Comparison and evaluation of cardiac biomarkers in patients with intermittent claudication: Results from the CAVASIC Study

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Applicable Methods in case-control studies

- **Scientific question**: Are biomarkers associated with the outcome of interest?

Method:

- Logistic regression analysis

- **Scientific question**: Do biomarkers improve discrimination / risk prediction?

Methods:

- **Deviance on nested models** (model fit)
- **C-statistic** (Area under the curve, ROC curve)

New upcoming tools:

- **IDI** (integrated discriminatory improvement)
- **NRI** (net reclassification improvement)

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CAVASIC (Cardiovascular Disease in Intermittent Claudication) Study

- **Case-control study (conducted between 2002 and 2006)**
  - Male cohort, age- and diabetes-matched controls
- **238 patients and 245 controls from 2 clinical centers**
  - Department of Vascular Surgery, Medical University Innsbruck
  - 3rd Medical Department of Metabolic Diseases and Nephrology, Hietzing Hospital, Vienna
- **Criterion for inclusion:**
  - History of symptomatic intermittent claudication (Peripheral arterial disease (PAD) IIa or IIb) regardless of past treatment procedure (bypass surgery or intervention)

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Peripheral arterial disease (PAD)

- Peripheral arterial disease (PAD) is a common manifestation of atherosclerosis
- Narrowing of the arteries of extremities (legs), causing circulatory disturbance
- Symptoms: Taking breaks during walking due to pain in the legs ("Schaufensterkrankheit")
- Patients with PAD have a high incidence of fatal and non-fatal cardiovascular and cerebrovascular events and mortality in general

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Cardiac markers to be evaluated in the CAVASIC Study

- **Mid-regional pro-adrenomedullin (MR-proADM) and Mid-regional pro-atrial natriuretic peptide (MR-proANP)**
  - Elevated in various cardiovascular conditions (e.g. myocardial infarction, coronary atherosclerosis, congestive heart failure)
- **C-terminal endothelin-1 precursor fragment (CT-proET-1)**
  - Increased concentrations in plasma related to all-cause mortality and mortality due to cardiovascular causes
- **N-terminal (NT) pro-B-type natriuretic peptide (pro-BNP)**
  - Established marker of cardiac stress (e.g. heart failure)
  - Reliable diagnostic and prognostic information in cardiac disease
  - Increased concentrations associated with an increased cardiovascular mortality in PAD patients

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Scientific questions

Hypotheses:

MR-proADM, MR-proANP and CT-proET-1 plasma concentrations are associated with symptomatic PAD

1. The association is **independent from** the **established cardiac marker NT-pro-BNP** and **persists after excluding those with prevalent cardiovascular disease**
2. The new markers help to **improve discrimination** between those individuals experiencing an event (= adverse outcome) and those who do not

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Logistic regression analysis: Hypothesis 1

Hypothesis 1: The association is independent from the established cardiac marker NT-pro-BNP and persists after excluding those with prevalent cardiovascular disease

~40-50 % higher risk per 1 SD increase of these 2 markers

Peripheral arterial disease (n=238)	OR 95% CI*	P value
MR-proADM (per 1 SD increase)	1.51(1.07-2.14)	0.019
CT-proET-1 (per 1 SD increase)	1.41 (1.02-1.94)	0.035

*** Adjusted for age, log-C-reactive protein, creatinine, HDL cholesterol and current smoking, log-NT-proBNP**

The association for MR-proADM and CT-proET-1 is still significant after adjusting for NT-proBNP and excluding those with prevalent cardiovascular disease

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Measures of performance of prediction models: Hypothesis 2

- **Deviance** (evaluate model fit)
- **IDI** (integrated discriminatory improvement)
- **NRI** (net reclassification improvement)
- **C-statistic** (Area under the curve, ROC curve)

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Test of deviance on nested models: Hypothesis 2

Hypothesis 2: The models including the new markers show improved model fits as compared to a basis model

	Deviance	Difference in deviance	P value
Basis model: including age, log-C-reactive protein, creatinine, HDL cholesterol, smoking status	457.17		
+ log-NT-proBNP (per 1 SD increase)	426.39	-30.78	$2.89*10^{-8}$
+ MR-proADM (per 1 SD increase)	444.47	-12.70	$3.65*10^{-4}$
+ MR-proANP (per 1 SD increase)	448.36	-8.81	0.003
+ CT-proET-1 (per 1 SD increase)	444.52	-12.66	$3.75*10^{-4}$

Deviance: All four markers provided improved model fits when compared to the basis model

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Test of deviance on nested models: Hypothesis 2

