Title Page

**HMG-CoA reductase inhibitors (Statins) and acute kidney injury: a secondary analysis of
renal study outcomes**

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HMG-CoA reductase inhibitors (Statins) and acute kidney injury: a secondary analysis of renal study outcomes

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Abstract

Background

Mortality in ICU patients with acute kidney injury (AKI) remains high. Previous studies have explored the role of HMG-CoA reductase inhibitors (statins) with variable findings.

Methods

The Randomised Evaluation of Normal vs. Augmented Level Replacement Therapy (RENAL) Study recruited 1508 participants requiring dialysis in ICU between 2006 and 2009. Statin use was recorded at study baseline. Multivariate Cox modelling was used to assess associations of such statin use and all-cause mortality. Propensity score analysis was performed for sensitivity analysis. The primary outcome was all-cause mortality at 90 days.

Results

Of the 1462 participants with the available data on statin usage, 187 (12.8%) received statin therapy at baseline. Participants who receiving statins were older ($P<0.001$), less likely to have sepsis or require mechanical ventilation ($P<0.001$). Multivariable analysis showed statin use did not have significant associations with mortality at both day 28 (HR 1.053, 95% CI 0.784-1.415, $P=0.730$) and day 90 (HR 1.091, 95% CI 0.836-1.424, $P=0.520$). Propensity score analysis confirmed the lack of association between statin use and mortality at day 90 (HR 1.042, 95% CI 0.734-1.479, $P=0.819$). However, in septic patients, multivariable analysis suggested statin therapy was associated with a trend to higher mortality at day 90 (HR 1.688, 95% CI 1.132-2.519, $p=0.010$) and continuation of statins was associated with higher mortality (HR 2.160, 95% CI 1.296-3.599, $P=0.003$), compared with statin withdrawal.

Conclusion

In the RENAL study cohort, baseline statin use was not associated with mortality. Our findings do not support a protective role of statins in ICU patients with severe AKI.

Key words: HMG-CoA reductase inhibitors, statins, acute kidney injury, dialysis, mortality, sepsis

Introduction

Acute kidney injury (AKI) is common in critically ill patients (1). When severe, patients with AKI often require renal replacement therapy (RRT) (2) and have a high mortality, prolonged hospitalisation, and increased risk of developing chronic kidney disease (1-3).

Previous studies have demonstrated that the use of HMG-CoA reductase inhibitors (statins) is associated with survival benefits in patients with chronic kidney disease (CKD) (4). Their use in AKI has mainly been investigated in the clinical settings of sepsis and peri-operative care (5), and controversy remains about their impacts upon patient outcomes. The effect of statins in preventing post-operative AKI remains unclear, mainly due to lack of consensus regarding the definitions of AKI in studies and significant patient heterogeneity (5, 6). The association between statin use and mortality also remains inconclusive in septic patients (7, 8). Furthermore, there is scant evidence on the association of statin therapy and survival in severe AKI patients undergoing RRT.

The Randomised Evaluation of Normal versus Augmented Level (RENAL) Renal Replacement Study assessed the effect of different dosing intensity of RRT on clinical outcomes of patients with severe AKI. This cohort of patients with dialysis requiring AKI, including all aetiologies of AKI that usually populate intensive care units, prospectively collected data on baseline statin use, allowing our investigation of the association of statin therapy and mortality in critically ill patients with severe AKI requiring RRT.

MATERIALS AND METHODS

The RENAL study was a prospectively randomised, parallel-group trial comparing high intensity (with effluent flow at 40 mL/kg/hr) versus low intensity (with effluent flow at 25 mL/kg/hr) of continuous RRT in 1508 critically ill patients with severe AKI admitted to ICU (9). The details of the study were reported elsewhere (9) and the primary outcome was all-cause mortality at day 90.

Statin therapy

Data on statin therapy were collected at hospital admission and at study baseline. Use of statin was documented as a binary variable (yes or no). The dose or name of the agent was not collected. Statin usage was collected as “statin baseline” (defined as the use of statins at the time of randomisation) and “statin arrival” (defined as use of statins at hospital admission).

