Prevention and Coronary Artery Disease

Progression of coronary artery calcification: risk and risk factors

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**Prevention and Coronary Artery Disease**  
**Progression of coronary artery calcification: risk and risk factors**

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Prevention and Coronary Artery Disease
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Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Prevalence of CAC (45 – 75y) in healthy
82 % Men
55 % Women

In CAD
Prevalence 6.8%
100% Men
84% Women

Schmermund A et al
Atherosclerosis 2006;185:177–182.
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Progression of coronary artery calcification: risk and risk factors

Comparative Analysis of Subjects with and without CHD

Schmermund A et al
Atherosclerosis 2006;185:177–182.
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Progression of coronary artery calcification: risk and risk factors

CAC-categories

1-100
Meta-analysis
HNR study
1.9 (1.3 - 2.8)
1.7 (0.8 - 3.5)

100-400
Meta-analysis
HNR study
4.3 (3.1 - 6.1)
4.0 (2.0 - 8.1)

400-1000
Meta-analysis
HNR study
7.2 (5.2 - 9.9)
5.4 (2.4-12.3)

>1000
Meta-analysis
HNR study
10.8 (4.2-27.7)
16.1 (8.0-32.2)

Relatives Risiko
(versus CAC = 0)

1 10 100
Lower Risk Higher Risk
## Prevention and Coronary Artery Disease
### Progression of coronary artery calcification: risk and risk factors

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</table>
Comparability of estimated percentiles from MESA with the Heinz Nixdorf Recall (HNR) Study (MESA estimates are for whites only).
What is the pathophysiology of CAC progression?
Potential mechanism of CAC progression

- Vascular dysfunction,
- Vasomotion abnormalities
- Inflammation
- Autoantibodies to oxidized LDL
- Increased apo B-100 immune complexes
- Lipoprotein (a)

independent of age, gender, traditional risk factors

Kiramijyan S et al AJC 2012, in press
Progression of coronary artery calcification: risk and risk factors

Increases in $\Delta$MBF to CPT after glucose-lowering treatment remained a statistically significant independent predictor of the progression of CAC.

CPT = cold pressure Test

$\Delta$MBF = myocardial blood flow by PET

Schindler Th H et al  Eur Heart J 2010
What is the change of CAC per year?
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Progression of coronary artery calcification: risk and risk factors

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Progression of coronary artery calcification: risk and risk factors

Schmermund et al.  
CAC progression dependent on baseline values

CAC progression = -1.080 + 79 \times (\log \text{baseline CAC quantity})
\[ P< 0.0001, \ R^2 = 0.57. \]
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Progression of coronary artery calcification: risk and risk factors

But what is the mean change of CAC per year?
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Progression of coronary artery calcification: risk and risk factors
MESA Results

5756 participants  average of 2.4 years

Median annual CAC change
21 CAC score in M
14 CAC score in F

Kronmal RA et al
Circulation 115:2722-2730, 2007
But what is the mean change for those with zero calcification?
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Progression of coronary artery calcification: risk and risk factors

during FU no CAC > 100

Follow-Up Scores (1-6 year follow-up)

Zero (n = 70) 1-9 (n = 9) >10 (n=2)

Budoff MJ et al

Am J Cardiol 86:8–11, 2000
incidence of new CAC averaged 6.6% per year.

<5% /year at 50 years, 12%/year 80 years

Kronmal RA et al

Circulation 115:2722-2730, 2007
Zero CAC means very low risk, but zero CAC does not mean zero for ever!

