Carotid Plaque & IMT Imaging: Where Do We Stand?
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Disclosures: None

Objectives
- Limits to FRS prediction
- Carotid ultrasound as tool to predict cardiovascular disease risk
  - Carotid plaque presence
  - Carotid intima-media thickness (CIMT) measurement
- Consensus statement from ASE/SVM

Limitations of Current CV Risk Prediction Models
- Heavily dependent on age
- Do not account on changes in patient’s health status over time
- Focused on short-term (10-year) risk
- Family history not incorporated into estimates
- Patients with high levels of a single risk factor may not be correctly classified solely on FRS
- Smoking considered as present or absent only
Advantages of Carotid Ultrasound as an Imaging Modality

- Non-invasive, safe
- Inexpensive
- Readily available, portable, and quick
- Plaque visualization
- Hemodynamics
- Office-based assessment

Ultrasound Assessment of Carotid IMT and Plaque Presence

Advantages of Carotid Study To Refine Risk Prediction

- Completely noninvasive – no radiation, no harmful exposures, no known biological effects
- Identifies range of disease – increased CIMT, non-occlusive plaque, stenosis
- Normal values are known – 25-85 years old, both sexes, most races/ethnicities
- Predicts future MI, CHD death, and stroke, with incremental predictive power
- Track serial changes
- Recommended by NCEP ATP III, AHA, ACC, ASE, SVM, SAIP, and ESC to assist with CVD risk stratification
Carotid Duplex Protocol

- Presence or absence of plaque
- Morphology of plaque
  - Calcified / echolucent / heterogeneous
- Degree of stenosis
  - Spectral doppler (angle-corrected)
  - Quantitative measurement of hemodynamic changes
  - Peak systolic velocity, end-diastolic velocity, ICA/CCA Ratio
- Sensitivity ~85%, specificity ~90%
- Similar to MRA for occlusion and stenosis > 70%

Color Mode: Echolucent Plaque

Case 1

- 50 year old female
  - Hypertension
  - Current smoker
  - No DM
  - No known CAD
  - TC 212, HDL 57, LDL 126, TG 144
  - FRS 6%
- Would the presence of carotid plaque on ultrasound alter her management?
How is Plaque Defined?

- Focal wall thickening that is at least 50% greater than that of surrounding vessel wall
- OR
- Focal thickening of IMT greater than 1.5 mm


Carotid Plaque and CAD

- Patients with occlusive carotid disease 7 times more likely to have positive exercise stress test than patients with normal carotid arteries
- Presence of carotid plaques associated with angiographic CAD
- Multi-vessel CAD associated with higher prevalence of carotid plaque than single-vessel disease


Prospective Studies Relating Carotid Plaque Presence to Incident CVD in Asymptomatic Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Event</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>12,375</td>
<td>45-64</td>
<td>MI, CHD death</td>
<td>2.96 (1.54-3.30)</td>
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<tr>
<td>KIHD</td>
<td>1,288</td>
<td>42-60</td>
<td>MI</td>
<td>4.15 (1.5-11.47)</td>
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<tr>
<td>MDCS</td>
<td>5,163</td>
<td>46-68</td>
<td>MI, CHD death</td>
<td>1.81 (1.14-2.87)</td>
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<tr>
<td>Northern Manhattan</td>
<td>1,839</td>
<td>&gt;40</td>
<td>Stroke</td>
<td>3.1 (1.1-8.5)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>6,399</td>
<td>&gt;55</td>
<td>MI</td>
<td>1.83 (1.27-2.62)</td>
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<tr>
<td>San Danielle</td>
<td>1,248</td>
<td>18-99</td>
<td>Stroke, TIA, vascular death</td>
<td>10.4 (4.4-17.1)</td>
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<tr>
<td>Yao City</td>
<td>1,289</td>
<td>60-74</td>
<td>Stroke</td>
<td>3.2 (1.4-7.1)</td>
</tr>
</tbody>
</table>

Case 1 Carotid Duplex: Screen for plaque

Does Plaque Presence (Increased CV Risk) Justify Initiation of Preventive Therapies?

