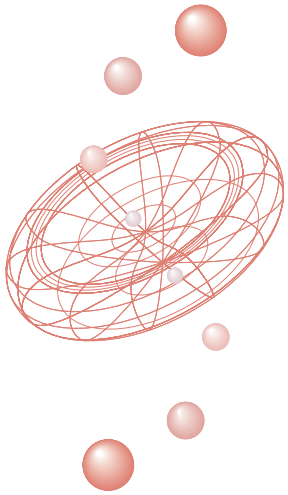
REVIEW ARTICLE



Significance of the Measurement and Evaluation of Albuminuria in Chronic Kidney Disease Patients

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SUMMARY

We have outlined above the significance of measuring albuminuria. Albuminuria is not only useful for diagnosing nephropathy but also important as a progression factor of kidney disease. As it is closely associated with cardiovascular events, it is a non-invasive marker that reflects the patient's prognosis. Because of this, even if a patient is negative for proteinuria in a dipstick test, albuminuria must be measured and evaluated proactively and suitable therapeutic intervention must be considered because of the possibility of progression to nephropathy and for improving the patient's prognosis.

INTRODUCTION

Currently there are an estimated 13.3 million patients with chronic kidney disease (CKD) in Japan, which means one out of about every 8 persons in the country has the disease. The number of CKD patients is expected to increase in the future. According to the latest survey by the Japanese Society for Dialysis Therapy, there are a total of 329,609 dialysis patients in Japan, an increase of 4,623 persons from the previous year. Thus CKD patients including those under dialysis are increasing year after year, and early detection and treatment of CKD have become urgent tasks. Against this background, in 2002, The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) proposed the concept of CKD which was defined in a way that could be understood by co-medical personnel and general practitioners. According to this definition, CKD is 1) the findings suggestive of kidney damage or 2) a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, or both of these conditions, continuing for 3 months or more[1]. The findings suggestive of kidney damage include urinary abnormalities like protein or occult blood in urine, blood abnormalities, image abnormalities such as only one functional kidney and polycystic kidney disease, and pathological signs. But the presence of proteinuria (albuminuria) has a particularly significant bearing. Albuminuria has recently been reported to be an independent risk factor for cardiovascular diseases. Based on such reports, and with the view that classification of albuminuria needs to reflect the prognosis of the patient, not just of the kidneys, Kidney Disease: Improving Global Outcomes (KDIGO), in 2009, published a new CKD classification[2] wherein

albuminuria was classified into three categories, which began use in Japan in 2012 (***Fig. 1***). It is important to avoid, or delay as much as possible, the inclusion of dialysis in a patient's treatment, as it sharply lowers the quality of life (QOL) of the patient and increases the chances of complications like cardiovascular disease and infections. According to a recent report, in 2016 diabetic nephropathy topped (43.2%) the list of diseases for which dialysis was initiated. This was followed by chronic glomerulonephritis (16.6%), renal sclerosis (14.2%), and unknown causes (12.8%). Although this share of diabetic nephropathy has remained more or less constant during the past few years, it continues to be a major disease for which dialysis is required. For these reasons, the early detection and treatment of nephropathy in diabetic patients is the most important issue for reducing the number of patients needing dialysis. Once diabetic nephropathy advances to kidney failure, the risk of mortality from cardiovascular complications increases almost 14-fold, to 19.2% per year from 1.4% per year in

