SUPPLEMENTARY DATA

**Supplementary Table 1.** Baseline characteristics of full cohort. Adapted from (Guyton et al, JACC 2008;51:1564-1572).

| Characteristic | ***N*** **(n=272)** | | ***E/S*** **(n=272)** | | ***E/S+N*** **(n=676)** | |
|---|---|---|---|---|---|---|
| **Age yr [Mean (SD)]** | 56.4 | (10.6) | 57.5 | (10.3) | 56.9 | (10.9) |
| **Sex n (%)** | | | | | | |
| Female | 136 | (50.0) | 120 | (44.1) | 352 | (52.1) |
| **Race n (%)** | | | | | | |
| Asian | 11 | ( 4.0) | 4 | (1.5) | 11 | (1.6) |
| Black | 13 | ( 4.8) | 17 | (6.3) | 38 | (5.6) |
| Hispanic | 14 | ( 5.1) | 11 | (4.0) | 49 | (7.2) |
| Other | 3 | (1.1) | 0 | (0.0) | 2 | (0.3) |
| White | 231 | (84.9) | 240 | (88.2) | 576 | (85.2) |
| **BMI (kg/m2) [Mean (SD)]** | 30.1 | (5.9) | 30.3 | (6.0) | 29.8 | (5.5) |
| **FSG (mg/dL) [Mean (SD)]** | 101.4 | (19.4) | 101.6 | (14.1) | 101.6 | (18.1) |
| **NCEP Risk Category n (%)** | | | | | | |
| CHD/CHD risk equivalent* | 69 | (25.4) | 84 | (30.9) | 183 | (27.1) |
| High risk with AVD† | 29 | (10.7) | 36 | (13.2) | 77 | (11.4) |
| CHD | 16 | (5.9) | 22 | (8.1) | 60 | (8.9) |
| Other forms of atherosclerosis‡ | 16 | (5.9) | 18 | (8.1) | 34 | (5.0) |
| High risk w/o AVD | 40 | (14.7) | 48 | (17.6) | 106 | (15.7) |
| Diabetes | 40 | (14.7) | 43 | (15.8) | 105 | (15.5) |
| ≥2 CHD (10yr>20%) risk factors | 15 | (5.5) | 22 | ( 8.1) | 42 | (6.2) |
| **Metabolic Syndrome§ n (%)** | 127 | (46.7) | 156 | (57.4) | 319 | (47.2) |
| Waist Circumference >102 cm (males) or >88 cm (females) | 142 | (52.2) | 150 | (55.1) | 363 | (53.7) |
| TG ≥1.69 mmol/L | 138 | (50.7) | 155 | (57.0) | 347 | (51.3) |
| HDL-C <1.01mmol/L (males) or <1.29mmol/L (females) | 94 | (34.6) | 91 | (33.5) | 217 | (32.1) |
| Blood pressure >130/85 mmHg or on antihypertensive medication | 166 | (61.0) | 181 | (66.5) | 431 | (63.8) |
| Fasting glucose >5.6mmol/L or diabetic | 117 | (43.0) | 153 | (56.3) | 305 | (45.1) |

***N*** = Extended release Niacin (titrated to 2 g)***; E/S*** = Ezetimibe / Simvastatin 10/20 mg***;*** BMI = Body Mass Index

*Patients with coronary heart disease (CHD) and CHD risk equivalents may be in more than one category of CHD, other forms of Atherosclerosis, and diabetes
(where diabetes is defined as: baseline fasting glucose >= 126 mg/dL on 2 or more occasions, or a diagnosis of diabetes, or use of antidiabetic medications).

† AVD = atherosclerotic vascular disease

‡ Other forms of atherosclerosis are peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, TIA, and stroke.

