Dual Therapy With Statins and Antioxidants Is Superior to Statins Alone in Decreasing the Risk of Cardiovascular Disease in a Subgroup of Middle-Aged Individuals With Both Diabetes Mellitus and the Haptoglobin 2-2 Genotype

Shany Blum, Uzi Milman, Chen Shapira, Rachel Miller-Lotan, Lawrence Bennett, Maria Kostenko, Michele Landau, Shlomo Keidar, Yishai Levy, Alexander Khemlin, Arman Radan, Andrew P. Levy

Diabetes Mellitus (DM) is associated with a state of increased oxidative stress. Paradoxically, however, antioxidants have not been found to provide CVD benefit to DM individuals in several prospective clinical trials. However, the inability to demonstrate benefit may have been attributable to inadequate patient selection as antioxidants may only benefit those with particularly high levels of oxidative stress.

A polymorphism in the Haptoglobin (Hp) gene, an antioxidant protein, appears to permit identification of individuals with high oxidative stress and who may benefit from antioxidant therapy. There exists 2 classes of alleles at the Hp genetic locus, 1 and 2, and the antioxidant capacity of the Hp 2 protein is inferior to the Hp 1 protein. Robust clinical data has shown that individuals homozygous for the Hp 2 allele (Hp 2-2 genotype), 40% of DM individuals, have an up to 500% increased risk of CVD. A vast amount of basic science, animal, and epidemiological data has provided the logic for targeting vitamin E administration specifically to DM individuals with the Hp 2-2 genotype. Most importantly we have recently reported in the ICARE study (Israel Cardiometabolic Risk and Cardiovascular Events Reduction with vitamin E [ClinicalTrials.gov# NCT00220831]) a prospective randomized placebo controlled trial of vitamin E therapy in DM individuals with the Hp 2-2 genotype, that vitamin E therapy results in a 50% reduction in CVD events. However, only about half of the Hp 2-2 DM participants in ICARE received statin therapy. Because statin therapy is currently recommended for all DM individuals we sought to determine whether antioxidant therapy could still be demonstrated to provide benefit to Hp 2-2 DM individuals also taking statins.

Results

Of the 801 Hp 2-2 individuals taking statins in the ICARE cohort, 386 were randomized to vitamin E and 415 to placebo. The study protocol of the ICARE study has previously been reported in detail. Briefly, participants were drawn from 47 primary health clinics of the Clalit Health Services in the northern sector of Israel. Patients were eligible for the study if they had Type II DM and were 55 years of age or older. 3054 individuals underwent Hp genotyping, and of these 1434 were found to have the Hp 2-2 genotype. These Hp 2-2 individuals were randomly assigned to treatment with either vitamin E or placebo. Hp 1-1 and Hp 2-1 individuals were not enrolled in the treatment phase of the study but were followed in a study registry for all major cardiovascular events using the same methodology for outcomes adjudication as for individuals with the Hp 2-2 genotype. The major study outcomes (MI, stroke, CVD death) were identified prospectively in this population over an 18-month period. A preplanned secondary analysis of ICARE was used to assess the ability of vitamin E therapy to influence outcomes in those ICARE participants who were also taking statins. Statin use as prospectively defined in ICARE was based on the use of statins by the participant in at least 8 of the 12 months preceding enrollment of the participant in the study. The decision to use statins for a particular participant was under the discretion of the patient’s primary care physician and was in no way influenced by the patient’s participation in the ICARE study.

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Of the 801 Hp 2-2 individuals taking statins in the ICARE cohort, 386 were randomized to vitamin E and 415 to placebo. There was no significant difference in the baseline characteristics, concurrent medications, or diabetes characteristics between those individuals taking statins who were randomized to placebo or vitamin E. We found that dual treatment with statins and vitamin E dramatically reduced the event rate compared with statin treatment alone. (1.3% 1/86 for vitamin E versus 4.1% 1/2415 for placebo, hazard ratio [HR] 0.31, 95% confidence interval [CI] 0.15 to 0.83, apparent adverse effect on the progression of coronary artery disease.23,24

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Conclusions

We conclude that dual therapy with antioxidants and statins appears to have provided superior cardiovascular protection to middle-aged Hp 2-2 DM individuals as compared with statins alone. These data provide further support for the role of Hp genotyping in individuals with DM to determine the optimal treatment regimen.

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Disclosures

Dr Levy is a consultant for Synvista Therapeutics.

References


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