Online Appendix Table-A: *Baseline characteristics of all randomized patients**

	All A N = 735	All E/S N = 494
Gender %		
Female	50.9	55.3
Age (years)		
Mean (SD)	59.7 (10.4)	59.3 (10.2)
Race %		
Asian	3.5	4.3
Black	10.5	14.6
Hispanic American	9.4	8.5
Native American	0.3	1.2
Other	1.0	2.2
White	75.4	69.2
BMI (kg/m^2)		
N	733	493
Mean (SD)	33.6 (7.4)	33.6 (7.2)
NCEP ATP III (%)		
CHD or CHD risk equivalent[†]	100	99.8
CHD	15.4	14.8
Other forms of atherosclerosis[‡]	12.2	10.9
Diabetes	100	99.8
≥2 CHD (10 years >20%) risk factors	11.3	8.3
Metabolic Syndrome (%)§	86.5	86.6
Waist Circumference >102 cm (males) or >88 cm (females)	76.1	75.9
TG ≥1.7 mmol/l	65.3	63.0
HDL-C <<1.04 (males) or <1.30 (females) mmol/l	53.1	52.6
Blood pressure ≥130/85 mmHg or on antihypertensive medication	84.2	83.6
Fasting glucose ≥5.6 mmol/l or diabetic	98.6	99.0
Visit 2 LDL-C Strata mmol/l (%)		
≥2.59-<3.36	36.7	36.8
≥3.36-<4.14	34.4	34.2
≥4.14-<4.92	19.2	19.4
≥4.92	9.7	9.5

All A=Atorvastatin (10, 20, 40 mg/day) pooled across all doses.
All E/S= Ezetimibe/Simvastatin (10/20, 10/40 mg/day) pooled across all doses.
ATP = Adult Treatment Panel; CHD = coronary heart disease; LDL-C = LDL-cholesterol; NCEP = National Cholesterol Education Program; TG=triglycerides.
*Data are derived from all patients randomized, including a patient in the E/S 10/40 group who was inadvertently randomized and did not have diabetes at baseline; [†]Patients with CHD and CHD-equivalent risk may be in more than one category of CHD, other forms of atherosclerosis, and diabetes (where diabetes is defined as baseline fasting glucose ≥7.0 mmol/l [≥126 mg/dl] on two or more occasions, or a diagnosis of diabetes, or use of antidiabetic medications); [‡]Other forms of atherosclerosis are peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, transient ischemic attack, and stroke. §Metabolic syndrome defined as 3 or more of the characteristics listed below (2); Conventional unit conversion factors: To convert LDL-C to mg/dl, divide by 0.0259; TG to mg/dl, divide by 0.0113; glucose to mg/dl, divide by 0.0555

On-line Appendix Table-B. ***Baseline and study-end values for efficacy parameters***

Efficacy Parameter†‡	A 10 mg (n=237)	E/S 10/20 mg (n=238)	A 20 mg (n=240)	E/S 10/40 mg (n=242)	A 40 mg (n=241)
LDL-C (mmol/l)					
Baseline mean (SD)	3.8 (0.8)	3.8 (0.8)	3.8 (0.8)	3.7 (0.8)	3.8 (0.8)
Endpoint mean (SD)	2.3 (0.6)	1.8 (0.6)	2.1 (0.7)	1.6 (0.6)	1.9 (0.7)
HDL-C (mmol/l)					
Baseline mean (SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Endpoint mean (SD)	1.2 (0.3)	1.2 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)
TG (mmol/l)					
Baseline median (SD) §	2.2 (1.2)	2.0 (1.2)	2.0 (1.2)	2.0 (1.1)	2.0 (1.3)
Endpoint median (SD) §	1.6 (0.9)	1.5 (0.8)	1.5 (0.7)	1.4 (0.7)	1.4 (1.0)
Non-HDL-C (mmol/l)					
Baseline mean (SD)	4.8 (1.0)	4.7 (1.0)	4.8 (1.0)	4.7 (0.9)	4.8 (0.9)
Endpoint mean (SD)	3.2 (0.8)	2.5 (0.7)	2.8 (0.8)	2.3 (0.7)	2.6 (0.8)
ApoB (g/l)					
Baseline mean (SD)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)
Endpoint mean (SD)	1.0 (0.2)	0.8 (0.2)	0.9 (0.3)	0.8 (0.2)	0.9 (0.2)
ApoAI (gl/l)					
Baseline mean (SD)	1.6 (0.2)	1.5 (0.2)	1.6 (0.3)	1.6 (0.3)	1.6 (0.2)
Endpoint mean (SD)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.3)	1.5 (0.2)
hsCRP (nmol/l)					
Baseline median (SD)§	22.9 (43.4)	27.6 (39.0)	23.8 (40.8)	27.6 (39.9)	24.8 (46.1)
Endpoint median (SD)§	21.0 (44.7)	20.0 (34.6)	21.9 (39.0)	16.2 (32.8)	15.2 (31.9)

