Using Computed Tomography Angiography In Personalised Medicine

Charalambos Antoniades MD PhD FESC
Professor of Cardiovascular Medicine
Deputy Head, Division of Cardiovascular Medicine University of Oxford
Director of Oxford Academic Cardiovascular CT Programme
Disclosures

Unrestricted grants from Sanofi
Unrestricted grants from NovoNordisk
Consultancies Mitsubishi-Tanabe
Founder, shareholder and CSO of Caristo diagnostics
Residual cardiovascular risk: the unmet need

If we detect coronary inflammation we may predict heart attacks, and direct deployment of novel therapeutics to prevent them!
Using imaging for risk stratification and treatment customization: Structural characteristics of the vulnerable plaque in CTA

The **vulnerable** plaque

**TABLE 3** Multivariable Logistic Regression Analysis for the Prediction of ACS Using Clinical Predictors and Coronary CTA Assessment

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>p Value</th>
<th>OR (95% CI)</th>
<th>p Value</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1 (1.0-1.1)</td>
<td>0.003</td>
<td>1.0 (1.0-1.1)</td>
<td>0.359</td>
<td>1.0 (0.9-1.1)</td>
<td>0.870</td>
</tr>
<tr>
<td>Female</td>
<td>0.2 (0.1-0.4)</td>
<td>&lt;0.001</td>
<td>0.3 (0.1-0.8)</td>
<td>0.020</td>
<td>0.4 (0.1-1.2)</td>
<td>0.104</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td>1.4 (1.0-1.8)</td>
<td>0.056</td>
<td>1.4 (0.9-2.2)</td>
<td>0.124</td>
<td>1.3 (0.8-2.0)</td>
<td>0.278</td>
</tr>
<tr>
<td>Stenosis &gt;50%</td>
<td>71.7 (27.1-189.9)</td>
<td>&lt;0.001</td>
<td>38.6 (14.2-104.7)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk plaque</td>
<td>8.9 (1.8-43.3)</td>
<td><strong>0.006</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clinical predictors were age, sex, and number of cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking status, and family history of premature CAD). Clinical predictors were those in model 1 plus stenosis >50%. Clinical predictors were those in model 2 plus high-risk plaque. Number of risk factors = number of cardiovascular risk factors (diabetes mellitus, hypertension, dyslipidemia, smoking status, and family history of premature CAD).

Analysis of 472 CTA scans from the ROMICAT-II trial

**But........ high risk plaque features are uncommon**

Hecht et al. JACC Cardiovasc Imaging. 2015;8(11)
Puchner et al. JACC. 2014;64(7):684–692.
Calcium Score: The prognostic value of coronary calcium on cardiovascular CT

The Multiethnic Study of Atherosclerosis (MESA) study (6000 + subjects)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR for model without CACS (95% CI)</th>
<th>P value</th>
<th>HR for model with CACS (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.30 (1.21-1.41)</td>
<td>&lt;0.001</td>
<td>1.08 (0.90-1.17)</td>
<td>0.29</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.21 (1.00-4.98)</td>
<td>&lt;0.001</td>
<td>1.68 (1.01-2.65)</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>1.10 (1.05-1.16)</td>
<td>0.003</td>
<td>1.18 (1.01-1.45)</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of blood pressure lowering medication</td>
<td>1.01 (1.21-2.15)</td>
<td>0.001</td>
<td>1.87 (1.03-1.42)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>1.07 (1.00-1.11)</td>
<td>0.001</td>
<td>1.05 (1.01-1.16)</td>
<td>0.01</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>0.81 (0.72-0.91)</td>
<td>&lt;0.001</td>
<td>0.84 (0.75-0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.91 (1.25-2.91)</td>
<td>0.003</td>
<td>1.54 (1.09-2.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>CACS (lnCACS + 1)</td>
<td></td>
<td></td>
<td>1.41 (1.23-1.33)</td>
<td>0.991</td>
</tr>
</tbody>
</table>

HR denotes hazard ratio, CACS coronary artery calcium score, and CI confidence interval.

But........ calcium is a sign of stable plaques and it increases with statins!

