Vascular Risk Prediction

TPA Course

Theoretical and practical aspects for the prevention of stroke and myocardial infarction using atherosclerosis imaging of carotid arteries

by Michel Romanens, MD
Ziegelfeldstr. 1
4600 Olten

[Links provided]

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Total Plaque Area (TPA)
A Tool for Targeting and Evaluating Vascular Preventive Therapy

Michel Romanens, MD
Cardiology Consultant Cantonal Hospital Olten
Coordinator Taskforce on Atherosclerosis imaging
President Vascular Risk Foundation
Key Messages

Coronary Risk Equations have a low sensitivity to detect subjects at high coronary risk, both in the age group 40-55 and 56-65 years.

TPA allows you to rapidly assess a patient's risk using images of atherosclerosis.

TPA is as good as a coronary calcium score obtained by Computed Tomography.
Total Plaque Area (TPA) - update

- Simple online tracing of plaque surfaces
- No fancy software needed
- Low cost imaging (e.g. CHF 75)
# Arteris Database

<table>
<thead>
<tr>
<th>Country</th>
<th>CH</th>
<th>DE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (N)</td>
<td>2202</td>
<td>2942</td>
</tr>
<tr>
<td>Female, N, %</td>
<td>1082</td>
<td>989</td>
</tr>
<tr>
<td>Mean age (N ± SD)</td>
<td>57 ± 9</td>
<td>46 ± 10</td>
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<tr>
<td>Family history for CAD (N, %)</td>
<td>386</td>
<td>660</td>
</tr>
<tr>
<td>Current smoker (N, %)</td>
<td>458</td>
<td>770</td>
</tr>
<tr>
<td>Blood pressure systolic, mm Hg mean ± SD</td>
<td>129 ± 16</td>
<td>123 ± 16</td>
</tr>
<tr>
<td>TPA mm² mean ± SD</td>
<td>52 ± 50</td>
<td>36 ± 50</td>
</tr>
<tr>
<td>Individuals with TPA≥80 mm² (N, %)</td>
<td>484</td>
<td>452</td>
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# Arteris Database

<table>
<thead>
<tr>
<th>TPA80</th>
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<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
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<tr>
<td>Women</td>
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<td>56-65</td>
<td>60</td>
<td>14.0</td>
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<td>66-75</td>
<td>78</td>
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<tr>
<td>Men</td>
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<td>15.7</td>
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<tr>
<td></td>
<td>56-65</td>
<td>150</td>
<td>37.2</td>
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<td>97</td>
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<td>66-75</td>
<td>175</td>
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### Sensitivity for TPA80

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<tbody>
<tr>
<td>0.0-2.5/1%</td>
<td>96</td>
<td>100</td>
<td>61</td>
<td>55</td>
<td>90</td>
<td>64</td>
<td>98</td>
<td>100</td>
<td>69</td>
<td>59</td>
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<tr>
<td>0.0-5.0/2%</td>
<td>86</td>
<td>95</td>
<td>26</td>
<td>21</td>
<td>61</td>
<td>36</td>
<td>91</td>
<td>96</td>
<td>34</td>
<td>27</td>
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<tr>
<td>0.0-7.5/3%</td>
<td>66</td>
<td>81</td>
<td>11</td>
<td>8</td>
<td>37</td>
<td>23</td>
<td>68</td>
<td>88</td>
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<td>13</td>
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<tr>
<td>0.0-10.0/4%</td>
<td>48</td>
<td>70</td>
<td>7</td>
<td>4</td>
<td>24</td>
<td>19</td>
<td>51</td>
<td>75</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>0.0-12.5/5%</td>
<td>28</td>
<td>55</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>8</td>
<td>39</td>
<td>59</td>
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<tr>
<td>0.0-15.0/6%</td>
<td>19</td>
<td>40</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>5</td>
<td>28</td>
<td>50</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.0-17.5/7%</td>
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<td>28</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>22</td>
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<td>0.0-20.0/8%</td>
<td>10</td>
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<td>0</td>
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<td>18</td>
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<td>0</td>
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<td>1</td>
<td>9</td>
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</tr>
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<td>21</td>
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<td>0.0-27.5/11%</td>
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<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>13</td>
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<tr>
<td>0.0-30.0/12%</td>
<td>0</td>
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<td>1</td>
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<td>0</td>
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</table>

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# Vascular Risk Prediction

## Sensitivity for TPA80

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>0.0-2.5/1%</td>
<td>100</td>
<td>100</td>
<td>96</td>
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<td>100</td>
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<td>88</td>
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<tr>
<td>0.0-10.0/4%</td>
<td>65</td>
<td>87</td>
<td>31</td>
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<td>23</td>
<td>72</td>
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</tr>
<tr>
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<td>23</td>
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<td>0.0-25.0/10%</td>
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<td>17</td>
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<td>5</td>
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</tbody>
</table>
Arteris Summary Observations

TPA80, a surrogate marker for coronary heart disease risk, is prevalent in over 10% of subjects up from the age of 40.

