Microalbuminuria: a valid marker for cardiovascular disease

As we aim to improve the identification and therapeutic management of those at high cardiovascular risk, certain less traditional risk markers are being more closely investigated. With growing evidence to support its relation to risk, microalbuminuria is becoming more widely recognised as an important marker in this assessment. Dr Paul Newman examines the evidence and seeks to rationalise a valid therapeutic strategy for high risk patients.

The release of the recent Joint British Societies 2 (JBS2) Guidelines on Prevention of Cardiovascular Disease in Clinical Practice in 2005, underlined the importance of the preventive measures to reduce cardiovascular risk in primary care. This concept has been reinforced by the recent release of the revised European Society of Hypertension–European Society of Cardiology 2007 Guidelines for the Management of Arterial Hypertension, which state that proper blood pressure measurement plus assessment of total cardiovascular (CV) risk is required to diagnose high blood pressure and guide treatment. Overall CV risk is now being used to assess whether treatment intervention is required, and stricter cholesterol targets have been included in JBS2 to further reduce the number of deaths due to heart disease in the UK.

Advanced age — together with male gender, smoking, diabetes mellitus, hypertension and dyslipidaemia — have long been recognised as the classic predictors of cardiovascular disease (CVD). Yet, as recent international data show, these risk factors alone do not sufficiently explain interpopulation variations in morbidity and mortality. This discovery has prompted researchers to investigate additional CVD markers, and there is now increasing evidence to suggest that the presence of small amounts of urinary albumin (microalbuminuria) may independently predict cardiovascular risk in patients, with and without type 2 diabetes and/or hypertension. This relationship has also been demonstrated in studies in elderly patients, where it has been shown that elderly patients with microalbuminuria have an increased CV risk. In fact, microalbuminuria was included in both the JBS2 and ESH/ESC 2007 guidelines as a marker of target organ damage and thus an indication to treat.

Microalbuminuria is a term used to describe a small amount of the protein albumin in the urine, and not, as is sometimes mistaken, a small type of albumin. Microalbuminuria is characterised by a raised albumin excretion rate of between 20 and 200µg/min (30–300mg in a 24-hour period). A urinary albumin level above this upper threshold is defined as macroalbuminuria. Urinary albumin-to-creatinine ratio measurements are also sometimes used to confirm diagnosis: a ratio between 30–300 (using mg of albumin and g of creatinine) or three–30 (using mg of albumin and mmol of creatinine) will usually verify microalbuminuric status.

However, it is important to note that the creatinine level can be affected by exercise and gender. The albumin level may also fluctuate due to certain conditions. Factors that can increase urinary albumin concentrations include: urinary tract infection, congestive heart failure, exercise, fever, poor glycaemic control and vaginal discharge. Therefore, since the amount of albumin and/or
Creatinine can vary, it is required that two out of three samples taken within one month are positive to confirm a diagnosis of microalbuminuria. Diagnosis with standard dipstick urinalysis can lead to some inaccuracies. For this reason laboratory based albumin creatinine ratios (ACRs) are the preferred prognostic tool. Additionally, concentrations of albumin and creatinine in the initial, morning, midstream sample correlate very well with 24-hour measurements, and it may not be necessary to request repeated samples throughout the day or take a 24-hour urine sample.

Multivariate analyses have revealed that microalbuminuria is strongly associated with increased age, hyperglycaemia, hypertension, smoking, non-Caucasian ethnicity and markers of inflammation such as C-reactive protein and raised lymphocytes. Pathophysiological studies investigating the link between microalbuminuria and macrovascular disease have suggested that these inflammatory markers are the principal aetiological mediators. Other hypotheses have proposed that albuminuria indicates an underlying endothelial dysfunction of the glomerular arteries, capillaries and/or intracellular matrix.

**CV risk**
Microalbuminuria affects around 11 per cent of people over the age of 40 years and may have significant consequences on long-term health. A prospective, population-based, six-year study of over 20,000 UK individuals aged between 40–79 years has shown that the presence of microalbuminuria significantly increases the risk of CV and all-cause mortality, and may be a useful marker for identifying older patients at the greatest absolute risk of fatal CV events.

The investigators found that compared to patients with normal albumin levels in their urine, microalbuminuria increased the likelihood of death by 48 per cent (1.20<95 per cent CI<1.79). Similarly, the risk of CV-related mortality was doubled (RR=2.03; 1.55<95 per cent CI<2.7). Both parameters reached statistical significance (p<0.001).

A study of 216 elderly patients reported similar findings. These patients, all of whom were aged 60–74 years, recorded a median urinary albumin excretion rate (UAER) of 7.52µg/min. During the seven-year study, only eight patients with a UAER below this threshold died, compared to 23 patients who met or exceeded it (p=0.0078). The investigators concluded that an association between microalbuminuria and mortality is present in the general elderly population, even when other known risk factors are taken into account.

**Patients with diabetes mellitus**
Microalbuminuria affects as many as 30 per cent of diabetic patients, with several prospective studies demonstrating that microalbuminuria is strongly associated with CV endpoints in both type 1 and type 2 diabetes.

A 10-year observational study of 939 adults with type 1 diabetes has shown that the presence of microalbuminuria is a predictor of CV mortality, irrespective of the status of classical risk factors (RR=1.45; 1.18<95 per cent CI<1.77). It is also known to be a strong predictor of renal disease. An 11-year study meta-analysis involving 2,138 patients concluded that microalbuminuria doubled CV morbidity and mortality in patients with type 2 diabetes (RR=2.0; 1.4<95 per cent CI<2.7). Importantly, this increased risk was even higher than those evoked by established atherosclerotic risk factors, and remained even after adjustments for concomitant risk factors such as age, hypertension, smoking and abdominal obesity. Microalbuminuric presence also significantly increased all cause-mortality in this group of patients (RR=2.4; 1.8<95 per cent CI<3.1).

