



Role of imaging in risk assessment models: the example of CIMT

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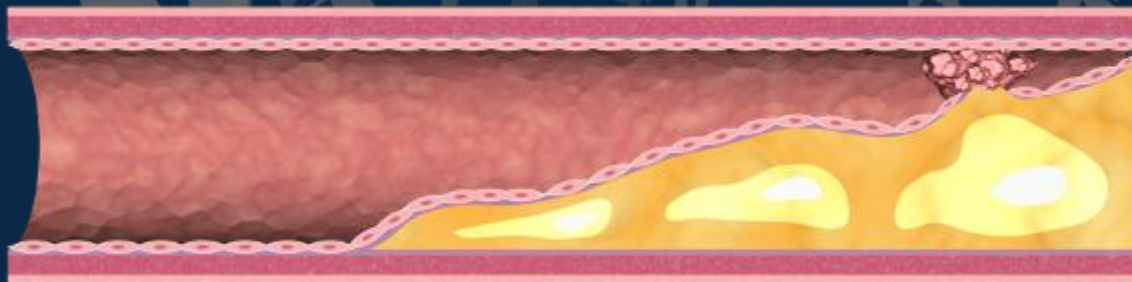
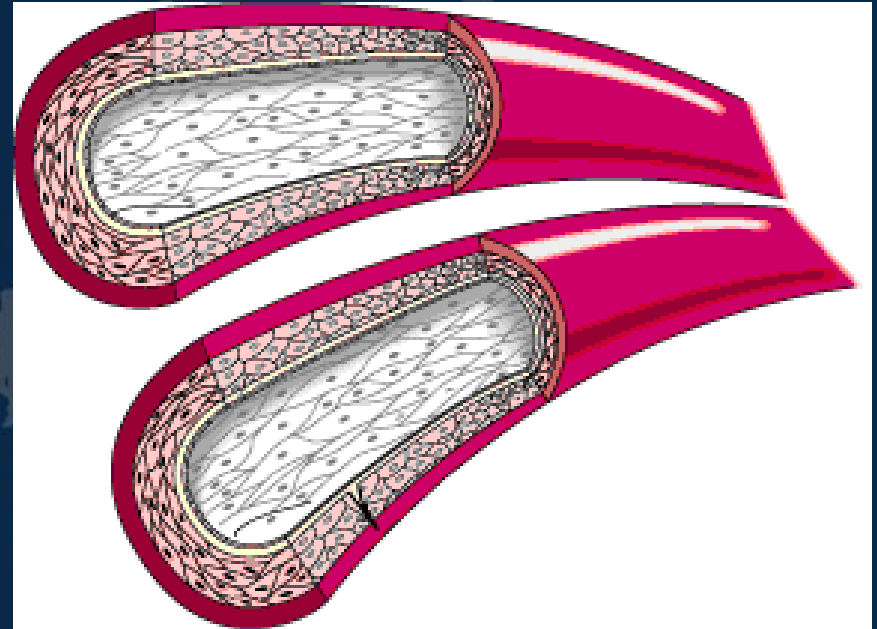
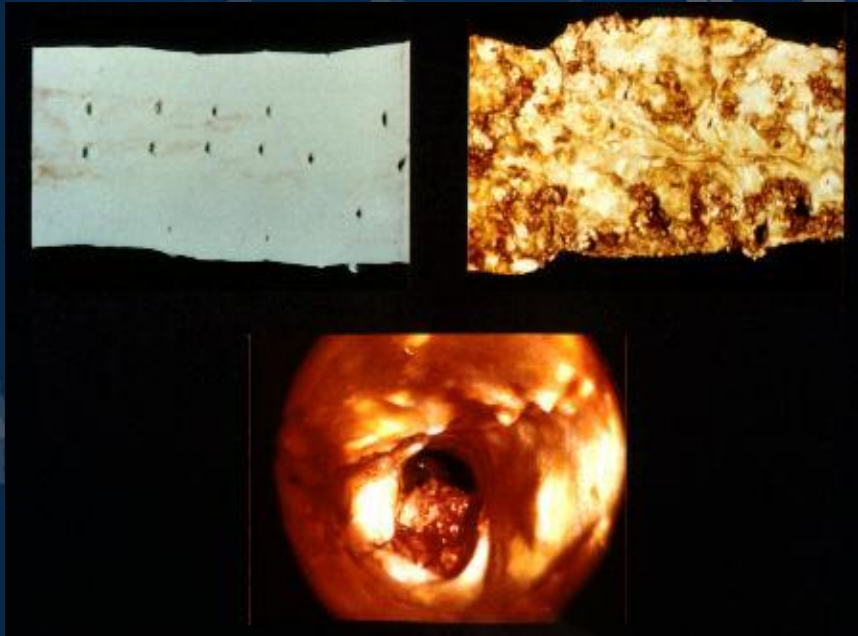
Disclosure



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I report being on an advisory boards for Organon, Pfizer, Roche, and Takeda; receiving consulting, lecture fees, and travel reimbursements from Roche, Takeda, Organon/Merck Schering Plough, AstraZeneca, and Servier; and research grants from Pfizer, AstraZeneca, Novartis, Organon/Merck Schering Plough, Wyeth, Unilever, GlaxoSmithKline, and Solvay.

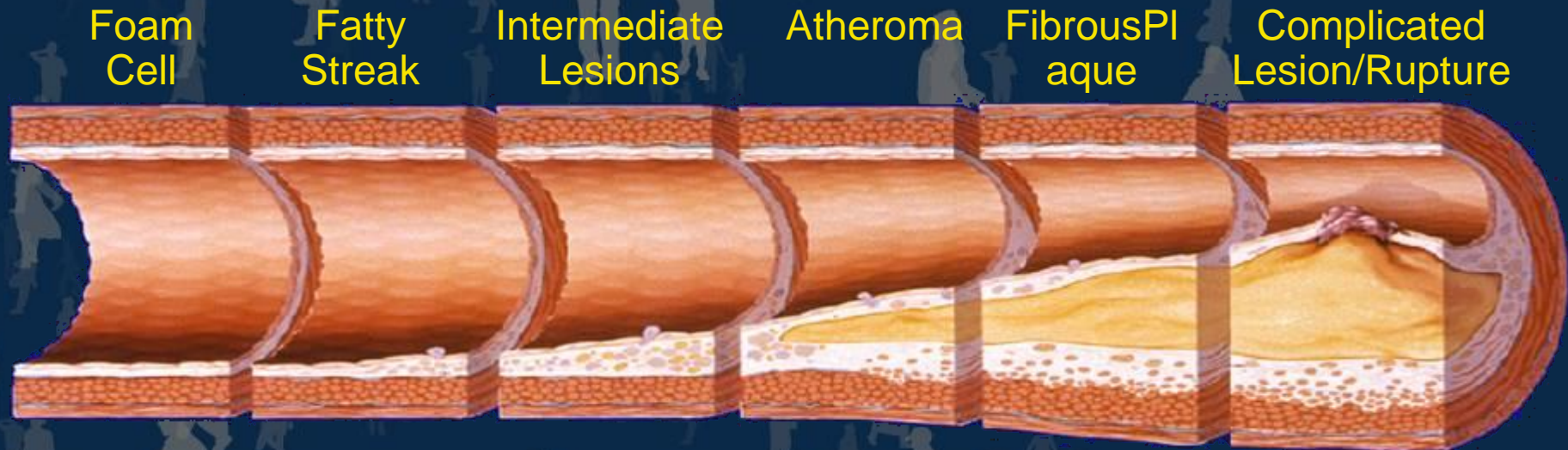
Phases and Faces of Cardiovascular Disease



