Game Strategy: High Intensity Statin in Stroke

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Cardiovascular Conference – PARM C
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No Disclosures
Are you Mind Full or Mindful?
Objectives

1. Discuss the correlation between dyslipidemia and stroke

2. Describe the evidence supporting the use of statin after stroke

3. State the optimal time to start statin therapy after stroke
Patient L.D.

53 yo male presents to the ED with right sided weakness that occurred 12 hours ago. CT scan of the brain shows acute lacunar stroke in the left basal ganglia. His fasting lipid panel shows:

- Cholesterol of 253 mg/dl
- LDL 165 mg/dl
- HDL 35mg/dl

The relationship between the level of LDL and the risk of stroke is best described as:

A. A strong association
B. No association
C. A weak association
D. Not known
Plasma Lipid Profile and Incident Ischemic Stroke

The Atherosclerosis Risk in Communities (ARIC) Study

Eyal Shahar, Lloyd E. Chambless, Wayne D. Rosamond, Lori L. Boland, Christie M. Ballantyne, Paul G. McGovern, A. Richey Sharrett
Stroke Risk and Lipid Levels in Men

Incident Ischemic Stroke vs Baseline LDL-Cholesterol Level
Knots: LDL = 2.08, 2.93, 3.54, 4.18, 5.20

Incident Ischemic Stroke vs Baseline HDL-Cholesterol Level
Knots: HDL = 0.72, 0.92, 1.10, 1.32, 1.82
Stroke Risk and Lipid Levels in Women

Incident Ischemic Stroke vs Baseline LDL-Cholesterol Level
Knots: LDL = 1.94, 2.78, 3.40, 4.11, 5.30

Incident Ischemic Stroke vs Baseline HDL-Cholesterol Level
Knots: HDL = 0.90, 1.17, 1.44, 1.74, 2.32
Dyslipidemia and Ischemic stroke

• The predictive power of dyslipidemia for stroke is weak.

• Lack of association may
  • a positive association with ischemic stroke
  • a negative association with hemorrhagic stroke

• Heterogeneity of ischemic stroke mechanisms

• Dyslipidemia maybe associated with:
  • large vessel intracranial and extracranial atherosclerosis
  • lacunar strokes
Heterogeneity of Stroke Etiology by Age group

Statin Drugs: Are They Worth the Risks
Patient H.D.

67 yo Female with CAD, hypertension, hyperlipidemia presents to the ED with acute neurologic deficit involving the right upper more than lower extremity. She got TPA by the neurologist in the ED. She takes amlodipine for hypertension. CT angiography of the brain shows significant intracranial stenosis involving the distal left MCA.

In addition to aspirin, 24 hours post tPA, which of the following will optimize secondary stroke prevention:

A. Simvastatin 40mg daily, no lipid panel required
B. Check lipid panel and start Pravastatin 80mg daily
C. Start Rosuvastatin 20mg daily, no lipid panel required
D. Check lipid panel and start Atorvastatin 40 mg daily
Statin trials and relative reduction of MACE
# Meta-analysis of Stroke Rates in Statin Trials

## Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug Dose</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>4S</td>
<td>Sim 40 mg</td>
<td>0.65 (0.48, 0.89)</td>
</tr>
<tr>
<td>CARE</td>
<td>Pra 40 mg</td>
<td>0.69 (0.49, 0.98)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pra 40 mg</td>
<td>0.83 (0.68, 1.02)</td>
</tr>
<tr>
<td>HPS</td>
<td>Pra 40 mg</td>
<td>0.77 (0.68, 0.87)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>Pra 40 mg</td>
<td>1.04 (0.82, 1.31)</td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>Pra 20 - 40 mg</td>
<td>0.91 (0.76, 1.09)</td>
</tr>
<tr>
<td>KLIS</td>
<td>Pra 20 - 40 mg</td>
<td>0.85 (0.56, 1.28)</td>
</tr>
<tr>
<td>GREACE</td>
<td>Ato 40 mg</td>
<td>0.53 (0.24, 1.19)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Ato 40 mg</td>
<td>0.74 (0.56, 0.96)</td>
</tr>
<tr>
<td>D+L Overall</td>
<td></td>
<td>0.81 (0.74, 0.89)</td>
</tr>
<tr>
<td>M-H Overall</td>
<td></td>
<td>0.81 (0.75, 0.87)</td>
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**Note:** Weights are from random effects analysis.
High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators

Stroke Prevention by Aggressive Reduction Cholesterol Level Trial (SPARCL Trial)
SPARCL Trial

• Eligibility
  • > 18 years
  • Ischemic or hemorrhagic stroke or TIA (diagnosed by a neurologist within 30 days after the event)
  • Event must have occurred 1 to 6 months before randomization.

