Disclosures

Speaker's bureau:	**Bayer, Merck Serono, Novartis, Amgen Servier International,**
Research grant:	**Boehringer Ingelheim, Novartis, Irbetch, Servier International**
Advisory Board:	**Boehringer Ingelheim, Novartis, Amgen, Abbott, Servier International**

BB e ARNI nello scompenso cardiac: perchè?

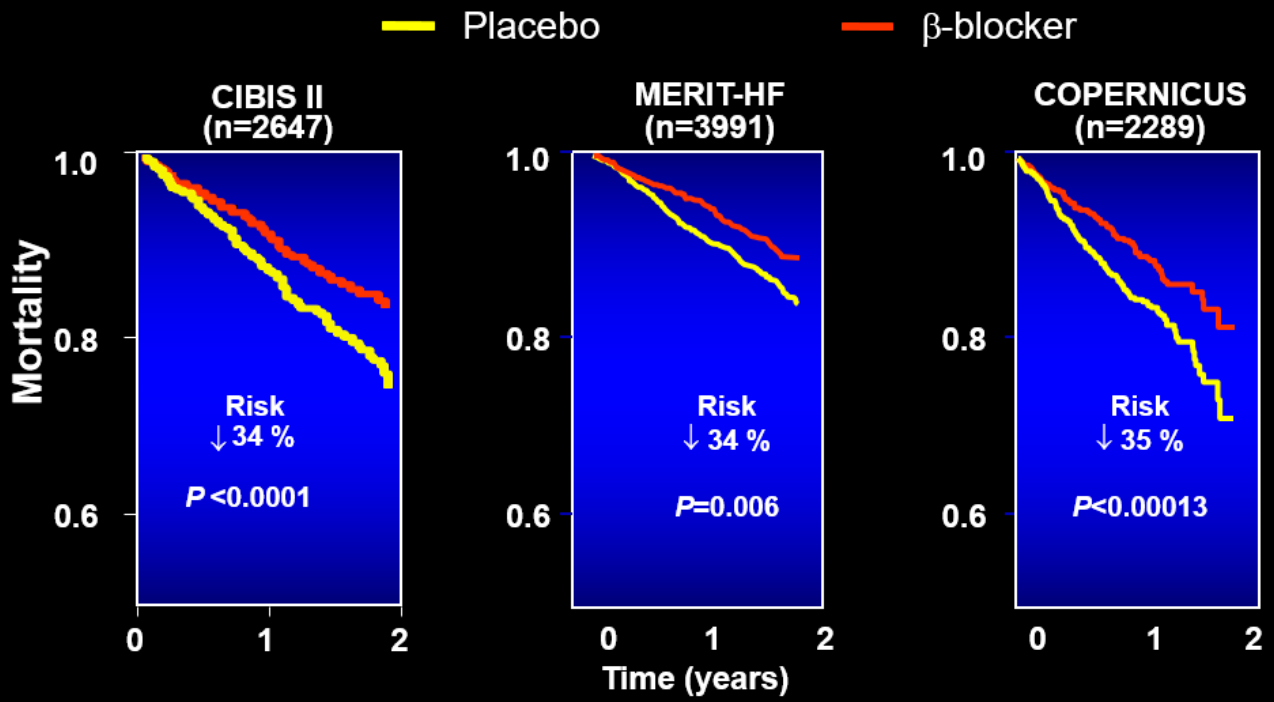
Prof. Roberto Ferrari

Indications for beta-blockers in HF

- Potentially **all patients** with stable mild or moderate systolic HF (*EF ≤ 40%*);
- First-line treatment, along with an ACE inhibitor and an MRA, in patients with **stabilized** HF
- Patients with **severe** HF also benefit from beta-blockers but treatment should be started under the care of a specialist
- Start **as early as possible** in the course of disease

ESC Guidelines

Effects of beta-blockers on mortality in CHF



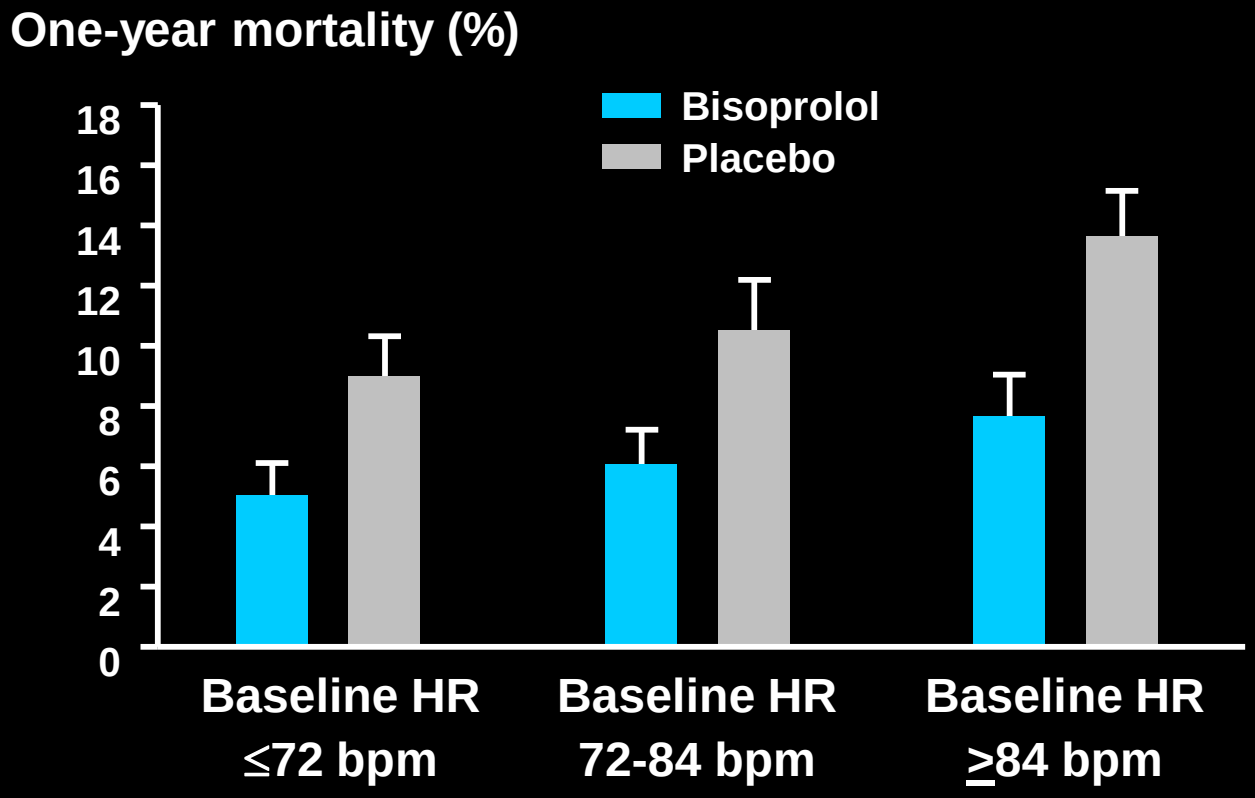
All cause mortality	34	34	35
Sudden Death	44	41	44
HF Hospitalizations	32	35	33

CIBIS = Cardiac Insufficiency Bisoprolol Study; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival Trial.

Reasons for beta-blocker therapy in HF with reduced EF

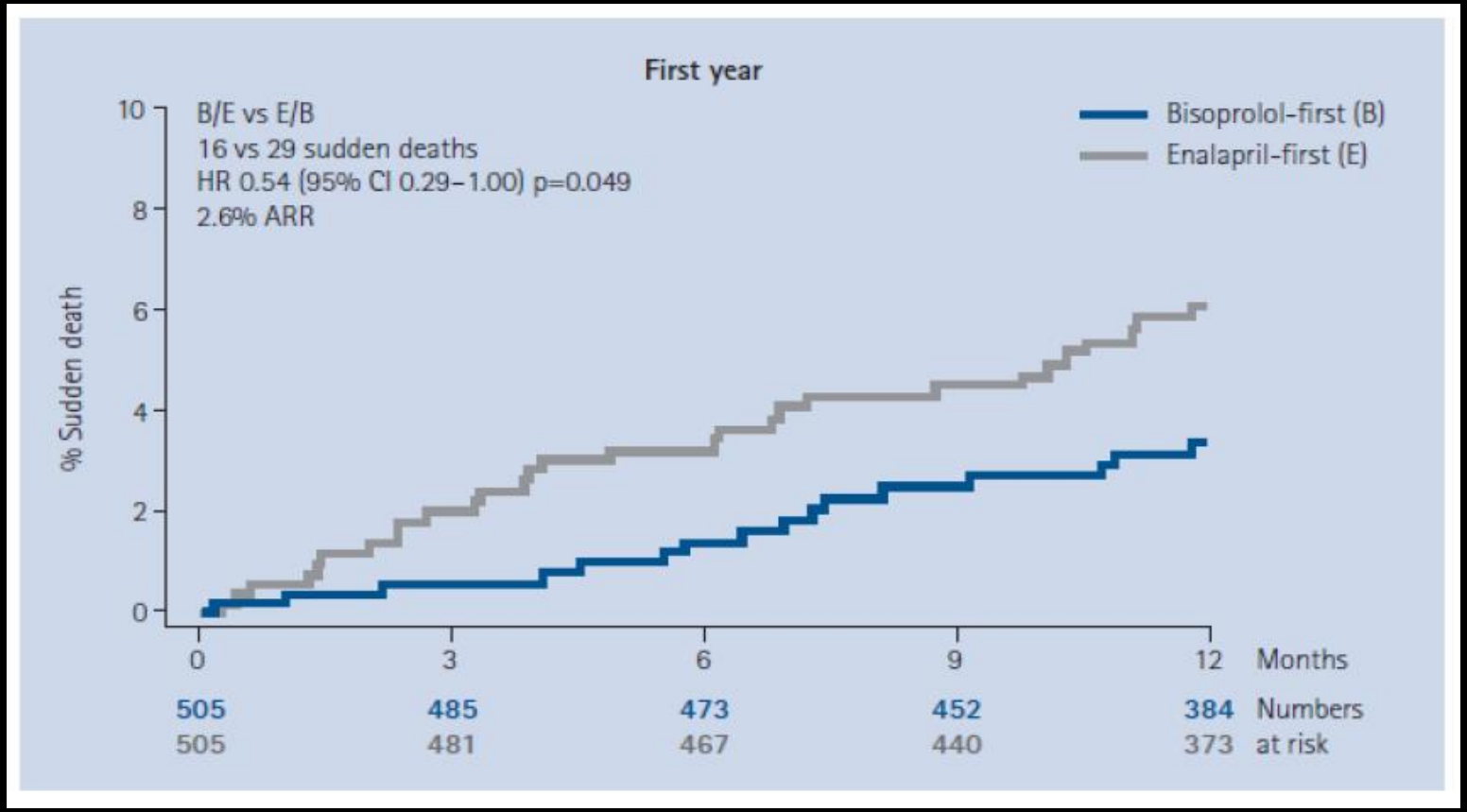
- Reduction of heart rate
- Reduction of sudden death
- Reduction of the negative effects of increased catecholamine levels on the myocardium
- Reduction of remodelling
- Improvement of contraction (*EF*)