Schematic presentation of how atherosclerosis develops

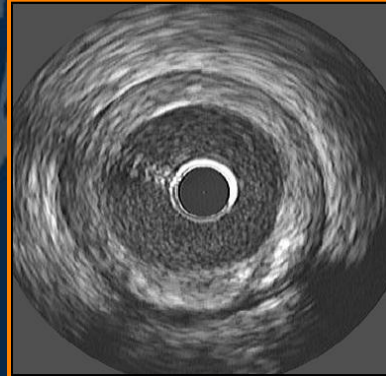
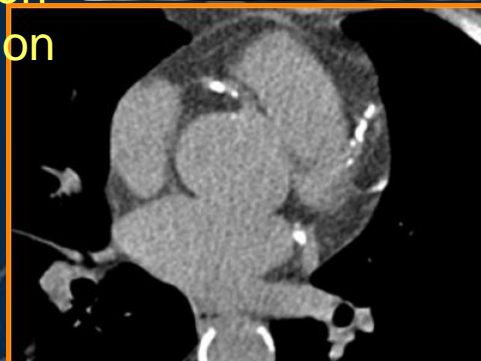
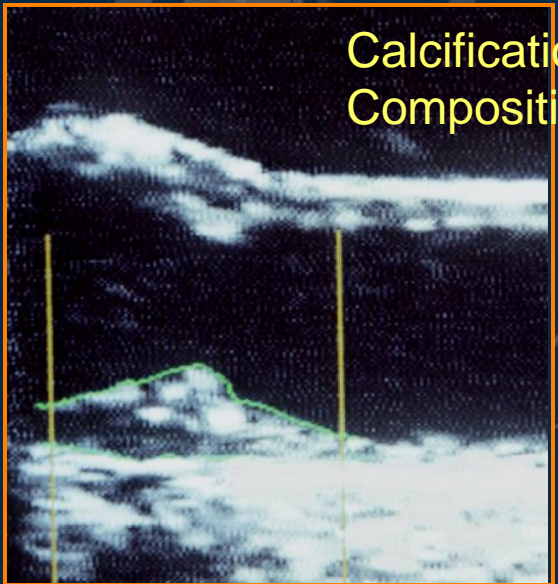
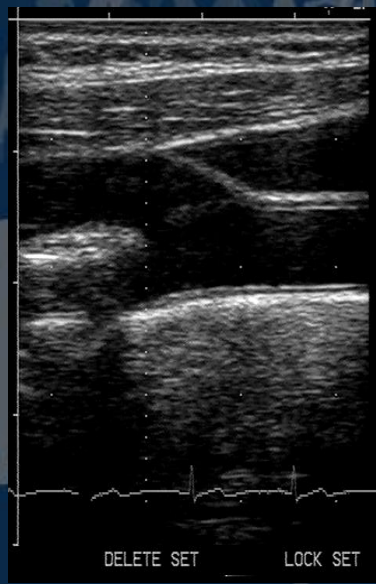
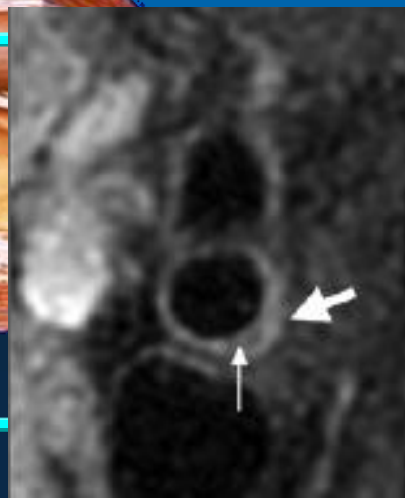
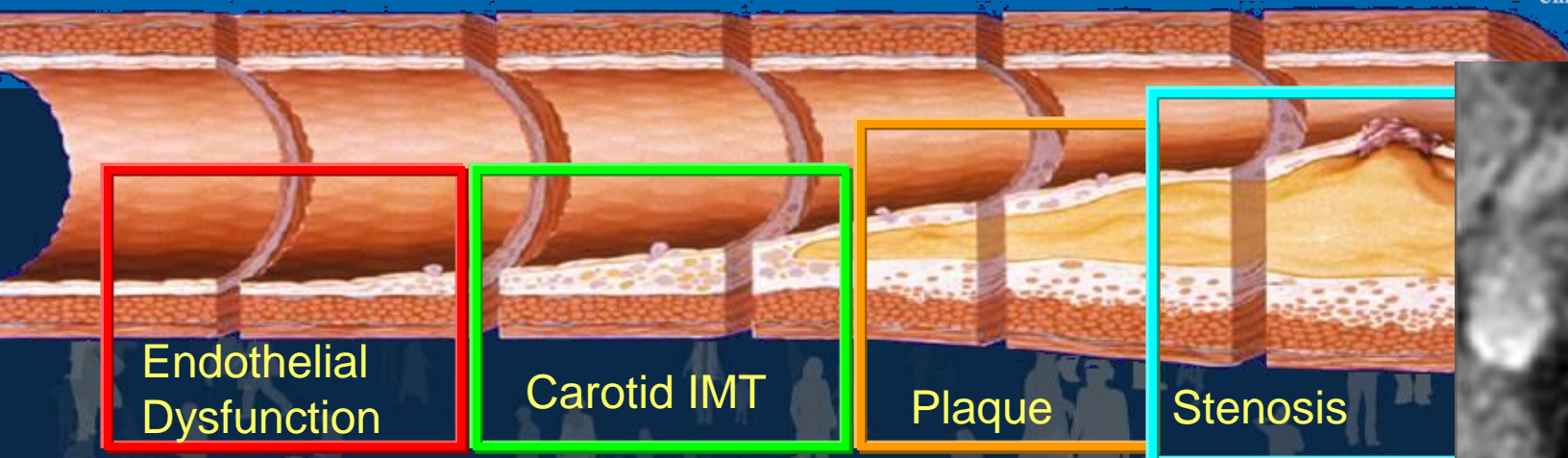


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Exposure to time and unfavourable risk factors

Imaging allows assessment of atherosclerosis progression



Monitoring atherosclerosis: options



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- Flow-mediated dilatation (FMD)
- Arterial compliance/ elasticity
- Pulse wave velocity
- Carotid artery intima-media thickness (CIMT)
- IVUS
- Coronary artery calcification
- Clinical signs and symptoms

Early

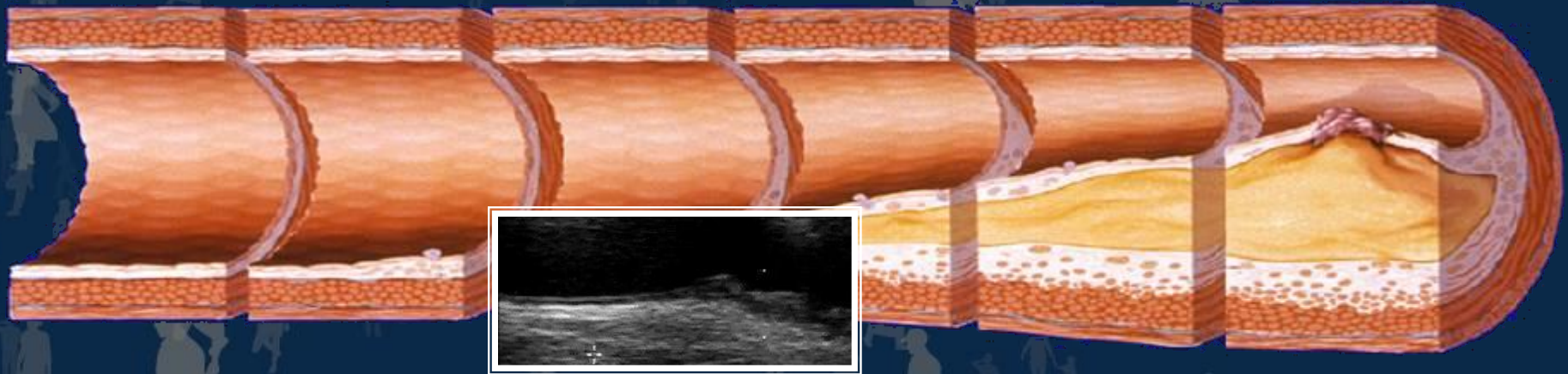


Late

Carotid IMT measurement: a window on the disease process



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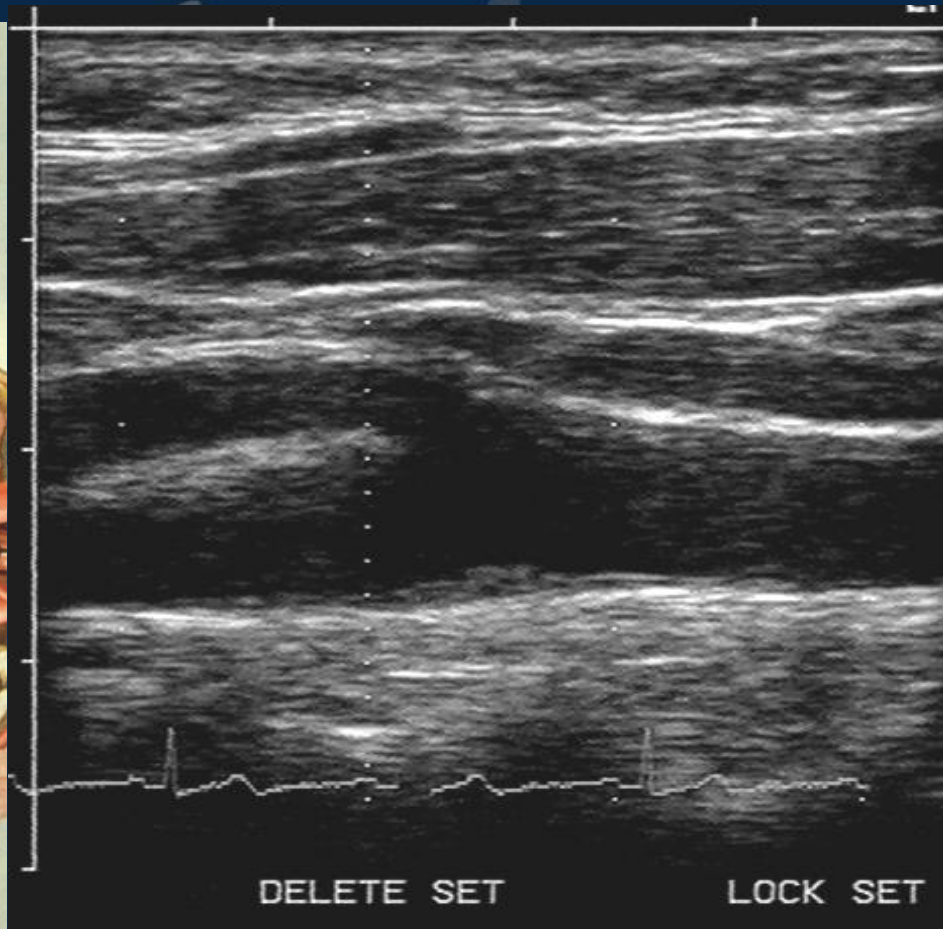
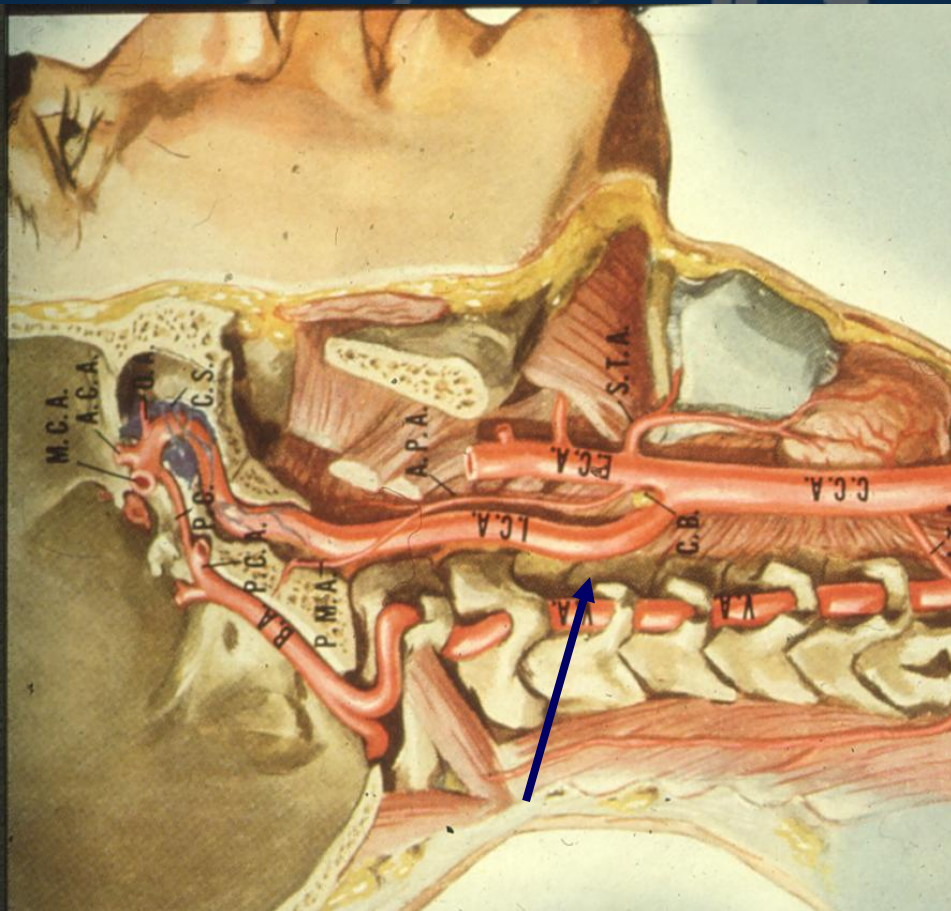
Carotid ultrasound imaging (CIMT)



