Atherosclerosis

Reversibility of Arterial Lesions

Animal models: documented in a wide range of species

Humans: There are growing evidences of plaque regression in mild atherosclerotic disease

*Atherosclerosis is usually viewed as a chronic progressive disease characterized by continuous accumulation of atheroma within the arterial wall.*
Presentation

- Evidences of plaque regression
- Predictors of plaque regression
- Clinical significance of regression
- Future perspective
Evidences of Plaque Regression

Carotid Artery
Effect of Lovastatin on Early Carotid Atherosclerosis & CV Events: ACAPS

In men & women with moderately elevated LDL cholesterol, lovastatin reverses progression of IMT in the carotid arteries & appears to reduce the risk of major CV events & mortality.

Circulation 1994;90:1679

Lovastatin (20-40 mg/d) versus placebo

919 asymptomatic patients with early carotid atherosclerosis

Primary outcome:
3-year change of mean maximum IMT
Aggressive LDL-cholesterol reduction was accompanied by regression of carotid intima media thickness in patients with familial hypercholesterolaemia, whereas conventional LDL lowering was not.
In patients with FHC, combined therapy with ezetimibe & simvastatin did not result in a significant difference in changes in IMT, as compared with simvastatin alone.
In middle-aged adults with an Framingham risk score of less than 10% & evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo.

# Summary of Major Lipid-Modifying Trials

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients No/ Duration (y)</th>
<th>Treatment</th>
<th>Target</th>
<th>Difference (mm/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAPS</td>
<td>919/3</td>
<td>L20-40/Pl</td>
<td>IMT</td>
<td>-0.015</td>
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<tr>
<td>ARBITER1</td>
<td>161/1</td>
<td>A80/P40</td>
<td>IMT</td>
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<tr>
<td>ASAP</td>
<td>325/2</td>
<td>A80/S40</td>
<td>IMT</td>
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<tr>
<td>CAIUS</td>
<td>305/3</td>
<td>P40/Pl</td>
<td>IMT</td>
<td>-0.0132</td>
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<tr>
<td>ENHANCE</td>
<td></td>
<td>S80+E1/S80</td>
<td>IMT</td>
<td>0.0026</td>
</tr>
<tr>
<td>KAPS</td>
<td>424/3</td>
<td>P40/Pl</td>
<td>IMT</td>
<td>-0.014</td>
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<tr>
<td>LIPID</td>
<td>522/4</td>
<td>R40/P1</td>
<td>IMT</td>
<td>-0.0145</td>
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<tr>
<td>METEOR</td>
<td>984/2</td>
<td>R80/R5</td>
<td>Volume</td>
<td>No change</td>
</tr>
<tr>
<td>PLAC-II</td>
<td>151/3</td>
<td>P20-40/Pl</td>
<td>IMT</td>
<td>-0.0082</td>
</tr>
<tr>
<td>RADIANCE1</td>
<td>850/2</td>
<td>T60+A/A</td>
<td>IMT</td>
<td>-0.0006</td>
</tr>
<tr>
<td>RADIANCE2</td>
<td>752/1.8</td>
<td>T60+A/A</td>
<td>IMT</td>
<td>0.0050</td>
</tr>
</tbody>
</table>

Evidences of Plaque Regression

Aorta
Effects of Simvastatin on Atherosclerotic Lesions: MRI Study

N=18
LDL-C $\geq$ 130 mg/dL, TG $\leq$ 445 mg/dL

Effective and maintained lipid-lowering therapy by simvastatin is associated with a significant regression of atherosclerotic lesions (reduction in lipid content -> plaque stabilization).

Circulation. 2001;104:249
Different Susceptibilities of Thoracic and Abdominal Aortic Plaques to Lipid Lowering

The effects of 20-mg versus 5-mg atorvastatin on thoracic and abdominal aortic plaques in 40 hypercholesterolemic patients (MRI) for 1 year.

