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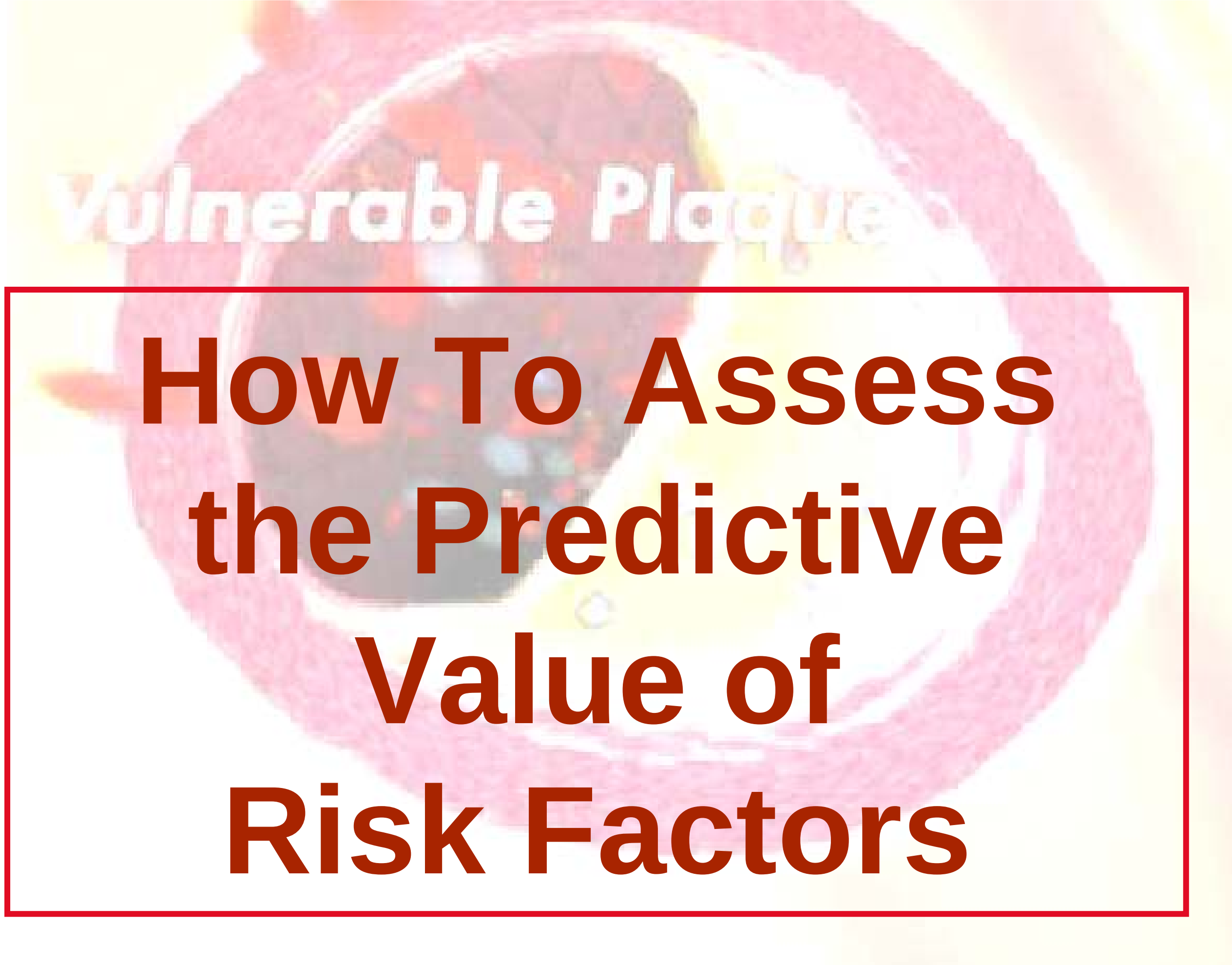



# How To Assess the Predictive Value of Risk Factors

**Michel Romanens, MD**
**Cardiology / Internal Medicine / Preventive Medicine / Cardioradiology**
**President Vascular Risk Foundation, www.varifo.ch**
**National Coordinator Taskforce Vascular Risk Prediction 2005-2008**
**National Coordinator Taskforce Atherosclerosis Imaging 2009- … ),**
**www.taskforce.atherosclerosisimaging.ch**

# Predictive Value of Risk Factors

Statistics in Medicine

Wolters Kluwer Health | Lippincott Williams & Wilkins

EUROPEAN SOCIETY OF CARDIOLOGY®

**Review**

**Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics**

Michel Romanens[a], Franz Ackermann[b], John David Spence[c], Roger Darioli[d], Nicolas Rodondi[d], Roberto Corti[e], Georg Noll[e], Matthias Schwenkglenks[f] and Michael Pencina[g]

[a]Cantonal Hospital, [b]Vascular Risk Foundation, Olten, Switzerland, [c]Stroke Prevention and Atherosclerosis Research Centre, London, Ontario, Canada, [d]Department of Ambulatory Care and Community Medicine, University of Lausanne, Medical Outpatient Clinic, University Hospital, Lausanne, [e]Cardiology Department, University Hospital, Zurich, [f]Head European Center of Pharmaceutical Medicine (ECPM) Research, Basel, Switzerland and [g]Department of Mathematics and Statistics, Framingham Heart Study, Boston University, Boston, Massachusetts, USA

# Predictive Value of Risk Factors

Statistics in Medicine

On Behalf of the
Dipartimento di Science Medico-Diagnostiche
E Terapie Speciali
Università degli Studi di Padova, Italia

