Baseline factors in diabetic dyslipidemia

Relationships Between Metabolic Syndrome and Other Baseline Factors and the Efficacy of Ezetimibe/Simvastatin and Atorvastatin in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia

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Running title: Baseline factors in diabetic dyslipidemia

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**Objective**—To investigate relationships between baseline factors and treatment-associated efficacy changes in type 2 diabetes.

**Research design and methods**—Multivariable analyses of treatment-response in 1,229 type 2 diabetes patients with hypercholesterolemia, who received ezetimibe/simvastatin or atorvastatin in a randomized, double-blind, 6-week study.

**Results**—Increasing age was related to improvements in all lipid assessments. Men had greater triglyceride and non-HDL-C reductions than women, and Black/Hispanic patients had less favorable lipid-effects than other races/ethnicities. Increasing baseline LDL-C was associated with improvements in most lipids; higher baseline non-HDL-C with improved HDL-C and triglycerides; higher baseline HDL-C with greater non-HDL-C and hsCRP reductions; and higher baseline hsCRP with smaller LDL-C, non-HDL-C and apolipoproteinB reductions. Patients with high baseline non-HDL-C or triglycerides less frequently attained LDL-C targets. Obesity was inversely related to HDL-C and hsCRP changes, and higher baseline HbA1C to apolipoproteinB reductions. Metabolic syndrome was not a significant predictor.

**Conclusions**—Treatment-responses in type 2 diabetes patients were related to baseline factors, though treatment-effects (ezetimibe/simvastatin>atorvastatin) remained consistent. The presence of predictive factors should be considered in planning lipid-altering therapy.
Treatment-response to statins can vary in patients with type 2 diabetes, attributed to various patient-related characteristics, including demographic and metabolic factors, baseline lipid levels, genetic polymorphisms and the metabolic syndrome (MetS) (1-6). This analysis explored relationships between various baseline characteristics and changes in lipids and high-sensitivity C-reactive protein (hsCRP) in the presence/absence of MetS in the Vytorin versus Atorvastatin in Patients With Type 2 Diabetes Mellitus and Hypercholesterolemia (VYTAL) study (7).

RESEARCH DESIGN AND METHODS
This was a post-hoc analysis of the randomized, double-blind, 6-week VYTAL study in 1,229 type 2 diabetes patients with hypercholesterolemia who received ezetimibe/simvastatin (10/20mg/day) versus atorvastatin (10 and 20mg/day) or 10/40mg ezetimibe/simvastatin versus 40mg atorvastatin (7). Type 2 diabetes patients, 18-80 years, with HbA1C levels ≤8.5%, triglycerides ≤4.52mmol/l and LDL-C levels ≥2.59mmol/l were included. This analysis was performed in randomized patients who had baseline and ≥1 post-baseline measurements (modified-intent-to-treat population) (7). Prespecified baseline factors found significant by univariate analysis for association with week-6 percent changes from baseline in lipids and hsCRP were assessed in multivariable linear-regression models using continuous and categorical variables in separate analyses. Factors were identified for inclusion in the final model using a model-based, variable-deletion process. Triglycerides and hsCRP were analyzed in this model using normal-scores-rank-transformations for percent changes. Proportions of patients attaining prespecified LDL-C levels (<1.81 and <2.59mmol/l) were assessed using similar logistic-regression models.

RESULTS
Baseline characteristics and levels of efficacy parameters at baseline and study-end are provided in the online appendix (available at http://care.diabetesjournals.org) Tables A and B (7). Baseline factors found to be significant predictors of percent change by univariate analysis (Appendix Table-C) were further assessed by multivariable analysis. Results of the analyses of baseline predictors on percent changes from baseline are displayed in Fig.1 and Appendix Fig.S1 (categorical), and Appendix Table-D (continuous). Increasing age was significantly related to all efficacy parameters analyzed except hsCRP. Patients ≥65 versus <65 years had greater reductions from baseline in LDL-C, non-HDL-C, apolipoproteinB and triglycerides, better LDL-C target attainment, and larger HDL-C and apolipoproteinA-I increases. Black/Hispanic patients had smaller LDL-C, non-HDL-C and apolipoproteinB reductions, and less LDL-C target attainment than White/Other race/ethnicities. Men had greater triglyceride and non-HDL-C reductions than women. Higher baseline LDL-C was associated with greater reductions in most lipids as well as smaller HDL-C increases and triglyceride reductions, and increasing baseline non-HDL-C with improvements in HDL-C and triglycerides. Higher baseline HDL-C was related to greater non-HDL-C and hsCRP reductions, and smaller HDL-C and apolipoproteinA-I increases. Patients with higher baseline non-HDL-C or triglycerides attained LDL-C targets less frequently. Higher baseline hsCRP levels were related to smaller LDL-C, non-HDL-C and apolipoproteinB reductions, and larger hsCRP reductions. Higher baseline BMI was associated with smaller HDL-C increases and hsCRP reductions, and higher baseline...
Baseline factors in diabetic dyslipidemia

HbA1C with smaller apolipoproteinB reductions. The presence of MetS had no effect. Ezetimibe/simvastatin treatment (versus atorvastatin) was associated with significantly greater improvements in all efficacy variables.