- in 106 (25.1%) of 422 patients rate of conversion
  
  13.4% in the first 4 years and 25.1% at 5 years

- progression non-linear, slow and flat in the first two and
  more rapid increase in the next 3 years,

reflecting the sex- and age-adjusted percentiles distribution of CAC
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What about changes in CAC in relation to other organs?
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Progression of coronary artery calcification: risk and risk factors
- Progression in association with disease at different organs -

Prospective Army Coronary Calcium (PACC) Project

n= 180

40 – 50 years M/F

1. CAC: 101 ± 259
2. CAC: 178 ± 417

FU 4.2±1.3 years
Range 1.5–6.6 years

Taylor AJ et al
Atherosclerosis 197, 339–345, 2008
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- Treatment options
### CARDIA Study
Coronary Artery Risk Development in Young Adults

2,831 subjects, 33-45 year old adults

<table>
<thead>
<tr>
<th>FRS</th>
<th>0 – 2.5%</th>
<th>2.6 – 5.0%</th>
<th>5.1 – 10%</th>
<th>&gt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAC&gt; 0</td>
<td>7.3%</td>
<td>20.2%</td>
<td>19.1%</td>
<td>44.8%</td>
</tr>
<tr>
<td>CAC&gt;100</td>
<td>1.3 %</td>
<td>2.4%</td>
<td>2.4%</td>
<td>17.2%</td>
</tr>
</tbody>
</table>
299 asymptomatic pts (227M/72F), 2 EBTs ≥1 year, range 1 – 6 years

Budoff MJ et al, Am J Cardiol 86:8–11, 2000
## Risk factors for incidental and progression of CAC

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated diabetes mellitus</td>
<td>26.8 (19.5 to 34.2)</td>
</tr>
<tr>
<td>Male gender</td>
<td>10.9 (6.3 to 15.5)</td>
</tr>
<tr>
<td>Lipid lowering medication</td>
<td>9.8 (4.2 to 15.4)</td>
</tr>
<tr>
<td>Family history of heart attack</td>
<td>9.0 (4.4 to 13.6)</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>8.8 (6.4 to 11.2)</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>8.0 (3.3 to 12.8)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.9 (0.8 to 3.1)</td>
</tr>
<tr>
<td>Smoking &gt;10 pack years</td>
<td>1.4 (0.2 to 2.6)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.9 (0.4 to 1.3)</td>
</tr>
</tbody>
</table>

### Baseline demographics at the time of the initial computed tomographic scan

<table>
<thead>
<tr>
<th>Variable</th>
<th>Matched Controls† (n = 300)</th>
<th>Patients With DM (n = 296)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 ± 6</td>
<td>59 ± 6</td>
<td>—</td>
</tr>
<tr>
<td>Women</td>
<td>29% (87)</td>
<td>29% (86)</td>
<td>—</td>
</tr>
<tr>
<td>Baseline CAC score</td>
<td>276 ± 41</td>
<td>291 ± 49</td>
<td>0.9</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>50% (150)</td>
<td>55% (163)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26% (78)</td>
<td>68% (201)</td>
<td>0.03</td>
</tr>
<tr>
<td>Family history of premature CAD§</td>
<td>50% (150)</td>
<td>40% (118)</td>
<td>0.7</td>
</tr>
<tr>
<td>Current tobacco smokers</td>
<td>16% (48)</td>
<td>19% (56)</td>
<td>0.6</td>
</tr>
<tr>
<td>Absolute annual CAC score change</td>
<td>34.3 ± 4.8</td>
<td>80.6 ± 10</td>
<td>0.00001</td>
</tr>
<tr>
<td>ΔCAC%*</td>
<td>10.2 ± 6.7</td>
<td>29.4 ± 8.7</td>
<td>0.00001</td>
</tr>
<tr>
<td>CAC progressors†</td>
<td>33.6% (101)</td>
<td>62.5% (185)</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

* CAC Progression (ΔCAC%) = (Annual change in CAC/baseline CAC) × 100.