§ Defined as having ≥3 of the following characteristics below

¶Percentages are based upon number (m) of partients with baseline HDL-C Levels

SUPPLEMENTARY DATA

**Supplementary Table 2.** Number of patients with new onset DM

| | 0-24 weeks n (%) | | | | | 24-64 weeks n (%) | | | Cumulative 64 weeks n (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***N**** (n=232) | ***E/S*** (n=229) | ***E/S+N*** (n=569) | ***P*-value‡** | ***P*-value§** | ***E/S*** (n=229) | ***E/S+N*** (n=569) | ***P*-value§** | ***E/S*** (n=229) | ***E/S+N*** (n=569) | ***P*-value§** |
| New-Onset of DM† | 5 (2.2) | 3‖ (1.3) | 25 (4.4) | 0.153 | 0.033 | 4 (1.7) | 3 (0.5) | 0.109 | 7 (3.1) | 28 (4.9) | 0.338 |
| Initiated use of anti-diabetic medications | 0 (0.0) | 2 (0.9) | 2 (0.5) | NA | NA | 1 (0.4) | 3 (0.5) | NA | 3 (1.3) | 5 (0.9) | NA |
| Consecutive elevations FG ≥7.0mmol/l | 5 (2.2) | 2 (0.9) | 24 (4.2) | NA | NA | 3 (1.3) | 1 (0.2) | NA | 5 (2.2) | 25 (4.4) | NA |
| Diagnosis of type 2 DM | 0 (0.0) | 1 (0.4) | 2 (0.4) | NA | NA | 1 (0.4) | 1 (0.2) | NA | 2 (0.9) | 3 (0.5) | NA |
| Criteria for DM still applicable at study-end§ | NA | NA | NA | NA | NA | NA | NA | NA | 6 (2.6) | 20 (3.5) | 0.661 |
| Remittance at study-end¶ | NA | NA | NA | NA | NA | NA | NA | NA | 1(0.4) | 8 (1.4) | 0.459 |

***N*** = Extended release Niacin (titrated to 2 g)***; E/S*** = Ezetimibe / Simvastatin 10/20 mg ‡ ***E/S+N*** vs ***N;*** § ***E/S+N*** vs ***E/S;*** *******patients were randomized and treated with ***N*** as described for 24 weeks (Guyton et al, JACC 2008;51:1564-1572), then switched to ***E/S+N*** or ***E/S*** based on a randomized pre-assignment (2:1) for 40 weeks additional; these patients were not included in the 64 week analysis and comprised a supportive secondary analysis group; †Defined as patients who had a DM diagnosis recorded as an adverse event, consecutive FG measurements ≥ 7.0 mmol/L, or initiated an antidiabetic medication during the course of the study; ¶On antidiabetic medication, persistent elevation of FG ≥7.0 mmol/L, or clinical diagnosis of type 2 DM at study-end; ‖Based on-time-to event analysis for new-onset diabetes, 1 additional patient in the ***E/S*** group is listed in the 24-week study that was previously reported in the 64-week study (Fazio et al, J Am J Cardiol. 2010;105:487-494).

