Detection of Vulnerable Plaque: Non-Invasive Imaging Is More Clinically Relevant

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Can non-invasive methods effectively image “vulnerable” plaques?
✓ Spatial resolution
✓ Temporal resolution
✓ Plaque composition
Non-invasive imaging does not have the ability to identify important plaque features.

- Thin cap fibroatheroma
- Necrotic core
- Plaque rupture
- Plaque erosion
- Calcified nodule
Why is non-invasive imaging preferable for assessing ‘at-risk’ individuals?
REASON #1: Non-invasive imaging offers a measure of overall coronary artery plaque burden.
## Plaque Characteristics by CCTA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACCURACY</strong></td>
<td>94</td>
<td>83</td>
<td>48</td>
<td>99</td>
</tr>
<tr>
<td></td>
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<tr>
<td>N=230, Stable Chest Pain; No known CAD; No exclusion (CACS, HR, BMI); CAD prevalence 13%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CorE64</td>
<td>85</td>
<td>90</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>N=291, Stable Chest Pain; No known and Known CAD; Exclusion CACS&gt;600; CAD prevalence 56%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meijboom</td>
<td>99</td>
<td>64</td>
<td>85</td>
<td>97</td>
</tr>
<tr>
<td>N=360, Acute and Stable Chest Pain; No known CAD; CAD prevalence 68%</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### plaque thickness

<table>
<thead>
<tr>
<th>Detected</th>
<th>Not Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque thickness</td>
<td>1.5 ± 0.3 mm</td>
</tr>
<tr>
<td>Vessel size (EEM CSA)</td>
<td>4.5 ± 1.2 mm</td>
</tr>
<tr>
<td>% Plaque cross-sectional area</td>
<td>42 ± 16%</td>
</tr>
</tbody>
</table>

p < 0.05 for all categories.

Budoff JACC 2008; Miller NEJM 2008; Meijboom JACC 2009; Leber JACC 2006
Plaque Features by CCTA

Volume (+/-)
- 64-slice CT

Composition (+/-)
- Overestimates calcified
- Underestimates non-calcified

Remodeling (+)
- Remodeling generally high agreement
- Overlap of HU for fibrous, and lipoid

Interobserver variability
- Any plaque (kappa = 0.75)
- Plaque volume (kappa = 0.37)

Plaque volume/vessel $\text{r}^2 = 0.69$, $p < 0.001$

Leber JACC 2006; Leber JACC 2004; Hoffman JACC 2006
Plaque features by CCTA

PQA vs. Agatston score (R²=0.989, p<0.001)

Dual Energy CCTA
CCTA Characteristics of Coronary Lesions in ACS

38 pts with ACS and 33 pts with SAP prior to PCI studied by CCTA.

Positive remodeling, NCP<30 HU and spotty calcification more frequent in culprit ACS lesions than SAP.

Motoyama et al. AHJ 2006
REASON #2:
Non-invasive imaging is prognostically valuable for identifying ‘at-risk’ individuals BEFORE events occur.


Plaque Severity

\[ \chi^2 = 44, \ p < 0.0001 \]

- \(<50\%\) Stenosis \((n=724)\)
  - 1 Vessel \((n=144), \ p = 0.94\)
- 2 Vessel \((n=63), \ p = 0.004\)
- 3 Vessel \((n=90), \ p = 0.001\)
- Left Main \(\geq 50\%\) \((n=106), \ p < 0.0001\)

R-A \(p < 0.001\) (controlling for risk factors + chest pain).

Min et al.  JACC 2007
Plaque Location

Cumulative Survival

Time to Follow-up (Years)

χ²=51, p<0.0001

<50% Stenosis (n=422)
≥2 Mild w 1 Prox. (n=64), p=0.192
1 Mod. (n=212), p=0.065
2 Mod. or 1 Severe (n=101), p=0.013
3 Mod. or 2 Severe or ≥70% prox. LAD (n=145), p=0.002
3 Severe or 2 Severe w Prox. LAD (n=86), p=0.001
≥50% Left Main (n=106), p<0.0001

R-A p<0.0001 (adjusting for risk factors, chest pain, + dyspnea), Mild (30%-49%), Mod. (50%-69%), & Severe (≥70%).

