

3618 A Cost-Consequences Analysis of Inpatient Tolvaptan Compared With Fluid Restriction Among SIADH Patients With Hyponatremia

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Background

- Hyponatremia is an electrolyte imbalance that is common among hospitalized patients, and severe acute hyponatremia can have serious consequences such as seizures, permanent brain damage, respiratory arrest, and even death.^{1,2}
- From a hospital perspective, the economic and resource use consequences of untreated hyponatremia include prolonged length of stay (LOS) in the hospital, increased risk of admission to the intensive care unit (ICU), and increased risk of 30-day rehospitalization.²
- Otsuka America Pharmaceutical, Inc. (OAPI) offers Samsca® (tolvaptan), a vasopressin antagonist that provides an alternative to fluid restriction (FR) for the treatment of hyponatremia in hospitalized patients.
- The efficacy of tolvaptan, compared with FR, as a treatment for hyponatremia was investigated in a prospective, multicenter, randomized, active-controlled, open-label trial.³ This trial is the only one to have been identified in the published literature that compares these two interventions.

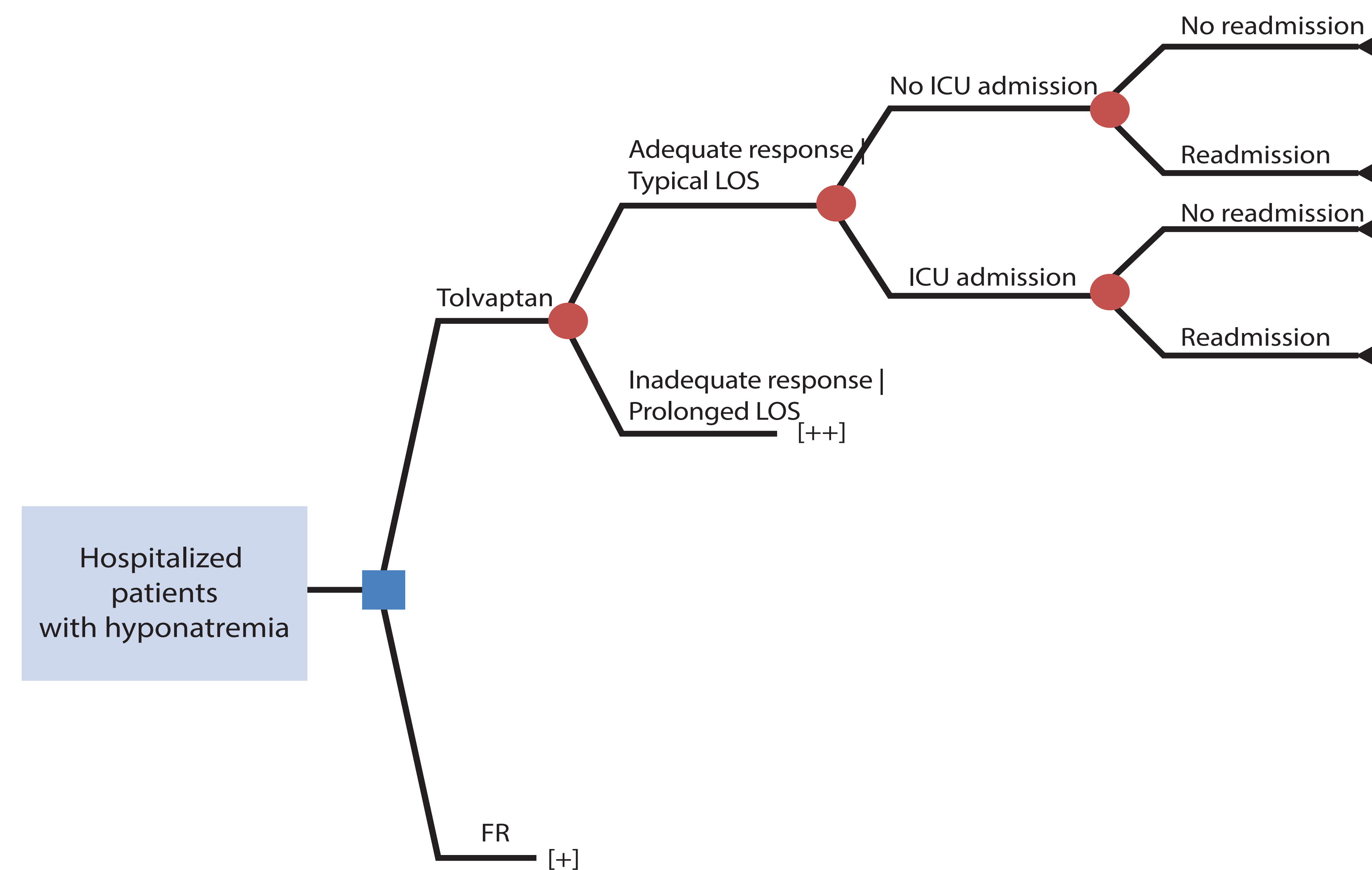
Objective

- The objective of this study was to estimate, from the perspective of a United States hospital, the economic and health consequences associated with the use of tolvaptan compared with FR in the treatment of hyponatremia in patients who are hospitalized due to syndrome of inappropriate diuretic hormone (SIADH).

Methods

- Based on the acute nature of the hyponatremia occurring during an inpatient hospitalization for SIADH, a decision-tree model structure was used (Figure 1).
- Patients with hyponatremia of two severity levels were considered in the model: serum sodium (SS) level < 125 mEq/L (hereafter referred to as severe hyponatremia) and SS level ≥ 125 mEq/L and < 136 mEq/L (hereafter referred to as mild-moderate hyponatremia).
- Patients with severe hyponatremia are treated with either tolvaptan or FR, and patients with mild-moderate hyponatremia with persistent resistance to initial treatment with FR can either receive tolvaptan or continue treatment with FR.

Figure 1. Model Structure



