

## MISE AU POINT/IN-DEPTH REVIEW

### INCREASED URINARY ALBUMIN EXCRETION

#### Définition, prevalence, clinical significance and therapeutic implications

Adel E. BIRBARI, Najla DAOUK, Ahmed FAWAZ

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#### INTRODUCTION

Recent studies indicate that increased urinary albumin excretion is an independent predictor of cardiovascular disease (CVD) and all-cause mortality in both diabetic and nondiabetic men and women and may be a stronger indicator for future cardiovascular (CV) events than systolic blood pressure (SBP) or serum cholesterol [1-2]. Detecting increased urinary albumin excretion is an important screening tool to identify people who are at high risk for CV events and the progression of kidney disease and who need more intensive therapy compared with subjects with normal albumin excretion rates [3].

#### DEFINITION AND CLASSIFICATION

Small amounts of albumin are present in the urine of healthy individuals [4]. However, excretion of albumin in the urine above a certain level is pathologic and becomes an independent risk marker for both CV and renal diseases [1].

Increased urinary albumin excretion is classified into two groups : (1) microalbuminuria, (2) macroalbuminuria.

(1) *Microalbuminuria* is a term used to define a sub-clinical increase in urine excretion which cannot be detected by the traditional dipstick technique used in urinalysis [5]. It does not denote the excretion of small albumin molecules.

By definition, microalbuminuria corresponds to the finding of an albumin excretion rate of 20-200 µg/min, 30-300 mg/24 h or an urinary albumin to creatinine ratio (ACR) of 2.5-25 mg/mmol (or 22-177 mg/g) in males and 3.5-30 mg/mmol (or 31-265 mg/g) in females (Table I) in a first morning urinary sample.

These conventional cut-off levels for defining microalbuminuria arose originally from studies of the association between urinary albumin and risk of nephropathy in patients with diabetes [6]. These cut-off levels have

been used to classify patients and predict renal events. However, recent evidence indicates that levels of urinary albumin much lower than the traditional thresholds also are predictors of clinical events, suggesting a continuous relationship between urinary albumin levels and clinical endpoints [1]. These data suggest that a different cut-off level for the definition of microalbuminuria may be necessary for predicting CV events. Lower cut-off levels such as urinary albumin excretion rate over 5 µg/min, urinary albumin concentration higher than 6 mg/l or urinary ACR over 0.7 mg/mmol have been suggested [7].

(2) *Macroalbuminuria* (proteinuria) denotes a urinary albumin excretion rate which is detectable by routine urinalysis dipstick, and which exceeds 300 mg/24 h or 200 µg/min in timed collections, corresponding to an urinary ACR greater than 20 mg/mmol (or greater than 177 mg/g) in males and greater than 30 mg/mmol (or greater than 265 mg/g) in females in spot first morning (first void) urine sample [5] (Table I).

#### PREVALENCE

Abnormally elevated urinary albumin excretion is a highly prevalent laboratory finding in several disease states as well as in the general population. However, prevalence rates vary widely across studies [1]. This has been attributed to the lack of consistency in urine collection times, methods of measurement of urinary albumin, ethnic origin and presence or absence of comorbid conditions.

In diabetes mellitus, the high prevalence of raised urinary albumin excretion rates is well documented [1, 3]. Worldwide surveys have shown that 20-40% of patients exhibit microalbuminuria while macroalbuminuria has been reported in 10% [3]. Prevalence rates are highest in Hispanic and Asian patients and lowest in Caucasian individuals [3].

In essential hypertension the presence of increased urinary albumin excretion is less consistent. Data obtained in many cross-sectional large scale studies have demonstrated large differences with prevalence rates varying from a low of 4.7% to a high of 46% [1, 3]. Although the cause of this wide variability is unclear, the presence of confounding factors has been postulated to explain these differences [3]. Prevalence rates of increased urinary albumin excretion are higher in hypertensive subjects with moderate to severe BP elevation, with evidence of target organ damage and/or atherosclerotic vascular disease, and of non Caucasian ethnicity [3]. Data on gender differences are inconsistent [3].

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Department of Internal Medicine/Nephrology & Physiology, American University of Beirut Medical Center.

