Supplemental Appendix

eTable 1. Kaplan-Meier cumulative incidence for drop-out over the 7-year study period, by treatment and level of eGFR

	eGFR <45		eGFR 45–59		eGFR 60–89		eGFR ≥90	
	S alone (N=532)	Ez/S (N=486)	S alone (N=1359)	Ez/S (N=1384)	S alone (N=4748)	Ez/S (N=4824)	S alone (N=2372)	Ez/S (N=2310)
Cumulative Incidence for Drop-Out (95% CI)								
Year 1	2.6 (1.6, 4.4)	3.5 (2.2, 5.5)	1.9 (1.3, 2.8)	2.9 (2.1, 3.9)	3.2 (2.7, 3.8)	3.2 (2.8, 3.8)	2.4 (1.9, 3.1)	3.8 (3.1, 4.7)
Year 2	3.6 (2.3, 5.5)	4.3 (2.8, 6.5)	3.6 (2.7, 4.7)	4.4 (3.5, 5.7)	4.5 (4.0, 5.2)	4.4 (3.8, 5.0)	3.9 (3.2, 4.8)	4.8 (4.0, 5.8)
Year 3	4.3 (2.9, 6.4)	4.9 (3.3, 7.3)	4.3 (3.4, 5.6)	4.9 (3.9, 6.2)	5.5 (4.9, 6.2)	5.3 (4.7, 6.0)	4.8 (4.0, 5.7)	5.9 (5.0, 6.9)
Year 4	4.9 (3.4, 7.1)	5.5 (3.8, 8.0)	5.1 (4.1, 6.5)	5.2 (4.2, 6.6)	6.1 (5.5, 6.9)	6.1 (5.5, 6.8)	5.7 (4.8, 6.7)	6.4 (5.5, 7.5)
Year 5	5.6 (3.9, 8.0)	6.7 (4.8, 9.4)	5.6 (4.5, 7.0)	6.4 (5.2, 7.8)	6.6 (5.9, 7.3)	6.7 (6.0, 7.4)	6.2 (5.3, 7.3)	7.0 (6.1, 8.2)
Year 6	6.5 (4.6, 9.1)	7.3 (5.3, 10.2)	5.6 (4.5, 7.0)	6.7 (5.5, 8.2)	7.4 (6.7, 8.2)	7.1 (6.4, 7.9)	7.5 (6.5, 8.7)	8.1 (7.0, 9.4)
Year 7	6.5 (4.6, 9.1)	7.7 (5.6, 10.7)	5.7 (4.6, 7.1)	6.9 (5.7, 8.5)	8.0 (7.2, 8.8)	7.5 (6.8, 8.3)	8.2 (7.1, 9.5)	8.6 (7.5, 9.9)

eGFR = estimated glomerular filtration rate; Ez/S = ezetimibe plus simvastatin; S = simvastatin monotherapy

eTable 2. Absolute incidence rates for the secondary and tertiary clinical composite endpoints, by level of eGFR

	Simvastatin monotherapy (N=9011)	Ezetimibe plus simvastatin (N=9004)
Secondary composite endpoints		
All-cause mortality, major coronary event, or nonfatal stroke		
eGFR <45 mL/min/1.73m^2	296/532 (55.6%)	242/486 (49.8%)
eGFR 45–59 mL/min/1.73m^2	594/1359 (43.7%)	593/1384 (42.8%)
eGFR 60–89 mL/min/1.73m^2	1614/4748 (34.0%)	1557/4824 (32.3%)
eGFR ≥90 mL/min/1.73m^2	723/2372 (30.5%)	683/2310 (29.6%)
Death from cardiovascular disease, nonfatal MI, or nonfatal stroke		
eGFR <45 mL/min/1.73m^2	191/532 (35.9%)	143/486 (29.4%)
eGFR 45–59 mL/min/1.73m^2	349/1359 (25.7%)	313/1384 (22.6%)
eGFR 60–89 mL/min/1.73m^2	792/4748 (16.7%)	764/4824 (15.8%)
eGFR ≥90 mL/min/1.73m^2	362/2372 (15.3%)	320/2310 (13.9%)
Tertiary composite endpoint		
All-cause mortality		
eGFR <45 mL/min/1.73m^2	205/532 (38.5%)	164/486 (33.7%)
eGFR 45–59 mL/min/1.73m^2	286/1359 (21.0%)	299/1384 (21.6%)
eGFR 60–89 mL/min/1.73m^2	540/4748 (11.4%)	564/4824 (11.7%)
eGFR ≥90 mL/min/1.73m^2	189/2372 (8.0%)	183/2310 (7.9%)

