Age corrected death rate cardiovascular disease in the Netherlands

- Male CVD
- Male Stroke
- Female CVD
- Female Stroke
Atherosclerosis: current concept

Stable plaque

Vulnerable plaque

Plaque rupture

Inflammation

Large lipid pool

Thin cap

Thrombus formation
Davies et al.
The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment.

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Abstract
The cardiovascular science community has pursued the quest to identify vulnerable atherosclerotic plaque in patients for decades, hoping to prevent acute coronary events. However, despite major advancements in imaging technology that allow visualization of rupture-prone plaques, clinical studies have not demonstrated improved risk prediction compared with traditional approaches. Considering the complex relationship between plaque rupture and acute coronary event risk suggested by pathology studies and confirmed by clinical investigations, these results are not surprising. This review summarizes the evidence supporting a multifaceted hypothesis of the natural history of atherosclerotic plaque rupture. Managing patients at risk of acute coronary events mandates a greater focus on the atherosclerotic disease burden rather than on features of individual plaques.
A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators

- Identified were 596 thin-cap fibroatheromas
- Major adverse cardiovascular events, 26 (51.0%) were thin-cap fibroatheromas
Trends in Acute Myocardial Infarction Incidence, Detection, and Treatment
Based on the 2015 50 Top Cardiovascular Hospitals Study

Figure 1: AMI Rate per 10,000 Aged Medicare Part A Beneficiaries

- Total (including unspecified)
- NSTEMI
- STEMI
Merged data from OCT and pathology studies

- **STEMI**
  - Rupture: 71%
  - Erosion: 29%

- **NSTEMI**
  - Rupture: 43%
  - Erosion: 57%

STEMI
NSTEMI

Total burden of ACS

STEMI
NSTEMI

Antihypertensive medication
Lipid lowering therapy
Smoking policy
Risk factor treatment

Nature reviews Cardiology 2016
Death rate following stroke, the Netherlands

Vaartjes et al. Stroke 2013
Athero-Express

• Collecting endarterectomy specimen (carotid, femoral and AAA) and blood (start 2002)

• Now >4000 patients included.

• GWAS data available of 1800 patients, whole genome methylation of 700 plaques.
Athero-Express

- Femoral + iliac
  - N= 1000

- Carotid
  - N= 2400

- AAA
  - N= 600
Time-Dependent Changes in Atherosclerotic Plaque Composition in Patients Undergoing Carotid Surgery

Guus W. van Lammeren, MD, PhD*; Hester M. den Ruijter, PhD*; Joyce E. P. Vrijinhoek, MD; Sander W. van der Laan, MSc; Evelyn Veilema, MSc; Jean-Paul P. M. de Vries, MD, PhD; Dominique P. V. de Kleijn, PhD; Aryan Vink, MD, PhD; Gert Jan de Borst, MD, PhD; Frans L. Moll, MD, PhD; Michiel L. Bots, MD, PhD; Gerard Pasterkamp, MD, PhD

Background—Time-dependent trends in the incidence of cardiovascular disease have been reported in high-income countries. Because atherosclerosis underlies the majority of cardiovascular diseases, we investigated temporal changes in the composition of atherosclerotic plaques removed from patients undergoing carotid endarterectomy.

Methods and Results—The Athero-Express study is an ongoing, longitudinal, vascular biobank study that includes the collection of atherosclerotic plaques of patients undergoing primary carotid endarterectomy in the province of Utrecht from 2002 to 2011. Histopathologic features of plaques of 1583 patients were analyzed in intervals of 2 years. The analysis included quantification of collagen, calcifications, lipid cores, plaque thrombosis, macrophages, smooth muscle cells, and microvessels. Large atheroma, plaque thrombosis, macrophages, and calcifications were less frequently observed over time, with adjusted odds ratios of 0.72 (95% confidence interval, 0.650-0.789), 0.62 (95% confidence interval, 0.569-0.679), 0.87 (95% confidence interval, 0.800-0.940), and 0.75 (95% confidence interval, 0.692-0.816) per 2-year increase in time, respectively. These changes in plaque characteristics were consistently observed in patient subgroups presenting with stroke, transient ischemic attack, ocular symptoms, and asymptomatic patients. Concomitantly, risk factor management and secondary prevention strategies among vascular patients scheduled for carotid endarterectomy significantly improved over the past decade.

