Multi-Modality Imaging of Atherosclerosis in HIV

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Disclosures

- Research Grants:
  - Actelion, Genentech, Takeda

- Consulting
  - Actelion, Amgen, Takeda
CV risk persists in treated HIV and inflammation predicts this risk

- Treated suppressed HIV infected individuals have high burden of vascular disease
  - Greater atherosclerosis burden after controlling for risk factors
  - More MI and strokes
  - Major cause of morbidity and mortality in HIV
- Atherosclerosis in HIV is **inflammatory**
  - Associated with higher IL-6, CRP, D-dimer levels
  - HIV-infected individuals have greater arterial inflammation

Hsue PY AIDS 2009; Hsue PY JAHA 2012; Subramanian S JAMA 2012; Duprez D PlosOne 2012; Nordell A JAHA 2014
HIV: Increased Risk of MI

Triant et al J Clin Endocrinol Metab. 2007
Multiple factors cause persistent inflammation during ART

- HIV production and replication
- ART toxicity, lipodystrophy, and traditional risk factors
- Cytomegalovirus and other copathogens

Loss of regulatory cells

Inflammation
- ↑ Monocyte activation
- ↑ T-cell activation
- ↑ Endothelium adhesion
- Dyslipidaemia
- Hypercoagulation

Comorbidities
- cardiovascular disease
- cancer
- kidney disease
- liver disease
- osteopenia/osteoporosis
- neurocognitive disease

Deeks, Lewin, Havir; Lancet 2013
Inflammation: A Central Player

From: Libby P. Nature 2002
Characteristics of High-Risk vs. Stable Plaques

- Thin fibrous cap
- Positive Remodeling
- Large lipid core
- Substantial inflammation

“High-Risk” plaque
- Area of detail

“Lower-Risk” plaque
- Lumen

- T lymphocyte
- Macrophage foam cell
- “Activated” intimal SMC
Outline

• IMT
• CT
• PET-CT & PET/MR
Non-Obstructive Plaques: an Important Locus of Plaque Rupture

Culprit Plaques:
Caused Insignificant Stenosis Within 6 Mo Prior to Rupture

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70%</td>
<td>14%</td>
</tr>
<tr>
<td>50-70%</td>
<td>18%</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>68%</td>
</tr>
</tbody>
</table>

Non-Obstructive CAD Assoc w Nearly 5-fold Increased 1-yr MI Risk

1-yr MI Risk

Falk et al. Circulation 1995
Maddox et al. JAMA 2014
### Risk of MI, Stroke, and CVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Event Follow-Up, y</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIHD$^2$</td>
<td>1.0 (MI)</td>
<td>2.2 (0.7–6.7)</td>
</tr>
<tr>
<td>ROT$^3$</td>
<td>2.7 (MI)</td>
<td>1.4 (1.2–1.8)</td>
</tr>
<tr>
<td>CHS$^4$</td>
<td>6.2 (MI)</td>
<td>3.2 (2.0–5.1)</td>
</tr>
<tr>
<td>MDCS$^5$</td>
<td>7.0 (MI)</td>
<td>2.1 (1.2–3.4)</td>
</tr>
<tr>
<td>CAPS$^6$</td>
<td>4.2 (MI)</td>
<td>2.2 (1.9–4.0)</td>
</tr>
<tr>
<td>ROT$^3$</td>
<td>2.7 (stroke)</td>
<td>1.4 (1.3–1.8)</td>
</tr>
<tr>
<td>CHS$^4$</td>
<td>6.2 (stroke)</td>
<td>2.8 (1.8–4.2)</td>
</tr>
<tr>
<td>CAPS$^6$</td>
<td>4.2 (stroke)</td>
<td>2.3 (0.9–6.3)</td>
</tr>
<tr>
<td>MDCS$^7$</td>
<td>7.0 (stroke)</td>
<td>3.0 (1.6–5.7)</td>
</tr>
<tr>
<td>Kitamura et al$^8$</td>
<td>4.5 (stroke)</td>
<td>3.5 (1.3–9.5)</td>
</tr>
<tr>
<td>MESA$^9$</td>
<td>5.3 (CVD)</td>
<td>2.3 (1.4–3.8)</td>
</tr>
<tr>
<td>CAPS$^6$</td>
<td>4.2 (CVD)</td>
<td>2.3 (1.4–3.8)</td>
</tr>
</tbody>
</table>
Plaque Composition – Lipid vs. Fibrous

