Costs associated with unplanned readmissions among patients with heart failure with and without hyponatremia

Alpesh N. Amin, M.D., Department of Medicine, Irvine School of Medicine, University of California, Irvine, CA

Jesse D. Ortendahl, M.S., Health Economics, Partnership for Health Analytic Research, LLC, Beverly Hills, CA

Amanda L. Harmon, M.P.H., Health Economics, Partnership for Health Analytic Research, LLC, Beverly Hills, CA

Siddhesh A. Kamat, M.S., M.B.A., Health Economics and Outcomes Research, Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ

Robert A. Stellhorn, M.S., Health Outcomes Data Analytics, Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ

Sandra L. Chase, Pharm.D., B.S., FCCP, Field Medical Affairs, Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ

Shirin V. Sundar, Ph.D., Field Medical Affairs, Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ

Address correspondence to Dr. Amin (anamin@uci.edu).

DOI 10.1093/ajhp/zxy064

Purpose. Costs associated with unplanned readmissions among patients with heart failure with and without hyponatremia were studied.

Methods. This study estimated the costs of patients hospitalized for heart failure (HF) discharged with or without corrected sodium. A model was developed to monetize the 30-day readmission risk based on hyponatremia correction. Costs of discharging patient with corrected versus uncorrected hyponatremia were estimated using readmission rates from a previously published study and hospitalization costs from the Healthcare Costs and Utilization Cost Project and the Premier Healthcare Database.

Results. Discharging patients with HF and hyponatremia increased costs from $488-$569 per discharge compared to patients with corrected hyponatremia. This range reflected differences in readmission rates and sources of hospitalization costs. Sensitivity analyses showed hospitalization costs and readmission rates had the largest impact on model results.

Conclusion. A retrospective study supports the value of upfront monitoring and correction of low serum sodium levels before discharge among patients with HF and hyponatremia by presenting an economic argument in addition to the clinical rational for reducing risk of readmission.

Keywords: heart failure, hospital costs, hyponatremia, readmission

Am J Health-Syst Pharm. 2019; 76:374-80

Heart failure (HF) is a disease associated with high morbidity and mortality rates and increasing healthcare costs.[1] Hyponatremia, defined as a serum sodium concentration of <135 meq/L, is the most common electrolyte disorder in hospitalized patients and occurs in 20–25% of patients hospitalized for HF.[2–5] Patients with HF develop hyponatremia due to the chronic activation of multiple neurohormonal pathways, leading to retention of sodium and excess of total body water (hypervolemic hyponatremia).[3] Several studies have associated hyponatremia with increased morbidity and mortality in patients hospitalized for HF.[3,6–11] In addition, an abnormal serum sodium level has been shown to be related to higher risks of avoidable hospital readmissions. Hernandez et al.[12] found that 30-day readmission rates in patients with HF were lowest among those with at least 2 factors including negative fluid balance, normal serum sodium level, and net reduction in the amino-terminal brain natriuretic peptide level. Similarly, the internationally validated HOSPITAL score uses sodium level at discharge as a predictor of a patients at risk of 30-day readmission, with a serum sodium concentration below 135 meq/L indicating an increased risk.[13]

Despite substantial evidence indicating a correlation between hyponatremia and worsening consequences in patients with HF, there is a lack of consensus on the modalities of correction and target sodium level at the time of discharge, leading to high variability in practice.[14] Standard practices for hyponatremia correction in hospitalized patients with HF and hyponatremia include fluid restriction and the use of diuretics; however, these options have varying effectiveness.[14] Vasopressin-receptor antagonists (vaptans) increase serum sodium levels by blocking vasopressin-mediated water reabsorption. Vaptans have been approved by the Food and Drug Administration for use in euvolemic and hypervolemic hyponatremia.[5,15] The 2013 American College of Cardiology and American Heart Association guideline for the management of HF recommends that in patients with HF who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of guideline-directed medical therapy, vasopressin antagonists may be considered in the short term to improve serum sodium concentration.[16] However, clinical trial data are lacking in regards to the independent association of hyponatermia correction and patient outcomes, including unplanned readmissions; therefore, correcting hyponatremia before hospital discharge is not consistently prioritized.[9,14] Specifically, an assessment of real-world data from a global hyponatremia registry found that the majority of patients with hyponatremia did not achieve a serum sodium level above 135 meq/L after initial treatment and did not receive subsequent treatment.[14]