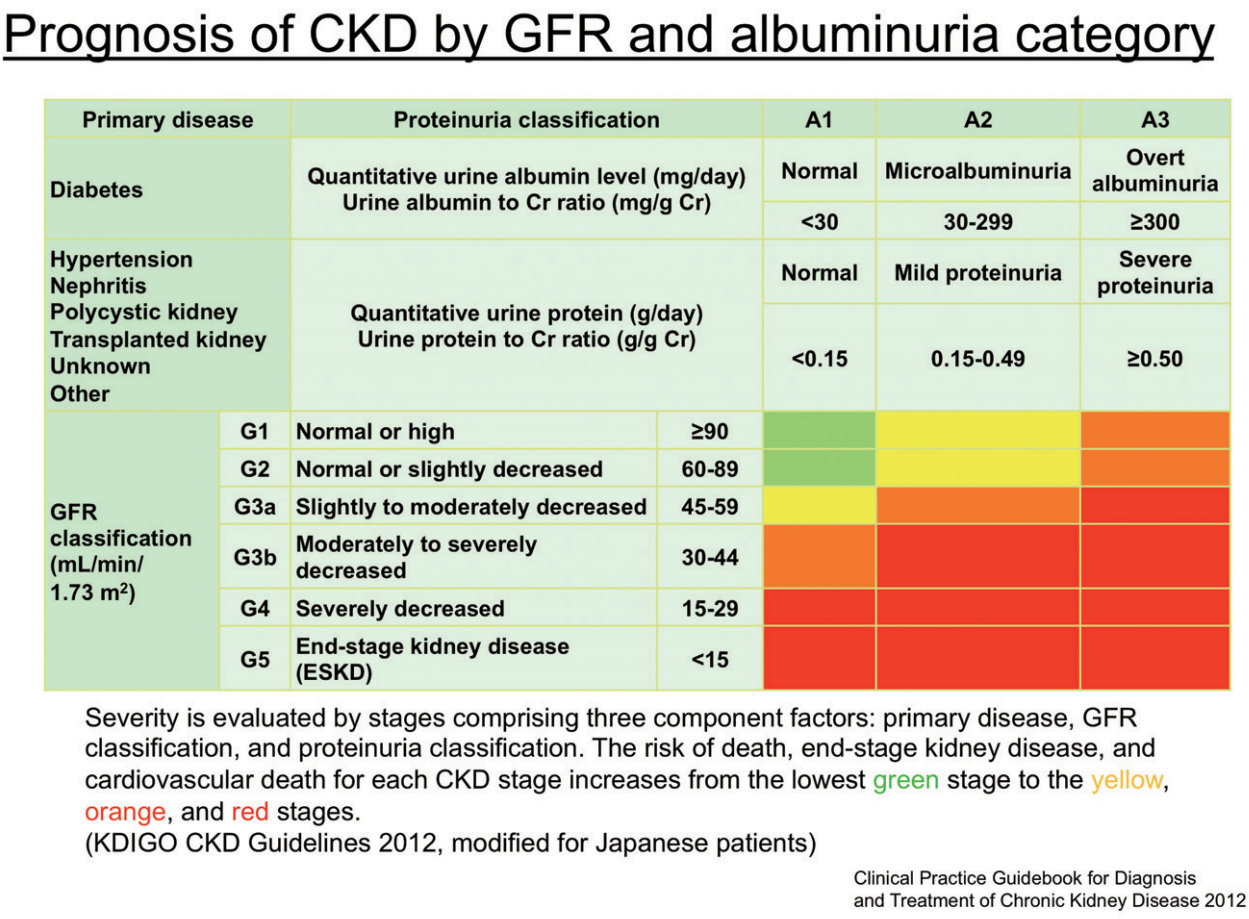

Fig. 1 *Definition and classification of CKD by GFR and albuminuria category*

diabetics without nephropathy (***Fig. 2***) [3]. From the medical economics point of view the burden of the cost of treatment of diabetes and hypertension, apart from the cost of the dialysis, has become a significant issue. Once kidney function declines, it is difficult to bring it back to normal levels. Therefore, early detection of urine protein may be the only way to avoid the induction of dialysis for CKD patients who might reach the stage of kidney failure because of diabetes and chronic nephritis or hypertension. Albuminuria is the most useful biomarker currently available for such early detection. We can alter the prognosis of CKD patients if we can determine the cause of CKD onset after detecting albuminuria, and provide treatment tailor-made for each patient.

We shall provide here an overview of the clinical significance of measuring albuminuria and methods of its evaluation as a marker of early-stage kidney damage.