**Risk Factor:**
Diabetes mellitus

**FU time**
56 ± 11 months

Kiramijyan S et al

AJC 2012, in press
Risk Factor: Inflammation

hs-CRP

Rotterdam Study

n= 1962

Risk Factors of CAC Progression from Zero to CAC > 0
Follow up time 27 years

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.09</td>
<td>0.99–1.20</td>
<td>0.09</td>
</tr>
<tr>
<td>Male</td>
<td>2.52</td>
<td>1.56–4.05</td>
<td>0.0001</td>
</tr>
<tr>
<td>Adolescence LDL-C</td>
<td>1.34</td>
<td>1.05–1.70</td>
<td>0.02</td>
</tr>
<tr>
<td>Adolescence systolic BP</td>
<td>1.38</td>
<td>1.08–1.77</td>
<td>0.01</td>
</tr>
<tr>
<td>(\Delta)LDL-C</td>
<td>1.07</td>
<td>0.84–1.37</td>
<td>0.58</td>
</tr>
<tr>
<td>(\Delta)Systolic BP</td>
<td>1.25</td>
<td>0.98–1.60</td>
<td>0.08</td>
</tr>
</tbody>
</table>
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Progression of coronary artery calcification: risk and risk factors

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Prevention and Coronary Artery Disease

Progression of coronary artery calcification: risk and risk factors

495 pts
2 scans within
1.9 ± 1 year
all on
statin therapy

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Progression of coronary artery calcification: risk and risk factors

Raggi et al.
Hypertension 46:238-243, 2005

1153 pts
157 DM
2 scans >1 year
CAC >15%/year
true progression
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Progression of coronary artery calcification: risk and risk factors

Kiramijyan S et al, AJC 2012, in press

Event Free Survival

No DM
DM

< 10  >10<20  >20<30  >30 ∆ % CAC

Kiramijyan S et al
AJC 2012, in press
Prevention and Coronary Artery Disease
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Kiramijyan S et al
AJC 2012, in press

same outcome
with or without DM
for non CAC progression
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Pharmacological Interventions for treatment of CAC

- statins -
Prevention and Coronary Artery Disease

Progression of coronary artery calcification: risk and risk factors

Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Verum:
- atorvastatin 20 mg
- vitamin C 1 g
- vitamin E 1,000 U
- aspirin 81 mg

Placebo:
- aspirin 81 mg

FU 2 years

FU 4 years

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>137 ± 310</td>
<td>155 ± 358</td>
<td>0.86</td>
</tr>
<tr>
<td>Percent</td>
<td>38 ± 75</td>
<td>36 ± 58</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Year four

<p>| | | | |</p>
<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>331 ± 421</td>
<td>323 ± 385</td>
<td>0.80</td>
</tr>
<tr>
<td>Percent</td>
<td>81 ± 89</td>
<td>73 ± 93</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Arad Y et al J Am Coll Cardiol 46:166–72, 2005
FU 24 months

Change in coronary artery calcium score (AU/year)

N= 39  
Atorvastatin 80 mg

N= 49  
Placebo

Houslay ES et al  
Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Percent change in LDL-C

---

Pravastatin 40 mg
Correlation coefficient -0.07
P=0.23

Atorvastatin 80 mg
Correlation coefficient -0.06
P=0.39

---

Raggi P et al
*Circulation.* 112:563-571, 2005
Prevention and Coronary Artery Disease Progression of coronary artery calcification: risk and risk factors

Schmermund A et al Circulation 113:427–37, 2006

Atorvastatin 10 mg versus 80 mg
As follow-up studies demonstrate CAC progression in the range of 15 – 25 % per year, the question arises: can we check the efficacy of the risk factor modification by CT?

