Pubmed: Studies of atherosclerosis progression/regression per year 1975 to current
Present status: Clinicaltrials.gov

- Recruiting studies: “Atherosclerosis” “Interventional”
  - IMT 58
  - Cardiac CT 31
  - CAC 41
  - IVUS 11
  - MRI 40
Imaging for Atherosclerosis Change

• Clinical tool
  – Detect changing cardiovascular risk, control of disease
    • Coronary calcium

• Research tool
  – Atherosclerosis as a surrogate for clinical benefit
    • Carotid ultrasound, Cardiac CT, MRI
Atherosclerosis progression portends risk

• Serial angiographic study in 335 pts, mean age 51, f/u 44 months

• QCA progression
  • >15% increase in diameter stenosis
  • 42%
  • 50% increase in adjusted risk for cardiac death/MI

Waters et al. Circulation 1993;87:1067-1075
IVUS progression predicts clinical events

• Essen University: Serial IVUS study of the left main coronary artery in 56 pts undergoing left coronary PCI

• Change in plaque area related to clinical risk factors

• Most events occurred in those with the greatest progression
  • P+M 25% vs. 6%

Will a serial scanning refine the risk prediction for CHD?

Achenbach et al. Circulation 2002;106:1077
How do we clinically monitor successful control of cardiovascular risk?

• Attainment of risk factor targets
  • BP, LDL-C, HDL-C
• Use of specific medication classes
• Compliance with therapeutic lifestyle changes
  • Tobacco, physical activity and diet

• Inference: Control of risk factors equates to control of the target disease… Atherosclerosis
CAC score progression

• ↑ progression in individuals with events

Open issues:
  • Calculation?
  • %/year
  • Volume
  • Determinants uncertain
  • Groups overlap

Raggi et al. ATVB. 2004;24(7):1272-7
Raggi et al. AJC. 2003;92:827
Signal vs. Noise

• Serial CAC testing depends upon detecting the difference between CAC progression vs. inter-scan variability

• CAC progression > inter-scan variability

MESA:
Mean SD absolute and % interscan variability and correlation (r) were 19.8 ± 59.6 20.82%

CAC score progression:
Typically exceeds 20% per year

Optimizing scan variability:
Cardiac position changes, partial volume effects, image noise, interobserver variation, coronary motion artifacts, attenuation, lesion number
Interscan variability is highest at lower scores

<table>
<thead>
<tr>
<th>Agatston Score</th>
<th>Scan 1</th>
<th>Scan 2</th>
<th>Absolute Difference</th>
<th>Variability (%)</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–10 (n = 30)</td>
<td>4.6 ± 3.2</td>
<td>4.5 ± 3.4</td>
<td>2.2 ± 2.3 (1.4)</td>
<td>65.8 ± 59.9 (58.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>11–50 (n = 54)</td>
<td>28.6 ± 14.4</td>
<td>28.1 ± 13.7</td>
<td>8.7 ± 9.6 (6.3)</td>
<td>34.6 ± 36.3 (23.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>51–100 (n = 36)</td>
<td>71.8 ± 18.2</td>
<td>75.6 ± 13.8</td>
<td>14.2 ± 12.8 (10.6)</td>
<td>19.8 ± 18.6 (15.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>101–400 (n = 71)</td>
<td>206.9 ± 83.5</td>
<td>205.3 ± 73.8</td>
<td>24.5 ± 22.9 (20.5)</td>
<td>13.1 ± 14.3 (10.2)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

• Under OPTIMAL conditions of patient on same day, un-moving, with heart-rate customized ECG trigger

Lu, Budoff et al.  Acad Radiol. 2002;9:654
Progression of Coronary Calcium and Incident Coronary Heart Disease Events

MESA (Multi-Ethnic Study of Atherosclerosis)

Matthew J. Budoff, MD,* Rebekah Young, PhD,† Victor A. Lopez, MS,‡ Richard A. Kronmal, PhD,† Khurram Nasir, MD, MPH,§∥ Roger S. Blumenthal, MD,§ Robert C. Detrano, MD, PhD,‡ Diane E. Bild, MD, MPH,** Alan D. Guerci, MD,†† Kiang Liu, PhD,‡‡ Steven Shea, MD, §§ Moyses Szklo, MD,||| Wendy Post, MD,§ Joao Lima, MD,§ Alain Bertoni, MD, MPH,¶¶ Nathan D. Wong, PhD, MPH‡

• N – 5682
• Serial CAC scans 2.5 years apart
• 7.5 year follow up
• Annual CAC score change average: 25 units
• Events:
  • Zero baseline: 1.3 per 100 unit change
  • CAC at baseline: HR 6.3 per 300 unit change

J Am Coll Cardiol 2013;61:1231–9
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Figure 1  Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons With CAC = 0 at Baseline

Figure 2  Kaplan-Meier Plot of Cumulative Incidence of Total CHD Among Persons with CAC > 0 at Baseline
Serial CAC scanning over mean of 3 years

Incident CAC: 40% increase likelihood per 5% increase in FRS

Progressive CAC: Increase in CAC score of 7 per 5% increase in FRS

Implication: Clinical response to changing CAC score should be intensification of risk factor control
What Is IMT?