HR reduction and outcome in CIBIS II

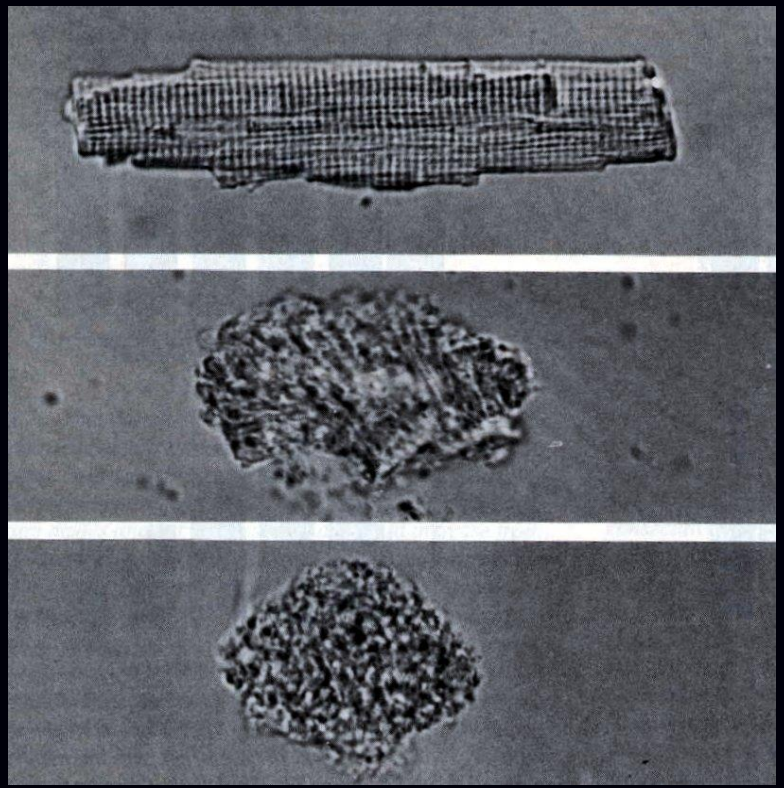


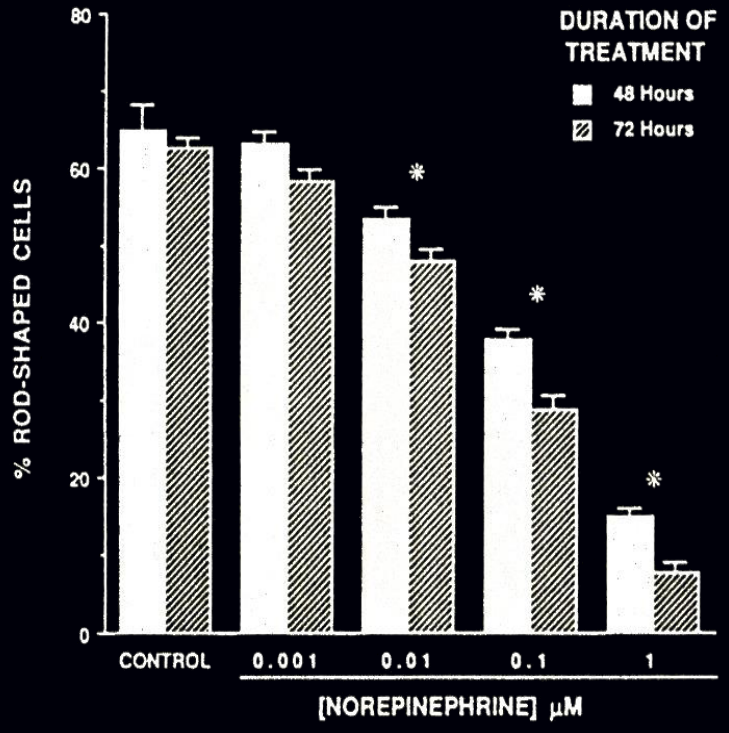
HR ≥72 bpm is associated with more CV events

Sudden cardiac death in CIBIS III



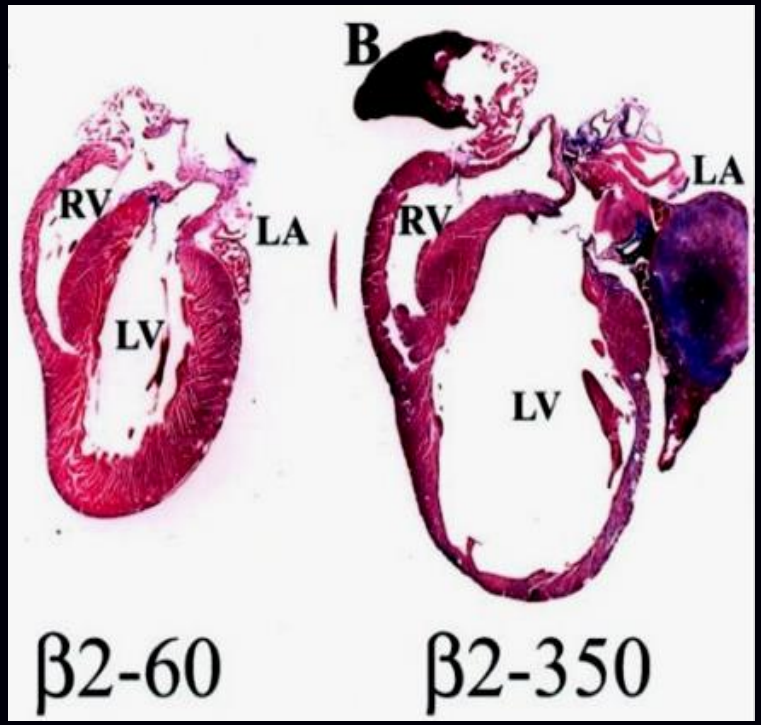
Adrenergic effects on viability of adult mammalian cardiocyte

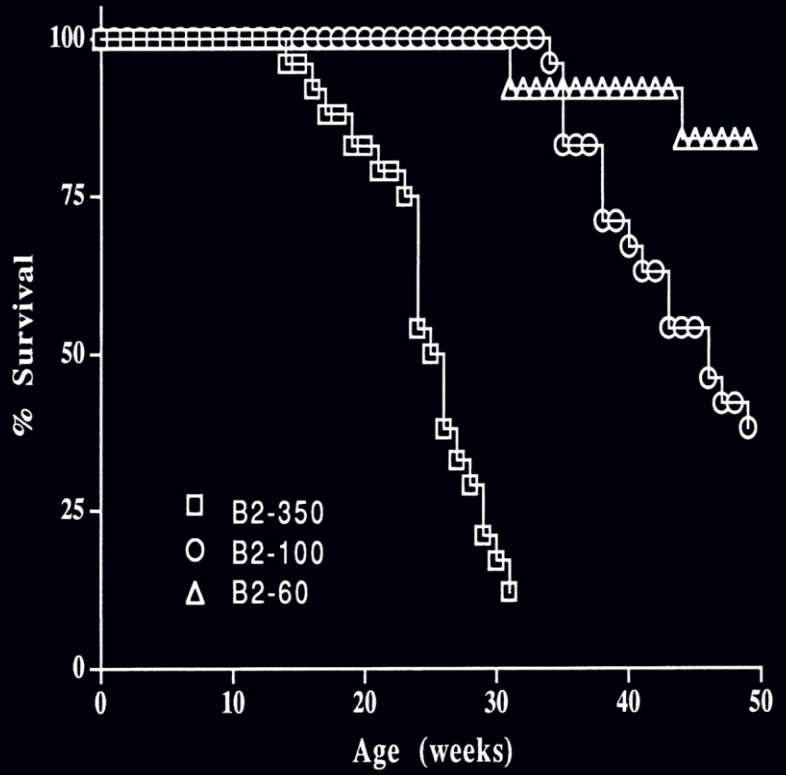




Mann et al, Circ 1992

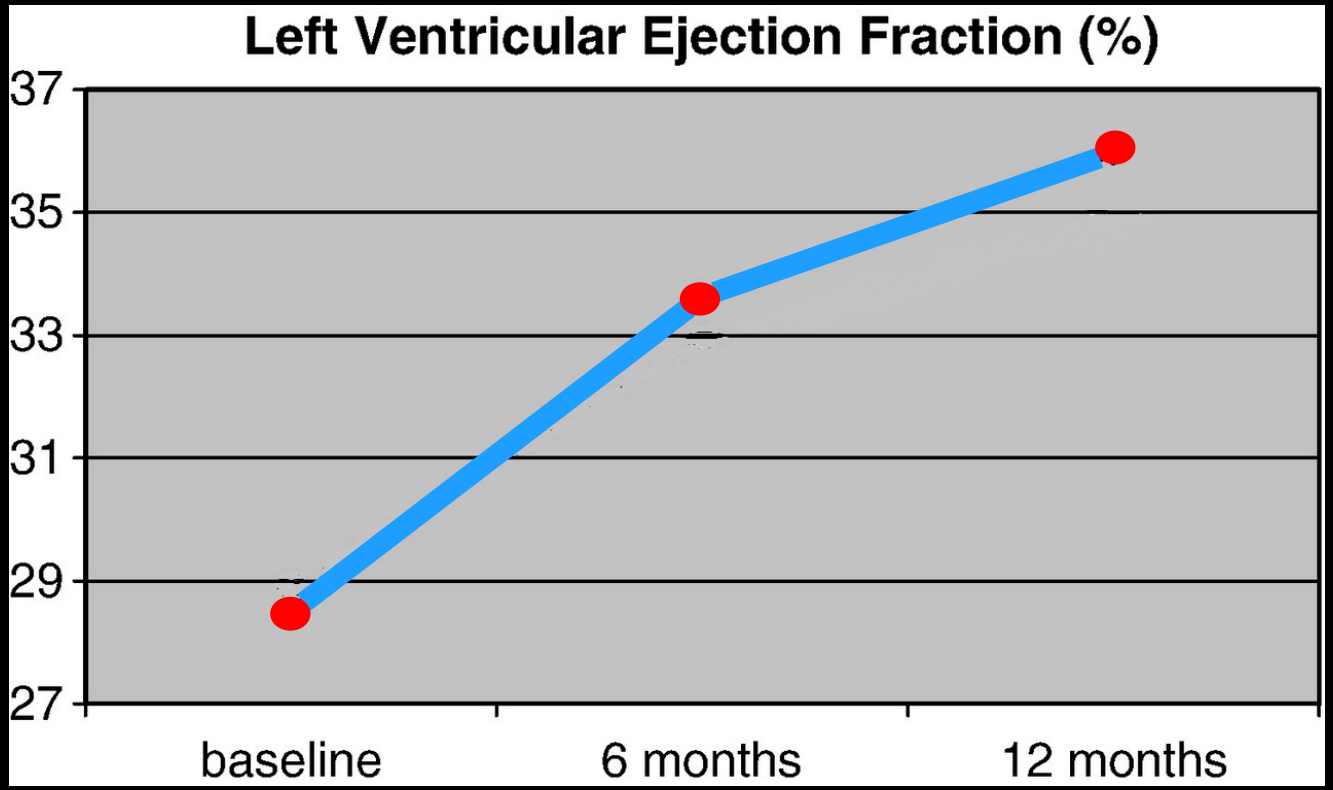
ß2-Adrenergic receptor over-expression





Ligget et al. Circ 2000

ECHO- substudy of CIBIS II shows that bisoprolol increases contraction (%*EF*)

