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Utilization and budget impact of tolvaptan in the inpatient setting among patients with heart failure and hyponatremia

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ABSTRACT

Objective: Assess characteristics of patients with heart failure (HF) and hyponatremia (HN) using tolvaptan, a selective vasopressin V2-receptor antagonist, for sodium correction, and estimate the budget impact of tolvaptan use in a hospital.

Methods: The Premier hospital database was analyzed to assess the utilization of tolvaptan, characteristics of users and non-users, and hospitalization costs among patients with HF and HN. Using these findings, a model was developed to estimate tolvaptan costs in proportion to total medical costs of managing patients with HF and HN, and the budget impact of tolvaptan use. Results were regenerated using data from the Healthcare Cost and Utilization Project (HCUP) database, and robustness was assessed in sensitivity analyses.

Results: Tolvaptan was used in 4.96% of inpatient visits among patients with HF and HN, more commonly among sicker patients as reflected in high utilization during intensive care stays (30.46%). Additionally, utilization increased by length of stay, which can serve as a proxy for disease severity. The model estimated that tolvaptan costs accounted for 0.3% of total hospitalization-related costs for patients with HF and HN, and the budget impact was \$52.42 per visit.

Conclusions: Results demonstrate that tolvaptan is used infrequently among patients with HF and HN, and is utilized among sicker patients. Tolvaptan accounted for 0.3% of total spending on management of inpatient visits with HF and HN, and had a marginal impact on hospital budget when compared with fluid restriction for HN correction. Availability of tolvaptan can provide an additional therapeutic option for sodium correction.

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Heart failure; hyponatremia; budget impact; sodium; hospitalization; economic model; tolvaptan

Introduction

Heart failure (HF) is a disabling disease with a rising incidence in the US that is associated with high morbidity and mortality rates¹. In 2013, one in nine death certificates (300,122 deaths) in the US mentioned HF, and HF was the underlying cause in 65,120 of those deaths¹. A common comorbidity in patients with HF is hyponatremia (HN), an electrolyte disorder characterized by serum sodium <135 mEq/L. HN is found in 20–25% of patients hospitalized for HF, and categorized as mild in patients with serum sodium between 130 and 135 mEq/L, moderate in patients with serum sodium 125–130 mEq/L, and severe in patients with serum sodium below 125 mEq/L². Compared to patients hospitalized for HF with normal sodium levels, those with HN have a higher proportion of comorbidities and increased mortality risk^{2–8}.

HF costs the US an estimated \$30.7 billion each year, including costs of health care services, medications to treat HF and missed days of work⁹. HN, even when mild and chronic, represents an economic and social burden⁷. Donzé *et al.*¹⁰ established an association between persistent HN

(serum sodium level <135 mEq/L at both admission and discharge) and increased risk of all-cause 30 day readmissions. Real-world evidence indicates that appropriate HN management reduces the likelihood of hospital readmissions^{4,10–12}.

Despite evidence highlighting the benefits of sodium correction, the lack of clinical guidelines leads to significant variability in treatment approaches. Treatment options for correcting HN in patients with HF include fluid restriction or diuretics, yet such approaches have either limited efficacy and/or low patient compliance^{13,14}. Fluid restriction involves restricting fluids to less than 800–1000 mL/d to achieve a negative water balance. However, many patients with HF and HN have increased thirst, which reduces compliance with fluid restriction^{6,13,14}. In the treatment of more advanced stages of HF, diuretics may fail to control salt and water retention^{15,16}.

Another potential therapy for HN in patients with HF is arginine vasopressin (AVP)-receptor antagonists or “vaptans”. AVP-receptor antagonists increase sodium levels and exhibit beneficial effects on hemodynamic variables, making their use promising in patients with HN^{13,17}. Tolvaptan is the only

oral, selective vasopressin V2-receptor antagonist¹⁸ available in the US. Tolvaptan is indicated for the treatment of clinically significant hypervolemic and euvolemic HN (serum sodium <125 mEq/L), or less marked HN that is symptomatic and has resisted correction with fluid restriction, including patients with HF and syndrome of inappropriate antidiuretic hormone (SIADH)¹⁸. While patients with HF and HN are being treated with tolvaptan, their sodium levels must be monitored to avoid an overly rapid correction. Therefore, the appropriate setting to initiate tolvaptan treatment is the hospital where sodium can be monitored. Tolvaptan treatment is discontinued when sodium has normalized.

