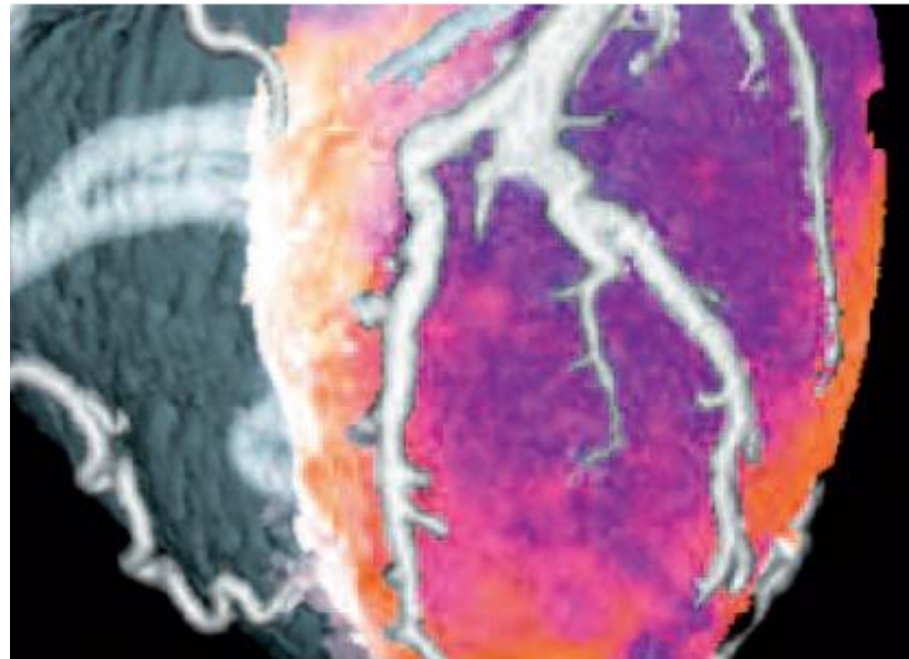


## Prevention and Coronary Artery Disease



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

Raimund Erbel  
Department of Cardiology  
West-German Heart Center Essen  
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erbel@uk-essen.de  
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German Cardiac Society



Swiss Society of Cardiology



University Hospital  
Zurich

#### Programme Directors

Thomas F. Lüscher, Zurich, Switzerland  
Bertram Pitt, Ann Arbor MI, USA

#### Scientific Coordinator

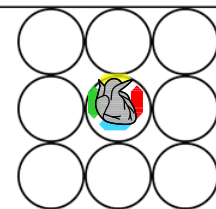
Ruth Amstein, Zurich, Switzerland



ZÜRICH  
HEART HOUSE

# Prevention and Coronary Artery Disease

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

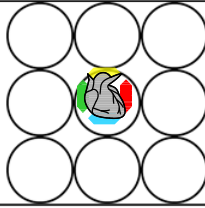


### Content

- Basic considerations
- Natural history
- Risk factors
- Cardiovascular events
- Treatment options

# Prevention and Coronary Artery Disease

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

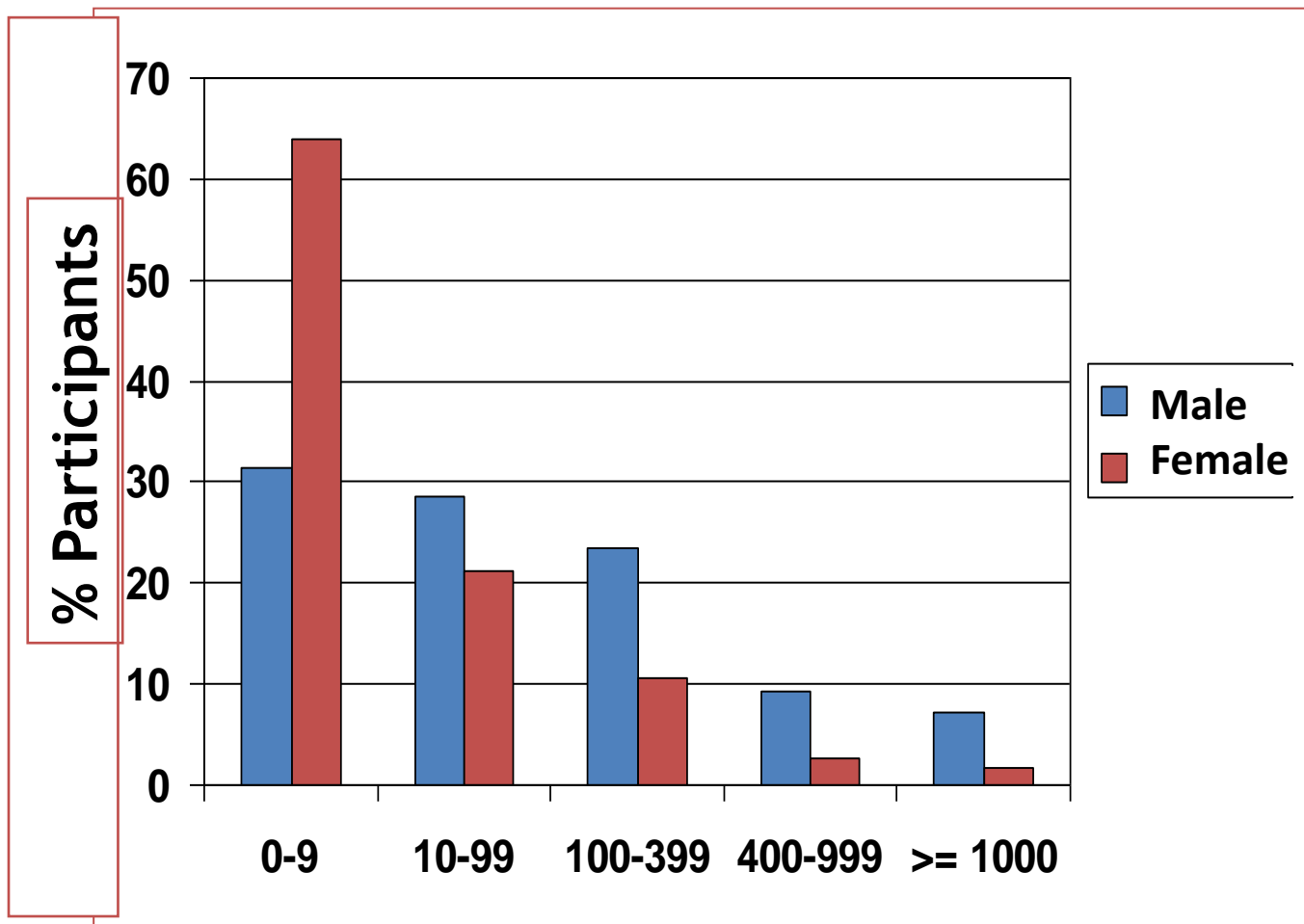


### Content

- Basic considerations
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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**

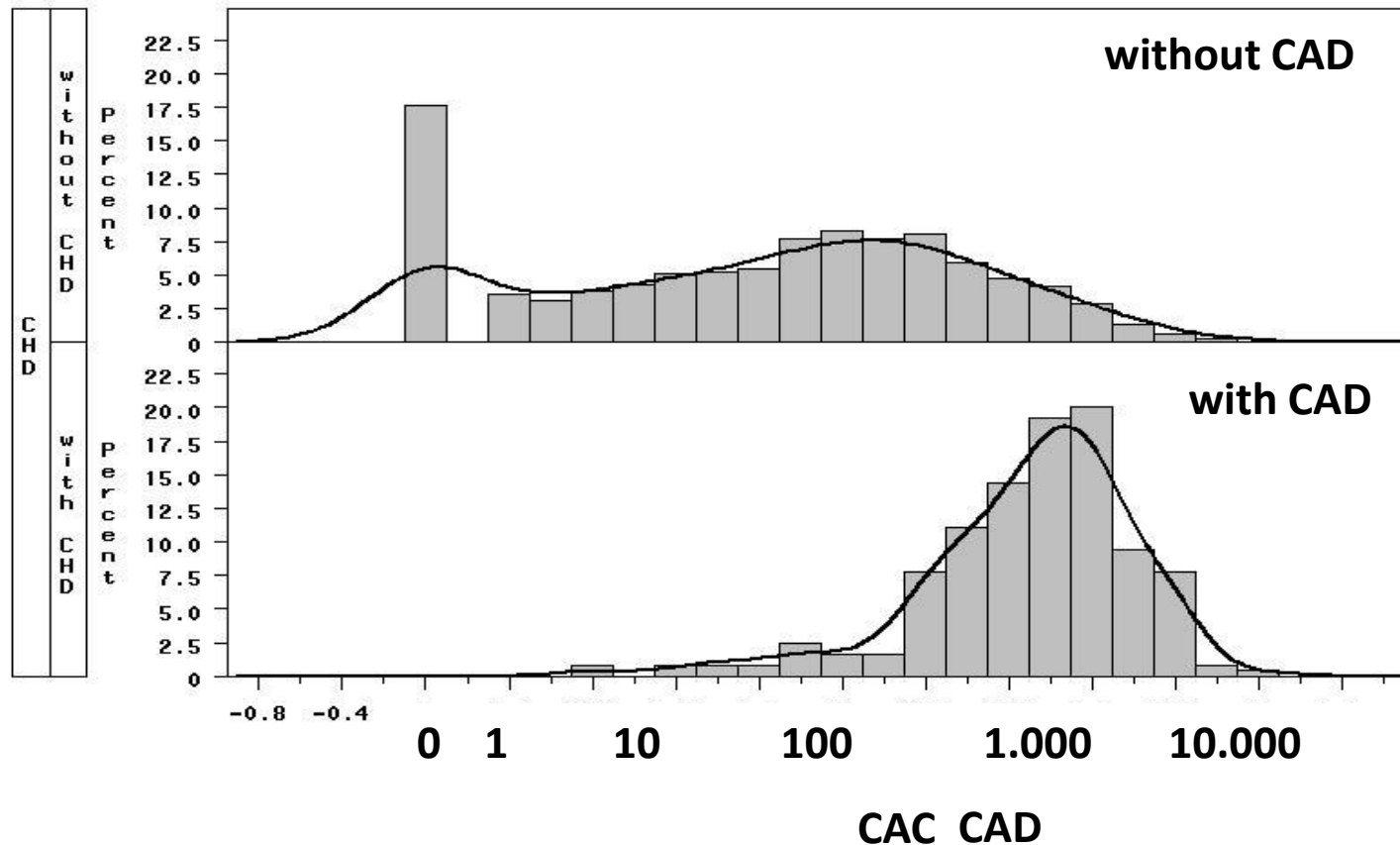
# Prevention and Coronary Artery Disease

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



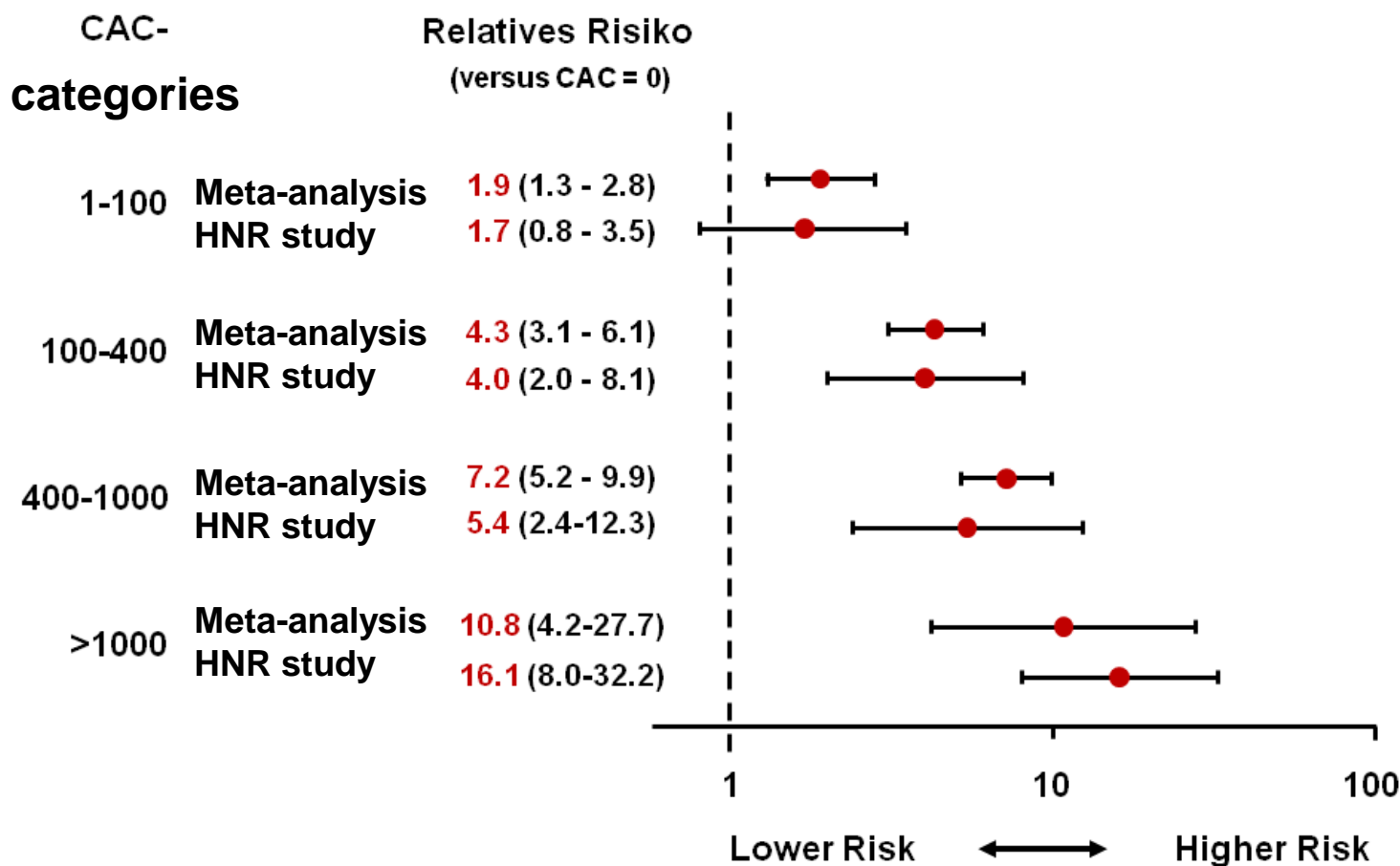
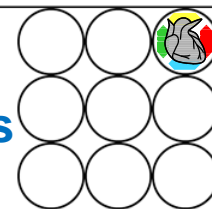
### Comparative Analysis of Subjects with and without CHD

Sex=Male



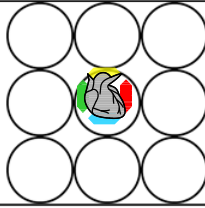
# Prevention and Coronary Artery Disease

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



# Prevention and Coronary Artery Disease

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



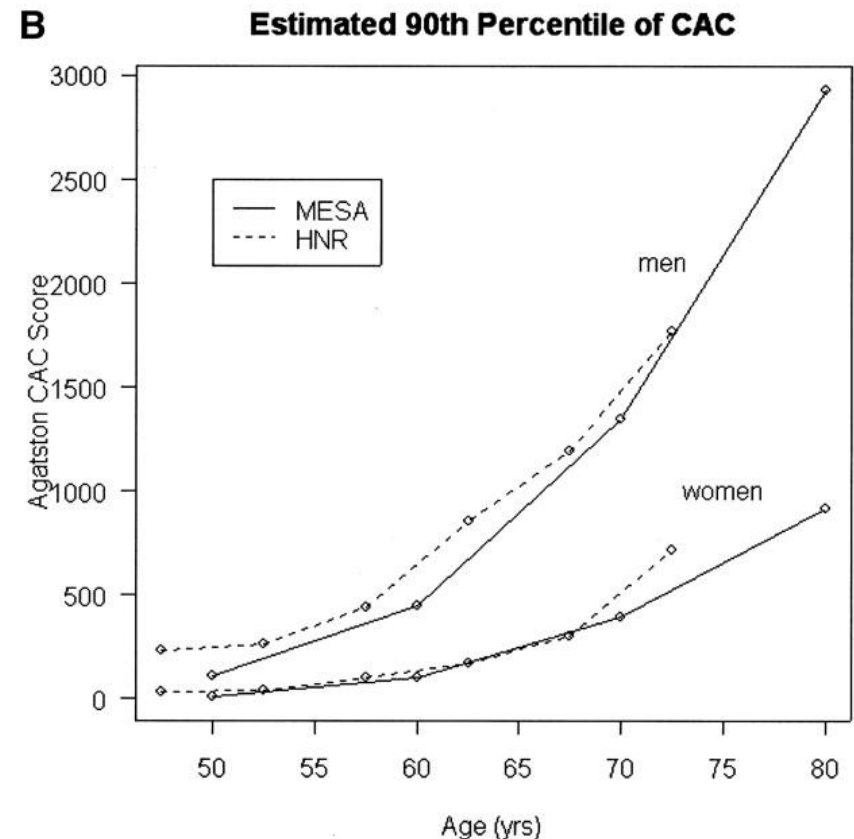
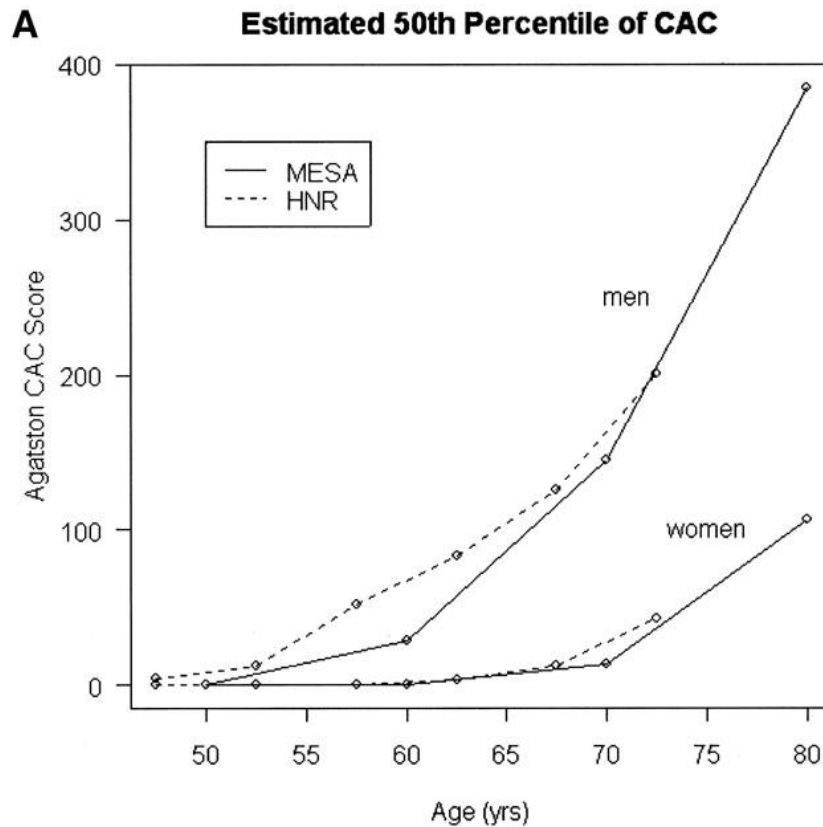
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# Prevention and Coronary Artery Disease

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

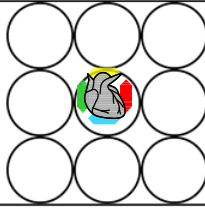
Comparability of estimated percentiles from MESA with the Heinz Nixdorf Recall (HNR) Study (MESA estimates are for whites only).





# Prevention and Coronary Artery Disease

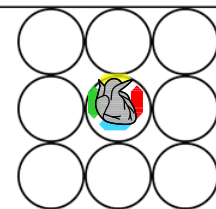
## Progression of coronary artery calcification: risk and risk factors



What is the pathophysiology of CAC progression ?

# Prevention and Coronary Artery Disease

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



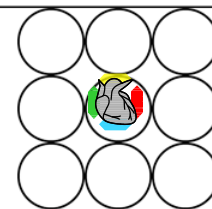
### Potential mechanism of CAC progression

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

independent of age, gender, traditional risk factors

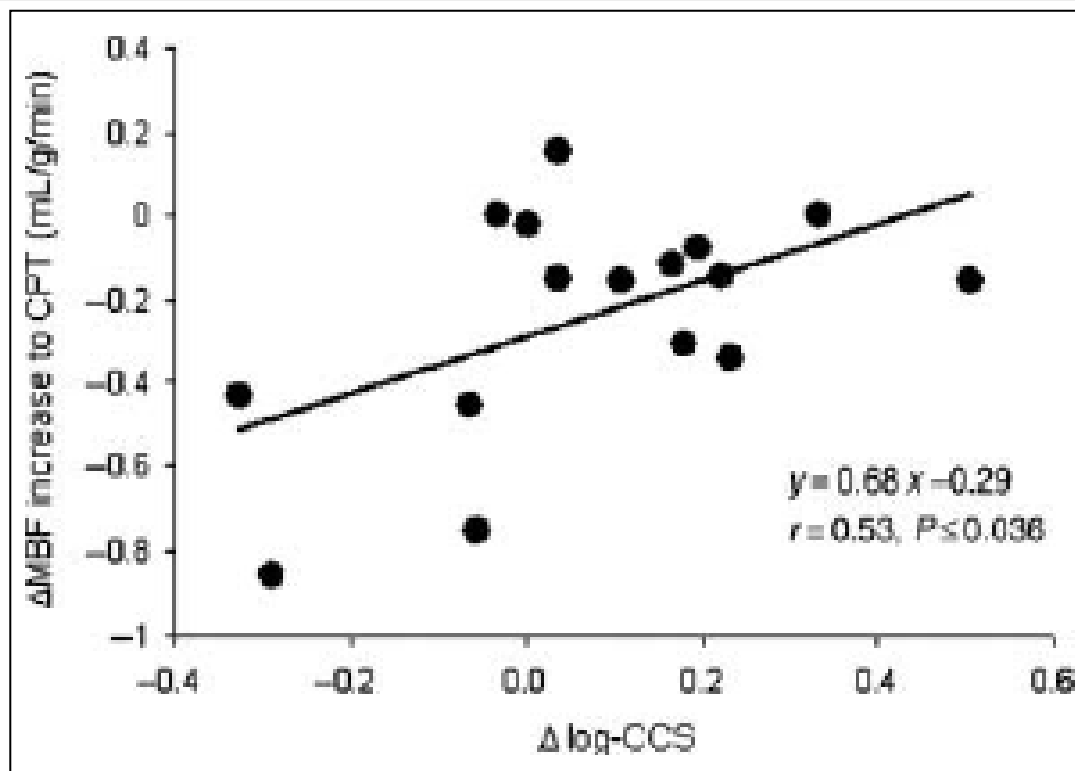
# Prevention and Coronary Artery Disease

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



CPT =  
cold pressure  
Test

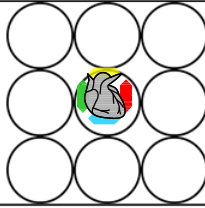
$\Delta$ MBF =  
myocardial blood  
flow by PET



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

# Prevention and Coronary Artery Disease

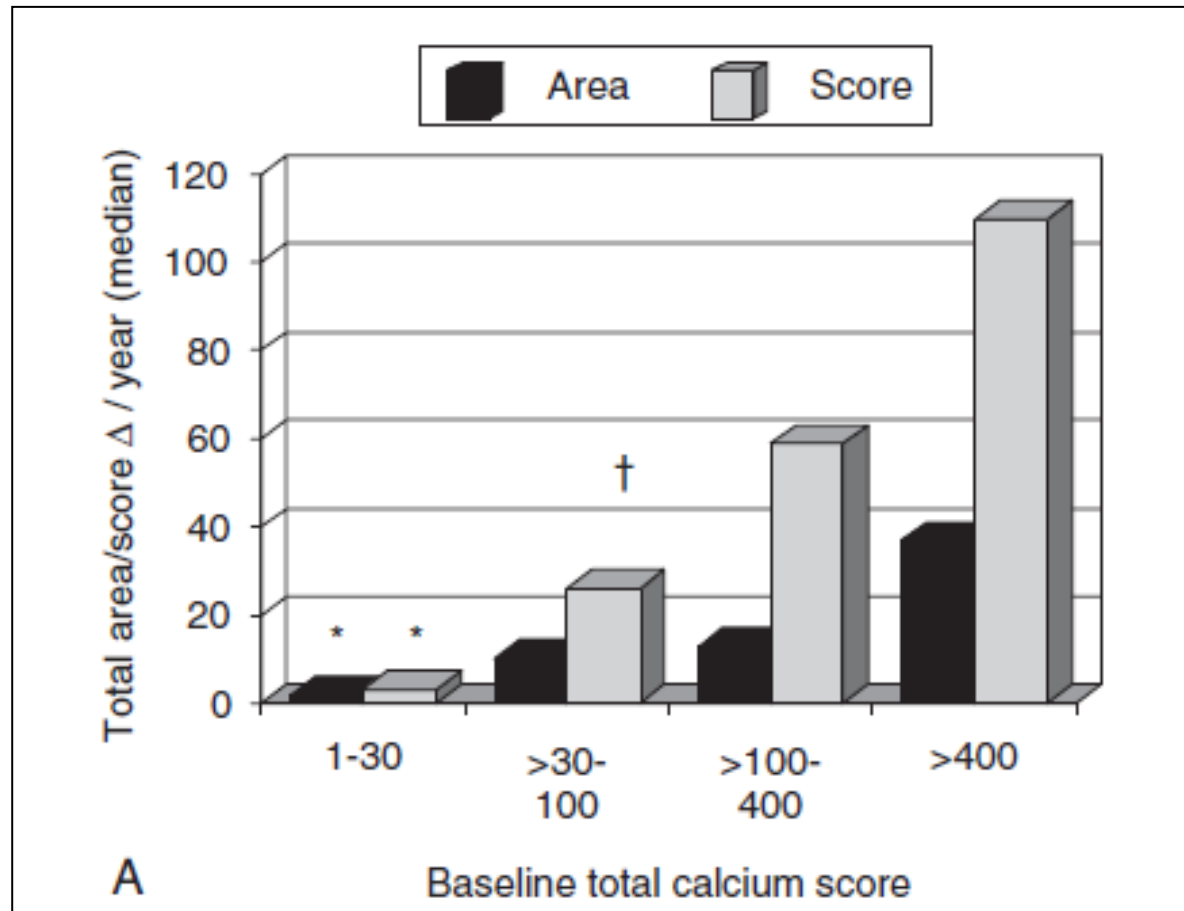
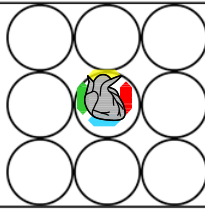
## Progression of coronary artery calcification: risk and risk factors



What is the change of CAC per year?

