Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Stroke Association
A Division of American Heart Association

Impact of Microalbuminuria on Incident Stroke : A Meta-Analysis

Meng Lee, Jeffrey L. Saver, Kuo-Hsuan Chang, Hung-Wei Liao, Shen-Chih Chang and Bruce Ovbiagele

Stroke 2010, 41:2625-2631: originally published online October 7, 2010
doi: 10.1161/STROKEAHA.110.581215
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Impact of Microalbuminuria on Incident Stroke
A Meta-Analysis

Meng Lee, MD; Jeffrey L. Saver, MD; Kuo-Hsuan Chang, MD; Hung-Wei Liao, MD; Shen-Chih Chang, PhD; Bruce Ovbiagele, MD, MS

Background and Purpose—Microalbuminuria, a marker of both kidney disease and endothelial dysfunction, may be associated with global vascular risk, but the nature and magnitude of the link between microalbuminuria and incident stroke has not been clearly defined. The purpose of this study was to assess the consistency and strength of the association of microalbuminuria with risk of stroke in prospective studies using meta-analysis.

Methods—We conducted a systematic search of electronic databases and bibliographies for studies reporting a multivariate-adjusted estimate, represented as relative risk with 95% CI, of the association between microalbuminuria and stroke risk. Studies were excluded if a majority of study participants had established kidney disease or pre-eclampsia. Estimates were combined using a random-effect model.

Results—We identified 12 studies, with a total of 48 596 participants and 1263 stroke events. Overall, presence of microalbuminuria was associated with greater stroke risk (relative risk, 1.92; 95% CI, 1.61 to 2.28; $P<0.001$) after adjustment for established cardiovascular risk factors. There was evidence of significant heterogeneity in the magnitude of the association across studies (P for heterogeneity <0.001, $I^2=68\%$), which was partially explained by differences in study population, microalbuminuria definition, and different microalbuminuria-related risk among stroke subtypes. However, in stratified analyses, microalbuminuria was associated with increased risk of subsequent stroke in all subgroups (general population, diabetics, those with known stroke).

Conclusions—Microalbuminuria is strongly and independently associated with incident stroke risk. Future studies should explore whether microalbuminuria is just a risk marker or a modifiable risk factor for stroke. **(*Stroke*. 2010;41:2625-2631.)**

Key Words: endothelial dysfunction ■ incidence ■ meta-analysis ■ microalbuminuria ■ stroke

Over the last 4 decades, several prospective clinical studies have identified a series of independent risk factors for symptomatic vascular events, including stroke.[1,2] However, a better understanding of the multifactorial pathogenesis of atherosclerosis, the underlying entity behind most vascular events, and the fact that many of these events occur in persons who do not harbor conventional vascular risk factors has prompted a search for novel risk factors for prediction of cardiovascular disease.[3] Nonetheless, the clinical value of many of these emerging risk factors remains uncertain largely due to inconsistency of data, paucity of prospective studies, or lack of evidence that their predictive ability is independent of conventional risk factors.[3]

One such emerging vascular risk factor is microalbuminuria.[4] Microalbuminuria is generally defined as a urinary albumin excretion rate (or albumin excretion rate) of 30 to 299 mg/day or an albumin:creatinine ratio of 2.5 to 25 mg/mmol in men and 3.5 to 25 mg/mmol in women.[4] Although often seen as a sign of early kidney disease (ie, impairment in glomerular filtration barrier), microalbuminuria interacts with several conventional vascular risk factors and is an independent marker of endothelial dysfunction.[4] Indeed, it is thought that assessing kidney structure using this relatively simple test could be a window to the systemic vasculature, that is, leaky renal vessels reflecting the permeability of the vasculature in general and an individual's susceptibility to target organ damage.[5]

There is convincing evidence of an independent positive relationship between overt proteinuria and stroke risk,[6] but the nature and magnitude of the link between microalbuminuria and incident stroke has so far not been systematically investigated. In this study, we aimed to assess the consistency and strength of the association of microalbuminuria with risk of stroke in prospective cohort studies using meta-analysis.

Methods

Literature Search

The search strategy was conducted according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology.[7] We performed a systematic search of PubMed (1966 to October 2009), EMBASE (1947 to October 2009), the Cochrane library (including CENTRAL), MEDLINE, and LILACS using the search strategy:

Received February 27, 2010; final revision received June 19, 2010; accepted June 30, 2010.

From the Stroke Center and Department of Neurology (M.L., J.L.S., B.O.), University of California, Los Angeles, Calif; the Department of Neurology, Chang Gung Memorial Hospital at Chiayi (M.L.) and Linkou (K.H.C.) and Chang Gung University College of Medicine, Taiwan; Ching-Ten Clinic (H.W.L.), Taiwan; the Department of Epidemiology (S.C.C.), School of Public Health, University of California, Los Angeles, Calif.

