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Clinical Study

Continuation or Discontinuation of Statin Therapy Did Not Influence Patient Outcomes after the Development of Acute Respiratory Distress Syndrome

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Background. The anti-inflammatory effects of statin therapy may be beneficial in the treatment and prevention of acute respiratory distress syndrome (ARDS). *Objectives*. Determine if continuation or discontinuation of prior statin therapy is associated with ventilator-free days (VFDs) at day 28 in patients with ARDS. *Methods*. Patients with ARDS admitted to the intensive care units of a tertiary care medical center were evaluated in this retrospective cohort study. Included patients were allocated to three groups: patients for whom statin therapy was given before and continued after ARDS diagnosis (Group 1), patients with statin therapy only before ARDS diagnosis (Group 2), and patients never exposed to statins (Group 3). *Results*. Of 244 patients evaluated, 187 were included; 17 (9.1%) patients in Group 1, 20 (10.7%) in Group 2, and 150 in Group 3. There were no differences among groups in APACHE II or SOFA scores. VFDs were not significantly different among groups (median 0 versus 4.5 versus 13.5 days, $P = 0.21$). After adjustment for baseline characteristics, including propensity for statin administration, statin therapy was not associated with increased VFDs on linear regression. *Conclusions*. Exposure to statins before or after ARDS diagnosis was not associated with improved VFDs in this cohort of patients with ARDS.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a common and devastating illness in the intensive care unit (ICU), with mortality rates exceeding 30–50% [1]. ARDS occurs secondarily in a number of disease processes, most commonly sepsis, pneumonia, aspiration, trauma, pancreatitis, blood transfusions, smoke or toxic gas inhalation, and certain types of drug toxicity [2]. The pathogenesis of ARDS is not completely clear. The disease process is characterized by diffuse damage to the alveoli resulting in disruption of the endothelium and epithelium. In the acute phase of ARDS, fluid accumulates in the alveolar spaces and is accompanied by severe inflammation, increased pulmonary vascular permeability, and gas exchange abnormalities. The subsequent fibrotic phase results in diffuse interstitial thickening, fibrosis, increased dead space, and loss of lung compliance [3].

Disappointingly, anti-inflammatory therapies for ARDS have been utilized with limited success in past studies [4–9]. Despite preliminary data suggesting reduced inflammation with ketoconazole and lisofylline, these effects were not demonstrated in clinical trials of patients with ARDS, and the studies were terminated early due to futility [4, 5]. Corticosteroids have been studied in a myriad of different doses, durations, and patient populations with ARDS [6–10]. While some studies suggest a mortality benefit with glucocorticoids [7, 8, 10], these results have not been replicated in other studies [6, 9]. Conflicting results on the benefit of corticosteroids have also been noted in meta-analyses of these trials [11–14]. Corticosteroids may have adverse effects in ARDS [15], adding to the controversy in the literature on the role of this therapy. 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) inhibitors, or statins, have been shown to have direct anti-inflammatory properties within atherosclerotic plaques [16]. There is also evidence showing that statins have pleiotropic effects on vascular endothelium, alterations of coagulation, and nitric oxide production [17, 18]. Since statins exhibit pleiotropic effects of immunomodulation and

anti-inflammation, studies were initiated to evaluate the role of statins in lung injury.

Although animal models [19–22] and a healthy-volunteer study [23] suggest that statins may prevent the development of ARDS, few studies have evaluated the effect of statins in patients with established ARDS [24]. In a retrospective study, Kor et al. [24] did not demonstrate a benefit with statin therapy on PaO_2/FiO_2 ratio or progression/prevention of organ failure (as assessed by change in Sequential Organ Failure Assessment (SOFA) scores) between days one and seven after the onset of ARDS. While the level of baseline organ dysfunction is associated with higher mortality and most patients with ARDS die from multiorgan failure, the relationship between changes in organ function (change in SOFA) over time and outcomes in patients with ARDS is not clear. A randomized controlled study by Craig and colleagues evaluated the biologic and physiologic effects of simvastatin in patients with ARDS. Although simvastatin did not improved pulmonary organ function as assessed by change in SOFA scores, it did lead to nonsignificant reductions in oxygenation index, plateau pressure and lung injury score [25]. We designed this retrospective cohort study primarily to evaluate the associations of continuing or discontinuing prior statin therapy and ventilator-free days (VFDs) in patients who developed ARDS. A portion of these data have been presented in the form of an abstract at the 2010 American Thoracic Society International Conference [26].