**Hypertensive patients**
Several studies have reported that the incidence of microalbuminuria in patients with mild to moderate hypertension is around 30 per cent. There is a close correlation between the level of albuminuria and the level of hypertension, with microalbuminuria being confirmed as a positive risk factor for CV morbidity and mortality in this patient cohort. In patients older than 45 years with stage 2 or higher hypertension (blood pressure ≥160/100mmHg), microalbuminuria appears to be strongly associated with several traditional and non-traditional risk factors, and with target organ damage.

A 10-year prospective study involving 2,085 non-diabetic, hypertensive patients found that the presence of microalbuminuria more than trebled the risk of ischaemic heart disease (RR=3.5; 1.0<95 per cent CI<12.1). In keeping with other analyses, these findings were adjusted for traditional atherosclerotic risk factors such as...
increased age, hyperlipidaemia, body mass index, and smoking status. The investigators concluded that urinary albumin excretion should be measured regularly in a hypertension clinic, and that a rigorous control of blood pressure and of other atherosclerotic risk factors should be performed in hypertensive patients with microalbuminuria.

**Evidence-based treatment — the current perspective**

Studies indicate that certain ACE inhibitors and ARBs have significant therapeutic effects in high risk patients with microalbuminuria, and that these effects are independent of their hypotensive benefits. The majority of these studies have been in patients with diabetes, but there is emerging data to show that there is also an effect on urinary albumin in those without diabetes. For example, in the two-year IRMA-2 study, 590 hypertensive patients with type 2 diabetes and microalbuminuria were randomised to receive either placebo or irbesartan (150–300mg/day). Additional antihypertensive medications (except dihydropyridine calcium-channel blockers, ACE inhibitors and other ARBs) were permitted in all groups to obtain target blood pressure (135/85 mmHg).

The study showed that compared to placebo, 300mg irbesartan reduced the time-to-onset of diabetic nephropathy by 70 per cent (0.14<95 per cent CI<0.61). Furthermore, only 5.2 per cent of patients receiving 300mg irbesartan (n=194) developed diabetic nephropathy; a significantly lower proportion than the placebo group (14.9 per cent; n=201; p<0.001), and as many as 34 per cent of these irbesartan patients reverted back to normoalbuminuric status.

During the two years of the study, the overall UAER was reduced by 38 per cent. In addition, when comparing systemic blood pressure in the irbesartan and control groups, there was no difference in diastolic blood pressure and a difference of one to three mmHg in systolic blood pressure indicating that these results were independent of the blood pressure achieved.

In a similar study, valsartan was also shown to have an effect on UAER, independent of its blood pressure lowering. The MARVAL trial investigated 332 patients with hypertension, type 2 diabetes and microalbuminuria that were randomised to receive either valsartan (80mg/day) or amlodipine (5mg/day) for 24 weeks. The UAER in the patients on the ARB was 44 per cent lower after 24 weeks, whereas the UAER was reduced by only eight per cent in the calcium channel blocker group in the same time. The levels of blood pressure achieved in each group were similar and there was no significant blood pressure difference throughout the study. The evidence in both early and late stage renal disease in diabetes has led the JBS2 guidelines to recommend the use of ACE inhibitors in type 1 diabetic nephropathy and ARBs in type 2 diabetic nephropathy and those who are intolerant of ACE inhibitors.

Both classes also have possible indications for chronic renal disease and proteinuric renal disease in those without diabetes, showing the importance of renin angiotensin aldosterone system (RAAS) blockade in patients with elevated urinary albumin. ACE inhibitors and ARBs have also been shown to delay the progression of chronic kidney disease.

In trials designed to measure the time taken to doubling of serum creatinine, the beneficial action of
RAAS blockage has been shown. For example, in the REIN study the decline in GFR per month was significantly lower in the ramipril group than the placebo group (p=0.03), independent of baseline, and follow-up arterial blood pressure\(^1\). In addition the IDNT trial, investigating 1,715 patients with hypertension and nephropathy due to type 2 diabetes, showed that the serum creatinine concentration in the irbesartan group increased 21 per cent more slowly than in the amlodipine group, with no significant difference in blood pressure levels\(^2\).

**Conclusion**

In an effort to identify those at increased CV risk, microalbuminuria is becoming a more recognised marker of both renal and cardiovascular complications. This is reflected by its inclusion in the JBS2 guidelines as a marker of target organ damage\(^3\). Identifying older patients at risk of CV events is of great importance and the addition of a further tool to help risk stratify the elderly represents a marked improvement. In addition, subsequent RAAS intervention in these patients has been shown to reduce both blood pressure and the level of urinary albumin excretion, greatly improving their CV risk profile.

**Conflict of interest:** Dr Newman has been a consultant to, and received honoraria and travel grants from, numerous companies in the pharmaceutical industry that market cardiovascular and diabetes therapies.

**Key points**

- Sufficient evidence now exists to warrant routine microalbuminuria screening in: patients with type 2 diabetes patients over age 40 with type 1 diabetes and/or with hypertension (stage 2 or higher).
- These patients are at high risk of CV morbidity and mortality and would benefit from early therapeutic interventions.
- Early treatment with certain ARBs or ACE inhibitors in patients who test positive for microalbuminuria reduces the risk of cardiovascular and renal complications.