Readmissions are costly to hospitals and health systems, and the reduction in avoidable readmissions is an important consideration being used to measure the quality of care.[17–19] The Agency for Healthcare Research and Quality (AHRQ) includes avoidable readmissions in their Prevention Quality Indicators and is currently quantifying readmissions due to HF in the Nationwide Readmissions Database. Recent initiatives that penalize hospitals for high readmission rates are leading to more scrutiny over potentially preventable hospitalizations.[20] The Centers for Medicare and Medicaid Services Hospital Compare publishes information about the quality of care at over 4,000 Medicare-certified hospitals—including information on 30-day readmission rates for patients with HF.[21] For HF, the age-sex adjusted rate of potentially preventable inpatient stays in 2012 was 341 per 100,000 population.[22]

KEY POINTS

- The economic impact of hyponatremia correction among patients with heart failure was assessed in a model-based analysis.
- Correcting sodium before hospital discharge decreases costs of readmission by 488–569 per discharge.
- Our results support the financial value of monitoring and correction of hyponatremia in this patient population.

Thus, potentially avoidable readmissions, such as those associated with patients with HF discharged with hyponatremia, have become a major focus for hospitals and health systems nationwide. Real-world evidence, including the well-validated HOSPITAL score, suggests the merits of management of hyponatremia in reducing unplanned hospital readmissions.[4,7,12,23] However, until recently, there was no direct link between correcting hyponatremia and reducing readmissions.

Donzé et al.[4] established a decrease in all-cause 30-day readmissions in patients who had hyponatremia corrected before discharge compared to those with persistent hyponatremia (serum sodium concentration of <135 meq/L at both admission and discharge). This economic model–based analysis estimates the medical costs among patients hospitalized for HF discharged with or without corrected hyponatremia, based on the Donzé study. Such an analysis can help hospital decision-makers and physicians quantify the potential cost savings associated with a reduction in avoidable readmissions and improve quality of patient care in the management of patients with HF and hyponatremia.

Methods

This study used an economic model to estimate the costs associated with readmissions for patients discharged following a HF admission with and without hyponatremia correction upon discharge. The goal of the analyses was to assess the cost savings associated with the decrease in readmission rates reported in a recent study by Donzé et al.[4] Specifically, we estimated the total hospitalization costs per person, separately for patients with and without correction of hyponatremia, by totaling the costs of initial hospitalization and readmissions and dividing by the number of patients initially hospitalized. The difference between these estimates was defined as the incremental cost increase or potential cost savings associated with correcting hyponatremia before discharge. Model inputs were based on published literature, an analysis of the Premier Healthcare Database, and the Healthcare Cost and Utilization Project (HCUP) database. The Premier Healthcare Database and HCUP are nationally representative databases containing information on hospitalizations. Model outcomes were reported as incremental costs of correcting hyponatremia on a per-person basis.

Model structure. The model was developed in an Excel spreadsheet (Microsoft Corp., Redmond, WA). Heart failure patients discharged either with or without hyponatremia were considered eligible to be analyzed using this model. Based on serum sodium level at discharge, patients faced differential risks of readmission. Those who required readmission accrued additional costs, whereas those not requiring readmission did not. We chose to use a simple model that did not incorporate the costs or potential additional benefits of hyponatremia correction to increase the transparency of the methods and make results easier to interpret.

