Optimizing clinical risk stratification in acute heart failure

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Introduction

Heart failure is a clinical syndrome characterized by a constellation of symptoms and signs caused by cardiac dysfunction. It is one of the major causes of morbidity and mortality in the developed countries, with a prevalence of 1-2%. Acute heart failure (AHF) is defined as a rapid onset of signs and symptoms of heart failure resulting in the need for urgent therapy which can occur as worsening of chronic heart failure or a presentation of a new heart failure. AHF is the leading cause of hospitalization in adults older than 65 years of age. Despite marked improvements in the prognosis of chronic heart failure patients primarily related to therapeutic advances over the past few decades, both short- and long-term outcomes remain very poor once patients are hospitalized for decompensated heart failure. Nearly 25% of patients hospitalized for AHF need readmission within 30 days of hospital discharge while <50% survive beyond 5 years after hospitalization. In addition to significantly reducing survival and quality of life of affected patients, the monetary burden of AHF on health care systems is enormous. The total cost of heart failure care was estimated to be $31 billion in the US alone in 2012 and majority of this cost is associated with inhospital care. This cost is projected to increase to an unprecedented $70 billion in 2030 due to ageing of populations.

There is a huge unmet medical need for therapeutic strategies that can improve survival and curb the high rates of hospital readmissions associated with hospitalization for AHF. Numerous strategies had been proposed and tested in randomized controlled trials with the goal of reducing the unacceptably high rates of readmission and mortality in AHF patients. However, development of such strategies remains highly elusive despite the massive effort to do so. A plethora of factors has been identified as contributing for the futility of these efforts among which the heterogeneous nature of the patient population in terms of etiology, pathophysiology and clinical needs is the most frequently cited. The ‘one-size-fits-all’ approach currently implemented both in the management of AHF and development of new therapeutic strategies fails to address this heterogeneity in the underlying patient population.

The necessity for the implementation of more targeted, need-based treatment strategies to curb the enormous burden of AHF on patients and health care systems is well recognized at this stage. There is already a decades old experience in preventive cardiology supporting the effectiveness of risk-based treatment strategies in terms of reducing both the humanitarian and monetary burdens of cardiovascular events in the general population. Interestingly, a glimpse of evidence suggesting that such strategies might also be promising in the management of AHF patients is available. Successful development of risk-based treatment strategies and translation into clinical practise require accurate and objective risk stratification tools. Nonetheless, risk stratification in AHF patients remains a clinical challenge.

Biomarkers are among the most promising contemporary tools for enhancing prognosis and risk stratification in patients hospitalized with AHF. Plenty of prognostic biomarkers reflecting diverse pathophysiologic pathways involved in heart failure have been identified over the past years. Clinical utility of these prognostic biomarkers is, however, highly limited. There are several methodologic drawbacks in many of the studies evaluating prognostic value of biomarkers. An important methodologic aspect that is often overlooked, not just in prognostic biomarker studies but also in heart failure research in general, is the presence of competing risks. Failure to deal with competing risks, particularly while evaluating non-mortality outcomes like rehospitalization, might lead to significantly biased findings. In addition, most studies focus on a single time-point, single biomarker-based strategy; an approach that fails to address the multitude of pathophysiologic mechanisms and clinical processes involved in the setting of AHF. Lack of data on optimal timing of measurement of biomarkers (besides the natriuretic peptides) is an additional factor that could hamper the clinical utility of prognostic biomarkers. Moreover, there is a significant gap with respect to defining mechanisms by which individual prognostic data can be utilized to facilitate the development and implementation of interventions that can improve outcome in AHF patients.

Overview of the thesis

Part I focuses on competing risks in the setting of prognostic heart failure research. The competing risks situation is an aspect of survival analysis which comes into play when the occurrence of one event precludes another event from occurring. This, for instance, can occur when one is interested in a readmission outcome after discharge for hospitalization for AHF. In this case, mortality acts as a competing event since the occurrence of death, by definition, precludes subsequent readmissions. Although the competing risks phenomenon is rampant in prognostic heart failure research, it is hardly dealt with the proper statistical methodology. Unless dealt with the appropriate statistical techniques, the presence of competing risks could lead to biased estimates of risk. In addition, it might also lead to inflation of estimates of performance for a prognostic variable/model under consideration.

