The Incidence of Kidney Injury for Patients Treated with a High-Potency versus Moderate-Potency Statin Regimen after an Acute Coronary Syndrome

Amy Sarma, Christopher P Cannon, Stephen D Wiviott, Marc S Sabatine, Marc A Pfeffer, Elaine B Hoffman, Jianping Guo, James A de Lemos, Michelle L O’Donoghue

Brigham and Women’s Hospital, Boston MA
Background

2,004,692 primary care pts in England/Wales aged 30-84yo

Risk of Renal Failure*

<table>
<thead>
<tr>
<th>Statin</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin</td>
<td>HR 1.61 (1.37-1.90)</td>
<td>HR 1.50 (1.23-1.83)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HR 1.63 (1.31-2.02)</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td>HR 1.57 (1.22-2.03)</td>
</tr>
</tbody>
</table>

*Risk of Renal Failure based on diagnosis codes in EMR

Hippisley-Cox & Coupland., BMJ 2010;340:c2197
Background (2)

2,004,692 primary care pts in England/Wales aged 30-84yo

Men

Risk of Renal Failure*

No statin

Simvastatin 10/20mg QD

Simvastatin 40/80mg QD

Atorvastatin 10mg QD

Atorvastatin 20/40/80mg QD

Women

Hippisley-Cox & Coupland., BMJ 2010;340:c2197

*Diagnosis of renal failure based on diagnosis codes in EMR
Background (3)

2,067,639 individuals >40 years old on newly dispensed statins

Population

- ≤ 120 days of therapy
  - Adjusted rate ratio (95% CI): 1.34 (1.25-1.43)
- > 120 to ≤ 365 days of therapy
  - Adjusted rate ratio (95% CI): 1.11 (1.04-1.19)

** Hospitalization for Acute Kidney Injury**

* High-potency statin defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, or ≥ 40 mg simvastatin

** Diagnosis of renal failure based on ICD-9 diagnosis codes

Dormuth et al., BMJ 2013;346:f880
2013 ACC/AHA Lipid Guidelines

Established CV disease (age <75yo)

1° Prevention: 10-y CV risk ≥7.5% (ages 40-75yo)

LDL ≥ 190 mg/dL

High-Potency Statin

Stone et al., *Circulation* 2013:epub
Study Design Considerations

**Large-scale observational study design:**
- High risk of confounding by indication since patients on a high-potency statin may differ from those not on the same regimen
- Larger sample size increases precision, but not accuracy

**Randomized trial design:**
- Randomized allocation of statin therapy obviates the risk of indication bias
- Smaller sample size, therefore diminished power to detect rare events within subgroups
Objectives

To examine trends in serum creatinine and the incidence of kidney injury for subjects randomized to an intensive versus moderate potency statin regimen across two large trials of patients after ACS.
**PROVE IT-TIMI 22**

4,162 patients randomized ≤ 10d post ACS

- **Standard Therapy**
  - (Pravastatin 40 mg)

- **Intensive Therapy**
  - (Atorvastatin 80 mg)

Duration: Mean 2 year follow-up

Subjects excluded if screening creatinine ≥ 2.0 mg/dl

Cannon CP et al, NEJM 2004;350:1495-504

del Lemos JA et al, JAMA 2004;292:1307-1316

**A-to-Z: Z phase**

4,497 patients randomized ≤ 5d post ACS

- **Placebo x4 months/ Simvastatin 20 mg**
- **Simva 40mg x1 month/ Simvastatin 80 mg**

Duration: Median 2 year follow-up

Subjects excluded if screening creatinine ≥ 2.0 mg/dl
Methods

• Serum creatinine (sCr) was to be assessed centrally at baseline and serial predefined timepoints during follow-up.

• The definition of kidney injury was adapted from the KDIGO* classification of acute kidney injury with baseline sCr as the referent.

• The incidence of adverse events (AEs) relating to kidney injury was determined through review of the serious and non-serious AE database.

• All analyses were conducted in the on-treatment study population.

