ΣΤΑΘΕΡΗ ΣΤΕΦΑΝΙΑΙΑ ΝΟΣΟΣ

Ανατομική ή λειτουργική μελέτη ως πρώτη επιλογή στην διαγνώση της στεφανιαίας νόσου.

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Διευθυντής Καρδ/κης Κλινικής , Ευρωκλινική Αθηνών

Disclosure : No conflict of interest to declare
FUNCTIONAL NON-INVASIVE IMAGING

Access to coronary anatomy: shift in paradigm

- **STEMI**
- **Non STEMI**
- **Acute coronary syndrome**
- ** Stable angina**
- **High risk subject**

**Invasive coronary angiography**

- High threshold functional evaluation = gatekeeper

**“Non invasive” coronary angiography**

- Low threshold functional evaluation guides therapy
Disagreement Anatomy and Function

Stenosis severity (MSCT) vs. Hemodynamic significance (FFR)

G 0 = no plaque; G 1 = <50%; G 2 = ≥50% D stenosis

One way ANOVA:
Tukey-Kramer multiple comparison

Sarno et al. JACC CV Interventions 2009
Stenting of lesions with an FFR 0.80 in the current era may actually be detrimental.
Impact of functional significance of stenosis in benefit of PCI: ISCHEMIA
Functional Testing Fails To Diagnose The Anatomic Extent Of CAD
Does a stenotic lesion means necessarily ischemic heart disease?  *(direct angiographic approach)*

The absence of ischemia precludes stenotic lesions of the coronary arteries  *(ischemia guided)*
Whether an individual does or does not have CAD it too simplistic and not enough....

Need to know what are the risks

Paradigm shift

From a focus on test performance to a focus on clinical end points to better determine the role of non invasive testing in the evaluation of CAD symptoms
The “COURAGE” Trial → Obstructive CAD

Removing obstructive CAD does not impact on prognosis. May exclude obstructive CAD but not predict “ischemia”

- Optimization of medical therapy alone without PCI is sufficient for initial treatment of patients SCAD.
- Less than half of >50% stenosis at CTA are associated with perfusion defect.
- Outstanding NPV but mediocre positive predictive values (29%-44%)

Boden et al. NEJM 2007
The “COURAGE” Trial → Ischemia

Removing ischemia (no matter how!) improves prognosis

COURAGE Trial: Nuclear Substudy (*Circulation* 2008)
Conclusions
Among individuals without known CAD, nonobstructive and obstructive CAD by CCTA are associated with higher rates of mortality, with risk profiles differing for age and sex. Importantly, absence of CAD is associated with a very favorable prognosis.
Patients were more likely to undergo cardiac catheterization after computed tomography angiography than after SPECT or PET after normal/nonobstructive and mildly abnormal study findings.

Post-imaging use of cardiac catheterization and medical therapy increase in proportion to the degree of abnormal study results, the frequency of catheterization.
# PACIFIC vs EVINCI

<table>
<thead>
<tr>
<th></th>
<th>PACIFIC</th>
<th>EVINCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>High Risk</td>
<td>Low Risk</td>
</tr>
<tr>
<td></td>
<td>Hemodynamically Significant CAD (44%)</td>
<td>Obstructive CAD (29%)</td>
</tr>
<tr>
<td><strong>Diagnostic End-Point</strong></td>
<td><strong>Mainly Functional</strong></td>
<td><strong>Mainly Anatomical</strong></td>
</tr>
<tr>
<td>at ICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local Imaging</strong></td>
<td>-</td>
<td>Better performance of CCTA than Stress Imaging</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Core Labs Imaging</strong></td>
<td>Similar performance of CCTA and SPECT</td>
<td>Similar performance of CCTA and SPECT/PET</td>
</tr>
<tr>
<td><strong>Analysis</strong></td>
<td></td>
<td>(in good quality exams)</td>
</tr>
<tr>
<td><strong>Quantitative PET</strong></td>
<td>Superior performance of quantitative PET (vs all other imaging)</td>
<td>-</td>
</tr>
</tbody>
</table>
1. CTA is the most accurate imaging modality for diagnosing the Primary End-Point.
2. Combination of CTA with perfusion nuclear imaging improves diagnostic accuracy of the non-invasive stress perfusion imaging alone.
3. Combinations of CTA with nuclear stress imaging were more accurate than combinations of CTA with non-nuclear stress imaging.

