Supplementary Online Content

Bach RG, Cannon CP, Giugliano RP, et al. Effect of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older: a secondary analysis of a randomized clinical trial. *JAMA Cardiol.* Published online July 17, 2019. doi:10.1001/jamacardio.2019.2306

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Definitions and Statistical Analysis

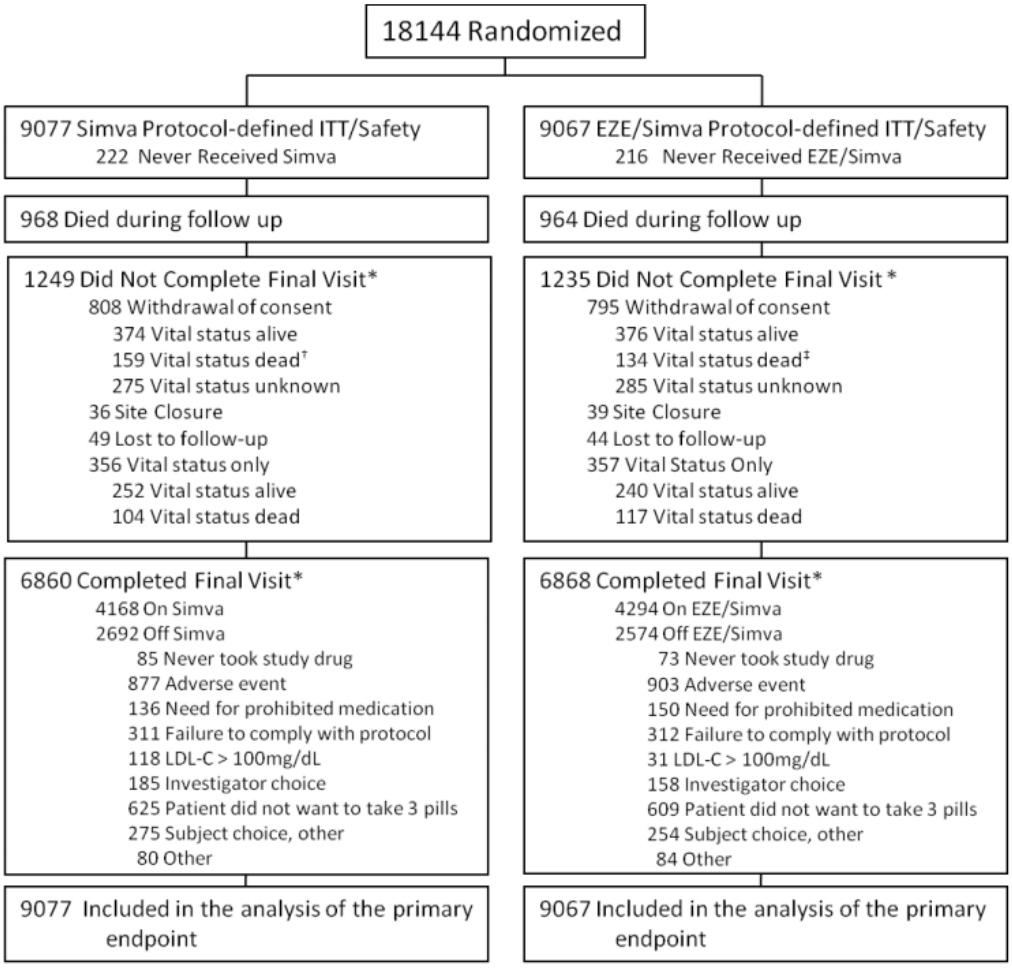
Endpoint definitions

Neurocognitive events included the following event terms: altered state of consciousness, amnesia, aphasia (not related to a stroke or transient ischemic attack), aphonia, cognitive disorder, dementia, altered or depressed consciousness, encephalopathy, lethargy, or impairment of memory, as previously described.[1]