The answer is **No**, because four randomized, placebo and verum controlled studies in different patient cohorts did not demonstrate any attenuation of CAC progression over time.
Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Pharmacological Interventions for treatment of CAC
- other than statins -
Budoff MJ et al. N = 19, 4 ml Aged Garlic Extract for 1 year.
Progression of coronary artery calcification: risk and risk factors

Budoff MJ et al
Preventive Medicine 39, 985–991, 2004
Prevention and Coronary Artery Disease
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RCT with 65 firefighters at intermediate risk (55±6 years
1200 mg age garlic extract and 120 mg Q 10 for 1 year

<table>
<thead>
<tr>
<th>Variables</th>
<th>AGE +CoQ10</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 6</td>
<td>54 ± 5</td>
<td>0.6</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>CAC</td>
<td>169 ± 29</td>
<td>211 ± 49</td>
<td>0.6</td>
</tr>
<tr>
<td>hsCRP</td>
<td>1.9 ± 2.1</td>
<td>1.9 ± 2.4</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 3</td>
<td>29 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>Absolute change at 1-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC</td>
<td>32 ± 6</td>
<td>58 ± 8</td>
<td>0.01</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-0.12 ± 0.24</td>
<td>0.91 ± 0.56</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.47 ± 0.82</td>
<td>0.28 ± 1.27</td>
<td>0.03</td>
</tr>
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Pharmacological Interventions for treatment of CAC
- optimized RF adjustment-
Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Follow-up in a healthy individual with all efforts and best risk factor management

At the age of 74, the score of 591 is above the 70th percentile.
At the age of 71, the score of 460 is above the 67th percentile.
At the age of 69, the score of 349 is above the 72nd percentile.

http://www.recall-studie.uni-essen.de
That means:

Once you are on a CAC percentile you will stay,

increase of CAC over time can be predicted and calculated.
Conclusion

Progression of CAC
- Natural history
- RF: known FRS and hs-CRP
- Diabetes
- High rate of progression means high risk
- No convincing data on drug treatment
- Progression genetically determined?
Conclusions—Evidence was found that many but not all genetic factors influencing baseline CAC quantity also influence CAC progression. The identification of common and unique genetic influences on these traits will provide important insights into the genetic architecture of coronary artery atherosclerosis. (Circulation. 2007;116:25-31.)

risk factors and CAC quantity, the estimated heritability of CAC progression was 0.40 (P<0.001). Baseline risk factors and CAC quantity explained 64% of the variation in CAC progression. Thus, genetic factors explained 14% of the variation [(100−64)×(0.40)] in CAC progression. After adjustment for risk factors, the estimated genetic correlation (pleiotropy) between baseline CAC quantity and CAC progression was 0.80 and was significantly different than 0 (P<0.001) and 1 (P=0.037). The environmental correlation between baseline CAC quantity and CAC progression was 0.42 and was significantly different than 0 (P=0.006).

Conclusions—Evidence was found that many but not all genetic factors influencing baseline CAC quantity also influence CAC progression. The identification of common and unique genetic influences on these traits will provide important insights into the genetic architecture of coronary artery atherosclerosis. (Circulation. 2007;116:25-31.)
...symptoms of atheroma are very rare.

There is neither a method

to detect an atheroma during life, nor,

if it is detected, to induce regression.

...die Symptomatologie des Atheroms ist sehr gering. Es gibt weder ein Mittel das Atheroma der Arterien sicher im Leben zu erkennen, noch, wenn es erkannt sein sollte, dasselbe rückgängig zu machen“

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**Zero CAC means very low risk, but zero CAC does not mean zero for ever!**

**Editorial**

Change of zero CAC to CAC > 0 does not mean primarily enhanced risk
as few go beyond CAC 100 or even higher in that time period.

Thus, cost savings in such a group of patients during a 3–5-year period

could be of great magnitude.
As follow-up studies demonstrate CAC progression in the range of 15 – 25 % per year, the question arises:

can the efficacy of the risk factor modification be assessed by CT?
Follow-up in a healthy individual with all efforts and best risk factor management.

At the age of 74, the score of 591 is above the 70th percentile.

At the age of 71, the score of 460 is above the 67th percentile.

