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Economic Evaluation of the Randomized Aldactone Evaluation Study (RALES): Treatment of Patients with Severe Heart Failure

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***Summary. Purpose*: To use data from the Randomized Aldactone Evaluation Study (RALES) to compare clinical outcomes and costs as part of the assessment of the economic implications of spironolactone treatment of advanced heart failure.**

***Methods*: RALES was a randomized, double-blinded, placebo-controlled trial that enrolled participants who had severe heart failure and a left ventricular ejection fraction of no more than 35% and who were receiving standard therapy, including an angiotensin-converting enzyme inhibitor, a loop diuretic, and, in some cases, digoxin. We used a decision analytic model that incorporated data from participants in RALES as well as cost data from five countries that participated in the study. Costs were calculated for nonfatal hospitalizations, ambulatory care, spironolactone therapy, and death. The primary health outcome was quality-adjusted life-years saved (QALYS). Outcomes were evaluated for the first 35 months of observation in RALES.**

***Results*: Spironolactone therapy during the first 35 months of follow-up in RALES increased quality-adjusted survival time (0.13 QALYS, 95% CI, 0.07 to 0.18) without increasing costs ($713 savings, 95% CI, $2123 savings to $783 in costs). Spironolactone therapy either dominated placebo or had a ratio of cost per QALYS that was unlikely to exceed $20,300. These results were robust in both one-way and multiway sensitivity analyses.**

***Conclusions*: Even after implementation of current clinical guidelines, addition of spironolactone therapy provides an opportunity to further reduce the large clinical and economic burden of patients with heart failure.**

***Key Words*. congestive heart failure, spironolactone, RALES, economics, cost-effectiveness**

Introduction

Congestive heart failure is a chronic, debilitating, and inexorably progressive disease characterized by significant morbidity and mortality. Despite advances in the medical management of heart failure, the incidence and prevalence of the disease continue to grow [1]. In the United States alone, nearly 5 million people are living with heart failure, and another 500,000 new cases are diagnosed each year [2]. The incidence of heart failure approaches 10 per 1000 population after the age of 65, and the 5-year mortality rate is approximately 50% [2].

Heart failure is also the most frequent and expensive reason for hospitalization among people age 65 years and older [3,4]. Each year in the United States, more than 900,000 people are hospitalized for heart failure and the direct costs of caring for all patients with heart failure exceed $8 billion [5]. Total costs of treatment of heart failure may approach $18 billion when evaluation and long-term care are considered [5,6]. The incidence and prevalence of heart failure in other industrialized nations are similar to those in the United States [7].

Current evidence-based clinical practice guidelines for the treatment of heart failure recommend an angiotensin-converting enzyme (ACE) inhibitor and a diuretic [8]. Recent studies of beta-blockers [9–12]

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and spironolactone [13] have shown that use of these drugs may further reduce heart failure-related morbidity and mortality. For example, the Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% reduction in the risk for death among patients with advanced heart failure who were also receiving ACE inhibitors, loop diuretics, and, in some cases, digoxin [13].

Appropriate treatment of heart failure should improve clinical outcomes and reduce morbidity-related costs. In this study, we used data from RALES to compare clinical outcomes and costs as part of the assessment of the economic implications of spironolactone treatment of advanced heart failure.

Methods

For this analysis, we adopted the structure of a previously published decision analytic model that we developed for the economic evaluation of the treatment trial in the Studies of Left Ventricular Dysfunction (SOLVD) [14]. We incorporated primary data from participants in RALES as well as cost data from five countries that participated in the study. Costs were calculated for nonfatal hospitalizations, ambulatory care, spironolactone therapy, and death. The primary health outcome was quality-adjusted life-years saved (QALYS); secondary health outcomes were years of survival according to New York Heart Association (NYHA) functional class and years of life saved. We evaluated incremental social costs (savings), expressed in 1999 U.S. dollars, and health outcomes for the first 35 months of observation in RALES (i.e., we adopted a truncated societal perspective that was limited to the evaluation of direct medical costs).