SUPPLEMENTARY DATA

**Supplementary Table 3.** Univariate and Multivariable Analyses of New-Onset Diabetes at 24 and 64 Weeks

| | Univariate | | | | Multivariate* | | | |
|---|---|---|---|---|---|---|---|---|
| | 24 weeks (n=1030) | | 64 weeks (n=798) | | 24 weeks (n=1015) | | 64 weeks (n=787) | |
| **Risk Factor** | **OR**† | **95% CI** | **OR**† | **95% CI** | **OR**‡ | **95% CI** | **OR**‡ | **95% CI** |
| Metabolic syndrome (with vs. without) | 9.21 | 3.21,26.44¶ | 6.29 | 2.58,15.32¶ | 6.07 | 2.00, 18.43‖ | 4.12 | 1.59, 10.68‖ |
| Baseline BMI (SD = 5.5), kg/m$^2$ | 1.76 | 1.33, 2.33¶ | 1.76 | 1.34, 2.31¶ | 1.64 | 1.13, 2.37‖ | 1.53 | 1.09, 2.15§ |
| Baseline hsCRP (SD = 57 nmol/L) | 1.28 | 1.06, 1.56§ | 1.43 | 1.18, 1.72¶ | NS | NS | 1.39 | 1.13, 1.70‖ |
| Baseline LDL-C (SD = 0.57 mmol/L) | 0.74 | 0.51, 1.06 | 0.91 | 0.65, 1.28 | 0.73 | 0.50, 1.06 | NT | NT |
| Gender | 1.47 | 0.72, 3.02 | 1.34 | 0.67, 2.65 | NT | NT | NT | NT |
| Race (white vs. non-white) | 0.76 | 0.29, 2.01 | 1.13 | 0.39, 3.27 | NT | NT | NT | NT |
| Age (SD = 10.7 years) | 1.45 | 1.00, 2.11 | 1.57 | 1.09, 2.25§ | 1.49 | 1.01, 2.21§ | 1.63 | 1.10, 2.43§ |
| Metabolic Syndrome Components††: | | | | | | | | |
| Waist circumference [>102 cm (males) or >88 cm (females) vs otherwise] | 2.76 | 1.22, 6.23§ | 2.00 | 0.96, 4.16 | NA | NA | NA | NA |
| Baseline TG (≥1.7 vs. <1.7 mmol/L) | 2.16 | 1.01, 4.60§ | 1.64 | 0.81, 3.29 | NA | NA | NA | NA |
| Baseline HDL-C [<1.0 mmol/L (males) or <1.3 mmol/L (females)] | 2.79 | 1.37, 5.69‖ | 2.38 | 1.21, 4.71§ | NA | NA | NA | NA |
| Blood pressure ≥130/85 mmHg or on antihypertensive medication (yes vs no) | 3.60 | 1.37, 9.42‖ | 2.58 | 1.11, 5.98§ | NA | NA | NA | NA |
| Fasting glucose (≥ 5.6 vs. < 5.6 mmol/L)‡‡ | NA | NA‖ | NA | NA‖ | NA | NA | NA | NA |
| Weight change (wk 24 minus baseline [SD=3.0 lbs]); (wk 64 minus baseline [SD=4.0 lbs]) | 0.98 | 0.68, 1.41 | 0.90 | 0.61, 1.34 | NT | NT | NT | NT |
| Treatment effect:§§ | | | | | | | | |
| ***E/S+N* vs. *E/S*** | 5.22 | 1.23, 22.20§ | 1.64 | 0.71, 3.81 | 7.34 | 1.66, 32.45§ | 2.33 | 0.94, 5.78 |
| ***E/S+N vs. N*** | 2.09 | 0.79, 5.52 | NA | NA | 2.18 | 0.80, 5.91 | NA | NA |

***E/S***=ezetimibe/simvastatin***; N***=Niaspan; NT=not tested, did not meet criterion for multivariate analysis; NA=not available. NS=non-significant; The 24 week analyses was performed in all nondiabetic patients at baseline treated with ***E/S, E/S+N*** and ***N*** and the 64-week analyses in all patients in the 24-week analysis originally randomized to ***E/S+N*** or ***E/S*** and continued these therapies during 64 weeks. *Factors with P<0.25 in the univariate analysis were assessed by multivariate analysis using multiple logistic-regression model. Factors with the largest P-value were removed, one at a time, by backwards-elimination, until all remaining factors had P-values <0.10. Treatment group was included in the model regardless of significance due to its primary role in the original study. †Odds Ratios (ORs), 95% CIs, and *P*-values estimated from simple logistic regression model; ORs for the continuous variables represent the increased odds of new-onset diabetes based on a 1-SD increase in the risk factor; ‡Adjusted ORs, 95% CIs, and *P*-values estimated from multiple logistic regression model; adjusted ORs for the continuous variables represent the increased odds of new-onset diabetes based on a 1-SD increase in the risk factor. ††Metabolic syndrome defined as ≥3 of the 5 of the characteristics below (Grundy et al., Circulation 2005; 112:2735-2752); the multivariate model excluded the 5 individual components due to their role in defining metabolic syndrome; ‡‡OR and 95% CIs not available for FG due to complete separation in the model as all patients with new-onset diabetes had baseline FG ≥5.6 mmol/L; §§Treatment effect (week 24: ***E/S+N*** vs. ***E/S*** and ***E/S+N*** vs. ***N***; week 64: ***E/S+N*** vs. ***E/S***); final model includes factors adjusting for treatment. §$P < 0.05$, ‖$P < 0.01$, ¶$P < 0.001$. To convert SI units to mg/dL: for cholesterol divide by 0.0259, triglycerides divide by 0.0113, glucose divide by 0.0555.