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Achenbach
## Progression of coronary artery calcification: risk and risk factors

### RCT for Evaluation of Statin Therapy on CAC

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Years</th>
<th>Pts</th>
<th>Statin/mg</th>
<th>Effect/ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arad</td>
<td>2005</td>
<td>4.3</td>
<td></td>
<td>20A+ vs 0</td>
<td>81 vs 73</td>
</tr>
<tr>
<td>Raggi</td>
<td>2005</td>
<td>1.0</td>
<td></td>
<td>80A vs 40P</td>
<td></td>
</tr>
<tr>
<td>Schmermund</td>
<td>2006</td>
<td>1.0</td>
<td>266</td>
<td>80A vs 10A</td>
<td>27 vs 25</td>
</tr>
<tr>
<td>Housley</td>
<td>2006</td>
<td>2.0</td>
<td>88</td>
<td>80A vs 0</td>
<td>26 vs 18</td>
</tr>
</tbody>
</table>
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FU 4.3 years, 1005 pts, 50 to 70 years ≥ 80 percentile of CAC, age and gender related

Verum:
atorvastatin 20 mg
vitamin C 1 g,
vitamin E 1,000 U
aspirin 81 mg

Placebo
aspirin 81 mg

Arad Y et al
J Am Coll Cardiol 46:166 –72, 2005
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<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Atorvastatin 80 mg (n=218)</th>
<th>Pravastatin 40 mg (n=257)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>268.6 (35.3)</td>
<td>267.7 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>268.6 (35.3)</td>
<td>267.7 (40.4)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>176.2 (41.6)</td>
<td>219.5 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Percent change to month 12</td>
<td>-33.8 (15.3)</td>
<td>-17.2 (13.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>175.3 (32.3)</td>
<td>173.6 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>175.3 (32.3)</td>
<td>173.6 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>92.2 (36.1)</td>
<td>129.0 (31.0)</td>
<td></td>
</tr>
<tr>
<td>Percent change to month 12</td>
<td>-46.6 (19.9)</td>
<td>-24.5 (18.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>56.3 (14.0)</td>
<td>58.7 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>56.3 (14.0)</td>
<td>58.7 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>57.0 (13.6)</td>
<td>60.5 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Percent change to month 12</td>
<td>2.3 (13.8)</td>
<td>3.9 (13.0)</td>
<td>0.0606</td>
</tr>
<tr>
<td>Apo B, mg/dL</td>
<td>166.5 (27.3)</td>
<td>164.7 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>166.5 (27.3)</td>
<td>164.7 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>101.1 (31.2)</td>
<td>128.9 (26.5)</td>
<td></td>
</tr>
<tr>
<td>Percent change to month 12</td>
<td>-39.0 (16.5)</td>
<td>-21.2 (14.9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Peripheral arterial disease
- Atorvastatin: 21 (6.9)
- Pravastatin: 21 (6.8)

Raggi P et al

Circulation. 112:563-571, 2005
Progression of coronary artery calcification: risk and risk factors

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin 80 mg (n=218)</th>
<th>Pravastatin 40 mg (n=257)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Median</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Total CVS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>204.7 (297.1)</td>
<td>107.1</td>
<td>267.0 (403.9)</td>
</tr>
<tr>
<td>12-Month follow-up</td>
<td>233.2 (350.1)</td>
<td>118.6</td>
<td>297.9 (408.3)</td>
</tr>
<tr>
<td>Absolute change</td>
<td>28.5 (87.4)</td>
<td>14.2</td>
<td>30.9 (65.1)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>20.1 (30.8)</td>
<td>15.1</td>
<td>19.8 (34.8)</td>
</tr>
</tbody>
</table>

Raggi P et al  
*Circulation.* 112:563-571, 2005
Progression of coronary artery calcification: risk and risk factors

Kiramijyan S et al

AJC 2012, in press
Conclusion of the study

- 2 year FU CAC for risk assessment
- risk modification
- medical optimization
- to control lipid levels on the basis of severity

CAC progression in DM

Kiramijyan S et al

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Breithaupt-Grögler K et al
Circulation 96: 2649-2655, 1997
Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