Min et al. JACC 2007
Plaque Composition and Mortality

Two-center study of 3,576 patients without obstructive CAD followed for 2.3 years.

Non-obstructive – Non-calcified
Non-obstructive and Obstructive – Mixed
Obstructive – Calcified

Min, preliminary data
Prognosis by Non-invasive Imaging

No Obstructive CAD

Pooled Statistic
0.6% (8/1,371)

Obstructive CAD

Pooled Statistic
14.5% (79/543)

Courtesy of Leslee Shaw
Totality of Prognostic Data Associated with Invasive Plaque Imaging
REASON #3: Non-invasive imaging concurrently identifies other information capable of predicting risk.
Which factors portend vulnerability?
Myocardial scar
Function

Stroke Volume: 78.0 ml
Ejection Fraction: 62.0%
Cardiac Output: 3.354.0 ml/min
Myocardial Mass: 97.3 g
ES Volume (55%): 46.0 ml
ED Volume (85%): 124.0 ml
PVR: 7.2 mmHg
DVR: 7.2 mmHg
BSA: 1.9 m²
Heart Rate: 43 bpm
Incremental Value of Perfusion to Anatomy

517 pts undergoing CCTA and MPS studied for SSS≥4 or coronary stenosis≥50%

Van Werkhoven et al. JACC 2009
Incremental Value of LVEF to Anatomy

5,646 consecutive patients undergoing CCTA followed for 2.3 years.

Min, preliminary data
**Incremental Value of Scar to Anatomy**

Adverse LV remodelling \((p=0.001)\) and \# of rehospitalizations for CHF \((p=0.0017)\) higher in TM DE.

<table>
<thead>
<tr>
<th></th>
<th>TM DE (n=18)</th>
<th>SE DE (n=20)</th>
<th>No DE (n=14)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CKMB</td>
<td>497</td>
<td>182</td>
<td>85</td>
<td>0.0004</td>
</tr>
<tr>
<td>Myocardial blush grade 3</td>
<td>22%</td>
<td>67%</td>
<td>75%</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>41%</td>
<td>53%</td>
<td>62%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Sato et al. EHJ 2008
REASON #4: Non-invasive imaging offers assessment beyond anatomy.
Inflammation and ACS (PET and CCTA)

Glycolytic activity by FDG uptake in the LM artery greater for pts with ACS than those who were stable (2.4 vs. 1.8, p 0.001).

O'Donnell and Voros AHA Scientific Sessions 2007
REASON #5: Non-invasive imaging by CCTA is safer than invasive imaging.
Near-term complications: Invasive Evaluation

Complication Rate, IVUS
- Any 1.1-2.9%
  - Spasm
- Major 0.4%
  - Occlusion
  - Dissection
  - Guidewire entrapment

Pinto FJ et al. Circulation 1993
# Near-term complications: Non-invasive imaging

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic bradycardia</td>
<td>0%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0%</td>
</tr>
<tr>
<td>Contrast-induced nephropathy</td>
<td>0%</td>
</tr>
<tr>
<td>Heart block</td>
<td>0%</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>0%</td>
</tr>
<tr>
<td>Any complication</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Using standard protocol involving 5mg increments of lopressor and iodixanol as contrast agent

Results from prospective multicenter ACCURACY trial, Budoff MJ et al. JACC 2008
Long-term Safety

Radiation dose with current generation CCTA: Multicenter Experience (3 months)

1.08 mSv (interquartile range 0.88-1.66)

ICA dose 5X the CCTA.
REASON #6: Non-invasive imaging by CCTA permits assessment of plaque progression.
Assessing Changes in Non-Calcified Atherosclerotic Plaque Volume in LM and LAD Over Time by 64-slice CCTA

50 patients with non-calcified plaque at baseline underwent f/u CCTA after 17±6 months. Mean plaque volumes were 92±81 mm³ at baseline MDCT and 115±110 mm³ on follow-up CCTA (p<0.001). Mean annualized volume change was 22% (95%CI, 14.7% vs. 29.7%). Weak but significant correlation to LDL levels for amount of baseline plaque volume, r=0.37, p<0.001)

Plaque areas manually traced. (PA = CSA – Luminal area)
Volume calculated by PA x (reconstruction increment)
Plaque volume = [PA1 + PA2 + . . . . . PA30] x 0.5mm

Achenbach et al. AJC 2008
REASON #7:  
You cannot invasively evaluate everyone.
Implicit in the evaluation of the “vulnerable” plaque is identification BEFORE clinical events occur.

