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Elevated urinary albumin excretion complements the Framingham Risk Score for the prediction of cardiovascular risk — response to treatment in the PREVEND IT trial☆

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ABSTRACT

Background: The PREVEND IT trial reported on a high cardiovascular (CV) event rate in subjects with a baseline urinary albumin excretion (UAE) rate of ≥50 mg/24 h. Here, we report on the observed 10-year CV outcome of this population and compare this with the predicted Framingham Risk Score (FRS). In addition, we evaluated the effect of four years of fosinopril treatment on this relation.

Methods and results: From the PREVEND IT cohort, 833 subjects without history of CV disease, randomized to fosinopril (N = 412) or placebo (N = 421), were studied. The primary endpoint included CV mortality and adjudicated hospitalization for CV disease during a 10-year follow-up period. Mean age was 51 ± 12 years and 65% were males, while prevalence of diabetes (2.6%) and use of CV drugs (3.5%) was low. Subjects were categorized to high UAE (≥50 mg/24 h) or low UAE (<50 mg/24 h). After 10 years of follow-up, the event rate in the high UAE group was almost twice as high as predicted by the FRS (29.5% vs. 17.2%). Treatment for four years with fosinopril reduced the event rate to comparable levels of that predicted by FRS. The addition of UAE ≥50 mg/24 h to the FRS improved the Integrated Discrimination Improvement (P = 0.033) and increased the area under the curve by 0.54% (P = 0.024).

Conclusions: The 10-year CV risk of subjects with an elevated UAE (≥50 mg/24 h) is substantially underestimated by the FRS. Treatment with fosinopril successfully reduced this increased event rate to FRS-predicted CV risk.

1. Introduction

Cardiovascular (CV) disease may be predicted by a variety of clinical, biochemical, and surrogate risk factors. Of these, endothelial dysfunction has also been linked to the development of atherogenesis [1,2]. Increased levels of urinary albumin excretion (UAE) do not only provide an indication of early renal dysfunction, but functions also as a marker of endothelial dysfunction [3]. Many trials have reported on a high prevalence of elevated UAE not only in high risk subjects suffering from diabetes [4,5], renal failure [6], or heart failure [7,8], but also in subjects from the general population [9]. An increased UAE was in every cohort associated with worse outcome. Recently, the Prevention of REnal and Vascular ENd-stage Disease Intervention Trial (PREVEND IT) confirmed these results and reported on a CV event rate of almost 30% in subjects with a baseline UAE ≥50 mg/24 h after 10 years of follow-up [10]. Some have proposed that UAE may be a useful surrogate marker for CV disease. It is unclear whether conventional CV risk prediction models, like the Framingham Risk Score (FRS) can be used in a population with albuminuria [11,12]. In addition, it remains unclear whether the addition of UAE could significantly improve prognostic performance of the FRS. In this analysis, we retrospectively investigate the quality of the CV risk estimations by the FRS by comparing it to the observed outcome in PREVEND IT.

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2. Material and methods

2.1. Study population

The study was performed using data of the PREVEND IT study, which has been described elsewhere [10,13]. Briefly, the aim of PREVEND IT was to assess the value of albuminuria as an indicator of increased CV risk in the general population. The key entry criteria of PREVEND IT were persistent microalbuminuria (one urinary albumin concentration ≥10 mg/L in an early morning spot urine test and at least one 15 to 300 mg/24 h in two 24 h urine samples), absence of antihypertensive and lipid-lowering medication, a blood pressure of <160/100 mm Hg and a total cholesterol of <8.0 mmol/L or <5.0 mmol/L in the case of previous myocardial infarction. From April 1998 to June 1999, 864 subjects were included in the PREVEND IT and were randomized to 20 mg fosinopril or matching placebo for the duration of four years (referred to as "active trial period"). At the end of this four year period, all subjects were taken off study medication and returned to the care of their general practitioners. Follow-up time was extended for an additional 6.0 years after the active trial period was ended, resulting in a total follow-up time of 10.0 years. To evaluate the FRS in our sample, we excluded subjects in which the variables of FRS were missing (N = 2, both missing values of HDL-cholesterol) or subjects with a history of CV disease (N = 29). Finally, a total of 833 subjects were eligible for the current analysis. An independent data and safety monitoring committee regularly monitored the progress of PREVEND IT during the entire follow-up period. The study was approved by the institutional medical ethics committee and conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

2.2. Endpoint collection and follow-up

The composite primary endpoint is the combined incidence of CV mortality and hospitalization for CV morbidity. CV morbidity was defined as hospitalization for documented nonfatal myocardial infarction or myocardial ischemia, heart failure, peripheral artery disease, and/or cerebrovascular accident. These endpoints are the same as for the FRS for general CV disease [14]. Follow-up for all surviving subjects after the active trial was collected via personal communication and electronic hospital files. Data on mortality were retrieved from the municipal register. Cause of death was obtained through the Dutch Central Bureau of Statistics and was coded according to the 10th revision of the International Classification of Diseases. Follow-up on hospitalization for CV morbidity was derived from records held by PRISMANT, the Dutch national registry of hospital discharge diagnoses [15]. In addition, personal communication was used to obtain data from subjects lost to follow-up. The date of admission was used as the date of the event. Details of each CV event were obtained from the treating physician. The independent end point committee of the active trial period reviewed all end points and the members had no knowledge of the subject's treatment assignments.