CT Attenuation: 46 HU

Pohle et al, Atherosclerosis 2007
Combined molecular and structural imaging (PET-CT) more accurate than structural imaging alone (CT or MR) for tumor staging and localization
- Lardinois NEJM 2003,
- Antoch, JAMA. 2003

Transformed Oncology practice and clinical trials

Prompted wide proliferation of PET/CT
PET Physics

Positron Emission

Annihilation

511 keV

511 keV
PET Physics

Annihilation Detector Crystals and PMT

Arrives first

Arrives late

Scattered photons NOT registered
PET Physics

Coincidental photons registered as true events

Detector Crystals and PMT

511 keV

β −

β +

Annihilation

511 keV
PET Physics

Exquisite (picomolar) sensitivity
Outstanding quantitation

Coincidental photons registered as true events

511 keV

β−

β +

Annihilation

Detector Crystals

and PMT
FDG-PET Accumulation: Measure of Tissue’s Glycolytic Rate

Rudd et al JACC 2010
FDG Uptake By Macrophages: Important in Tumor Imaging

Kubota et al JNM 1994
FDG Uptake Linked to Pro-Inflammatory Activation

Satomi et al. JNM 2013
Linear Relationship between Macrophage Glycolysis and Pro-inflammatory Activity

- Normoxia
- Hypoxia

R = 0.97
P < 0.001

TNF-α, pg/ml vs. Fru-2,6-P₂, pmol/mg protein
Arterial FDG Uptake Relates to Plaque Inflammation

CT coronal +LAP +PR

PET/CT coronal High FDG uptake

PET/CT axial Low FDG uptake

Histopathology axial

FDG uptake (TBR) vs. Macrophage Density

R=0.70, p<0.001

Figueroa Circ CV Imaging 2011
Tawakol JACC 2006
Arterial Inflammation Predicts Subsequent Plaque Progression

Baseline Inflammation (by PET) Precedes Subsequent Local Plaque Calcification (by CT)

Relative FDG Uptake

2-yr Follow-up

Baseline
PET
CT

2-yr Follow-up
CT

p = 0.001

Subsequent Incident Calcium Deposition

Abdelbaky et al Circ Imaging 2013
Arterial FDG Signal Predicts Risk of Subsequent CVD Events

**Risk Categories**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>NRI [95% bootstrap CI]</th>
<th>Events correctly reclassified</th>
<th>Non-events correctly reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% risk</td>
<td>29.44% [13.45,48.42]</td>
<td>12.20%</td>
<td>17.24%</td>
</tr>
<tr>
<td>10-20% risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20% risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carotid FDG Uptake Predicts Early Stroke Recurrence


<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Mean SUV</th>
<th>Maximum SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Clinical stroke recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6.4 (1.4–30.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted</td>
<td>6.1 (1.3–28.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical and subclinical stroke recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>7.4 (1.7–31.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Adjusted</td>
<td>7.6 (1.6–35.3)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Effects of Therapy
Human Treatment Studies

- FDG PET/CT arterial imaging
  - Widely employed to test effects of therapy
  - Over a dozen MCTs

- 4 drug classes
  - Both PET/CT data and outcomes data.
  - How predictive are PET/CT imaging results?
Hi vs Low-Dose Atorvastatin

**PET/CT Imaging Trial**
- Δ = 7% for Atorvastatin 10 mg
- Δ = 6% for Atorvastatin 80 mg
- P < 0.05

**Clinical Endpoint Trial**
- Δ = 13% for Atorvastatin 80 mg
- Δ = 15% for Atorvastatin 80 mg
- HR = 0.78 (0.69–0.89)
- P < 0.001