Correspondence to Bruce Ovbiagele, MD, MS, UCLA Stroke Center, 710 Westwood Plaza, University of California, Los Angeles, CA 90095. E-mail Ovibes@mednet.ucla.edu

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.110.581215**

Table 1. Definition of Microalbuminuria

Measurement Method	Microalbuminuria
Urine albumin excretion	30–300 mg/day or 20 to 200 μg/min or nearest equivalent interval
Spot UAC	20–300 mg/L or nearest equivalent interval
Spot UACR	25–300 mg/g or 2.8–35 mg/mmol or nearest equivalent interval

"proteinuria" or "albuminuria" or "microalbuminuria" or "macroalbuminuria" crossed with "stroke" or "cerebrovascular disease" or "cerebrovascular attack" or "cerebral ischemia" or "brain ischemia" or "intracranial hemorrhage." We restricted the search to human studies. There were no language restrictions. Manual searches of bibliographies of all relevant studies and review articles were reviewed and identified by 2 investigators (M.L. and K.H.C.).

Study Selection and Data Abstraction

Studies were selected if they met the following entry criteria: (1) prospectively collected data obtained within cohort studies or clinical trials; (2) reported quantitative estimates of the multivariate-adjusted relative risk (RR) and 95% CI for stroke associated with microalbuminuria; and (3) follow-up duration was at least 1 year. Studies were excluded if (1) the study design was cross-sectional, case–control, or retrospective cohort studies; (2) the majority of the participants had chronic kidney disease (ie, estimated glomerular filtration rate <60 mL/min/1.73 m^2, kidney transplant, Fabry disease, eclampsia, or preeclampsia; (3) only reported unadjusted or age-and sex-adjusted RR; and (4) did not report 95% CI. The prespecified definitions of microalbuminuria are listed in Table 1.[8] Studies that used slightly varying definitions were included if they were otherwise comparable. All data from eligible studies were abstracted independently by 2 investigators (M.L. and K.H.C.). Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

Assessment of Study Quality

We assessed quality of all articles that met the selection criteria with the following 8 characteristics: (1) prospective study design; (2) maintenance of comparable groups; (3) adjustment of potential confounders; (4) documented loss of follow-up rate; (5) outcome assessed blind to exposure status; (6) clear and proper definition of exposures (microalbuminuria) and outcomes (stroke); (7) temporality (microalbuminuria measured at baseline, not at time of outcomes assessment) and (8) follow-up of at least 1 year. Studies were graded as good quality if they met 6 to 8 criteria; fair if they met 3 to 5; and poor if they met <3 criteria.

Statistical Analysis

Data analysis used multivariate-adjusted outcome data (expressed as RRs and 95% CIs). We converted these values in every study by using their natural logarithms, and the SEs were calculated from these logarithmic numbers and their corresponding 95% CIs. The statistical analysis used the inverse variance approach to combine log RRs and SEs. We used a random-effect model and explored for sources of inconsistency (I^2) and heterogeneity. A fixed-effect model was also conducted for the comparison to the random-effects model on the overall risk estimate. The Cochrane Collaboration's Review Manager Software Package (RevMan 5) was used for the meta-analysis. All reported probability values were 2-sided with significance set <0.05. Heterogeneity was assessed by probability value of χ^2 statistics and I^2, which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance.[9,10] We regarded I^2 of <40% as "heterogeneity might not be important" and >75% as "considerable heterogeneity" based on the suggestion of *Cochrane Handbook for Systemic Review of Interventions*.[11]

All available data were included in the primary analysis. Subsequent subgroup analyses were conducted according to population (general versus diabetes versus stroke history), ethnicity (whites versus Asians and American Indians), microalbuminuria prevalence at entry (<30% versus ≥30%), measurement methods of microalbuminuria (spot urine albumin concentration [UAC] versus urine albumin creatinine ratio [UACR]), follow-up duration (<7 years versus ≥7 years), participant number (<2000 versus ≥2000), end point (fatal stroke versus fatal+nonfatal stroke), stroke subtypes (ischemic versus hemorrhagic versus nonspecific type), study type (observational cohorts versus secondary analysis of clinical trials), microalbuminuria versus stroke assessed as a primary study objectives compared with secondary objectives, and whether definitions of microalbuminuria found in each study completely versus partially corresponded to our prespecified microalbuminuria definition.

Finally, we also did a sensitivity analysis to further explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we removed each individual trial from the meta-analysis 1 at a time. A funnel plot based on the primary outcome was conducted to evaluate potential systematic bias in studies, including publication bias.