2.3. Measurements

At trial follow-up visits, various clinical and biochemical measurements were performed and two 24-hour urine collections were obtained. Systolic and diastolic blood pressures were calculated as the mean of the last two of ten consecutive measurements, using an automatic Dinamap XL model 9300 series device (Johnson & Johnson Medical Inc.). Serum creatinine, plasma cholesterol and glucose were determined in one laboratory by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), using an automated enzymatic method. The intra- and interassay variation coefficient of serum creatinine were respectively 0.9% and 1.1%. Serum triglycerides were measured enzymatically. A commercially available assay system was used to assess high-density lipoprotein (HDL) cholesterol (Abbott Inc., Abbott Park, IL, USA). Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/L and intra-assay and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic). 10-year risk for CV events according to the FRS was calculated as described by D'Agostino [14] and divided into three risk categories: low (<10%), intermediate (10–20%) and high (>20%), as recommended by Wilson [16]. UAE was categorized by low (<50 mg/24 h) vs. high (≥50 mg/24 h), according to the quintiles used in PREVEND IT [10,13].

2.4. Statistical methods

Baseline continuous data are reported as mean (standard deviation) for normal data. Normality of variables was assessed by standard numerical methods, using skewness/kurtosis tests. UAE and triglycerides showed a log-linear functional shape with the response variable and were transformed to a 2-log scale and reported as median (interquartile range). This means that risk estimates should be interpreted as the relative risk of values were doubled (e.g. 1 to 2 mg/L or 10 to 20 mg/24 h). Times to first occurrence of outcomes are presented as Kaplan–Meier estimates, and statistical differences between placebo and active treatments were analyzed by log-rank testing. To assess the additive value of UAE over the FRS, we evaluated the Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) indices for UAE (both as a continuous variable as well as dichotomized to high vs. low, using a cut-off of 50 mg/24 h) according to FRS. All reported probability values are two-tailed and $P < 0.05$ was considered as the nominal level of statistical significance. All analyses were performed using StataIC (version 11.0 software for Windows).

3. Results

Baseline characteristics of subjects divided by low (<50 mg/24 h) vs. high UAE (≥50 mg/24 h) are summarized in Table 1. These characteristics show a middle-aged population with a low prevalence of conventional CV risk factors, exemplified e.g. by a low prevalence of diabetes mellitus (4.0%), and little use of CV drugs (3.5%). The subjects in the high UAE group were at baseline older and had higher levels of systolic and diastolic blood pressures and a higher resting heart rate. Also, levels of glucose, triglycerides and serum creatinine were slightly increased in the high UAE group. Baseline median FRS was 12.7% and was different between UAE groups, namely 11.9% (IQR 5.2–23.9) and 17.1% (IQR 7.8–30.7) for the low UAE and the high UAE group ($P = 0.001$), respectively. Mean follow-up was 10.0 years (range 9.8 to 10.3) from start of the active trial until 1 January 2009.

At baseline, median UAE was 19 mg/24 h (IQR 15–29) in the low UAE group and 77 mg/24 h (IQR 59–115) for the high UAE group ($P < 0.001$). The following changes, during the entire follow-up period are depicted in Fig. 1. The low and high groups of UAE are divided by treatment group. In the low UAE group, 4 years of treatment with fosinopril during the active trial resulted in a decrease in median UAE from 20 mg/24 h to 15 mg/24 h ($P = 0.003$ compared to baseline). In the high UAE group, fosinopril treatment decreased UAE to 55 mg/24 h ($P = 0.003$ compared to baseline). Three months after cessation of fosinopril, median UAE increased in both groups and remained stable during further follow-up. UAE was unaffected by placebo during the entire follow-up period.

During the entire follow-up, the primary endpoint occurred in 119 subjects. The event rate in the high UAE group was significantly higher, compared to the low UAE group (22.0% vs. 12.3%, respectively, $P = 0.001$). Treatment with fosinopril lowered the event rate in the high UAE group to the same height as subjects with low UAE levels at start (15.6% vs. 12.3%, respectively, $P = 0.436$).

The observed ten-year event rate for both the low UAE group as well as the high UAE group is plotted against the FRS-predicted risk, in Fig. 2A