[+] = same as the potential outcomes following the choice of tolvaptan in the top branch.
 [+] = same as the potential outcomes following the response outcome (adequate response) in the top branch.

Model Inputs

- Input parameters to the model are summarized in Table 1.

Table 1. Model Input Parameters

Parameter	Value (Source)	
	SIADH, Severe Hyponatremia	SIADH, Mild-Moderate Hyponatremia, Resistant to FR
Probability of adequate response (tolvaptan)	0.73 (Gheorghide et al., 2006 ³)	
Probability of adequate response (FR)	0.38 (Gheorghide et al., 2006 ³)	0.00 (Assumption)
Hospital LOS in days (adequate response)	5.50 (Callahan et al., 2009 ^{5,b})	
Hospital LOS in days (inadequate response)	7.50 (Callahan et al., 2009 ^{5,a})	7.10 (Callahan et al., 2009 ^{5,a})
Probability of ICU admission (adequate response)	0.144 (Callahan et al., 2009 ^{5,b})	
Probability of ICU admission (inadequate response)	0.223 (Callahan et al., 2009 ^{5,a})	0.178 (Callahan et al., 2009 ^{5,a})
Probability of readmission (adequate response)	0.115 (Deitelzweig et al., 2013 ^{6,b})	
Probability of readmission (inadequate response)	0.133 (Deitelzweig et al., 2013 ^{6,b})	
Average hospital cost per day (general ward)	\$1,412 (HCUP/ICD-9 253.6 ^c ; Amin et al., 2012 ^{8,b})	
Average additional cost of an ICU admission (adequate response)	\$10,414 (Amin et al., 2012 ^{8,b})	
Average additional cost of an ICU admission (inadequate response)	\$11,686 (Amin et al., 2012 ^{8,b})	
Average cost of readmission	\$10,089 (HCUP/ICD-9 code 253.6 ^{7,d})	

HCUP = Healthcare Cost and Utilization Project; ICD-9 = International Classification of Diseases, Ninth Edition.
^aSource reported outcomes by hyponatremia severity level.
^bSource did not report outcomes by hyponatremia severity level.
^cTo estimate the cost per day (general ward), the average hospitalization cost (less the cost of an ICU stay, obtained from Amin et al., 2013⁸) for ICD-9 code 253.6 (other disorders of neurohypophysis, which includes SIADH) was divided by the corresponding mean LOS (both from HCUP). The costs from HCUP⁸ and Amin et al. (2013)⁸ were inflated to 2014 costs using Consumer Price Index estimates from the Bureau of Labor Statistics (2014)⁹ prior to performing the cost-per-day derivation.

