ORIGINAL RESEARCH

Cost-Effectiveness of de novo Simvastatin as Adjunctive Therapy in Patients Critically Ill with Sepsis

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OBJECTIVE: To evaluate the cost-effectiveness of de novo simvastatin plus standard therapy versus standard therapy alone in patients with sepsis during a 1-year period.

METHODS: A total of 145 critically ill patients were recruited in an open-label, randomized, controlled clinical trial. Of these, 80 patients received standard therapy according to Surviving Sepsis Campaign Guidelines 2012, and 65 received oral simvastatin plus standard therapy. The outcomes assessed include survival at the end of 1-year follow-up and intensive care unit (ICU) length of stay. Per protocol analysis was used.

RESULTS: The ICU length of stay was significantly decreased in the simvastatin group (P = .001). At 1 year, 46% of patients in the simvastatin group survived compared with 35% in the standard therapy group, although this was not significant (P = .173). However, a Kaplan-Meier curve showed a significant difference that favored the standard arm (P = .01). Simvastatin was the dominant treatment option based on lower total direct costs versus the standard group. Savings related to ICU length of stay was the main determinant of the cost-saving results of simvastatin. Incremental cost-effectiveness ratio was negative and thus was not calculated. Probabilistic sensitivity and one-way sensitivity analyses were done, and results were robust to change.

CONCLUSION: de novo simvastatin as an adjunct to standard therapy in ICU patients with sepsis lowered the overall cost by shortening ICU length of stay and its associated costs, but generalization to patients with different magnitudes of sepsis severity and to different ethnic groups requires further investigation.

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KEY WORDS: adjunctive simvastatin, ICU costs, ICU length of stay, sepsis, statins

Sepsis is a prevalent healthcare issue, as emphasized by the high consumption of resources when caring for patients with this condition. It is a leading cause of death in the United States and the most frequent cause of death in noncardiac critically ill patients.[1] No specific treatment has been found for antisepsis; management relies mostly on antimicrobial agents directed against the confirmed or suspected pathogen, surgical drainage/debridement if needed, and organ support.[2,3] Nevertheless, studies of new treatments with promising results are ongoing, and they should be assessed for possible benefits for a particular population (efficacy), for their subsequent employment in real-world situations (effectiveness), and for economic costs (efficiency).[3-8]

A previously published work by the authors of the present study assessed the result of the addition of 40 mg of simvastatin to that of standard therapy[9] on mortality and intensive care unit (ICU) length of stay in critically ill septic patients. The results showed that simvastatin is a probable cost-effective therapy as it decreased the ICU length of stay in this population.[10] Another study also showed a significant effect of de novo statin use on ICU length of stay in septic patients.[11]

Due to limited financial resources, especially in developing countries, economic evaluations are becoming more important with respect to reimbursement decisions. Countries such as Canada and Australia now require economic analyses to reimburse a new pharmaceutical agent under their drug benefit program.[12]

The goal of this study was to conduct a cost-effectiveness analysis to examine the use of de novo simvastatin

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plus standard therapy versus standard therapy alone in patients with sepsis during 1 year of follow-up.

Methods

All patients newly admitted to the ICU of Ain Shams and Cairo University Hospitals in Egypt in whom sepsis was suspected were screened for inclusion into the study. Of 400 patients screened between February 2014 and January 2016, 145 patients were enrolled. Within the first 24 hours of ICU admission, suspected sepsis was confirmed in patients based on the definitions established by the American College of Chest Physicians.[13]

Patients aged >70 years were excluded because the mortality rate may be increased in this population when treated with statins based on findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial study.[14] Patients with end-stage renal disease were also excluded because the use of statins in this population is relatively contraindicated.[15] In addition, patients with active liver disease and pregnancy were excluded by the investigators to avoid the risk of adverse effects of statins on the liver and fetus.[16] Moreover, those with extensive burns[17] or receiving drugs known to interact with simvastatin[16] were excluded because of the high risk of rhabdomyolysis. Finally, those with previous statin use were excluded to investigate the benefits from acute administration of statins.

This was a randomized, open-label, controlled clinical trial that took place at 2 medical centers in Egypt (Ain Shams and Cairo University Hospitals). The clinical and economic analyses were conducted per protocol. The perspective of the economic study was healthcare payer (government), thus only direct medical and nonmedical costs were incurred. The study was approved by the Research Ethics Committee at Faculty of Pharmacy, Ain Shams University (number 97) and was registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02067949). Consent forms were obtained from all patients or if unable from a relative.