Hypothesis 2: The models including the new markers show improved model fits as compared to a basis model

	Deviance	Difference in deviance	P value
Basis model: including age and log-NT-proBNP	598.79		
+ MR-proADM (per 1 SD increase)	586.40	-10.53	0.001
+ CT-proET-1 (per 1 SD increase)	589.72	-9.07	0.003

Deviance: Both markers provided improved model fits when compared to the basis model

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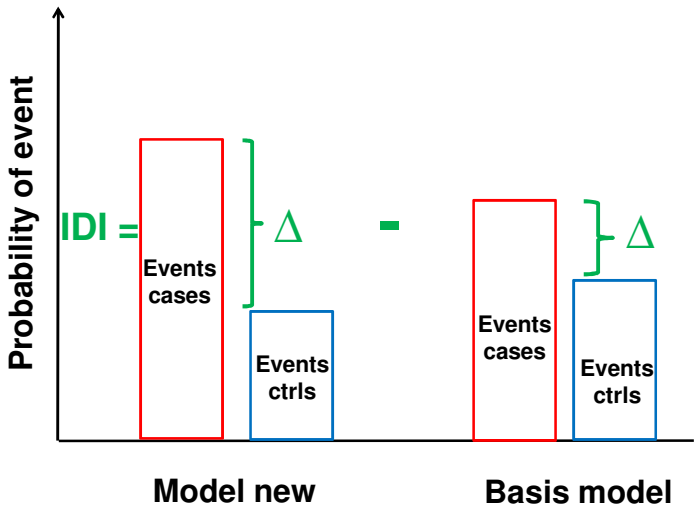
IDI: integrated discriminatory improvement



ctrls = controls

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IDI: integrated discriminatory improvement

- IDI=integrated discriminatory improvement

Δ_{new} = Difference in the predicted probabilities for an event in the new model between cases and controls (= discriminatory ability of new model)

Δ_{basis} = Difference in the predicted probabilities for an event in the basis model between cases and controls (= discriminatory ability of basis model)

IDI = $\Delta_{new} - \Delta_{basis}$

Aim: Better discrimination between cases and controls by new model compared to basis model

→ the higher IDI, the better is the discrimination
→ but dependent on prevalence / incidence within a population

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IDI: integrated discriminatory improvement: Hypothesis 2

Hypothesis 2: The new models offer better discrimination between cases and controls as compared to the basis model

Basis model including age, log-C-reactive protein, creatinine, HDL cholesterol, smoking status	IDI 95% CI	P value
	0.358*	
+ log-NT-proBNP (per 1 SD increase)	0.053 [0.033-0.073]	$1.9*10^{-07}$
+ MR-proADM (per 1 SD increase)	0.013 [0.002-0.024]]	0.02
+ MR-proANP (per 1 SD increase)	0.022 [0.010-0.035]	$1.1*10^{-03}$
+ CT-proET-1 (per 1 SD increase)	0.019 [0.010-0.032]	$4.0*10^{-03}$

Positive IDI: Increased mean predicted probabilities for events for cases and decreased for controls

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*** discrimination slope of basis model**

IDI: integrated discriminatory improvement: Hypothesis 2

Hypothesis 2: The new models offer better discrimination between cases and controls as compared to the basis model

Basis model including age + log-NT-proBNP	IDI 95% CI	P value
	0.118*	
+ MR-proADM (per 1 SD increase)	0.020 [0.007-0.033]	0.002
+ CT-proET-1 (per 1 SD increase)	0.019 [0.007-0.033]	0.002

Positive IDI: Increased mean predicted probabilities for events for cases and decreased for controls

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*** discrimination slope of basis model**

NRI: net reclassification improvement

- P(event) = probability for an event
- **Category-free NRI:**

NRI for cases= (proportion of cases, for whom P(event) increases) **-** (proportion of cases, for whom P(event) decreases)

NRI for controls= (proportion of controls, for whom P(event) decreases) **-** (proportion of controls, for whom P(event) increases)

Category-free NRI = NRI for cases + NRI for controls

Theoretically maximum category-free NRI = calculated risks for all subjects with events are increased, and for all subjects without events are decreased