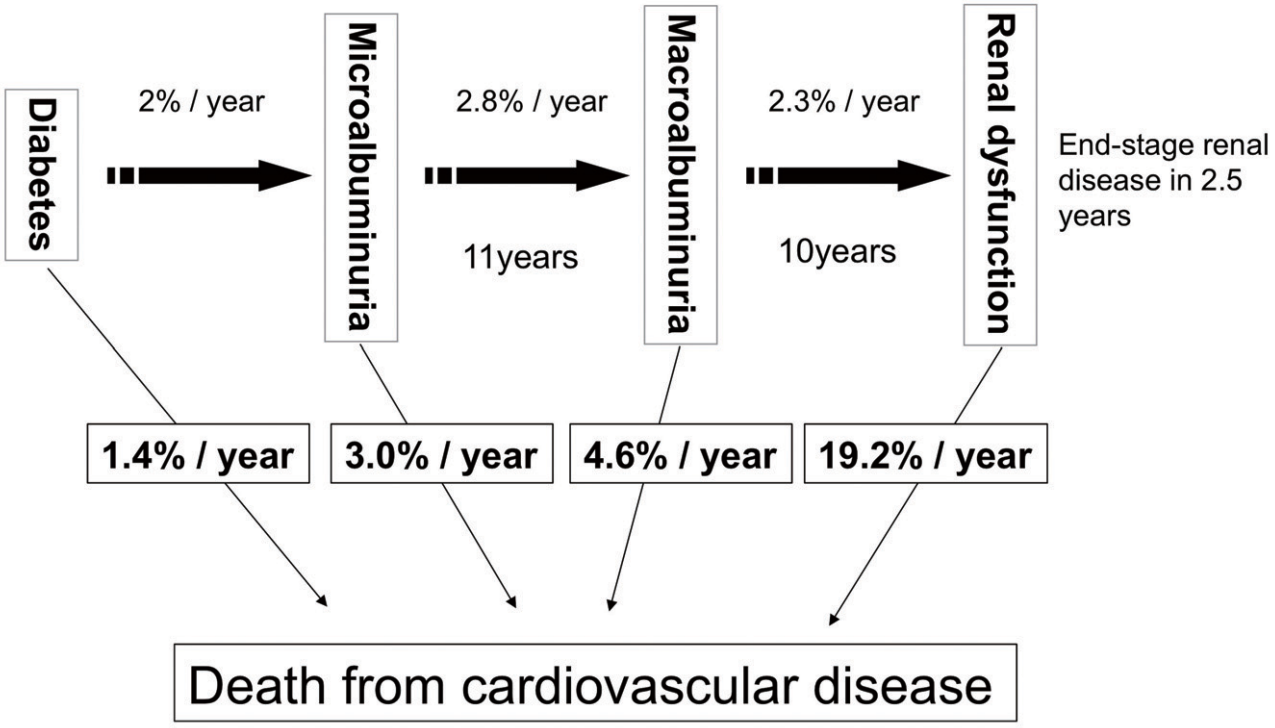

Fig. 2 *Natural history of diabetic nephropathy and the risk of cardiovascular disease in patients with type 2 diabetes (~UKPDS 64~)*

ALBUMINURIA

The phenomenon of albumin leaking into the urine has been explained as a breakdown of the albumin barrier in glomeruli or decreased albumin reabsorption in renal tubules. Albumin leaks into the urine when there is some disturbance in the negative charge of the basal membrane, the glomerular epithelial cells or glomerular endothelial cells which act as barriers. Moreover, the glycocalyx - which is made of glycoproteins and covers the glomerular endothelial cells - acts as a charge barrier. A reduction in glycocalyx is associated with increased albumin discharge into the urine [4]. The albumin passing through the glomeruli is reabsorbed by megalin, which is a receptor protein of the proximal renal tubules. When, however, there is some damage to renal tubules, the albumin does not get reabsorbed and appears in urine. In humans, reportedly about 3.3 g of albumin normally passes through the glomeruli each day, and about 3.2 g of this is reabsorbed through proximal renal tubules and the remaining albumin is excreted outside the body [5].
Albuminuria is easy to measure and is the most useful among currently available biomarkers of early-stage kidney damage. As albuminuria is also a progression factor of the disease, it must be more widely measured at the point of care in the future as an important target in the treatment of CKD.

