Atherosclerosis: Progression- Regression

Brown BG, Zhao XQ, Sacco DE, Albers JJ.

Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease.

Circulation. 1993;87:1781-1790.

• Dissociation between angiography and clinical outcomes.
• Negligible improvement of luminal caliber: 1-3 %
### Statins Prevent Major Coronary Events

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>High Risk</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>AF/TexCAPS</td>
<td>WOS</td>
<td>ASCOT</td>
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<tr>
<td><strong>N</strong></td>
<td>6605</td>
<td>6595</td>
<td>10305</td>
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<tr>
<td><strong>ΔLDL</strong></td>
<td>-27%</td>
<td>-26%</td>
<td>-26%</td>
</tr>
</tbody>
</table>

**Reduction (%)**


*P<0.001; †P=0.0005; ‡P<0.0001; §P=0.002.

Apo A-I Milano trial

Effect of recombinant Apo A-I Milano on coronary atherosclerosis in patients with acute coronary syndromes. A randomized controlled trial

Steven E. Nissen et al.

Cleveland Clinic

Apo A-I Milano trial

Rilevant issues

- First compelling evidence of atherosclerosis regression in humans
- HDL therapy
- Role of IVUS
Apo A-I Milano

- Variant of Apo A I
- 40 carriers
- Very low HDL
- Longevity
Apo A-I Milano trial

- ACS pts within 14 days
- Lesions > 20% > 50% at angiography
- 5 weekly recombinant Apo A-I Milano intravenous infusions
- IVUS at baseline and after treatment

SE Nissen et al. JAMA 2003;290:2292-2300
IVUS emerges as the "gold standard" in the study of atherosclerosis progression-regression

Higher Frequency Imaging

30 MHz  40 MHz  50 MHz
Determinazione IVUS dell’area dell’ateroma

Area ateroma = Area EEM – Area lume
Apo A-I Milano trial

Results

The absolute reduction in atheroma volume was:

-14.1 mm$^3$ or

4.2% decrease from baseline (p<.001)

In five weeks

40 000 $ / treatment

SE Nissen et al. JAMA 2003;290:2292-2300
REVERSAL trial

Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial.

*Nissen SE, Tsunoda T, Tuzcu EM, et al.*

Disegno dello Studio REVERSAL

654 pazienti in 32 centri
CAD sintomatica, stenosi angiografica documentata >20%
LDL 125-210 mg/dL, dopo 8 settimane di wash-out

Ecografia intravascolare con trasduttore a 30 MHz
Trascinamento della registrazione 0,5 mm/sec per >30 sec

18 mesi trattamento

Pravastatina 40mg
- 78 pazienti ritirati dallo studio
- Pravastatina: 249 pazienti

Atorvastatina 80mg
- 74 pazienti ritirati dallo studio
- Atorvastatina: 253 pazienti

American Heart Association, Scientific sessions, Orlando; Nov. 2003
Nissen SE et al. JAMA 2004;291:1071-1080
Endpoint primario
Variazione percentuale del volume dell’ateroma

- Progressione (p=0,001*)
- Nessuna variazione (p=0,98*)

Pravastatina
Atorvastatina

* Wilcoxon signed rank test
** Wilcoxon rank sum test

American Heart Association, Scientific sessions, Orlando; Nov. 2003
Nissen SE et al. JAMA 2004;291:1071-1080
Variazioni IVUS

American Heart Association, Scientific sessions, Orlando; Nov. 2003
Nissen SE et al. JAMA 2004;291:1071-1080
HPS: Effects of Fixed Dose Statin by LDL-C Subgroups

HPS LDL-C Subgroup Analysis

LDL-C (mg/dL)

LDL-C > 135 (>3.5 mmol) 39%
LDL-C 116-135 (3-3.5 mmol) 37%
LDL-C < 116 (<3 mmol) 35%

LDL-C ↓ 35%
LDL-C ↓ 37%
LDL-C ↓ 35%

Relative Risk Reduction (Major vascular events):

Placebo LDL-C levels
Simvastatin LDL-C levels
Evolution of Atherosclerosis model

- Gradual luminal narrowing
- Plaque rupture
- Inflammation
Atherosclerosis: traditional model

Atheroma accumulation leads to luminal narrowing from the onset of the disease process

Gradual luminal narrowing
“like rust in a pipe”

The Traditional View of Atherosclerosis
Atherosclerosis is more than luminal narrowing

• 99% of atherosclerotic disease is in vessel wall
• Does not narrow the lumen
• Hidden from angiographic view

Steven Nissen
European Atherosclerosis Society  april 2004 meeting, Seville, Spain
Relationship Plaque/Lumen

