Inflammation & Imaging

Ahmed Tawakol, MD
Co-Director Cardiac MR PET CT Program
Massachusetts General Hospital
Harvard Medical School
Disclosures

• Research Grants:
  – Genentech, Takeda, Actelion

• Consulting
  – Actelion, Amgen, Astra Zeneca, Takeda
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

Falk et al. Circulation 1995
Maddox et al. JAMA 2014
1) Stenosis evaluation
   • inadequate for plaque evaluation and risk stratification.

2) Evaluation of wall composition and biology
   • may provide important insights.

3) Achieved via
   • combination of molecular and structural imaging.
Oncology: Demonstrated Clinical Utility of Combined Biological and Structural Imaging

- 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
Inflammation: A Central Player

From: Libby P. Nature 2002
Inflammation: Many Targets
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
Macrophage Glycolysis
Increased after M1 Activation

Rodriguez-Prados et al. J Immunol 2010
Inflammation and Metabolism in an Atherosclerotic Environment

Glycolytic Flux

normoxia

hypoxia
Inflammation and Metabolism in an Atherosclerotic Environment

**A**

Pro-Inflammatory Activity

- ** normoxia **
- ** hypoxia **

![Graph](image)

**B**

Glycolytic Flux

- ** Fru-2,6-P_2**

![Graph](image)

Tawakol et al ATVB 2015
Inflammation and Metabolism in an Atherosclerotic Environment

Glycolytic Flux

Pro-Inflammatory Activity

(normoxia) PG/ml

Pro-Inflammatory Activation
(TNF alpha pg/ml)

Glycolytic Flux

Fru-2,6-P₂, pmol/mg protein

LDL oxLDL GM

(normoxia) PG/ml

Fru-2,6-P₂, pmol/mg protein

R=0.97
P<0.001

Tawakol et al ATVB 2015
FDG Uptake Linked to Pro-Inflammatory Activation

Satomi et al. JNM 2013
PET-CT

Axial

Coronal

Axial measurements every 5 mm

Measured ROI Values

<table>
<thead>
<tr>
<th>Mean Value</th>
<th>Max Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>2.0</td>
<td>2.2</td>
</tr>
<tr>
<td>2.2</td>
<td>2.5</td>
</tr>
<tr>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Imaging Endpoints

Most Diseased Segment (MDS)

Whole Vessel TBR

1.77

MDS TBR

2.23

Whole Vessel

1.2

2.2

2.2

2.5

2.0

1.3

1.4

1.5 cm
Arterial FDG Uptake Relates to Plaque Inflammation

CT
- coronal
- High FDG uptake
- Calcified plaque

PET/CT
- coronal
- Low FDG uptake

PET/CT
- axial

Histopathology
- axial
- Lumen
- NC1
- NC2
- NC3

FDG uptake (TBR) vs. Macrophage Density
- \( R = 0.70, \ p < 0.001 \)
Multi-group Confirmation

R=0.8, p<0.005

MA Font et al, Frontiers in Bioscience 2009

R=0.64, P<0.001

M. Graabe et al, Eur J Vasc Endovasc Surg 2009

: r = 0.67, P = 0.03

Taqueti et al Circ Imaging 2014
Arterial FDG Uptake: Relationship to Cardiac Risk Factors

Kim et al. Circulation Imaging 2010
Arterial Inflammation Predicts Subsequent Plaque Progression

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

Baseline PET 
Baseline CT 
2-yr Follow-up PET 
2-yr Follow-up CT 

Relative FDG Uptake

p = 0.001

Abdelbaky et al Circ Imaging 2013
Changes in Arterial Inflammation Predict Plaque Progression: Wall thickness by MR

Early Changes in Inflammation (by PET) Predict Long-Term Changes in Wall Thickness, (by MRI)

Fayad et al Lancet 2011; Tawakol et al ESC 2012

PET 1 → 6M → PET 2 → 24M → MR 1 → MR 2

Change in Wall Thickness over 24 Mo

![Graph showing change in wall thickness over 24 months with decreased and increased TBR.]