Clinical inputs. Patient enrollment through the model was determined by clinical outcomes reported in the Donzé et al.[4] study. Briefly, that study was a retrospective cohort analysis examining 4,295 patients admitted to a tertiary care hospital over a 6-year period. Rate of readmissions and mortality within 30 days of discharge for patients with and without hyponatremia correction were assessed, both before adjusting for baseline differences between groups and as an adjusted odds ratio after controlling for demographic and clinical characteristics. In our model, we only considered readmissions, which the original authors found occurred in 27.5% of HF patients with persistent hyponatremia and 23.4% of those with sodium correction before discharge. In addition, we conducted the analysis with both the unadjusted rates as reported and using the adjusted odds ratio of 1.28 (95% confidence interval [CI], 1.11–1.48). To convert from the adjusted odds ratio to probabilities for use in the model, we used the reported rate for patients discharged with uncorrected hyponatremia and multiplied this baseline rate by the reported odds ratio.

Cost inputs. To assess the economic implications of hyponatremia correction, the model required the cost of a hospitalization. Model cost inputs were inflation adjusted to 2016 U.S. dollars, as commonly done in economic modeling, to account for differences in the years that costs were reported and to make such costs directly comparable. As hospitalization costs can vary between facilities, we used 2 alternative sources to estimate the cost of a hospitalization and considered the costs for prespecified subgroups. By considering different sources for a variable that is known to be uncertain and vary between settings, we were able to assess the robustness of results and the extent to which findings were driven by this input.

The first approach for estimating the costs of hospitalization was based on an analysis we conducted of the Premier Healthcare Database. Premier provides utilization and cost information for 20% of the U.S. hospital discharges, totaling more than 45 million visits. Using this database, we assessed patients of all ages hospitalized from January 1 through December 31, 2014 with primary *International Classification of Diseases, Ninth Edition* (ICD-9) codes 428.xx, reflecting HF. There were 591 hospitals included in the data analyzed. All costs were inflated to 2016 US dollars using the medical component of the Consumer Price Index inflation calculator, which was 1.093 when converting from 2014 to 2016.[24]

The second approach used publicly available hospitalization cost data from the HCUP database.[25] HCUP is a collection of databases sponsored by AHRQ that provides data collected from state data organizations, hospital associations, private data organizations, and the federal government to create a national information resource of patient-level healthcare data. The National Inpatient Sample is the inpatient database contained in HCUP and includes data on roughly 8 million hospital stays each year from a national sample of over 1,000 hospitals. The cost estimate from HCUP included patients with any diagnosis and was updated from 2014 U.S. dollars to 2016 U.S. dollars to maintain consistency in the model.[24]

Analyses. In the base case, we estimated the per-patient costs related to unplanned readmissions among those patients with HF and hyponatremia discharged with corrected and without corrected hyponatremia. Costs for those with corrected hyponatremia were calculated as the sum of the cost per initial hospitalization multiplied by the number of HF patients initially hospitalized and the cost per readmission times the number of HF patients readmitted, all divided by the total number of HF patients with corrected hyponatremia. Costs for those without corrected hyponatremia were calculated similarly. The incremental costs associated with correcting hyponatremia before discharge were calculated as the difference between these two measures. The incremental costs were estimated for a hypothetical cohort of 1,000 hospitalized patients, using the proportion of patients with hyponatremia correction from the study by Donzé et al.[4] We assessed 1,000 hospitalized patients, as it is likely more tangible to a hospital than when presenting results on a per-patient basis. The base case analysis used the Premier-based hospitalization costs and rates of readmission using the adjusted odds ratio. Scenario analyses were also conducted to assess the impact of using different sources for inputs or assumptions related to data. In such analyses, the results were regenerated using the HCUP-based costs and using the unadjusted rates of readmission as reported directly from the Donzé et al.[4] study. In another set of scenario analyses, we estimated the cost impact when varying the length of stay on readmission. In this scenario, we used data from an additional analysis of the Premier database, limited to those patients with HF and hyponatremia. We also conducted 3 subgroup analyses among patients ≥ 65 years old, those requiring an intensive care unit (ICU) stay, and those with severe disease. In addition, to assess the impact of parameter uncertainty on model results, we conducted one-way sensitivity analyses on all model parameters. To compare characteristics of those with and without hyponatremia correction from the Premier Hospital Database, we conducted statistical testing using *t*-tests for comparing mean values and chi-square tests for comparing proportions.