Correspondence : Adel E. Birbari, MD. AUBMC. POBox 113-6044. Beirut. Lebanon.

Tel. : +961 1 353465 Fax : 961 1 744464  
E-mail : ab01@aub.edu.lb

**TABLE I**  
THRESHOLD LEVELS FOR URINARY ALBUMIN EXCRETION

	TIMED COLLECTIONS		SPOT COLLECTIONS		
	24 h mg/D	Overnight µg/min	mg/l	Alb/Cr mg/mmol	Alb/Cr mg/g
NORMAL	< 30	< 20	< 20	< 3	< 27
MICROALBUMINURIA	30-300	20-200	20-200	2.5-20 M 3.5-30 F	22-177 31-265
MACROALBUMINURIA (PROTEINURIA)	> 300	> 200	> 200	> 20 M > 30 F	> 177 > 265

Alb : albumin   Cr : creatinine   M : male   F : female

Large population studies have demonstrated that microalbuminuria is detected in 5 to 15% in the general population and in 3 to 8% of healthy individuals without diabetes or hypertension [3, 8].

Some hypertensive patients with an initial urinary albumin level in the high normal range from 15-29 mg/24 h may progress towards microalbuminuria despite anti-hypertensive treatment [9].

#### METHODS FOR ASSESSMENT AND EXPRESSION OF URINARY ALBUMIN EXCRETION

Urinary albumin excretion does not remain constant, but varies from day to day. It is influenced by a large number of factors including circadian pattern, state of hydration, physical activity and presence of pathologic conditions. Night-time recumbency and overhydration cause a reduction while physical activity, in particular strenuous exercise, elevate urinary albumin excretion [3]. Likewise fever, hematuria, menstrual bleeding, urinary tract infection and heart failure are associated with a transient microalbuminuria which is more or less persistent depending on the cause, intensity and duration of the respective condition [3]. Further, day to day variability in urinary albumin excretion is also influenced by the method of urine sampling, absolute amount of albumin in the urine and the type of underlying renal disease [3]. Reproducibility is poorer in high range than in low range albuminuria, and in type 1 diabetic compared to essential hypertensive patients [3].

Urinary albumin excretion can be assessed in one of the four urine collection procedures : 2 timed collections (24 h and timed-overnight) and 2 spot sampling collections (random and morning/first void) (Table II).

#### Which sample should be collected ?

For improved precision for the diagnosis of microalbuminuria and to overcome the various pitfalls, 24 h urine collection is the gold standard. The next best is a timed overnight urine collection [3]. However, these timed collections are subject to collection errors and require significant effort from and compliance of the patient. Further, they may not be practical for clinical

evaluation and follow-up [3].

Taking these considerations into account and to avoid confounders associated with timed urine collections, methods based on spot urine sampling have been advocated [3]. The diagnostic performance of measuring urinary albumin concentration in spot sampling in predicting urinary albumin equal or greater than 30 mg/24 h in subsequent 24 h urine collections is satisfactory [3]. A spot first-morning (first void) urine sample has the advantage over a random spot urine sample because it is always performed at the same time of the day and is least influenced by hydration status and physical activity of the patient, reducing the variability that is caused by these factors [3]. Further, for untimed samples, the determination of ACR may be more reliable than just a urinary albumin concentration, particularly as it may correct variability in timing collection [3]. Likewise, in case a specific patient is followed over time with serial urine samples, the ACR may offer an advantage over albumin concentration alone [11-12].

However, there are pitfalls in standardizing urine ACR for men and women. Urine creatinine excretion is influenced by gender, age, race and ethnicity while urinary albumin excretion is independent of these factors [11]. Creatinine, a metabolic byproduct of skeletal muscle creatine and phosphocreatine metabolism, is lower in subjects with smaller muscle mass such as women and the elderly [11]. Because the denominator in the urine ACR is lower in women, different definitions of an abnormal value have been recommended for men and women [11-12].