SUPPLEMENTARY DATA

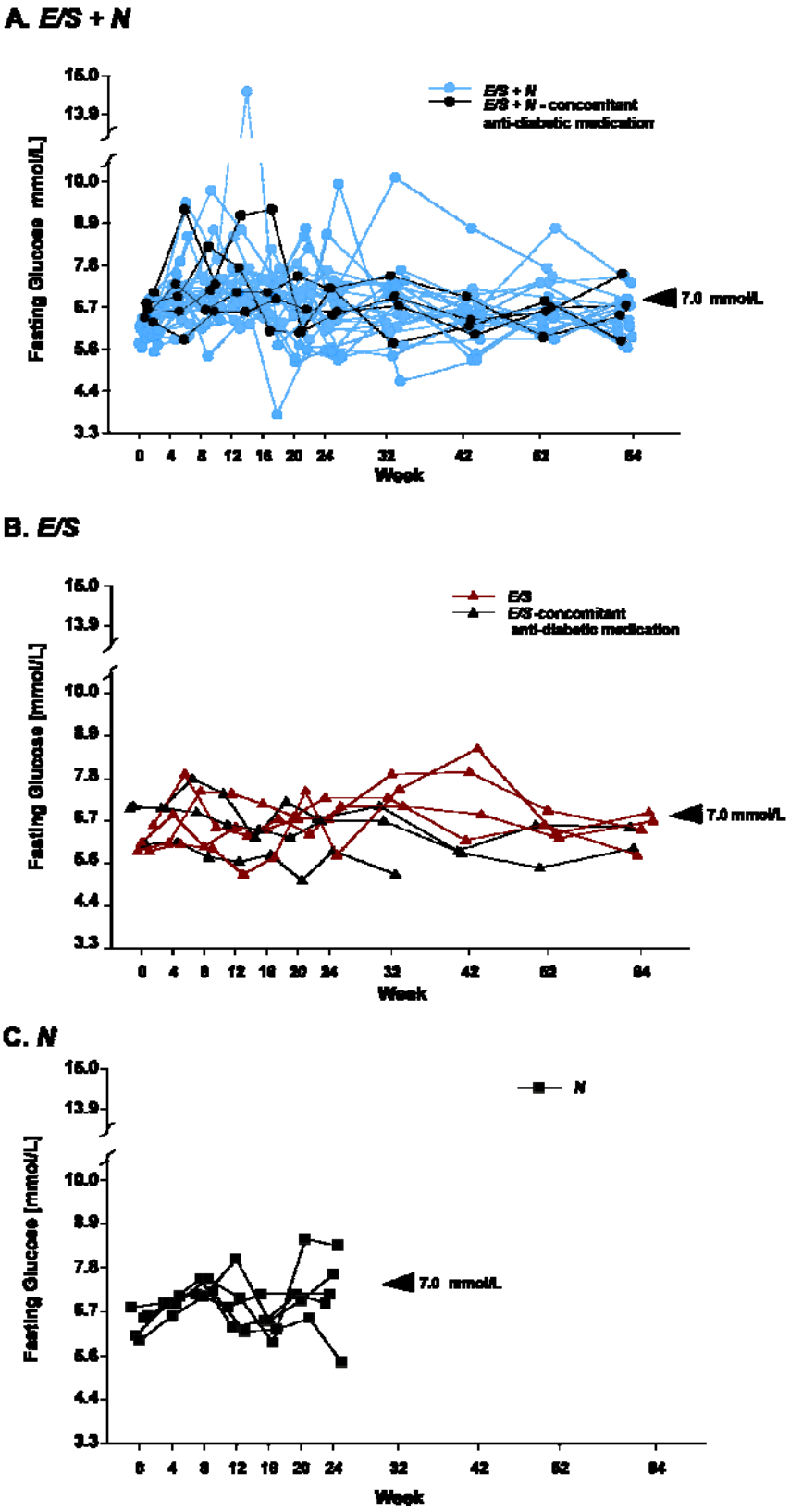
**Supplementary Table 4.** Univariate and Multivariate Analyses of Fasting Glucose Changes (mmol/L) from baseline for Various Risk Factors*