Cost-effectiveness analysis based on the mortality rate at the end of 1 year of follow-up was the primary outcome; the secondary outcome was ICU length of stay.

The full cohort of 145 patients were divided into 2 groups: 80 patients received standard therapy (standard group) according to Surviving Sepsis Campaign Guidelines 2012,[9] and 65 patients received oral simvastatin plus standard therapy (statin group).

From the first day of inclusion in the study, the statin group received simvastatin daily as a single oral 40-mg tablet (doses ≥40 mg were associated with significantly reduced hospital mortality).[18] Patients continued the daily regimen until they were discharged from the ICU. Because tablets can be crushed and suspended in water, enteral feeding or gastric drainage tubes were used in patients who were not able to swallow.[19]

This phase 3 clinical trial compared new treatment to standard therapy with a sample size of 145 patients.[20] A computer-generated randomization sequence was used with random block size.[21]

Direct medical cost was calculated as the whole cost per day plus statin cost in the intervention arm. The cost was reimbursed by the government except for the statin cost, whereas direct nonmedical costs were collected directly from the patient. Patients' medical records were used to obtain the diagnostic data of sepsis. Patients' economic data were collected during ICU length of stay, and mortality data were collected during ICU length of stay and at 3, 6, and 12 months. Laboratory values and adverse events were all recorded throughout the patients' ICU length of stay.

Statistical Analysis

The IBM SPSS statistics (v 25.0) software platform was used. For quantitative nonparametric measures, data were expressed as median and percentiles (as data were skewed).

KEY POINTS

- Sepsis is a prevalent healthcare issue, as emphasized by the high consumption of resources when caring for patients with this condition, and a leading cause of death in the United States.
- This study was an open-label, randomized, controlled clinical trial, assessing a total of 145 critically ill intensive care unit (ICU) patients with sepsis; 80 patients received standard therapy and 65 received oral simvastatin plus standard therapy.
- Outcomes assessed include survival at the end of 1-year follow-up and ICU length of stay.
- By month 3, 52 patients in the standard group and 35 patients in the simvastatin group had died. However, at 6 and 12 months, no additional deaths were recorded, and at 12 months, a nonsignificant decrease in mortality was detected in the simvastatin group compared with the standard group.
- The standard group showed a significantly higher ICU length of stay compared with the statin group (8.2 ± 4.3 days vs 5.3 ± 2.6 days, respectively; $P = .0001$).
- In the present study, although statins had no impact on mortality, de novo simvastatin as an adjunct to standard therapy in ICU patients with sepsis decreased the overall cost by reducing the ICU length of stay and its associated costs.

Table 1 Demographic and Clinical Characteristics of the Recruited Patients at Baseline

Variables	Group 1 (standard group) (n = 28)	Group 2 (simvastatin group) (n = 30)	*P* value
Weight, kg (median, IQR)	80 (70-80)	80 (70-97.5)	.96[a]
Age, years (median, IQR)	42 (31.5-62)	52 (33.5-60)	.60[a]
Sex distribution (male %)	20 (71.4)	15 (50)	.308[b]
Charlson comorbidity index (median, IQR)	0 (0-2.25)	2 (0-4)	.11[a]
SOFA admission (median, IQR)	5 (2.75-8)	6 (3.25-7)	.88[a]
APACHE II score (median, IQR)	13 (5-17)	14 (10.25-17.75)	.50[a]
Creatine kinase, IU/L (median, IQR)	207 (100-291)	315 (180-441.75)	.03[a]
Alanine transaminase, IU/L (median, IQR)	27.50 (14.75-49.25)	18.50 (14-35.25)	.20[a]
Aspartate transaminase, IU/L (median, IQR)	30 (21.75-46.25)	24.50 (18.25-37.50)	.20[a]

[a]Wilcoxon rank sum test.
[b]Chi-squared test at level of significance $P \leq .05$.
APACHE indicates Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

Categorized data were expressed as number and percentage. For nonparametric data, the Wilcoxon rank sum test was used to compare 2 independent variables, whereas Wilcoxon signed rank test was used to compare between 2 dependent variables. Categorized data were compared using the chi-squared test, and a *P* value of ≤.05 was considered significant.