SIGNIFICANCE OF MEASURING ALBUMINURIA IN PATIENTS OF DIABETIC KIDNEY DISEASE

The albuminuria test is an important tool for detecting early-stage kidney damage. It is possible to estimate the severity of nephropathy in a patient and evaluate the prognosis by measuring urine creatinine (Cr) also while testing albumin in random urine samples in outpatient departments and obtaining the albumin secretion per day into urine as "mg/gCr". The test results are categorized into A1: normoalbuminuria (< 30 mg/gCr), A2: microalbuminuria (early-stage diabetic nephropathy) (30-299 mg/gCr) and A3: macroalbuminuria (≥ 300 mg/gCr) (***Fig. 3***). Patients with advanced diabetic nephropathy present with macroalbuminuria and their kidney tissues often show characteristic nodular lesions. Even in early-stage nephropathy, the kidney tissues sometimes have diffuse or nodular lesions. For early detection and treatment of diabetic nephropathy, it is necessary to measure albuminuria while the patient is still negative or mildly positive for urine protein in a dipstick test, in order to proactively discover early-stage diabetic nephropathy. Because such patients sometimes have the complication of some other kidney disease such as nephritis, a kidney biopsy must be done without hesitation if there is hematuria or signs suggestive of

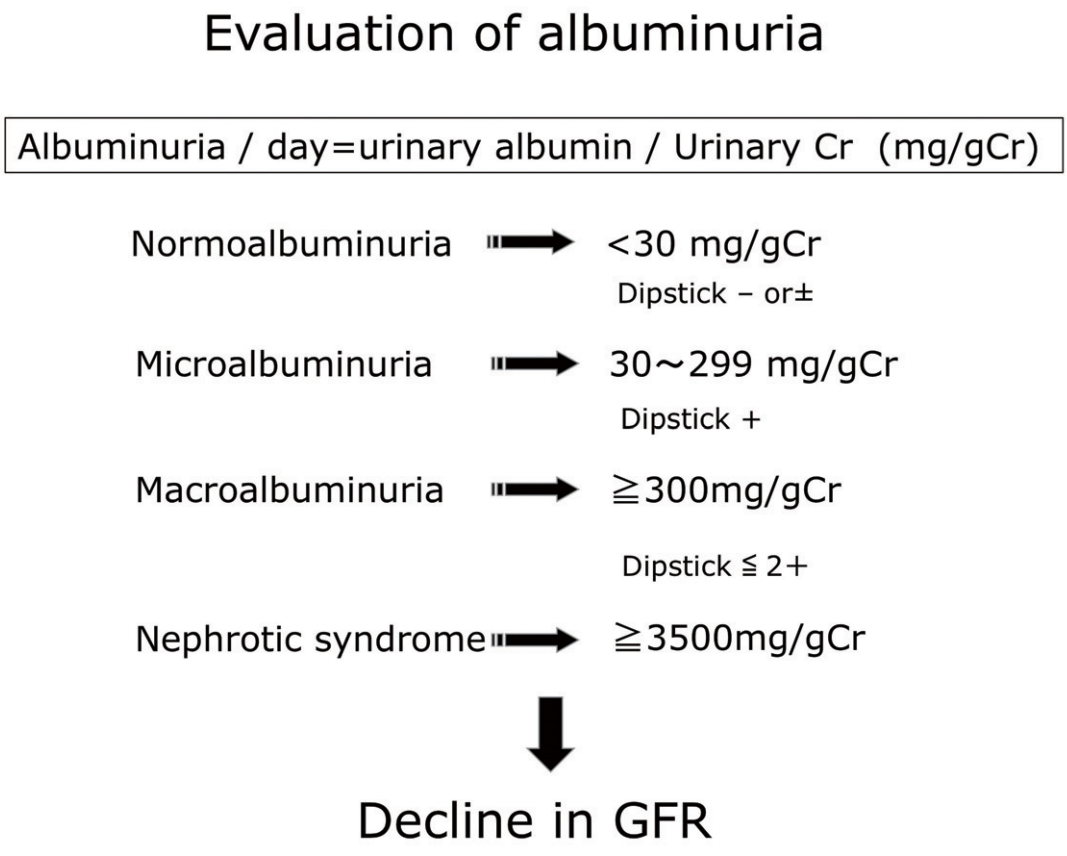

Fig. 3 *Evaluation of albuminuria in CKD patients*

nephritis in urine sediment findings.
Another mechanism of albumin excretion into urine in diabetes is the hyperfiltration caused by glomerular hypertension. Apart from increased systemic blood pressure and breakdown of autoregulation of afferent glomerular arterioles by impairment of tubuloglomerular feedback system, the cause of glomerular hypertension can be the constriction of the efferent arterioles due to activation of the renin-angiotensin system (RAS) (***Fig. 4***) which leads to hyperfiltration that causes leakage of albumin into the urine. Moreover, there have been reports of RAS functioning in a cytotoxic manner on glomerular epithelial cells, mesangial cells, and renal tubular cells. Therefore, an RAS inhibitor like renin inhibitor, angiotensin converting enzyme inhibitor (ACE-I) or an angiotensin II type 1 receptor blocker (ARB) is used at the point of care. Active use of ARB in cases with severely compromised renal function reduced the risk of