2. Methods

2.1. Study Design. This study is a retrospective cohort study of patients who were screened or included in ARDS Network study protocols at our institution between January 2001 and December 2005. Patients were included in the study if they presented with the acute onset of PaO_2/FiO_2 less than or equal to 300, new bilateral infiltrates on chest radiograph, and no clinical evidence of left atrial hypertension. Patients were excluded if they had any of the following medical comorbidities: malignant or other irreversible condition and estimated 28-day mortality greater than 50%, moribund patients not surviving 24 hours after endotracheal intubation, chronic respiratory failure with baseline $PaCO_2$ greater than 55 mmHg, autoimmune deficiency syndrome, short-bowel syndrome in the absence of gastrointestinal tract, or age less than ten years. This study was approved by our local Institutional Review Board as well as the NIH NHLBI ARDS Network.

A chart review was performed and included patients who were divided into three groups: (a) patients who received statin therapy prior to hospital admission and was continued (≥1 dose) after ARDS diagnosis (Group 1), (b) patients whom statin therapy was given prior to admission to the hospital and discontinued prior to ARDS diagnosis (Group 2), or (c) patients whom statin therapy was never given, no record of statin administration prior to hospital admission or during hospital stay (Group 3).

2.2. Data Collection. Data collected from the medical records of patients on the date of ARDS diagnosis included criteria for ARDS diagnosis, study exclusion criteria, demographics, medical comorbidities, etiology of ARDS, ventilator parameters, vasopressor administration, and components of the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores. Additionally, administration of statin therapy prior to admission to the hospital and throughout the ICU stay was collected along with administration of neuromuscular blocking agents and corticosteroids. To assess for the primary and secondary endpoints, dates of intubation, extubation, reintubation within 28 days (if applicable), ICU admission and discharge dates, hospital admission and discharge dates, and vital status at ICU and hospital discharge were collected. Applicable data for patients enrolled in ARDS Network trials were provided by the NIH NHLBI ARDS Network.

2.3. Statistical Analysis. An *a priori* power analysis revealed that at least 294 patients would need to be included to detect a 2.5 day difference in VFDs, assuming 14.5 VFDs in the group receiving statins before and after ARDS, 10 VFDs in the group receiving statins before but not after ARDS group, 12 VFDs in the group never receiving statins [27], patient allocation ratio of 1 : 1 : 3 (resp.), 2-sided α error of 0.05, and power of 80%. Because the proportion of patients receiving statin therapy was much lower than estimated (approximate allocation ratio of 1 : 1 : 8), the data were analyzed after collection of data from patients screened and/or enrolled in the Fluid and Catheter Therapy Trial (FACTT) only. The results of this analysis are presented in this paper.

The primary endpoint for this study was ventilator-free days (VFDs), 28 days after ARDS diagnosis with secondary endpoints of ICU, hospital, and 28-day mortality. VFDs were calculated per the method of the ARDS Network [28]. Dichotomous variables are presented as counts (%), while continuous data are presented as median (IQR), unless otherwise noted. Univariate analyses for categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Mann-Whitney U-test was used to compare continuous variables. All tests were 2-tailed, and a P value of <0.05 was considered statistically significant.

A propensity score model, using nominal logistic regression, was generated to estimate the probability of receiving statin therapy after the development of ARDS based on patient characteristics. Patient baseline characteristic covariates were entered into the propensity scoring model if they were significantly different on univariate analysis or when there were strongly plausible biologic associations. The variables entered included gender, coronary artery disease, hyperlipidemia, hypertension, congestive heart failure, peripheral vascular disease, prior stroke, chronic pulmonary disease, diabetes mellitus, medical admission, septic cause of ARDS, age, and APACHE II score at the time of ARDS. The propensity scores generated for each patient were separated into quintiles and used for regression adjustments for the primary and secondary variables.