Polonsky et al. JAMA. 2010 303(16): 1610–1616
Detrano et al. NEJM. 2008; 358:1336-1345
Could detection of any calcium or plaque trigger prevention measures? (SCOTT-HEART study)

But... it leads to over-medication.

Unmet need: If we detect inflamed vessels or plaques we could direct treatments in a targeted way
Perivascular FAI: a “sensor” of vascular inflammation

Healthy, non-inflamed artery

“Healthy,” inflamed artery

Can we **visualize** and **quantify** these changes in PVAT composition non-invasively in humans?

Perivascular Fat Attenuation Index (FAI\textsubscript{PVAT})

Low FAI

- Healthy
- (STEMI 3 years later)

High FAI

- Healthy

**Weighted FAI:** An artificial intelligence-enhanced, radiotranscriptomic biomarker

Can FAI_{PVAT} “track” coronary inflammation?

Antonopoulos A et al. Science Translational Medicine 2017
Can FAI predict cardiovascular risk?
The CRISP-CT study

Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data

~4000 participants with CCTA at baseline
Derivation (Erlangen), n~2000
Validation (Cleveland Clinic), n~2000

Up to 10y follow up

199 deaths/74 cardiac deaths
FAI has prognostic value for cardiac death

Erlangen cohort

All-cause mortality

Cardiac mortality

Oikonomou E et al; Lancet 2018; 392(10151):929-939
FAI has prognostic value for cardiac death

Erlangen cohort

Cleveland cohort

Adjusted HR 3.69, 95% CI 2.25-6.02
p<0.0001

Adjusted HR 5.62, 95% CI 2.90-10.88
p<0.0001

Oikonomou E et al; Lancet 2018; 392(10151):929-939
FAI predicts non-fatal myocardial infarction

Oikonomou E et al; Lancet 2018 (in press)
FAI improves prediction of cardiac death over and above current state-of-the-art

**Model 1**: age, sex, hypertension, hypercholesterolaemia, diabetes mellitus, smoker status, epicardial fat volume, modified Duke CAD index and number of high-risk plaque features on CCTA.

**Model 2**: Model 1 + FAI

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Oikonomou E et al; Lancet 2018; 392(10151):929-939

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**Areas under the curve**:

- **Derivation**: 0.913 (95% CI 0.867–0.958) to 0.962 (0.940–0.983), *P*=0.0054
- **Validation**: 0.763 (95% CI 0.669–0.858) to 0.838 (0.764–0.912), *P*=0.0069
The risk identified by FAI may be modifiable by statins/aspirin

Cardiac mortality prediction in Erlangen cohort, after treatment initiation

Risk for all groups together: Adjusted HR 9.04 [3.35 - 24.4]

Editorial:
Imaging of coronary inflammation for cardiovascular risk prediction.

Oikonomou E et al; Lancet 2018
FAI: A powerful, novel technology for CV risk stratification

✓ **Biology/Science**: FAI detects coronary inflammation by phenotyping perivascular fat attenuation changes in CCTA

✓ **Clinical value**: FAI has a striking prognostic value for cardiac death and non-fatal AMI, over and above current risk scores and state-of-the-art interpretation of CCTA (risk modifiable?)

✓ **Potential to use in clinical practice**: The FAI technology is applicable to any standard CCTA, from any scanner and with any scan settings (with appropriate weighting)

✓ **FAI as a “clever” biomarker**: Developed via artificial intelligence, and keeps evolving as we include data from more outcomes studies

✓ **Pitfalls**: FAI needs appropriate corrections for obesity, scanner type, scan settings and other technical and biological factors, so *crude measurement of “mean perivascular attenuation” is of limited value in clinical practice*. Consistent and validated image analysis tools will allow quality-assured delivery of FAI technology for patient benefit.
Acknowledgments

Funding bodies

Collaborators

Oxford Cardiac CT team
- Dr Nik Sabharwal
- Dr Andrew Kelion
- Dr Cheerag Shirodaria

OUH NHS Trust
- Mr Rana Sayeed
- Mr Mario Petrou
- Mr G Krasopoulos
- Prof Keith Channon
- Prof Barbara Casadei
- Prof Stefan Neubauer
- Prof Hugh Watkins