Limitations

- Frequent suboptimal imaging protocol: Sub-maximal stress was reported in 41% of Echo examinations and 23% of patients remained on medical therapy.
- Lack of quantitative measurements: MBF by PET, perfusion by CMR and CFR by TTE-Doppler were not included in the main analysis.
- Population: low prevalence of High Risk CAD
- Primary End-Point: did not include criteria for High Risk CAD

**EVINCI Study** demonstrated that, in patients with suspected CAD and intermediate-low probability of disease:
Prospective comparison of Cardiac PET/CT, SPECT/CT perfusion imaging and CT coronary angiography with Invasive Coronary angiography

PACIFIC Results | Lancet 2017

Quantitative PET has a Better performance than SPECT or CCTA
EVINCI/PACIFIC Studies: Take Home Messages

- In populations with stable chest pain symptoms and lower prevalence of CAD, anatomical imaging by CTCA is an effective first line diagnostic examination with at least similar performance than functional perfusion imaging.

- In populations with stable chest pain symptoms and higher prevalence of CAD, functional imaging by quantitative PET is the most accurate approach to detect “high risk” hemodynamically significant disease.

- Diagnostic performance of non invasive imaging critically depends on the Pre-Test Probability of “high risk” CAD in the individual patient as well as on the quality of the test and of its interpretation.

- Efforts are needed to improve current predictive models of “High Risk” CAD prior to imaging, to achieve better imaging performance and reduce risks.
<table>
<thead>
<tr>
<th></th>
<th>SCOT-HEART Trial</th>
<th>PROMISE Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>UK</td>
<td>North America</td>
</tr>
<tr>
<td>Sample Size</td>
<td>4,146</td>
<td>10,003</td>
</tr>
<tr>
<td>Comparators</td>
<td>CCTA + Standard of Care versus Standard of Care</td>
<td>CCTA versus Functional Stress test</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Open-Label</td>
<td>Open-Label</td>
</tr>
<tr>
<td>Recruiting Centres</td>
<td>12</td>
<td>193</td>
</tr>
<tr>
<td>Length of Follow Up</td>
<td>20 months</td>
<td>25 months</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Certainty of diagnosis of angina due to coronary heart disease</td>
<td>Death, non-fatal MI, hospitalization for unstable angina, major procedural complications (anaphylaxis, bleeding and renal failure)</td>
</tr>
</tbody>
</table>

*Lancet* 2015;385:2383-2391  
Short-term Effects of CTCA
Clinical Outcomes

The SCOT-HEART Trial
CHD death or non-fatal myocardial infarction
HR 0.62 (95% CI, 0.38-1.01), P=0.053
Excluding the 50-day treatment delay

JACC 2016;67:1759-1768

Anatomical vs. functional testing
Hazard ratio, 1.04 (95% CI, 0.83–1.29)
P=0.75

The promise Trial
Death or non-fatal myocardial infarction
HR 0.66 (95% CI, 0.44-1.00), P=0.049

Anatomical testing 3.3%
Functional testing 3.0%

N Engl J Med 2015;
Short-term Effects of CTCA
Invasive Coronary Angiography & Coronary Revascularisation

The SCOT-HEART Trial

The promise Trial

CT Coronary Angiography
Standard of Care

HR 1.20 (95% CI, 0.99-1.45), P=0.06

Frequency @ 90 Days (%)

Invasive Coronary Angiography
Coronary Revascularisation

P<0.001
8.1
3.2

P<0.001
12.2
6.2

Number at risk
CTCA 2073
Standard care 2073
1413
1413
733
733
770
770

Lancet 2015;385:2383-2391
Η ταφή του κομητα Οργκαθ
Η αμφισβήτηση
Μουσείο Τολέδου

Δομίνικος Θεοτοκόπουλος (1541-1614)
Which First-Line Imaging Modality Is Better?

ESC GL prefer STRESS Imaging!
International guidelines recommendations

AHA
- FUNCTIONAL evaluation of myocardial ischemia (class IA) with provisional CTA for those with inconclusive stress test or those unable to exercise

ESC
- FUNCTIONAL evaluation of myocardial ischemia with intermediate probability (class IB) and CTA as an alternative for those with inconclusive stress test or those unable to exercise (class IIa C)

- CTA is recommended for patients in the lower range of intermediate pretest probability after non-conclusive exercise ECG or stress imaging (class IIa C)
Future Considerations

How to improve the detection of coronary artery disease functionally significant with new emerging techniques?

