Landmark clinical trials have firmly established implantable cardioverter defibrillator (ICD) therapy as the cornerstone of sudden death prevention in patients with systolic heart failure stemming from both ischemic and nonischemic cardiomyopathies. Despite the widespread use of ICDs, a recent analysis of the Get With The Guidelines Heart Failure Registry suggested that an ICD may be indicated to prolong survival for an additional 800000 patients with heart failure in the United States. Guideline recommendations for primary prevention ICD therapy are based on efficacy demonstrated among highly selected outpatients with stable, mild-to-moderate heart failure symptoms. These efficacy data have in turn been used to generate estimates of cost-effectiveness. In contrast to those patients enrolled in the pivotal trials, a substantial proportion of real-world ICD recipients are older, hospitalized at implant, or have a greater burden of comorbid medical conditions. Each of these factors may increase the risk of nonarrhythmic death and attenuate the incremental survival benefit conferred by primary prevention ICDs in otherwise eligible patients. Clearer identification of those patients whose dominant risk is from decompensated heart failure or noncardiac comorbidities will allow more focused ICD therapy in those for whom the device promises to provide meaningful prolonging of life.

Most primary prevention ICD recipients never experience an appropriate defibrillator shock. Multiple strategies have been studied to better target ICD therapy to those at highest risk. Sophisticated tools, such as magnetic resonance imaging, invasive electrophysiology study, and surface ECG analysis, have unfortunately proven to be neither a practical nor an efficient means of stratifying sudden death risk. Only a persistently reduced left ventricular ejection fraction ≤35% has endured in the guidelines as the central risk marker to triage candidates with chronic heart failure to a prophylactic ICD. As might be expected, there remains considerable risk heterogeneity for sudden death within this broadly defined group of patients with a low ejection fraction group. Clinicians are left with little actionable information from which to personalize recommendations and inform shared decisions about this invasive, life-long therapy. Increased awareness of the burgeoning costs of the heart failure epidemic has also now converged with the precision medicine movement to create an opportunity to revisit risk stratification strategies for ICD candidates.

In this issue of Circulation: Heart Failure, Lee et al present a timely new conceptual model for exploring the competing risks of appropriate shocks and mortality in patients receiving an ICD for the primary prevention of sudden death. Their analysis is derived from a prospective, population-based registry of referrals for ICD implantation in Ontario, the most populous province of Canada and home to a single-payer system that facilitates comprehensive data capture. The study excluded inpatient recipients, patients with special indications for ICD therapy, and those patients who refused a device. The final cohort of 3445 primary prevention ICD recipients largely mimics those patients enrolled in the landmark trials. All ICD recipients were ambulatory patients. A majority were men with an ischemic cardiomyopathy, whereas the median age was 66 years. Most recipients had less symptomatic heart failure, including 65% with New York Heart Association Class I/II functional capacity, and only 38% had experienced a prior heart failure hospitalization.

Unlike previous studies of post-ICD outcomes, Lee et al used routinely available clinical variables to develop 2 separate models for predicting both appropriate ICD shock and all-cause mortality and then juxtaposed these 2 competing risk models. Median follow-up after implant was 2 years, which captured 4.9 deaths/100 person-years and 3.6 shocks/100 person-years, event rates reflecting a stable ambulatory cohort with a low heart failure burden. Cumulative incidence of appropriate shock at 1 year ranged =10-fold from lowest to highest decile and nearly 20-fold for mortality. Multivariable predictors of the 2 events were established, and 17 of 22 predictor variables in the competing risk models were associated with only a single outcome. After regression modeling and bootstrap correction of the estimates, the Bimodal Survival and Implantable defibrillator Shocks (BaSIS) risk scoring system was established. Using the model, the adjusted hazard ratio for appropriate shock was nearly 8-fold from lowest to highest risk group and was 36-fold for death, suggesting an impressive ability to risk stratify across both domains of risk.

The study authors then cleverly plotted modeled risk for individuals according to both mortality and appropriate shock to better conceptualize the multiple dimensions of risk. The highest risk decile for mortality and lowest risk for shock were set as potential thresholds for reconsidering implant. The vast majority of ICD implants (82.6%) were in the high benefit sweet spot of patients at high shock risk and low mortality risk. Only 2.5% of recipients were in the lowest benefit group as defined by high risk of mortality and low risk of ICD shock.
Most of these low benefit ICD recipients had a heavy burden of heart failure as defined by high New York Heart Association class or recent heart failure hospitalization, risk markers well established in the literature to predict post-ICD mortality. It is not yet clear how much net reclassification away from an ICD recommendation would result from deploying this new framework, particularly because the cohort implanted were already reflective of clinical trial participants.

Overall, these findings confirm the broad appropriateness of ICD use in this large regional cohort, while at the same time identifying potential thresholds for reconsidering the decision to proceed with implant. The BaSIS model provides a novel conceptual framework for approaching the assessment of risk after ICD implantation. By exploring the overlapping risk features for both shock and death, the study provides a balanced view of the uncertainties patients and clinicians face when weighing the decision to implant a primary prevention ICD. These data reinforce that the conversations between physician and patient surrounding ICD implant should serve as a milestone in heart failure care, as well as an opportunity to review expectations of the heart failure disease trajectory.