**TABLE II**  
METHODS FOR ASSESSMENT OF URINARY ALBUMIN EXCRETION

- 1. Timed urine collection**
  - (a) 24 h urine volume collection
  - (b) Overnight timed urine collection
- 2. Spot urine sampling**
  - (a) Random urine sampling
  - (b) Spot morning (first void) urine collection

### **Gender-specific definitions of urinary albumin excretion**

The recommended ACRs to define microalbuminuria (30-300 µg/mg) which do not account for gender and racial differences in urine creatinine excretion may underestimate microalbuminuria in subjects with higher muscle mass (men) or overestimate it in subjects with lower muscle mass [11]. Therefore, several investigators have advocated using separate ACR cutpoints in men and women to detect microalbuminuria to help avoid overestimating or underestimating the prevalence/incidence of microalbuminuria in subjects with different muscle mass. To determine gender-specific ACR values, Warren compared ACR in spot urine samples to albumin excretion rates measured in timed urine specimens. He reported that single ACR values of 30-300 µg/mg corresponded to ACR of 17-250 µg/mg in men and 25-355 µg/mg in women [11-12]. By dividing the ACR by 8.84 converts the units (from µg/mg to mg/mmol) [12].

Using the traditional ACR definition (30-300 µg/mg) to examine the prevalence of microalbuminuria in US using the National Health and Nutrition Examination Survey (NHANES) III, Knight reported that women were significantly more likely than men to have microalbuminuria [11]. However, when the gender-specific criteria were applied, no significant gender differences were observed in the prevalence of microalbuminuria.

### **CLINICAL SIGNIFICANCE**

Prospective studies confirm that microalbuminuria is predictive, independently of classical risk factors, of CV events and all-cause mortality within groups of patients with diabetes or hypertension and in the general population.

#### **Diabetes mellitus**

In type 1 diabetes mellitus, microalbuminuria is a predictor of CV events [1]. A 10-year observational study in adults with type 1 diabetes mellitus at the Steno Diabetes Center documented increased CV mortality independent of classical risk factors [1]. This association has been observed also in type 2 diabetes mellitus. Denneau and Gerstein demonstrated a twofold increased risk of total and CV mortality in microalbuminuric patients with type 2 diabetes mellitus [1]. Increased urinary albumin excretion is also an independent risk factor in these patients. In the Durango study it was associated with a threefold increased risk of ischemic stroke [1, 13]. Further, abnormal urinary albumin levels are related to other CV events such as heart failure and lower extremity amputation [14-15].

#### **Hypertension**

Numerous studies document a link between microalbuminuria and CVD in essential hypertension. Hypertensive patients with increased urinary albumin excretion display (1) an atherosclerotic risk profile characterized by higher than normal levels of atherogenic lipoproteins such as low-density lipoprotein cholesterol (LDL-C) and lipo-

protein (a), greater than normal insulin response to a glucose load, and insulin resistance ; (2) abnormal 24 h BP pattern characterized by less than normal nocturnal dipping (fall) of BP ; (3) heightened levels of systemic inflammatory markers such as hsCRP (high sensitivity C-reactive protein) ; (4) evidence of target organ damage including unfavorable alterations of left ventricular geometry, increased intima-media thickness (a sign of carotid atherosclerosis), augmented arterial stiffness and renal dysfunction ; (5) greater risk of CV complications independently of the degree of BP control [1].

#### **General population**

There is increasing evidence from large population-based studies that increased urinary albumin excretion is related to fatal and non fatal CV events, not only in individuals with hypertension, diabetes mellitus or high CV risk background, but also in apparently healthy individuals.

In nonhypertensive, and nondiabetic participants in the PREVEND (Prevention of Renal and Vascular End-stage Disease), HUNT (Nord-Trondelag Health Study) and EPIC (European Prospective Investigation) studies, presence of microalbuminuria was associated with a 29-50% increased risk of CV mortality and 40% increased risk of incident coronary heart disease [1, 8].

In addition to CV events, microalbuminuria has been associated also with cerebrovascular disease. In the EPIC study, microalbuminuric individuals had a 50% increased risk of ischemic stroke [1]. Further, the level of urinary albumin was a predictor of severity of the neurological deficit and risk of recurrence of stroke [1].

