



We are all aware of the role of ACE inhibitors and Angiotensin-II blockers in managing chronic heart failure and how B-blockers went from HF bad boy to recommended therapy, led largely by Carvedilol.

Spironolactone has become an established part of therapy following the publication of the [RAL ES trial](#)

waaaay back in 1999, with mortality and morbidity benefits and decreased frequency of hospital admission for acute exacerbations of chronic heart failure. Other aldosterone receptor blocking agents have been added to the mix, with agents like Eplerenone (

[EMPHASIS-HF](#)

, NEJM 2011 - a trial that was stopped early when a pre-planned threshold had been crossed. Watch out!) looking similarly promising, though you need to be aware of the inclusion and exclusion criteria.

So what's new in heart failure management?

There is a brief [update on acute heart failure pharmacotherapy](#) on Medscape here (You may need to log in, but registration is free)

A novel agent, called relaxin-2 (drug name = Serelaxin), has recently been examined with the publication this month in The Lancet of the [RELAX-AHF trial](#) . The trial was industry-sponsored, multi-centre, international, double blind and placebo controlled with n=1161 and intention-to-treat analysis. The countries that contributed were based in East and West Europe, the USA, Argentina and Israel. Both the relaxin and placebo were administered as infusions

over 48 hours, starting within 16 hours of presentation (Mean = 7hours, which is fairly impressive). The average patient age was 72 years, 55% of the trial population had an LVEF < 40% and all classes of heart failure were represented, though NYHA II and III accounted for 70 - 80%.

Relaxin-2 is a hormone expressed during pregnancy that, amongst a number of effects, contributes to vasodilation and enhanced renal function; both desirable effects in acute exacerbations of heart failure.

The results of RELAX-AHF are interesting. There were two measures of the primary outcome (dyspnoea), one of which showed an improvement with therapy, while the other showed no difference. Whether this difference is due to the treatment or the measurement tool would take someone smarter than me to explain. So as a primary outcome, there doesn't appear to be much to hang on to. Therefore the author go to the secondary outcomes next ... so beware! These are secondary outcomes and should really only be used to direct future trials, not change practice yet.

There was no difference in cardiovascular outcomes, mortality or hospitalisation at 60 days between serelaxin and placebo, despite an improvement in symptoms, signs and biomarkers of heart failure. However, by 6 months, there was a 37% reduction in risk of all-cause mortality and an identical reduction in risk of cardiovascular mortality with serelaxin. The absolute reduction in cardiovascular deaths at 6 months was 3.5%, yielding an NNT of 29 to prevent one cardiovascular death by six months. To my mind this delay to an detectable outcome is plausible given the mechanism of action of hormones. Oddly, though 6 month mortality appeared to have been reduced, the frequency of hospitalisation was unaffected, causing some concern about how to interpret the results overall.

Of interest, they included analysis of patients admitted to the ICU in the study and report a reduced ICU/CCU stay of a third of a day; not a huge or practical reduction, but a signal nonetheless. However, the paper does not tell us anything about this group of patients, including the size of this cohort. We only know that exclusion criteria included patients who had already been started on some other form of acute failure therapy (presumably inotropes), or a mechanical assist device (e.g. IABP) more than 2 hours before starting serelaxin and that the mean systolic BP at entry to the trial was 142mmHG in both the study and placebo groups.

There is a useful discussion with the lead author of this trial at an American Heart Association

meeting on YouTube [here](#) .

It may not be a game changer yet, but it may contribute to a pattern of therapy. Watch out for further studies of this drug.

Articles and links

- Teerlink JR, Cotter G, Davison BA, et al. [Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure \(RELAX-AHF\)](#) : A randomised, placebo-controlled trial. The Lancet, Volume 381, Issue 9860, Pages 29 - 39, 5 January 2013.
- [The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure](#) . Bertram Pitt, M.D., Faiez Zannad, M.D., Willem J. Remme, M.D., Robert Cody, M.D., Alain Castaigne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D. for the Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709-717 (Full text)
- [Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms](#) . Faiez Zannad, M.D., Ph.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J. Pocock, Ph.D., and Bertram Pitt, M.D. for the EMPHASIS-HF Study Group. N Engl J Med 2011; 364:11-21. (Full text)
- Medscape [presentation on heart failure pharmacotherapy](#) with Dr. Ileana Piña (Montefiore Einstein Medical Center in the Bronx, New York)

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