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Editorial

Drug discovery and development for acute heart failure drugs: Are expectations too high?

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The development of drugs for acute heart failure (AHF) over the last two decades has resembled a particularly scary roller coaster ride. I have followed developments in this field from the beginning of the nineties: over twenty years of great enthusiasm, hard work, great expectations, and, alas, many disappointments.

A search of the literature for clinical trials in AHF identifies 25 medium-to-large double-blind trials (phases IIb and III) on new chemical entities published after 2000 (Fig. 1). Some of the drugs under scrutiny are well known, others less so; some reached the market long ago, some are still not approved. The reader will certainly recognize names such as dopamine, istaroxime, milrinone, enoximone, levosimendan, and omecamtiv mecarbil in the inotrope/inodilators group; cinaciguat, clevidipine, tezosentan, nesiritide and serelaxine among the vasodilators; and the diuretics tolvaptan and rolofylline.

Recently, promising data were disclosed which bring some hope [1,2]. However, clear-cut results on a handful of new drugs are still awaited for (see the large study NCT01870778 on the efficacy, safety and tolerability of serelaxin when added to standard therapy in AHF, to be completed in June 2016), and the field at the moment continues to be characterized by paucity of evidence [3].

From my position in the industry I feel that the development of novel treatments for AHF is not going as smoothly as it might. I would like to sketch what I believe are the five most tenacious problems contributing to this state of affairs (see Table 1), and list some of the few strategies which in my opinion are promising.

The first pitfall is that the therapeutic field of AHF is complicated: the definition of the syndrome itself is not straightforward, with many etiologies and various manifestations [4]. A comparison between the two latest versions of the European Society of Cardiology guidelines for treatment of heart failure (from 2008 and 2012, respectively) [5,6] shows that the definition is still evolving: even nowadays some of the typical symptoms and signs of heart failure are still considered non-discriminating and therefore of limited diagnostic value [7]. As candidly stated in the latest guidelines, the treatment of AHF "remains largely opinion-based with little good evidence to guide therapy" [6].

Secondly, the armamentarium of drugs used to keep patients alive (and with as little permanent cardiac damage as possible) through the acute phase of heart failure is limited, and among the hemodynamically active *i.v.* drugs, certain families such as vasodilators, diuretics, inotropes, and vasopressors, currently dominate the field [8,9]. Many of those agents are so inexpensive that whatever incremental improvement a newcomer might possibly demonstrate would be offset (even eclipsed) by a premium price (and incremental cost) that would be difficult to justify to payers who are more and more pressed by budget limitations [10].

Thirdly, in recent times the pharmaceutical industry has experienced a rising attrition rate, defined as failure of the discovery, development, registration and launch phases [11]. Pharmaceutical companies have responded in various ways, including streamlining and 'de-risking' their research strategies — that is to say focusing on fewer therapeutic fields and more limited objectives. Moreover it must be recognized that even for 'Big Pharma' the R&D budget is not limitless. Cardiovascular product innovation in general is reported to be declining [12,13] and other therapeutic areas may appear much less risky than a fragmented field such as AHF. In short, AHF does not appear a good prospect for the emergence of block-buster drugs: [14] that in turn discourages the sort of ambitious investment that might produce a breakthrough.

Fourthly, AHF is a life-threatening syndrome and all regulatory clinical trials are targeted not only to the short-term relief of symptoms, but to reduction in longer-term mortality. The barrier to new entrants is thus set very high. Significant and meaningful increases in survival are difficult to demonstrate if patients in the referent group receive the full gamut of existing *p.o.* and *i.v.* drugs. As an example, it is worth mentioning the REVIVE II study (levosimendan vs. placebo, each on top of

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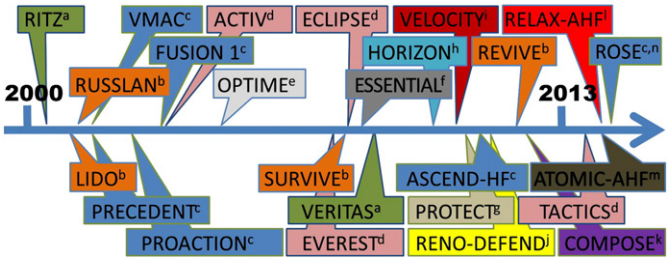

Fig. 1. Latest clinical trials on drugs for acute heart failure. PubMed was searched for papers describing ((("acute heart failure" *or* "acutely decompensated heart failure")) *and* "clinical trial") *and* ("2000/01/01" [date–publication]:"2014/01/01" [date–publication]). The 113 articles found by this search strategy allowed to identify 25 medium-large sized double-blind trials on new chemical entities (phases IIb and III). The acronyms of the trials are marked as follows: (a) trials on tezosentan, (b) levosimendan, (c) nesiritide, (d) tolvaptan, (e) milrinone, (f) enoximone, (g) rolofylline, (h) istaroxime, (i) clevidipine, (j) SLV320, (k) cinaciguat, (l) serelaxine, (m) omecamtiv mecarbil, and (n) dopamine.

standard of care, in patients hospitalized for worsening heart failure and LV ejection fraction ≤35%) [15] in which 87% of the patients in the placebo arm vs 92% in the active drug arm improved their dyspnea over 5 days. Similarly, in the more recent RELAX-HF study (serelaxin vs. placebo in patients admitted to hospital for AHF, with SBP > 125 mm Hg) [16], improvement in dyspnea (Likert scale) was reached by 26% of the patients in the placebo arm vs 27% in the active drug arm.