| | Univariate | | | | Multivariate | | | |
|---|---|---|---|---|---|---|---|---|
| | 24 weeks (n=650) | | 64 weeks (n=418) | | 24 weeks (n=648) | | 64 weeks (n=410) | |
| **Risk Factor** | **FG change†** | **95% CI** | **FG change†** | **95% CI** | **FG change†** | **95% CI** | **FG change†** | **95% CI** |
| Metabolic syndrome (with vs. without) | 0.31 | -1.39, 2.01 | -1.31 | -3.33,0.71 | NT | NT | NS | NS |
| Baseline BMI (SD=5.4) | 1.15 | 0.31,1.99‖ | 0.35 | -0.66, 1.36 | 1.18 | 0.35, 2.01‖ | NT | NT |
| Baseline hsCRP (SD=61 nmol/L) | 0.15 | -0.69,0.99 | 1.16 | 0.15, 2.16§ | NT | NT | 1.08 | 0.10, 2.07§ |
| Baseline LDL-C (SD=0.6 mmol/L) | -0.18 | -1.03, 0.66 | 0.07 | -0.94, 1.08 | NT | NT | NT | NT |
| Gender (male vs. female) | 0.03 | -1.66, 1.72 | -1.00 | -3.03, 1.03 | NT | NT | NT | NT |
| Race (white vs. non-white) | 0.57 | -2.33, 3.46 | -1.02 | -5.00, 2.96 | NT | NT | NT | NT |
| Age (SD=10.4 years) | 0.27 | -0.58, 1.11 | 0.74 | -0.27, 1.75 | NT | NT | 0.92 | -0.07, 1.90§ |
| Metabolic Syndrome Components:†† | | | | | | | | |
| Waist circumference [>102 cm (males) or >88 cm (females) vs. otherwise] | 1.37 | -0.33, 3.06 | 0.21 | -1.82, 2.25 | NA | NA | NA | NA |
| Baseline TG (≥1.7 vs <1.7 mmol/L) | 1.73 | 0.04, 3.42§ | 1.32 | -0.70, 3.35 | NA | NA | NA | NA |
| Baseline HDL-C [<1.0 (males) or <1.3 (females) mmol/L vs otherwise] | 0.87 | -0.95, 2.68 | 1.41 | -0.78, 3.60 | NA | NA | NA | NA |
| Blood pressure ≥130/85 mmHg or on antihypertensive medication (yes vs no) | 0.41 | -1.32, 2.14 | -0.35 | -2.45, 1.76 | NA | NA | NA | NA |
| Fasting Glucose (5.6 vs.<5.6 mmol/L ) | -4.63 | -6.32, -2.94¶ | -5.52 | -7.51,-3.53¶ | NA | NA | NA | NA |
| Weight change baseline to wk 24 (SD=3.0 lbs) | 0.82‡‡ | -0.03, 1.66 | 1.16‡‡ | 0.16, 2.17§ | NT | NT | NT | NT |
| Treatment effect:§§ | | | | | | | | |
| ***E/S+N*** vs ***E/S*** | 3.10 | 1.12, 5.08‖ | 4.16 | -2.10, 6.21¶ | 3.16 | 1.20, 5.13¶ | 4.24 | 2.21, 6.28¶ |
| ***E/S+N*** vs ***N*** | -0.80 | -2.95, 1.35 | NA | NA | -0.74 | -2.88, 1.40 | NA | NA |