Chapter 1 illustrates estimation of cumulative incidence in the presence of competing events in the setting of AHF.

Chapter 2 evaluates the potential impact of ignoring competing events on cardiovascular risk prediction and stratification using a classic prognostic model utilized in preventive cardiology (i.e. the Systematic COronary Risk Evaluation (SCORE) model)

Part II addresses biomarker-based risk stratification in AHF patients. There is an ever growing interest in biomarkers in AHF based on the premise that they can serve as simple, objective yet inexpensive prognostic tools. These attributes make biomarkers ideally suited to augment risk stratification in AHF which is currently a significant challenge for the clinicians treating these patients. Plenty of prognostic biomarkers have been defined in AHF, yet clinical utility remains very limited. Current strategies focus on single biomarkers, a strategy that is highly unlikely to be adequate in the light of the complex array of pathophysiologic pathways involved. Moreover, serial evaluation might be needed for most biomarkers considering the multitude of clinical and hemodynamic changes that occur in these patients during the inhos-

pital treatment phase and post-discharge. However, evidence on the optimal timing of measurements and added value of serial evaluation of biomarkers is lacking at this stage except for the natriuretic peptides. **Chapter 3** assesses the added prognostic value of a combination of biomarkers reflecting diverse pathophysiologic pathways and further evaluates the timing of biomarker measurements, during hospitalization or early post-discharge phase, that maximize prognostic performance. **Chapter 4** investigates the incremental value of a multimarker panel of serially evaluated biomarkers over a single time-point-based single marker strategy.

Assessment of added value on top of readily available patient-related parameters is an essential first step towards ascertaining the potential role of an individual biomarker or a multimarker panel for prognostication and risk stratification of AHF patients. Translation of this potential to clinical utility demands further evaluation of the role of biomarkers in terms of solving the day-to-day risk stratification related clinical challenges doctors involved in the management of AHF face. One of these clinical challenges is diagnosis of bacterial infections. Bacterial infections are among the major precipitating factors for AHF hospitalizations and carry worse outcome unless treated timely and adequately. However, diagnosis of bacterial infections in AHF, particularly respiratory infections, is difficult primarily due to overlapping clinical and radiologic features. Procalcitonin is gaining prominence as a highly specific marker of bacterial infections and could play an essential role in facilitating identification of potentially high risk AHF patients with otherwise underdiagnosed bacterial infections. **Chapter 5** examines the prognostic implications of significantly elevated procalcitonin levels in patients hospitalized with AHF with no overt clinical signs of bacterial infection. Another risk stratification related clinical problem in AHF patients is predischarge risk ascertainment. The need for objective decision-making regarding length of hospital stay and intensity of post-discharge care could not be overstated. A strategy that combines early discharge of patients at low-risk for post-discharge events and more intensive and extended hospital stay with intensive post-discharge care in high risk patients can play a crucial role in terms

of facilitating efficient utilization of scarce health care resources and, ultimately, leading to improved outcomes. **Chapter 6** presents findings of a comparative analysis evaluating the value of biomarkers evaluated close to discharge for the identification of hospitalized AHF patients at low and high risk for post-hospital discharge events.

Part III introduces one mechanism by which risk stratification tools could be used to facilitate the development and implementation of new interventions that can improve outcome in AHF patients. The presence of significant differences among the AHF patient population in terms of etiology, pathophysiology and plenty of clinical factors prompts the consideration of the possibility that different subpopulations of patients might differentially respond to a specific pharmacologic or non-pharmacologic therapeutic intervention. This concept, commonly referred to as heterogeneity in treatment effect (HTE), is well recognized in clinical trials involving AHF patients. The conventional approach for the evaluation of HTE in these trials, however, fails to address the complex interactions among factors that can influence treatment response besides being prone to notable methodologic deficiencies. Risk prediction models could serve as methodologically robust alternatives that can facilitate the detection, interpretation and extrapolation of clinically relevant differences in treatment response among subpopulations. **Chapter 7** presents findings of a post-hoc analysis of the PROTECT trial in which risk-based heterogeneity in the efficacy of rolofylline in patients hospitalized with AHF was evaluated.

PART I

Competing risks in AHF research