Clinical Inputs

- Clinical inputs to the model included probabilities of response to treatment, hospital LOS, probabilities of ICU admission, and probabilities of 30-day readmission.
- Probabilities of response to treatment with tolvaptan and FR were based on the proportions of patients with hyponatremia experiencing SS level normalization in the tolvaptan and FR arms of the trial documented in Gheorghide et al. (2006).³
- Probabilities of response to treatment with tolvaptan and FR were assumed to be the same for both hyponatremia severity levels. This assumption is supported by a study conducted by Berl et al. (2010),⁴ who found SS level correction rates to be similar among patients with hyponatremia with different baseline SS levels.
- Data for response to treatment specific to the patients with persistent resistance to initial treatment with FR were not available. The analysis assumed tolvaptan's effectiveness among these patients to be the same as that among patients without having been treated first with FR.
- The model assumed the response rate to continued FR among FR-resistant patients to be 0%.
- Patients respond to treatment either adequately or inadequately, and their response to treatment determines the hospital LOS, the likelihood of an ICU admission, and the likelihood of a 30-day all-cause hospital readmission.
- Estimates of hospital LOS, probabilities of ICU admission, and probabilities of 30-day readmission were obtained from published studies that compared patients with and without hyponatremia (hospital LOS and probability of ICU admission among adequate and inadequate responders⁵; probability of 30-day readmission among adequate and inadequate responders⁶).

Cost Inputs

- Cost inputs to the model included costs of treatment with tolvaptan and FR, average cost per day of a hospital stay (general ward), average additional cost of an ICU admission, and cost of a readmission.
- The cost per day of treatment with tolvaptan was assumed to be \$312.50, and the treatment duration was assumed to be 4 days, as provided by OAPI. The cost of FR was assumed to be \$0.

Sensitivity Analyses

- Uncertainty information was obtained from the literature for the input parameters for one-way sensitivity analyses (OSA) and probabilistic sensitivity analyses (PSA), where available; reasonable assumptions were made otherwise. For the PSA, the beta distribution was used for probabilities, and the Gaussian distribution was used for cost and resource use parameters.
- For the OSA, parameter estimates were varied across their 95% confidence intervals, estimated based on distributional assumptions (where available), or by ± 20% of their default estimates.

Results

Economic Outcomes

- Among patients hospitalized for SIADH and treated for severe hyponatremia, the use of tolvaptan yielded total cost-savings of \$223 per patient when compared with FR. The estimated cost-savings were higher (\$966) among patients with mild-moderate FR-resistant hyponatremia when tolvaptan use was compared with continued FR.
- The estimated savings in general ward costs are approximately \$1,012 and \$1,657 per patient in patients with severe and mild-moderate hyponatremia, respectively. The cost-savings in general ward costs alone exceeded the costs of treatment with tolvaptan (\$1,250 per patient) in patients with mild-moderate hyponatremia.

Health Outcomes

- Among patients hospitalized for SIADH and treated for severe hyponatremia with tolvaptan compared with FR, the model suggested reductions of 14.6% and -5.1% in the numbers of ICU admissions and 30-day readmissions, respectively.
- The model suggested reductions of 14.0% and 9.9% in the numbers of ICU admissions and 30-day readmissions, respectively, among patients treated for mild-moderate FR-resistant hyponatremia with tolvaptan compared with continued FR.
- Base-case economic and health outcomes for the population hospitalized for SIADH and treated for hyponatremia are summarized in Table 2.

