A Cost-Consequences Analysis of Inpatient Tolvaptan Compared With Fluid Restriction Among CHF 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 significant 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 congestive heart failure (CHF).

Methods

- Based on the acute nature of the hyponatremia occurring during an inpatient hospitalization for CHF, a decision-tree model structure was used (Figure 1).

- Patients with hyponatremia of two severity levels are 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
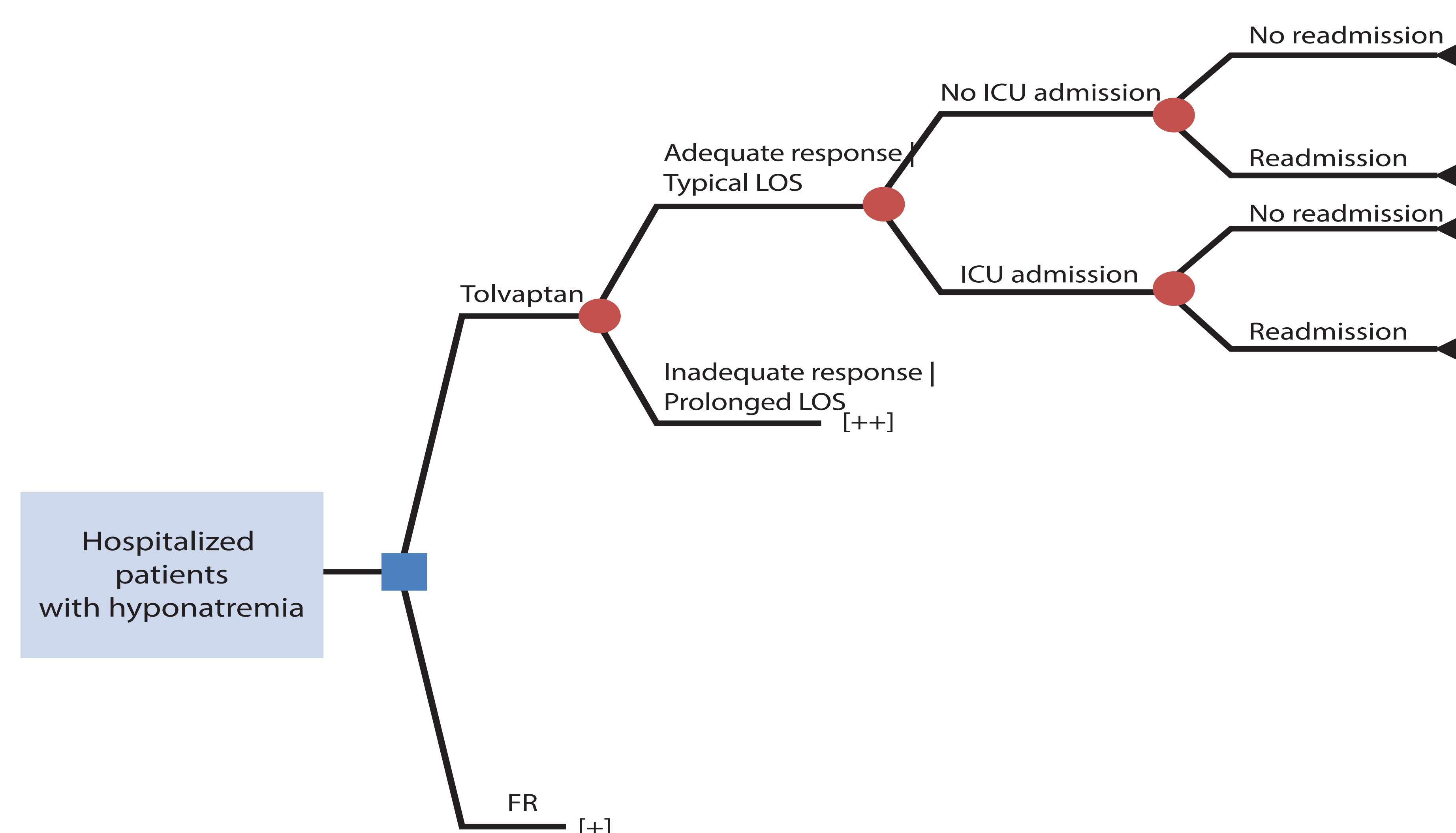
[+] = same as the potential outcomes following the choice of tolvaptan in the top branch.
[++] = same as the potential outcomes following the response outcome (adequate response) in the top branch.