Results

In the Premier Healthcare Database, 571 hospitals were found to have at least 1 record of a patient admitted with HF. In total, there were 62,122 hospitalizations with ICD-9 codes 428.xx, reflecting HF. Characteristics of these patients are shown in Table 1. The costs per hospitalization calculated from both Premier and HCUP are shown in Table 2, both in their original currency and in 2016 U.S. Dollars.

In the base case analysis, using the Premier database, we found that discharging HF patients with uncorrected hyponatremia resulted in readmission costs of $3,401 per discharge, compared with $2,832 when discharging patients with corrected hyponatremia. Thus, correcting hyponatremia resulted in a savings of $569 per patient. When using costs from the HCUP database for hospitalization, this incremental cost decreased to $547. Based on the adjusted odds ratio, we calculated the risk of readmission among those with corrected hyponatremia was 22.9%, compared to an unadjusted rate of 23.4%. With the adjusted

Table 1. Descriptive Analysis of Patients in the Premier Database With Heart Failure and With and Without Hyponatremia[a]

Variable	Patients With HF and hyponatremia	Patients with HF Without hyponatremia	Total patients with HF	*p*
n	7,022	55,100	62,122	
Mean age, yr	69.0	68.6	68.7	0.0618
Male, % pts	50.6	51.0	51.0	0.4840
3M APR DRG severity of illness, % pts				<0.0001
Minor	0.2	5.3	4.7	
Moderate	18.3	31.1	29.7	
Major	59.6	52.5	53.3	
Extreme	21.9	11.1	12.3	
Length of stay, mean days	7.8	5.1	5.4	<0.0001
Inpatient stays with ICU admissions, % stays	24.7	16.4	17.3	<0.0001

[a] HF = heart failure, APR = all-patient refined, DRG = diagnosis-related group, ICU = intensive care unit.

Table 2. Original and Inflated Cost per Hospitalization From Different Sources[a]

Variable	Hospitalization Cost (Per Event) 2014 US Dollars ($)	2016 US Dollars[b] ($)
Premier Database		
Patients with HF[c]	11,318	12,366
Patients with HF and hyponatremia[d]	16,999	18,573
Patients with HF and hyponatremia and age ≥ 65 years	15,399	16,825
Patients with HF and hyponatremia and admission to the ICU	33,207	36,281
Patients with HF and hyponatremia with 3M APR DRG severity of illness of “major” or “extreme”	18,683	20,413
HCUP Database		
Patients with HF[c]	10,885	11,893

[a] ICU = intensive care unit, APR = all-patient refined, DRG = diagnosis-related group, HCUP = Healthcare Costs and Utilization Cost Project, HF = heart failure.
[b] 2014 U.S. dollars inflated to 2016 using a factor of 1.093 based on the medical component of the Consumer Price Index.[24]
[c] Defined as patients with International Classification of Diseases, Ninth Revision (ICD-9) codes 428.xx.
[d] Defined as patients with primary ICD-9 codes of 428.xx and secondary or tertiary ICD-9 codes of 276.1x. Only considered in scenario analysis.

risk of unplanned readmissions, the cost savings resulting from correcting hyponatremia increased to $488–$507 per patient when using HCUP and Premier costs, respectively. All per-patient costs can be found in Table 3 and Figure 1.

When estimating the cost impact among patients ages 65 or older, we found that the cost savings associated with correcting hyponatremia was $690 when using the unadjusted rate of readmission after hyponatremia correction and $774 when incorporating the adjusted rate. Cost savings were largest when limiting the analysis to those with an ICU stay, as patients without hyponatremia correction accrued costs of $9,977 where as those with hyponatremia correction had costs of $8,308 (adjusted readmission rate) and $8,490 (unadjusted readmission rate). Results of all subgroup analyses are found in Table 4.

In the scenario assuming a length of stay for readmitted patients increased from a base case value of 5.4 days to 7.8 days, we found that the mean per-person cost for patients with hyponatremia correction was $4,248. The corresponding cost for patients with uncorrected hyponatremia was $4,992, or an increase of $744.