Statistical analysis

We reported continuous variables as means with standard deviations (SD) for normally distributed variables and as medians and interquartile ranges (IQR) for non-normally distributed variables. Comparisons of means and medians were made using Student’s t test or the Mann-Whitney U test when appropriate. Categorical variables were reported as proportions and the chi-square test was performed for comparison.

Baseline variables including statin usage were used to construct Cox proportional hazards models, using mortality at 90 days as a dependent variable. The selection of variables was

based on identifying all measured clinical variables of known or suspected prognostic importance for mortality. The baseline variables that were assessed included demographic data (age (10, 11) and gender (12)), biochemical (haemoglobin (13), potassium (14), creatinine (15), albumin (16), pH (17)), clinical (mechanical ventilation (18, 19), severe sepsis at baseline (20)), urine output (21)), and illness severity scores (Acute Physiology and Chronic Health Evaluation III (APACHE III) score) (19). A survival curve adjusted for covariates was estimated by the relevant Cox model to compare survival between the statins and non-statin groups. Multivariable analysis was then performed to assess the association of statin use with all-cause mortality at 90 and 28 days.

A propensity score analysis matching for age, gender, mechanical ventilation, severe sepsis status at baseline, urine output, and APACHE III scores was performed as a sensitivity analysis. A priori subgroup analysis of patients with sepsis and post operation was also performed. Due to multiple comparisons, a two-sided $p < 0.01$ was used to indicate statistical significance. Statistical analyses were performed with the use of SAS software version 9.3.

RESULTS

Patient Characteristics at Baseline

Of the 1508 patients enrolled in the RENAL study, complete information on statin therapy was available for 1462 participants (97.0%), with 187 participants (12.8%) receiving statins at the time of randomisation. In addition, 437 (29.9%) patients were recorded as being on

pre-morbid statin therapy at hospital arrival. Among them, only 166 patients remained on statin therapy at the time of randomisation (Figure 1).

The baseline characteristics and laboratory parameters of patients with and without statin therapy at the time of randomisation are summarised in Table 1. Participants who were on statins were older (mean age of 72.0 vs. 63.5, $P<0.001$), had lower disease severity as assessed by APACHE III score (98.2 vs 103.1, $P=0.006$), were less likely to be septic at baseline (32.1% vs. 51.9%, $P<0.001$), and had less requirement for mechanical ventilation (57.8% vs 76.2%, $P<0.001$) (Table 1).

Primary and secondary outcomes

Univariate Cox analysis showed that advanced age, more severe illness at the time of randomisation (higher APACHE III score, the presence of sepsis, use of ventilation), lower urine output and creatinine value, hypoalbuminaemia, as well as metabolic acidosis were associated with an increased risk of all-cause mortality at 90 days. However, there was no survival difference at day 90 between the patients receiving statin or not receiving statin therapy at randomization (HR 0.951, 95% CI 0.753-1.200, $P=0.670$) (Table 2). Likewise, statin therapy at randomization was not significantly associated with a decreased mortality at 90 days (HR 1.091, 95% CI 0.836-1.424, $P=0.520$) when adjusted for baseline variables in the multivariate Cox proportional hazard model (Table 2). Kaplan-Meier survival plots from

randomisation to day 90 showed no statistically significant difference in 90 days mortality between statin and non-statin therapy group (log rank $P=0.666$) (Supplementary Figure 1).

Similarly, statin therapy at randomisation was not significantly associated with lower mortality at 28 days (HR 1.053, 95% CI 0.784-1.415, $P=0.730$) (Supplementary Table 1).

Higher mortality at 28 days was associated with advanced age, more severe illness assessed by APACHE III and sepsis, less UO on ICU admission, and lower creatinine levels.