The largest trial of tolvaptan in patients with HF is the EVEREST outcome study, which included 4,133 patients hospitalized for worsening HF who were randomly assigned to tolvaptan or placebo. Among the 330 patients with a baseline serum sodium concentration below 134 mEq/L, tolvaptan significantly increased serum sodium within the first 7 days (5.5 versus 1.9 mEq/L with placebo)^{19,20}. In a similar subset analysis²¹ of patients with HN in the EVEREST trial, tolvaptan was associated with greater likelihood of normalization of serum sodium, greater weight reduction, greater relief of dyspnea at discharge and lower use of diuretics than placebo. Tolvaptan did not improve long-term outcomes compared with placebo among patients with serum sodium below 135 mEq/L. However, tolvaptan use in patients with pronounced HN (<130 mEq/L; $n = 92$) resulted in a significant reduction in cardiovascular morbidity and mortality after discharge²¹. A separate phase II study and real-world data also indicated that tolvaptan corrected sodium levels more quickly than did fluid restriction^{14,22}.

Understanding the clinical characteristics of patients with HF and HN who use tolvaptan in the real-world setting may facilitate the formulary decision-making process. Additionally, this study also provides estimates of the budget impact of tolvaptan that can be useful for guiding access decisions.

Methods

Methods overview

This study evaluated the utilization rate and dose of tolvaptan among patients with HF and HN using the Premier hospital database. Additionally, the average length of stay and hospitalization costs were estimated from both the Premier and the Healthcare Cost and Utilization Project (HCUP) databases. The Premier hospital database and HCUP are nationally representative databases containing information on hospitalizations, and are described in more detail below. Information on dose and duration of tolvaptan use during inpatient visits recorded in the database was used to estimate the costs of tolvaptan use. A Microsoft Excel based model was used to project the total costs of inpatient visits for HF and HN, including costs related to fluid restriction for sodium correction. The budget impact was also estimated, and defined as the additional tolvaptan-related product acquisition costs to a hospital when using tolvaptan compared to the fluid restriction per HF and HN inpatient visit.

Costs were reported in 2016 US dollars from the hospital payer perspective.

Model structure

To assess the impact of tolvaptan use, a model was developed in which the costs associated with an episode of HF and HN related hospitalization were estimated. The initial cohort of patients included in the model were those hospitalized with HF, based on the total number of patients identified in the Premier hospital database. Patients without HN were excluded from further analysis, whereas those with HN were deemed eligible for tolvaptan and assessed. The hospitalization costs for visits associated with HF and HN, and tolvaptan product costs, were considered in the model. Costs of fluid restriction were not separately included, as it was assumed that these would be captured in the estimate of total hospitalization costs. Similarly, cost of potential adverse events was assumed to be factored into total hospitalization costs. The model was developed following guidelines on best practices in budget impact modeling as outlined by the International Society for Pharmacoeconomics and Outcomes Research²³. Specifically, the analysis was conducted from the budget holder's perspective, which in this study was the hospital, including the pharmacy, and therefore did not include indirect costs or any costs accrued after discharge. Additionally, the population eligible for treatment was carefully estimated, relevant comparators were included in the analysis, the data used to inform model parameters was transparently reported and the impact of uncertainty on model results was methodically explored.

Model inputs

Model inputs, including clinical parameters and costs, were based on the Premier hospital database analysis and supplemented with HCUP data and PriceRx, a guide that reports historic and current prices of individual drugs²⁴. The total number of patients with HF, along with the proportion with HN and those treated with tolvaptan, were calculated from the hospital database. The daily costs of tolvaptan, either 15 mg or 30 mg tablets, were based on the wholesale acquisition costs. As of November 2016, these prices were \$357.81 per 15 mg tablet and \$371.17 per 30 mg tablet²⁴. The proportion of patients receiving each dose, and duration of therapy, were based on estimates from Premier among patients with HF and HN treated with tolvaptan. The per-day cost of hospitalization, inclusive of all services rendered besides tolvaptan use, and average length of stay, were estimated from the Premier database among those patients with HF and HN.

Premier hospital database analysis

Premier provides utilization and cost information for 20% of the US hospital discharges, totaling more than 45 million visits. An analysis of 2014 data from the Premier hospital database was conducted to evaluate the number of inpatient visits attributed to HF and HN in the real-world, characterize

Table 1. Model Inputs.

