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# Albuminuria and Risk of Cardiovascular Events, Death, and Heart Failure in Diabetic and Nondiabetic Individuals

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**D**IABETES MELLITUS (DM) IS A strong risk factor for cardiovascular (CV) disease.<sup>1</sup>

Compared with those who do not have DM, people with DM have a 2- to 4-fold increased risk of subsequent CV disease.<sup>2-4</sup> Risk factors that independently increase CV risk in people with DM include smoking, hypertension, dyslipidemia,<sup>3</sup> renal dysfunction,<sup>5</sup> and hyperglycemia.<sup>6-10</sup> Recently, data from several studies have established microalbuminuria (MA), or dipstick-negative albuminuria, as another CV risk factor. Microalbuminuria is reported in approximately 30% of middle-aged patients with either type 1 or type 2 DM and in approximately 10% to 15% of middle-aged individuals who do not have DM.<sup>11-13</sup> Although MA is associated with other risk factors in those with or without

**Context** Microalbuminuria is a risk factor for cardiovascular (CV) events. The relationship between the degree of albuminuria and CV risk is unclear.

**Objectives** To estimate the risk of CV events in high-risk individuals with diabetes mellitus (DM) and without DM who have microalbuminuria and to determine whether levels of albuminuria below the microalbuminuria threshold increase CV risk.

**Design** The Heart Outcomes Prevention Evaluation study, a cohort study conducted between 1994 and 1999 with a median 4.5 years of follow-up.

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

**Participants** Individuals aged 55 years or more with a history of CV disease (n=5545) or DM and at least 1 CV risk factor (n=3498) and a baseline urine albumin/creatinine ratio (ACR) measurement.

**Main Outcome Measures** Cardiovascular events (myocardial infarction, stroke, or CV death); all-cause death; and hospitalization for congestive heart failure.

**Results** Microalbuminuria was detected in 1140 (32.6%) of those with DM and 823 (14.8%) of those without DM at baseline. Microalbuminuria increased the adjusted relative risk (RR) of major CV events (RR, 1.83; 95% confidence interval [CI], 1.64-2.05), all-cause death (RR, 2.09; 95% CI, 1.84-2.38), and hospitalization for congestive heart failure (RR, 3.23; 95% CI, 2.54-4.10). Similar RRs were seen for participants with or without DM, even after adjusting for other CV risk factors (eg, the adjusted RR of the primary aggregate end point was 1.97 [95% CI, 1.68-2.31] in those with DM and 1.61 [95% CI, 1.36-1.90] in those without DM). Compared with the lowest quartile of ACR (<0.22 mg/mmol), the RRs of the primary aggregate end point in the second quartile (ie, ACR range, 0.22-0.57 mg/mmol) was 1.11 (95% CI, 0.95-1.30); third quartile, 1.38 (95% CI, 1.19-1.60; ACR range, 0.58-1.62 mg/mmol); and fourth quartile, 1.97 (95% CI, 1.73-2.25; ACR range, >1.62 mg/mmol) (*P* for trend <.001, even after excluding those with microalbuminuria). For every 0.4-mg/mmol increase in ACR level, the adjusted hazard of major CV events increased by 5.9% (95% CI, 4.9%-7.0%).

**Conclusions** Our results indicate that any degree of albuminuria is a risk factor for CV events in individuals with or without DM; the risk increases with the ACR, starting well below the microalbuminuria cutoff. Screening for albuminuria identifies people at high risk for CV events.

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DM,<sup>11,13,14</sup> it is also an independent predictor of future strokes, death, and myocardial infarction (MI).<sup>15-19</sup> Moreover, MA may also predict future congestive heart failure (CHF). However, at

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present, there are few prospective data regarding this association.<sup>20-23</sup>

Despite being increasingly recognized as a CV risk factor, the definition of MA was based on its ability to predict diabetic nephropathy (ie, macroalbuminuria or clinical proteinuria). Whether individuals with albumin excretion rates below the MA threshold are also at risk for CV disease or whether there is a progressive graded relationship between different degrees of albuminuria and CV events is unclear.

