Vulnerable Plaque is a Systemic Disease: Insights from BioImage Study

Roxana Mehran MD, FACC, FSCAI, FAHA, FESC

Professor of Medicine (Cardiology),

Population Health Science and Policy

The Icahn School of Medicine at Mount Sinai

Cardiovascular Research Foundation

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

Affiliation/Financial Relationship	Company
• Grant/Research Support (Institutional)	• The Medicines Co., BMS, Astra Zeneca, Lilly/Daiichi Sankyo; Orbus Neich
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Prevalence, Impact and Predictive Value of Detecting Subclinical Coronary and Carotid Atherosclerosis in Asymptomatic Adults:

The BioImage Study

Usman Baber MD MS, Roxana Mehran MD, Samantha Sartori PhD, Mikkel Malby Schoos MD PhD, Henrik Sillesen MD DMSc, Pieter Muntendam MD, Mario J. Garcia MD, John Gregson PhD, Stuart Pocock PhD, Erling Falk MD DMSc, Valentin Fuster MD, PhD

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Background

- Methods to enhance cardiovascular risk prediction are needed given the imprecision in traditional risk factor (Framingham) assessment alone.

- While recent studies have shown that quantifying atherosclerosis using coronary artery calcification (CAC) is superior to indirect markers of atherosclerosis (cIMT) for long-term risk prediction, its' utility in shorter term risk prediction is less clear.

- Moreover, there are limited data comparing CAC to other imaging-based biomarkers that also directly quantify atherosclerosis.

Objectives

- *To determine the incremental impact of detecting subclinical coronary or carotid atherosclerosis over traditional risk factors for short-term CVD risk prediction among a contemporary cohort of asymptomatic, at-risk individuals*

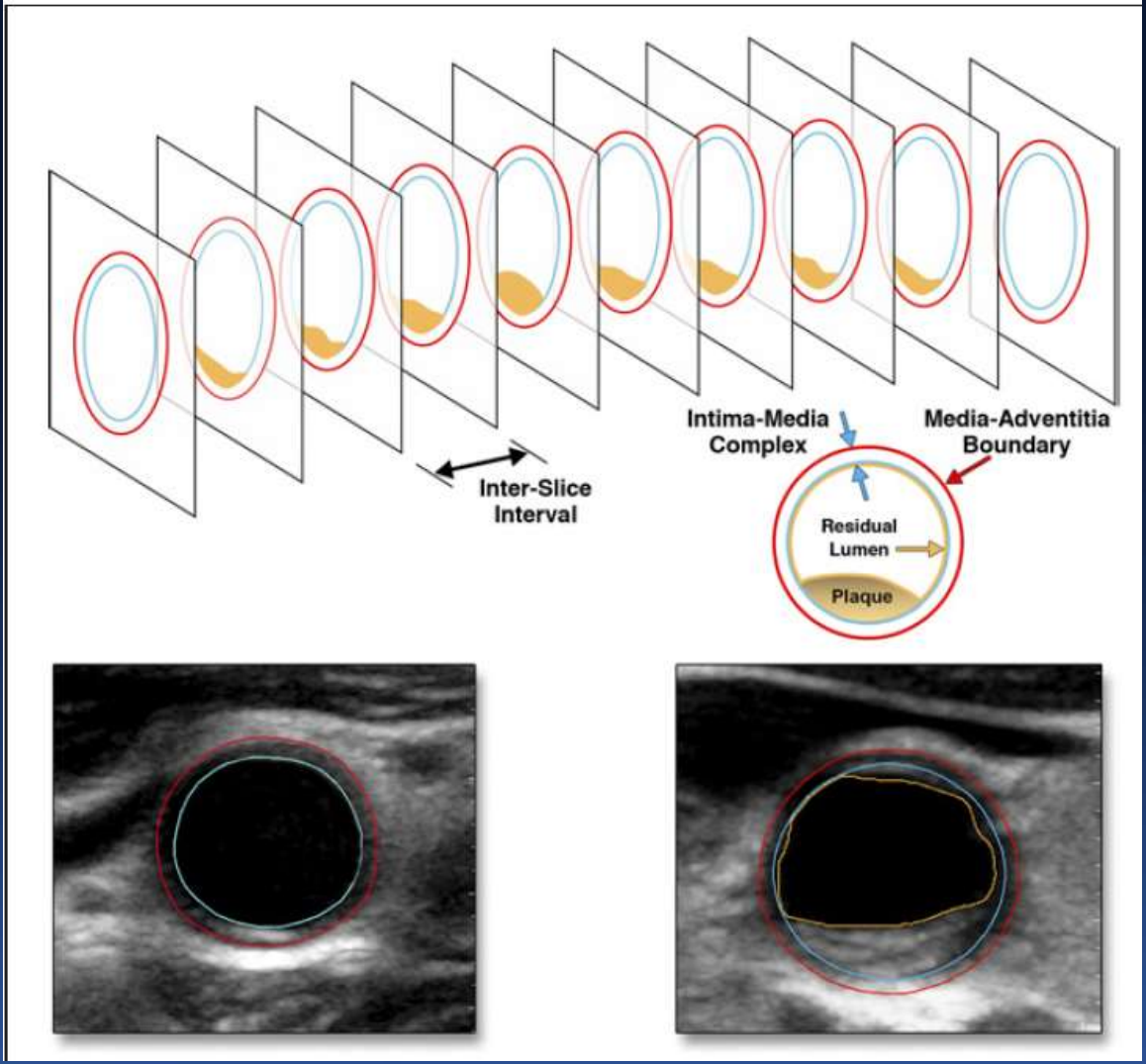
Methods

- Study Design/Population
  - Observational study embedded within a health insurance network (Humana) designed to identify imaging-based biomarkers that improve near-term CVD risk prediction
  - Collaborative effort between insurance, imaging, biomarker and pharmaceutical companies and led by a consortium of international academic investigators
  - Eligible participants comprised asymptomatic, at-risk (men >55 years; women >60 years) US adults without established CVD recruited from 2 cities (Chicago, IL; Fort Lauderdale, FL)
  - In each location, temporary mobile research facilities with mobile imaging equipment were established. Recruited between 2008-2009; follow-up ~ 3 years

Methods

- Assessment and follow-up
  - All participants underwent assessment of traditional risk factors, imaging of the coronary (CAC) and carotid ultrasound using a novel “3D cross-sectional sweep”
  - Imaging results were read by independent and blinded core labs
  - Putative adverse events were identified using insurance claims and death index. Adverse events were adjudicated by an independent committee.
  - Primary endpoint included cardiovascular death, spontaneous myocardial infarction or ischemic stroke. Broader secondary endpoint included all-cause death, unstable angina and coronary revascularization.