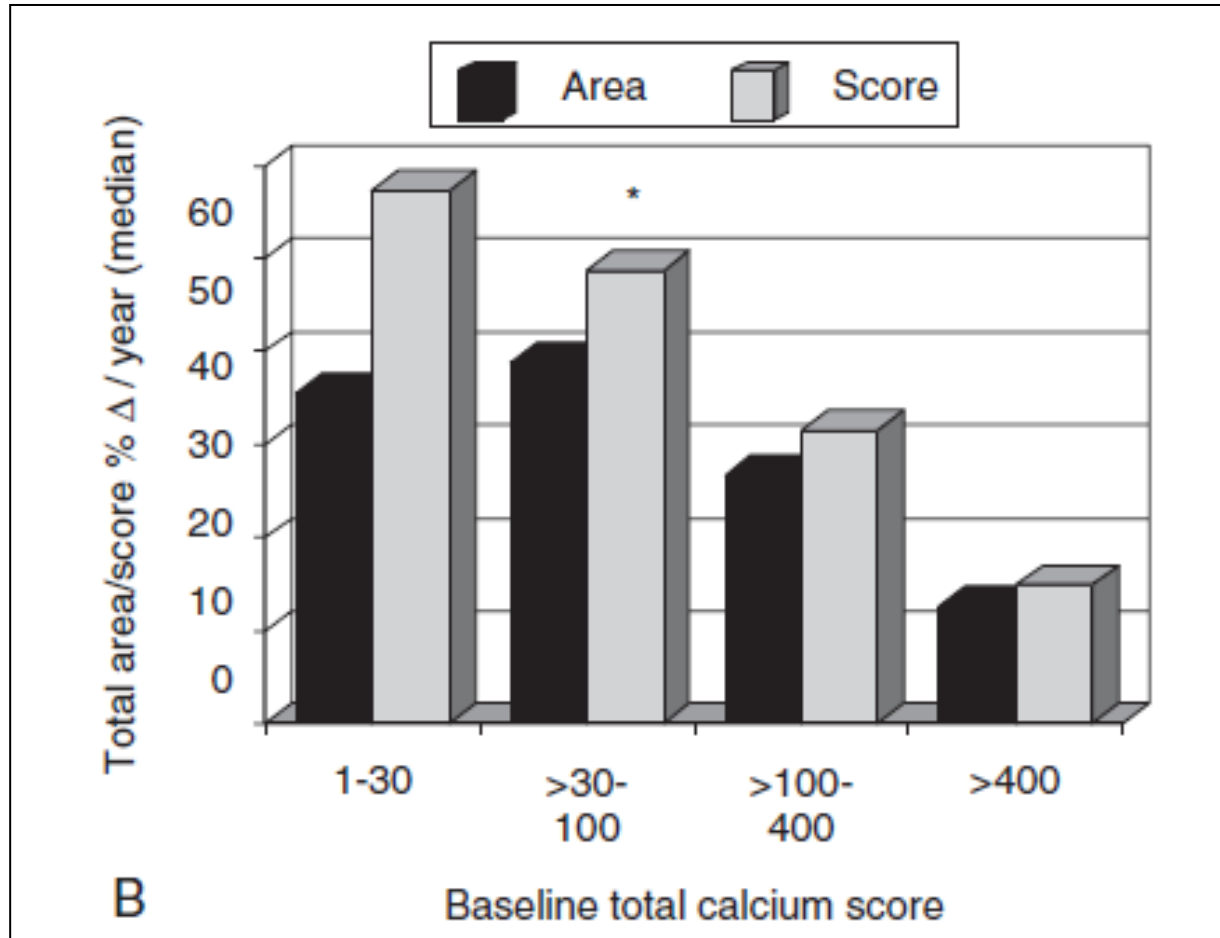
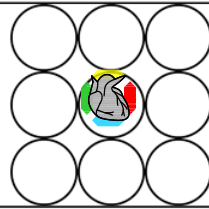
# Prevention and Coronary Artery Disease

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



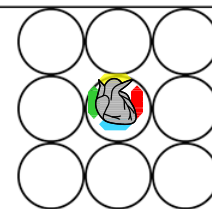
# Prevention and Coronary Artery Disease

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

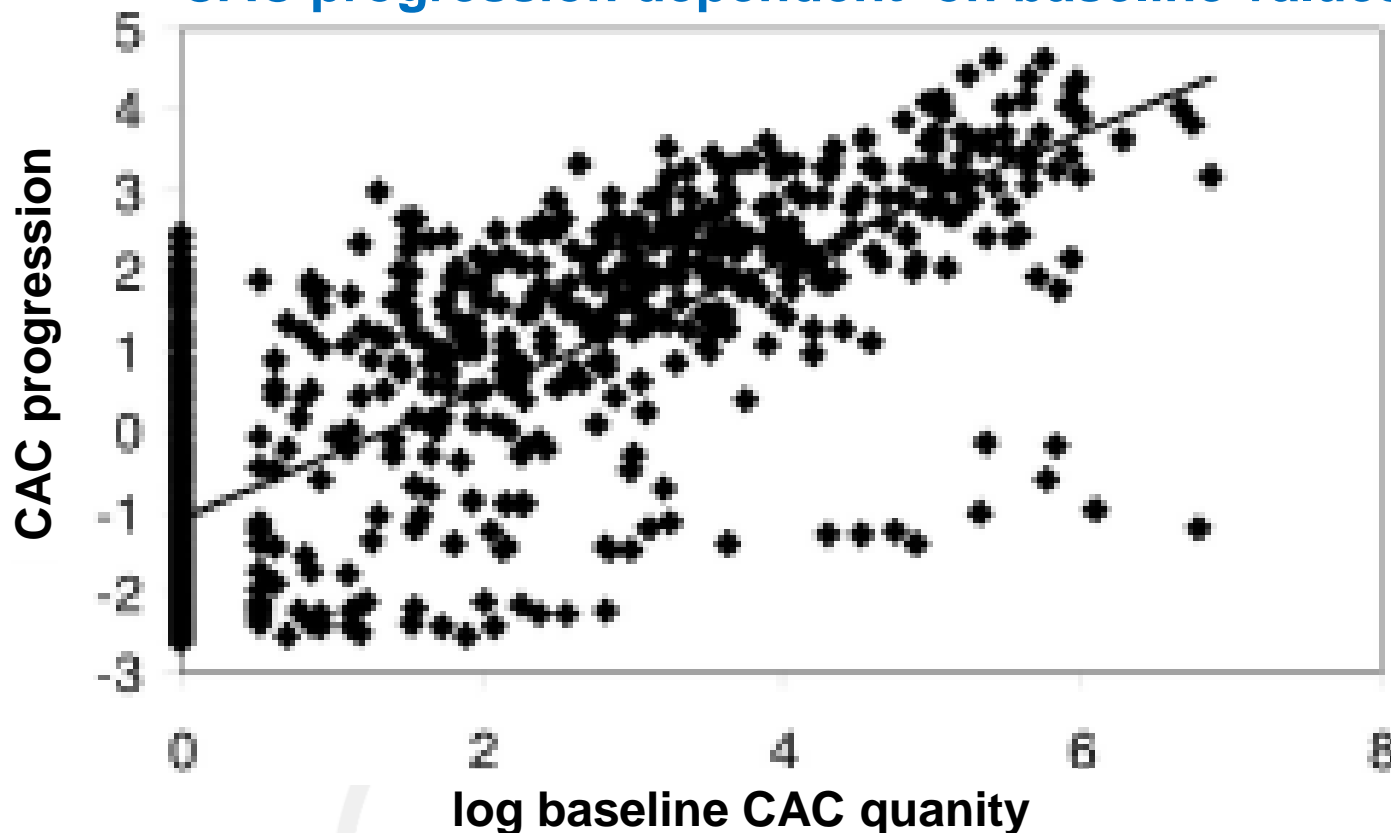


# Prevention and Coronary Artery Disease

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



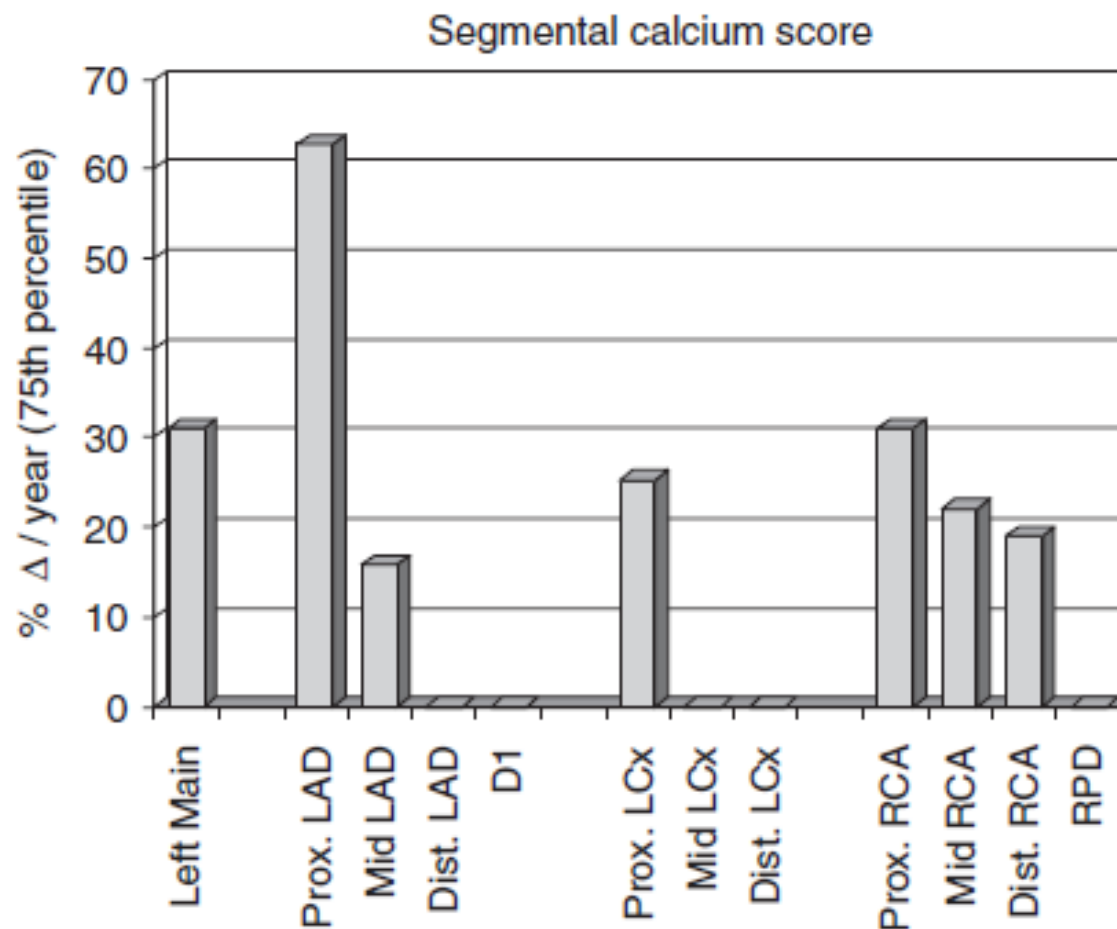
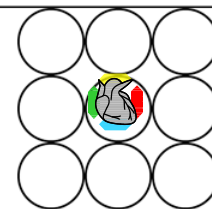
### CAC progression dependent on baseline values



$\text{CAC progression} = -1.080 + 79 \times (\text{log baseline CAC quantity})$   $P < 0.0001$ ,  $R^2 = 0.57$ .

# Prevention and Coronary Artery Disease

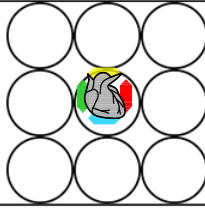
## Progression of coronary artery calcification: risk and risk factors





# Prevention and Coronary Artery Disease

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

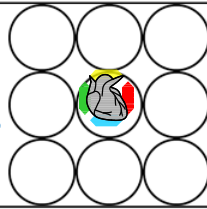


But what is the mean change of CAC per year?

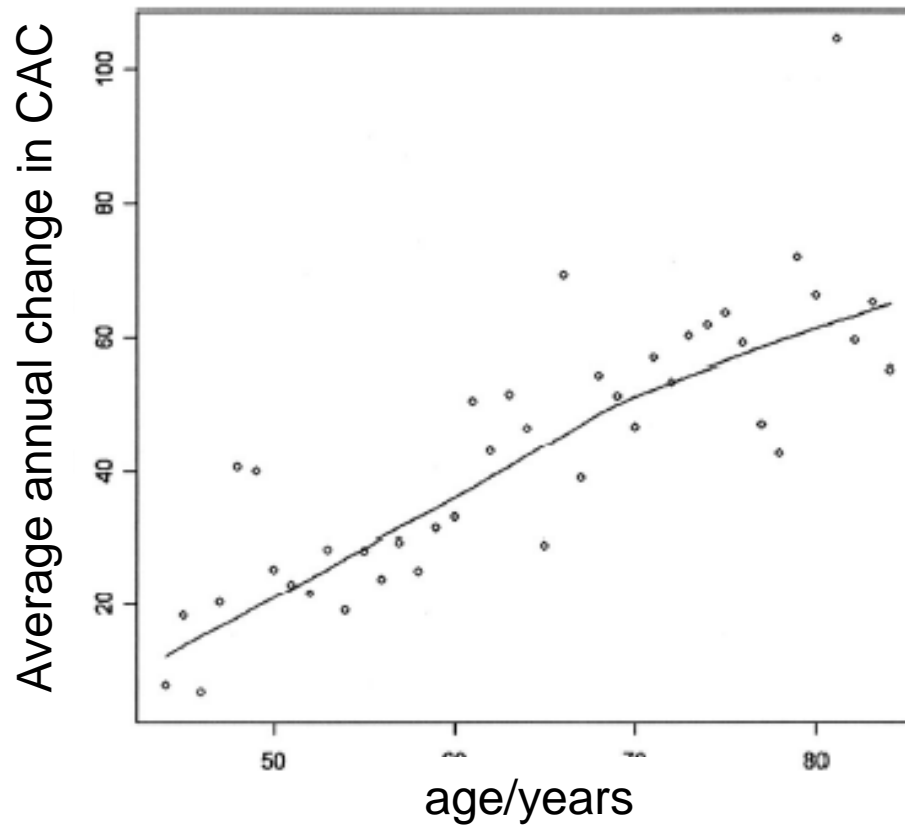
# Prevention and Coronary Artery Disease

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

### MESA Results



5756 participants average of 2.4 years



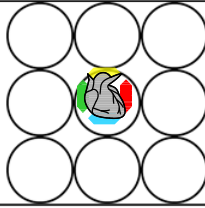
Median annual  
CAC change

21 CAC score in M

14 CAC score in F

# Prevention and Coronary Artery Disease

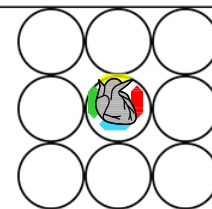
## Progression of coronary artery calcification: risk and risk factors



But what is the mean change for those  
with zero calcification?

# Prevention and Coronary Artery Disease

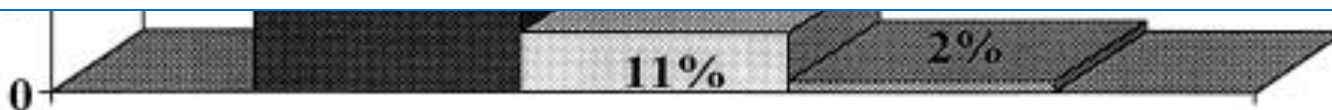
## Progression of coronary artery calcification: risk and risk factors



100  
80



**during FU no CAC > 100**

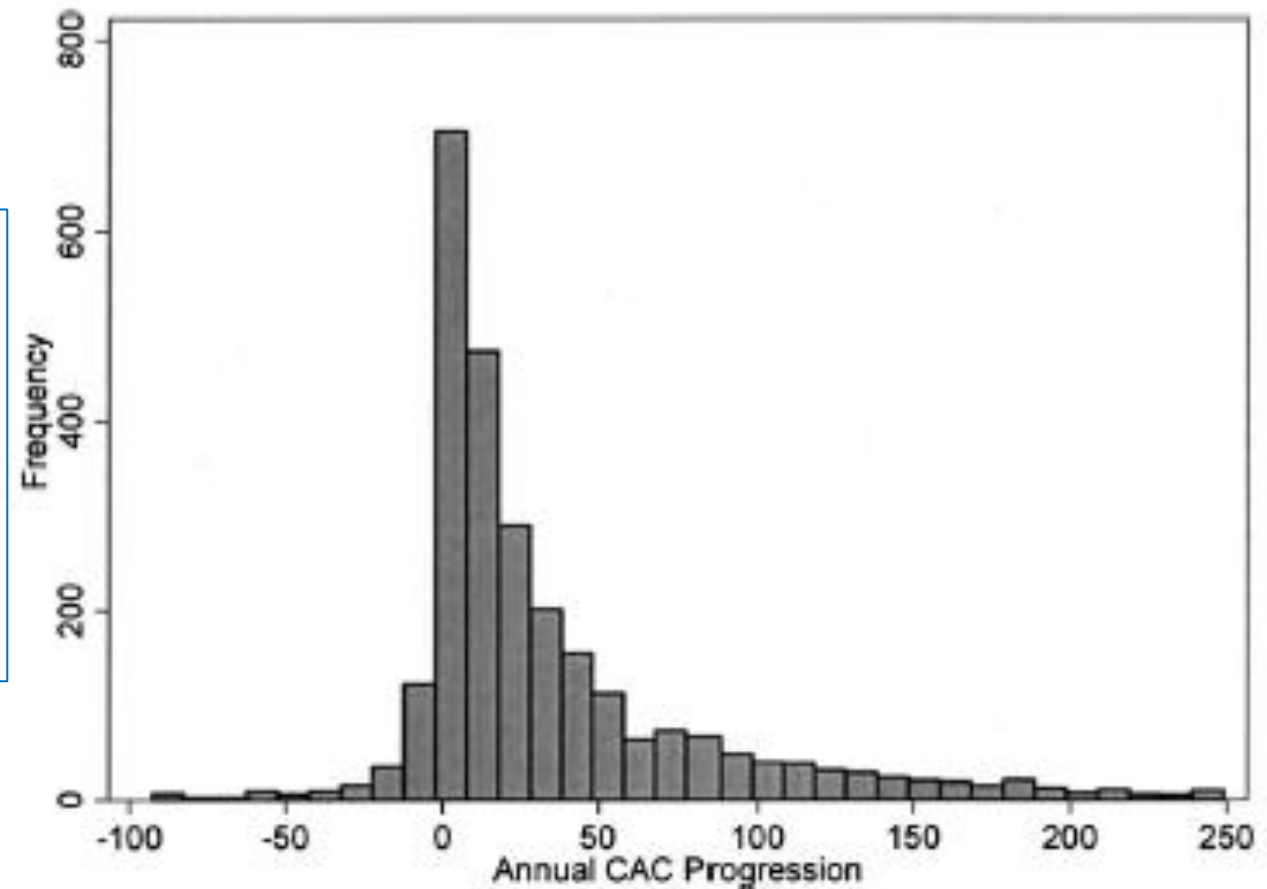
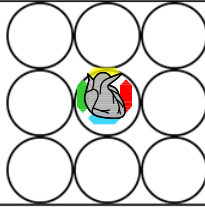


**Follow-Up Scores (1-6 year follow-up)**  
**Zero (n = 70) 1-9 (n = 9) >10 (n=2)**

# Prevention and Coronary Artery Disease

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

### - Effect of age on incidence of new CAC -

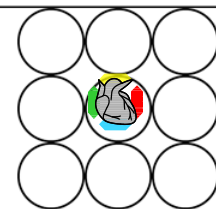


incidence  
new CAC  
averaged  
6.6% per year.

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

# Prevention and Coronary Artery Disease

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

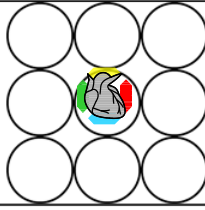


Zero CAC means very low risk, but zero CAC does not mean zero for ever!

- 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

# Prevention and Coronary Artery Disease

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

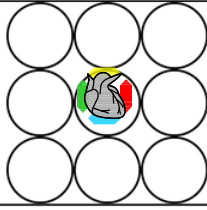


What about changes in CAC in relation to other organs?

# Prevention and Coronary Artery Disease

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

- Progression in association with disease at different organs -



### Prospective Army Coronary Calcium (PACC) Project

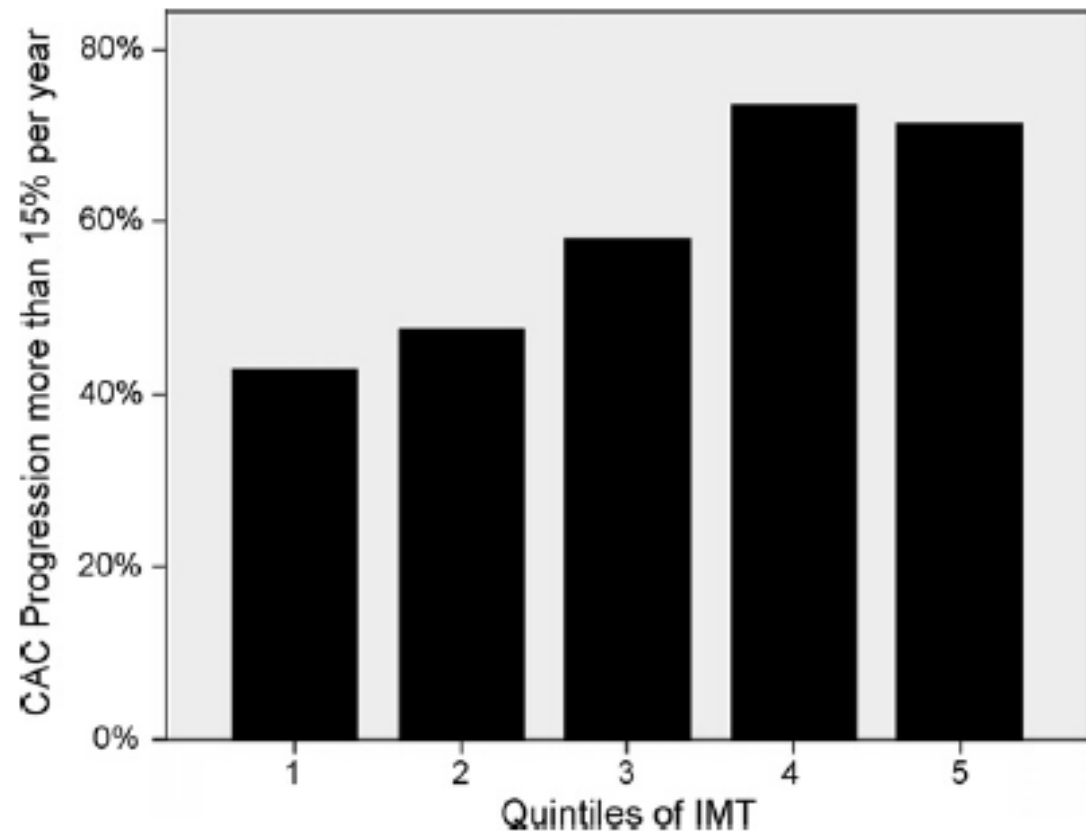
**n= 180**

**40 – 50 years M/F**

**1. CAC:  $101 \pm 259$**

**2. CAC:  $178 \pm 417$**

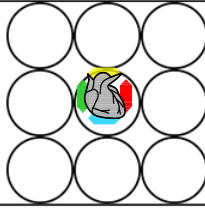
**FU  $4.2 \pm 1.3$  years**  
**Range 1.5–6.6 years**





# Prevention and Coronary Artery Disease

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

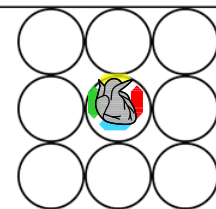


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# Prevention and Coronary Artery Disease

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



CARDIA Study

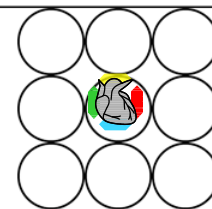
Coronary Artery Risk Development in Young Adults

