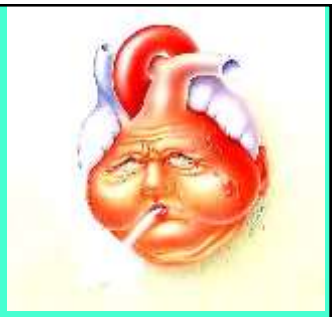

Nebrilysin pathway in heart failure

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- Chronic heart failure (HF) is a complex and progressive clinical syndrome resulting from any abnormality of cardiac structure or function.
- HF prevalence and the number of HF-related hospitalizations are increasing, and the prognosis remains poor, with a 5-year mortality worse than many cancers.

- There has been significant progress in HF therapy, but mostly in HF with reduced ejection fraction (HFrEF), while for patients with preserved ejection fraction (HFpEF), no therapy has improved clinical outcomes. Despite such advances, however, morbidity and mortality of HFrEF still remains high.

The Role of the Renin-Angiotensin-Aldosterone System and sympathetic system in Heart Failure

- Neurohumoral activation, in particular, of the renin-angiotensinaldosterone system (RAAS) and the sympathetic nervous system, plays a major role in the development and progression of HF.
- The RAAS is an essential component in the regulation of cardiovascular homeostasis that exerts its actions through the hormones angiotensin II and aldosterone. The RAAS regulates vascular tone and blood pressure

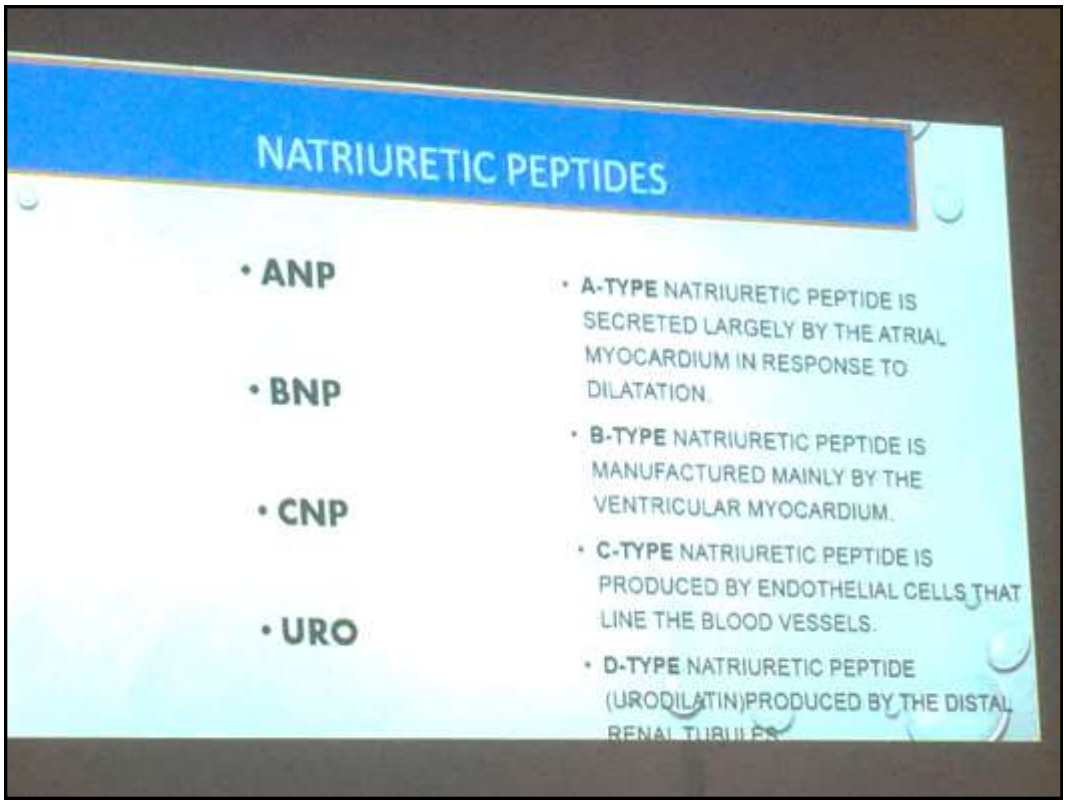
- Abnormalities in cardiac function in HF activate the RAAS and sympathetic nervous system in order to maintain perfusion of vital organs.
- However, prolonged activation of these systems increases systemic vascular resistance and causes sodium and water retention, myocardial hypertrophy, fibrosis and apoptosis, which accelerates the progression of HF and promotes end-organ damage.
- The blockade of beta-adrenergic receptors leads to symptomatic improvement and reduced morbidity and mortality in patients with HFrEF.