Results

The literature review identified 160 full articles for detailed assessment, among which 124 were excluded for no stroke estimate, 6 for no adjusted estimate or only age-and sex-adjusted estimate, and 18 for only proteinuria and stroke risk estimate. Our final primary analysis included 12 prospective cohort studies[12–23] with 13 estimates because 1 study reported diabetes mellitus (DM) and non-DM population separately (Figure 1).[16] The study characteristics are shown in Table 2. There were a total 48 596 participants and 1263 stroke events in the current meta-analysis. Among 13 estimates, 6 derived from the general population,[15–18,22,23] 5 from a Type 2 DM population,[13,14,16,19,20] and 2 from a population with a stroke history.[12,21] Nine studies were from a white-dominant population,[12–19,22] 2 from an Asian population,[20,21] and 1 from an American Indian population.[23] The participant number ranged from 370[21] to 23 433.[22] The follow-up duration ranged from 1.1 years[21] to 13.4 years.[23] Three of the 12 studies used UAC[12,16,19] for microalbuminuria measurement, whereas 9 used UACR.[13–15,17,18,20–23] Eleven studies reported fatal plus nonfatal stroke as a primary end point, whereas 1 reported fatal stroke as a primary end point.[19] Three studies used ischemic stroke as a primary end point[15,18,20] and others used all reported stroke as a primary end point.[12–14,16,17,19,21–23] Overall quality of studies was good (median, 6; range, 5 to 7).

Overall, presence of microalbuminuria was associated with greater subsequent stroke risk (RR, 1.92; 95% CI 1.61 to 2.28; $P<0.001$) after adjustment for established cardiovascular risk factors (Figure 2). There was evidence of significant heterogeneity in the magnitude of the association across studies (P for heterogeneity <0.001, $I^2=68\%$). The exclusion of any single study from the analysis did not alter the overall finding in a sensitivity test (data not shown). There was mild asymmetrical appearance lacking studies on the left lower part of the funnel plot (Figure 3). The RR from a fixed-effect model was 1.82 (95% CI, 1.65 to 1.99; $P<0.001$).

Table 3 shows microalbuminuria was associated with increased risk of subsequent stroke in all subgroups when we stratified the estimates by population, study type, ethnicity, microalbuminuria prevalence at entry, follow-up duration, participant number, measurement methods of microalbuminuria, and end point. Significant heterogeneity was found between the DM population and the population with a stroke

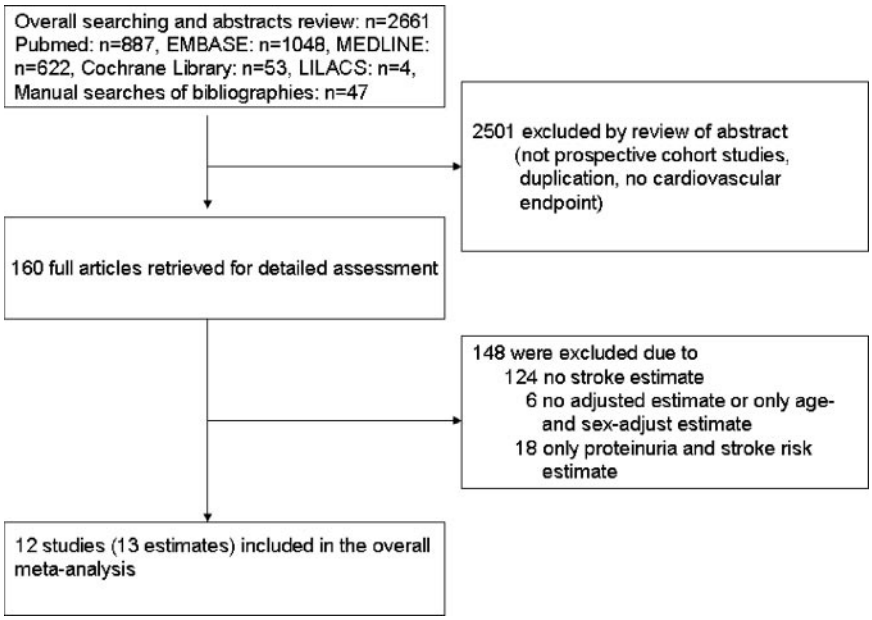

Figure 1. Study selection flow.

history (RR, 1.70; 95% CI, 1.43 to 2.04 versus RR, 2.92; 95% CI, 1.12 to 7.64; *P* for heterogeneity among groups=0.04, I^2=77%). Also, the association with ischemic stroke risk (RR, 2.21; 95% CI, 1.44 to 3.38) was significantly higher than hemorrhagic stroke risk (RR, 1.03; 95% CI, 0.68 to 1.55) and unspecified stroke risk (RR, 1.66; 95% CI, 1.48 to 1.87; *P* for heterogeneity among groups <0.01, I^2=82%). Heterogeneity was noted for studies, which completely (RR, 1.61; 95% CI, 1.43 to 1.81) versus partially (RR, 2.26; 95% CI, 1.66 to 3.07; *P* for heterogeneity among groups <0.001, I^2=91%) corresponded to our prespecified microalbuminuria definition.