A multivariate linear regression was performed to identify independent determinants of ventilator free days. Covariates were entered into the model if they were statistically

relevant on univariate analysis or if they had plausible interactions with VFDs. The model was developed with forward and backward stepwise regression while accounting for covariate colinearity. Variables entered into the linear regression model including statin group, gender, and fluid balance during ARDS episode, use of corticosteroids, propensity score quintiles, age, APACHE II score, and tidal volume. A logistic regression to determine independent risk factors for ICU mortality was performed using similar techniques. For both multivariate analyses, patients who never received statins (Group 3) were used as the reference group. All statistics were computed using SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographics. During the study period, a total of 244 patients met criteria for ARDS and were screened for inclusion in an ARDS Network study. Of these patients, 57 were excluded (26 met $\geq$ 1 exclusion criterion and 31 had incomplete data) and 187 patients were included for analysis. Most patients included in the study were never exposed to statin therapy ($n = 150$; 80.2% of the entire cohort), while the distribution of statin continuation ($n = 17$; 9.1%) and discontinuation ($n = 20$; 10.7%) after ARDS diagnosis was similar. The predominant etiology of ARDS in the entire cohort was pneumonia (47.6%), 31.6% of patients were enrolled in FACTT, and a relatively high proportion were in shock requiring vasopressors (40.6%) on the day of ARDS diagnosis.

Patient characteristics of the three study groups are presented in Table 1. There were several expected differences in patient characteristics between groups receiving and not receiving statin therapy, such as age and medical comorbidities with indications for statin administration. Additionally, patients in Group 1 more frequently received a neuromuscular blocking agent on the day of ARDS diagnosis ($P = 0.05$). Importantly, there were no differences between groups in baseline severity of illness (as assessed by APACHE II, SOFA, PaO_2/FiO_2 ratio, and vasopressor administration) or ventilator parameters. Atorvastatin was the most commonly administered statin in both Group 1 (71%) and Group 2 (65%). Patients in Group 1 received statins for a median of 7 days (2.5–15.5 days) after ARDS diagnosis.

3.2. Outcomes. There was no difference in median VFDs among study groups (Table 2). On multivariate analysis, male gender, fluid balance during ARDS episode, and treatment with corticosteroids were the only variables independently associated with VFDs (Table 3). All three of these variables were associated with a decrease in VFDs, while statin continuation or discontinuation was not independently associated with change in VFDs.

The incidence of ICU and hospital mortality was significantly higher on univariate analysis for patients in Group 1 (Table 2). In light of this significant difference, a multivariate analysis of ICU mortality was performed, which accounted for study group, age, baseline APACHE II, and tidal volume on ARDS diagnosis date. In this logistic regression analysis, age was the only variable independently associated with ICU mortality ($P = 0.001$).

In an exploratory analysis, the patients were regrouped into patients with any statin exposure ($n = 37$) versus no statin exposure ($n = 150$). On the day of ARDS diagnosis the two groups had similar APACHE II (26.0 versus 26.0, $P = 0.94$) and SOFA scores (8.0 versus 8.0, $P = 0.66$), as well as a similar PaO_2/FiO_2 ratio (95.0 versus 121.8, $P = 0.26$). Similar to the primary analysis, there were no differences between groups in median VFDs (2.0 versus 13.5 days, $P = 0.08$) or ICU length of stay (12.0 versus 11.0 days, $P = 0.54$), but patients exposed to statins had a significantly higher ICU mortality rate (43.2% versus 24.7%, $P = 0.04$). On multivariate logistic regression analysis which included the same variables as mentioned previously, age was again the only variable independently associated with ICU mortality ($P = 0.001$).

4. Discussion

In this retrospective cohort study of patients who had statin therapy continued, discontinued, or never given after ARDS diagnosis, there was no difference in median ventilator-free days. After adjustment for baseline characteristics, logistic regression analysis confirmed that statin therapy was not associated with a decrease in VFDs. Differences in survival by statin exposure observed on univariate analyses were not significant in a multivariate analysis, which showed age as the only variable independently associated with ICU mortality.

