EDITORIAL COMMENT

The Challenge of Drug Development in Acute Heart Failure
Balancing Mechanisms, Targeting Patients, and Gambling on Outcomes*

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Nearly 40 years ago, recommendations to treat acute heart failure (AHF) included oxygen, diuretic agents, vasodilators, and inotropes (1). Although the addition of rotating nitrates and phlebotomy have become historical footnotes, a clinician treating AHF today would essentially use the same therapeutic modalities. A layperson might conclude that significant reductions in morbidity and mortality over time have obviated the need for improvements in medical therapy. Unfortunately, the statistics are much more sobering. With >1 million AHF hospital stays annually in the United States, death and rehospitalization rates after discharge remain unacceptably high, affecting 30% to 40% of patients within 90 days (2,3). At 1 year after discharge, nearly one-third of patients have died. Remarkably, the last drug approved to treat AHF was nesiritide in 2001, but the evidence for efficacy was modest at best, and the benefits were overstated and oversold. The need for new therapies to improve outcomes is unquestionable.

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Failure to substantially improve post-discharge outcomes mirrors the lack of progress in identifying or discovering new treatments. Even drugs that have become standard of care, including intravenous diuretic agents and vasodilators, lack contemporary evidence of benefit. Although decades of use speak to their symptomatic and hemodynamic effects, conclusive outcomes trials have yet to be performed. The economic realities of conducting clinical trials for generic therapies are the most commonly cited reason; lack of clinical equipoise is another. Against this background, novel drug therapies have been actively pursued. However, with 1 exception, all phase 3 clinical trials have been disappointing due to lack of efficacy and/or safety concerns.

In this issue of JACC: Heart Failure, Chan et al. (4) report their findings from the UNICORN (Urocortin-2 in the Treatment of Acute Heart Failure as an Adjunct Over Conventional Therapy) study, a phase 2, single-center, randomized, double-blind, placebo-controlled trial of urocortin-2 in patients with AHF. After screening ~800 patients for eligibility, 53 patients were randomly assigned to receive a 4-h infusion of urocortin-2 (5 ng/kg/min) or placebo, in addition to standard AHF therapy. Urocortin-2 is 1 of 3 endogenous peptides that comprise the known corticotropin-releasing factor (CRF) family, which bind to CRF-1 and 2 (G-protein coupled receptors). Urocortin-2 binds primarily to the CRF-2 receptor, which is found in particularly high concentrations in the heart and vasculature. Past work by the investigators has demonstrated inotropic, lusitropic, natriuretic, and vasodilatory properties of urocortin-2 in heart failure (HF). However, these benefits were less pronounced in chronic human HF compared to animal models (5,6). Combined with its rapid onset of action and relatively short half-life (both approximately 15 min) (5), these salutary benefits suggested promise for AHF. The current study was therefore designed to assess the acute hemodynamic, renal, and neurohormonal effects of urocortin-2 in patients with AHF, irrespective of ejection fraction or history of HF.

In the overall cohort, urocortin-2 exerted a rapid and potent hypotensive effect with a reduction in systolic blood pressure of 16 mm Hg greater than time-matched placebo. Indeed, in 15% of patients, systolic blood pressure fell to <85 mm Hg. In the subgroup of patients that underwent right heart catheterization, urocortin-2 resulted in marked reductions in peripheral resistance and (secondary) improvements in cardiac output presumably due to vasodilation. No significant changes in cardiac filling pressures or pulmonary artery pressure, however, were observed. Although natriuretic peptide levels fell more in urocortin-2–treated patients at 12 and 24 h, these “late” beneficial effects were counterbalanced by significantly decreased urine output, sodium excretion, and creatinine clearance, as well as increases in plasma renin activity, during drug infusion. Increased flushing was also observed in the active treatment group.

Although the groups were well matched at baseline, the level of AHF acuity was modest (average systolic blood pressure 112 mm Hg, heart rate 81 beats/min, estimated GFR 58 ml/min, NT-proBNP 450 pmol/l), and it is unclear when intravenous diuretic agents were held before infusion. Furthermore, only “varying” doses of vasodilators or inotropes were held within 3 h of randomization, suggesting the

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possibility that stable doses were allowed. In addition, medications that might lead to hypotension were “ideally held” 2 h before infusion, but it is unclear which patients this affected. These differences, especially in a small study population, could easily confound the changes observed.

