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Lessons from Lisbon on AHF drug treatment: Is it really true that *all-old-failed-all-new-will-succeed*? ☆☆

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The authors of this letter, a pre-clinical scientist, a translational researcher, and a clinical trialist, just returned back from a particularly interesting annual meeting of the Heart Failure Society of the ESC in the gorgeous city of Lisbon. In the program, ample space was also dedicated to drugs for the treatment of acute heart failure (AHF) and large audiences enjoyed lectures, discussions, posters, industry-sponsored satellites and expert panels focused on the past, present and future of diuretics, vasodilators and inotropes. It's indeed a hot topic, as it has been for many years.

We three have been active in our respective research fields for at least two decades each and reacted, again, to a disturbing phenomenon which in waves appears in the scientific community: the paean for "*all-old-failed-all-new-will-succeed*" pervading all discussions, being them focused on molecular targets or on clinical trials.

Taking a helicopter view over two decades or preclinical, translational and clinical research, and having seen several molecules coming into use, we would like to recommend caution to our colleagues. Our message can be summarized in two points: (I) all old did not fail but possibly reached its proper niche of use, and (II) all new will not possibly succeed if it will not strive to arrive to its proper niche of use.

The conundrum is in fact in the definition of "failure". It is in fact proper to speak about "failure" of a drug when it does not reach the market for lack of regulatory approval on the basis of safety and efficacy reasons, and, to some extent, it is too understandable when industry defines "failure" a drug which does not pay back its investment costs as planned. It is, however, less understandable when clinicians define "failure" a drug which misses some end points in clinical regulatory trials on populations large enough but often very heterogeneous. Just as an example, limiting our discussion on inotropes and inodilators, molecules such as dobutamine, dopamine, digoxine, amrinone, milrinone, enoximone, and the most recent levosimendan have indeed been all taken in use, albeit often not in general use, after more or less broad and successful development and regulatory phases.

At the horizon new targets and molecules are appearing, and seem to be as promising as the old have been in the corresponding stage of their lives. Activators of myosin or other targets in the contractile apparatus [1] are currently described with vivid colors by often overenthusiastic scientists. The scientific community sees a dichotomy between old drugs and promising molecules, and often a new

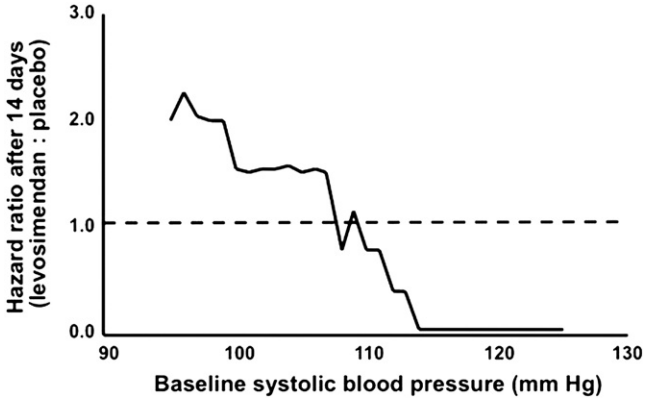

Fig. 1. Hazard ratio for all-cause mortality (levosimendan vs. placebo on top of standard of care) at 14 days in the REVIVE-II study as function of the systolic blood pressure at randomization [8] (with permission).

☆☆ Potential conflict of interest: PP is full-time employed of Orion Pharma, which developed and presently markets one of the drugs cited in the text, ZP and MSN has received honoraria from the same company for educational lectures.

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promise become suddenly an old failure: like in the description of père Champmathieu in Viktor Hugo's *Les Miserables*: "*Quand j'étais enfant, on m'appelait Petit, maintenant on m'appelle Vieux*". We heard key opinion leaders at the annual congress describing the current inotropes and inodilators as "old failures" despite used by a broad segment of colleagues who do not like to feel *passé* just because they collected good experiences in daily practice with those treatments in acute settings.

Dobutamine, milrinone, and levosimendan did indeed find their own place in therapy, as demonstrated by recent surveys on the use of inotrope and inodilator in general practice [2,3] and deserve proper consideration also in the light of recent studies (smaller but more focused) which demonstrate their benefits in some population segment and in some stages of the disease. Let's remember that acute (decompensated or de novo) heart failure has a complex definition and presents a variety of etiologies, symptoms and manifestations [4]. In some segments, drugs as levosimendan are doing great [5]. Such drugs cannot be defined as a panacea for AHF, but surely not as "failed" drugs. According to this, we recommend Industries who develop new drug for AHF to focus on smaller but better defined segment. The dream for a *good-for-all* drug which could complement diuretics and vasodilators in the treatment of AHF is alluring and could bring the newcomers to a failure, in the more strict regulatory definition.

Industry, in our opinion, should not be seeking for block busters in the complex field of AHF, and the scientific community (or at least the loud part of it which gives lecture at the annual congresses) should also realistically recognize the merit of what is on the market before treating it as "old and failed" in waiting for the "new-and-promising". This draconian attitude could generate the never ending and frustrating feeling well described by Beckett in his "*Waiting for Godot*", and create a bigger fracture between current use and ideal-guidelines.

At this regard we wish also to point out how the positioning of inodilators in the recent Heart Failure guidelines, compared to the previous, is misleading, in some cases dangerously. As an example the vasodilator and inotrope levosimendan, which was in the 2005 [4] and 2008 version of the guidelines [6] duly recommended for patients with baseline pressure over 100 mm Hg is now recommended for patients with pressures under 85 mm Hg [7]. A paramount change is not justified by any new study or publication in this sense. On the contrary, the newly published REVIVE study [8] (which data were indeed known to the scientific community and to the regulatory authorities from November 2005) [9,10] corroborates the use of this drug to patients with higher pressure, as seen also in the specification for the use of the drug (see Fig. 1) [8].

We are particularly excited by the decision of the newly renewed Translational Committee of the Heart Failure Association to focus on sarcomere and/or excitation–contraction coupling in one of the upcoming workshops: we hope that the discussion will not be spoiled by confounding "non-blockbuster" drugs with "failed" target molecules. A target in fact is not a drug and a drug has very often several targets and several effects which can be in different forms proven in clinical trials. We conclude with a hope that the field of AHF drug therapy will not become what Yeats described as "*No country for old men…*": we wish in fact to expect the new without throwing the old. The "new" in fact could become "old" in an eyeblink.

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