Risk assessment models: What is to come?

Role of biomarkers in improving risk assessment models

Europrevent 2010, Praque

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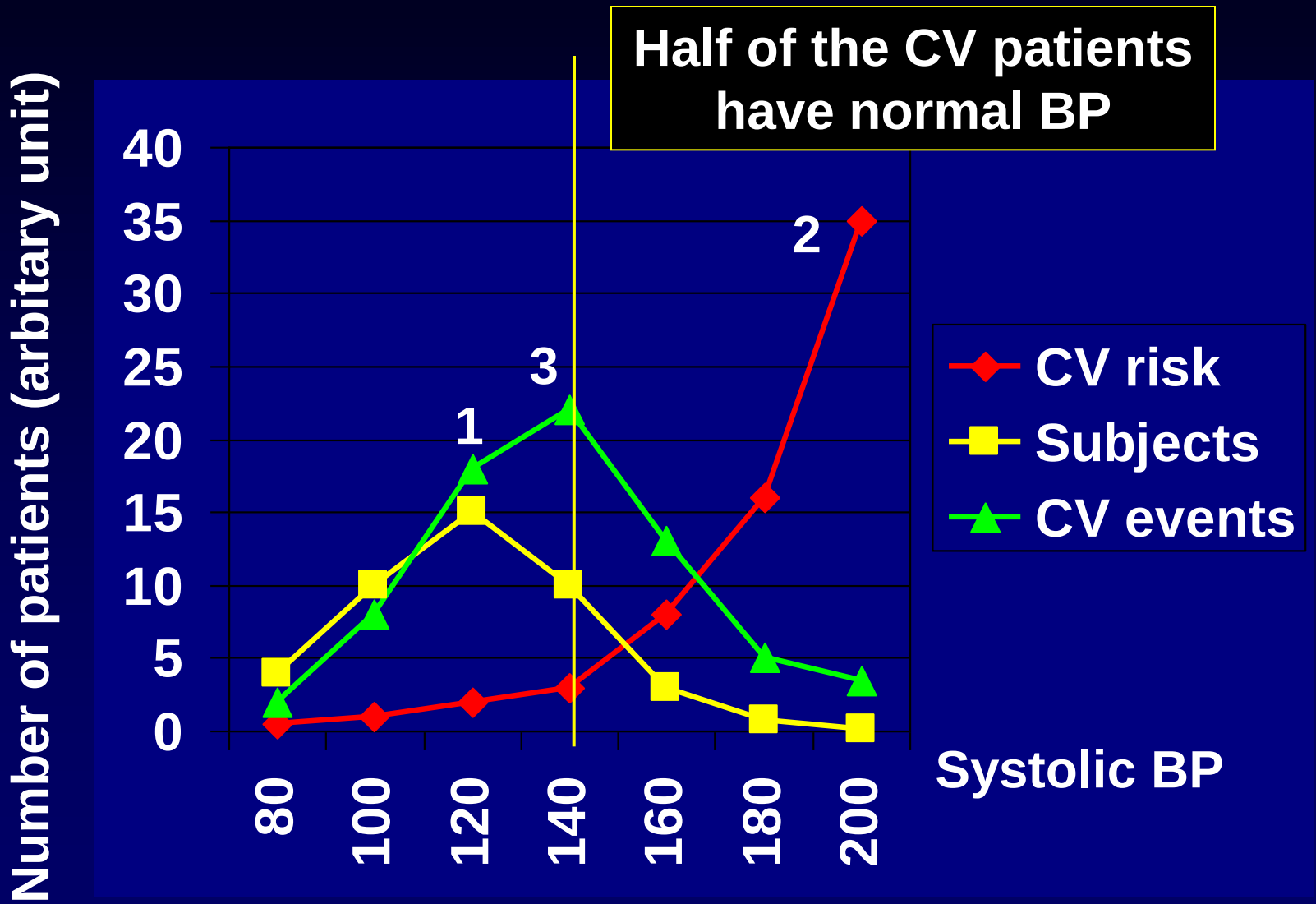
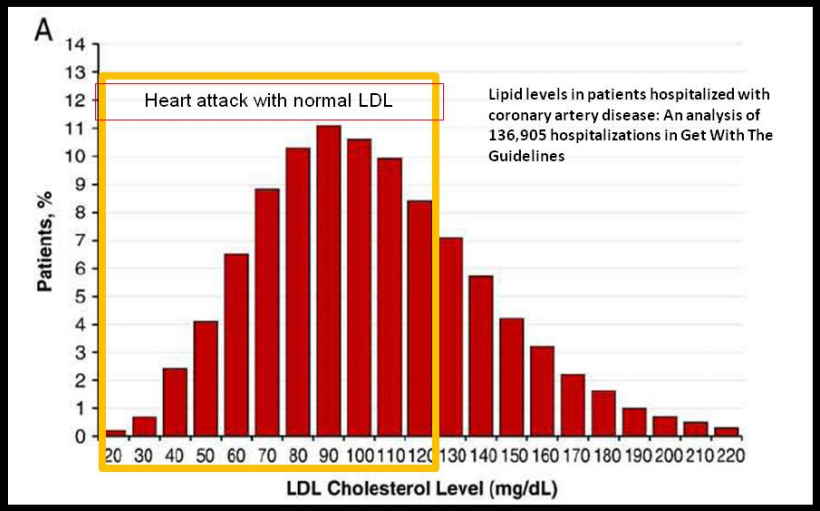
Despite prognostic importance, traditional CV risk factors have problems predicting individual CV risk



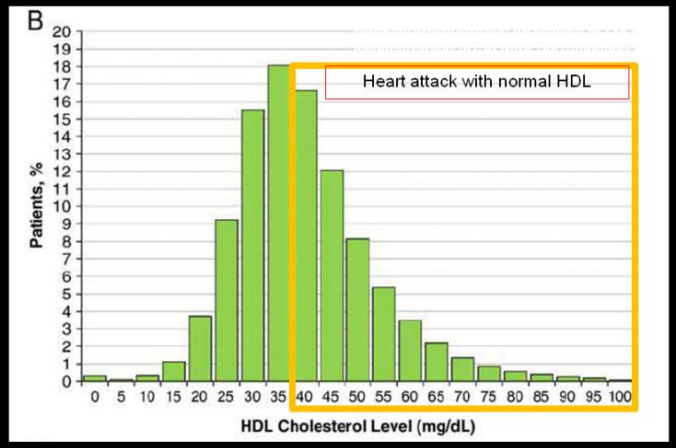
Also lipids are normal in half of the patients hospitalized for acute myocardial infarction

Of 136,905 patients hospitalized with CAD, more than 70% had LDL levels below 130 mg/dl



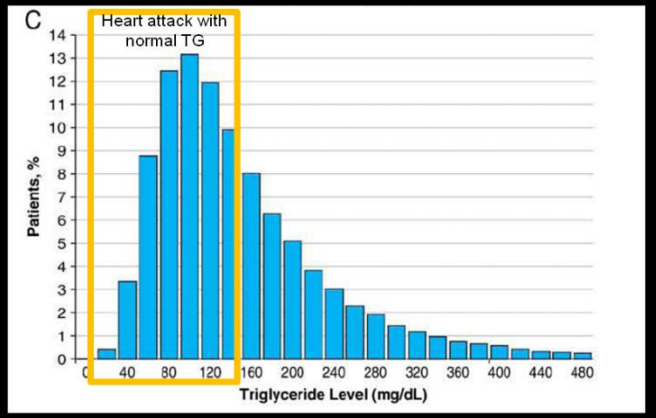
Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009

Of 136,905 patients hospitalized with CAD, more than 45% had HDL levels above 40 mg/dl



