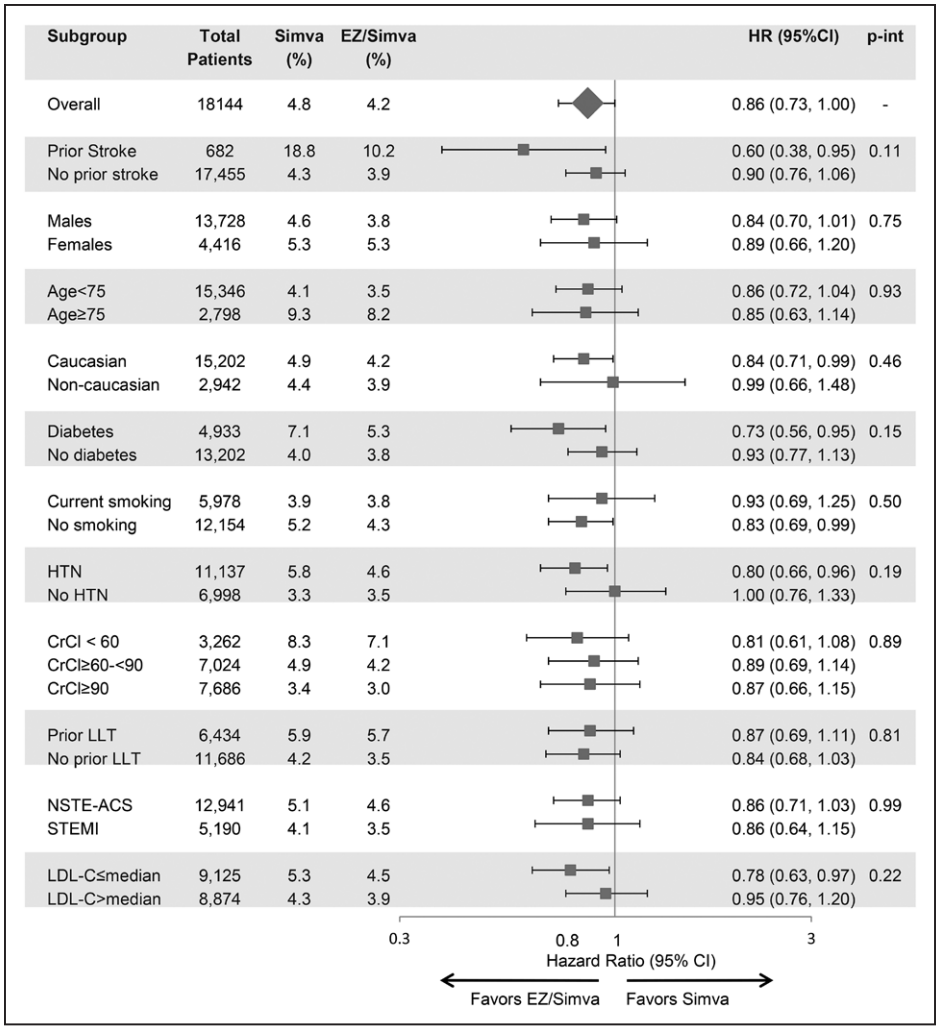

Figure 4. Subgroup analysis for the outcome of stroke of any etiology.
Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for ezetimibe/simvastatin versus placebo/simvastatin within subgroups are shown for the end point of stroke of any etiology. *P* interactions for treatment by subgroup are shown. % indicates 7-year Kaplan-Meier rate; ACS, acute coronary syndrome; CrCl, creatinine clearance by Cockcroft-Gault in ml/min; EZ, ezetimibe; HTN, hypertension; LLT, lipid-lowering therapy; LDL-C, low-density lipoprotein-calculated; NSTE, non—ST elevation; p-int, p-interaction; simva, simvastatin; and STEMI, ST-elevation MI.