Non-invasive assessment of ‘at-risk’ patients is clinically more relevant than invasive assessment of ‘at risk’ plaques.
Thank you.
Non-invasive assessment of plaque vulnerability is preferable because:

1. People will do it.
2. It is safer.
3. It permits serial assessment.
4. It permits assessment of overall plaque burden.
5. It is prognostic.
6. It offers data beyond plaque.
7. It permits concurrent evaluation of anatomy and physiology.
BEAL 2.5 mSv
RCA aneurysm
Totally occluded OM
Severely diseased LAD
Chronic Total Occlusions
NPV / PPV based upon disease prevalence
SVG to OM; SVG to RPL
LM and LAD
810 patients who underwent CCTA with non-obstructive CAD but with low dense plaques with CT HU density <68 HU, accompanied by mild-moderate coronary artery stenosis (25-75%). Follow-up 1,062+/−544 days for MACE (ACS, incl AMI and UA; cardiac death).

Only prior MI and low dense CT plaques predictive of MACE.
Low density plaques OR 4.60 (95% CI, 1.08-5.92)

Matsumoto et al. Circ J 2007
## MDCT: CABG 64-row MDCT Studies

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>MDCT Rows</th>
<th># Grafts</th>
<th>% Assessable</th>
<th>Basis</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
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<tr>
<td>Pashka Eur Heart J 2006</td>
<td>31</td>
<td>64</td>
<td>96</td>
<td>94</td>
<td>Sten &amp; Occl</td>
<td>97.8</td>
<td>89.3</td>
<td>90</td>
<td>87.7</td>
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<tr>
<td>Ropers et al Circulation. 2006</td>
<td>50</td>
<td>64</td>
<td>138</td>
<td>100</td>
<td>Sten</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>92</td>
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<tr>
<td>Dikkers J Cardio Imag 2006</td>
<td>34</td>
<td>64</td>
<td>69</td>
<td></td>
<td>Sten Occl</td>
<td>100</td>
<td>100</td>
<td>98.7</td>
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<tr>
<td>Meyer J Am Coll Cardiol 2007</td>
<td>138</td>
<td>64</td>
<td>418</td>
<td></td>
<td>Sten &amp; Occl</td>
<td>97</td>
<td>97</td>
<td>93</td>
<td>99</td>
</tr>
</tbody>
</table>
TAKE HOME POINT 1:
Spatial resolution is the most needed improvement to cardiac CT.
CASE #1: No known CAD

- 60 y/o female
  - H/o dyslipidemia, HTN
  - Chest pain: exertional, better with rest
Contrast-enhanced Quantification of Plaque Volumes
Calcium score vs. Contrast-enhanced calcium measurement

By total calcium score

Volumetric vs. Contrast-Enhanced Calcium Score

Agatston vs. Contrast-Enhanced Calcium Score

Correlation coefficient = 98.9%, P<0.0001
Calcium score vs. Contrast-enhanced calcium measurement

By artery

Volumetric vs. Contrast-Enhanced Calcium Score

Agatston vs. Contrast-Enhanced Calcium Score
Plaque composition

Non-calcified plaque
14-51 HU

Calcified plaque
391-715 HU

Mixed plaque
91-116 HU

Schroeder et al., Leber et al., Viles-Gonzales et al.
20 patients – 64-row CT

Comparison to IVUS
- 54/65 (83%) non-calcified
- 50/53 (94%) mixed
- 41/43 (95%) calcified
- 192/204 (94%) accurate identification

$r^2 = 0.69$
- Underestimate mixed and non-calcified plaque

Leber AW et al. JACC 2006
Plaque Characterization - IVUS

- 32 patients – 16-row CT
- IVUS  252 sites
- Hyper-echogenic IVUS
  - $121 \pm 34$ HU
- Hypo-echogenic IVUS
  - $43 \pm 58$ HU

Pohle K et al. Atherosclerosis 2006
Risk of Death with Medical Therapy vs. Revascularization: Observational Data