Economic analysis was performed using Microsoft Excel 2010. The gross domestic product (GDP) per capita for Egypt, based on World Bank figures, was $3525.02 (US dollars) in the year 2016. The World Health Organization (WHO) recommendation for the willingness-to-pay threshold for low- and middle-income countries is 1 to 3 times GDP per capita.[22] Accordingly, an incremental cost-effectiveness ratio of less than E£85,000 (Egyptian pounds; ie, $9095 US dollars based on average exchange rate in 2016 of $0.107 US dollars) was considered to be cost-effective. To convert cost into a common currency base (dollar), all costs were divided by the purchasing power parity rate 2016 (2.5).

Power analysis was done by IBM SPSS sample power (v 3.0.1, July 2012) and yielded a power of 0.939 (94%, meaning 94% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the means are equal).

Sensitivity Analysis

Based on the Consolidated Health Economic Evaluation Reporting Standards: Professional Society for Health Economics and Outcomes Research (ISPOR) Task Force report, various one-way sensitivity analyses were performed to assess uncertainty around the incremental cost-effectiveness ratio and to test the stability of the study results through variations in the key variables.[23] Variations in key variables occurred in reasonable ranges.

A probabilistic sensitivity analysis was conducted to evaluate how incremental cost-effectiveness ratio is affected by simultaneous alteration in numerous variables. In this method, a large number of simulations (here 100) are made by repetitively drawing samples from probability distributions of input variables. Accordingly, it offers a probability distribution of the output variable, ie, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios.[24,25] Microsoft Excel 2010 was used to conduct all the analyses.

Results

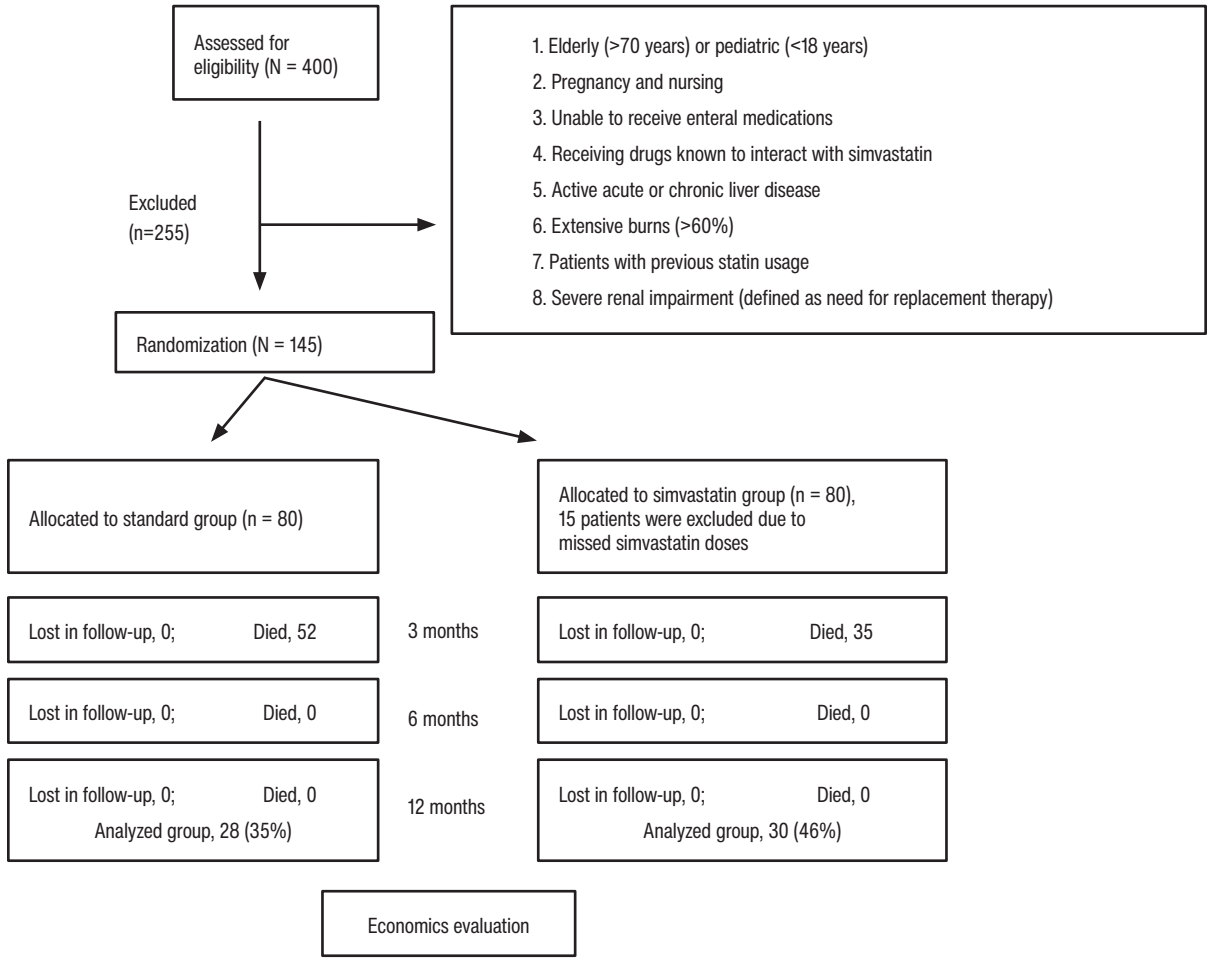
The patient demographics and clinical characteristics of the 2 study groups at baseline were comparable except for creatine kinase (CK) levels, but CK levels in both groups did not exceed the upper limit as shown in **Table 1**. The most frequent comorbidity was cardiovascular disease, followed by diabetes mellitus, cerebrovascular disease, renal disease, and immunocompromised disease or cancer.