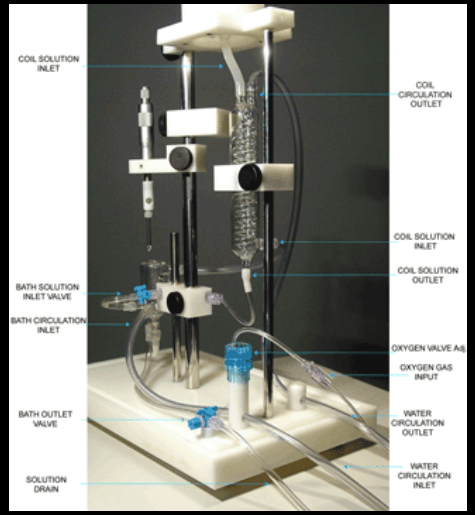


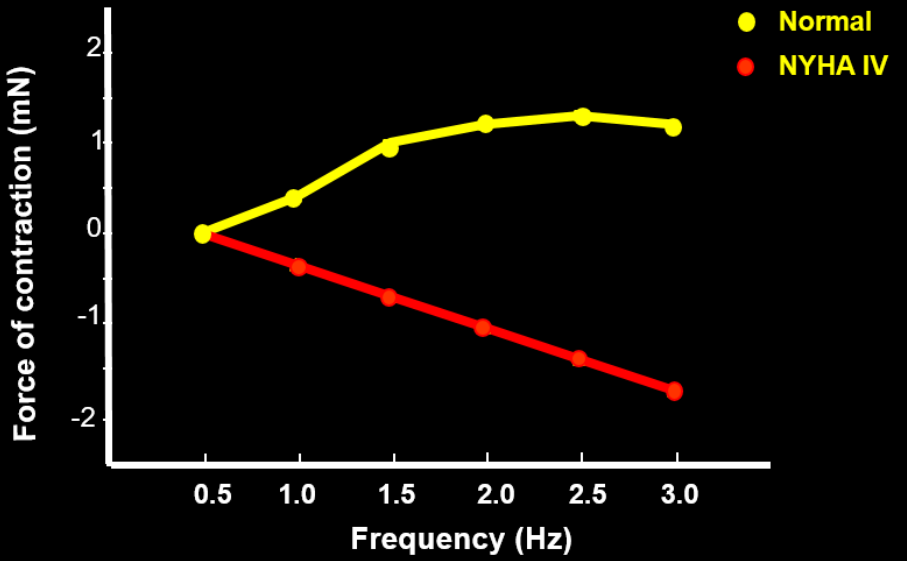
LLM Van de Ven et al, International Journal of Cardiology 2010

The paradox: BB are negative inotrope agents and yet in HF increase % EF:

- Why reducing HR with beta blockers causes a positive inotropic effect?
- Why do beta blockers reduce remodelling?

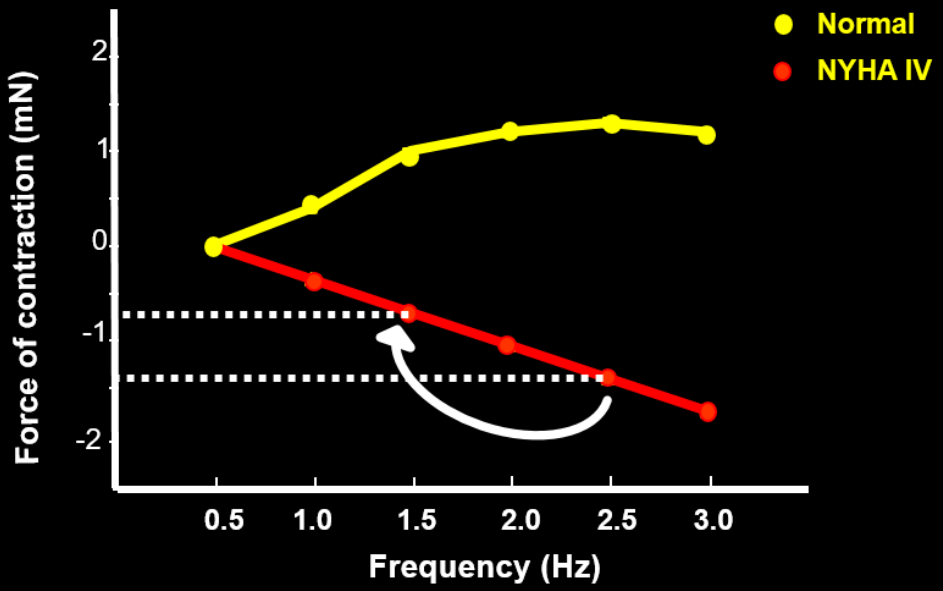
Human papillary strips from normal and HF patients have a different relationship between Frequency (*HR*) and Force (*%EF*)





Böhm M, et al. *Clin Invest.* 1992;70:421-5.

In HF, a reduction of HR (*frequency*) causes an increase of %EF (*force*)

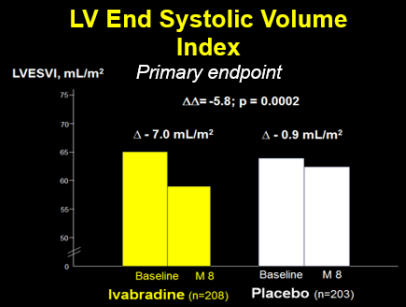


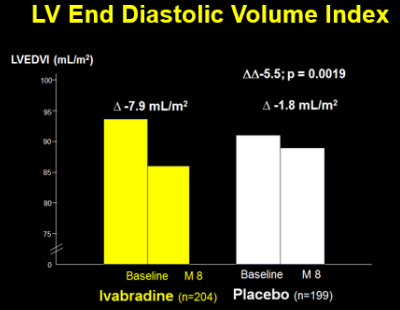
But… is this true in HF patients?

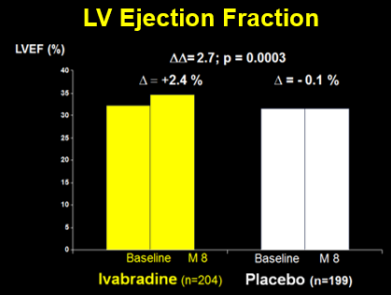
Böhm M, et al. *Clin Invest.* 1992;70:421-5.

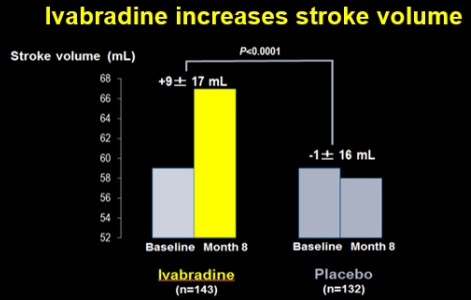
Yes, echo sub-studies (*SHIFT and BEAUTIFUL*) also confirm that HR reduction with ivabradine increase %EF and cardiac output

SHIFT





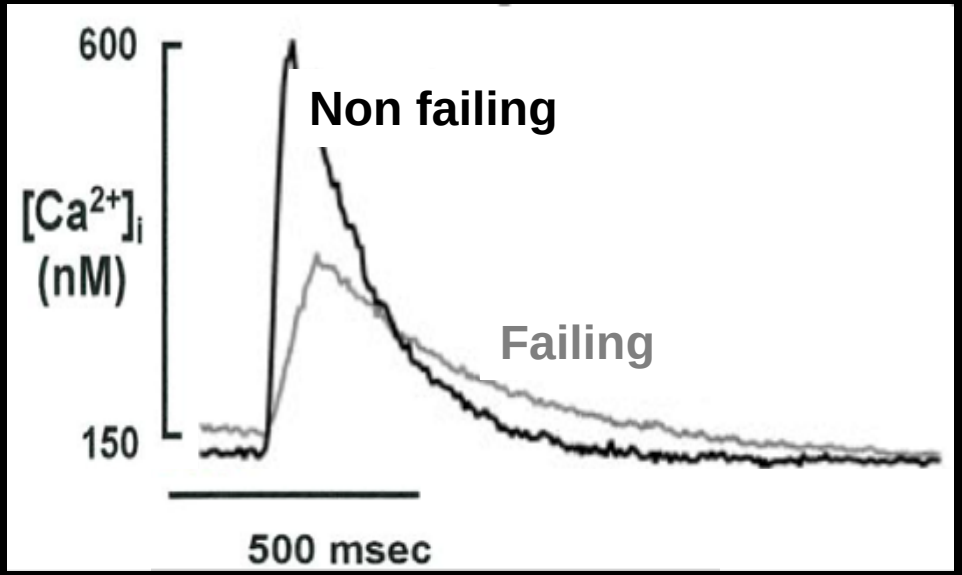


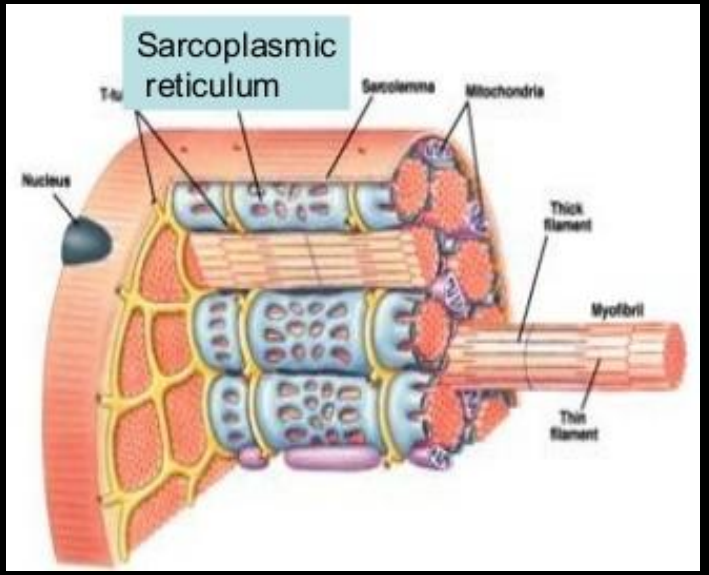


- BB and ivab in HF are the "*ideal inotropes*"
- Improve %EF without increasing O_2 need

Why?...

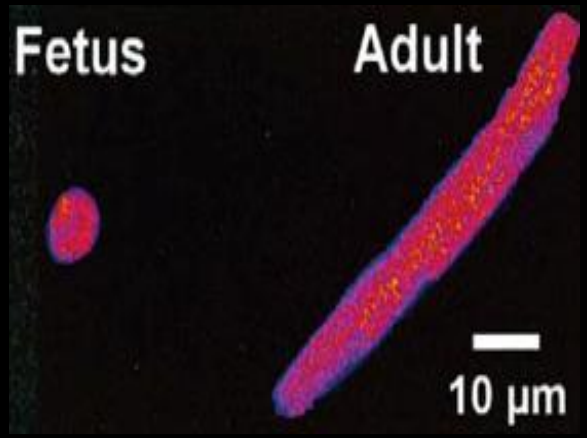
In HF, calcium movement from sarcoplasmic reticulum to myofilaments and vice versa is abnormal: Ca^{2+} peak is smaller and delayed

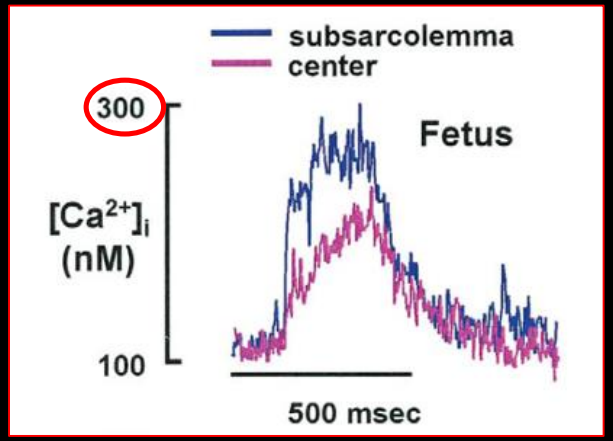


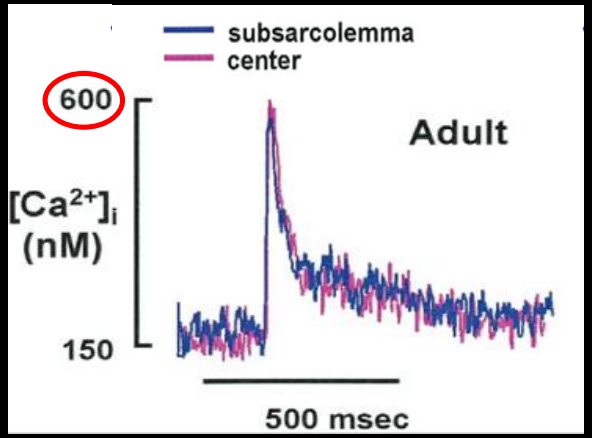


But…Why?