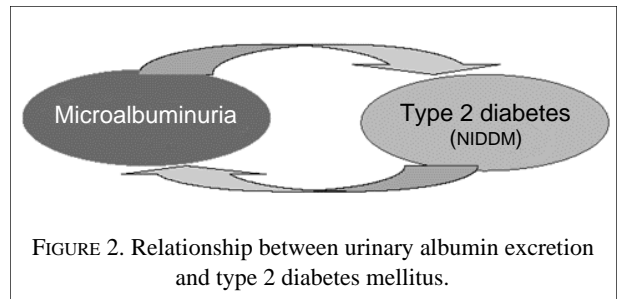
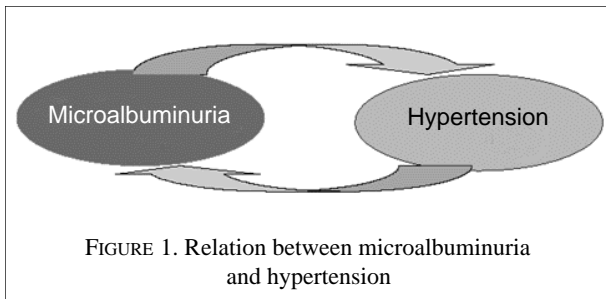
#### **Relation between albuminuria and renal outcome**

Numerous studies indicate that albuminuria is a strong predictor for progression of renal disease in overt proteinuric nephropathy, as well as in patients with diabetes mellitus, hypertension and in the general population [1, 18-19].

Elevated urinary albumin excretion is an early predictor of progressive loss of renal function in type 1 and type 2 diabetes mellitus [16-17]. Albuminuria appears to be associated with worse renal outcome also in nondiabetic patients. In the PREVEND Study, after a 4.2-year follow-up, the number of individuals who progressed to renal insufficiency/failure was related to baseline microalbuminuria [8].

#### **Associations with other CV risk factors**

Although it is well recognized that elevated urinary albumin excretion frequently occurs in patients with hypertension or diabetes mellitus, it appears also to be a sensitive marker for the development of de novo hypertension (Fig. 1) or new onset diabetes mellitus (Fig. 2). Microalbuminuric individuals have a twofold increased risk for the development of de novo hypertension, as well as a fourfold increased risk for new onset diabetes mellitus, even after correcting for baseline glucose and insulin



levels and excluding those with impaired glucose metabolism or the metabolic syndrome [5]. Further, normotensive microalbuminuric individuals are at risk to progress to higher BP levels [1].

### Which levels of albuminuria predict CV events ?

Recent studies have added novel findings to the well established association between albuminuria and risk of CVD. First, the association between albuminuria and risk of CVD appears at urinary albumin excretion rates much lower than the conventionally defined threshold levels of 30 mg/24 h or 20 µg/min in timed collections, or an urinary ACR ratio of 2.5 mg/mmol in men and 3.5 mg/mmol in women, regardless of the population studied. In a population-based cohort of 2085 consecutive subjects, an urinary ACR of only 0.65 mg/mmol was associated with a relative risk of 2.3 of ischemic heart disease [2]. Similarly, in an elderly population, subjects with a timed overnight urinary albumin excretion greater than 7.5 µg/min had a higher mortality rate than those with lower values [1]. In hypertensive patients, an overnight urinary albumin excretion rate between 5 and 10 µg/min was associated with an increased risk of 70% and 50% of coronary heart disease and mortality respectively [20]. The risk of both events increases to 100% with a urinary albumin excretion greater than 10 µg/min [20]. In the cohort of subjects included in the HOPE study, compared with the lowest quartile of ACR, the relative risk of primary endpoint in the fourth quartile, defined as an ACR greater than 1.62 mg/mmol, was 1.97. Second, in diabetic patients, progression of albuminuria is associated with a further increase in the risk of CVD independently of the initial urinary albumin excretion [22]. Third, the relation between urinary albumin excretion and risk of CV and renal disease is a continuum, both increasing in a graded fashion. In the Microalbuminuria, Cardiovascular and Renal Outcomes (MICRO) Heart Outcomes Prevention Evaluation (HOPE) substudy, the risk for primary outcome (myocardial infarction, stroke and CV death) increased in a graded fashion with increasing urinary ACR, even below the traditional microalbuminuria threshold [22].

