Clinical and Population Studies

Vitamin E Supplementation Reduces Cardiovascular Events in a Subgroup of Middle-Aged Individuals With Both Type 2 Diabetes Mellitus and the Haptoglobin 2-2 Genotype
A Prospective Double-Blinded Clinical Trial

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Objective—Clinical trials of vitamin E have failed to demonstrate a decrease in cardiovascular events. However, these studies did not address possible benefit to subgroups with increased oxidative stress. Haptoglobin (Hp), a major antioxidant protein, is a determinant of cardiovascular events in patients with Type 2 diabetes mellitus (DM). The Hp gene is polymorphic with 2 common alleles, 1 and 2. The Hp 2 allelic protein product provides inferior antioxidant protection compared with the Hp 1 allelic product. We sought to test the hypothesis that vitamin E could reduce cardiovascular events in DM individuals with the Hp 2-2 genotype, a subgroup that comprises 2% to 3% of the general population.

Methods and Results—1434 DM individuals ≥55 years of age with the Hp 2-2 genotype were randomized to vitamin E (400 U/d) or placebo. The primary composite outcome was myocardial infarction, stroke, and cardiovascular death. At the first evaluation of events, 18 months after initiating the study, the primary outcome was significantly reduced in individuals receiving vitamin E (2.2%) compared with placebo (4.7%; P=0.01) and led to early termination of the study.


Key Words: diabetes mellitus ■ vitamin E ■ cardiovascular events ■ pharmacogenomics ■ haptoglobin genotype

Extensive preclinical and observational studies showing the apparent benefit from vitamin E in preventing cardiovascular events created an atmosphere in which more than 40% of cardiologists were routinely prescribing high dose vitamin E.1 Over the past 10 years, several prospective randomized clinical trials have investigated whether vitamin E supplementation provides cardiovascular protection.2-9 The overwhelming consensus from these studies is that vitamin E supplementation does not provide cardiovascular benefit.10-11 To the contrary, meta-analysis of these studies suggests high dose vitamin E supplementation may increase mortality,12 and several opinion articles have called for a moratorium on prescription of high dose vitamin E supplements.10-12

A possible explanation for why these studies failed in spite of solid preclinical data are the inadequate nature of patient selection in these studies.13 High-dose antioxidant therapy may only provide benefit to individuals who suffer from particularly high levels of oxidative stress.

The haptoglobin (Hp) genotype may help identify patients with high levels of oxidative stress and who may benefit from antioxidant therapy with vitamin E.14 The Hp gene is polymorphic with 2 common classes of alleles denoted 1 and 2.15 We and others have demonstrated that the Hp 2 allele protein product is an inferior antioxidant compared with the Hp 1 allele protein product.16-20 These differences in antioxidant protection are profoundly accentuated in the diabetic state resulting in a marked relative increase in oxidative stress in Hp 2 transgenic mice and Hp 2-2 individuals with DM.16-20

The distribution of the 3 Hp genotypes in Western societies is approximately 16% Hp 1-1, 36% Hp 2-2, and 48% Hp 2-1.15 We have demonstrated an interaction between the Hp genotype and DM on the development of cardiovascular events. In multiple longitudinal studies Hp 2-2 DM individuals have been shown to have a 2- to 5-fold increase in cardiovascular events as compared with Hp 1-1 and Hp 2-1 DM individuals.21-24

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These data prompted us to examine whether antioxidant therapy with vitamin E might have reduced cardiovascular events in Hp 2-2 DM individuals in the HOPE study. We assessed the Hp genotype in stored blood samples from HOPE and found that in Hp 2-2 DM individuals vitamin E significantly reduced myocardial infarction and cardiovascular death by 43% and 55%, respectively. However, because of the retrospective nature of this analysis as well as the inability to demonstrate a statistical interaction between vitamin E use and Hp type for either the HOPE composite outcome (stroke, CVD death, MI) or any of its components these data were interpreted with considerable caution. We sought to test the validity of these findings in Hp 2-2 DM individuals in a prospective, double-blind, placebo-controlled trial of vitamin E.

Methods

Participants

Study Location

The study protocol was approved by the Independent Ethics Committee (IEC) of the Carmel Medical Center in Clalit Health Services (CHS) and the Israeli Ministry of Health. The study took place within 47 primary health care clinics in the Haifa and Western Galilee district of CHS.