* KDIGO = Kidney Disease: Improving Global Outcomes Classification
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PROVE IT-TIMI 22</th>
<th></th>
<th>A-to-Z</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prava 40mg N=2063</td>
<td>Atorva 80mg N=2099</td>
<td>Plac/Simva 20mg N=2232</td>
<td>Simva 40/80mg N=2265</td>
<td></td>
</tr>
<tr>
<td>Age, yr (mean)</td>
<td>58.3</td>
<td>58.1</td>
<td>60.6</td>
<td>60.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Male sex</td>
<td>78%</td>
<td>78%</td>
<td>75%</td>
<td>76%</td>
<td>0.72</td>
</tr>
<tr>
<td>White race</td>
<td>91%</td>
<td>91%</td>
<td>85%</td>
<td>85%</td>
<td>0.84</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18%</td>
<td>18%</td>
<td>24%</td>
<td>23%</td>
<td>0.76</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49%</td>
<td>51%</td>
<td>50%</td>
<td>50%</td>
<td>0.76</td>
</tr>
<tr>
<td>sCr, mg/dL (mean)</td>
<td>1.04</td>
<td>1.03</td>
<td>1.14</td>
<td>1.14</td>
<td>0.80</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m² (MDRD, mean)</td>
<td>79.0</td>
<td>80.0</td>
<td>60.1</td>
<td>60.3</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Baseline eGFR by treatment arm

eGFR (ml/min/1.73 m², MDRD)

PROVE IT-TIMI 22

A-to-Z

No difference between treatment arms in either trial
Temporal changes in sCr by treatment arm

PROVE IT-TIMI 22

% change in mean sCr from baseline

P values reflect difference in mean change from baseline between treatment arms
Temporal changes in sCr by treatment arm A-to-Z

% change in mean sCr from baseline

- Placebo/Simva 20mg
- Simva 40/80mg

P values reflect difference in mean change from baseline between treatment arms

P=0.60
P=0.84
P=0.98
P=0.81
P=0.87

% change in mean sCr from baseline

- 3.48%
- 1.74%
- 0.87%
- 0.87%
- -0.87%
- -0.88%
Incidence of kidney injury
PROVE IT-TIMI 22

Baseline creatinine as referent. Data through long-term follow-up.

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>Pravastatin 40mg N=1798</th>
<th>Atorvastatin 80mg N=1828</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.45</td>
<td>2.84</td>
</tr>
<tr>
<td>1</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>1.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR 1.16 (95% CI 0.60-1.38)  
P=0.46

OR 0.98 (95% CI 0.32-3.03)  
P=0.98
Incidence of kidney injury
A-to-Z

Baseline creatinine as referent. Data through long-term follow-up.
Incidence of kidney injury
High-potency statin vs placebo
- First 4 months of A-to-Z -

OR 0.83 (0.47-1.45)
P=0.51

Placebo N=2064
Simvastatin 40mg/80mg N=2117

OR 3.42 (0.71-16.48)
P=0.18

Incidence (%)
High Risk Subgroup
- Baseline eGFR < 60ml/min/1.73m² -

**PROVE IT-TIMI 22**

- Pravastatin 40mg QD: OR 1.79 (0.59-5.56), P=0.29
- Atorvastatin 80mg QD: OR 2.94 (0.31-33.3), P=0.62

**A-to-Z**

- Placebo/ Simva 20mg QD: OR 0.63 (0.33-1.18), P=0.15
- Simva 40/80mg QD: OR 1.32 (0.30-5.92), P=1.00

Incidence (%)

- ≥ 1.5-fold increase in sCr: 1.93
- ≥ 2.0-fold increase in sCr: 3.42

Incidence (%)
Incidence of kidney injury-related AE/SAEs
Combined PROVE IT-TIMI 22 and A-to-Z

Incidence (%)

- Moderate-potency statin regimen
- High-potency statin regimen

**First 4 Months**
- Incidence: 0.42
- OR: 1.15 (0.61-2.16)
- P: 0.67

**Long-term follow-up**
- Incidence: 0.86
- OR: 1.06 (0.68-1.67)
- P: 0.78

**Incidence: 0.92**
Limitations

• A strength was that sCr was centrally assessed at pre-specified timepoints; however, a change in sCr between study visits could have been missed.

• However, consistent results were observed when we examined the incidence of investigator-reported kidney injury events using the AE database.

• Few patients with eGFR <30ml/min/1.73m$^2$ at baseline
Conclusions

• Across two large randomized statin trials, a high-potency statin regimen did not raise sCr or the risk of kidney injury.

• Considering the recently updated lipid guidelines, these findings provide important reassurance that a high-potency statin regimen will not increase the incidence of adverse renal events.