Tawakol et al. JACC 2013

LaRosa et al. NEJM 2005
Non-pharmacologic LDL Llowing Rapidly Reduces Arterial Inflammation

Impact of Apheresis in FH

**A**

<table>
<thead>
<tr>
<th></th>
<th>Pre-apheresis</th>
<th>Post-apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial TBR (all vessels)</td>
<td>2.20</td>
<td>1.60</td>
</tr>
</tbody>
</table>

P<0.001

**A**

R=0.52

P=0.009

van Wijk et al JACC 2014
Response To Therapy: Pioglitazone

PET/CT Imaging Trial

ΔTBR

Change in PET Signal

Pio
Glimepiride

p < 0.02

Clinical Endpoint Trials

Nissen et al JAMA 2007
Erdmann et al JACC 2007

Mizoguchi et al JACC CV Imaging 2011
### PET/CT Imaging Trial

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo Mean (SE)</th>
<th>Dalcetrapib Mean (SE)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid MRI‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vessel area at 24 months§ (mm²)</td>
<td>5.72 (1.45)</td>
<td>1.71 (1.43)</td>
<td>0.04</td>
</tr>
<tr>
<td>Wall area at 24 months§ (mm²)</td>
<td>2.69 (1.05)</td>
<td>0.49 (1.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>Wall thickness at 24 months¶ (mm)</td>
<td>0.05 (0.03)</td>
<td>0.02 (0.03)</td>
<td>0.45</td>
</tr>
<tr>
<td>Normalised wall index at 24 months§ (%)</td>
<td>-0.40 (0.80)</td>
<td>0.30 (0.80)</td>
<td>0.57</td>
</tr>
<tr>
<td>Index vessel PET/CT¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most diseased segment mean of maximum TBR at 6 months**</td>
<td>-0.26 (0.08)</td>
<td>-0.19 (0.08)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

### Clinical Endpoint Trials

- N=15,871

![Graph showing cumulative incidence of primary outcome (% of patients)](image)

P=0.52 by log-rank test
Effect of LPPLA2 Inhibition on Arterial FDG Uptake

PET/CT Imaging Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 84</th>
<th>Difference</th>
<th>(95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole vessel (primary endpoint)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilapladi, n = 35</td>
<td>2.21 (0.402)</td>
<td>2.09 (0.279)</td>
<td>0.05</td>
<td>-0.06 to 0.16</td>
<td>0.3717</td>
</tr>
<tr>
<td>Placebo, n = 36</td>
<td>2.11 (0.388)</td>
<td>1.99 (0.320)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Most diseased segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilapladi, n = 35</td>
<td>2.27 (0.432)</td>
<td>2.14 (0.304)</td>
<td>0.04</td>
<td>-0.08 to 0.16</td>
<td>0.4947</td>
</tr>
<tr>
<td>Placebo, n = 36</td>
<td>2.21 (0.423)</td>
<td>2.07 (0.365)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>All active segments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilapladi, n = 38</td>
<td>2.21 (0.40)</td>
<td>2.10 (0.28)</td>
<td>-0.00</td>
<td>-0.16 to 0.15</td>
<td>0.9653</td>
</tr>
<tr>
<td>Placebo, n = 39</td>
<td>2.12 (0.39)</td>
<td>2.00 (0.32)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Tawakol et al JACC 2014

Clinical Endpoint Trials

N=15,828

Hazard ratio, 0.94 (95% CI, 0.85–1.03)  
P=0.20

N=13,026

HR, 1.00 (95% CI, 0.91–1.09)  
χ² P= .93

HIV
CIMT in HIV

PY Hsue et al JAHA 2012

Longenecker1 et al CROI 2015
Associations Between HIV Infection and Subclinical Coronary Atherosclerosis
Atorvastatin Reduces Progression of Non-Calcified Plaque

Lo et al JAMA HIV 2015
Arterial Inflammation is Increased in HIV

Subramanian et al. JAMA 2012
Aortic Inflammation is Associated with High Risk Coronary Plaques