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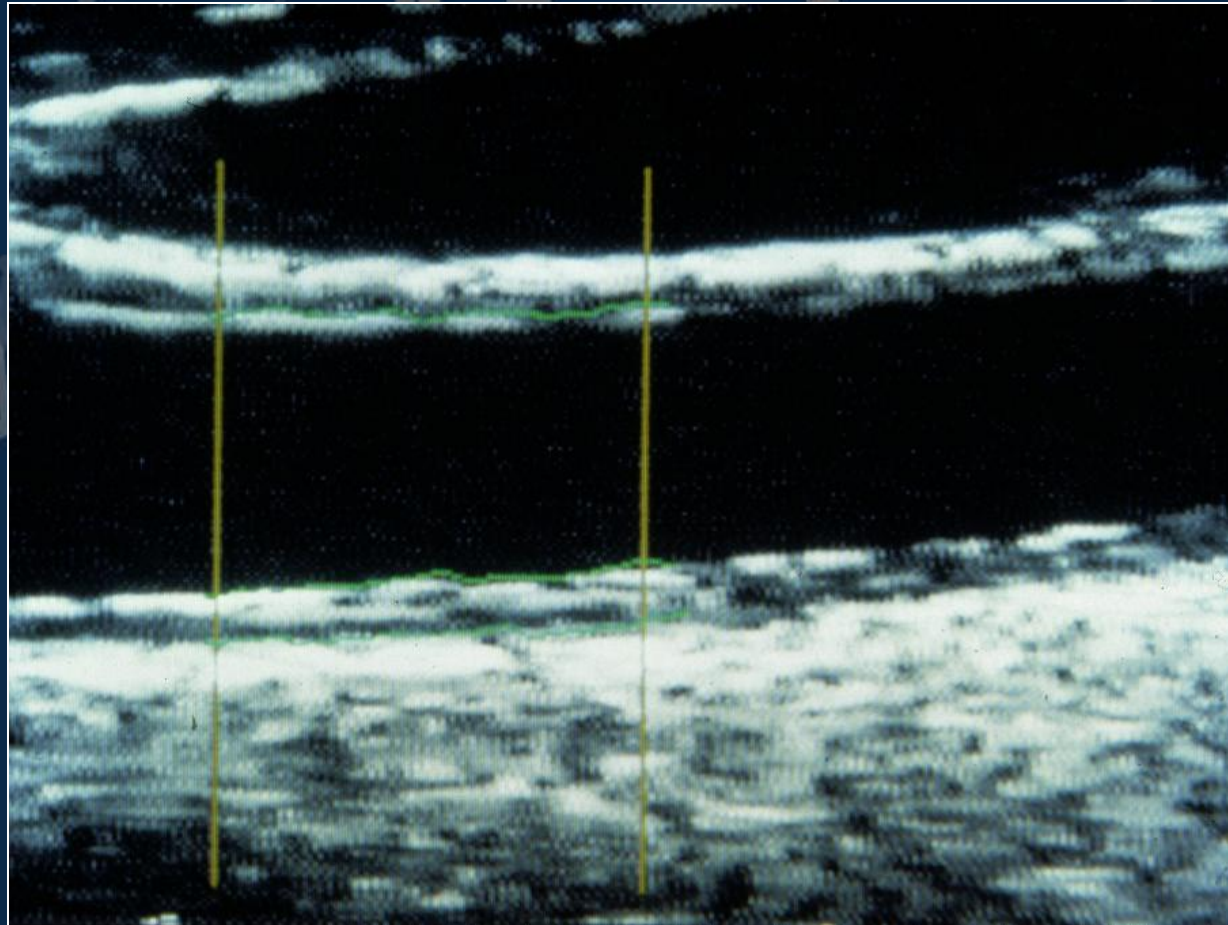
Carotid scan: anatomy and images



