WACARDIOLOGY

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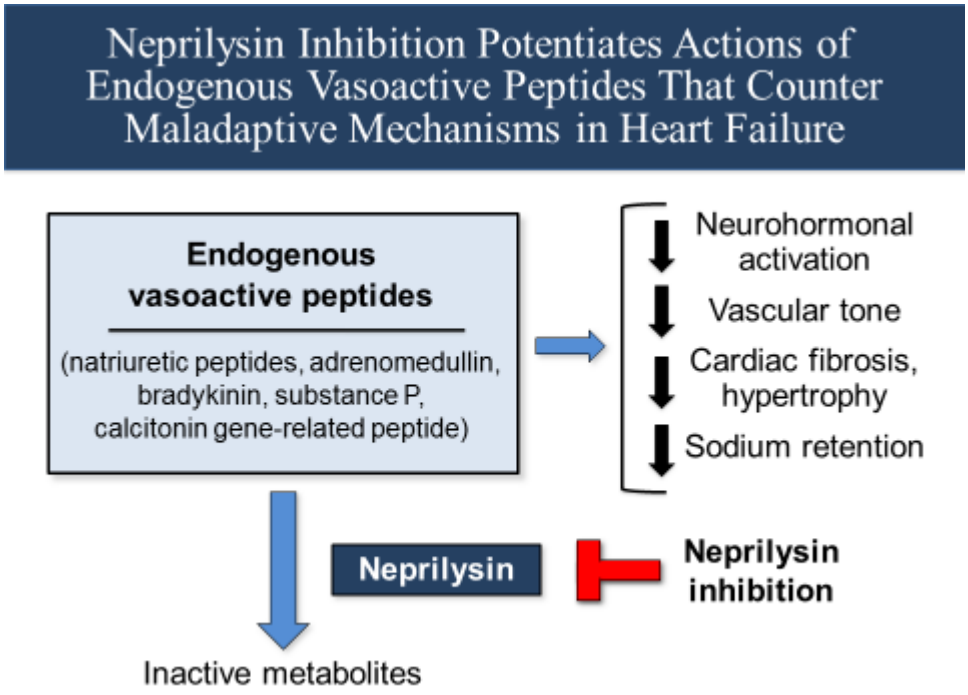
A PARADIGM SHIFT IN THE MANAGEMENT OF CCF – THE PARADIGM HF TRIAL

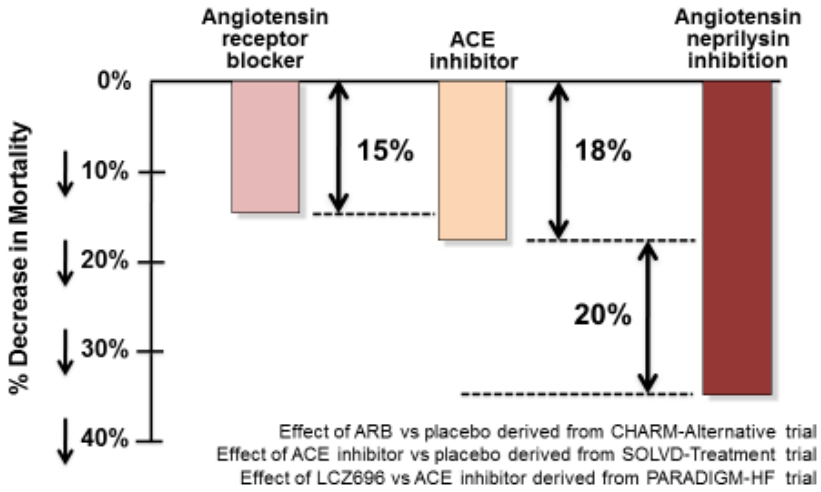
We now have a new class of drug, an Angiotensin Receptor Neprilysin inhibitor (ARNI) called sacubitril/valsartain which has been approved by the FDA for the treatment of chronic heart failure/heart failure with reduced ejection fraction. This drug should become available in Australia in the next 12 months.

A Neprilysin inhibitor prevents the breakdown of vasoactive peptides such as BNP, substance P and bradykinin. By enhancing the levels of these vasoactive peptides, it is hypothesised that neurohormonal activation is reduced which results in less cardiac fibrosis/positive remodelling.



PARADIGM-HF was a large, 8440-patient trial, comparing two treatments: the ACE inhibitor enalapril, 10 mg twice a day, and this new agent. The primary end point was cardiovascular death or heart-failure hospitalization. The trial was stopped early on the recommendation of the data safety and monitoring board [DSMB] after a meeting at 27 months because there was a highly statistically significant 20% reduction in the primary end point in the two components of that composite, so in both cardiovascular death and heart-failure hospitalization. Even overall mortality was reduced by 16%. The inclusion criteria was patients with NYHA II-IV heart failure with an EF <35%.

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Please note that the dose of valsartain 103mg bd used in the trial is equivalent to the dose of 160mg bd in our current formulation. It cannot be combined with an ACEi due to the development of angioedema. Both the neprilysin inhibitor and an ACEi inhibit the breakdown of bradykinin.

If you are going to monitor response of the patient by means of a BNP level, this drug will result in a higher BNP levels but a lower pro-BNP levels. The BNP levels go up as a direct result of the drug but the pro-BNP levels go down as a result of reduced wall stress. Patients may also need less diuretics due to the higher BNP levels (increases diuresis) and as a result of the improved LVEF.

It is a very well tolerated drug with less cough, hyperkaelamia or renal impairment. There is slightly more hypotension seen in the ARNI group but no significant increase in discontinuations.

The following table summarises the Paradigm HF trial which is no doubt a paradigm shift in the management of patients with HFREF (Heart failure with Reduced Ejection Fraction).

PARADIGM-HF: Summary of Findings

In heart failure with reduced ejection fraction, when compared with recommended doses of enalapril:

LCZ696 was *more effective* than enalapril in . . .

- Reducing the risk of CV death and HF hospitalization
- Reducing the risk of CV death by *incremental* 20%
- Reducing the risk of HF hospitalization by *incremental* 21%
- Reducing all-cause mortality by *incremental* 16%
- *Incrementally* improving symptoms and physical limitations

LCZ696 was *better tolerated* than enalapril . . .

- Less likely to cause cough, hyperkalemia or renal impairment
- Less likely to be discontinued due to an adverse event
- More hypotension, but no increase in discontinuations
- Not more likely to cause serious angioedema

Ed.

Dr Edmund Lee
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