Eligibility and Informed Consent

Individuals were eligible for inclusion in the study if they had Type II DM and were 55 years of age or older. 22 142 individuals were identified meeting these requirements in the 47 health clinics described above. Study exclusion criterion were (1) uncontrolled hypertension; (2) myocardial infarction or stroke within 1 month before enrollment; (3) unwillingness to stop antioxidant supplements; (4) known allergy to vitamin E. Further details regarding eligibility and the informed consent process are described in an online supplement.

Hp Typing

Hp phenotyping was performed on hemoglobin-enriched serum by polyacrylamide electrophoresis. An Hp phenotype (Hp 1-1, Hp 2-1, or Hp 2-2) is obtained using this method in over 98% of individuals with reproducibility of greater than 99%. This method provides a signature banding pattern for each of the 3 possible Hp phenotypes with which we have demonstrated 100% correspondence to the 3 possible Hp genotypes of identical nomenclature as determined by polymerase chain reaction (PCR).

Interventions and Monitoring Compliance

DM individuals with the Hp 2-2 genotype were randomly allocated to either placebo or vitamin E (natural source d-alpha tocopherol) at a dose of 400 IU per day for the duration of the study. Placebo pills were identical to vitamin E pills except that they contained no vitamin E. Pills were supplied in bottles identical in appearance having only the participant’s enrollment number on the bottle. Treatment allocation was blinded for all study participants, physicians, and the study staff. All treatment decisions regarding routine care remained at the discretion of the individual’s primary care physician. Assessment of compliance was based on telephone interviews.

Randomization Procedure

A computer generated randomization was used to allocate individuals to the 2 treatment groups and is described in an online supplement.

Primary and Secondary Outcomes

The primary outcome of the study was the composite of cardiovascular death, nonfatal myocardial infarction, and stroke. Definitions of these components of the primary outcome are provided in an online supplement. Prespecified secondary end points were: total mortality, hospitalization for congestive heart failure, and coronary revascularization.

Sample size determination, method of ascertainment and adjudication of events, and the planned method of interim analysis of the data for safety and efficacy are provided in an online supplement.

Hp 1-1 and Hp 2-1 Genotype Study Participants

Individuals with the Hp 1-1 and Hp 2-1 genotypes were not eligible for the treatment phase of this study, but they 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 baseline characteristics of the Hp 1-1 and Hp 2-1 individuals are supplied as an online data supplement, and major events in these individuals are reported in the results section of the article.

Statistical Analysis

Analysis of the effects of vitamin E on cardiovascular events in Hp 2-2 DM individuals was performed according to the intention to treat principle on all Hp 2-2 DM individuals who were allocated to vitamin E or placebo. Categorical data are presented as absolute values and percentages. Differences in demographic variables and medications between the 2 groups were compared by chi-squared test or Fisher exact test, as appropriate. Kaplan-Meier estimates, stratified according to the treatment allocation or according to the Hp genotype for the primary composite end point, are presented as event curves, and compared using the log-rank test. For the Kaplan-Meier estimates the time of patient exposure and events was calculated beginning from the day the patient underwent Hp typing until the first event or until September 30, 2006 in patients who did not have an event. The hazard ratio (HR) and corresponding confidence interval (CI) for the primary composite study end point was computed using a Cox proportional hazards model without adjustments for other baseline covariates.

Because Hp 1-1 and Hp 2-1 individuals were followed for all primary events in a registry, we had the opportunity to assess how vitamin E meaningfully modified the increased cardiovascular risk associated with the Hp 2-2 genotype. For this analysis we divided the whole cohort (randomized and registry subjects) into 4 groups: Hp 1-1, Hp 2-1, Hp 2-2 randomized to placebo and Hp 2-2 randomized to vitamin E. Estimates of hazard ratios were obtained with the use of Cox proportional-hazards models using Hp 2-1 individuals as reference. Variables thought to have clinical importance and those with P<0.1 in the univariate analysis were included in a stepwise Cox multivariable model. The following baseline clinical characteristics were considered in the model: age, gender, prior MI, prior stroke, HDL levels, LDL levels, and smoking.

Statistical analysis was performed using SPSS statistical software Version 15.0. All reported probability values are 2-sided.

Results

Participant Flow

Figure 1 provides a flow diagram of the trial comparing vitamin E versus placebo in individuals with the Hp 2-2 genotype and DM.