Conclusions—In conclusion, over the past decade, atherosclerotic plaques harvested during carotid endarterectomy show a time-dependent change in plaque composition characterized by a decrease in features currently believed to be causal for plaque instability. This appears to go hand in hand with improvements in risk factor management. (Circulation. 2014;129:2269-2276.)

Key Words: endarterectomy, carotid ■ histology ■ plaque, atherosclerotic ■ primary prevention

Reproduced in femoral artery plaques
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>&gt; 40% lipid (%)</td>
<td>33</td>
<td>36</td>
<td>27</td>
<td>21</td>
<td>14*</td>
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<tr>
<td>Intra plaque bleeding (%)</td>
<td>74</td>
<td>75</td>
<td>62</td>
<td>49</td>
<td>37*</td>
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<tr>
<td>Vessel density (AU)</td>
<td>6.7</td>
<td>8.5</td>
<td>7.7</td>
<td>7.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>
Intra plaque bleeding over time
Calcification over time

For females:
- 2003-2004: 60%
- 2005-2006: 40%
- 2007-2008: 60%
- 2009-2010: 40%
- 2011-2012: 60%

For males:
- 2003-2004: 40%
- 2005-2006: 60%
- 2007-2008: 40%
- 2009-2010: 60%
- 2011-2012: 40%
Adjusted odds ratio for the presence of plaque characteristics, per 2 year increase in time

- Plaque thrombosis: 0.62 [0.569-0.679] (<0.001)
- Atheromatous plaque: 0.72 [0.650-0.789] (<0.001)
- Calicified plaque: 0.75 [0.692-0.816] (<0.001)
- Macrophage rich: 0.87 [0.800-0.940] (0.001)
- Collagen rich: 0.99 [0.877-1.068] (0.515)
- Smooth muscle cell rich: 1.05 [0.961-1.146] (0.286)

Lammeren et al. Circulation 2014
Femoral artery plaques (% of plaques)

Atheromatous calcification

IPH collagen

Macrophages SMC
If underlying pathology is shifting: implications

- In the presence of (a)symptomatic disease: much more stable lesions are observed.
- For increasing number of patients: Are we still chasing the right target, e.g. the “vulnerable plaque”?
- What does this imply for tissue and plasma biobanks (biomarkers): Do data and samples obtained before 2000 still represent current patient population?
Patients undergoing carotid endarterectomy
Governmental policy in the Netherlands: smoking banned from public areas since 2004.
All organs and cells share the same DNA
But how the genetic information is used differs for each organ
Are plaque characteristics determined by genetic architecture?

- kalk
- vet
- bloedingen
Associations of 57 Cardiovascular Risk Loci with atherosclerotic plaque traits
To what extent do the 57 known CAD susceptibility loci correlate with (vulnerable) plaque characteristics?
19 out of 57 CAD risk variants associate with a plaque characteristic