“Manual 3D” Cross-sectional Carotid Sweep



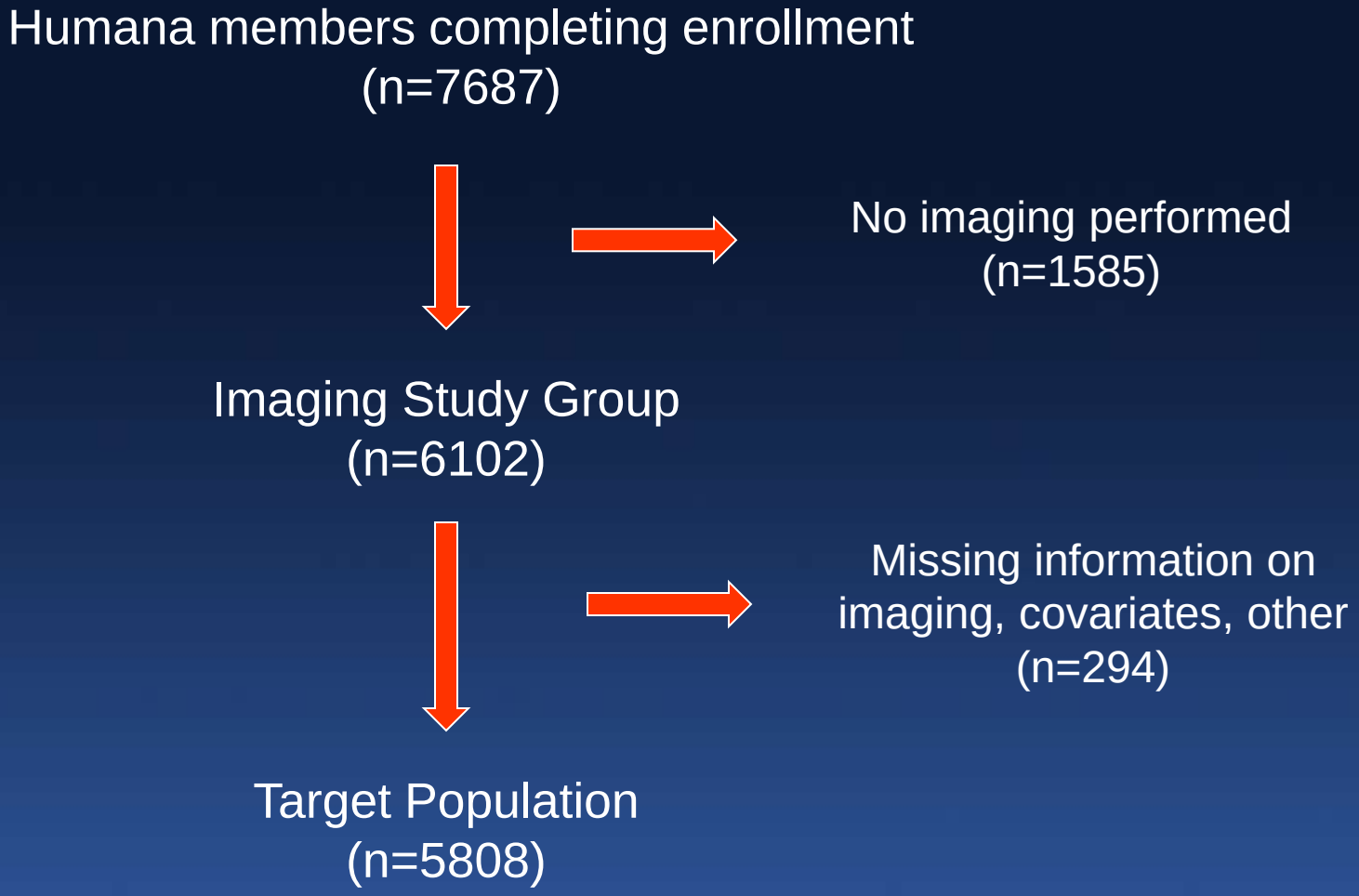
Area of all carotid plaques was summed yielding a continuous metric of total carotid atherosclerosis: carotid plaque burden (cPB)

Sillesen et al., JACC Img 2012

Methods

- **Statistical Approach**
  - Participants were grouped as either having no measurable atherosclerosis or by tertile of increasing CAC or carotid plaque burden (cPB).
  - Incidence of adverse events was calculated using KM method and compared across CAC/cPB groups
  - Associations between CAC, cPB and MACE were assessed using Cox proportional hazards regression
  - Metrics of model performance (global fit, discrimination, calibration) were compared between models with traditional risk factors alone and traditional risk factors with CAC or cPB, respectively
  - Net reclassification was compared between models with and without CAC and cPB

Study Flow

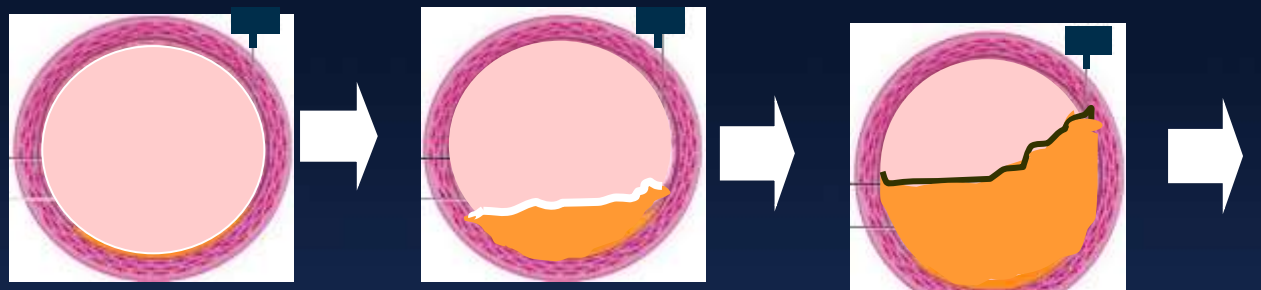

Humana members completing enrollment
(n=7687)
No imaging performed
(n=1585)
Imaging Study Group
(n=6102)
Missing information on
imaging, covariates, other
(n=294)
Target Population
(n=5808)