2.831 subjects, 33-45 year old adults

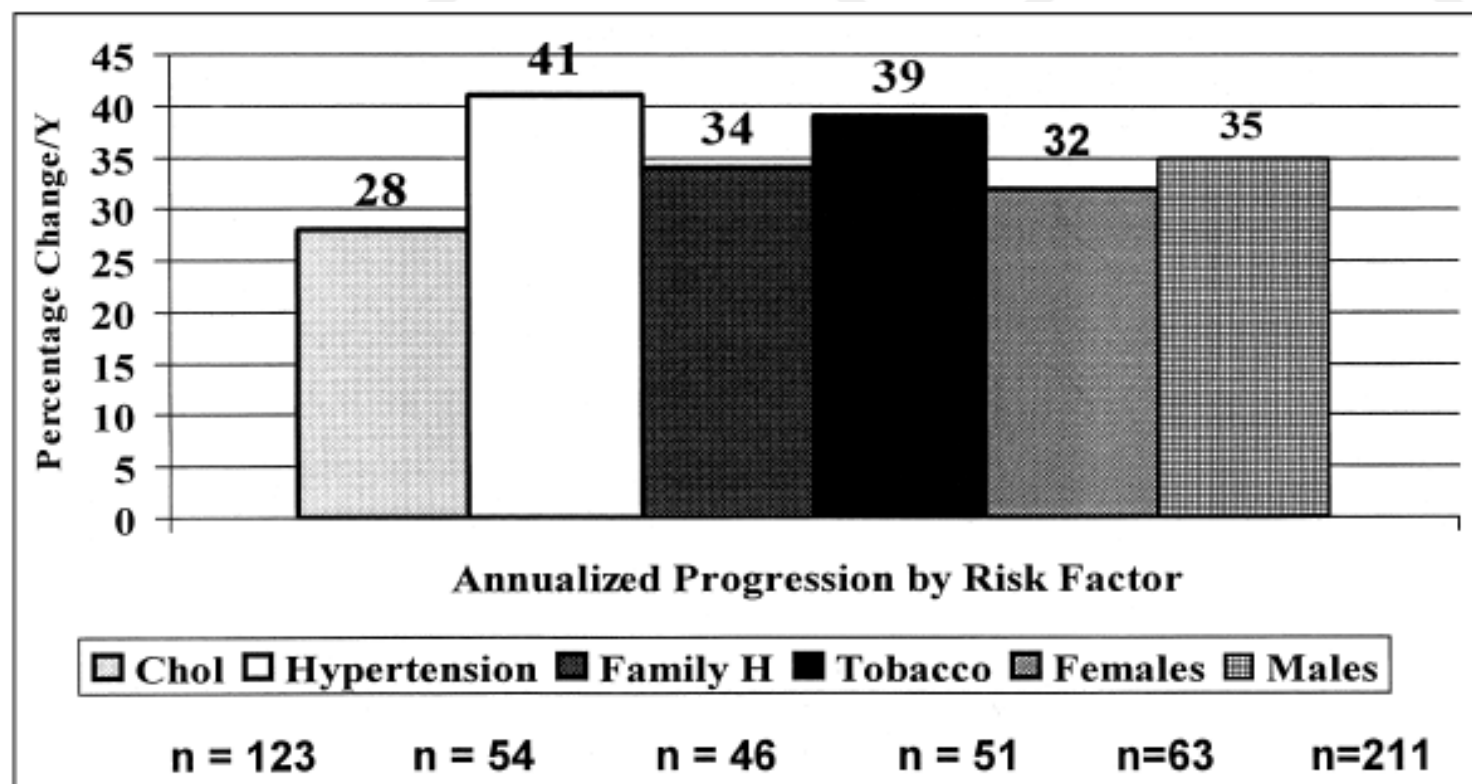
| FRS     | 0 – 2.5% | 2.6 – 5.0% | 5.1 – 10% | > 10% |
|---------|----------|------------|-----------|-------|
| CAC> 0  | 7.3%     | 20.2%      | 19.1%     | 44.8% |
| CAC>100 | 1.3 %    | 2.4%       | 2.4%      | 17.2% |

# Prevention and Coronary Artery Disease

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



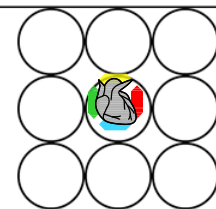
299 asymptomatic pts (227M/72F), 2 EBTs  $\geq 1$  year, range 1 – 6 years



# Prevention and Coronary Artery Disease

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

### MESA Study

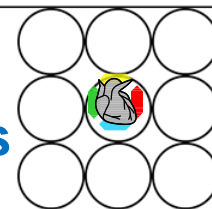


#### Risk factors for incidental and progression of CAC

|                                |                     |
|--------------------------------|---------------------|
| Treated diabetes mellitus      | 26.8 (19.5 to 34.2) |
| Male gender                    | 10.9 ( 6.3 to 15.5) |
| Lipid lowering medication      | 9.8 ( 4.2 to 15.4)  |
| Family history of heart attack | 9.0 ( 4.4 to 13.6)  |
| Age (10 y)                     | 8.8 ( 6.4 to 11.2)  |
| Antihypertensive medication    | 8.0 ( 3.3 to 12.8)  |
| Systolic BP                    | 1.9 ( 0.8 to 3.1)   |
| Smoking >10 pack years         | 1.4 ( 0.2 to 2.6)   |
| Body mass index                | 0.9 (0.4 to 1.3)    |

# Prevention and Coronary Artery Disease

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



**Risk Factor:  
Diabetes mellitus**

**FU time**

**56 ± 11 months**

Baseline demographics at the time of the initial computed tomographic scan

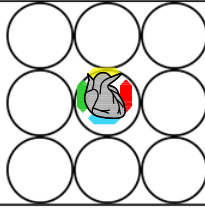
| Variable                                     | Matched<br>Controls <sup>†</sup><br>(n = 300) | Patients<br>With DM<br>(n = 296) | p<br>Value |
|----------------------------------------------|-----------------------------------------------|----------------------------------|------------|
| Age (yrs)                                    | 59 ± 6                                        | 59 ± 6                           | —          |
| Women                                        | 29% (87)                                      | 29% (86)                         | —          |
| Baseline CAC score                           | 276 ± 41                                      | 291 ± 49                         | 0.9        |
| Statin therapy                               | 50% (150)                                     | 55% (163)                        | 0.8        |
| Hypertension                                 | 26% (78)                                      | 68% (201)                        | 0.03       |
| Family history of premature CAD <sup>§</sup> | 50% (150)                                     | 40% (118)                        | 0.7        |
| Current tobacco smokers                      | 16% (48)                                      | 19% (56)                         | 0.6        |
| Absolute annual CAC score change             | 34.3 ± 4.8                                    | 80.6 ± 10                        | 0.0001     |
| ΔCAC%*                                       | 10.2 ± 6.7                                    | 29.4 ± 8.7                       | 0.0001     |
| CAC progressors <sup>†</sup>                 | 33.6% (101)                                   | 62.5% (185)                      | 0.0001     |

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

# Prevention and Coronary Artery Disease

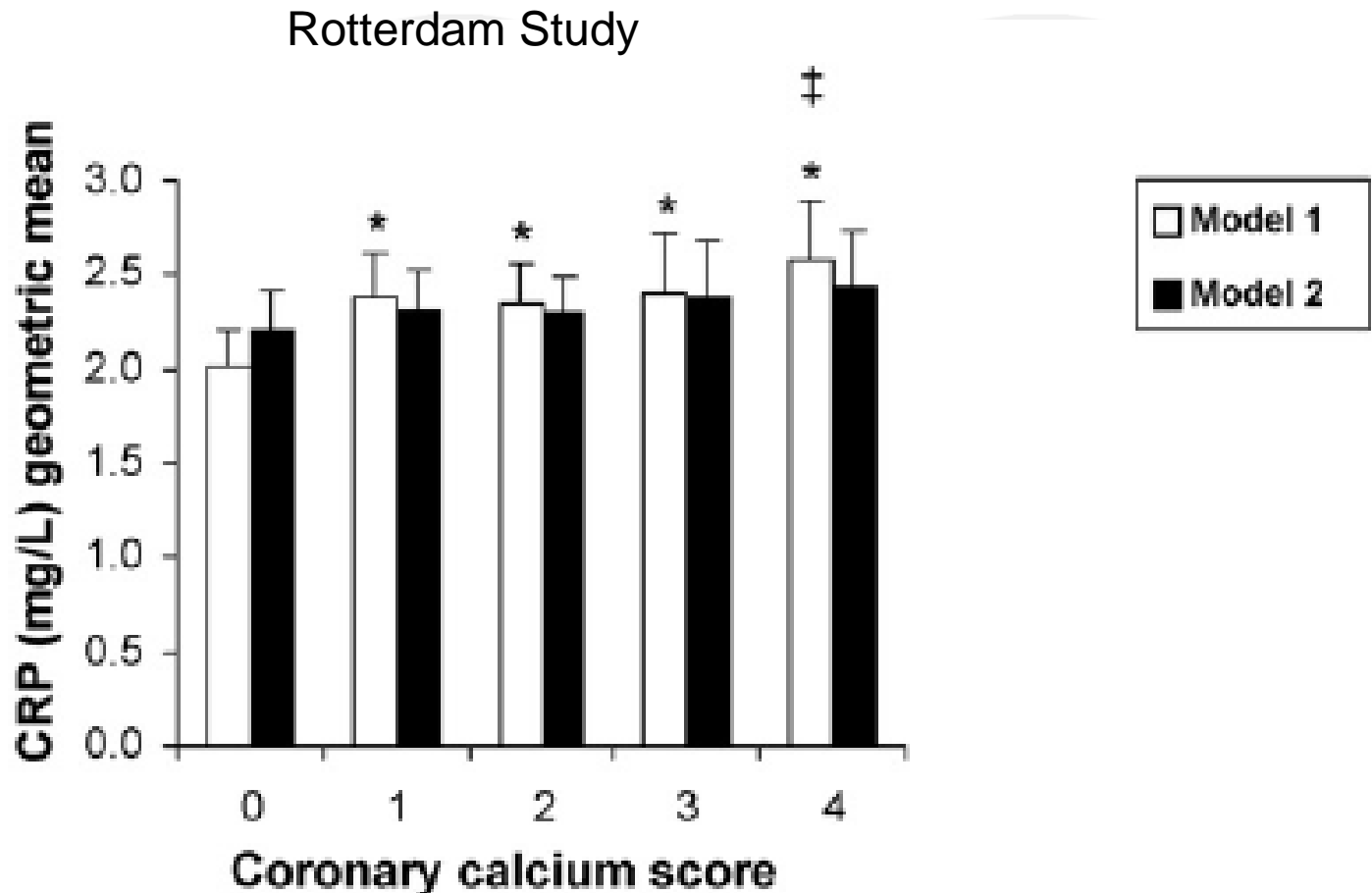
## Progression of coronary artery calcification: risk and risk factors

### Risk Factor: Inflammation



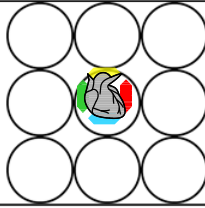
hs-CRP

n= 1962



# Prevention and Coronary Artery Disease

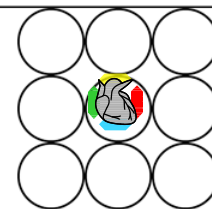
## Progression of coronary artery calcification: risk and risk factors



Risk Factors of CAC Progression  
from Zero to  $CAC > 0$

# Prevention and Coronary Artery Disease

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



Follow up time 27 years

**Table 2**

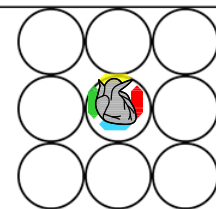
**ORs and 95% CIs for CAC in Adulthood  
in a Multivariable Logistic Regression Model  
(N = 563) Adjusted for All of the Listed Variables**

|                         | OR   | 95% CI    | p Value |
|-------------------------|------|-----------|---------|
| Age                     | 1.09 | 0.99–1.20 | 0.09    |
| Male                    | 2.52 | 1.56–4.05 | 0.0001  |
| Adolescence LDL-C       | 1.34 | 1.05–1.70 | 0.02    |
| Adolescence systolic BP | 1.38 | 1.08–1.77 | 0.01    |
| $\Delta$ LDL-C          | 1.07 | 0.84–1.37 | 0.58    |
| $\Delta$ Systolic BP    | 1.25 | 0.98–1.60 | 0.08    |



# Prevention and Coronary Artery Disease

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

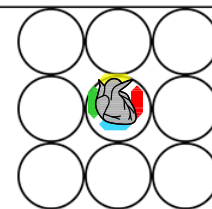


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# Prevention and Coronary Artery Disease

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



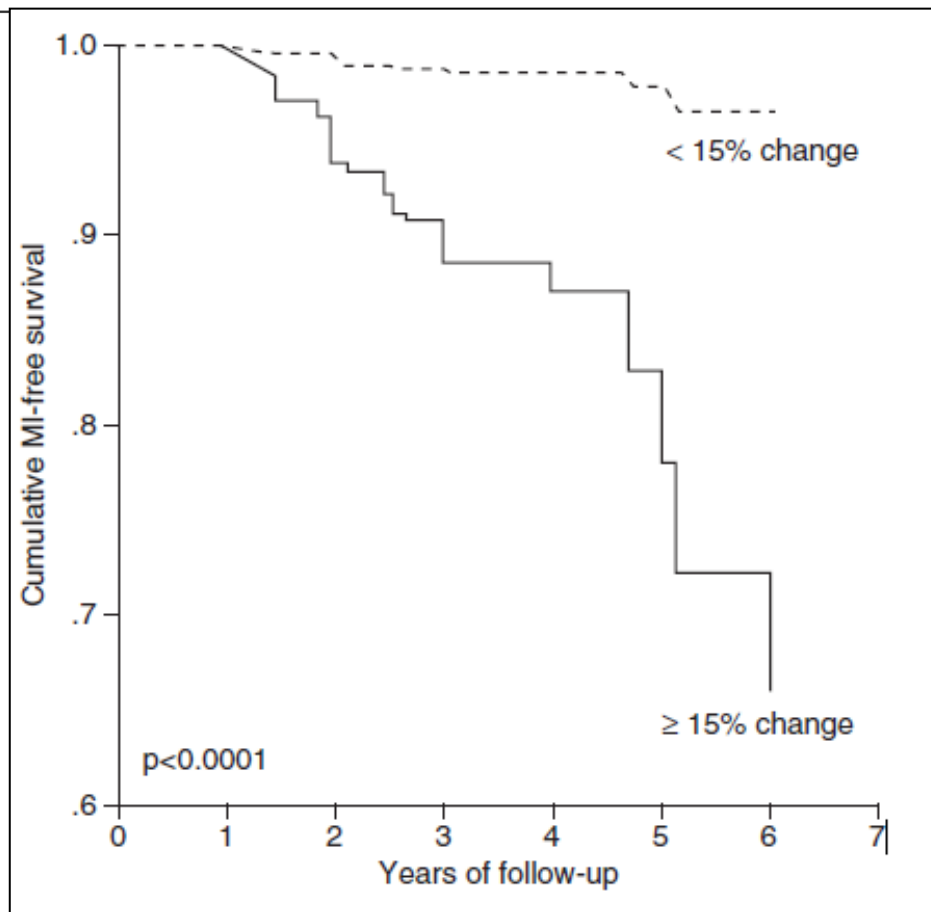
495 pts

2 scans within

$1.9 \pm 1$  year

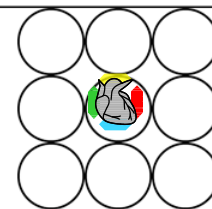
all on

statin therapy



# Prevention and Coronary Artery Disease

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



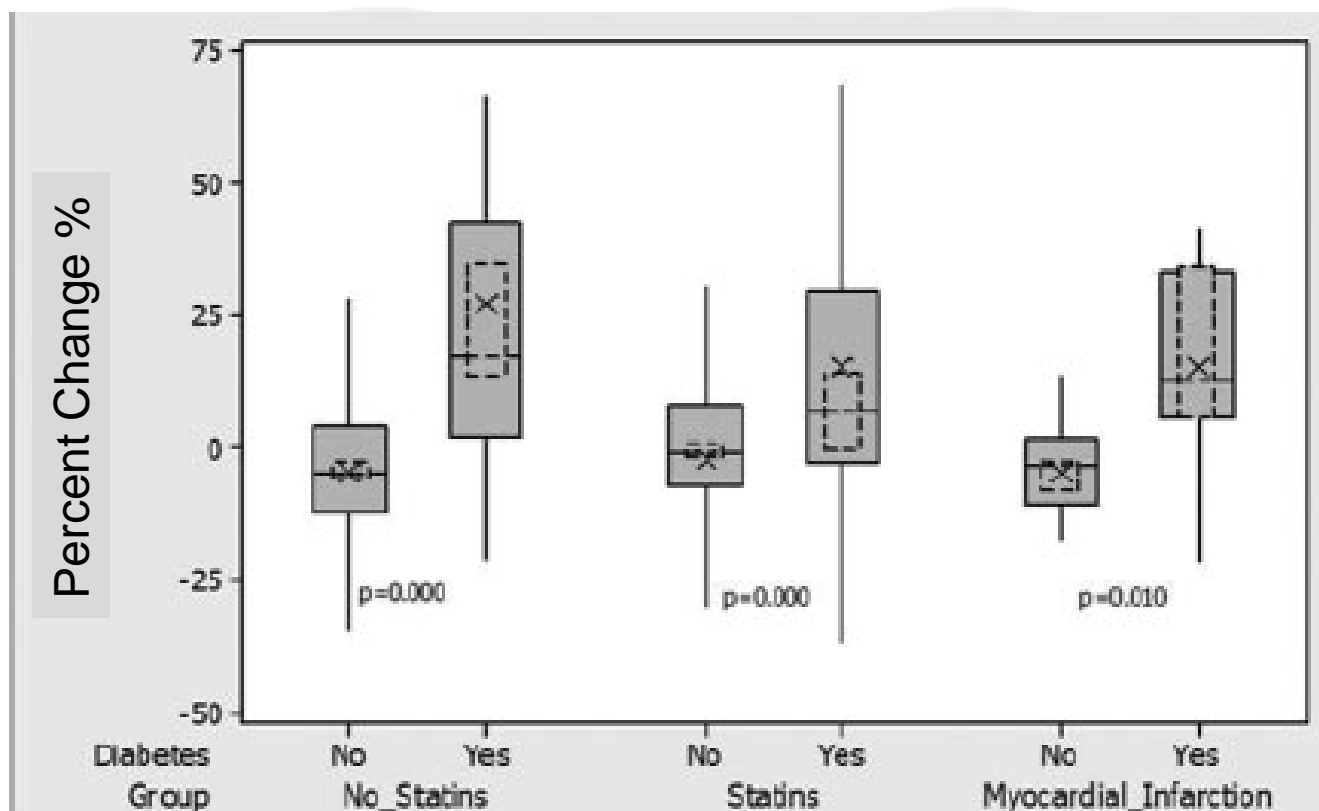
1153 pts

157 DM

2 scans >1 year

CAC >15 %/year

true progression

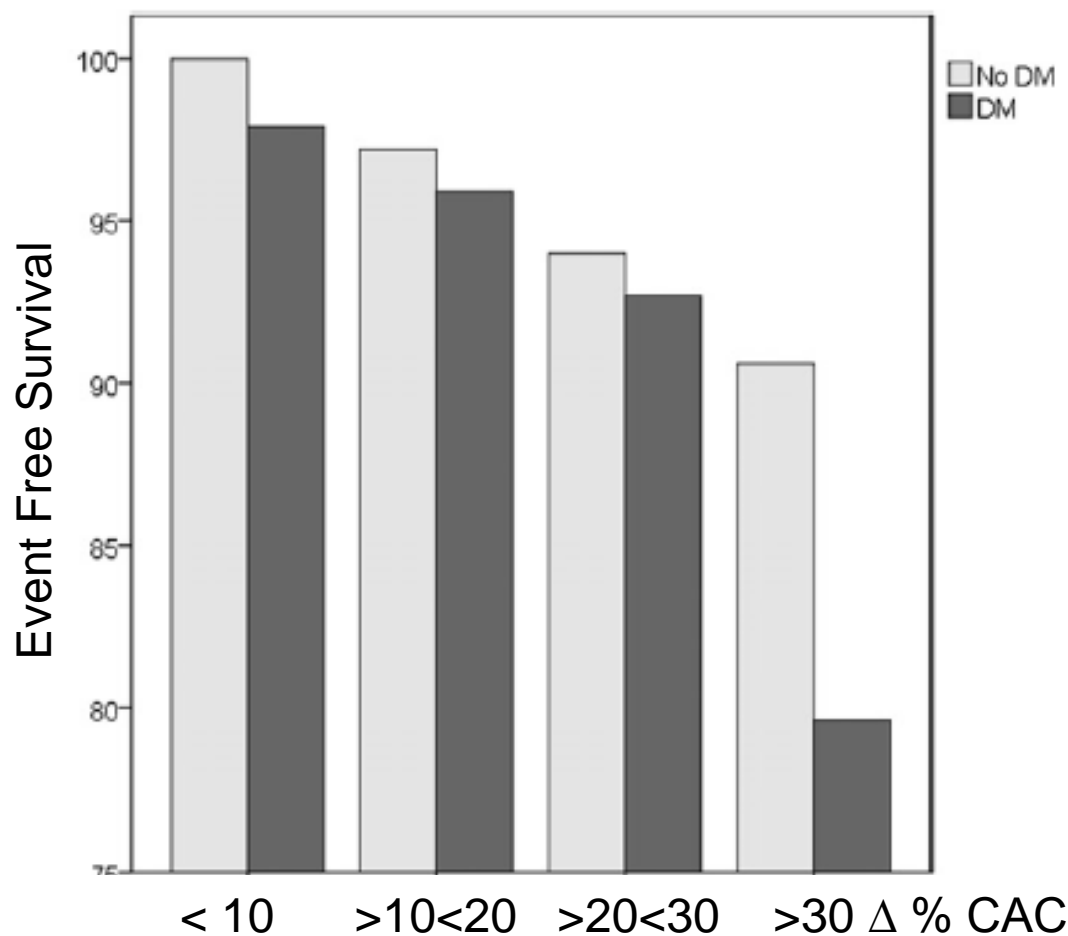
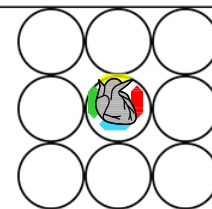


Raggi et al.