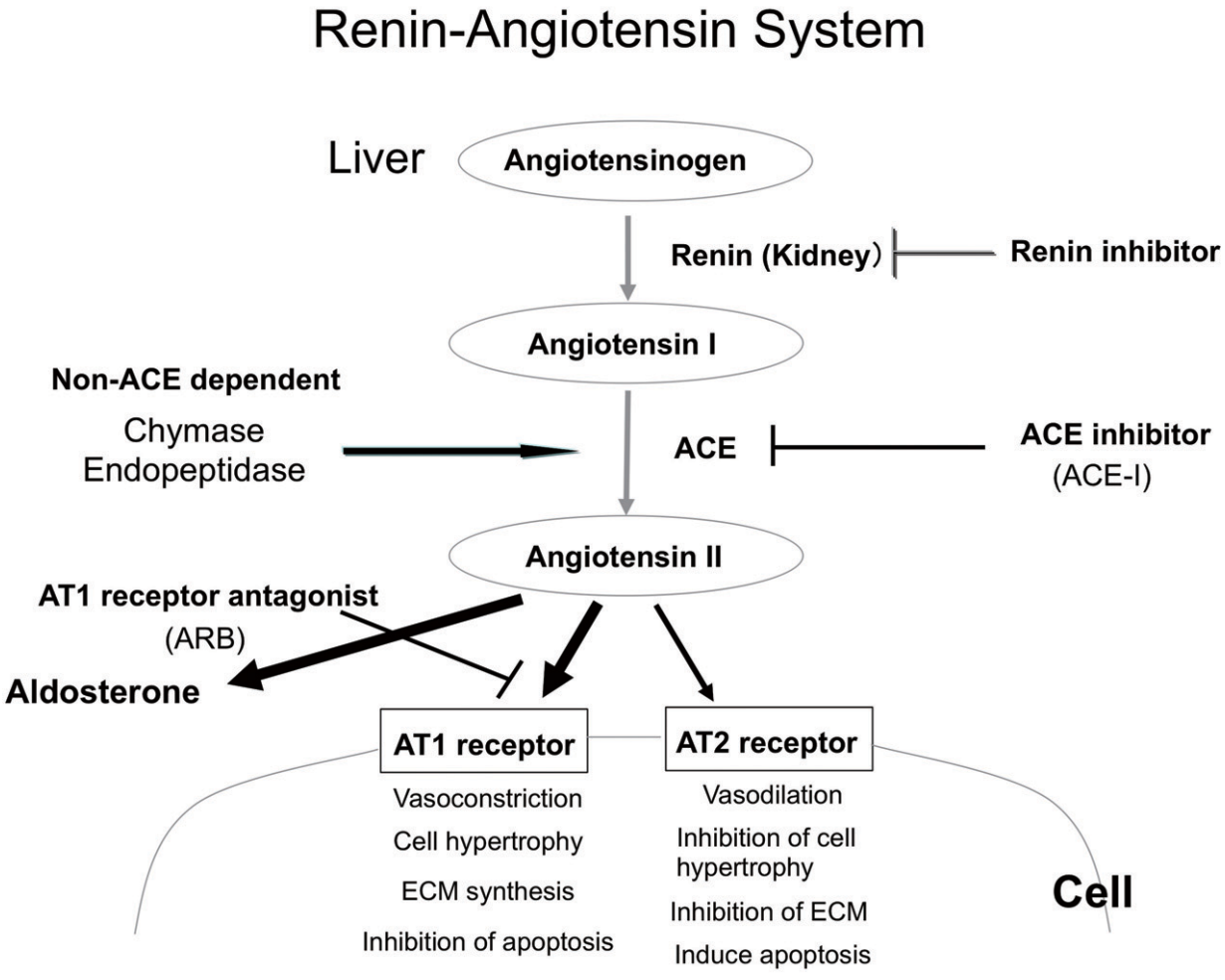

Fig. 4 *Scheme of the renin-angiotensin system and renal cell damages*

progression to renal failure and the need to start dialysis by 28% (***Fig. 5***) [6]. Albuminuria can be suppressed even without using an RAS inhibitor, by strict control of blood pressure and blood glucose. The CARTER study examined the proteinuria suppressing action of Ca channel blockers (CCB) in diabetic nephropathy patients under treatment with an RAS inhibitor. The study report stated that the group treated with cilinidipine, an N/L type CCB, had significantly lower urine protein compared to the group treated with amlodipine, an L-type CCB that showed no lowering of urine protein, although the hypotensive effect was about the same in the two groups [7]. Apparently in diabetic nephropathy patients, because of their higher glomerular pressure compared to the systemic blood pressure, N-type or T-type CCB which can dilate not only the afferent but also the efferent arterioles are more effective than the L-type CCB which dilate only the afferent arterioles [8]. Recently there have been reports of oral hypoglycemic agents showing an albuminuria lowering effect. It is known that DPP4 inhibitors and SGLT2 inhibitors lower albuminuria independently of blood glucose control and suppress the lowering of eGFR. The market for SGLT2 inhibitors in particular has shown a sharp expansion in the recent past. A sub-analysis of the EMPA-REG OUTCOME study showed that the empagliflozin treatment group showed reduced albumin excretion into the urine earliest after 12 weeks of treatment, irrespective of whether