HF myocytes resemble the foetal ones where Ca^{2+} movements are slow and contraction is weak

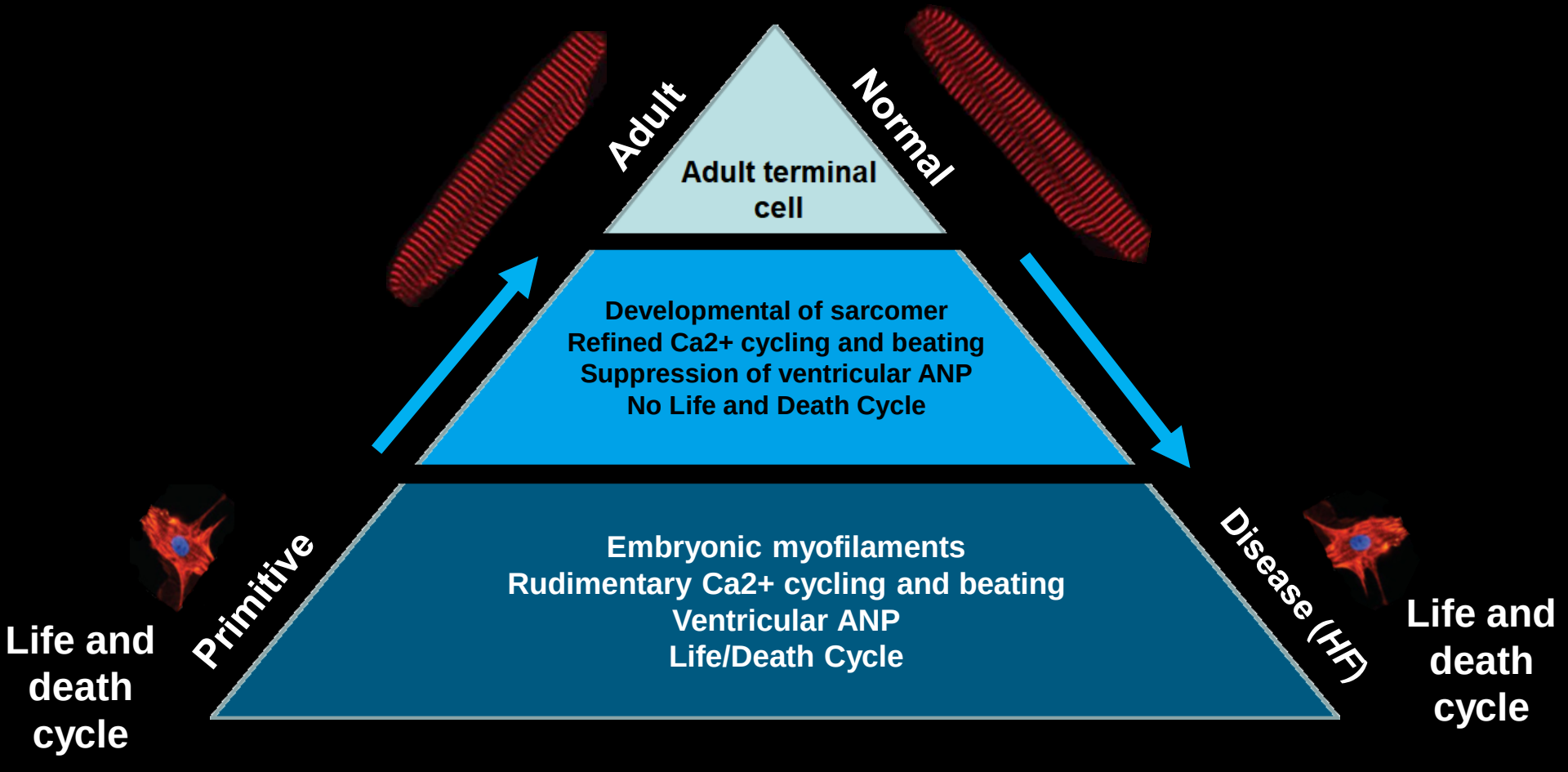




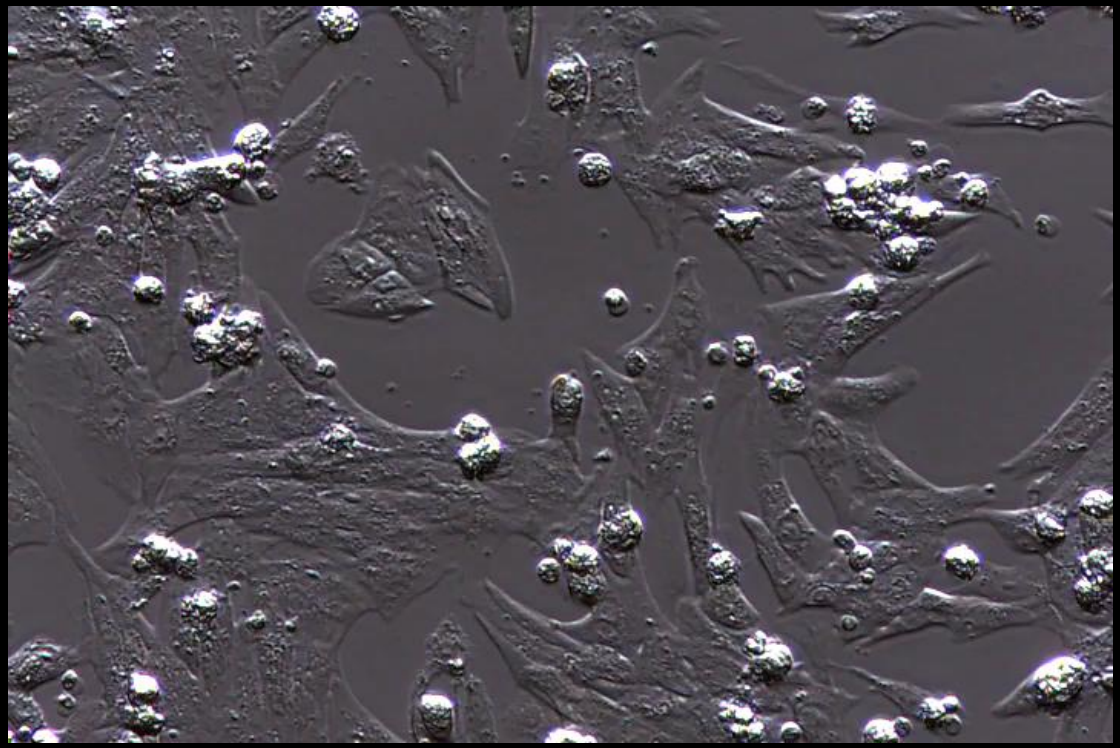


In HF, heart rate reduction allows more time for Ca^{2+} to reach myofilaments. It is a "*Ca^{2+} sensitizer*"!

But…why in HF are there embyonic myocytes?

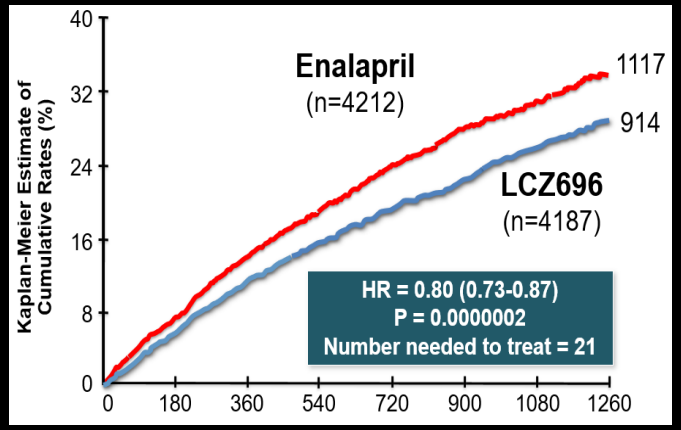


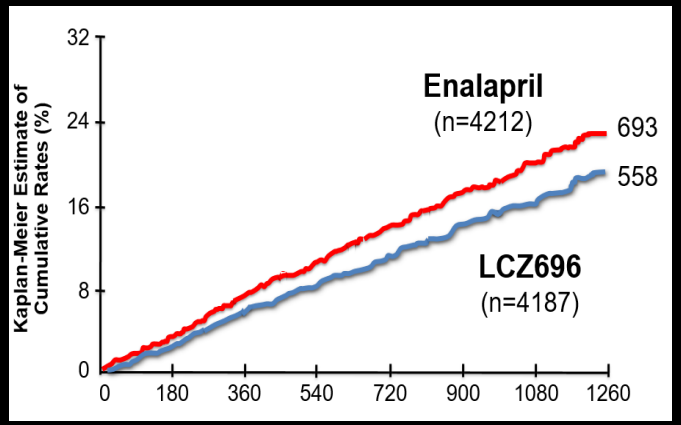
Isolated alive and dead myocytes from failing hearts



Difficult questions in HF treatment: why are ARNIs so successful in HFrEF?

PARADIGM - HF





Absolute benefits

- **Switching 1000 patients from an ACE inhibitor/ARB to LCZ696 avoided:**

31	cardiovascular deaths
28	patients hospitalized for HF
37	patients hospitalized for any reason
53	admissions for HF
111	admissions for any reason

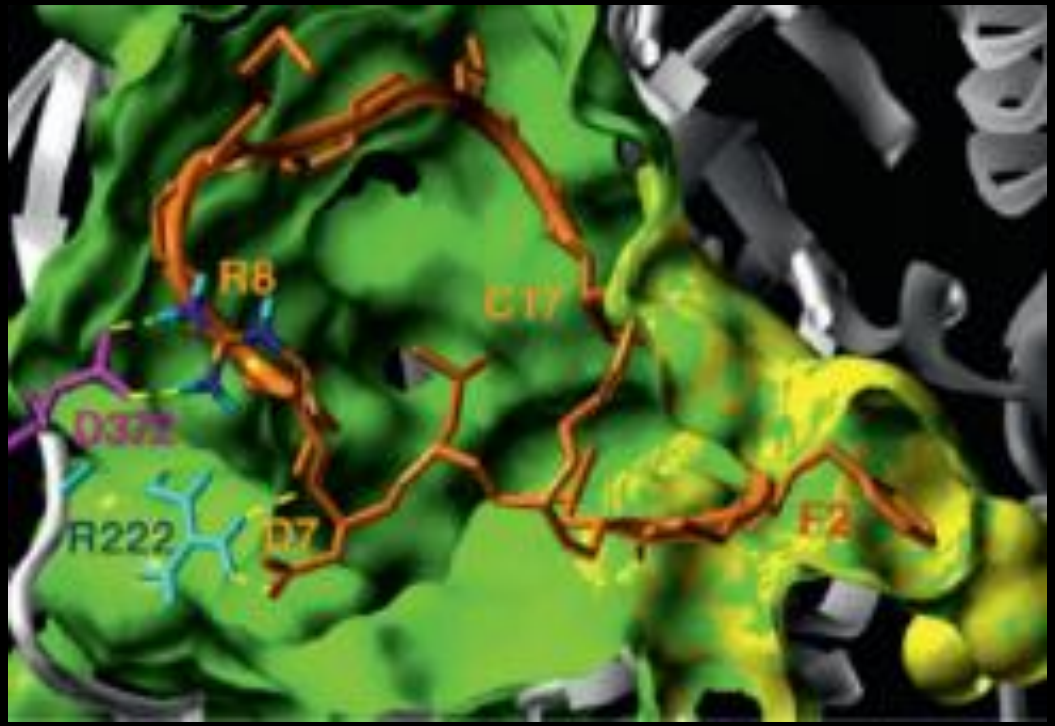
- **Considering NNT to prevent 1 death of 80, in USA ARNI therapy would prevent 28484 death/year**