Eligibility, Recruitment, and Allocation

From a target population of 22 142 individuals, 3054 underwent Hp genotyping between April 2005 and September 2006. An Hp genotype was obtained on 3044 individuals with the distribution: Hp 1-1 285 (9.4%); Hp 2-1 1248 (41.0%); Hp 2-2 1511 (49.6%). Hp 1-1 and Hp 2-1 individuals were
excluded from randomization but were followed for primary and secondary end points. Of 1511 DM individuals identified as Hp 2-2, 1434 were randomized to vitamin E or placebo. 77 Hp 2-2 individuals were not randomized because of their failure to satisfy the study inclusion or exclusion criterion. 726 Hp 2-2 individuals were randomized to vitamin E and 708 Hp 2-2 individuals were randomized to placebo. 450 Hp 2-2 individuals who had been randomized (229 placebo and 221 vitamin E) did not receive the allocated intervention for reasons explained in the description of the randomization procedure in the online supplement. However, all 1434 Hp 2-2 individuals who were randomized were followed for primary and secondary end points.

Baseline Demographic and Clinical Characteristics of Study Participants
Hp 2-2 DM individuals randomized to placebo or vitamin E treatment groups were well balanced for baseline characteristics, with the exception of statins and ACE inhibitors which were higher in the placebo group, as shown in Table 1. The prevalence of cardiovascular disease in this study cohort at baseline was 25%.

Follow-Up
Two Hp 2-2 participants were lost to follow up (1 in each group). Seven individuals discontinued intervention because of advice from a physician (5 in vitamin E group, 2 in placebo). Eleven individuals discontinued the study because of perceived side effects (5 in vitamin E and 6 in placebo). Fifty-five participants taking vitamin E and 61 participants taking placebo were noncompliant with taking the respective pills based on telephone interviews.
who were also this rate to that observed in Hp 2-1 and Hp 1-1 individuals and that vitamin E supplementation could reduce that the rate of cardiovascular events was increased in Hp 2-2 individuals allocated to vitamin E or placebo. We sought evidence participants) into 4 groups according to Hp genotype and We divided the entire study cohort (randomized and registry outcomes stratified by Hp genotype.

Study Outcome
At the first interim analysis the primary study outcome among all randomized Hp 2-2 DM individuals was significantly reduced in participants randomized to vitamin E when compared with placebo (2.2% for vitamin E versus 4.7% for placebo, hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.27 to 0.82, P = 0.01 by log-rank; Figure 2). Analysis of the cohort of Hp 2-2 DM individuals who received the allocated intervention (505 vitamin E and 479 placebo) demonstrated an even more impressive benefit from vitamin E (1.6% for vitamin E versus 4.6% for placebo, HR 0.30, 95% CI 0.16 to 0.70; P = 0.003 by log-rank). The reduction in the primary outcome in the vitamin E group was in large part attributable to a significant reduction in the incidence of nonfatal myocardial infarction (Table 2). None of the prespecified secondary outcomes were significantly different between the 2 treatment groups (Table 2).

Outcomes Stratified by Hp Genotype
We divided the entire study cohort (randomized and registry participants) into 4 groups according to Hp genotype and randomization to vitamin E or placebo. We sought evidence that the rate of cardiovascular events was increased in Hp 2-2 individuals and that vitamin E supplementation could reduce this rate to that observed in Hp 2-1 and Hp 1-1 individuals (who were also >55 years old and had Type 2 DM). The event curves for Hp 1-1 and Hp 2-1 individuals superimposed on the event curves for Hp 2-2 (randomized to placebo) and

<table>
<thead>
<tr>
<th>End Point</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>16 (2.2)</td>
<td>33 (4.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (1.0)</td>
<td>17 (2.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (0.8)</td>
<td>11 (1.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>3 (0.4)</td>
<td>5 (0.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>11 (1.5)</td>
<td>18 (2.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8 (1.1)</td>
<td>8 (1.1)</td>
<td>0.96</td>
</tr>
<tr>
<td>Total mortality</td>
<td>11 (1.5)</td>
<td>12 (1.7)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). P values are based on chi-square tests or Fisher exact test.

Hp 2-2 (randomized to vitamin E) are shown in Figure 3. Whereas the event rate (unadjusted or adjusted by Cox regression) was increased more than 2-fold in Hp 2-2 individuals randomized to placebo as compared with Hp 1-1 and Hp 2-1 individuals, the event rate in Hp 2-2 individuals randomized to vitamin E was remarkably similar to that of Hp 1-1 and Hp 2-1 individuals (Table 3).