Invited Speaker
Michel Romanens, MD

International Conference on Laboratory Medicine
BEYOND „NORMAL“ VALUES
Padova, October 14$^{th}$, 2010
Aula Magna del Bo – University of Padova

# Predictive Value of Risk Factors



## Lectures at the meeting

Carl Heneghan, Oxford, UK: **How clinicians use laboratory results**
Gerard Siest, Nancy, France: **Development and evolution of the IFCC theory on reference values. Need for more practical recommendations**
Ferruccio Ceriotti, Milano, Italy: **Towards common reference intervals.**
Mauro Panteghni, Milano, Italy: **Impact of standardization approaches on the suitability and interpretation of laboratory results.**
Per Hyltoft Peterson, Bergen, Norway. **Analytical performance, reference values and decision limits.**
David Armbruster, Abbott Park, Illinois, USA: **The role of the IVD industry in generating reference intervals.**
Callum Fraser, Dundee, Scotland, UK: **Biochemical individuality and reference change values.**
Michel Romanens, Basel. Switzerland: **How to assess the predictive Value of risk factors.**
Giuseppe Novelli, Roma, Italy. **Assessment of genetic testing in clinical practice.**
Sophie Visvikis-Siest, Nancy, France: **Biobanks and reference values.**
George D. Lundberg, San Francisco, California, USA. **Laboratory information: the brain-to-brain loop 40 years later.**
Mario Plebani, Padova, Italy: **Current threats and challenges to the brain-to-brain loop theory.**

# Predictive Value of Risk Factors



## How do I Tell the Patient

- ✓ (My) Clinical approach to statistics in medicine
- ✓ look at absolute differences
- ✓ be aware of small number statistics
- ✓ statistical methods and results should “make sense” in clinical thinking

# Predictive Value of Risk Factors

Statistics in Medicine

## Further Reading and Downloads


✓ Pencina M, et al. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond.

- Statist. Med. 2008; 27:157–172

✓ Hlatky M, Greenland P, Arnett D, et al. Criteria for Evaluation of Novel Markers of Cardiovascular Risk. A Scientific Statement From the American Heart Association.

- Circulation. 2009;119:2408-2416

✓Romanens M, Ackermann F, Spence J et. al. Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics.

- European Journal of Cardiovascular Prevention and Rehabilitation 2010, 17:18–23


This talk and involved papers can be downloaded at www.scopri.ch/stats.pdf and www.scopri.ch/stats.zip

# Predictive Value of Risk Factors



Problem with small numbers

- ✓ Communication of risk: absolute versus relative
- ✓ Absolute Risk: 1:10'000 / 10 years = 0.01%
- ✓ Absolute Risk: 2:10'000 / 10 years = 0.02%,
  but a relative decrease of 50%!

# Predictive Value of Risk Factors

Statistics in Medicine

Small numbers: Risk Avoidance Creep

✓ Paper: “The Public Health Hazards of Risk Avoidance Associated With Public Reporting of Risk-Adjusted Outcomes in Coronary Intervention”

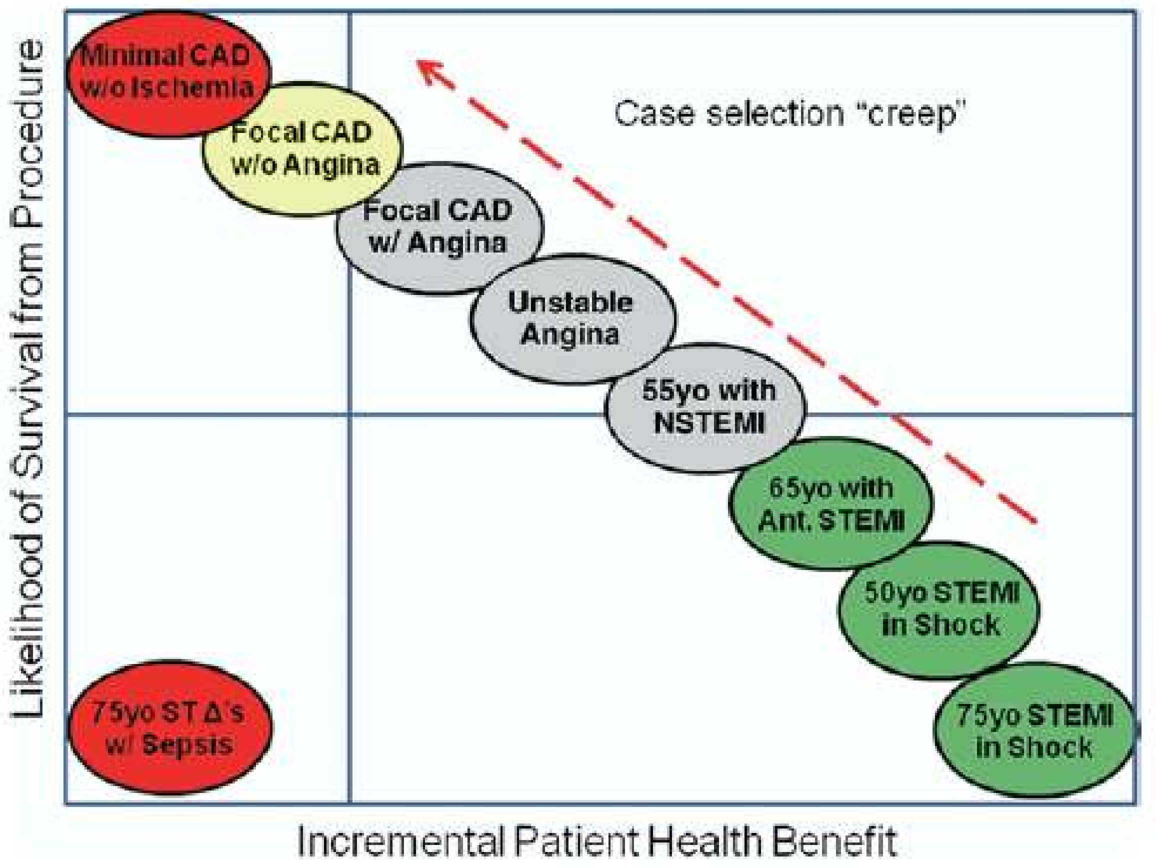
- Publically reporting of mortality rates for PCI
- New York PCI registry 2003: Mortality 0.58/year
- PCI in cardiogenic shock: 2003 2.28%; 2004: 1.9%, 2005: 1.29 %
- Observation: decrease of PCI in highest risk patients