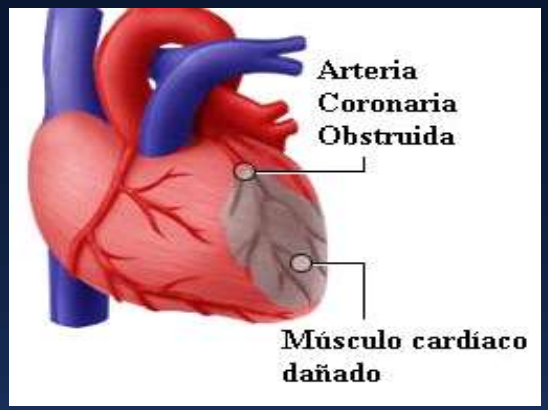
Baseline Characteristics of HRP BioImage Cohort

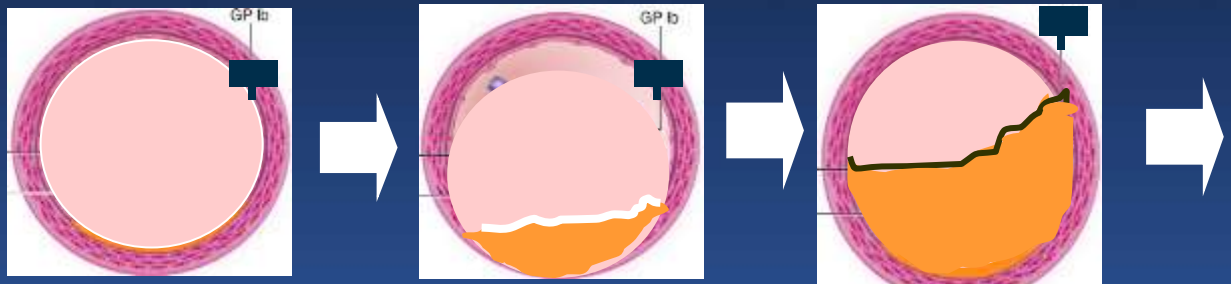
Age, mean (SD), y	68.9 (6.0)
Female, No. (%)	3281 (56.5)
White Race, No. (%)	4301 (74.0)
Diabetes mellitus, No. (%)	857(14.8)
Current Smoker, No. (%)	496 (8.5)
Hypertension, No. (%)	3614 (62.2)
BMI, mean (SD), kg/m^2	29.0 (5.5)
LDL-C, mean (SD), mg/dl	114.2 (33.2)
HDL-C, mean (SD), mg/dl	55.7 (15.3)
Total Cholesterol , mean (SD), mg/dl	202.5 (38.6)
Systolic BP, mean (SD), mm Hg	139.4 (18.5)
Diastolic BP, mean (SD), mm Hg	78.2 (9.1)
Lipid lowering Therapy, No. (%)	1993 (34.3)
Chronic Kidney Disease, No. (%)	1115 (19.1)

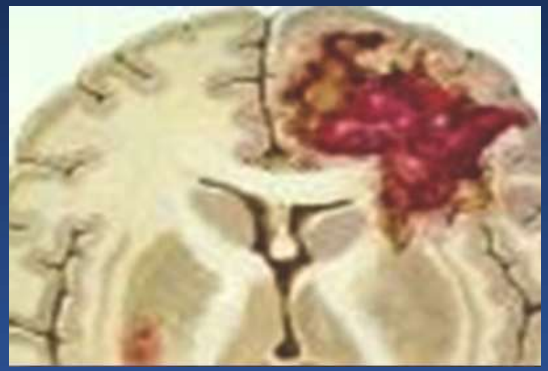
PESA & AWHS
40-54y, N= 4,060 , FU 0,3,6 y