In sensitivity analyses, when varying all parameters ± 20%, we found that the parameters with the greatest impact on model results were the probabilities of readmission conditional on serum sodium levels. When the rate of readmission among patients without hyponatremia correction was increased by 20%, the economic burden associated with uncorrected hyponatremia increased from ~$500 to $1,249 per hospitalization. The readmission rates had a higher impact on the costs associated with uncorrected hyponatremia compared to the costs of hospitalization. Figure 2 depicts the cost savings when each parameter was varied.

Discussion

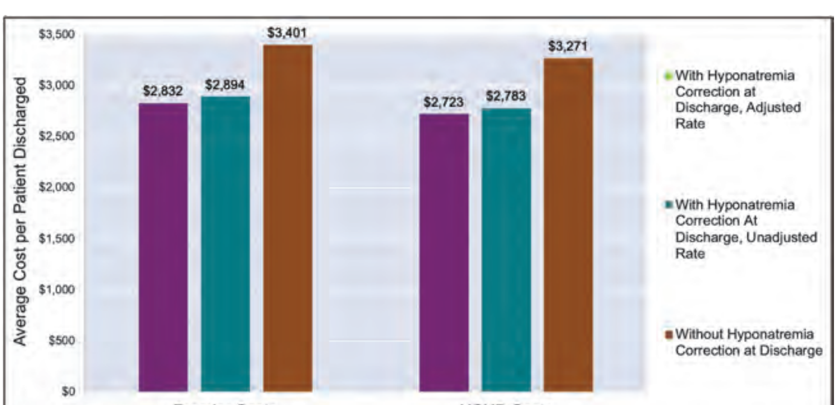
This study quantified the potential cost savings in terms of readmissions avoided by correcting hyponatremia before discharge in patients with HF. The

Table 3. Model-Projected Incremental Costs of Sodium Correction Among All Patients[a]

Variable	Cost per Patient ($) With Hyponatremia Correction	Cost per Patient ($) Without Hyponatremia Correction	Incremental Costs[b] ($)
Based on Premier hospitalization cost inputs and adjusted unplanned readmission rates[c]	2,832	3,401	569
Based on HCUP hospitalization cost inputs and adjusted readmission rates[c]	2,723	3,271	547
Based on Premier hospitalization cost inputs and unadjusted readmission rates	2,894	34,01	507
Based on HCUP Hospitalization cost inputs and unadjusted readmission rates	2,783	3,271	488

[a] HCUP = Healthcare Costs and Utilization Cost Project.
[b] Incremental costs defined as cost savings with hyponatremia correction.
[c] Adjusted rates were calculated using the adjusted odds ratio reported in Donzé et al.[4] Adjusted ratio accounted for between-group differences in age, sex, race, admissions within 6 months preceding index admission, unplanned index admission versus elective, length of stay, atrial flutter or atrial fibrillation, ischemic heart disease, cancer, chronic obstructive pulmonary disease, diabetes, and chronic kidney disease. The severity of congestive heart failure was assessed using the last available laboratory value of the brain natriuretic peptide or the last measurement of ejection fraction before discharge.

Figure 1. Per-Patient Costs per Discharge by Source of Hospitalization Cost. Adjusted rates were calculated using the adjusted odds ratio reported in Donzé et al.[4] Adjusted ratio accounted for between-group differences in age, sex, race, admissions within 6 months preceding index admission, unplanned index admission versus elective, length of stay, atrial flutter or atrial fibrillation, ischemic heart disease, cancer, chronic obstructive pulmonary disease, diabetes, and chronic kidney disease. The severity of congestive heart failure was assessed using the last available laboratory value of the brain natriuretic peptide or the last measurement of ejection fraction before discharge. HCUP = Healthcare Costs and Utilization Cost Project.



magnitude of the economic benefit varied depending on the assumed cost of hospitalizations and rate of decrease in readmission with hyponatremia correction, but in all scenarios, the cost-savings were substantial. When considering subgroups, such as older HF patients or those requiring intensive care, the cost-savings increased. These findings highlight the economic benefits of reducing unplanned readmissions. In addition to the economic savings, reducing preventable readmissions can provide additional benefits.

