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

Ronald B. Goldberg, md[1]
John R. Guyton, md[2]
Theodore Mazzone, md[3]
Ruth S. Weinstock, md, phd[4]
Adam B. Polis, ma[5]
Diane Tipping, ms[5]
Joanne E. Tomassini, phd[5]
Andrew M. Tershakovec, md, mph[5]

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 diabetic 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 cholesterol reductions than women, and black/Hispanic patients had less favorable lipid effects than other races/ethnicities. Increasing baseline LDL cholesterol was associated with improvements in most lipids; higher baseline non-HDL cholesterol with improved HDL cholesterol and triglycerides; higher baseline HDL cholesterol with greater non-HDL cholesterol and high-sensitivity C-reactive protein (hs-CRP) reductions; and higher baseline hs-CRP with smaller LDL cholesterol, non-HDL cholesterol, and apolipoprotein B reductions. Patients with high baseline non-HDL cholesterol or triglycerides less frequently attained LDL cholesterol targets. Obesity was inversely related to HDL cholesterol and hs-CRP changes, and higher baseline A1C to smaller apolipoprotein B reductions. Metabolic syndrome was not a significant predictor.

CONCLUSIONS — Treatment responses in type 2 diabetic patients were related to baseline factors, although treatment effects (ezetimibe/simvastatin being more effective than atorvastatin) remained consistent. The presence of predictive factors should be considered in planning lipid-altering therapy.

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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 (hs-CRP) 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 diabetic patients with hypercholesterolemia who received ezetimibe/simvastatin (10/20 mg/day) versus atorvastatin (10 and 20 mg/day) or 10/40 mg ezetimibe/simvastatin versus 40 mg atorvastatin (7). Type 2 diabetic patients, 18–80 years, with A1C levels ≤8.5%, triglycerides ≤4.52 mmol/l, and LDL cholesterol levels ≥2.59 mmol/l were included.

This analysis was performed in randomized patients who had baseline and one or more postbaseline 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 hs-CRP 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 hs-CRP were analyzed in this model using normal-score rank transformations for percent changes. Proportions of patients attaining prespecified LDL cholesterol levels (<1.81 and <2.59 mmol/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 (supplementary Tables A and B, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1762/DC1) (7). Baseline factors found to be significant predictors of percent change by univariate analysis (supplementary 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 supplementary Fig. S1 (categorical) and supplementary Table D (continuous). Increasing age was significantly related to all efficacy parameters analyzed except hs-CRP. Patients aged ≥65 vs. <65 years had greater reductions from baseline in LDL cholesterol, non-HDL cho-

