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The effect of vitamin E supplementation on cardiovascular risk in diabetic individuals with different haptoglobin phenotypes

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To the Editor

The role of antioxidant supplementation with vitamin E in the prevention of cardiovascular disease (CVD) has been a topic of considerable recent interest and controversy. Motivated by preclinical studies demonstrating an important role of oxidation in the atherogenicity of lipoproteins (oxidative modification hypothesis) [1] and observational epidemiological studies showing that serum vitamin E concentrations were inversely correlated with the risk of disease, vitamin E supplements were routinely prescribed by cardiologists for the primary and secondary prevention of CVD. However, over the past 10 years numerous placebo controlled randomized clinical trials have failed to demonstrate benefit from vitamin E on CVD risk [2-10]. In fact, in over 80% of these studies total mortality was actually increased in those individuals who received high dose vitamin E supplementation and meta-analysis of these studies has shown that high dose vitamin E supplementation may increase all-cause mortality [11]. This has led many thought leaders to call for a moratorium on high dose vitamin E supplements [12,13].

One possible reason for the failure of these prospective studies to show benefit was the lack of proper patient selection for treatment with vitamin E [14]. We have recently proposed that one subgroup of patients that may benefit from vitamin E therapy are individuals with diabetes mellitus (DM) and the haptoglobin (Hp) 2-2 genotype (approximately 36% all DM individuals). The Hp 2-2 genotype has been shown to be associated with a 2-5 fold increased risk of CVD in DM in multiple independent longitudinal cohorts [15-19]. A mechanistic link between the Hp 2-2 protein, oxidation and CVD in DM may be the increased production of oxidatively modified HDL in Hp 2-2 DM individuals [20]. Hemoglobin is bound to the HDL of Hp 2-2 DM individuals resulting in the oxidative modification of HDL and a loss of the ability of the HDL to promote reverse cholesterol transport [20]. Vitamin E supplementation can prevent HDL oxidation and restores HDL function in Hp 2-2 DM individuals [20]. Proof of concept that vitamin E supplementation provides concrete cardiovascular benefit to Hp 2-2 DM individuals has been provided in two independent studies. In the HOPE study [3], in the 399 Hp 2-2 DM individuals for whom serum samples were archived when the study was initiated, the odds ratio (OR) for the primary study endpoint of the composite of CV death, myocardial infarction and stroke in individuals who received each day 400 IU of natural source vitamin E (d-alpha tocopherol acetate) as compared to placebo was 0.69 (95% CI 0.42-1.13)

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[21]. Subsequently, this hypothesis was tested prospectively in 1434 Hp 2-2 DM individuals in the ICARE study where the OR for Hp 2-2 DM individuals receiving each day 400 IU of natural source vitamin E (d-alpha tocopherol acetate) as compared to placebo for the same primary study endpoint as used in HOPE was 0.46 (95% CI 0.25-0.85) [18,21].

We have sought to test this hypothesis further in randomized trials of vitamin E assessing CVD endpoints in individuals with DM which have already been concluded. Studies in which vitamin C was included in an antioxidant cocktail cannot be used to test this hypothesis due to the deleterious interaction between vitamin C and the Hp 2-2 genotype in DM [22,23]. The only study in which natural source vitamin E (d-alpha tocophorol) alone was administered and in which samples were archived was the Women's Health Study (WHS) [9]. In WHS approximately 40,000 female health professionals (2.6% of which had DM) aged 45 or over were randomized to 600 IU every other day of natural source vitamin E (d-alpha tocopherol) or placebo and followed for an average of 10.1 years. We recognized that as a result of the small number of DM participants in WHS to be included in this analysis (277 Hp 2-2 DM participants), as well as the lower CVD event rate in WHS as compared to HOPE and ICARE (secondary to the lower age and female gender of WHS participants), that the WHS cohort would be underpowered to show a significant effect of vitamin E on CVD endpoints in DM participants stratified by Hp genotype. Nonetheless, we thought that demonstration of a trend similar to what was observed in HOPE and ICARE would provide important preliminary data to encourage additional pharmacogenomic outcomes studies which are needed to determine whether a pharmacogenomic strategy of typing all DM individuals for Hp and then giving vitamin E only to those with the Hp 2-2 genotype is clinically effective. With these limitations and goals clearly in mind prior to the analysis, serum was aliquoted from all DM participants of WHS who had submitted serum specimens upon study enrollment and the Hp type was determined on these specimens by polyacrylamide gel electrophoresis [24].

