



Hypertension and Diabetes – A Deadly Combination

Hypertension and diabetes often coexist (upto 40-65% of Type 2 patients with diabetes have hypertension depending on their age) and when they do, the risk of developing target organ disease in the heart, eyes and kidneys and the risk of premature cardiovascular events and premature death is greatly increased. Diabetes patients already have a three fold increased risk of death from coronary heart disease. The importance of “tight” blood pressure control was confirmed in the UKPDS study when an achieved blood pressure of 144/82 mm Hg significantly reduced the risk of a number of diabetes-related cardiovascular outcomes including any diabetes related end point, diabetes related death, stroke, microvascular end points, heart failure and retinopathy.

It has been appreciated for some time, that blockage of the renin-angiotensin system does more than just reduce blood pressure and reduce hypertensive target organ damage. The important role of this system in promoting atherosclerotic vascular events was confirmed in a large intervention trials (the HOPE study) where it was shown that ramipril, an ACE inhibitor, was shown to reduce a whole raft of cardiovascular end points including cardiovascular death, stroke, myocardial infarction, nephropathy, TIAs, and heart failure with only a 3/1 mm Hg reduction in blood pressure.

A close inspection of the major biological effects of Angiotensin II allows one to see how blockade of its action can have such profound effects. Angiotensin II is known to contribute significantly to vascular remodelling, decreasing the diameter of arteriolar resistance vessels, increasing the wall to lumen ratio, amplifying the responsiveness to vasoconstrictor stimuli and increasing vessel stiffness. It leads to left ventricular hypertrophy and dilatation, impaired cardiac function and heart failure and a loss of 50% of capillaries in peripheral vascular beds with a concomitant increase in peripheral vascular resistance. It is known to be a promoter of endothelial dysfunction, smooth muscle cell proliferation and migration and is a facilitator of LDL oxidation, promoting the uptake of oxidized LDL (in human coronary artery endothelial cells). It plays a part in the recruitment of monocytes and macrophages in the the arterial wall.

ACE inhibitors are first line drugs used in the treatment of hypertension and diabetes but there are a number of increasing indications for the use of AT1 receptor blockers. It would seem unlikely that ACE inhibitors are able to completely suppress the renin angiotensin system and it is known that circulating angiotensin II levels recover in some patients on ACE inhibitors. When angiotensin 1 receptor blockers are used, a rebound increase in angiotensin II occurs which is free to interact to the unblocked AT2 receptor neutralizing the harmful effects of AT1 receptor activation. A number of these drugs have been shown to protect against diabetic nephropathy and without the side effects of cough that occurs in some patients taking ACE inhibitors. It seems that AT1 receptor blockers have additional benefits out of proportion to their blood pressure lowering effects and these are likely to lead to their more extensive use.

Some of these actions include:

- Involvement in endothelial dysfunction
- Modulation of vascular smooth muscle cell growth, differentiation and death



- Simulation of vascular wall matrix deposition
- Acceleration of vascular cell aging
- Involvement in vascular inflammation and pathogenesis of atherosclerotic lesions, plaque instability and thrombosis
- Sodium and fluid retention
- Sympathetic activation

The inhibitory effect of candesartan is more prolonged than many other AT1 receptor blockers in keeping with its known slow dissociation from the AT1 receptor. There is increasing evidence now that it also possesses other properties which are important in reducing cardiovascular events in the long term.

Some of them are listed below:

- Left ventricular hypertrophy is now established as an independent and significant cardiovascular risk factor and candesartan has a favourable impact on left ventricular arterial structure and function in hypertensive patients.
- Arterial stiffness, measured by a fall in augmentation index, is also reduced by treatment with candesartan.
- Candesartan has been shown to improve flow-dependent vasodilatation and it seems that both bradykinin and nitrous oxide are involved in the increase in flow dependent vasodilatation mediated by this AT1 blocker.
- Candesartan improves tonic nitrous oxide release and reduces vasoconstriction to endogenous endothelin-1.
- Candesartan treatment prevents the uptake of oxidized LDL cholesterol by cultured mouse macrophages and reduces plaque formation and cholesterol accumulation in the thoracic aorta of the Watanabe heritable hyperlipidaemic rabbit.
- Myointimal hyperplasia arising from endothelial denudation is significantly attenuated by either ACE-1 or AT1 blockers such as candesartan.
- Candesartan leads to a significant increase in the rate of endothelialisation after balloon catheter injury to the thoracic aorta in New Zealand white rabbits

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