This work should be considered in the context of other published analyses assessing the characteristics of patients with hyponatremia and economic impact of correcting sodium imbalances. The assessment of patients with and without hyponatremia was consistent with previous studies that found that those with hyponatremia were typically sicker, had longer lengths of stays, more comorbidities, and more ICU visits.[3,6–11] A previous meta-analysis of eight U.S. studies found hyponatremia to be associated with approximately $3,000 higher hospital costs per patient when compared with the cost of normonatremic subjects.[10] This cost estimate was higher than the results of the current study; however, the $3000 figure was based on an analysis of patients with any underlying condition, as opposed to being limited to patients with HF. In the present study, discharging patients with HF with uncorrected hyponatremia increased costs from $488–$507 per discharge compared with patients whose serum sodium concentration exceeded135 meq/L. While the estimates of cost savings ranged across analyses and settings, the findings of a decrease in costs after hyponatremia correction was consistent.

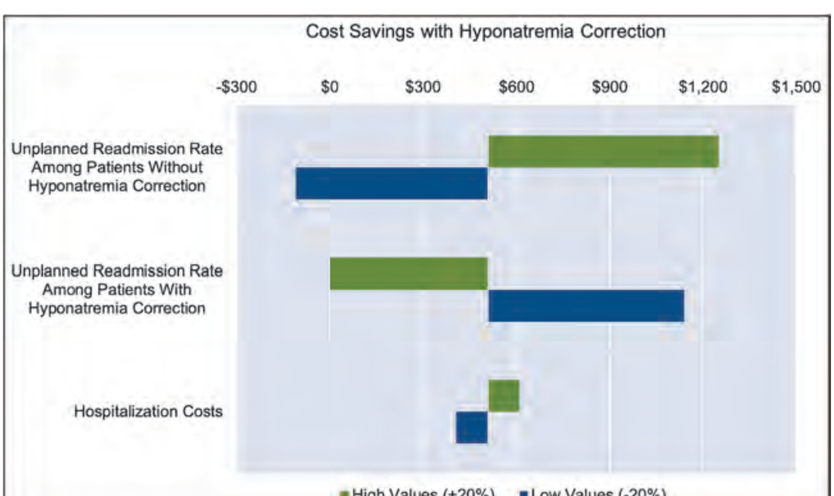
Patients with HF and hyponatremia represent a population in which improvement in inpatient care and post-discharge outpatient follow up may effectively avoid recurrent hospitalizations. Gheorghiade et al.[7] reported that the risk of death or readmission for patients with HF increased by 8.6% (95% CI, 0.740–0.998) for each 3-meq/L decrease in serum sodium concentration

Table 4. Model-Projected Incremental Costs of Sodium Correction Among Patient Subgroups[a]

	Cost per Patient ($)		
Variable	**With Correction of Hyponatremia**	**Without Correction of Hyponatermia**	**Incremental Costs[b] ($)**
Costs among patients with HF and hyponatremia and age ≥ 65 years			
Adjusted unplanned readmission rates[c]	3,853	4,627	774
Unadjusted unplanned readmission rates	3,937	4,627	690
Costs among patients with HF and hyponatremia and admission to the ICU			
Adjusted unplanned readmission rates[c]	8,308	9,977	1,669
Unadjusted unplanned readmission rates	8,490	9,977	1,488
Costs among patients with HF and hyponatremia with 3M APR DRG severity of illness of "major" or "extreme"			
Adjusted unplanned readmission rates[c]	4,675	5,614	939
Unadjusted unplanned readmission rates	4,777	5,614	837

[a] Subgroup analyses based on hospitalization costs identified in Premier Database. APR = all patient refined, DRG = diagnosis-related group, HF = heart failure, ICU = intensive care unit.
[b] Incremental costs defined as cost savings with hyponatremia correction.
[c] Adjusted rates were calculated using the adjusted odds ratio reported in Donzé et al.[4] Adjusted ratio accounted for between-group differences in age, sex, race, admissions within 6 months preceding index admission, unplanned index admission versus elective, length of stay, atrial flutter or atrial fibrillation, ischemic heart disease, cancer, chronic obstructive pulmonary disease, diabetes, and chronic kidney disease. The severity of congestive HF was assessed using the last available laboratory value of the brain natriuretic peptide or the last measurement of ejection fraction before discharge.