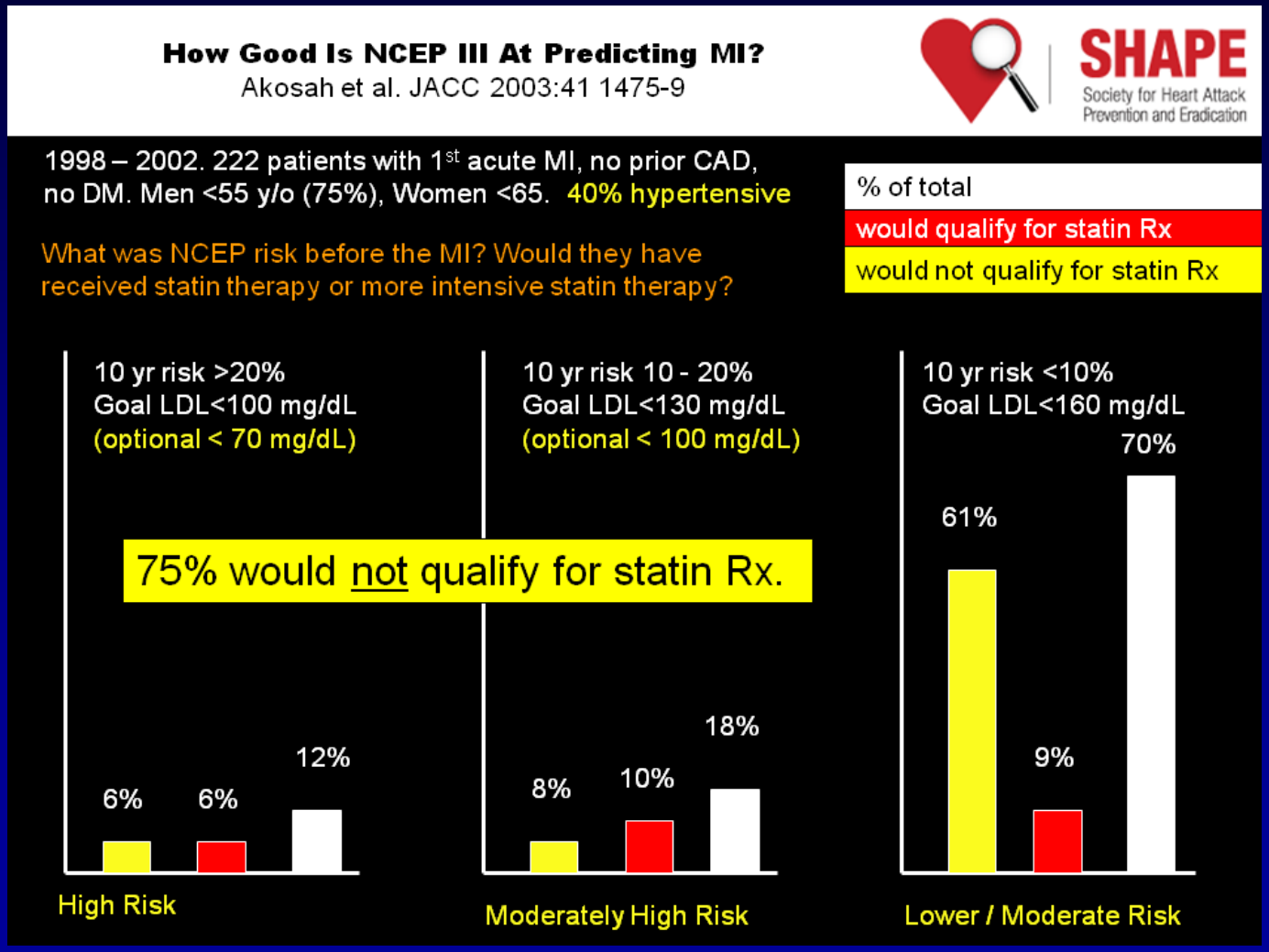
Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009

Of 136,905 patients hospitalized with CAD more than 50% had TG levels below 160 mg/dL



Sachdeva et al. AHJ, Vol 157, 111-117 Jan 2009

Traditional risk factors are inadequate to predict CV events making primary prevention difficult



The additive predictive values of non-traditional CV risk markers are also controversial

REVIEW

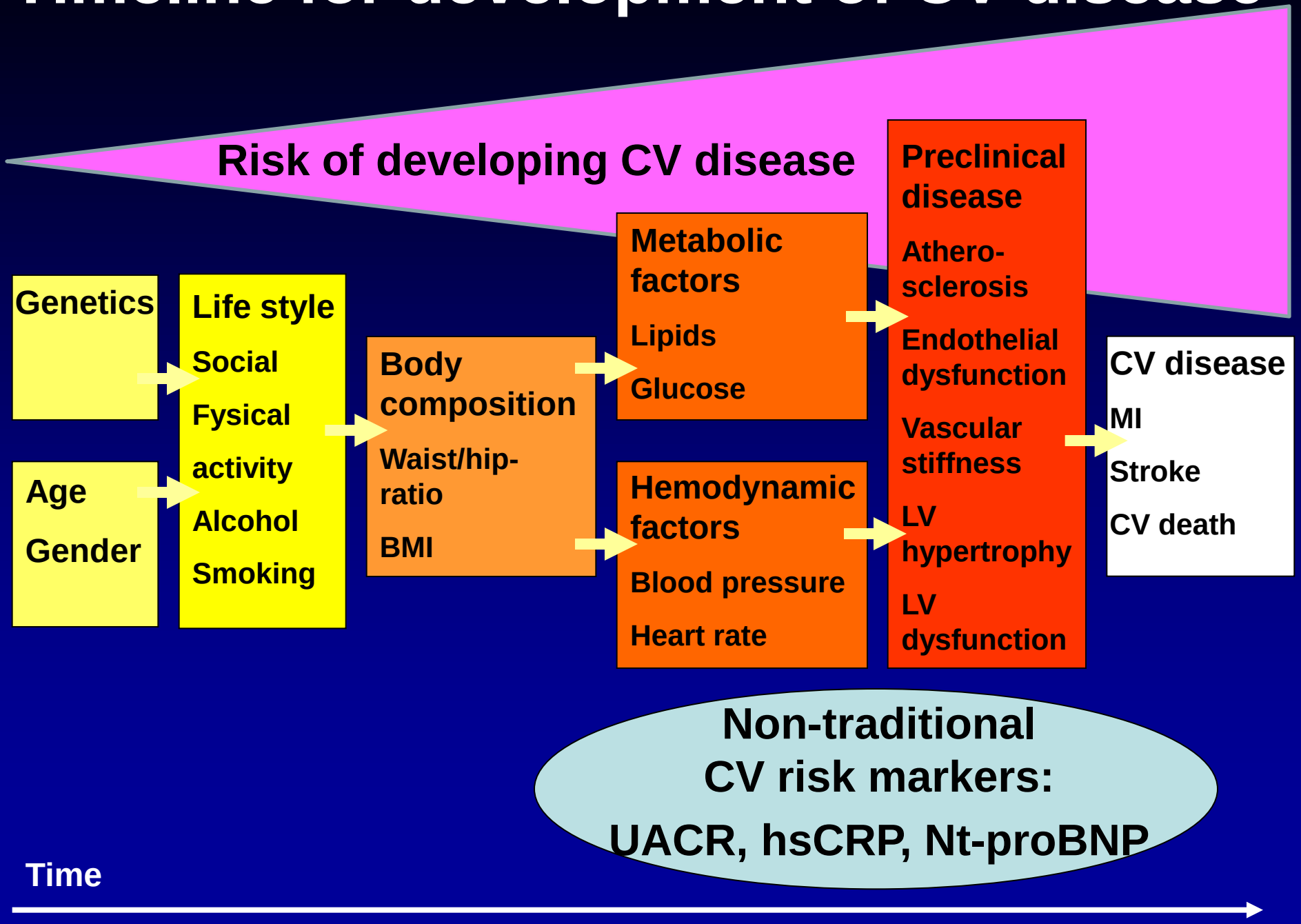
Assessment of Claims of Improved Prediction Beyond the Framingham Risk Score

JAMA. 2009;302(21):2345-2352

Results We evaluated 79 eligible articles. Forty-nine studies (62%) did not calculate the FRS as it has been proposed, 15 (19%) modeled the additional predictor in more than 1 way and presented only the best fit or area-under-the-curve (AUC) results for only 1 model, 41 (52%) did not examine the original outcome that the FRS was developed for, 33 (42%) studied a

Conclusion The majority of examined studies claimed that they found factors that could offer additional predictive value beyond what the FRS could achieve; however, most had flaws in their design, analyses, and reporting that cast some doubt on the reliability of the claims for improved prediction.

Timeline for development of CV disease



Five important questions

1. What do these non-traditional risk markers reflect?
2. Do they predict outcome independently of traditional CV risk factors?
3. Are they especially strong in certain subgroups?
4. Can they supplement SCORE in selecting subjects for primary prevention?
5. Do changes during treatment have prognostic importance?