Erlangen, Germany
- Prof S Achenbach
- Dr M Marwan

Cleveland Clinic, USA
- Prof M Desai

Athens Medical School, Greece
- Prof D Tousoulis
- Dr N Koumallos
- Dr Nikos Alexopoulos

Caristo Diagnostics
- Dr Cheerag Shirtodaria
- Dr David Scottlander
- Dr Danniel Green
FAI predicts cardiac mortality across all risk groups

<table>
<thead>
<tr>
<th>Patients (n)/Events (n)</th>
<th>Adjusted HR (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derivation cohort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive coronary artery disease No 1405/14</td>
<td>6.66 (1.93-22.96)</td>
<td>p=0.0%, p=0.78</td>
</tr>
<tr>
<td>Yes 467/12</td>
<td>8.54 (2.41-30.21)</td>
<td></td>
</tr>
<tr>
<td>Coronary calcium score &lt;300 1153/6</td>
<td>10.62 (1.49-75.48)</td>
<td>p=0.0%, p=0.82</td>
</tr>
<tr>
<td>≥300 162/6</td>
<td>4.66 (0.85-25.44)</td>
<td></td>
</tr>
<tr>
<td>N/A 457/14</td>
<td>6.37 (1.73-23.48)</td>
<td>p=0.0%, p=0.65</td>
</tr>
<tr>
<td>Duke coronary artery disease index 1-2 1562/16</td>
<td>6.91 (2.24-21.29)</td>
<td>p=72.9%, p=0.06</td>
</tr>
<tr>
<td>3-6 310/10</td>
<td>10.86 (3.32-50.66)</td>
<td></td>
</tr>
<tr>
<td>High-risk plaque features No 1407/20</td>
<td>4.88 (1.79-13.29)</td>
<td>p=0.0%, p=0.40</td>
</tr>
<tr>
<td>Yes 465/16</td>
<td>73.53 (5.57-945.10)</td>
<td></td>
</tr>
<tr>
<td><strong>Validation cohort</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive coronary artery disease No 1754/33</td>
<td>7.01 (3.27-15.66)</td>
<td>p=0.0%, p=0.41</td>
</tr>
<tr>
<td>Yes 285/15</td>
<td>3.85 (1.21-12.27)</td>
<td></td>
</tr>
<tr>
<td>Duke coronary artery disease index 1-2 1902/38</td>
<td>6.25 (3.08-12.71)</td>
<td>p=43.2%, p=0.18</td>
</tr>
<tr>
<td>3-6 138/10</td>
<td>3.25 (0.80-13.16)</td>
<td></td>
</tr>
<tr>
<td>High-risk plaque features No 1582/28</td>
<td>8.24 (3.63-18.70)</td>
<td>p=0.0%, p=0.40</td>
</tr>
<tr>
<td>Yes 458/20</td>
<td>3.45 (1.26-9.30)</td>
<td></td>
</tr>
</tbody>
</table>

Oikonomou E et al; Lancet 2018; 392(10151):929-939
Can perivascular adipocytes sense inflammation coming from the neighbouring artery?