	Value ^a
Patient population	
HF related inpatient visits per year (patients)	62,122
Proportion of HF visits with diagnosed HN (<i>n</i> , %)	7022, 11.30
Real-world utilization of tolvaptan among patients with HF and HN (<i>n</i> , %)	348, 4.96
Tolvaptan acquisition costs for use during inpatient visit related to HF and HN	
% of patients using 30 mg (opposed to 15 mg)	27.9
Average number of days of tolvaptan use during inpatient stay	2.9
Cost per 15 mg tablet ^b	\$357.81
Cost per 30 mg tablet ^b	\$371.18
Hospitalization costs	
Length of stay for inpatient visit	
Premier hospital database analysis: mean (SD) per patient with HF and HN	7.8 (8.35)
HCUP database analysis: mean per patient with HF	7.0
Cost per day of inpatient stay (\$) ^c	
Premier hospital database analysis: mean per patient with HF and HN (SD)	\$2389.27 (\$4605.90)
HCUP database analysis: mean per patient with HF	\$2437.98

^aCosts inflated to 2016 using the medical care component of the Consumer Price Index²⁹.

^bBased on wholesale acquisition costs as of November 2016 as reported in PriceRx²⁴.

^cNot including tolvaptan acquisition costs.

Abbreviations. HCUP, Healthcare Cost and Utilization Project; HF, heart failure; HN, hyponatremia; mg, milligram; SD, standard deviation.

the patients treated with tolvaptan in terms of demographic characteristics, utilization of intensive care unit services, length of stay and dosage distribution of tolvaptan used, and finally to estimate the relevant costs to a hospital. Patients included in the analysis had a primary International Statistical Classification of Diseases and Related Health Problems (ICD)-9 code of 428.xx, indicating HF, and a secondary or tertiary ICD-9 code of 276.1, indicating HN²⁵. Tolvaptan users were identified in Premier using the charge master codes 250250110160000 (15 mg) and 250250110170000 (30 mg)²⁶. The proportion of patients with each code was identified from the database analysis, and the demographic/epidemiologic characteristics of tolvaptan users were examined along with the corresponding hospitalization costs and length of stay. The measures examined in Premier among tolvaptan users included the average length of stay, proportion of visits requiring an ICU admission, and 3M all patient refined diagnosis related group (3M APR DRG) categorization²⁷. The 3M APR DRG is a widely used metric by payers for defining disease severity and predicting the risk of mortality, and can be used as a proxy for disease severity. The 3M APR DRG severity of illness levels are minor, moderate, major and extreme.

Healthcare Utilization Program database analysis

The analysis was also repeated using hospitalization costs and length of stay from the HCUP database among patients with ICD-9 codes 428.xx²⁸. HCUP is a collection of databases sponsored by the Agency for Healthcare Research and Quality (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 health care data. The National Inpatient Sample (NIS) 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. All costs reported in years prior to 2016 were

updated to year 2016 US dollars using the medical component of the Consumer Price Index, a method commonly used in economic analyses to incorporate inflation²⁹. All model inputs are found in [Table 1](#).

Analyses

In the base case analysis, the costs for a typical patient with HF and HN were estimated, and separated by those related to hospitalization and those related to tolvaptan treatment. These costs were reported both on a per-visit basis, and for the cohort of patients identified in the Premier analysis. Additionally, the costs to a hospital using tolvaptan were estimated and compared to the costs without tolvaptan use. These results were reported as total annual costs to the hospital, as well as on a per-hospitalization per-patient basis. The difference between scenarios (i.e. with and without tolvaptan use) was calculated to reflect the incremental costs of using tolvaptan. Sensitivity analyses were conducted to assess the impact of parameter uncertainty on model results. In such analyses, the proportion of patients utilizing tolvaptan, as well as tolvaptan dosing and costs, were varied individually $\pm 20\%$ of the base case value. For each model iteration, the incremental costs of tolvaptan use were recalculated.