Our study examines the relationship between baseline albuminuria levels and future CV events using data collected from individuals with or without DM enrolled in the Heart Outcomes Prevention Evaluation (HOPE) Study. Participants were followed-up for a median of 4.5 years

## METHODS

### Participants and Overview of Study Design

Detailed descriptions of the HOPE study and MICRO (Microalbuminuria, Cardiovascular and Renal Outcomes) HOPE substudy have been published previously.<sup>24-27</sup> In brief, individuals with or without DM aged 55 years or older with a history of previous CV disease (either coronary artery disease, stroke, or peripheral vascular disease) or with a history of DM plus at least 1 other CV risk factor (total cholesterol >200 mg/dL [ $>5.2$  mmol/L], high-density lipoprotein cholesterol  $\leq 35$  mg/dL [ $\leq 0.9$  mmol/L]), hypertension, known MA, or current smoker) were studied between 1994 and 1999 in North and South America and Europe. Key exclusion criteria included dipstick-positive proteinuria or established diabetic nephropathy, other significant renal disease, hyperkalemia, CHF, low-ejection fraction, or hypersensitivity to vitamin E or angiotensin-converting enzyme inhibitors.<sup>24</sup> The aggregate primary end point of the study was the development of either MI, stroke, or CV death. This analysis is restricted to the 97% of all HOPE participants (3498 with DM and 5545 without DM) randomized to receive ei-

ther 10 mg of ramipril or placebo and in whom baseline urine albumin measurements were available.

### Clinical Data Collection

Diabetes status and other demographic and clinical variables were determined by history and physical examination. Glycated hemoglobin was assayed for participants with a history of DM in each study center's local laboratory. Results were expressed as the percentage above the upper limit of normal for the assay used. Serum creatinine was measured at each study site in all participants at baseline and was only measured in the participants with DM at follow-up visits. The results were expressed in International System of Units.

### Urine Collection and Analysis

Urinary albumin was measured in 9043 (97%) of HOPE study participants at baseline; the assays used have been described previously.<sup>24,25</sup> A first morning urine was collected at baseline, 1 year, and study end. Urinary albumin levels were measured by either radioassay (Europe and North America) or immunoturbidimetry (South America), and urinary creatinine levels were measured by the Jaffe method.<sup>25</sup> The degree of albuminuria, expressed as the albumin/creatinine ratio (ACR), was entered into the database so that the relationship between baseline ACR and future outcomes could be analyzed. Microalbuminuria was defined as an ACR of 2 mg/mmol or more for both men and women; dipstick-positive (ie,  $\geq 1+$ ) proteinuria (ie, a level with  $>70\%$  sensitivity and 90% specificity for detecting MA) was an exclusion criteria.<sup>28</sup>

### Outcome Assessment

Participants were assessed every 6 months. Myocardial infarction, stroke, CV death (the primary aggregate end point), and hospitalization for CHF (a secondary end point), were documented and adjudicated centrally as described previously. As reported, the study was approved by local ethics boards, and all participants signed written informed consent.<sup>27</sup>

### Statistical Analysis

The univariate and multivariate relative risks (RRs) of the primary study end point MI, stroke, or CV death; all-cause mortality; and hospitalization for CHF in participants with and without MA were calculated using Cox regression models. The proportionality assumption of the Cox model was assessed by inspection of the Kaplan Meier curves for those with and without MA; these showed no evidence of a time-dependent hazard. Variables entered into the multivariate model for all participants included age, sex, smoking status, hypertension, history of dyslipidemia (ie, a total cholesterol  $>200$  mg/dL [ $>5.2$  mmol/L] or high-density lipoprotein cholesterol  $\leq 35$  mg/dL [ $\leq 0.9$  mmol/L]), DM status, abdominal obesity, and baseline serum creatinine level; for participants with DM, duration of DM, use of oral glucose-lowering agents or insulin, and glycated hemoglobin level were also included. Population attributable risk for MA in all participants (ie, the proportion of events attributable to MA) was estimated as the proportion of all people with MA  $\times$  (the difference in event rates between those with and without MA)/the overall event rate.

