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EDITORIAL COMMENT

# Theory and Fact

## Revisiting Association and Causation*

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*"I pass with relief from the tossing sea of Cause and Theory to the firm ground of Result and Fact."*
—Winston S. Churchill,
The Story of the Malakand Field Force (1)

*"One of the first things taught in introductory statistics textbooks is that correlation is not causation. It is also one of the first things forgotten."*
—Thomas Sowell,
The Vision of the Anointed:
Self-Congratulation as a Basis for Social Policy (2)

The concentration of endothelin (ET)-1 has been repeatedly demonstrated to be prognostic in patients with heart failure (3,4). Indeed, it has been shown to be more predictive of both mortality and hospitalization than most hemodynamic, inflammatory, and fibrotic biomarkers (5). Furthermore, ET has hemodynamic and physiologic effects that appear to be detrimental in the presence of cardiac dysfunction. Thus, it was very reasonable to assume that ET antagonism would be beneficial. The ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) trials, now published after a long delay (6) in this issue of *JACC: Heart Failure*, tested the hypothesis that bosentan, a dual ET receptor antagonist, would improve the clinical status of heart failure patients.

The trials took into account problems in prior studies. Fluid retention has been previously seen, so the fluid status of patients was watched carefully. There was concern that high doses might not be initially tolerated, so the dose of bosentan was titrated. There was enough optimism to design a study in which 1,613 severely ill patients were enrolled.

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Despite an excellent study design and implementation, blockade of ET actually worsened outcomes. This result emphasizes the need for well controlled and designed studies to bring us from "Cause and Theory to the firm ground of Result and Fact" (1). Despite excellent reasoning and highly prognostic biomarkers, only such studies can teach us how to treat patients.

The field of heart failure is ripe with examples of successful interventions based upon prognostic factors (beta-adrenergic antagonists and renin-angiotensin-aldosterone system interventions rapidly come to mind). However, we also know that prognostic factors might only identify high-risk individuals with the association not indicating causation. Is renal dysfunction the cause of worsening heart failure or a consequence? When is tachycardia the problem or reflection of the problem? What do we make of the obesity paradox?

Preventing 30-day readmissions has been the latest cause of health care providers forgetting that association is not causation. Hospital administrators are developing complicated algorithms to predict those at risk. Does knowing that patients with cancer are more likely to be readmitted help us to personalize care? While focusing on social issues to prevent readmission has been important, those who assume that decreasing 30-day readmission rates will decrease mortality have forgotten the basic statistical teachings.

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We must therefore be very careful before assuming that addressing hypotension or cardiac output or the latest prognostic biomarker will improve outcomes. Perhaps they will. Conventional inotropes have not been proven effective, but it is certainly reasonable to assess the impact of the hemodynamic effects of omecamtiv mecarbil. Although natriuretic peptides are prognostic, interventions to lower them appear to work only when proven therapies (unrelated to natriuretic peptide concentrations) are increased. Prognostic factors are worth assessing because they teach us about physiology and suggest possible interventions. But any intervention needs to be carefully tested in studies we can trust.

The ENABLE studies did carefully evaluate an ET antagonist, leading to the conclusion that ET-1 antagonists should not be used for the treatment of heart failure. Nevertheless, there is still much to learn and studies about the physiology that might provide clinically important information should be continued. For example, although ET theoretically causes salt and fluid retention, these studies show that its antagonism leads to retention. Complex renal cortical, proximal tubule, blood pressure, renin-angiotensin-aldosterone system axis, and sympathetic nervous system effects all make prediction of net renal outcomes in patients difficult. The cardiac effects are also complicated. Not only has ET receptor antagonism been reported to exacerbate autoimmune myocarditis (in mice), but ET-1 also modulates coronary blood flow, affects cardiac muscle function, induces cardiomyocyte growth, and is associated with maladaptive cardiac remodeling. Careful studies may lead us to illuminate specific beneficial effects of antagonizing a powerful prognostic factor, but for now we can be confident that ET antagonists should be avoided in patients with heart failure. The facts are clear because of the well-designed, placebo-controlled ENABLE studies.

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