HRP > 55y,
N=5808 FU3y



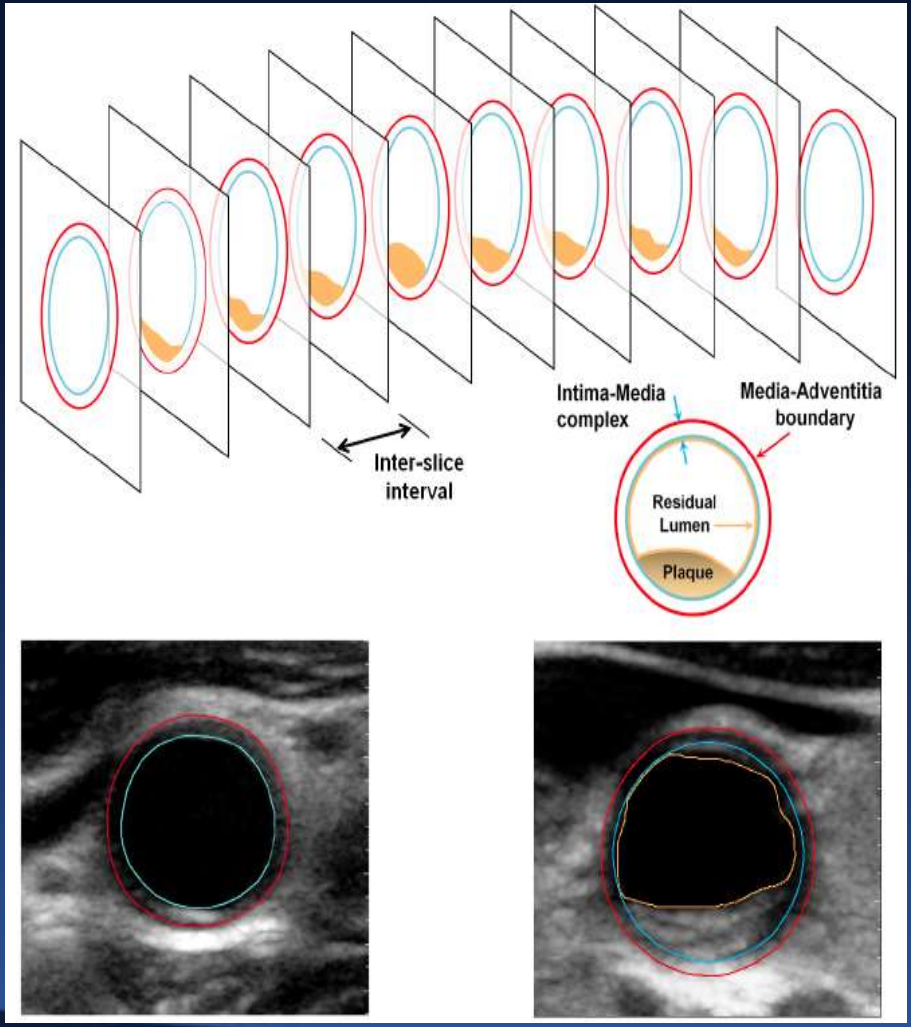


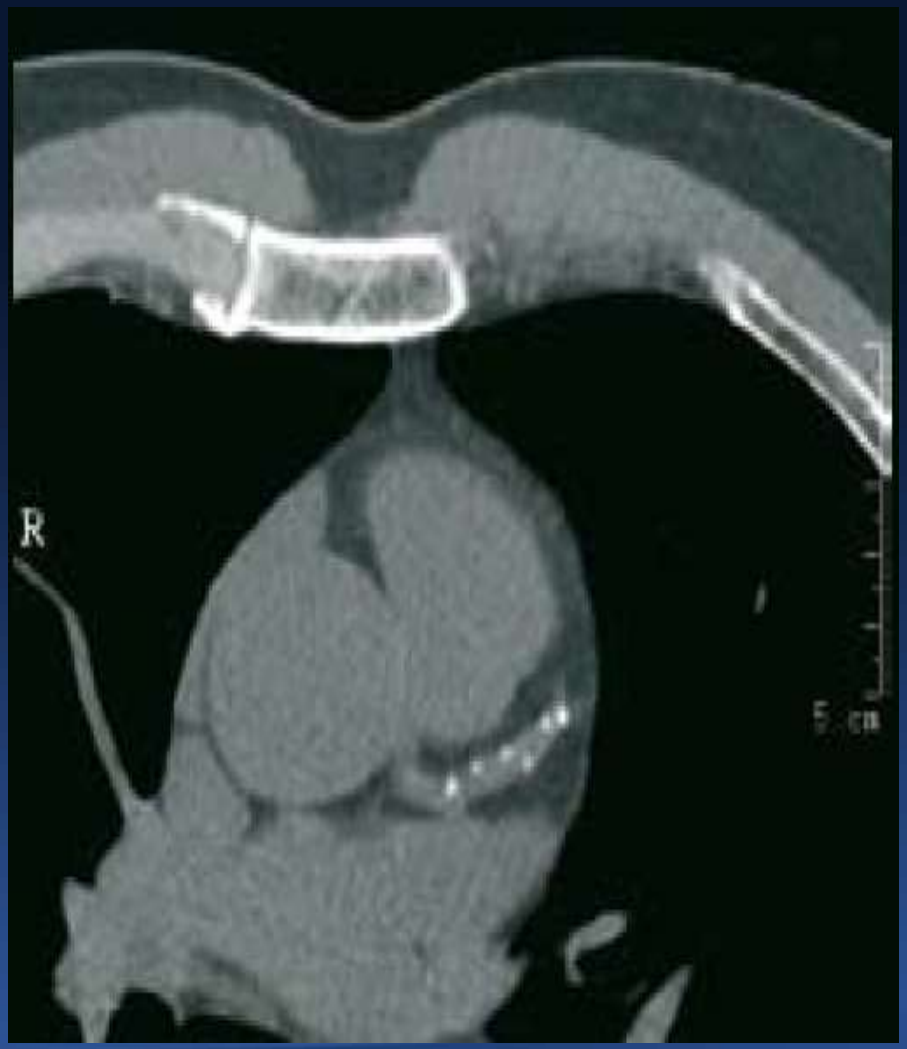




Baber, et al. J. Am. Coll. Card. 2015; 65: 1065

Plaque Burden (N=5808)
Carotid 3D-US, Coronary Calcification





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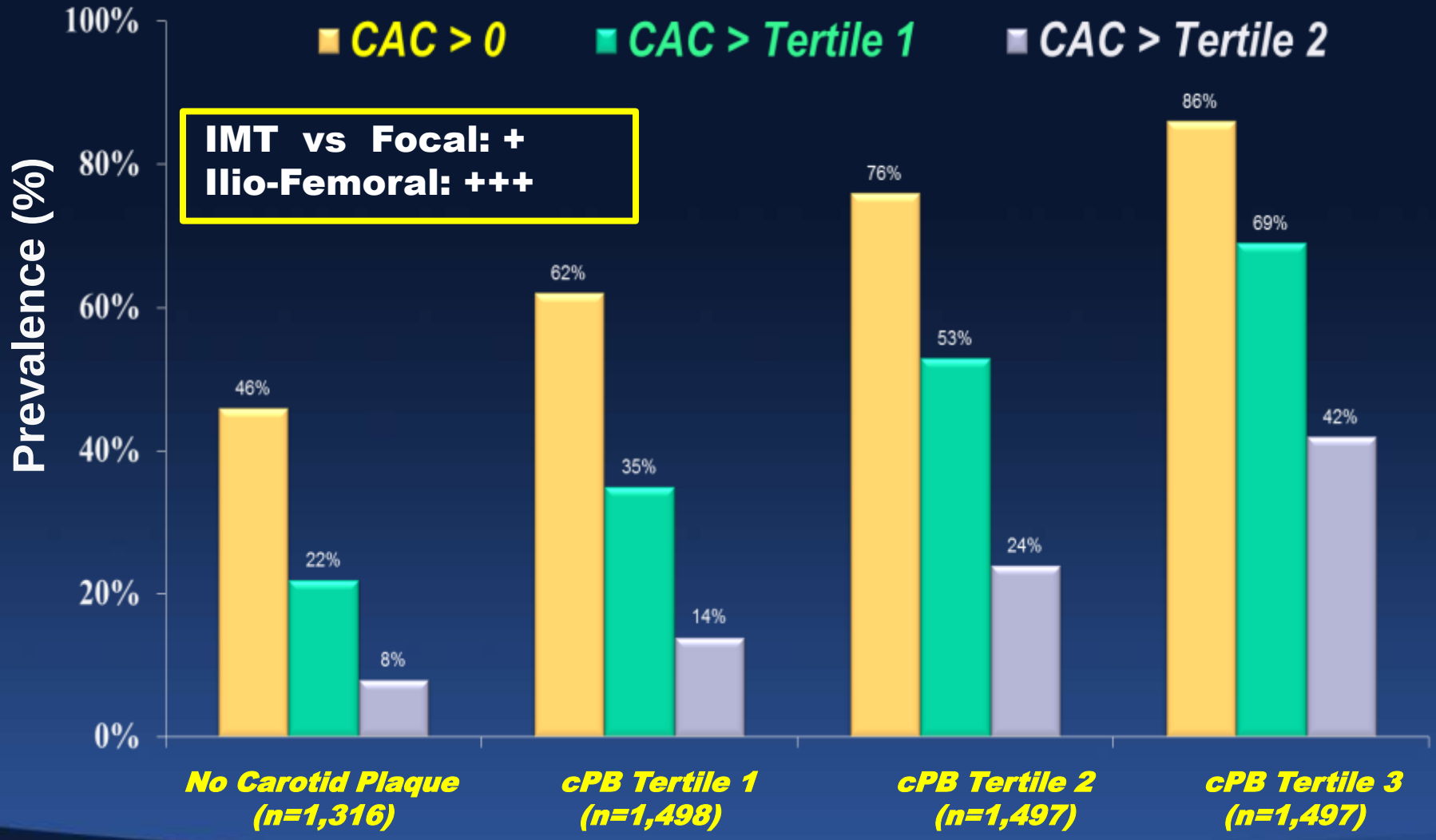
Sillesen, H et.al JACC Imag. 2012;7:681.