TPA80 prevalence increases with age.

Sensitivity of Risk Equations are low at current thresholds (AGLA maximal 23% sensitivity at the 10% threshold in age 40-65).
Total Plaque Area (TPA) - update

- In multivariable regression analyses, traditional coronary risk factors account for
- only 15-17% of IMT (16)
- only 13% of carotid stenosis (17)
- but account for 52% of TPA (17)

**Total Plaque Area (TPA) - update**

- Progression Rate of TPA is about 10 mm² / year
- Progression Rate of IMT is about 0.0147 to 0.0176 mm / year, image resolution is 0.3 mm
- Therefore: Sample size to assess effect of medical intervention
  - TPA: 120 patients per year (41)
  - IMT: 469 patients for 2 years (41)
  - IVUS: 500 patients for 1.5 years (42)

TPA outcome study  Stroke. 2002;33:2916-2922

<table>
<thead>
<tr>
<th>Plaque Area</th>
<th>5-Year Risk (%)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.00–0.11</td>
<td>6.3</td>
<td>1.0*</td>
<td></td>
</tr>
<tr>
<td>0.12–0.45</td>
<td>11.3</td>
<td>1.8 (1.1 to 3.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>0.46–1.18</td>
<td>13.2</td>
<td>2.1 (1.2 to 3.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>1.19–6.73</td>
<td>19.1</td>
<td>3.0 (1.8 to 4.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted†</td>
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<td></td>
</tr>
<tr>
<td>0.00–0.11</td>
<td>5.6</td>
<td>1.0*</td>
<td></td>
</tr>
<tr>
<td>0.12–0.45</td>
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<td>1.9 (1.1 to 3.3)</td>
<td>0.02</td>
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<td>19.5</td>
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</tr>
</tbody>
</table>

*Reference category.
†Adjusted for all baseline patient characteristics listed in Table 1.
TPA outcome study  Stroke. 2002;33:2916-2922
Total Plaque Area (TPA) - update

- TPA in ROC analysis
- Vascular Mortality, Spence Cohort

<table>
<thead>
<tr>
<th>N=</th>
<th>AUC</th>
<th>p=</th>
<th>95CI%</th>
<th>Sens</th>
<th>Spec</th>
</tr>
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<tbody>
<tr>
<td>Vasc Mort</td>
<td>1686</td>
<td>77</td>
<td>&lt;0.001</td>
<td>71-84</td>
<td>86%</td>
</tr>
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</table>

Hence: TPA as modifier of risk using EU-SCORE

Stroke. 2002;33:2916-2922
Total Plaque Area (TPA) - update

- TPA in ROC analysis
- AMI (N=13), Spence Cohort

<table>
<thead>
<tr>
<th></th>
<th>N=</th>
<th>AUC</th>
<th>p-value</th>
<th>95CI%</th>
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<td>AMI ATP III</td>
<td>684</td>
<td>68</td>
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<td>56-80</td>
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<td>AMI TPA PTP</td>
<td>684</td>
<td>74</td>
<td>&lt;0.001</td>
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<tr>
<td>Contrast</td>
<td>+6</td>
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</table>
**Total Plaque Area (TPA) - update**

- TPA in ROC analysis versus Calcium Scoring
- This database is currently being updated

### Table

<table>
<thead>
<tr>
<th>CS&lt;1000</th>
<th>n</th>
</tr>
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<tbody>
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<td>0</td>
<td>8</td>
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<table>
<thead>
<tr>
<th>Curve</th>
<th>Area</th>
<th>SE</th>
<th>p</th>
<th>95% CI of Area</th>
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<tbody>
<tr>
<td>TPA</td>
<td>0.904</td>
<td>0.0777</td>
<td>&lt;0.0001</td>
<td>0.852 to 0.957</td>
<td>have higher values</td>
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</tbody>
</table>