### Pathogenetic mechanisms

The pathophysiologic mechanism of the association between albuminuria, CV and renal disease remains unclear.

Impaired endothelial function has been postulated to link microalbuminuria and risk of CVD [23]. Several groups of investigators have demonstrated increased levels of biochemical markers of endothelial dysfunction as well as decreased flow-mediated dilatation of the brachial artery in diabetic and in hypertensive subjects [24-25]. However, in the PREVEND Study, in apparently healthy nondiabetic/nonthypertensive subjects, increasing levels of urinary albumin excretion were accompanied by a significant increase in age, SBP/DBP, body mass index (BMI) and serum triglycerides and a preponderance of males whereas flow-mediated dilatation of brachial artery was normal [26]. In these studies, urinary albumin excretion correlated with BP, BMI and serum triglycerides but not with flow-mediated dilatation [26]. These investigators proposed that, in the light of these observations, the presence of atherogenic risk factors precedes the development of endothelial dysfunction in microalbuminuric otherwise healthy individuals [26] (Fig. 3).

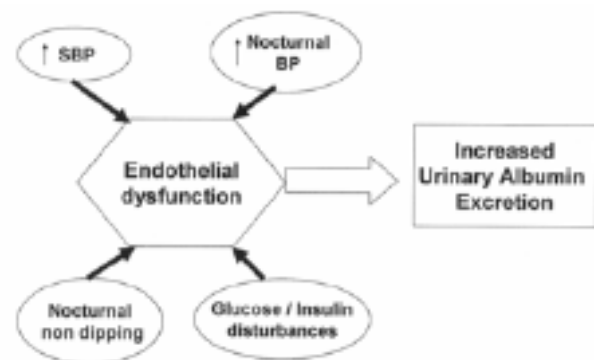


FIGURE 3. Relation between cardiovascular risk and urinary albumin excretion.

*What is the mechanism of urinary albumin excretion in the presence of normal endothelial function ?* It is very likely that the transmission of increased systemic BP to the glomerulus particularly SBP will lead to increased glomerular pressure and increased urinary albumin excretion [27]. Further, in the obese, the secretion of cytokines from adipocytes may be involved in initiating an atherosclerotic process and increase vascular permeability which might be an additional pathophysiologic mechanism underlying increased urinary albumin excretion [28]. At this stage, albuminuria reflects renal functional and potentially reversible glomerular hemodynamic and basement

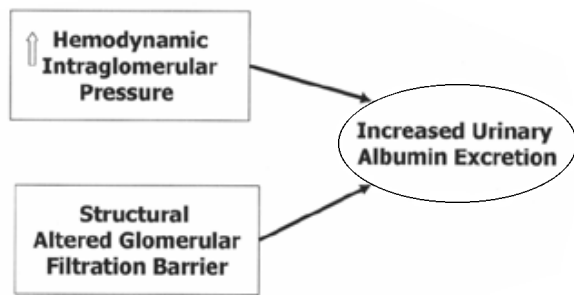


FIGURE 4. Relation between hemodynamic and structural changes in urinary albumin excretion.

membrane alterations [26-27]. However, with increasing severity of albuminuria, with levels in excess of 200 µg/min, renal structural changes occur, leading to overt proteinuria, worsening renal function, higher BP and significantly elevated risk of CVD [29] (Fig. 4).

#### THERAPEUTIC IMPLICATIONS

##### Aims of therapy

The mainstay of therapy should be adequate BP control to levels of less than 130/80 mmHg and maximization of albuminuria by upward titration of antihypertensive medications, although tolerability may limit the dose used.

There is increasing evidence that reduction of microalbuminuria is associated with reduction in the incidence of CV events as well as in renal outcomes in different patient populations, including healthy individuals, patients with hypertension or diabetes.

Several strategies are available to lower urinary albumin excretion in the microalbuminuria range. Widely known is the albuminuria reducing effect of antihypertensive agents. In this respect, agents that block the renin-angiotensin-aldosterone system confer a greater reduction in urinary albumin excretion and greater cardioprotection as well as renoprotection than conventional therapy, despite equal BP reduction.