N=13,555; 3,893 deaths; F/U 8.7 yrs

Hachamovitch et al, ACC 2008
Inducible Ischemia Pre-Treatment and Following 6-18 Months of OMT with or without PCI


*Changes by treatment were adjusted by index ischemia. Dotted lines indicate no significant reduction in ischemia. Solid lines indicate ≥5% reduction in myocardial ischemia.
Event-Free Survival in 105 Patients with Moderate-to-Severe Baseline Ischemia

Residual Ischemia and Outcome


Unadjusted p=0.001
Risk adjusted p=0.09
Accuracy of CCTA (16-slice) to Identify and Differentiate Plaque Composition

58 vessels in 37 consecutive patients (33 male, 63 ± 8 yrs) patients undergoing CCTA and IVUS, examined for accuracy of CCTA for detection of any plaque and plaque composition. 92% (484/525) atherosclerotic lesions correctly excluded.

Leber et al. JACC 2004
DE-CMR of the Coronary Arteries and CCTA

20 pts (14 with CV risk factors, 6 healthy subjects without RF). DE-CMR noted in 2/30 (7%) coronary segments with no plaque by CCTA, 1/10 (10%) segments with non-calcified plaque, 16/44 (36%) segments with calcified plaque (p=0.035). DE-CMR noted in 8/15 (53%) segments with >20% coronary artery stenosis by QCA but also in 12/80 (15%) segments w/o stenosis (p=0.01).

Yeon et al. JACC 2008
A patient.
Another patient.
Spotty Calcification Typifies the Culprit Plaque in AMI (IVUS)

% Patients with Positive Remodeling and Calcification Patterns

Haegawa et al. AHJ 2006
Utilization of non-invasive and invasive testing.

- 50% of all imaging relates to CV imaging
- 3 fold increase non-invasive imaging ‘93-’01

Non-invasive imaging is more clinically relevant because . . .

- It can identify vulnerable patients \textit{before} not after an acute coronary event.
- It is prognostically valuable.
- It provides incremental information about risk beyond plaque.
- It is safer.
- Patients will do it.
### NPV for death

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>PATIENTS (N)</th>
<th>DEAD (N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery plaque score= 0</td>
<td>333</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>No left main plaque</td>
<td>951</td>
<td>20</td>
<td>2.1%</td>
</tr>
<tr>
<td>No proximal LAD plaque</td>
<td>551</td>
<td>9</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Negative predictive value 97.9-99.7% for death.
Stable Chest Pain

Long-term Risk Stratification for All-Cause Death

2,538 consecutive patients undergoing CCTA by EBCTA followed for 6.5 years.
NPV for death for individuals with no CAD 0.3% per year.

Ostrom JACC 2008
Stable Chest Pain

Two Center 64-Detector Row CCTA Risk Stratification for All-Cause Death

5,646 consecutive patients without prior bypass surgery undergoing CCTA followed for 2.3 years.
64-slice CCTA for Classification and Quantification of Plaque Volume in Proximal Coronary System

19 patients underwent 64-slice CCTA and IVUS in 36 vessels. Vessels divided into 3mm sections, evaluated for correct detection of plaque.

Non-calcified plaque: 54/65 (83%)
Mixed Plaque: 41/43 (94%)
Calcified Plaque: 41/43 (95%)

Leber et al. JACC 2006
64-slice CCTA for Classification and Quantification of Plaque Volume in Proximal Coronary System

19 patients underwent 64-slice CCTA and IVUS in 36 vessels. Vessels divided into 3mm sections, evaluated for correct detection of plaque.

Plaque volume/vessel: $r^2=0.69$, $p<0.001$

- Underestimates mixed and non-calcified volumes
- Overestimates calcified plaque volume

Interobserver variability:
- Any plaque (kappa=0.75)
- Plaque volume (kappa=0.37)

7/10 (70%) correct for “lipid pool”
27/30 (90%) correct for spotty calcification.

Leber et al. JACC 2006
Accuracy of CCTA to Identify and Differentiate Plaque Composition

Current generation CCTA can NOT differentiate effectively between lipoid, fibrolipoid or fibrous plaque because HU densities overlap.

Leber et al. JACC 2004
Assessment of Coronary Remodeling by CCTA

44 patients undergoing CCTA and ICA. CSA measured for respective lesion and for reference segment proximal to the lesion.