given an RAS inhibitor concurrently, and that the effect was maintained for at least three years [9]. These findings were consistent with the following CANVAS program study using canagliflozin [10]. SGLT2 inhibitors suppressed Na reabsorption by proximal renal tubules by inhibiting SGLT2 which is excessively expressed in proximal renal tubules under hyperglycemic conditions. This in turn increases NaCl arrival at the macula densa and normalizes the tubuloglomerular feedback [11]. It is believed that albumin leakage is lowered because of the vasoconstriction of afferent arterioles and the consequent lowering of glomerular pressure [12]. This type of multi-disciplinary therapy that combines strict control of blood pressure and blood glucose can improve micro- and macroalbuminuria to the level of normoalbuminuria, i.e., achieve "remission" of diabetic nephropathy.

Recently, DKD, instead of diabetic nephropathy is widely used in the world. Diabetic nephropathy defined as massive proteinuria and rapid decline in GFR with characteristic nodular lesion in the kidney biopsy. On the other hand, DKD is broadly defined by elevated urine albumin excretion or reduction of GFR or both. Recently, it has been reported that a portion of diabetic patients with normoalbuminuria have progressive renal insufficiency, and epidemiologic research has demonstrated that normoalbuminuric DKD is common. The main renal pathological findings are atherosclerotic changes in the renal arteries, but some nodular lesions are seen. Therefore, even in normoalbuminuric range, we should be careful to decline rapid decline of GFR in DKD patients.

