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Framingham score and microalbuminuria: Combined future targets for primary prevention?

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Framingham score and microalbuminuria: Combined future targets for primary prevention?

Background. Risk assessment is the cornerstone of primary prevention of cardiovascular disease. Our objective was to evaluate the prognostic value of the Framingham score in microalbuminuric subjects without a history of cardiovascular disease and whether this risk score can predict the benefit of treatment with fosinopril or pravastatin.

Methods. Subjects were randomized to fosinopril 20 mg or matching placebo, and to pravastatin 40 mg or matching placebo (mean age 51 ± 12 years, 65% men, $N = 830$). Prediction of 10-year risk for coronary heart disease by the Framingham score was performed using the risk factor categories with LDL cholesterol.

Results. Albuminuria was correlated with Framingham score at baseline ($P < 0.001$). In the population with a Framingham risk score $< 20\%$, both albuminuria and Framingham risk score were independent predictors of the primary end point. A two-fold increase of albuminuria or the Framingham risk score was associated with a hazard ratio of 1.60 (95% CI 1.10–2.31), $P = 0.013$ and 3.00 (95% CI 1.40–6.44), $P = 0.005$, respectively. In contrast to fosinopril, pravastatin showed a significant beneficial effect on Framingham risk score after 4 years of follow-up ($P < 0.001$). Furthermore, the observed absolute risk reduction in cardiovascular events was greater than calculated by the Framingham risk score.

Conclusion. The Framingham score is useful in microalbuminuric subjects as a prognostic tool. In addition, when considering the risk score as a target of intervention, the beneficial effects of therapies might be underestimated. Combining the Framingham score with the level of urinary albumin excretion is suggested as a primary prevention strategy with higher efficiency.

It has been generally accepted that early detection of cardiovascular risk and subsequent intervention can prevent coronary heart disease (CHD). The traditional cardiovascular risk factors are male gender, age, cigarette smoking, elevated blood pressure, high LDL cholesterol, low HDL cholesterol, and diabetes. All these cardiovascular risk factors are included in the Framingham cardiovascular risk score. This score can help physicians to predict 10-year risk for major cardiovascular events in

the individual patient. Studies also show that the higher the risk for developing CHD, the higher the efficacy of the intervention is. However, several primary prevention trials have demonstrated a significant effect of intervention on cardiovascular events in patients with a lower risk score [1, 2]. Limited data are available on the recommended strategy in lower risk populations with a 10-year risk between 10% to 20%. New tools such as noninvasive imaging and novel serum markers are in development to use in clinical practice. These markers may be used after assessment of traditional cardiovascular risk factors to identify the persons whom need aggressive intervention despite their moderate risk. A new relatively inexpensive to be measured risk indicator is microalbuminuria, which has been associated with an increased risk for cardiovascular disease in subjects with hypertension and diabetes, but also in the general population [3]. The Prevention of Renal and Vascular Endstage Disease Intervention Trial demonstrated that treatment with fosinopril had a significant effect on urinary albumin excretion, and was associated with a trend in reducing cardiovascular events. Treatment with pravastatin did not result in a significant reduction in urinary albumin excretion or a reduction in the primary end point [4]. All these subjects had no indication for primary prevention at inclusion. In this supplementary-analysis of the PREVENT IT, we evaluated the prognostic value of the Framingham risk score in microalbuminuric subjects without a history of cardiovascular disease and whether this risk score can predict the benefit of treatment with fosinopril or pravastatin.

METHODS

The PREVENT IT was an investigator-initiated, single-center, double-blind, randomized, placebo-controlled trial with a 2×2 factorial design. Subjects were randomized to fosinopril 20 mg or matching placebo, and to pravastatin 40 mg or matching placebo ($N = 864$). The key entry criteria were persistent microalbuminuria (once a urinary albumin concentration > 10 mg/L in an early morning spot urine, and at least

Key words: microalbuminuria, Framingham score, primary prevention.

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Table 1. Baseline characteristics

	Framingham risk score			Total
	<10%	10% to 20%	>20%	
Age years	43 ± 9	52 ± 9	62 ± 9	51 ± 12
Male gender	44.6%	74.1%	88.7%	64.9%
Systolic blood pressure mm Hg	122 ± 14	131 ± 16	141 ± 17	130 ± 18
Diastolic blood pressure mm Hg	71 ± 8	78 ± 9	82 ± 9	76 ± 10
LDL-cholesterol mmol/L	3.7 ± 0.8	4.2 ± 0.9	4.5 ± 1.0	4.1 ± 1.0
HDL-cholesterol mmol/L	1.1 ± 0.3	1.0 ± 0.3	0.9 ± 0.2	1.0 ± 0.3
Current smoking	29.8%	48.2%	47.4%	39.8%
Diabetes	0.3%	3.1%	5.7%	2.5%
Albuminuria mg/24h	19.6 (13.9–36.8)	22.9 (16.0–38.9)	28.6 (18.2–50.6)	22.6 (15.6–40.8)
Framingham risk score %	5.2 (3.0–7.2)	13.8 (11.6–16.8)	29.9 (24.3–39.5)	11.1 (5.6–21.2)

