Statin Use in Patients Undergoing Hemodialysis:

A Nationwide Population-based Study in Taiwan

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I have nothing to disclose.
Introduction

- The size of the end-stage renal disease (ESRD) population is increasing and expanding at a rate of 7% per year worldwide.
• According to the US Renal Data System 2009 annual data report, there were more than 530,000 patients receiving treatment for ESRD, with 370,000 undergoing chronic dialysis treatment.
Observational study of ESRD patients: Statins reduce mortality

Statin treatment was associated with a 32% reduction in the adjusted relative risk of death: RR=0.68 (95% CI 0.53–0.86) p=0.002

CI=confidence interval; RR=relative risk

4D study:
No benefit of statin therapy in diabetic hemodialysis patients

No. at risk:
Placebo 636 532 383 252 136 51 19
Atorvastatin 619 515 378 252 136 58 29

Cumulative incidence of primary endpoint (%)

Time (years)

Placebo
Atorvastatin

p=0.37

AURORA study:
No benefit of statin therapy in diabetic hemodialysis patients
Kaplan-Meier estimate of time to first major CV event

Cumulative incidence of primary endpoint (%)

No. at risk:
Rosuvastatin 1390 1152 962 826 551 148
Placebo 1384 1163 952 809 534 153

Years from randomization

0 1 2 3 4 5

Placebo
Rosuvastatin

HR=0.96 (95% CI 0.84–1.11)
P=0.59

SHARP study:

No sufficient power to assess the effects on major atherosclerotic events separately in dialysis and non-dialysis patients.

<table>
<thead>
<tr>
<th></th>
<th>Eze/simva (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis (n=6247)</td>
<td>296 (9.5%)</td>
<td>373 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Dialysis (n=3023)</td>
<td>230 (15.0%)</td>
<td>246 (16.5%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>↓ 16.5% SE 5.4 (P=0.0022)</td>
</tr>
</tbody>
</table>

No significant heterogeneity between non-dialysis and dialysis patients (P=0.25).

• In the post hoc analysis of the 4D study, treatment with atorvastatin in diabetic patients undergoing hemodialysis (HD) significantly reduced the risk of fatal and nonfatal cardiac events and death from any cause.

• In the post hoc analysis of the AURORA trial, treatment with rosuvastatin in diabetic patients undergoing HD reduced atherosclerotic coronary events by 32%.

The beneficial effects of statins in patients undergoing HD are still controversial.
Study Purpose

• Our study aimed to investigate the use of statins and the subsequent risk of cardiovascular morbidity and mortality in patients with HD by using the Taiwan National Health Insurance Research Database (NHIRD).
Methods

Data sources

• The National Health Insurance program in Taiwan has operated since 1995 and enrolls nearly all the inhabitants of Taiwan (21,869,478 beneficiaries out of 22,520,776 inhabitants at the end of 2002).

• Currently, the NHIRD at the National Health Research Institute (NHRI) in Miaoli (Taiwan) manages the complete National Health Insurance claims database.
Methods

Data sources

• In this dataset, each patient’s original identification number has been encrypted to protect privacy.

• The encrypting procedure is consistent, so that the linkage of claims belonging to the same patient is feasible within the NHIRD.

• This study was exempt from full review by the Institutional Review Board of Taipei Veterans General Hospital, because the dataset used consisted of de-identified secondary data released to the public for research purposes.
The National Health Insurance database specifies 31 illnesses as “catastrophic illness”. Patients with such catastrophic illness must be reviewed by specialists in the committee of the Bureau of National Insurance, and then they can be exempted from co-payment for catastrophic expenditures, if approved.

• HD is listed in the category of catastrophic illness and all patients undergoing HD in this study are identified from those with catastrophic illness certificates in the Taiwan National insurance dataset.

Methods

Study population
Methods

Study population

- We identified two cohorts from the patients who started to receive HD between 1998 and 2003.
- The statin cohort included the HD patients with statin use.
- The comparison cohort was selected from those HD patients without any history of statin use.
- The age and gender were matched in the two cohorts.
Methods

Study endpoints

• All of the patients were followed up for 3 years.
• The endpoints of the study included
  (1) Acute myocardial infarction,
  (2) Ischemic stroke,
  (3) Hospitalization for unstable angina,
  (4) Deep vein thrombosis,
  (5) Pulmonary emboli,
  (6) Cardiovascular mortality, and
  (7) All-cause mortality.
Results

Flow charts

68,345 New cases of HD
1998 - 2003

21,910 cases with previous statins use were excluded
10,202 cases with the history of acute myocardial infarction, ischemic stroke, or hospitalization for unstable angina were excluded
342 cases with the history of hospitalization for venous thromboembolism were excluded