Data presented as n/N (%).
eGFR = estimated glomerular filtration rate; MI = myocardial infarction.

eTable 3. Unadjusted and adjusted hazard ratios comparing combination therapy with monotherapy for adverse safety events of special interest, at prespecified eGFR values

Safety Endpoint	Unadjusted Models		Adjusted Models*	
	HR (95% CI)	Interaction P-value	HR (95% CI)	Interaction P-value
Gallbladder-related events		0.716		0.748
eGFR 45 mL/min/1.73m^2	0.84 (0.62, 1.13)		0.84 (0.62, 1.13)	
eGFR 60 mL/min/1.73m^2	0.86 (0.71, 1.05)		0.86 (0.70, 1.05)	
eGFR 75 mL/min/1.73m^2	0.88 (0.75, 1.03)		0.87 (0.75, 1.03)	
eGFR 90 mL/min/1.73m^2	0.90 (0.73, 1.11)		0.89 (0.72, 1.10)	
eGFR 105 mL/min/1.73m^2	0.92 (0.67, 1.26)		0.91 (0.67, 1.25)	
ALT, AST, or both ≥3x ULN		0.333		0.323
eGFR 45 mL/min/1.73m^2	0.89 (0.63, 1.26)		0.89 (0.63, 1.26)	
eGFR 60 mL/min/1.73m^2	1.11 (0.87, 1.42)		1.11 (0.87, 1.42)	
eGFR 75 mL/min/1.73m^2	1.25 (0.94, 1.67)		1.26 (0.95, 1.68)	
eGFR 90 mL/min/1.73m^2	1.16 (0.91, 1.47)		1.17 (0.92, 1.49)	
eGFR 105 mL/min/1.73m^2	1.07 (0.72, 1.60)		1.09 (0.74, 1.63)	
Myopathy, rhabdomyolysis, or myalgia with CK ≥5x ULN		0.588		0.632
eGFR 45 mL/min/1.73m^2	0.91 (0.51, 1.62)		0.93 (0.52, 1.66)	
eGFR 60 mL/min/1.73m^2	1.08 (0.66, 1.74)		1.07 (0.66, 1.74)	
eGFR 75 mL/min/1.73m^2	1.10 (0.62, 1.94)		1.08 (0.61, 1.91)	
eGFR 90 mL/min/1.73m^2	0.84 (0.51, 1.40)		0.84 (0.51, 1.40)	
eGFR 105 mL/min/1.73m^2	0.66 (0.28, 1.51)		0.65 (0.28, 1.54)	

*Adjusted for age, sex, race, weight, diabetes, hypertension, smoking status, baseline Killip class, and baseline medications (beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, aspirin, statin therapy) at time of qualifying event.

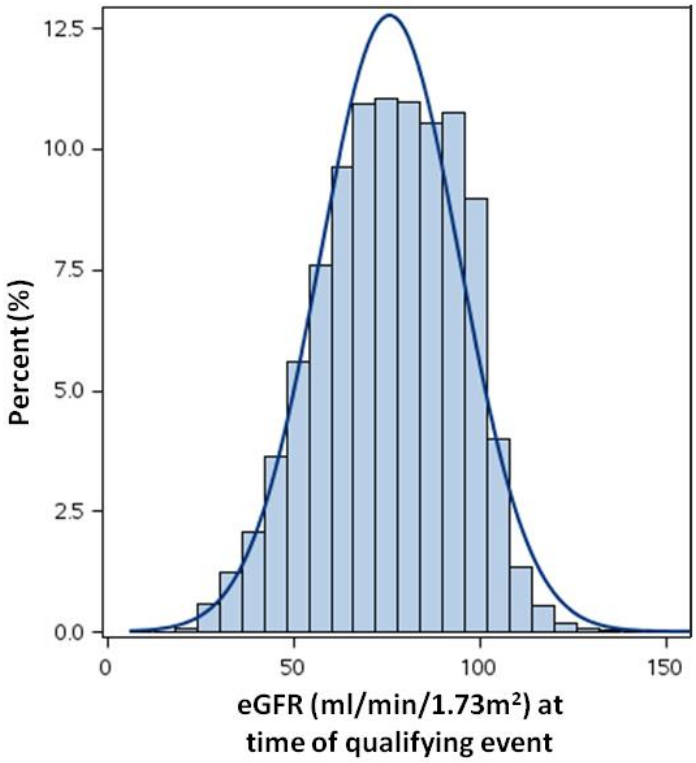
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; CK = creatine kinase; eGFR = estimated glomerular filtration rate; Ez/S = ezetimibe plus simvastatin; HR = hazard ratio; S = simvastatin monotherapy; ULN = upper limit of normal.