Data are given as mean ± standard deviation, except for albuminuria and Framingham risk score, which are presented as median (interquartile range).

once 15 to 300 mg/24 hours in 2 × 24-hour urine samples), blood pressure <160/100 mm Hg without the use of antihypertensive medication, and total cholesterol <8.0 mmol/L or <5.0 mmol/L in case of previous myocardial infarction, and without the use of lipid-lowering drugs. The laboratory and diagnostic methods to measure risk factors and the definition of the primary end point are described previously [5]. Prediction of CHD risk by the Framingham risk score was performed using the risk factor categories with LDL cholesterol reported by Wilson et al [6]. The scores provide estimates of CHD risk during a period of 10-year based on the Framingham study in men and women aged 30 to 74. To evaluate the Framingham risk score in our population, we excluded subjects with a history of cardiovascular disease. From the 864 subjects, 34 subjects were excluded, 29 because of a history of cardiovascular disease, and 5 subjects due to missing LDL-cholesterol values at baseline. Finally, 830 subjects were eligible to analyze the prognostic value of the Framingham risk score at baseline. The effect of intervention on reduction in Framingham risk score was evaluated by comparing three months' treatment data with baseline scores. Nonparametric Mann-Whitney tests were used to test the difference in Framingham risk score between placebo and active treatment after four years of follow-up. Cox regression analysis was used to investigate the prognostic value of albuminuria and Framingham risk score. Albuminuria and the Framingham risk score showed a log-linear functional form with the response variable, and were subsequently transformed to a two-log scale. Using this transformation, the relative risk estimates should be interpreted as if values of albuminuria or Framingham risk score were doubled (e.g., 20 mg/24h vs. 10 mg/24h, or 10% vs. 5%). All calculations were performed with SPSS version 11.0.1 software (SPSS, Chicago, IL, USA). The study was approved by the Institutional Review Board, and conducted in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

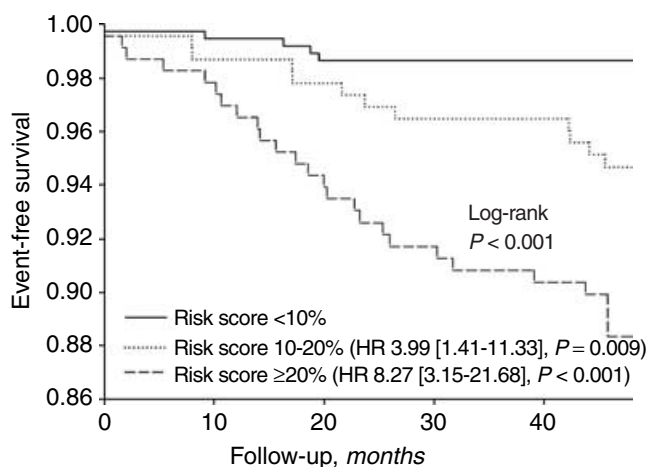


Fig. 1. Kaplan-Meier analysis illustrating the prognostic value of Framingham risk score in microalbuminuric subjects. The population is divided in three groups according to 10-year risk on cardiovascular disease. Hazard ratios (95% CIs) are given for the groups with a score between 10% to 20% and >20%.

RESULTS

The baseline characteristics for the total population and the three Framingham risk strata are summarized in Table 1. Almost half of our population (44.8%) has a Framingham risk score <10%, 27.5% has a risk score between 10% to 20%, and 27.7% has a risk score >20%. The level of albuminuria itself was significantly correlated with the Framingham score at baseline (P for linear trend <0.001). As illustrated in Figure 1, the Framingham risk score has prognostic value in microalbuminuric subjects. In the population with a Framingham risk score <20%, albuminuria and Framingham risk score itself were independent predictors of the primary end point. A two-fold increase of albuminuria or Framingham risk score was associated with a hazard ratio of 1.60 (95% CI 1.10–2.31), $P = 0.013$, and 3.00 (1.40–6.44), $P = 0.005$, respectively.