via upregulation of the LDL receptor—underlies the benefit seen with certain lipid-lowering strategies (eg, statins, ezetimibe, bile acid sequestrants, and ileal bypass).[9] This hypothesis is further supported by findings from the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) with another nonstatin lipid-lowering agent, the PCSK9 (proprotein convertase subtilisin–kexin type 9) inhibitor evolocumab, which demonstrated a significant reduction in cardiovascular events, including ischemic stroke.[10]

Hemorrhagic Stroke

Although hemorrhagic stroke was rare at a rate of <0.6% over 7 years in the control arm, a nonsignificantly greater number of hemorrhagic strokes occurred in patients treated with the simvastatin-ezetimibe combination compared with simvastatin alone. Epidemiological studies have observed an association between low LDL-C and intracranial hemorrhage, a finding not consistently replicated in observational and randomized studies.[11] For example, the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), which randomized patients with recent history of stroke or transischemic attack to high-dose atorvastatin versus placebo, identified a significant increase in hemorrhagic stroke with atorvastatin that was independent of achieved LDL-C and was primarily observed in patients with a prior history of intracranial hemorrhage.[12,13] Hemorrhagic stroke was not significantly increased in the larger CTT meta-analysis of randomized trials with statin therapy (HR, 1.12; 95% CI, 0.93–1.35), which included >500 hemorrhagic strokes.[4] Similarly, a meta-analysis of randomized and observational studies in-

Table 3. Outcomes in Subgroups With and Without a Stroke Before Baseline by Randomized Treatment

End point	Prior Stroke				No Prior Stroke				*P* interaction
	Simva N=346 n (%)	EZ/Simva N=336 n (%)	HR (95% CI)	ARR (95% CI)	Simva N=8728 n (%)	EZ/Simva N=8727 n (%)	HR (95% CI)	ARR (95% CI)	
Stroke of any etiology	48 (18.8)	29 (10.2)	0.60 (0.38–0.95)	8.6% (2.1–15.1)	297 (4.3)	267 (3.9)	0.90 (0.76–1.06)	0.4% (–0.4 to 1.0)	0.11
Ischemic stroke	44 (16.3)	23 (8.7)	0.52 (0.31–0.86)	7.6% (1.6–13.6)	253 (3.7)	213 (3.2)	0.84 (0.70–1.01)	0.5% (–0.2 to 1.1)	0.078
Hemorrhagic stroke	3 (2.4)	5 (2.1)	1.69 (0.40–7.06)	0.3% (–3.2 to 3.7)	40 (0.6)	54 (0.7)	1.35 (0.90–2.04)	–0.1% (–0.5 to 0.1)	0.77
Primary trial end point	141 (48.3)	119 (41.0)	0.84 (0.66–1.07)	7.3% (–1.6 to 16.2)	2601 (34.2)	2453 (32.4)	0.94 (0.89–0.99)	1.8% (0.5–3.1)	0.37
Other individual and exploratory end points									
MI	60 (22.0)	51 (19.1)	0.85 (0.59–1.24)	2.9% (–4.4 to 10.2)	1058 (14.6)	926 (12.9)	0.87 (0.80–0.95)	1.7% (0.6–2.7)	0.91
Coronary revascularization	61 (21.9)	55 (19.5)	0.92 (0.64, 1.33)	2.4% (–4.8 to 9.7)	1732 (23.4)	1635 (21.9)	0.95 (0.89–1.01)	1.5% (0.3–2.7)	0.89
Urgent coronary revascularization	27 (9.7)	18 (6.5)	0.67 (0.37–1.21)	3.2% (–1.5 to 8.1)	599 (8.5)	492 (7.0)	0.82 (0.73–0.92)	1.5% (0.6–2.4)	0.51
Unstable angina	7 (2.2)	8 (2.8)	1.16 (0.42, 3.21)	–0.6% (–3.3 to 2.1)	141 (1.9)	148 (2.0)	1.05 (0.84–1.33)	–0.1% (–0.6 to 0.3)	0.85
CV death	34 (11.1)	38 (13.6)	1.11 (0.70, 1.76)	–2.5% (–8.3 to 3.2)	504 (6.7)	499 (6.7)	0.99 (0.88–1.12)	0.0% (–0.8 to 0.8)	0.66
Coronary heart disease death	26 (8.1)	31 (11.4)	1.18 (0.70–1.99)	–3.3% (–8.4 to 1.8)	435 (5.8)	409 (5.5)	0.94 (0.82–1.08)	0.3% (–0.5 to 1.0)	0.41
All-cause mortality	85 (29.3)	83 (29.6)	0.96 (0.71–1.30)	–0.3% (–8.6 to 8.1)	1146 (14.8)	1132 (14.8)	0.99 (0.91–1.08)	0.0% (–1.2 to 1.0)	0.85
CV death, MI, or stroke	117 (40.3)	93 (33.2)	0.78 (0.59–1.02)	7.1% (–1.5 to 15.8)	1587 (21.6)	1451 (19.9)	0.91 (0.85–0.98)	1.7% (0.4–2.9)	0.27