NT=not tested, did not meet criterion for multivariate analysis; NA=not available; NS=non-significant. *The risk analysis of FG changes from baseline was performed in the same manner as for new-onset diabetes (Table–S3); however, single and multiple linear-regressions were used for the univariate and multivariable analyses, respectively at 24 and 64 weeks in patients who were nondiabetic at baseline with baseline and week-24 and -64 FG assessments. †Parameter estimates, 95% CIs and p-values were assessed by simple regression; estimates and 95% CIs for the continuous variables represent the increase in mean FG changes for a 1 SD unit (mmol/l) increase in the risk factor; estimates and 95% CIs for the categorical variables represent the relative difference in mean FG changes from one level of the risk factor to the second level of the risk factor; ‡Adjusted parameter estimates, 95%CI, and p-values were assessed by multiple regression model using backwards elimination; ††MS defined as ≥3 of the 5 characteristics below (Grundy et al., Circulation 2005; 112:2735-2752); the multivariate model excluded the 5 individual components due to their role in defining metabolic syndrome ‡‡Weight change was excluded from multivariate model, and when included it gave similar estimates; §§Treatment effect (week 24: ***E/S+N*** vs. ***E/S*** and ***E/S+N*** vs. ***N***; week 64: ***E/S+N*** vs. ***E/S***); §p<0.05, ‖p<0.01, ¶p<0.001; To convert SI units to mg/dL: for cholesterol divide by 0.0259, triglycerides divide by 0.0113, glucose divide by 0.0555.

SUPPLEMENTARY DATA

**Supplementary Figure 1.** Individual changes in FG over time in patients with new-onset DM. Those who initiated antidiabetic medication are indicated