Statistical Analysis

For the analysis of age by treatment group using age as a categorical variable, Kaplan Meier event rates were produced for each outcome by treatment group and age subgroup (defined above). Hazard ratios were generated from Cox models that included age subgroup, treatment, age by treatment interaction and the randomization strata. Continuous variables are shown by means ± standard deviation, median, 25th and 75th percentiles, minimum and maximum values. Categorical variables are shown with counts and percentages. Database management and all analyses were performed by the Duke Clinical Research Institute using raw data, independent of the sponsor.

eFigure. Consort Diagram of the Total ITT Population of IMPROVE-IT[2]



*Final visits occurred on or after May 1, 2014; Vital status recorded in 2014.
†Includes 28 CV deaths, 16 non-CV deaths during follow up and 115 deaths > 4 months after last contact (30 non-CV death, 85 unknown deaths); ‡Includes 14 CV deaths, 14 non-CV deaths during follow up and 106 deaths > 4 months after last contact (27 non-CV death, 79 unknown deaths)

The final study disposition of all study participants is summarized in eFigure 1. Vital status after January 1, 2014 was obtained in 96.0% of all randomized participants. At study conclusion, there were 93 participants who were lost to follow-up and 75 participants from closed sites without known vital status. Vital status was identified for 713 participants who were lost prior to the close out period. During the study, 1603 subjects withdrew consent (1.6%/year) where vital status was obtained in 1043 subjects, including 42 subjects experiencing a cardiovascular death. The number of subjects categorized as site closure, lost to follow-up and withdrawn of consent was similar between randomized treatment groups. Assessment of percent of potential follow-up for the primary endpoint and all-cause mortality: For the primary endpoint subject-years of follow-up was based on the day of randomization to the day of the first occurrence of a primary endpoint event or the last office or phone visit, or day of death during follow-up; potential subject-years of follow-up was based on the day of randomization to the day of the 39 first occurrence of a primary endpoint event or the end of study, which was 5/1/2014 or the last visit on or after 5/1/2014, or the day of death. For all-cause mortality subject-years of follow-up was based on the day of randomization to the last known alive day or day of death; potential subject-years of follow-up was based on the day of randomization to the end of study, or the day of death. Percent of potential follow-up equals (subject-years of follow-up / potential subject-years of follow-up) x 100. Reproduced from Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372(25):2387-2397. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

eTable 1. Patient Disposition and Follow-up for the Total ITT Population and According to Age Group

	Total		Age < 65		Age 65-74		Age >= 75	
	Simva N=9077	**Simva/Ez N=9067**	**Simva N=5129**	**Simva/Ez N=5044**	**Simva N=2520**	**Simva/Ez N=2653**	**Simva N=1428**	**Simva/Ez N=1370**
Subjects randomized	9077	9067	5129	5044	2520	2653	1428	1370
Received at least one dose of allocated drug	8853/9077 (97.5%)	8847/9067 (97.6%)	5023/5129 (97.9%)	4932/5044 (97.8%)	2457/2520 (97.5%)	2597/2653 (97.9%)	1373/1428 (96.1%)	1318/1370 (96.2%)
Never received drug	222/9077 (2.4%)	216/9067 (2.4%)	105/5129 (2.0%)	110/5044 (2.2%)	62/2520 (2.5%)	56/2653 (2.1%)	55/1428 (3.9%)	50/1370 (3.6%)
Disposition								
Completed final visit (a)	6860/9077 (75.6%)	6868/9067 (75.7%)	4077/5129 (79.5%)	4037/5044 (80.0%)	1944/2520 (77.1%)	2009/2653 (75.7%)	839/1428 (58.8%)	822/1370 (60.0%)
Died before final visit (b)	968/9077 (10.7%)	964/9067 (10.6%)	316/5129 (6.2%)	301/5044 (6.0%)	290/2520 (11.5%)	333/2653 (12.6%)	362/1428 (25.4%)	330/1370 (24.1%)
Completed on study drug	4168/9077 (45.9%)	4294/9067 (47.4%)	2564/5129 (50.0%)	2617/5044 (51.9%)	1166/2520 (46.3%)	1249/2653 (47.1%)	438/1428 (30.7%)	428/1370 (31.2%)
Completed off study drug	2692/9077 (29.7%)	2574/9067 (28.4%)	1513/5129 (29.5%)	1420/5044 (28.2%)	778/2520 (30.9%)	760/2653 (28.6%)	401/1428 (28.1%)	394/1370 (28.8%)
Reasons for drug discontinuation								
Never took study drug	85	73	45	33	21	21	19	19
Adverse event	877	903	455	499	293	285	129	119
Need for prohibited medication	136	150	67	77	48	50	21	23
Failure to comply with protocol	311	312	195	189	81	77	35	46
LDL > 100	118	31	88	29	26	2	4	0
Investigator choice	185	158	107	87	48	44	30	27
Patient did not want to take 3 pills	625	609	329	306	173	192	123	111
Subject choice, other	275	254	179	141	63	72	33	41
Other	80	84	48	59	25	17	7	8