Starting in the Rotterdam Study, early nineties: Common far wall

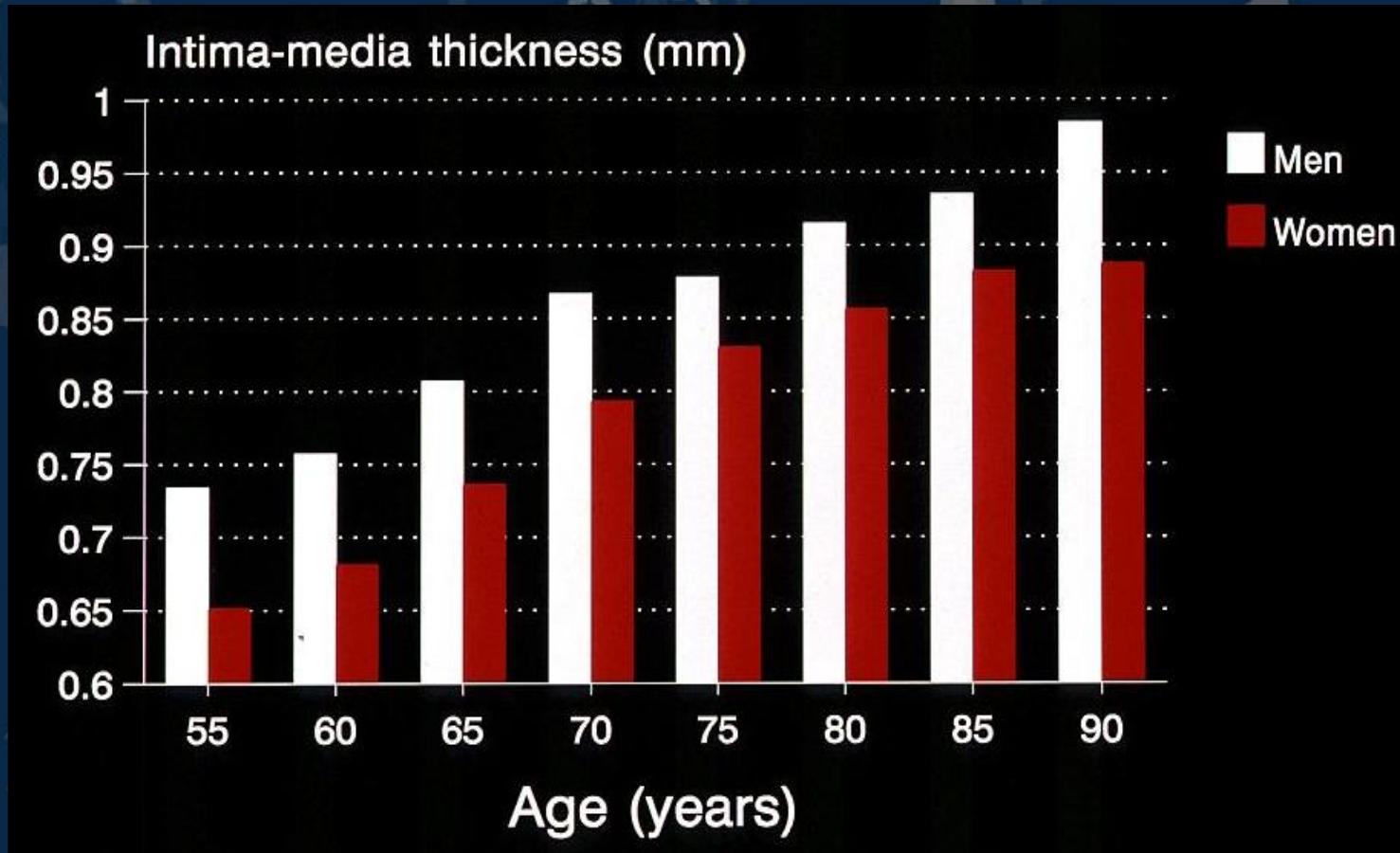


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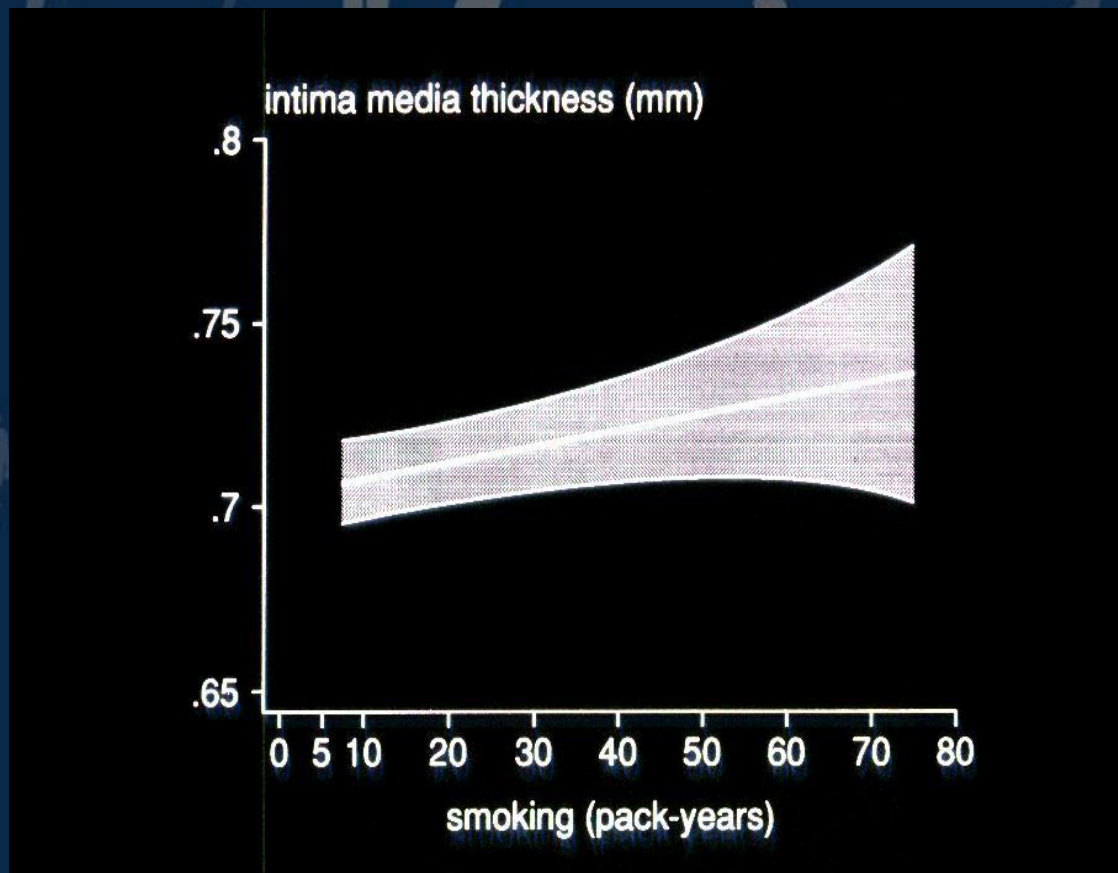
Picture from PhD thesis Michiel Bots, currently professor of cardiovascular disease epidemiology Utrecht University

Carotid IMT and Risk Factors: Age and Gender



Bots ML, Grobbee DE. Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. J Intern Med. 1994;236:567-73

Carotid IMT and Risk Factors: Smoking



Bots ML, Grobbee DE. Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. J Intern Med. 1994;236:567-73

Rotterdam Study and ARIC showed that

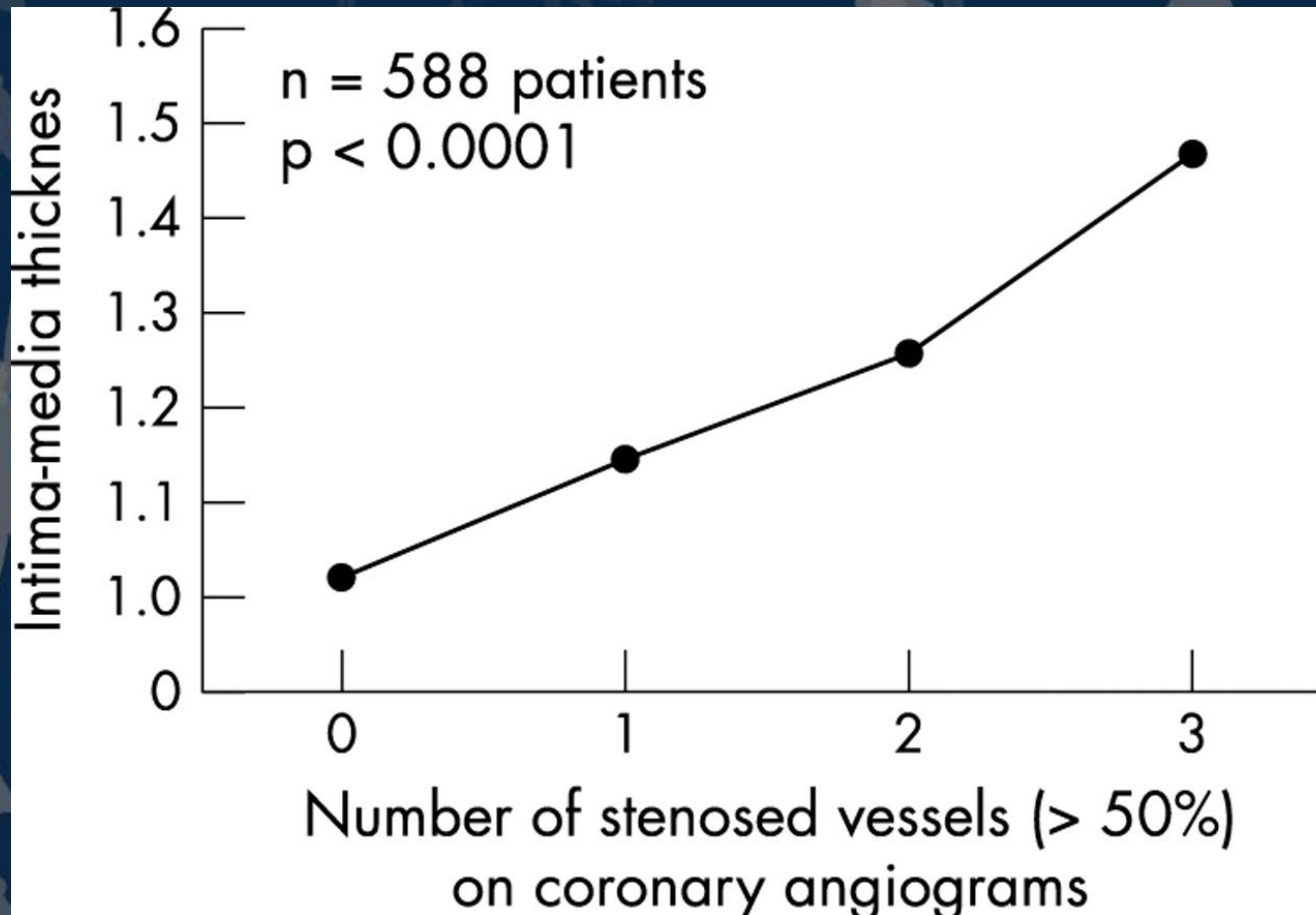


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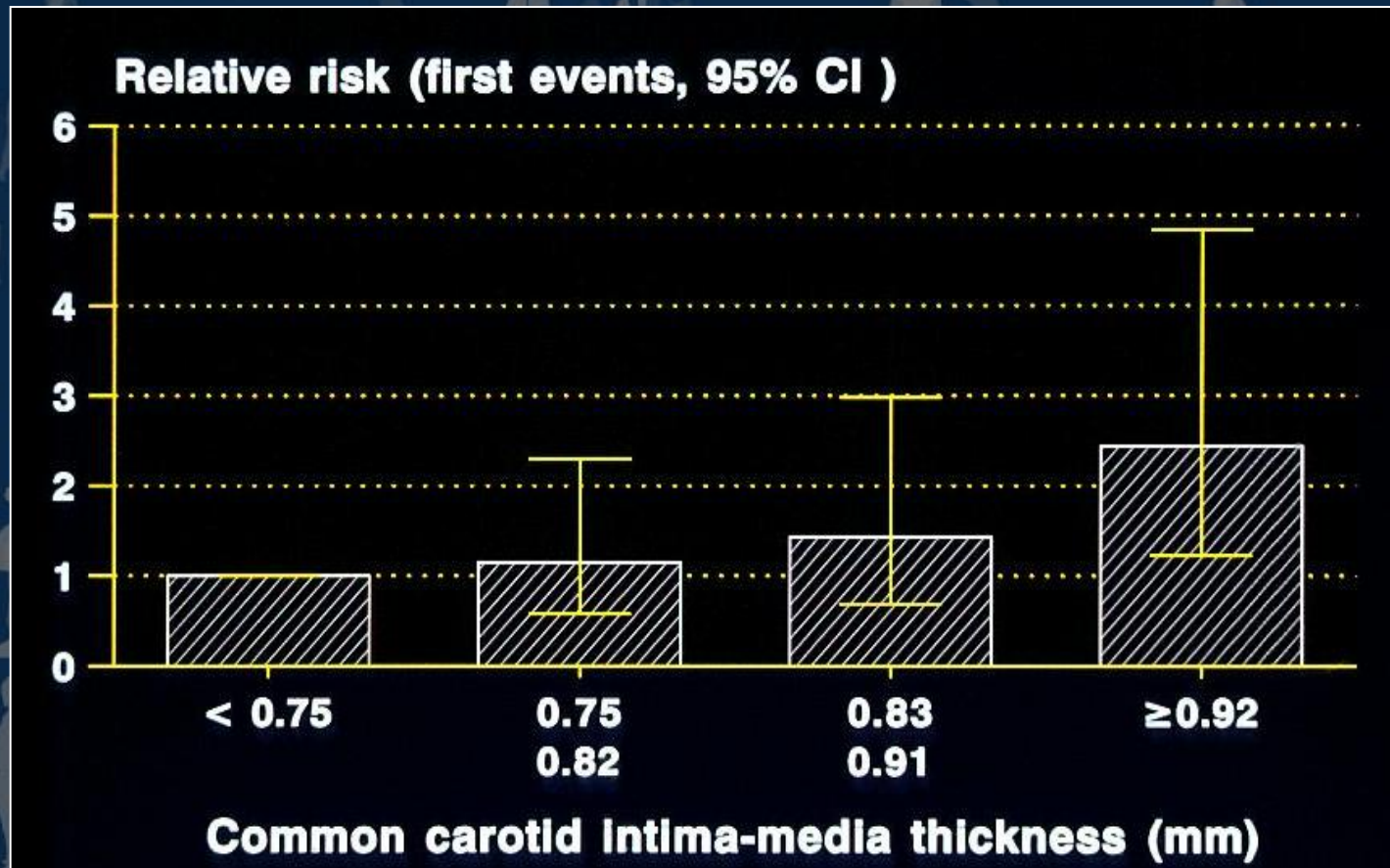
- Age, sex, smoking, total cholesterol, LDL, HDL, fibrinogen, CRP, blood pressure, alcohol...
are all consistently related to thickness of carotid intima-media
- Note: even if not measure of *local* atherosclerosis, it is a measure of *total* atherosclerotic burden

