Should cardiologists be interested in albuminuria?

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Abstract

Excretion of excess urinary albumin is a marker of generalised endothelial dysfunction and both progressive renal disease and cardiovascular events in those with and without diabetes; its detection provides a simple way of identifying patients at particularly high risk. Effective management of cardiovascular risk factors and the use of angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors have been shown to retard or prevent progression of microalbuminuria to more profound albuminuria. Microalbuminuria can be reversed by such therapy and recently an ACE inhibitor has been shown to prevent the development of microalbuminuria in hypertensive patients with type 2 diabetes. Given the increasing prevalence of type 2 diabetes and the corresponding ascendancy of ensuing cardiovascular disease and renal failure, strict control of multiple risk factors, including microalbuminuria, is to be encouraged.

Key words: albuminuria, type 2 diabetes, cardiovascular risk, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors.

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Introduction

Cardiologists have an ambivalent view of renal impairment. They recognise the association between chronic kidney disease and cardiovascular events, and are aware that risk factors (e.g. diabetes and hypertension) are shared.[1,2] They appreciate that renal impairment is a marker of adverse outcomes in both acute coronary syndrome[3] and following coronary surgery, and that some cardiological interventions can be nephrotoxic (e.g. radio-contrast induced nephropathy). A more detailed knowledge of the natural history of renal diseases is unusual and as the practice of cardiology moves increasingly towards interventional approaches, it's possible that an understanding of the importance of kidney disorders, their presentation and management, will be designated the responsibility of other specialists.

Furthermore, while most cardiologists are well aware of the details of the National Service Framework (NSF) for Coronary Heart Disease (CHD),[4] their knowledge of the content (or even the existence) of the NSF for Diabetes[5] and the NSF for Renal Services[6] is lacking. This is important because the former recommends regular surveillance for diabetic complications (including renal dysfunction) and the latter advises routine screening, using existing diabetes and CHD networks of 'at-risk' patients with single (early morning) urine protein detection and formula-based estimation of glomerular filtration rate (GFR) (see table 1). This might seem removed from cardiological practice until the 'at-risk' group are defined – those treated for hypertension, diabetes, heart failure or vascular disease, and those taking diuretics, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs); i.e. the bulk of a general cardiology out-patient clinic. So cardiologists are ideally placed to identify those at risk of developing chronic kidney disease and to play an important role in the prevention or palliation of renal impairment; hoping that by so doing they can intervene to reduce associated cardiovascular morbidity.

Table 1. Subdivisions of protein detected in the urine

	24-hour urinary albumin excretion	Albumin: creatinine ratio (mg/mmol)
Normal	< 30 mg	< 2.5 men, < 3.5 women
Microalbuminuria	30–300 mg	2.5–25 men, 3.5–25 women
Macroalbuminuria	> 300 mg	> 25 men, > 25 women

NB. The National Service Framework for chronic kidney disease recommends assessment on a single urine sample (preferably early morning sample)

Proteinuria and the link to cardiovascular disease

Microalbuminuria is not a disease but is simply a description of a level of urinary protein loss that lies within an arbitrary range (see table 1), in the same way that hypertension is a measure of blood pressure rather than a disease state. It may be present in the absence of any evidence of renal disease, certainly before any reduction in GFR, and is seen in 'healthy' individuals as well as

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those with diabetes and/or hypertension. In such healthy individuals it predicts a later diagnosis of diabetes or hypertension.[7,8] Its presence also predicts an increased likelihood of developing overt proteinuria, end-stage renal disease (ESRD) and manifestations of cardiovascular disease (CVD).[9,10] The magnitude of increased cardiovascular risk is equivalent to that of cigarette smoking or an absolute increase in total cholesterol by 1.5–2.0 mmol/L.[11] In a British study of 20,911 people aged 40–79 years followed for an average of 6.3 years, after adjusting for other risk factors, microalbuminuria was associated with a doubling in the risk of dying of CVD and a 48% increased risk of all-cause mortality.[12] This relationship, independent of renal function, hypertension or diabetes, has been confirmed in another cohort study.[13]

Initially, microalbuminuria may be transient and reversible[14] (though seldom in type 2 diabetes, in which condition an understanding of urinary protein loss and its management is most advanced). Microalbuminuria precedes the diagnosis of type 2 diabetes in 25% of patients.[15] It goes on to develop in 2% of the remainder per annum and 2.8% progress to proteinuria.[16] While worsening diabetic nephropathy is characterised by a gradual transition from 'normo-' through 'micro-' and 'macro-albuminuria' (overt proteinuria) to ESRD, patients with all degrees of albuminuria are at risk of sudden cardiac events and, in any given year, patients with proteinuria have a greater risk of dying than of requiring dialysis.[15]

Microalbuminuria was present at baseline in 32.2% of people with diabetes (compared with 14.7% in people without diabetes) in the Heart Outcomes Prevention Evaluation (HOPE) study, and in both groups was associated with increasing age, smoking, hypertension, left ventricular hypertrophy and abnormal waist:hip ratio, an indicator for insulin resistance and a component of the metabolic syndrome.[17]

The putative mechanisms by which microalbuminuria is linked to increased CVD risk includes a chronic inflammatory state, a prothrombotic state and a generalised state of vascular damage/endothelial dysfunction, of which increased urinary albumin excretion is a manifestation.[18-20]

Is albuminuria an appropriate target in preventive cardiology?

