Randomized clinical trials have established the efficacy of certain therapies to reduce all-cause mortality for patients with heart failure and reduced ejection fraction (HFrEF), but uptake in clinical practice has been variable. More recently, the angiotensin receptor neprilysin inhibitor (ARNI, sacubitril/valsartan) has been demonstrated to reduce cardiovascular death and HF hospitalization compared with enalapril in the Prospective Comparison of ARNI With ACEI To Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. A prior study has determined the potential mortality reductions that could be achieved with optimal implementation of other HFrEF therapies. However, to date, the potential magnitude of benefits of implementation with ARNI therapy in terms of preventing or postponing deaths has not been quantified at the population level.

**Methods**

Potential patient eligibility for ARNI therapy and the expected mortality benefits with ARNI treatment were identified using published sources, following the methods applied in a previous study. Eligibility for ARNI therapy was based on the population of patients with HF covered in the current US Food and Drug Administration-approved labeling. The number of patients with HF in the United States was based on data selected for the 2016 American Heart Association Heart Disease and Stroke Statistics Update. Rates of medical exceptions, potential contraindications, intolerance, or other patient, physician, or system reasons for not applying angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/ARNI therapy were derived from published sources.
The magnitude of mortality reduction for ARNI was determined from the PARADIGM-HF trial. The number needed to treat (NNT), standardized to 12 months, was used to calculate the number of potential lives saved per year with ARNI therapy, as previously described. We also evaluated benefit in a multiple-way sensitivity analysis, using the analysis-of-extremes method. This approach assigns a lower value and an upper value, using ±20% relative differences for the number of patients eligible for treatment and risk reduction variables. An additional sensitivity analysis was performed, applying additional inclusion criteria from the PARADIGM-HF trial based on natriuretic peptide levels, renal function, ACEI/ARB dosing, and dropouts during the run-in phase.

Results

The prevalence of HF is 5,700,000 cases per the entire US population, and 48% of these patients have a left ventricular ejection fraction of less than 40%. Of the 2,736,000 patients with HFrEF, there were additional exclusions applied for patients under hospice or comfort care—only measures (4%) and those receiving continuous inotropic agents, requiring ventricular assist devices, or requiring urgent heart transplantation (1%). For the remaining 2,599,200 patients with HFrEF, 7% were excluded based on contraindications/intolerance of ACEI/ARB/ARNI, and an additional 5% for having systolic blood pressure of less than 95 mm Hg, leaving 2,287,296 patients as candidates for ARNI therapy (Figure).

The magnitude of benefit demonstrated with ARNI therapy incremental to ACEI therapy, along with those for other evidenced-based HFpEF therapies, are shown in the Table. The NNT to prevent 1 death, standardized to 12 months, was calculated to be 80.3. The number of deaths that could potentially be prevented each year with optimal implementation of ARNI therapy would be 28,484. Multiple-way sensitivity analyses using the analysis-of-extremes method yields the range of deaths potentially avoided from a lower limit of 18,230 to an upper limit of 41,017. Using product limit survival rates and actual follow-up times from the PARADIGM-HF trial yields a NNT of 71.3. Based on this alternative NNT value, 32,080 patient deaths could potentially be prevented each year. Applying additional exclusions (totaling an additional 35% excluded) based on the PARADIGM-HF trial entry criteria yields 1,486,742 patients eligible and 18,515 deaths potentially prevented per year.

Discussion

Heart failure continues to result in more than 300,000 deaths a year, highlighting the need for therapies that provide additional benefits beyond previously established therapies. Based on the findings of this study, if ARNI therapy were comprehensively applied to eligible patients with HFrEF in the United States, then 28,484 deaths per year could be prevented or postponed. These findings have significant clinical and public health implications, providing the first quantification of the magnitude of the survival benefits at the population level that may result from full implementation of ARNI therapy for patients with HFrEF.