Cross Interaction (n=5808) Between Carotid Plaque & CAC



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U Baber, et al. J. Am. Coll. Card. 2015; 65: 1065

Cumulative Primary MACE by Carotid Plaque Burden (cPB)

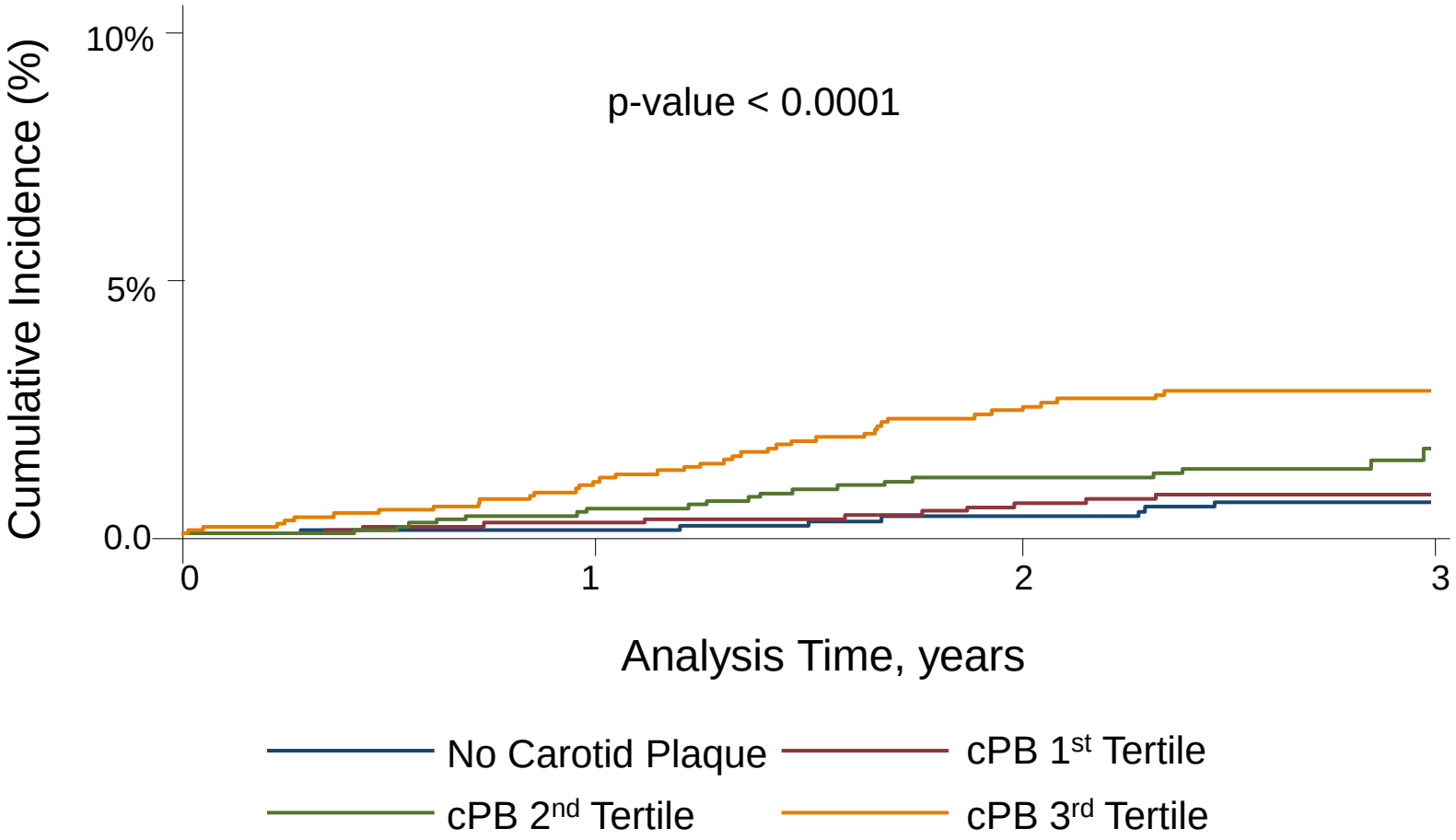


Figure 3A. Cumulative Incidence of Primary MACE Endpoint (cardiovascular death, spontaneous myocardial infarction, ischemic stroke) by cPB over 3 years

Cumulative Primary MACE by Coronary Artery Calcium (CAC)