- Smoking cessation
  - Smokers shown images of carotid plaques were more likely to stop smoking at 6 months
    - Quit Rates 22% versus 6%, p=0.003 in those who had plaque

- Lifestyle modification
  - Patients more likely to adhere to diet and exercise recommendations after seeing pictures of plaque

- Would you initiate treatment with a statin?
- What should be her target LDL-C?

“Less is Not More”

“PPIs for persons with nonulcer dyspepsia, opioid medications for persons with chronic nonmalignant pain, and STATIN medications for persons without CAD are all examples of the widespread use of medications with known adverse effects despite the ABSENCE of DATA FOR PATIENT BENEFIT for these indications.”

Case 2

43 year old female
- Family history of premature CHD
  - Father CABG at age 49, brother MI at age 47
- No hypertension, no DM
- Non-smoker
- TC 192, HDL 52, LDL 122, TG 92
- Framingham Risk < 1%

Carotid Ultrasound: No Plaque

Do CIMT Measurement
Carotid Intima-Media Thickness (IMT)

US Measure of ATH

Normal and Abnormal Carotid
Intima-Media Thickness

CAROTID IMT CALCULATION

\[
\text{TOTAL IMT} = \sum_{i=1}^{n} \text{IMT}_i
\]

where \( \text{IMT}_i = \text{Mean} (A_i - B_i) \) or \( \text{Max} (A_i - B_i) \)
Why Use the Distal CCA?

- Size of vessel
- Superficial location
- Ease of accessibility
  - In comparison to ICA and bulb which is more dependent on technical expertise
- Limited movement


Clinical CIMT Measurement

ASE Task Force Recommendation
- Distal 1 cm of far wall of each CCA
- Obtain measurement and compare with values from normative data set

Distribution of CIMT in the General Population: ARIC Study

Distribution of CIMT in General Population: AXA Study


Prospective Studies Relating CCA CIMT to Incident CVD Events in Asymptomatic Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Yrs</th>
<th>CV Event</th>
<th>Cutpoint</th>
<th>Adjusted RR (95% CI)</th>
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<tbody>
<tr>
<td>ARIC</td>
<td>12,841</td>
<td>45-64</td>
<td>5</td>
<td>MI, CHD death</td>
<td>tertile</td>
<td>2.53 (1.02-6.26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>stroke</td>
<td>tertile</td>
<td>2.02 (1.32-3.09)</td>
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<tr>
<td>CAPS</td>
<td>5,895</td>
<td>19-60</td>
<td>4</td>
<td>MI, stroke, death</td>
<td>quartile</td>
<td>2.32 (1.09-4.94)</td>
</tr>
<tr>
<td></td>
<td>5,776</td>
<td>&lt;60</td>
<td>4</td>
<td>MI</td>
<td>quartile</td>
<td>2.57 (1.94-3.42)</td>
</tr>
<tr>
<td>KISS</td>
<td>1,387</td>
<td>65-85</td>
<td>3</td>
<td>MI</td>
<td>&lt;1.0 mm</td>
<td>1.85 (1.09-3.15)</td>
</tr>
<tr>
<td>MESA</td>
<td>8,880</td>
<td>&gt;65</td>
<td>6</td>
<td>MI, CHD death</td>
<td>quartile</td>
<td>3.61 (2.13-6.11)</td>
</tr>
<tr>
<td>CHS</td>
<td>4,476</td>
<td>&gt;65</td>
<td>6</td>
<td>MI</td>
<td>quintile</td>
<td>2.57 (1.64-4.02)</td>
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<tr>
<td>Tromsø</td>
<td>6,226</td>
<td>25-85</td>
<td>5</td>
<td>MI</td>
<td>quartile</td>
<td>2.86 (1.07-7.65)</td>
</tr>
<tr>
<td>Yao City</td>
<td>1,289</td>
<td>60-74</td>
<td>5</td>
<td>stroke</td>
<td>quartile</td>
<td>5.6 (3.2-10.1)</td>
</tr>
</tbody>
</table>

