Sacubitril/valsartan vs ACEi/ARB at hospital discharge and 5-year survival in older patients with heart failure with reduced ejection fraction: A decision analysis approach

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Abstract

Background In clinical trials, sacubitril/valsartan has demonstrated significant survival benefits compared to angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARB). Whether older patients with heart failure with reduced ejection fraction (HFrEF) benefit as much, due to higher rates of comorbidities, frailty and drug discontinuation, is unknown.

Methods and results Using a cohort of Medicare beneficiaries hospitalized with HFrEF between 2016 and 2018, we determined all-cause mortality and HF-readmission rates among patients not given ACEi/ARB or sacubitril/valsartan at hospital discharge, by age. We then used risk reductions from the SOLVD, PARADIGM-HF and PIONEER-HF trials to estimate the benefits of ACEi/ARB and sacubitril/valsartan. We then incorporated age-specific estimates of drug discontinuation from Medicare. A Markov decision process model was used to simulate 5-year survival and estimate number needed to treat, comparing discharge on ACEi/ARB vs sacubitril/valsartan by age. After accounting for drug discontinuation rates, which were surprisingly slightly higher among those discharged on ACEi/ARB (2.3%/month vs 1.9%/month), there was a small but significant survival advantage to discharge on sacubitril/valsartan over 5 years (+0.81 months [95% CI 0.80, 0.81]). The benefit of sacubitril/valsartan over ACEi/ARB did not decrease with increasing age – the number needed to treat among 66 to 74-year-old patients was 84 and among 85+ year-old patients was 67.

Conclusions Even after accounting for "real world" rates of drug discontinuation, discharge on sacubitril/valsartan after conferred a small, but significant, survival advantage which does not appear to wane with increasing age. (Am Heart J 2022;250:23–28.)

Based on the results of the PARADIGM-HF study,[1] in 2016 the American Heart Association, American College of Cardiology and Heart Failure Society of America issued a Class I recommendation that all patients with heart failure with reduced ejection fraction (HFrEF) on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEi/ARB) should be transitioned to sacubitril/valsartan.[2] Supported by the results of the PIONEER-HF study[3] and other recent work,[4] hospitalization is now viewed as an ideal opportunity to initiate or switch appropriate HFrEF patients to sacubitril/valsartan.

However, due to higher comorbidity burdens and increased frailty, there are concerns that older patients with HFrEF may not derive as much benefit from sacubitril/valsartan.[5] In PARADIGM-HF, the average participant was 64 years old.[1] In PIONEER-HF, the mean age was 61 years.[3] In contrast, today's average Medicare beneficiary hospitalized with HFrEF is 80 years old.[6] Given the potential for increased adverse event rates and the high cost of sacubitril/valsartan for many with Part D prescription coverage,[7] uncertainty remains as to whether older pa-

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Journal Subject Terms: *Heart Failure, Quality and Outcomes, Pharmacology, ACE/Angiotensin Receptors/Renin Angiotensin System*

Submitted August 31, 2021; accepted April 17, 2022

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0002-8703

https://doi.org/10.1016/j.ahj.2022.04.007

tients with HFrEF will reap the same benefits from sacubitril/valsartan as younger patients.

The aim of this study is to use "real world" rates of drug discontinuation and switching from Medicare claims and clinical trial estimates of mortality and readmission reduction to determine the association between discharging HFrEF patients on sacubitril/valsartan vs ACEi/ARB and mortality, and then determine if this association varies with age.

Methods

Study population

We created a cohort of fee-for-service (FFS) Medicare beneficiaries hospitalized with a primary diagnosis of HFrEF (Supplementary Table I) between 2016 and 2018 who had ≥1 year of FFS coverage before admission and ≥1 year of FFS coverage after admission or until death, whichever occurred first. Patients ineligible for sacubitril/valsartan or ACEi/ARB due to end-stage renal disease, hyperkalemia, hypotension or a history of allergy/angioedema were excluded. We then stratified beneficiaries based on drug fill within 30 days of discharge into 3 groups: (1) sacubitril/valsartan (n = 45,346); (2) ACEi/ARB (n = 45,846); (3) neither drug (n = 59,667). We used inverse probability weighting to balance baseline differences in socio-demographics, geographic location, comorbidities, type of HFrEF, prior health care utilization and prior medication use (Supplementary Table II).