Adapted from Packer M. et al., Circulation 2015

Sacubitril/valsartan and PARADIGM

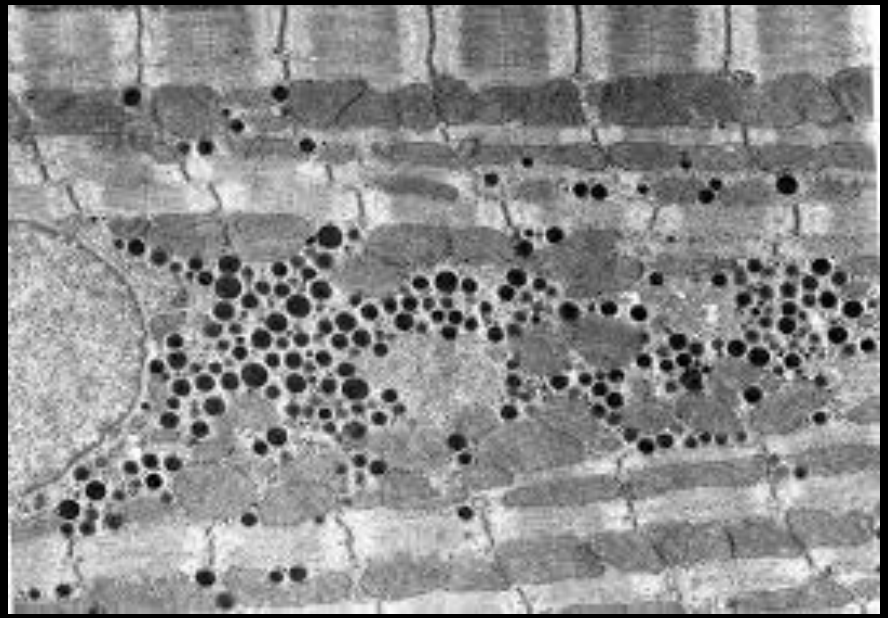
- What lies behind such good results?
- Is it just because sacubitril/valsartan exerts a particularly strong vasodilation? Or a strong diuresis?
- Or are there other reasons?

There is a new -*important*- target: neprylisin, which is inhibited by sacubitril

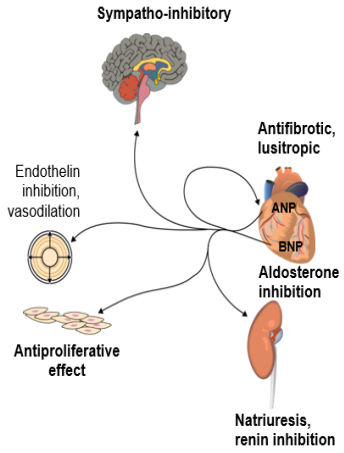


- Neprilysin (*NEP*) is an ubiquitous enzyme which metabolizes low molecular weight peptides, potentially useful in HF

Which peptide? Atrial Natriuretic Peptide



ANP protects the heart, vessels, and kidneys



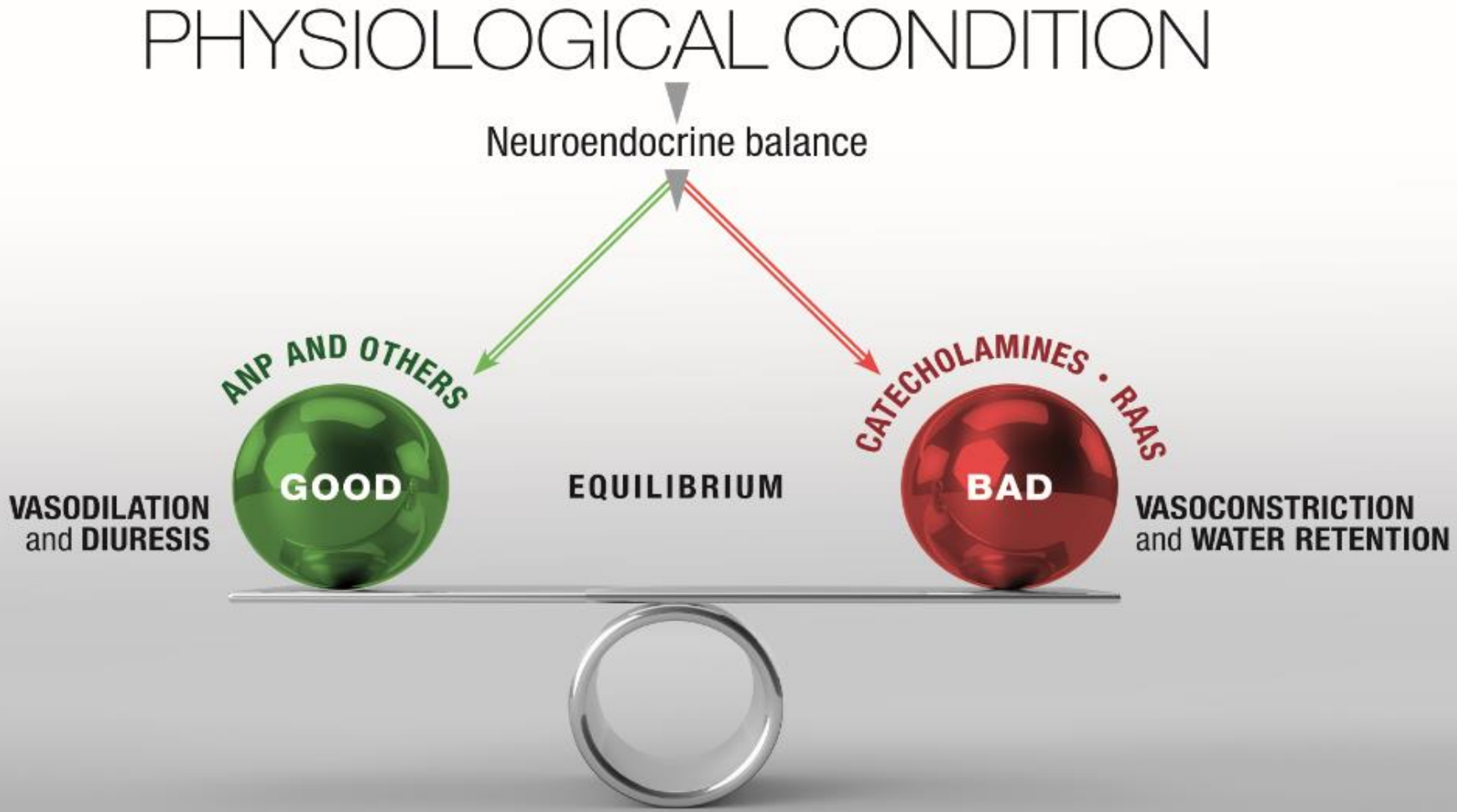
- NPs are released in response to cardiac wall stress and act in the brain, adrenal gland, kidney, vasculature and heart, leading to:
  - natriuresis and diuresis
  - vasodilation
  - inhibition of RAAS and sympathetic activity
  - attenuation of cardiac remodeling (LVH) and fibrosis
  - reverse vascular remodeling (arterial stiffness)
  - attenuation of renal fibrosis and improved renal hemodynamics
  - enhanced endothelial function
  - lipid mobilization

ANP=atrial natriuretic peptide; LVH=left ventricular hypertrophy
Boerrigter & Burnett. Expert Opin Invest Drugs 2004;3:643–52; Rubattu et al. Am J Hypertens 2008;21:733–41

In HF ventricles (*like in the foetus*) express granuli of ANP

The change of PARADIGM

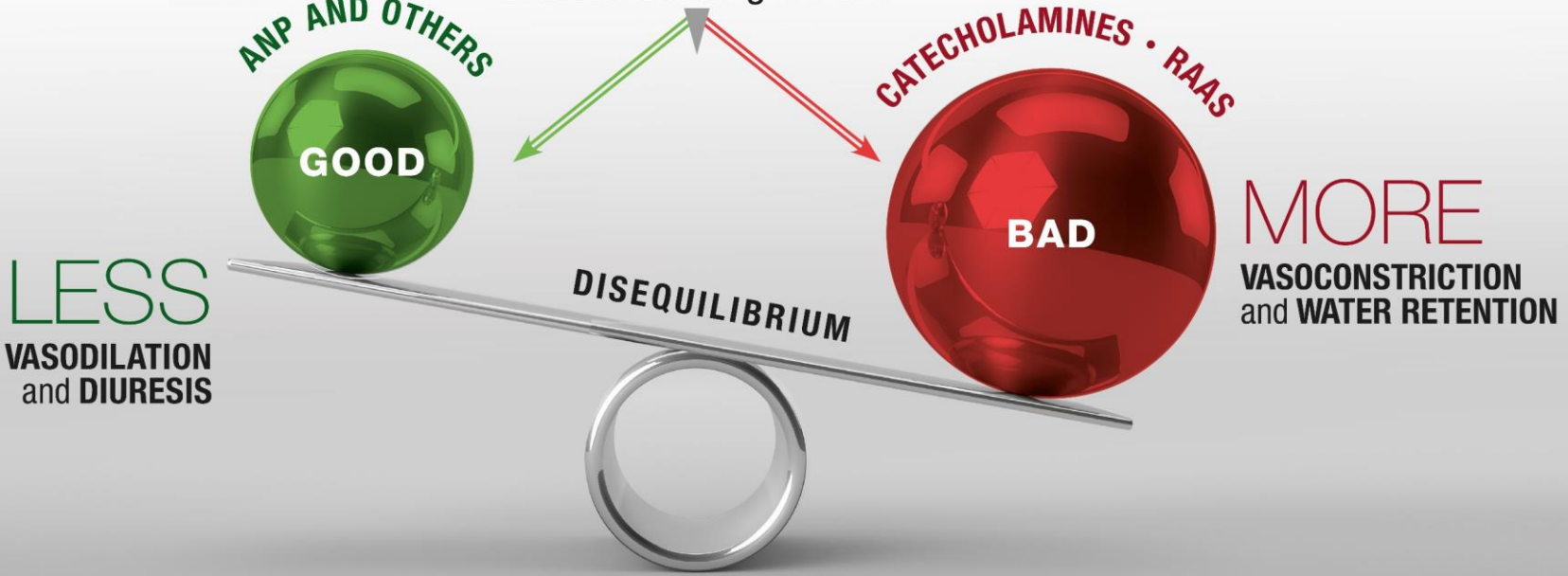
- **Sacubitril, by inhibiting neprylisin, reduces degradation and increases availability of ANP**
- **ARNI, instead of just blocking with valsartan the renin angiotensin activation, recruits the "*good and forgotten*" neuroendocrine response increasing ANP, thus improving the "*neuroendocrine balance*"**
- **This allows a '*physiological*' vasodilatation and increse of diuresis**
- **Previous attempts to use synthetic ANP as therapy for HF have always failed**