Table 2. Base-Case Outcomes for Patients Hospitalized for SIADH and Treated for Hyponatremia With Tolvaptan or FR

Outcome	Severe Hyponatremia			Mild-Moderate Hyponatremia, Resistant to FR		
	Tolvaptan	FR	Difference (%)	Tolvaptan	FR	Difference (%)
Economic outcomes (per person)						
Total expected costs	\$12,772	\$12,995	-\$223 (-1.7%)	\$12,481	\$13,446	-\$966 (-7.2%)
General ward	\$8,518	\$9,530	-\$1,012 (-10.6%)	\$8,368	\$10,024	-\$1,657 (-16.5%)
ICU	\$1,795	\$2,191	-\$396 (-18.1%)	\$1,654	\$2,080	-\$426 (-20.5%)
30-day rehospitalization	\$1,209	\$1,274	-\$65 (-5.1%)	\$1,209	\$1,342	-\$133 (-9.9%)
Hyponatremia medication	\$1,250	\$0	\$1,250 (n/a)	\$1,250	\$0	\$1,250 (n/a)
Health outcomes (per person)						
Number responding adequately to therapy	0.73	0.38	0.36 (95.6%)	0.73	0.00	0.73 (n/a)
Number admitted to the ICU	0.17	0.19	-0.03 (-14.6%)	0.15	0.18	-0.02 (-14.0%)
Number rehospitalized at 30 days	0.12	0.13	-0.01 (-5.1%)	0.12	0.13	-0.01 (-9.9%)

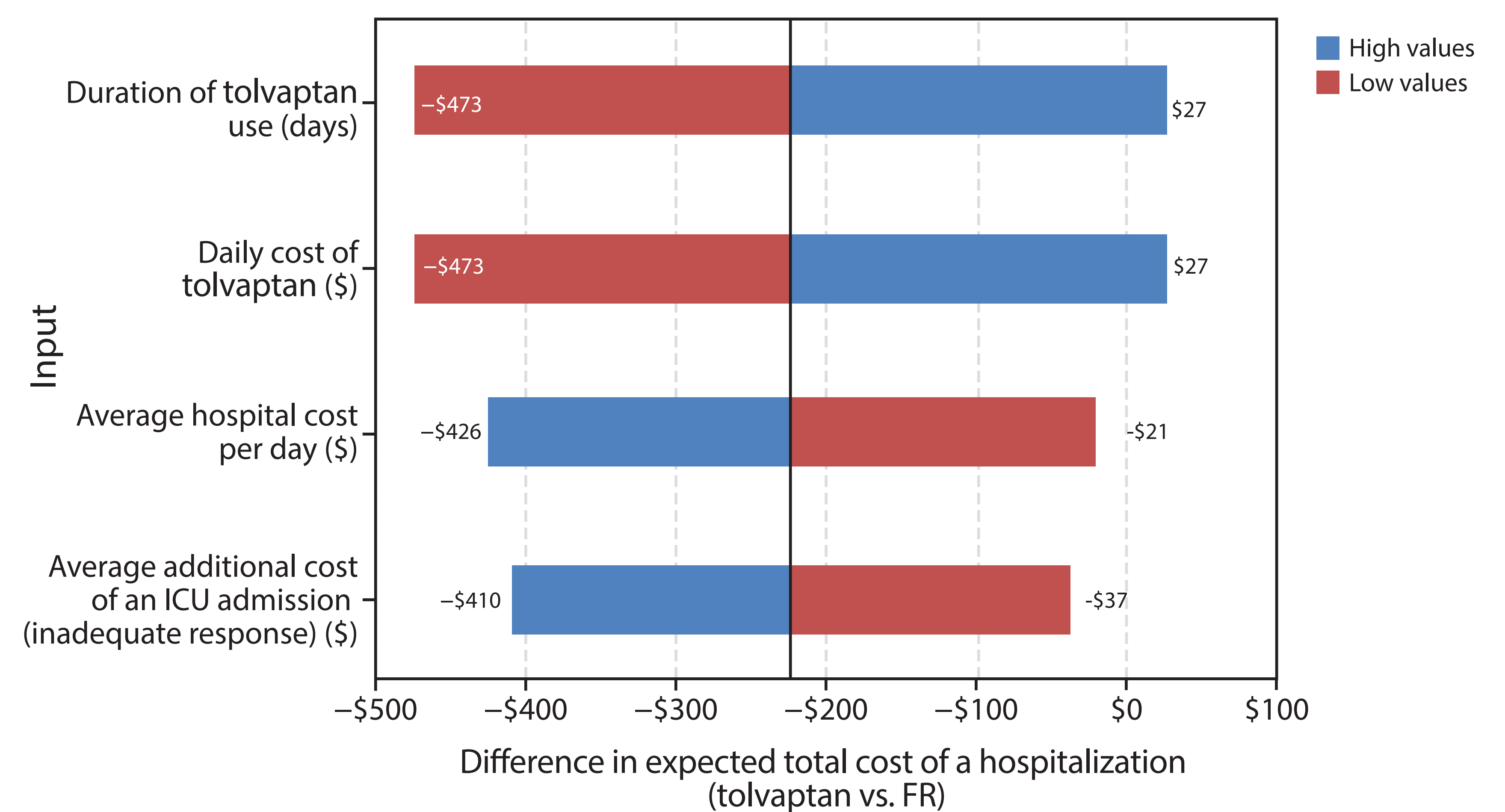
n/a = not applicable.

