The Effect of Statin Therapy on Risk of Intracranial Hemorrhage

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Objectives

- Review benefits of statin therapy after ischemic stroke
- Discuss controversies surrounding increased risk of intracranial hemorrhage with statins
- Review literature regarding safety and efficacy of statin use after ischemic stroke, tPA administration, and acute ICH

Background

- Statin therapy shown to reduce risk of ischemic stroke by 20-25%
  - Decreased cholesterol synthesis
  - Pleotropic effects
  - Benefit may be offset by increased risk of intracranial hemorrhage (ICH)
  - Antithrombotic effects
  - Reduced platelet aggregation
  - Excessive lowering of cholesterol
  - Controversy regarding statins and risk of ICH

Cholesterol and ICH Risk

- Low cholesterol may increase fragility of endothelium
- Rotterdam study
  - Examine relationship between cholesterol levels and risk of ICH
  - Prospective cohort study
  - 7,983 patients ≥55 years with no history of stroke
  - Followed until first stroke, death or study end (median 10 years)

<table>
<thead>
<tr>
<th>Cholesterol Type</th>
<th>No Lipid Lowering Medications (HR 95% CI)</th>
<th>Lipid Lowering Medication (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.92 (0.67-1.28)</td>
<td>1.29 (0.81-3.97)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.21 (0.94-1.55)</td>
<td>1.86 (0.76-4.55)</td>
</tr>
<tr>
<td>LDL</td>
<td>0.94 (0.68-1.28)</td>
<td>1.33 (0.89-2.17)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.65 (0.46-0.92)</td>
<td>0.64 (0.24-1.70)</td>
</tr>
</tbody>
</table>

- Low triglycerides associated with increased risk of ICH
- Lipid lowering therapy did not increase risk

The SPARCL Trial

- Examine benefit of statin therapy for secondary prevention of stroke
- Enrollment
  - 4,731 patients ≥18 with stroke (ischemic, hemorrhagic, or TIA) in past 30 days
  - Absence of coronary heart disease
  - LDL 100-190 mg/dL
- Methods
  - Randomized to atorvastatin 80 mg daily versus placebo
  - Mean follow up of 5 years
- Primary outcome was time to first nonfatal or fatal stroke
Results

- Statin use showed benefit for secondary prevention of stroke
- Increased risk of hemorrhagic stroke seen in post-hoc analysis

### Risk of ICH after Ischemic Stroke

- **Design**
  - Retrospective cohort study
- **Population**
  - 17,862 patients ≥ 66 after ischemic stroke
  - Statin users compared to nonusers
  - Median of 4.2 years
- **Results**
  - 213 episodes of ICH
  - No association with statin use; HR 0.87 (95% CI 0.65-1.17)

### Meta-Analysis of Statin Therapy and ICH Risk

- **Inclusion**
  - A total of 182,803 patients included from 31 different studies
  - Randomized controlled trials of statin therapy reporting ICH or hemorrhagic stroke as an outcome
  - Primary or secondary prevention of stroke
- **Methods**
  - Statins compared to usual care, placebo, or lower dose statins
- **Outcomes**
  - Rate of ICH, all stroke, and mortality

- **Results**
  - Statin use not associated with increased risk of ICH
  - Reduction in all stroke and mortality
  - Benefits of statin therapy likely outweigh any potential risk of ICH
Statin Use After tPA

- **Design**: Retrospective, observational, multi-center
- **Population**: 1,446 patients who received IV thrombolytic for ischemic stroke
- **Methods**:
  - Statins categorized in 3 groups based on potency
    - Low dose: LDL reduction of <35%
    - Medium dose: LDL reduction of 35-44%
    - High dose: LDL reduction of ≥45%
- **Primary outcome**: was occurrence of ICH and favorable outcome at 3 months (Modified Rankin 0-2)


<table>
<thead>
<tr>
<th>Statin Group</th>
<th>Incidence of ICH</th>
<th>Odds Ratio (95% CI) for ICH</th>
<th>Odds Ratio (95% CI) for Favorable Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>1.7%</td>
<td>0.59 (0.14-2.51)</td>
<td>1.88 (1.19-2.98)</td>
</tr>
<tr>
<td>Medium dose</td>
<td>6.0%</td>
<td>2.38 (1.07-5.33)</td>
<td>1.78 (1.11-2.84)</td>
</tr>
<tr>
<td>High dose</td>
<td>12.7%</td>
<td>5.34 (2.30-12.28)</td>
<td>1.66 (0.89-3.16)</td>
</tr>
</tbody>
</table>