Overall, Chan et al. (4) conducted a detailed, proof-of-concept study with a novel agent in a challenging patient population. They built on their prior findings with urocortin-2 in animals and patients with stable HF, and expanded the database to include AHF. Furthermore, they characterized the drug carefully through invasive hemodynamic, neurohormonal, biomarker, and renal function assessments, although true invasive measures of inotropy and lusitropy and validated symptom measures were lacking. On the basis of the resultant benefits of increased cardiac output, lowered peripheral resistance, and reduced natriuretic peptides, the investigators suggest that urocortin-2 “may warrant further research” albeit at a lower dose. Although lower doses may indeed mitigate risks of urocortin-2, the present data engender skepticism regarding future development.

In the UNICORN study, unloading of the heart appears to be the primary hemodynamic effect. While the absence of significant reflex tachycardia (p = 0.07) is reassuring—the investigators speculate that this is due to suppressive effects of urocortin-2 on cardiac sympathetic nerve activation—the trend raises concerns, particularly in light of the target population and the drug’s other effects: namely, marked hypotension, decreased urine output, decreased renal function, and increases in plasma renin activity. Although these concerning safety issues might be attenuated by a lower dose, the absence of any significant decreases in right atrial, pulmonary capillary wedge, or mean pulmonary artery pressures raises doubts as to whether lower doses would lead to any beneficial venodilatory effects in congested patients. With the benefit of hindsight, what are the lessons learned from this study?

**Primum, no nocere.** Chan et al. (4) correctly highlight the dangers of hypotension, yet their pre-specified stopping rule for asymptomatic hypotension was 85 mm Hg. Perhaps more than any other signal, hypotension has derailed development programs in AHF involving agents with vasodilatory properties, particularly first-dose hypotension with bolus dosing (7). Earlier experiences with endothelin antagonists, synthetic natriuretic peptides, and calcium sensitizing agents come to mind. Current phase 2 and phase 3 trial designs deliberately mitigate the threat of hypotension with rigid stopping rules, and in some cases, higher inclusion blood pressure (8). A silver lining from the UNICORN trial may be the identification of the maximal tolerated dose.

**Dose.** Deciding on the correct dose is particularly difficult in AHF. The dose used in the UNICORN study matched the lower dose used in a chronic HF study; however, plasma concentrations were similar to the higher dose, for reasons that are not clear. In healthy humans, the higher dose activated plasma renin activity, angiotensin II, and norepinephrine, but not the lower dose (9). Despite similarities between chronic and acute HF, differences in dose effects during the transition from chronic HF to acute decompensation have been observed (7). In addition, concomitant therapy, comorbidities, and degree of neurohormonal activation may be quite different in these 2 disease stages. Although studying a drug first in chronic HF is understandable, meritorious, and perhaps even necessary, chronic HF is not acute HF, and studies such as UNICORN highlight these differences. Ideally, dose-ranging studies should be performed to demonstrate the maximal tolerated and lowest effective doses. Financial constraints, however, are recognized, as well as the threat to any development program of even a single unexpected serious adverse event. Although serial, single-dose studies are an option, negative or neutral studies dampen the enthusiasm of clinical investigators and investors alike. Bayesian adaptive designs have been used in other fields and represent a valid option for dose-finding studies, although they have yet to be used in AHF (10).

**Study population and power.** Although designed as a randomized controlled trial with appropriate power calculations, the UNICORN study enrolled a relatively small number of patients, with multiple hypothesis testing, introducing the potential for type I and type II error. Adding in the heterogeneity of the AHF patient population and known regional differences raises questions as to whether a different and larger patient population may have yielded different results. The low mean natriuretic peptide levels and higher estimated GFR relative to recent AHF clinical trials suggest a lower risk group. The increase in plasma renin activity (and trend toward increases in endothelin and aldosterone) might also be a reflection of lower neurohormonal activation. Although this is counterintuitive for AHF, urocortin-2 infusion in chronic HF demonstrated suppression of the renin-angiotensin-aldosterone system compared to studies involving healthy volunteers, suggesting that some UNICORN study patients may have been less acute (5,6,9). A population of patients with acute pulmonary edema or patients with hypertensive urgency might be a more appropriate target for urocortin-2, at least at the dose studied.