There are several cohort studies demonstrating a short-term (in-hospital or 30 day) mortality benefit of statin exposure compared to no statin exposure in patients with bacteremia [29, 30], pneumonia [31, 32], multiple organ dysfunction syndrome [33], and sepsis [34–37]. Cohort studies have also suggested a long-term mortality benefit (180 to 365 days) in general ICU patients [38] and patients with pneumonia [39] exposed to statins. On the other hand, there are observational cohort studies that did not find an association between statin exposure and early mortality in patients with these inflammatory conditions [39–42]. A meta-analysis of cohort trials suggested a treatment benefit with statins (relative risk of death 0.55, 95% confidence interval 0.36–0.83) but also noted significant heterogeneity ($I^2 = 76.5\%$) and possible publication bias (Egger test $P = 0.15$) [43]. These disparate results suggest that outcomes with statin exposure may not be consistent in all patient populations. In addition, benefits demonstrated in one disease state may not be applicable to other inflammatory conditions, such as ARDS.

In a murine model of acute lung injury, Fessler et al. demonstrated that pretreatment with lovastatin was associated with decreased lipopolysaccharide- (LPS-) induced pulmonary inflammation [22]. In a similar design in healthy human volunteers, Shyamsundar et al. randomized subjects to four days of pretreatment with simvastatin or placebo prior to inhalation of LPS [23]. Subjects who received simvastatin had significantly lower markers of pulmonary and systemic inflammation after LPS inhalation compared to subjects receiving placebo [23]. These studies suggest that statins may

Table 1: Patient demographics.

Characteristic	Statin before and after ARDS (n = 17)	Statin before but not after ARDS (n = 20)	Statin never (n = 150)	P value
Age (years)	68.0 (52.0–77.0)	68.5 (55.5–76.5)	55.0 (40.8–68.3)	0.004
Male gender	8 (47.1)	13 (65.0)	66 (44.0)	0.21
APACHE II	24.0 (19.0–28.0)	27.0 (22.3–30.8)	26.0 (20.0–30.0)	0.38
SOFA	7.0 (6.5–9.5)	9.0 (7.0–10.0)	8.0 (7.0–11.0)	0.59
Ethnicity				0.97
White, non-Hispanic	13 (76.5)	15 (75.0)	111 (74.0)	
Black, non-Hispanic	4 (23.5)	5 (25.0)	37 (24.7)	
Other	0	0	2 (1.3)	
Medical comorbidities				
CAD	7 (41.2)	10 (50.0)	26 (17.3)	0.001
Prior MI	1 (5.9)	6 (30.0)	13 (8.7)	0.012
Hyperlipidemia	12 (70.6)	12 (60.0)	11 (7.3)	<0.001
Hypertension	11 (64.7)	13 (65.0)	68 (45.3)	0.10
Heart failure (Class I–III)	6 (35.3)	7 (35.0)	29 (19.3)	0.12
PVD	3 (17.6)	4 (20.0)	10 (6.7)	0.065
Stroke	5 (29.4)	1 (5.0)	11 (7.3)	0.009
Diabetes mellitus	12 (70.6)	10 (50.0)	42 (28.0)	0.001
Dementia	0	2 (10.0)	5 (3.3)	0.23
Chronic pulmonary disease	1 (5.9)	5 (25.0)	30 (20.0)	0.30
Arthritis	2 (11.8)	1 (5.0)	7 (4.7)	0.47
Chronic dialysis	0	1 (5.0)	7 (4.7)	0.66
Leukemia	0	1 (5.0)	4 (2.7)	0.64
Lymphoma	1 (5.9)	0	6 (4.0)	0.60
Immune suppression	4 (23.5)	4 (20.0)	38 (25.3)	0.87
Cirrhosis	0	0	6 (4.0)	0.47
Ethanol abuse	0	1 (5.0)	12 (8.0)	0.44
Transplant	1 (5.9)	1 (5.0)	11 (7.3)	0.91
Acute renal failure	4 (23.5)	2 (10.0)	30 (20.0)	0.51
Admission type				
Medical	16 (94.1)	20 (100.0)	143 (95.3)	0.59
Elective surgical	1 (5.9)	0	5 (3.3)	0.59
Emergent surgical	0	0	2 (1.3)	0.78
Category of lung injury				
Pneumonia	10 (58.8)	10 (50.0)	69 (46.0)	0.59
Sepsis	4 (23.5)	7 (35.0)	47 (31.3)	0.74
Aspiration	2 (11.8)	2 (10.0)	15 (10.0)	0.97
Multiple transfusion	0	0	0	
Trauma	0	0	0	
Corticosteroid administration	11 (64.7)	12 (60.0)	80 (53.3)	0.60
Fluid balance during ARDS (liters)	10.9 (1.5–25.6)	6.0 (1.6–10.4)	4.9 (0–13.4)	0.32
Values on ARDS diagnosis date				
$PaO_2 : FiO_2$	130 (71–233)	93 (71–176)	122 (89–188)	0.35
Tidal volume (mL/kg PBW)	8 (7–8.5)	7.7 (7.3–8.8)	7.3 (6.7–8.6)	0.5
Vasopressor administration	9 (52.9)	7 (35.0)	60 (40.0)	0.51
NMBA	6 (35.3)	3 (15.0)	19 (12.7)	0.05
Fluid balance (liters)	1.1 (0.4–3.1)	2.3 (0.5–4.0)	1.5 (0.5–3.2)	0.71
Enrolled in the ARDS Network Fluid and Catheter Treatment Trial	8 (47.1)	7 (35.0)	44 (29.3)	0.31