Sensitivity analysis - propensity score analysis

Among 1275 patients who were not on statin therapy at the time of randomisation, 185 patients were matched to the statin therapy group ($n=187$) for age, gender, sepsis, mechanical ventilation and APACHE III scores at the time of randomisation (Supplementary table 2). When analysed, statin therapy was not associated with survival benefits at day 90 in both univariate (HR 0.898, 95% CI 0.664-1.186, $P=0.484$) and multivariate analysis (HR 1.042, 95% CI 0.734-1.479, $P=0.819$) (Table 3).

Subgroup analysis of patients on pre-admission statin therapy

Among 437 patients who were on statins at the hospital admission, 166 patients remained on statin therapy at the time of randomization, while statin therapy was ceased in 271 patients. When comparing the statin continuation to statin withdrawal, there was no mortality difference at 90 days between these two groups in both univariate (HR 0.952, 95%

CI 0.707-1.282, P=0.745) and multivariate analysis (HR 1.201, 95% CI 0.851-1.696, P=0.298) (Table 4).

Statin therapy in patients with sepsis

Further subgroup analysis was performed in the patients admitted to ICU with sepsis.

Among 1462 patients with information on statin therapy at the time of randomisation, 722 patients were septic on ICU admission. Among them, 60 patients (8.3%) were on statins, and 662 patients (91.7%) were not on statin therapy at randomisation. There was no interaction between sepsis and statin therapy at randomisation (P=0.110).

On univariate analysis, there was no statistically significant difference in mortality between statin and non-statin therapy group. However, in multivariable analysis, statin therapy at baseline was associated with a trend to higher mortality at day 90 (HR 1.688, 95% CI 1.132-2.519, p=0.010). In addition, advanced age (HR 1.016, 95%CI 1.006-1.025, P=0.001), male sex (HR 1.474, 95% CI 1.151-1.887, P=0.002), higher APACHEIII scores (HR 1.009, 95%CI 1.004-1.014, P<0.001), low urine output (HR 0.916, 95%CI 0.846-0.992, P=0.031), lower serum creatinine (HR 0.997, 95%CI 0.996-0.998, P<0.001, and lower serum haemoglobin (HR 0.988, 95%CI 0.981-0.995, P<0.001) were associated with higher mortality at day 90 (Supplementary Table 3).

Among 437 patients who were on statins at hospital admission, 171 patients had sepsis on ICU admission. Overall, 53 patients remained on statin therapy at the time of randomisation while statins were ceased in 118 patients. In these patients, multivariate analyses showed that continuation of statin use was associated with higher mortality at day 90 (HR 2.160, 95% CI 1.296-3.599, $P=0.003$), compared with statin withdrawal (Supplementary Table 4).

Statin use in post-operative patients

There were 368 patients who were admitted to ICU after an operation. Among them, 60 patients (14.1%) were on statins at the time of randomisation, while 316 patients (85.9%) were not. There was no survival difference between the statin and non-statin group (HR 0.943, 95%CI 0.553-1.160, $P=0.830$) (Supplementary Table 5).

Discussion

Key findings

We assessed the association between statin therapy and mortality in patients with severe AKI and receiving renal replacement therapy (RRT) using the data from a large, multicenter randomized trial of ICU. We found that patients receiving statins had important baseline differences in clinical variables and, after multivariate adjustment, that such use did not have a significant impact on mortality at 28 days or 90 days. Moreover, this finding was also

confirmed by the propensity score matching analysis. Finally, in the subgroup of patients with sepsis, our analysis raises the possibility of greater mortality when statins were used but this finding should be interpreted with caution.

Relationship to previous studies

In animal studies, statins have demonstrated immunomodulatory effects with an increase in the production of vasodilatory nitric oxide (22) and IL-6 (23, 24) and decreased renal ischemic-reperfusion injury and AKI induced by sepsis (24). However, a multicenter randomised trial assessed statin use in 250 patients with severe sepsis found no survival difference in mortality at day 28 and 90 between statin and non-statin use (8). In contrast, in our study, statin use was associated with increased mortality risk at day 90 in patients with sepsis. This significance may be spurious owing to the small sample size of patients (only 60 patients were on statins at the time of randomisation) analysed. However, a recent randomised controlled trial (25) demonstrated that statin (Rosuvastatin in this trial) therapy was associated with fewer days free of renal and hepatic failure in patients with sepsis-associated ARDS, indicating that statin may have detrimental effects on kidney and hepatic function, although no significant effect on mortality with statin therapy was still noted. Furthermore, the previous studies assessing the effect of statins on sepsis did not specifically examine patients with severe AKI receiving dialysis. Our patients came from a unique population. The combination of sepsis and severe AKI receiving RRT may have