- IMT is the distance between the lumen-intima interface and the media-adventitia interface.
- First described by Pignoli et al. when imaging, with ultrasound, the wall of the abdominal aorta.

B-Mode Image of the Carotid Artery Wall

- plaque
- intima
- media
- adventitia

Courtesy of W. Riley media
Carotid Intima-media Thickness

• Far wall
  • Acoustic shadowing in near wall

• Which site?
  • CCA most reproducible
  • ICA/Bulb: more difficult
    • Plaque more common
    • Greater magnitude of change

• Measurement
  • ABD or manual, 1cm length
  • Easy - takes minutes
  • Accurate - .0x mm

Selection of end-diastolic images
Systolic expansion/IMT thinning
IMT Variability: Improving signal:noise

Sources of variability for measuring changes in IMT progression

Proposed solutions
   - Replicates
   - Increase time interval

Implicit solution
   - Increase sample size

Present Protocol

- 13 MHz
  - ECG gated, diastolic images
- Common carotid
  - 2 views
  - 2 full sets
- Analysis
  - Single observer, masked
  - Manual and ABD
    - All measurements performed twice on each image set
      - Mean CC IMT, Max CC IMT
Reproducibility with Present Protocol

- CIMT images from 148 participants of a clinical trial were examined.

- Imaging protocol:
  - 2 complete sets of anterior and lateral views of the far wall of the distal CCA
  - Single sonographer using a 13 MHz linear probe
  - Quantified by a single observer using an off-line workstation with manual and automated border detection (ABD) software
  - Digital image acquisition was gated to diastole

Mean CIMT of the cohort in the anterior and lateral views was approximately 0.90 mm
- No relationship between the mean difference between measurement pairs and image quality.
- Reader drift was .0001 mm or less.

<table>
<thead>
<tr>
<th>Difference between image sets</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior- manual</td>
<td>.0045 mm</td>
<td>-.0139 to .0049 mm</td>
</tr>
<tr>
<td>Lateral- manual</td>
<td>.0029 mm</td>
<td>-.0162 to .0033 mm</td>
</tr>
<tr>
<td>Anterior- ABD</td>
<td>.0087 mm</td>
<td>-.0182 to .0008 mm</td>
</tr>
<tr>
<td>Lateral- ABD</td>
<td>.0073 mm</td>
<td>-.0037 to .0184 mm</td>
</tr>
</tbody>
</table>
CIMT Progression: Related to risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Change in Intima-media Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM (yes/no)</td>
<td>1.97 microns</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.82 microns</td>
</tr>
<tr>
<td>HDL (17.1 mg/dL)</td>
<td>-.59 microns</td>
</tr>
<tr>
<td>LDL (39.4 mg/dL)</td>
<td>.22 microns</td>
</tr>
<tr>
<td>Triglycerides (90 mg/dL)</td>
<td>.43 microns</td>
</tr>
<tr>
<td>Systolic BP 19 mm Hg</td>
<td>.36 microns</td>
</tr>
</tbody>
</table>

Intima-media thickness of the common carotid arteries is a marker of atherosclerosis and has been shown to be associated with prevalent and incident coronary heart disease and with coronary heart disease risk factors. The authors examined the association of baseline risk factors or change in risk factors with change in intima-media thickness over follow-up (1987–1998) in the Atherosclerosis Risk in Communities (ARIC) population-based cohort (baseline: age 45–64 years, n = 15,792). Subjects were members of households sampled in four areas of the United States. Either not adjusting for baseline intima-media thickness or doing so with correction for its measurement error resulted in statistically significant associations of change in intima-media thickness with baseline diabetes, current smoking, high density lipoprotein cholesterol, pulse pressure, white blood cell count, and fibrinogen. The associations were of a similar order of magnitude as anticipated from the authors’ cross-sectional findings. Statistically significant associations were found between change in intima-media thickness and change in low density lipoprotein cholesterol and triglycerides and with onset of diabetes and hypertension. In summary, established risk factors for coronary heart disease are associated with the rate of change of subclinical atherosclerosis. *Am J Epidemiol* 2002;155:38–47.
IMT measures treatment effect