J Am Coll Cardiol 2009;53:825–30

# Predictive Value of Risk Factors



## Small numbers: Risk Avoidance Creep




J Am Coll Cardiol 2009;53:825–30

# Predictive Value of Risk Factors

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Statistics in Medicine

Small numbers: Risk Avoidance Creep

- ✓ Institution A: mortality 6/1000/year
- ✓ Institution B: mortality 3/1000/year
  - Difference: - 3/1000/year = 50% lower mortality
  - Difference = perceived as better quality of Inst, B
  - Incentive for Inst. A: reduce mortality = do not treat highest risk patients (those who benefit most from intervention)

J Am Coll Cardiol 2009;53:825–30

# Predictive Value of Risk Factors

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Statistics in Medicine

Small Numbers: Prostate Cancer

✓ Paper: “Screening and Prostate-Cancer Mortality in a Randomized European Study”

- Conclusion: “PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis.”

N Engl J Med 2009;360;13:1320-1328

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# Predictive Value of Risk Factors

Statistics in Medicine

## Small Numbers: Prostate Cancer

- ✓ 182’000 men aged 50-74 years in Europe
- ✓ PSA cutoff: 3.0 ng/ml → biopsy
  - Deaths: screening 0.35/1000/year, control 0.41/1000/year; Δ 0.06/1000/year; p=0.01
    - Model used: Cox prop. hazard ratio
- ✓ Prostate-Cancer Deaths CH for 65-84 years:
  - 1.7/1000/year = 0.2%/year
  - 1.7% in 10 years
  - Guidelines CH: stop PSA screening

N Engl J Med 2009;360;13:1320-1328

# Predictive Value of Risk Factors

Statistics in Medicine

Small Numbers: Prostate Cancer

- ✓ Improved Guides for Patients
- ✓ Communicate absolute and not relative risk!
- ✓ Do not scare patients with small numbers
- ✓ Avoid over-medicalization and harms to patients

N Engl J Med 2009;360;13:1320-1328

# Predictive Value of Risk Factors

Statistics in Medicine

## Further Topics of this Talk

- ✓ Diagnostic Sensitivity / Specificity versus Likelihood Ratio and other Tools
- ✓ Differences between ROC and Hazard Ratio
- ✓ Difference between Diagnosis and Prevention
- ✓ Value of Pre- and Post-test probabilities
- ✓ Examples in the Field of Vascular Prevention

# Predictive Value of Risk Factors

Statistics in Medicine

## Criteria for a good test (Overview)

- ✓ Independent comparison with a gold standard
- ✓ Large spectrum of pretest probabilities
- ✓ Ability to change clinical decisions
- ✓ High reproducibility
- ✓ Validation in several populations
- ✓ High accuracy to discriminate individuals with and without disease

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# Predictive Value of Risk Factors



## Methods to Evaluate Model Performance (Overview)

- ✓ Measures of relative risk: relative risk, odds ratios, hazard ratios.
- ✓ Measures of model performance: c-statistics, calibration $\chi^2$
- ✓ Measures of model improvement: difference in c-statistics, NRI, IDI.
  - IDI: Integrated Discrimination Improvement equals NRI over all cutoffs of the new test
- ✓ Methods to add new test: posttest risk calculation, redevelopment of the model with new test variable.

# Predictive Value of Risk Factors

Statistics in Medicine

Two-by-Two Table
is a Basic Concept

| | |
|---|---|
| TRUE POSITIVE | TRUE NEGATIVE |
| FALSE POSITIVE | FALSE NEGATIVE |

# Predictive Value of Risk Factors

## Definitions of a Test Performance

**Table 1 Calculation of test performances (modified from Ref. [7])**

| |
|---|
| SE = TP/(TP + FN) |
| SP = TN/(TN + FP) |
| PPV = TP/(TP + FP) |
| NPV = TN/(TN + FN) |
| pLR = SE/(1 − SP) |
| nLR = (1 − SE)/SP |
| ACC = (TP + TN)/(TP + TN + FP + FN) |

For the calculation of probabilities, a range from zero to 1.00 is used. Multiply by 100 to obtain percentages and accordingly, sensitivities and specificities are not expressed in percent but in percent divided by 100. ACC, accuracy; FN, false negative; FP, false positive; nLR, negative likelihood ratio; NPV, negative predictive value; pLR, positive likelihood ratio; PPV, positive predictive value; SE, sensitivity; SP, specificity; TN, true negative; TP, true positive.