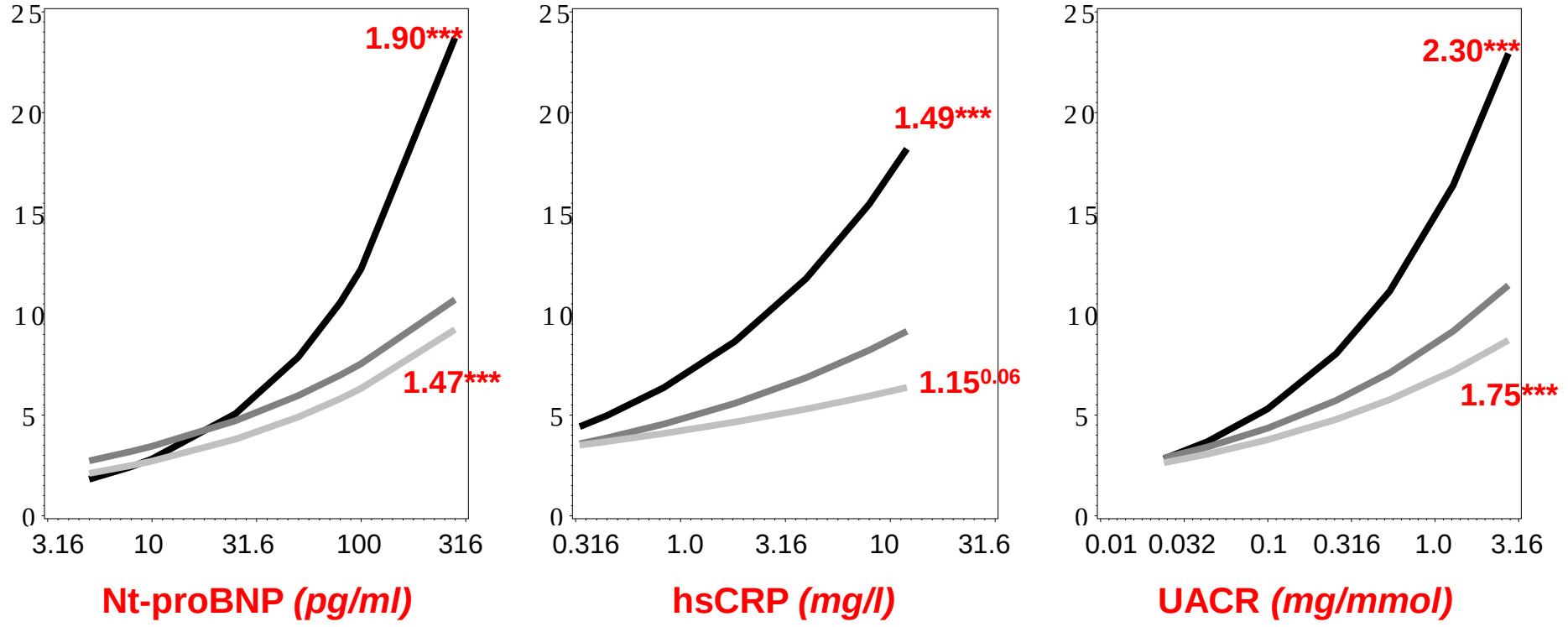
What do these non-traditional risk markers reflect?

- **High sensitivity C-reactive protein (hsCRP)**
  - Reflects the subclinical inflammation associated with development of atherosclerosis and unstabil plaques
- **Urin albumin/creatinin ratio (UACR)**
  - Reflects systemic microvascular damage (not only glomeruli) with increased risk of lipid-insudation and later development of atherosclerosis
- **N-terminal pro brain natriuretic peptide (Nt-proBNP)**
  - Reflects hemodynamic load on the myocardium and thereby cardiovascular hypertrophy/fibrosis

Five important questions

1. What do these non-traditional risk markers reflect?
2. Do they predict outcome independently of traditional CV risk factors?

In the general population the risk of CEP increases with increasing levels of non-traditional risk markers



The calculated absolute risk of the composite endpoint as functions of log(Nt-proBNP), log(hsCRP) or logUACR unadjusted (black), adjusted for prior stroke or myocardial infarction, known diabetes, CV medication gender and mean age (dark grey), and further adjusted for smoking and mean heart rate, systolic blood pressure, plasma glucose and serum low density lipoprotein (light grey).

Olsen MH *et al*. Eur Heart J 2007;28:1374-81

Five important questions cont.

1. What do these non-traditional risk markers reflect?
2. Do they predict outcome independently of traditional CV risk factors?
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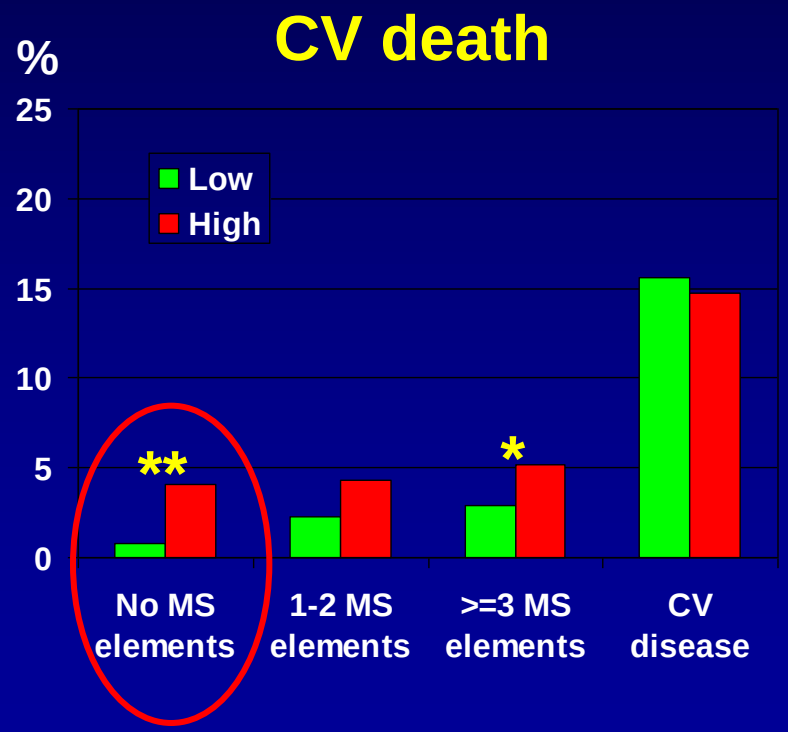
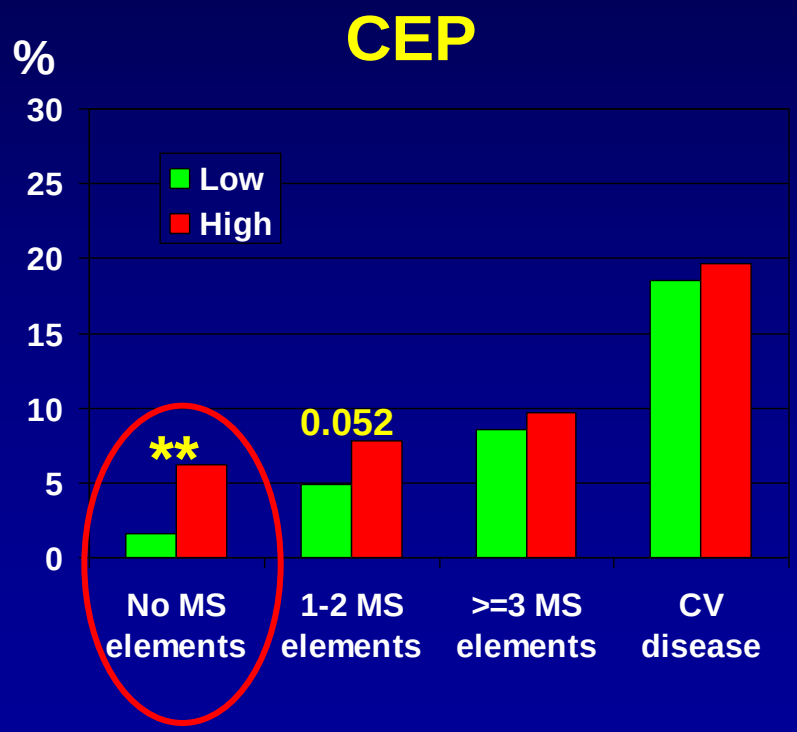
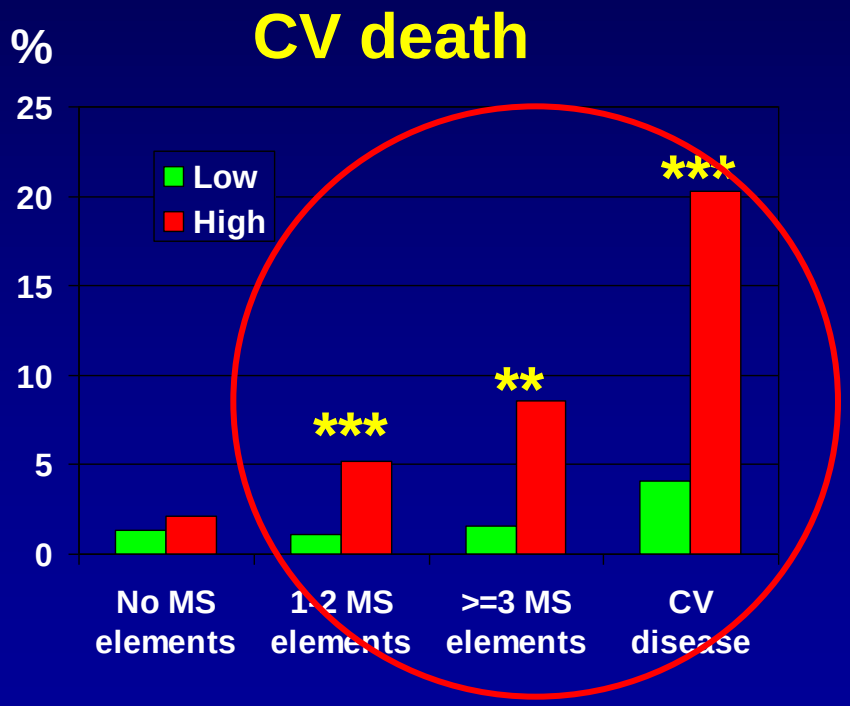
High hsCRP predicted CV events in low risk subjects - a marker of early atherosclerosis