Data presented as n (%) or median (IQR). ARDS: acute respiratory distress syndrome; APACHE: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; CAD: coronary artery disease; MI: myocardial infarction; PVD: peripheral vascular disease; PBW: predicted body weight.

Table 2: Outcome results.

Characteristic	Statin before and after ARDS ($n = 17$)	Statin before but not after ARDS ($n = 20$)	Statin never ($n = 150$)	P value
VFDs through day 28	0 (0–19)	4.5 (0–16.0)	13.5 (0–20.0)	0.21
ICU mortality	9 (52.9)	7 (35.0)	37 (24.7)	0.04
Hospital mortality	12 (70.6)	7 (35.0)	49 (32.7)	0.009
28-day mortality	9 (52.9)	6 (30.0)	39 (26.0)	0.067
ICU LOS	14.0 (5.5–23.5)	12.0 (7.0–23.8)	11.0 (7.0–20.0)	0.83
Hospital LOS	21 (15.5–33.0)	28.0 (15.5–40.5)	23.0 (15.0–35.3)	0.79

Data presented n (%) or as median (IQR). ARDS: acute respiratory distress syndrome; VFDs: ventilator-free days; ICU: intensive care unit; LOS: length of stay.

Table 3: Linear regression of ventilator-free days.

Variable[a]	Effect estimate (days)	Confidence interval (95%)	P value
Male gender	−3.51	−6.32 to −0.71	0.015
Fluid balance (per liter positive)	−0.30	−0.40 to −0.21	<0.001
Corticosteroids	−2.71	−5.36 to −0.05	0.046
Statins before and after ARDS	−1.18	−6.77 to 4.42	0.679
Statins before but not after ARDS	−1.39	−5.66 to 2.88	0.521

[a]Variables entered into equation: statin administration before and after ARDS diagnosis, statin before but not after ARDS diagnosis, quintile of propensity to receive statins, age, male gender, APACHE II (per point), tidal volume (per mL/kg of predicted body weight above 6 mL/kg), corticosteroids, and overall fluid balance (per liter positive). ARDS: acute respiratory distress syndrome; APACHE: Acute Physiology and Chronic Health Evaluation.

prevent the occurrence of ARDS, but the benefit of statins on outcomes in patients who have already developed acute lung injury has not been established.

In a prospective observational study of patients with ARDS, statin use was associated with a numerically lower but not statistically significant, ICU mortality rate (20.8% versus 33.5%, $P = 0.2$). After correction for baseline factors with logistic regression, treatment with statins was not independently associated with improved mortality (odds ratio 0.27, 95% confidence interval 0.06–1.21, $P = 0.09$) [44]. Additionally, a retrospective cohort study [24] and a prospective randomized trial [25] of patients with ARDS did not demonstrate a difference in ICU mortality rate or VFDs between patients exposed to statins and those who never receive statins. The present study also did not demonstrate a significant improvement in VFDs or ICU mortality with statin exposure.