Results

In the Premier database, 4.96% of patients with HF and HN were treated with tolvaptan. Due to the observational nature of this database and lack of baseline information on patients prior to their inpatient visit, tolvaptan users included in the analysis tended to be sicker, leading to biased observations due to confounding by severity of disease. This bias was evident from the utilization rates of tolvaptan increasing by decades of length of stay, which can serve as a proxy for disease severity ([Figure 1](#)). This was further reflected by 30.46% of

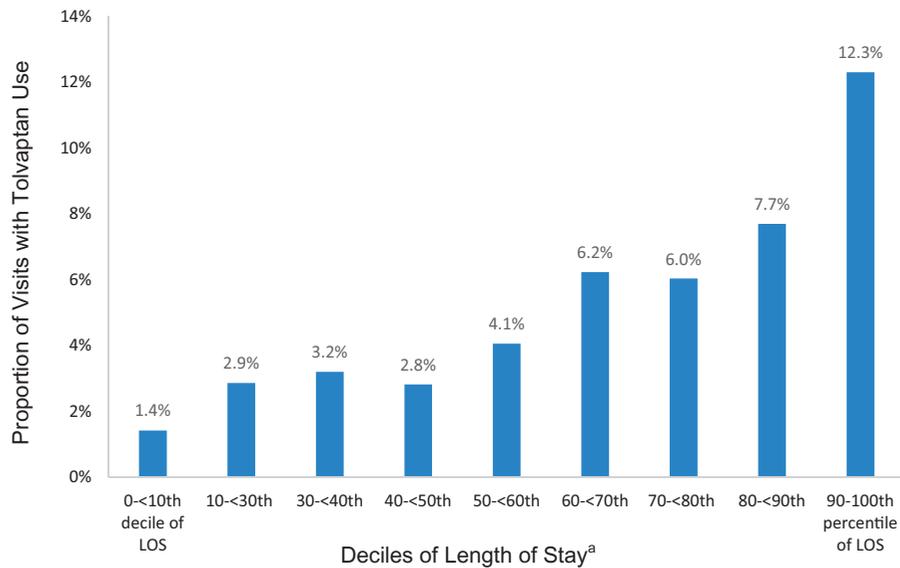


Figure 1. Proportion of tolvaptan use increases by severity of inpatient visit (total number of visits with HF and HN = 7022). ^aNo patients within the 10th–20th decile were tolvaptan users, such that the 10th–30th percentiles were combined into a single group. Abbreviation. LOS, length of stay.

Table 2. Budget impact to the hospital of using tolvaptan.

	Annual tolvaptan costs ^a	Annual hospitalization costs ^b	Total annual costs to the hospital ^c
Using premier database analysis costs for hospitalization			
Fluid restriction ^c	\$0	\$130,822,880	\$130,822,880
Fluid restriction + tolvaptan use	\$368,001	\$130,822,880	\$131,190,881
Using HCUP costs for hospitalization			
Fluid restriction	\$0	\$119,798,685	\$119,798,685
Fluid restriction + tolvaptan use	\$368,001	\$119,798,685	\$120,166,686

^aTolvaptan accounted for 0.28% of total hospitalization costs when using Premier data, and 0.31% of total hospitalization costs when using HCUP data. For fluid restriction, it is assumed that no patients receive tolvaptan.

^bHospitalization costs include all inpatient costs other than tolvaptan.

^cTotal costs calculated as the sum of tolvaptan costs and hospitalization costs. Abbreviation. HCUP, Healthcare Cost and Utilization Project.

patients treated with tolvaptan receiving intensive care services. Additionally, inpatient visits with tolvaptan use were associated with the 3M APR DRG categories of extreme disease severity (23.3%) and major severity (59.5%).

When estimating the costs to hospitals for treating patients with HF and HN, costs attributable to therapy for correcting HN were minimal. On a per-patient basis, total hospitalization costs were \$18,636 per event when using length of stay and per-day costing information from the Premier hospital database analysis, and \$17,066 when using data from HCUP. The corresponding drug costs per utilizing patient for those with HF and HN using tolvaptan were \$1,048. When considering tolvaptan costs among all hospitalized patients, as opposed to among the subset using tolvaptan, these per-patient costs dropped to \$52.42. When assessing the full cohort of patients with HF and HN in the Premier database analysis, tolvaptan acquisition costs accounted for 0.28%–0.31% of total hospitalization costs of managing patients with HF and HN, depending on the source used for hospitalization costs (Table 2).