**ASAP (Simva 40 vs Atorva 80)**

![Graph showing CCA-IMT over months for ASAP (Simva 40 vs Atorva 80)]

**ARBITER 2 (Nicotinic acid)**

![Bar chart showing change in CIMT for Placebo + Statin vs ER Niacin + Statin]

**RADIANCE 1 (Torcetrapib)**

![Graph showing CCA-IMT over months for RADIANCE 1 (Torcetrapib)]

**PREVENT (Amlodipine)**

![Bar chart showing change in CIMT for Placebo vs Amlodipine]
Figure 1: Hazard ratios (HRs) per one SD increase in mean common carotid intima-media thickness progression for four endpoints.
Coronary CT angiography

• Coronary CT Angiography (CTA) can characterize non-calcified (NCP) and calcified plaque (CP)

• Current reference standard for quantifying plaque volume is the expert observer
  • Time-consuming
  • Variable

Software approaches

ATLANTA TRIAL
- Prospective
- 60 patients
- CTA, invasive cath and VH-IVUS

- Correlation $R = 0.6 - 0.84$ for CP, NCP volume with VH-IVUS
Automated Three-dimensional Quantification of Noncalcified Coronary Plaque with Coronary CT Angiography: Comparison with Intravascular US Quantification

Purpose: To determine the accuracy of an automated algorithm (AUTOPLAQ-APQ) versus manual tracing for quantification of noncalcified plaque with coronary computed tomographic (CT) angiography in comparison with quantification with intravascular ultrasonography (US).
NCP volume measurement

Coronary CTA

External elastic membrane

Lumen intima border

IVUS
NCP volume measurement (N=22)

IVUS: 105.9 mm$^3$
Manual CCTA: 100.8 mm$^3$
APQ: 116.6 mm$^3$

Dey et al Radiology 2010
Comparison with IVUS (N=22)

\[ y = 1.03x \]

\[ R = 0.94, \ p < 0.0001 \]

Dey et al Radiology 2010
Quantitative Plaque Analysis

Reproducibility: Quantitative Measurements

1. Centerline extraction
2. Lumen segmentation
3. Anatomical segments
4. Measurements
   1. MLD
   2. %DS
   3. MLA
   4. %AS
   5. Plaque volume
   6. Percent atheroma volume
   7. Remodeling index
   8. Plaque components

Figure 1. Lesion analysis by X-ray angiography and multi-slice computed tomography (MSCT). (A) X-ray angiography demonstrates severe stenosis in the proximal left anterior descending artery. (B and D) MSCT demonstration of severe stenosis. (C) Severe stenosis with plaque characterization. (E and F) Minimal luminal diameter of plaque with and without plaque characterization. Green = lumen; Red = low-density noncalcified plaque; Blue = high-density noncalcified plaque; Yellow = calcified plaque.

Quantitative Plaque Analysis

Reproducibility: Quantitative Measurements

Plaque

Calcified Plaque (CAP)

Non-Calcified Plaque (NCP)

Low-Density NCP (LD-NCP)

High-Density NCP (HD-NCP)

?Lipid-rich necrotic core?

?Fibrous and fibro-fatty tissue?

Quantitative Plaque Analysis
Reproducibility

Limits of agreement:
- Calcified Plaque: ±4.1%
- Non-Calcified Plaque: ±4.0%
- Low-density non-calcified plaque: ±3.0%
- High-density non-calcified plaque: ±4.7%

Challenges

• Plaque quantification requires good-excellent image quality

• Artifacts - effect on automated plaque quantification
CTA Characteristics of Plaques Subsequently Resulting in ACS

1059 pts suspected or known CAD
27+10 mo f/u

<table>
<thead>
<tr>
<th>Feature</th>
<th>ACS+</th>
<th>ACS-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>127%</td>
<td>113%</td>
<td>.003</td>
</tr>
<tr>
<td>PV</td>
<td>135 mm³</td>
<td>58 mm³</td>
<td>.003</td>
</tr>
<tr>
<td>LAP V</td>
<td>20 mm³</td>
<td>1.1 mm³</td>
<td>.001</td>
</tr>
<tr>
<td>%LAP/ plaque area</td>
<td>21.4%</td>
<td>7.7%</td>
<td>.001</td>
</tr>
</tbody>
</table>
Plaque Progression on CTA

69 chest pain pts; 8311 coregistered cross sections
Repeat imaging 2 yrs
% of slices with either CP or NCP