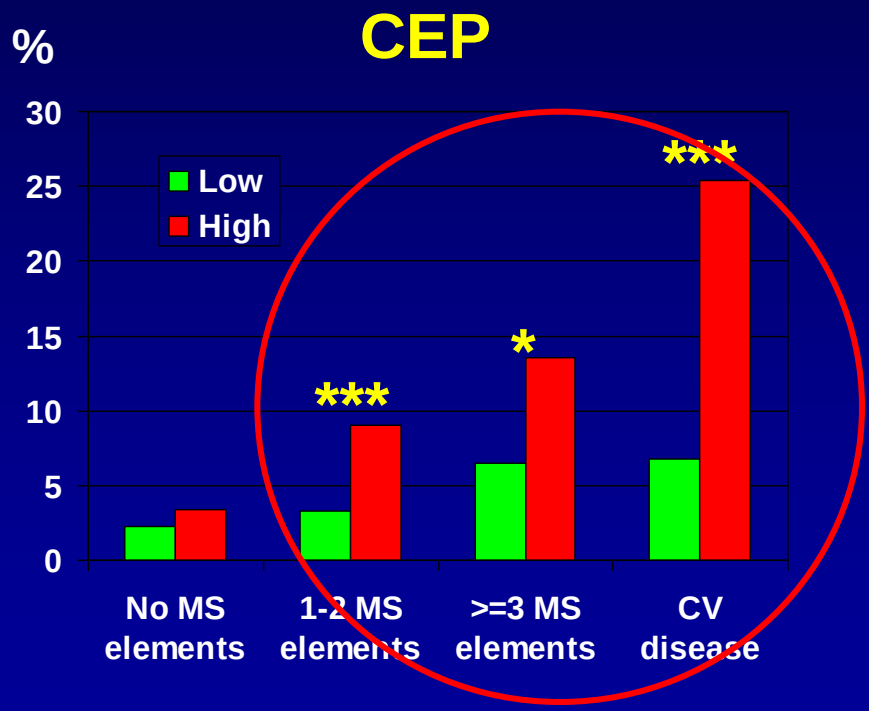




Olsen MH *et al.* J Hum Hypertens 2008;22(9):634-40

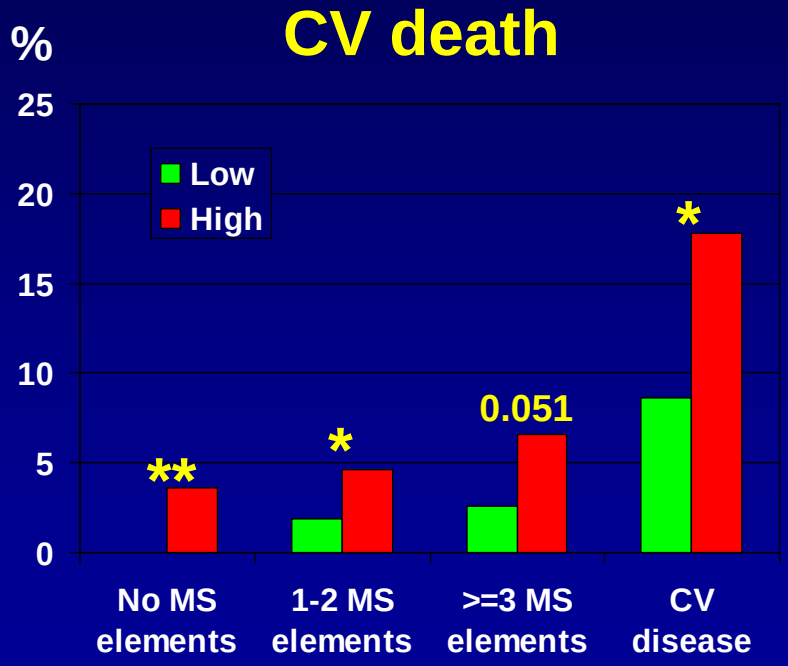
High Nt-proBNP predicted CV events in high risk subjects – a marker of later CV damage