Hypertension 46:238-243, 2005

# Prevention and Coronary Artery Disease

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

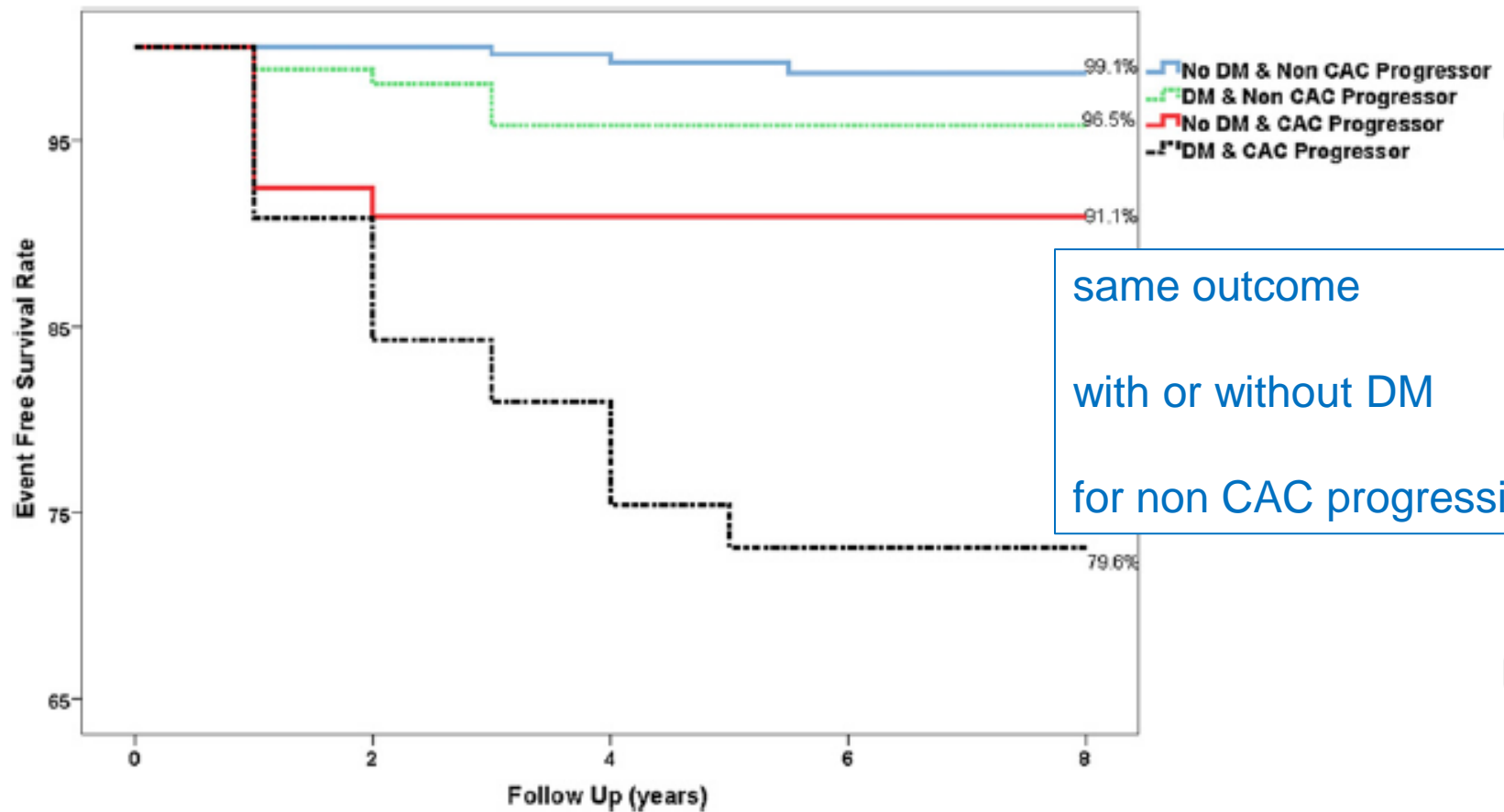
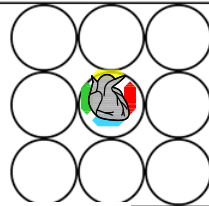


Kiramijyan S et al

AJC 2012, in press

# Prevention and Coronary Artery Disease

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



same outcome

with or without DM

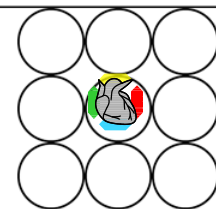
for non CAC progression

Kiramijyan S et al

AJC 2012, in press

# Prevention and Coronary Artery Disease

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

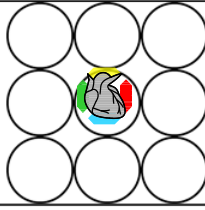


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# Prevention and Coronary Artery Disease

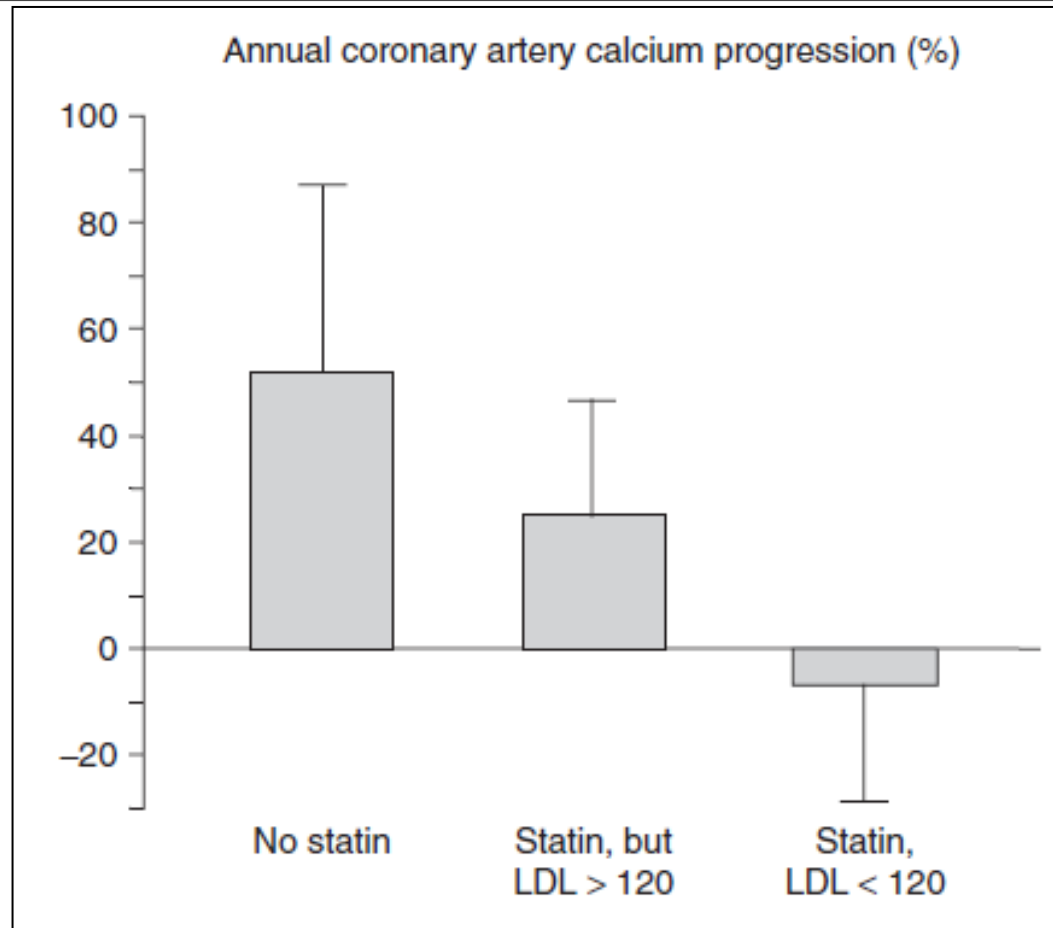
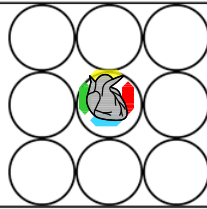
## Progression of coronary artery calcification: risk and risk factors



Pharmacological Interventions  
for treatment of CAC  
- statins -

# Prevention and Coronary Artery Disease

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



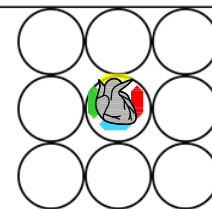
Callister TQ et al.

New Engl J Med 339: 1972–78, 1998



# 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**

|                                   | Treatment  | Control    | p Value |
|-----------------------------------|------------|------------|---------|
|                                   | 490        | 515        |         |
|                                   | 528        | 563        | —       |
|                                   | 379        | 370        | 0.96    |
| th percentiles                    | 184, 636   | 183, 671   | —       |
|                                   | 417        | 431        | —       |
|                                   | 647        | 723        | —       |
|                                   | 482        | 505        | —       |
| th percentiles                    | 231, 820   | 251, 901   |         |
| Change (year two minus baseline)  |            |            |         |
| Absolute                          | 137 ± 310  | 155 ± 358  | 0.86    |
| Percent                           | 38 ± 75    | 36 ± 58    | 0.86    |
| Year four                         |            |            |         |
| n                                 | 281        | 288        |         |
| Mean                              | 846        | 922        | —       |
| Median                            | 623        | 673        | —       |
| 25th, 75th percentiles            | 335, 1,077 | 343, 1,138 | —       |
| Change (year four minus baseline) |            |            |         |
| Absolute                          | 331 ± 421  | 323 ± 385  | 0.80    |
| Percent                           | 81 ± 89    | 73 ± 93    | 0.76    |

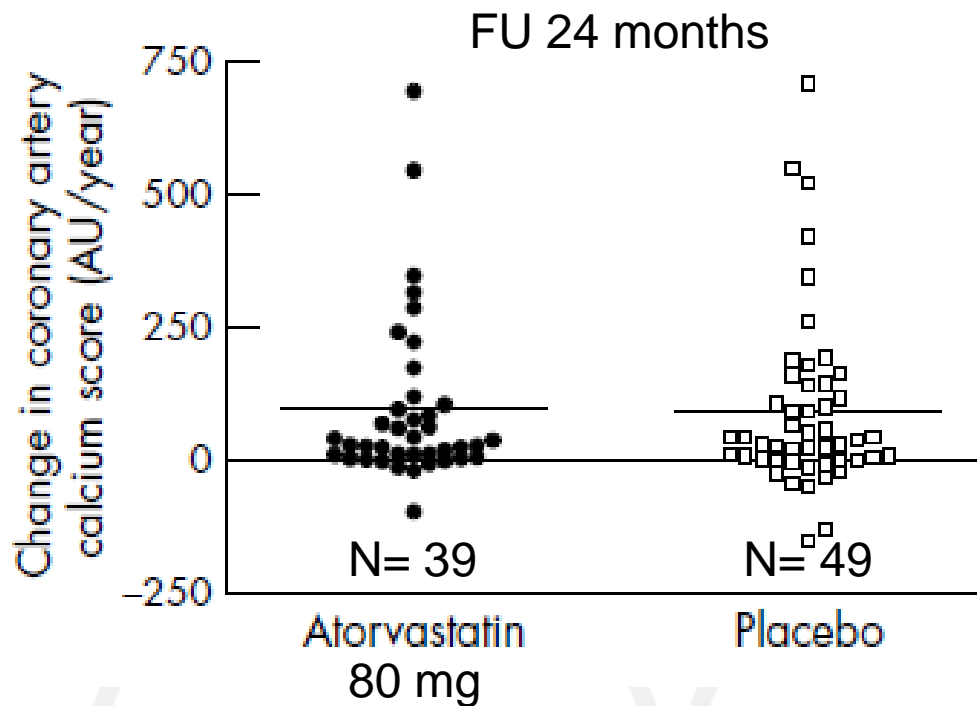
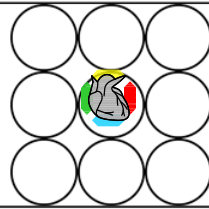
Because baseline calcium scores were not normally distributed, p values are based on the distribution of calcium scores (median, interquartile range [Wilcoxon rank sum test]), rather than mean values. Change in calcium scores was normally distributed and the p value is based on comparison of the mean values and their respective variances.

Arad Y et al

J Am Coll Cardiol 46:166 –72, 2005

# Prevention and Coronary Artery Disease

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

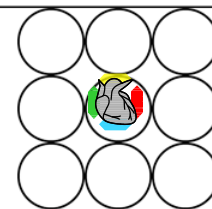


Houslay ES et al

Heart 92:1207–1212, 2006.

# Prevention and Coronary Artery Disease

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



# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



### **Aggressive Versus Moderate Lipid-Lowering Therapy in Hypercholesterolemic Postmenopausal Women: Beyond Endorsed Lipid Lowering With EBT Scanning (BELLES)**

Paolo Raggi, Michael Davidson, Tracy Q. Callister, Francine K. Welty, Gloria A. Bachmann, Harvey Hecht and John A. Rumberger

*Circulation* 2005;112;563-571; originally published online Jul 11, 2005;

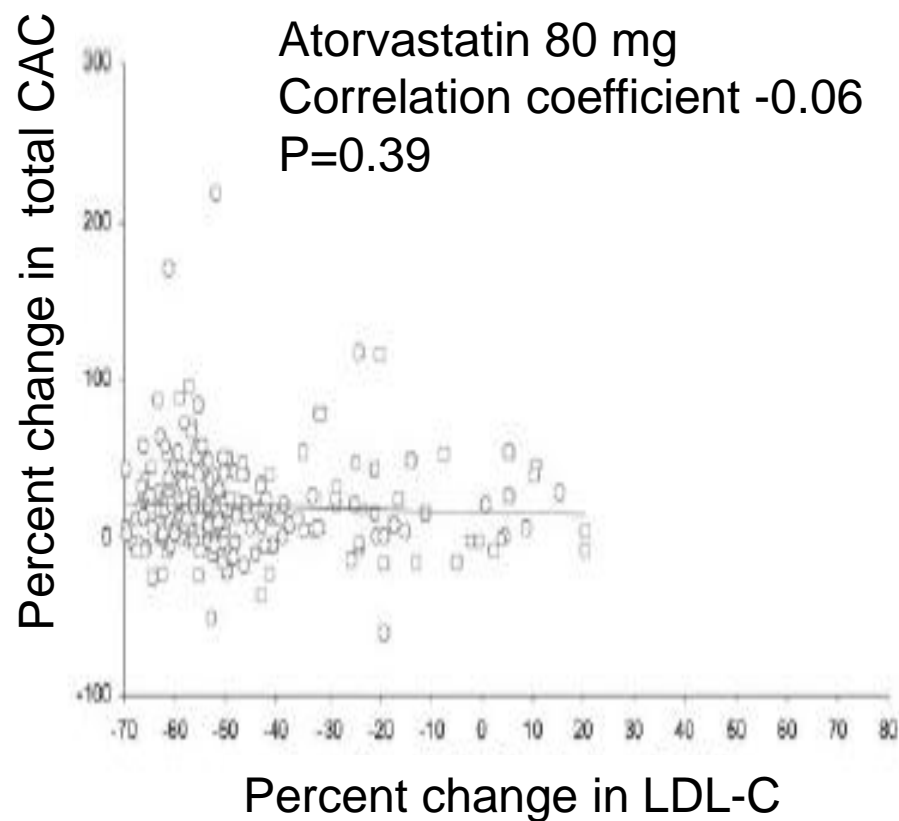
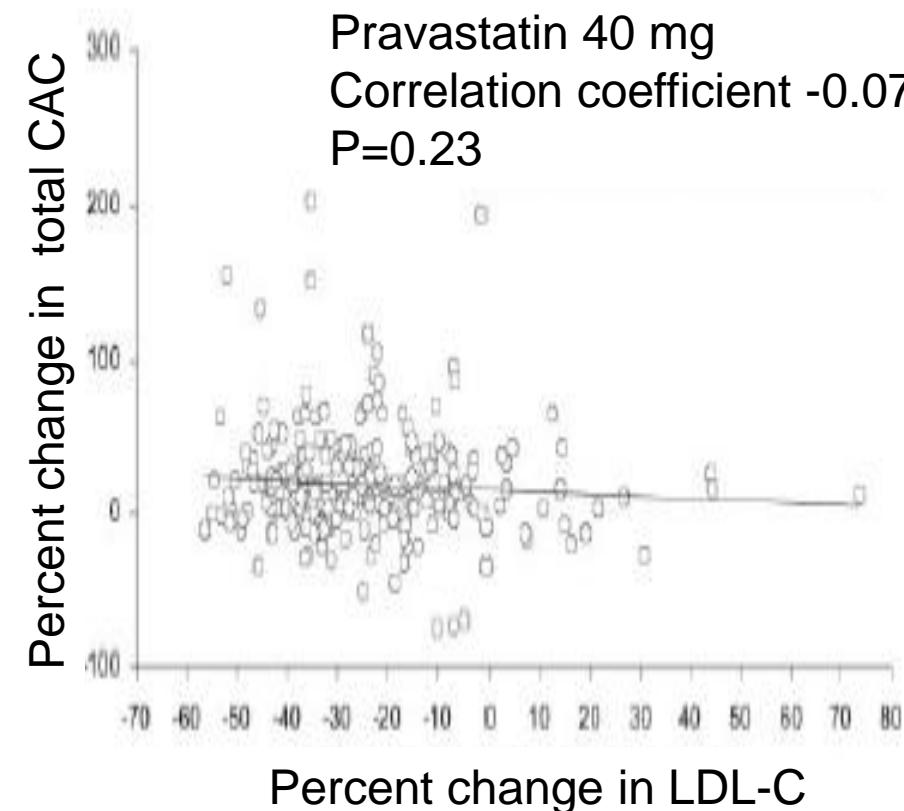
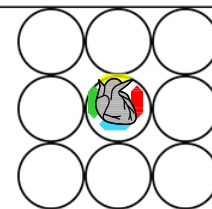
DOI: 10.1161/CIRCULATIONAHA.104.512681

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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# Prevention and Coronary Artery Disease

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

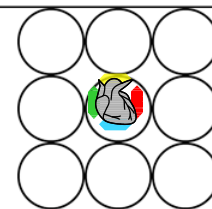


**Raggi P et al**

***Circulation. 112:563-571, 2005***

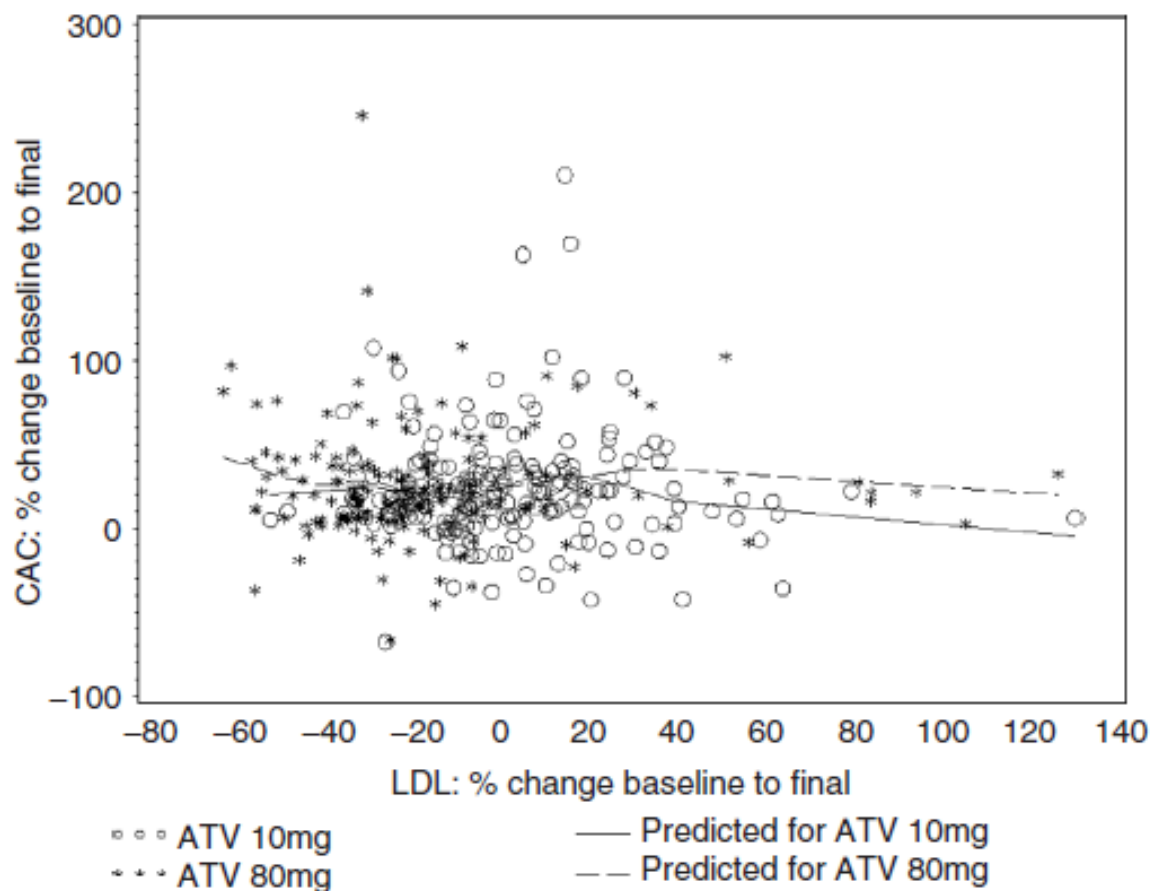
# Prevention and Coronary Artery Disease

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



**Atorvastatin**

**10 mg  
versus  
80 mg**

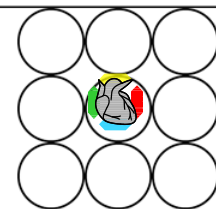


Schmermund A et al

Circulation 113:427–37, 2006

# Prevention and Coronary Artery Disease

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



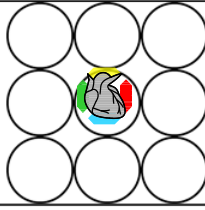
As follow-up studies demonstrate CAC progression in the range of 15 – 25 % per year, the question arises: can we check the efficacy of the risk factor modification by CT?

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

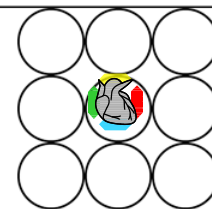
## Progression of coronary artery calcification: risk and risk factors



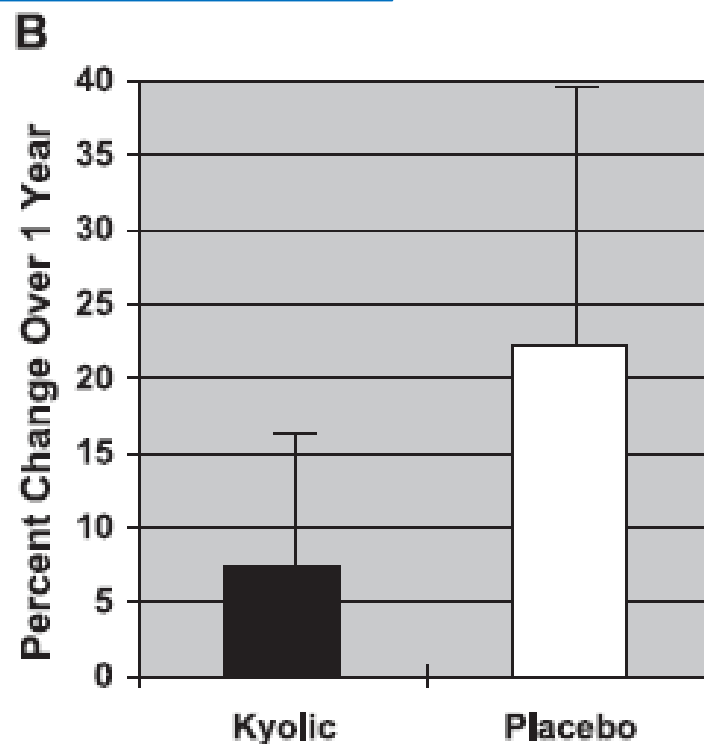
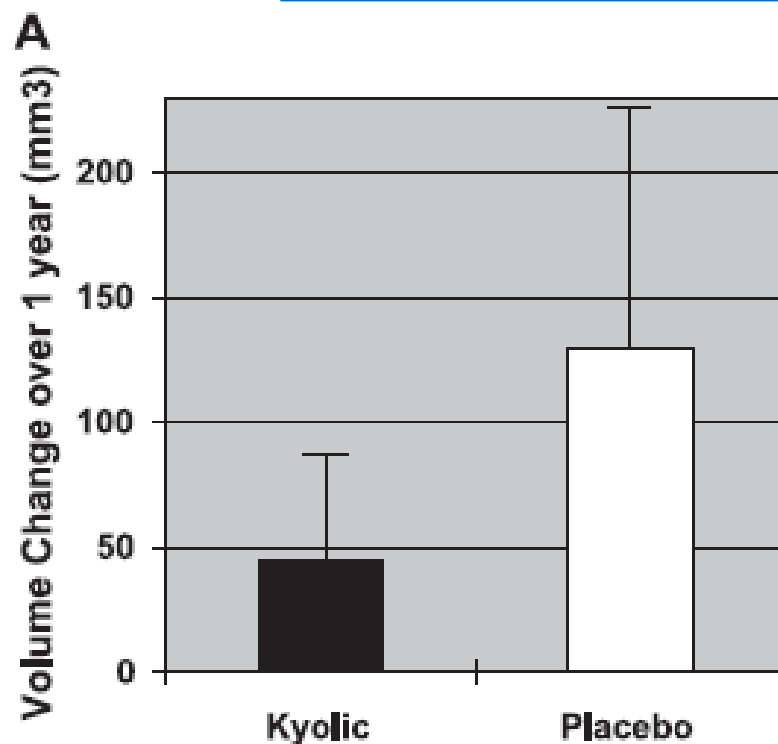
Pharmacological Interventions  
for treatment of CAC  
- other than statins -

# Prevention and Coronary Artery Disease

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



N = 19, 4 ml Aged Garlic Extract for 1 year



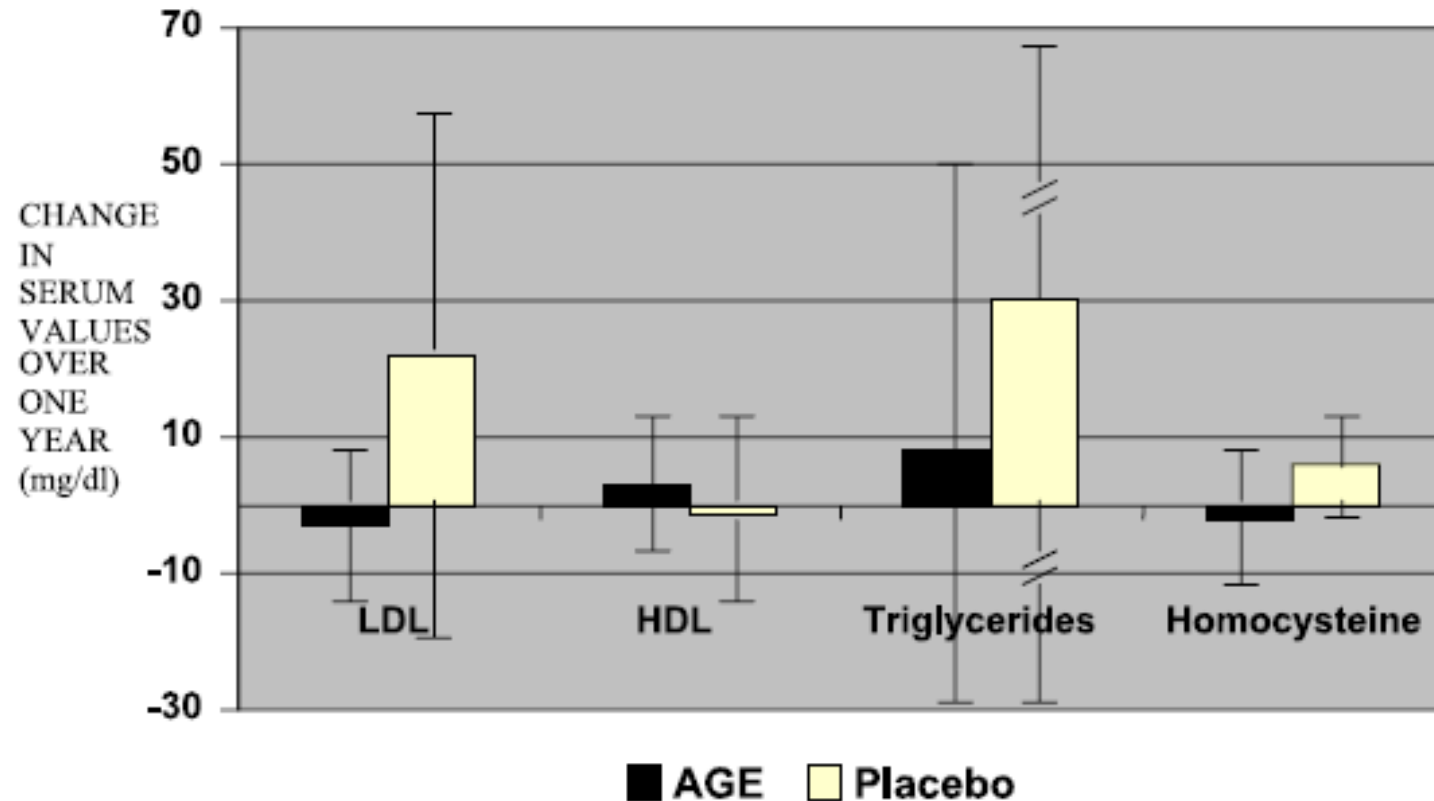
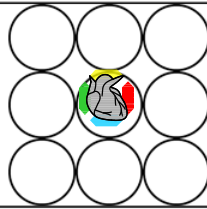
Budoff MJ et al