Discussion

In this meta-analysis of 12 prospective cohort studies, among almost 49 000 individuals experiencing >1200 stroke events, we found that persons with baseline microalbuminuria have a risk of future stroke that is approximately 90% greater than those without microalbuminuria. This relationship was consistent across diverse population subgroups (ie, general populations, diabetic populations, and populations with a stroke history). Furthermore, the size and inclusion of only prospective data strengthen the robustness of our findings, because issues of selection bias, recall bias, and reverse causality are unlikely. In addition, all studies included in our meta-analysis reported a multivariate-adjusted RR, which probably mitigated the possibility of known confounding influencing our results.

We observed that the impact of microalbuminuria was greatest in the population with a history of stroke and relatively modest in the diabetic population. It is conceivable that this distinction is because among the diabetics, microalbuminuria may have more likely been a reflection of "earlier stage" nephropathy and not necessarily widespread vascular disease that could have precipitated future strokes. On the other hand, microalbuminuria among those with prior cerebrovascular bed damage (stroke) may have signified persons with extensive interaction of vascular factors[24,25] and vascular instability at highest risk for further cerebrovascular events.[4] We found microalbuminuria had the greatest impact on ischemic stroke, which would be expected given the aforementioned postulated underlying mechanisms for this association, followed by unspecified stroke type, and then an almost neutral effect on hemorrhagic stroke, further underscoring the likelihood that atherosclerosis might be the pathological link between microalbuminuria and stroke.

Our meta-analysis, based on observational studies, cannot prove causality and mechanistically it is unclear how albuminuria would directly cause stroke. However, there was some evidence implying that stroke risk might be reduced when we reduced microalbuminuria. A study showed that short-term reduction in albuminuria after initiation of blood pressure-lowering treatment has been associated with lower long-term stroke risk.[26] Among various blood pressure-lowering agents, for a similar level of attained blood pressure, modulators of the renin–angiotensin system lower urine albumin excretion or decrease incidence of new-onset microalbuminuria more effectively than other agents among patients with diabetes.[27,28] In fact, among microalbuminuric subjects, treatment with fosinopril had a significant effect on lessening urinary albumin excretion and was associated with a trend in reducing cardiovascular events, results that could not completely be attributed to the reduction in arterial blood pressure.[29,30] Future studies are needed to investigate whether limiting urinary albumin excretion with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers may reduce cardiovascular events, including strokes, beyond their blood pressure-lowering effects.

Compared with studies whose definitions completely corresponded to our prespecified microalbuminuria definition, those that only partially did so appeared to have a stronger link to stroke risk. Most of the studies in the latter category did not set an upper limit of UACR, which means participants with macroalbuminuria were also included. As such, it is not surprising that stroke risk was higher with data likely comprising the entire albuminuria range (microalbuminuria+macroalbuminuria).