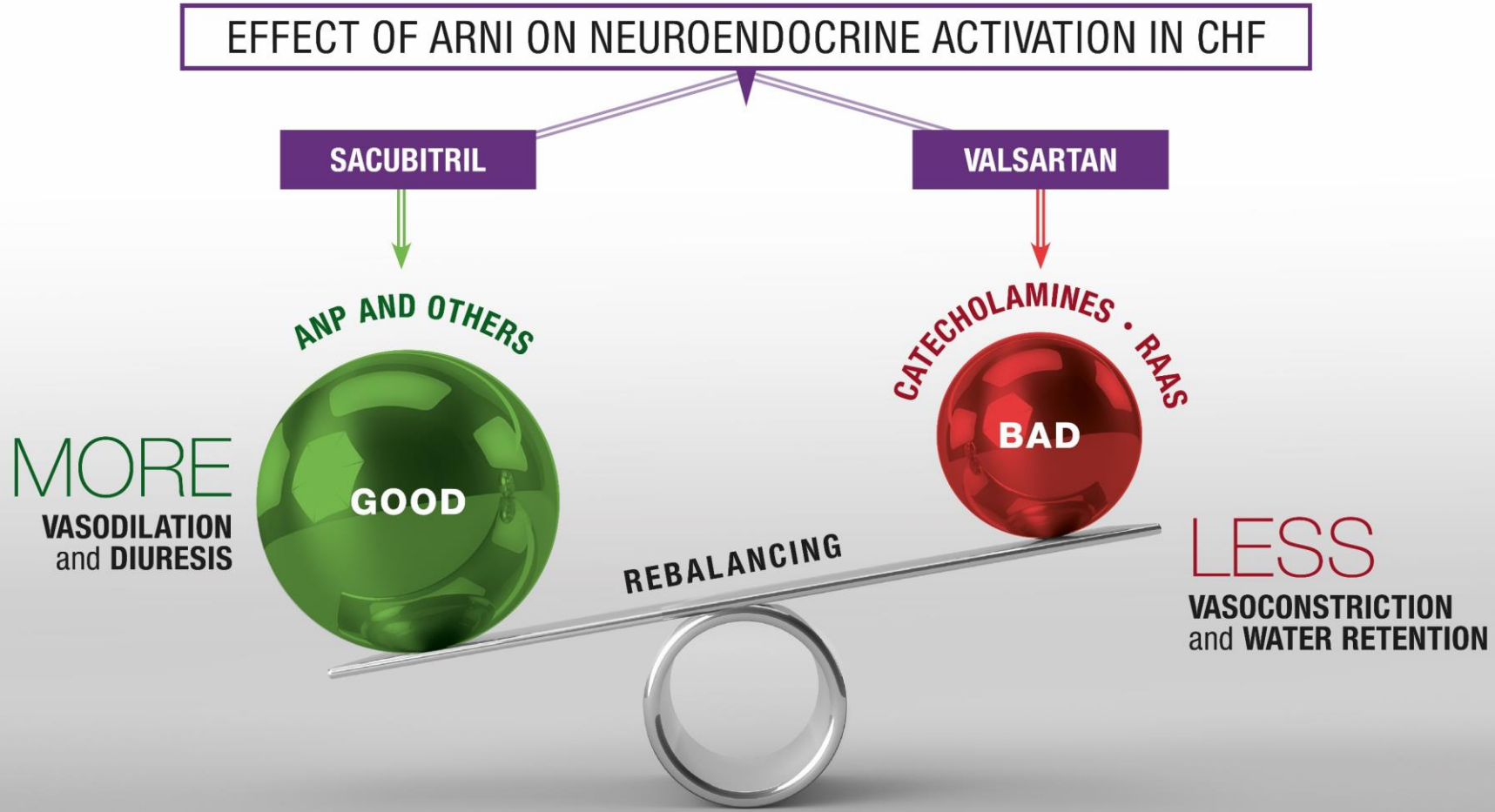

PHYSIOLOGICAL CONDITION
Neuroendocrine balance
ANP AND OTHERS
GOOD
VASODILATION
and DIURESIS
EQUILIBRIUM
CATECHOLAMINES • RAAS
BAD
VASOCONSTRICTION
and WATER RETENTION

CHRONIC HEART FAILURE (CHF)

Decreased cardiac output and blood pressure

The bad neuroendocrine activation overcomes the good one




EFFECT OF ARNI ON NEUROENDOCRINE ACTIVATION IN CHF
SACUBITRIL
VALSARTAN
ANP AND OTHERS
CATECHOLAMINES • RAAS
GOOD
BAD
MORE
VASODILATION
and DIURESIS
REBALANCING
LESS
VASOCONSTRICTION
and WATER RETENTION

FINAL RESULTS OF ARNI THERAPY

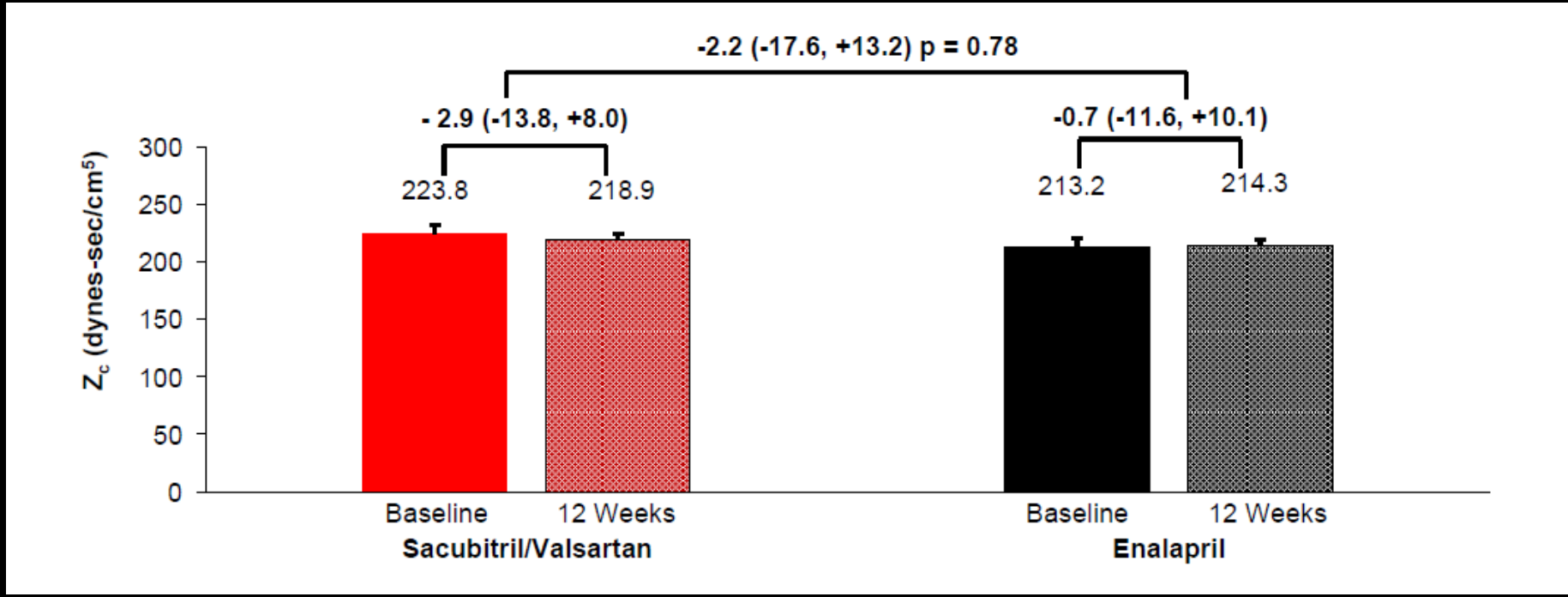
MORE PHYSIOLOGICAL DILATION AND DIURESIS

Which translates in less remodelling

EVALUATE-HF

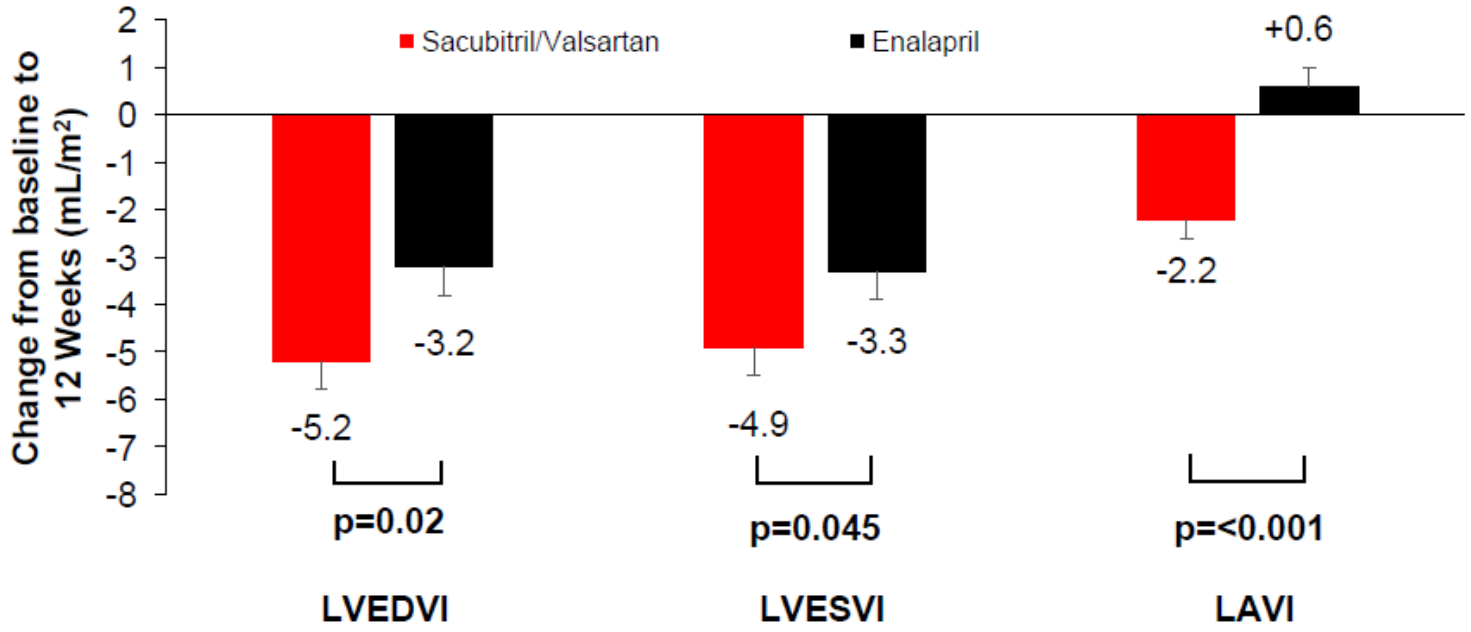
Primary endpoint: change in aortic impedance

Z_c from Baseline to week 12: no effect!



EVALUATE-HF

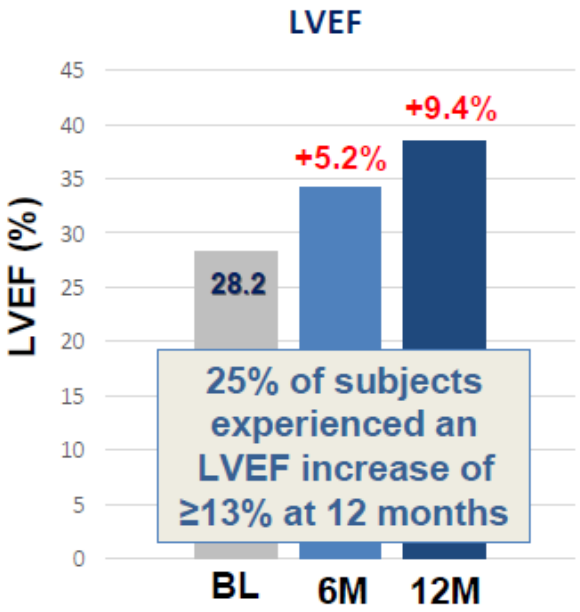
Secondary Endpoints: change in remodelling from baseline to 12 weeks, by Treatment

