Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease

JOHANNES F.E. MANN, QI-LONG YI, and HERTZEL C. GERSTEIN

Department of Cardiology and of Endocrinology, and Population Health Research Institute, McMaster University, Hamilton, Canada; Schwabing General Hospital, Ludwig Maximilians University Munchen, Germany; and German Institute for High Blood Pressure Research, Heidelberg, Germany

Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease.

Background. Microalbuminuria predicts elevated cardiovascular risk in those with and without diabetes. In diabetes, microalbuminuria also heralds overt diabetic nephropathy. The predictive value of albuminuria below the microalbuminuria cutoff, and the development of overt nephropathy in nondiabetics with microalbuminuria, have not been well studied. We review findings of the HOPE Study.

Methods. The HOPE Study database includes data on first morning urine albumin/creatinine ratio (ACR) in 9043 participants at baseline, and in 7674 participants at baseline and at last follow-up. Inclusion criteria were known vascular disease or diabetes, plus one other cardiovascular risk factor; exclusion criteria included heart failure or known impaired left ventricular function, dipstick-positive proteinuria (>1+), and serum-creatinine >2.3 mg/dL (200 lµmol/L). Microalbuminuria was defined as an ACR ≥ 2 mg/mmol.

Results. Microalbuminuria at baseline approximately doubled the relative risk (RR) of the primary outcome (myocardial infarction, stroke, or CV death). For every 1 mg/mmol rise of ACR, even below the level of microalbuminuria, the adjusted hazard of the primary outcome increased by about 15%. Baseline microalbuminuria predicted subsequent clinical proteinuria, RR 17.5, similarly in participants without and with diabetes. New microalbuminuria developed in 1542 participants, and clinical proteinuria in 317.

Conclusion. Albuminuria is a continuous risk factor for CV events even below the level of microalbuminuria. Microalbuminuria predicts clinical proteinuria in nondiabetics.

Microalbuminuria was initially defined as a range of dipstick-negative albuminuria that predicted future overt nephropathy in people with type 1 diabetes mellitus [1–3]. Further research established similar associations in people with type 2 diabetes mellitus, albeit with wider estimates of risk than those reported for type 1 diabetes [1–3]. The significance of microalbuminuria as a risk factor for renal outcomes in nondiabetic people is even less clear [4].

In addition to predicting renal disease, microalbuminuria is a powerful predictor of cardiovascular events both in people with and without diabetes mellitus [5–15]. The fact that microalbuminuria predicts both cardiovascular and renal events, and the fact that microalbuminuria is observed in 10% to 15% of adults, and in about 30% of people with diabetes mellitus [1], highlights the importance of identifying affected people. For example, the INSIGHT Study evaluated an extensive list of cardiovascular risk factors in hypertensive subjects, and albuminuria turned out to be the single most important [16].

The HOPE Study was a prospective trial of 4.5 years duration that included people with and without a history of diabetes who were at risk for cardiovascular events [17–20]. People with a serum-creatinine ≤2.3 mg/dL (200 µmol/L) who had no evidence of clinical proteinuria were included. The urine albumin/creatinine ratio (ACR) was measured at baseline and at last follow-up in all participants; in people with diabetes it was also measured at one year. This paper reviews the HOPE Study observations regarding albuminuria as a predictor of cardiovascular and renal events [4, 21].

RESULTS OF THE HOPE STUDY

Cardiovascular impact of baseline microalbuminuria

Microalbuminuria (albumin/creatinine ratio, ACR, ≥2 mg/mmol or 18 mg/g) was detected in 1140 (32.6%) diabetic participants, and 823 (14.8%) nondiabetic participants at baseline. Figure 1 displays the risk for important outcomes according to the presence or absence of microalbuminuria. After controlling for randomization to ramipril, baseline microalbuminuria increased the risk of major cardiovascular events by 1.83-fold (95% CI 1.64–2.05; P < 0.0001); all-cause mortality by 2.09-fold (95% CI 1.84–2.38); and hospitalization for heart failure by 3.23-fold (95% CI 2.54–4.10). Similar estimates
Cardiovascular impact of albumin/creatinine ratio below the microalbuminuria threshold

Figure 2 shows the relationship between the risk of cardiovascular outcomes and baseline ACR; this relationship extended into the “premicroalbuminuric” range. Indeed, this linear trend for major cardiovascular events, all-cause mortality, and hospitalization for congestive heart failure in all participants was significant, after controlling for age, gender, systolic blood pressure, diastolic blood pressure, waist/hip ratio, diabetes status (presence or absence in all participants and the glycated hemoglobin in diabetic participants) (P < 0.0001), and after randomization to ramipril (P for trend <0.0001).

Renal impact of baseline microalbuminuria

Microalbuminuria predicted clinical proteinuria regardless of a history of diabetes. This risk was independent of other cardiovascular risk factors, including hypertension. Approximately 5% of microalbuminuric participants with no history of diabetes, and 20% of microalbuminuric participants with a history of diabetes developed clinical proteinuria or overt nephropathy within four years (Fig. 3). In participants with microalbuminuria, the risk for clinical proteinuria/overt nephropathy was about 15- to 20-fold higher than in participants without microalbuminuria.