(continued)

	Total		Age < 65		Age 65-74		Age >= 75	
	Simva N=9077	**Simva/Ez N=9067**	**Simva N=5129**	**Simva/Ez N=5044**	**Simva N=2520**	**Simva/Ez N=2653**	**Simva N=1428**	**Simva/Ez N=1370**
Did not complete final visit (a)	1249/9077 (13.8%)	1235/9067 (13.6%)	736/5129 (14.3%)	706/5044 (14.0%)	286/2520 (11.3%)	311/2653 (11.7%)	227/1428 (15.9%)	218/1370 (15.9%)
Withdrew consent	808/9077 (8.9%)	795/9067 (8.8%)	439/5129 (8.6%)	436/5044 (8.6%)	199/2520 (7.9%)	215/2653 (8.1%)	170/1428 (11.9%)	144/1370 (10.5%)
Vital status - alive	374	376	219	217	91	105	64	54
Vital status - dead	159	134	44	34	45	40	70	60
Vital status - searched, unknown	275	285	176	185	63	70	36	30
Site closure	36/9077 (<0.5%)	39/9067 (<0.5%)	20/5129 (<0.5%)	29/5044 (0.6%)	10/2520 (<0.5%)	9/2653 (<0.5%)	6/1428 (<0.5%)	1/1370 (<0.5%)
Vital status only	356/9077 (3.9%)	357/9067 (3.9%)	235/5129 (4.6%)	207/5044 (4.1%)	74/2520 (2.9%)	79/2653 (3.0%)	47/1428 (3.3%)	71/1370 (5.2%)
Vital status - alive	252	240	197	170	35	44	20	26
Vital status - dead	104	117	38	37	39	35	27	45
Lost to follow-up	49/9077 (0.5%)	44/9067 (0.5%)	42/5129 (0.8%)	34/5044 (0.7%)	3/2520 (<0.5%)	8/2653 (<0.5%)	4/1428 (<0.5%)	2/1370 (<0.5%)