##### General population

The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT) is the only randomized trial that evaluated the effect of reduction of albuminuria in microalbuminuric healthy individuals. Asselbergs demonstrated that reduction of albuminuria with the angiotensin converting enzyme inhibitor fosinopril tended to be cardioprotective [30].

##### Hypertension

Similar results were reported in hypertensive patients. In the LIFE Study, in patients with hypertension and left ventricular hypertrophy, compared to atenolol, losartan, an angiotensin receptor blocker, conferred a greater reduction in urinary albumin excretion and better cardioprotection for similar BP levels [31]. Further, the greater the reduction in the levels of baseline and in-treatment

albuminuria, the greater the reduction in risk of CVD [32]. Interestingly, reduction in albuminuria explained about 17% of the benefits of losartan relative to atenolol on the composite endpoint of CV death, myocardial infarctus and stroke after 4.8 years of follow-up [33].

##### Diabetes mellitus

In patients with diabetes mellitus, blockade of the renin-angiotensin-aldosterone system has been shown to reduce progression to overt proteinuria, decrease in renal function and endstage renal disease. In the IRMA-2 Study (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria), irbesartan, an angiotensin receptor blocker reduced albuminuria substantially in microalbuminuric hypertensive patients with diabetes mellitus type 2 and this was associated with renoprotection and some degree of CV protection [34]. This renoprotective action appeared to be dose-dependent. Further, the beneficial effect of irbesartan on urinary albumin excretion could not be explained by a reduction in BP solely [34]. The angiotensin receptor blocker valsartan has also been shown to reduce albuminuria, independent of its BP lowering action in hypertensive and normotensive albuminuric patients with type 2 diabetes mellitus [35]. In the RENAAL Trial, in diabetic type 2 patients with nephropathy, losartan 50-100 mg/D reduced significantly albuminuria, loss of renal function and hospitalization for heart failure [36-37]. In this study, the level of residual albuminuria during treatment also had a strong effect on renal outcome [37].

##### Combination therapy

Dual blockade of the renin-angiotensin system with angiotensin converting enzyme inhibitor and angiotensin receptor blocker in patients with type 2 diabetes mellitus and albuminuria is more effective in reducing BP and decreasing albuminuria than either agent alone even in maximal recommended doses [38-39]. Whether dual therapy will translate to a reduced incidence of endstage renal disease in patients with diabetes mellitus is unknown. However, the recent combination treatment of angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor in nondiabetic renal disease (COOPERATE study) has demonstrated that dual therapy in nondiabetic proteinuric patients was superior to monotherapy in retarding progression to endstage renal disease, despite the achievement of similar BP in the different groups [40].

Combination treatment of an angiotensin-converting enzyme inhibitor with a dihydropyridine calcium channel blocker or a diuretic may also be associated with a greater reduction in albuminuria than angiotensin-converting enzyme inhibitor alone in patients with type 2 diabetes mellitus, albuminuria and hypertension [41-42].

Other therapeutic approaches such as statins and glucosamineglycans have been shown to reduce albuminuria in microalbuminuric diabetes type 2 patients [43].

## CONCLUSION

Microalbuminuria is a powerful and independent risk factor for renal and CVD. It is frequent in the general population, hypertensives, diabetics and patients with CVD. It is also often associated with evidence of target organ damage and high incidence of CV complications.

Regular detection of albuminuria is indicated for risk stratification, particularly in patients with high atherosclerotic burden.

Cardiovascular protection requires reduction or even normalization of albuminuria with hypertensive agents that block the renin-angiotensin-aldosterone system. Mere BP reduction is insufficient for cardiovascular protection (Fig. 5).