ARR indicates absolute risk reduction; CI, confidence interval; CV, cardiovascular; EZ, ezetimibe; HR, hazard ratio; MI, myocardial infarction; and simva, simvastatin. Event rate (%) represents 7-year Kaplan-Meier estimate. Stratified Cox modeling was performed within each subgroup to generate hazards by treatment for each end point. *P* interaction values were calculated in a Cox model including all patients with a term for subgroup treatment for each end point. The primary trial end point was a composite of death from CV disease (CV death), a major coronary event (nonfatal MI, documented unstable angina requiring hospital admission, or coronary revascularization occurring ≥30 days after randomization), or nonfatal stroke.

cluding >200 000 patients and 14 000 intracranial hemorrhages did not identify a significant association with statin therapy and intracranial hemorrhage.[14] If present, the link between statins and CNS hemorrhage has been hypothesized to be related to an antithrombotic effect of statins rather than to LDL-C reduction.[15]

In IMPROVE-IT, hemorrhagic stroke risk was independent of achieved LDL-C, where those with the lowest achieved LDL-C did not experience a higher rate of intracranial hemorrhage.[16] Furthermore, the rates of hemorrhage stroke were no different between treatment arms in an on-treatment analysis in IMPROVE-IT (placebo/simvastatin n=34 [0.4%] versus ezetimibe/simvastatin n=32 [0.4%], *P*=0.79), indicating that the numeric imbalance in hemorrhagic stroke occurred after discontinuation of the study medication.[17] The FOURIER trial with the PCSK9 inhibitor evolocumab also demonstrated no significant increase in hemorrhagic stroke (HR, 1.16; 95% CI, 0.68–1.98) despite achieving a median LDL-C of 30 mg/dL in the evolocumab arm.[10] Findings from 2 other cardiovascular outcomes trials with the PCSK9 inhibitors bococizumab and alirocumab may help to further clarify the risk of LDL-C reduction through a nonstatin mechanism as it relates to intracranial hemorrhage.[18,19]

Independent Predictors of Stroke

A history of prior stroke was the dominant risk factor for recurrent stroke, with a >3-fold increased risk after adjustment for other predictors. It is interesting to note that the remainder of the independent predictors for stroke in this patient population with established ischemic heart disease closely mirror those contained in the CHA_2DS_2-VASc scoring system, which was derived and validated as a tool for stroke risk stratification in patients with atrial fibrillation.[20,21] Notably, treatment with ezetimibe/simvastatin was protective for ischemic stroke, a benefit that was particularly robust in patients with a history of stroke because of the high absolute risk of recurrent strokes. The only independent predic-