All participants were categorized by quartiles of albuminuria levels. Tests for linear trend across quartiles were performed using Cox regression after adjusting for (1) age and sex; (2) age, sex, systolic blood pressure, diastolic blood pressure, waist-hip ratio, DM status (in all participants), and glycated hemoglobin (in diabetic participants) in all the participants and in those with no MA (ie, with an ACR  $<2$  mg/mmol); and (3) randomization to receive ramipril in the previous model. The unadjusted RR and 95% confidence intervals (CIs) of outcomes in each quartile with reference to the first quartile were also calculated. Model fit was assessed using the likelihood ratio test. All statistical analyses were performed using SAS version 6.11.

## RESULTS

### Baseline Associations

Microalbuminuria was detected in 1140 (32.6%) of participants with DM and

823 (14.8%) of participants without DM at baseline. A detailed description of the baseline characteristics of the HOPE participants according to the presence or absence of MA has been published previously.<sup>11</sup> Both diabetic and nondiabetic individuals with MA were older, had higher systolic and diastolic blood pressure, had a lower ankle-arm blood systolic pressure ratio, and had a higher serum creatinine concentration than individuals without MA; patients with DM and with MA also had a longer duration of DM and had higher glycated

hemoglobin level and waist-hip ratio than those without MA.

### Impact of MA

TABLE 1 and TABLE 2 list the incidence and risk of the primary aggregate end point of the HOPE study MI, stroke, or CV death; all-cause mortality; and hospitalization for CHF according to the presence of MA. After controlling for randomization to receive ramipril, baseline MA increased the adjusted RR for major CV events by 1.83-fold (95% CI, 1.64-2.05;  $P < .001$ ); (2) all-cause mor-

tality by 2.09-fold (95% CI, 1.84-2.38); and (3) hospitalization for heart failure by 3.23-fold (95% CI, 2.54-4.10). Similar estimates were noted in individuals with and without a history of DM at the time of randomization (Tables 1 and 2). The close association between MA and these outcomes persisted even after controlling for other CV risk factors in the placebo and ramipril groups (Table 2). The population attributable RRs were 12.7% (95% CI, 9.9%-15.5%) for major CV events; 16.9% (95% CI, 13.4%-20.4%) for all-cause mortality; and

**Table 1.** Incidence and Risk of Cardiovascular Events in HOPE Study Participants With and Without Baseline Microalbuminuria\*

Variables	With Microalbuminuria, %	Without Microalbuminuria, %	Crude Risk (95% CI)†	Adjusted Risk (95% CI)†
All participants				
MI, stroke, or CV death	23.1	13.8	1.67 (1.51-1.85)	1.83 (1.64-2.05)
All-cause mortality	18.2	9.4	1.93 (1.72-2.18)	2.09 (1.84-2.38)
CHF hospitalization	6.9	2.2	3.08 (2.49-3.82)	3.23 (2.54-4.10)
Diabetes history				
MI, stroke, or CV death	25.0	13.9	1.80 (1.56-2.07)	1.97 (1.68-2.31)
All-cause mortality	18.6	9.3	2.01 (1.69-2.39)	2.15 (1.78-2.60)
CHF hospitalization	8.5	2.5	3.34 (2.49-4.50)	3.70 (2.64-5.17)
No diabetes history				
MI, stroke, or CV death	20.4	13.8	1.48 (1.27-1.73)	1.61 (1.36-1.90)
All-cause mortality	17.4	9.4	1.85 (1.55-2.20)	2.00 (1.65-2.41)
CHF hospitalization	4.6	2.1	2.23 (1.55-3.19)	2.20 (1.40-3.26)

\*Time-to-event analyses using Cox regression were performed to calculate the risk for cardiac events and total mortality. CI indicates confidence interval; CV, cardiovascular; MI, myocardial infarction; and CHF, congestive heart failure.

†Adjusted for randomization to receive ramipril. All are  $P < .001$ .