While excess urinary protein excretion is a risk marker for both chronic kidney disease and CVD, it remains possible that interventions aimed at moderating proteinuria may have beneficial effects with respect to renal function without reducing cardiovascular risk. There are no completed randomised controlled trials with a primary purpose of proving that reducing urinary protein excretion causes lower cardiovascular risk. Evidence from other sources does suggest the existence of such a link.

In a sub-study of the Losartan Intervention for End point Reduction in Hypertension (LIFE) study, there was a 'dose-response' relationship between baseline albuminuria and risk of cardiovascular events across all deciles of protein excretion, in a population that predominantly consisted of patients without diabetes.[21] When the amount of albumin excretion decreased during treatment, the composite cardiovascular end point did so as well, and this was not explained by the level of blood pressure achieved.[22] Similarly, a *post-hoc* analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study confirmed that patients with diabetes with a higher baseline albuminuria had a higher cardiovascular risk. It showed that the degree of reduction in albuminuria after six months' treatment predicted later cardiovascular outcome. A 50% reduction in albuminuria was associated with a 27% reduction in heart failure and an 18% reduction in the composite cardiovascular end point.[23] These authors described albuminuria as a "therapeutic target for cardiovascular protection", while others have stated, "If albuminuria is not decreased by patients' current antihypertensive and other treatments, further intervention directed towards blood pressure control and other modifiable risk factors should be considered."[22]

How can we target albuminuria?

Risk factor management

Given the association between proteinuria and established cardiovascular risk markers,[17] it is not surprising that optimisation of these risk markers has benefits with respect to urinary protein excretion. In diabetes, strict control of glycaemia and blood pressure is associated with a reduction in both proteinuria and microvascular and macrovascular complications.[24,25] Intensive insulin therapy for a mean of 6.5 years in patients with type 1 diabetes was associated with a prolonged beneficial effect on both the development of microalbuminuria and cardiovascular events – both almost halved.[26] A long-term intensive intervention targeting multiple risk factors in patients with type 2 diabetes with microalbuminuria, the Steno-2 study, also reported a reduction in the risk of cardiovascular and microvascular events, including nephropathy, by about 50%.[27] The implication is that continuing to treat existing risk factors will, *de facto*, lead to reasonable management of proteinuria.

ACE inhibitors and ARBs

There is evidence for differential effects on protein loss between agents despite similar improvements in established risk factors. In particular, blockade of the renin-angiotensin system using ACE inhibitors or ARBs appears to be the most reliable method of preventing progressive renal disease in diabetics. Angiotensin II plays an important role in the development of proteinuria by adversely altering intrarenal haemodynamics, glomerular capillary permeability, and filtration surface area, and stimulating extracellular matrix protein synthesis in glomerular mesangial cells and hypertrophy in glomerular cells.[28,29] Protection from the effects of angiotensin II can therefore be achieved either by inhibiting angiotensin II generation by ACE inhibition or by antagonising its effect on the AT_1-receptor sites. Beneficial effects on vascular endothelial function will also occur.

In the LIFE study, for example, the reduction in albuminuria in those hypertensives receiving losartan was significantly greater than in those taking atenolol (33% *vs.* 25% at two years) despite a similar reduction in blood pressure.[21] Losartan treatment was

also associated with a significantly lower rate of stroke. In a randomised controlled trial in patients without diabetes with chronic renal disease who were all receiving ramipril, the addition of felodipine failed to show either additional benefit with respect to progressive renal disease or with respect to cardiovascular events, in spite of better blood pressure control in the felodipine group.[30]

In patients with type 2 diabetes, the weight of evidence for renal protection supports ARB use.[31] The RENAAL study and the Irbesartan Diabetic Nephropathy Trial (IDNT)[32] showed the renoprotective effects of losartan and irbesartan respectively in diabetics with macroalbuminuria, whilst the effect of long-acting calcium channel blockers was similar to placebo. The IRbesartan in patients with type 2 diabetes and MicroAlbuminuria study group (IRMA 2) showed that irbesartan reduced the likelihood of progression from micro- to macroalbuminuria and, at higher doses, was associated with significantly more regression to 'normoalbuminuric' levels, albeit small. Significant differences existed in systolic blood pressure between treatment and control groups.[33] The shorter Microalbuminuria Reduction with Valsartan in Patients with Type 2 Diabetes study (MARVAL)[34] showed valsartan to significantly reduce urinary protein excretion compared with treatment with amlodipine, despite similar blood pressure control. A comparison was also made with amlodipine in IDNT, and again the ARB proved more effective, despite similar blood pressure control.