The design of our study prevents definitive conclusions on the true reason we did not find an association between statins and improved outcomes, but several plausible explanations exist. Although we did not find a difference in baseline APACHE II or SOFA scores between groups, we cannot rule out that the patients in the statins before and after ARDS group were more ill at baseline. Patients in both statins groups had a numerically higher, but not statistically significant, requirement for vasopressors and tidal volume on the day of ARDS diagnosis. In addition, patients in Group 1, in which statins were continued, more frequently required neuromuscular blockade. While several of these factors were accounted for in the multivariate analysis, this potential difference in baseline severity of illness may have masked a potential beneficial effect of statin exposure. Indeed, the development of ARDS despite statin exposure itself may have been an indicator of a higher severity of illness. In addition, patients receiving statin therapy may have chronic conditions that portend worse outcomes, which are not accounted for with APACHE II or SOFA scores. Furthermore, most of the patients included in our study likely met criteria for severe sepsis, a disease state where several studies support the benefit of statins on short-term outcomes. The majority of our patients exposed to statins were receiving atorvastatin after ARDS development, which has been shown to have a wide range of plasma levels after a single dose in patients with sepsis [45]. This may suggest that patients in our cohort were not exposed to adequate plasma levels of statins to experience beneficial effects. Importantly, our data do not provide insight into the initiation of *de novo* statin therapy in patients who develop ARDS, which is the subject of an ongoing study (NCT00979121).

Preliminary data from patients with sepsis suggested that discontinuation of statins after the development of this inflammatory condition led to a higher mortality rate when compared to patients who had statins continued or were never exposed to statins [30]. Therefore, we hypothesized that patients who had statins discontinued after the development of ARDS would have the fewest VFDs and patients who had statins continued would have the most VFDs. Our data do not support an increase in morbidity when statins were abruptly discontinued after the development of ARDS, which is in line with a recently published randomized trial of statin discontinuation in patients with presumed infection [46].

Our study demonstrated that male gender, positive fluid balance during ARDS episode, and administration of corticosteroids were each independently associated with

a decrease in VFDs. These data coincide with previous studies regarding the association between gender [47] and positive fluid balance [27] with worse outcomes in ARDS but seem in opposition to previous data with administration of corticosteroids [7, 9]. Patients from the current trial were treated for ARDS during a time period when corticosteroids were predominantly used for persistent ARDS [8] and universally in patients with septic shock [48]. This use of corticosteroids may be an indicator of more severe disease or prolonged mechanical ventilation.

As with any retrospective analysis, our study has the intrinsic limitations of this design. Many of the confounders and biases with this design have been accounted for with the use of propensity scores for statin administration and multivariate analyses of the endpoints. While these statistical methods are not perfect, they may increase the external validity of our study. Relatively few patients in our study received a statin in light of the frequency of comorbid conditions with indication for statin administration. The assumptions of our *a priori* power analysis of distribution of patients by statin group were not upheld in our cohort study; therefore we terminated data collection prior to including the suggested number of patients. As a result, we cannot exclude the possibility that true differences between groups exist and the study may be underpowered to detect these differences. However, given the existing data it would require an extreme reversal of current trends, if further data were included, to find a favorable association with statin exposure. The strengths of our study include the similarity of the groups in APACHE II and SOFA scores on the day of ARDS diagnosis. We designed the study to evaluate VFDs, a clinically important endpoint for patients with ARDS that incorporates both duration of mechanical ventilation and death [28]. We utilized a propensity score for statin administration in multivariate analyses of our endpoints, which has been shown to minimize biases between study groups by accounting for factors associated with receipt of the therapy [49]. These factors may enhance the applicability of our data to other settings.

5. Conclusions

Exposure to statins before or after ARDS diagnosis was not associated with improved ventilator-free days in this cohort of patients with ARDS. Differences noted in ICU mortality by statin exposure on univariate analysis were not confirmed in multivariate analysis. Our data do not support a beneficial effect of continuation of statin therapy, or detrimental effect of statin discontinuation, on outcomes in patients with ARDS.

Conflict of Interests

All authors have no conflict of interests to declare.

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