Discussion
In this study we have demonstrated in a prospective, randomized, double-blinded placebo controlled trial that vitamin E provides cardiovascular benefit to DM individuals with the Hp 2-2 genotype. The rationale for this study was based on a solid foundation of in vitro, animal, and human studies demonstrating impaired antioxidant protection and increased cardiovascular risk in Hp 2-2 DM individuals coupled with a retrospective analysis of the HOPE cohort showing that vitamin E may have reduced cardiovascular death and myocardial infarction in Hp 2-2 DM individuals.14

Several important caveats must be stated clearly to prevent misinterpretation of this data. First, these data showing apparent benefit from vitamin E are relevant to a distinct population, Hp 2-2 DM individuals over 55 years of age (approximately 2% to 3% of the general population), and should not be generalized to the entire population. Second, these data should not be used to promote vitamin E therapy in place of other proven therapies (such as statins) to prevent cardiovascular disease.

A vast amount of epidemiological, animal, and basic science data has provided the logic for the present study targeting Hp 2-2 DM individuals.14 First, we have demonstrated in 4 independent longitudinal studies that Hp 2-2 DM individuals have a 2- to 5-fold increased risk of CVD as compared with DM individuals without the Hp 2-2 genotype.21–24 Secondly, we have recapitulated the association between cardiovascular disease and the Hp 2-2 genotype in mice genetically modified at the Hp locus.28–30 Specifically, we have shown that Hp 2-2 ApoE−/− mice have increased atherosclerotic plaque macrophage content, iron and oxidation as compared with Hp 1-1 ApoE−/− mice.29 Moreover, we have shown that reverse cholesterol transport is impaired in Hp 2-2 DM mice.30 Thirdly, we have demonstrated that the Hp 2 protein is an inferior
The antioxidant function of Hp is attributable to its ability to neutralize hemoglobin which is capable of generating the highly reactive hydroxyl radical. Micro-hemorrhages resulting in liberation of extravascular extracorpuscular hemoglobin are of increased frequency and severity in diabetic atherosclerosis. The Hp 1-1 protein is superior to the Hp 2-2 protein in protecting against extracorpuscular hemoglobin as a result of its better ability to prevent release of heme from the Hp-hemoglobin complex and to promote uptake of the Hp-hemoglobin complex via the macrophage CD163 receptor.

The choice not to include Hp 1-1 and Hp 2-1 individuals in this study was similarly based on prior epidemiological and animal studies. In HOPE vitamin E was not found to provide benefit to Hp 1-1 or Hp 2-1 DM individuals but may have provided benefit to Hp 2-2 DM individuals. In mice antioxidant therapy did not provide protection against myocardial ischemic-reperfusion injury in Hp 1-1 DM mice but benefit was provided to Hp 2-2 DM mice.

There exists prior support that antioxidant therapy may be beneficial in specific subgroups with increased oxidative stress. SPACE, a trial of vitamin E in hemodialysis patients who have very high levels of oxidative stress, demonstrated significant cardiovascular benefit from vitamin E. However, the choice of antioxidant may be critical. Many studies have used a combination of vitamin E and vitamin C to boost antioxidant protection, but vitamin C may offset the beneficial affects of vitamin E. Vitamin C has been associated with increased mortality in DM individuals in a large longitudinal study. The toxicity of vitamin C in DM may be the result of the increased amount of redox-active iron in DM which can convert vitamin C into a prooxidant. Vitamin C may therefore be particularly harmful in Hp 2-2 DM individuals who have exceptionally high levels of redox-active iron, which may account for the apparent acceleration of lesion progression in a small study of vitamin C administration with vitamin E to DM Hp 2-2 subjects.

The present study has limitations. First, this was a primary care “real-life” study. No attempt was made to optimize or manage the administration of medications that the primary care physician prescribed for study participants. Second, a large number of Hp 2-2 individuals who were randomized to vitamin E or placebo did not receive this intervention. Nonetheless, the apparent large benefit of vitamin E to those individuals who did receive the allocated intervention was sufficient to permit the demonstration of a benefit from vitamin E in an intention to treat analysis.