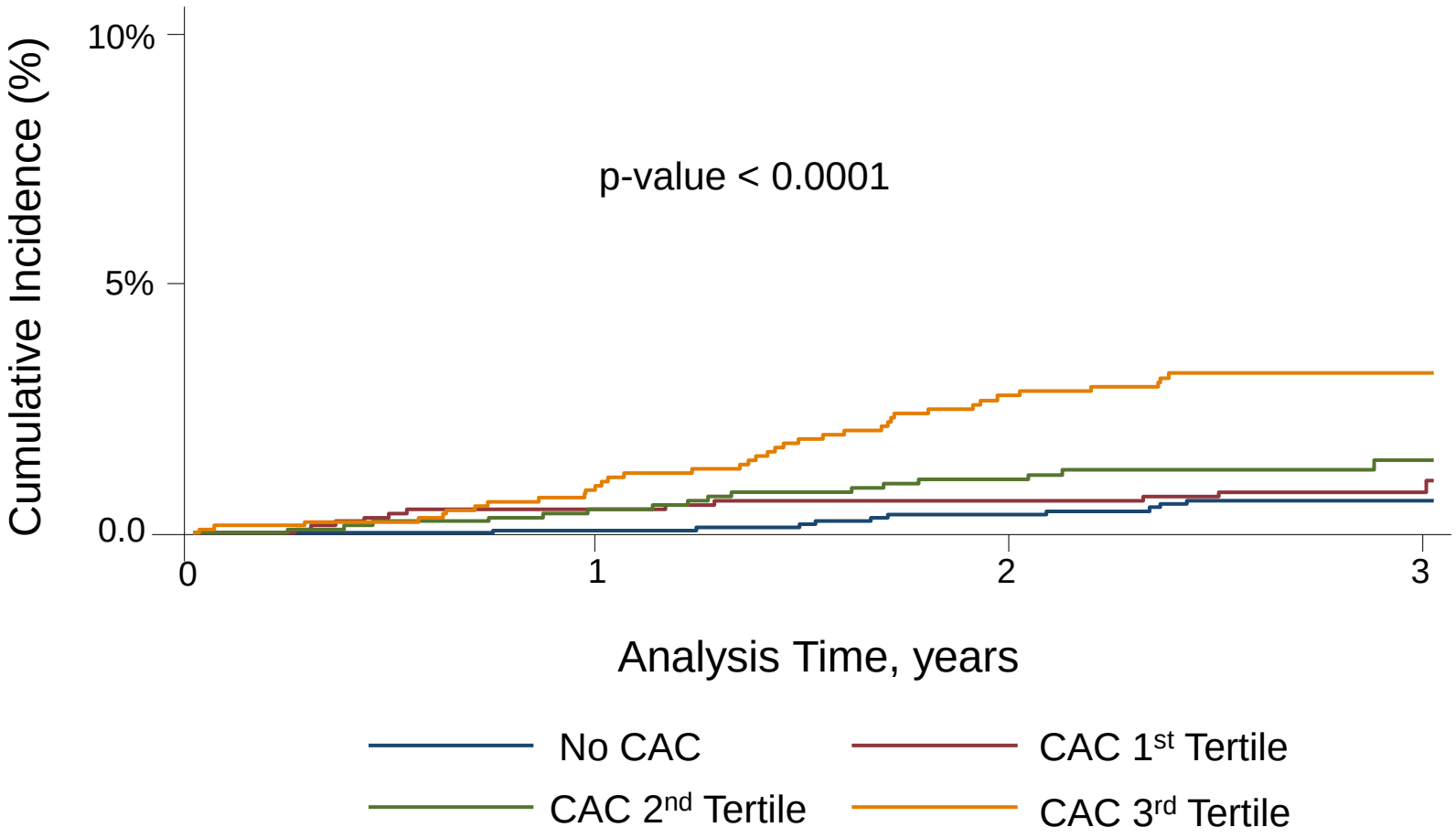
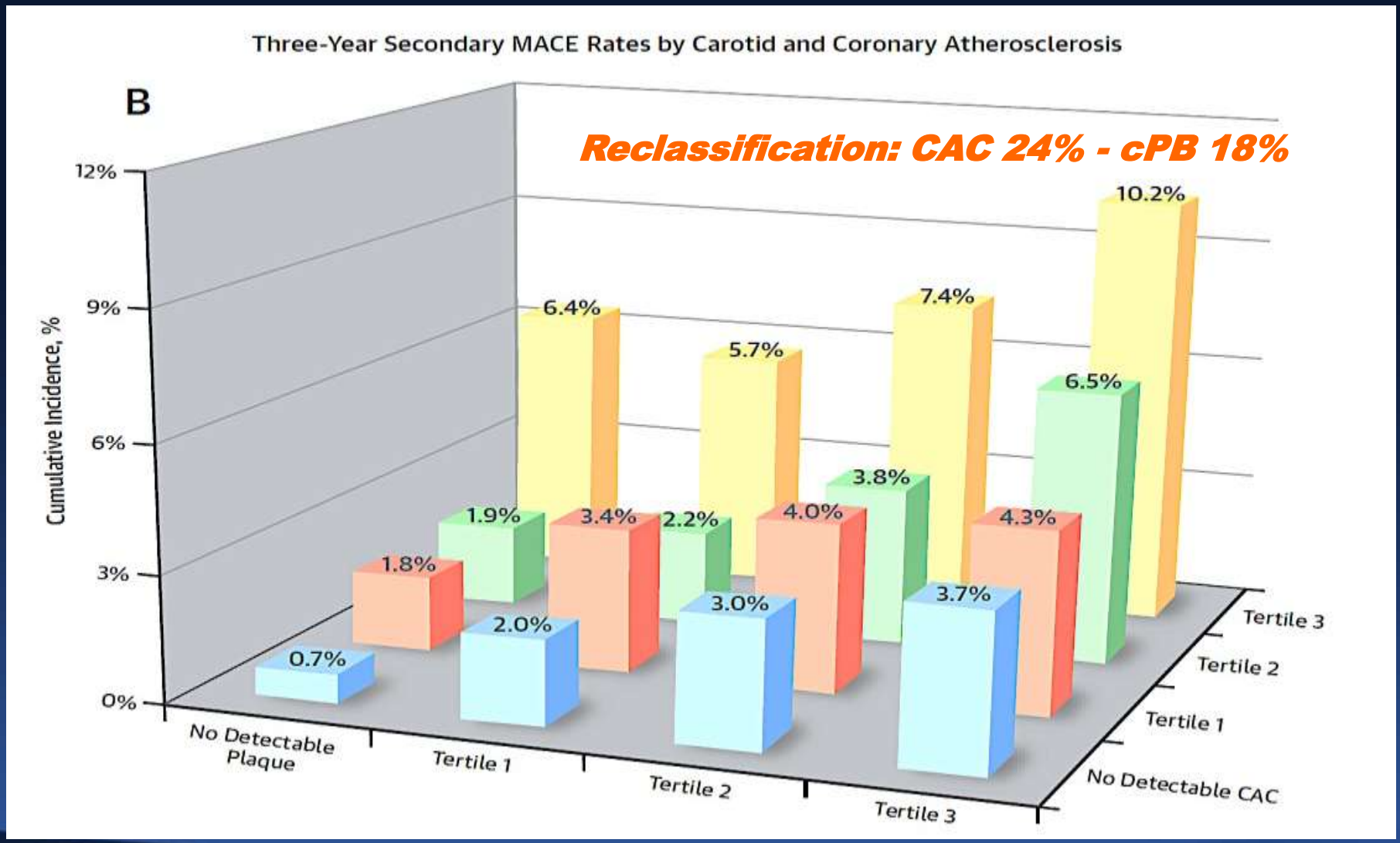


Figure 3C. Cumulative Incidence of Primary MACE Endpoint (cardiovascular death, spontaneous myocardial infarction, ischemic stroke) by CAC over 3 years

Three Year All-Cause MACE Rates (N=216) by Carotid and Coronary Atherosclerosis



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U Baber, et al. J. Am. Coll. Card. 2015; 65: 1065

Limitations

- Findings may not be broadly generalizable to individuals without health insurance
- Longer-term follow-up of this cohort is needed to assess durability of the present findings
- Reliance on claims for event ascertainment may have introduced ascertainment or misclassification bias

Conclusions

- Detection of subclinical atherosclerosis by CAC or “3D” carotid ultrasound is strongly and independently associated with short-term MACE events among asymptomatic US adults
- Improvements in risk prediction and reclassification with cPB are comparable to CAC, suggesting these modalities may be complementary in CVD assessment
- Imaging-based modalities that enable direct quantification of subclinical atherosclerosis, irrespective of anatomic territory, may be the optimal adjuncts to traditional risk factors in CVD risk prediction
- Cost-effective analyses are warranted to determine the potential value of such imaging in clinical decision making.