altered pharmacokinetics of statins, which may have modified the relationship between statin therapy and outcomes in septic patients and contributed to the differences between our finding and previous studies results.

Most studies of the use of statins in AKI have mainly focussed on the post-operative setting and have reported conflicting results (26, 27). A retrospective observational study of 324 patients who underwent elective cardiac surgery showed that early postoperative statin use was associated with a lower incidence of AKI and withdrawal of statin was associated with increased incidence of AKI (26). However, a randomised clinical trial of 615 post cardiac surgery patients demonstrated no difference in the incidence of AKI with or without statin therapy (27). In contrast, a systematic review and meta-analysis of 5 randomised controlled trials (RCT) and 19 observational studies in patients undergoing major surgery (5) found that analysis confined only to RCTs did not show any renal protective effect of statin use in this setting. Similarly, another systematic review, including 7 RCTs and 662 adult patients undergoing cardiac bypass surgery (6) showed that pre-operative statin administration did not result in a significant reduction in post-operative AKI, all-cause mortality or the need for RRT. However, there was no clear consensus on the criteria used to define AKI in most of the studies included in these systematic reviews (5, 6), making it difficult to draw robust conclusions. However, the results of our study, the first in patients receiving RRT, were consistent with the findings from the most recent systematic review.

Implications of study findings

Our study findings imply that in patients with severe AKI receiving renal replacement therapy, treatment with statins either pre-morbid or continued in ICU is unlikely to be of benefit. Moreover, by showing a potential signal for harm in septic patients, it implies that it is statin therapy may be particularly unlikely to be of benefit in critically ill patients with combined severe AKI and sepsis.

Strengths and limitations

To our knowledge, this is the first study assessing the association of statin therapy and clinically important outcomes in patients with severe AKI receiving RRT. Importantly, we used data from a large cohort of patients in a randomised controlled trial with extensive and prospectively collected baseline data which was independently monitored. We were able to assess the use of, the continuation of and the cessation of statin therapy in relation to mortality and to assess such relationship in different clinically relevant subgroups, providing a comprehensive analysis of this relationship. The lack of association provides evidence that statin therapy in such patients is unlikely to be beneficial. However, our findings suffer from the limitations inherent to all observational studies, including the fact that residual confounding may still be at play in our analysis and may have impacted on the results. Another limitation is lack of information on the dose of statin used at the baseline. Finally, the daily use of statin was not collected, making it impossible to assess the possible impact of duration of therapy.

In conclusion, the statin therapy did not demonstrate any statistically significant beneficial impact upon mortality in critically ill patients with severe AKI on RRT and in selected subgroup was associated with a signal of harm. Our findings do not support a role for statin therapy in ICU patients with severe AKI receiving RRT.

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Conflict of Interest Statement