Bots ML, Grobbee DE. Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. J Intern Med. 1994;236:567-73

CIMT and angiographic coronary atherosclerosis

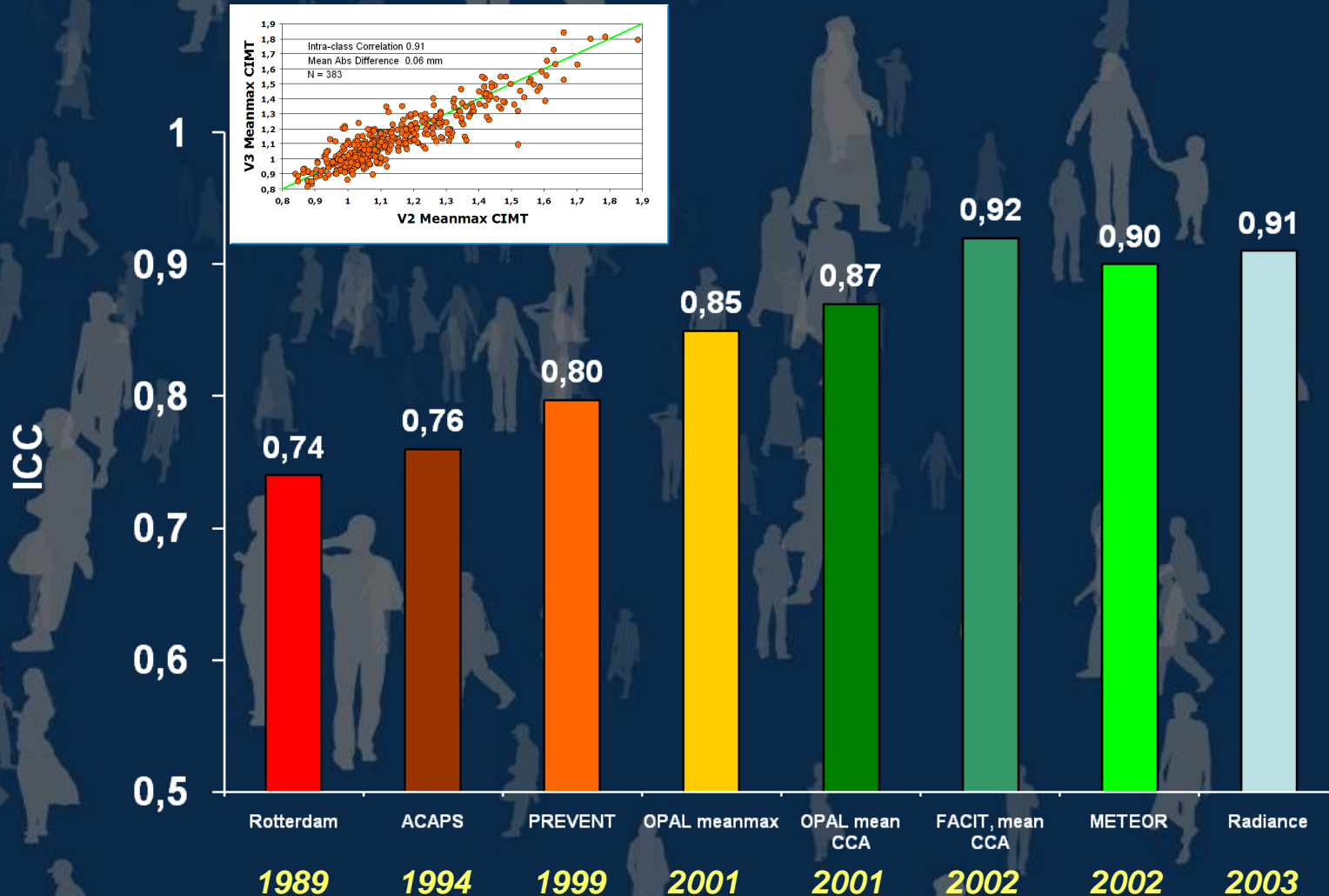


Carotid Disease as a Marker of Cardiovascular Risk : IHD



Bots, Grobbee, et al. Circulation 1997

Carotid IMT Measured Using B-mode Ultrasound: Progress in reproducibility since the early days



Parental Smoking and Vascular Damage in Young Adult Offspring: Is Early Life Exposure Critical?

The Atherosclerosis Risk in Young Adults Study

Caroline C. Geerts, Michiel L. Bots, Diederick E. Grobbee, Cuno S.P.M. Uiterwaal



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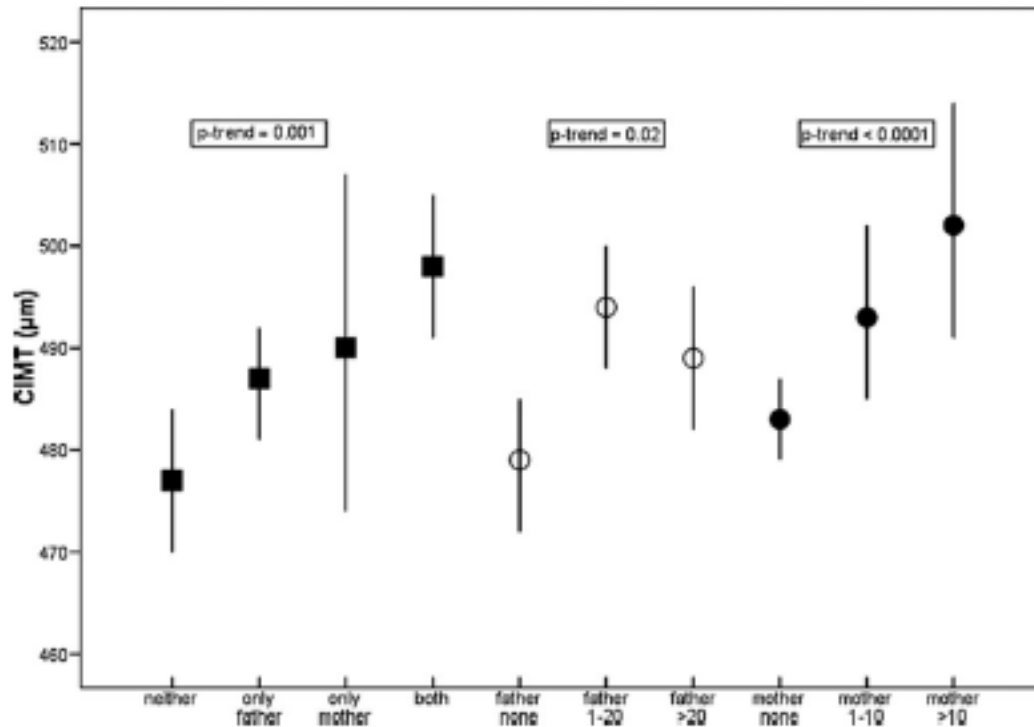


Figure 2. Mean carotid artery intima-media thickness (CIMT) of young adults by dose of tobacco smoke exposure from either or both parents in pregnancy (closed squares), and by number of cigarettes smoked by father (open circles) and by mother (closed circles).

Arterioscler Thromb Vasc Biol. 2008;28:2296-2302



CIMT today: Many options to chose from

Comments, Opinions, and Reviews

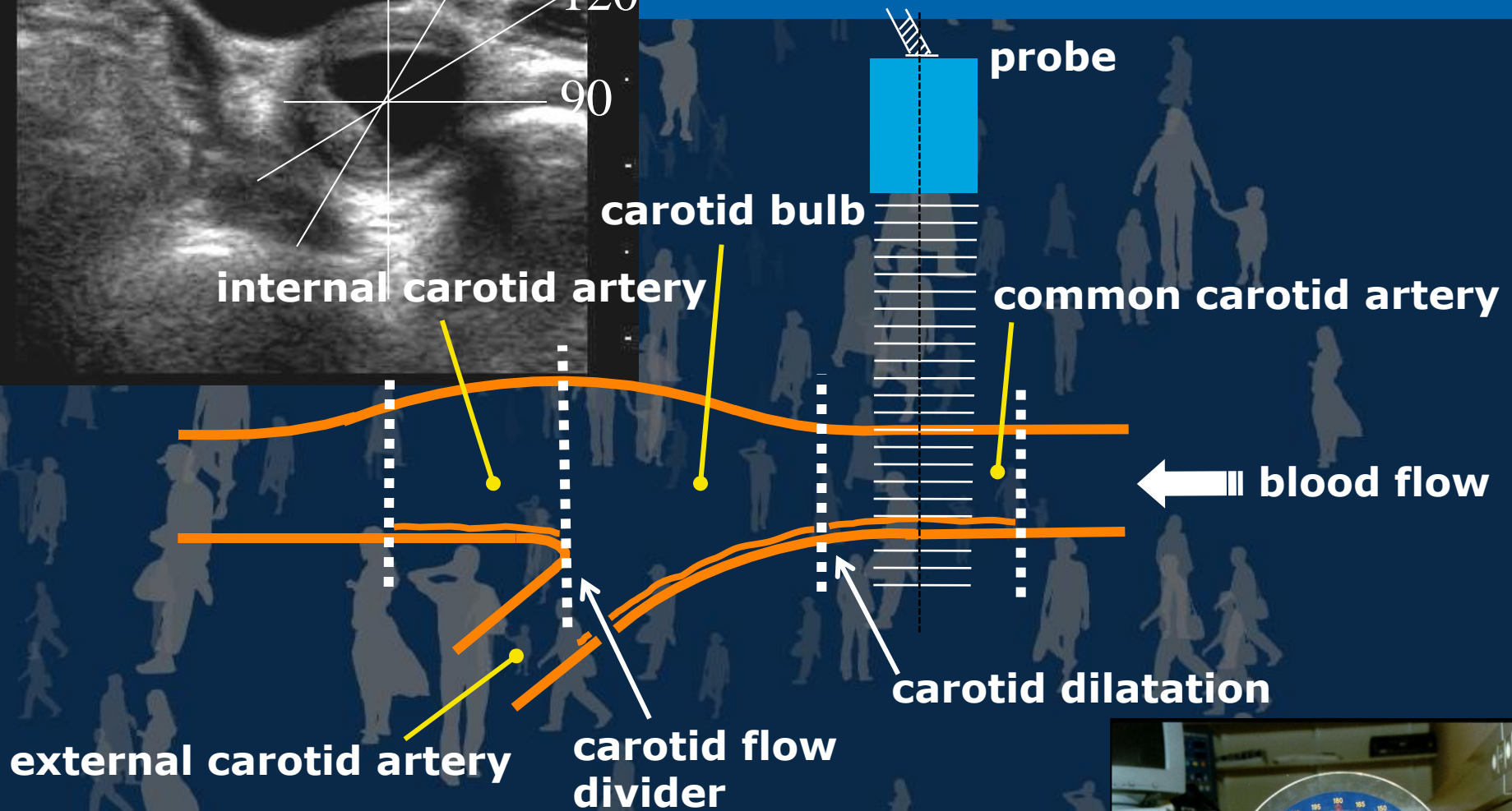
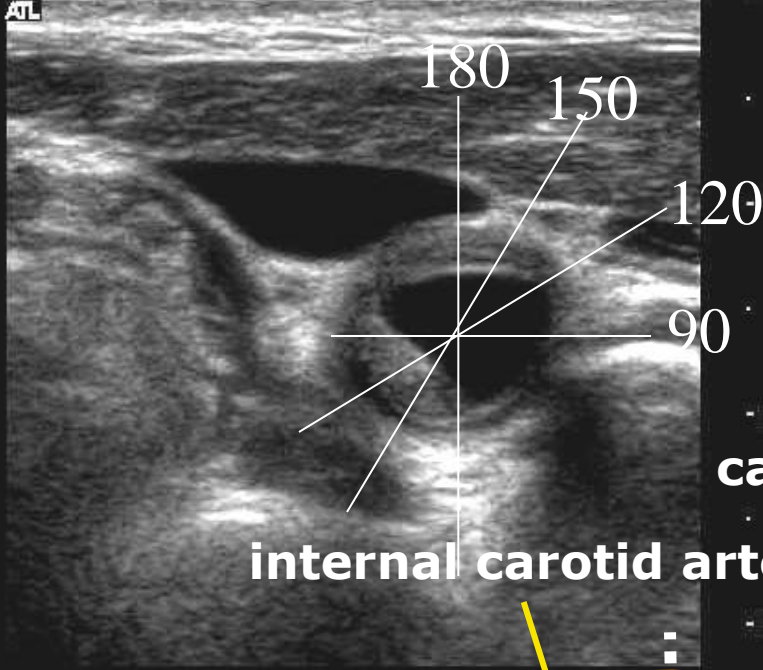
Carotid Intima-Media Thickness Measurements in Intervention Studies

