Are Biomarkers the Answer to the Heart Failure Readmissions Problem?

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Readmissions after hospitalization for heart failure (HF)3 are an increasingly important problem, with 1 in 4 patients rehospitalized within 30 days of discharge. Given the economic and public health implications of readmissions, several health care–related institutes and payers have focused on this metric as an indicator of the quality of care. On October 1, 2012, the Centers for Medicare and Medicaid Services (CMS) began to financially penalize hospitals with higher than expected 30-day readmission rates for pneumonia, acute myocardial infarction, and HF. This has led to advocacy for a variety of approaches to reduce readmissions, including improved coordination of care in the postdischarge period, earlier postdischarge follow-up, more home-based follow-up, and enhanced patient education and self-management. Because biomarkers play an important role in the diagnosis and management of HF, there has been interest in understanding their potential as part of a strategy to reduce readmissions.

There are two potential roles for the use of biomarkers in a strategy to reduce readmissions in HF. First, biomarkers may help to predict which patients are at increased risk for readmission. Second, monitoring serial values in the outpatient setting may allow for early intervention aimed at reducing readmissions. Although the use of biomarkers in identifying patients at highest risk for readmissions seems like a natural extension of their current use, there are several problems to address.

What biomarkers would be most useful in this setting? Although a wide variety of biomarkers have been demonstrated to predict death in patients with HF, their record is more mixed in regard to predicting readmission. Natriuretic peptides are the most commonly used markers in this regard. In a single-center study of patients admitted with acute decompensated HF, B-type natriuretic peptide (BNP) measured at hospital discharge was a strong predictor of 1-year mortality, having an area under the ROC curve (AUC) of 0.78, but was no better than a flip of a coin at predicting 1-year readmission for HF (AUC of 0.47) (1). While other studies have demonstrated a slightly more promising role for natriuretic peptides in predicting readmission, the cutoff values used for prediction vary from study to study. Furthermore, the biological variation associated with this these analytes means that marked changes are necessary to be sure they are not simply due to spontaneous variation. Serial values may be more helpful, but there is more work to be done to understand how to use these values and devise treatment strategies to assist in patient care.

Novel biomarkers, such as ST2 and galectin-3, may have potential use either alone or as part of a multimarker strategy to predict readmissions. ST2, a member of the interleukin-1 receptor family, has been linked to the development of cardiac fibrosis, hypertrophy, and ventricular dysfunction and has emerged as a novel cardiovascular biomarker. Galectin-3 plays a central regulatory role in several biological and pathological disease processes. In the heart, galectin-3 is believed to contribute to maladaptive cardiac remodeling by augmenting fibrosis. Both ST2 and galectin-3 have been demonstrated to independently predict death in HF. In a Mayo Clinic study, ST2 was the most potent predictor of rehospitalization of all biomarkers assessed (2). Recent reports have also suggested that galectin-3 is a potent predictor of readmissions in patients with HF.

Even if biomarkers are useful in predicting readmissions, several additional questions must be addressed before one can implement such a strategy. For example, when should the biomarkers be measured? Whereas most postdischarge prognostic models rely on variables measured on the day of hospital discharge, in the case of readmission, there has been interest in the prognostic value of information gathered during the widely advocated 1-week follow-up visit. However, readmissions occur frequently in the early days after hospital discharge. By postdischarge day 7, 31.7% of all 30-day readmissions have already occurred (3) and would be ineligible for interventions informed by a strategy that relied on data from a 1-week visit. Thus, given the short-term nature of the 30-day metric, a focus on values obtained at the time of hospital discharge may represent the most prudent approach.