Randomized aldactone evaluation study

RALES was a randomized, double-blinded, placebo-controlled trial that enrolled 1663 participants with severe heart failure (NYHA class III or IV with a history of class IV within the 6 months before enrollment) and a left ventricular ejection fraction of no more than 35% who were receiving standard therapy, including an ACE inhibitor and a loop diuretic, with or without digoxin [13]. A total of 822 participants were randomly assigned to receive 25 mg of spironolactone daily, and 841 were assigned to receive placebo. Participants were enrolled in 195 centers in 16 countries. The primary clinical end point was death from all causes; secondary clinical end points included cardiovascular hospitalizations.

The trial was discontinued early, after a mean follow-up of 24 months, because an interim analysis determined that spironolactone was efficacious. The study showed that spironolactone was associated with a relative risk for death of 0.70 (95% confidence interval [CI], 0.60 to 0.82; $P < 0.001$) compared with placebo. The drug also had a relative risk for cardiac hospitalization of 0.65 (95% CI, 0.54 to 0.77; $P < 0.001$). The design and results of the study have been previously reported [13].

The model

Survival. Monthly survival probabilities for participants receiving spironolactone and those receiving placebo were estimated from Kaplan-Meier curves for the first 35 months of observation in RALES. From these curves we estimated the survival probabilities at the beginning of months 1, 2, ..., 36. We used the trapezoidal method to estimate the area under the survival curve during each of the 35 months, e.g., $ST_{t,j} = (S_{t,j} + S_{t+1,j})/2$, where $ST_{t,j}$ equals the survival time (in months) in month t for patients who received treatment j, $S_{t,j}$ equals the proportion of patients who received treatment j who were alive at the beginning of month t, and $S_{t+1,j}$ equals the proportion of patients who received treatment j who were alive at the beginning of month $t + 1$. These areas represented average survival time during that month. The sum of these areas represented survival time during the 35 months of RALES.

Functional status and quality-adjusted survival. At each follow-up visit, NYHA classes of persons in the study were evaluated by their physicians. We estimated the proportion of time that study participants were in each of the four NYHA classes during each month.

Quality-adjusted survival was assessed by multiplying our estimates of the number of years that study participants spent in NYHA classes I through IV by a set of quality-adjustment factors equaling 0.71, 0.61, 0.52, and 0.47, respectively [14,15]. These factors were derived from responses of 1601 participants in SOLVD to a visual analogue scale, the Ladder of Life questionnaire. This questionnaire was used to rate current health of persons in the four NYHA classes as a fraction of healthy life (where 0 = worst possible life and 1 = best possible life).

Hospitalizations and deaths outside the hospital. We estimated treatment-specific monthly probabilities of nonfatal hospitalization conditional upon participants' being available for follow-up in a month from data on hospitalizations that were recorded prospectively during the trial. To do so, we counted the number of hospitalizations in a month and divided the total by the total follow-up time (in months) in the month. Figure 1 shows the monthly probabilities of all-cause nonfatal hospitalizations. Probabilities were estimated for each of eight primary reasons for admission (atrial flutter, angina, heart failure, myocardial infarction, stroke, ventricular arrhythmia, other cardiovascular conditions, and other noncardiovascular conditions). Total hospitalizations during the 35 months of follow-up were estimated by multiplying the monthly probabilities by the survival time in a month.

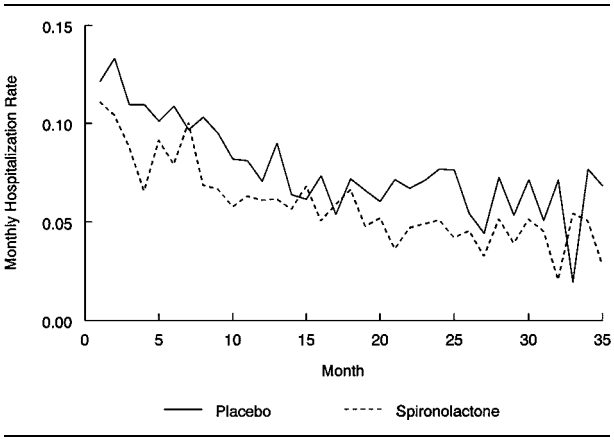

Fig. 1. *Nonfatal hospitalization rates during the first 35 months of the Randomized Aldactone Evaluation Study (RALES). Dashed line represents rates for patients receiving spironolactone; solid line represents rates for patients receiving placebo.*

We also estimated monthly probabilities of death both within (by cause) and outside the hospital.