Design Options, Progression Rates, and Sample Size Considerations: A Point of View

Michiel L. Bots, MD, PhD; Gregory W. Evans, MA; Ward A. Riley, PhD; Diederick E. Grobbee, MD, PhD

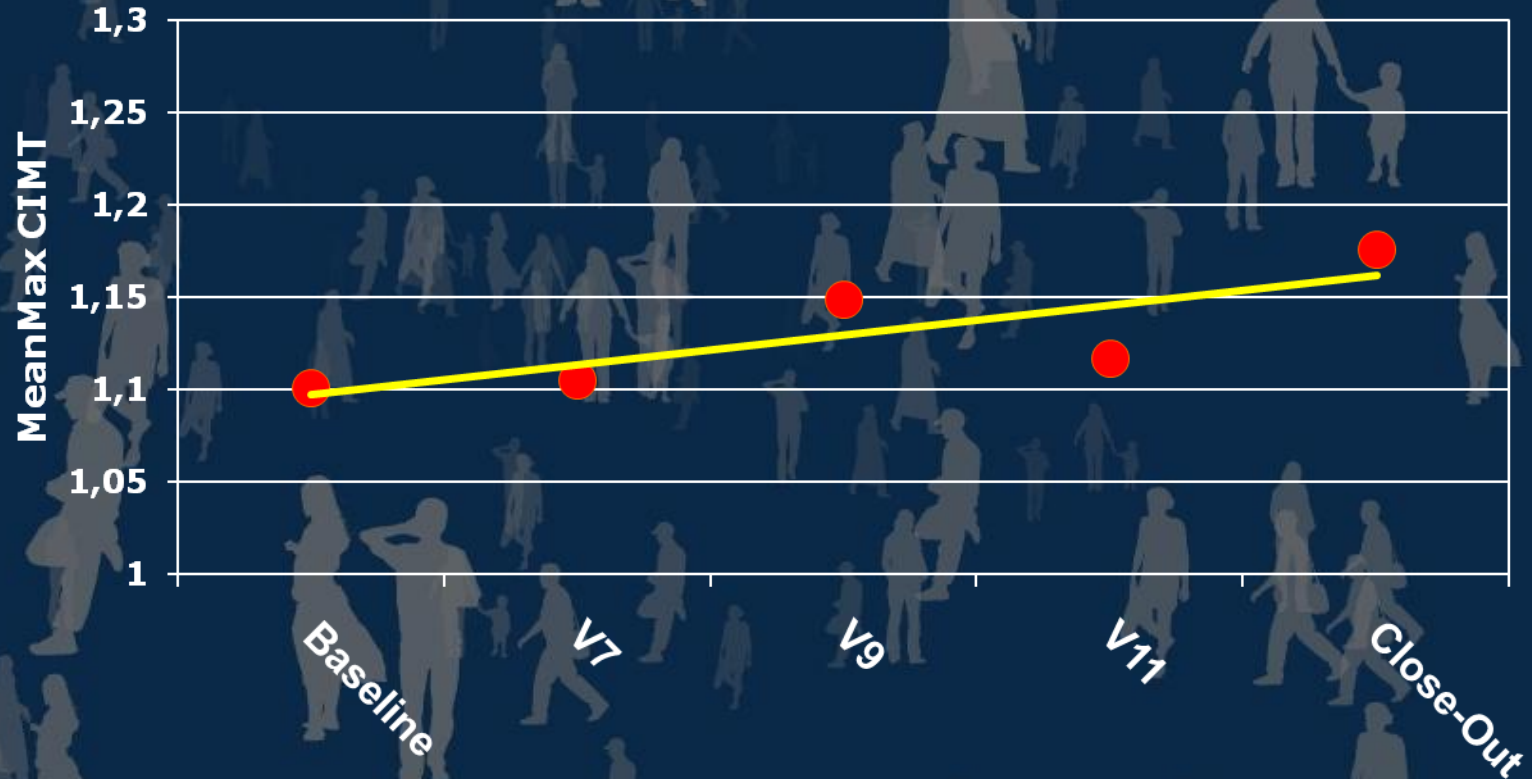
Background—Carotid intima-media thickness (CIMT) measurements are currently widely used in randomized controlled trials (RCTs) to study the efficacy of interventions. In designing a RCT with CIMT as a primary outcome, several ultrasound options may be considered. We discuss the various options and provide a pooled estimate of CIMT progression. In addition, we quantify the effect of these choices on the sample size for a RCT.

Summary of Comment—To estimate the average CIMT progression rate, we performed a pooled analysis using CIMT progression rates of control groups from published RCTs. The pros and cons of the following ultrasound options are discussed: which arterial segments may be studied; whether near and far wall CIMT measurements should be performed; whether a single image (1 angle of interrogation) or multiple images (more angles of interrogation) should be used; whether a manual or an automated edge detection reading system should be used; and whether images should be read in a random fashion or in batches. The pooled analysis showed an annual rate of change in mean common CIMT of 0.0147 mm (95% CI, 0.0122 to 0.0173) and in mean maximum CIMT of 0.0176 mm (95% CI, 0.0149 to 0.0203).



- Use of CIMT measurements enables to detect effects on atherosclerosis earlier with smaller sample sizes
- Can indicate value (or lack thereof) of new compounds faster
- Examples
 - Rosuvastatin (METEOR)
 - Torcetrapib (Radiance)

Measurement of change in CIMT over time (example for Meteor)



Meteor - Study design



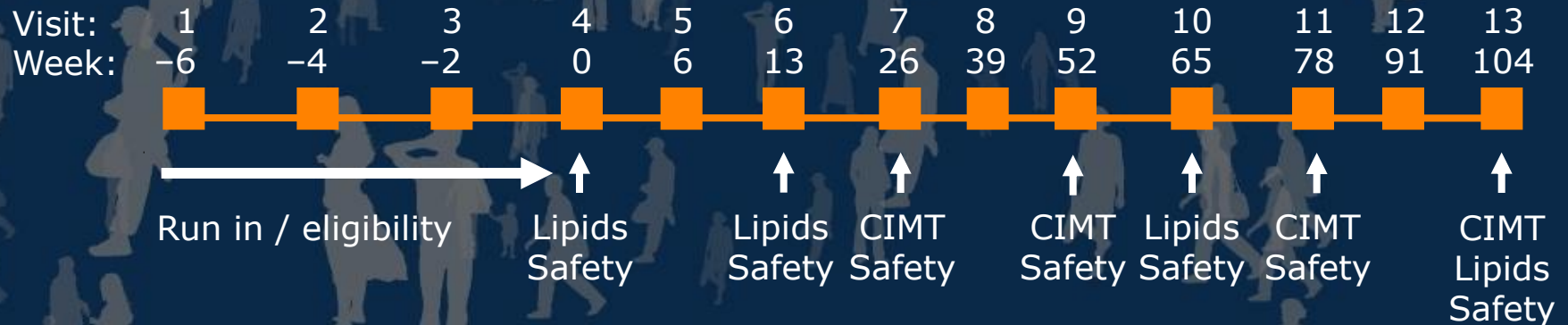
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Patients

Asymptomatic for CHD
Maximum IMT ≥ 1.2 – < 3.5 mm
Modest hypercholesterolaemia
Men (aged 45–70)
Women (aged 55–70)

