New study reveals that reversing albuminuria reduces cardiovascular

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New study reveals that reversing albuminuria reduces cardiovascular events in patients with diabetic nephropathy

The RENAAL study, published in 2001 demonstrated that Merck's Losartan slows diabetic nephropathy and reduces the risk of heart failure. In a more recent analysis of the RENAAL database, researchers have shown that albuminuria predicts heart failure as well as other cardiovascular events and that the degree of success with which Losartan can reduce albumin levels is related to the extent of cardiovascular protection.

(Editorial note: In depth reports on diabetic nephropathy and cardiovascular risk can be found at *LeadDiscovery's* report center or click here for suggested reading)

DailyUpdates 7 September, 2004: Cardiovascular disease is a leading cause of mortality and prevention of acute events is a high priority. Major risk factors include hypertension, dyslipidemia and diabetes. Many at risk individuals carry multiple risk factors and considerable emphasis is being placed on the development of cross-risk factor treatment with fixed dose combinations (for example Pfizer's Caduet). The development of multi-modal drugs which can target a number of risk factors may be of even greater benefit and the angiotensin II receptor antagonists (ATIIAs) is emerging as one such class of agent.

Of the 150 million+ type II diabetics 10-40% develop nephropathy, a progressive decline in glomerular filtration rate associated with albuminuria. Albumin levels may be reduced through the use of antiproteinuric strategies that interrupt the renin-angiotensin system via either angiotensin converting enzyme (ACE) inhibition or through the use of ATIIAs. Guidelines now recommend these approaches as first line renoprotective therapies.

Angiotensin II, which is formed from angiotensin I in a reaction catalyzed by ACE, is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. Losartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor. Over recent years the ATIIAs, or 'sartans', have been the fastest-growing antihypertensives with sales of losartan hitting $1.4 billion in the first half of 2004. This growth has been accelerated by a series of studies, starting with the PRIME study focusing on irbesartan, which demonstrated that ATIIAs protected against the progression of kidney disease in patients with hypertension and Type 2 diabetes. The renoprotective activity of these agents is in part independent of anti-hypertensive effects and instead related to their ability to reduce angiotensin II-mediated efferent arteriolar vasoconstriction and hence intraglomerular pressure.

Although the reasons are not entirely clear albuminuria is also a risk factor for hypertension. Consequently the use of ACE inhibitors or ATIIAs may reduce hypertension both directly and also through the reversal of albuminuria. Like nephropathy, hypertension is common in type II diabetics with 60-65% of patients displaying high blood pressure. Since both of these comorbities are predictive of cardiovascular events, albuminuria may be an independent cardiac risk marker in type 2 diabetes with nephropathy. Likewise, albuminuria reduction may represent a cardiovascular-protection treatment strategy. To investigate this possibility de Zeeuw et al have recently performed a *post hoc* analysis of the RENAAL database.

The RENAAL trial was conducted to investigate the ability of losartan to reduce endpoints in type II diabetes. The study demonstrated the renoprotective effects of losartan and in addition one of the secondary end-points, the rate of first hospitalization for heart failure, was significantly lower with losartan. In their recent analysis of the RENAAL database reported in the August edition of ***Circulation***, de Zeeuw et al demonstrate that high levels of baseline albumin predicted heart failure or a combination of myocardial infarction, stroke, unstable angina, coronary or peripheral revascularization and cardiovascular death. Likewise the degree of short-term albumin reduction during the RENAAL trial predicted long-term outcome. This relationship was predominantly seen in patients with renal events.

This study therefore suggests that in diabetics with nephropathy, losartan reduces the risk of heart failure or other non-heart failure types of cardiovascular disease. This study also shows that increasing levels of albumin result in a greater risk of suffering cardiovascular events and that protection against these events increases as the reduction of albuminuria becomes more successful. These findings are important for two reasons. Firstly, the study suggests that measuring albumin levels may represent a simple and inexpensive marker of cardiovascular protection in patients with diabetic nephropathy. Secondly, targeting albuminuria may offer a strategy for reducing the risk of cardiovascular events in these patients.

Source: Albuminuria, a Therapeutic Target for Cardiovascular Protection in Type 2 Diabetic Patients With Nephropathy. Circulation. 2004 Aug 24

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