A total of 52 patients in the standard group and 35 patients in the simvastatin group died by month 3. However, at 6 and 12 months, no additional deaths were recorded (**Figure 1**). Accordingly, at 12 months, a nonsignificant decrease in mortality was detected in the simvastatin group compared with the standard group ($P = .173$).

Because data regarding mortality were collected at 28 days, 3 months, 6 months, and 12 months, Kaplan-Meier test could not be constructed daily over the entire year. Thus, when the Kaplan-Meier curve was constructed against the ICU length of stay only, it showed a significant difference that favored the standard arm ($P = .010$; **Figure 2**).

By contrast, the standard group showed a significantly higher ICU length of stay compared with the statin group (8.2 ± 4.3 days vs 5.3 ± 2.6 days, respectively; $P = .0001$). In addition, of the patients who died, the mean ICU length of stay of the standard group was significantly higher than that in the statin group (8 ± 4.8 days vs 5.1 ± 2.2 days, respectively; $P = .002$). Among survivors, the mean ICU length of stay of the standard group was significantly higher than that in the statin group (8.4 ± 3.3 days vs 5.4 ± 3 days, respectively; $P = .002$). Hence, the controversy between total percent mortality during 1 year of follow-up and Kaplan-Meier test may be explained by the fact that the standard arm increased the length of stay without any improvement in patients' Sequential Organ Failure Assessment (SOFA) scores, which apparently increased the

Figure 1 Patient Drop Out from the Cost-Effectiveness Analysis at 12 Months



ICU length of stay and survival at 28 days; however, at 3 months, 6 months, and 12 months the mortality percentage was higher in the standard group, although it did not reach statistical significance. Thus, the statin group showed decreased ICU length of stay and improved 1-year survival rate.

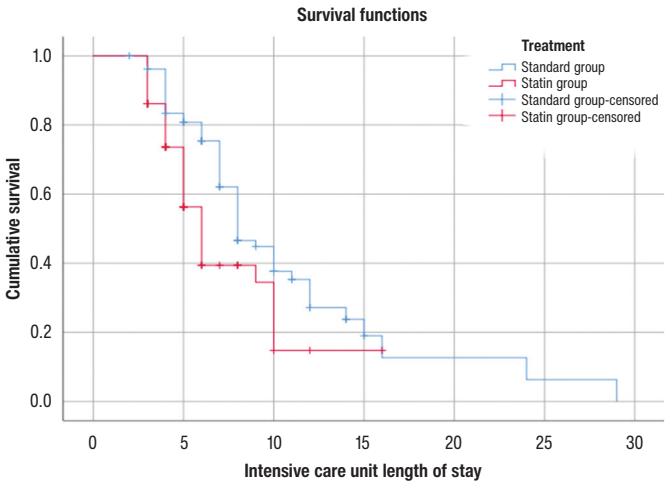
Simvastatin was the dominant treatment option based on lower total direct costs and nonmedical costs versus the standard group. Saving in costs of the ICU length of stay was the main determinant of the cost-saving results of simvastatin (**Table 2**). So, the incremental cost-effectiveness ratio was negative and thus was not calculated.