Preventive Medicine 39, 985–991, 2004



# Prevention and Coronary Artery Disease

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

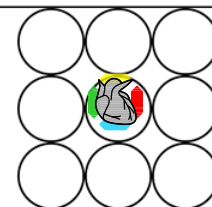


Budoff MJ et al

Preventive Medicine 39, 985–991, 2004

# Prevention and Coronary Artery Disease

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



RCT with 65 firefighters at intermediate risk ( $55 \pm 6$  years)  
1200 mg age garlic extract and 120 mg Q 10 for 1 year

**CAC progression  
annual rate  
 $32 \pm 6$   
vs  
 $58 \pm 8$**

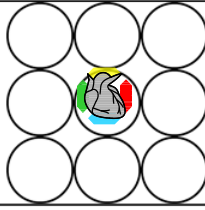
| Variables                                  | AGE +CoQ10       | Placebo         | P value |
|--------------------------------------------|------------------|-----------------|---------|
| <i>Baseline</i>                            |                  |                 |         |
| Age (years)                                | $55 \pm 6$       | $54 \pm 5$      | 0.6     |
| Gender (Male)                              | 100%             | 100%            | -       |
| CAC                                        | $169 \pm 29$     | $211 \pm 49$    | 0.6     |
| hsCRP                                      | $1.9 \pm 2.1$    | $1.9 \pm 2.4$   | 0.9     |
| BMI                                        | $28 \pm 3$       | $29 \pm 4$      | 0.5     |
| <i>Absolute change at 1-year follow-up</i> |                  |                 |         |
| CAC                                        | $32 \pm 6$       | $58 \pm 8$      | 0.01    |
| hsCRP                                      | $-0.12 \pm 0.24$ | $0.91 \pm 0.56$ | 0.01    |
| BMI                                        | $-0.47 \pm 0.82$ | $0.28 \pm 1.27$ | 0.03    |

Zeb I et al

J Cardiovasc Dis Res 3: 185-190, 2012

# Prevention and Coronary Artery Disease

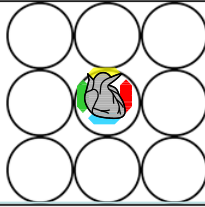
## Progression of coronary artery calcification: risk and risk factors



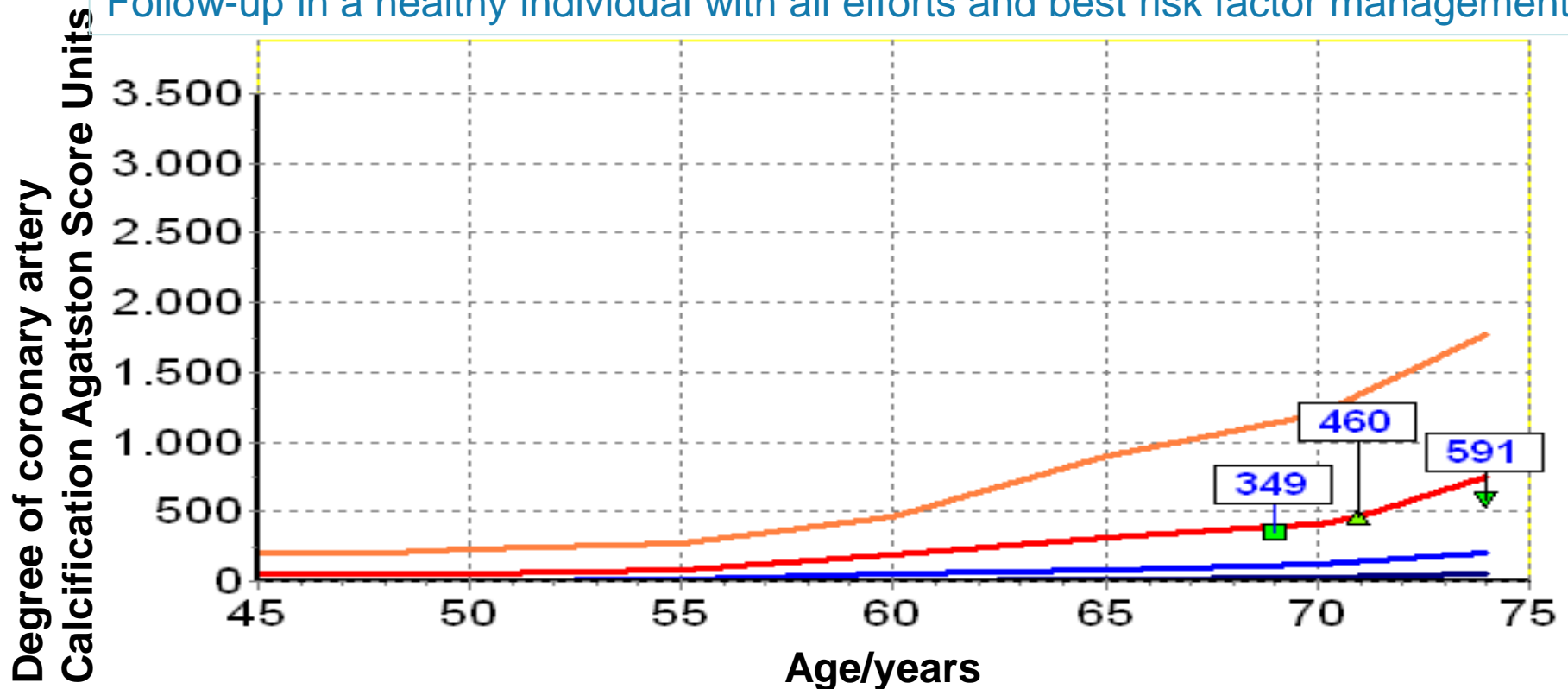
Pharmacological Interventions  
for treatment of CAC  
- optimized RF adjustment-

# 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



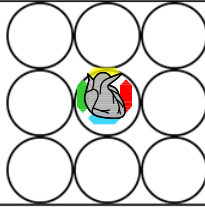
At the age of 71, the score of 460 is above the 67th percentile



At the age of 69, the score of 349 is above the 72nd percentile

# Prevention and Coronary Artery Disease

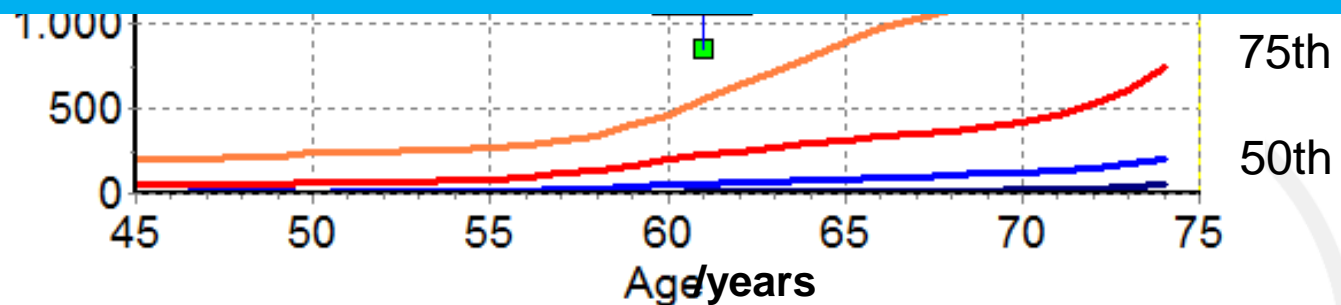
## Progression of coronary artery calcification: risk and risk factors



10-year Follow-up EBCTs in a healthy check-up individual

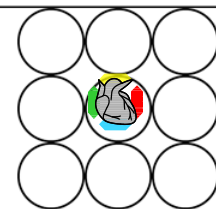
That means:

Once you are on a CAC percentile you will stay,  
increase of CAC over time can be predicted and calculated.



# Prevention and Coronary Artery Disease

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



### Conclusion

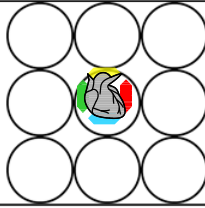
#### Progression of CAC

- 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?



# Prevention and Coronary Artery Disease

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



...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.

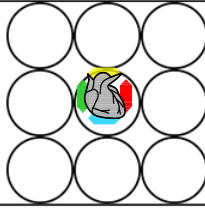
...die Symptomatologie des Atheroms ist sehr gering.  
Es gibt weder ein Mittel das Atheroma der Arterien sicher  
im Leben zu erkennen, noch, wenn es erkannt sein sollte,  
dasselbe rückgängig zu machen“

Lobstein. Stuttgart, 1835, Bd II 465 u folg.



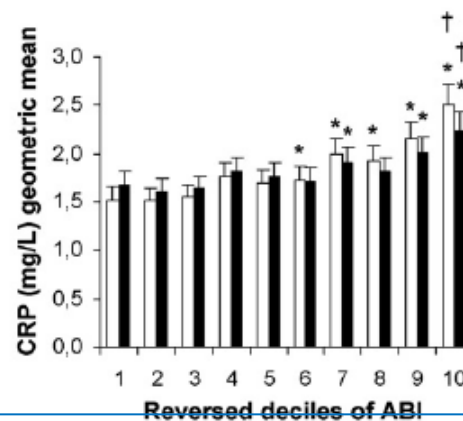
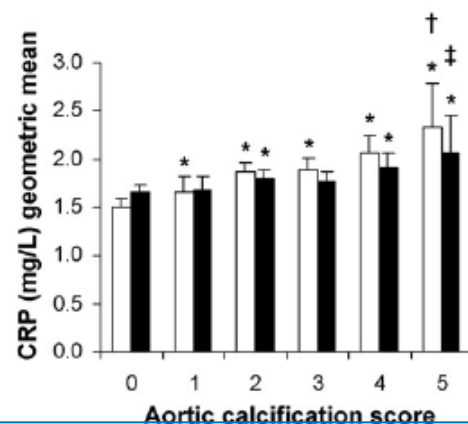
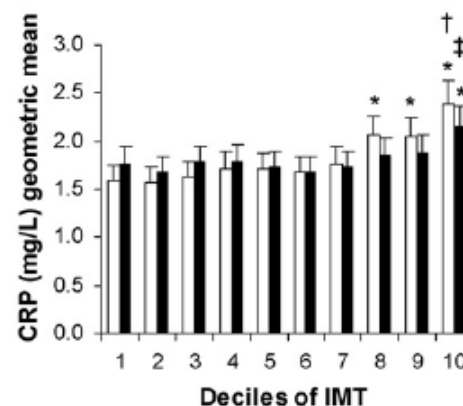
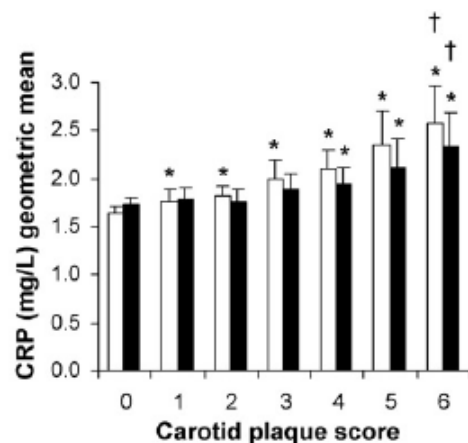
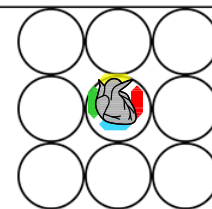
# Prevention and Coronary Artery Disease

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



# Prevention and Coronary Artery Disease

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

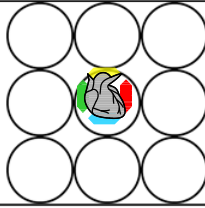


Elias-Smale SE et al. /

Atherosclerosis 195, e195–e202, 2007

# Prevention and Coronary Artery Disease

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



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

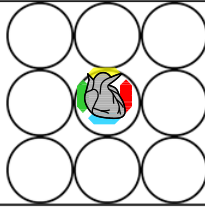
Editorial

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.

# Prevention and Coronary Artery Disease

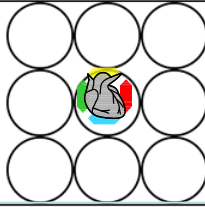
## Progression of coronary artery calcification: risk and risk factors



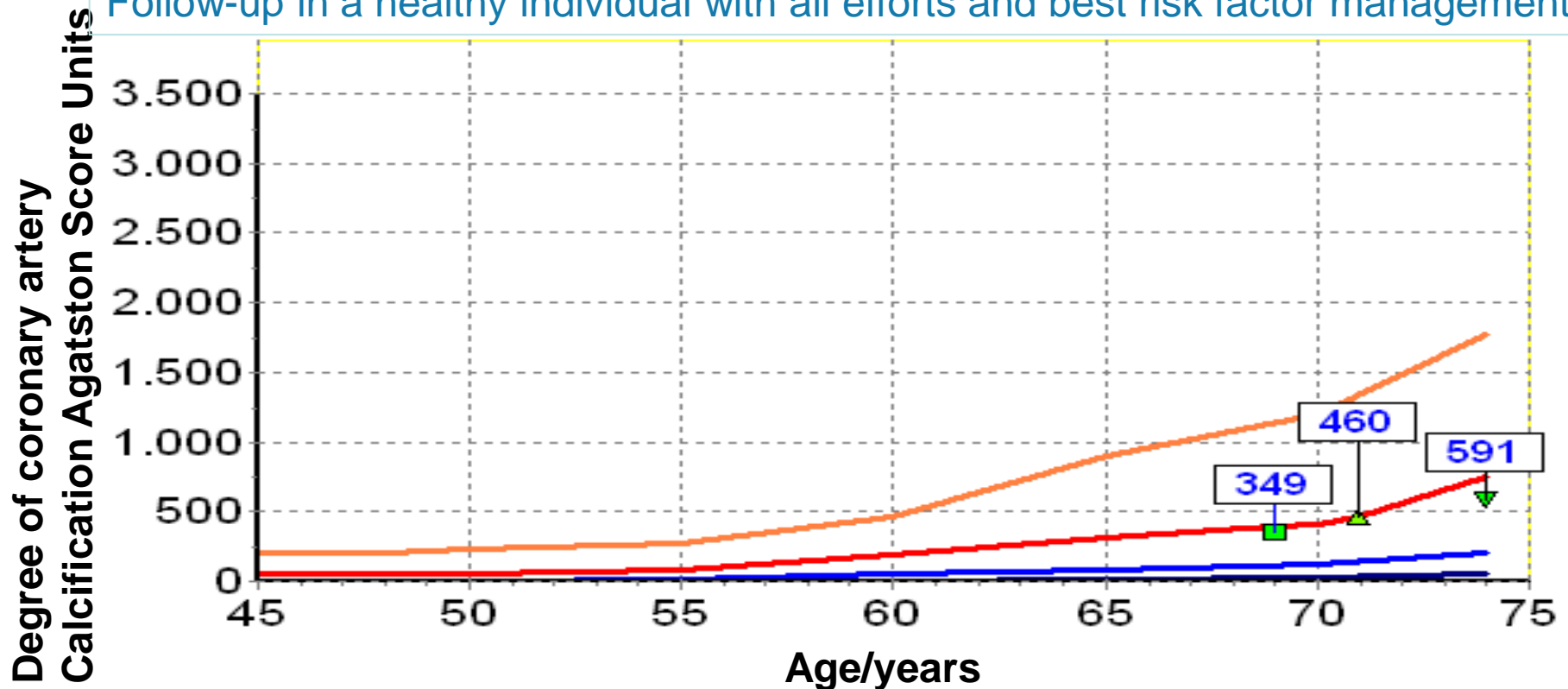
**As follow-up studies demonstrate CAC progression  
in the range of 15 – 25 % per year, the question arises:  
can the efficacy of the risk factor modification  
be assessed by CT?**

# 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



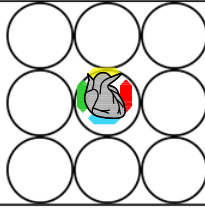
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At the age of 69, the score of 349 is above the 72nd percentile

# Prevention and Coronary Artery Disease

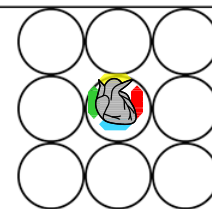
## Progression of coronary artery calcification: risk and risk factors



Achenbach

# Prevention and Coronary Artery Disease

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

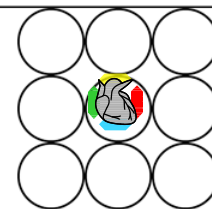


### RCT for Evaluation of Statin Therapy on CAC

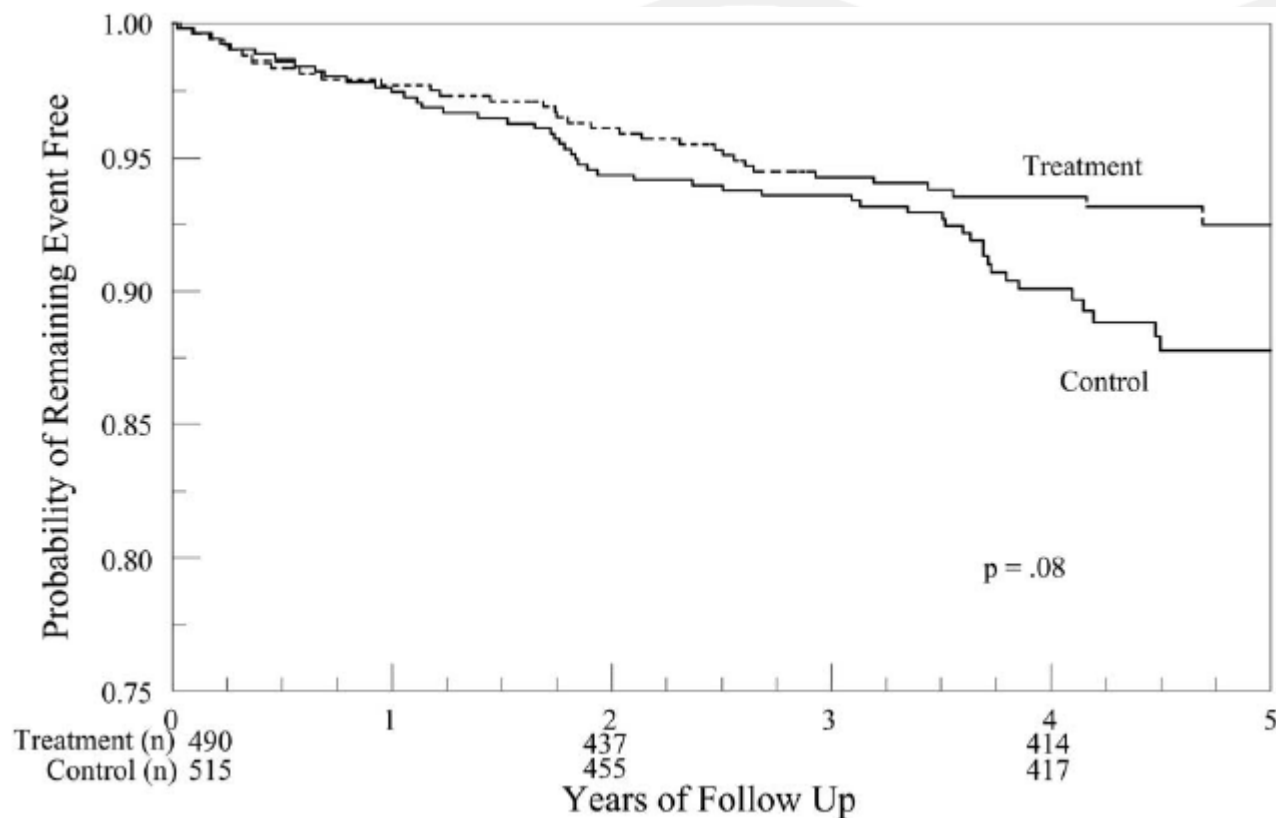
|            | Year | N | Years | Pts | Statin/mg  | Effect/ % |
|------------|------|---|-------|-----|------------|-----------|
| Arad       | 2005 |   | 4.3   |     | 20A+ vs 0  | 81 vs 73  |
| Raggi      | 2005 |   | 1.0   |     | 80A vs 40P |           |
| Schmermund | 2006 |   | 1.0   | 266 | 80A vs 10A | 27 vs 25  |
| Housley    | 2006 |   | 2.0   | 88  | 80A vs 0   | 26 vs 18  |

# Prevention and Coronary Artery Disease

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



FU 4.3 years, 1005 pts, 50 to 70 years  $\geq$  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

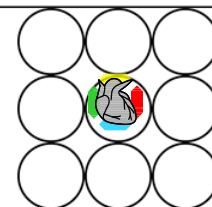
Arad Y et al

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# Prevention and Coronary Artery Disease

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



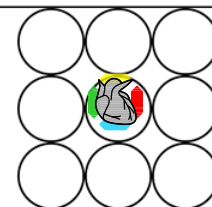
| Lipid Parameter             | Atorvastatin<br>80 mg<br>(n=218) | Pravastatin<br>40 mg<br>(n=257) | P       |
|-----------------------------|----------------------------------|---------------------------------|---------|
| Total cholesterol, mg/dL    |                                  |                                 |         |
| Baseline                    | 268.6 (35.3)                     | 267.7 (40.4)                    |         |
| Month 12                    | 176.2 (41.6)                     | 219.5 (35.4)                    |         |
| Percent change to month 12  | -33.8 (15.3)                     | -17.2 (13.1)                    | <0.0001 |
| LDL-C, mg/dL                |                                  |                                 |         |
| Baseline                    | 175.3 (32.3)                     | 173.6 (35.6)                    |         |
| Month 12                    | 92.2 (36.1)                      | 129.0 (31.0)                    |         |
| Percent change to month 12  | -46.6 (19.9)                     | -24.5 (18.5)                    | <0.0001 |
| HDL-C, mg/dL                |                                  |                                 |         |
| Baseline                    | 56.3 (14.0)                      | 58.7 (14.2)                     |         |
| Month 12                    | 57.0 (13.6)                      | 60.5 (14.7)                     |         |
| Percent change to month 12  | 2.3 (13.8)                       | 3.9 (13.0)                      | 0.0606  |
| Apo B, mg/dL                |                                  |                                 |         |
| Baseline                    | 166.5 (27.3)                     | 164.7 (29.9)                    |         |
| Month 12                    | 101.1 (31.2)                     | 128.9 (26.5)                    |         |
| Percent change to month 12  | -39.0 (16.5)                     | -21.2 (14.9)                    | <0.0001 |
| Peripheral arterial disease |                                  |                                 |         |
|                             | 21 (6.9)                         | 21 (6.8)                        |         |

Raggi P et al

*Circulation.* 112:563-571, 2005

# Prevention and Coronary Artery Disease

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



|           | Atorvastatin 80 mg (n=218) |        | Pravastatin 40 mg (n=257) |        |    |
|-----------|----------------------------|--------|---------------------------|--------|----|
|           | Mean (SD)                  | Median | Mean (SD)                 | Median | P* |
| Total CVS |                            |        |                           |        |    |

|                    | Atorvastatin 80 mg (n=218) |        | Pravastatin 40 mg (n=257) |        |      |
|--------------------|----------------------------|--------|---------------------------|--------|------|
|                    | Mean (SD)                  | Median | Mean (SD)                 | Median | P*   |
| Total CVS          |                            |        |                           |        |      |
| Baseline           | 204.7 (297.1)              | 107.1  | 267.0 (403.9)             | 132.9  | 0.04 |
| 12-Month follow-up | 233.2 (350.1)              | 118.6  | 297.9 (408.3)             | 160.3  |      |
| Absolute change    | 28.5 (87.4)                | 14.2   | 30.9 (65.1)               | 18.5   | 0.21 |
| Percentage change  | 20.1 (30.8)                | 15.1   | 19.8 (34.8)               | 14.3   | 0.64 |