From the [1]University of Miami Miller School of Medicine, Miami, Florida; [2]Duke University, Durham, North Carolina; the [3]University of Illinois, Chicago, Illinois; the [4]State University of New York Upstate Medical University and VA Medical Center, Syracuse, New York; and [5]Merck, North Wales, Pennsylvania.
Corresponding author: Ronald B. Goldberg, rgoldber@med.miami.edu.
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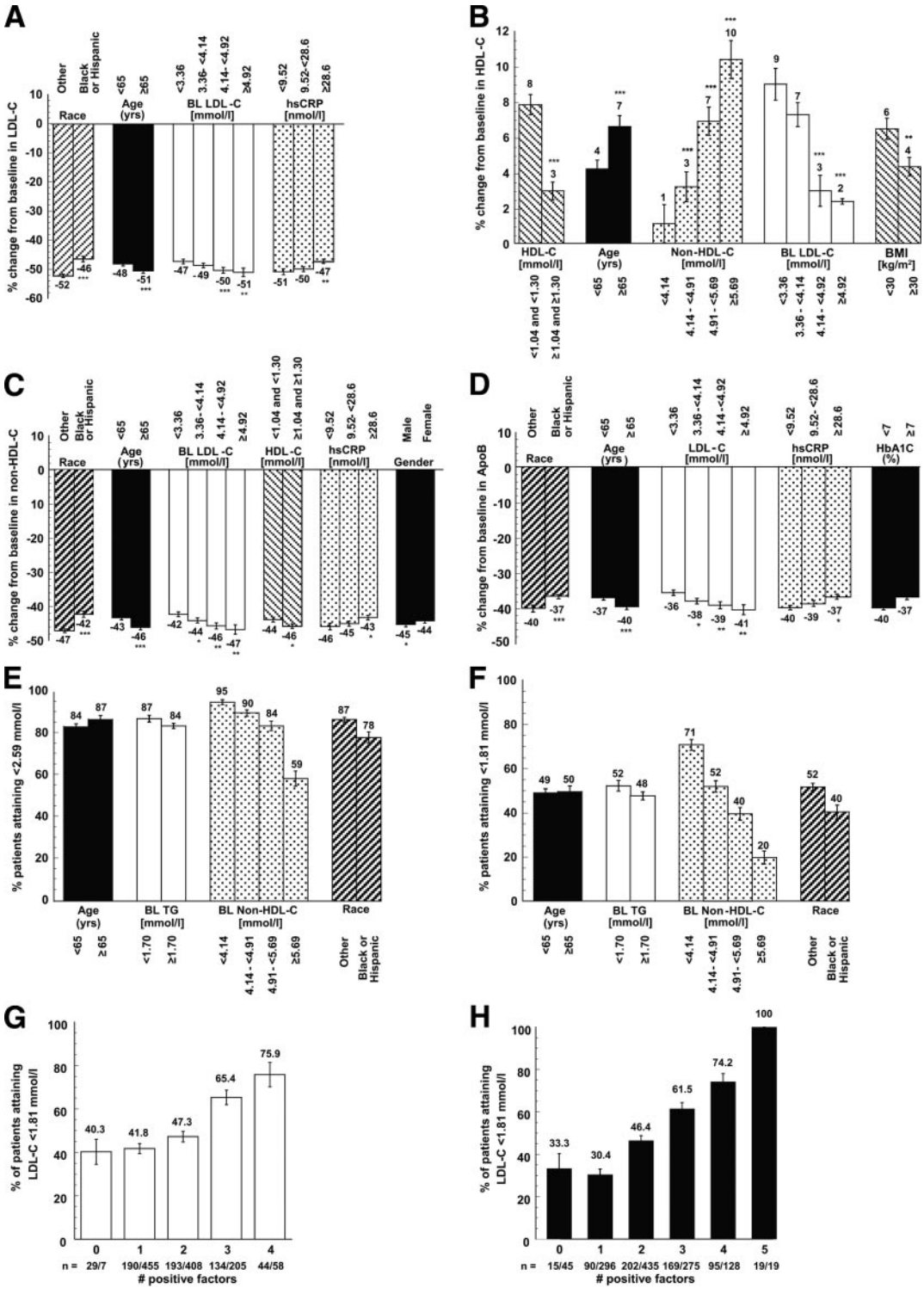

Figure 1—*Multivariable association of categorical factors with the percent change from baseline in LDL cholesterol (LDL-C)* (A)*, HDL cholesterol (HDL-C)* (B)*, non–HDL cholesterol* (C)*, and apolipoprotein B* (D). P *values (*P < 0.05, **P < 0.01, ***P < 0.001) in* A–D *correspond to the significance of marked (*) category compared with lowest category for the variable. Association (logistic regression) of categorical factors with the attainment of LDL cholesterol <2.59 mmol/l (<100 mg/dl)* (E) *and <1.81 mmol/l (<70 mg/dl)* (F) *is shown. (Note: When non-HDL cholesterol was removed from the multivariable model, baseline LDL cholesterol was a significant factor for attainment of these LDL cholesterol levels, presumably because of the high correlation [r = 0.90] of baseline non-HDL cholesterol with baseline LDL cholesterol levels.)* G *and* H*: Proportion of patients who attained LDL cholesterol <1.81 mmol/l (<70 mg/dl) by the number of positive predictive factors in the multivariate model. The four baseline factors associated with LDL cholesterol <1.81 mmol/l, i.e., age ≥65 years, baseline triglycerides <1.70 mmol/l (<150 mg/dl), baseline non-HDL cholesterol <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 (vs. atorvastatin) treatment are shown in* H*. 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. TG, triglyceride.*