CIMT Progression and Clinical CV Events

N=188
Non-smoking
Men ages 45-59
Prior CABG
Clinical Trials: Carotid IMT as an outcome measure

**Carotid IMT and Statins**

**Pravastatin:**
- PLAC-II (Pravastatin, Lipids, and Ath in Carotid Arteries)
- KAPS (Kuopio Atherosclerosis Prevention Study)
- REGRESS (Regression growth Evaluation Statin Study)
- LIPID (Long-term Intervention with Pravastatin in Ischemic Dis)

**Lovastatin:**
- MARS (Monitored Atherosclerosis Regression Study)
- ACAPS (Asymptomatic Carotid Artery Progression Study)

*Carotid IMT progression meets accepted definitions of a surrogate for cardiovascular disease endpoints in statin trials

*NOT FDA-approved surrogate end point of vascular events

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**METEOR Trial**

- 984 subjects
  - Age as only CVD risk factor (mean 57 yrs) OR
  - FRS < 10%
  - Modest CIMT thickening (focal CIMT > 1.2 mm)
  - Elevated LDL-C (range 120-190 mg/dL)
- Randomized to 40 mg rosuvastatin versus placebo
- CIMT progression rate over 2 years assessed

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**METEOR: Change in Maximum CIMT for the Primary End Point**

\[
\Delta \text{CIMTmax} = -0.0145 \text{ mm/year}
\]
AIM-HIGH Study Design

- 3414 subjects: age 64, 34% with T2DM and 71% with MetS; 94% prior statins
- Randomized to simvastatin to reduce LDL-C < 80 mg/dL; then niacin ER 2 gm in 1718 or PBO in 1696
- Baseline lipids: LDL-C 71
  TG 161
  HDL 35
- Primary endpoint composite: no difference after 32 months; trial stopped for futility after 511 events of 800 planned.

(AIM HIGH) Results
CIMT Challenges

- Ultrasound protocol heterogeneity
  - Image acquisition segment: CCA/Bulb/ICA
  - Wall: near, far
  - Type of measure: max, mean of max (2-12)
  - Unilateral or bilateral
- Measurement variability
  - Scanning equipment
  - Sonographers
  - Reading equipment
  - Readers
- Limited Reimbursement

Back to Case 2

- 43 year old female
  - Family history of premature CHD
    - Father CABG at age 49, brother MI at age 47
  - No hypertension, no DM
  - Non-smoker
  - TC 192, HDL 52, LDL 122, TG 92
  - Framingham Risk < 1%

Case 2: CIMT Measurement

- CIMT 0.70 mm
- Between 90th and 95th Percentiles
- CV Risk: Increased
- Although FRS < 1%, CIMT measurement indicates increased CV risk in this patient
ASE Consensus Statement

ASE CONSENSUS STATEMENT
Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk: A Consensus Statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force
Endorsed by the Society for Vascular Medicine


Who Should be Screened?

- Intermediate CVD risk
  - FRS 6%-20% without established CHD, DM
  - Family history of premature CVD in first degree relative (men < 55 years, women < 65 years)
  - Women younger than 60 years with at least 2 CVD risk factors
  - Not recommended in patients with established atherosclerotic disease

ASE Consensus Statement: CV Risk

- CVD Risk Increased
  - If CIMT ≥ 75th percentile for age, race, sex
  - If carotid plaque is present
    - Greater than 50% protrusion
    - Focal IMT > 1.5 mm