Regression of thoracic aortic plaques, whereas only retardation of plaque progression in abdominal aorta.
Coronary Artery

Evidences of Plaque Regression
REVERSAL

Screening Visit*

Placebo Run-in Phase

Randomization
654 patients

Double-blind period

Atorvastatin 80 mg/day

Pravastatin 40 mg/day

18-month follow-up with IVUS

*Includes baseline intravascular ultrasound (IVUS)
Intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. The progression rate at any level of LDL-C reduction was lower with atorvastatin compared with pravastatin.
To evaluate whether long-term treatment with rosuvastatin 40 mg in CAD pts resulted in coronary plaque regression (single arm study)

Patients
CAD, undergoing coronary angiography
Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment
No cholesterol entry criteria
≥18 years

Rosuvastatin 40 mg
(n=349 evaluated serial IVUS examinations)
Primary Endpoint: $\Delta$% Atheroma Volume

Very high-intensity statin therapy using rosuvastatin 40mg/d resulted in significant regression of atherosclerosis,
A recombinant ApoA-I Milano/phospholipid complex (ETC-216) administered intravenously for 5 doses at weekly intervals produced significant regression of coronary atherosclerosis as measured by IVUS.

-14.1 mm³ or a 4.2% decrease from baseline
Summary

There are convincing evidences to support that high-dose statin or HDL-raising therapies may induce regression of mild to moderate atherosclerotic lesions in humans.
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The probability of a decrease in IMT was significantly related to decrease in LDL-C but not significantly related to a decrease in SBP.

Conversely, probability of decreases in LVMI were significantly related to decreases in SBP but not to LDL-C decreases.

Reducing LDL-C (<70mg/dl vs.100 ) & SBP (<115mmHg vs. 130) to lower targets resulted in regression of carotid IMT & greater decrease in LV mass in type 2 DM.
**REVERSAL:** Continuous Relationship between LDL-C, CRP, and Percent Atheroma Volume

<table>
<thead>
<tr>
<th>Change in Percent Atheroma Volume (%)</th>
<th>Change in CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LDL-C (mg/dL)</td>
<td></td>
</tr>
</tbody>
</table>

In **REVERSAL,** greatest decrease in disease progression observed among patients with greatest reductions in CRP for any given change in LDL-C.

Usefulness of Follow-Up LDL–C Level as an Independent Predictor of Changes of Coronary Atherosclerotic Plaque Size After Statin Therapy

When patients achieved a follow-up LDL cholesterol level <100 mg/dl, regression or no progression of coronary plaque was expected.

N=103, 1 year follow-up

Hong MK et al. AJC 2006;98:866
In ASTEROID, there was no plaque regression in patients with LDL-C > 100 mg/dL, and little change in patients with LDL-C of 70-100 mg/dL. Plaque regression was only seen in patients with LDL-C ≤ 70 mg/dL.
The regressible plaque

Summary

• Plaque regression is associated with a substantial reduction of LDL-C, and lipids and inflammatory substances may be responsible for this change.

• It remains uncertain whether plaque consisting of connective tissue and calcium may be regressible.
Presentation

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• Future perspective
Association between Carotid IMT and Clinical Endpoints

Are surrogate imaging markers of the arterial wall are representative for clinical outcomes?

Imaging trials and clinical endpoints trials that evaluated similar drugs indicates good correlations between CIMT & clinical events.

Limitations:  
- different imaging protocols  
- different outcomes measures

Effect of Rosiglitazone on Carotid IMT Progression in CAD Patients Without DM

Rosiglitazone reduces common carotid IMT progression in nondiabetic CAD patients, & insulin-sensitization may be one contributory mechanism.

Placebo
Progression rate = 0.031 mm/48 weeks (0.0016, 0.0604)

Rosiglitazone 8 mg/day
Progression rate = -0.012 mm/48 week (-0.0414, 0.0174)
Estrogen in the Prevention of Atherosclerosis
A Randomized, Double-Blind, Placebo-Controlled Trial

The average rate of progression of IMT was slower in healthy postmenopausal women taking unopposed ERT with 17ß-estradiol than in women taking placebo.
ENHANCE vs. ASAP
What’s the differences?