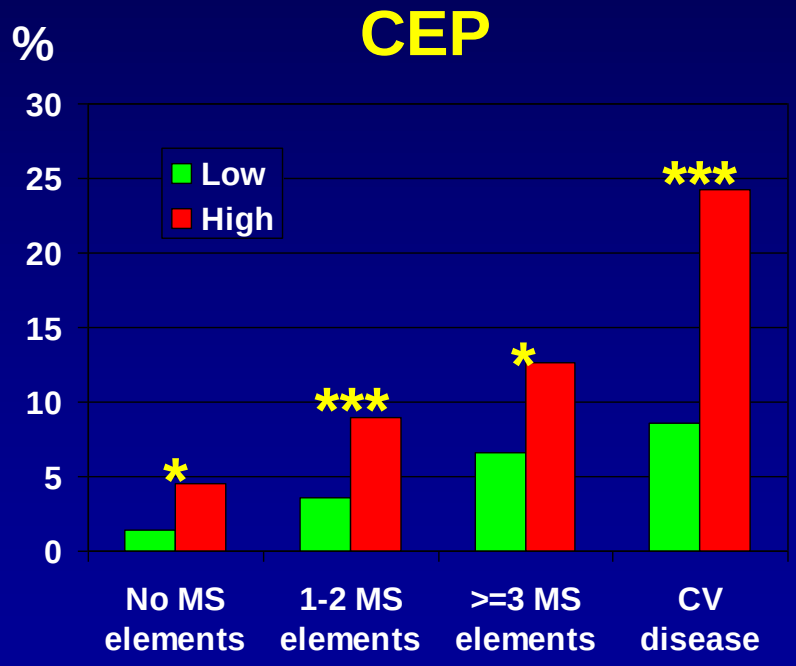




Olsen MH *et al.* J Hum Hypertens 2008;22(9):634-40

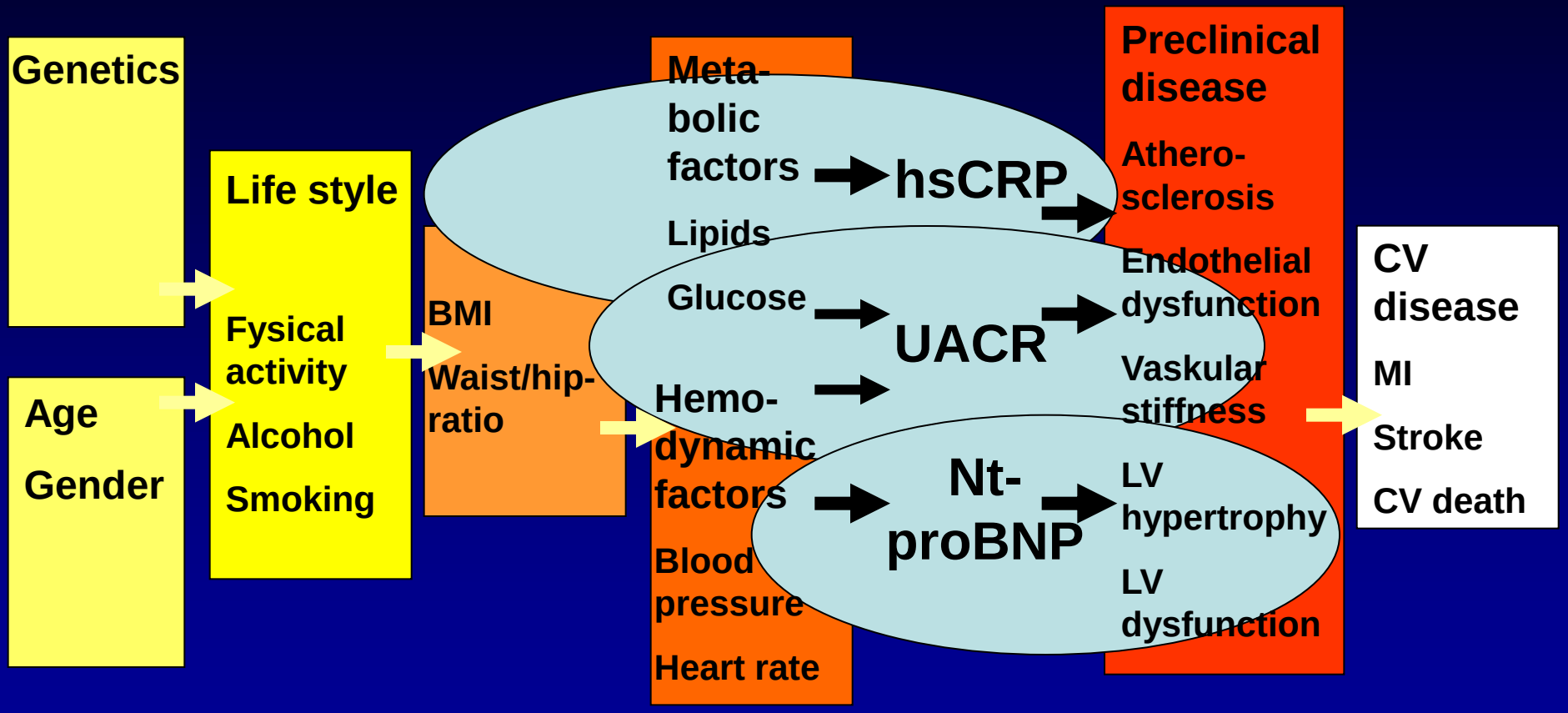
High UACR predicted CV events in all subjects – a marker of early (endothelial dysfunction) and later (microvascular damage) atherosclerosis





Olsen MH *et al.* J Hum Hypertens 2008;22(9):634-40

Non-traditional risk markers predict events partly independently of the traditional risk factors



But do they provide additive information leading to clinical changes in daily practise?

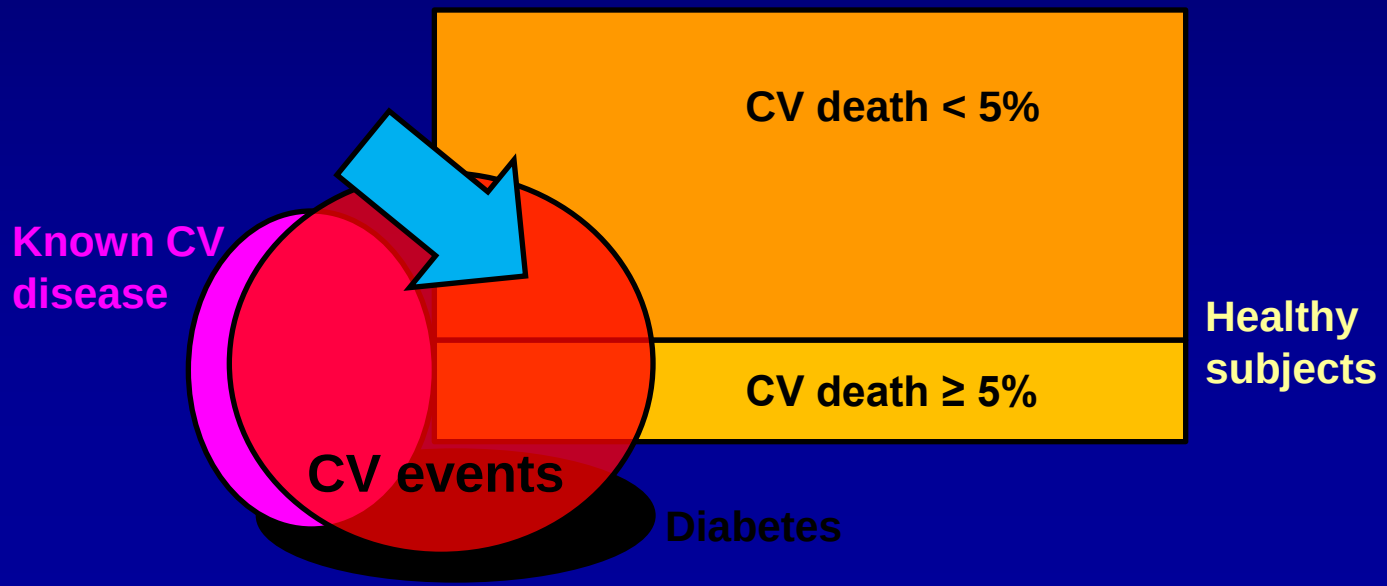
Time

Five important questions cont.

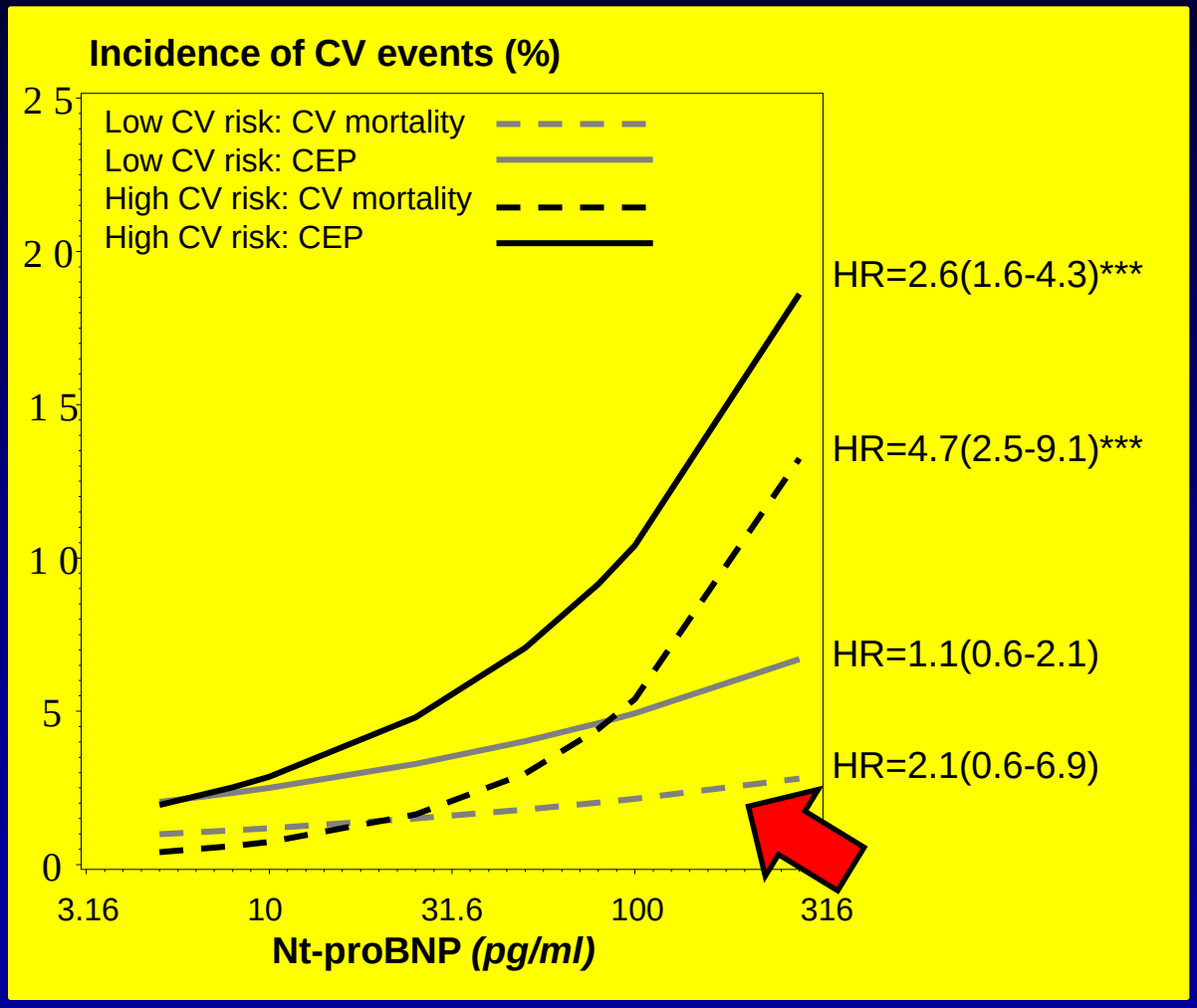
1. What do these non-traditional risk markers reflect?
2. Do they predict outcome independently of traditional CV risk factors?
3. Are they especially strong in certain subgroups?
4. Can they supplement SCORE in selecting subjects for primary prevention?