**Table 2.** Incidence and Risk of Cardiovascular Events in HOPE Study Participants With and Without Baseline Microalbuminuria by Randomized Group\*

Variables	Placebo						Ramipril					
	%		Crude Risk (95% CI)	P Value	Adjusted Risk (95% CI)†	P Value	%		Crude Risk (95% CI)	P Value	Adjusted Risk (95% CI)†	P Value
	With MA	Without MA					With MA	Without MA				
All participants												
MI, stroke, or CV death	26.4	15.2	1.73 (1.52-1.98)	<.01	1.75 (1.49-2.05)	<.001	19.6	12.4	1.58 (1.35-1.85)	<.01	1.42 (1.18-1.71)	<.001
All-cause mortality	20.3	9.8	2.07 (1.77-2.42)	<.01	1.92 (1.59-2.31)	<.001	15.7	8.9	1.77 (1.48-2.12)	<.01	1.52 (1.23-1.88)	<.001
CHF hospitalization	6.9	2.5	2.77 (2.06-3.73)	<.01	2.42 (1.70-3.45)	<.001	6.9	2.0	3.47 (2.54-4.73)	<.01	2.59 (1.78-3.77)	<.001
Diabetes history												
MI, stroke, or CV death	28.6	15.3	1.87 (1.55-2.25)	<.01	1.84 (1.46-2.31)	<.001	21.1	12.6	1.68 (1.35-2.10)	<.01	1.44 (1.11-1.86)	.006
All-cause mortality	20.8	10.6	1.96 (1.56-2.46)	<.01	1.85 (1.41-2.43)	<.001	16.3	7.9	2.05 (1.57-2.68)	<.01	1.64 (1.21-2.22)	.002
CHF hospitalization	8.2	2.5	3.24 (2.11-4.96)	<.01	4.51 (2.55-7.96)	<.001	8.9	2.6	3.46 (2.29-5.23)	<.01	2.91 (1.79-4.73)	<.001
No diabetes history												
MI, stroke, or CV death	23.3	15.2	1.53 (1.25-1.88)	<.01	1.60 (1.27-2.02)	<.001	17.4	12.3	1.41 (1.11-1.80)	.005	1.31 (0.99-1.73)	.06
All-cause mortality	19.7	9.5	2.09 (1.65-2.63)	<.01	1.86 (1.42-2.43)	<.001	14.9	9.4	1.60 (1.22-2.09)	<.01	1.36 (1.01-1.85)	.04
CHF hospitalization	5.0	2.5	2.04 (1.26-3.30)	.004	1.41 (0.81-2.45)	.2	4.2	1.7	2.49 (1.45-4.28)	<.01	1.94 (1.03-3.64)	.04

\*Time-to-event analyses using Cox regression were done to calculate the risk for cardiac events and total mortality. CV indicates cardiovascular; MI, myocardial infarction; and CHF, congestive heart failure.

†Adjusted for age, sex, smoking status, hypertension, dyslipidemia, diabetes status, abdominal obesity, and serum creatinine concentration in all participants and also for diabetes duration, use of oral agents or insulin, and glycated hemoglobin in patients with diabetes.

31.1% (95% CI, 24.0%-38.3%) for hospitalization for heart failure.

### Impact of ACRs Below the MA Threshold

These CV outcomes were also analyzed according to the level of albuminuria (expressed in quartiles) to determine the CV importance of ACRs below the MA threshold. The ACR cutpoints for each quartile of all HOPE participants who had a baseline determination for albuminuria are shown in TABLE 3. There was a graded relationship between the baseline ACR and the risk of both CV outcomes and mortality; this relationship extended into the "submicroalbuminuric" range. For example, the RR of all-cause death for each quartile compared with the first quartile (ACR <0.22 mg/mmol), was 1.08 (95% CI, 0.89-1.42) for an ACR of 0.22 to 0.57 mg/mmol, 1.46 (95% CI, 1.21-1.75) for an ACR of 0.58 to 1.62 mg/mmol, and 2.34 (95% CI, 1.99-2.77) for an ACR >1.62 mg/mmol. For major CV events, all-cause mortality and hospitalization for CHF in all participants, this linear trend was significant after (1) controlling for age and sex ( $P<.001$ ); (2) controlling for age, sex,