As expected, the budget impact model predicted that, compared to fluid restriction alone, adding tolvaptan to

fluid restriction would increase costs to the hospital. On a per-inpatient stay basis, the inpatient visit costs including fluid restriction was \$18,636. These costs were attributable solely to the initial hospitalization, as opposed to any costs specifically related to sodium correction or readmission. When using tolvaptan in 4.96% of patients with HF and HN, as found in the Premier database analysis, costs per inpatient stay increased to \$18,689. This resulted in an incremental cost of \$52.42 for each patient admitted with HF and HN (Figure 2).

Two hospital-wide scenarios were also compared, differing by tolvaptan use. In the first scenario tolvaptan was not used, whereas in the second scenario it was used by the proportion of patients identified in the Premier database analysis as being tolvaptan users. In the cohort of 7,022 patients with HF and HN, and based on tolvaptan dosing as observed in the Premier database analysis, total tolvaptan related costs for all patients were \$368,001. Hospitalization-related costs were assumed to be equal for patients in both scenarios, and ranged from \$120 million to \$130 million depending on the source of cost inputs (i.e. HCUP or Premier). The costs by component (i.e. related to tolvaptan acquisition or

hospitalization) are shown using both sources of hospitalization data in Table 2.

To assess the impact of parameter uncertainty on model results, sensitivity analyses were conducted in which the utilization patterns and costs of tolvaptan were varied individually ±20% of the base case values. Such an exploration into the impact of changing each parameter is recommended in budget impact modeling to help identify which model inputs are most influential. In these analyses, the parameters with the greatest impact on model results were the proportion of patients treated with tolvaptan, the duration of treatment and the product acquisition costs. The proportion using 15 mg versus 30 mg tolvaptan was less influential, as the difference in costs between doses is minimal. Results of all sensitivity analyses are found in the tornado diagram (Figure 3).

Discussion

Our analysis demonstrated the marginal impact of tolvaptan use on payer and hospital budgets when compared with fluid restriction for HN correction among patients with HF. Accounting for <1% of total spending on HF and with a

slight increase in per-patient cost, tolvaptan use in this patient population will only minimally impact payers and hospitals and will provide an additional therapeutic option for sicker patients with HF and HN. The incremental cost per patient using tolvaptan of \$1,048 provides an estimate for the impact of using tolvaptan for a given patient compared to not using it in that patient, whereas the incremental cost per visit of \$52 can help illustrate to a hospital payer the impact of tolvaptan use in context of their overall HF and HN patient population. In other words, the pharmacy cost impact of tolvaptan for all the HF and HN visits managed by the hospital is \$52 per visit since only a small proportion of all these visits show evidence of tolvaptan use. The latter metric can be more meaningful as the expectation is that tolvaptan use will be restricted to those with more severe disease and the hospital's cost impact in managing their HN and HF patient population will be minimal.

The medical costs associated with HF place a heavy financial burden on the US economy and healthcare system, and are projected to more than double to nearly \$70 billion by 2030^{9,30}. It is important to control these high costs. A previous meta-analysis study of US data found HN to be associated with approximately \$3,000 higher hospital costs per patient when compared with the cost of normonatremic subjects⁷. A cost-analysis study based on the EVEREST trial estimated total cost savings when treating patients with HF and HN with tolvaptan of \$265 per admission¹⁷. In other studies, correcting HN has been found to convey additional economic benefits, including decreased length of stay and reduced HN-related medical conditions^{7,8,31}. Our current study did not consider a difference in duration of hospitalization or decrease in risk of readmission with sodium correction, rather the model strictly estimated the product costs. However, one would expect that the inclusion of such factors would further highlight the financial benefits of tolvaptan use.

One area not directly addressed in our financial analysis but should be considered is that avoidable readmissions lead to considerable suffering and additional costs. For HF, the age–sex adjusted rate of potentially preventable inpatient

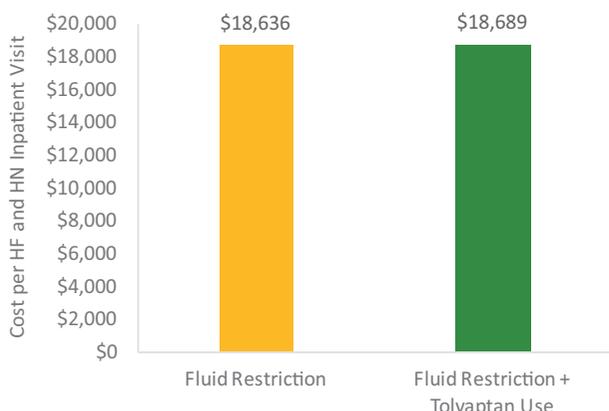


Figure 2. Cost per visit for fluid restriction based solely on hospitalization costs. For the scenario with tolvaptan use, cost per visit based on hospitalization costs for all patients and tolvaptan costs for the 4.96% found to be tolvaptan users in the Premier analysis. Abbreviations. HF, heart failure; HN, hyponatremia.

