Multi-modality Molecular and Cellular Imaging to Predict

Abdominal Aortic Disease Progression: Towards Personalised

Assessment of Disease

Rachael Forsythe
University of Edinburgh & Royal Infirmary of Edinburgh
UK
Disclosure

Speaker name:

Rachael Forsythe

☑️ I do not have any potential conflict of interest
The Hubble Space Telescope
Molecular & Cellular Imaging:
The Hubble Space Telescope of Cardiovascular Research
Natural History of AAA Disease

INITIATION  EXPANSION  RUPTURE (REPAIR)
Scope of the Problem

“Staccato” growth

Rupture at small diameters

Complications & reintervention

Kurvers et al, JACC 2004

Evolving management

Cost & cost-effectiveness

Abdominal aortic aneurysm: diagnosis and management

NICE guideline
Draft for consultation, May 2018
Should my patient undergo aneurysm repair?

If so, when?

And by which method?

Is there any treatment that I can give to reduce their risk?
“Humans as the model organism”

**TARGET**

Biological Target-specific Imaging with adequate spatial resolution for imaging

**PROBE**

Safe & available

**MODALITY**

**AGENT**
Our Research Studies

MACROPHAGE-MEDIATED INFLAMMATION → USPIO MRI

MICRO-CALCIFICATION → \(^{18}\text{F-NaF}\) PET-CT
Ultrasmall superparamagnetic particles of iron oxide (USPIO)

- Engulfed by macrophages
- MRI signal change correlates with macrophage density
- USPIO demonstrated in rupture prone rather than stable carotid plaque

Morishige et al. (2010)
Tang et al. (2009)
USPIO Reduces MRI Signal Decay

Pre-USPIO
Low USPIO uptake
High USPIO uptake

Reductions in T2* value identify USPIO accumulation
USPIO ‘Colour Maps’

USPIO negative
Periluminal USPIO uptake only, which is not thought to represent true inflammation

USPIO positive
Area of mural USPIO enhancement of >10 contiguous voxels at the aneurysm wall, representing inflammation
MRI in AAA to Predict Rupture or Surgery
The MA³RS Study

- Patients identified from surveillance and screening at 3 study sites
- 350 patients with AAA >40mm on US
- Baseline Assessment (2 days)
  - DAY 1
    - MRI Pre
    - US
  - DAY 2
    - MRI Post 24 h
    - CT Aortogram
- 6 monthly US assessments
- Final 2 year assessments
  - US
  - CT Aortogram

Edinburgh Imaging
www.ed.ac.uk/edinburgh-imaging
MA³RS Study Results

56% USPIO NEGATIVE

43% USPIO POSITIVE

*1% indeterminate

Current Smoking (p=0.0003)

AAA diameter (p=0.0002)

CIA Aneurysm (p=0.0289)

342 Participants
End Points

During follow up: 1005±280 days

- Rupture: 5% (17)
- Repair: 37% (126)
- Death: 14% (48)
Primary Endpoint: Aneurysm Rupture or Repair

<table>
<thead>
<tr>
<th>Primary endpoint: Rupture &amp; Repair</th>
<th>36% (68)</th>
<th>47% (69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPIO -ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USPIO +ve</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*95% CI: 1.1-22.2, p=0.0308
Secondary Endpoint: Aneurysm Growth

**USPIO -ve**

**USPIO +ve**

<table>
<thead>
<tr>
<th>Aneurysm growth rate (mm/year)</th>
<th>2.5±2.4</th>
<th>3.1±2.5</th>
</tr>
</thead>
</table>

*95% CI: 0.2-1.2 mm/yr, p=0.0424*
The Predictive Value of USPIO MRI in AAA

- USPIO enhancement predicts AAA rupture / repair and AAA growth

- BUT it is not an independent predictor
  - C-statistic 0.7924-0.7926
  - Unconditional net reclassification -13.5%; 95% CI -36.4 to 9.3

- It highlights a central role for cellular inflammation

- Interesting size observation:
  - If <50mm - double the rate of repair / rupture if USPIO+ve, no effect on mortality
  - If >50mm - double the rate of mortality if USPIO+ve, no effect on rupture / repair
18F-NaF PET-CT to Investigate Microcalcification

**CALCIUM DYSTROPHY**

- Apoptosis
- Necrotic inflammation
- Micronodules of calcification
- Dense calcification