In four years of follow-up, 41 primary end points occurred, 1.3% of the subjects with a Framingham <10%

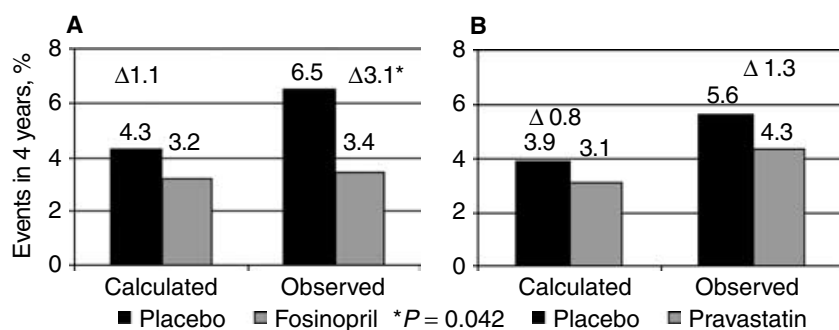


Fig. 2. The effects of foscinopril and pravastatin on the calculated Framingham risk score and the observed incidence of cardiovascular events during four years of follow-up.

had an end point, 5.3% in the group between 10% to 20%, and 10.4% in the group with a Framingham >20%. These incidences were comparable with the predicted incidence of cardiovascular events over the four-year period: 2.1%, 5.5%, and 11.9%, respectively. As shown in Figure 2, foscinopril and pravastatin both decreased the event rate over four years calculated by Framingham risk score by 1.1% and 0.8%, respectively. Interestingly, the observed reduction during the four-year follow-up was greater than the calculated reduction (3.1% and 1.3%, respectively).

Despite a significant reduction of foscinopril in cardiovascular events, no beneficial effect could be demonstrated on Framingham risk score after four years of follow-up. Median (interquartile range) delta Framingham risk score was 6.01% in the foscinopril group versus 6.42% in the placebo group. In contrast to foscinopril, pravastatin did show a positive and long-term effect on Framingham risk score. In the pravastatin group a median (interquartile range) delta Framingham risk score of 3.74% was observed in comparison to 8.53% in the placebo group ($P < 0.001$).

DISCUSSION

In a microalbuminuric population, a strong prognostic value of the Framingham risk score was observed. Microalbuminuria itself, as indicator of increased cardiovascular risk, is correlated with this Framingham risk score, and was an independent predictor of primary end points in subjects with a Framingham risk score <20%. In contrast to foscinopril, pravastatin showed a significant beneficial effect on Framingham risk score after four years' follow-up ($P < 0.001$). Furthermore, the observed absolute risk reduction in cardiovascular events was greater than calculated by the Framingham risk score.

In our main report on the results of the PREVENT IT study, we already observed that foscinopril, but not pravastatin, had an effect on microalbuminuria. Many studies have shown that the presence and magnitude of risk factors is associated with the level of microalbuminuria. The fact that the calculated effect of pravastatin on the risk score is lower than the calculated effect for

foscinopril is in line with the observed difference in their effect on microalbuminuria. Furthermore, the predicted difference in incidence of cardiovascular events between the pravastatin and foscinopril group is in line with the observed incidence. However, it is also evident that for both groups the Framingham score is underestimating the beneficial effect of treatment substantially. This suggests that including microalbuminuria in the algorithm for the Framingham score could improve the prediction for those treatments, which have an effect on the level of urinary albumin excretion. Especially microalbuminuria could improve the predictive value of the Framingham risk score in subjects with a risk score below 20%.

CONCLUSION

The Framingham risk score predicts also in microalbuminuric subjects the incidence of cardiovascular events. However, the beneficial effects of therapies reducing albumin excretion are underestimated. Combining the Framingham score with the level of urinary albumin excretion is suggested as a primary prevention strategy with high efficiency.

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REFERENCES

1. DOWNS JR, CLEARFIELD M, WEIS S, *et al*: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279:1615-1622, 1998
2. SHEPHERD J, COBBE SM, FORD I, *et al*: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 333:1301-1307, 1995

3. HILLEGE HL, FIDLER V, DIERCKX GF, *et al*: Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 106:1777–1782, 2002
4. ASSELBERGS FW, DIERCKX GF, HILLEGE HL, *et al*: Effects of fosinopril and pravastatin on cardiovascular events in microalbuminuric subjects. Results of PREVEND IT. *Circulation*, in press
5. DIERCKX GF, JANSSEN WM, VAN BOVEN AJ, *et al*: Rationale, design, and baseline characteristics of a trial of prevention of cardiovascular and renal disease with fosinopril and pravastatin in nonhypertensive, nonhypercholesterolemic subjects with microalbuminuria (the Prevention of RENal and Vascular ENdstage Disease Intervention Trial [PREVEND IT]). *Am J Cardiol* 86:635–638, 2000
6. WILSON PW, D'AGOSTINO RB, LEVY D, *et al*: Prediction of coronary heart disease using risk factor categories. *Circulation* 97:1837–1847, 1998