eTable 4. Summary changes of eGFR over 7-year follow-up, on-treatment.

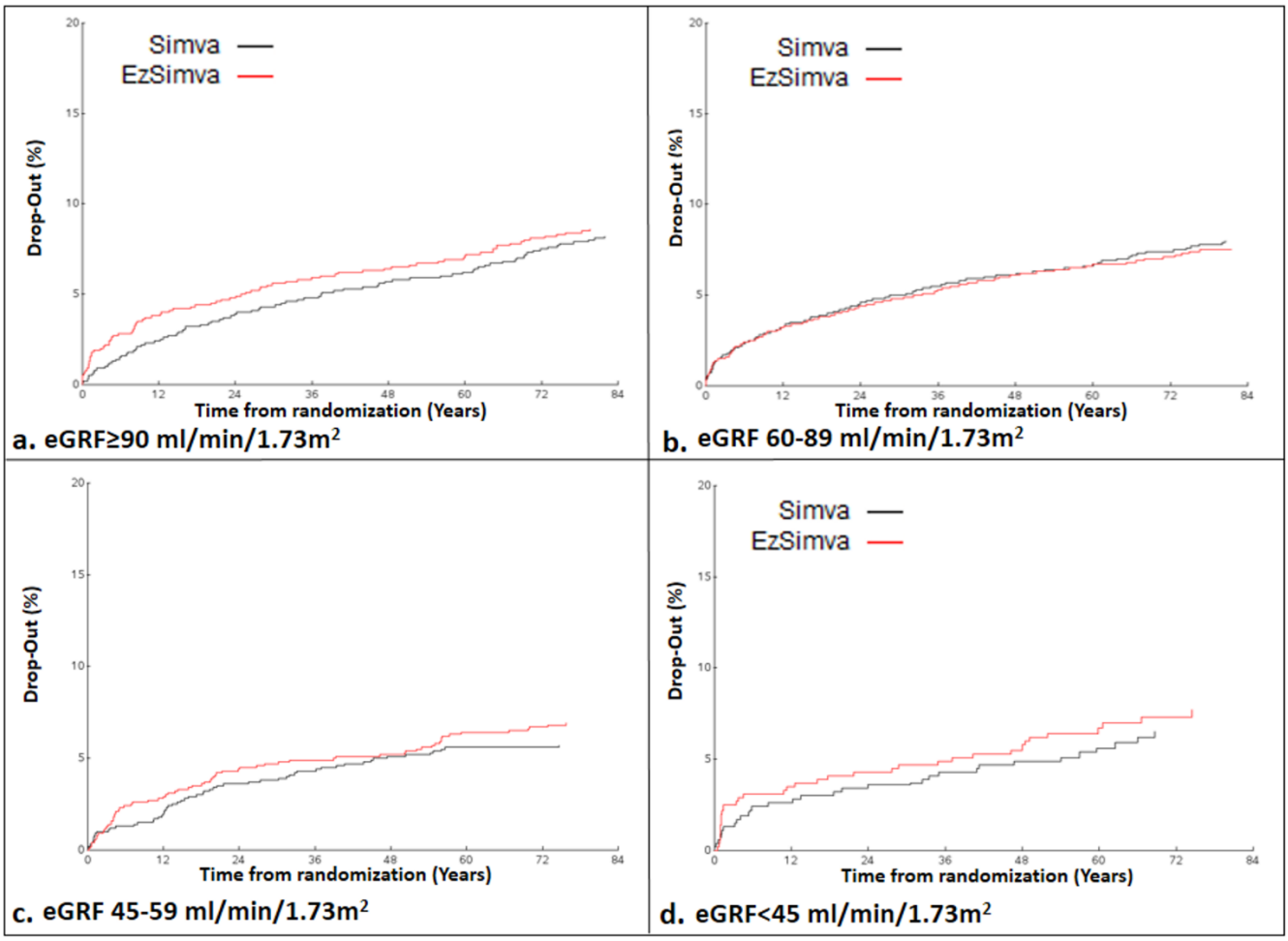
	Simvastatin monotherapy	Ezetimibe plus simvastatin	Total
Qualifying event (N)	8799	8793	17592
Mean (SD)	76.0 (18.9)	75.8 (18.6)	75.9 (18.7)
Median (IQR)	76.7 (62.7, 90.9)	76.3 (62.9, 90.4)	76.6 (62.8, 90.6)
Year 1 (N)	7081	7026	14107
Mean (SD)	72.1 (16.6)	72.0 (16.8)	72.1 (16.7)
Median (IQR)	72.4 (61.3, 84.0)	72.2 (60.9, 83.9)	72.3 (61.1, 84.0)
Year 2 (N)	6032	6119	12151
Mean (SD)	72.4 (16.9)	72.1 (16.8)	72.2 (16.9)
Median (IQR)	72.6 (61.1, 84.6)	72.4 (61.1, 84.1)	72.5 (61.1, 84.3)
Year 3 (N)	5454	5527	10981