Baseline event rates and risk reduction estimates

Using patients from Group 3 (who received neither ACEi/ARB nor sacubitril/valsartan at discharge), we used Medicare claims to determine rates of all-cause mortality and readmission due to heart failure (HF) by age group (66-74, 75-84 and 85+) during and after the first 2 months following initial discharge. To estimate the risk reduction for ACEi/ARB, we applied hazard ratios from the SOLVD Treatment[8] and SOLVD Prevention[9] studies to the baseline Medicare rates, since the placebo group in the SOLVD studies did not receive any neurohormonal therapy. To estimate the risk reduction of sacubitril/valsartan relative to ACEi/ARB, we then applied the risk reductions from PIONEER-HF[3] and PARADIGM-HF[1]. As PIONEER-HF focused on patients immediately after hospitalization and PARADIGM-HF[1] focused on stable HFrHF outpatients, we used all-cause mortality and rehospitalization for HF for first 2 months with the risk reductions from PIONEER-HF[3], then used the risk reductions from the PARADIGM-HF trial for the subsequent months (Table I). We then incorporated age-group specific and drug-specific estimates of drug discontinuation and switching from Medicare claims.

As a sensitivity analysis, we accounted for the fact that survival benefits attributable to either medication regimen will likely be restricted to cardiovascular-specific mortality, which was found to be the underlying cause in 55% of deaths in an analysis of Framingham Heart Study participants with HFrEF.[10] Given that this study observed the proportion of noncardiovascular deaths to increase with age among patients with HFrEF, we adapted their estimates for probability of cardiovascular vs noncardiovascular death by age group, applied these to Medicare mortality estimates and used hazard ratios representing risk reductions for cardiovascular death from SOLVD Treatment[8] and PARADIGM-HF.[1]

Modeling approach

We developed a discrete-time Markov decision model (Figure 1) comparing survival for hospitalized HFrEF patients discharged on either sacubitril/valsartan or ACEi/ARB. We used Markov chain Monte Carlo simulations (N = 10,000) with a 1-month cycle length and simultaneously varying lognormal distributions reflecting published confidence intervals (CI) for all hazard ratios to estimate the 5-year differences in all-cause mortality after discharge on sacubitril/valsartan vs ACEi/ARB for the full cohort and then by age category. Simulated cohort survival times were compared by Welch's *t* test. We calculated the number needed to treat (NNT) by calculating the Bayesian conditional probabilities of survival for each initial discharge regimen based on the fundamental matrix solutions for each Markov model with fixed probabilities. The proportion of patients alive after 5 years under each strategy was then used to calculate absolute risk differences. All Medicare analyses were performed using SAS version 9.4. All decision analysis modeling was done using TreeAge Pro Health Care version 20.1.2. This project was approved by the Institutional Review Board at Dartmouth-Hitchcock Medical Center.

Results

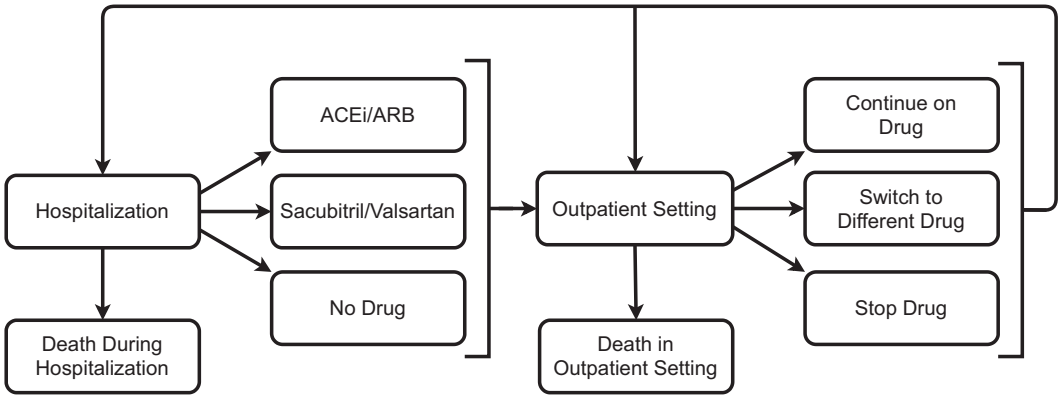
As detailed in Table II, overall, HFrEF patients discharged on sacubitril/valsartan had an estimated life expectancy of 41.61 months (95% CI, 41.19-42.02) compared to 40.80 months (95% CI, 40.38-41.22) for those discharged on ACEi/ARB ($P = .008$). This represents an absolute difference of +0.81 months (95% CI, 0.80-0.81) and a relative difference of +1.97% (95% CI, 1.94-2.01) favoring sacubitril/valsartan. Interestingly, the rate of drug discontinuation/switching was higher with ACEi/ARB than sacubitril/valsartan (2.3% vs 1.9% monthly discontinuation rate, $P < .001$), a trend that was consistent across age strata.