systolic blood pressure, diastolic blood pressure, waist-hip ratio, and DM status (in all participants) or glycated hemoglobin in diabetic participants ( $P<.001$ ); and (3) after removing individuals with MA and then controlling for age, sex, systolic blood pressure, diastolic blood pressure, waist-hip ratio, and DM status in all participants or glycated hemoglobin in participants with DM ( $P<.001$  for major CV events and all-cause mortality, and  $P=.05$  for CHF hospitalization). Similar findings were noted in the subgroups of participants with or without DM (Table 3). Finally, the linear trends remained significant when the 3 models were repeated for all participants and for the subgroups of participants with or without DM after randomization to receive ramipril was also included in the model ( $P$  for trend  $<.001$  except where indicated in Table 3).

### The ACR as a Continuous Risk Factor

To further assess the ACR as a continuous CV risk factor, the incidence of the primary outcome, all-cause death, and hospitalization for CHF was plotted against the ACR (partitioned accord-

ing to deciles in all participants with a baseline measurement). The FIGURE illustrates the progressive nature of this relationship. In addition, the hazard for these events for every increment in the ACR (by Cox regression) was calculated after adjustment for age, sex, and randomization to receive ramipril: for every 0.4-mg/mmol increase in ACR, the hazard of the primary outcome increased by 5.9% (95% CI, 4.9-7.0); all-cause death increased by 6.8% (95% CI, 5.6-8.0%); and hospitalization for CHF increased by 10.6% (95% CI, 8.4-13.0).

### COMMENT

A growing number of prospective epidemiologic studies have reported that MA is a strong independent risk factor for CV events.<sup>15-19</sup> The data presented herein support this conclusion and also show that MA is a strong independent risk factor for hospitalization for CHF and for all-cause mortality in people with no prior history of CHF and show that the relationship between albuminuria and experiencing a CV event is not restricted to the MA range. Indeed, they indicate that the relationship between the ACR and CV disease extends at least as

**Table 3.** Relative Risk of Outcomes According to Quartile of Albuminuria in HOPE Participants

Variables	Quartile, RR (95% Confidence Interval)				P for Trend†	P for Trend‡	P for Trend§
	First	Second	Third	Fourth			
Albumin/creatinine, mg/mmol	<.22	0.22-0.57	0.58-1.62	>1.62			
All patients (n = 9043)							
MI, stroke, or CV death	1	1.11 (0.95-1.30)	1.38 (1.19-1.60)	1.97 (1.73-2.25)	<.001	<.001	<.001
All-cause mortality	1	1.08 (0.89-1.32)	1.46 (1.21-1.75)	2.34 (1.99-2.77)	<.001	<.001	<.001
CHF hospitalization	1	1.19 (0.77-1.83)	1.95 (1.32-2.88)	3.79 (2.65-5.41)	<.001	<.001	.05 .05¶
Diabetes mellitus patients (n = 3498)							
MI, stroke, or CV death	1	0.85 (0.63-1.14)	1.11 (0.86-1.43)	1.89 (1.52-2.36)	<.001	<.001	.005 .006¶
All-cause mortality	1	0.86 (0.58-1.28)	1.41 (1.01-1.95)	2.38 (1.80-3.20)	<.001	<.001	.0006
CHF hospitalization	1	0.72 (0.32-1.63)	1.83 (0.98-3.43)	3.65 (2.06-6.46)	<.001	<.001	.39 .38¶
Patients without diabetes mellitus (n = 5545)							
MI, stroke, or CV death	1	1.24 (1.03-1.49)	1.54 (1.29-1.85)	1.83 (1.52-2.20)	<.001	<.001	<.001
All-cause mortality	1	1.17 (0.93-1.47)	1.49 (1.19-1.87)	2.27 (1.82-2.82)	<.001	<.001	.0002
CHF hospitalization	1	1.45 (0.87-2.44)	1.86 (1.12-3.10)	2.93 (1.79-4.81)	.001 .001¶	.006 .007¶	.13 .14¶

\*Relative risks of outcomes with reference to the first quartile are tabulated. The fourth quartile includes participants with microalbuminuria as well as lesser degrees of albuminuria; dipstick positive proteinuria was an exclusion criteria. MA indicates microalbuminuria; CV, cardiovascular; MI, myocardial infarction; and CHF, congestive heart failure.