A Transatlantic Project

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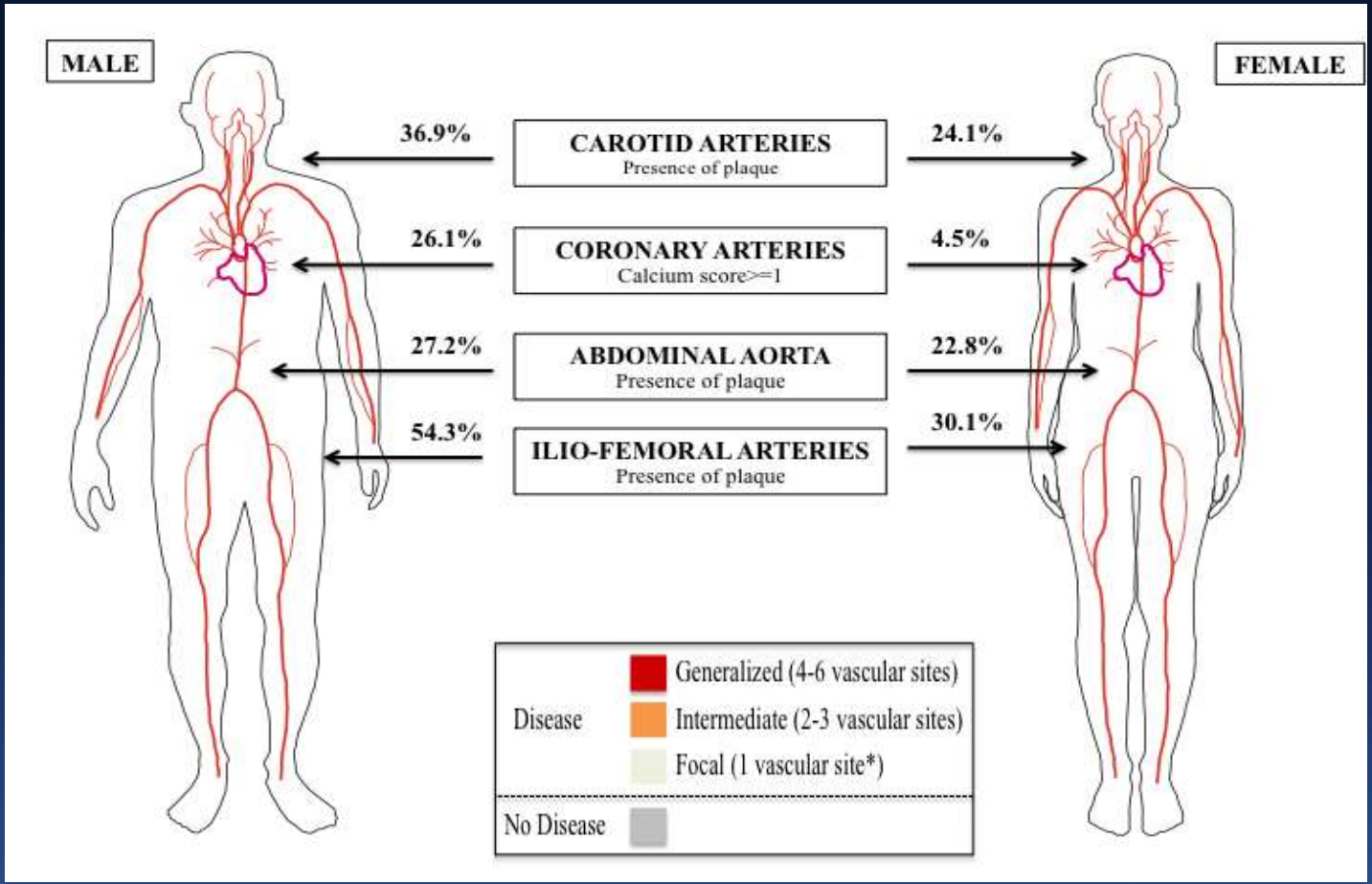
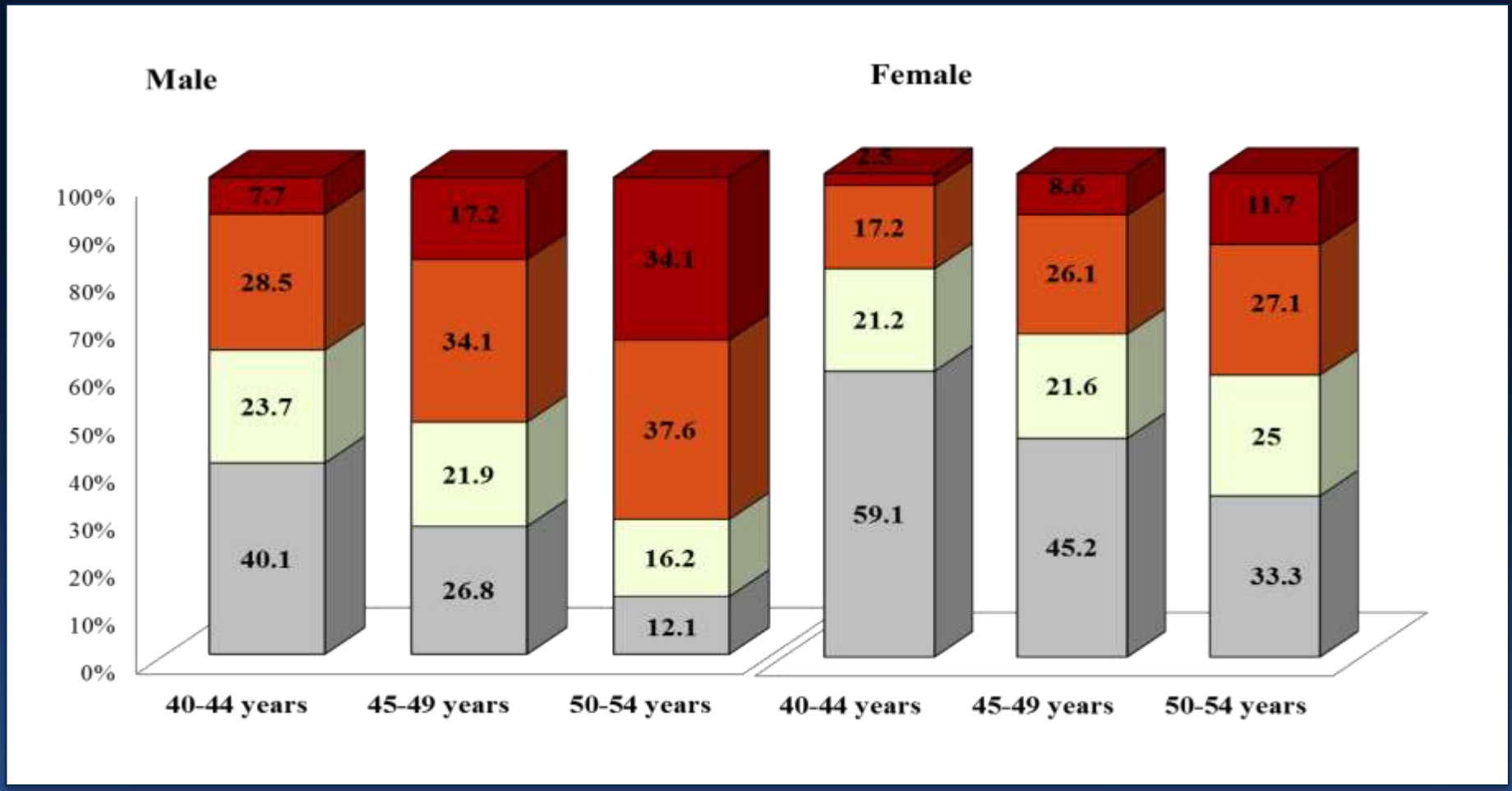
Sub-Clinical Atherosclerosis (n=4060)
Ilio-femoral More Sensitive Than Carotid (6 regions)