- CVD Risk Average (unchanged)
  - CIMT in the 25th to 75th percentile

- CVD Risk Lower
  - CIMT ≤ 25th percentile
Proposed Screening Algorithm

FRS 6%-20%
Family History Premature CVD
F < 60 years with 2 CVD Risk Factors

SCREENING CAROTID DUPLEX

PLAQUE PRESENT

STOP

PLAQUE ABSENT

CIMT MEASUREMENT

ARIC Study: CIMT and Plaque in CHD Risk Prediction

- 13,145 subjects free of CHD or stroke (45-65yr)
- Mean follow up 15.1 years
- 1,812 incident CHD events
- Risk Prediction Models (10-yr CHD risk)
  - Traditional Risk Factors (TRF)
  - TRF + CIMT
  - TRF + Plaque
  - TRF + CIMT + Plaque


CIMT and Plaque Definitions

- CIMT
  - Mean of mean of distal CCA, bifurcation, and proximal ICA measurements (both right and left)
  - Categorized as: <25th, 25th-75th, >75th percentiles
- Plaque – 2 of 3 criteria:
  - Abnormal wall thickness (CIMT > 1.5 mm)
  - Abnormal wall shape (protrusion into lumen)
  - Abnormal wall texture (brighter echoes)
ARIC Results: CHD Incidence Rate

Nambi et al. JACC 2010;55:1600-7

ARIC Results: Effect on AUC

Table 2: Adjusted AUC for Different Models, With 95% Confidence Interval for Difference in Adjusted AUC Comparing Various Models With TRF-Only Model

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall</th>
<th>Man</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRF only</td>
<td>0.742</td>
<td>0.574</td>
<td>0.759</td>
</tr>
<tr>
<td>TRF + CIMT</td>
<td>0.742</td>
<td>0.574</td>
<td>0.759</td>
</tr>
<tr>
<td>TRF + CIMT + plaque</td>
<td>0.739</td>
<td>0.566</td>
<td>0.733</td>
</tr>
<tr>
<td>TRF + CIMT + plaque</td>
<td>0.739</td>
<td>0.566</td>
<td>0.733</td>
</tr>
<tr>
<td>TRF + CIMT + plaque vs. TRF + CIMT</td>
<td>0.002 to 0.005</td>
<td>0.001 to 0.006</td>
<td>0.002 to 0.010</td>
</tr>
</tbody>
</table>

Nambi et al. JACC 2010;55:1600-7

ARIC: Reclassification of Subjects

- TRF + CIMT + Plaque resulted in reclassification of ~23% of subjects
- More subjects reclassified to lower risk group
  - 12.4% vs. 11%
- No subjects were reclassified from low (<5%) to high risk (>20%)
- No subjects reclassified from high to low risk
- Results similar in FRS-based TRF model
- www.ARICnews.net (CHD risk calculator)
**2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults**

**Recommendation for Measurement of Carotid Intima-Media Thickness**

CLASS IIa (Level of Evidence: B)

“Measurement of carotid artery intima-media thickness is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (43,44). Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results (44).”


**ASE/SVM Consensus Statement**

- Increased CVD risk if
  - CIMT ≥75th percentile for age, sex, race
  - Presence of carotid plaque (> 50% protrusion or focal IMT ≥1.5 mm)
- Recommendations
  - Scanning technique
  - Interpretation
  - Reporting
  - Training and certification


**ASE/SVM Consensus Statement**

**Patient Selection**

- “Intermediate” risk
  - 10-year Framingham risk of 6-20%
  - Not already at high risk
- Family history of premature CV disease in a first-degree relative (men <55, women <65 yo)
- Younger people with severe abnormalities in a single risk factor who are not being treated with medications (e.g., genetic dyslipidemia, heavy smoker)
- Women <60 years old with ≥2 CV risk factors

Objective: To determine whether CIMT has added value in the 10-year risk prediction (FRS) of first-time MI or stroke.