Any progression of proteinuria occurred in 1859 participants (24%); this includes progression from normal urine albumin excretion to either microalbuminuria or to clinical proteinuria, or the progression from microalbuminuria to clinical proteinuria. Progression was more often observed in diabetic (N = 3243) than in nondiabetic (N = 4431) participants (34% vs. 17%, P < 0.001). New microalbuminuria developed 1542/6055 participants (25.5%, comprising 38.2% of the diabetic and 18.1% of the nondiabetic participants) (Fig. 3). New clinical proteinuria developed in 317/7674 participants (4.1%, comprising 8% of the diabetic and 1% of the nondiabetic participants) (Fig. 3).
DISCUSSION

The HOPE and MICRO-HOPE trials predominantly included people with definitive evidence of atherosclerotic cardiovascular disease [17] and a large number of people with diabetes mellitus [20]. As such, its findings are directly applicable to the patients that internists and family physicians encounter on a daily basis.

How should we interpret albuminuria levels that are below and above the threshold for microalbuminuria (ACR 2 mg/mmol)?

The cardiovascular outcome data presented here show that microalbuminuria predicts hospitalization for congestive heart failure and all-cause mortality. This is new information in addition to the growing number of prospective studies that portrayed microalbuminuria as a strong independent risk for CV events [5–15]. Most importantly, we show that the relationship between albuminuria and all cardiovascular events is not restricted to the microalbuminuria range. Indeed, they indicate that the ACR is a continuous risk factor for CV disease, and that the relationship extends well below currently accepted screening thresholds for microalbuminuria [21]. As such, the ACR is similar to the blood pressure, with no clear “normal” cutoff. This is consistent with a recent prospective study in which individuals with an albumin/creatinine ratio >0.65 mg/mmol had a relative risk for ischemic heart disease of 2.3 (P = 0.002) compared to people with a lower degree of albuminuria [22]. Thus, an albumin/creatinine ratio of 2.0 mg/mmol (18 mg/g) may not be relevant when considering the risk for cardiovascular outcomes; lower degrees of albuminuria are also predictive.

The renal outcome data show that the microalbuminuria cutoff is relevant as a strong risk factor for the development of clinical proteinuria in both diabetic and nondiabetic people at high risk for cardiovascular events. We also confirm the predictive value of microalbuminuria for overt nephropathy [1] in type 2 diabetes, with about 5% new cases per year. We do not have further nephrologic details of the participants. Based on the high likelihood of generalized atherosclerosis in most participants of the HOPE trial, and on the exclusion of proteinuric participants, we can assume that the progression from microalbuminuria to clinical proteinuria in the nondiabetic people is suggestive evidence of progressive nephrosclerosis [23]. We do not know, however, whether this progression heralds future renal failure, as is the case in diabetes. Considering the high number of patients with terminal renal failure due to nephrosclerosis [23–26], the latter point deserves further study.

Progression of albuminuria, defined as a new microalbuminuria or new clinical proteinuria, was found in a substantial number of participants in the HOPE Study, although they were extensively treated by antihypertensives, statins, aspirin, etc. Also, only participants with controlled hypertension could be included, and most were normotensive at baseline [18, 20]. Nevertheless, progression of albuminuria was found in one of five participants in 4.5 years, in one of three participants with diabetes, and in one of seven without diabetes. In particular, one of three participants with diabetes developed new microalbuminuria, and one of five diabetic participants with microalbuminuria developed overt nephropathy [4].

From trials in patients with renal diseases and significant proteinuria it is known that the amount of proteinuria on treatment is also predictive of future renal outcomes [27]. Unpublished data of the MICRO-HOPE Study suggest that this is also true for cardiovascular events. At least, microalbuminuria at baseline and during treatment was equally predictive for cardiovascular events.

The data reported here have a number of limitations. A substantial number of participants could not provide follow-up urines, mainly because they had died. It is conceivable or even likely that participants that died during the trial developed new microalbuminuria or new proteinuria more frequently than did those that did not die [4]. Therefore, the data may underestimate the true rate of progression of proteinuria in a population at high cardiovascular risk. Urine albumin was measured only once at each time point. Albuminuria is variable and most organizations recommend that 2 out of 3 measurements need to be positive to establish the presence of microalbuminuria [1, 2]. Nevertheless, the large sample size and the fact that the ACR was assayed centrally, can compensate for the variance associated with only one measurement. Moreover, the fact that the regression dilution bias introduced by a single measurement of a risk factor is an underestimate and not an overestimate of the importance of that risk factor [28] provides further indication of the robustness of these observations.

CONCLUSION

Taken together, these observations support the conclusion that albuminuria reflects underlying vascular disease. These data also suggest that measurement of urinary albumin—before starting treatment and during treatment—may be a useful tool to identify both diabetic and nondiabetic patients at high risk of renal and cardiovascular disease. These patients can then be more aggressively targeted for preventive interventions.

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Reprint requests to Johannes F.E. Mann, M.D., Dept. of Nephrology and Hypertension, Schwabing General Hospital, LMU, Kohler Platz 1 D–80804 Munchen, Germany.
E-mail: johannes.mann@kms.mhn.de