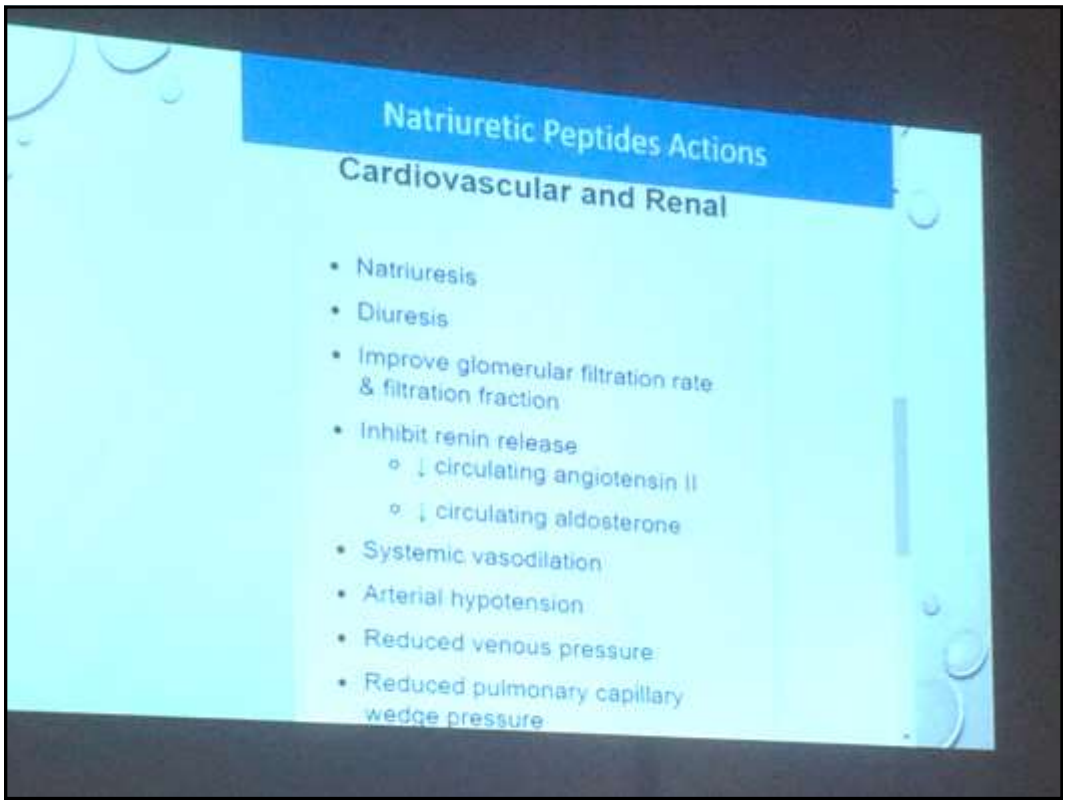
The natriuretic peptide system

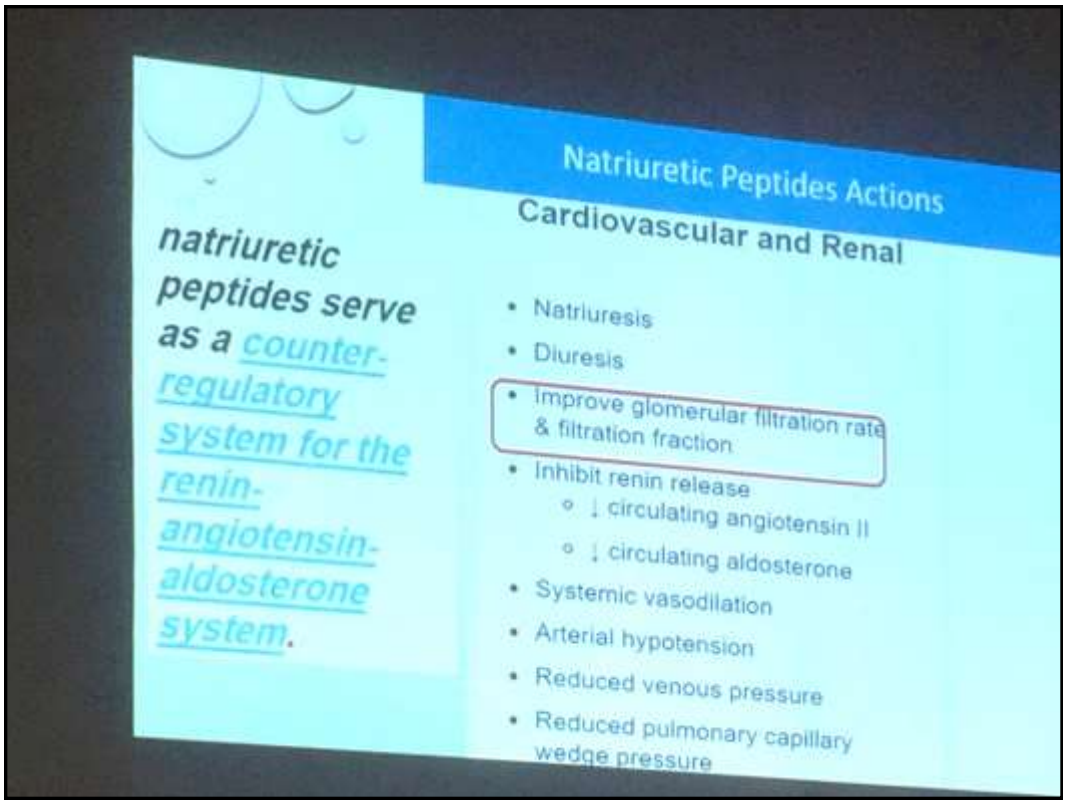
- The natriuretic peptide system counter regulates the detrimental effects of the up regulation of RAAS that occurs in HFrEF.
- Sodium and water retention and vasoconstriction caused by activation of RAAS and the sympathetic nervous system, and the action of vasopressin, lead to increased ventricular preload and afterload and elevated wall stress which in turn lead to production of pre-pro B-type natriuretic peptide (BNP) which is cleaved to BNP and N-terminal proBNP (NT-proBNP).