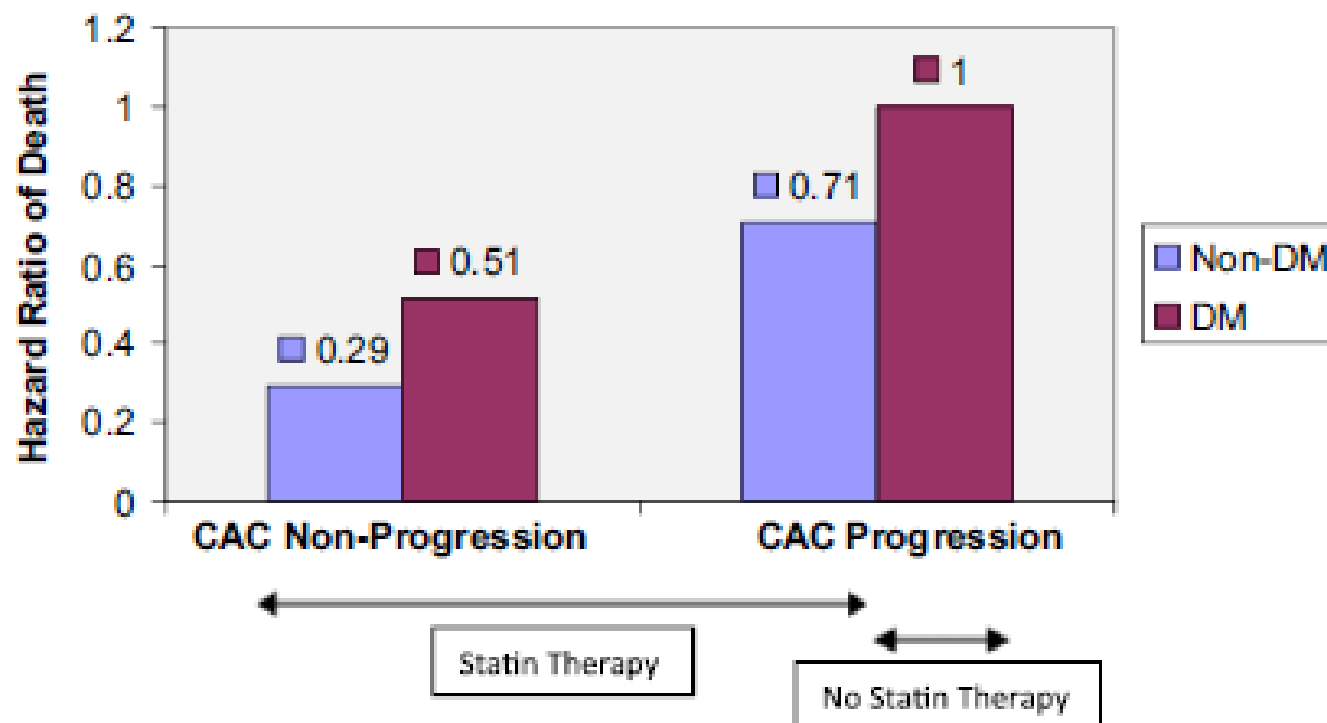
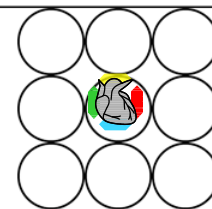
|                        |              |      |               |      |      |
|------------------------|--------------|------|---------------|------|------|
| 12-Month follow-up     | 28.7 (88.4)  | 0.0  | 41.8 (102.8)  | 0.0  |      |
| Absolute change        | 6.6 (59.5)   | 0.0  | 5.3 (25.9)    | 0.0  | 0.35 |
| Right coronary artery† |              |      |               |      |      |
| Baseline               | 65.2 (144.9) | 7.2  | 94.0 (213.4)  | 13.7 | 0.14 |
| 12-Month follow-up     | 72.8 (154.5) | 13.1 | 102.0 (205.4) | 18.1 |      |
| Absolute change        | 7.7 (31.2)   | 0.0  | 8.0 (43.4)    | 0.0  | 0.95 |

Raggi P et al

*Circulation.* 112:563-571, 2005

# Prevention and Coronary Artery Disease

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

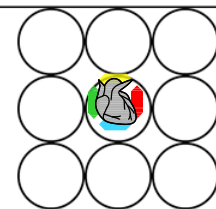


Kiramiyan S et al

AJC 2012, in press

# Prevention and Coronary Artery Disease

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



### Conclusion of the study

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

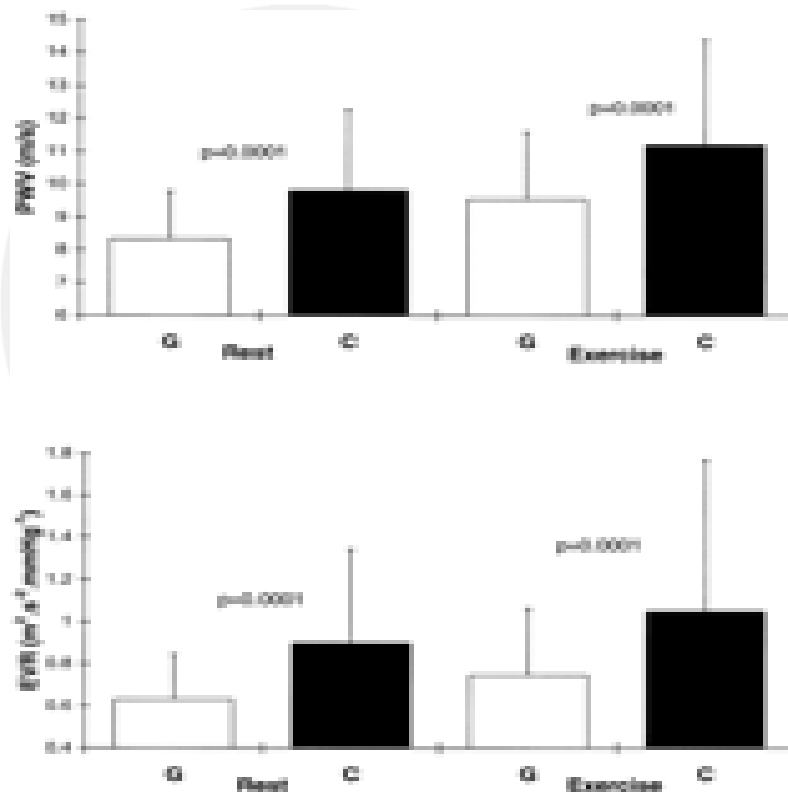
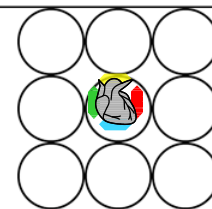
### CAC progression in DM

Kiramijyan S et al

AJC 2012, in press

# Prevention and Coronary Artery Disease

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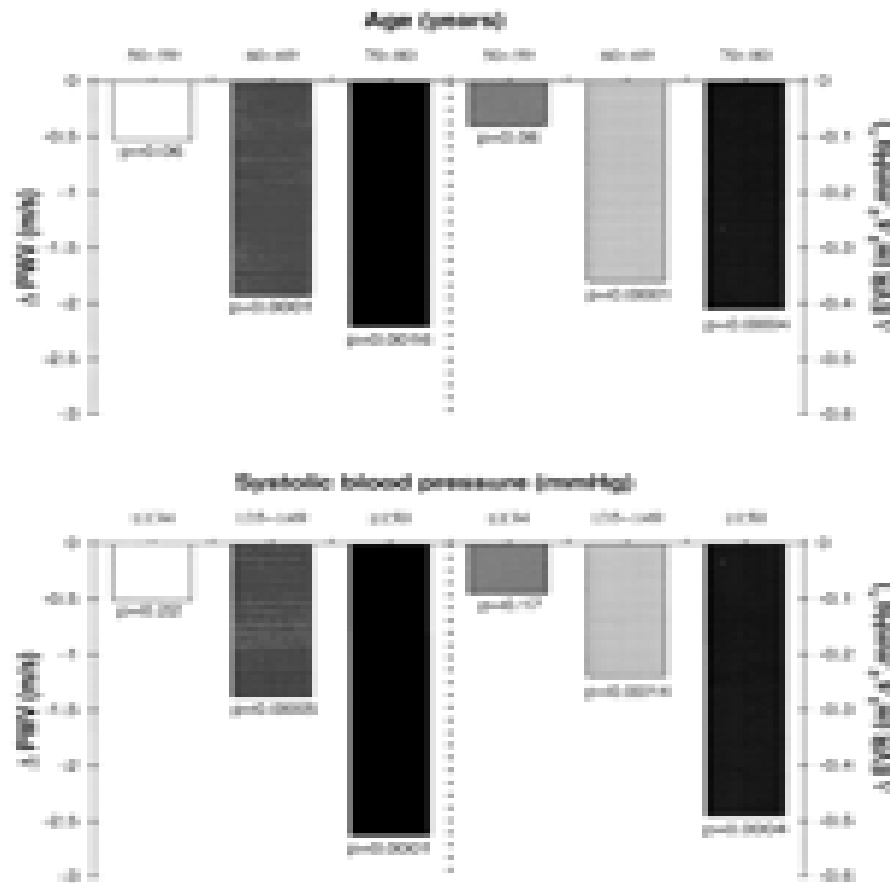
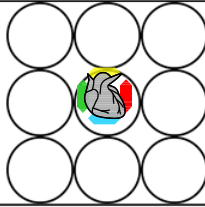


Breithaupt-Grögler K et al

Circulation 96: 2649-2655, 1997

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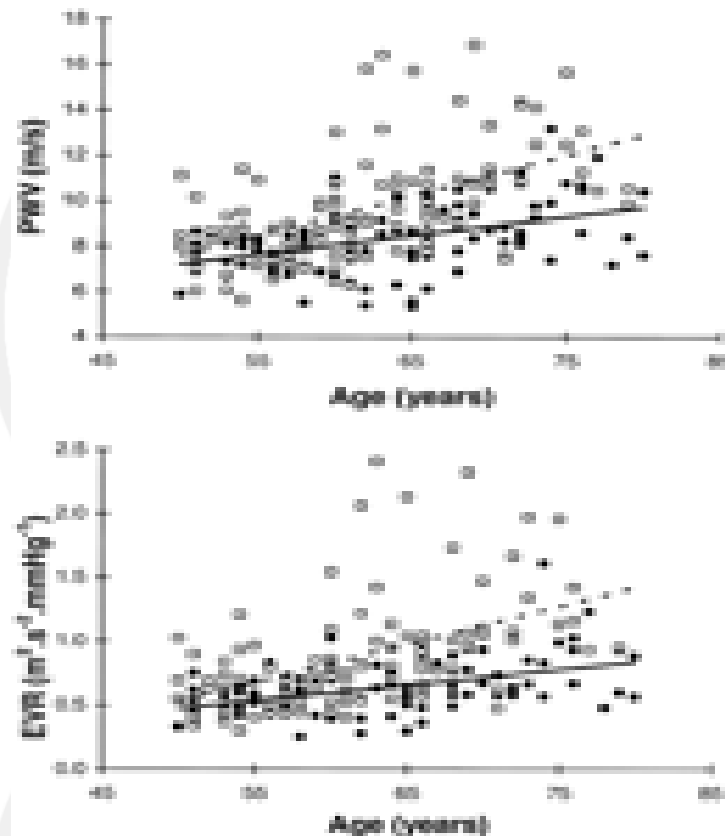
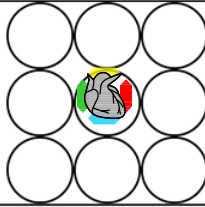


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# Prevention and Coronary Artery Disease

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

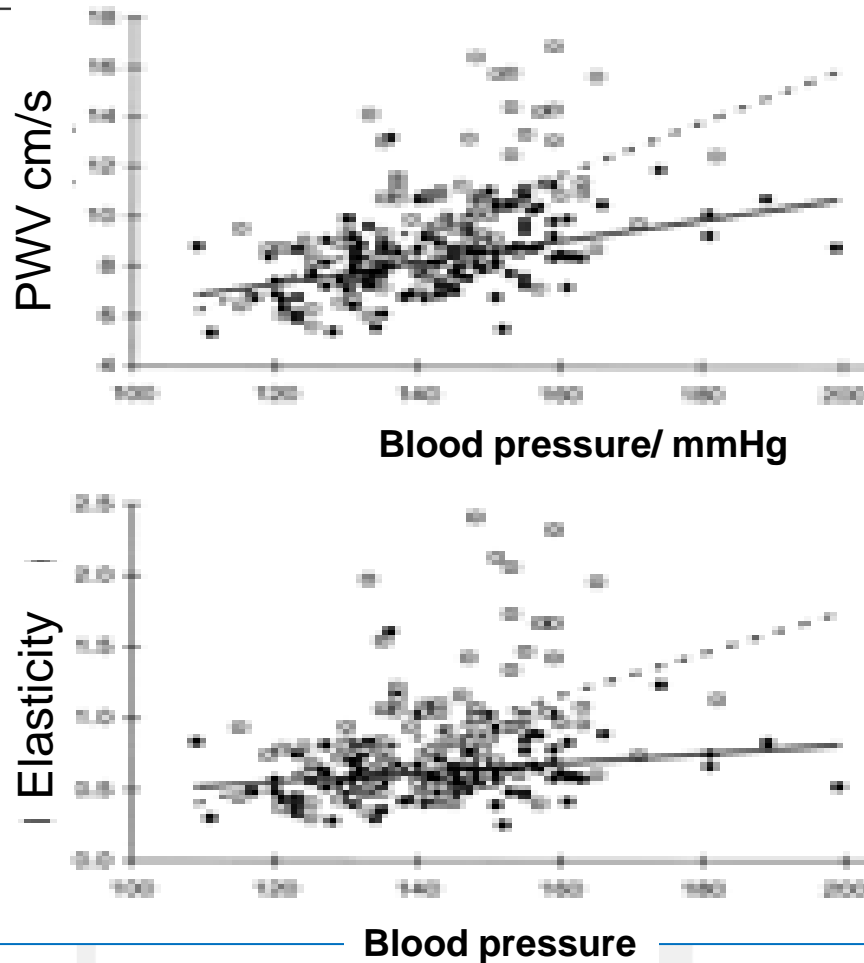
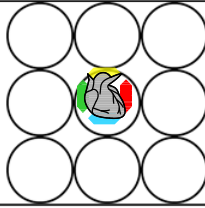


**Breithaupt-Grögler K et al**

**Circulation 96: 2649-2655, 1997**

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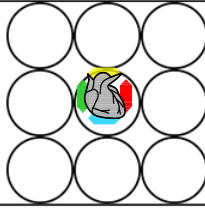
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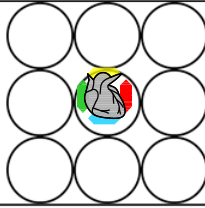
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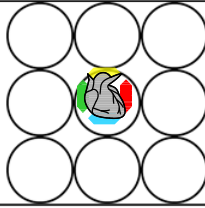
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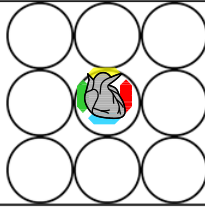
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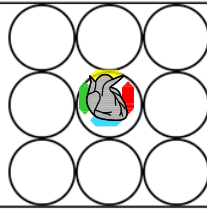
## Progression of coronary artery calcification: risk and risk factors



CAC Progression as a sign of coronary atherosclerosis is  
genetic determined and not influencable!?

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### Heritability estimates for log baseline CAC quantity and CAC progression

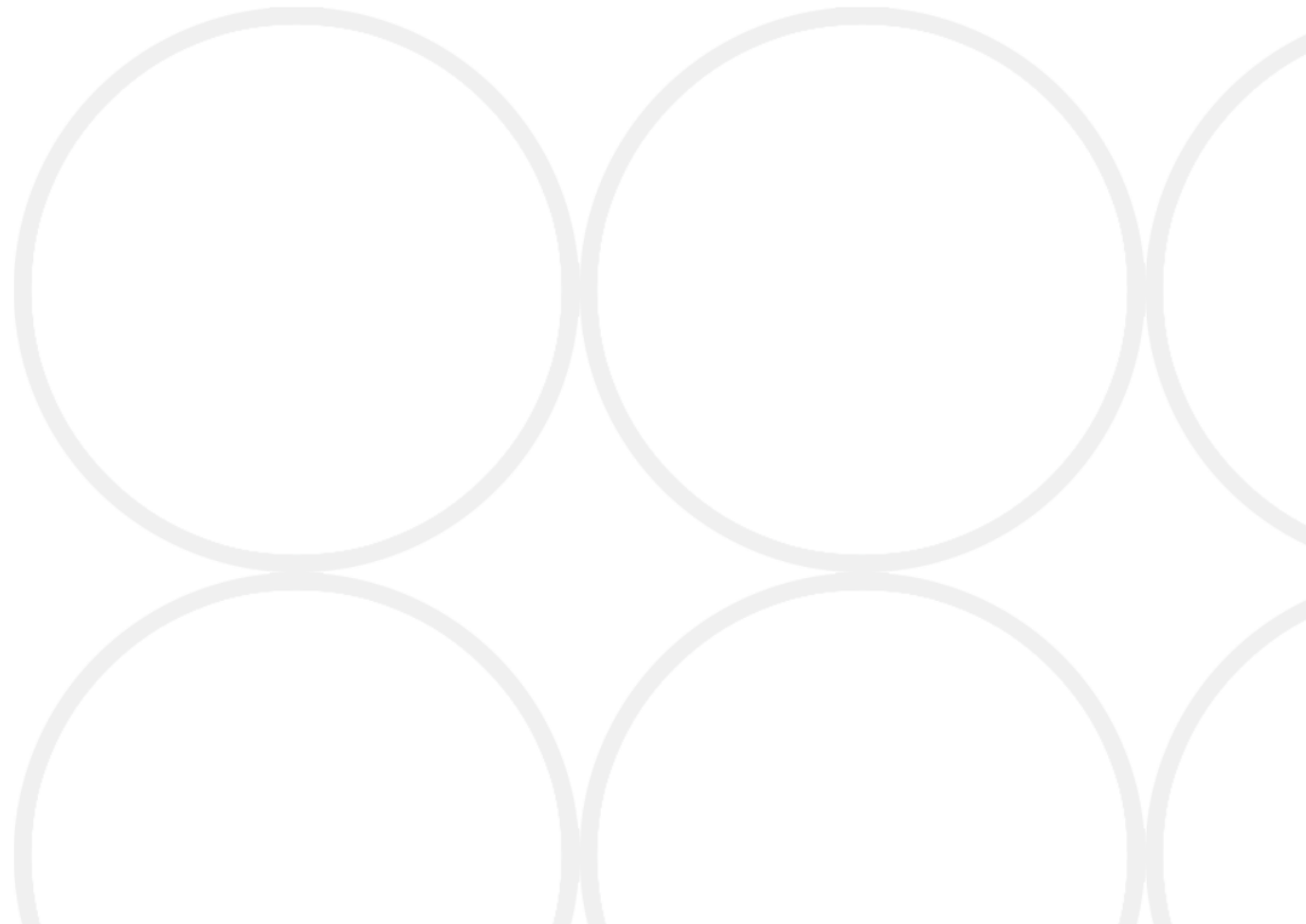
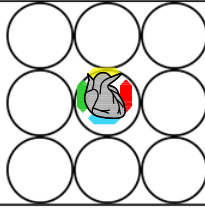
| Trait                     | $h^2$ (SE)    | Covariate Variance* | Covariates Adjusted for:                                                                                                           | % of Variance Explained by Genetic Factors† |
|---------------------------|---------------|---------------------|--------------------------------------------------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

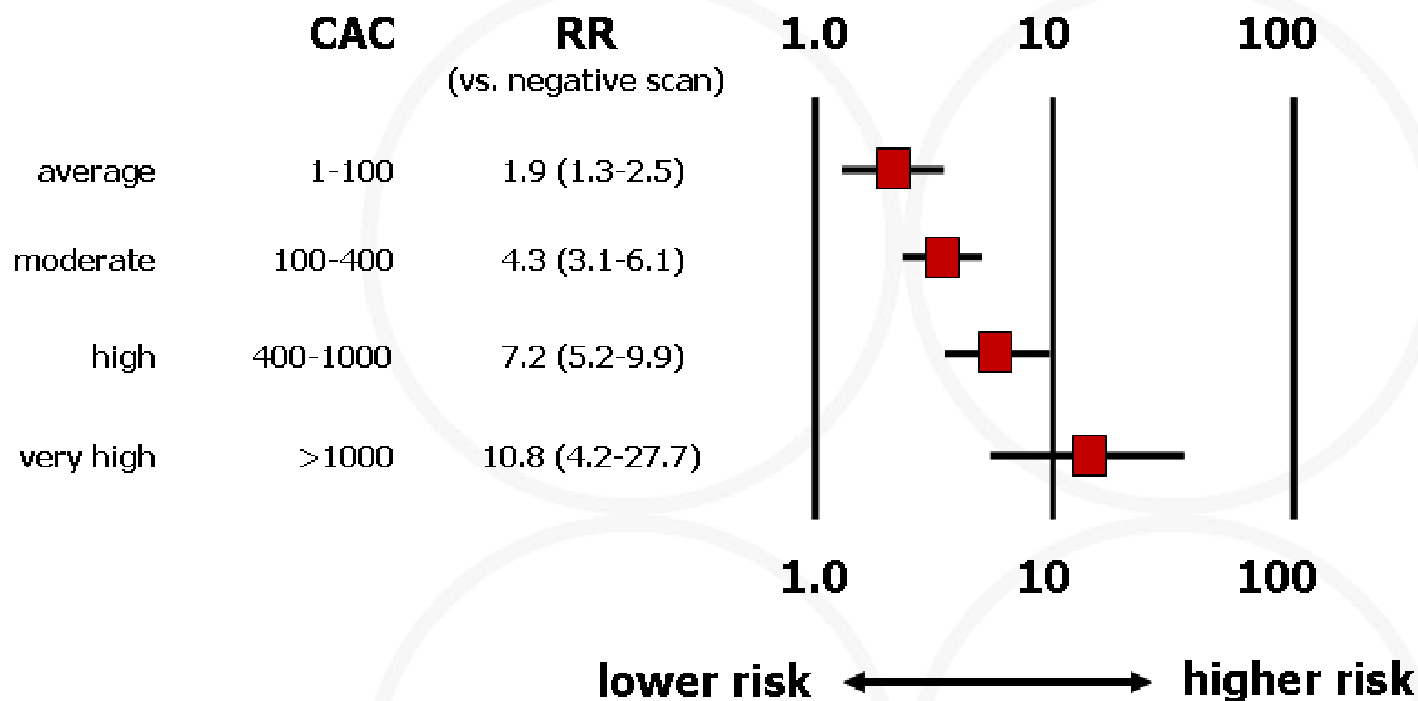
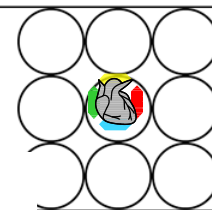
Cassidy-Bushrow, AE et al

Circulation 116:25-31, 2007

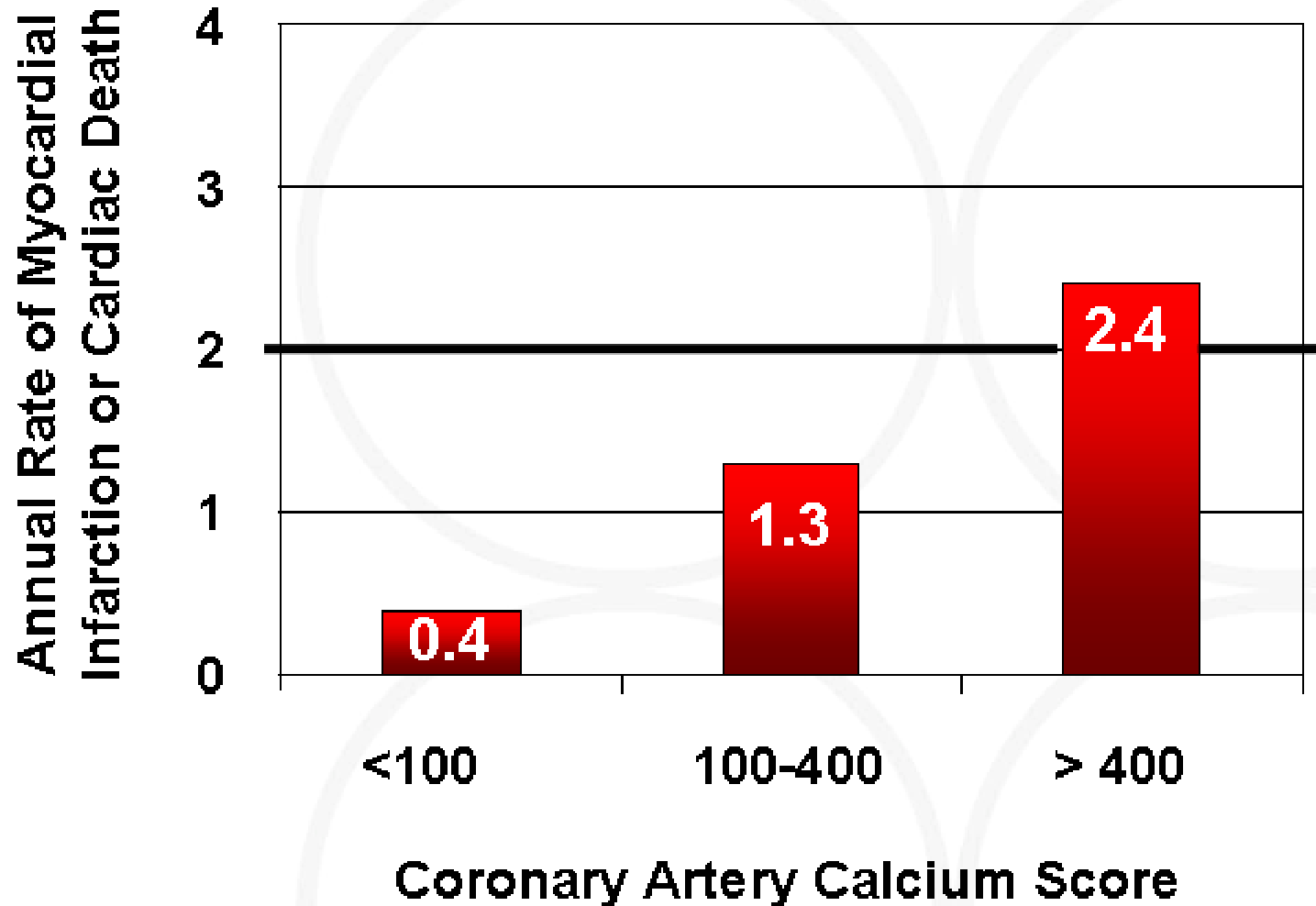
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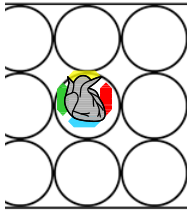




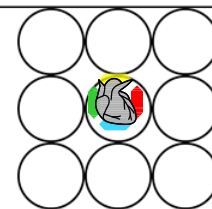
**Figure 1:** Increase in relative risk (RR) with increasing CAC scores in asymptomatic persons in comparison to asymptomatic persons without CAC (modified from (13)).