Percentage of Cross Sections Containing Plaque

- Any Plaque
- Non-Calcified Plaque
- Calcified Plaque

Significant by multivariate analysis
baseline plaque
number of risk factors
smoking

<table>
<thead>
<tr>
<th></th>
<th>Any</th>
<th>NCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>16.5</td>
<td>3.1</td>
</tr>
<tr>
<td>2 yrs</td>
<td>18.6</td>
<td>4.4</td>
</tr>
<tr>
<td>p</td>
<td>0.01</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Intraobserver 0.95
Interobserver 0.93

Lehman I. JACCImg 2009;2:1262–70.
Serial Coronary CTA Verified Changes in Plaque Characteristics: Effect of Statin Intervention

32 treatment naïve pts: 24 fluvastatin 20 mg, 8 no rx
15: 16 slice, 17: 64 slice
12 month rescan

Decreased total plaque volume due to decreased LAP
No change in lumen volume
MR Plaque Imaging

- High SNR
- High resolution
- Clear delineation between the blood, vessel wall and surrounding tissues
  - Black-blood imaging
    - In-flow suppression (IS), double inversion recovery (DIR) and motion-sensitized driven equilibrium (MSDE)
- Evaluation of imaging biomarkers

Multi-Contrast Carotid Artery Images

- Arrows = LRNC
- Arrowheads = thick fibrous cap

# Multi-Contrast MR Imaging

<table>
<thead>
<tr>
<th>Plaque Component</th>
<th>T1-weighted</th>
<th>T2-weighted</th>
<th>Proton density-weighted</th>
<th>Time-of-flight</th>
<th>Post-Gadolinium based contrast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid rich, Necrotic core</td>
<td>Isointense to slightly hyperintense</td>
<td>Hypointense</td>
<td>Isointense to hyperintense</td>
<td>Isointense</td>
<td>Slower uptake, less enhancement</td>
</tr>
<tr>
<td>Hemorrhage (recent)</td>
<td>Hyperintense</td>
<td></td>
<td></td>
<td></td>
<td>Enhancement</td>
</tr>
<tr>
<td>Calcification</td>
<td>Hypointense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose Matrix</td>
<td>Hypointense to isointense</td>
<td>Hyperintense</td>
<td>Hyperintense</td>
<td>Hypointense</td>
<td>No change</td>
</tr>
</tbody>
</table>

MR Imaging Biomarkers of Atherosclerosis

- **Morphology**
  - Lumen and plaque dimensions
    - (6-10% measurement error)

- **Composition**
  - Calcification (sens 76%, spec 86%)
  - Lipid-rich necrotic core (sens 85-95%, spec 76-92%)
  - Hemorrhage (sens 87-97%, spec 70-98%)
  - Thrombus (sens 88%, spec 98%)
  - Fibrous cap (sens 89%, spec 96%)

- **Activity**
  - Inflammation
  - Neovasculature

Clinical Trials using MR Based Evaluation of Atherosclerotic Plaque

- Aorta
- Carotid
- Femoral
Aorta

- 27 patients with known atherosclerosis followed for 6 months after beginning simvastatin (Lima et al.)
  - Serial MRI of thoracic aorta
  - LDL-C decreased from 125+/-32 to 97+/-27

- 18 patients with known carotid or aortic atherosclerotic disease (Corti et al.)
  - Reduction in LDL-C by 38% and TC by 21%

(2) Corti R et al. Circulation 2001;104:249-252
Serial T2-weighted images of the same patient

Corti R et al. Circulation 2001;104:249-252
Serial MRI after simvastatin therapy

Corti R et al. Circulation 2001;104:249-252
Change in Carotid Plaque Composition with Lipid Therapy

- 33 patients with measurable lipid-rich necrotic core at baseline started on atorvastatin therapy and followed for 3 years
- Decrease in plaque lipids after 1 year
  - This preceded plaque regression

From: MR Imaging of Carotid Plaque Composition During Lipid-Lowering Therapy: Title and subTitle BreakA Prospective Assessment of Effect and Time Course

From: MR Imaging of Carotid Plaque Composition During Lipid-Lowering Therapy: Title and subTitle Break
Prospective Assessment of Effect and Time Course

Noninvasive imaging for atherosclerosis regression

- **Clinical tool: CAC**
  - Progression on serial scans predicts events independent of baseline score

- **Research tools:**
  - **IMT:** Simple, reproducible, small changes
  - Questions about relationship to events
  - **Coronary CT:** Robust, accurate
    - Plaque volume and characteristics
  - **MRI:** Peripheral arteries