- The peptide BNP acts to promote natriuresis and vasodilation (NT-proBNP is physiologically inactive).
- Atrial stretch leads to the production of pre-proatrial or A-type natriuretic peptide and ultimately atrial natriuretic peptide (ANP) which has similar biological properties to BNP.
- Urodilatin is derived from the same precursor in the kidneys.
- C-type natriuretic peptide (CNP) is released from endothelial cells and acts in a paracrine fashion but is only found in low concentrations in circulating blood.


NEW THERAPEUTIC TARGET
NATRIURETIC PEPTIDE SYSTEM


NATRIURETIC PEPTIDES
• ANP
• BNP
• CNP
• URO
• A-TYPE NATRIURETIC PEPTIDE IS SECRETED LARGELY BY THE ATRIAL MYOCARDIUM IN RESPONSE TO DILATATION.
• B-TYPE NATRIURETIC PEPTIDE IS MANUFACTURED MAINLY BY THE VENTRICULAR MYOCARDIUM.
• C-TYPE NATRIURETIC PEPTIDE IS PRODUCED BY ENDOTHELIAL CELLS THAT LINE THE BLOOD VESSELS.
• D-TYPE NATRIURETIC PEPTIDE (URODILATIN)PRODUCED BY THE DISTAL


Natriuretic Peptides Actions
Cardiovascular and Renal
• Natriuresis
• Diuresis
• Improve glomerular filtration rate & filtration fraction
• Inhibit renin release
◦ ↓ circulating angiotensin II
◦ ↓ circulating aldosterone
• Systemic vasodilation
• Arterial hypotension
• Reduced venous pressure
• Reduced pulmonary capillary wedge pressure


natriuretic peptides serve as a counter-regulatory system for the renin-angiotensin-aldosterone system.
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Cardiovascular and Renal
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- ANP, BNP, CNP and urodilatin are cleaved and inactivated by a membrane bound endopeptidase, neprilysin.
- Neprilysin is found in a number of tissues but in especially high concentrations in the kidney.

- Two strategies have been employed to try and improve outcomes in HFrEF via modulation of this pathway:
- The 1st is the administration of exogenous natriuretic peptides e.g.; Nesiritide which initially showed promising beneficial effects on hemodynamics' and natriuresis in patients with HFrEF. However, in a large-scale randomized controlled trial, Nesiritide failed to improve outcomes.
- The 2nd strategy is to inhibit the breakdown of natriuretic peptides by using Neprilysin inhibitors.

Neprilysin inhibitors

(1) Initial Neprilysin inhibitors:

- Initial attempts at inhibiting neprilysin using an oral (racecodotril) and intravenous (candoxatrilat) formulation were successful in promoting natriuresis and increasing urinary excretion of ANP.
- However, a study of chronic use of the oral candoxatril showed that the initial reduction in blood pressure was not sustained this might be explained by the finding that neprilysin also breaks down angiotensin II.

- Therefore inhibiting neprilysin alone, while raising natriuretic peptides levels, also increases angiotensin II levels with its harmful effect on the heart, potentially counteracting the actions of the former peptides.