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Total Plaque Area (TPA) - update

- rightTPA in cumulative probability to detect AMI
- Tromso Cohort, N=6226, FU 6 years, age 60 years
- Only right Plaques were measured

Stroke 2007;38;2873-2880

Michel Romanens, © Varifo Foundation Olten 2010
Vascular Risk Prediction

Imaging Examples – just look and tell me your impression at the end
Imaging Examples – just look and tell me your impression at the end
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Vascular Risk Prediction

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Imaging Examples – just look and tell me your impression at the end
Vascular Risk Prediction

Imaging Examples – just look and tell me your impression at the end
Imaging Examples – just look and tell me your impression at the end
TABLE 2. Unadjusted and Adjusted 5-Year Risks and Relative Risks of Combined Outcome of Stroke, Myocardial Infarction, and Vascular Death by Quartile of Carotid Plaque Area (cm$^2$)

<table>
<thead>
<tr>
<th>Plaque Area</th>
<th>5-Year Risk (%)</th>
<th>Relative Risk (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Adjusted†</td>
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<td>$&lt;0.001$</td>
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*Reference category.
†Adjusted for all baseline patient characteristics listed in Table 1.
## Integrative Risk Prediction for the Individual

Additional information from atherosclerosis imaging

<table>
<thead>
<tr>
<th>Total plaque area (TPA) in mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPA mm²</td>
</tr>
<tr>
<td>PROCAM (%)</td>
</tr>
<tr>
<td>TPA-Posttest (%)</td>
</tr>
</tbody>
</table>

**Coronary Calcium Score Percentiles**

<table>
<thead>
<tr>
<th>CS%</th>
<th>&lt;25</th>
<th>25-49</th>
<th>50-74</th>
<th>75-89</th>
<th>90+</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCAM (%)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>CS%-Posttest (%)</td>
<td>2</td>
<td>15</td>
<td>26</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

Michel Romanens www.kardiolab.ch Juli 2008
Imaging Examples – the result of TPA was 1.04 cm$^2$

How to tell the result to the patient:

**TPA mm$^2$**

- **00-09**  green zone, excellent result
- **10-49**  orange zone, usually life style modifications
- **50-99**  red zone, prognostically relevant, ev. medications
- **100 +**  dark red zone, throw in all you have

do not talk about „severe“ atherosclerosis
this scares patients
Total Plaque Area (TPA) – update

When 25 patients were re-scanned by two technologists, the kappa was 0.85.

Total Plaque Area (TPA) – update

- In my experience since 03/2002 with > 2000 pts
  - View carotids in short axis, look for plaques
  - Trace plaques as appropriate
  - Risk categories based on quartiles:
    - Low <10, im 10-49, high 50-99, very high 100+ mm²
  - Reliable tracking of TPA during follow up with TPA < 100 (acceptable reproducibility)
  - With TPA > 100 highest risk, therefore no tracking needed, but maximal medical preventive therapy
  - The most important is to have a look at carotids
**Total Plaque Area (TPA) – update**

**How I do TPA**
- Patient in supine position
- Head slightly retroflected
- Head turned to right or left about 45°
- Transverse scan from jaw to clavicle
- Adjust brightness and gain optimally
- Look for plaques
- Find the largest longitudinal area of each plaque
- Freeze image
- If necessary, zoom in
- Measure TPA for each plaque
- Sum all plaques from both sides to the total plaque area
- Eventually record area of each plaque
- Eventually record TPA for right and left side separately
Vascular Risk Prediction

**Plaque area (mm²)**
- Q1: 0 to 9
- Q2: 10 to 49
- Q3: 50 to 99
- Q4: 100 +

**Quality of Plaque**
- small (1)
- small (1-3)
- large (3-5)
- complex

**Vascular risk**
- low
- intermediate
- high
- very high

**Reproducibility**
- very high
- high
- intermediate
- low

**Atherosclerosis tracking feasibility**
- very good
- good
- acceptable
- low

**Suitability for risk management using tracking**
- low
- high
- high
- low

**Qualitative Quartile definition by pure inspection**
- high
- low
- low
- high
Part 2: Statistics in Medicine

Beyond ROC analysis
Integrative Risk Prediction
Bayes Theorem
Posttest Risk
Net Reclassification Improvement
Activated Atherosclerosis

The same amount of plaque has different prognosis: example in current smokers versus non-smokers