The authors acknowledge and address most of the important limitations of this analysis. First, the BaSIS model is presented as a decision support tool before ICD implant, yet all patients modeled actually received an ICD after considerable attrition from initial referral population. The modeled cohort was generally at low risk of death so that predictive variables might be different or of different magnitude in a different ICD cohort enriched with older, hospitalized heart failure patient with a greater number of comorbid conditions. This problem of healthy candidate bias in the derivation cohort of ICD recipients partially undermines the claims that the BaSIS model has been validated by the bootstrap correction. Despite the good track record of bootstrapping methods, concerns will inevitably remain about the calibration and discrimination of any model in the absence of split-cohort validation or confirmation in a separate cohort. As such, the BaSIS model must be considered exploratory. Indeed, it is relatively easy to discriminate risk profiles of patients in a cohort where the outcomes are already known. It is a far harder task to estimate the probability of an outcome for a given individual then be confident enough in that prediction to sway a decision when the stakes are high and there is an effective, readily available therapy. Without more robust validation, the direct applicability of this exploratory model to individual patient care is likely to be limited.

Another notable limitation is that the model exclusively covers early risks experienced after ICD implantation. The risk stratification curves presented are confined to only the first year and do not present confidence boundaries. Given the dynamic nature of risk profiling in heart failure, this is an easy approach to defend. However, an early time horizon of risk may be an inappropriate means to inform decisions surrounding what nearly always amounts to a lifelong therapy. In the landmark trials, the survival curves with and without ICD do not separate until around 1 year after implant, suggesting latency to ICD benefit. Because intermediate or long-term outcomes are not available for risk modeling in this cohort, the authors suggest that the BaSIS score can simply be used as a means to recalculate risk each year and reset expectations. Indeed, the BaSIS model can at best only shine a light on the immediate road ahead. Despite these limitations, any effort to make risk assessment a centerpiece of any annual heart failure review remains laudable, even though the tools at our disposal to assay competing risks remain imperfect.

Several important considerations about device selection and configuration in this study are worth noting. ICD programming in the study was not mandated, but most of the enrollees in this study received their device after the Primary Prevention Parameters Evaluation (PREPARE) trial was published. Although delayed or high-rate therapy was not made explicit, we can expect appropriate shocks to approximate aborted sudden death. Each episode of an ICD shock was carefully adjudicated before being declared to be appropriate. Next, 38% of ICD recipients had cardiac resynchronization (CRT) coimplanted. The authors took great pains to remodel risk and interaction of the model with CRT and show that CRT did not significantly change model performance for risk stratification. However, the mortality and shock risk that BaSIS explores are not the only considerations for the CRT-eligible population. The decision to implant a CRT device also centers on the hope for an improved functional capacity and quality of life.

Finally, only ambulatory patients receiving an ICD were included in the derivation cohort. More than one third of Medicare beneficiaries in the United States are implanted during a nonselective inpatient hospitalization, most often for heart failure management. Such patients have a greater cumulative burden of comorbidities and more severe heart failure, likely reflecting a different landscape of competing risk. It is not yet known whether the BaSIS model can be applied to patients implanted during a hospitalization intended to stabilize another illness. Furthermore, heart failure hospitalization itself has been shown to predict early death and lower ICD efficacy in the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II). Patients with repeated heart failure hospitalizations are more likely to die from nonarrhythmic causes of death, such as progressive heart failure or noncardiac causes. The decision to implant a primary prevention ICD in a patient with multiple previous heart failure hospitalizations should be made cautiously and with appropriately calibrated expectations of heart failure survival.

It is in older patients with heart failure and multiple comorbidities where the need for competing risk assessment remains greatest and where the decision to implant an ICD often becomes the most difficult. More than one third of Medicare ICD recipients are dead within 3 years of implant. This stark fact reflects a real-world population of ICD recipients who in aggregate has more advanced age and disease than seen in trial populations for primary prevention. Appropriately selected Medicare beneficiaries with a low heart failure burden have been shown to have outcomes and survival similar to trial ICD recipients, and so age alone is clearly not the only factor in play. Thoughtful candidate selection for ICD therapy is the linchpin of responsible and cost-effective patient care.

This thought-provoking article by Lee et al adds to the momentum to change the conversation surrounding ICD implantation and highlights the complex matrix of considerations influencing this seemingly straightforward decision. The article offers a fresh framework for estimating competing risk of appropriate shock and mortality in a patient with heart failure referred for a...
primary prevention ICD. Current guidelines for both heart failure and device-based therapy suggest ICD use in chronic heart failure patients with reduced ejection fraction when there is anticipated survival of at least a year with good functional capacity.9,10 It is imperative that we continue to explore how best to estimate and then communicate these expectations of survival and quality of life to our patients with heart failure. Because physicians and healthcare systems are increasingly motivated by value-driven care, assessment of both ICD benefit and cost-effectiveness must be inevitably recalibrated based on factors, such as frailty and comorbidity burden not reflected in current guidelines. We would do well as a community of caregivers to redouble our efforts to map the uneven terrain of competing risk over which our patients with heart failure must travel.

Acknowledgments
Thank you to the Kenneth L. Baughman Master Clinician Scholar in Cardiovascular Medicine Program at Brigham and Women’s Hospital for its ongoing support.

Disclosures
None.

References

Key Words: Editorials || idiopathic dilated cardiomyopathy || heart failure || implantable cardioverter-defibrillator || risk stratification || sudden death
Mapping the Terrain of Competing Risk Following Primary Prevention Defibrillator Implantation
Garrick C. Stewart

Circ Heart Fail. 2015;8:847-849
doi: 10.1161/CIRCHEARTFAILURE.115.002503

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/8/5/847

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/