Rosuvastatin 40 mg

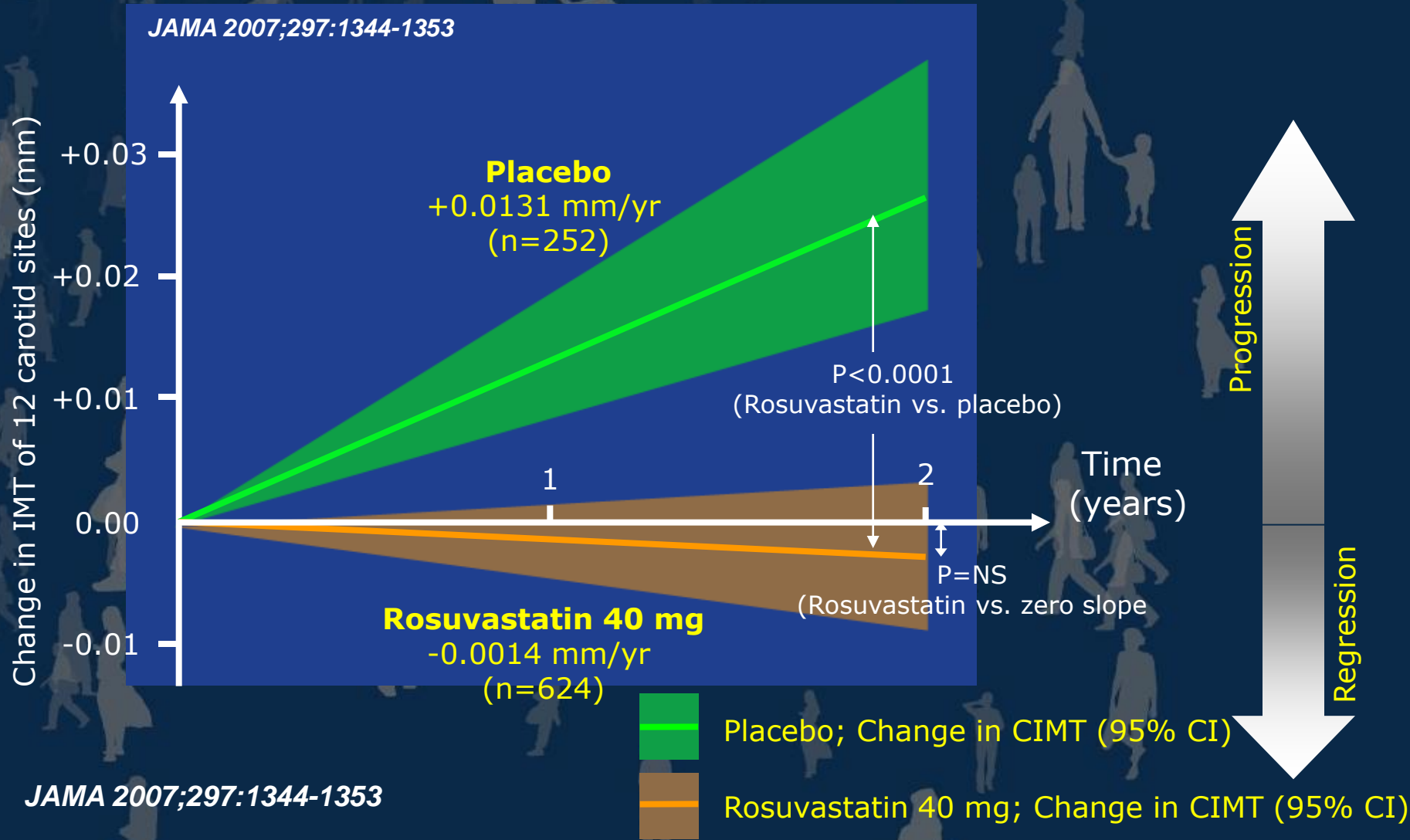
Placebo



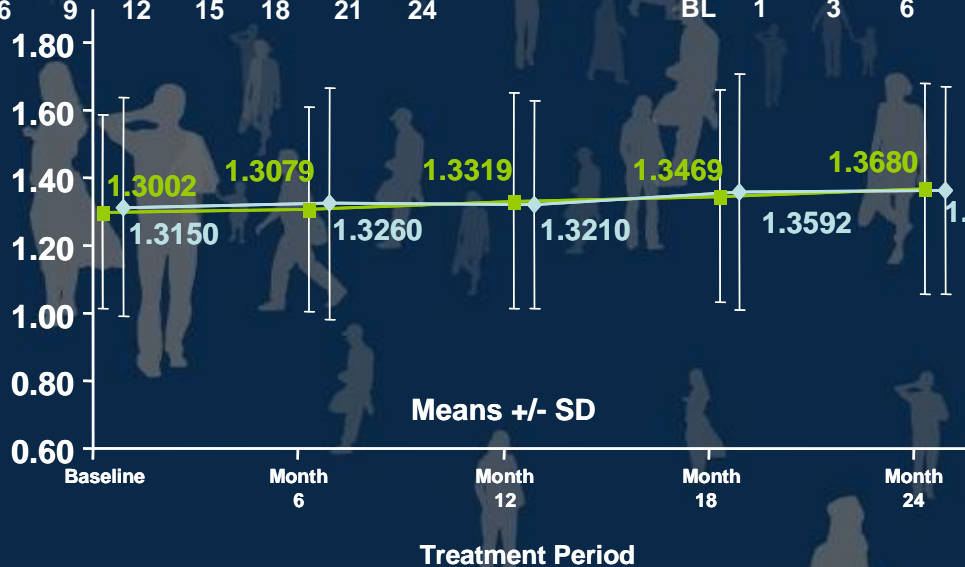
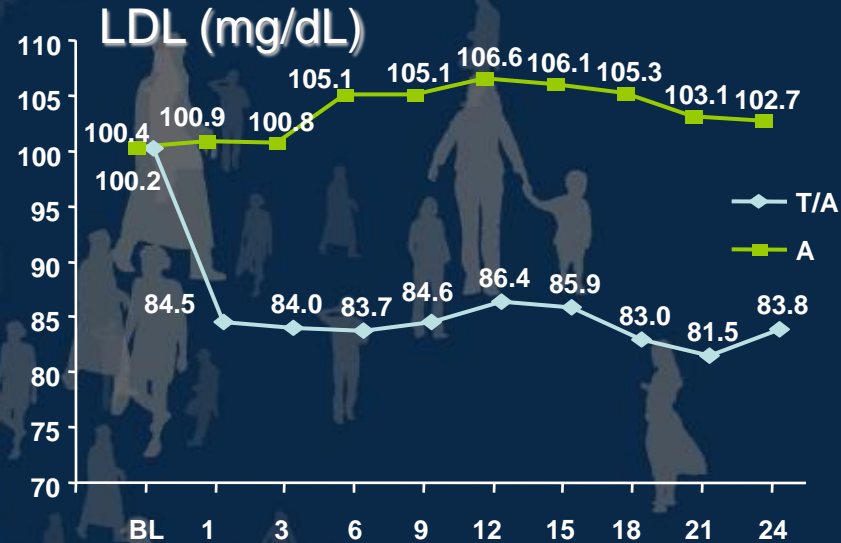
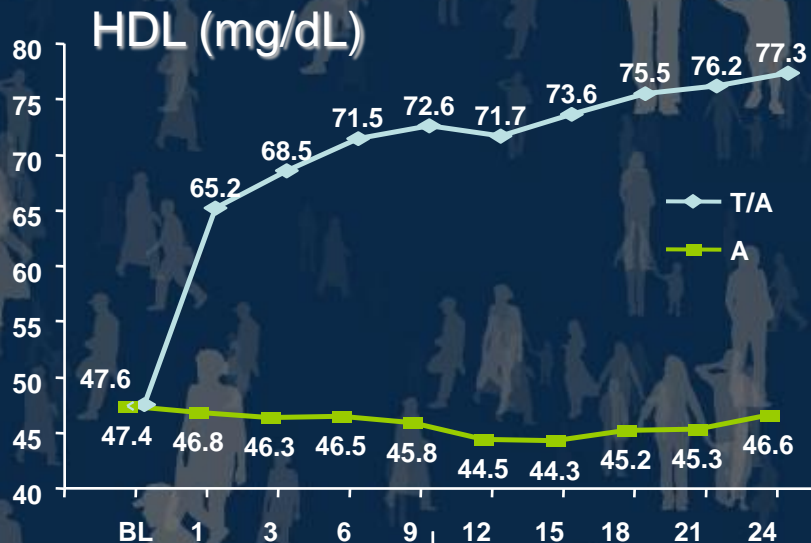
CIMT= carotid intima media thickness

Adapted from Crouse JR, Bots ML, Grobbee DE, et al. *Cardiovasc Drugs Ther* 2004; 18: 231–8

METEOR primary endpoint: Rate of change of maximum IMT Rosuvastatin vs placebo



Radiance: the end of a bright future for Torcetrapib



CIMT: Established measure of atherosclerosis



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- Use of CIMT in cohort studies showed
 - Consistent relations between risk factors and CIMT
 - Already early in life
 - Consistent relations between CIMT at various segments and future risk of MI and stroke
- Use of CIMT in trials (OPAL, Meteor, Facit, Radiance, etc.) showed
 - Changes in thickness of time can be reproducibly measured
 - Changes in CIMT over time reflect changes in risk
 - Differential effects of drugs and diet on CIMT progression

- Very often papers end with
 - ‘CIMT measurements may help to further characterise the patient’
 - ‘CIMT measurements may help us in risk stratification’
- Meaning that the value of CIMT alters the treatment strategy (risk stratification)

Recommendations



- 2000 AHA working group on identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden (Circulation 2000;101:e12-e15)
- 2003 ESH/ESC guidelines for management of arterial hypertension (J Hypertens 2003, 21:1011)
- 2003 European guidelines on cardiovascular disease prevention in clinical practice (Eur Heart J 2003; 24:1601)
- 2004 & 2007 Mannheim Intima-media thickness consensus (Cerebro Dis 2007;23:75)
- 2006 SHARP statement (Am J Cardiol)

The issue is ...



Does the result of the imaging test for atherosclerosis in one individual lead to a shift from one risk function category to another and is this shift indeed followed by different treatment consequences for that individual?

-> Increased risk or decreased risk !