†P for trend after controlling for age and sex.

‡P for trend after controlling for age, sex, systolic and diastolic blood pressure, waist-hip ratio, diabetes or (in diabetic participants) glycated hemoglobin.

§P for trend after removing individuals with MA (albumin/creatinine  $\geq 2$  mg/mmol) and then controlling for age, sex, systolic, and diastolic blood pressure, waist-hip ratio, diabetes mellitus, or glycated hemoglobin in participants with diabetes.

¶P for trend after including randomization to ramipril in each of the models is identical to the P value before including ramipril except where indicated.

low as 0.5 mg/mmol (Table 3), well below currently accepted screening thresholds for a diagnosis of MA.<sup>29</sup> This is consistent with a recent prospective study in which individuals with an ACR of >0.65 mg/mmol had an RR for ischemic heart disease of 2.3 ( $P = .002$ ) compared with people with a lower degree of albuminuria.<sup>30</sup> Thus, an ACR of 2.0 mg/mmol—a threshold used to screen for MA and risk for diabetic nephropathy—may not be relevant when considering the risk for CV outcomes; lower degrees of albuminuria are also predictive.

Taken together these observations support the suggestion that albuminuria reflects underlying vascular disease. These data also suggest that measurement of urinary albumin may help estimate the absolute risk of experiencing a CV event for individuals with or without DM. Patients with a high absolute risk will experience a higher absolute risk reduction when given preventive interventions than patients with a lower absolute risk. Therefore, a test that identifies high-risk patients provides useful information that will help clinicians estimate the benefits that may be expected from adding a proven preventive therapy.

Why is albuminuria a risk factor for CV disease? Clearly, a very small concentration of urinary albumin is unlikely to be a direct cause. Albuminuria is, however, associated with several other risk factors that may themselves be causal or linked with causal processes. These include both diabetic and nondiabetic degrees of hyperglycemia,<sup>31-33</sup> hypertension,<sup>34,35</sup> renal dysfunction,<sup>36</sup> dyslipidemia,<sup>31</sup> hyperhomocysteinemia,<sup>37</sup> dietary protein,<sup>37</sup> smoking,<sup>38</sup> and markers of an acute phase response.<sup>39</sup> Albuminuria also reveals increased renal endothelial permeability and may be an easily measured marker of diffuse endothelial dysfunction.<sup>40</sup> Thus albuminuria is an easily measured marker of other CV factors, as well as existing endothelial dysfunction, that likely reflects underlying macrovascular and microvascular disease.