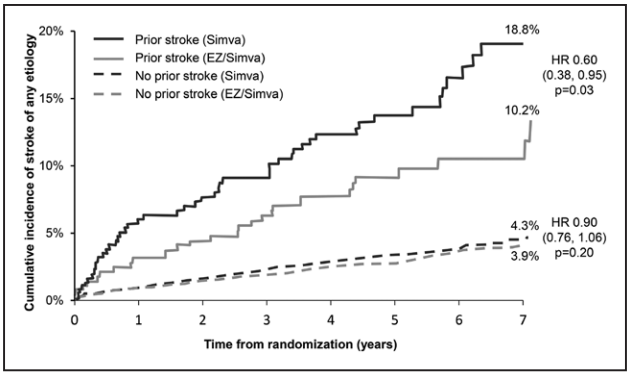

Figure 5. Kaplan-Meier curves for stroke in subgroups with and without a prior stroke by randomized treatment.

Kaplan-Meier curves for the first event of stroke of any etiology stratified by a history of stroke before baseline and treatment with placebo/simvastatin versus ezetimibe/simvastatin. Hazard ratio (HR) and 95% confidence interval are shown. The *P* interaction value for prior stroke subgroup and treatment is 0.11. EZ indicates ezetimibe; and simva, simvastatin.

tors identified for hemorrhagic stroke (N=102) were atrial fibrillation, heart failure, and hypertension. It is likely that the predictive value of atrial fibrillation for hemorrhagic stroke may in part reflect the bleeding risk of warfarin based on an observation of higher rates of warfarin use in patients with atrial fibrillation who suffered a hemorrhagic stroke during follow-up.

Limitations

A number of limitations may be noted of this exploratory analysis. Although stroke fatalities were collected, modified Rankin scores were not available. As a result, we cannot comment on any differential disability as determined by Rankin scores because of stroke across subgroups or between treatments. We do not have data on prerandomization stroke subtype (eg, prior hemorrhagic stroke), which would have been useful to better understand the hemorrhagic stroke risk in general and between randomized treatment groups. With regard to the total events analyses, after a first nonfatal event, subjects may discontinue a blinded study drug, which can result in a higher proportion of subsequent events occurring off the study drug. A total events analysis for the entire IMPROVE-IT population found consistent results in an on-treatment analysis using multiple statistical methods, including the negative binomial approach applied here.[6]

IMPROVE-IT evaluated patients with a recent ACS event, so the results are most relevant to such a population. However, with a median follow-up of 6 years, much of the data were accrued during the stable phase of atherosclerotic disease. Finally, the IMPROVE-IT evaluated a strategy of the addition of ezetimibe to a moderate- to high-intensity statin (simvastatin 40–80 mg) versus moderate- to high-intensity simvastatin alone. The proportionate reduction in LDL-C attributed to ezetimibe beyond statin therapy alone in this study (24%) was similar to that seen in other studies regardless of the background dose (or type) of statin.[22,23] Although it is not possible to specifically address the cardiovascular benefit of the addition of ezetimibe to other statin regimens (eg, atorvastatin 80 mg daily) because it was not studied in IMPROVE-IT, it may be hypothesized that the magnitude of benefit for the addition of ezetimibe would be related to the baseline LDL-C (and therefore the absolute reduction in LDL-C based on a consistent, proportionate reduction in LDL-C with ezetimibe added to statin therapy), rather than the specific statin regimen.[4,5]

Conclusions

The addition of ezetimibe to simvastatin in patients stabilized after ACS reduces the frequency of ischemic stroke, with a particularly large effect seen in patients with a prior stroke.

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AFFILIATIONS

TIMI Study Group, Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (E.A.B., S.D.W., R.P.G., J.-G.P., S.A.M., C.P.C., E.B.). Duke Clinical Research Institute, Durham, NC (M.A.B., J.A.W.). Cardiology Dvision, Geneva University Hospital, Switzerland (F.M.). Departments of Cardiovascular Medicine and Cardiovascular Sciences, University of Leuven, Belgium (F.V.d.F.). Milpark Hospital, Johannesburg, South Africa (A.J.D.). Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand (H.D.W.). Merck & Co., Inc, Kenilworth, NJ (A.M.T.).

FOOTNOTES

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