A corollary of this situation is that convincing regulatory studies need to be both large and lengthy. The consequence of such lengthy development is that patent life begins to be worryingly short and business cases are less prone to show a return over investment.

Finally, clinical studies have been often – and with some justification – criticized for not representing the full diversity of AHF patients encountered in the "real world". Such questions, although old [17], have not yet generated good answers, and this becomes an additional confounding factor which may delay reception of new drugs into the market. Moreover, trials in emerging markets are becoming an issue. The need on one hand for global quality standards in international big clinical trials and on the other for locally arranged clinical trials to secure regulatory approval in some big national markets cannot always be reconciled without additional considerable costs.

In this complicated business environment a handful of companies still support innovative research and expensive clinical development [18]. In order to attract and retain the support of investors it is crucial for these companies to create expectations. Yet, as I have argued in this Editorial, AHF is an arena where it is wrong (I would say both morally and commercially) to encourage expectations that are too high. I hope not to be over-simplistic or unduly negative when I state that there cannot be one cure-all drug for AHF. There can be no realistic expectation of a blockbuster in such a multi-dimensional condition and no defensible reason to encourage hopes that such a drug is just around the corner. In the era of personalized therapies we should search for drugs targeted to sub-settings of AHF (e.g. cardiogenic shock, AHF with low ejection fraction, or others), not for panaceas.

Striving after a magic bullet has been the downfall of much research in the past. As an example levosimendan was developed as an inotrope and meant to be used independent of the SBP value of the patient. Its vasodilatory effect very soon became evident, however, and nowadays its use is restricted to patients with SBP >100 mm Hg [15]. During the process much fuss was created, much time was lost, some opportunities vanished. I hope the lesson was learned: the newcomer drugs should be developed bearing in mind the variety of manifestations of AHF.

Pharma industry seems to have, alas, surprisingly short memory. As it regards Omecamtiv mecarbil, for example, it appears that the earlier discussion on sarcomere-active drugs has been forgotten. Decades ago, molecules which prolong the contractility transient were ditched because potentially harmful in case of ischemic conditions [19]. Omecamtiv shares some of these characteristics [20] and the latest clinical trial on this positive inotropic drug (ATOMIC-AHF) indeed showed a sign (albeit only a non-significant numerical unbalance) of myocardial infarction [21]. It could be a play of chance, or it could be somehow related to the sign of cardiac ischemia described by a previous Phase II trial [22].

Is it time to be rethinking the strategy? I believe so, and I suggest some possible solutions.

Pharmacogenetic targeting of drugs for heart failure has been advocated recently as a development strategy and business solution which would provide a blend of clinical, commercial and health-care cost benefits [23]. A concrete suggestion, which I fully endorse, was recently made by the Forbes analyst David Shaywitz, with the observation that "The explosion of sensors and mobile technologies, and of digital health more generally has dramatically increased our ability to understand a patient's experience of disease, providing the opportunity for continuous versus episodic assessment, and understand phenotype at a far more granular level" [24]. This could be a possible way for increasing the possibility of success in the discovery and development of new AHF drugs.

Another possible way would be to go beyond the "mega trial", as Collins and co-workers suggest [25], and move towards Bayesian adaptive trial design in acute heart failure syndromes. This approach is suited for investigating heterogeneous conditions such as AHF and allows investigators to study multiple treatment approaches and therapies in multiple patient phenotypes within a single trial, while maintaining a reasonable sample size.

I would finally recommend that the scientific societies in the field of cardiology strengthen their discussions with pharmaceutical companies and identify new ways of cooperation for the early phases of discovery and development. A good start was the decision of the Heart Failure Association of the European Society of Cardiology to re-name the Basic Science working group as "Committee on Translational Research" and give it a new focus of promoting the development, application and translation of basic science knowledge to clinically relevant questions and targets in the field of heart failure.

Conflict of interest

The author was among the inventors of levosimendan, one of the drugs cited in the editorial, and is currently employed by the company which has the global rights for this drug.

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Table 1
The main problems in the development of novel treatments for AHF.

- The definition of AHF is still evolving. Typical symptoms and signs of heart failure are still considered of limited diagnostic value,
- No new families of drugs in sight. Many generic inotropes, vasodilators, and diuretics. Difficulties in justifying a premium price to institutional payers with rising budget limitations,
- Harsh competition for R&D financing between therapy areas within pharmaceutical industry,
- Rising costs of clinical trials. Need for long term mortality data. Difficulties in showing advantages vs. placebo on top of existing standard of care,
- Risk of running clinical trials on populations which do not fully represent the real patients.

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