Figure 2. Incremental costs of hyponatremia correction in one-way sensitivity analyses.



below 140 meq/L at admission. A meta-analysis by Corona et al.[26] found that among patients with HF, the risk ratio for overall mortality among those with hyponatremia was 2.47 (95% CI, 2.09–2.92) compared with those without hyponatremia. A study by Amin et al[23]. showed that hyponatremia was associated with an increased risk (14–17%) for early hospital readmission for any cause and a more than 5-fold greater risk (95% CI, 4.77–5.46; $p < 0.001$) of going back to the hospital within 30 days for hyponatremia among patients with HF.[23,27]

While we followed published guidelines for model development[28] and used the best available evidence in utilizing the model, results should be considered in light of the limitations of this study. This analysis excluded all costs other than those related to readmission. The impact of excluding other costs is expected to be mixed, as there would be a cost of correcting hyponatremia that would decrease the incremental costs found in this analysis; however, there may also be further benefits of hyponatremia correction beyond, or associated with, reduced readmission rates (e.g., reduced caregiver costs, decreased patient burden, decreased risk of hospital-acquired infections). These excluded costs could be an area for future research.

Also, this analysis focused solely on the financial consequences of reduced readmissions associated with corrected hyponatremia. The benefits in terms of greater quality of life and decreased patient burden are important additional considerations. Finally, the rates of readmission used in this analysis were based on a retrospective analysis from a single hospital—a large, tertiary care, referral center.[4] While this was the best available evidence and the findings in the assessed study appear unbiased, the generalizability of the results is unclear. The Donzé et al.[4] study also did not consider the severity of disease, assess the therapies utilized during the initial hospitalization, or measure serum sodium levels between admission and discharge to determine whether those discharged with hyponatremia had consistently low sodium levels.

Conclusion

A retrospective study supports the value of upfront monitoring and correction of low serum sodium levels before discharge among patients with HF and hyponatremia by presenting an economic argument in addition to the clinical rationale for reducing risk of readmission.

Disclosures

Mr. Kamat, Mr. Stellhorn, Dr. Chase, and Dr. Sundar are employees of Otsuka Pharmaceutical Development and Commercialization. Mr. Ortendahl and Ms. Harmon are employees of Partnership for Health Analytic Research, LLC, and received consulting fees for conducting the research described in this article. Dr. Amin received consulting fees for conducting the research described in this manuscript.