Indications for prevention

- **Secondary prevention**
  - Known CV disease
- **Primary prevention**
  - Diabetes
  - Healthy subjects with a 10-year risk of CV death ≥ 5% as estimated by SCORE

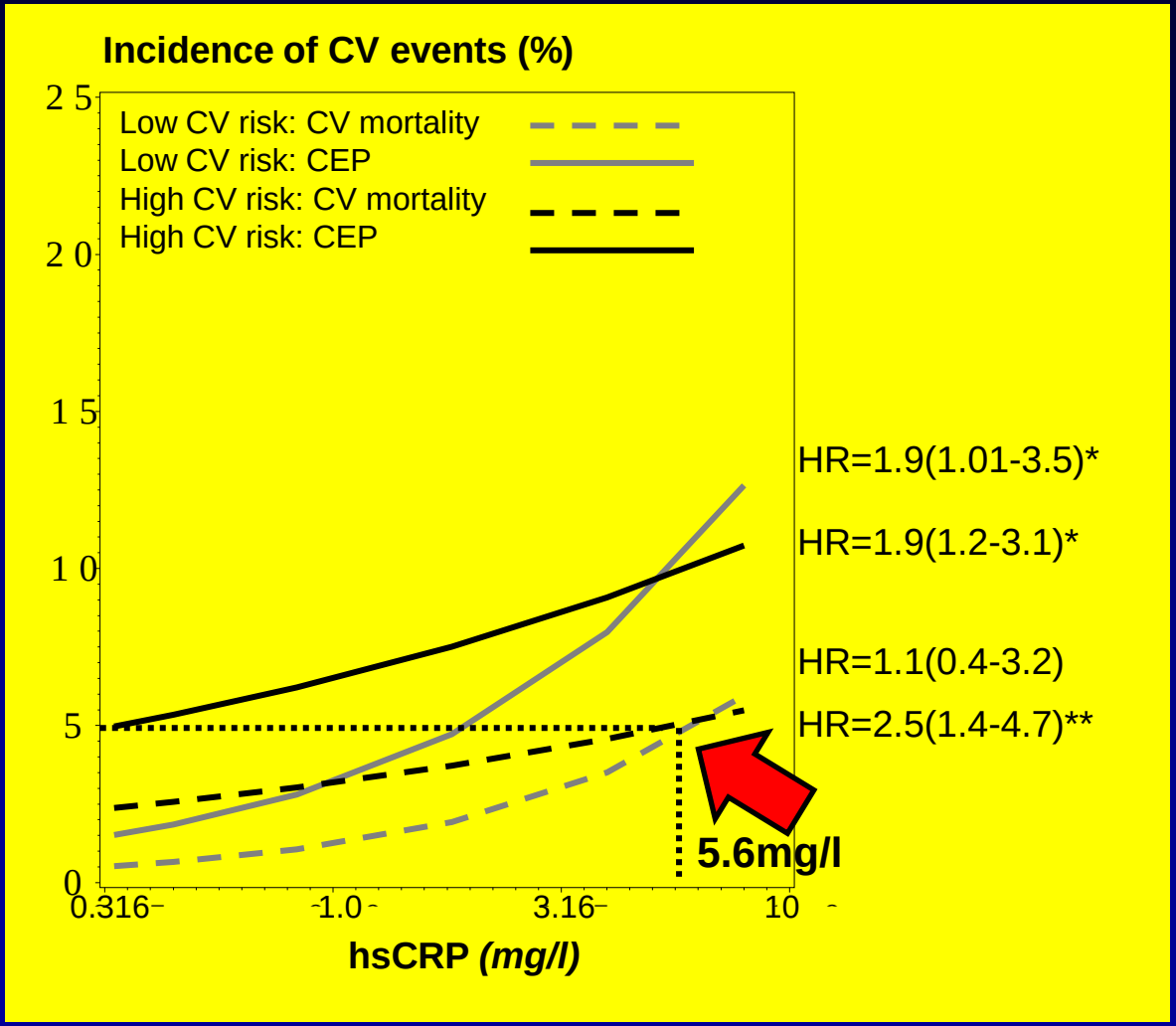


Nt-proBNP was not associated with CV risk in the low-moderate risk group (SCORE < 5%)



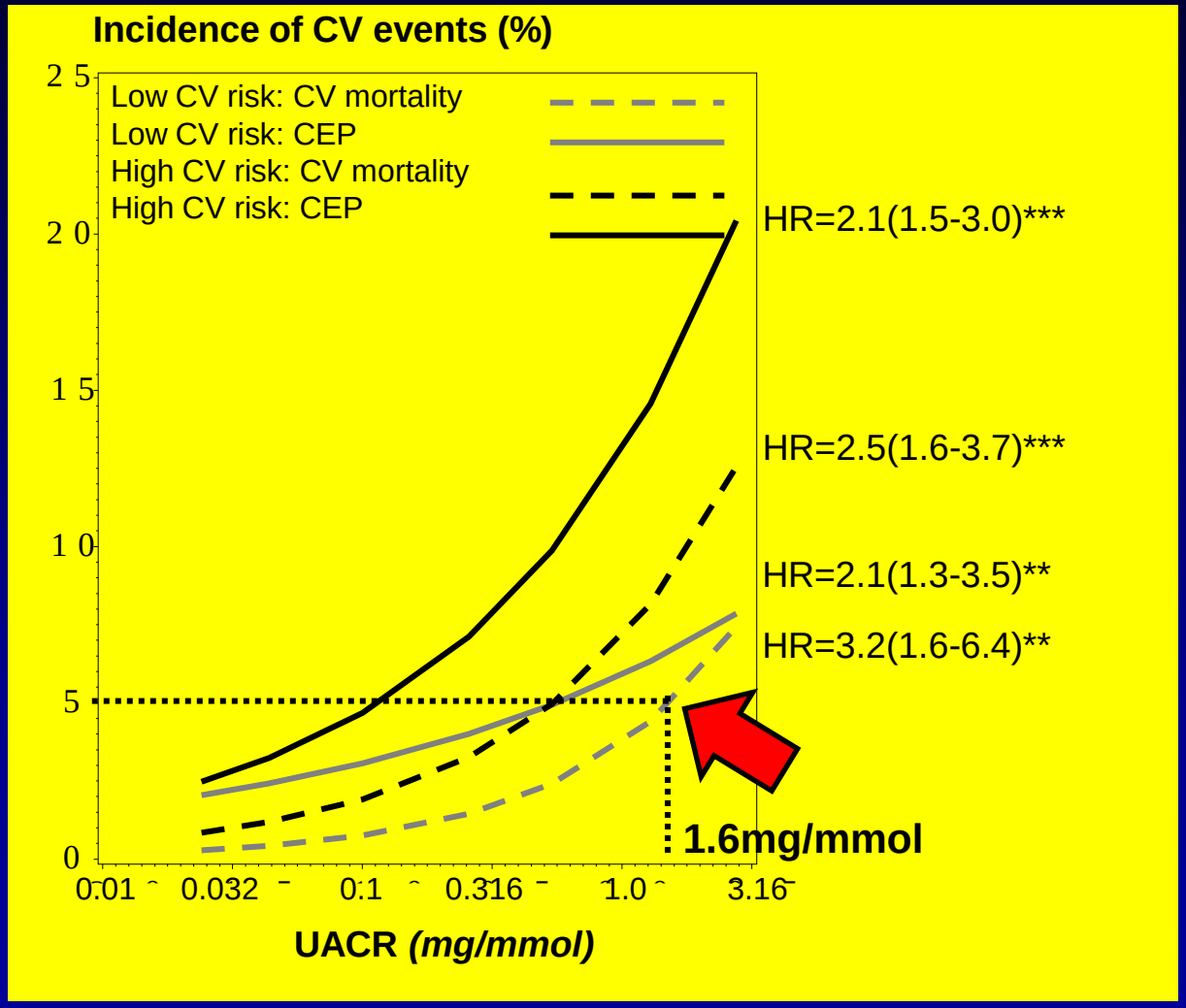
Olsen MH *et al*. J Hum Hypertens 2008;23(2):105-112