eTable 2. Baseline Characteristics by Age Subgroup and Treatment

	Age <65		Age 65-74		Age ≥75	
	Simva N=5129	**Simva/Ez N=5044**	**Simva N=2520**	**Simva/Ez N=2653**	**Simva N=1428**	**Simva/Ez N=1370**
Demographics						
Age (yrs)						
Mean +/- SD	57.0 +/- 5.3	57.0 +/- 5.3	69.7 +/- 2.9	69.6 +/- 2.8	79.8 +/- 3.7	79.8 +/- 3.7
Median (25th, 75th percentiles)	57.6 (53.5, 61.1)	57.6 (53.5, 61.1)	69.6 (67.1, 72.2)	69.5 (67.2, 71.9)	79.2 (77.0, 81.9)	79.0 (76.9, 81.9)
(Min, Max)	(22.9, 65.0)	(24.5, 65.0)	(65.0, 75.0)	(65.0, 75.0)	(75.0, 98.5)	(75.0, 95.8)
Male - no. (%)	4085 (79.6%)	4020 (79.7%)	1860 (73.8%)	1912 (72.1%)	941 (65.9%)	910 (66.4%)
Caucasian - no. (%)	4201 (82.0%)	4115 (81.7%)	2149 (85.3%)	2259 (85.2%)	1274 (89.3%)	1204 (87.9%)
Weight (kg)						
Mean +/- SD	85.8 +/- 18.3	85.7 +/- 18.5	81.5 +/- 15.8	81.2 +/- 15.7	75.5 +/- 13.6	76.0 +/- 13.5
Median (25th, 75th)	84.0 (73.0, 96.0)	83.9 (73.5, 95.3)	80.0 (70.0, 91.0)	80.0 (70.0, 90.7)	75.0 (66.0, 84.5)	75.0 (67.0, 84.4)
(Min, Max)	(40.0, 189.2)	(34.9, 224.5)	(40.8, 159.0)	(35.9, 149.2)	(40.0, 128.6)	(42.3, 134.5)
Body mass index (kg/m^2)						
Mean +/- SD	28.9 +/- 5.6	28.8 +/- 5.5	28.1 +/- 4.8	28.1 +/- 4.8	26.7 +/- 4.1	26.9 +/- 4.2
Median (25th, 75th)	27.9 (25.1, 31.7)	27.8 (25.2, 31.5)	27.5 (24.8, 30.5)	27.4 (24.9, 30.6)	26.6 (24.1, 29.1)	26.4 (24.1, 29.2)
(Min, Max)	(16.1, 90.1)	(13.0, 87.7)	(14.5, 66.5)	(15.1, 52.9)	(15.2, 48.0)	(13.0, 50.6)
Comorbidities - no. (%)						
Diabetes	1265 (24.7%)	1241 (24.6%)	791 (31.4%)	816 (30.8%)	418 (29.3%)	402 (29.3%)
Hypertension	2821 (55.0%)	2801 (55.6%)	1700 (67.5%)	1776 (67.0%)	1036 (72.6%)	1003 (73.2%)
Current smoker	2380 (46.4%)	2234 (44.3%)	511 (20.3%)	589 (22.2%)	144 (10.1%)	120 (8.8%)
History of CVD	234 (4.6%)	204 (4.0%)	236 (9.4%)	262 (9.9%)	168 (11.8%)	162 (11.8%)
History of PAD	206 (4.0%)	185 (3.7%)	180 (7.1%)	185 (7.0%)	132 (9.3%)	117 (8.5%)
MI prior to index ACS	913 (17.8%)	951 (18.9%)	585 (23.2%)	635 (23.9%)	383 (26.9%)	339 (24.8%)
PCI prior to index ACS	900 (17.6%)	886 (17.6%)	561 (22.3%)	585 (22.1%)	335 (23.5%)	295 (21.5%)
CABG prior to index ACS	304 (5.9%)	307 (6.1%)	296 (11.8%)	345 (13.0%)	242 (17.0%)	190 (13.9%)

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SD, standard deviation; Simva, simvastatin monotherapy; Simva/Ez, simvastatin plus ezetimibe.

eTable 3. Serum LDL Cholesterol and the Effects of Simvastatin Monotherapy and Combination Simvastatin-Ezetimibe by Age at Randomization