Apo =apolipoprotein; HDL-C =HDL-cholesterol; hsCRP =high-sensitivity C-reactive protein; LDL-C =LDL-cholesterol; SD=standard deviation; TG =triglycerides

†LS mean values for efficacy parameters at baseline and week 6 in the modified intent-to-treat population.

‡Clinical laboratory measurements were performed at a certified central laboratory (Pharmaceutical Product Development, Inc/Medical Research Laboratories International [PPD/MRLI], Highland Heights, Kentucky, USA). Lipid measurements were performed according to standards specified by the National Heart, Lung, and Blood Institute, and the Centers for Disease Control and Prevention. LDL-C values were calculated by the method of Friedewald (LDL-C = TC-(HDL-C + TG/5)30. When triglyceride levels were >400 mg/dL (>4.5 mmol/L), direct LDL-C measurements were obtained using the beta-quantitative method. High-sensitivity CRP was measured by the immunonephelometric method (Dade Behring, Inc., Deerfield, Illinois, USA). The highest LDL-C observed was 202.6 mg/dl (5.25 mmol/l) during 6 weeks in these patients.

§Robust SD = interquartile range (IQR)/1.075, where IQR=3rd quartile -1st quartile

Conventional unit conversion factors: To convert cholesterol to mg/dl, divide by 0.0259; TG to mg/dl, divide by 0.0113; Apo to mg/dL, divide by 0.01; hsCRP to mg/l, divide by 9.524

Online Appendix Table-C: Range of effects for baseline factors on efficacy changes by univariate analysis

Factor	Range of Baseline Effects on Treatment-Associated Changes in Efficacy Variables*								
	LDL-C	**% LDL-C† <1.81 mmol/l**	**% LDL-C† <2.59 mmol/l**	**HDL-C**	**TG‡**	**Non–HDL-C**	**ApoB**	**ApoA-I**	**hsCRP‡**
Demographic									
Age <65 vs ≥65 yrs	-5.0 to -1.4§	-7.1 to 11.5¶	-2.6 to 7.0§	1.4 to 4.1‖	-8.8 to 0.8‖	-6.0 to -2.1§	-5.4 to -2.1§	NS	NS
Race/ethnicity other vs Black/Hispanic	2.5 to 11.0§	-21.3 to -6.1§	-15.6 to -1.6§	-4.6 to -2.3§	0.7 to 11.7‖	0.9 to 8.7§	-3.0 to 8.4§	NS	NS
Gender female vs male	-5.3to 1.1‖	3.4 to 17.8¶	4.3 to 8.6¶	0.5 to 4.5‖	-5.3 to -0.5¶	-4.7 to 0.5‖	NS	-1.6 to 3.9‖	NS
Metabolic									
Metabolic syndrome#	NS	NS	NS	-5.8 to -1.7§	1.7 to 14.8§	NS	NS	NS	NS
BMI <30 vs ≥30 kg/m^2	NS	NS	NS	-3.3 to 0.6¶	NS	NS	NS	NS	NS
HbA1C <7 vs ≥7%	0 to 5.2‖	NS	NS	-4.0 to 1.5‖	-4.4 to 9.4‖	2.1 to 4.7§	1.4 to 6.2§	NS	NS
hsCRP <9.52 vs >28.57 nmol/l	0.2 to 5.8§	-16.3 to 9.8¶	NS	NS	NS	0.6 to 4.9§	-1.4 to 5.7§	NS	NS
Baseline lipids (mmol/l)									
LDL-C stratum >2.59 - ≤3.36 vs >4.92	-8.7 to 2.8‖	58.8 to -26.1§	-68.1 to -6.5§	NS	NS	-9.3 to 1.5§	-8.1 to -1.7‖	NS	NS
HDL-C <1.04 vs ≥1.04 (men) <1.30 vs ≥1.30(women)	NS	NS	NS	-5.8 to -4.1§	0.9 to10.4‖	-4.1 to 0.0¶	NS	-4.0 to -1.2§	NS
TG <1.70 vs ≥1.70	NS	NS	NS	1.4 to 7.2§	-14.0 to -9.1§	NS	NS	NS	-8.8 to 13.2¶