References

1. Mozaffarian D, Benjamin EJ, Go AS et al. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation.* 2016; 133:447–54.
2. Farmakis D, Filippatos G, Parissis J et al. Hyponatremia in heart failure. *Heart Fail Rev.* 2009; 14:59–63.
3. Bettari L, Fiuzat M, Shaw LK et al. Hyponatremia and long-term outcomes in chronic heart failure–an observational study from the Duke Databank for Cardiovascular Diseases. *J Card Fail.* 2012; 18:74–81.
4. Donzé JD, Beeler PE, Bates DW. Impact of hyponatremia correction on the risk for 30-day readmission and death in patients with congestive heart failure. *Am J Med.* 2016; 129:836–42.
5. Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. *World J Cardiol.* 2013; 5:317–28.
6. Gheorghiade M, Rossi JS, Cotts W et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial. *Arch Intern Med.* 2007; 167:1998–2005.
7. Gheorghiade M, Abraham WT, Albert NM et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J.* 2007; 28:980–8.
8. Klein L, O'Connor CM, Leimberger JD et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF) study. *Circulation.* 2005; 111:2454–60.
9. Yancy CW. Acute heart failure: searching for a new evident truth. *J Am Coll Cardiol.* 2017; 69:1420–3.
10. Corona G, Giuliani C, Parenti G et al. The economic burden of hyponatremia: systematic review and meta-analysis. *Am J Med.* 2016; 129:823–835.e4.
11. Madan VD, Novak E, Rich MW. Impact of change in serum sodium concentration on mortality in patients hospitalized with heart failure and hyponatremia. *Circ Heart Fail.* 2011; 4:637–43.
12. Hernandez MB, Schwartz RS, Asher CR et al. Predictors of 30-day readmission in patients hospitalized with decompensated heart failure. *Clin Cardiol.* 2013; 36:542–7.
13. Donzé JD, Williams MV, Robinson EJ et al. International validity of the HOSPITAL score to predict 30-day potentially avoidable hospital readmissions. *JAMA Intern Med.* 2016; 176:496–502.
14. Greenberg A, Verbalis JG, Amin AN et al. Current treatment practice and outcomes. Report of the Hyponatremia Registry. *Kidney Int.* 2015; 88:167–77.
15. Chiong JR, Kim S, Lin J et al. Evaluation of costs associated with tolvaptan-mediated length-of-stay reduction among heart failure patients with hyponatremia in the US, based on the EVEREST trial. *J Med Econ.* 2012; 15:276–84.
16. Yancy CW, Bozkurt B, Butler J et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013; 128:e240–327.
17. Claudia Steiner. New AHRQ database tracks hospital readmission rates (2015). https://www.ahrq.gov/news/blog/ahrqviews/112015.html (accessed 2017 Apr 28).
18. Agency for Healthcare Research and Quality. AHRQ Quality Indicators www.qualityindicators.ahrq.gov/Modules/pqi_resources.aspx (accessed 2017 Apr 28).
19. Halfon P, Eggli Y, Prêtre-Rohrbach I et al. Validation of the potentially avoidable hospital readmission rate as a routine indicator of the quality of hospital care. *Med Care.* 2006; 44:972–81.
20. Centers for Medicare and Medicaid Services. Readmissions reduction program (2016). www.cms.gov/medicare/medicare-fee-for-service-payment/acuteinpatientpps/readmissions-reduction-program.html (accessed 2017 Apr 7).
21. Centers for Medicare and Medicaid Services. Medicare Hospital Compare www.medicare.gov/hospitalcompare/About/What-Is-HOS.html (accessed 2017 Apr 7).
22. Fingar KR, Barrett ML, Elixhauser A et al. Trends in potentially preventable inpatient hospital admissions and emergency department visits (2015). www.hcup-us.ahrq.gov/reports/statbriefs/sb195-Potentially-Preventable-Hospitalizations.jsp (accessed 2017 Apr 7).
23. Amin A, Deitelzweig S, Christian R et al. Healthcare resource burden associated with hyponatremia among patients hospitalized for heart failure in the US. *J Med Econ.* 2013; 16:415–20.
24. U.S. Department of Labor, Bureau of Labor Statistics. CPI (consumer price index) inflation calculator (2017). www.bls.gov/data/inflation_calculator.htm (accessed 2018 Jan 2].
25. Agency for Healthcare Research and Quality. HCUPnet: a tool for identifying, tracking, and analyzing national hospital statistics. http://hcupnet.ahrq.gov/HCUPnet.jsp?Id=38928A2C495EB62F&Form=DispTab&JS=Y&Action=Accept (accessed 2016 Aug 10].
26. Corona G, Giuliani C, Parenti G et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. *PLoS ONE.* 2013; 8:e80451.
27. Amin A, Deitelzweig S, Christian R et al. Evaluation of incremental healthcare resource burden and readmission rates associated with hospitalized hyponatremic patients in the US. *J Hosp Med.* 2012; 7:634–9.
28. Sullivan SD, Mauskopf JA, Augustovski F et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health.* 2014; 17:5–14.