



# THE INTERNET STROKE CENTER

PRESENTATIONS AND DISCUSSIONS ON STROKE MANAGEMENT

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## Can Statins Prevent the First Stroke?



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### 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.

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## TABLE OF CONTENTS

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

# Pharmacology of Statins

## Natural Statins:

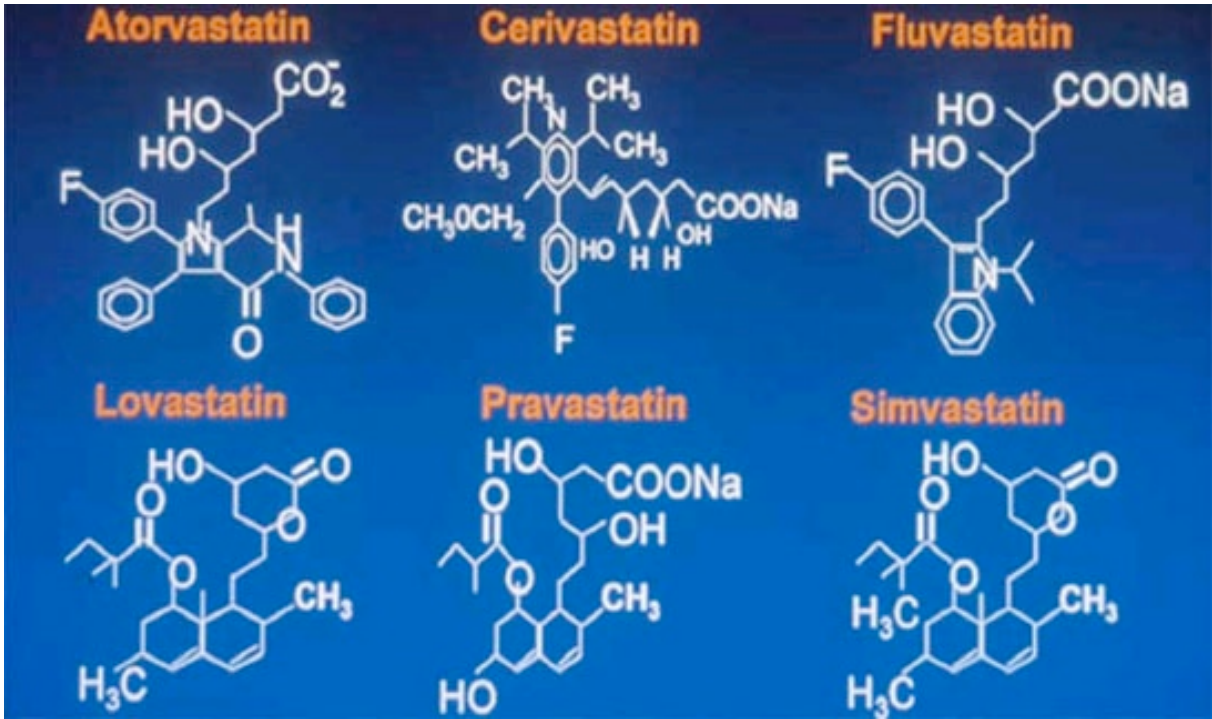
- Lovastatin\*
- Simvastatin\*
- Pravastatin†

## Synthetic Statins:

- Fluvastatin‡
- Atorvastatin\*
- Cervistatin\*

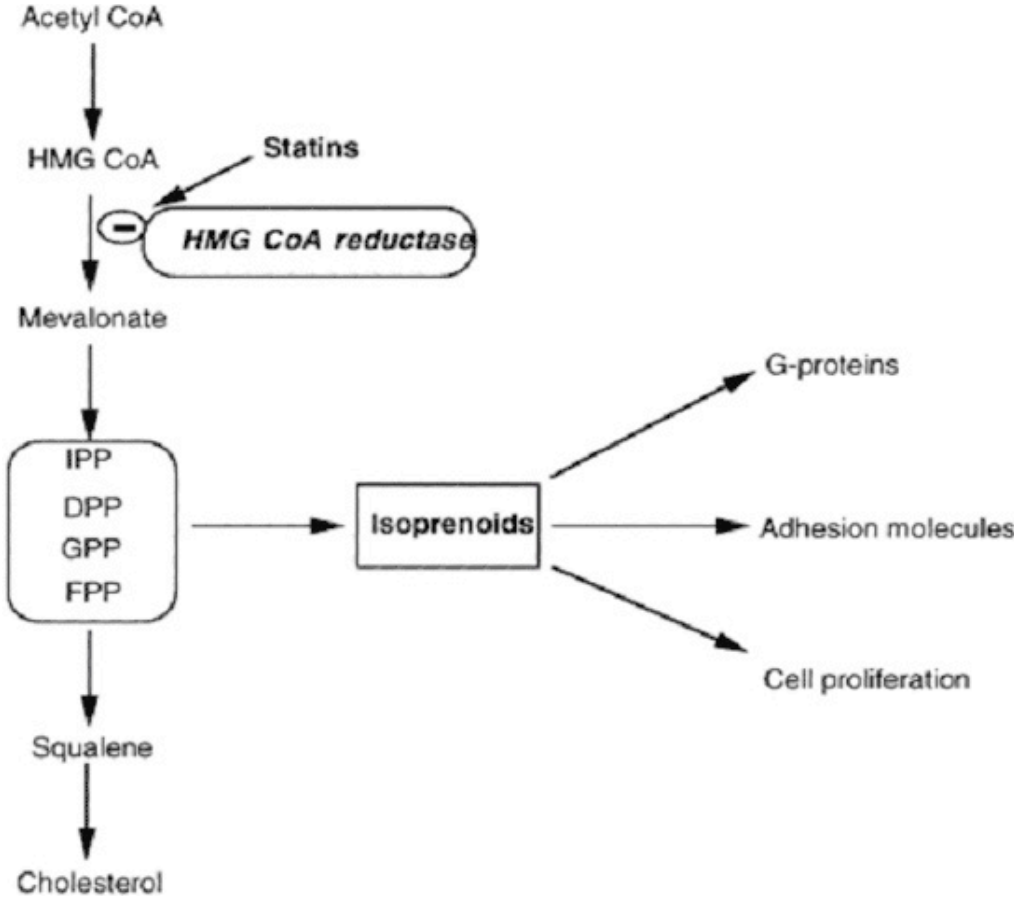
\*Utilizes P450 CYP 3A4; ‡CYP 2C9; †dose note utilize CYP

# 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

Study	Agent	LDL @ baseline mg/kl	% LDL reduction	On trila LDL mg/dl	% reduction in total death	% reduction coronary events	% reduction CABG, PTCA	NTT
<b>4S</b> n=4444	Simvast 20-40mg	188	35	120	30 P<0.003	34 P<0.0001	37 P<0.0001	15
<b>CARE</b> n=4159	Pravast 40mg	139	32	95	9 P=NS	24 P<0.003	27 P<0.001	33
<b>LIPID</b> n=9014	Pravast 40mg	150	25	113	22 P<0.0001	24 P<0.0001	22 cabg P<0.001	28
<b>WOSCO</b> n=6599	Pravast 40mg	192	26	142	22 P<0.051	31 P<0.001	37 P<0.009	42
<b>TexCAP</b> n=6605	Lovast 20-40mg	150	25	113	0 P=NS	37 P<0.001	33 P<0.001	24

## 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 OCSF, 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.