Incremental value of CIMT on top of risk factors in the prediction of CVD events



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- Literature review on studies addressing incremental value
- Not relative risk / odds ratios
- But,
 - Area under the receiver operating curve
 - C-statistic
 - Prediction rule

Plantinga Y, et al. European Journal of Cardiovascular Prevention and Rehabilitation 2009, 16:639–644

Incremental value of CIMT on top of risk factors in the prediction of CVD events



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380 hits

- 29 studies IMT & follow-up events
- 6 studies dealt with ‘incremental value’
- 3 in diabetes or known CVD included
- Remaining:
 - Del Sol, Stroke 2001
 - Folsom, Diabetes Care 2003
 - Bernard, Diabetes Care 2006

The added value of CIMT measurements in risk stratification: Rotterdam Study



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Contribution of Different IMT Measures to Model 1 in the Prediction of Coronary Heart Disease and Stroke

Model	ROC* Area (95%CI)
Model 1	0.72 (0.67–0.77)
Model 1+maximum CCA IMT	0.74 (0.69–0.78)
Model 1+maximum BIF IMT	0.74 (0.69–0.78)
Model 1+maximum ICA IMT	0.75 (0.70–0.79)
Model 1+combined IMT	0.75 (0.71–0.80)

Adding CIMT to conventional risk factors for coronary heart disease and stroke does not result in a material increase in the predictive value when used as a screening tool

The added value of CIMT measurements in risk stratification: ARIC



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	AUC using traditional risk factors only	AUC using traditional risk factors and CIMT >75th percentile
Combined (N=13,145)	0.748	0.757
Women (N=7,463)	0.802	0.809
Men (N=5,682)	0.684	0.703

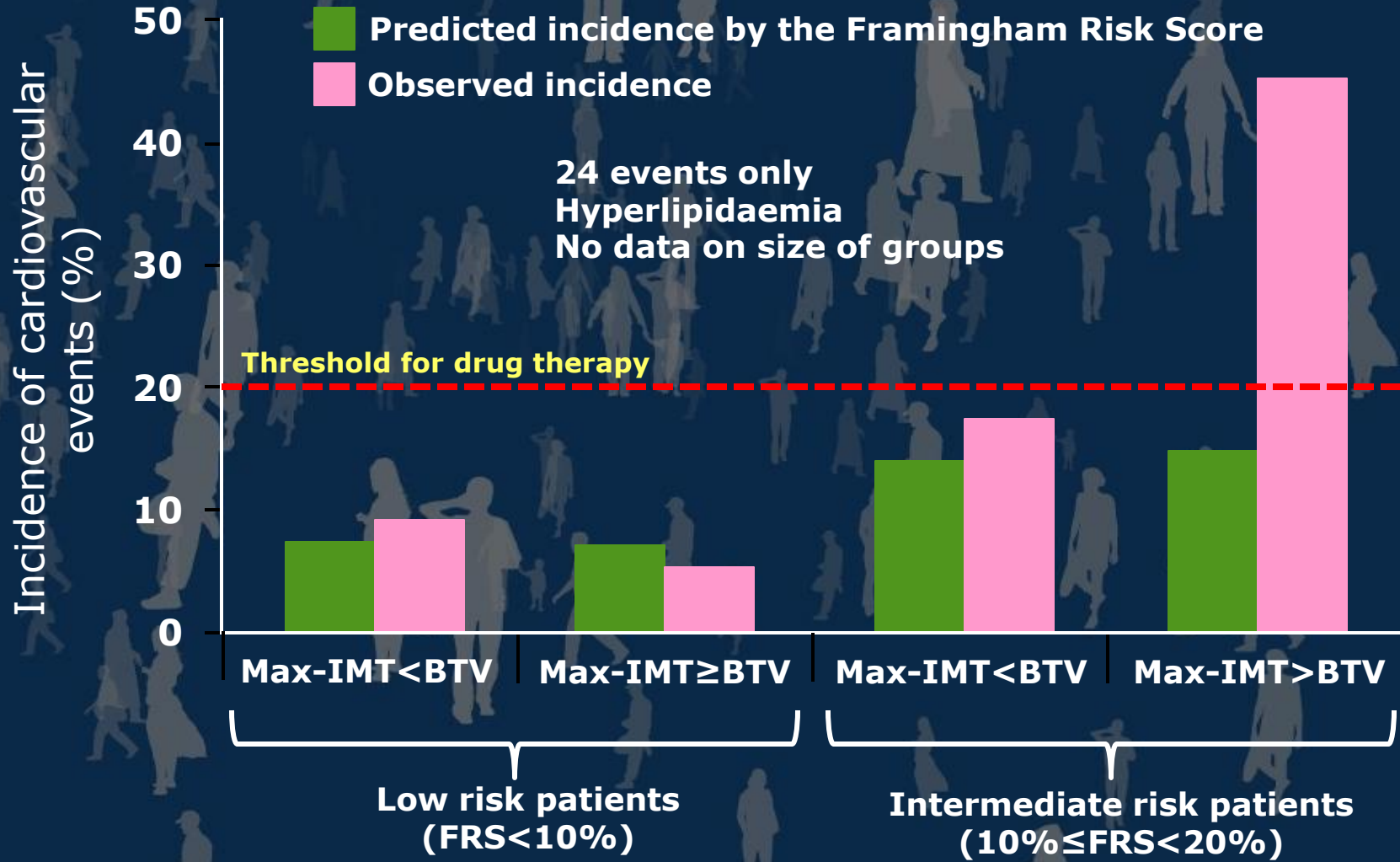
CIMT 75th percentile: 0.78 mm entire population, 0.73 mm women, 0.84 mm men

The added value of CIMT measurements in risk stratification

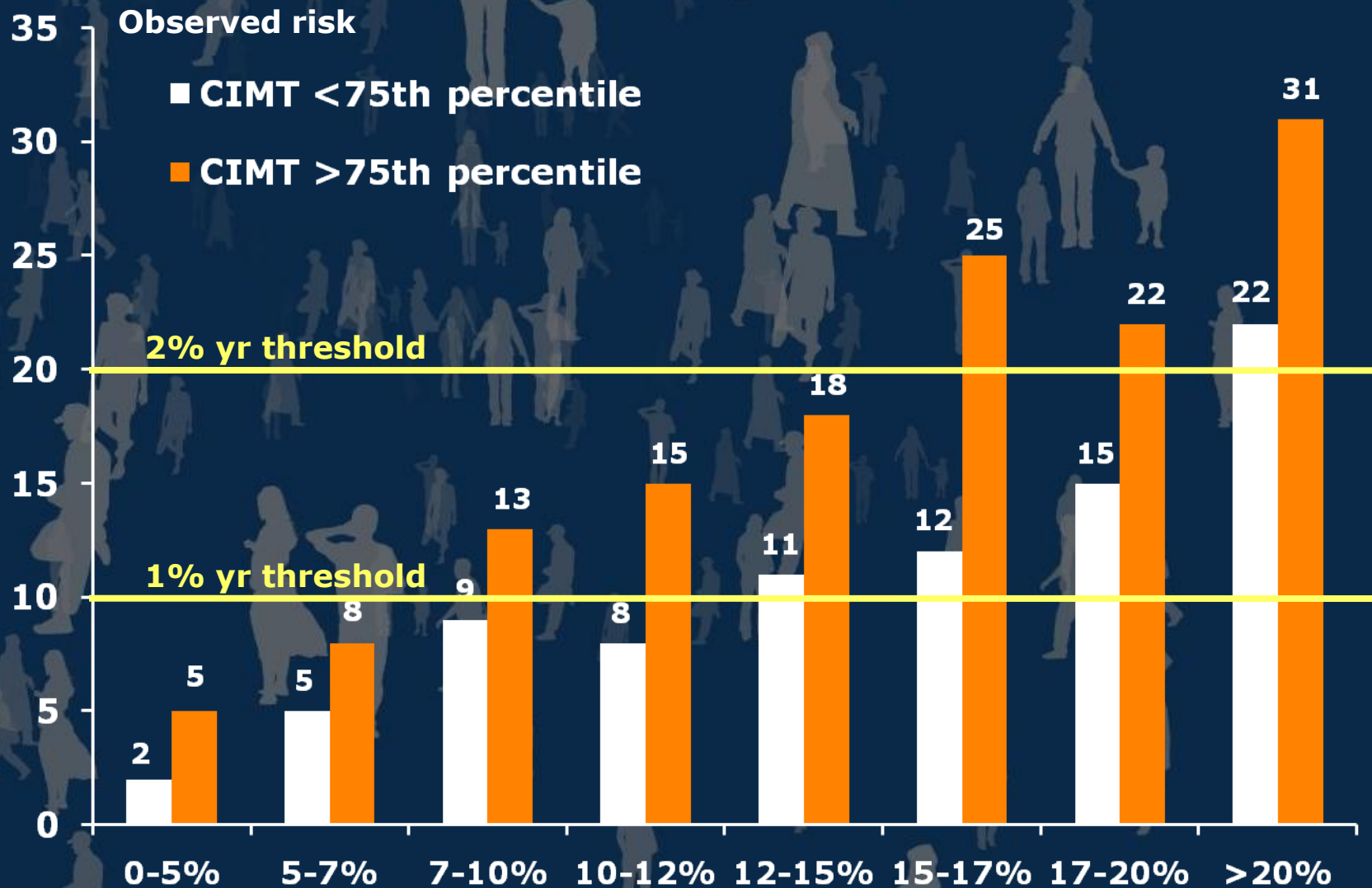


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- Small effects:
Change of 0.01 – 0.03 in AUC ROC
- But is AUC the most appropriate measure of performance in clinical practice?
- Alternative: Can CIMT measurement lead to a change in risk category and thereby trigger a different treatment approach?



ARIC: observed risk in various risk categories classified by CIMT



Conclusions



- Carotid IMT measurements offer a well established method for imaging atherosclerosis in observational research
- Carotid IMT measurements can validly be used as a proxy marker for disease progression and regression in clinical trials

Conclusions



- Carotid IMT measurements integrate the effects of conventional risk factors on atherosclerosis occurrence and progression and therefore add little overall improvement of risk prediction models
- In patients in intermediate categories of risk Carotid IMT measurements may improve risk classification and assist in selecting those that have an indication for risk factor modification but the evidence is limited and additional research is needed to position their utility in clinical practice

Acknowledgements: my team



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+ a group of excellent PhD fellows

+ numerous participants