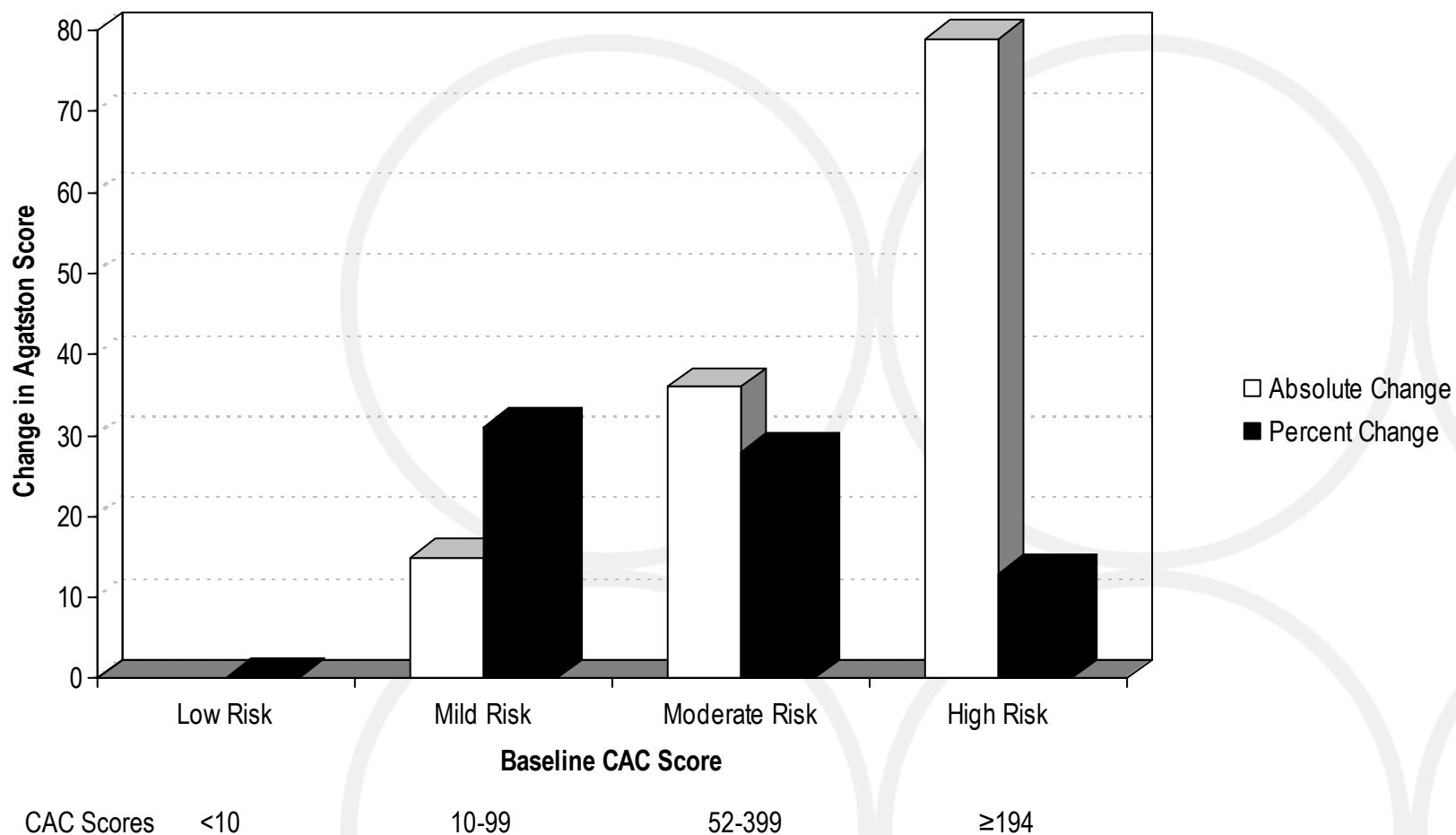
**Figure 2** Annual rate of myocardial infarction or cardiac death in categories of CAC burden in persons at intermediate risk based on convention risk factor assessment. In persons with a high CAC score (>400), the annual event rate exceeds the threshold for intensive risk factor modification, i.e. >2% per year (black line). A CAC score > 400 in intermediate risk persons may therefore be considered as a risk equivalent (modified from (13))



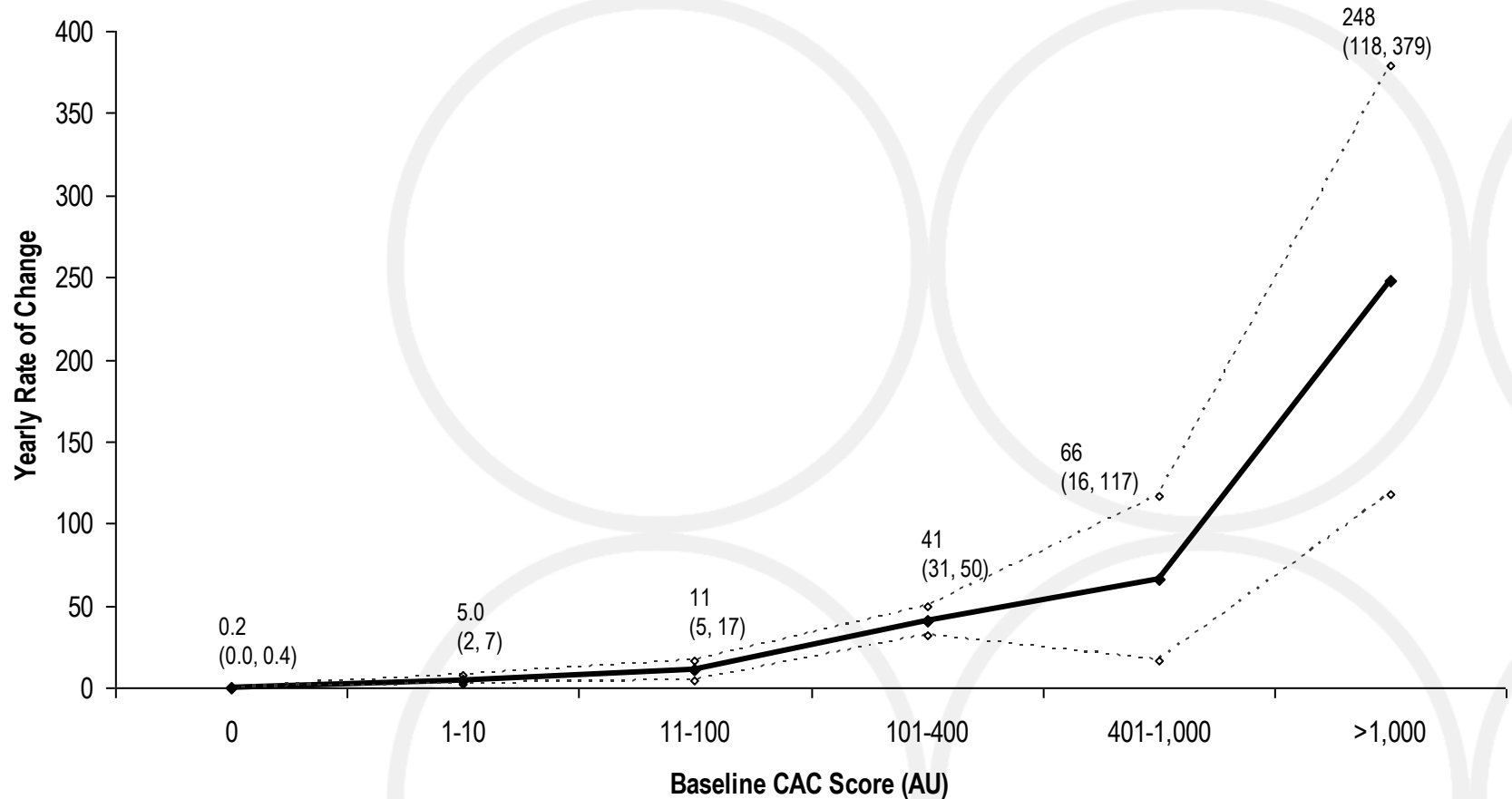
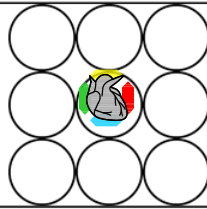


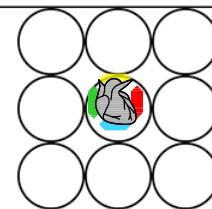


**Figure 3.** The Absolute and Percent Change in Baseline Agatston Score on Serial CT Imaging

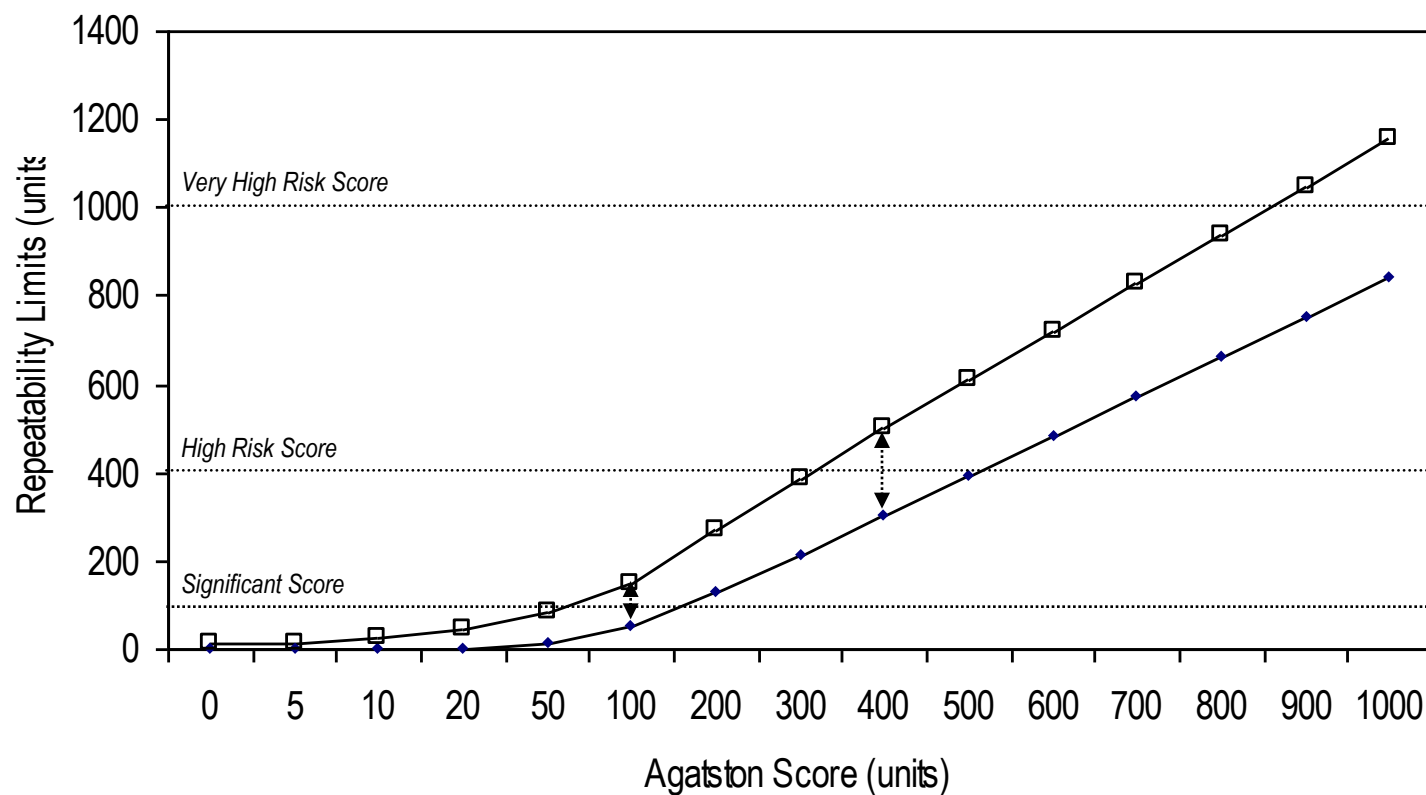


**Figure 4.** Expected Yearly Rate of Change (95% Confidence Intervals) from Baseline for Coronary Artery Calcium Scores Ranging from 0 to  $\geq 1,000$  Agatston Units (AU)

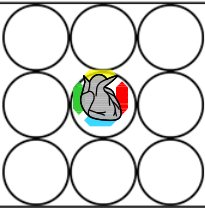




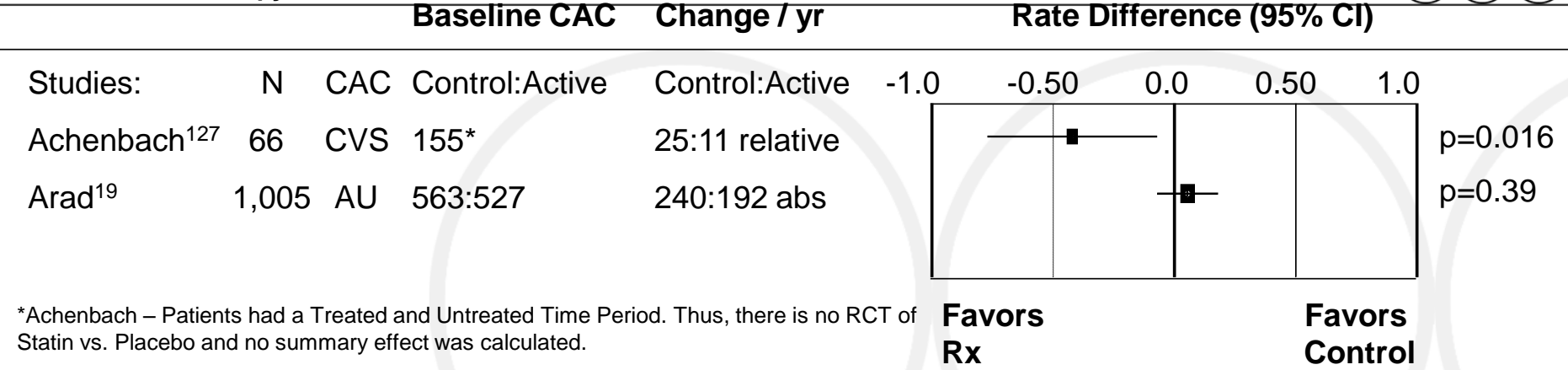
**Figure 5.** 95% Confidence Intervals for Repeatability of Coronary Artery Calcium Scores from 0 to  $\geq 1,000$



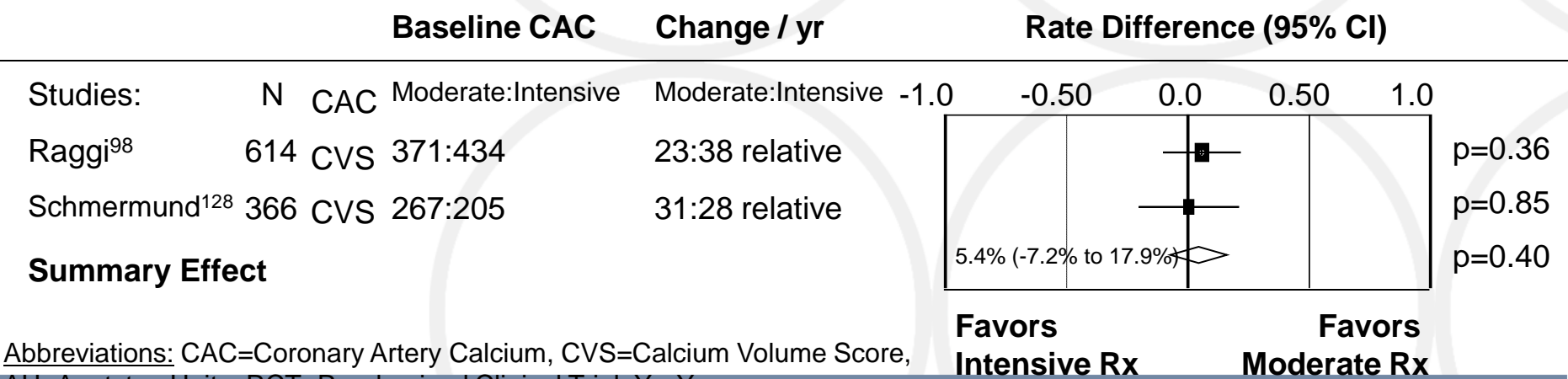
**Figure 6.** Summary Meta-Analysis of Randomized Control Trials (RCT) on the Effect of Statin Therapy (Rx) on CAC Progression



**RCTs of Statin Therapy vs. Placebo**



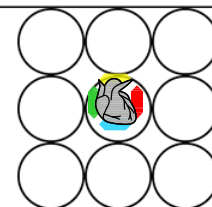
**RCTs of Moderate vs. Intensive Statin Therapy**



Abbreviations: CAC=Coronary Artery Calcium, CVS=Calcium Volume Score, AU=Agatston Units, RCT=Randomized Clinical Trial, Yr=Year,

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### Cardiovascular Risk

## Adolescence Risk Factors Are Predictive of Coronary Artery Calcification at Middle Age

The Cardiovascular Risk in Young Finns Study

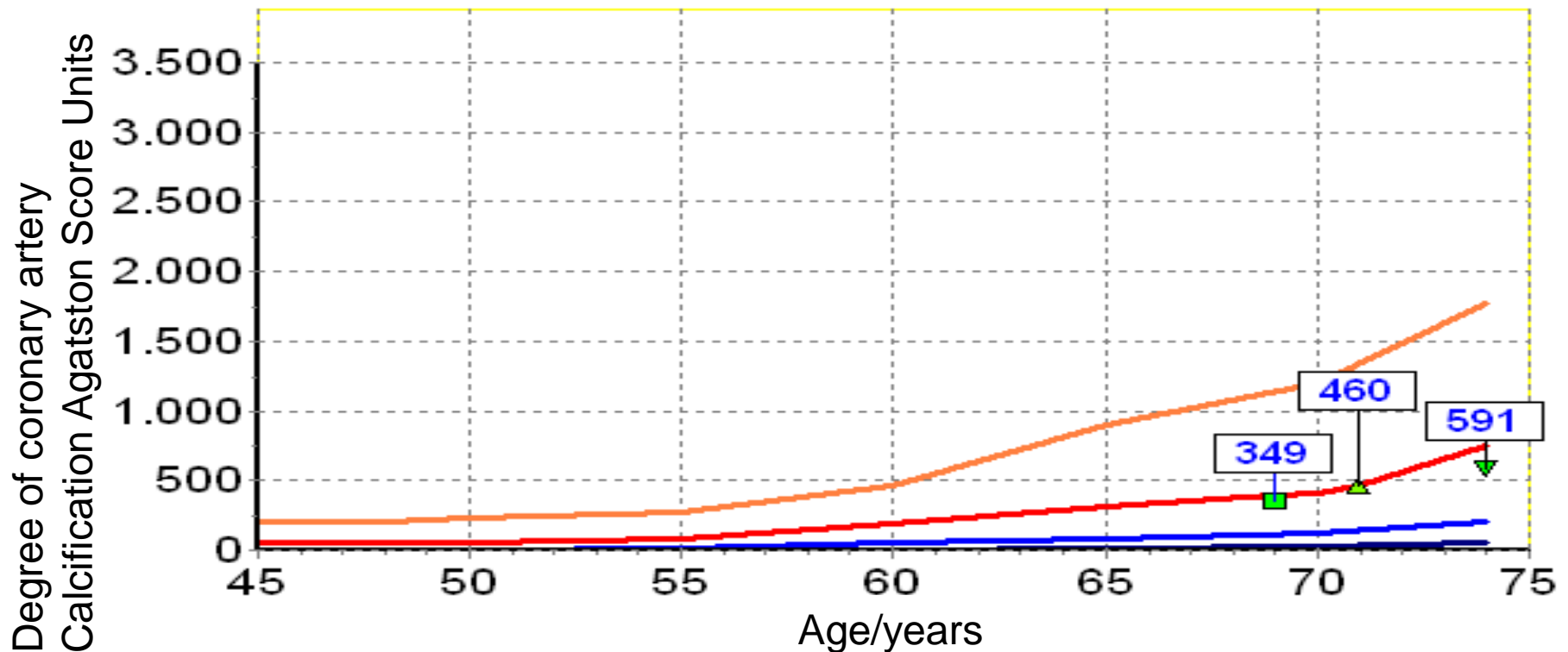
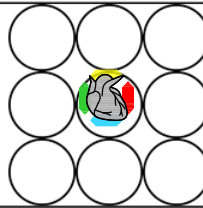
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Olli T. Raitakari, MD, PhD\*§§

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Hartiala O t al

J Am Coll Cardiol 2012;60:1364–70)

# Non Invasive Assessment of Subclinical Coronary Sclerosis: EBCT

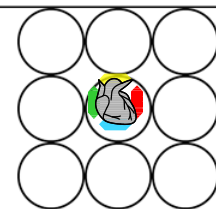


- ▼ Im Alter von 74 liegt der Verkalkungswert von 591 oberhalb der 70. Perzentile.
- ▲ Im Alter von 71 liegt der Verkalkungswert von 460 oberhalb der 67. Perzentile.
- Im Alter von 69 liegt der Verkalkungswert von 349 oberhalb der 72. Perzentile.

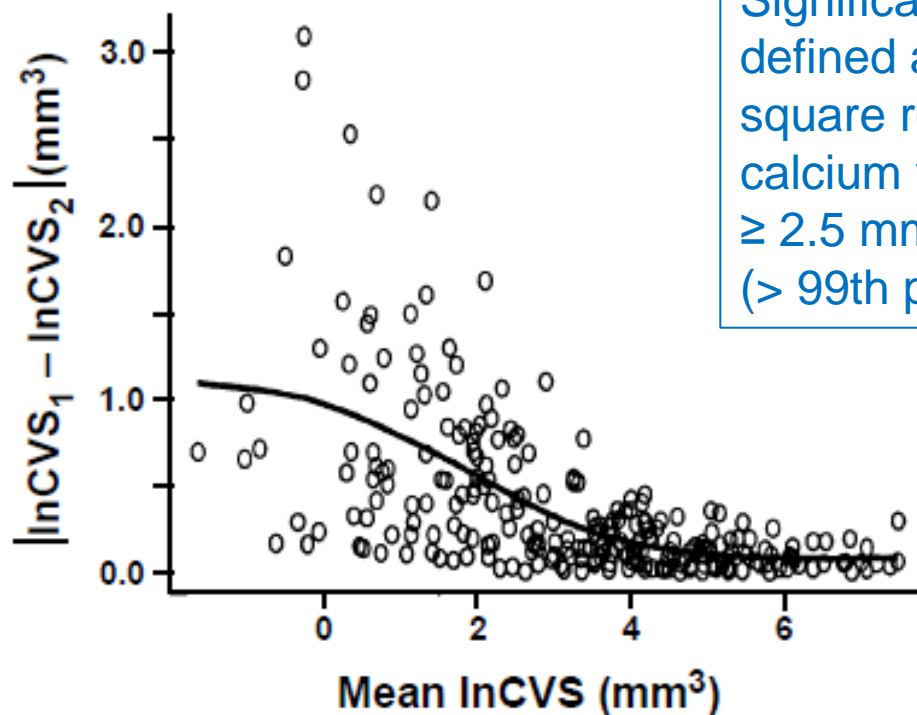
- 90. Perzentile
- 75. Perzentile - oberhalb hat der Wert eine größere klinische Bedeutung
- 50. Perzentile
- 25. Perzentile

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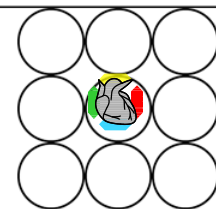
calcium volume scores taken a mean of 2.7 years apart in 109 diabetics



Significant change in CVS defined as a difference between square root-transformed to calcium volume scores  $\geq 2.5 \text{ mm}^3$  ( $> 99\text{th}$  percentile interscan variat..)