<table>
<thead>
<tr>
<th>Cardiac mortality</th>
<th>Model performance</th>
<th>Discrimination (IDI [95% CI])</th>
<th>Risk reclassification</th>
<th>Risk reclassification NRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in $\chi^2$</td>
<td>p value*</td>
<td>Events Risk up</td>
<td>Events Risk down</td>
</tr>
<tr>
<td>Derivation</td>
<td>20.29</td>
<td>&lt;0.0001</td>
<td>0.038 (0.000-0.174)</td>
<td>0.64</td>
</tr>
<tr>
<td>Validation</td>
<td>25.30</td>
<td>&lt;0.0001</td>
<td>0.032 (0.001-0.090)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>Model performance</th>
<th>Discrimination (IDI [95% CI])</th>
<th>Risk reclassification</th>
<th>Risk reclassification NRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in $\chi^2$</td>
<td>p value*</td>
<td>Events Risk up</td>
<td>Events Risk down</td>
</tr>
<tr>
<td>Derivation</td>
<td>16.54</td>
<td>&lt;0.0001</td>
<td>0.017 (0.003-0.052)</td>
<td>0.48</td>
</tr>
<tr>
<td>Validation</td>
<td>25.60</td>
<td>&lt;0.0001</td>
<td>0.030 (0.008-0.068)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Perivascular FAI comparison was ≥70.1 HU vs <70.1 HU. IDI and NRI were calculated at 6 years. Baseline model (current state-of-the-art model 1): age, sex, hypertension, hypercholesterolaemia, diabetes mellitus, active smoker status, epicardial adipose tissue volume, modified Duke coronary artery disease index (reference: group 1, mild or no disease), and number of high-risk plaque features. New model (model 2): model 1 plus high perivascular FAI values. FAI=fat attenuation index. IDI=integrated discrimination improvement. NRI=net reclassification improvement index. *Likelihood ratio test.
Applying FAI Analysis as a new dimension of routine CTA

Antonopoulos A, Sanna F et al. Science Translational Medicine 2017
Can the inflamed human coronary artery affect adipocyte size in PVAT, in vivo?

Biopsies: 2mm 20mm

Adipocyte size (fold differences)

Distance from RCA

pp<0.05

PPARγ gene expression (fold differences)

C/EBPα gene expression (fold differences)

FABP4 gene expression (fold differences)

P<0.05

Does FAI tell you about fat inflammation in vivo?

Low inflammation

- **PET**: PET heat map (SUV)
  - PET images
- **Adipocytes exposed to inflammation**
  - Large adipocytes
    - More lipophilic phase
    - Less aqueous phase
- **FAI in standard CT**
  - FAI heat map (HU)

High inflammation

- **PET**: PET heat map (SUV)
  - PET images
- **Adipocytes exposed to inflammation**
  - Small adipocytes
    - Less lipophilic phase
    - More aqueous phase
- **FAI in standard CT**
  - FAI heat map (HU)

Antonopoulos A, Sanna F et al. Science Translational Medicine 2017
How do adipocytes “sense” inflammation …. and how do they change in response to it?

Human primary adipocytes

- Exogenous inflammation
  - Inhibits adipogenesis
  - Induces lipolysis
  - Small, “fat free” adipocytes

Antonopoulos A et al, Science Transl Med 2017
Can we “see” these changes in adipocyte content?

Non-inflamed fat

Adipocytes

Inflamed fat

Adipocytes + IL6+TNFα+IFNγ

↑Lipolysis
↓Adipogenesis
↑Oedema

Fat Attenuation and texture

Fat Attenuation and texture

Fat Attenuation

Fat Attenuation and texture

-30HU -190HU

-30HU -190HU
Development of Fat Attenuation Indexing (FAI)

Image reconstruction/engineering exercise

CT attenuation histograms

Biology?

Adipocyte Size
FABP4
CEBPA
PPAR-γ

EpAT

Tertiles of FAI in tissue explants

FAI in vivo (HU)

Conversion of FAI_{explants} to FAI_{in vivo}

EPAT

Low Mid High

P<0.05

FAI in vivo (HU)


FAI in vivo (HU)

-110 -105 -100 -95 -90 -85 -80 -75 -70 -65 -60 -55 -50 -45 -40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110

Antonopoulos et al. Science Translational Medicine 2017
What does Fat Attenuation Index describe?

- Adipocyte size
- Adipogenesis
- Tissue inflammation

How is epicardial fat related with coronary inflammation?


New approaches in detecting vascular inflammation

Classic approach (outside to inside signals)

Paracrine signals

Antonopoulos A et al; Obes Rev. 2009;10:269-79
Margaritis et al; Circulation 2013;127:2209-21

New approach (inside to outside signals)

PVAT "Sensing"

PPARγ is the “hub” for PVAT’s sensing of vascular signals

Antonopoulos et al; Arterioscler Thromb Vasc Biol. 2014;34:2151-2159

Antonopoulos et al; Diabetes 2015; 112:213-222