Among those aged 66 to 74, sacubitril/valsartan had an absolute benefit of +0.80 months (95% CI, 0.79-0.82) and a relative benefit of +1.74% (95% CI, 1.70-1.78). Among those aged 75 to 84, sacubitril/valsartan had an absolute benefit +0.75 months (95% CI, 0.74-0.76) and

Table I. Model inputs

All-cause mortality (monthly)	Source	Hazard ratio (95% CI)	Probability			
			Overall	Age 66-74	Age 75-84	Age 85+
Death on ACEi/ARB (0-2 mo)	Medicare	NA	.0248	.0157	.0182	.0327
Death on sacubitril/valsartan vs ACEi/ARB (0-2 mo)	PIONEER-HF[3]	0.66 (0.30-1.48)	.0164	.0104	.012	.0215
Death on no drug (0-2 mo)	Medicare	NA	.0415	.0191	.0271	.0560
Death on ACEi/ARB vs no drug (>2 mo)	SOLVD Treatment[8]	0.84 (0.74-0.95)	.0118	.0075	.0092	.0145
Death on sacubitril/valsartan vs ACEi/ARB (>2 mo)	PARADIGM-HF[1a]	0.84 (0.76-0.93)	.0099	.0063	.0077	.0122
Death on no drug (>2 mo)	Medicare	NA	.0140	.0089	.0109	.0172
Readmission for heart failure (monthly)						
Readmission on ACEi/ARB (0-2 mo)	Medicare	NA	.1167	.1163	.1181	.1155
Readmission on sacubitril/valsartan vs ACEi/ARB (0-2 mo)	PIONEER-HF[3]	0.56 (0.37-0.84)	.0653	.0651	.0661	.0647
Probability of readmission on no drug (0-2 mo)	Medicare	NA	.1330	.1327	.1328	.1334
Readmission on ACEi/ARB vs no drug (>2 mo)	SOLVD Prevention[9]	0.64 (0.54-0.78)	.0181	.0185	.0180	.0180
Readmission on sacubitril/valsartan vs ACEi/ARB (>2 mo)	PARADIGM-HF[1a]	0.79 (0.71-0.89)	.0143	.0146	.0143	.0142
Probability of readmission on no drug (>2 mo)	Medicare	NA	.0282	.0288	.0282	.0281
Mortality during readmission						
Death, admitted on ACEI/ARB	Medicare	NA	.038	.033	.035	.044
Death, admitted on sacubitril/valsartan	Medicare	NA	.032	.026	.028	.033
Death, admitted on no drug	Medicare	NA	.068	.050	.070	.087
Drug switching during/after readmission						
Admitted on no drug						
Discharge on no drug	Medicare	NA	.719	.695	.711	.730
Discharge on ACEi/ARB	Medicare	NA	.255	.269	.260	.248
Discharge on sacubitril/valsartan	Medicare	NA	.027	.037	.029	.023
Admitted on ACEi/ARB						
Discharge on no drug	Medicare	NA	.080	.050	.066	.094
Discharge on ACEi/ARB	Medicare	NA	.547	.576	.555	.531
Discharge on sacubitril/valsartan	Medicare	NA	.373	.374	.379	.375
Admitted on sacubitril/valsartan						
Discharge on no drug	Medicare	NA	.053	.022	.053	.085
Discharge on ACEi/ARB	Medicare	NA	.471	.465	.460	.458
Discharge on sacubitril/valsartan	Medicare	NA	.476	.513	.487	.457
Drug discontinuation/switching in outpatient setting						
On ACEi/ARB, stop ACEi/ARB	Medicare	NA	.023	.017	.024	.025
On sacubitril/valsartan, stop sacubitril/valsartan	Medicare	NA	.019	.014	.018	.022
On no drug						
Continue on no drug	Medicare	NA	.058	.051	.054	.061
Start ACEi/ARB	Medicare	NA	.024	.030	.027	.021
Start sacubitril/valsartan	Medicare	NA	.002	.003	.003	.002
Upon stopping ACEi/ARB						
Continue on no drug	Medicare	NA	.011	.012	.010	.011
Restart ACEi/ARB	Medicare	NA	.070	.069	.071	.070
Switch to sacubitril/valsartan	Medicare	NA	.002	.003	.002	.002
Upon stopping sacubitril/valsartan						
Continue on no drug	Medicare	NA	.015	.014	.015	.014
Switch to ACEi/ARB	Medicare	NA	.007	.011	.006	.006
Restart sacubitril/valsartan	Medicare	NA	.062	.063	.062	.058