Model Inputs

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

Table 1. Model Input Parameters

Parameter	Value (Source)	
	CHF, Severe Hyponatremia	CHF, Mild-Moderate Hyponatremia, Resistant to FR
Probability of adequate response (tolvaptan)	0.73 (Gheorghiade et al., 2006[3])	
Probability of adequate response (FR)	0.38 (Gheorghiade et al., 2006[3])	0.00 (Assumption)
Hospital LOS in days (adequate response)	5.40 (Shorr et al., 2011[4,b])	
Hospital LOS in days (inadequate response)	6.90 (Shorr et al., 2011[4,a])	6.10 (Shorr et al., 2011[4,a])
Probability of ICU admission (adequate response)	0.171 (Amin et al., 2013[5,b])	
Probability of ICU admission (inadequate response)	0.210 (Amin et al., 2013[5,b])	
Probability of readmission (adequate response)	0.222 (Amin et al., 2013[5,b])	
Probability of readmission (inadequate response)	0.253 (Amin et al., 2013[5,b])	
Average hospital cost (inflated to 2014 US$) per day (general ward)	$2,042 (HCUP/ICD-9 428[6]; Amin et al., 2013[5,b]c)	
Average additional cost (inflated to 2014 US$) of an ICU admission (adequate response)	$7,701 (Amin et al., 2013[5,b])	
Average additional cost (inflated to 2014 US$) of an ICU admission (inadequate response)	$9,863 (Amin et al., 2013[5,b])	
Average cost (inflated to 2014 US$) of readmission	$11,261 (HCUP/ICD-9 code 428[6,b])	

HCUP = Healthcare Cost and Utilization Project; ICD-9 = International Classification of Diseases, Ninth Edition.
[a]Source reported outcomes by hyponatremia severity level.
[b]Source did not report outcomes by hyponatremia severity level.
[c]To estimate the cost per day (general ward), the average hospitalization cost for heart failure (less the cost of an ICU stay, obtained from Amin et al., 2013[5]) was divided by the corresponding mean LOS (both from HCUP). The costs from HCUP and Amin et al. (2013)[5] were inflated to 2014 costs using Consumer Price Index estimates from the Bureau of Labor Statistics (2014)[7] 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 Gheorghiade 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)[8] 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 among adequate and inadequate responders to treatment for hyponatremia were obtained from published studies that compared patients with and without hyponatremia (hospital LOS[4]; probability of ICU admission and probability of 30-day readmission[5]).

Cost Inputs

- Cost inputs to the model included costs of treatment with tolvaptan and FR, average cost per day of hospital stay (general ward), average additional cost of an ICU admission, and cost of 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 is used for probabilities and the Gaussian distribution is used for cost and resource use parameters.

- For the OSA, parameter estimates were varied across their 95% confidence intervals (CIs), estimated based on distributional assumptions (where available), or by ± 20% of their default estimates.

Results

Economic Outcomes

- Among patients hospitalized for CHF and treated for severe hyponatremia, the use of tolvaptan yielded total cost-savings of $243 per patient when compared with FR. The estimated cost-savings were higher ($608) among patients with mild-moderate FR-resistant hyponatremia when tolvaptan use was compared with continued FR.

- The estimated savings in general ward costs from tolvaptan were approximately $1,050 and $1,100 per patient among patients treated for severe and mild-moderate hyponatremia, respectively. The cost-savings in general ward costs alone offset more than 80% of the $1,250 cost per patient of treatment with tolvaptan.

Health Outcomes

- Among patients hospitalized for CHF and treated for severe hyponatremia with tolvaptan compared with FR, the model suggested reductions of 7.2% and 4.6% in the numbers of ICU admissions and 30-day readmissions, respectively.

- The model suggested reductions of 13.6% and 9.0% 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 CHF and treated for hyponatremia are summarized in Table 2.

Table 2. Base-Case Outcomes for Patients Hospitalized for CHF 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	$17,206	$17,449	−$243 (−1.4%)	$16,770	$17,378	−$608 (−3.5%)
General ward	$11,845	$12,943	−$1,098 (−8.5%)	$11,409	$12,458	−$1,048 (−8.4%)
ICU	$1,518	$1,788	−$270 (−15.1%)	$1,518	$2,071	−$553 (−26.7%)
30-day rehospitalization	$2,593	$2,718	−$125 (−4.6%)	$2,593	$2,849	−$256 (−9.0%)
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	0.18	0.20	−0.01 (−7.2%)	0.18	0.21	−0.03 (−13.6%)
Number rehospitalized at 30 days	0.23	0.24	−0.01 (−4.6%)	0.23	0.25	−0.02 (−9.0%)

n/a = not applicable.

Sensitivity Analyses

OSA

- The OSA in the population hospitalized for CHF 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 $243 to $493 per patient. These results are illustrated in a tornado diagram in Figure 2.

- When all model parameters were varied in the OSA, the probability of adequate response to treatment with tolvaptan was found to be the most influential variable in terms of its effect on difference in total costs between tolvaptan and FR. Setting the probability of adequate response to treatment with tolvaptan to the lower bound of its 95% CI resulted in the total cost difference due to tolvaptan (vs. FR) changing from −$243 to $368 per patient, and when set to its upper bound, the cost-savings due to tolvaptan (vs. FR) increased from $243 to $854 per patient (not shown).

- In patients hospitalized for CHF 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 additional cost of an ICU admission was the most influential variable, resulting in an increase of cost-savings from $608 to $911 when its value was increased by 20% (not shown).