HsCRP was associated with CV events in the low-moderate risk group, and risk of CV death ≥ 5% for hsCRP>5.6mg/l



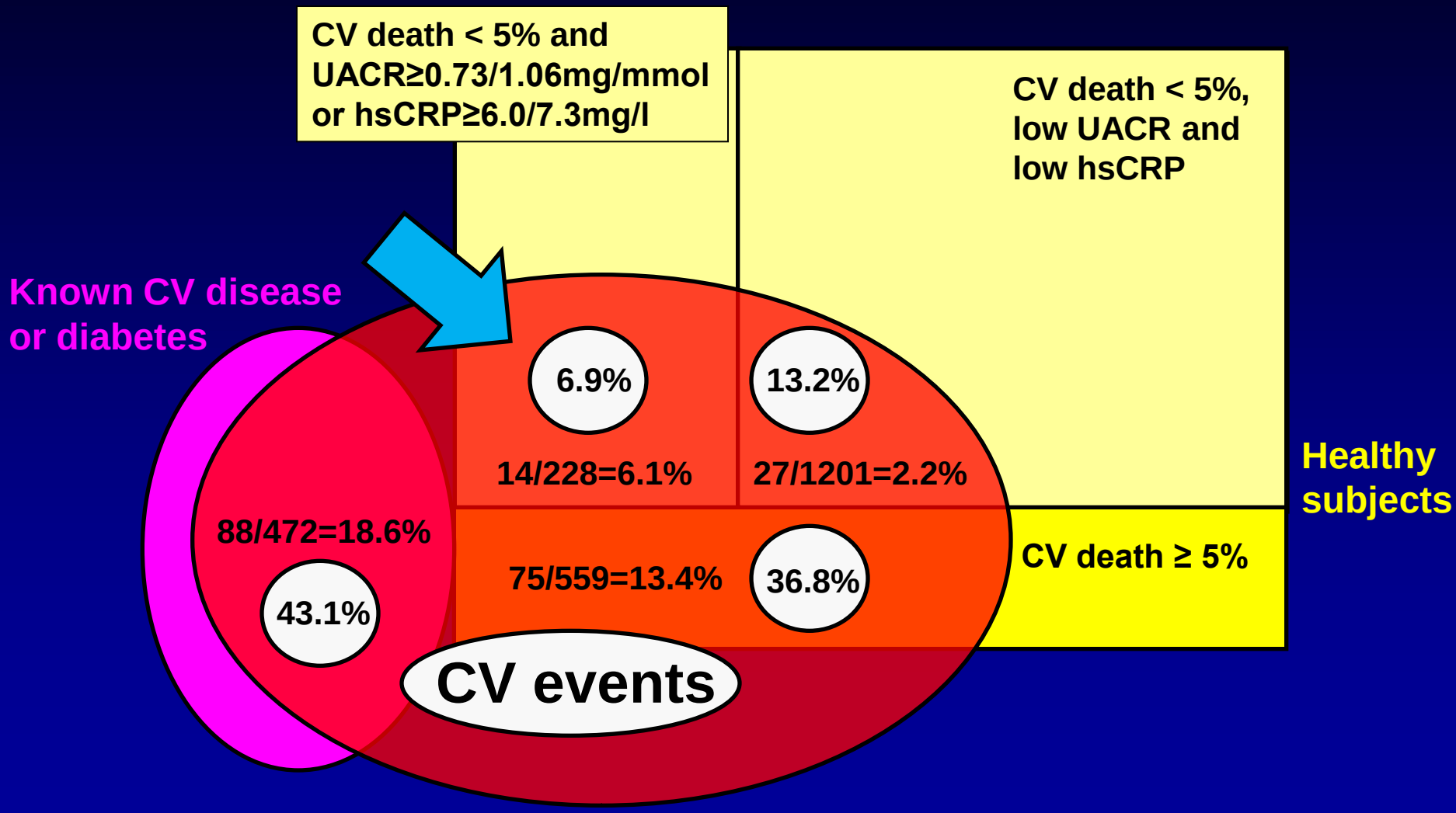
Olsen MH *et al*. J Hum Hypertens 2008;23(2):105-112

UACR var associeret med CV events independently of CV risk, and CV death ≥ 5% in the low-moderate risk group for UACR>1.6mg/mmol



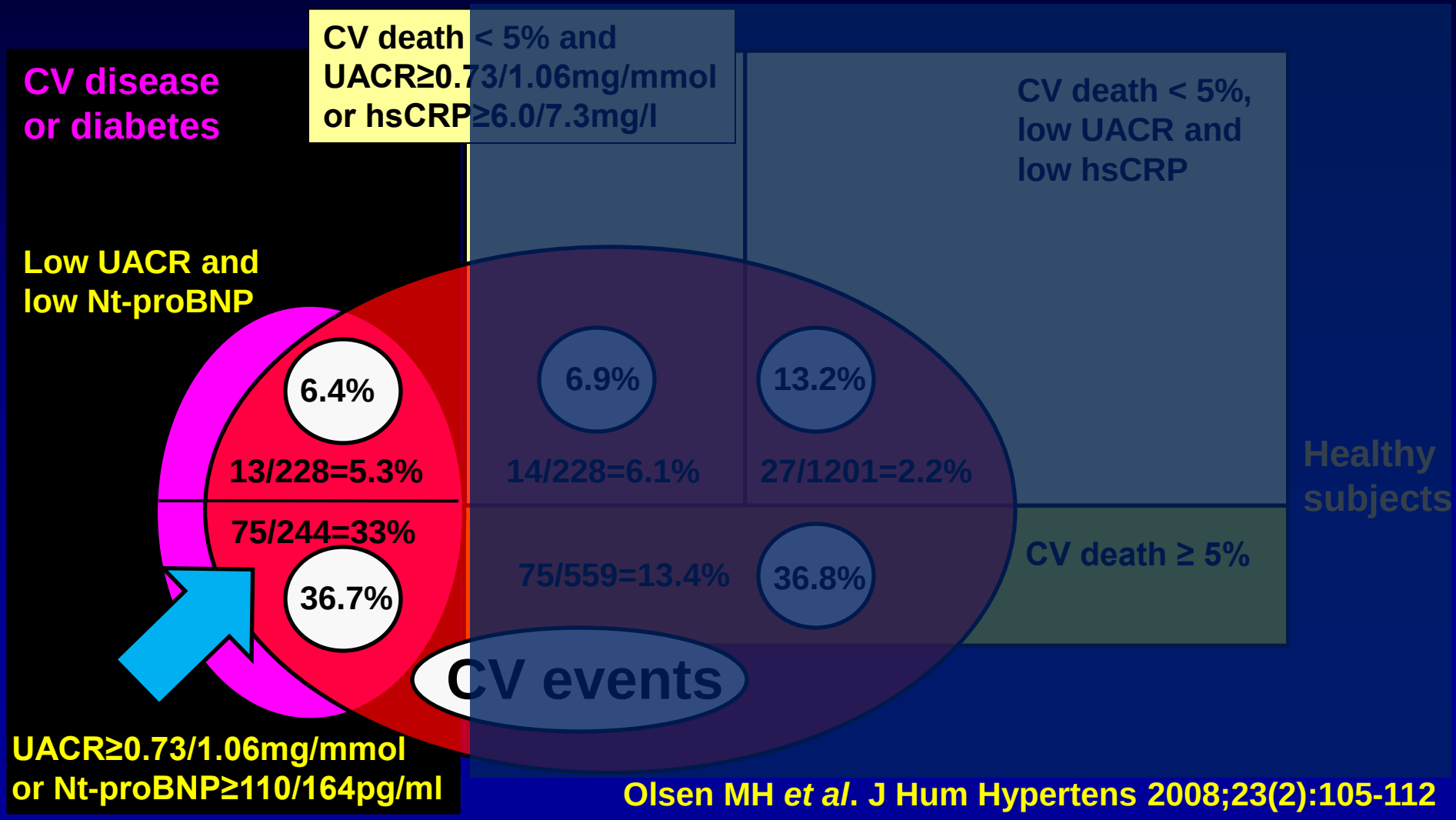
Olsen MH *et al*. J Hum Hypertens 2008;23(2):105-112