Figure 1



Markov Decision Model Summary. This figure shows the possible patients flows though the model. After hospitalization for HFrEF, patients who survived could be discharged on sacubitril/valsartan, ACEi/ARB or no drug. They then transitioned to the outpatient setting where they either died, were readmitted, continued on initial therapy, switched to another therapy or stopped therapy entirely. They then could continue in the outpatient setting alive, die in the outpatient setting or be readmitted.

Table II. Survival times and NNT based on discharge drug

Age strata	Discharged on sacubitril/ valsartan (mo) mean (95% CI)	Discharged on ACEi/ARB (mo) mean (95% CI)	*P*-value	Absolute benefit of sacubitril/ valsartan over ACEi/ARB (mo) (95% CI)	Relative benefit of sacubitril/ valsartan over ACEi/ARB (%) (95% CI)	Number needed to treat (NNT)
Overall	41.61 (41.19-42.02)	40.80 (40.38-41.22)	.008	0.81 (0.80-0.81)	1.97 (1.94-2.01)	72
66-74	46.93 (46.55-47.30)	46.12 (45.74-46.51)	.004	0.80 (0.79-0.82)	1.74 (1.70-1.78)	84
75-84	44.72 (44.32-45.12)	43.97 (43.57-44.38)	.01	0.75 (0.74-0.76)	1.70 (1.66-1.73)	77
85+	38.64 (38.21-39.06)	37.54 (37.10-37.97)	<.001	1.10 (1.09-1.11)	2.93 (2.88-2.99)	67

a relative benefit of +1.70% (95% CI, 1.66-1.73). Finally, among those aged 85 and older, there was an absolute benefit of +1.10 months (95% CI, 1.09-1.11) and a relative benefit of +2.93% (95% CI, 2.88-2.99) with sacubitril/valsartan over ACEi/ARB. Overall, the NNT with sacubitril/valsartan rather than ACEi/ARB to save one 1 life over 5 years was 72. In the youngest age group (66-74 years), the NNT was 84. In the oldest age group (85+ years) the NNT was 67.

We performed sensitivity analyses by limiting benefits from treatment to cardiovascular mortality risk and varying the contribution of non-cardiovascular mortality risk by age (Supplementary Table III). Among patients aged 66 to 74, the absolute survival benefit of sacubitril/valsartan over ACEi/ARB using this more conservative approach was +0.80 months (95% CI, 0.79-0.81), the relative benefit was +1.75% (95% CI, 1.71-1.79) and the NNT was 84. In the 85 and older group, the absolute benefit was +0.93 months (95% CI, 0.92-0.94) with a relative benefit of +2.53% (95% CI, 2.48-2.58) and NNT of 77.