- When all model parameters were varied in the OSA, the probability of adequate response to treatment with tolvaptan was found to be the most influential variable in terms of its effect on difference in total costs between tolvaptan and FR. Setting the probability of adequate response to treatment with tolvaptan to the lower bound of its 95% CI resulted in the total cost-savings due to tolvaptan (vs. FR) decreasing from $608 to $236 per patient, and when set to its upper bound, the cost-savings due to tolvaptan (vs. FR) increased from $608 to $979 per patient (not shown).

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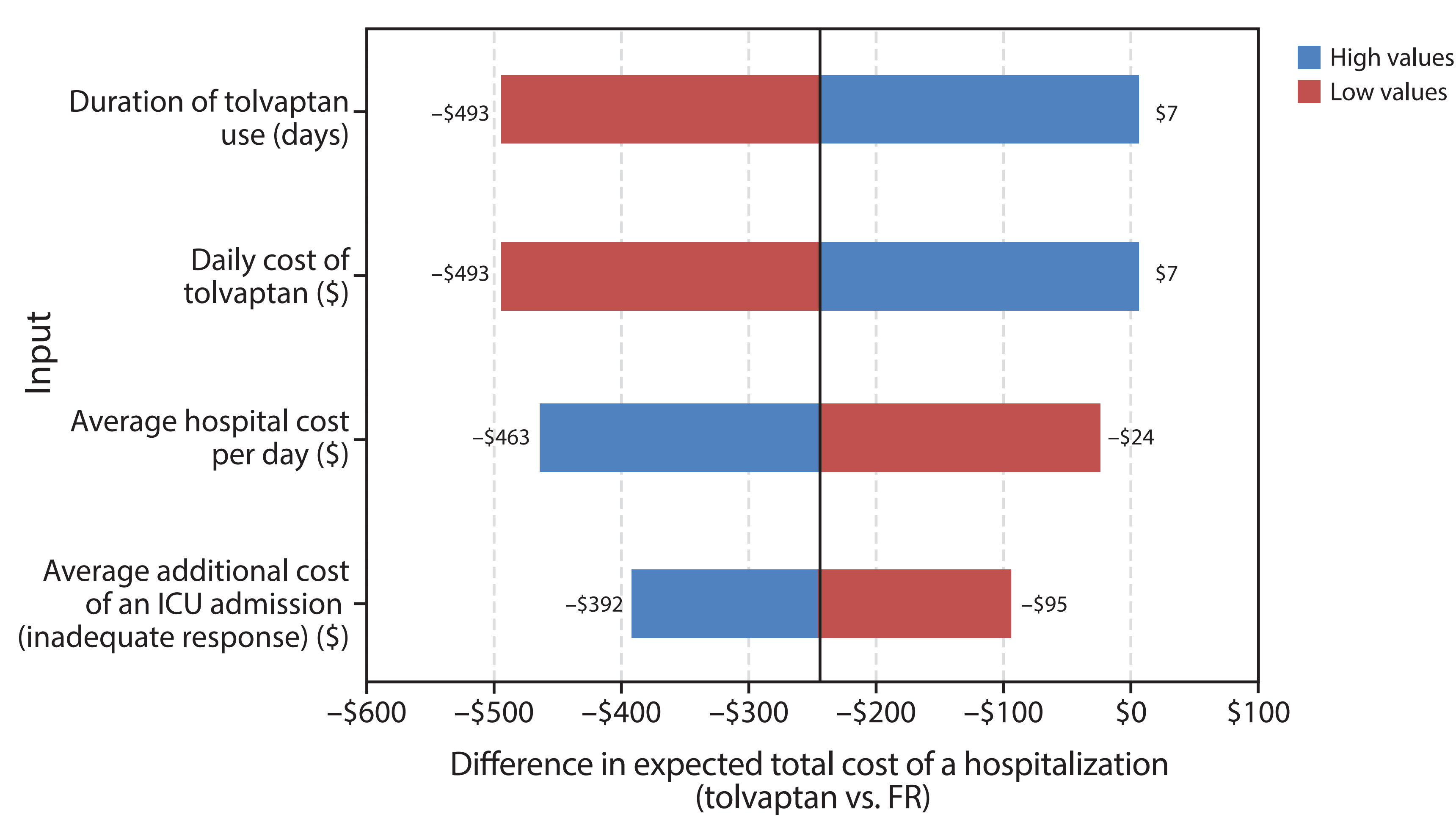
PSA

- The PSA showed that, under base-case assumptions of uncertainty in the model input parameters, the use of tolvaptan to treat hyponatremia yielded cost-savings in approximately 77% of the simulations conducted in a population of patients hospitalized for CHF and treated for with severe hyponatremia. Approximately 95% of the simulations conducted in a population of patients hospitalized for CHF and treated for mild-moderate hyponatremia and 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 CHF, tolvaptan, in comparison with FR, is expected to save hospitalization costs.

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