

Any "new" antihypertensive drugs we should know about?

Carvedilol (freely available and fully funded in NZ)

This drug has been available in NZ for a few years. It was initially promoted for the management of heart failure where studies had shown it to be more effective than metoprolol and other beta blockers. More recently it has been recognised as an effective antihypertensive agent, and as it no longer requires Special Authority approval it can be freely prescribed.

Carvedilol is a 3rd generation, non-cardioselective beta blocker that also possesses alpha₁adrenergic-blocking, antioxidant and calcium antagonist effects. It has several potential advantages over 1st and 2nd generation beta blockers as an antihypertensive agent including an apparently favourable metabolic profile (neutral or beneficial effect on insulin resistance and lipid profile), and apparently a markedly lower incidence of traditional beta blocker side effects, including fatigue and sexual dysfunction. The usual precautions and contraindications when considering beta blocker therapy should still be observed with this drug.

Long term outcome studies with this drug are still in progress, but where a beta blocker is considered for treatment of hypertension this drug is certainly worth consideration. The only disadvantage is that the LA preparation is not currently available in NZ and it must be dose twice daily (dose range 6.25 – 25mg BD). Certainly it is worth a try in individuals intolerant of traditional beta blockers

Eplerenone (obtainable, but not funded in NZ)

This is an aldosterone receptor antagonist, like spironolactone, but unlike spironolactone (which also has affinity for androgen and progesterone receptors) is more selective of the mineralocorticoid receptor. It has the same therapeutic benefits as spironolactone without the potential anti-androgenic side effects. Spironolactone is now in common use as an add-on 4th or 5th drug in resistant hypertension¹, where it has proven itself extremely effective. In the up to 10% of men who experience painful gynaecomastia or sexual dysfunction on spironolactone, eplerenone allows the possibility of effective aldosterone antagonism without unacceptable side effects. It is weaker than spironolactone – suggested dose range 25-50mg daily (equates approximately to spironolactone 12.5- 25mg daily). Unfortunately it is not freely available in New Zealand, nor subsidised by Pharmac. Community pharmacies are able to access it though and the approximate cost to the patient would be about \$NZ 130 per month at the 25mg per day dose. **In my view this drug should be available in NZ on Special Authority for men with heart failure or hypertension who require an aldosterone antagonist but experience anti-androgenic side effects with spironolactone.**

Aliskerin (not currently available in NZ)

Blockade of the renin-angiotensin-aldosterone system (RAAS) is an important tool in the management of hypertension. Previously we have been able to interrupt it at the level of angiotensin converting enzyme (which converts inactive angiotensin 1 to active angiotensin 2 - with ACE-inhibitors like enalapril), the action of angiotensin 2 on its AT1 receptor (angiotensin receptor blockers, like losartan), and at the level of the aldosterone receptor (with aldosterone receptor antagonists like spironolactone). Aliskerin is the first of a class of drugs called "oral direct renin inhibitors" – it works by blocking the cleavage of angiotensinogen to angiotensinogen 1 which is the first and rate-limiting step in the RAS cascade. It was approved for use in the USA in 2007 and appears to be a safe and effective antihypertensive agent – approximately as effective in monotherapy as an ACE-inhibitor or an ARB, and can be effectively combined with thiazide diuretics. Side effect profile is similar to ARB's. Dose range is 150-300mg daily.

This drug is not available in NZ currently, and my reading of the current literature suggests that additive antihypertensive effect in a patient on an adequate dose of ACE-inhibitor or ARB is modest (somewhat analogous to addition of ARB to ACE-inhibitor). Long term cardiovascular outcome studies are not available yet, but one study (AVOID) did suggest some additional antiproteinuric effect in patients with diabetic nephropathy already on a maximum dose of losartan². **I am not convinced (on evidence available to date) that it is a big step forward in the pharmacology of hypertension;** - it may find a niche in the management of patients intolerant of both ACE-inhibitors and angiotensin receptor blockers.

Darusentan (for interest only)

This is not yet available clinically in the USA but likely will be in the near future (unlikely to be available in NZ in the foreseeable future). It is from a new class of antihypertensive drug called Endothelin Receptor Antagonists. Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor implicated in the pathogenesis and progression of CV disease, including hypertension. It has been trialled in mild hypertension and is effective, but there are concerns about toxicity (liver, and possibly teratogenic) so it is unlikely that it will be used extensively. It does however have a possible niche as an add-on drug in resistant hypertension, and in a recent phase 2 clinical trial³ in patients with resistant hypertension (blood pressure not at target on a

minimum of 3 antihypertensive drugs, one of which is a diuretic) the group randomised to receive darusentan had an average 11.5/3.1 blood pressure drop compared with those randomised to receive placebo. The drug was generally well tolerated and commonest side effects were oedema and headaches.

1. Chapman N, Dobson J, Wilson S et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension;Anglo-Scandinavian Cardiac Outcomes Trial Investigators. *Hypertension* 2007;49:839-45.

2. Aliskerin combined with losartan in type 2 diabetes and nephropathy. Parving HH et al. *N.Engl.J.Med.*2008;358:2433-46

3. Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomised, double-blind, placebo-controlled dose-ranging study. Black HR et al.