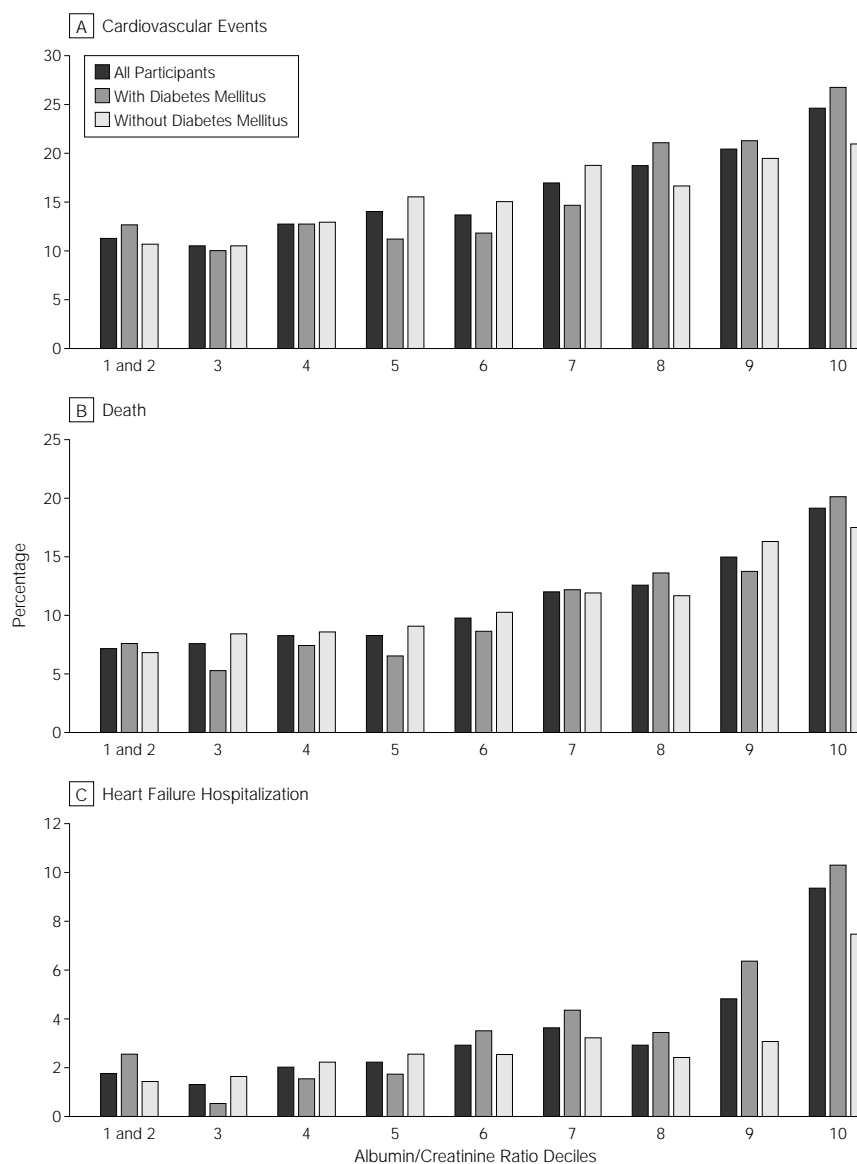
The measurement of only 1 ACR at baseline and previous observations that the degree of albuminuria varies from day-to-day are 2 limitations of the data.<sup>41</sup>

Nevertheless, the large sample size, central assay of the ACR, and the high diagnostic accuracy of a single urine collection<sup>42-45</sup> minimize the uncertainty associated with a single measurement. Moreover, the regression dilution bias introduced by a single measurement of a risk factor tends to underestimate the strength of the risk factor. This sug-

gests that the true association between ACR and CV events is likely to be even stronger than observed in our study.<sup>46,47</sup>

Albuminuria is therefore a robust independent continuous risk factor for future CV events, CHF, and all-cause mortality in middle-age dipstick-negative individuals with or without DM at high risk for CV disease. It is also relatively inex-

**Figure.** Incidence of Cardiovascular Outcomes According to Degree of Albuminuria



Panels A, B, and C show the rate of major cardiovascular events (myocardial infarction, stroke, or cardiovascular death), all-cause mortality, and hospitalization for congestive heart failure in each decile of albumin/creatinine ratio (ACR) for all participants, participants with diabetes mellitus, and participants without diabetes mellitus. Decile 1 and 2 are combined because of very low incidence rates in these 2 deciles. The 8th decile includes ACR of 2 mg/mmol, which is the microalbuminuria threshold.

pensive and can be assayed for less than \$10 in most laboratories. It can therefore be used as a simple test to identify individuals at high risk for future events who could be targeted for preventive strategies.

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**A complete listing of Hope investigators** appeared in 2 previously published articles (*Lancet*. 2000;255:253-259 and *N Engl J Med*. 2000;342:145-153).

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