Table 3. Unadjusted and Adjusted Cox Regression Models According to Hp Genotype and Treatment Assignment

<table>
<thead>
<tr>
<th>Hp genotype</th>
<th>n</th>
<th>Events (%)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hp 2-1</td>
<td>1248</td>
<td>25 (2.0)</td>
<td>1.0 (0.4–2.5)</td>
<td>0.93</td>
<td>1.0 (0.4–2.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Hp 1-1</td>
<td>285</td>
<td>6 (2.1)</td>
<td>1.1 (0.6–2.1)</td>
<td>0.74</td>
<td>1.1 (0.6–2.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hp 2-2 Vitamin E</td>
<td>726</td>
<td>16 (2.2)</td>
<td>2.4 (1.4–4.0)</td>
<td>0.001</td>
<td>2.3 (1.4–3.9)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*The model adjusted for age, gender, prior MI, prior stroke, HDL levels, LDL levels, and smoking. Hp 2-1 was used as the reference group for calculating hazard ratios.
The pendulum of scientific thought at the time that this study was designed and executed was such that proposals for clinical trials of vitamin E could inspire little enthusiasm and financial support.\textsuperscript{10–12} The primary goal of this study was to test the hypothesis that significant cardiovascular protection may be obtained from Vitamin E supplementation to Hp 2–2 DM individuals.\textsuperscript{25} The study was terminated early for 2 reasons. First, at the first evaluation of end points, as a result of a stronger apparent benefit of Vitamin E therapy than was anticipated in the study design, we were able to meet the stated primary goal of the study. Second, it was felt that the results of the study should be reported to motivate establishment of a platform for a substantially larger trial without the limitations of the current study, and which could therefore constitute the basis for conclusive treatment guidelines.

In conclusion, this study suggests that a pharmacogenomic approach may be useful to identify a large subgroup of DM individuals who could potentially derive cardiovascular benefit from a very inexpensive treatment. Such an approach\textsuperscript{14} to determine which DM individuals should receive vitamin E appears warranted based on several meta-analyses showing that vitamin E may be harmful when given indiscriminately to all individuals.

Acknowledgments
A list of physicians participating in this study is provided in an online supplement.

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Disclosures
Dr Levy is a consultant for Synvista Therapeutics.

References


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Methods

Eligibility and Informed consent procedure

Individuals were eligible for inclusion in the study if they had Type II DM and were 55 years of age or older. 22,142 individuals were identified meeting these requirements in the 47 health clinics described above. Study exclusion criterion were (1) uncontrolled hypertension; (2) myocardial infarction or stroke within 1 month prior to enrollment; (3) unwillingness to stop antioxidant supplements; (4) known allergy to vitamin E. Potentially eligible study participants were invited by their primary care physician to undergo Hp typing between April 2005 and September 2006.

All individuals undergoing Hp typing signed an informed consent form (ICF) stating that they agreed to undergo Hp typing to identify their cardiovascular risk and that they understood that (1) if they had the Hp 1-1 or Hp 2-1 genotypes then they would be followed prospectively for cardiovascular events but they would not be invited to participate in the treatment phase of the study; (2) if they had the Hp 2-2 genotype then they would be followed prospectively for cardiovascular events, randomized to treatment with either placebo or vitamin E and invited to participate in the treatment phase of the study. However, as stipulated by the IEC, study participants identified as Hp 2-2 were required to sign an additional ICF agreeing to participate in the treatment phase of the study prior to receiving the study drug. Participants were not aware to which treatment (vitamin E or placebo) they had been randomized when deciding on whether or not to begin treatment with the study drug. Participants were also told that their treatment and medical care in the clinic would be unaffected by their decision on whether or not to take the study drug. Physicians received no compensation for individuals participating in the study and were blinded to their patient’s treatment assignment.

Randomization

A computer generated randomization was used to allocate individuals to the two treatment groups. At the site of study drug manufacture all medication bottles were labeled with a number in accordance with the computer generated randomization key. A medication bottle number was assigned in the study coordination center immediately after receiving notification from the Hp core laboratory that an individual was Hp 2-2. The coordination center assigned that individual the next available bottle number in sequence and that bottle was sent to the
individual's primary care clinic where it was to be distributed by the primary physician only after the individual signed the second ICF. A large number (approximately 1/3) of Hp 2-2 individuals who underwent randomization did not receive the allocated intervention. The major reason why these individuals did not receive the allocated intervention was that they were not called back to the clinic to sign the second ICF and to receive the study drug, a direct result of the limited resources of this study with no dedicated study administrative personnel in the clinics. It is critical to note that the identity of the contents of the bottles was not known to any participant, physician, or individual involved in the study during enrollment, randomization, follow-up or adjudication of events. Furthermore, individuals who were randomized but did not sign the second ICF and did not begin treatment, were unaware to what treatment group they had been allocated. Finally, all individuals who were randomized were included in the intention to treat analysis.