* ~6.5-fold enrichment, $p = 3.8 \times 10^{-11}$

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Locus</th>
<th>OR [95% CI]</th>
<th>P</th>
<th>Disease</th>
<th>GWAS dir.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification</td>
<td><em>WDR12</em></td>
<td>0.74 [0.58 - 0.94]</td>
<td>0.012</td>
<td>CAD</td>
<td>+</td>
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<tr>
<td>Calcification</td>
<td><em>ZNF259-APOA5-APOA1</em></td>
<td>1.26 [1.01 - 1.58]</td>
<td>0.043</td>
<td>CAD</td>
<td>+</td>
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<tr>
<td>Calcification</td>
<td><em>LDLR</em></td>
<td>1.59 [1.21 - 2.07]</td>
<td>6.29x10$^{-4}$</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Calcification</td>
<td><em>KCNE2 (gene desert)</em></td>
<td>0.71 [0.55 - 0.91]</td>
<td>7.92x10$^{-3}$</td>
<td>CAD</td>
<td>-</td>
</tr>
<tr>
<td>Collagen</td>
<td><em>NOS3</em></td>
<td>1.73 [1.03 - 2.90]</td>
<td>0.031</td>
<td>CAD</td>
<td>-</td>
</tr>
<tr>
<td>Collagen</td>
<td><em>SMG6</em></td>
<td>0.78 [0.64 - 0.95]</td>
<td>0.012</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Fat</td>
<td><em>MIA2</em></td>
<td>1.27 [1.02 - 1.56]</td>
<td>0.029</td>
<td>CAD</td>
<td>+</td>
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<tr>
<td>Fat</td>
<td><em>ZEB2-ACO74093.1</em></td>
<td>1.38 [1.00 - 1.92]</td>
<td>0.049</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Fat</td>
<td>7q22</td>
<td>0.63 [0.51 - 0.77]</td>
<td>5.09x10$^{-6}$</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Fat</td>
<td><em>NOS3</em></td>
<td>1.73 [1.03 - 2.90]</td>
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<td>CAD</td>
<td>-</td>
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<tr>
<td>Fat</td>
<td><em>TRIB1</em></td>
<td>0.77 [0.65 - 0.92]</td>
<td>3.54x10$^{-3}$</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Fat</td>
<td><em>ABO</em></td>
<td>1.27 [1.02 - 1.59]</td>
<td>0.034</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>IPH</td>
<td><em>LIPA</em></td>
<td>1.27 [1.07 - 1.52]</td>
<td>6.33x10$^{-3}$</td>
<td>CAD</td>
<td>-</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Locus</th>
<th>$\beta$ [s.e.m.]</th>
<th>P</th>
<th>Disease</th>
<th>GWAS dir.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td><em>BCAS3</em></td>
<td>-0.137 [0.054]</td>
<td>0.011</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>SMCs</td>
<td><em>LIPA</em></td>
<td>0.083 [0.040]</td>
<td>0.036</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>SMCs</td>
<td><em>COL4A1/A2</em></td>
<td>0.103 [0.042]</td>
<td>0.015</td>
<td>CAD</td>
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<td>Vessels</td>
<td><em>SWAP70</em></td>
<td>0.079 [0.040]</td>
<td>0.046</td>
<td>CAD</td>
<td>+</td>
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<tr>
<td>Vessels</td>
<td><em>KSR2</em></td>
<td>0.109 [0.040]</td>
<td>6.97x10$^{-3}$</td>
<td>CAD</td>
<td>-</td>
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<tr>
<td>Vessels</td>
<td><em>UBE2Z</em></td>
<td>-0.080 [0.038]</td>
<td>0.034</td>
<td>CAD</td>
<td>-</td>
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</table>

Variant rs12539895 on 7q22 is associated with **less intraplaque fat content** (OR = 0.63, A-allele)

Same allele associated with **decreased susceptibility for CAD** (OR = 0.96)

Most significant:
chr7:106,901,393:I:D, TG > T in the intron of **COG5** (OR = 0.52 [0.40-0.66 95% CI] per A-allele, p = 2.14x10^{-7}, CAF= 0.17)
Methylation: no transcription
Case: the hunger study

- Winter 1944-1945
  - 3.5 million people
  - 20,000 deaths
Case: the Hongerwinter studie

Normal birthweight

Early

low birthweight

Late
Case: the Hongerwinter studie

Later age:

- Obesity +
- Normal weight

Early

Late
• Genetische code is bij een individu hetzelfde in ieder orgaan.
• Maar of de code wordt “afgeschreven”, is niet hetzelfde per orgaan of cel.
Athero-Express: de grootste verzameling van:

- beenvaten • N= 1000
- halsslagader • N= 2300
- aneurysma • N= 600
DNA methylation: smoking
DNA methylation in plaques: smoking

- AHRR demethylation, more transcription
Epigenetic gene transcription regulation

- DNA-methylation only occurs at Cytosine-Guanine (CpG)

- DNA-methylation is cell type specific
Next step: did methylation of DNA in plaques change in non smokers after banning smokers in public areas?
Acknowledgements