6M Change in TBR

Decreased

Increased

**
Arterial FDG Signal Predicts Risk of Subsequent CVD Events

### Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>NRI</th>
<th>Events correctly reclassified</th>
<th>Non-events correctly reclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% risk</td>
<td>29.44%</td>
<td>12.20%</td>
<td>17.24%</td>
</tr>
<tr>
<td>10-20% risk</td>
<td>29.44%</td>
<td>12.20%</td>
<td>17.24%</td>
</tr>
<tr>
<td>&gt; 20% risk</td>
<td>[13.45,48.42]</td>
<td>12.20%</td>
<td>17.24%</td>
</tr>
</tbody>
</table>
Carotid FDG Uptake predicts early stroke recurrence.

### Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Mean SUV</th>
<th></th>
<th>Maximum SUV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>(p)</td>
<td>HR (95% CI)</td>
<td>(p)</td>
</tr>
<tr>
<td>Clinical stroke recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6.4 (1.4–30.1)</td>
<td>0.02</td>
<td>3.1 (1.4–6.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Adjusted(^a)</td>
<td>6.1 (1.3–28.8)</td>
<td>0.02</td>
<td>3.1 (1.4–6.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical and subclinical stroke recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>7.4 (1.7–31.8)</td>
<td>0.009</td>
<td>3 (1.5–6.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted(^a)</td>
<td>7.6 (1.6–35.3)</td>
<td>0.009</td>
<td>3.1 (1.4–6.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Effect 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 Atorva

PET/CT Imaging Trial

- BL
- Wk 4
- Wk 12

Δ = 7%  
P = 0.04

Δ = 6%  
P = 0.04

Clinical Endpoint Trial

- BL
- Wk 4
- Wk 12

Δ = 13%  
P < 0.001

Δ = 15%  
P < 0.001

Tawakol et al JACC 2013

LaRosa et al NEJM 2005
Non-Pharmacologic LDL Lowering: Apheresis

P = 0.03

R = 0.71

P = 0.01

Van Wijk et al JACC 2014
Response To Therapy: Pioglitazone

PET/CT Imaging Trial

Change in PET Signal

ΔTBR

p < 0.02

Pio  Glimepiride

Clinical Endpoint Trials

Mizoguchi et al JACC CV Imaging 2011

Erdmann et al JACC 2007

Nissen et al JAMA 2007
# Effect of the CETP Antagonist Dalcetrapib

## PET/CT Imaging Trial

<table>
<thead>
<tr>
<th>Least squares mean of absolute change from baseline (SE)</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Dalcetrapib</td>
</tr>
<tr>
<td>Carotid MRI‡</td>
<td></td>
</tr>
<tr>
<td>Total vessel area at 24 months§ (mm²)</td>
<td>5.72 (1.45)</td>
</tr>
<tr>
<td>Wall area at 24 months§ (mm²)</td>
<td>2.69 (1.05)</td>
</tr>
<tr>
<td>Wall thickness at 24 months¶ (mm)</td>
<td>0.05 (0.03)</td>
</tr>
<tr>
<td>Normalised wall index at 24 months§ (%)</td>
<td>-0.40 (0.80)</td>
</tr>
<tr>
<td>Index vessel PET/CT†</td>
<td></td>
</tr>
<tr>
<td>Most diseased segment mean of maximum TBR at 6 months**</td>
<td>-0.26 (0.08)</td>
</tr>
</tbody>
</table>

## Clinical Endpoint Trials

N=15,871

Cumulative Incidence of Primary Outcome (% of patients)

- Placebo
- Dalcetrapib

P=0.52 by log-rank test

Schwartz et al, NEJM 2012

Fayad et al, Lancet 2011
Effect of LPPLA2 Inhibition on Arterial FDG Uptake

PET/CT Imaging Trial

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

Clinical Endpoint Trials

N=15,828

N=13,026

Tawakol et al JACC 2014

O'Donoghue et al JAMA 2014

Physiologic Insights
Arterial Inflammation is Increased in HIV

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

% Subjects with High-Risk Coronary Plaques

Low Attenuation

Low Attenuation and Positive Remodeling

P = 0.02

P = 0.04

Aortic TBR

< Median Value

> Median Value

High-Risk Coronary Plaque Morphology
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

Increased extramedullary monocytopoiesis

MI

β3-Adrenoceptor

Progenitor release from BM niche
Does this axis exist in humans?

Hematopoietic Activation: Relates to Pro-Inflammatory Gene Activation in Leucocytes

Emami et al. JACC Imaging 2015
Does Hematopoietic tissue activity predict CVD Risk?

