

# Cardiovascular events were increased in high cardiovascular risk patients with albuminuria

Gerstein HG, Mann JF, Yi Q, et al., for the HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001 Jul 25;286:421-6.

## QUESTION

Is any degree of albuminuria a risk factor for cardiovascular (CV) events in high-risk patients with or without diabetes mellitus (DM)?

## DESIGN

Cohort study of patients enrolled in the Heart Outcomes Prevention Evaluation (HOPE) study with a median follow-up of 4.5 years.

## SETTING

Community and academic practices in Europe and North and South America.

## PARTICIPANTS

9043 patients  $\geq 55$  years of age who had a history of previous CV disease (either coronary artery disease, stroke, or peripheral vascular disease) or a history of DM plus  $\geq 1$  other CV risk factor (total cholesterol level  $> 5.2$  mmol/L, high-density lipoprotein cholesterol level  $\leq 0.9$  mmol/L, hypertension, known microalbuminuria, or current smoker). Exclusion criteria included dipstick-positive proteinuria or established diabetic nephropathy, other renal disease, hyperkalemia, congestive heart failure (CHF), low-ejection fraction, and hypersensitivity to vitamin E or angiotensin-converting enzyme inhibitors.

## ASSESSMENT OF RISK FACTORS

Baseline data were collected on age, sex, smoking status, hypertension, history of dyslipidemia, DM status, abdominal obesity, and serum creatinine level. In patients with DM, duration of DM, use of oral glucose-lowering agents or insulin, and glycated hemoglobin levels were also assessed. Urinary creatinine and albumin levels were measured at baseline, first visit, and the end of the study in all patients; the serum creatinine level was measured at follow-up visits in patients with DM.

## MAIN OUTCOME MEASURES

CV events (myocardial infarction, stroke, or CV death), all-cause mortality, and hospitalization for CHF.

## MAIN RESULTS

Microalbuminuria was detected in 33% of patients with DM and 15% of patients with-

out DM, and it increased the risk for major CV events, all-cause mortality, and hospitalization for CHF (Table). The risk increased with the albumin/creatinine ratio, beginning below the microalbuminuria cut point (2 mg/mmol). Similar relative risks (RRs) were seen for patients with or without DM and after adjustment for other CV risk factors.

## CONCLUSION

Patients with increased cardiovascular risk, with or without diabetes mellitus, and any degree of albuminuria were at increased risk for major cardiovascular events.

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### Incidence and relative risk (RR) of major cardiovascular (CV) events (myocardial infarction, stroke, or cardiovascular death), all-cause mortality, and hospitalization for congestive heart failure (CHF) in all high-risk patients

Outcomes at median 4.5 y	With microalbuminuria	Without microalbuminuria	Adjusted RR (95% CI)†
Major CV events	23%	14%	1.83 (1.64 to 2.05)
All-cause mortality	18%	9%	2.09 (1.84 to 2.38)
CHF hospitalization	7%	2%	3.23 (2.54 to 4.10)

†Adjusted for randomization to receive ramipril.

## COMMENTARY

This large, international, multicenter, CV disease prevention trial—which found ramipril, but not vitamin E, protective—has clearly shown that the presence of albuminuria indicates increased risk for myocardial infarction, stroke, CV death, CHF, and all-cause mortality. This increase was true in patients with or without diabetes and in those receiving ramipril or placebo. The increase in risk began even below the threshold level for microalbuminuria used to indicate incipient diabetic nephropathy in patients with DM.

The authors point out that many CV risk factors are associated with microalbuminuria, including smoking, dyslipidemia, hypertension, hyperhomocystinemia, dietary protein, and markers of acute phase response. Although the authors adjusted for many of these factors in the analyses, further research is necessary to more clearly assess the independent CV risk signaled by albuminuria. More important, researchers need to clarify whether increasing albuminuria is a causal risk factor for CV disease or simply a marker of diffuse endothelial disease characteristic of early atherosclerosis.

The steady increase in CV risk by deciles of albuminuria to a doubling of risk at the traditional level of microalbuminuria is so

striking that clinicians may want to direct interventions to decrease albuminuria, but this approach may be premature. The study was based on one measure of albuminuria; thus, the individual variability in levels of albuminuria this low may be of concern. Cut points to stratify risk would have to be established. The clarity of the intervention must also be determined: Should we intervene more aggressively in the areas of blood pressure, lipid levels, glucose intolerance, and smoking, which most physicians already try to do, or should we prescribe something more specific for albuminuria?

Before clinicians begin measuring albuminuria for CV risk stratification, it will be necessary to assess whether albuminuria is a risk factor or just a marker for CV disease, to determine the mechanism of any increased risk, and to evaluate whether a specific intervention to lower albuminuria results in reduced CV risk. Meanwhile, clinicians should concentrate on reducing proven CV risk factors that have cleared these hurdles.

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