Can Statins Prevent the First Stroke?

Abdullah Nassief, M.D.
Assistant Professor of Neurology
Washington University School of Medicine

About this Presentation
The content of these pages was written by Dr. Abdullah Nassief of Washington University School of Medicine, based on a presentation given in October of 2000.

TABLE OF CONTENTS

Pharmacology of Statins 2
Structure of Statins 3
Mechanism of Statins 4
Overview of Clinical Trials 5
Primary Stroke Prevention and Statins 6
Meta-Analysis 7
Is Statins’ Benefit Mediated Only Through Cholesterol Reduction? 8
Which Statin to Use? 9
Are Statins Interchangeable? 10
Should We Follow an Absolute LDL Level or a % Reduction? 11
Which Stroke Patient Might Benefit from a Statin? 12
Conclusion 13
# Pharmacology of Statins

<table>
<thead>
<tr>
<th>Natural Statins</th>
<th>Synthetic Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin*</td>
<td>Fluvastatin‡</td>
</tr>
<tr>
<td>Simvastatin*</td>
<td>Atorvastatin*</td>
</tr>
<tr>
<td>Pravastatin†</td>
<td>Cervistatin*</td>
</tr>
</tbody>
</table>

*Utilizes P450 CYP 3A4; ‡CYP 2C9; †dose note utilize CYP
Structure of Statins
Mechanism of Statins

Isoprenoids have effects on G-protein, adhesion molecules, and cell proliferation. Anti-inflammatory effects of the statins is believed to be related to reduction in isoprenoids.
## Overview of Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>LDL @ baseline mg/dl</th>
<th>% LDL reduction</th>
<th>On trila LDL mg/dl</th>
<th>% reduction in total death</th>
<th>% reduction coronary events</th>
<th>% reduction CABG, PTCA</th>
<th>NTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simvast 20-40mg</td>
<td>188</td>
<td>35</td>
<td>120</td>
<td>30 P&lt;0.003</td>
<td>34 P&lt;0.0001</td>
<td>37 P&lt;0.0001</td>
<td>15</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravast 40mg</td>
<td>139</td>
<td>32</td>
<td>95</td>
<td>9 P=NS</td>
<td>24 P&lt;0.003</td>
<td>27 P&lt;0.001</td>
<td>33</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravast 40mg</td>
<td>150</td>
<td>25</td>
<td>113</td>
<td>22 P&lt;0.0001</td>
<td>24 P&lt;0.0001</td>
<td>22 cabg P&lt;0.001</td>
<td>28</td>
</tr>
<tr>
<td>WOSCO</td>
<td>Pravast 40mg</td>
<td>192</td>
<td>26</td>
<td>142</td>
<td>22 P&lt;0.051</td>
<td>31 P&lt;0.001</td>
<td>37 P&lt;0.009</td>
<td>42</td>
</tr>
<tr>
<td>TexCAP</td>
<td>Lovast 20-40mg</td>
<td>150</td>
<td>25</td>
<td>113</td>
<td>0 P=NS</td>
<td>37 P&lt;0.001</td>
<td>33 P&lt;0.001</td>
<td>24</td>
</tr>
</tbody>
</table>
Primary Stroke Prevention and Statins

- Only the CARE trial evaluated stroke as a predefined secondary endpoint in pts with MI and average level of LDL; Pravastatin produced RRR of 32% (from 7.3/1000 to 5.0/1000 person-year). 435 NNT per year to prevent one stroke. 85% of pts in this trial were on antiplatelet therapy.

- Post hoc analysis from 4S showed 29% RRR with simvastatin. Stroke incidence in the placebo was 7.7/1000 person-years (similar to CARE).
Meta-Analysis

- Meta-analysis of primary MI prevention (pravastatin, and lovastatin) trials found 11% (P=NS) relative risk reduction in first ever stroke.

- Meta-analysis of secondary MI prevention (simvastatin, pravastatin) trials found 30% relative risk reduction in first ever stroke
Is Statins’ Benefit Mediated Only Through Cholesterol Reduction?

Meta-analysis of published trials strongly suggested that there may be a cholesterol independent effects. Some of these effects include:

- Improve endothelial cell function
- Anti-inflammatory effect and antiplatelet effect
- Anti-oxidant effect
- Plaque stabilization
- Antithrombotic effect
Which Statin to Use?

- Only natural statins (simvastatin, pravastatin, and lovastatin) have been shown to prevent first and second MI and first ever stroke.
- There is no direct evidence to support use of synthetic statins for prevention of MI and/or stroke.
Are Statins Interchangeable?

- Statins were classified based on their ability to inhibit HMG CO A reductase.
- There is no established clinical or scientific definition of class effect.
- FDA defines a class as “all products within a class are assumed to be closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions”.
- Differences have been shown in statins’ ability to inhibit cholesterol accumulation in macrophages.
- Inhibition of SMC varies among the statins.
- Lipophilic (not hydrophilic) statins suppress tissue factor expression, initiator of coagulation.
- Lipophilic (not hydrophilic) statins were shown to impair recovery of myocardial cells after ischemia.
- Atorvastatin has been shown to increase PAI-1 antigen level. It was also shown to increase fibrinogen and produce molecular changes in fibrinogen structure.
- Atorvastatin at higher doses was shown to affect HDL unfavorably.
Should We Follow an Absolute LDL Level or a % Reduction?

- The correlation between the degree of cholesterol reduction and the extent of statins’ clinical benefit is controversial.
- Post hoc analysis from WOSCOPS and CARE showed no additional benefit to further reduction of LDL (>24%).
- On the other hand the relationship was curvilinear in the 4S.
- The ongoing SEARCH trial (simvastatin 20mg vs. 80mg) will help resolve this issue.
Which Stroke Patient Might Benefit from a Statin?

- Hankey et al., prospectively followed a cohort of 469 pts with TIA for an average of 4.1 years. There were 82 deaths, 51% due to coronary events.

- In the OCSP, 675 patients with first ever stroke were followed for 6.5 years. In the first 30 days, most deaths were related to the stroke; after that, cardiovascular causes were most common.

- The estimated annual absolute risk of coronary events in pts with TIA or stroke is between 2.9 and 4.5%.

- Typically TIA and stroke pts have a high prevalence of vascular disease and risk factors.

- A TIA and/or stroke patients with CHD and high or average cholesterol.

- A TIA and/or stroke patients with vascular risk factors (HTN, DM etc) and high or average cholesterol.

- No evidence supports the use of statins in a TIA or stroke patient without CHD and without vascular risk factor. Those with elevated cholesterol should be treated.
Conclusion

- Cholesterol independent mechanisms are likely to contribute to the cardioprotective and cerebroprotective effects of the statins.

- While statins are similar in their ability to inhibit HMG CO A reductase. There are differences at the cellular level that cast doubt about the scientific merits of the poorly defined class effect.

- Only natural statins have been shown to offer primary and secondary cardiovascular disease prevention, and primary stroke prevention.

- TIA and stroke patients are more likely to die of a coronary event than any other cause, therefore every patient who qualifies should be considered for a natural statin.