Arterial Inflammation

Increased extramedullary monocytopoiesis

Progenitor release from BM niche

Dutta et al Nature 2012
Hematopoietic Tissue Activity Correlate w Arterial Activity in Individuals without known Athero
Splenic Activity Predicts Subsequent CVD

![Graph showing the proportion free of CVD over follow-up years for different FDG uptake levels. The graph indicates a significant difference (P=0.003) between the two groups, with the median split.](Image)

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>FDG Uptake &lt; median:</th>
<th>227</th>
<th>222</th>
<th>208</th>
<th>175</th>
<th>112</th>
<th>55</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG Uptake ≥ median:</td>
<td>228</td>
<td>206</td>
<td>190</td>
<td>164</td>
<td>118</td>
<td>62</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

Emami et al JACC Imaging 2015
Splenic Activity Predicts Subsequent CVD

Emami et al JACC Imaging 2015
Other CV Targets
FDG Uptake
Aortic Valve Calcification

Marincheva et al, JACC 2011
FDG-PET/CT: Characterization of Inflammation in DVT

Mice

- Neutrophil depleted DVT FDG signal
- Control mice
- TBR vs. # Neutrophils / 5 HPF
  - $r = 0.62$, $p < 0.001$

Humans

- (A) DVT
- (B) No DVT

- SUVmax
  - DVT age: $\leq 16$, 17-58, $\geq 59$, No DVT
  - $*p = 0.002$

Hara et al. Circulation 2014
How could we use inflammation imaging clinically today?
Clinical Imaging

- **Sarcoidosis**: Predictive of Death/VT
- **Prosthetic Valve Endocarditis**: Increases sensitivity of modified Duke criteria
- **Device Infection**: Improved detection

References:
- Blankstein JACC 2014
- Saby et al JACC 2013
- Serrazin et al JACC 2012
Future uses:

• Moderate to severe carotid stenosis
  – Risk stratification to guide treatment

• Chronic Coronary Atherosclerosis
  – Fine-tune risk
  – Allocation of treatments
    • New treatments will be available
      – Mounting costs and side effects
    • Need to improve ability to allocate treatments
      – Think like oncologists
  – Follow response to expensive/toxic treatments
    – Switch course when drugs are not working

• Venous Thromboembolism
  – Predict post thrombotic syndrome
  – Identify young clots susceptible to thrombolysis
Coronaries?
Culprit Coronary Lesions Have Higher Arterial FDG Uptake

Rogers et al JACC CV Imaging 2010
18F NaF Imaging of Micro-calcification

Localizes to culprit lesions
Far less background uptake than FDG

- Unclear mechanism leading to its uptake in culprit
- Unclear if its modifiable by therapy
- Unclear if provides additional prognostic info above CAC

Joshi et al, Lancet 2014
NAF UPTAKE IS NOT CELL-SPECIFIC
Technological Advances
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
Ga DOTATATE

Courtesy of James Rudd
PET/MR
# Acknowledgements

## MGH CV Imaging Team

- Amr Abdelbaky, MD
- Hamed Emami, MD
- Amparo Figueroa, MD
- Brian Ghoshhajra, MD
- Amorina Ishai, MD
- Philip Joseph, MD
- Udo Hoffmann, MD
- Hoey Chyi Lim, BA
- Megan Macnabb, BA
- Thomas Neilan, MD
- Parmanand Singh, MD
- Sharath Subramanian, MD
- Richard Takx, MD

## Key Collaborators

- Lisardo Bosca, MD
- Ciprian Catana, MD
- Marcelo DiCarli, MD
- Michael E Farkouh MD
- Zahi A Fayad PhD
- Henry Gewirtz, MD
- Michael Jaff, DO
- Farouc Jaffer, MD, PhD
- Peter Ganz, MD
- Stephen Grinspoon, MD
- Linda Hemphill, MD
- Priscilla Hsue, MD
- Janet Lo, MD
- Matthias Nahrendorf, MD
- Jagat Narula, MD
- Miguel Pampaloni, MD
- Roger Pitman, MD
- James HF Rudd MD PhD
- Bruce Rosen, MD, PhD
- Marielle Scherer-Crosbie, MD
- Lisa Shin, PhD
- David Sosnovik, MD
- Quinh Truong, MD