1. Stress Cardiac Magnetic Resonance (CMR)
2. Fractional Flow Reserve CT (FFRct)
3. Hybrid Imaging
CMR stress T1 mapping accurately detected and differentiated between obstructive epicardial CAD and microvascular dysfunction, without contrast agents or radiation.
CMR Stress T1 mapping for the assessment of epicardial and microvascular CAD

- Stress ΔT1 > 4.0%: Likely no obstructive epicardial CAD or microvascular dysfunction
- Stress ΔT1 1.5 - 4.0%: Likely microvascular dysfunction
- Stress ΔT1 < 1.5%: Likely obstructive epicardial CAD

FFR = fractional flow reserve
IMR = index of microvascular resistance
How to increase to cost/effectiveness of the gatekeeper to ICA

Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFRct: outcome and resource impacts study

- 61% patients in FFRct group: ICA cancelled
- Rate of ICA without obstructive CAD
  - By QCA: 73.3% usual care; 12.4% FFR_{CT}
  - By site-read angiographic
  - data: 56.7% usual care; 9.3% FFR_{CT}

Douglas P, Pontone G et al EHJ 2015 (PLATFORM Primary Endpoint)
CCTA, ICA and $\text{FFR}_{\text{CT}}$ vs FFR

Norgaard et al. JACC 2014
CAD 10 years from now
My predictions and how to get yourself ready

Eugene Braunwald, MD
Brigham and Women’s Hospital
Harvard Medical School

August 27, 2018
PET-MR combine the high-spatial resolution morphological and functional assessment afforded by the ability of PET for quantification of metabolism, diffusion, and inflammation from a single scan."
Future of Atherosclerotic Evaluation
Integrative Imaging of Biological Systems

Multi-Modality Imaging

SPECT PET/CT and PET /MR

- take a systems-wide view of biological processes.
- Simultaneously measure:
  - arterial inflammation
  - myocardial function & biological processes
  - adipose tissue volume and inflammation
  - hematopoietic activity
  - brain activity
  - many other targets
Κλινική Έρευνα

Υβριδική Απεικόνιση στη Στεφανιαία Νόσο

Ιωάννης Βασιλειάδης, Ευσταθίος Δεσποτόπουλος, Δολαδίου Ζαφειράκης

1Καρδιολογικό Τμήμα, Ευρωπαϊκή Αθηνών, 2Διαγνωστικό Κέντρο Ευρωμέδεα-Ευρώπη
PET/MR Imaging of Atherosclerosis

FDG-PET

<table>
<thead>
<tr>
<th></th>
<th>SUV\textsubscript{mean} (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESSION</td>
<td>0.792 (±0.053)</td>
<td>0.681</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.774 (±0.052)</td>
<td></td>
</tr>
<tr>
<td>REGRESSION</td>
<td>0.834 (±0.092)</td>
<td>0.015</td>
</tr>
<tr>
<td>6 Months</td>
<td>0.511 (±0.044)</td>
<td></td>
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</tbody>
</table>
18F-Fluoride CT Coronary Angiography

Identifying Plaque Rupture

Joshi et al. Lancet 2014;383:705-713
Future directions

**PRE18FFIR**

Prediction of Recurrent Events with 18F-Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction

PRE18FFIR - Heart attacks are caused by a blood clot which stops blood flowing to part of the heart muscle. The blood clots form in areas of blood vessels (arteries) that are damaged (inflamed) by a build-up of small fatty lumps (plaques). The fatty lumps can break and cause blood to stick to the wall of the blood vessel. It appears that this process can also occur without causing any symptoms and may put patients at increased risk of heart attacks in the future. It has also been shown that patients with a heart attack often have more than one damaged plaque. Previous research has shown a specialised scanning technique known as PET (positron emission tomography) using a tracer called 18F-sodium fluoride can identify these damaged plaques in patients with a recent heart attack. The aim of this study is to confirm whether this tracer can be used identify patients who are at risk of having a heart attack or other heart problems in the future.

Chief Investigator: Professor David Newby

Number and location of participating sites (by region/ country): Multicentre study with 6 UK centres based in Aberdeen, Edinburgh, Manchester, Oxford, Leeds and Birmingham.

EudraCT number: 2014-004021-41

The Clinical Trials gov number is NCT02278211.

Funder: Wellcome Trust

Start and End date of grant award: Jan 2015 – Dec 2019
$^{68}$Ga-DOTATATE

FDG

$^{68}$Ga-DOTATATE
Which Imaging Strategy is more cost-effective to guide treatment and improve prognosis? Still UNDEFINED!!!
### Important criteria that might influence choice of cardiovascular test costs