High-Risk Coronary Plaque Morphology

% Subjects with High-Risk Coronary Plaques

Low Attenuation: $P = 0.02$

Low Attenuation and Positive Remodeling: $P = 0.04$

Aortic TBR

- < Median Value
- ≥ Median Value

Tawakol et al J AIDs 2014
Ongoing Athero Imaging Trials in HIV

- Effect of Methotrexate on Atherosclerosis
  - FDG PET/CT Imaging
  - ACTG, NHLBI

- REPRIEVE
  - Statins in HIV
  - ACTG, NHLBI
Myocardial Fibrosis in HIV

Holloway et al. Circulation 2013
Development of New Tracers

**TSPO Imaging**

Pugliese et al JACC 2010

**Ado Receptor Imaging**

Elmaleh et al PNAS 2006

**Manose Receptor Imaging**

Tahara et al Nature Medicine 2014
Atherosclerotic mechanisms may have important components that exist outside the vessel wall
MI (LAD Ligation) Triggers $\beta_3$AR-mediated progenitor cell release from bone marrow

... increase in splenic granulocyte macrophage progenitors (GMPs)

... and subsequent aortic plaque inflammation

Arterial Inflammation

MI

β3-Adrenoceptor

Progenitor release from BM niche

Increased extramedullary monocytosis

Dutta et al Nature 2012
Does this axis exist in humans?
Hematopoietic Activation: Relates to Pro-Inflammatory Gene Activation in Leucocytes

ACS

Stable CAD

<table>
<thead>
<tr>
<th>Bone Marrow FDG Uptake</th>
<th>Spleen FDG Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum biomarkers</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.62</td>
</tr>
<tr>
<td>TNF</td>
<td>0.19</td>
</tr>
<tr>
<td>IL-1β</td>
<td>0.43</td>
</tr>
<tr>
<td>Gene expression in leukocytes</td>
<td></td>
</tr>
<tr>
<td>CD36</td>
<td>0.05</td>
</tr>
<tr>
<td>MSR-1</td>
<td>0.53</td>
</tr>
<tr>
<td>S100A9</td>
<td>0.15</td>
</tr>
<tr>
<td>TLR-2</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Does Hematopoietic tissue activity predict CVD Risk?
Hematopoietic Tissue Activity Correlate w Arterial Activity in Individuals without known Athero

Emami et al JACC Imaging 2015
Splenic Activity Predicts Subsequent CVD

Spleen FDG Uptake

Proportion free of CVD

P=0.003

Follow-up (years)

Number at Risk

FDG Uptake < median: 227 222 208 175 112 55 12

FDG Uptake ≥ median: 228 206 190 164 118 62 22

Emami et al JACC Imaging 2015
Aortic TBR is strongly correlated with Splenic TBR

HIV infected: red
Controls: blue

HIV+ (n=21): Spearman correlation = 0.53, p=0.014
HIV- (n=21): Spearman correlation = 0.73, p=0.00016

P. Hsue et al CROI 2014
### Predictors of Splenic TBR in Treated Suppressed HIV:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Beta, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>%CCR2 within monocytes</td>
<td>1.04 (1, 1.07, p=0.04)</td>
</tr>
<tr>
<td>sCD14 ug/ml</td>
<td>1.55 (1.05, 2.28, p=0.026)</td>
</tr>
<tr>
<td>Log IL6 pg/ml</td>
<td>1.17 (1.02, 1.35, p=0.03)</td>
</tr>
<tr>
<td>sCD163 per 100 ng/ml</td>
<td>1.05 (1.01, 1.09, p=0.02)</td>
</tr>
<tr>
<td>% of total CD4 T cells in T cells</td>
<td>1.01 (1.00, 1.01, p=0.026)</td>
</tr>
<tr>
<td>% of total CD8 T cells within total T cells</td>
<td>0.99 (0.99, 1.00, =0.019)</td>
</tr>
<tr>
<td>HIV integrated DNA (copies/10^6 CD4 T cells)</td>
<td>1.14 (1.04, 1.26, p=0.008)</td>
</tr>
</tbody>
</table>

P. Hsue et al CROI 2014
Thank You!
# Acknowledgements

**MGH CV Imaging Team**

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