Table 2. Study Characteristics

Study	Study Design and Population	Country	No. of Participants (Women, %)	Prevalence of Microalbuminuria at Entry	No. of Stroke	Age, Mean±SD, Years	Follow-Up, Years	End Point	Definition of Microalbuminuria	Adjusted Variable
Beamer, 1999[12]	Stroke cohort from a hospital	USA	121 (11)	21%	26	66±8	1.5	All recurrent stroke	UAC 20–200 mg/L	HTN, DM, smoking status
Gillett, 2003[13]	Type 2 diabetic cohort, no stroke history at entry	Australia	1083 (52)	40%	89	66±10	4.9	All stroke	UACR ≥3.0 mg/mmol	Age, sex, BMI, waist circumference, diabetes duration, glycemic control, BP, BP treatment, lipid, lipid-lowering therapy, aspirin, atrial fibrillation/flutter, smoking, alcohol, exercise status, and carotid bruit status
Hitman, 2007[14]	Type 2 diabetic cohort without CVD history at entry from a clinical trial	UK	2838 (32)	24%	60	62±8	3.9	All stroke	UACR >2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 μg/min	Age, sex, retinopathy, proteinuria, DM duration, systolic BP, HbA1C, atorvastatin use
Kistorp, 2005[15]	Population-based cohort without CVD history at entry	Denmark	537 (58)	NR	21	68±11	5	Ischemic stroke	UACR >18.4 mg/g	Age, sex, current smoking, DM, HTN, AF, LVEF <50%, LVH, total cholesterol, and serum creatinine
Miettinen, 1996a[16]	Nondiabetic cohort, stroke history at entry was 1%	Finland	1375 (52)	NR	30	58±0.2	7	All stroke	UAC 150–299 mg/L	Sex, area, age, history of stroke, total cholesterol, HDL cholesterol, TG, smoking, HTN
Miettinen, 1996b[16]	Type 2 diabetic cohort, stroke history at entry was 6%	Finland	1056 (45)	NR	125	58±0.2	7	All stroke	UAC 150–299 mg/L	Sex, area, age, history of stroke, total cholesterol, HDL cholesterol, TG, smoking, HTN
Schrader, 2006[17]	HTN, nondiabetic cohort with all received ACEI, stroke history at entry was 2%	Germany	2582 (62)	32%	15	63±8	3.5	All stroke	UACR 20–300 mg/g	Age, sex, HF, CHD, MI, hyperlipidemia, hyperuricemia
Solbu, 2009[18]	Population-based, nondiabetic cohort, no CVD history at entry	Norway	5215 (49)	33%	225	60±10	9.7	Ischemic stroke	UACR 0.75–30 mg/mmol	Age, sex, metabolic syndrome, current smoking, hard physical activity ≥1 hour per week, eGFR
Valmadrid, 2000[19]	Population-based older-onset diabetic cohort	USA	668 (57)	31%	65	67±11	12	Fatal stroke	UAC 30–299 mg/L	Age, sex, glycemic control, insulin use, alcohol intake, physical activity, history of CVD, intake of anti-HTN agents, presence and severity of diabetic retinopathy
Yang, 2008[20]	Type 2 diabetic clinic-based cohort, no stroke history at entry	China	5403 (55)	25%	91	57 (interquartile range, 46–67 years)	5.4	Ischemic stroke	UACR 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women	Age, sex, smoking status (current and former), HTN, BMI, HDL cholesterol, duration of DM, eGFR, and use of drugs at baseline (lipid-lowering drugs, oral antidiabetic drugs, and insulin)
Yokota, 2009[21]	Ischemic stroke cohort from a hospital	Japan	370 (34)	NR	49	70±11	1.1	All recurrent stroke	UACR 20–300 mg/g	Sex, DM, high BP (factors with $P<0.05$ in univariate analysis)
Yuyun, 2004[22]	Population-based cohort, no stroke history at entry	UK	23433 (53)	12%	237	58±9	7.2	All stroke and stroke subtypes	UACR 2.5–25 mg/mmol	Age, sex, smoking, hypertension treatment, systolic BP, total cholesterol, DM, BMI, physical activity, family history of stroke, and baseline CHD
Zhang, 2008[23]	Population-based cohort, stroke history at entry was 1%	USA (American Indians)	3915 (60)	22%	228	57±9	13.4	All stroke	UACR 30–299 mg/g	Age, sex, systolic and diastolic BP, BMI, waist circumference, LDL and HDL cholesterol, TG, physical activity, smoking, alcohol use, and fasting glucose

CVD indicates cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitor; NR, not reported; BMI, body mass index; BP, blood pressure; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; HDL, high-density lipoprotein; TG, triglycerides; HF, heart failure; CHD, coronary heart disease; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein.

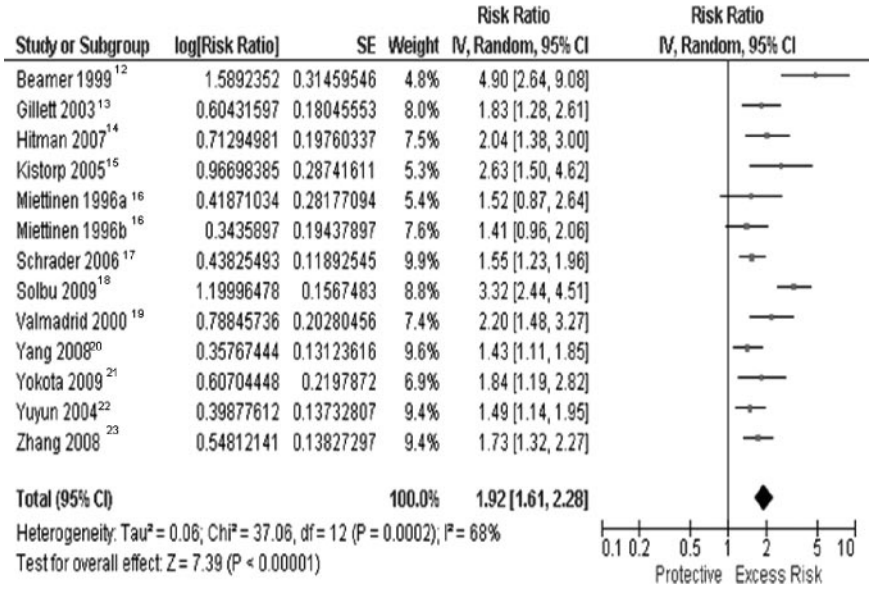

Figure 2. Overall risk ratio (RR) for the association of microalbuminuria and stroke risk.