None

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Tables and Figure

Table 1: Baseline characteristics of the study patients

Baseline characteristics of the study patients	Pre-randomization enrollment (n=1462)		P value
	Use of statin		
	No (n=1275, 87.2%)	Yes (n=187, 12.8%)	
Age – yr*	63.5±15.2	72.0±9.9	<0.001
Male – no. (%)	819/1275 (64.4)	125/187 (67.2)	0.49
Weight - kg*	80.6±12.8	80.6±13.5	0.98
Mechanical ventilation – no. (%)	972/1275 (76.2)	108/187 (57.8)	<0.001
Severe sepsis – no. (%)	662/1275 (51.9)	60 (32.1)	<0.001
APACHE III score*	103.1±26.1	98.2±21.9	0.006
SOFA*	10.2±3.0	9.2±2.5	<0.001
Non renal SOFA*	7.5±3.0	6.3±2.7	<0.001
Urine output on day 1#	165 (40-495)	140 (35-400)	0.25
Creatinine (μmol/L) *	334±212	352±179	0.20
Potassium (mmol/L) *	4.8±0.9	4.9±0.9	0.20
pH*	7.25±0.13	7.27±0.13	0.08
Albumin (mg/L) *	25.7±7.0	27.9±7.5	<0.001
Haemoglobin (gm/L) *	100±20	98±19	0.30
Source of admission – no. (%)			<0.001
Emergency department	319/1196 (26.7)	29/172 (16.9)	
Hospital ward	320/1196 (26.8)	67/172 (39.0)	
Transfer from another ICU	102/1196 (8.5)	9/172 (5.2)	
Transfer from another hospital	139/1196 (11.6)	15/172 (8.7)	
OR after emergency surgery	190/1196 (15.9)	16/172 (9.3)	
OR after elective surgery	126/1196 (10.5)	36/172 (20.9)	

* values expressed as means±SD;

values expressed as median and interquartile range;

Abbreviations: APACHE III score, Acute Physiology and Chronic Health Evaluation III scores which range from 0 to 299, with higher scores represent more disease severity; SOFA score, Sequential Organ Failure Assessment, with a higher score indicating more disease severity.

Table 2: Association of clinical parameters at baseline with the risk for 90-day mortality using Cox proportional hazard analysis (patients who were on statins at the time of randomisation, n=187 vs 1275)

Variables	Unit	Univariable model		Multivariable model	
		HR (95% CI)	P value	HR (95% CI)	P value
Statin*	Yes / No	0.951 (0.753-1.200)	0.670	1.091 (0.836-1.424)	0.520
Age - yr	Per 1 year	1.014 (1.008-1.020)	<0.001	1.014 (1.007-1.020)	<0.001
Male	Male vs Female	1.039 (0.885-1.221)	0.639	1.095 (0.914-1.313)	0.324
APACHE III	Per 1 score	1.014 (1.011-1.017)	<0.001	1.009 (1.005-1.013)	<0.001
Sepsis	Yes / No	1.310 (1.123-1.528)	<0.001	1.288 (1.075-1.544)	0.006
Mechanical ventilation	Yes / No	1.855 (1.521-2.263)	<0.001	1.269 (0.994-1.620)	0.058
Urine output	Log (mL)	0.885 (0.840-0.932)	<0.001	0.938 (0.885-0.993)	0.028
Creatinine	Per $\mu\text{mol/L}$	0.998 (0.997-0.998)	<0.001	0.998 (0.997-0.999)	<0.001
Potassium	Per mmol/L	0.946 (0.870-1.030)	0.200	1.047 (0.940-1.167)	0.404
pH	Per 0.01	0.990 (0.984-0.995)	<0.001	1.001 (0.993-1.008)	0.888
Albumin	Per gm/dL	0.973 (0.963-0.984)	<0.001	0.994 (0.982-1.007)	0.380
Haemoglobin	Per gm/dL	0.996 (0.992-1.000)	0.055	0.995 (0.990-1.000)	0.031

*Statin usage at the time of randomisation from all study participants.

Abbreviations: APACHE III score, Acute Physiology and Chronic Health Evaluation III scores; SOFA score, Sequential Organ Failure Assessment

Multivariate model analysis was adjusted for age, gender, APACHE III, Sepsis, Mechanical ventilation, Urine output, serum creatinine, potassium, PH value, albumin and haemoglobin.