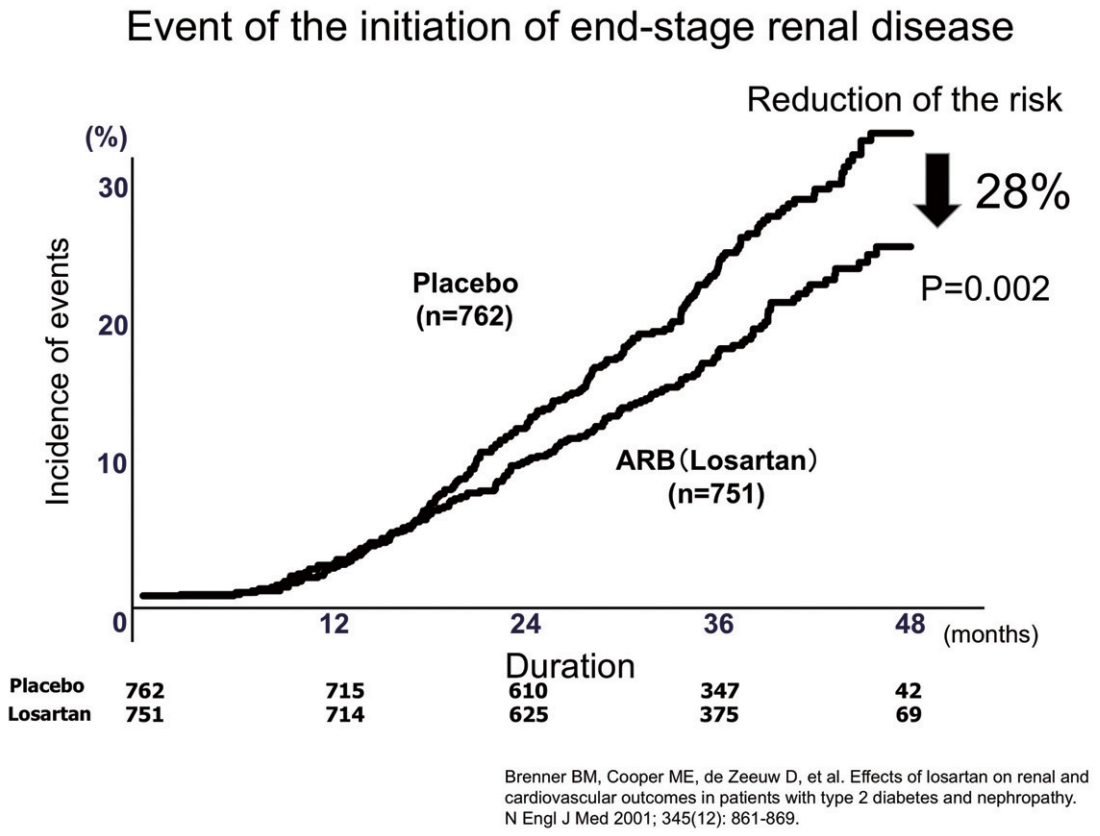

Fig. 5 *Composite renal outcome (a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death) in the RENAAL study*

URINE ALBUMIN AS A MARKER OF CARDIORENAL DISEASES

Urine albumin has been demonstrated not only to be a marker of kidney damage but also to be associated with arteriosclerosis and mortality. In a study covering 691 diabetics aged 65 or more, albuminuria was shown to have significant correlation with total mortality and mortality from cardiovascular disease, and to be an independent predictor [13]. Interestingly, a study that examined albuminuria, cardiovascular complications and mortality in 1,568 healthy persons who did not have hypertension or diabetes showed that in groups with urine albumin excretion ≥ 3.9mg/gCr in males and ≥ 7.5 mg/gCr in females, even within this normal range, the higher the albuminuria the higher was the risk of mortality from cardiovascular disease [14]. From these results we may conclude that urine albumin is a significant predictive marker of death from cardiovascular disease, apart from being an early marker of kidney damage. What is the reason for urine albumin to be a risk factor for both cardiovascular and renal diseases? Glomeruli and renal tubules are normal parts of cortical nephrons close to the kidney surface and juxtamedullary nephrons in the interior parts of the kidneys. Blood vessels connected to the glomeruli of juxtamedullary nephrons branch out directly from thick blood vessels and therefore are constantly exposed to higher blood pressure than the cortical nephrons, and they are called "strain vessels". Strain vessels are also present in perforating branches of the middle cerebral arteries and brain stem arteries. The development of albuminuria because of arteriosclerosis-associated renal lesions reflects injury in these strain vessels and can therefore be considered as a factor related to renal and cardiovascular diseases (***Fig. 6***) [15]. In a study that examined the effect of ARB in high risk groups with cardiovascular diseases, patients with aggravated albuminuria showed decline of cognitive functions, and these functions improved in a group where the urine albumin level was lowered by treatment with ARB, suggesting a brain-kidney linkage [15].

