

Another CV Risk Factor

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This *Heartbeat* will discuss an easily measured yet frequently overlooked screening tool for cardiovascular (CV) risk—*microalbuminuria*. The presence of microalbumin in the urine of persons with Type 2 diabetes (T2DM) or hypertension is perhaps the most important early signal of systemic vasculopathy and associated disease to the brain, heart and kidney. Microalbuminuria identifies patients who need more aggressive CV risk management to prevent early CV death and progressive renal disease. Therapeutic strategies to control blood pressure (BP), preferably < 130/80 to reduce microalbuminuria, along with strict attention to glycemic control and lipid levels, are the most effective ways to slow not only the progression of renal disease but also of CV disease. **The identification and normalization of urine microalbumin excretion should be an important consideration in all those with hypertension, diabetes or metabolic syndrome.**

Marker for CVD and Renal Injury

Screening for microalbuminuria is one of the most important and simple clinical tools in practice. In T2DM, it is the earliest clinical sign indicating vascular damage to the glomerulus, which is reflective of vascular disease throughout the body. Although only 20% - 40% of T2DM patients with microalbuminuria progress to end stage renal disease (ESRD), many feel this percentage would be a lot higher if many didn't die from myocardial infarction (MI) or stroke, i.e. they don't live long enough.

There appears to be a linear relationship between increasing levels of urinary albumin and both MI and stroke, and this is evident well below the standard microalbuminuria threshold (30mg/dL).¹ Microalbuminuria is also commonly associated with a cluster of CV risk factors known as metabolic syndrome (MetS) which is associated with increased CV risk.² This means that early screening can have predictive value to identify patients early in the

disease process so that preemptive CVD risk reduction therapy can be initiated as soon as possible.

Screening

A spot determination is the easiest and cheapest to use and provides accurate information (at least 90% sensitive for determining microalbuminuria compared with a 24-hour urine collection).³ The relationship between albuminuria and progressive renal injury is not completely understood, but elevated protein in the urine points to a derangement in the glomerular filtration barrier. Normal is defined as < 30mg/dL. Microalbuminuria is 30-300mg/dL, and macroalbuminuria is defined as \geq 300 mg/dL. Spot specimens can also be used as a means for determining response to therapy.

Rationale for Treatment

The rationale for reducing microalbuminuria or proteinuria is based on the clinical evidence linking proteinuria not only to CV events but also to progressive renal dysfunction. The severity of albuminuria parallels renal disease progression. Albuminuria and hypertension are predictors of poor renal and CV outcome in diabetic patients. This is also true for patients without diabetes. Consequently, antihypertensive and antiproteinuric renal protective strategies are of great interest. *The key clinical questions are: How low should we reduce BP pressure in the proteinuric patient and specifically, what drugs should we use?*

Antihypertensive agents that target the renin-angiotensin system, such as the angiotensin-converting enzyme (ACE) inhibitors or the angiotensin II receptor blockers (ARB), have been demonstrated to have more potent antiproteinuric effects with similar degrees of BP reduction compared with other antihypertensive drug classes in multiple studies. BP reductions of < 130/80 per the American Diabetic Association (ADA) are associated with improved outcomes.

ACE inhibitors and angiotensin II receptor blockers have been convincingly demonstrated to have renal-protective benefits. The majority of the data with the ACE inhibitor is in type 1 diabetics and in patients with non-diabetic renal disease.^[4,5] The more recent data with angiotensin II receptor blockers is confined to patients with T2DM.^[6,7,8] However, more often than not these patients will require multiple drugs to achieve the lower levels of BP, which may be important in correcting glomerular capillary hypertension and optimally reducing proteinuria. Newer strategies to use combinations of drugs will likely prove to be important. The addition of a thiazide diuretic or a nondihydropyridine calcium antagonist may also amplify the antiproteinuric effects of drugs that block the renin-angiotensin system.⁹ *Most of the renal outcome studies with ACE inhibitors or ARBs included diuretic and/or calcium antagonists to achieve better BP control.*

Early studies indicate that using an ACE inhibitor and an angiotensin II receptor blocker together may be better than using either one alone in the approved dosing range to reduce microalbuminuria or proteinuria. A more recent study in April 2003 documented a superior effect on BP and a tendency to a more pronounced drop in urine albumin excretion of dual blockade of the renin-angiotensin system compared with single blockade.¹⁰

The HOPE study showed the ACE inhibitor ramipril reduced the level and progression of microalbuminuria and reduced the risk of a CV event.¹¹ It is most likely that ramipril affected a disease process (vasculopathy—*inflammation and endothelial dysfunction*) that was reflected by changes in albuminuria and CV event rates.

Current methods of reducing microalbuminuria include strict glycemic control. Recent data has shown the superiority of glitazones when compared

to metformin and gliburide for reduction of microalbuminuria.^{12 13} Glitazones have many important effects beyond lowering blood glucose.

Summary/Conclusions

Most of the practice of modern medicine deals with prevention of the consequences of chronic conditions like hypertension or T2DM. To achieve this end, identifying people at risk for these consequences and then initiating evidence-based preventive therapies are key. *Microalbuminuria is a risk factor which is causally related to outcome, and its modification by a wide range of interventions almost certainly will improve outcomes.*

- Screening for microalbuminuria should be performed yearly on all patients with hypertension, MetS or T2DM as recommended by the ADA.¹⁴
- The presence of microalbuminuria is an indicator of inflammation and vasculopathy and therefore higher CV and renal risk.
- Consequently the presence of microalbuminuria requires lower BP goals (<130/80); more aggressive lipid goals (LDL-C of < 100mg/dL—*statins*); tight glucose control—consider glitazones; *aspirin* for platelets; as well as anti-microalbuminuric therapies—*an ACE inhibitor and/or ARB*.
- Therapeutic lifestyle changes (TLC)—exercise, diet and tobacco cessation—have to be part of all CV and renal risk reduction strategies.

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¹ Gerstien HC et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA*. 2001; 286: 421-426.

² Sowers JR et al. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001; 37: 1053-1059.

³ Bennett PH et al. Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. *Am J Kidney Dis*. 1995; 25: 107-112.

⁴ Jafar TH et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int*. 2001; 60: 1131-1140.

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- ⁵ Lewis EJ et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993; 329: 1456-1462.
- ⁶ Parving HH et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001; 345: 870-878.
- ⁷ Brenner BM et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001; 345: 861-869.
- ⁸ Lewis EJ et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001; 345: 851-860.
- ⁹ Bakris GL, Weir MR, DeQuattro V, et al. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int.* 1998; 54: 1283-1289.
- ¹⁰ Jacobson P et al. Dual rennin-angiotensin system blockade best in DM nephropathy. *J Am Soc Nephrol* 2003; 14: 992-999.
- ¹¹ HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of HOPE study and MICRO HOPE study. *Lancet* 2000; 255: 253-259.
- ¹² Imano E et al. Effect of triglitazone in patients with incipient diabetic nephropathy. *Diabetes Care* 1998; 12: 2135-2139.
- ¹³ Bakris GL et al. Rosiglitazone reduces urinary albumin excretion in T2DM. *J Hum Hypertens* 2003; 17: 7-12.
- ¹⁴ American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care.* 2003; 26 (suppl 1): S33-S50.