A seemingly perfect analogue

LDL-C differences:
ΔENHANCE: 17%
ASAP: 9%

Not the end of the world!

The results of IMPROVE-IT, which will not be available until 2012, are expected not only to help define the role of ezetimibe in the treatment of hypercholesterolemia but also to provide insight into the use of IMT as a surrogate indicator of coronary events.
The REVERSAL study used the same treatment regimen as the PROVE-IT. Although the REVERSAL & PROVE-IT studies were distinct studies, their results provided evidence that plaque progression measured by IVUS is predictive of an increased risk of CV events.
Torcetrapib & Regression ILLUSTRATE

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Torcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>% atheroma volume</td>
<td>0.19 vs 0.12 (p=0.72)</td>
<td>0.12 vs 0.19 (p=0.72)</td>
</tr>
<tr>
<td>AV of most diseased 10 mm</td>
<td>-3.3 vs -4.1 (p=0.12)</td>
<td>-4.1 vs -3.3 (p=0.12)</td>
</tr>
</tbody>
</table>

IVUS-derived indexes of coronary plaque progression

- Pitfall of PAV (average atheroma area/average EEM area): -5%↑ of atheroma (progression), 10%↑ of EEM (positive remodeling) → 4.5%↓ of PAV (regression)
- It remains uncertain what’s the best surrogate for clinical benefits.
Summary

- The CIMT or IVUS studies provide proof of concept, giving us the answer with only a few hundred patients.

- Although plaque regression does not guarantee a reduction in the rate of clinical events, it may not be expected without a reduction in plaque progression.

- However, imaging surrogates will not be a substitute for clinical endpoint trials because regression does not necessarily mean plaque stabilization.
Presentation

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## Effect of Rosuvastatin Therapy on Coronary Artery Stenosis Assessed by QCA in ASTEROID

### Clinically Relevant Changes

<table>
<thead>
<tr>
<th>Change Description</th>
<th>Stenosis Reduced by</th>
<th>Stenosis Changed by</th>
<th>Stenosis Increased by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosis reduced by</td>
<td>≥ 10% (regression*)</td>
<td>22</td>
<td>7.5%</td>
</tr>
<tr>
<td>Stenosis changed by</td>
<td>&lt; 10%</td>
<td>261</td>
<td>89.4%</td>
</tr>
<tr>
<td>Stenosis increased by</td>
<td>≥ 10% (progression*)</td>
<td>9</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

* Proportion of regressors greater than progressors, both p <0.03

### Effect of Rosuvastatin Therapy on Coronary Artery Stenosis Assessed by QCA in ASTEROID

<table>
<thead>
<tr>
<th>Change Description</th>
<th>MLD Change</th>
<th>MLD Smaller by</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD larger by</td>
<td>≥ 0.2mm (regression*)</td>
<td>34</td>
</tr>
<tr>
<td>MLD Change</td>
<td>&lt; 0.2mm</td>
<td>261</td>
</tr>
<tr>
<td>MLD smaller by</td>
<td>≥ 0.2mm (progression*)</td>
<td>9</td>
</tr>
</tbody>
</table>

* Proportion of regressors greater than progressors, both p <0.03
Progression of coronary atherosclerosis can be associated with a paradoxical increase in lumen cross-sectional area, whereas regression is not associated with any change in lumen area (REVERSAL trial).
Future Perspective and Unanswered Questions

• Study duration:
  - Most studies lasted for only $\leq 2$ years

Plaque Quantity vs. Quality

- Minimal cosmetic improvement does not improve myocardial ischemia.
- Plaque regression does not necessarily mean plaque stabilization, requiring imaging tools for accurate evaluation of plaque quality.
Conclusions

Regression is a surrogate marker (unproven stand-in) waiting for definitive outcome trials.

Any drug taken by patients every day for the rest of their life should be backed with accepted outcome data (Level A evidence).