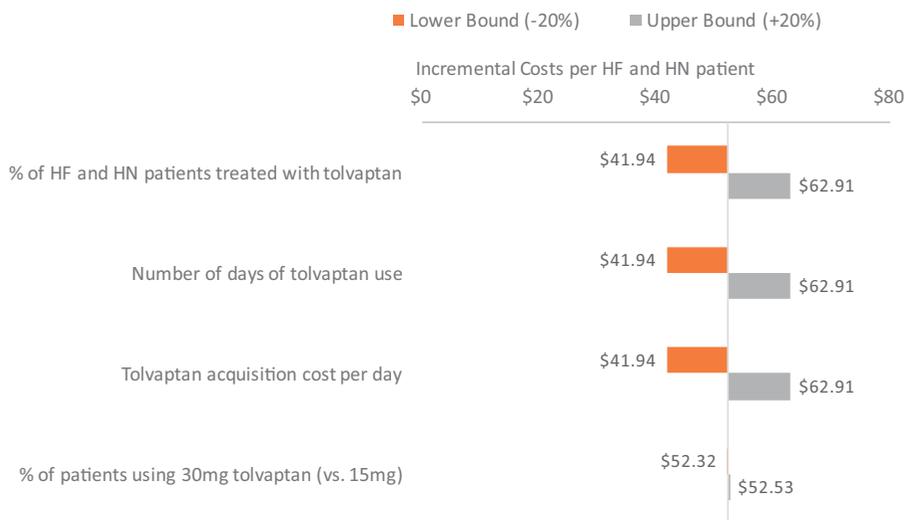


Figure 3. Incremental costs defined as change in costs with tolvaptan use compared with no tolvaptan use. Abbreviations. HF, heart failure; HN, hyponatremia; mg, milligram.

stays is 341 per 100,000 population. The Hospital Readmissions Reduction Program, a component of the Affordable Care Act, is designed to reduce readmission frequency among Medicare patients by penalizing hospitals with excessive readmission rates for certain conditions, including HF³². 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 of patients with HF³³. Much attention has been drawn to the topic of readmissions, with avoidable readmissions the target of many healthcare reforms.

Improvement in inpatient and outpatient care of patients with HF and HN, including sodium correction, may prevent hospital readmissions, reduce mortality and lead to other health improvements^{34–36}. Specifically, Gheorghiadu *et al.*⁴ reported that the risk of death or readmission for patients with HF increased by 8% for each 3 mEq/L decrease in serum sodium concentration below 140 mEq/L at admission. A study by Amin *et al.*¹¹ showed that, among patients with HF, HN was associated with a 14–24% increased risk of early all-cause hospital readmission and an over five-fold greater risk of 30 day HN-specific readmission. These lower readmission rates associated with improved sodium management may ultimately lead to cost savings. Additional studies have found that hyponatremia can increase the risk of falls and osteoporosis-related fractures, as well as a functional and cognitive decline^{37,38}.

Findings from our analyses and prior research indicate that tolvaptan is used in a specific patient population, which is consistent with reports from a global HN registry that found that approximately 5% of patients were prescribed tolvaptan as initial therapy for hyponatremia¹⁴. Limited use of tolvaptan, despite evidence of effectively correcting sodium, is driven by the indication, which allows for treatment among HF and SIADH patients with HN. Additionally, within HF patients, tolvaptan can only be used as a first-line therapy among those with severe HN, whereas for those with mild HN it is indicated after fluid restriction and only in symptomatic patients. Thus, appropriate use of tolvaptan will be limited by the clinical indication and only used among HF patients who do not respond to other therapies. Therefore, it is expected that utilization will remain low. This translates into optimized drug benefits with marginal impact on payer budgets – an ideal scenario for any novel treatment. Our analysis was designed to examine the characteristics of tolvaptan users, as a study assessing the comparative efficacy of tolvaptan was not possible given the selection bias present in retrospective real-world data. However, the inpatient hospital data indicate that tolvaptan users accrue higher costs and are sicker than non-users, with a higher rate of ICU admissions. Also, our study showed that the use of tolvaptan increased among those patients with a longer length of stay, which is similar to findings from the subset of HN patients with HF from the HN registry³¹. Real-world characteristics of those who utilize this product indicate that it serves an unmet need in a small, high-risk patient population. Additionally, tolvaptan should only be initiated in the hospital setting because of monitoring requirements, therefore

its use prior to discharge would allow for an increase in continuity of care. Pharmacists and hospital formulary decision-makers should consider these findings when discussing appropriate tolvaptan access.