lesterol, apolipoprotein B, and triglycerides; better LDL cholesterol target attainment; and larger HDL cholesterol and apolipoprotein A-I increases. Black/Hispanic patients had smaller LDL cholesterol, non-HDL cholesterol, and apolipoprotein B reductions and less LDL cholesterol target attainment than white/other races/ethnicities. Men had greater triglyceride and non-HDL cholesterol reductions than women. Higher baseline LDL cholesterol was associated with greater reductions in most lipids as well as smaller HDL cholesterol increases and triglyceride reductions and increasing baseline non-HDL cholesterol with improvements in HDL cholesterol and triglycerides. Higher baseline HDL cholesterol was related to greater non-HDL cholesterol and hs-CRP reductions and smaller HDL cholesterol and apolipoprotein A-I increases. Patients with higher baseline non-HDL cholesterol or triglycerides attained LDL cholesterol targets less frequently. Higher baseline hs-CRP levels were related to smaller LDL cholesterol, non-HDL cholesterol, and apolipoprotein B reductions and larger hs-CRP reductions. Higher baseline BMI was associated with smaller HDL cholesterol increases and hs-CRP reductions and higher baseline A1C with smaller apolipoprotein B 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 cholesterol <1.81 mmol/l was related to the number of positive predictive baseline factors (Fig. 1*G* and *H*). Approximately 31% of patients with zero or one factor achieved LDL cholesterol <1.81 mmol/l compared with 46.4% with two factors, 61.5% with three factors, 74.2% with four factors, and 100% with all five factors. Without the treatment factor in the model, 41.6% with zero to one factor and 75.9% with all four factors achieved LDL cholesterol <1.81 mmol/l.

CONCLUSIONS — 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 VLDL particle production) may account for the more robust therapeutic LDL cholesterol lowering in older patients (9,10). Attenuated LDL cholesterol–lowering responses in black patients after statin treatment have been linked to single-nucleotide polymorphisms in HMG-CoA reductase (11). The age-associated HDL cholesterol increases observed in this study may reflect altered HDL-mediated cholesterol efflux and/or other physiological functions in older patients (12).

The diminished LDL cholesterol–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 cholesterol levels were negatively related to percent change from baseline in HDL cholesterol, as reported previously (5). Whether MetS provides greater clinical value than its individual components is debated (13). In this analysis, factors that contribute to MetS (BMI, A1C, triglycerides, HDL cholesterol) and the inflammatory marker hs-CRP were significant predictors of lipid changes; however, MetS itself was not related to treatment responses, although there were relatively few subjects without MetS (2,3,6). Higher baseline hs-CRP levels were associated with attenuated LDL cholesterol lowering, an effect not previously noted to our knowledge, and perhaps related to heightened levels of inflammation (9). Obesity-related changes in HDL cholesterol metabolism may account for the smaller HDL cholesterol increases associated with higher BMI (5,14). Because adipose tissue inflammation in obese patients may strongly influence hs-CRP levels, smaller hs-CRP 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 A1C and smaller apolipoprotein B reductions may be related to the presence of small dense LDL particles in these patients that vary inversely with A1C levels (15).

When considered cumulatively, the baseline factors positive for treatment response, namely age ≥65 years, baseline triglycerides <1.7 mmol/l, baseline non-HDL cholesterol <4.14 mmol/l, and race/ethnicity other than black/Hispanic, predicted attainment of LDL cholesterol <1.81 mmol/l irrespective of treatment. These results indicated that black or Hispanic subjects, individuals aged <65 years, and patients with elevated triglycerides and non-HDL cholesterol levels may require more intensive therapy to attain LDL cholesterol 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 diabetic patients with hypercholesterolemia after 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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