# Predictive Value of Risk Factors

Statistics in Medicine

## Definitions of a Test Performance

✓ Sensitivity: rate of true positives in a positive test result (TP / TP + FN)

✓ Specificity: rate of true negatives in a negative test result (TN / TN + FP)

- Sensitivity and Specificity results are dependent of the prevalence / pretest probability

Nancy Cook. Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction. Circulation. 2007;115:928-935

# Predictive Value of Risk Factors



Definitions of a Test Performance

✓ Positive predictive value: rate of false positives in a positive test result (TP / TP + FP)
✓ Negative predictive value: rate of false negatives in a negative test result (TN / TN + FN)

- Predictive values are dependent of the prevalence / pretest probability

# Predictive Value of Risk Factors

Statistics in Medicine

Definitions of a Test Performance

- ✓ Likelihood ratio: may change the pretest probability to a posttest probability
- ✓ PROCAM 10 year coronary risk function (IAS)

  - Example: SE 30%, SP 90%
  - pLR of 30/(100–90) = 3.00
  - nLR of (100–30)/90 = 0.78
  - PROCAM: good pLR, weak nLR

# Predictive Value of Risk Factors

Statistics in Medicine

Odds ratio versus relative risk:

✓ Titanic drama:
✓ 154 of 462 women died; 308 survived
✓ 709 of 851 men died; 142 survived

- Odds for women: 154:308 = 0.5
- Odds for men: 709:142 = 5 (4.993)
- Odds ratio: 5:0.5 = 10 (9.986)
- Risk for women: 33%
- Risk for men: 83%
- Relative Risk: 0.83:0.33 = 2.5

# Predictive Value of Risk Factors

Statistics in Medicine

Odds ratio versus relative risk:

- ✓ Odds ratio (OR) and relative risk (RR) compare the relative likelihood
- ✓ The relative risk is easier to interpret and consistent with the general intuition.
- ✓ Odds ratio has wider use:
  - logistic regression works with the log of the odds ratio, not relative risk.
  - Odds ratio is favored for case-control and retrospective studies.
  - Relative risk and hazard risk is used in randomized controlled trials and cohort studies

http://www.musc.edu/dc/icrebm/oddsratio.html

# Predictive Value of Risk Factors

Statistics in Medicine

Are You Looking for Diagnosis or Prognosis ?

✓ In preventive medicine ‘establishing a diagnosis’ – is replaced by ‘estimating a risk for a future diagnosis’

✓ In Preventive Vascular Medicine:
- amount of atherosclerosis is largely defined by risk factors (=prognosis) and is related to the risk of future atherothrombosis (=diagnosis)
- This remains true in subjects after a clinical vascular event
- Good control of cardiovascular risk factors reduces atherosclerotic burden and risk for clinical events

Statistics in Medicine

# Predictive Value of Risk Factors

Relative Indicators of Test Performance – ROC

- ✓ ROC curves (c-statistic): plot of SE versus 1 – SP over all possible risk thresholds after inclusion of a continuous predictor.
- ✓ Area under the ROC curve (AUC): measure of ability to distinguish future events from non-events.
- ✓ Incremental value of a new test: additional diagnostic information of e.g. 0.12 (or 12%).
- ✓ Statistical difference: usually by the DeLong-DeLong method for comparison of ROC curves

# Predictive Value of Risk Factors



## Relative Indicators of Test Performance – ROC

✓ a value of 74% (AUC 0.74) means that the probability for the predicted risk is 74% higher in cases than in non-cases

# Predictive Value of Risk Factors



ROC versus Other Measures of Risk

✓ ROC Curves may refute a clinically meaningful new test (e.g. HDL)

✓ ROC Curves refute additional benefit despite significant increases in

- Hazard Ratios: ROC = no time analysis, hazard ratios: time to event included in the model
- Net Reclassification Improvements (NRI)

# Predictive Value of Risk Factors

Statistics in Medicine

## ROC versus Relative Risk / Likelihood Ratios

✓ Example: Cardiovascular Disease Prediction in the Women's Health Study (estimates from COX proportional Hazard Models)

| | RR | p | AUC |
|---|---|---|---|
| Age, BPs, Smoking | | | 0.76 |
| Adding HDL | 1.7 | .0001 | 0.77 |
| Adding total Cholesterol | 1.4 | .0001 | 0.77 |
| Adding LDL | 1.4 | .0001 | 0.77 |

RR compares risk across 2 SD units, except for smoking, which is yes versus no
RR: The likelihood ratio statistic tests the significance of the addition of each variable separately to a predictive model that included age only

Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293–1304.

# Predictive Value of Risk Factors

Statistics in Medicine

ROC versus Relative Risk / Likelihood Ratios

✓ Example: Cardiovascular Disease Prediction in the Women's Health Study (estimates from COX proportional Hazard Models)
✓ ?AUC or COX models, relative risk, odds ecc?
✓ an ongoing scientific debate
✓ a nice way around: NRI (Michael Pencina, Medicine and Statistics, 2008)
  - Co-Editor of Statistics in Medicine
  - Principal Statistician of the Framingham Heart Study, University of Boston

# Predictive Value of Risk Factors



## Net Reclassification Improvement (NRI)

| Model without HDL | Model with HDL | | | Total |
|---|---|---|---|---|
| **Participants who experience a CHD event** | | | | |
| Frequency row percentage | <6% | 6–20% | >20% | |
| <6% | 39 | 15 | 0 | 54 |
| | 72.22 | 27.78 | 0.00 | |
| 6–20% | 4 | 87 | 14 | 105 |
| | 3.81 | 82.86 | 13.33 | |
| >20% | 0 | 3 | 21 | 24 |
| | 0.00 | 12.50 | 87.50 | |
| Total | 43 | 105 | 35 | 183 |
| **Participants who do not experience a CHD event** | | | | |
| Frequency row percentage | <6% | 6–20% | >20% | |
| <6% | 1959 | 142 | 0 | 2101 |
| | 93.24 | 6.76 | 0.00 | |
| 6–20% | 148 | 703 | 31 | 882 |
| | 16.78 | 79.71 | 3.51 | |
| >20% | 1 | 25 | 72 | 98 |
| | 1.02 | 25.51 | 73.47 | |
| Total | 2108 | 870 | 103 | 3081 |

# Predictive Value of Risk Factors



Net Reclassification Improvement NRI using HDL in the Framingham Cohort

- Participants within different risk rates
  - Risk I: 0-5%; Risk II: 6-20%; Risk III: >20%
- Participants with and without an event
- Model without and with HDL
- Example 1: 15 of 54 Risk I → II in those with events = correct shift (counted: +15)
- Example 2: 4 of 105 Risk II → Risk I in those with events = incorrect shift (counted: - 4)
- NRI: 22/183 +1/3081 = 12.02 + 0.03% = 12.1%.