Ambulatory care. Data on the use of outpatient services were not recorded in RALES. We thus used responses of 2704 family and general practitioners, internists, and cardiologists to an American Heart Association survey on outpatient management of participants with heart failure [16] to estimate this utilization. We assumed that physicians saw participants four times a year; measured electrolytes three times a year; and used standard chest radiography, echocardiography, radionuclide ventriculography, and exercise testing less than once a year.

Spironolactone dose. To calculate the probability that participants took 12.5, 25, and 50 mg of spironolactone per day during each month of the trial, we used data from case report forms that recorded prescribed study medication and changes in this medication.

Cost data

Costs were estimated for eight types of nonfatal and fatal hospitalization, deaths outside the hospital, ambulatory care, and spironolactone therapy itself. Daily costs of hospitalizations (by reason for admission) were derived from Belgium, Brazil, France, Spain, and the United Kingdom (these five countries enrolled 1165 out of the 1663 [70%] participants in the trial). To estimate per-patient total hospital costs in these countries, we multiplied days in the hospital (by reason for admission) by the admission-specific daily cost estimates. To estimate hospitalization costs for other developing countries (Mexico, South Africa, and Venezuela), we multiplied days in the hospital by the daily cost estimates derived in Brazil. To estimate costs for other developed countries (Australia, Canada, Germany, Japan, the Netherlands, New Zealand, Switzerland, and the United States), we multiplied days in the hospital by the admission-specific average of cost estimates from Belgium, France, Spain, and the United Kingdom.

We estimated that death outside of the hospital would cost $1000 and that this cost included the costs of an ambulance, emergency services, and emergency department care [14]. A year of ambulatory care was estimated to cost $436 [14].

The cost of spironolactone therapy was based on the U.S. average wholesale price ($48.30 per 100 25-mg tablets).

Economic analysis

We present undiscounted and discounted years of survival (overall and by NYHA class), discounted years of survival adjusted for the quality of survival, and discounted costs. When one therapy dominated another (i.e., had lower costs and greater QALYS), we report this fact. When costs of care and QALYS were greater for one therapy, we report ratios of discounted cost per discounted QALYS. We used a discount rate of 3% [17].

We used a bootstrap procedure to assess stochastic uncertainty in the analysis [18]. The model was replicated 1000 times, and we report confidence intervals for our estimates of undiscounted survival, discounted survival, discounted QALYS, discounted costs, and the ratio of cost per QALYS. We also used the results of the bootstrap procedure to estimate the probability that spironolactone has a cost-effectiveness ratio that falls below $20,000 per QALYS.

Sensitivity analyses

Effects of five assumptions used in the models were tested in one-way sensitivity analysis by varying the following data: (1) the survival benefit (±33%), based on the 95% CI for the relative risk for death among the participants who received spironolactone; (2) the costs of spironolactone (±50%); (3) the daily costs of hospitalization (±50%); (4) ambulatory care costs (±50%); and (5) the discount rate, at 0% and 7%.

In the primary analysis, the QALYS results were driven by heart failure class, not by side effects such as gynecomastia (which was reported in 10% of patients receiving spironolactone and 1% of placebo recipients [13]). To address the ways in which gynecomastia may affect quality of life, we performed a sensitivity analysis that assumed that (1) gynecomastia had an additive quality-adjustment factor of −0.10 (e.g., someone in NYHA class I who experienced gynecomastia would have had a quality-adjustment factor of 0.61 [0.71 minus 0.10]), and (2) patients who developed this side effect experienced it for the duration of the trial.

Finally, we report best-case and worst-case scenarios by combining the values of variables that led to more optimistic results for spironolactone as well as those that led to more pessimistic results. For the best case, we assumed an increased survival benefit

of +33%, decreased spironolactone costs (−50%), decreased hospital costs (−50%), decrease ambulatory care costs (−50%), and a lower discount rate (0%). For the worst case, we assumed a reduced survival benefit (−33%), increased spironolactone costs (+50%), increased hospital costs (+50%), increased ambulatory care costs (+50%), a higher discount rate (7%), and a quality-adjustment factor for gynecomastia (−0.10).

