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Acute Heart Failure Deserves a Log-Scale Boost in Research Support

Call for Multidisciplinary and Universal Actions

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With 2 recent neutral trials (1), many physicians caring daily all around the world for acute heart failure (AHF) patients were disappointed. Are we going to manage those patients like we did in past years and keep facing high mortality and a high rate of readmission?

In fact, those neutral trials are clear indications that we still do not understand AHF and that we should join forces and support our understanding of what mechanisms lead to acute heart failure before performing new large phase III trials.

WE STILL DO NOT UNDERSTAND: WHAT IS ACUTE HEART FAILURE?

We likely performed trials in AHF without a clear understanding of AHF. Patients were included based on circulating natriuretic peptides and subjective symptoms. Misunderstanding AHF likely translated into the bad outcome associated with AHF. Indeed, many national surveys showed in-hospital and mid-term mortality remained high and unchanged in the last years. This is confirmed in the very recent AHF trials.

Furthermore, the term "acute heart failure" is not ideal, although no other term has achieved consensus. It is not ideal because the word "heart" does not represent the disease (2). AHF starts with an alteration in heart properties followed by alterations in many other extracardiac, including neuroendocrine, systems that lead to congestion and AHF. In addition, most drugs administered in AHF (except in cardiogenic shock) have little influence on the heart. By contrast, in the term acute heart failure, "acute" is correct as emergency and critical medicine define "patient admitted for unscheduled visit with a high risk of death" as "acute" (3). As pointed out by recent Heart Failure Association of the European Society of Cardiology guidelines, the precipitating factors of AHF were overlooked and often not treated. Patients admitted with a combination of cardiogenic pulmonary edema and acute coronary syndrome or infection are admitted in critical condition and at high risk of death (**Figure 1A**) (4). Similarly acute decompensated COPD (chronic obstructive pulmonary disease represent) patients have been admitted for pneumonia that lasted several days before admission and for whom antibiotic therapy improved outcome.

Oral heart failure therapies (OHFT) are necessary to prevent worsening conditions and sometime even partially restore heart function. However, those therapies will not reduce the rate of AHF in the short term. Indeed one should keep in mind that: 1) the first episode of AHF (also named de novo HF) represents up to 40% of AHF patients; 2) OHFT have proven to be active only in heart failure with reduced left ventricle ejection fraction (LVEF) that are the minority of AHF patients, dominated by patients with preserved LVEF; 3) many patients with optimal OHFT are still admitted with AHF; and 4) optimization of OHFT is still an unresolved challenge as only 30% of HF patients receive optimal doses and even much <30% in the oldest old patients who are becoming the majority of AHF. Indeed, failure in implementation of OHFT contributes to the excessively high rate of short-term readmission, a phenomenon that is unique in medicine. Management of AHF after discharge raises other issues. For example, should we and how can we generalize about HF nurses? Should we have other health care providers in the loop? Those questions and many others are now included in the "post-discharge vulnerable phase," although no clear indications are given to the physicians in

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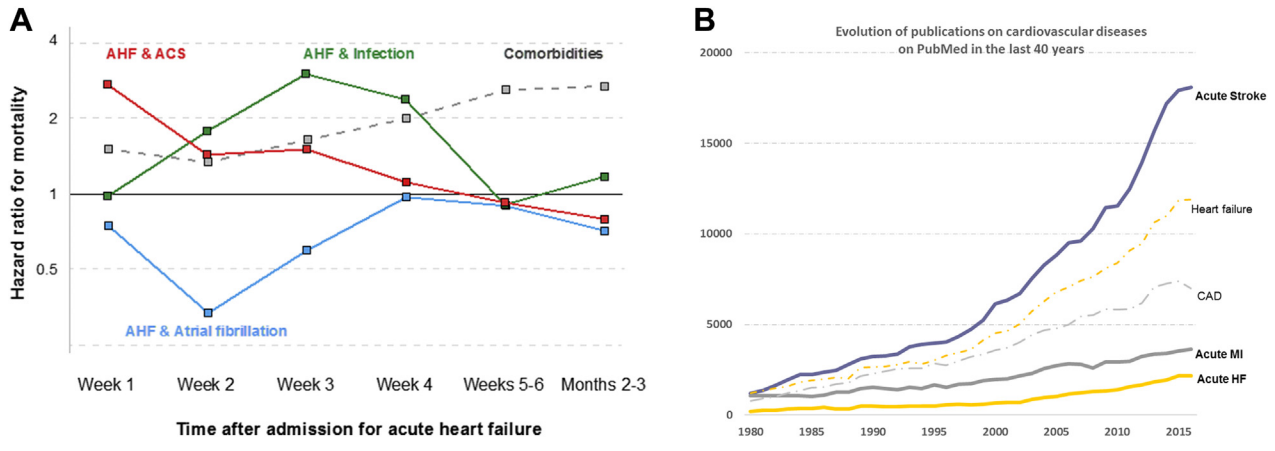
FIGURE 1 **AHF Is Misunderstood Because It Is Not Studied Enough**



(A) Time after admission for AHF. Combination of AHF and ACS, infection, and atrial fibrillation alter very short-term mortality while comorbidities play important roles on 3-month mortality (3). **(B)** Evolution of publications on cardiovascular diseases in PubMed in the last 40 years. Much more research was performed in acute stroke than in AHF. ACS = acute coronary syndrome; AHF = acute heart failure; CAD = coronary artery disease.

charge, who are largely noncardiologists, throughout the world.

WHAT HAVE WE LEARNED FROM THE LAST 30 YEARS OF ACUTE HEART FAILURE TRIALS?

No trial to date assessing effects of drug therapy on AHF has been positive, although we were eager to find new therapies for AHF patients. To do so, various intravenous agents, mostly with either vasodilator or positive inotropic properties, or both, were tested using similar trial designs: short-term administration to achieve improvement in mid-term outcome. All drugs tested showed benefits in hemodynamics in phase II but neutral effects in large phase III randomized clinical trials. Mid-term mortality in AHF, the coprimary of TRUE-AHF (Efficacy and safety of Ularitide for the treatment of acute decompensated heart failure) and RELAX-AHF (Effect of serelaxin versus standard of core in acute heart failure patients), was neutral. Benefits for mortality may not be achievable because mid-term mortality is influenced by many factors, some of them not actionable (comorbidities). Improvement in short-term symptoms, however, seems achievable, although transient. In the 2 recent trials, benefits for symptoms were minimal, knowing that many patients were included with mild decompensation of severe chronic heart failure.

The 2 very recent trials have focused on "time to start" the administration of active therapies. Time to start the administration of an active drug in AHF trial is an unresolved issue, although emergency department (ED) physicians think it matters. The 2 trials failed to demonstrate that ularitide or serelaxin were effective for AHF, although both drugs were administered earlier than in former AHF trials. It is also possible that 6 h after presentation was not early enough. Indeed, today, in most EDs, AHF patients receive intravenous drugs often within 90 min after presentation. Furthermore, studies showed that noninvasive ventilation and very recently intravenous diuretics given within <30 min of presentation were associated with the best outcome (5). Keeping the parallel between AHF and other diseases that appear several days before presentation, for example, sepsis, several recent studies showed that administration of antibiotics at presentation saves lives, whereas early administration of volume, another recommended tool, was not associated with additional benefits. In summary, it is likely a general rule that we better administer active agents as early as possible, any active agent in critically ill patients, in order to prevent worsening. However, which drug(s) may be considered as active agent(s) in AHF?

Although it would be ideal to better understand AHF before moving forward with large clinical trials, some agents are already in the pipeline. As advised by many famous people: "If you always do what you've