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### Potential mechanism of CAC progression

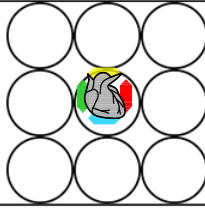
Inverse relationship to

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



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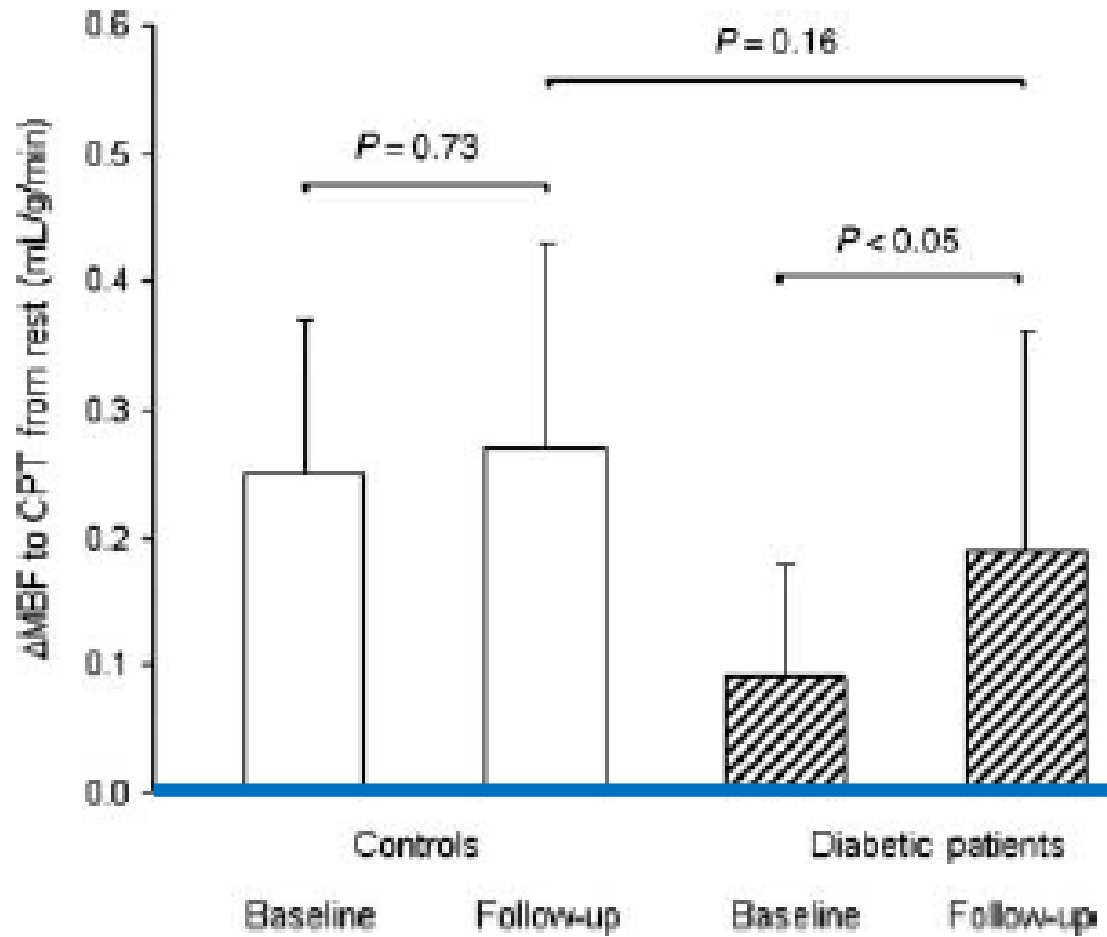
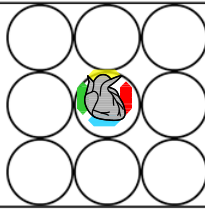


What is the Pathophysiology of CAC Progression in Relation  
to Endothelium Function and Myocardial Blood Flow

# Prevention and Coronary Artery Disease

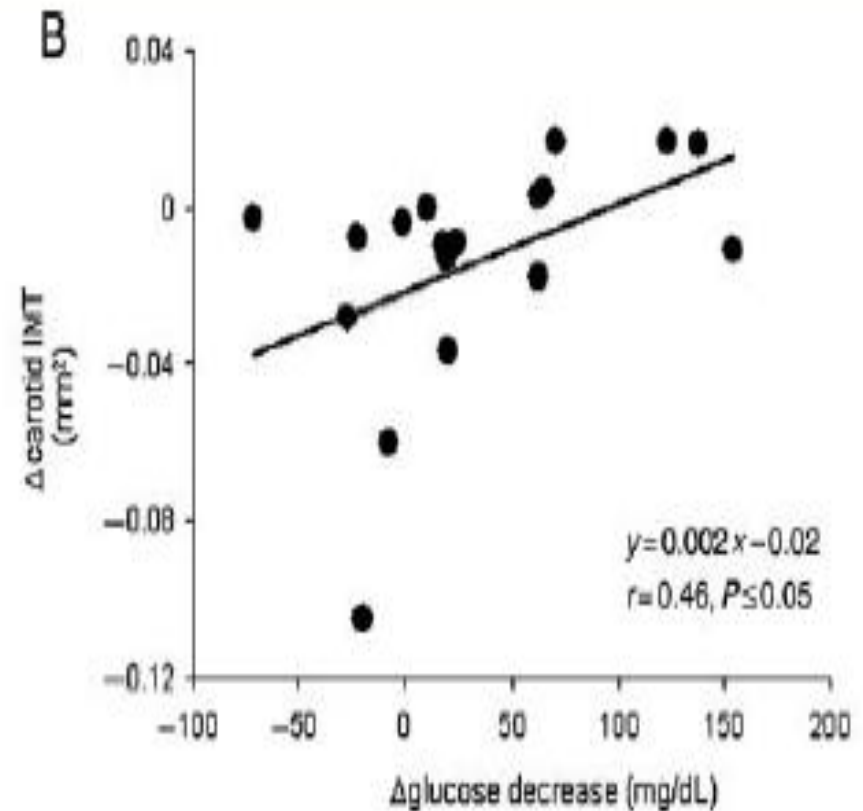
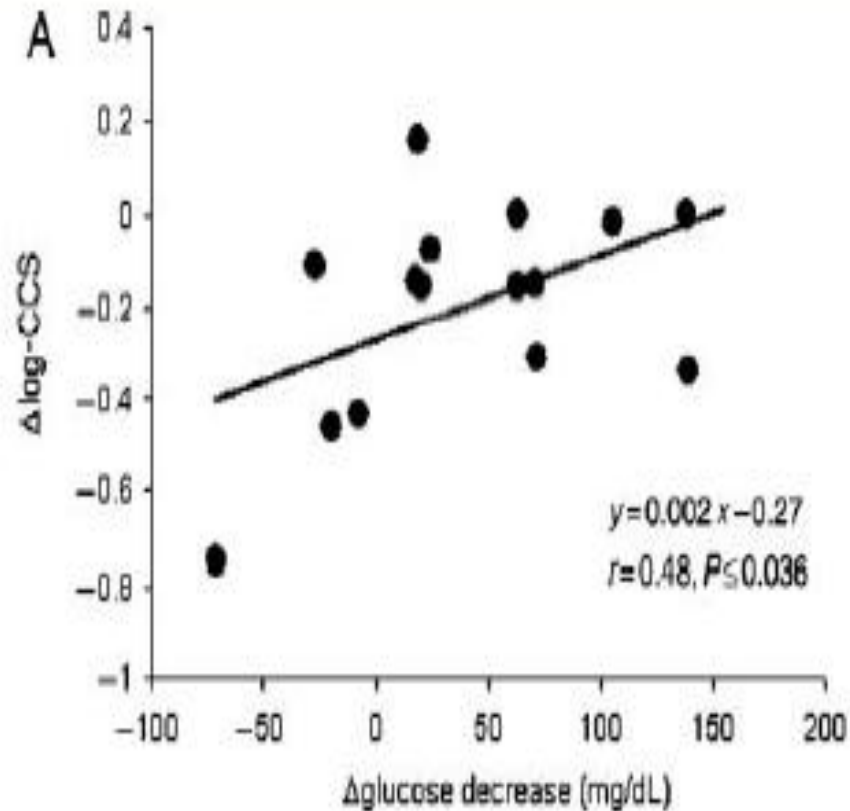
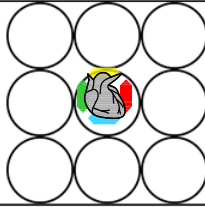
## Progression of coronary artery calcification: risk and risk factors

### Relation to Myocardial Blood flow



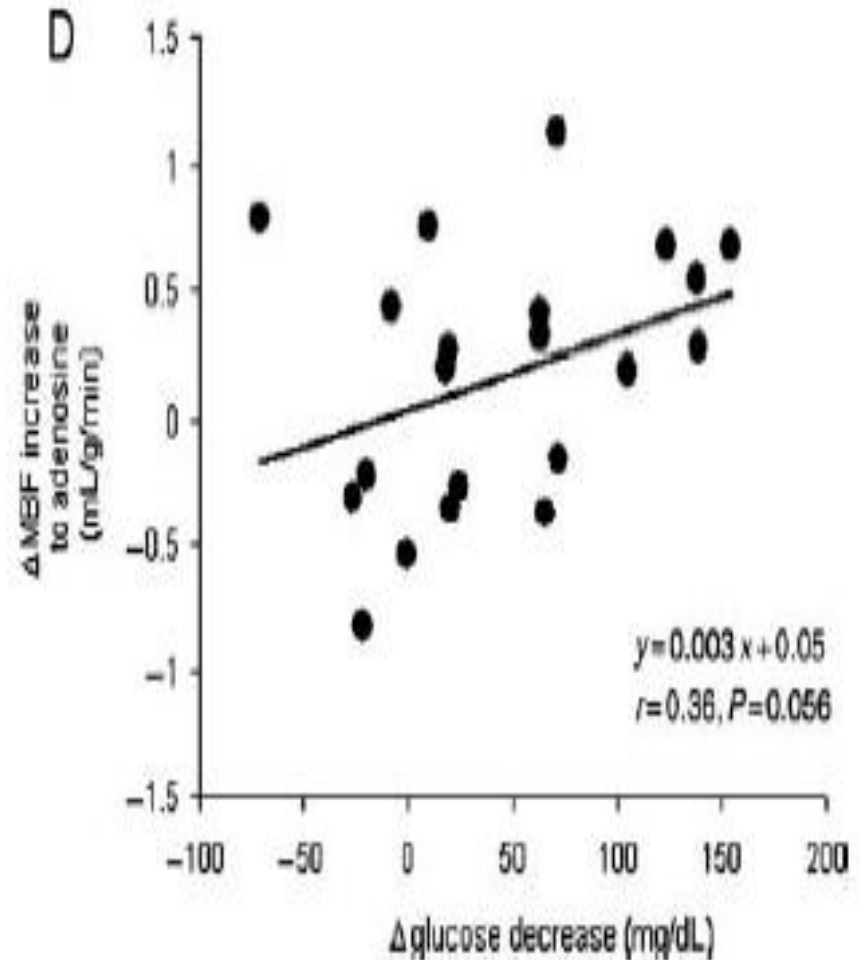
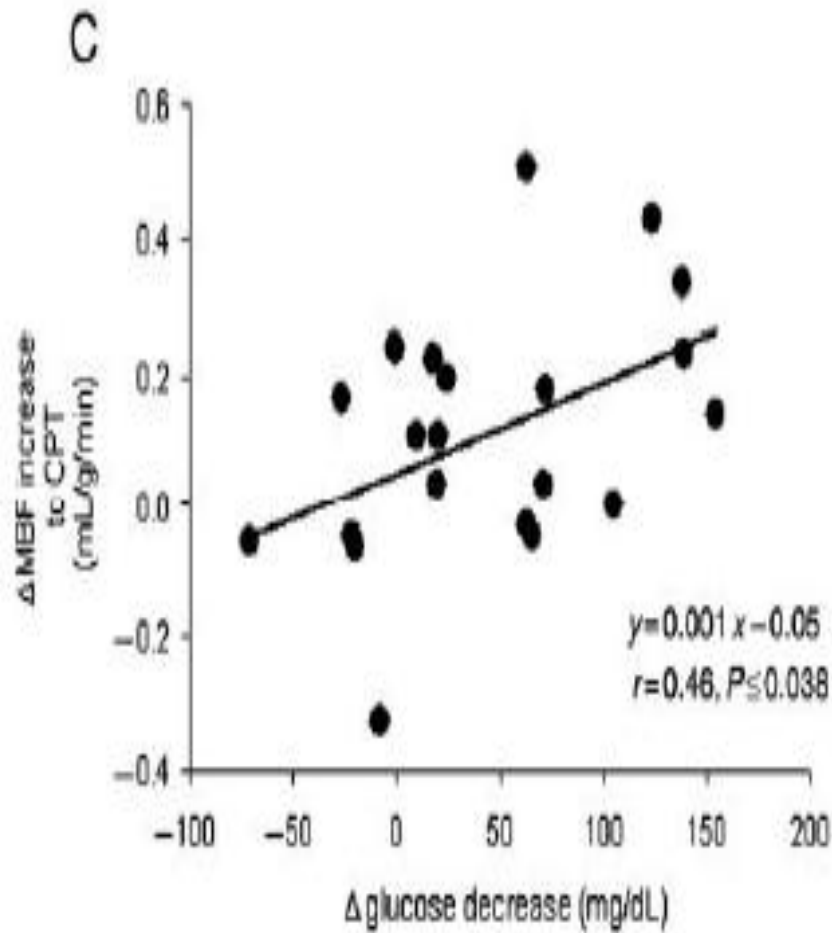
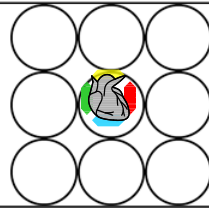
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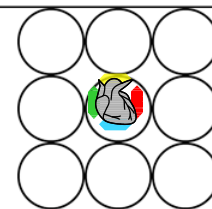
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### Models of coronary artery calcium progression

| Model | $\Delta$ CAC%   | Matched Controls | Patients With DM  | p Value |
|-------|-----------------|------------------|-------------------|---------|
| 1     | 10%–20% vs <10% | 1.0 (reference)  | 1.88 (1.51–2.36)  | 0.0001  |
| 2     | 21%–30% vs <10% | 1.0 (reference)  | 2.29 (1.56–3.38)  | 0.0001  |
| 3     | >30% vs <10%    | 1.0 (reference)  | 6.95 (2.23–11.53) | 0.0001  |

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).

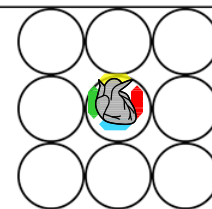
Adjusted for age, gender, hypertension, hyperlipidemia, family history of CHD, baseline CAC, and smoking.

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Risk factor—adjusted event-free survival (depicted in Figure 1)

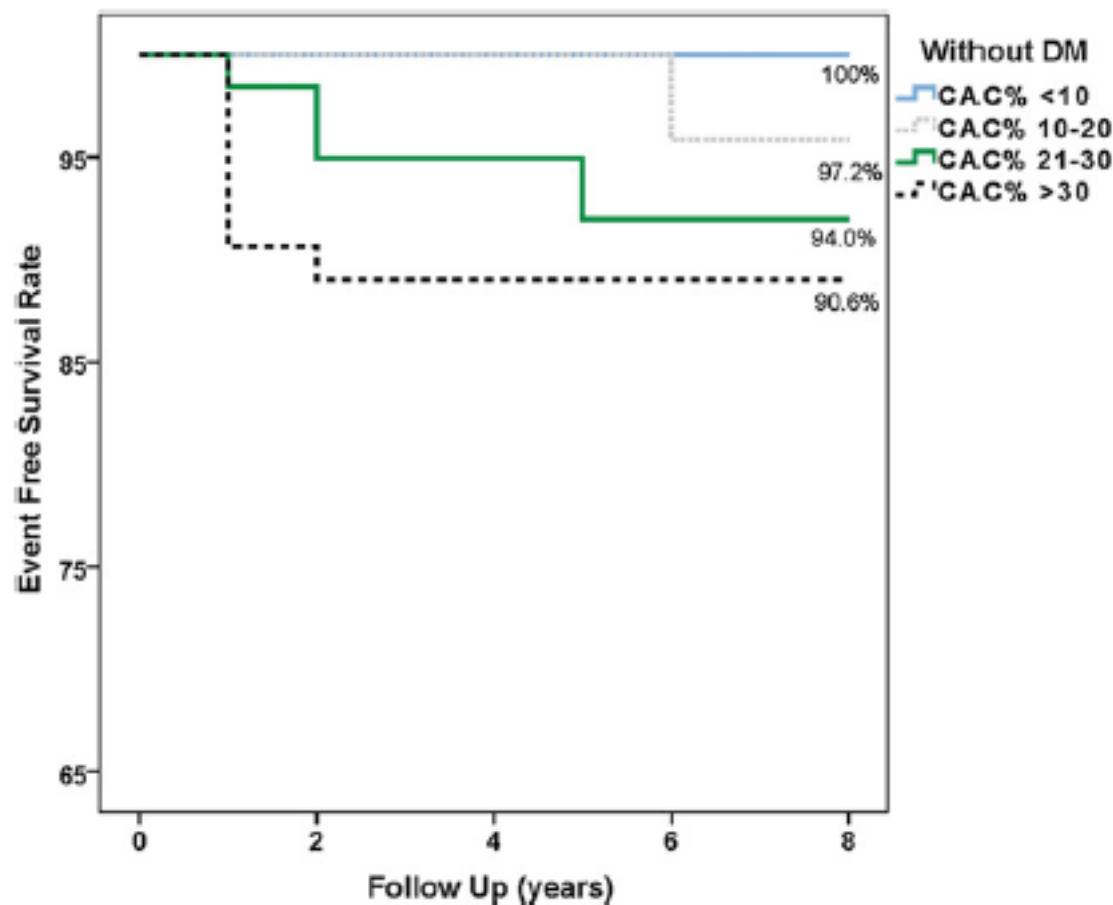
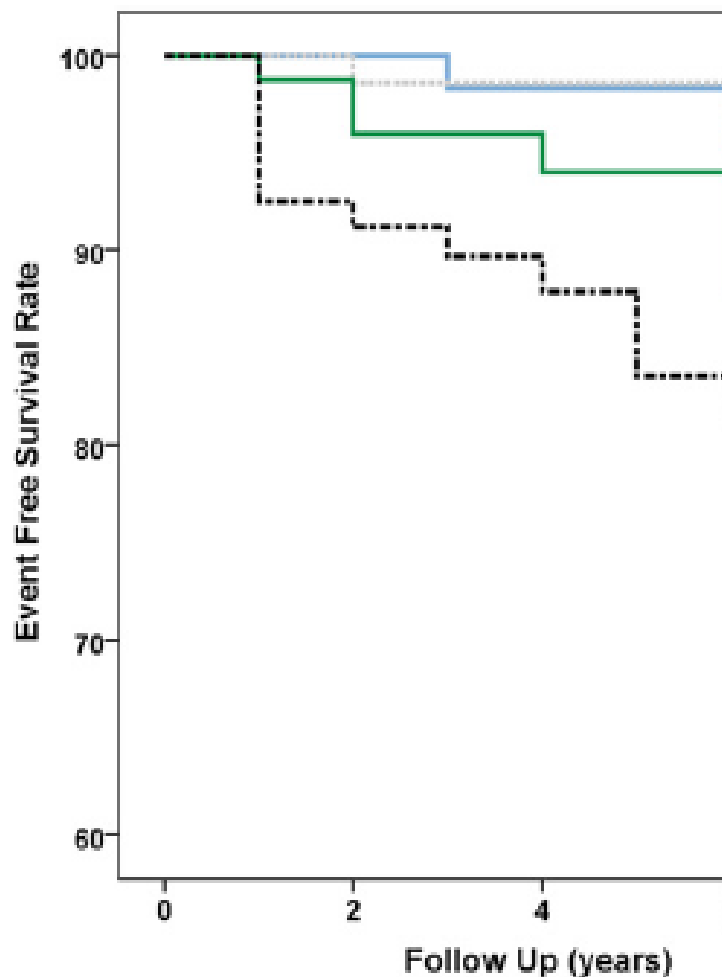
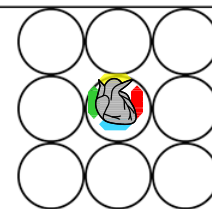
| Variable ( $\Delta$ CAC) | DM    | No DM | p Value |
|--------------------------|-------|-------|---------|
| <10%                     | 97.9% | 100%  | 0.50    |
| 10%–20%                  | 95.9% | 97.2% | 0.01    |
| 21%–30%                  | 92.7% | 94%   | 0.01    |
| >30%                     | 79.6% | 90.6% | 0.0001  |

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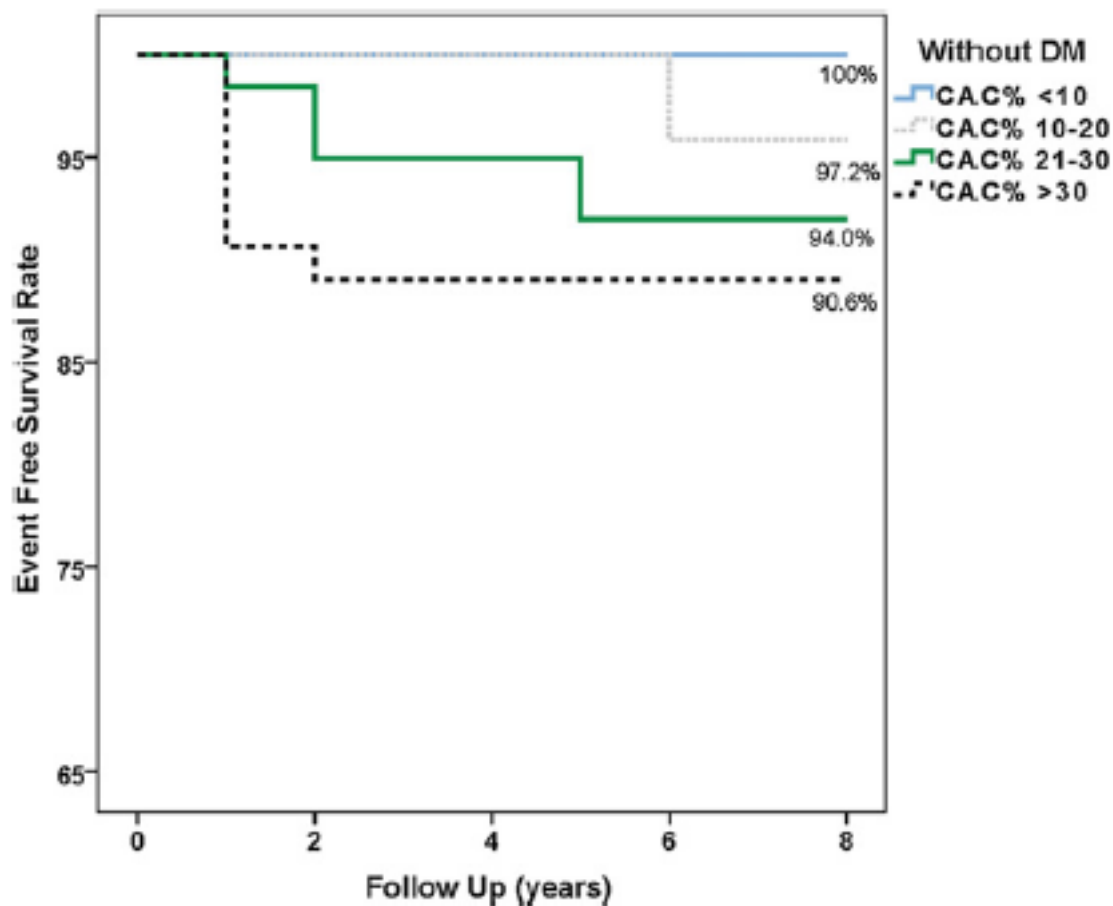
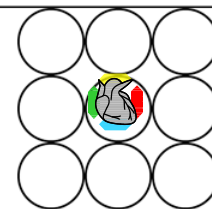
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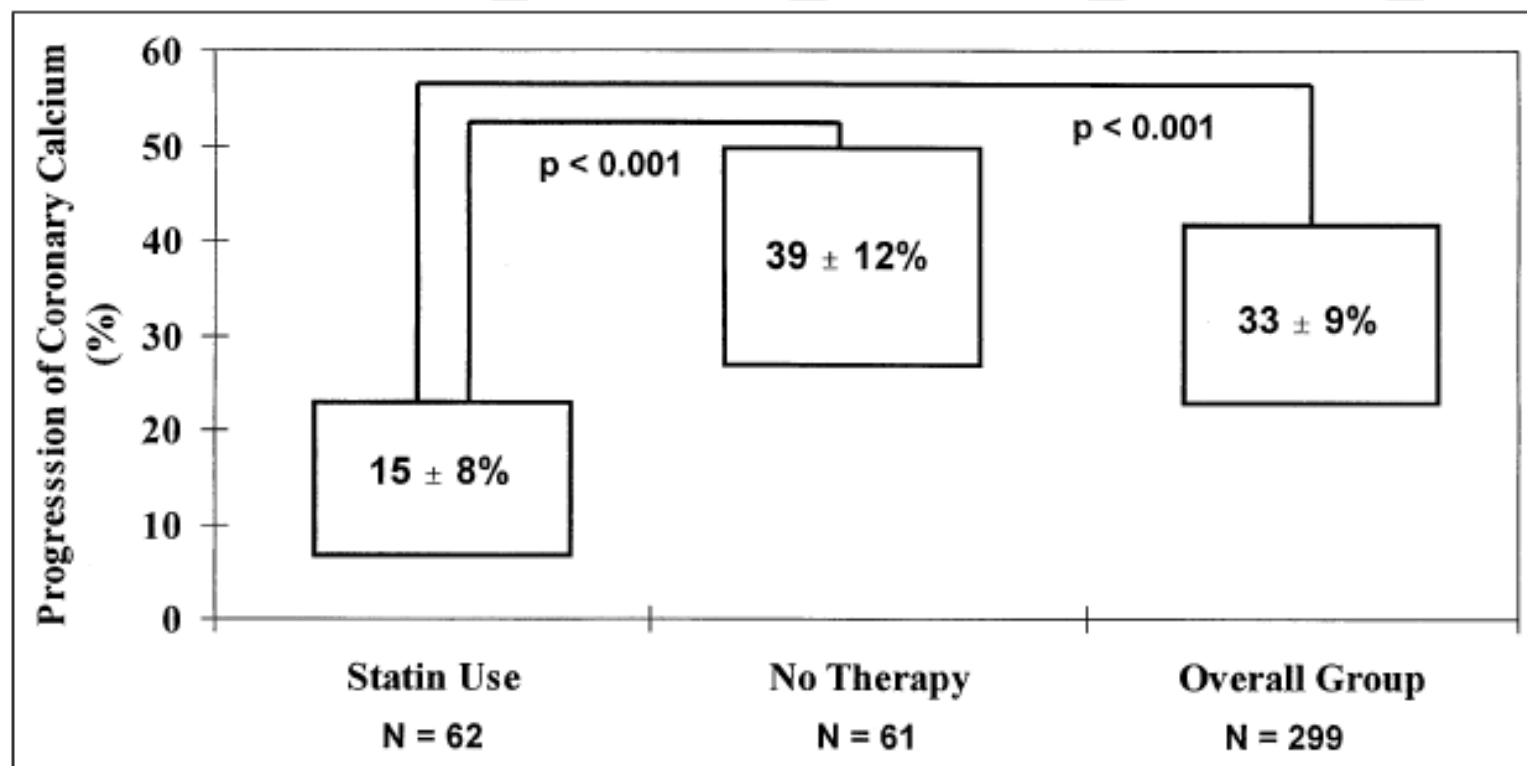
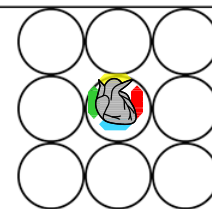
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Am J Cardiol 86:8–11, 2000