**Timing of enrollment.** As with acute coronary syndromes, recent studies suggest that earlier initiation of diuretic and vasoactive therapy may benefit patients with AHF by decreasing wall stress and subsequent myocardial injury that could have an impact on late outcomes (11). Even small increases in cardiac troponins carry negative prognostic import (12). Whether there is a window of opportunity for urocortin-2 in AHF is unknown. As the average time to enrollment was 22 h after IV loop diuretic and as long as 36 h post-admission, standard therapy was likely to have affected the pathophysiologic milieu. Early changes in neurohormones and renal function also exert important influences on drug effect (vs. toxicity). Alternatively, salutary clinical and hemodynamic changes may have already occurred, limiting the observed benefits of urocortin-2.

The absence of a clear definition of AHF reinforces the heterogeneity of the syndrome (13). If presentation to the
emergency room is the most acute phase, is it still acute 36 h later? Does it matter? Does “acute” define 30-day or 90-day risk (or longer), or does it reflect acuity of presentation (and how is that defined)? Although the argument is academic, from a research perspective, it is imperative. A simple thought experiment highlights this point: 10 different physicians who manage AHF are asked to describe a patient in detail: cause, precipitant, background therapy, comorbidities, bedside hemodynamic status, and treatment options, including when and where to treat and which doses to target. Although there will be many similarities, the differences will be striking. AHF trialists have much to learn from acute coronary syndrome investigators, who would not group patients with ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina, or leave background therapy up to investigator discretion.

**Biomarker-guided trials.** Using a broad definition of biomarker, the UNICORN trial used biomarker surrogates as endpoints—a reasonable approach, especially in a proof-of-concept study. Although absence of an efficacy signal may be due to type II error and should not immediately exclude a therapy from further development, positive signals support the hypothesis. A more narrow definition of biomarkers could also be used to target patients. Individual or even a small panel of biomarkers that reflect the pathophysiole target of interest and inform illness severity and prognosis might be considered to carefully select patients for inclusion on the basis of a drug’s known profile or intended benefit. For phase 2 clinical trials of modest size, increasing the number of endpoints may be critical to achieving power.

**Standard therapy.** Every AHF trial to date uses standard therapy in the placebo arm. This implies that these therapies are safe and effective, and that withholding them would be unethical. Yet no study has definitively proven longer-term benefits or harm from standard therapy. Standard therapy is, in fact, not standard and introduces confounding, even in large trials (14). Whereas certain novel agents may have the regulatory goal of being labeled as add-on therapy, others may not. A significant advance in the field would come from simply knowing the benefit versus safety signals of IV furosemide or nitroglycerin. Given the persistently high morbidity and mortality of AHF despite years of efforts, sticking to tradition may, in certain instances, create its own moral hazard.

To date, AHF trials largely follow a similar pattern, iterative in subsequent design, tweaked modestly by a specific drug action. Initial large trials conducted a decade ago were truly bold, exploring a poorly defined entity for the first time. Subsequently, creative endpoints have been developed, new statistical methods have been introduced, and even enrollment windows have been shortened. Although such iteration is essential to discovery, “creative destruction” may also play a role in drug development. The audacity to hypothesize that short-term therapy can impact longer-term outcomes challenges conventional wisdom. Bold hypotheses, even if scientifically sound, typically raise concerns as the potential high reward is coupled with greater risk. The UNICORN study is such an example. Such carefully constructed, scientifically sound, yet bold experiments are absolutely necessary, and should be reported with transparency. The more we learn from our patients and share with the greater AHF community, the better our trials become. A decade of efforts, multiple disappointing trials, and dismal patient outcomes warrants new approaches. Hopefully, 10 years from now, a similar commentary does not begin with “Nearly 50 years ago…” Our patients deserve better.

**References**


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