(2) Dual neprilysin and ACE inhibition

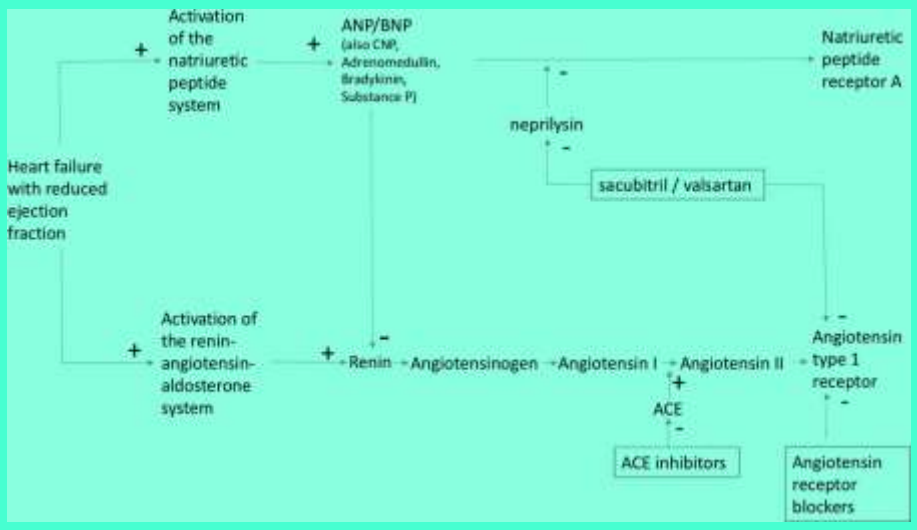
- The solution to the problem of lone neprilysin inhibition appeared to be dual blockade of RAAS and the natriuretic peptide system.
- As ACE inhibitors are known to improve outcomes it seemed logical to combine an ACE inhibitor with a neprilysin inhibitor.
- The combined ACE and neprilysin inhibitor omapatrilat was studied in a large randomized controlled trial against enalapril 10 mg twice daily in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial.

- The primary end point, death from any cause or HF hospitalizations were not reduced by omapatrilat.
- Although the excessive potentiation of bradykinin and resultant high rates of serious angioedema led to the discontinuation of the clinical development of this drug.

(3) Angiotensin receptor blocker neprilysin inhibitors

- Combining an angiotensin receptor blocker (ARB) and a neprilysin inhibitor was the logical next step and potential solution to the problem encountered with omapatrilat.
- The angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan (formerly known as LCZ696) was designed with the aim of inhibiting neprilysin while blocking the adverse effects of RAAS and reducing bradykinin potentiation.

Pathways blocked by ACE inhibitors, angiotensin receptor blockers and neprilysin inhibitors.



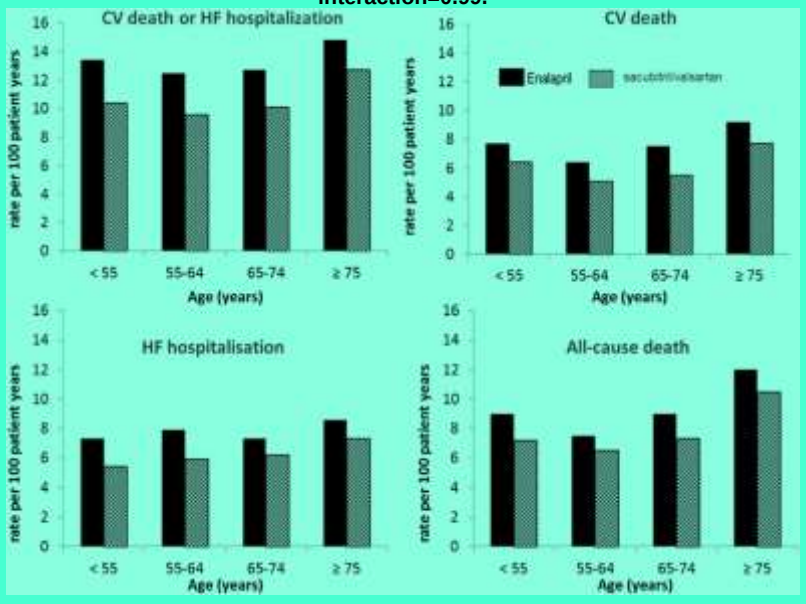
Pardeep S Jhund, and John J V McMurray Heart 2016;102:1342-1347

Heart

PARADIGM-HF

- The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) was conducted to test whether twice daily dose of sacubitril/valsartan was superior to enalapril 10 mg twice daily in reducing the primary end point of CV death or HF hospitalization.
- The trial was terminated early, due to a sustained and highly significant reduction in the risk of the primary composite end point and in CV mortality in the sacubitril/valsartan group compared with the enalapril group.

Effect of sacubitril/valsartan on the rate of primary end point and component and all-cause mortality in patients randomised in the PARADIGM-HF trial according to age group.27 p for interaction for cardiovascular (CV) death or heart failure (HF) hospitalisation=0.94, for CV death p for interaction=0.92, for HF hospitalisation p for interaction=0.81 and all-cause death p for interaction=0.99.



Thank you