- Plaque size in itself is not the sole predictor of luminal narrowing:
- Marked compensatory enlargement of the coronary artery with plaque progression
- Lumen size is not correlated with plaque size

Renu Virmani

Armed Forces Institute of Pathology, Washington, DC
Interazione placca-parete: Rimodellamento

“Compensatory enlargement of human atherosclerotic coronary artery”

Glagov hypothesis
Normal

wall

lumen

EEM
Remodeling: compensatory enlargement

Lumen is normal

Plaque grows in outward fashion

Remodeling permits large accumulation before lumen narrowing
Lumen stenosis is delayed until the lesion occupies 40% of the potential lumen area.
Remodeling classification

Dicotomous Classification of Remodeling

Positive remodeling

Intermediate remodeling

Negative remodeling

Proximal reference

Lesion

Distal reference

Atherosclerosis and vascular remodeling

A

B

C

D

Diameter Stenosis

Angio

Pathology

Normal

Moderate

+ Disease

++ Disease

Area Stenosis

0%

0%

50%

75%

50%

89%

75%

50%

95%

% cross-sectional involvement by atheroma

Actual luminal area decrease

M.C. Fishbein & R.J. Siegel, Circulation. 1996;94:2662-2666
Atherosclerosis & coronary remodeling
IVUS views

M.C. Fishbein & R.J. Siegel, Circulation. 1996;94:2662-2666
Irregolarità luminali: significato patologico

Il riscontro angiografico di alterazioni del lume indica quindi un’estensione della placca di almeno il 40% dell’area del vaso.

In questo caso la maggior parte dell’intero albero coronarico è già interessata dall’aterosclerosi
Placca/stenosi
patologia/angiografia

- La stenosi visibile all’angiografia è un’impronta nella proiezione del lume
- punta affiorante dell’ateroma parietale
- falsa impressione di interessamento focale
ACS: Tip of the Atherothrombotic “Iceberg”

Acute Plaque Rupture ACS (UA/NSTEMI/STEMI)

Clinical

Subclinical

Presence of Multiple Coronary Plaques

Persistent Hyperreactive Platelets

Vascular Inflammation

ACS, acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
Adapted from Goldstein JA. J Am Coll Cardiol. 2002;39:1464-1467.
Our preoccupation with coronary luminology.

The dissociation between clinical and angiographic findings in ischemic heart disease.

*Eric J. Topol, Steven E. Nissen*


After 50 years coronary angiography is still considered as “gold standard”

Coronary angiography: simple two-dimensional projection of the lumen (stenosis)

Atherosclerosis: disease of the arterial wall (plaque)
Limitation of angiographic projection

False-negative angiogram
Coronary remodeling

Steven E. Nissen, MD; Paul Yock, MD. *Circulation*. 2001;103:604
Angiographic underestimation of disease

Steven E. Nissen, MD; Paul Yock, MD.  Circulation. 2001;103:604
False-negative angiogram: bifurcation

False-negative angiogram: severe concentric disease

Overestimation of lumen gain by angiography after PTCA

Positive remodeling

AMI after lysis

Steven E. Nissen, MD; Paul Yock, MD. Circulation. 2001;103:604
Negative remodeling

Steven E. Nissen, MD; Paul Yock, MD. Circulation. 2001;103:604
Vulnerable plaque
The propensity for plaques to rupture is independent of plaque size

Michael C. Fishbein, MD; Robert J. Siegel, MD
AMI Evolve Most Frequently From Plaques With Mild to Moderate Obstruction

Coronary stenosis severity prior to AMI

Non-Stenotic Vulnerable Plaques overall are More Dangerous Since they are far More Frequent than Stenotic Ones.
Atherothrombosis* is the Leading Cause of Death Worldwide\textsuperscript{1}

<table>
<thead>
<tr>
<th>Causes of Mortality (%)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
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<td>Pulmonary Disease</td>
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<td>Injuries</td>
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<tr>
<td>Atherothrombosis*</td>
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<td></td>
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</table>

\* Atherothrombosis defined as ischemic heart disease and cerebrovascular disease.

In ACS inflammatory response is largely independent from global atherothrombotic burden.

“A. Maseri at the 2nd Vulnerable Patient Symposium held by AEHA on March 6th in conjunction with the ACC 2004 New Orleans, LA

Dissociation between Atherosclerosis and atherothrombosis

“I’m impressed as a physician that some patients have a lot of atheroma and yet they didn’t have an infarction and others had very little atheroma and they have an infarction. I’m even more impressed by the fact that some patients have an infarction, have that atheroma and then for years and years have absolutely nothing with the same atheroma staying there, the same atheromatic burden.”