Mean (SD)	72.2 (17.0)	72.2 (17.3)	72.2 (17.2)
Median (IQR)	72.5 (61.0, 84.5)	72.4 (60.8, 84.6)	72.5 (60.8, 84.6)
Year 4 (N)	4954	5059	10013
Mean (SD)	72.6 (17.6)	72.8 (17.6)	72.7 (17.6)
Median (IQR)	72.8 (61.0, 85.2)	73.1 (60.7, 85.7)	73.0 (60.9, 85.4)
Year 5 (N)	3981	4095	8076
Mean (SD)	74.4 (18.4)	74.6 (18.1)	74.5 (18.3)
Median (IQR)	75.1 (61.7, 88.4)	75.2 (62.3, 88.3)	75.2 (62.0, 88.4)
Year 6 (N)	2967	3039	6006
Mean (SD)	75.0 (18.5)	75.7 (18.5)	75.3 (18.5)
Median (IQR)	75.7 (62.6, 89.6)	76.4 (63.5, 90.0)	76.1 (63.0, 89.7)
Year 7 (N)	2193	2254	4447
Mean (SD)	77.3 (18.5)	77.7 (18.9)	77.5 (18.7)
Median (IQR)	78.5 (64.8, 92.1)	79.3 (64.7, 92.9)	78.9 (64.7, 92.5)