The current systematic review found the prevalence of microalbuminuria ranged from 12%[22] to 40%.[13] The high prevalence rate of microalbuminuria raises a question whether it is cost-effective to screen microalbuminuria in diabetic and general populations. Health economic analyses have shown that screening for albuminuria in the Type 2 diabetic patients and subsequent initiation of angiotensin II antagonists treatment in those found positive contributed to better outcomes, including reduction of cardiovascular event, and may represent an excellent value.[31,32] On the other hand, some have argued that simply treating all middle-aged diabetic patients with angiotensin-converting enzyme inhibitors is a simple strategy that provides additional benefit at modest additional cost.[33] For the general population, a strategy of annual dipstick screening for gross proteinuria with follow-up testing and treatment with an angiotensin-converting enzyme inhibitor may not be cost-effective with regard to slowing progression of kidney disease or decreasing mortality.[34] This is because the yield is so low due to the low prevalence (<1%) of gross proteinuria in the general population.[35] However, screening for the general population for microalbuminuria and subsequently treating those found positive with fosinopril may be more cost-effective compared with no screening and adopting an ordinary healthcare perspective given the substantially higher rates of microalbuminuria in the general population.[36]

Some limitations need to be mentioned. First, meta-analyses can be constrained by comprehensiveness of searches, methodological rigor of the included studies, and publication bias, especially when the meta-analysis was conducted of epidemiological studies rather than randomized controlled trials. Second, the studies varied with respect to the characteristics of participants, definition of stroke in outcome assessment, follow-up duration, among others and indeed, heterogeneity was found by formal analysis. Still, our sensitivity analysis showed that removing any 1 study did not alter the main meta-analysis findings. Finally, there was evidence of a publication bias as

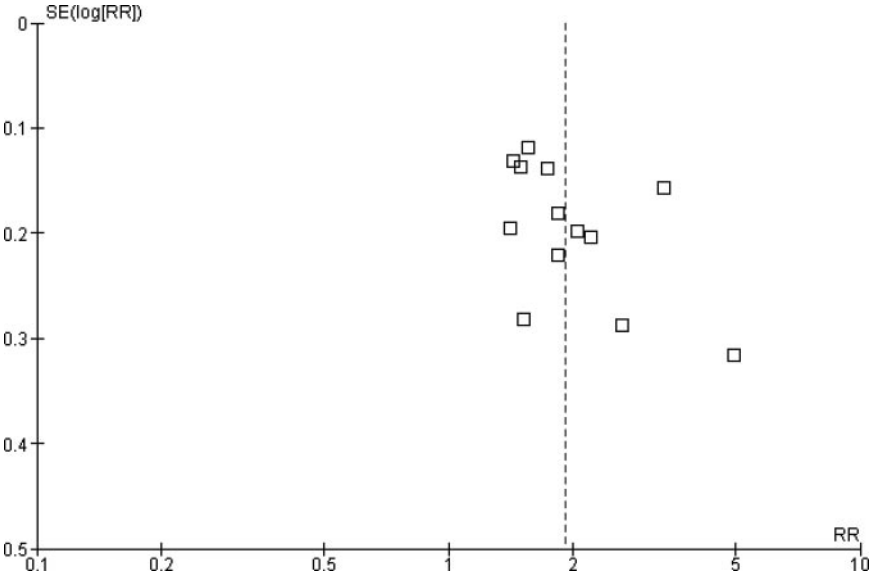

Figure 3. The funnel plot of included studies.