Finally, and most importantly, once patients at highest risk for readmission are identified, what should

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1 Nonstandard abbreviations: HF, heart failure; CMS, Centers for Medicare and Medicaid Services; BNP, B-type natriuretic peptide; AUC, area under the ROC curve.
be done about it? Biomarkers may also be useful as a monitoring parameter to guide interventions to reduce rehospitalizations in high-risk HF patients. Although attractive, the use of biomarker-guided therapy, perhaps most notably tested with the natriuretic peptides, has not been particularly effective at reducing readmissions. In the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) trial (4), patients discharged after an HF hospitalization were randomized to clinically guided therapy or therapy based on N-terminal BNP concentrations. Although most HF events (64%) were preceded by an increase in N-terminal BNP concentration, which often resulted in intensification of diuretic therapy, there was no difference in rates of cardiovascular or HF rehospitalization between the two arms. Importantly, this signifies that even if worsening HF can be predicted, it might not be preventable. Some would argue that this is because the increment of reduction in natriuretic peptides was inadequate given the large biological variation. Biological variation is high for the natriuretic peptides, but it is unclear what the comparable variation is for ST2. It appears that galectin-3 does not change markedly, and thus only solitary values appear necessary. Further, perhaps clinicians were implementing the wrong therapies based on the biomarker concentrations. Natriuretic peptides, ST2, and galectin-3 all interface with pathways that facilitate fibrosis. Therefore, aldosterone antagonists may have therapeutic value in the setting of increased biomarker values and are worthy of further investigation. However, although their use is already advocated in the HF guidelines, biomarkers remain underused.

Regardless of the approach, its success will depend on the etiologies of the readmissions. Recent data suggest that most readmissions after a HF hospitalization are due to conditions other than HF (3). Although the most common reason for readmission within 30 days of HF hospital discharge is HF, it still only accounts for 35.2% of all 30-day readmissions (3). Because patients with HF are often elderly with several comorbidities, they are at high risk for readmission for noncardiovascular issues. This multi-morbidity makes efforts to reduce readmissions particularly challenging because adequately treating the patient’s HF alone is unlikely to prevent most patients from returning to the hospital. This highlights the importance of a comprehensive approach when designing strategies to target the readmissions problem. Even if biomarkers are 100% successful in preventing readmissions due to HF, it seems less plausible that they would have value in predicting noncardiovascular readmissions. Thus, even in the best-case scenario, it is likely they would only be able to predict a modest portion of the problem.

To date, in a scramble to avoid readmission penalties, institutions have primarily implemented blunt, one-size-fits-all strategies based on little evidence. Although there have been some anecdotal reports of reduced readmission rates with various approaches, most tactics have fallen short (5). Unfortunately, accurately predicting which patients are at highest risk for readmission so that therapies can be targeted to that population has proven to be difficult. The models developed have suffered from poor discrimination and have often identified factors, such as patient demographics, that are not amenable to modification or intervention. Approaches that include biomarkers may suffer the same fate unless incorporated into a comprehensive strategy. The family physician who integrates care is gone from many of our systems, and in our increasingly subspecialized world, comprehensive approaches are more difficult. However, without an integrated approach it is unlikely that the use of biomarkers will be successful in reducing readmissions.

Diagnostic companies often want to do simplistic studies that point toward the value of their products while avoiding intricate designs. Such an approach may not serve us well in this complex environment.

Thirty-day readmission is currently the parameter being followed most closely by CMS, and thus has the greatest potential financial implication to institutions. Patients who have been hospitalized once with HF are likely to be hospitalized again, even if the 30-day mark can be avoided. While reimbursement metrics may change, improving the quality of life for patients living with HF will remain a goal of research efforts and care. Because hospitalizations remain a significant contributor to morbidity in HF, future research should continue to focus on developing strategies to avoid preventable hospitalizations over the course of the disease.

Biomarkers have the potential to be helpful in the effort to reduce hospitalizations in patients with HF. Future research efforts should include investigating which biomarkers, alone or in combination, best predict readmission due to HF and probing therapeutic options. Ideally, these biomarkers will be incorporated into better, more clinician-friendly risk assessment tools. Such approaches will require collaboration between individuals involved in biomarker development, outcomes research, and the development of systems for more facile care of the individual patient. This problem is emblematic of our need to expand our thinking into the better integration of overall care as our population ages. Only then will the contribution of biomarkers to the subset of patients with HF be potentially realized.

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