Hypolipidemic drugs in stroke prevention

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Declaration of Interest

DECLARATION

Participation in the « Life Medical Control » company
A medical device company.
STROKE PREVENTION

PHYSICAL ACTIVITY AS A DRUG: LipoProtein Lipase
ACC/AHA versus ESC/EAS

Guidelines

2013 ACC/AHA

Cholesterol is NOT a target.
No treat-to-target strategy. Instead each risk category..
RISK Threshold : Pooled cohorts Equation : 10-year risk from ARIC, CHS, CARDIA, FHS.
Model variables : Age, Sexe, TC, HDLC, SBP & HT, DM, Smoking.
    > 13 millions newly eligible

1) Secondary ASCVD - 2) primary LDL-C ≥ 190
2) ASCVD DM @ LDL-C 70-189 - 4) ASCVD LDL-C 70-189 & RISK ≥ 7.5%.

2016 ESC/ESA

Cholesterol is a target
RISK Threshold : SCORE system : age, Total cholesterol (total or HDL-C), SBP, smoking (Fatal).
Low risk charts and high risk charts according to countries.
Recalibration with HDL-C, apoB, Lp(a), TGs, CAC, ABI.
**RISK LEVELS ESC/EAS**

**Total cholesterol, age, SBP**

**> VERY HIGH-RISK**
Documented CVD, clinical or imaging

**> HIGH-RISK**
Increased risk factors:
Cho > 310 - BP ≥ 180/110 - DM - CKD (30-59)
SCORE 5-10%

**> MODERATE-RISK**
SCORE 1-5%

**> LOW-RISK**
SCORE <1%
<table>
<thead>
<tr>
<th>Total CV risk (SCORE) %</th>
<th>LDL-C levels</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&lt;70 mg/dL</td>
<td>70 to &lt;100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>1.8 to &lt;2.6 mmol/L</td>
<td>2.6 to &lt;4.0 mmol/L</td>
</tr>
<tr>
<td>&lt;1</td>
<td>No lipid intervention</td>
<td>No lipid intervention</td>
</tr>
<tr>
<td>≥1 to &lt;5</td>
<td>No lipid intervention</td>
<td>No lipid intervention</td>
</tr>
<tr>
<td>Class*/Levelb</td>
<td>I/C</td>
<td>I/C</td>
</tr>
<tr>
<td>≥5 to &lt;10, or high-risk</td>
<td>No lipid intervention</td>
<td>Lifestyle intervention, consider drug if uncontrolled</td>
</tr>
<tr>
<td>Class*/Levelb</td>
<td>IIa/A</td>
<td>IIa/A</td>
</tr>
<tr>
<td>≥10 or very high-risk</td>
<td>Lifestyle intervention, consider drug</td>
<td>Lifestyle intervention and concomitant drug intervention</td>
</tr>
<tr>
<td>Class*/Levelb</td>
<td>IIa/A</td>
<td>IIa/A</td>
</tr>
</tbody>
</table>
**Stroke Primary Prevention**

**Analysis 1.8. Comparison | Mortality and Morbidity, Outcome 8 Total Number of Stroke Events.**

Review: Statins for the primary prevention of cardiovascular disease

Comparison: Mortality and Morbidity

Outcome: Total Number of Stroke Events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Statin Therapy Group</th>
<th>Usual Care or Placebo</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS 1994</td>
<td>0/160</td>
<td>5/459</td>
<td>1.2 %</td>
<td>0.09 [0.01, 1.64]</td>
<td></td>
</tr>
<tr>
<td>Adult Japanese MEGA Study</td>
<td>503866</td>
<td>62/3966</td>
<td>13.8 %</td>
<td>0.83 [0.57, 1.20]</td>
<td></td>
</tr>
<tr>
<td>ASPEN 2006</td>
<td>27/959</td>
<td>29/946</td>
<td>6.6 %</td>
<td>0.92 [0.55, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Bone 2007</td>
<td>1/485</td>
<td>0/119</td>
<td>0.2 %</td>
<td>0.74 [0.03, 18.07]</td>
<td></td>
</tr>
<tr>
<td>CARDS 2008</td>
<td>30/1429</td>
<td>50/1412</td>
<td>11.3 %</td>
<td>0.59 [0.36, 0.93]</td>
<td></td>
</tr>
<tr>
<td>JUPITER 2008</td>
<td>33/8901</td>
<td>64/8901</td>
<td>14.4 %</td>
<td>0.52 [0.34, 0.78]</td>
<td></td>
</tr>
<tr>
<td>KAPS 1995</td>
<td>2/214</td>
<td>5/212</td>
<td>1.1 %</td>
<td>0.40 [0.08, 2.02]</td>
<td></td>
</tr>
<tr>
<td>PHYSIS 2004</td>
<td>1/253</td>
<td>0/254</td>
<td>0.1 %</td>
<td>3.01 [0.12, 73.58]</td>
<td></td>
</tr>
<tr>
<td>PREVEND IT 2004</td>
<td>7/433</td>
<td>4/431</td>
<td>0.9 %</td>
<td>1.74 [0.51, 5.91]</td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>194/3302</td>
<td>223/3293</td>
<td>50.3 %</td>
<td>0.87 [0.72, 1.05]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>20302</strong></td>
<td><strong>19993</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.78 [0.68, 0.89]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 345 (Statin Therapy Group), 442 (Usual Care or Placebo)
Heterogeneity: Chi² = 12.08, df = 9 (p = 0.21); I² = 26%
Test for overall effect: Z = 3.56 (p = 0.00037)
Test for subgroup differences: Not applicable