For each analysis, we report the impact of the change in the assumption on the point estimates of discounted costs, discounted years of life saved, discounted QALYS, and the ratio of discounted cost per discounted QALYS. We also report the impact of the change on the 95% CI for the ratio of cost per QALYS. The confidence intervals reflect both the uncertainty related to the specific measures being evaluated and stochastic uncertainty.

Results

Survival time

Estimates of survival time during the first 35 months of follow-up in RALES (overall and by NYHA class) are reported in Table 1. Average survival time for participants who received spironolactone was 2.28 years (95% CI, 2.01 to 2.34 years), which was 0.22 year (95% CI, 0.11 to 0.30 year) longer than the 2.07 years (95% CI, 1.86 to 2.13 years) of survival time among participants who received placebo. In addition to lengthening survival, spironolactone therapy also led to improved functional status. Of the 0.22-year increase in survival, 0.05 year was spent in NYHA class I and 0.13 year was spent in NYHA class II; there was also a small substitution of survival time between classes III and IV. Given the short time horizon of the study and a discount rate of 3%, results for discounted survival time were similar to those for undiscounted time.

Because of the relatively large diminutions in the quality-adjustment factors associated with survival time in the four NYHA classes, discounted quality-adjusted survival time was substantially less than discounted survival time. Patients who received spironolactone experienced 1.27 QALYS (95% CI, 1.12 to 1.30 QALYS) during the 35 months of follow-up; those who received placebo experienced 1.14 QALYS (95% CI, 1.02 to 1.18 QALYS). Thus, spironolactone therapy was associated with a gain of 0.13 discounted QALYS (95% CI, 0.07 to 0.18 QALYS).

Costs

Table 2 shows the discounted costs for participants receiving either spironolactone or placebo for the first 35 months of follow-up in RALES. Costs were $8762 (95% CI, $7612 to $9860; data not shown in table) for participants who received spironolactone and $9475 (95% CI, $8197 to $10,434; data not shown in table) for placebo recipients. The apparent cost saving of $713 (95% CI, $2123 in savings to $783 cost) associated with spironolactone therapy was not statistically significant (one-tailed $P = 0.2$).

Cost-effectiveness

Figure 2 shows the distribution of the bootstrap replicates comparing costs and QALYS among participants who received spironolactone or placebo. The point estimate indicates that spironolactone therapy dominated placebo (i.e., it saved $713 and lengthened discounted quality-adjusted survival time by 0.13 year). A total of 80.4% of the bootstrap replicates fell in the dominant, southeast quadrant of the cost-effectiveness plane [19], and 19.6% of the replicates fell in the northeast quadrant (in which spironolactone therapy increases costs and discounted QALYS). The 95% CI for the comparison of costs and QALYS indicated that spironolactone

Table 1. *Years of survival for participants treated with spironolactone or placebo during the first 35 months of the randomized aldactone evaluation study*[a]

	New York Heart Association Class					
Variable	I	II	III	IV	Total[a]	95% Confidence interval
Within-trial						
Undiscounted years of life						
Spironolactone	0.21	0.94	0.99	0.15	2.28	2.01 to 2.34
Placebo	0.16	0.81	0.93	0.17	2.07	1.86 to 2.13
Difference	0.05	0.13	0.06	−0.02	0.22	0.11 to 0.30
Discounted years of life[b]						
Spironolactone	0.20	0.92	0.96	0.15	2.23	1.97 to 2.28
Placebo	0.15	0.79	0.91	0.17	2.02	1.82 to 2.08
Difference	0.05	0.13	0.05	−0.02	0.21	0.11 to 0.29
Discounted quality-adjusted years of life[b]						
Spironolactone	0.14	0.56	0.50	0.07	1.27	1.12 to 1.30
Placebo	0.11	0.48	0.47	0.08	1.14	1.02 to 1.18
Difference	0.03	0.08	0.03	−0.01	0.13	0.07 to 0.18

[a] Differences due to rounding.

[b] Discount rate = 3% per year.