Figure 3 shows an incremental cost-effectiveness ratio plane of 2 treatments with different possible scenarios. Based on this, an incremental cost-effectiveness ratio plane was made to consider uncertainty around the point estimates. The plane revealed that the southeast quadrant included most of the 100 iterations of cost-outcome difference pairs (**Figure 4**). This shows that a statin treatment strategy is less costly and more effective (ie, higher survival). A small level of variation around the presence and magnitude of cost-savings and effectiveness is designated by the small number of points lying outside of this area.

All variables were varied simultaneously over 100 iterations within various error distributions, as shown by the probabilistic sensitivity analysis. The cost-effectiveness acceptability curve shown in **Figure 5** illustrates the probabilistic sensitivity analysis results. It indicates that cost-effectiveness of simvastatin was robust to these changes in the assumptions. Accordingly, the probability of being cost-effective at incremental cost-effectiveness ratio of less than E£85,000 (Egyptian pounds) per survival is 0.64.

One-way sensitivity analysis showed that the direct medical costs of statin and standard therapy had the ut-

Figure 2 The Survival Curve of the 2 Studied Groups



most influence on the results (**Figure 6**). The sensitivity analysis using assumed reasonable ranges showed no effect on treatment decisions, given the uncertainty surrounding the point estimates of the number of survived patients. Our conclusions were not changed by the sensitivity analysis using the uncertainty ranges assumed from the standard error. Treatment decision was not significantly affected by the majority of the other variables over plausible ranges.

Discussion

This is the first pragmatic trial to evaluate the cost-effectiveness of statin use in sepsis. The research was conducted according to the ISPOR Task Force on Good Research Practices: Randomized Clinical Trials–Cost-Effectiveness Analysis.[26] The results of clinical outcomes showed that de novo simvastatin use in living patients was accompanied by a significant decline in the ICU length of stay ($P = .001$). Although mortality was lower in the statin arm, this was not statistically significant.

In addition, when the Kaplan-Meier curve was constructed, it significantly favored the standard therapy. This could be attributed to the fact that the curve represented cumulative survival against ICU length of stay only, which was significantly longer in the standard arm. On the other hand, all the recorded deaths were at 3 months; otherwise, no deaths were recorded at 6 and 12 months.

This shows that the apparent increase in survival in the standard arm despite the nonsignificant difference between the 2 groups in SOFA score at the end of therapy is related to the increased ICU length of stay in the standard arm, indicating further deterioration and increases in costs. On this basis, an economic evaluation of simvastatin therapy was conducted. The results showed that simvastatin was a dominant treatment option in patients with sepsis.

Table 2 Total Cost Allocation Between Alive Patients in Both Groups

Patient number	Standard group, E£ (n = 28)	Statin group, E£ (n = 30)
1.	6960	2628
2.	2710	5556
3.	10,680	5478
4.	5400	5530
5.	13,120	3098
6.	2850	3624
7.	2750	3068
8.	2700	5424
9.	5750	4224
10.	2680	3086
11.	4160	2724
12.	2900	6524
13.	3450	3998
14.	11,100	5324
15.	4220	3930
16.	1400	4924
17.	3100	4086
18.	3650	5530
19.	6180	4824
20.	3560	3736
21.	12,750	5424
22.	10,700	4430
23.	12,950	3930
24.	3300	3330
25.	8000	5324
26.	2000	5030
27.	12,780	3074
28.	3330	3430
29.	------	3830
30.	------	3848
Sum of total cost	165,130 E£ ($66,052)[a]	128,966 E£ ($51,586.4)[a]

[a]All costs were calculated in E£; to convert total costs into a common currency base (US dollar), all costs were divided by the purchasing power parity rate 2016 (2.5).
E£ indicates Egyptian pound.