## REFERENCES

1. Yuyun MF, Adler AI, Wareham NJ. What is the evidence that microalbuminuria is a predictor of cardiovascular disease events? *Curr Opin Nephrol Hypertens* 2005; 14: 271-6.
2. Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in nondiabetic subjects. Islington Diabetes Survey. *Lancet* 1988; 2: 530-3.
3. De Zeeuw PE, Curhang C. Screening, monitoring and treatment of albuminuria: Public health perspectives. *J Am Soc Nephrol* 2006; 17: 2120-6.
4. Zandi-Nejad K, Eddy AE, Glasscock RJ, Brenner BM. Why is proteinuria an ominous biomarker of progressive kidney disease? *Kidn Intern* 2004; 66: (Suppl 92): S76-S89.
5. De Zeeuw D, Parving HH, Henning RH. Microalbuminuria as an early marker for cardiovascular disease. *J Am Soc Nephrol* 2006; 17: 2100-5.
6. Mogensen CE, Keane WF, Bennett PH et al. Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; 346: 1080-4.
7. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension and diabetes. *Circulation* 2004; 110: 32-5.
8. Hillege HL, Janssen WM, Bak AA et al. PREVENT Study Group: Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 2001; 249: 519-26.
9. Brantsma AH, Attobari J, Bakker SJ et al. What causes progression and regression of urinary albumin excretion in the general population? (Abstract). *J Am Soc Nephrol* 2005; 16: 324A.
10. Gansevoort RT, Verhave JC, Hillege HL et al, for the PREVENT Group. The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. *Kidn Intern* 2005; 67 (Suppl 94): S28-S35.
11. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002; 13: 1034-9.
12. Verhave JC, Hillege HL, de Zeeuw D, de Jong PE. How to measure the prevalence of microalbuminuria in relation to age and gender? *Am J Kidn Dis* 2002; 40: 436-7.
13. Yuyun MF, Khaw KT, Luben R et al. Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *J Intern Med* 2004; 255: 247-56.
14. Vaur L, Gueret P, Lievre M et al. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, HYpertension, Cardiovascular events and Ramipril) study. *Diabetes Care* 2003; 26: 855-60.
15. Resnick HE, Carter EA, Sasenko TM et al. Incidence of lower-extremity amputation in American Indians: the Strong Heart Study. *Diabetes Care* 2004; 27: 1885-91.
16. Veharti GC, Hill RD, Jarret RJ et al. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982; 1: 1430-2.
17. Fioretto P, Mauer M, Brocco E et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 1996; 39: 1569-76.
18. Sarafides PA, Bakris GL. Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease. *Nephrol Dial Transplant* 2006; 21: 2366-74.
19. Pinto-Sietsma ST, Janssen WMT, Hillege HL et al. Urinary albumin excretion is associated with renal functional abnormalities in a nondiabetic population. *J Am Soc Nephrol* 2000; 11: 1882-8.
20. Wang TJ, Evans JC, Meigs JB et al. Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation* 2005; 111: 1370-6.
21. Borch-Johnsen K, Feldt-Rasmussen B, Stranggaard S et al. Urinary albumin excretion: An independent predictor of ischemic heart disease. *Arterioscler Thromb Vasc Biol* 1999; 19: 1992-7.
22. Mann JFE, Gerstein HC, Qi-Long YI et al. Development of renal disease in people at high cardiovascular risk: Results of the HOPE randomized study. *J Am Soc Nephrol* 2003; 14: 641-7.
23. Deckert T, Feldt-Rasmussen B, Borch Johnsen K et al. Albuminuria reflects widespread vascular damage: the Steno Hypothesis. *Diabetologia* 1989; 32: 219-26.

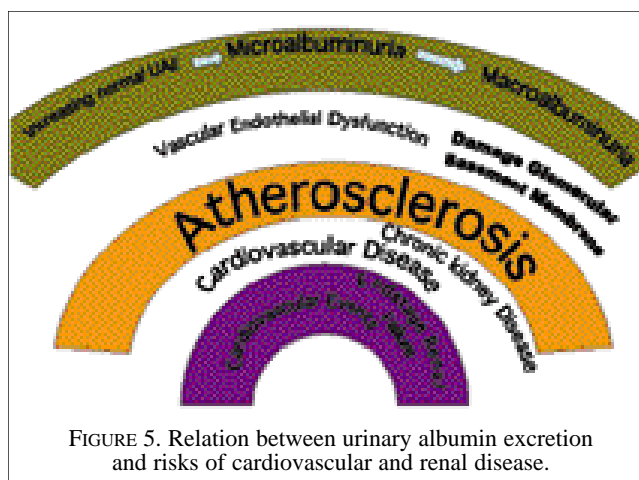


FIGURE 5. Relation between urinary albumin excretion and risks of cardiovascular and renal disease.