Table 2. *Costs by category for participants treated with spironolactone or placebo during the first 35 months of the randomized aldactone evaluation study*[a]

Variable	Spironolactone	Placebo	Difference[b]	95% Confidence interval
Nonfatal hospitalization	6096	7109	−1012	−2305 to 368
Fatal hospitalization	1113	1241	−128	−597 to 377
Deaths outside hospital	178	265	−86	−131 to −30
Ambulatory care	948	861	87	44 to 119
Spironolactone	427	0	427	377 to 441
Total cost	8762	9475	−713	−2123 to 783

[a]Discount rate = 3% per year.
[b]Differences due to rounding.

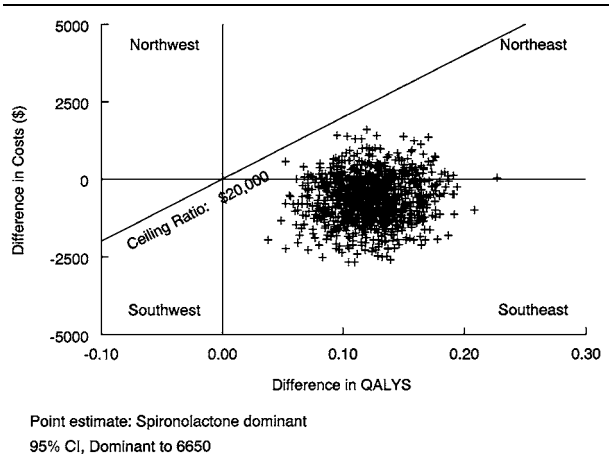

Fig. 2. *1000 bootstrap replicates of incremental costs and quality-adjusted life-years saved (QALYS) during the first 35 months of the Randomized Aldactone Evaluation Study (RALES).*

may have dominated placebo (lower limit) or may have had a cost per QALYS ratio as high as $6650 (upper limit). The probability approaches 100% that the cost per QALYS ratio was less than $20,000 (represented by the fact that none of the replicates were above and to the left of the line representing a ceiling ratio of $20,000).

Sensitivity analysis

Sensitivity analyses reported in Table 3 indicate that our results were robust for the six variables we evaluated in one-way sensitivity analysis. In all cases, the point estimate indicated that spironolactone dominated placebo; in all cases the lower limit of the 95% CI for the comparison of costs and QALYS indicated that spironolactone dominated placebo, and in no case was the upper limit of the 95% CI above $9050 (it equaled this value when we reduced the survival benefit of spironolactone by 33%).

Our sensitivity analysis evaluating diminutions in preferences related to the development of gynecomastia indicated that this condition might reduce the incremental QALYS associated with spironolactone by 0.02, from 0.13 to 0.11. The resulting 95% CI for the difference ranged from 0.05 to 0.16 (data not shown in table). As with all of the other sensitivity analyses, the point estimate and lower limit of the 95% CI indicated that spironolactone dominated placebo; the upper limit of the ratio was no higher than $8050 per QALYS.

Results of the multiway best- and worst-case sensitivity analyses also indicated that the results were robust. In the best case, the point estimate and the lower limit of the 95% CI suggested that spironolactone dominated placebo, whereas the upper limit was $2400. In the worst-case analysis, the point estimate and lower limit of the 95% CI indicated that spironolactone dominated placebo, while the upper limit of the ratio was $20,300 per QALYS.

Discussion

Spironolactone therapy during the first 35 months of followup in RALES increased quality-adjusted survival time (0.13 QALYS, 95% CI, 0.07 to 0.18) without increasing costs ($713 savings, 95% CI, $2123 savings to $783 in costs). Spironolactone therapy either dominated placebo or had a ratio of cost per QALYS that was unlikely to exceed $20,300. These results were robust in both one-way and multi-way sensitivity analysis.

Spironolactone therapy also reduced the burden of heart failure related to hospitalizations. This finding is one of the primary reasons that spironolactone, in addition to treatment with an ACE inhibitor, loop diuretic, and, in some cases, digoxin, appears to be economically attractive for patients with severe heart failure.

Comparisons with economic results of other heart failure treatments should be made with caution. For instance, patients with less severe disease may not be as responsive to spironolactone therapy as patients with a more severe condition (or vice versa). In addition, differences in mortality- and morbidity-related costs may be associated with varying severity of heart failure. Therefore, the effectiveness of spironolactone treatment among patients with less severe disease requires further study.