Sample size determination

A sample size of 1000 Hp 2-2 participants in each group was selected to provide power of at least 80% to detect a risk reduction with vitamin E of 20% using a 2-sided statistical significance level of P<0.05. This assumed, based on the HOPE study, a 20% incidence rate in the placebo group over the course of the study.

Primary and secondary outcomes

The primary outcome of the study was the composite of cardiovascular death, non-fatal myocardial infarction and stroke. Cardiovascular death was defined as either (1) unexplained death due to ischemic cardiovascular disease occurring within 24 hours after the onset of symptoms or (2) death from myocardial infarction or stroke within 7 days after the myocardial infarction or stroke. Myocardial infarction was defined by the typical rise and fall of serum markers of myocardial necrosis (CK-MB or troponin) with at least one of the following: (a) typical ischemic symptoms; (b) development of pathologic Q-waves on the ECG; (c) ECG changes diagnostic of ischemia.\footnote{1} Stroke was defined as a neurologic deficit lasting more than 24 hours. Prespecified secondary endpoints were: total mortality, hospitalization for congestive heart failure, and coronary revascularization.

Ascertainment and adjudication of events
All CHS hospitalizations, as well as out of hospital deaths, are documented in a computerized database. Events were ascertained by reviewing all hospitalizations of study participants. Adjudication of events corresponding to the primary and secondary outcomes was based on the hospitalization discharge summary by a panel of physicians blinded to treatment allocation. For out-of-hospital deaths, adjudication was based on interviews with the participant's physician and family.

**Interim analysis of data for safety and efficacy and termination of the study**

The data were reviewed for the first time in November, 2006 inclusive of events to September 30, 2006, and were to be reviewed every six months thereafter. The trial was intended to last 4 years. As will be outlined in Results, the initial review led to early termination of the study.

**Table 1. Baseline characteristics of Hp 1-1 and Hp 2-1 participants**

<table>
<thead>
<tr>
<th></th>
<th>Hp 1-1</th>
<th>Hp 2-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>285</td>
<td>1248</td>
</tr>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD) years</td>
<td>69.0 (8.6)</td>
<td>68.3 (9.0)</td>
</tr>
<tr>
<td>Duration of DM (SD)</td>
<td>11.3 (9.0)</td>
<td>10.9 (8.4)</td>
</tr>
<tr>
<td>Males [n (%)]</td>
<td>131 (46)</td>
<td>593 (47.5)</td>
</tr>
<tr>
<td>Minorities [n (%)]</td>
<td>31 (10.9)</td>
<td>157 (12.6)</td>
</tr>
<tr>
<td><strong>History [n (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>33 (11.6)</td>
<td>175 (14.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>25 (8.8)</td>
<td>66 (5.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>209 (73.3)</td>
<td>933 (74.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>17 (6)</td>
<td>122 (9.8)</td>
</tr>
<tr>
<td><strong>Lab Results (mean (SD))</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.3 (1.3)</td>
<td>7.3 (1.3)</td>
</tr>
<tr>
<td>Test</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>188.8 (33.0)</td>
<td>186.2 (37.3)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>46.1 (10.8)</td>
<td>46.0 (10.5)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>104.0 (24.6)</td>
<td>102.9 (29.1)</td>
</tr>
</tbody>
</table>

**Medications [n (%)]**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinic 1</th>
<th>Clinic 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>121 (42.4)</td>
<td>455 (36.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>144 (50.5)</td>
<td>664 (53.2)</td>
</tr>
<tr>
<td>B-blockers</td>
<td>106 (37.2)</td>
<td>481 (38.5)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>122 (42.8)</td>
<td>615 (49.3)</td>
</tr>
<tr>
<td>Metformin</td>
<td>166 (58.2)</td>
<td>725 (58.1)</td>
</tr>
</tbody>
</table>

**Participating clinics (italics) and physicians in this study:**

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Online data supplement

References for on-line supplement.