Statistics in Medicine

# Predictive Value of Risk Factors

Net Reclassification Improvement NRI using HDL in the Framingham Cohort

- 12.1% were correctly categorized into a higher or lower risk category
- statistically significant
- Using ROC analysis, no improvement would have been observed (Women's Health Study)
- changes in risk categories in 12% of participants: this has important clinical implications
- e.g. lower LDL levels need to be achieved in higher risk subjects
- based on NRI: HDL improves sensitivity without a loss in specificity in the Framingham Cohort

# Predictive Value of Risk Factors



Example 1: Sensitive Troponin Assays (STA), Integration in Different Pretest Probabilities for Acute Myocardial Infarction (AMI)

- ✓ Measure Myocardial Cell Injury
- ✓ Early (3 h) Detection of Acute Myocardial Infarction
- ✓ Test Performance assessed in a population with 17% pretest probability for AMI
- ✓ Poor Sensitivity in Patients with Unstable Angina

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

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# Predictive Value of Risk Factors

Statistics in Medicine

## Example 1: Sensitive Troponin Assays (STA)

| | Sens | Spec | PPV | NPV |
|---|---|---|---|---|
| Sensitive Troponin Assays | | | | |
| Abbott–Architect Troponin I | | | | |
| 99th percentile, 0.028 µg/liter | 86 | 92 | 97 | 69 |
| Roche High-Sensitive Troponin T | | | | |
| 99th percentile, 0.014 µg/liter | 95 | 80 | 99 | 50 |
| Roche Troponin I | | | | |
| 99th percentile, 0.160 µg/liter | 84 | 94 | 97 | 73 |
| Siemens Troponin I Ultra | | | | |
| 99th percentile, 0.040 µg/liter | 89 | 92 | 98 | 68 |
| Standard Troponin Assay | | | | |
| Roche Troponin T 4th Generation | | | | |
| Limit of detection, 0.010 µg/liter | 83 | 93 | 97 | 72 |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

# Predictive Value of Risk Factors

Statistics in Medicine

Example 1: Sensitive Troponin Assays (STA)

✓ Clinical Utility of Troponins ?

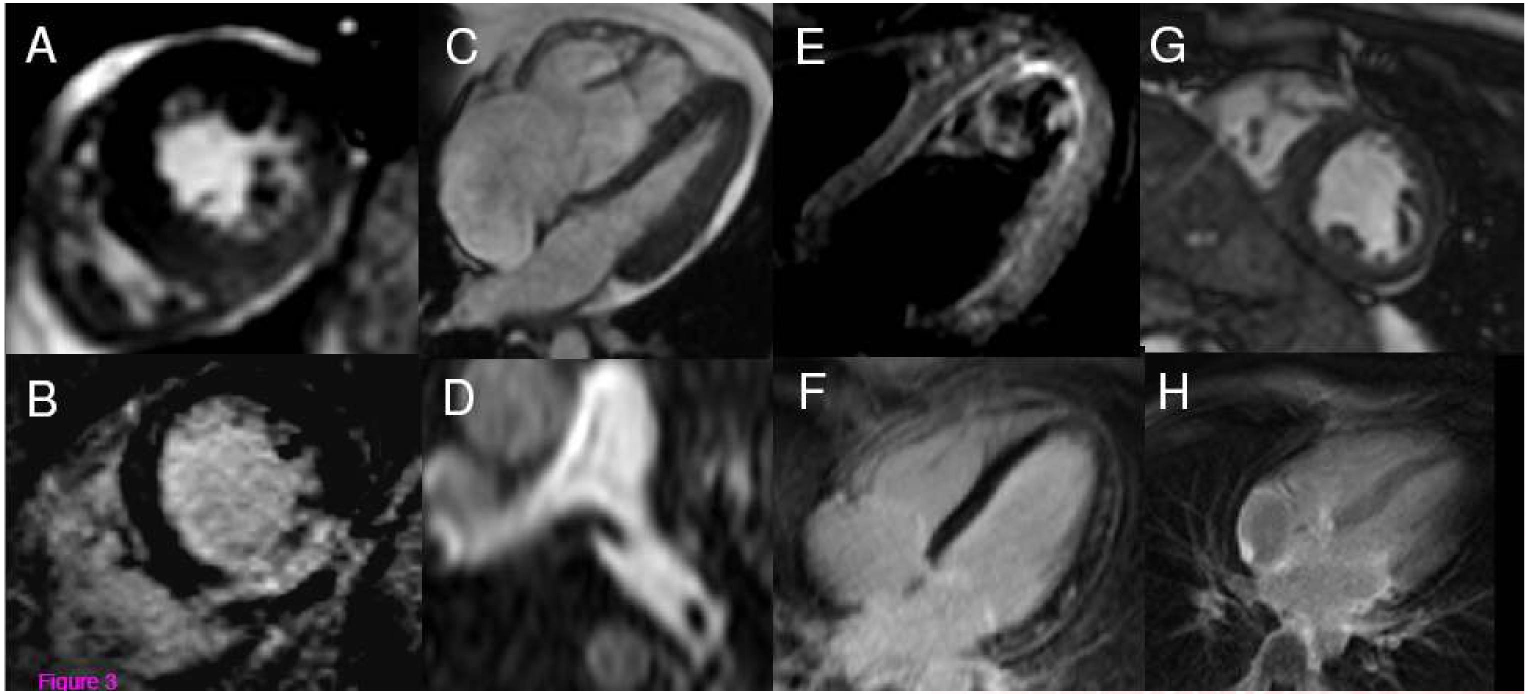
- Problem with False Positives (Injury of myocardial Cells from other causes)
- Effect of Pretest Probability on Posttest Risk for Myocardial Infarction