24. Clausen P, Feldt-Rasmussen B, Jensen G et al. Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects : a 4-year prospective study. *Clin Sci* 1999 ; 97 : 37-43.
25. Stehouwer CDA, Henry RMA, Dekker JM et al. Microalbuminuria is associated with impaired brachial artery flow-mediated vasodilation in elderly individuals without and with diabetes : Further evidence for a link between microalbuminuria and endothelial dysfunction. The Hoor Study. *Kidn Intern* 2004 ; 66 (Suppl 92) : S42-S46.
26. Diercks GFH, Stroes ESG, van Boven AJ et al. Urinary albumin excretion is related to cardiovascular risk indicators, not to flow-mediated vasodilation, in apparently healthy subjects. *Atherosclerosis* 2002 ; 163 : 121-6.
27. Stehouwer CDA, Smulders YM. Microalbuminuria and risk for cardiovascular disease : Analysis of potential mechanisms. *J Am Soc Nephrol* 2006 ; 17 : 2106-11.
28. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects - Association with obesity, insulin resistance and endothelial dysfunction : a potential role for cytokines originating from adipose tissue ? *Arterioscler Thromb Vasc Biol* 1999 ; 19 : 972-8.
29. Ruggenti P, Remuzzi G. Time to abandon microalbuminuria ? *Kidn Intern* 2006 ; 70 : 1214-22.
30. Asselbergs FW, Diercks GFH, Hillege H et al. Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) investigators : Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation* 2004 ; 110 : 2809-16.
31. Wachtell K, Ibsen H, Olesen MH et al. Microalbuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy : the LIFE Study. *Ann Intern Med* 2003 ; 139 : 901-6.
32. Ibsen H, Wachtell K, Olsen MH et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy ? A LIFE substudy. *J Hypertens* 2004 ; 22 : 1805-11.
33. Ibsen H, Wachtell K, Borch-Johnsen K et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy : the LIFE Study. *Kidn Intern* 2004 ; 66 (Suppl 92) : S56-S58.
34. Parving HH, Lehnert H, Brochner-Mortensen J et al. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group : The effect of Irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001 ; 345 : 870-8.
35. Ziberti G, Wheeldon NM. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus : a blood pressure independent effect. *Circulation* 2002 ; 106 : 672-8.
36. Brenner BM, Cooper ME, de Zeeuw D et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2006 ; 345 : 861-9.
37. De Zeeuw D, Remuzzi G, Parving HH et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy : Lessons from RENAAL. *Kidn Intern* 2004 ; 65 : 2309-20.
38. Jacobsen P, Andersen S, Rossing K et al. Dual blockade of the renin-angiotensin system versus maximal recommended dose of ACE inhibition in diabetic nephropathy. *Kidn Intern* 2003 ; 63 : 1874-80.
39. Rossing K, Christensen PK, Jensen BR, Parving HH. Dual blockade of the renin-angiotensin system in diabetic nephropathy : a randomized double-blind crossover study. *Diabetes Care* 2002 ; 25 : 95-100.
40. Nakao N, Yoshimura A, Morita H et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in nondiabetic renal disease (COOPERATE) : a randomized controlled trial. *Lancet* 2003 ; 361 : 117-24.
41. Fogari R, Preti P, Zoppi A et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. *Am J Hypertens* 2002 ; 15 : 1042-9.
42. Mogensen CE, Viberti G, Halimi S et al. Effect of low-dose perindopril/endozapamide on albuminuria in diabetes : preterox in albuminuria regression : PREMIER. *Hypertension* 2003 ; 41 : 1063-71.
43. Gambaro G, Kinalska I, Oksa A et al. Oral Sulodexide reduces albuminuria in microalbuminuric type 1 and type 2 diabetic patients : the Di. N. A. S. randomized trial. *J Am Soc Nephrol* 2002 ; 13 : 1615-25.