**PET-CT**

**CT**
18F-NaF PET-CT in Vascular Calcification

**CORONARY**

Joshi et al, Lancet 2014

**CAROTID**

Vesey et al, Circ Cardiovasc Imaging 2017

**AORTIC VALVE**

Dweck et al, Circ Cardiovasc Imaging 2014
The SoFIA$^3$ Study

Sodium Fluoride Imaging ($^{18}$F-NaF PET-CT) in Abdominal Aortic Aneurysms

SoFIA³ Study: Methods

Control Group

Normal aorta ≤ 30mm

Observational Cohort

Asymptomatic AAA ≥ 40mm

CT Aortogram

¹⁸F-NaF PET-CT

Calcium scoring CT

No further follow up

USS every 6 months
‘Most-Diseased Segment’ Analysis

Tawakol et al, JACC 2013
Results: Case-Control & ex-vivo Studies
Results: Aneurysm Growth
Tertiles of $^{18}$F-NaF Uptake in the MDS

72 Participants


18 months of follow up
Results: AAA Rupture or Repair

Tertiles of $^{18}$F-NaF Uptake in the MDS

Repair or rupture

Repair alone

## Multivariable Analysis: $^{18}$F-NaF Uptake

<table>
<thead>
<tr>
<th></th>
<th>Increase in Expansion (mm/year; 95% CI)</th>
<th>P-value</th>
<th>Hazards Ratio (95% CI) for AAA events</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.365 (0.34, 1.90)</td>
<td>0.006</td>
<td>2.16 (1.03, 4.51)</td>
<td>0.041</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.375 (0.39, 1.91)</td>
<td>0.004</td>
<td>2.26 (1.97, 4.76)</td>
<td>0.033</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.259 (0.029, 1.56)</td>
<td>0.042</td>
<td>2.49 (1.07, 5.78)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Model 1: unadjusted  
Model 2: adjusted for age, sex  
Model 3: adjusted for age, sex, body mass index, systolic blood pressure, smoking, aneurysm diameter
The Predictive Value of $^{18}$F-NaF PET-CT in AAA

- This is the largest clinical PET-CT study in AAA

- Increased $^{18}$F-NaF uptake occurs in aneurysmal aortae vs controls

- Uptake is associated with histological markers of cell death / early calcification

- $^{18}$F-NaF uptake on PET-CT is an independent predictor of AAA growth, rupture or repair

This is the first imaging biomarker to independently predict disease progression in a clinical study
Other Targets and PET Tracers

Angiogenesis
- $^{18}$F-NOTA-RGDfK
- $^{18}$F-NS14490

Fibrosis
- $^{18}$F-NOTA-RGDfK

Inflammation
- $^{11}$C-PK11195
- $^{18}$F-NS14490
- $^{68}$Ga DOTATATE (FDA)

Thrombus
- ENC2015
- GP1
Current and Future $^{18}$F-NaF Studies in Edinburgh

- **SoFIA³-PREDICT**
  - Multi-centre efficacy study: can $^{18}$F-NaF PET-CT be used for personalised assessment of AAA disease?
  - EVERLAST – predicting EVAR durability

- **FAAAST**
  - $^{18}$F-NaF PET-CT in acute aortic syndromes: can we predict clinical progression of TBAD, IMH and PAU?

- **Blue SAFFIRE**
  - $^{18}$F-NaF PET-CT in carotid artery disease: does $^{18}$F-NaF predict future stroke in patients with carotid atherosclerosis?
    - + coronary, aortic valve, drug trial endpoints etc etc...
    - + other tracers
Translational Value of Imaging Biomarkers

Personalised evaluation of future disease potential

1. Management according to biological risk in addition to clinical features

2. Decision-making in medically high risk patients

3. Person-specific intervention thresholds

Serial non-invasive assessments of the vasculature

Evaluation of new drug therapies – surrogate endpoint
Moving Towards Personalised Medicine

DEEP PHENOTYPING → PRECISION HEALTHCARE
Professor David Newby
And
University of Edinburgh:
Dr MR Dweck, Dr JMJ Robson, Dr AT Vesey, Dr OMB McBride, Dr J Kaczynski, Dr ASV Shah, Dr A Tavares, Dr S Semple, Dr C Gray, Prof EJR van Beek, Dr A Fletcher, Dr C Lucatelli, Dr A Marin, Mr P Burns, Prof OJ Garden, Dr T MacGillivray, Dr C Wang, Miss A Cooper, Dr YG Koutrakli, Dr W Ho, Miss L Fraser, Miss H Cuthbert, Prof P Hoskins, Dr B Doyle, Dr N Conlisk, Dr L Milne, Dr F Strachan, Dr F Wee, Dr K Oatey, Dr C Graham, Prof G Murray, Mr G Milne, Dr M Bucukoglu, Dr K Goodman
Royal Infirmary of Edinburgh:
Prof W Wallace, Dr RTA Chalmers, Mr N Mitchard, Dr G Weir, Dr G McKillop
Western Infirmary, Glasgow:
Dr W Stuart, Prof C Berry, Dr G Roditi, Miss L Murdoch
Forth Valley Royal Hospital:
Dr R Holdsworth, Dr E Scott

Acknowledgements