Analysis of the relationship between Hp type and total incident CVD (CV death, non-fatal MI, non-fatal stroke, or coronary revascularization) [25] was restricted to Caucasians (n=721) who represented 95% of the WHS cohort [26] in order to avoid genetic admixture. Logistic regression analysis comparing the effect of vitamin E on the time to any one of the components of the study endpoint of total CVD by Hp type was done based on a Cox proportional hazards model adjusting for traditional risk factors [25].

Table 1 provides the absolute number of CVD events and the adjusted hazard ratios (HR) associated with treatment with vitamin E compared to placebo in WHS participants stratified by Hp type. Due to the lack of statistical significance of any of these relationships and their wide 95% confidence intervals (CI) these results must be viewed with extreme caution. Vitamin E supplementation was associated with an approximately 15% reduction in total CVD in Hp 2-2 DM individuals and a 20-25% increase in total CVD in non Hp 2-2 DM individuals.

Analysis of individual components of the total CVD endpoint was also hampered by the small study size and the extremely small number of events for individual components of the total CVD endpoint. The only individual endpoint that approached statistical significance was among Hp 2-1 DM individuals where there was a statistically significant increase in non-fatal ischemic stroke with vitamin E (absolute events (9) 5.7% with vitamin E vs. (2) 1.2% with placebo p=0.02; adjusted HR 4.483 [0.927-21.672], p=0.06). These data on stroke are of possible significance given the recent demonstration in several cohorts that vitamin E supplementation increases blood pressure [27,28] and that this effect may be Hp genotype specific (A.P. Levy, unpublished observation).

Finally, with regard to total mortality vitamin E supplementation was associated with a non-significant reduction in total mortality in Hp 2-2 DM participants HR 0.922 [0.739-2.600] and

a non-significant increase in total mortality in Hp 1-1 and Hp 2-1 DM participants (HR 1.088 [0.292-4.057] in Hp 1-1 and HR 1.387 [0.739-2.600] in Hp 2-1). Total mortality was also decreased (non-significantly) with vitamin E supplementation in Hp 2-2 DM participants of HOPE and ICARE.

In conclusion, while the analysis of the effects of vitamin E on total CVD in DM participants of the WHS cohort did not show significant benefit for any Hp type and therefore the trends presented could simply be due to chance, the effect estimates from vitamin E supplementation to Hp 2-2 DM or non Hp 2-2 DM individuals are in the same beneficial or harmful direction respectively as seen in ICARE and HOPE. Given that the non Hp 2-2 DM group makes up close to two-thirds of the total DM population the apparent harm shown to this group may help to explain why prior clinical studies assessing the efficacy of vitamin E supplementation in genetically unselected populations not only didn't show benefit (masking benefit to Hp 2-2 DM individuals) but showed an overall trend towards harm.

Given all the limitations of this study mentioned above why should these results be reported? Clearly stemming from the numerous failed vitamin E studies and meta-analysis showing possible harm from vitamin E there appears to exist among a very high percentage of the medical community an almost knee-jerk reaction to the possibility that vitamin E may have some role in preventing CVD. However, with the public health burden of DM increasing at an alarming rate it would be a shame to throw the baby out with the bathwater and reject the possibility that a very inexpensive treatment might benefit a subgroup of DM individuals (approximately one-third of the DM population) who are at extremely high risk for CVD. We believe that the study presented here, taken in the context of HOPE and ICARE, adds one more piece of data that we hope will help to motivate a large prospective study investigating the pharmacogenomic application of the Hp genotype to prevent CVD with vitamin E which could constitute the basis for conclusive treatment guidelines.

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Table 1

The effect of vitamin E vs. placebo stratified by Hp type on total CVD

	Hp 1-1	**Hp 2-1**	**Hp 2-2**
N (vit E/placebo)	112 (56/56)	332 (159/173)	277 (146/131)
Absolute events n(%) total CVD	12(21.4%) vs. 10(17.9%) Increase 19.6%	37(23.3%) vs. 30(17.3%) Increase 34.7%	31(21.2%) vs. 31(23.7%) Decrease 10.5%
Adjusted total CVD HR [95%CI]	1.192 [0.456-3.117]	1.254 [0.766-2.055]	0.857 [0.511-1.435]

Total CVD defined as the composite endpoint comprising the first of any of these events: non fatal MI, non fatal stroke, cardiovascular death, PTCA or CABG.