**STATINS**

Cholesterol decrease of -1.00 mmol/L
40 mg/dL

**STROKE DECREASE BY 22%**

*Cochrane 2013. Taylor F.*
**Drug choice**

**STATINS.**

**EZETIMIBE**: inhibits uptake w/o affecting absorption of fat-nutrients
- In association with Statins.

**PCKS9 inhibitors**  When STATINS fails or hereditary hypercholesterolemia

**Drug combinations**

**STATINS** and **EZETIMIBE**: 21% less stroke (IMPROVE-IT).

**No more consideration**

Bile Acid Sequestrants (BAS).
Nicotinic Acid

*NEJM 2006, 355,6:549*
Stroke Overall Prevention: more or less intensive statins

Initial & More vs Less intensive therapy
Cholesterol down 0.51 mmol/L (mean).

In any case, per 1.0 mmol/L reduction:
- Coronary: -13%
- Coronary revascularisation: -19%
- Ischemic stroke: -16%

Even if ...
Initial low cholesterol

CTT. Cholesterol Treatment Trialists
The LANCET 2010, 376:1670-1681
**TRIGLYCERIDES**

Target value

- < 1.7 mmol/L (150 mg/dL)
- > 10.0 mmol/L (880 mg/dL)

**Choice - [Threshold 2.7 mmol/L (200 mg/dL)]**

**STATINS**: strong (atorvastatin, rosuvastatin, pitavastatin)

**Less interest**

**FIBRATES**: HHS, (Helsinki Heart Study), VA-HIT, BIP, FIELD, and ACCORD (only ACCORD targeted Fibrates).

**NICOTINIC ACID**: Unavailable in Europe.
HDL-C

TARGET, minimum

- HDL-C Increase ≥ 7.5%
- LDL-C < 80 mg/dL

Choice

LIFE STYLE: LPL (Lipo Protein Lipase).
STATINS: modest, 5-10%.

Less interest

FIBRATES: Modest.
NICOTINIC ACID.
CPET: deleterious
Energy flux

Alimentary fats + cholesterol

Bile acids, cholesterol

Bile

Chylomicrons

Residues

VLDL

B 48

B 100

E

LDL

Muscle, fat tissue

Peripheral tissues

HDL 1 (trigly.)

HDL 2

C. E.

HDL 3

FFA (portal vein)

Muscle, fat tissue

athérosclerosis

arteries

alimentary fats + cholesterol

LPLh

Transformation de B48 et B100, peroxydation des triglycérides

LPL capillary

Bile capillary

Residues

VLDL

B 48

B 100

E

LDL

Muscle, fat tissue

Peripheral tissues

FFA (portal vein)

Energy flux

Alimentary fats + cholesterol

Bile acids, cholesterol

Bile

Chylomicrons

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LDL

Muscle, fat tissue

Peripheral tissues

HDL 1 (trigly.)

HDL 2

C. E.

HDL 3

FFA (portal vein)
SPECIFIC POPULATIONS

Older adults:
- established CVD: same rules than youngers
- Careful titration
- Free from CVD but many CVRF

METS, STATINS:
- target decrease at least 50% - regardless of initial LDL-C value

ACS or PTCA: Target cholesterol < 70 mg/dL
- STATINS: Initial HIGH DOSE
- If needed add EZETIMIBE +/- PCKS9 inhibitors
- Short loading or pre-treatment if elective PCI

HEART FAILURE: not an indication by itself

AUTO-IMMUNE DISEASE: no indication

CKD: YES for Very high CV risk (CKD 3-5).
- if dialysis dependent and free of atherosclerotic CVD
- if transplant recipients, considered.
STATINS
VACCINE AT04A
Antibodies against PCSK9

CLINICAL PHASE 1 (Vienna)
- Running

Animals: mice Western Diet
- Cholesterol: - 50 %
- Atherosclerotic diseases: - 60 %
- Inflammation: decrease

RNAi
Interfering RNA

CHARITE (Berlin) and IMPERIAL COLLEGE (Londres): « Interfering RNA »
- Inhibition of the PCKS9 mRNA

High Risk PATIENTS (n=500)
- Cholesterol decrease up to 50 %
- Long-term effect of one single administration, still active after a 9-month Follow-Up.
### RISK LEVELS

**ESC/EAS**

**RISK SCORE:**
- Total cholesterol
- Age
- SBP

#### > VERY HIGH-RISK
Documented CVD, clinical or imaging

#### > HIGH-RISK
Increased risk factors:
- Cho > 310
- BP ≥ 180/110
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### Recommendations

**Lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)**

PAD is a very high-risk condition and lipid lowering therapy (mostly statins) is recommended in these patients.

**Class** | **Level**
--- | ---
I | A

**Lipid-lowering drugs for primary and secondary prevention of stroke**

Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.

**Class** | **Level**
--- | ---
I | A

Lipid-lowering therapy is recommended in patients with other manifestations of CVD for primary prevention of stroke.

**Class** | **Level**
--- | ---
I | A

Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke.

**Class** | **Level**
--- | ---
I | A
PREVENTION IS COST-EFFECTIVE and would decrease DALYs

STROKE COST

70,000 € each

Europe: 45 Billions a year or 5 Millions € each hour.

HEALTH RISK BEHAVIOURS WOULD PREVENT AT LEAST 80 % OF CVD

Disability Adjusted Life years. OMS 2002
The Stroke Prevention by **Aggressive Reduction in Cholesterol Levels (SPARCL)** Investigators.

High-dose atorvastatin after stroke or transient ischemic attack.