Table 3: Association of clinical parameters at baseline with the risk for 90-day mortality using Cox proportional hazard analysis – propensity score matched analysis

Variables	Unit	Univariable model		Multivariable model	
		HR (95% CI)	P value	Multivariable	P value
Statin*	Yes / No	0.898 (0.664-1.186)	0.484	1.042 (0.734-1.479)	0.819
Age - yr	Per 1 year	1.009 (0.994-1.024)	0.242	1.014 (0.996-1.032)	0.139
Male	Male vs Female	1.017 (0.728-1.421)	0.922	1.147 (0.772-1.705)	0.496
APACHE III	Per 1 score	1.018 (1.012-1.024)	<0.001	1.007 (0.999-1.016)	<0.001
Sepsis	Yes / No	1.590 (1.166-2.168)	0.003	1.612 (1.103-2.355)	0.014
Mechanical ventilation	Yes / No	2.112 (1.527-2.919)	<0.001	1.427 (0.812-1.023)	0.105
Urine output	Log (mL)	0.852 (0.771-0.942)	0.002	0.911 (0.812-1.023)	0.115
Creatinine	Per $\mu\text{mol/L}$	0.998 (0.997-0.998)	<0.001	0.999 (0.998-1.000)	0.068
Potassium	Per mmol/L	0.847 (0.714-1.004)	0.041	0.814 (0.649-1.020)	0.074
pH	Per 0.01	0.975 (0.963-0.988)	<0.001	0.985 (0.968-1.002)	0.076
Albumin	Per mg/dL	0.957 (0.963-0.977)	<0.001	0.980 (0.954-1.006)	0.125
Haemoglobin	Per gm/L	0.999 (0.990-1.007)	0.750	0.997 (0.986-1.009)	0.649

* Statin at baseline compared with patient who never received statin (not include statin at arrival) (PS MATCHED n=187+185=372).

Abbreviations: APACHE III score, Acute Physiology and Chronic Health Evaluation III scores; SOFA score, Sequential Organ Failure Assessment

Multivariate model analysis was adjusted for age, gender, APACHE III, Sepsis, Mechanical ventilation, Urine output, serum creatinine, potassium, PH value, albumin and haemoglobin.

Table 4: Association of clinical parameters at baseline with the risk for 90-day mortality using Cox proportional hazard analysis according to continued use or cessation of statins

Variables	Unit	Univariable model		Multivariable model	
		HR (95% CI)	P value	Multivariable	P value
Statin*	Yes / No	0.952 (0.707-1.282)	0.745	1.201 (0.851-1.696)	0.298
Age - yr	Per 1 year	1.034 (1.017-1.051)	<0.001	1.042 (1.022-1.062)	<0.001
Male	Male vs Female	1.024 (0.880-1.648)	0.246	1.286 (0.895-1.848)	0.175
APACHE III	Per 1 score	1.013 (1.007-1.019)	<0.001	1.003 (0.996-1.011)	0.409
Sepsis	Yes / No	1.248 (0.933-1.669)	0.136	1.602 (1.127-2.277)	0.009
Mechanical ventilation	Yes / No	2.568 (1.762-3.744)	<0.001	1.886 (1.181-3.011)	0.008
Urine output	Log (mL)	0.885 (0.802-0.977)	0.002	0.928 (0.825-1.043)	0.210
Creatinine	Per $\mu\text{mol/L}$	0.998 (0.997-0.999)	<0.001	0.998 (0.997-0.999)	0.003
Potassium	Per mmol/L	1.035 (0.876-1.224)	0.683	1.055 (0.844-1.318)	0.639
pH	Per 0.01	0.986 (0.974-0.997)	0.017	0.990 (0.975-1.004)	0.166
Albumin	Per mg/dL	0.980 (0.960-1.001)	0.060	0.995 (0.971-1.020)	0.712
Haemoglobin	Per gm/L	0.996 (0.987-1.004)	0.301	0.994 (0.984-1.004)	0.213

* Among 437 patients who were on statins on the hospital admission, 166 patients remained on statin at the time of randomization while statins were ceased in 271 patients. Abbreviations: APACHE III score, Acute Physiology and Chronic Health Evaluation III scores; SOFA score, Sequential Organ Failure Assessment. Multivariate model analysis was adjusted for age, gender, APACHE III, Sepsis, Mechanical ventilation, Urine output, serum creatinine, potassium, PH value, albumin and haemoglobin.

Figure 1: Flow chart of statin therapy in the RENAL study

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