The analysis was conducted from a governmental perspective; productivity cost wasn't calculated to avoid underestimating the societal benefits of treatment.[27] Moreover, in Egypt, direct cost estimation is recommended.[28]

Patients with sepsis are generally treated in ICUs. Based

on various studies conducted between 1989 and 2001 and converted based on the July 2003 exchange rate (ie, €1 = $1.15 [US dollar]), the average total cost per ICU day for countries with a highly developed healthcare system is estimated at approximately €1200 ($1380).[29]

In addition, sepsis is the most costly disease managed in US hospitals at $23.7 billion, based on the 2013 Healthcare Cost and Utilization Project Statistical Brief.[30] Moreover, a 2022 study by Madkour and colleagues showed that the prevalence of sepsis in a respiratory ICU was approximately 270 sepsis cases per 100,000 persons per year, with a 26% mortality rate.[31]

It is important to note that ICU length of stay is the main factor responsible for the high proportion of fixed costs in ICU treatment and the total cost of ICU care. In addition, saving beds is crucial around the world. However, efforts to decrease ICU costs through various means, such as a reduction in length of stay, are difficult to achieve.[32] On that basis, significant reductions in total inpatient cost can be achieved through interventions that reduce ICU length of stay and/or duration of mechanical ventilation.[33]

ICU length of stay has long been used as a measure of resource utilization because of its surprising consistency among most diagnoses.[34] In one analysis, length of stay ranged from 24 hours to 132 days.[34] Even though the ICU occupies less than 10% of total hospital beds, one-third of total healthcare costs accrue in ICU care.[35] Furthermore, impaired physical function and neuromuscular weakness acquired in the ICU are the 2 long-term complications that ICU survivors often have[36] and may result in extra costs to government and society. According to WHO information reported by the website Al-Monitor, the Egyptian Ministry of Health provides 30% to 35% of medical services in the country.[37]

Adverse drug reactions leading to hospital admission, prolongation of hospital stay, and emergency department visits have significant economic and clinical costs.[38] In the present study, no significant adverse drug reactions were seen between the 2 groups in terms of CK, alanine transaminase, and aspartate transaminase levels at the end of therapy (ICU discharge). This is consistent with most studies that included patients pretreated with statins[39] and those with acute administration of statins after sepsis diagnosis, whether using atorvastatin[11] or simvastatin.[40]

Similarly, a meta-analysis evaluating the efficacy and safety of statins compared with placebo for the treatment of sepsis in adults showed that the rate of adverse events was comparable in the 2 groups of the study.[41] It is important to note that the 30-day all-cause mortality was not affected by statin use in the entire cohort of patients and in a subgroup of patients with severe sepsis. Accordingly, the investigators' conclusion was against using statins in adult patients with sepsis.[41]

Figure 3 Incremental Cost-Effectiveness Ratio Plane of 2 Treatments with Different Possible Scenarios

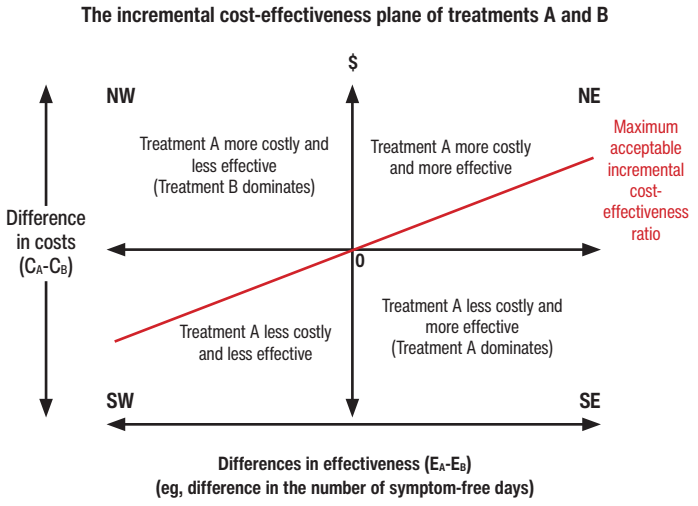
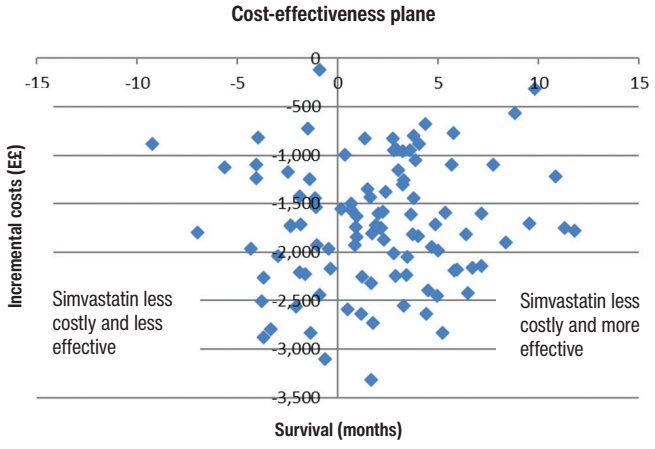