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

# Predictive Value of Risk Factors



## Example 1: Sensitive Troponin Assays (STA)




A+B: acute myocardial Infarction

C+D: acute pulmonary embolism

E+F: myocarditis

G+H: amyloidosis

Steen H, Madadi M, Lehrke S. Staged cardiovascular magnetic resonance for differential diagnosis of Troponin T positive patients with low likelihood for acute coronary syndrome. Journal of Cardiovascular Magnetic Resonance 2010, 12:51

# Predictive Value of Risk Factors

Statistics in Medicine

Example 1: Sensitive Troponin Assays (STA)

✓ Posttest Risk Using the Bayes Theorem
✓ Test gives positive result:

$$(PV \times SE) / [PV \times SE + (1 - PV) \times (1 - SP)]$$

✓ Test gives negative result:

$$[PV \times (1 - SE)] / [PV \times (1 - SE) + SP \times (1 - PV)]$$

| | |
|---|---|
| PV | Prevalence for a disease |
| SE | sensitivity |
| SP | specificity |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

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# Predictive Value of Risk Factors

Statistics in Medicine

## Example 1: Sensitive Troponin Assays (STA)
## Definition of Risk For AMI without STA / Troponin

| | Risk Points |
|---|---|
| Age <58 | 0 |
| Age 58-65 | 2 |
| Age 66-74 | 5 |
| Age > 74 | 5 |
| Weight kg <69 | 0 |
| Weight kg 69-75 | 1 |
| Weight 76-85 | 2 |
| Weight > 85 | 4 |
| Creatin Cl ml/min > 99 | 0 |
| Creatin Cl ml/min 77-99 | 3 |
| Creatin Cl ml/min 58-76 | 5 |
| Creatin Cl ml/min <58 | 9 |
| ST depression 0.0 | 0 |
| ST depression 0.1-0-9 | 1 |
| ST depression 1-0-1.8 | 6 |
| ST depression > 1.9 | 14 |
| BBB configuration (e.g. LBBB) | 10 |

Death / AMI at 30 d (%)

| Points | Risk (%) |
|---|---|
| 0 | 1 |
| 10 | 2 |
| 15 | 3 |
| 20 | 5 |
| 25 | 8 |
| 30 | 12 |
| 35 | 18 |

Westerhout C, Fu Y, Lauer M et al. Short- and Long-Term Risk Stratification in Acute Coronary Snycdromes. JACC 2006;48:939-947.

# Predictive Value of Risk Factors

Statistics in Medicine

## Example 1: Sensitive Troponin Assays (STA)

| | Sens | Spec | PPV | NPV |
|---|---|---|---|---|
| Sensitive Troponin Assays | | | | |
| Abbott–Architect Troponin I | | | | |
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| 99th percentile, 0.014 μg/liter | 95 | 80 | 99 | 50 |
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| Siemens Troponin I Ultra | | | | |
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| Standard Troponin Assay | | | | |
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| Limit of detection, 0.010 μg/liter | 83 | 93 | 97 | 72 |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

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# Predictive Value of Risk Factors



## Example 1: Sensitive Troponin Assays (STA) Posttest Risk for Death / AMI at 30 d in a low risk subject with a clinical pretest probability of 1%

**Low Risk subject**

| **Test positive** | Abbott | Roche 1 | Roche 2 | Siemens | Standard |
|---|---|---|---|---|---|
| PRETEST PROBABILITY | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.10 | 0.05 | 0.12 | 0.10 | 0.11 |
| | | | | | |
| **Test negative** | | | | | |
| PRETEST PROBABILITY | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

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# Predictive Value of Risk Factors



## Example 1: Sensitive Troponin Assays (STA) Posttest Risk for Death / AMI at 30 d in a intermediate risk subject with a clinical pretest probability of 5%

| Intermediate Risk Subject | | | | | |
|---|---|---|---|---|---|
| **Test positive** | Abbott | Roche 1 | Roche 2 | Siemens | Standard |
| PRETEST PROBABILITY | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.36 | 0.20 | 0.42 | 0.37 | 0.38 |
| | | | | | |
| **Test negative** | | | | | |
| PRETEST PROBABILITY | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.01 | 0.00 | 0.01 | 0.01 | 0.01 |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

# Predictive Value of Risk Factors

Statistics in Medicine

## Example 1: Sensitive Troponin Assays (STA) Posttest Risk for Death / AMI at 30 d in a high risk subject with a clinical pretest probability of 15%

**High Risk Subject**

| **Test positive** | Abbott | Roche 1 | Roche 2 | Siemens | Standard |
|---|---|---|---|---|---|
| PRETEST | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.65 | 0.46 | 0.71 | 0.66 | 0.68 |
| | | | | | |
| **Test negative** | | | | | |
| PRETEST PROBABILITY | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| SENSITIVITY | 0.86 | 0.95 | 0.84 | 0.89 | 0.83 |
| SPECIFICITY | 0.92 | 0.80 | 0.94 | 0.92 | 0.93 |
| RESULT | 0.03 | 0.01 | 0.03 | 0.02 | 0.03 |