1/3 of CV events occur in subjects with moderate risk by standard risk factors



Olsen MH *et al*. J Hum Hypertens 2008;23(2):105-112

85% of CV events in subjects with known CV disease or diabetes was predicted by high UACR or high Nt-proBNP

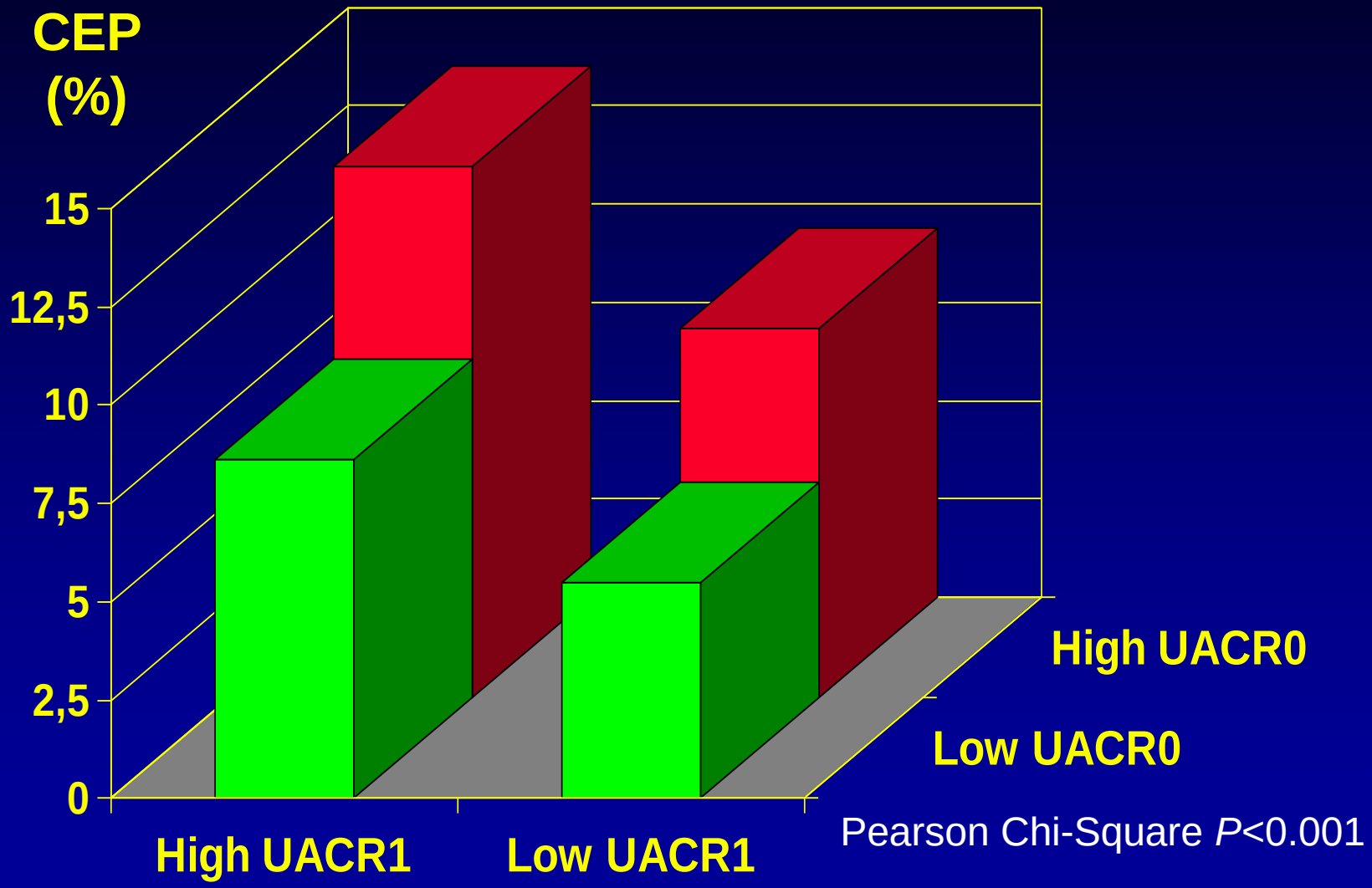


Olsen MH *et al*. J Hum Hypertens 2008;23(2):105-112

Five important questions cont.

1. What do these non-traditional risk markers reflect?
2. Do they predict outcome independently of traditional CV risk factors?
3. Are they especially strong in certain subgroups?
4. Can they supplement SCORE in selecting subjects for primary prevention?
5. **Do changes during treatment have prognostic importance?**

Baseline as well as 1-year UACR has prognostic importance



Pearson Chi-Square *P*<0.001

Ibsen *et al*: Hypertension 2005;45(2):198-202

Five important answers

1. These 3 non-traditional risk markers reflect different aspects of cardiovascular damage
2. They predict outcome independently of traditional CV risk factors, but do not in general provide additional clinically relevant prognostic information
3. They are stronger in selected subgroups
4. They may supplement SCORE in selecting subjects for primary prevention
5. Changes in UACR during treatment have prognostic importance

Conclusion

1. The impact of new non-traditional CV risk factors/markers are dependent on which part of the CV disease process they reflect
2. Therefore, better understanding of the complex mechanisms leading to CV disease is essential.
3. Thereby identifying the right risk markers/factors with the right cut-off values for the right populations
4. Leading to improved risk assessment, better targeted prevention and more individualized treatment

Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association.

Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE Jr, Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, McConnell JP, Normand SL, O'Donnell CJ, Smith SC Jr, Wilson PW; American Heart Association Expert Panel on Subclinical Atherosclerotic Diseases and Emerging Risk Factors and the Stroke Council.

Circulation. 2009 May 5;119(17):2408-16

1. Design and outcomes according to accepted standards
2. Risk stratification based on traditional cardiovascular risk factors
3. Associated risk of the non-traditional risk marker:
   a) Relative risk, odds ratio, or hazard ratio conveyed by the non-traditional risk marker alone, with the associated confidence limits and *P*-value (standardized hazard ratios)
   b) Relative risk, odds ratio, or hazard ratio for non-traditional risk marker after statistical adjustment for traditional risk factors, with the associated confidence limits and *P*-value (standardized hazard ratios)
   c) P-value for addition of the non-traditional risk marker to a model of traditional risk factors (The likelihood ratio partial chi^2)
4. Discrimination of the non-traditional marker:
   a) C-index and its confidence limits for model with traditional risk factors
   b) C-index and its confidence limits for model including non-traditional risk marker and traditional risk factors
   c) Integrated discrimination index (correctly revises upward/downward the predicted risk in cases/non-cases)
   d) Graphic or tabular display of predicted risk in cases and non-cases separately, before and after inclusion of the non-traditional risk marker
5. Accuracy of the non-traditional risk marker:
   a) Display observed vs. expected event rates across the range of predicted risk for models without and with the non-traditional risk marker (Goodness-of-fit test)
   b) Using generally and clinically recognized risk thresholds, report the number of subjects reclassified and the event rates in the reclassified groups (clinical utility)
6. Clinical outcome (randomized) and Cost-effectiveness analyses

I hope to see many of you in Oslo

The predictive values for CEP using predefined gender specific cut-off values

	Nt-proBNP			hsCRP			UACR		
Specificity *(%)* *Part of cont. healthy with low risk*	75	90	95	75	90	95	75	90	95
Sensitivity *(%)* *Part of future sick with high risk*	45	23	15	45	19	8	47	30	20
Positive PV*(%)* *Part of high risk getting an event*	10.1	12.8	16.2	10.1	10.9	9.9	10.5	15.8	20.5
Negative PV*(%)* *Part of low risk avoiding an event*	96	95	95	96	95	94	96	95	95

Cut-off values at 90% specificity for

Nt-proBNP	**(men/women):**	**110/164 pg/ml**
HsCRP:	**(men/women):**	**6.0/7.3 mg/l**
UACR:	**(men/women):**	**0.73/1.06 mg/mmol**

Olsen MH *et al.* J Hypertens 2008;26(1):26-34