Shaw, European Heart Journal 2006;27:968–975
Sequential Testing Rationale

Mortality from any cause further stratified for calcium score

Framingham Risk

Pretest

Posttest Risk

<10
11-100
101-400
401-1000
>1000

Low Risk
n=1,302

Intermediate Risk
n=5,876

High Risk
n=3,194

Event Rate

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Integrative Risk Prediction

Risk Calculators („global risk“)

+ 

New Test

= 

New Risk Category ? („new global risk“?)
Integrative Risk Prediction

Risk Calculators + New Test = New Risk Category

Miss too many with future AMI

Improve detection of high risk subjects

Better allocation of resources
Integrative Risk Prediction

Risk Calculators + New Test = New Risk Category

Miss too many with future AMI Pretest Probability

Improve detection of high risk subjects Sensitivities + Specificities

Better allocation of resources Posttest Probability
Integrative Risk Prediction

PTP = posttest probability of Newtest

A stepwise approach to improve c-statistics in cohorts re-discovered by Kardiolab (1)

1. Calculate Quartiles of Newtest in your cohort
2. Define de positivity cutoff of Newtest
3. Calculate Sens and Spec for every quartile of Newtest
4. Apply Bayes formula to every subject using a pretest-probability of your choice (e.g. PROCAM RISK)
5. Calculate PTP of Newtest
6. Recalculate ROC for PROCAM and Newtest-PTP
7. Assess level of statistical significance by Delong-Delong Method (2)


Integrative Risk Prediction

Calculation of Absolute Global Risk is accepted today

The Bayes Theorem allows you to exactly calculate posttest absolute risk of New Test

TPA, eventually in combination with ABS and hsCRP has greatest potential to improve

- prediction of absolute vascular risk
- adherence of patients to life style changes and medications (images tell more ...)
Integrative Risk Prediction

Perform your own posttest risk calculations on

www.scopri.ch/posttestcalculators1.html
NEWS FROM TPA FRONT

TPA and Risk Prediction for Stroke

• The Tromso study showed, that TPA was an independent predictor of stroke (paper not published yet)
NEWS FROM TPA FRONT

TPA amount not explained by risk factors

- Spence showed that an important amount of TPA is due to genetic factors
NEWS FROM TPA FRONT

Treating Arteries Instead of Risk Factors
A Paradigm Change in Management of Atherosclerosis

(Stroke. 2010;41:00-00.)

J. David Spence, BA, MBA, MD, FRCPC, FAHA; Daniel G. Hackam, BSc, MD, PhD, FRCPC

Figure 1. Plaque regression is much faster than most would expect. Left panel, a soft plaque at the origin of the left external carotid in a 64-year-old man using ezetimibe alone because of myalgias and cramps with statins. His plaque had progressed from 20 mm² the previous year to 26 mm² after stopping rosuvastatin. After restarting rosuvastatin 5 mg daily with CoQ10 200 mg daily to prevent myalgias, the plaque area regressed to 0.19 mm² over 3.5 months. The plaque had also become denser with regression of the soft plaque and more calcification.

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Vascular Risk Prediction

NEWS FROM TPA FRONT

Treating Arteries Instead of Risk Factors
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**Key Arguments against Imaging**

- no incremental value on top of CV risk factors, that explain > 90% of disease incidence
  - answer: based on ROC analysis, posterior probabilities and possibly on net reclassification improvements, several emerging risk factors give statistically significant incremental values
- It is not proven, that imaging helps to reduce events
  - answer: the ultimate proof is lacking, indeed. However, what we measure is atherosclerosis.
- Cost efficiency of imaging has to be clarified
  - this is true and could be performed easily using posttest probabilities and risk reduction calculations, if treatment goals were achieved.
- Imaging scares patients
  - that is a semantic problem. What we need is to talk frankly about posterior risk in absolute 10 year risk.

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Conclusions and future perspectives

- TPA has a high diagnostic value to predict events
- Useful to predict future AMI and vascular Death
- Should not be used per se but using posttest risk calculators (Bayes theorem)
- Can guide preventive therapy
- Can be used for atherosclerosis tracking
- Is as good as calcium scoring
- Imaging based risk prediction remains in the hands of the clinician
Conclusions and future perspectives

- TPA 2D is validated, but for the future, 3D is probably more desirable
- for now, 2D is ok and 3D fancy medicine should not prevent us from imaging our patients
- In TPA between 0 -100 2D imaging correlates probably very well with 3D imaging
Quantitative Decision Making in Sequential Testing

Thank You!