Methods: Meta-analysis of 14 population based cohorts, 45,828 individuals median follow-up 11 years: 4,007 MI or strokes observed.
"... the added value of common CIMT measurements to the Framingham risk score in the general population was small": Of 45,828 individuals from 14 cohort studies worldwide, 0.8% were correctly reclassified.

"In individuals at intermediate risk, the added value was 3.2% in men and 3.9% in women. Our results suggest, that common CIMT measurements should not be routinely performed in the general population because the overall added value is small and unlikely to be of clinical importance"

Objective: to compare improvement in prediction of incident CHD of 6 risk markers: 1) coronary artery calcium 2) IMT 3) ABI 4) brachial flow-mediated dilatation 5) hsCRP 6) FHx

Methods: 6814 MESA participants from 6 US Field centers (1330 intermediate risk participants). 7.6 years follow-up: 94 CHD and 123 CVD events. AUC and NRI were calculated.
Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals

"Coronary artery calcium, ABI, hsCRP and family history were independent predictors of incident CHF in intermediate-risk individuals. CAC provided superior discrimination and risk reclassification compared with other risk markers."

"CIMT [...] was not associated with incident CHD in multivariable analyses."

Coronary Artery Calcification Compared With Carotid Intima-Media Thickness in the Prediction of Cardiovascular Disease Incidence

Prospective cohort study, n=6698, age 45-84.
IMT and CAC measured at baseline in 6 field centers
Main outcome: risk of incident CVD (CAD, stroke, CVD death) over 5.3 yrs. of f/u.

MESA: CVD Prediction with CIMT and CAC

- Highest quartile CIMT predicted CVD events: adjusted HR 2.3 (1.4 – 3.8) to 3.8 (2.2 – 6.4)
- But: adjusted HR higher with CAC (6.0, 3.9 – 9.1)
  - Risk factors = 0.772
  - RFs + CIMT = 0.782
  - RFs + CAC = 0.808
  - RFs + CIMT + CAC = 0.811
- CIMT predicted stroke (HRSD = 1.3, p=0.01), but CAC did not (HRSD = 1.1, p=0.71)
Objective: To compare improvement in prediction of incident CHD with addition of CIMT to Framingham Risk Score

Methods: Mean IMT of ICA and CCA in 2965 participants of Framingham Offspring Study were measured. 7.2 years follow-up: 296 cardiovascular events. C-statistic and NRI were calculated.

“We conclude that the intima-media thickness of the common carotid artery and the intima-media thickness of the ICA are independent predictors of cardiovascular events among participants in the Framingham Offspring Study.”

“The maximum intima-media thickness of the ICA […], contributed significantly but modestly to the predictive power of the risk factors used in calculating the FRS and improved risk classification on the basis of the FRS.”

Unanswered Questions and Future Directions

- No study has shown that treatment based on carotid plaque presence or CIMT alters long-term outcomes
- Does plaque screening and subsequent intensification of medical regimens in patients with plaque or increased CIMT prevent cardiovascular events?
- Is this cost-effective?
- Need prospective studies to determine effectiveness of carotid ultrasound imaging in improving CVD outcomes
For example:
- Established Atherosclerotic CVD
- FRS, RRS, or Global Risk ≥10%
- Most patients w/ DM or CKD
- CAC>100

High 10-Year Risk

Lifestyle Changes
+ Potent Statin

High Lifetime Risk

Lifestyle Changes
+ Discuss Statin

Low Risk

Focus on Ideal CV Health

For example:
- Age ≥50 + major RF
- FRS, RRS, or Global Risk 5-10%
- CAC=0 + ≤100
- FHxor MetS+ age >40 years
- Consider CAC scan

None of above
- 10-yr risk <5%
- Lifetime risk <39%

Low Risk

Lifestyle Changes
+ Potent Statin

High 10-Year Risk

Lifestyle Changes
+ Discuss Statin

High Lifetime Risk

Focus on Ideal CV Health