Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, Takeda.

## References

References are available as supplementary material at *European Heart Journal* online.

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# Understanding ARNIs

## Harmonizing the 'good and bad' of the neuroendocrine response in heart failure is a balancing act discussed and illustrated by Roberto Ferrari, José Silva-Cardosa, and Maria Candida Fonseca

The results of the PARADIGM-HF study have shed a new light on the treatment of heart failure (HF).[1] PARADIGM is a trial of 'three firsts':

a. The first time a trial in HF has used a new drug to replace a pre-existing drug, instead of adding it to the usual therapy;
b. The first time a drug for HF has reduced total mortality in comparison with a comparator;
c. The first time a drug balances, instead of antagonizing, the neuroendocrine response to HF.

This last point (c) represents a real change in PARADIGM and explains the robust results of PARADIGM-HF after 30 years of unsuccessful research. During these years, the neuroendocrine activation in HF was considered deleterious. The 'dogma' was to antagonize it and research has produced different drugs to counteract the increased renin–angiotensin axis and the sympathetic system.[2]

*Figure 1*, however, shows in an extremely simple manner, that the body's neuroendocrine response is more complex and, at least, two distinct and opposite systems are activated: those aimed at vasoconstriction and water retention and those bringing about vasodilation and natriuresis. Under normal physiological conditions these systems are balanced and represent the classic dance of nature between opposites: 'the good and the bad'. However, in HF, with progression of the disease, water retention and vasoconstriction evoked by the 'bad' neuroendocrine response overcome the 'good' natriuretic and vasodilatory influences resulting in a disequilibrium, responsible for the worsening of symptoms and prognosis.[3]

*Figure 2* shows that the introduction of sacubitril inhibits neprylisin, a ubiquitous neutral endopeptidase that degrades several peptides such as atrial natriuretic peptides (ANPs), angiotensin II, bradykinin, substance P, calcitonin gene-related peptide, and others, all known to play a role in congestive heart failure (CHF). Consequently, neprylisin is a pharmacological bio target in CHF (*and not only*). Its inhibition leads to the gradual increase of plasma concentration of all this substrate including ANPs.

Thus, angiotensin receptor-neprylisin inhibitors (ARNIs) recruiting the 'good' vasodilatory and diuretic influences contribute to rebalance the neuroendocrine activation to HF (*Figure 3*). The presence of valsartan in the ARNIs molecule is useful to counteract the deleterious effects of angiotensin II that is increased in response to the disease and is not metabolized due to the inhibition of neprylisin by sacubitril.

It follows that sacubitril/valsartan represents a shift in HF medical therapy which, for years, has been directed to counteract the 'bad' hormones with angiotensin converting enzyme inhibitors, angiotensin II inhibitors, antialdosterone drugs, and beta-blockers. ARNIs stimulate the 'good' and blocks, in part at least, the 'bad' neuroendocrine response. In so doing, it reinstates a more physiological neuroendocrine balance resulting in improvement of natural diuresis, reduction of peripheral resistance, and blood pressure with amelioration of symptoms and prognosis (*Figure 4*).

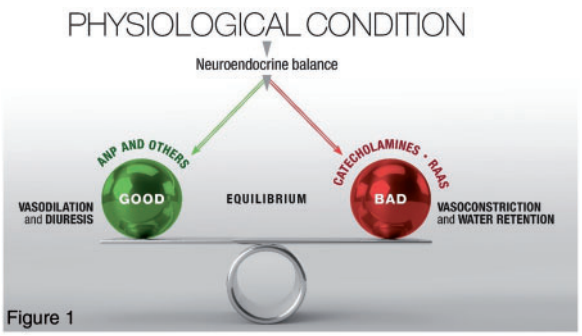

Figure 1

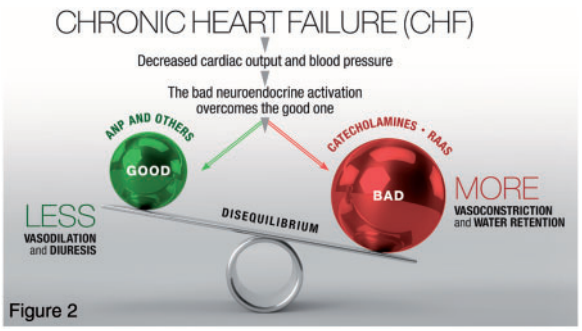

Figure 2

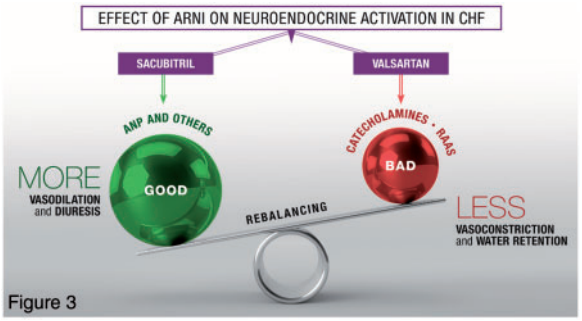

Figure 3

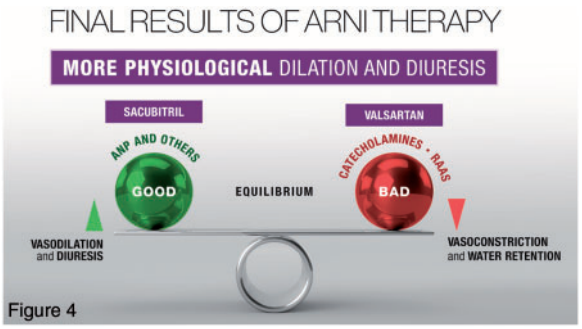

Figure 4


Roberto Ferrari MD
Department of Cardiology and LTTA Centre,
University Hospital of Ferrara and Maria Cecilia Hospital,
GVM Care & Research, Cotignola (RA), Italy
Chair of Cardiology
Azienda Ospedaliero-Universitaria di Ferrara
Ospedale di Cona
Via Aldo Moro 8, 44124 (Cona) Ferrara, Italy
Email: fri@unife.it
Tel: +39 0532 239882


José Silva-Cardoso
Department of Cardiology,
Faculty of Medicine,
CINTESIS-Center for Health
Technology and Services Research,
University of Porto, São João
Medical Center, Porto, Portugal.


Maria Candida Fonseca
Heart Failure Unit,
Internal Medicine Department,
São Francisco Xavier Hospital –
Western Lisbon Hospital Centre (CHLO),
Lisbon, Portugal and NOVA Medical School,
Faculty of Medical Sciences,
New University of Lisbon, Portugal.

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## References

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Cardio Pulse contact: Andros Tofield, Managing Editor. Email: docandros@bluewin.ch