PESA (L Fernandez-Friera, A Fernandez-Ortiz, V Fuster et.al) Circ 2015, 4/20

Distribution Of The Systemic Extent Of Subclinical Atherosclerosis



PESA (L Fernandez-Friera, et.al) Circulation 2015, 4/20

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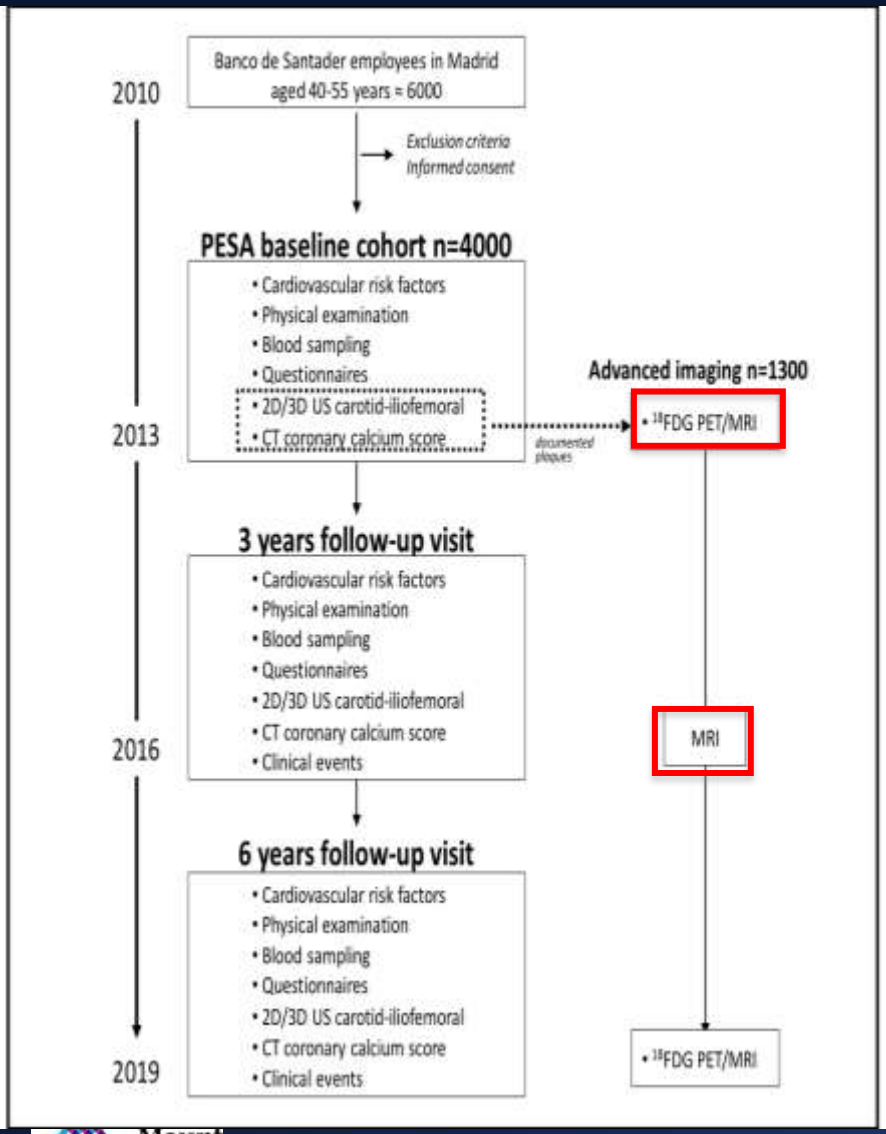
PET / MRI Protocol



Study population

≈950 individuals who had baseline vascular PET/MRI and will returned for follow-up vascular MRI to CNIC

Imaging protocol

A cardiac MRI study, including cine (LV function and structure), T1- and T2-mapping (Inflammation and diffuse fibrosis) and LGE (scar)

Advantages / Requirements

- Instead of having a vascular PET (30 min), they will have a cardiac MRI (novel heart assessment in PESA)
- Fibrosis quantification: creatinin / Hb
- Additional Budget: contrast for 950 cardiac MRI: 46.400 € (personal included)

Thank you!

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