Establishing the potential population-level benefits with optimal implementation of a new HF therapy may be of considerable importance when weighing the extent to which resources should be devoted to implementation of the new therapy relative to other ongoing national quality-improvement efforts. Some have advocated that a substantial period of time (2-7 years) should pass from when a new therapy is first approved to when it is routinely prescribed in clinical practice, allowing for potential issues regarding safety to emerge.
These findings suggest that there may be substantial downsides in delaying implementation of this new therapy in clinical practice, even if subsequent unforeseen safety issues were to emerge, with potentially tens of thousands of deaths resulting that otherwise could have been prevented or postponed with more timely and complete implementation.

This analysis is based on the premise that the magnitude of efficacy demonstrated in the PARADIGM-HF trial will translate into a similar degree of effectiveness when applied to the population of patients with HFrEF encountered in clinical practice. Prior observational studies of the clinical effectiveness of ACEI/ARB therapy suggest that the observed relative risk reductions are similar to those observed in clinical trials, even in older patients. In a study of national patterns of discharge prescription of either ACEI or ARB in Medicare patients, the risk-adjusted relative risk reduction in 1-year mortality was 17%, as seen in the clinical trials. However, because the age, sex, race/ethnicity, comorbid conditions, and other characteristics of patients with HFrEF in clinical practice do differ from those enrolled in randomized clinical trials, including the PARADIGM-HF trial, the efficacy established in this trial may not translate to the same degree of clinical effectiveness in practice. This may particularly be the case for patient cohorts not adequately represented in the trial. In addition, the expected survival benefits of implementation of ARNI are also fully contingent on being able to apply this therapy with similar safety, tolerability, and dosing as achieved in clinical trials.

While this study focused on mortality, ARNI therapy has been shown to have other clinical benefits that are incremental to ACEI therapy, including reduced HF hospitalizations and the possibility of improved health status. The adoption of ARNI therapy would involve a substantial increase in medication costs, yet HF itself is a costly condition and cost-effectiveness studies suggest that ARNI therapy may provide high to intermediate value. Nevertheless, additional analyses of the financial implications of implementation at the population level are warranted.

The limitations of this study include that the proportion of patients eligible and with contraindications for ARNI therapy may deviate from the estimates used in this study. Application of more restrictive criteria would reduce the number of patients eligible and projected to benefit. If the broader HFrEF population has a greater proportion of patients with lesser or no response to ARNI or who tolerate therapy less well, the potential benefits would be less in real-world use. In the primary analysis, we accounted for 17% of patients with HFrEF who were ineligible, had contraindications, or were intolerant to ARNI, yet the actual rates could be higher. Outcomes other than mortality, adverse events, and the cost-effectiveness (ie, value) of ARNI therapy were not evaluated, but they should be evaluated in future studies.

Conclusions

We have demonstrated the potential gains that may be achieved with the application of ARNI therapy for patients with HFrEF in the United States. Given the substantial HF burden and potential benefits of implementation for preventing deaths, efforts to ensure comprehensive implementation of ARNI therapy should be considered.

ARTICLE INFORMATION
Accepted for Publication: May 4, 2016.
Published Online: June 22, 2016.
Author Contributions: Dr Fonarow had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fonarow, Hernandez, Solomon.
Acquisition, analysis, or interpretation of data: Fonarow, Yancy.
Drafting of the manuscript: Fonarow.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Fonarow, Solomon.
Administrative, technical, or material support: Fonarow, Yancy.
Study supervision: Fonarow.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
Dr Fonarow reported receiving research grants from the National Institutes of Health and consulting fees from Amgen, AstraZeneca, Merck, and Novartis. Dr Hernandez reports receiving research support from Brigham and Women’s Hospital and consulting fees from Amgen, AstraZeneca, Merck, and Novartis. Dr Solomon reports receiving research grants from Novartis to Brigham and Women’s Hospital and consulting fees from Amgen, AstraZeneca, Merck, and Novartis. Dr Yancy is a Deputy Editor, JAMA Cardiology, and they were not involved in the review process or decision to accept the manuscript for publication.
REFERENCES