• 4,731 underwent randomization

• Intervention/Comparator - atorvastatin 80mg daily / Placebo

• Follow up from 4.4 – 6.6 years

• Outcome: Time to fatal and non-fatal stroke
<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Atorvastatin (N = 2365)</th>
<th>Placebo (N=2366)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.0 ± 0.2</td>
<td>62.5 ± 0.2</td>
</tr>
<tr>
<td>Male sex</td>
<td>1427 (60.3%)</td>
<td>1396 (59.0%)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>138.9 ± 0.4</td>
<td>138.4 ± 0.4</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>82.0 ± 0.2</td>
<td>81.4 ± 0.2</td>
</tr>
<tr>
<td>Ischemic stroke/TIA</td>
<td>97.3%</td>
<td>97.7%</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.9%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Others/Unclassified</td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>132.7 ± 0.5</td>
<td>133.7 ± 0.5</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>50.0 ± 0.3</td>
<td>50.0 ± 0.3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>211.4 ± 0.6</td>
<td>212 ± 0.6</td>
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</table>
NNT = 46

HR, 0.84 (95% CI, 0.71–0.99); P=0.03

HR, 0.57 (95% CI, 0.35–0.95); P=0.03

HR, 0.87 (95% CI, 0.73–1.03); P=0.11

HR, 0.77 (95% CI, 0.67–0.88); P<0.001
NNT = 29

HR, 0.58 (95% CI, 0.46–0.73); P<0.001

HR, 0.65 (95% CI, 0.49–0.87); P=0.003

HR, 0.80 (95% CI, 0.69–0.92); P=0.002

HR, 0.74 (95% CI, 0.66–0.83); P<0.001
## Adverse Events from Statin Use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin (N=2365)</th>
<th>Placebo (N=2366)</th>
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</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>5.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Myopathy</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>ALT or AST &gt; 3x ULN at 2 consecutive measurements</td>
<td>2.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Creatine kinase &gt; 10x ULN at 2 consecutive measurements</td>
<td>0.1%</td>
<td>0.0%</td>
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**2018 Stroke Guidelines - Statin**

<table>
<thead>
<tr>
<th>Guideline on Statins use in Acute Ischemic Stroke</th>
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<tbody>
<tr>
<td><strong>High intensity statin therapy</strong> should be initiated or continued as first line-line therapy in patient ≤75 years who have clinical ASCVD, unless contraindicated.</td>
</tr>
<tr>
<td>In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, and is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, <strong>moderate-intensity statin</strong> should be used as the second option if tolerated.</td>
</tr>
<tr>
<td>Patients with ischemic stroke and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines, which include <strong>lifestyle modification, dietary</strong> recommendation and medication recommendations.</td>
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When to Get a Lipid Panel?

Guideline on Statins use in Acute ischemic stroke

| Routine measurement of blood cholesterol levels in all patients with ischemic stroke presumed to be of atherosclerotic origin who are not already taking a high-intensity statin | III – No Benefit | B-R |

Measurement of blood cholesterol levels in patients with ischemic stroke presumed to be of atherosclerotic origin who are already taking an optimized regimen of statin therapy | IIb | B-R |

It may be **useful for identifying patients who would be candidates for outpatient Proprotein Convertase Subtilisin/Kexin type 9 (PCSK-9) inhibitor treatment** to reduce the risk of subsequent cardiovascular death, MI, or stroke.

It has to be done when???
Patient: M.R.

58 yr old male was admitted through the ED after he presents with headaches and right homonymous hemianopsia. He had an MRI that showed left parieto-occipital infarct.

In addition to aspirin, when is appropriate time to start statin?

A. Within 24 hours after stroke
B. 7 days after of stroke event
C. Should be started prior to discharge
D. 90 days after discharge
Statins in Acute Ischemic Stroke: A Systematic Review

Keun-Sik Hong, Ji Sung Lee
A. In-hospital statin effect on good functional outcome

B. In-hospital statin effect on short-term mortality (OR)

C. In-hospital statin effect on short-term mortality (HR)
Randomized Controlled Trial of Early Versus Delayed Statin Therapy in Patients With Acute Ischemic Stroke

ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient)

Shinichi Yoshimura, Kazutaka Uchida, Takashi Daimon, Ryuzo Takashima, Kazuhiro Kimura, Takeshi Morimoto, on behalf of ASSORT Trial Investigator*
In hospital vs outpatient
Guideline on Statins use in Acute ischemic stroke

For patients with an AIS who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable.

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<tr>
<th>Guideline</th>
<th>Ila</th>
<th>C-LD</th>
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PAR Ischemic Stroke Patients Discharged on High Dose Intensive Statin

Goal: ≥ 95% Compliance Rate

Month Range: January 2016 - December 2017

Project Start
• What are some of the common pitfalls in the use of statin in the clinical setting?
Why Physicians are not Using High Intensity Statin

• Fear of future hemorrhagic stroke

• The LDL – C is already < 200 mg/dl

• Fear of liver toxicity

• Fear of rhabdomyolysis and myopathy
Major Take Home Points

• Dyslipidemia may be a predictor of atherosclerotic stroke but not all ischemic strokes

• Good evidence for high intensity statins for stroke

• Use high intensity statin for secondary prevention.

• Start statins before discharge for ischemic stroke
Acknowledgements

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