Figure 4 Cost-Effectiveness Plane for the Cost-Effectiveness Analysis Showing Bootstrapped Replications of Mean Incremental Costs and Survival



E£ indicates Egyptian pound.

This conclusion was criticized by Zhou and Tang in 2019, who pointed out that meta-analysis included a limited number of studies, which can result in random errors and false results, such as false-negative errors (type II errors).[42] Trial sequential analysis has been suggested to analyze these potential errors.[42,43] Zhou and Tang also mentioned that Pertzov and colleagues' criteria were incorrect where they incorporated studies of septic patients as well as those with infection and on mechanical ventilation.[40,42,44-47] They highlighted the importance of differenti-

Figure 5 Cost-Effectiveness Acceptability Curves Showing the Probability of Simvastatin Being Cost-Effective Compared with Standard Therapy

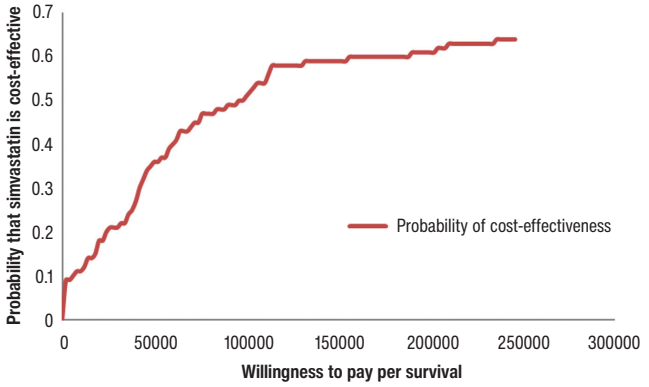
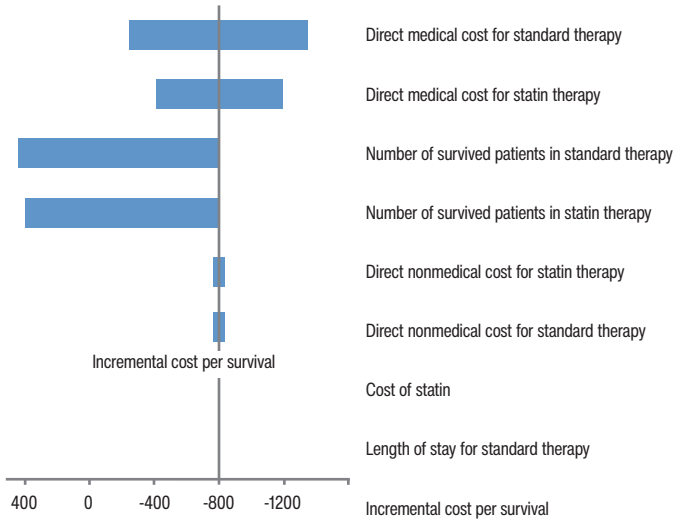


Figure 6 One-Way Sensitivity Analysis (Tornado Diagram)



ating between sepsis as a composite of systemic inflammatory response and infection and the definition of infection alone.[41,42] They also mentioned that the 2016 study by Shao and colleagues had no data on mortality and hence should have been excluded.[48]

Accordingly, including publications of nonseptic patients plus the bounded number of studies included might undervalue the actual impact of statins on septic patients and make them appear ineffective. Furthermore, Pertzov and colleagues did not assess ICU length of stay. In contrast, our results showed that de novo simvastatin use was associated with a significant decrease in ICU length of stay, which affected the total cost positively.