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WEST-GERMAN HEART CENTER
CARDIOLOGY - UNIVERSITY HOSPITAL ESSEN
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Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors
CAC Progression as a sign of coronary atherosclerosis is genetic determined and not influencable!?
Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors

Heretability estimates for log baseline CAC quantity and CAC progression

<table>
<thead>
<tr>
<th>Trait</th>
<th>$h^2$ (SE)</th>
<th>Covariate Variance*</th>
<th>Covariates Adjusted for</th>
<th>% of Variance Explained by Genetic Factors†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log baseline CAC quantity</td>
<td>0.488 (0.104)</td>
<td>0.00</td>
<td>None</td>
<td>48.8</td>
</tr>
<tr>
<td></td>
<td>0.391 (0.097)</td>
<td>0.35</td>
<td>Age, sex</td>
<td>25.4</td>
</tr>
<tr>
<td></td>
<td>0.376 (0.096)</td>
<td>0.43</td>
<td>Age, sex, LDL-C, SBP, DBP, log pack-years of smoking +1, diabetes, family history of CHD, sex x LDL-C</td>
<td>21.4</td>
</tr>
<tr>
<td>CAC progression</td>
<td>0.782 (0.101)</td>
<td>0.00</td>
<td>None</td>
<td>78.2</td>
</tr>
<tr>
<td></td>
<td>0.671 (0.108)</td>
<td>0.35</td>
<td>Age, sex</td>
<td>43.6</td>
</tr>
<tr>
<td></td>
<td>0.592 (0.109)</td>
<td>0.44</td>
<td>Age, sex, waist-to-hip ratio, LDL-C, log pack-years of smoking +1, diabetes, hypertension, family history of CHD</td>
<td>33.2</td>
</tr>
<tr>
<td></td>
<td>0.396 (0.133)</td>
<td>0.64</td>
<td>Age, sex, waist-to-hip ratio, LDL-C, log pack-years of smoking +1, hypertension, baseline CAC quantity, age x baseline CAC quantity</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Prevention and Coronary Artery Disease
Progression of coronary artery calcification: risk and risk factors
Figure 1: Increase in relative risk (RR) with increasing CAC scores in asymptomatic persons in comparison to asymptomatic persons without CAC (modified from (13)).
Figure 2: Annual rate of myocardial infarction or cardiac death in categories of CAC burden in persons at intermediate risk based on conventional risk factor assessment. In persons with a high CAC score (>400), the annual event rate exceeds the threshold for intensive risk factor modification, i.e. >2% per year (black line). A CAC score > 400 in intermediate risk persons may therefore be considered as a risk equivalent (modified from (13)).
Figure 3. The Absolute and Percent Change in Baseline Agatston Score on Serial CT Imaging

Change in Agatston Score

Low Risk   Mild Risk   Moderate Risk   High Risk

Absolute Change

Percent Change

Baseline CAC Score

CAC Scores

<10

10-99

52-399

≥194

Figure 4. Expected Yearly Rate of Change (95% Confidence Intervals) from Baseline for Coronary Artery Calcium Scores Ranging from 0 to ≥1,000 Agatston Units (AU)

Adapted from Yoon (117).
Figure 5. 95% Confidence Intervals for Repeatability of Coronary Artery Calcium Scores from 0 to ≥1,000
**Figure 6.** Summary Meta-Analysis of Randomized Control Trials (RCT) on the Effect of Statin Therapy (Rx) on CAC Progression

**RCTs of Statin Therapy vs. Placebo**

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>CAC</th>
<th>Change / yr</th>
<th>Rate Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achenbach(127)</td>
<td>66</td>
<td>CVS</td>
<td>155*</td>
<td>-1.0</td>
</tr>
<tr>
<td>Arad(19)</td>
<td>1,005</td>
<td>AU</td>
<td>563:527</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

* Achenbach – Patients had a Treated and Untreated Time Period. Thus, there is no RCT of Statin vs. Placebo and no summary effect was calculated.