Despite this wealth of evidence supporting the renoprotective effects of ARBs, a subsequent meta-analysis failed to show a significant beneficial effect on mortality.[35] The same meta-analysis included outcomes from 4,008 patients with diabetes (type 1 and type 2) in trials of ACE inhibitors versus placebo. This reported a statistically significant reduction in all-cause mortality, largely driven by the results of the subgroup with diabetes in the HOPE study. In addition, a recent three-year prospective study (too late for inclusion in the meta-analysis) of 3,773 Chinese patients with type 2 diabetes, with varying degrees of albuminuria (from normo- through to macroalbuminuria) found that ACE inhibition was associated with a significant reduction in mortality for the entire study group.[36]

There have been few 'head-to-head' comparisons of ACE inhibitor and ARBs though the recently completed Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study in patients with type 2 diabetes with nephropathy reported similar renoprotective effects, but was too small to allow meaningful comparison of cardiovascular outcome.[37]

Finally, there may be added benefit in treating with a combination of ACE inhibitor and an ARB. In a randomised, controlled trial of Japanese patients without diabetes but with kidney impairment, the renoprotective effects of trandolapril and losartan were similar and additive,[38] and the additive effect was more than could be explained by blood-pressure lowering effects.

Can we prevent albuminuria?

Preventing or delaying the development of microalbuminuria is a key goal for renoprotection and, if it really does reflect endothelial dysfunction, for cardioprotection. Animal studies in streptozocin-induced diabetes demonstrate that proteinuria can be reversed if an ACE inhibitor is started early in the course of glomerular injury, yet the same treatment started later only slows the rate of decline in kidney function.[39] Humans with type 2 diabetes develop changes in the 'glomerular barrier' to macromolecules that are not affected by ACE inhibitors.[40] So early treatment of those at risk of proteinuria is advisable.

Strict blood pressure control with captopril or atenolol (144/82 mmHg *vs.* 154/87 mmHg) in the UK Prospective Diabetes Study (UKPDS) was associated with both a significant reduction in stroke and heart failure, and a 29% reduction in the development of microalbuminuria.[25] So prevention is possible.

To more clearly demonstrate the feasibility of a preventive strategy, the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) was designed to assess whether a long-acting ACE inhibitor could prevent microalbuminuria in hypertensive diabetic patients with normal urinary albumin excretion.[41] Trandolapril treatment was associated with a halving (5.7% *vs.* 10.0%) in the development of persistent microalbuminuria over a median 3.6 years compared with placebo. Although there was a slight, though significant improvement in blood pressure control in the group taking trandolapril (average trough pressure 139/81 mmHg *vs.* 142/83 mmHg), the renoprotective effects exceeded that expected based upon this difference. Further evidence for a specific renoprotective effect of trandolapril was the fact that sustained-release verapamil had no effect on development of microalbuminuria, a finding that remained valid even after adjustment for blood pressure differences (verapamil:141/82 mmHg *vs.* placebo:142/83 mmHg).

Key messages

- Microalbuminuria is a marker of generalised vascular dysfunction
- It can be reversed and/or prevented by drugs that inhibit the renin-angiotensin system
- It may become a target for therapy in patients at risk of vascular disease

Conclusion

There is evidence for a strong relationship between renal and cardiac disease. Microalbuminuria occurs early in many conditions and is a marker of generalised vascular disease, and there is evidence (mainly in trials of diabetic patients) that ACE inhibitors and ARBs reduce urinary albumin excretion and deterioration of renal function, probably by effects that are in addition to blood-pressure lowering. It is too early to recommend that microalbuminuria be a specific target of treatment to prevent cardiovascular events, irrespective of other risk factors, though its presence should at least encourage more strict control of such factors. However, it seems likely that a major potential benefit would result from

screening for microalbuminuria in many cardiology patients, and instituting earlier treatment with ACE inhibitors or ARBs.

Conflict of interest

CW* and JV† have received honoraria from a variety of pharmaceutical companies that manufacture ACE inhibitors and ARBs. These include Abbott*, Bristol-Myers Squibb*†, Boehringer Ingelheim*, Merck Sharp & Dohme*†, Sankyo*, Sanofi-Aventis* and Servier†.

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