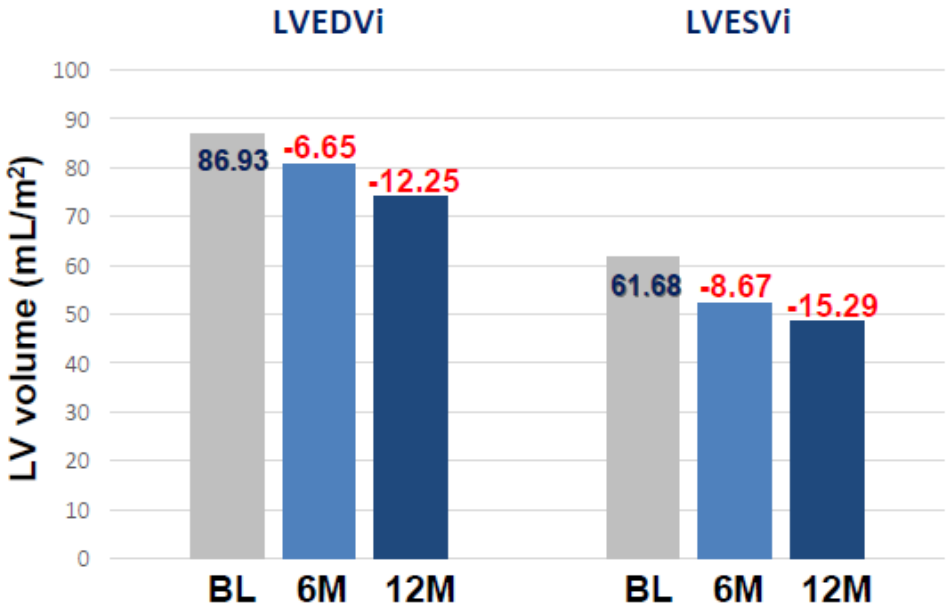


Reverse cardiac remodeling (1)

PROVE-HF

Baseline to 12 months: all P <.001



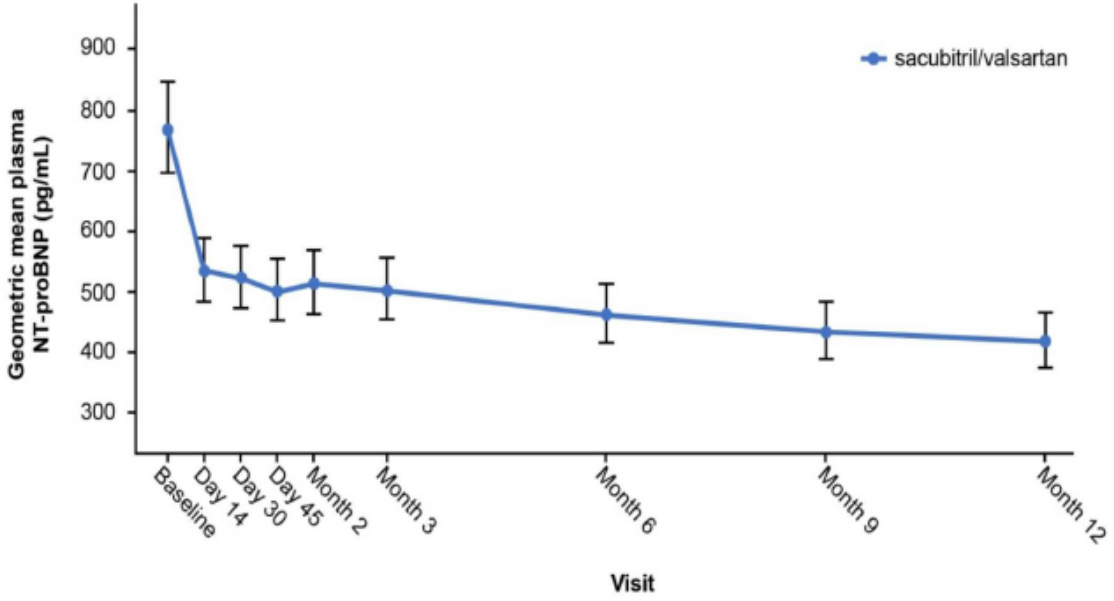


BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index

NT-proBNP concentrations

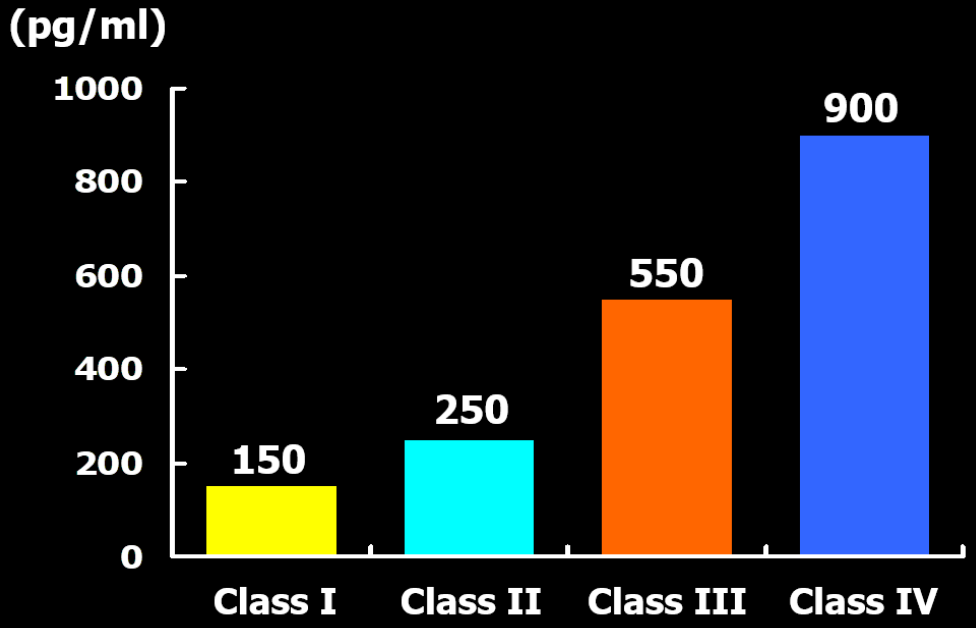
PROVE-HF

Rapid and significant reduction of NT-proBNP was observed, with majority of reduction within the first 2 weeks



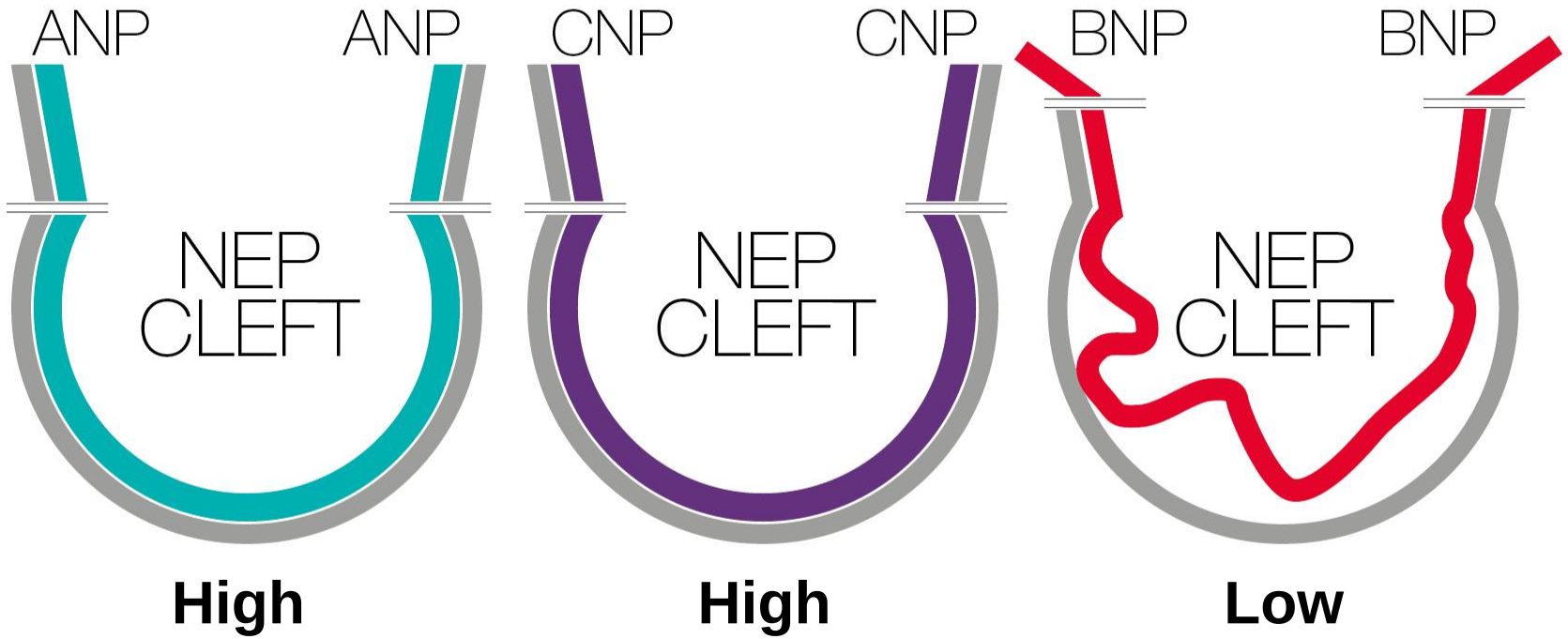
Time point	N	Median NT-proBNP (25th, 75th percentile), pg/mL
Baseline	760	816 (332, 1822)
Day 14	754	528 (226, 1378)
Day 30	740	546 (211, 1321)
Day 45	734	514 (192, 1297)
Month 2	721	535 (210, 1299)
Month 3	719	488 (211, 1315)
Month 6	699	473 (179, 1163)
Month 9	659	444 (170, 1153)
Month 12	638	455 (153, 1090)

But BNP (*a parent of ANP*) is a negative prognostic marker! *How is this possible if Neprilyesin inhibition improves prognosis increasing ANP?*



- NEP Cleaves ANP (*Atrial Natriuretic Peptide*) and CNP (*C-type Natriuretic Peptide*) but not BNP
- The avidity of NEP for natriuretic peptides is CNP >ANP > BNP

NEPRILYSIN AFFINITY FOR NATRIURETIC PEPTIDES

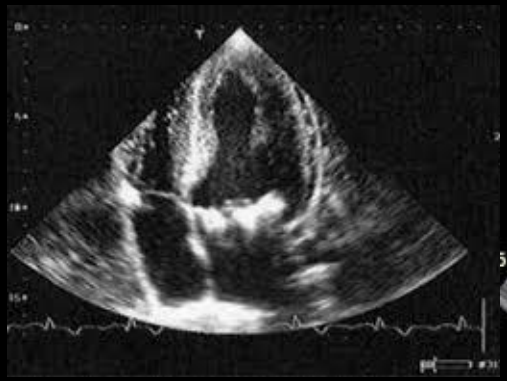


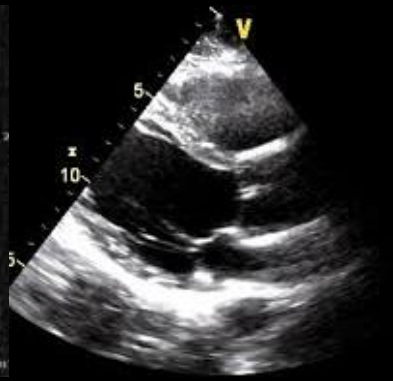
- But…is this true? Do we have some other evidence?
- This takes me back to the "*Indian*" period of my research on untreated HF

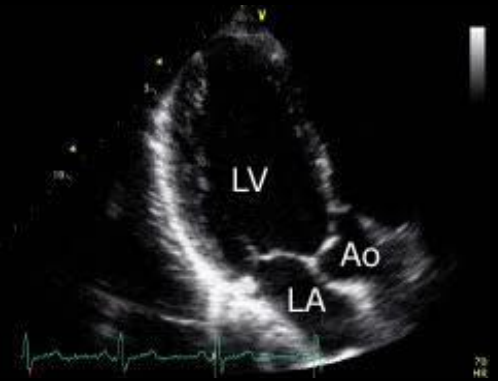


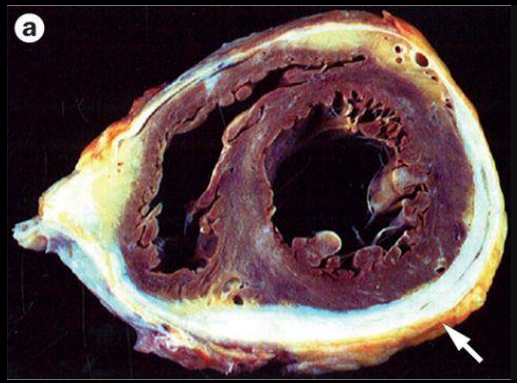
- **There, we found severely symptomatic patients (*NYHA IV*) despite normal haemodynamic and cardiac output**
- **It was a puzzling dilemma at the time**
- **They had a thick calcified constrictive pericarditis involving also the atria**