SUPPLEMENTARY DATA

## Table of data for Supplementary Figure-1.

| Patient | FG levels [mmol/L]† by Treatment Week | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **0** | **4** | **8** | **12** | **16** | **20** | **24** | **32** | **42** | **52** | **64** |
| ***E/S+N*** | | | | | | | | | | | |
| **1** | 5.8 | 6.9 | 6.8 | 7.3 | 7.5 | 6.5 | 6.4 | 6.3 | na | na | na |
| **2** | 6.2 | 6.5 | 6.2 | 7.8 | 7.5 | 6.8 | 6.1 | 6.3 | 6.5 | 6 | 6.3 |
| **3** | 6.2 | 7.3 | 7 | 6.7 | 6.4 | 5.3 | 5.6 | 6.2 | 6.7 | na | na |
| **4** | 6.3 | 7.3 | 7.5 | 8.6 | 6.7 | 5.4 | 8.7 | 7.1 | 6.3 | 7.4 | 6.2 |
| **5** | 5.7 | 7.2 | 6.2 | 6.4 | 6.8 | 6.9 | 7.7 | 7.3 | 6.9 | 6.4 | 6 |
| **6** | 6.4 | 7.3 | 7.4 | 7 | 7.4 | na | na | na | na | na | na |
| **7** | 6 | 5.9 | 6.3 | 7 | 6.9 | 7.9 | 6.2 | 6 | 6.4 | 6.3 | 6.9 |
| **8** | **6.4** | **7.3** | **6.7** | **7.1** | **7.1** | **7.5** | **7.2** | **7.5** | **7** | **5.9** | **6.5** |
| **9** | 6.4 | 6.6 | 7.1 | 6.8 | 7 | 7.1 | 6.3 | 7.4 | 6.7 | 6.1 | 6.7 |
| **10** | 5.9 | 7.6 | 5.4 | 6.3 | 6.5 | 5.7 | 5.7 | 5.4 | 6.4 | 6 | na |
| **11** | **6.8** | **7** | **8.3** | **7.8** | **6.1** | **6** | **7.2** | **5.8** | **6.2** | **6.9** | **5.8** |
| **12** | 6 | 6.8 | 7.1 | 6.2 | 8.3 | 7 | 5.6 | 7.4 | 6.2 | na | na |
| **13** | **6.7** | **6.6** | **7.2** | **9.2** | **9.3** | **6.1** | **6.5** | **7** | **6.4** | **6.6** | **7.6** |
| **14** | 6.9 | 7.9 | 9.8 | 8.8 | 7.5 | 7.2 | 7 | 10.2 | 8.8 | 7.8 | na |
| **15** | 6.4 | 6.6 | 6.7 | 7.8 | 6.2 | 7.7 | 7.4 | 7.3 | 5.3 | 6.7 | 5.7 |
| **16** | 5.9 | 6.4 | 7.4 | 7.4 | 7.3 | 8.6 | 7.2 | 6.9 | 7.2 | 7 | 6.8 |
| **17** | 6.3 | 7.1 | 7.2 | 6.9 | 7 | 7.2 | 6.8 | 6.2 | 7 | 7.4 | 7.5 |
| **18** | 5.9 | 6.7 | 8.8 | 7 | 7.2 | 8.8 | 6.4 | 6.5 | 6.5 | 6 | 6.9 |
| **19** | **6.3** | **5.9** | **6.6** | **6.6** | **6.9** | **6.7** | **6.6** | **6.8** | **6** | **6.7** | **6.8** |
| **20** | **7.1** | **9.3** | **7.3** | na | na | na | na | na | na | na | na |
| **21** | 5.6 | 7.3 | 7.2 | 6.9 | 3.9 | 5.6 | 5.3 | 6.9 | 5.5 | 6.8 | 5.7 |
| **22** | 6.5 | 9.5 | 8 | 14.6 | 5.7 | 6.5 | 10 | 4.8 | 5.3 | na | na |
| **23** | 6.7 | 6.7 | 7.4 | 7.7 | 7.4 | 8.3 | 7.2 | 7.7 | 6.8 | 7.5 | 6.9 |
| **24** | 6 | 8.6 | 6.4 | 7.1 | 7.8 | 5.9 | 6.7 | 6.9 | 6.2 | 6.4 | 6.4 |
| **25** | 5.7 | 5.9 | 6.8 | 7.8 | 6.2 | 7.2 | 6.8 | 6.4 | 6.7 | 6.5 | 6.2 |
| **26** | 6.1 | 6.3 | 6.4 | 6.3 | 7.4 | 7 | 5.4 | 5.7 | 5.9 | 5.9 | 6.8 |
| **27** | 6.9 | 7 | 6.7 | 6.8 | 7 | 7.3 | 6.8 | 6.5 | 6.8 | 8.8 | 7.4 |
| **28** | 6.8 | 6.9 | 7.5 | 7 | 6.3 | 6.5 | 7.3 | 7.4 | 6.5 | 6.8 | 5.9 |
| ***E/S*** | | | | | | | | | | | |
| **1** | **7** | **7** | **7.8** | **7.4** | **6.2** | **7.2** | **6.7** | **7** | **5.9** | **6.5** | **6.5** |
| **2** | **7** | **7** | **6.9** | **6.5** | **6.4** | **6.2** | **6.7** | **6.7** | **5.8** | **5.4** | **5.9** |
| **3** | 5.9 | 6.1 | 7.4 | 7.4 | 7.1 | 6.8 | 7.3 | 7.3 | 6.2 | 6.5 | 5.8 |
| **4** | 6.1 | 6.8 | 6 | 6.5 | 6.4 | 6.7 | 6.7 | 7.9 | 7.9 | 6.9 | 6.4 |
| **5** | **6** | **6.1** | **5.7** | **5.6** | **5.8** | **5.1** | **5.9** | **5.3** | na | na | na |
| **6** | 5.9 | 6 | 5.9 | 5.3 | 5.7 | 7.4 | 5.8 | 7.5 | 8.5 | 6.3 | 6.9 |
| **7** | 6.5 | 7.9 | 6.5 | 6.3 | 6.7 | 6.3 | 7 | 7 | 6.8 | 6.2 | 6.7 |
| ***N*** | | | | | | | | | | | |
| **1** | 6.8 | 6.9 | 7.1 | 6.8 | 7.1 | 7.1 | 6.9 | na | na | na | na |
| **2** | 6 | 6.9 | 7.5 | 6.3 | 6.4 | 7.1 | 7.1 | na | na | na | na |
| **3** | 5.9 | 6.5 | 7 | 8 | 6.4 | 6.9 | 7.6 | na | na | na | na |
| **4** | 6.5 | 6.9 | 7.5 | 7 | 5.9 | 8.5 | 8.3 | na | na | na | na |
| **5** | 6.5 | 7 | 7.2 | 6.2 | 6.2 | 6.5 | 5.4 | na | na | na | na |

***N*** = Extended-release niaspan (titrated to 2 g); ***E/S*** = Ezetimibe/Simvastatin 10/20 mg; na=not applicable; †Bolded data indicates concomitant medication usage

SUPPLEMENTARY DATA

**Supplementary Figure 2.**