**RCTs of Moderate vs. Intensive Statin Therapy**

<table>
<thead>
<tr>
<th>Studies</th>
<th>N</th>
<th>CAC</th>
<th>Change / yr</th>
<th>Rate Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raggi(98)</td>
<td>614</td>
<td>CVS</td>
<td>371:434</td>
<td>-1.0</td>
</tr>
<tr>
<td>Schmermund(128)</td>
<td>366</td>
<td>CVS</td>
<td>267:205</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

**Summary Effect**

- **Moderate vs. Intensive**
  - 5.4% (-7.2% to 17.9%)

**Abbreviations:** CAC=Coronary Artery Calcium, CVS=Calcium Volume Score, AU=Agatston Units, RCT=Randomized Clinical Trial, Yr=Year,
Adolescence Risk Factors Are Predictive of Coronary Artery Calcification at Middle Age

The Cardiovascular Risk in Young Finns Study

Olli Hartiala, BM,* Costan G. Magnusson, PhD,*†‡ Sami Kajander, MD, PhD,§
Juhani Knuuti, MD, PhD,§ Heikki Ukkonen, MD, PhD,|| Antti Saraste, MD, PhD,§
Irina Rinta-Kiikka, MD, PhD,¶ Sakari Kainulainen, MD,# Mika Kähönen, MD, PhD,**
Nina Hutri-Kähönen, MD, PhD,† Tomi Laitinen, MD, PhD,¶ Terho Lehtimäki, MD, PhD,‡‡
Jorma S.A. Viikari, MD, PhD,|| Jaakko Hartiala, MD, PhD,§ Markus Juonala, MD, PhD,*||
Olli T. Raitakari, MD, PhD*§§

Turku, Tampere, and Kuopio, Finland; and Melbourne, Victoria, and Tasmania, Australia
Non Invasive Assessment of Subclinical Coronary Sclerosis: EBCT
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calcium volume scores taken a mean of 2.7 years apart in 109 diabetics

Significant change in CVS defined as a difference between square root–transformed to calcium volume scores ≥ 2.5 mm³ (> 99th percentile interscan variat..)

Potential mechanism of CAC progression

Inverse relationship to

- changes in vascular function
- oxidized phospholipids/apolipoprotein B-100 complexes
  lipoprotein (a)

Kiramijyan S et al
AJC 2012, in press
What is the Pathophysiology of CAC Progression in Relation to Endothelium Function and Myocardial Blood Flow
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Relation to Myocardial Blood flow

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<table>
<thead>
<tr>
<th>Model</th>
<th>ΔCAC%</th>
<th>Matched Controls</th>
<th>Patients With DM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10%–20% vs &lt;10%</td>
<td>1.0 (reference)</td>
<td>1.88 (1.51–2.36)</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>21%–30% vs &lt;10%</td>
<td>1.0 (reference)</td>
<td>2.29 (1.56–3.38)</td>
<td>0.0001</td>
</tr>
<tr>
<td>3</td>
<td>&gt;30% vs &lt;10%</td>
<td>1.0 (reference)</td>
<td>6.95 (2.23–11.53)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Hazard ratios of risk for death and 95% CIs (in parentheses) across various categories of CAC progression in subjects with diabetes compared to subjects without DM as a reference using Cox proportional-hazard regression analysis (n = 596).

Adjusted for age, gender, hypertension, hyperlipidemia, family history of CHD, baseline CAC, and smoking.

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<table>
<thead>
<tr>
<th>Variable (ΔCAC)</th>
<th>DM</th>
<th>No DM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>97.9%</td>
<td>100%</td>
<td>0.50</td>
</tr>
<tr>
<td>10%–20%</td>
<td>95.9%</td>
<td>97.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>21%–30%</td>
<td>92.7%</td>
<td>94%</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>79.6%</td>
<td>90.6%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

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Budoff MJ et al. Am J Cardiol 86:8–11, 2000