Discussion

After incorporating drug discontinuation and switching rates, across all age strata discharge on sacubitril/valsartan after a HFrEF admission was associated with a small, but significant decrease in all-cause mortality, compared to ACEi/ARB. Annualized discontinuation of sacubitril/valsartan was 22.8%, marginally higher – as anticipated – than the 19.6% of PIONEER-HF participants and 17.8% of PARADIGM-HF participants in each trial's respective sacubitril/valsartan arm for whom treatment was discontinued.[1,3] The association between discharge on sacubitril/valsartan and long-term mortality did not appear to decrease with age. Even adjusting for the smaller contribution of underlying cardiovascular causes among overall deaths for the oldest patients, these patients appeared to realize both the largest absolute and relative survival benefits with discharge on sacubitril/valsartan as compared to ACEi/ARB.

These results have important implications for clinical practice and policy. First, consistent with prior work, this

study found a net survival benefit of sacubitril/valsartan over ACEi/ARB and observed the relative benefit may increase with patient age.[11,12] However, by incorporating "real world" rates of drug discontinuation and switching, this study found a smaller net benefit and a larger NNT than previously reported.[12] This underscores the importance of encouraging therapy continuation to optimize the clinical benefits of sacubitril/valsartan. This has policy implications for Medicare Part D coverage, since the "donut hole" has been identified as a barrier to ongoing sacubitril/valsartan therapy.[13]

In contrast to prior studies, this study focused on whether the association between sacubitril/valsartan and outcomes varied across the age spectrum. Recent work has shown that the benefits of beta-blockers and ACEi/ARB for HFrEF are preserved across the age spectrum.[14] This work extends those findings to sacubitril/valsartan.

Limitations

This study is constrained first by its use of claims data limited to the over-65 population. Recent work has indicated that improper coding of heart failure with preserved ejection fraction as HFrEF has been observed in Medicare data despite improvements achieved with the ICD-10 coding paradigm[15] and our identification of patients with HFrEF from claims is limited by the sensitivity and specificity of the claims-based algorithm we used. Second, there may be residual confounding from unmeasured variables when generating estimates. To mitigate effects due to confounding, patients ineligible for sacubitril/valsartan and/or ACEi/ARB were excluded, and inverse probability weighting was used to match the populations receiving sacubitril/valsartan and ACEi/ARB on all available variables. Third, as treatment efficacy for mortality and readmission was not reported in the trial estimates by age, we used fixed relative treatment effects across age groups. As well, we are not able to distinguish drug discontinuation due to side effects or intolerance from potentially appropriate drug discontinuation at end-of-life. Fifth, to account for variations in the contribution of HF-related risk to total mortality risk by age, we used death from any cause as our primary outcome in the primary analysis. This does, however, limit our ability to observe any effect modification by age on disease-specific mortality when medication regimes are compared. We thus performed a sensitivity analysis that accounted for the approximate contribution of noncardiovascular deaths to all-cause mortality in HFrEF patients by age, based on estimates from an analysis of participants in the Framingham Heart Study from 1971 to 2004. Future studies of underlying causes of death in HFrEF patients by age might allow for more accurate survival modeling. Finally, estimates for readmission were limited to HF-specific readmissions, since the clinical trials used did not include all-cause readmission estimates.

Conclusions

Across all age strata, after accounting for "real world" rates of drug discontinuation and switching discharge on sacubitril/valsartan after HFrEF hospitalization conferred a small, but significant, survival advantage compared to ACEi/ARB. In addition, the benefit of sacubitril/valsartan may increase with age.

Acknowledgments

The authors would like to thank Christopher Leggett for his contribution to this work.

Funding

This work is supported by the National Heart Lung and Blood Institute (NHLBI) [K23HL142835 to LG]; the National Institute on Aging (NIA) [P01AG019783 to JOM]; and the National Center for Advancing Translational Science (NCATS) [UL1TR001086 to ANAT]. None of the funding sources (NHLBI, NIA, AHA or NCATS) had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Author contributions

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Conflict of interest

The authors have no relationships with industry to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.04.007.

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