Table 3. Subgroup Analyses

	No. of Estimates	RR (95% CI)	Heterogeneity Within Subgroup	Heterogeneity Among Subgroups
Population				General versus DM: $P=0.39$, $I^2=0\%$; General versus stroke history: $P=0.09$, $I^2=65\%$; DM versus stroke history: $P=0.04$, $I^2=77\%$
General (including hypertension cohort)	6	1.91 (1.46–2.52)	$P<0.001$, $I^2=76\%$	
Diabetes mellitus	5	1.70 (1.43–2.04)	$P=0.26$, $I^2=24\%$	
Stroke history	2	2.92 (1.12–7.64)	$P=0.01$, $I^2=85\%$	
Ethnicity				$P=0.09$, $I^2=65\%$
White	10	2.04 (1.63–2.55)	$P<0.001$, $I^2=73\%$	
Asian and American Indian	3	1.60 (1.35–1.90)	$P=0.49$, $I^2=0\%$	
MA prevalence at entry				$P=0.09$, $I^2=66\%$
<30%	5	1.87 (1.41–2.48)	$P<0.01$, $I^2=73\%$	
≥30%	5	2.12 (1.48–3.04)	$P<0.01$, $I^2=76\%$	
Follow-up duration, year				$P=0.49$, $I^2=0\%$
<7 years	7	1.95 (1.54–2.46)	$P=0.01$, $I^2=64\%$	
≥7 years	6	1.87 (1.24–2.47)	$P<0.01$, $I^2=75\%$	
Participants No.				$P=0.27$, $I^2=17\%$
<2000	7	2.05 (1.58–2.65)	$P=0.03$, $I^2=56\%$	
≥2000	6	1.82 (1.43–2.31)	$P<0.001$, $I^2=77\%$	
Measurement method				$P=0.46$, $I^2=0\%$
UAC	4	2.12 (1.31–3.44)	$P<0.01$, $I^2=76\%$	
UACR	9	1.86 (1.55–2.24)	$P<0.01$, $I^2=67\%$	
End points				$P=0.96$, $I^2=0\%$
Fatal stroke	2	1.79 (1.21–2.66)	$P=0.15$, $I^2=52\%$	
Fatal+nonfatal stroke	12	1.90 (1.58–2.28)	$P<0.001$, $I^2=70\%$	
Stroke subtypes				$P<0.01$, $I^2=82\%$
Ischemic	4	2.21 (1.44–3.38)	$P<0.001$, $I^2=83\%$	
Hemorrhagic	1	1.03 (0.68–1.55)	…	
Unspecified	10	1.66 (1.48–1.87)	$P=0.55$, $I^2=0\%$	
Study type				$P=0.55$, $I^2=0\%$
Observational cohorts	12	1.91 (1.59–2.30)	$P<0.001$, $I^2=70\%$	
Secondary analysis of clinical trials	1	2.04 (1.38–3.00)	…	
Association of MA and stroke in study objectives				$P=0.33$, $I^2=0\%$
Primary objective	5	1.85 (1.31–2.62)	$P<0.01$, $I^2=70\%$	
Secondary objective	8	1.97 (1.60–2.42)	$P<0.01$, $I^2=69\%$	
Prespecified MA definitions				$P<0.001$, $I^2=91\%$
Completely measure up	6	1.61 (1.43–1.81)	$P=0.52$, $I^2=0\%$	
Partly measure up	7	2.26 (1.66–3.07)	$P<0.01$, $I^2=73\%$	

MA indicates microalbuminuria.

seen in the funnel plot (Figure 3). Some studies did not report RR with 95% CI when an insignificant result was found after adjusting for known cardiovascular risk factors[37] and, as such, could not be included in our meta-analysis. This issue probably resulted in an overestimation of the association between microalbuminuria and stroke risk. However, when we exclude 3 estimates with larger SEs, the overall RR between microalbuminuria and stroke risk decreased to 1.61 (95% CI, 1.39 to 1.85).

In conclusion, our formal meta-analysis found a significant and strong association between microalbuminuria and subsequent stroke risk across various population subtypes after adjustment of established cardiovascular risk factors. Future studies, preferably randomized controlled studies of agents that lower or prevent microalbuminuria, should explore whether microalbuminuria is just a risk marker or a potentially modifiable risk factor for stroke.

Acknowledgments

We thank Yueh Lee, MS, for article retrieval.

Sources of Funding

Supported by CMPRG 660311, Taiwan (M.L.), National Institutes of Health Specialized Program for Translational Research in Acute Stroke (SPOTRIAS; J.L.S.), and University of California–Los Angeles RCMAR under National Institutes of Health/National Institute on Aging Grant P30-AG021684 (B.O.).

Disclosures

J.L.S. has received honoraria from universities as a visiting professor; is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to Concentric Medical, Talecris, and Ev3; is a site investigator in multicenter trials sponsored by Lundbeck for which the UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the National

Institutes of Health Interventional Management of Stroke (IMS) 3 and Combination Therapy of rt-PA and Eptifibatide to Treat Acute Ischemic Stroke (CLEAR-ER) multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; has declined consulting/honoraria monies from Genentech since 2002; and is funded by National Institutes of Health–National Institute of Neurological Disorders and Stroke Awards P50 NS044378 and U01 NS 44364.