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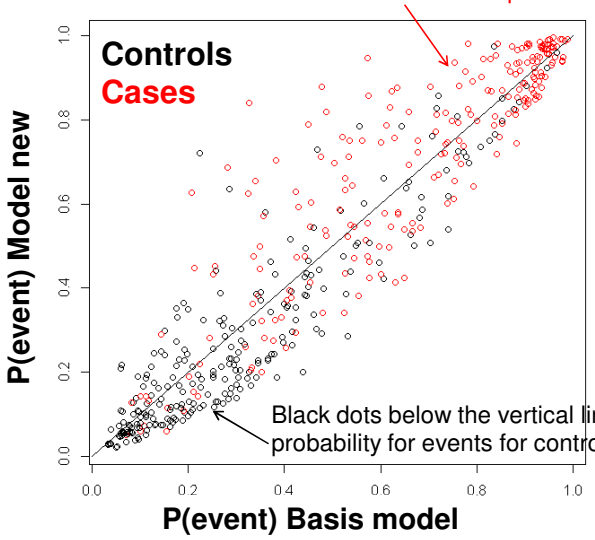
NRI: net reclassification improvement

Red dots above the vertical line: increased probability for events for cases



Aim: All red dots (=cases) above vertical line, all black dots (controls) below this line

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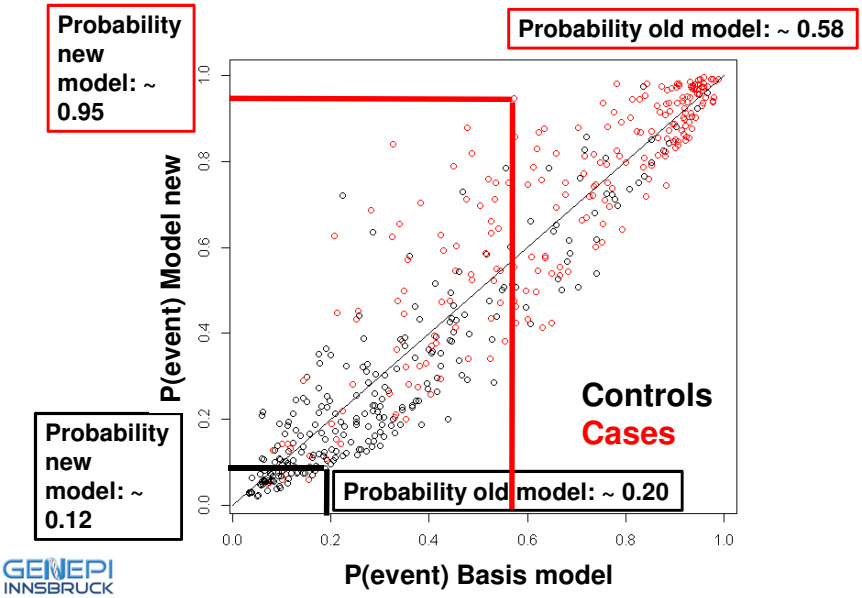
NRI: net reclassification improvement

What is more important: correctly classifying cases or controls → optimal: both!



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Discriminatory improvement: IDI, NRI and C-Statistic : Hypothesis 2

Basis model including age, log-C-reactive protein, creatinine, HDL cholesterol, smoking status		P value
+ log-NT-proBNP (per 1 SD increase)		
IDI of basis model	0.358	
IDI of new model [95% CI]	0.05 [0.03-0.07]	$1.9*10^{-07}$
Relative IDI of new model in %	0.15	
Overall category-free NRI [95% CI]	0.51 [0.33-0.69]	$3.2*10^{-08}$
NRI for cases [95% CI]	0.09 (-0.04-0.22)	0.16
NRI for controls [95% CI]	0.42 (0.29-0.55)	$7.7*10^{-11}$
C statistic basis model [95% CI]	0.846 [0.808-0.879]	
C statistic new model [95% CI]	0.867 [0.832-0.897]	

New model including NT-proBNP improved discriminatory ability in comparison to the basis model

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Summary of Main Clinical Findings in the CAVASIC Study

- MR-proADM, MR-proANP and CT-pro-ET1 concentrations were significantly associated with symptomatic peripheral arterial disease
- The effect of MR-proADM and CT-pro-ET1 was independent from the established cardiac marker NT-pro-BNP and persisted after exclusion of those with prevalent cardiovascular diseases
- NT-proBNP is the strongest marker for PAD risk determination

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Summary for measures of performance of prediction models

- **Models** containing **new markers provided improved model fits** when compared to a basis model
- **IDI seems more sensitive than C-statistic** in judging improvement in model performance (**detecting small changes**)
  - IDI weights sensitivities equally across all possible cut-points
  - C-statistic weights large sensitivities more heavily
  - IDI is directly based on event probabilities
- **Category-free NRI** gives quite similar results as IDI
- **At the end:** Deviance, C-statistic, IDI and NRI should lead to the same conclusion (e.g. either for very large or very small differences)

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GOLD

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