	Age <65		Age 65-74		Age 65-74	
	Simva N=5129	**Simva/Ez N=5044**	**Simva N=2520**	**Simva/Ez N=2653**	**Simva N=1428**	**Simva/Ez N=1370**
LDL cholesterol (mg/dL)						
Baseline						
Mean +/- SD	83.3 +/- 24.0	82.8 +/- 24.2	79.0 +/- 23.4	79.1 +/- 22.8	78.5 +/- 22.5	77.8 +/- 23.1
Median (25th, 75th)	82.0 (67.0, 99.0)	82.0 (66.0, 97.0)	77.0 (62.0, 93.0)	78.0 (64.0, 92.0)	76.0 (63.0, 91.0)	76.0 (62.0, 91.0)
Year 1						
Mean +/- SD	72.0 +/- 23.6	54.9 +/- 23.1	67.0 +/- 20.8	51.7 +/- 22.0	66.5 +/- 22.3	49.4 +/- 20.5
Median (25th, 75th)	69.0 (57.0, 83.0)	51.0 (41.0, 64.0)	66.0 (53.0, 77.0)	48.0 (38.0, 60.0)	64.0 (53.0, 76.0)	46.0 (36.0, 57.0)
Change from baseline (Year 1)						
Mean +/- SD	-11.0 +/- 27.0	-27.9 +/- 27.8	-12.2 +/- 26.2	-27.2 +/- 27.7	-11.6 +/- 25.8	-28.6 +/- 26.2
Median (25th, 75th)	-11.0 (-29.0, 5.0)	-28.0 (-45.0, -13.0)	-12.0 (-27.0, 3.0)	-27.0 (-44.0, -12.0)	-11.0 (-27.0, 3.0)	-28.0 (-44.0, -14.0)

LDL, low-density lipoprotein; Simva, simvastatin monotherapy; Simva/EZ, simvastatin plus ezetimibe; SD, standard deviation.

eTable 4. HDL-C, Triglycerides, and hs-CRP by Age Group and Treatment

	Simva			Simva/Ez		
	Age <65 N=5129	**Age 65-74 N=2520**	**Age ≥75 N=1428**	**Age <65 N=5044**	**Age 65-74 N=2653**	**Age ≥75 N=1370**
HDL-C (mg/dL)						
Baseline						
N	5041	2480	1403	4946	2604	1344
Mean +/- SD	40.0 +/- 10.6	42.4 +/- 11.6	43.9 +/- 12.1	40.0 +/- 10.9	42.0 +/- 10.7	43.9 +/- 11.1
Median (25th, 75th)	38.0 (33.0, 45.0)	41.0 (34.0, 49.0)	42.0 (35.0, 51.0)	38.0 (33.0, 45.0)	41.0 (35.0, 48.0)	43.0 (36.0, 50.0)
Year 1						
N	4094	1899	949	3931	2017	923
Mean +/- SD	47.0 +/- 13.2	49.1 +/- 13.2	51.0 +/- 13.8	47.2 +/- 12.5	50.2 +/- 12.8	52.2 +/- 13.3
Median (25th, 75th)	45.0 (38.0, 54.0)	47.0 (40.0, 56.0)	49.0 (41.0, 59.0)	45.0 (39.0, 54.0)	49.0 (41.0, 57.0)	51.0 (43.0, 61.0)
Change from baseline (Yr 1)						
N	4050	1883	937	3882	1993	914
Mean +/- SD	7.0 +/- 9.4	6.9 +/- 9.0	7.4 +/- 9.7	7.4 +/- 9.2	8.2 +/- 9.3	8.2 +/- 9.6
Median (25th, 75th)	6.0 (1.0, 12.0)	6.0 (1.0, 12.0)	7.0 (1.0, 13.0)	7.0 (2.0, 12.0)	8.0 (2.0, 13.0)	8.0 (2.0, 14.0)
Triglycerides (mg/dL)						
Baseline						
N	5044	2482	1404	4950	2604	1345
Mean +/- SD	148.7 +/- 67.9	134.1 +/- 57.1	123.2 +/- 50.9	147.9 +/- 69.5	135.8 +/- 58.6	125.7 +/- 51.5
Median (25th, 75th)	134.0 (102.0, 178.0)	122.0 (95.0, 159.0)	113.0 (89.0, 145.0)	133.0 (102.0, 177.0)	124.5 (96.0, 161.0)	115.0 (91.0, 150.0)
Year 1						
N	4097	1902	951	3935	2020	923
Mean +/- SD	145.1 +/- 97.0	128.6 +/- 71.5	119.2 +/- 59.4	126.6 +/- 78.0	114.8 +/- 58.0	105.9 +/- 50.3
Median (25th, 75th)	122.0 (86.0, 177.0)	110.0 (83.0, 156.0)	107.0 (80.0, 139.0)	108.0 (79.0, 150.0)	101.0 (76.0, 135.0)	94.0 (73.0, 123.0)