Apo =apolipoprotein; HDL-C =HDL-cholesterol; hsCRP =high-sensitivity C-reactive protein; LDL-C =LDL-cholesterol; NS=nonsignificant, $P \geq 0.05$; TG =triglycerides

Univariate analysis of prespecified factor subgroups in the mITT population of the VYTAL study cohort (7). Data were analyzed using SAS software (SAS Institute, Inc. Cary, North Carolina). Treatment by subgroup interactions and subgroup effects on the percent changes in efficacy variables were carried out using an ANCOVA model with terms for statin (E/S and A), baseline LDL-C stratum (≥2.59-<3.36, ≥3.36-<4.14, ≥4.14-<4.92, and ≥4.92 mmol/l), and statin-by-subgroup interaction. Estimates of between-treatment group differences, corresponding 95% CIs and p-values were derived from a similar model where statin was replaced by treatment group (E/S 10/20mg vs A10mg, E/S 10/20mg vs A 20mg, or E/S 10/40mg vs A 40mg). *The difference in least-squares means of percent change from baseline at 6 weeks between the highest (second) and lowest (first) subgroup strata for each treatment group was calculated. The minimum and maximum values are presented for the range of calculated differences (see example below). †Proportion of patients attaining LDL-C <1.81 and 2.59 mmol/l assessed by logistic regression analysis. ‡Analyses based on transformed data, using normal scores rank-transformations for TG and hsCRP; §$P < 0.001$; ‖$P < 0.01$; ¶$P < 0.05$ for subgroup effect. #Metabolic syndrome defined as having 3 or more of the following characteristics: 1) Waist Circumference >102 cm (males) or >88 cm (females), 2) TG ≥1.7 mmol/l, 3) HDL-C <1.04 (males) or <1.30 (females) mmol/l, 4) Blood pressure ≥130/85 mmHg or on antihypertensive medication, 5) Fasting glucose ≥5.6 mmol/l or diabetic (2); Conventional unit conversion factors: To convert cholesterol to mg/dl, divide by 0.0259; TG to mg/dl, divide by 0.0113; hsCRP to mg/l, divide by 9.524.

Range for % change in LDL-C by baseline LDL-C strata:

Treatment	*≥2.59 -≤3.36 mmol/l*	*≥4.92mmol/l*	*Difference*	
A 10	*–35.6*	*–40.9*	*-5.3*	
A 20	*–42.3*	*–45.7*	*-3.4*	
A 40	*–50.1*	*–47.3*	*2.8*	*maximum*
E/S 20	*–53.0*	*–56.8*	*-3.8*	
E/S 20	*–54.5*	*–63.2*	*-8.7*	*minimum*

Online Appendix Table-D—*Associations between baseline factors and efficacy variables in multivariable model*