Patients with less severe disease may be more affected by, or less tolerant of, the adverse effects of

Table 3. *Sensitivity analysis*

Variable	Disc costs	Disc YOLS	Disc QALYS	Cost/QALYS	95% Confidence interval
Principal analysis	−715	0.21	0.13	Dom+	Dom+ to 6650
Survival benefit					
−33%	−750	0.14	0.09	Dom+	Dom+ to 9050
+33%	−680	0.28	0.17	Dom+	Dom+ to 5800
Spironolactone costs					
−50%	−925	0.21	0.13	Dom+	Dom+ to 4850
+50%	−500	0.21	0.13	Dom+	Dom+ to 8750
Hospitalization costs					
−50%	−145	0.21	0.13	Dom+	Dom+ to 5300
+50%	−1285	0.21	0.13	Dom+	Dom+ to 8400
Gynecomastia					
−0.1 Quality-adjustment	−715	0.21	0.11	Dom+	Dom+ to 8050
Ambulatory care costs					
−50%	−755	0.21	0.13	Dom+	Dom+ to 6350
+50%	−670	0.21	0.13	Dom+	Dom+ to 7000
Discount rate					
0%	−750	0.22	0.14	Dom+	Dom+ to 6350
7%	−665	0.20	0.12	Dom+	Dom+ to 7000
Multi-way sensitivity analysis					
Best case	−415	0.29	0.18	Dom+	Dom+ to 2400
Worst case	−1020	0.13	0.07	Dom+	Dom+ to 20,300

+Results rounded to the nearest $5 (discounted costs), 0.01 (discounted years of life saved [YOLS] and quality-adjusted years of life saved [QALYS]), and $50 (cost/QALYS). Disc = discounted; Dom+ = spironolactone dominates placebo.

therapy. In RALES, gynecomastia occurred in 10% of the spironolactone-treated patients vs 1% of the placebo recipients ($P < 0.001$). Other adverse reactions related to spironolactone include digestive conditions (gastric bleeding, ulceration, diarrhea, nausea, and vomiting) and other endocrine effects (in addition to gynecomastia), including inability to achieve or maintain erection, irregular menses or amenorrhea, and postmenopausal bleeding (Aldactone Package Insert, G.D. Searle & Co., Chicago, Illinois, 1998). Spironolactone also carries a warning because it has been shown to be a tumorigen in long-term toxicity studies, prompting the recommendation that unnecessary use of this drug should be avoided. while this side effect profile may limit patients' acceptance of the therapy, these potential adverse outcomes should be weighed against spironolactone's positive effects on both morbidity and mortality among patients with severe heart failure.

Our study had several limitations. First, there were substantial amounts of censored data in RALES, principally because patients were enrolled over a period of 21 months, and all follow-up stopped on August 24, 1998. This type of censoring generally falls under the category of "missing completely at random," which has been referred to by Rubin as MCAR [20]. To address the potential problems posed by such censoring, for our analysis we adopted a method similar to the one proposed by Lin et al. (referred to as the Lin interval method) [21]. This method has been shown to be reliable in the face of missing data mechanisms that are MCAR [21].

Second, our QALYS results were driven by heart failure class, not by preference data collected directly in the trial, because the trial did not assess preferences. We used sensitivity analysis to address the QALYS diminutions that may be associated with gynecomastia. We found that even if the quality-adjustment factor associated with gynecomastia was as high as 0.10, it had little impact on the cost-effectiveness of spironolactone.

Third, we used average variable costs per day of hospitalization to estimate hospital costs. We did not have data indicating whether the intervention affected the intensity of hospitalization. When we addressed this issue through the sensitivity analysis related to the cost of hospitalization, however, we found that it probably had little effect on our results.

Fourth, we had no direct measurement of the costs of ambulatory care, and we accounted only for differences in these costs that were associated with spironolactone's longer survival time. As with the cost of hospitalizations, sensitivity analysis indicated this variable probably had little effect on our results.

Our results indicate that even after implementation of current clinical guidelines, there are opportunities to further reduce the large clinical and economic burden of patients with heart failure. Spironolactone therapy increased quality-adjusted survival and may have reduced the cost of treatment of advanced heart failure, but the latter difference was not significant. Additional study may be required to confirm these findings and evaluate the cost-effectiveness of this drug in patients with less severe disease.

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