Patients manifesting symptomatic pulmonary congestion during an acute myocardial infarction have long been recognized to be at heightened risk of both short- and long-term mortality. Acute heart failure (AHF) complicates acute myocardial infarction as a result of a complex interaction of structural, hemodynamic, neurohormonal, and genetic maladaptations. Abrupt myocyte loss leading to contractile dysfunction and AHF is an obvious mechanism, and the extent of biomarker elevation correlates with prognosis and the range of functional recovery. In those without extensive myocyte necrosis, postischemic left ventricular systolic dysfunction (LVSD) leading to AHF can result from transient myocardial stunning or hibernation depending on the extent of coronary reperfusion. Ventricular remodeling can increase wall stress to viable regions that may be relatively underperfused, furthering ischemia and adding to this cycle. Ischemia-induced impairment in myocardial relaxation can increase left ventricular filling pressures irrespective of global systolic function and lead to AHF. Furthermore, ischemia can also precipitate acute mitral regurgitation in some patients, contributing to the risk of pulmonary congestion. Recent data also suggest that AHF potentiates apoptosis in and outside the infarct zone, which focuses attention beyond mechanics, hemodynamics, and perfusion to alterations in signaling pathways and genetic expression. Regardless of which processes dominate in individual patients, it is clear that the intersection of AHF and myocardial infarction remains deadly even in the current era of acute reperfusion.

The authors provide important new data implicating AHF equally across the spectrum of acute ischemic syndromes. For example, the adverse prognostic implications of AHF complicating ACS are not relegated only to those who manifest evidence of myocardial necrosis. The approximately 4-fold increased risk of in-hospital mortality was strikingly similar across all groups. Nonetheless, as expected, a stepwise increase in absolute risk was found for AHF across the ACS spectrum with unstable angina patients, with AHF patients having an in-hospital mortality of 6.7% and myocardial infarction patients with AHF without and with ST-segment elevation incurring a 10.3% and 16.5% in-hospital mortality, respectively. Furthermore, the GRACE investigators confirm previous reports that AHF develops in a sizeable number (5.6%) of patients after admission regardless of biomarker elevation or ST-segment deviation. The authors provide revealing that many patients with unstable angina (8.2%) present with AHF. The investigators chose to exclude 2459 patients (15%) from their analyses because of chronic heart failure and the smaller proportion of patients presenting with overt cardiogenic shock. Therefore, the prevalence presented in their cohort must be considered a conservative estimate of the magnitude of AHF complicating ACS regardless of ST-segment deviation or biomarker evidence of myocardial necrosis.

AHF complicating ACS does not require evidence of LVSD or myocardial necrosis at presentation, and the majority do not have distinguishable LVSD at discharge. Although ejection fraction correlates with the risk of AHF, both provide independent information. This disconnect between LVSD and AHF in ACS is highlighted by the following 2 points: (1) the majority of such patients are discharged free of symptoms and (2) only a minority of patients have been observed to develop chronic heart failure later (although this number may be increasing as a result of therapeutic advances in ACS management and an aging population). For example, in infarct patients randomized into the SAVE trial (Survival And Ventricular
Enlargement\(^{12}\) in which postinfarction LVSD was required, 60% were asymptomatic; conversely, in the VALIANT trial (VALsartan In Acute myocardial iNfarctIon) trial,\(^{13}\) in which patients could be enrolled with either AHF, LVSD, or both, 42% of the cohort presented with AHF and did not have quantitative evidence of LVSD. Unfortunately, the GRACE investigators do not report data on co-incidence, timing, or extent of LVSD in association with AHF status, which limits further understanding of the magnitude of the interaction between AHF and LVSD across the continuum of coronary syndrome presentations.

Regardless of LVSD, AHF in the presence of ACS is associated with a striking increase in short-term mortality. Predictive models for AHF constructed in observational and clinical trial ACS data sets and across ST-segment deviation subpopulations\(^{9,10,14}\) report similar determinants of in-hospital and short-term mortality risk, including increasing age, female gender, prior infarction, diabetes, hypertension, and higher heart rate, among others. The GRACE analysis confirms the importance of these AHF promoters and expands their clinical relevance to those without biomarker necrosis. Because a clinical profile exists of an ACS patient with an increased likelihood to develop AHF and death, careful attention on intake should lead to earlier recognition and/or therapeutic modifications minimizing the likelihood of AHF development across all ACS patients. Focusing early aggressive pharmacological, procedural, and interventional strategies at this group may lead to early benefits in overall survival. Even if only a relatively small modification in risk for the heart failure subgroup were achieved, significant absolute reduction would occur in morbidity and mortality for the entire ACS population, as upwards of 80% of all in-hospital morbidity and mortality is concentrated in the AHF group with and without LVSD.\(^{15,16}\)

Even though clinical AHF profiling is currently realizable, the GRACE investigators, building on previous findings,\(^{15–17}\) report on the alarming heterogeneity in the care of ACS patients who present or develop AHF compared with those at lower mortality risk. We strongly concur with Steg et al\(^{8}\) that ACS patients with AHF would derive the greatest absolute risk reduction from any intervention because they have such a significantly greater mortality risk. Thereby, clinicians should intensify their application of proven therapies. Yet, contrary to this principle, ACS patients who develop AHF are significantly less likely to undergo cardiac catheterization and subsequent revascularization and also are less likely to receive pharmacotherapies with established mortality reduction such as ACE inhibitors, β-blockers, and statins.

A critical window exists to improve the survival of those with AHF complicating ACS. Although AHF is present on admission or develops early during ACS, the mortality risk in patients continues to accelerate beyond the early period out to at least 30 days.\(^{18}\) In Figure 1 of their article, the GRACE investigators provide further credence to this important premise because the slope of the Kaplan-Meier curves for the AHF group continued to increase through \(\approx\)1 month after ACS presentation. This brief window of opportunity should draw attention to all ACS patients with AHF regardless of LVSD, electrocardiographic, or biomarker presentation. Recent data with β-blockers\(^{19}\) and aldosterone antagonists\(^{20}\) strongly support that targeting the ACS patient with AHF early can dramatically alter short- and long-term mortality.

The intersection of AHF and ACS is deadly. Although some have reported encouraging improvements in early survival over recent decades,\(^7\) the current report from the GRACE registry reminds us that the incidence, in-hospital mortality, and long-term survival remain unacceptably high. Clinical predictors now exist, and health system strategies may be needed to correct the alarming observations that AHF complicating ACS leads to lesser and later intensive management. Further investigations should target patients with AHF; they are at the highest risk, have the most to gain, and provide the medical community with the greatest possibility of continuing to decrease the human and economic burden of ACS.

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