IQR = interquartile range; SD = standard deviation

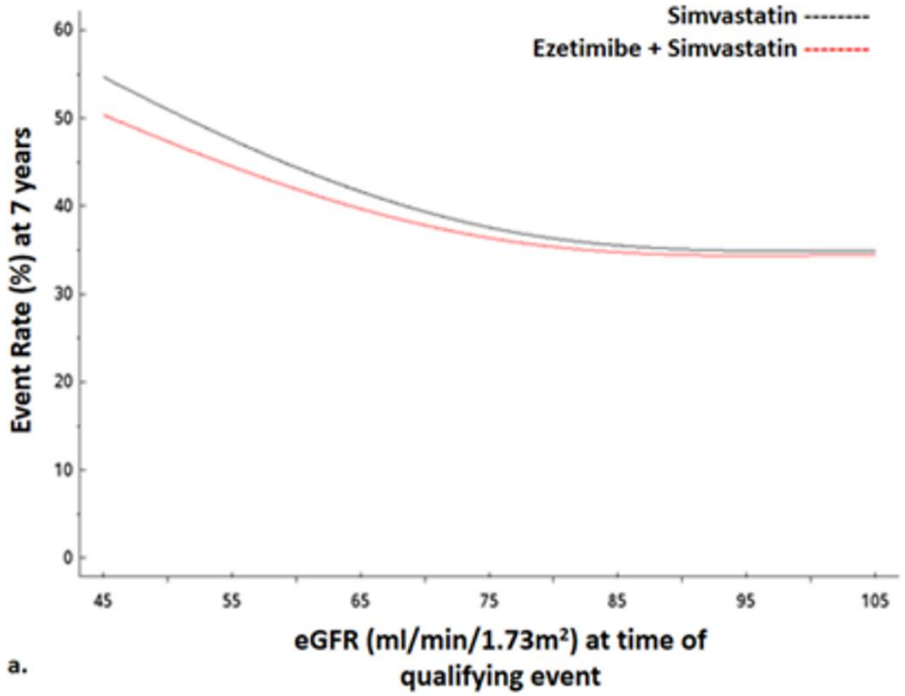
eFigure 1. A histogram with an overlying normal distribution bell-curve showing the distribution of eGFR at the time of qualifying event for individuals in IMPROVE-IT (N=18,015)



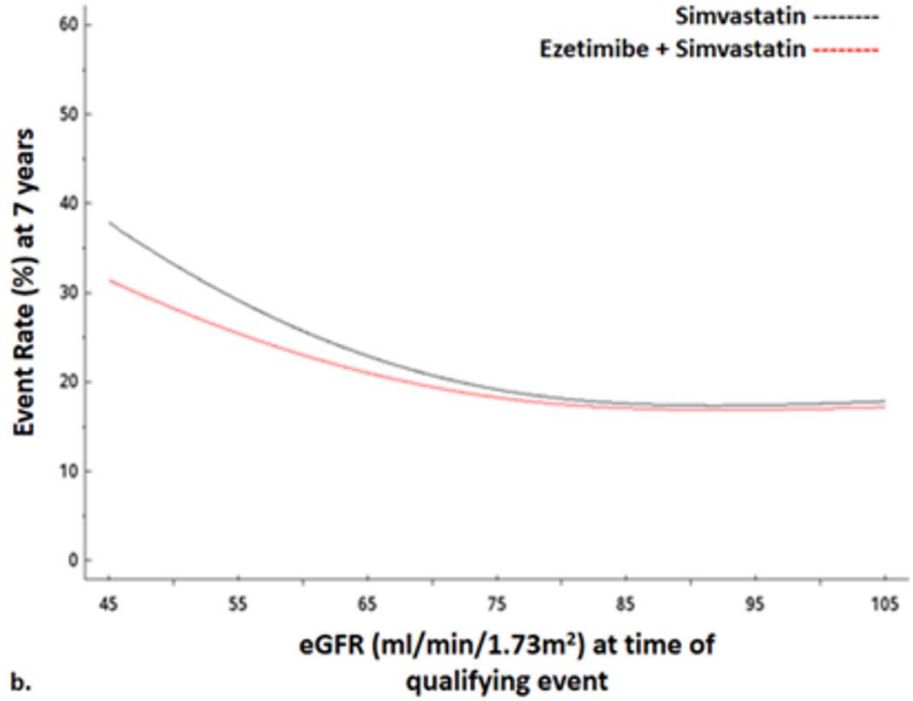
eFigure 2. Kaplan-Meier curves for drop-out during the overall 7-year study period, stratified by: a) eGFR ≥90 mL/min/1.73m^2; b) eGFR 60–89 mL/min/1.73m^2; c) eGFR 45–59 mL/min/1.73m^2; and d) eGFR <45 mL/min/1.73m^2



eFigure 3. Cox proportional hazards models, by eGFR, with respect to the secondary endpoints of (**a**) all-cause mortality, major coronary events, or nonfatal stroke (p=0.246), and (**b**) death from cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke (p=0.067)



a.



b.

eFigure 4. On-treatment changes in mean eGFR over the 7-year follow-up period, with corresponding 95% confidence intervals