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

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# Predictive Value of Risk Factors

Statistics in Medicine

## Example 1: Sensitive Troponin Assays (STA): Messages

- ✓ Sensitive Troponin Assays: high sensitivity and specificity for AMI and Early Detection of risk for AMI
- ✓ All assays have a relatively low posttest risk in low risk subjects – defined by clinical, ECG variables and renal function
- ✓ In low posttest risk: use of medical intervention (e.g. heparin, aspirin, clopidogrel in combination, and coronary angiography) may expose patients at unnecessary risks

Reichlin T Hochholzer W, Bassetti S. Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays. N Engl J Med 2009;361:858-67.

# Predictive Value of Risk Factors

Statistics in Medicine

Example 2: does hs CRP improve risk prediction ?

**Epidemiology**

**C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction**

**The Reynolds Risk Score for Men**

Paul M Ridker, MD; Nina P. Paynter, PhD; Nader Rifai, PhD;
J. Michael Gaziano, MD; Nancy R. Cook, ScD

Riedker P, Paynter N, Rifai N et al. C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction. The Reynolds Risk Score for Men. Circulation. 2008;118: 2243-2251

# Predictive Value of Risk Factors

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Statistics in Medicine

Example 2: does hs CRP improve risk prediction ?

- ✓ N=10'724 men FU 10.8 years
- ✓ Why was NRI reported only for the combination of hsCRP+FamilyHx ?

Riedker P, Paynter N, Rifai N et al. C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction. The Reynolds Risk Score for Men. Circulation. 2008;118: 2243-2251

# Predictive Value of Risk Factors



## Example 2: does hs CRP improve risk prediction ?

**Table 2. Model Fit, Discrimination, and Reclassification Indices in a Global Risk Prediction Algorithm Based on Traditional* Factors (Model A) and on Traditional Factors Plus hsCRP and Parental History of Myocardial Infarction Before Age 60 Years (Model B)**

| End Point/ Measure | Model A: Without CRP or Parental History | Model B: With CRP and Parental History | *P*† |
|---|---|---|---|
| CVD | | | |
| BIC | 23 048 | 23 008 | <0.001 |
| C-index | 0.699 | 0.708 | <0.001 |
| $J^2$ | 40.1‡ | 15.6 | ... |
| NRI, % | ... | 5.3 | <0.001 |
| CNRI, % | ... | 14.2 | <0.001 |
| CHD | | | |
| BIC | 19 196 | 19 157 | <0.001 |
| C-index | 0.689 | 0.700 | <0.001 |
| $J^2$ | 50.1‡ | 12.3 | ... |
| NRI, % | ... | 6.8 | <0.001 |
| CNRI, % | ... | 13.6 | <0.001 |

CVD indicates cardiovascular disease; CHD, coronary heart disease.
*Traditional factors include age, blood pressure, smoking status, total cholesterol and HDLC. The J-squared and c-statistics are based on survival estimates at 7 years, and the NRI and CNRI are based on case-control status as of 7 years, ignoring censored observations.
†Likelihood ratio test for comparison of models, bootstrap for comparison of C-indices.
‡P<0.01, indicating significant deviation of observed and predicted risk in reclassified strata.

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Example 2: does hs CRP improve risk prediction ?

✓ Standard Variables included in Risk Calculators

| | PROCAM Europe | SCORE Europe | NCEP III USA |
|---|---|---|---|
| Age | yes | yes | yes |
| Gender | yes | yes | yes |
| T-Cholesterol | no | yes | yes |
| LDL | yes | no | no |
| HDL | yes | no | yes |
| Triglycerides | yes | no | no |
| Smoker | yes | yes | yes |
| Blood Press | yes | yes | yes |
| Fam Hx | yes | yes | no |

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Example 2: does hs CRP improve risk prediction ?

✓ Consider a PROCAM risk (low risk population x 0.7)

| | | | |
|---|---|---|---|
| Man age | 65 years | | |
| HDL | 1.5 mmol/l | | |
| LDL | 3.5 mmol/l | | |
| TG | 1.3 mmol/l | | |
| BPs | 130 mm Hg | | |
| Smoker | no | | |
| Fam Hx for CAD | no | | |
| CRP mg/l | 1.0 | 5.0 | 10.0 |
| PROCAM RISK | 6.7% | 6.7% | 6.7% |
| Reynolds RISK | 6.3% | 7.4% | 7.9% |

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## Example 2: does hs CRP improve risk prediction ?

✓ Computational formula for the Reynolds Risk Score for men

10-year cardiovascular disease risk (%)

$$= [1 - 0.8990^{(\exp[B - 33.097])}] \times 100\%$$

B=

| | |
|---|---|
| Age | 4.385 |
| BP | 2.607 |
| CHOL | 0.963 |
| HDL | 0.772 |
| SMOKER | 0.405 |
| Fam Hx | 0.541 |
| hs CRP | 0.102 |

**Appendix C**: Computational formula for the Reynolds Risk Score for men

**10-year cardiovascular disease risk (%)** = $[1 - 0.8990^{(\exp[B-33.097])}] \times 100\%$ where

B = 4.385 x natural logarithm(age) + 2.607 x natural logarithm(systolic blood pressure) + 0.963 x natural logarithm(total cholesterol) - 0.772 x natural logarithm(high-density lipoprotein cholesterol) + 0.405 (if current smoker) + 0.102 x natural logarithm(high-sensitivity C-reactive protein) + 0.541 (if parental history of premature myocardial infarction)

Riedker P, Paynter N, Rifai N et al. C-Reactive Protein and Parental History Improve Global Cardiovascular Risk Prediction. The Reynolds Risk Score for Men. Circulation. 2008;118: 2243-2251

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Example 2: does hs CRP improve risk prediction ?