35,861 New cases of HD
Results

Flow charts

**Statin cohort**
4,074 New cases of HD who received statin

**Comparison cohort**
8,116 New cases of HD without any history of statin use

Follow up for 3 years
## Results

### Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Statin cohort (n=4,074)</th>
<th>Comparison cohort (n= 8,116)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.3 ± 13.5</td>
<td>53.3 ± 13.3</td>
<td>0.931</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>1,422 (34.9)</td>
<td>2,884 (35.0)</td>
<td>0.881</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>2,984 (73.2)</td>
<td>5,616 (69.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n(%)</td>
<td>1,321 (32.4)</td>
<td>2,641 (32.5)</td>
<td>0.898</td>
</tr>
<tr>
<td>Coronary artery disease, n(%)</td>
<td>661 (16.2)</td>
<td>1,272 (15.7)</td>
<td>0.431</td>
</tr>
<tr>
<td>Atrial fibrillation, n(%)</td>
<td>431 (10.6)</td>
<td>934 (11.5)</td>
<td>0.125</td>
</tr>
<tr>
<td>Heart failure, n(%)</td>
<td>623 (15.3)</td>
<td>1,398 (17.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Valvular heart disease, n(%)</td>
<td>90 (2.2)</td>
<td>160 (2.0)</td>
<td>0.382</td>
</tr>
<tr>
<td>Peripheral artery disease, n(%)</td>
<td>221 (5.4)</td>
<td>452 (5.6)</td>
<td>0.742</td>
</tr>
<tr>
<td>Thyrotoxicosis, n(%)</td>
<td>85 (2.1)</td>
<td>175 (2.2)</td>
<td>0.801</td>
</tr>
</tbody>
</table>
# Results

## Demographic data

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>Statin cohort (n=4,074)</th>
<th>Comparison cohort (n= 8,116)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin, n(%)</td>
<td>346 (8.49)</td>
<td>398 (4.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ticlopidine, n(%)</td>
<td>37 (0.91)</td>
<td>28 (0.34)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Clopidogrel, n(%)</td>
<td>60 (1.47)</td>
<td>61 (0.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Coumadin, n(%)</td>
<td>279 (6.85)</td>
<td>502 (6.19)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
## Results

**Statin cohort (n=4,074)**

<table>
<thead>
<tr>
<th>Statin</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>1,006</td>
<td>24.69</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>606</td>
<td>14.87</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>372</td>
<td>9.13</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>529</td>
<td>12.98</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1,483</td>
<td>36.40</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>78</td>
<td>1.91</td>
</tr>
</tbody>
</table>
# Results

Incidence of endpoints in the patients undergoing HD

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Statin cohort (n=4,074)</th>
<th>Comparison cohort (n= 8,116)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI, n(%)</td>
<td>86 (2.11)</td>
<td>134 (1.65)</td>
<td>0.072</td>
</tr>
<tr>
<td>Ischemic stroke, n(%)</td>
<td>85 (2.09)</td>
<td>248 (3.06)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Hospitalization for UA, n(%)</td>
<td>131 (3.22)</td>
<td>275 (3.39)</td>
<td>0.616</td>
</tr>
<tr>
<td>Deep vein thrombosis, n(%)</td>
<td>5 (0.12)</td>
<td>71 (0.87)</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>Pulmonary emboli, n(%)</td>
<td>3 (0.07)</td>
<td>7 (0.09)</td>
<td>0.819</td>
</tr>
<tr>
<td>Cardiovascular mortality, n(%)</td>
<td>21 (0.52)</td>
<td>105 (1.29)</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>All-cause mortality, n(%)</td>
<td>183 (4.49)</td>
<td>510 (6.28)</td>
<td>&lt;<strong>0.001</strong></td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; UA, unstable angina.
Results

Adjusted Hazard Ratios (3-year follow-up)

<table>
<thead>
<tr>
<th>Event</th>
<th>HR</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocardial infarction</td>
<td>0.79</td>
<td>(0.60 - 1.05)</td>
<td>0.100</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.46</td>
<td>(0.36 - 0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.59</td>
<td>(0.48 - 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0.10</td>
<td>(0.04 - 0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>0.55</td>
<td>(0.14 - 2.17)</td>
<td>0.391</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.27</td>
<td>(0.17 - 0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.45</td>
<td>(0.38 - 0.54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The HRs are adjusted for age, gender, comorbidities, and concomitant medication. HR= hazard ratio; C.I.= confidence interval.
Study limitation

- The diagnoses were identified using the ICD-9 code from the database.
- Personal information such as body weight, smoking habits, and biochemistry profiles were not available in this database.
- We didn’t have data on the patency of arteriovenous fistula.
- We didn’t compare the effects of each statins.
Conclusion

• Statin use was associated with a lower incidence of cardiovascular morbidity and mortality in patients undergoing HD, mainly in ischemic stroke, hospitalization for unstable angina, deep vein thrombosis, cardiovascular mortality, and all-cause mortality.
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