The likelihood of attaining LDL-C <1.81mmol/l was related to the number of positive predictive baseline factors (Fig.1,G-H). Approximately 31% of patients with 0 or 1 factor achieved LDL-C <1.81mmol/l compared with 46.4% with 2 factors, 61.5% with 3 factors, 74.2% with 4 factors and 100% with all 5 factors. Without the treatment factor in the model, 41.6% with 0-1 factors and 75.9% with all 4 factors achieved LDL-C <1.81mmol/l.

DISCUSSION

In this study, age and race/ethnicity significantly predicted LDL-lowering, consistent with previous findings in statin-treated patients (4,5,8). These effects were not attributable to differences in study-therapy adherence, which was high for both age (98.1%-98.2%) and race/ethnicity (95.9%-98.7%) subgroups. Alterations in LDL-metabolism (e.g. diminished very-low-density-lipoprotein particle production), may account for the more robust therapeutic LDL-C-lowering in older patients (9,10). Attenuated LDL-C-lowering responses in Black patients following statin treatment have been linked to single-nucleotide polymorphisms in HMG-CoA reductase (11). The age-associated LDL-C increases observed in this study may reflect altered HDL-mediated cholesterol efflux and/or other physiological functions in older patients (12).

The diminished LDL-C-lowering response observed in hypertriglyceridemic patients may be attributed to the increased prevalence of small, dense LDL-particles in these patients that bind less effectively to LDL-receptors (5,6). Higher baseline HDL-C levels were negatively-related to percent change from baseline in HDL-C, as reported previously (5). Whether MetS provides greater clinical-value than its individual components is debated (13). In this analysis, factors which contribute to MetS (BMI, HbA1C, triglycerides, HDL-C), and the inflammatory marker, hsCRP, were significant predictors of lipid changes; whereas MetS itself was not related to treatment-responses, although there were relatively few subjects without MetS (2,3,6). Higher baseline hsCRP levels were associated with attenuated LDL-C-lowering, an effect not previously noted to our knowledge, and perhaps related to heightened levels of inflammation (9). Obesity-related changes in HDL-C metabolism may account for the smaller HDL-C increases associated with higher BMI (5,14). Since adipose-tissue inflammation in obese patients may strongly influence hsCRP levels, smaller hsCRP reductions observed in obese patients could reflect lesser statin-effectiveness in suppressing adipose versus vascular sources of inflammation (6,9). The association between increasing baseline HbA1C and smaller apolipoproteinB reductions may be related to the presence of small, dense LDL-particles in these patients that vary inversely with HbA1C levels (15).

When considered cumulatively, the baseline factors positive for treatment-response, namely age >65 years, baseline triglycerides <1.7mmol/l, baseline non-HDL-C <4.14mmol/l and race/ethnicity other than Black/Hispanic, predicted attainment of LDL-C <1.81mmol/l irrespective of treatment. These results indicated that Black or Hispanic subjects, those <65 years, and patients with elevated triglycerides and non-HDL-C levels, may require more intensive therapy to attain LDL-C goal than patients without these factors.

It should be noted this exploratory analysis had limited statistical power, and some observations may have been influenced by chance-variation because of multiple
comparisons. Nonetheless, several observations, notably the impact of age and race/ethnicity, are consistent with previous statin studies. In summary, patient-related characteristics can influence efficacy in type 2 diabetes patients with hypercholesterolemia following ezetimibe/simvastatin and atorvastatin treatment. These factors, and particularly the collective presence of positive predictors, should be considered in planning lipid-altering therapies in these patients.

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**Figure Legend**

**Figure 1.** Multivariable association of categorical factors with the percent change from baseline in LDL-C (A), HDL-C (B), non–HDL-C (C) and apolipoproteinB (D). P-values (*p<0.05, **p<0.01, ***p<0.001) in A-D correspond to the significance of marked (*) category compared with lowest category for the variable. Association (logistic-regression) of categorical factors with the attainment of LDL-C <2.59mmol/l (<100mg/dl) (E) and <1.81mmol/l (<70mg/dl) (F). (Note: When non-HDL-C was removed from the multivariable model, baseline LDL-C was a significant factor for attainment of these LDL-C levels, presumably because of the high correlation [r=0.90] of baseline non-HDL-C with baseline LDL-C levels). Proportion of patients who attained LDL-C <1.81 mmol/l (<70 mg/dl) by the number of positive predictive factors in the multivariate model (G and H). The four baseline factors associated with LDL-C <1.81mmol/l: age ≥65 years, baseline triglycerides <1.70 mmol/l (<150 mg/dL), baseline non-HDL C <4.14 mmol/l (160 mg/dl), and race/ethnicity other than black or Hispanic are shown in (G). The four baseline factors additionally with ezetimibe/simvastatin (versus atorvastatin) treatment are shown in (H). n/N=the number of patients with the indicated number of positive factors in the category of all patients assessed for that number. To convert mmol/l to mg/dl, divide by 0.0259. BL=baseline