References

1. Bineau S, Dufouil C, Helmer C, Ritchie K, Empana JP, Ducimetiere P, Alperovitch A, Bousser MG, Tzourio C. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. *Stroke*. 2009;40:1564–1570.
2. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302:1993–2000.
3. Ovbiagele B. Optimizing vascular risk reduction in the stroke patient with atherothrombotic disease. *Med Princ Pract.* 2010;19:1–12.
4. Ovbiagele B. Microalbuminuria: risk factor and potential therapeutic target for stroke? *J Neurol Sci*. 2008;271:21–28.
5. de Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol*. 2006;17:2100–2105.
6. Ninomiya T, Perkovic V, Verdon C, Barzi F, Cass A, Gallagher M, Jardine M, Anderson C, Chalmers J, Craig JC, Huxley R. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis*. 2009;53:417–425.
7. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
8. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension*. 2003;42:1050–1065.
9. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
11. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* Oxford, UK: The Cochrane Collaboration; 2008.
12. Beamer NB, Coull BM, Clark WM, Wynn M. Microalbuminuria in ischemic stroke. *Arch Neurol*. 1999;56:699–702.
13. Gillett M, Davis WA, Jackson D, Bruce DG, Davis TM. Prospective evaluation of carotid bruit as a predictor of first stroke in type 2 diabetes: the Fremantle Diabetes Study. *Stroke*. 2003;34:2145–2151.
14. Hitman GA, Colhoun H, Newman C, Szarek M, Betteridge DJ, Durrington PN, Fuller J, Livingstone S, Neil HA. Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabet Med*. 2007;24:1313–1321.
15. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA*. 2005;293:1609–1616.
16. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects. *Stroke*. 1996;27:2033–2039.
17. Schrader J, Luders S, Kulschewski A, Hammersen F, Zuchner C, Venneklaas U, Schrandt G, Schnieders M, Rangoonwala B, Berger J, Dominiak P, Zidek W. Microalbuminuria and tubular proteinuria as risk predictors of cardiovascular morbidity and mortality in essential hypertension: final results of a prospective long-term study (MARPLE Study). *J Hypertens*. 2006;24:541–548.
18. Solbu MD, Kronborg J, Jenssen TG, Njolstad I, Lochen ML, Mathiesen EB, Wilsgaard T, Eriksen BO, Toft I. Albuminuria, metabolic syndrome and the risk of mortality and cardiovascular events. *Atherosclerosis*. 2009;204:503–508.
19. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med*. 2000;160:1093–1100.
20. Yang X, Ko GT, So WY, Ma RC, Kong AP, Lam CW, Ho CS, Chow CC, Tong PC, Chan JC. Additive interaction of hyperglycemia and albuminuria on risk of ischemic stroke in type 2 diabetes: Hong Kong Diabetes Registry. *Diabetes Care*. 2008;31:2294–2300.
21. Yokota C, Minematsu K, Ito A, Toyoda K, Nagasawa H, Yamaguchi T. Albuminuria, but not metabolic syndrome, is a significant predictor of stroke recurrence in ischemic stroke. *J Neurol Sci*. 2009;277:50–53.
22. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ. Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC–Norfolk) population study. *J Intern Med*. 2004;255:247–256.
23. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, Howard WJ, Wang W, Best L, Lee ET. Incidence and risk factors for stroke in American Indians: the Strong Heart Study. *Circulation*. 2008;118:1577–1584.
24. Rodicio JL, Campo C, Ruilope LM. Microalbuminuria in essential hypertension. *Kidney Int Suppl*. 1998;68:S51–S54.
25. Tebbe U, Bramlage P, Thoenes M, Paar WD, Danchin N, Volpe M, Schrader J, Noll G, Burnier M, Bohm M. Prevalence of microalbuminuria and its associated cardiovascular risk: German and Swiss results of the recent global i-SEARCH survey. *Swiss Med Wkly*. 2009;139:473–480.
26. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlof B, Devereux RB, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wan Y. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension*. 2005;45:198–202.
27. Viberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation*. 2002;106:672–678.
28. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G, Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR, Remuzzi G. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med*. 2004;351:1941–1951.
29. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, de Zeeuw D, de Jong PE, van Veldhuisen DJ, van Gilst WH. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110:2809–2816.
30. van de Wal RM, Gansevoort RT, van der Harst P, Boomsma F, Thijs Plokker HW, van Veldhuisen DJ, de Jong PE, van Gilst WH, Voors AA. Predictors of angiotensin-converting enzyme inhibitor-induced reduction of urinary albumin excretion in nondiabetic patients. *Hypertension*. 2006;48:870–876.
31. Boersma C, Atthobari J, Gansevoort RT, de Jong-Van den Berg LT, de Jong PE, de Zeeuw D, Annemans LJ, Postma MJ. Pharmacoeconomics of angiotensin II antagonists in type 2 diabetic patients with nephropathy: implications for decision making. *Pharmacoeconomics*. 2006;24:523–535.
32. Palmer AJ, Valentine WJ, Chen R, Mehin N, Gabriel S, Bregman B, Rodby RA. A health economic analysis of screening and optimal treatment of nephropathy in patients with type 2 diabetes and hypertension in the USA. *Nephrol Dial Transplant*. 2008;23:1216–1223.
33. Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. *Ann Intern Med*. 1999;131:660–667.
34. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. *JAMA*. 2003;290:3101–3114.
35. Gansevoort RT, de Jong PE, Postma MJ. Cost-effectiveness of screening for proteinuria. *JAMA*. 2004;291:1442–1443; author reply 1443.
36. Atthobari J, Asselbergs FW, Boersma C, de Vries R, Hillege HL, van Gilst WH, Gansevoort RT, de Jong PE, de Jong-van den Berg LT, Postma MJ. Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: a pharmacoeconomic analysis linked to the prevention of renal and vascular endstage disease (PREVEND) study and the prevention of renal and vascular endstage disease intervention trial (PREVEND IT). *Clin Ther*. 2006;28:432–444.
37. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. *Arch Intern Med*. 1999;159:1097–1103.