It is worth mentioning that some studies favor the role of simvastatin in sepsis over other statins. This is attributed to animal and in vitro studies demonstrating that simvastatin showed promising antimicrobial activity, mitigated the symptoms of early sepsis, protected vascular endothelium from damage, and improved coagulation disorders in sepsis.[49-53]

In addition, Lee and colleagues evaluated sepsis, statin use, and mortality data from the Taiwan's National Health Insurance Database from 2000 to 2011. The authors reviewed mortality data at 30 days and 90 days in 52,737 patients diagnosed with sepsis.[54] Atorvastatin, simvastatin, and rosuvastatin were the statins assessed in this analysis. In looking at the effect of statins on 30-day mortality, the investigators determined that simvastatin provided the most significant benefit on mortality (28% risk reduction), followed by atorvastatin (22% risk reduction). The positive impact of statins was seen to decrease at 90 days, although it remained significant for the 3 statins.[54] In brief, among the different statins, simvastatin provided the most potent antibacterial activity and the greatest benefit on mortality in patients with sepsis, and it was the most effective statin when used as a novel adjuvant antibiotic.[55,56]

Our conclusion that simvastatin is cost-effective is in accordance with Agus and colleagues,[57] who reported that mortality in the simvastatin group at 12 months was lower than that in the placebo group, but the difference was not significant (P = .20). The investigators also found that the cost-effectiveness of simvastatin for the treatment of acute respiratory distress syndrome from different causes (including sepsis) was associated with a significant quality-adjusted life-year gain and a cost-saving. The high unit costs associated with the higher mean number of ICU days and the high-dependency unit bed days in the placebo group were the main reasons for cost-saving.

It is worth mentioning that ethnic differences in statin efficacy have been shown only in African Americans and Asians compared with other ethnicities.[58,59] Although the United States has a racially and ethnically diverse population, the clinical results of our study, which was conducted in Egypt (the second most highly populated country in the Middle East and North Africa), can be adopted in a large group of Americans and in other countries as well.

Healthcare in Egypt consists of both a public and a private sector. For several decades, the government has provided a subsidized healthcare system that is meant to ensure healthcare for those who cannot afford it.[60,61]

The present study was conducted at 2 large governmental university hospitals in Egypt. Thus, the costs were reimbursed by the government except for the cost of the statins. In the present study, results were converted to common currency (dollar) by dividing by purchasing power parity

rate. However, our calculations were based on Egyptian market prices, GDP of low- to middle-income countries, and insurance coverage percentage of total cost, which is different from the United States. Although the healthcare system in Egypt differs from that in the United States, study results support that statin cost in sepsis can be cost-effective and would be covered as a medical benefit in the hospital through a diagnosis-related group system in the United States.

Moreover, COVID-19 has been closely related to sepsis, which suggests that most deaths in ICUs in infected patients are produced by viral sepsis.[62,63] As statins are known for their pleiotropic anti-inflammatory, antithrombotic, and immunomodulatory effects, they have been suggested to possess a potential role as adjunctive therapy to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection.[64,65] Accordingly, the study results support the further investigations of statins as a promising cost-effective therapy in sepsis.

Limitations

It is important to note that most of the patients in our study were diagnosed with early sepsis, and only 7 had severe sepsis. Lee and colleagues mentioned that the positive impact of statins did not occur in patients needing to be admitted to the ICU or patients with acute organ dysfunctions.[54] This may be credited to the fact that the potential benefits of statins occur by decreasing inflammation via intracellular signaling, lowering catecholamine levels, or decreasing Toll-like receptor activation by pathogen-associated molecular patterns.[56] Thus, the main limitation of the present study is that sepsis affects diverse levels of severity, so generalization of the results would be difficult.

Moreover, although the intention-to-treat population is the ideal choice for the primary analysis because it maintains sample size and eliminates bias,[66] missed data for those who died during the study period led to using per-protocol primary analysis. However, based on the Consolidated Standards of Reporting Trials guidelines, although intention-to-treat analysis is the standard practice, they recommend a per-protocol analysis to be performed alongside an intention-to-treat approach to allow the effect of any lost data to be studied.[67]

Conclusion

In the present study, although statins had no impact on mortality, de novo simvastatin as an adjunct to standard therapy in ICU patients with sepsis decreased the overall cost by reducing the ICU length of stay and its associated costs.

Author Disclosure Statement

The authors have no conflicts of interest to report.

This trial was registered at ClinicalTrials.gov (Clinical Trials.gov Identifier: NCT02067949). Consent forms were obtained from all patients or if unable from one of their relatives.

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