Change from baseline (Yr 1)						
N	4055	1887	940	3889	1996	915
Mean +/- SD	-2.3 +/- 90.4	-5.2 +/- 63.7	-2.8 +/- 53.6	-21.3 +/- 79.4	-20.1 +/- 58.2	-21.5 +/- 48.9
Median (25th, 75th)	-9.0 (-42.0, 26.0)	-9.0 (-36.0, 20.0)	-5.0 (-31.0, 20.0)	-22.0 (-56.0, 10.0)	-20.0 (-48.0, 7.0)	-19.0 (-45.0, 2.0)
hs-CRP (mg/dL)						
Baseline						
N	5024	2459	1388	4931	2586	1332
Mean +/- SD	20.9 +/- 30.8	20.8 +/- 28.9	24.9 +/- 33.1	21.2 +/- 31.0	23.0 +/- 33.3	23.5 +/- 32.9
Median (25th, 75th)	9.2 (3.9, 25.5)	9.3 (3.9, 25.4)	12.2 (4.6, 31.7)	9.2 (3.8, 25.3)	9.8 (3.8, 28.1)	11.1 (4.1, 29.0)
Year 1						
N	4137	1921	961	3983	2034	937
Mean +/- SD	3.6 +/- 8.0	4.2 +/- 12.6	4.2 +/- 12.2	3.2 +/- 9.8	3.5 +/- 9.7	3.3 +/- 7.6
Median (25th, 75th)	1.6 (0.8, 3.6)	1.6 (0.8, 3.5)	1.6 (0.8, 3.4)	1.3 (0.6, 2.8)	1.3 (0.7, 2.9)	1.2 (0.6, 2.7)
Change from baseline (Yr 1)						
N	4077	1890	940	3920	1996	918
Mean +/- SD	-17.3 +/- 30.7	-16.2 +/- 29.3	-19.7 +/- 33.8	-17.8 +/- 31.4	-19.0 +/- 32.8	-17.7 +/- 28.5
Median (25th, 75th)	-6.6 (-21.0, -1.7)	-6.5 (-20.8, -1.5)	-8.0 (-24.9, -1.9)	-7.0 (-21.8, -1.9)	-7.5 (-24.8, -2.1)	-7.7 (-21.6, -2.2)

HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; Simva, simvastatin monotherapy; Simva/Ez, simvastatin plus ezetimibe; SD, standard deviation.

eTable 5. Hemorrhagic Strokes in IMPROVE-IT Occurring >30 Days After Stopping Study Drug, by Age Group and Treatment (Cox Proportional Hazards Model)

	Simva	Simva/Ez
Age group (at risk for late ICH*)		
Late hemorrhagic stroke and <75	7/7452 (0.1%)	18/7505 (0.2%)
Late hemorrhagic stroke and ≥75	2/1369 (0.1%)	9/1315 (0.7%)

* Patients at risk for late hemorrhagic strokes (post treatment) include all patients that received treatment. Late hemorrhagic stroke events are hemorrhagic strokes that occur >30 days after stopping drug. Patients that had a hemorrhagic stroke while on treatment were not included. Analysis by Cox proportional hazards model adjusted for qualifying event diagnosis, lipid-lowering experience, and EARLY-ACS treatment assignment.

Simva, simvastatin monotherapy; Simva/Ez, simvastatin plus ezetimibe.

eReferences

1. Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol : A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol.* 2017;2(5):547-555.

2. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med.* 2015;372(25):2387-2397.