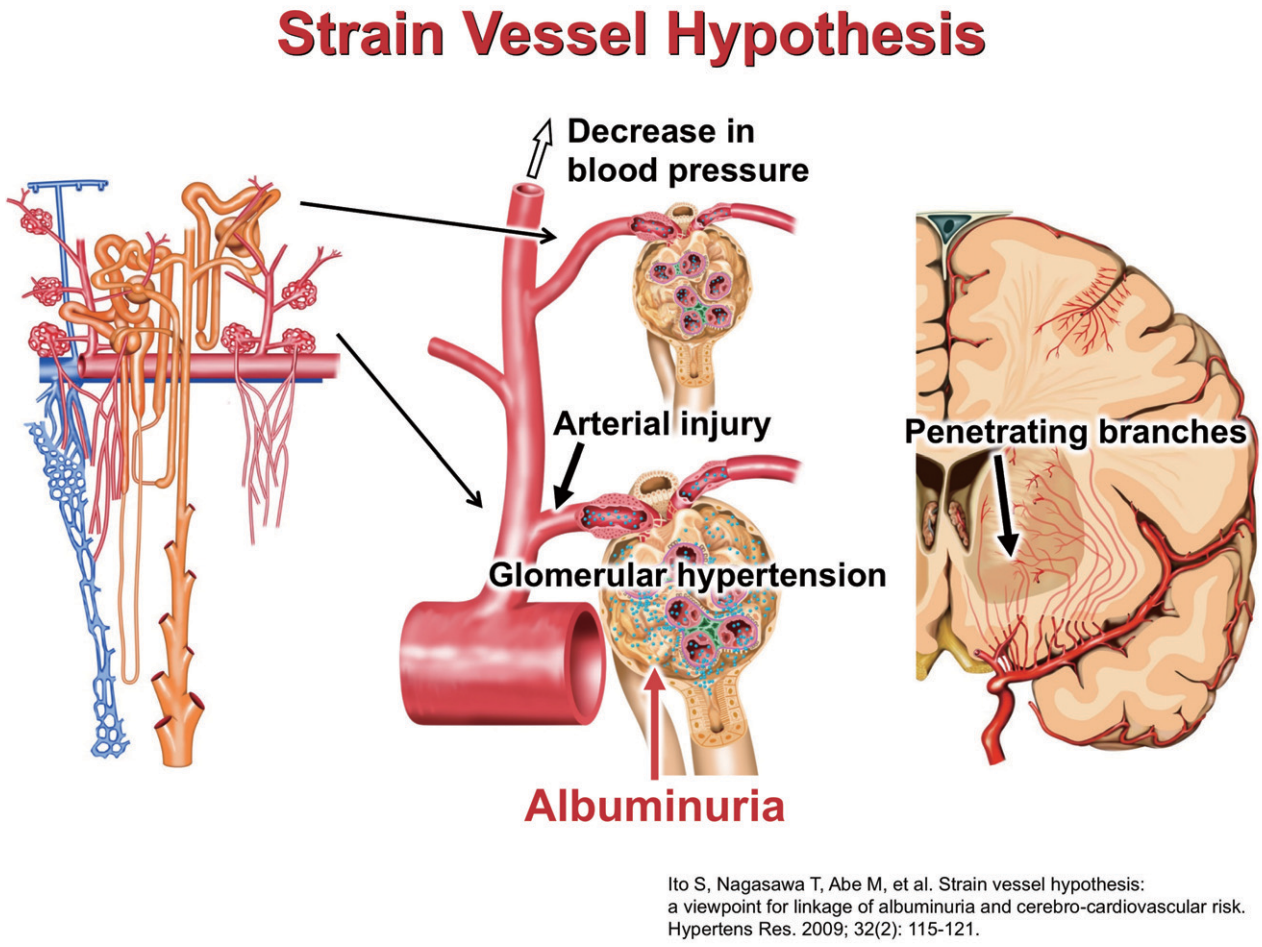

Fig. 6 *Scheme of the strain vessel hypothesis (crosstalk between albuminuria and cerebrovascular disease)*

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