Sensitivity Analyses

OSA

- The OSA in the population hospitalized for SIADH and treated for severe hyponatremia showed that among the hospital-related costs and resource use inputs, the duration of tolvaptan use and the daily cost of tolvaptan were the most influential variables in terms of their effect on difference in total costs between tolvaptan and FR. When the duration of tolvaptan use or the daily cost of tolvaptan were decreased by 20%, the cost-savings achieved by using tolvaptan (vs. FR) increased from \$223 to \$473 per patient. These results are illustrated by a tornado diagram in Figure 2.
- When all model parameters were varied in the OSA, LOS in patients with inadequate response to treatment was found to be the most influential variable in terms of its effect on difference in total costs between tolvaptan and FR. Decreasing its value by 20% resulted in the total cost difference due to tolvaptan (vs. FR) changing from -\$223 to \$536 per patient, and when increased by 20%, the cost-savings due to tolvaptan (vs. FR) increased from \$223 to \$982 per patient (not shown).
- In patients hospitalized for SIADH and with mild-moderate hyponatremia that is resistant to FR, among the hospital-related cost and resource use inputs, the OSA showed that the average hospital cost per day (general ward) was the most influential variable, resulting in an increase of cost-savings from \$966 to \$1,297 when its value was increased by 20% (not shown).
- When all model parameters were varied in the OSA, LOS in patients with inadequate response to treatment was found to be the most influential variable in terms of its effect on difference in total costs between tolvaptan and FR. Decreasing its value by 20% resulted in the total cost difference due to tolvaptan (vs. FR) changing from -\$966 to \$505 per patient, and when increased by 20%, the cost-savings due to tolvaptan (vs. FR) increased from \$966 to \$2,436 per patient (not shown).

Figure 2. OSA Results, Patients Hospitalized for SIADH and Treated for Severe Hyponatremia



PSA

- The PSA showed that, under base-case assumptions of uncertainty in the model input parameters, the use of tolvaptan to treat hyponatremia yields cost-savings in approximately 65% of the simulations conducted in a population of patients hospitalized for SIADH and treated for severe hyponatremia. Approximately 83% of the simulations conducted in a population of patients hospitalized for SIADH and treated for mild-moderate hyponatremia resistant to FR show tolvaptan to be cost-saving compared with FR.

Limitations

The primary limitations of this modeling analysis stem from assumptions around parameters for which data were not available in the literature.

Conclusion

As an effective treatment for hyponatremia among patients hospitalized for SIADH, tolvaptan, in comparison with FR, is expected to save hospitalization costs.

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Disclosures

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