Limitations

This study should be considered in light of its limitations. The budget impact analysis did not include clinical effects and only considered the costs of tolvaptan acquisition and costs of hospitalization in patients with HF and HN. Given that sodium correction may reduce hospital readmissions, our findings may be considered an upper bound of costs associated with tolvaptan use. On the other hand, potential adverse effects associated with tolvaptan use may cause associated costs to be slightly higher than found in our analysis. However, data from the EVEREST trial has shown that the adverse events related to tolvaptan are associated with its aquaretic properties consistent with its mechanism of action, and serious adverse events occurred more frequently in the placebo group of the trial^{19,20}. The estimates used in our analysis were based on findings from hospital data and published literature and may not be generalizable to all patients with HF and HN. However, our findings of marginal budget impact were consistent when varying these model inputs in sensitivity analyses and when using inputs from multiple sources, suggesting that our conclusions would remain valid even in the case of “perfect” model inputs. Also related to model inputs, the database analysis only included estimates through 2014 due to the lag in data availability. Future studies could utilize more recent observations to determine whether there are temporal trends influencing the utilization of tolvaptan or costs of hospitalization; however, there is no reason to believe results would be impacted substantially. Additionally, the study database did not contain information on serum sodium levels at treatment initiation; however, further research could support previous findings that tolvaptan is used more frequently in those with severe hyponatremia than in cases of mild hyponatremia^{14,31}. Such findings could help inform whether tolvaptan would be optimally used in all patients with HN, or just among those with serum sodium below 125 mEq/L. Finally, the only HN treatment approaches considered in this analysis were the guideline-recommended alternatives, tolvaptan and fluid restriction³⁹. While alternatives exist, data from a HN registry capturing 762 patients with HF and HN from 146 sites indicated that fluid restriction was the most commonly used initial therapy in clinical practice (44%), followed by no treatment (23%), isotonic saline (5%), hypertonic saline (2%) and salt tablets (1%)³¹. Given the low utilization of alternative therapies, we compared tolvaptan to the commonly used approach of fluid restriction.

Conclusions

Considering the larger economic impact of patients hospitalized with HF and HN, tolvaptan costs are low and convey

minimal incremental costs compared with fluid restriction. Given that tolvaptan is used among sicker patients with HF towards the end of their hospital stay, and is typically used among patients who have failed to respond to fluid restriction and diuretics, it is expected that the budget impact would remain low if tolvaptan was added to a hospital formulary and utilization was limited to those patients currently targeted for treatment. With these findings, hospital payers can better understand the limited impact of tolvaptan on their budgets and may consider these estimates during formulary decision making.

Transparency

Declaration of funding

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Author contributions: S.A.K., S.L.C. and S.V.S. were involved in the conception and design. J.D.O., R.A.S. and A.L.H. were involved in data collection. A.N.A., J.D.O. and A.L.H. were involved in analysis and interpretation of that data. J.D.O. and A.L.H. drafted the paper. A.N.A., S.L.C. and S.V.S. revised it critically for intellectual content. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Declaration of financial/other relationships

R.A.S., S.L.C. and S.V.S. have disclosed that they are employees of Otsuka Pharmaceutical Development & Commercialization Inc., who manufacture tolvaptan. At the time of preparation and submission of this manuscript, S.A.K. was an employee of Otsuka Pharmaceutical Development & Commercialization Inc., who manufacture tolvaptan. J.D.O. and A.L.H. have disclosed that they are employees of PHAR LLC, which was paid as a consultant to conduct the research described in this manuscript. A.N.A. has disclosed that he was paid as a consultant to conduct the research described in this manuscript.

A reviewer on this paper is a consultant to Otsuka in hyponatremia; however, was not involved with this study. All other *CMRO* peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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