	Multivariable Efficacy Variables Coefficient Estimates (*P*-value)*								
Factors†	LDL-C	LDL-C‡ <1.81 mmol/l	LDL-C‡ <2.59 mmol/l	HDL-C	TG§	Non-HDL-C	ApoB	ApoA-I	hsCRP§
Treatment (All E/S>All A)	-11.28¶	4.82¶	3.75¶	3.67¶	-0.15‖	-9.54¶	-7.39¶	2.78¶	-0.18¶
Demographic									
Age (years)	-0.23¶	1.03¶#	1.04¶	0.15¶	-0.01¶	-0.22¶	-0.24¶	0.08‖	NS
Race/ethnicity (black/Hispanic vs other)	5.49¶	0.50¶	0.40¶	NS	NS	4.46¶	3.05‖	NS	NS
Gender (male vs female)	NS	NS	NS	NS	-0.11#	-1.98#	NS	NS	NS
Metabolic									
Baseline BMI (kg/m^2)	NS	NS	NS	-0.14‖	NS	NS	NS	NS	0.01¶
Baseline HbA1C (%)	NS	NS	NS	NS	NS	NS	1.10#	NS	NS
Baseline hsCRP (nmol/l)	0.11#	NS	NS	NS	NS	0.10#	0.13#	NS	-0.04‖
Baseline lipids (mmol/l)									
LDL-C	-0.03#	NS	NS	-0.10¶	0.02¶	-0.04¶	-0.05¶	NS	NS
HDL-C	NS	NS	NS	-0.24¶	NS	-0.10‖	NS	-0.17¶	-0.01#
TG	NS	1.01¶	1.01¶	NS	NS	NS	NS	NS	NS
Non–HDL-C	NS	0.96¶	0.96¶	0.11¶	-0.02¶	NS	NS	NS	NS

Apo = apolipoprotein; BMI = body mass index; A1C = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; All ezetimibe/simvastatin (E/S) = 10/20 and 10/40 mg/day pooled across doses; All atorvastatin (A) = 10, 20, 40 mg pooled across doses.

* % change from baseline by multiple regression analysis. Data were compiled and analyzed using SAS software (SAS Institute, Inc. Cary, North Carolina).Coefficient estimates indicate the percent change in efficacy variables and percentage point increase for attainment of LDL-C <1.81 and <2.59 mmol/l related to the continuous (age, BMI, A1C, lipids, hsCRP) and categorical (treatment, race, gender) factors. For example, the coefficient estimate for the treatment effect on LDL-C lowering was -11.28% indicating an 11.28 percentage point larger reduction in LDL-C for patients on ezetimibe/simvastatin versus atorvastatin, while the coefficient for race/ethnicity was 5.49% indicating a 5.49 percentage point smaller reduction in LDL-C for Black/Hispanic subjects compared to Others.

†Factors assessed as continuous variables were: age (each 1-yr increase), BMI (each 1-kg/m2 increase); HbA1C (each 1% increase); hsCRP (each 1-nmol/l increase) and LDL-C, HDL-C, TG and non-HDL-C (each 1-mmol/l increase). For these continuous baseline factors, the coefficients represent the percentage change associated with a one unit increase with the baseline factor. Factors for inclusion in the final model were identified using a backward selection process, removing factors one-at-a-time until all remaining factors were significant at 5% levels, ‡Odds ratio by logistic regression analysis; §Analyses based on transformed data, using normal scores rank-transformations for TG and hsCRP; #Although age was significant in the continuos model, it was no longer significant in the categorical model, possibly due to a loss of power in the dichotomous classification (<65 and ≥65years). Model robustness was assessed by comparison of results with a model that included MetS (2).

¶P<0.001; ‖P<0.010; #P<0.05; NS=not significant (P>0.05). Conventional unit conversion factors: To convert cholesterol to mg/dl, divide by 0.0259; TG to mg/dl, divide by 0.0113; Apo to mg/dL, divide by 0.01; hsCRP to mg/l, divide by 9.524.

On-line appendix Figure S1. Multivariable association of categorical factors with the percent change from baseline in triglycerides (A), ApolipoproteinA-I (B) and hsCRP (C). Percent change for A and C are based on medians due to non-normal distribution. P-values (*p<0.05, **p<0.01,***p<0.001) correspond to the significance of marked (*) category compared with lowest category for the variable. BL=baseline.