- ✓ In the U.S. the Reynolds calculator may be more appropriate than the Framingham risk calculator (no Fam History included in NCEP III)
- ✓ However, NRI is low for the whole population (≈5%) and only acceptable for intermediate risk subjects (≈15%)
- ✓ In Europe, the addition of CRP is unlikeli to change risk categories, because CRP is a weak risk modifier
- ✓ Refer to http://scopri.ch/riskalgorithms.htm

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## Example 3: Does Coronary Calcium Improve Coronary Risk Prediction

✓ Heinz Nixdorff Recall Study

- N= 4‘129 participants
- Incidence at 5 years: 2.3% for Death / AMI
- NRI for pretest of 6-20%: 31%
- AUC Framingham 0.69
- AUC CAC 0.74 (p=0.00001)

Erbel R, Möhlenkamp S, Moebus S. Coronary Risk Stratification, Discrimination, and Reclassification Improvement Based on Quantification of Subclinical Coronary Atherosclerosis. J Am Coll Cardiol

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## Example 4: Should we do coronary calcium then?

- ✓ No!
- ✓ Need for more comparative studies
- ✓ CAC versus Carotid Plaque
- ✓ Work in Progress at our institution

Kappa agreement was 0.23 (p<0.0001) for quartiles of TPA and CAC, with 49 (14%) of subjects exhibiting the 3. or 4. quartile of TPA, but having the 1. quartile CAC and 29 (9%) of subjects exhibiting the 3. or 4. quartile of CAC but the first quartile of TPA (Pearson's X2 statistic 5.8, p=0.016, Table 2).

| | CAC quartiles | | | | |
|---|---|---|---|---|---|
| TPA quartiles | 1 | 2 | 3 | 4 | Total |
| 1 | 40 | 13 | 18 | 11 | 82 |
| 2 | 48 | 11 | 21 | 12 | 92 |
| 3 | 29 | 10 | 27 | 22 | 88 |
| 4 | 20 | 9 | 15 | 44 | 88 |
| Total | 137 | 43 | 81 | 89 | 350 |

Romanens M, Ackermann F, Schwenkglenks M et al. Emerging Risk Modifiers Based on Atherosclerosis Imaging: Fancy Radiology or Simple Bedside Ultrasound? Abstract, Swiss Society of Internal Medicine 2008

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Example 4: Should we do coronary calcium then?

✓ N=428 with CAC and TPA in the same individual

| | | % |
|---|---|---|
| TPA = 0 | CAC = 0 | 5 |
| TPA = 0 | CAC ≠ 0 | 3 |
| TPA ≠ 0 | CAC = 0 | 30 |
| TPA ≠ 0 | CAC ≠ 0 | 62 |

Romanens M, Ackermann F, Schwenkglenks M et al. Emerging Risk Modifiers Based on Atherosclerosis Imaging: Fancy Radiology or Simple Bedside Ultrasound? Abstract, Swiss Society of Internal Medicine 2008

# Predictive Value of Risk Factors

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Example 4: Should we Do Coronary Calcium then?

- ✓ Simple tracing of longitudinal plaque surfaces ($mm^2$)
- ✓ reproducible, use for atherosclerosis tracking +++
- ✓ no radiation burden
- ✓ low cost examination

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Summary (1)

- ✓ Differences among groups: large spectrum of statistical prodedures
- ✓ Clinical Relevance of A New Test
  - First: are observed differences clinically important ?
  - Second: are differencies statistically significant
- ✓ Small number statistics as a quality benchmark?
- ✓ Statistics may cause harm
  - risk avoidance creep
  - Extensive testing in patients with suspicion of prostate cancer

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# Predictive Value of Risk Factors

## Summary (2)

- ✓ Improved Risk Prediction using NRI
  - Intuitively correct
  - Allows for better allocation of resources
  - gives clinical meaningful results
- ✓ Improvements in pretest probabilities needed
  - High sensitivity and specificity does not exlude low posttest risk in a positive test
- ✓ CRP is unlikeli to improve risk in Europe

# Predictive Value of Risk Factors



## Summary (3)

✓ Last but not least:

- More studies are needed comparing different emerging risk factors in the same population, e.g. laboratory tests versus atherosclerosis imaging

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## Multiple Choice Questions (1)

A statistically non significant difference in AUC of a standard versus a new test can be interpreted as follows

A) New test is not superior to the other and should not be used in clinical practice

B) Each new test is valid, if relative risk exceeds at least 2.0, irrespective of AUC (e.g. using hazard ratios).

C) The clinical significance of a test is high, if there is a statistically significant shift in risk classification using the net reclassification improvement (NRI), even if differences in AUC are not statistically significant.

D) Non superiority and therefore clinical irrelevance is only proven, when the difference in AUC is not significant based upon the Delong-Delong Method (Biometrics 1988;44:837–45)

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## Multiple Choice Questions (2)

Posttest risk calculations are

A) Based upon Sensitivity and Specificity
B) Based upon Test accuracy
C) Based upon The Youden Index
D) Dependent on pretest probabilities

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## Multiple Choice Questions (3)

Criteria for a good test to predict coronary risk are

A) Large Spectrum of Pretest-Probabilities
B) Validation in Several Populations
C) Results are obtained within few minutes
D) High Reproducibility