- Increased risk of ICH with medium and high dose statins
- Statin use associated with improvement in functional outcome at 3 months


Statin Use After Recanalization

- **Design**: Retrospective, observational, single-center
- **Population**: 337 patients who received recanalization therapy for ischemic stroke
- **Methods**: Statins categorized in 3 groups based on day of initiation
  - First day (D1 = 13.4%), second day (D2 = 20.8%), third day (D3 = 15.4%)
  - Nonusers = 50.4%
- **Primary outcome**: Modified Rankin score of 0-1 at 3 months
- **Secondary outcomes**: included hemorrhagic transformation and neurologic improvement


- Early use of statins improved functional outcome with the most benefit seen at day 1
- No increase in symptomatic ICH

Statin Use During Hospitalization for ICH

- **Design**: Retrospective, cohort study, single center
- **Patients**: 4,481 patients ≥50 over a 10 year period with a primary discharge diagnosis of ICH
- **Known details of statin use before and during hospitalization
- **Primary outcome**: 30 day survival and discharge home/inpatient rehabilitation


- Statin use associated with improved mortality at 30 days; OR 4.25 (95% CI 3.46-5.23)
- Inpatient statin use associated with improved outcome
- Statin discontinuation had mortality rate of 57.8% compared with 18.9% for those using a statin before and during hospitalization (p=0.001)

Effect of Statin Use on Hematoma Growth

- Design
  - Pooled data from INTERACT 1 and 2
  - Prospective RCTs assessing intensive blood pressure reduction
- Patients
  - 3243 patients with spontaneous ICH
  - Repeat head CT at 24 hours
- Primary outcome was death or disability (Modified Rankin 3-6)
- Secondary outcome was growth of hematoma volume at 24 hours


- Lipid lowering therapy not associated with worse clinical outcomes or with increased growth of hematoma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lipid Lowering</th>
<th>No Lipid Lowering</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or dependency</td>
<td>68.1%</td>
<td>52.1%</td>
<td>0.781</td>
</tr>
<tr>
<td>Hematoma growth</td>
<td>9.2 mL</td>
<td>6.8 mL</td>
<td>0.130</td>
</tr>
</tbody>
</table>

Statin Use and Microbleeds (MB) in Patients with ICH

- Design
  - Retrospective review of prospectively collected ICH database
- Patients
  - 337 patients with spontaneous ICH over a 3 year period
  - Follow-up 30 days of ICH
- Primary outcome was the presence or absence of MB in statin users compared to non-users

- Results
  - Statin users had a higher occurrence of MB (31% versus 17%, p = 0.039)
  - No data on outcomes with this finding, unknown if this represents increased ICH risk


- Statin use After ICH Based on Location
  - Design
    - Use of Markov decision modeling to determine risk of statin therapy depending on ICH location (deep versus lobar)
  - Patients
    - Mathematical modeling done based on a 65 year-old with a ICH to simulate several clinical trials
  - Primary outcome was impact of statin of quality-adjusted life expectancy (QALY)

- Results
  - Statin therapy had a net loss of 2.2 QALYs for lobar ICH and 0.8 QALYs for deep ICH
  - In the setting of high risk of ICH recurrence avoiding statins may be preferred, especially in lobar ICH

Conclusions

- Increased risk of ICH with statin use after ischemic stroke was seen in post-hoc analysis in SPARCL trial
- Studies designed specifically to assess effect of statins after ischemic stroke have found no association with increased ICH
- Statin therapy found to be safe and reduce risk of stroke and mortality
- Statin therapy following recanalization associated with improved functional outcomes but may increase risk of ICH
- Statin use during hospitalization for ICH associated with improved outcomes and not shown to increase hematoma volume
- May increase incidence of MB but has unknown clinical significance
- Patients with lobar ICH may have worse outcomes with statin therapy
- Based on only one poorly designed study, weigh risk versus benefit

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