‘Remodeling Index’ = vessel area/ reference segment.

Results correlated to IVUS and ICA stenosis measurements >50%.

Hoffman et al. JACC 2006
Vulnerable Plaque

A **vulnerable plaque** is an atheromatous plaque, an unstable collection of white blood cells (primarily macrophages) and lipids (including cholesterol) in the wall of an artery which is particularly prone to produce sudden major problems, such as heart attack.

- Susceptible to physical injury.
  - Implies a state which has not yet occurred, i.e., before the event occurs.
Prospective enrollment of 318 asymptomatic HD patients (male/female: 170/148; 64 yrs), without known CAD who underwent dual SPECT using 123I–BMIPP and 201-thallium. 3.6+/1.0 yr f/u. 50 died of cardiac events (MI=22, CHF=17, SCD=11). Cox hazard analysis associated cardiac death with age (70 years) and with abnormal BMIPP SPECT images (BMIPP SSS>12: HR 21.9; p 0.0001).

Nishimura et al. JACC 2008
Prediction of Cardiac Death by Myocardial Fatty Acid Imaging

Mean BMIPP–Tl mismatch score higher in pts with cardiac death than in those w/o (14.0 +/-8.1 [n =50] vs. 2.9+/-4.6 [n =268]; p<0.001).

Nishimura et al. JACC 2008
REASON #8: Non-invasive imaging is less costly.
Spending on Health Care as a Percentage of Gross Domestic Product Under an Assumption That Excess Cost Growth Continues at Historical Averages

Ezekiel J. Emanuel, MD, PhD: NIH
Noninvasive imaging is cost effective.

Cost-Effectiveness Analysis
At Chest Pain

Extended Dominance
\( 0.176 \leq k \leq 0.532 \)
\( 0.584 \leq k \leq 0.956 \)

Min, preliminary data
Prediction of Cardiac Death in Hemodialysis Patients by Myocardial Fatty Acid Imaging

Prospective enrollment of 318 asymptomatic HD patients (male/female: 170/148; 64 yrs), without known CAD who underwent dual SPECT using 123I–BMIPP and 201-thallium. 3.6+/-1.0 yr f/u. 50 died of cardiac events (MI=22, CHF=17, SCD=11). Cox hazard analysis associated cardiac death with age (70 years) and with abnormal BMIPP SPECT images (BMIPP SSS>12: HR 21.9; p 0.0001).

Nishimura et al. JACC 2008
Extent and Direction of Arterial Remodeling in Stable Versus Unstable Coronary Syndromes: An IVUS Study

85 pts with ACS and 46 pts with stable coronary syndromes studied by IVUS prior to PCI.

Remodeling ratio (RR) = (EEM_{lesion})/(EEM_{prox}).

Positive remodeling: RR > 1.05;
Negative remodeling: RR < 0.95.

ACS vs. Stable Angina:
1. Plaque area
   (13.9±5.5 vs 11.1±4.8 mm2; P=0.005)
2. EEM area
   (16.1±6.2 vs 13.0±4.8 mm2; P=0.004)
3. Relative Remodeling
   (1.06±0.2 vs 0.94±0.2; P=0.008)

Schoenhagen et al. Circulation 2000
Compared with the 3 other morphology groups, echolucent plaques were more frequent in the unstable than in the stable angina group (19% versus 4%; P=0.02).
Spotty Calcification in Culprit Plaques in AMI: An IVUS Study

171 pts—61 AMI, 70 UAP, 47 SAP. Frequency and # of calcium deposits within arc <90º for all calcium deposits measured.
Plaque Morphology in Men with CAD Who Died Suddenly

113 men: 59 acute thrombus; 54 severe narrowing by plaque without thrombosis (stable plaque). Thrombosis divided into 2 groups: 41 from rupture of a vulnerable plaque (a thin fibrous cap overlying a lipid-rich core); 18 resulting from the erosion of a fibrous plaque rich in smooth-muscle cells and proteoglycans.

MULTIFACTORIAL ASSESSMENT OF PLAQUE IDENTIFIES PATIENTS WITH UNHERALDED SUDDEN CARDIAC DEATH

Vermani NEJM