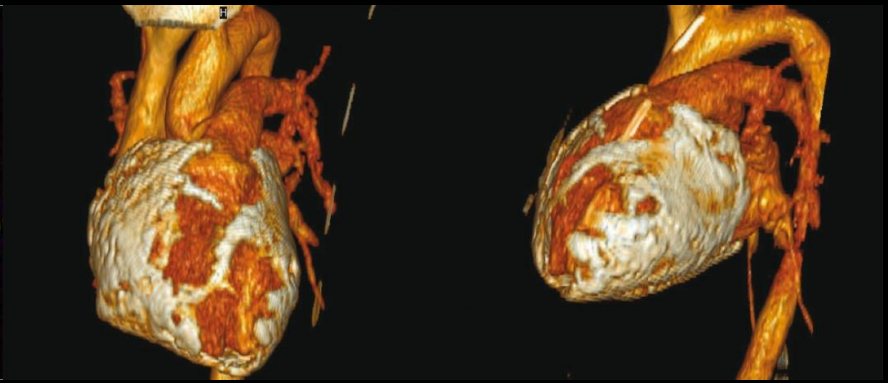
CONSTRICTIVE PERICARDITIS





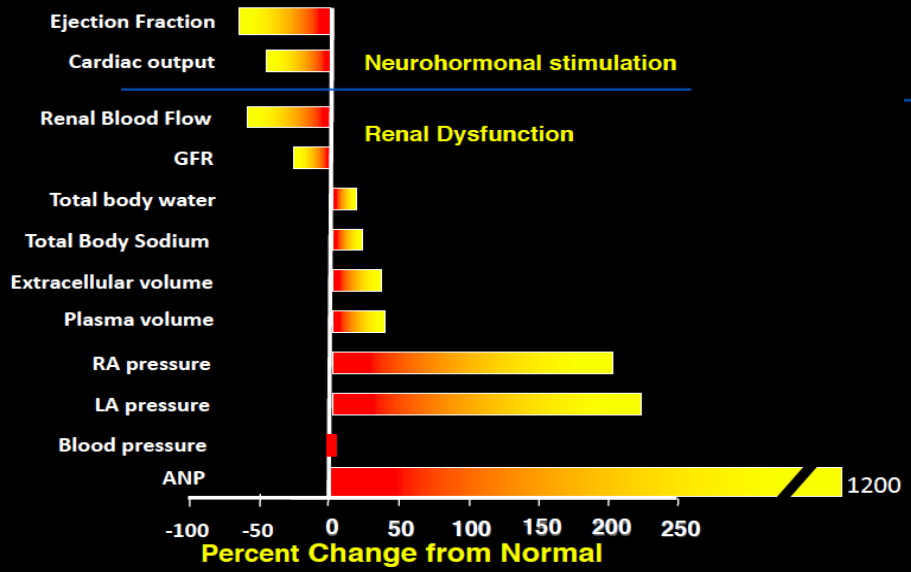




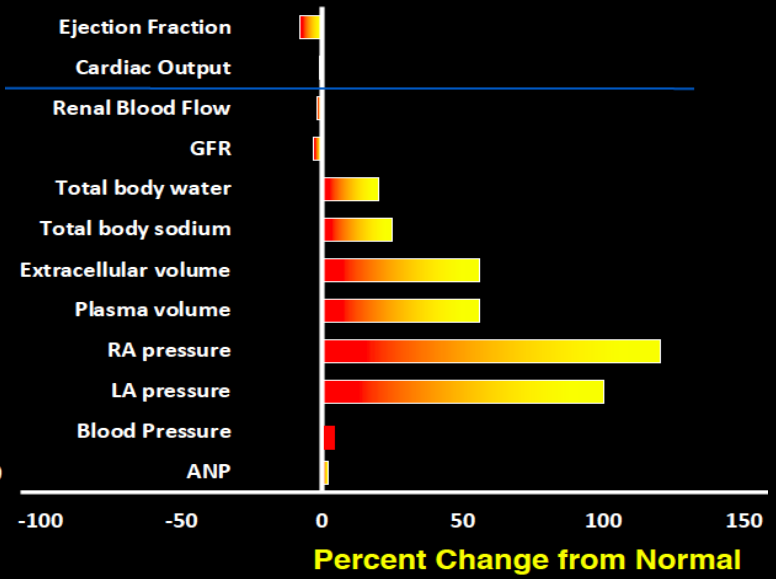


Comparison of untreated forms of HF

Ischaemic



Constrictive pericarditis



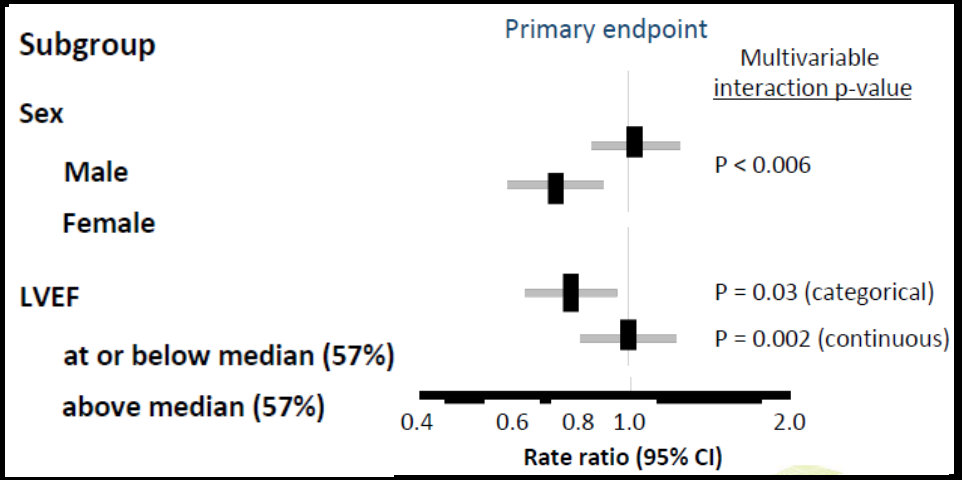
It is the availability of ANP that makes the difference!

But…the real confirmation comes from PARAGON-HF

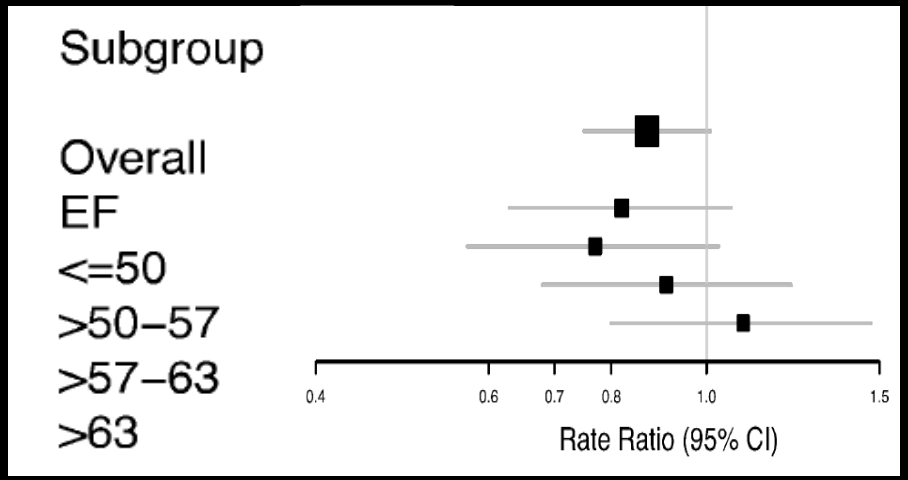
- **When the ventricle is normal, cardiac output is normal and the neuroendocrine balance is maintained!**

- **When the ventricle is just abnormal (*EF 45-57*), there is a possible benefit**

Significant heterogeneity by Ejection Fraction and Sex

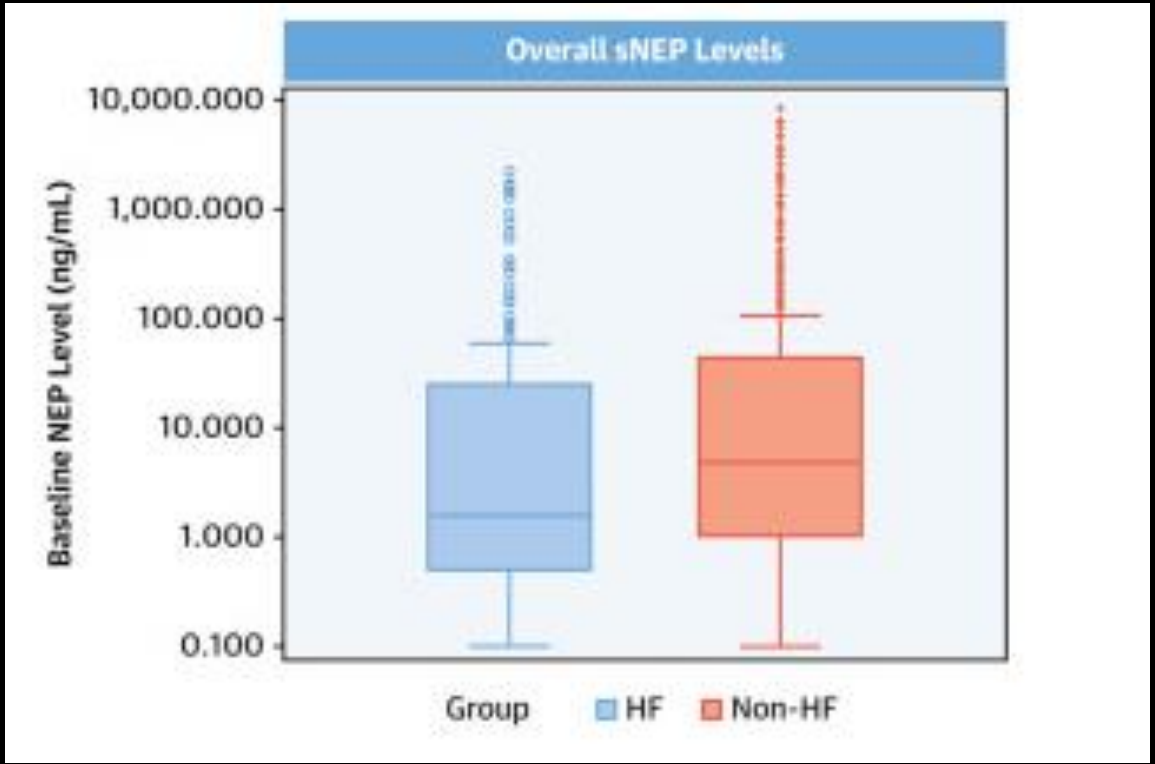


Treatment effect by Ejection Fraction quartiles



Another problem of PARAGON-HF:

neprylisin in HFpEF is not increased



Conclusions

- BB are ideal inotropes as they do not further increase O_2 consumption
- ARNIs are the ideal physiological diuretics and vasodilators resulting in reverse remodelling
- When the ventricle is normal (*PARAGON*) ARNIs have little or no effect
- This is a confirmation that ARNIs act on failing ventricles which, in turn, evoke a neuroendocrine response (*PARADIGM*)