#### 2012 Medicare Fee Schedule For Selected Cardiovascular Tests

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Physician Payment</th>
<th>Non-Facility Payment</th>
<th>Facility Payment</th>
<th>Total Non-Facility</th>
<th>Total Facility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Technical)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Hospital Owned</td>
<td>Hospital Owned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex ECG</td>
<td>$37</td>
<td>$51</td>
<td>$178</td>
<td>$89</td>
<td>$215</td>
</tr>
<tr>
<td>Stress Echo</td>
<td>$87</td>
<td>$155</td>
<td>$581</td>
<td>$243</td>
<td>$668</td>
</tr>
<tr>
<td>Stress Nuclear</td>
<td>$114</td>
<td>$478*</td>
<td>$850</td>
<td>$592*</td>
<td>$964</td>
</tr>
<tr>
<td>Stress MR</td>
<td>$186</td>
<td>-</td>
<td>$575*</td>
<td>$713</td>
<td>$761*</td>
</tr>
<tr>
<td>CT Angio</td>
<td>$114</td>
<td>$262*</td>
<td>$262</td>
<td>$376*</td>
<td>$376</td>
</tr>
<tr>
<td>Diagnostic Cath</td>
<td>$316</td>
<td>$782</td>
<td>$2,720</td>
<td>$1098</td>
<td>$3,036</td>
</tr>
</tbody>
</table>

*services include a contrast agent or radionuclide – paid at cost to practice and not factored into number.

Cath = Catheterization; CT Angio, coronary computed tomography angiography; CV, cardiovascular; ECG, electrocardiogram; Echo, echocardiography, MR, magnetic resonance.

Greek reality: EOPYY Cost – Physician payment in private sector

Wall MJ et al, JACC 2014
Συμπεράσματα

• Η αλλαγή στο τρόπο σκέψης (Paradigm shift) θέτει σε εκκίνηση μια νέα διαδικασία επιλογής ανατομικής η λειτουργικής δοκιμασίας στη διερεύνηση συμπτωματολογίας ύποπτης στεφανιαίας νόσου, στοχεύοντας περισσότερο στην κλινική έκβαση και λιγότερο στην διαγνωστική πληροφορία.

• Η αξονική στεφανιογραφία (CTA), ως πρώτη επιλογή μπορεί να εφαρμοστεί σε συμπτωματικούς με χαμηλή πιθανότητα ΣΝ ή σε ασυμπτωματικούς με προδιαθεσικούς παράγοντες, ενώ ο ρόλος των λειτουργικών δοκιμασιών με SPECT ή ECHO εκτρέπεται από ελεγκτικό μηχανισμό (gatekeeper) σε καθοδηγητικό ρόλο επιλογής επαναιμάτωσης ή συντηρητικής θεραπείας.

• Ο υπολογισμός της pre-test πιθανότητας ΣΝ (PTP) αποτελεί κλειδί για την επακόλουθη διαγνωστική μέθοδο. Το νέο Consortium PTP Scores της ESC εμφανίζει μεγαλύτερη ακρίβεια πρόβλεψης ΣΝ συγκρινόμενη με το ιστορικό μοντέλο D.F Score της USA. Σε ασθενείς με χαμηλή προς ενδιάμεση PTP (15-65%) ΣΝ προτιμάται η λειτουργική δοκιμασία, Σε ενδιάμεση προς υψηλή PTP (66-85%) ενδείκνυται ο έλεγχος της ανατομίας με CTA or ICA και σε εξεταζόμενους με χαμηλή PTP (<15%) η CTA μπορεί να έχει αξία.

• Η επιλογή μιας αναίμακτης διαγνωστικής μεθόδου θα πρέπει να λαμβάνει υπόψη διαφόρους παράγοντες όπως τα κριτήρια καταληλότητας, η εμπειρία του διενεργούντος την εξέταση, η υποκειμενικότητα της μεθόδου, η διαθεσιμότητα, το κόστος και η ακτινική επιβάρυνση.

• Συνδυαστική απεικόνιση (Fusion imaging) και FFR_{CT} θα αποτελέσουν το μέλλον της διάγνωσης.
Επαναπροσανατολισμός από το να στοχεύει κανείς στο αποτέλεσμα μιας διαγνωστικής μεθόδου στην ικανότητα πρόβλεψης κλινικών καταληκτικών σημείων της μεθόδου επί ασθενών με συμπτωματολογία στεφανιαίας νόσου
Vascular Calcification
Pathognomonic of Atherosclerosis

Allam et al. JACC Cardiovasc Imaging 2011;4:315-327
Primary Clinical End Point

Excluding the 50-day treatment delay

*Hazard Ratio 0.53
(95% CI, 0.36 to 0.78)
P=0.001

JACC 2016;67:1759-1768

No. at Risk
Standard Care 2073 2033 2008 1994 1572 856
CCTA 2073 2051 2028 2015 1585 872

Follow up (years)

Coronary Heart Disease Death or Non-fatal Myocardial Infarction

Standard Care Alone — CTCA + Standard Care

N Engl J Med 2018; on line
## Primary Clinical End Point

### Subgroups of Interest

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>CCTA Hazard Ratio (95% CI)</th>
<th>Standard Care Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>1383</td>
<td>0.98 (0.92, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>0.98 (0.92, 1.05)</td>
<td>0.43 (0.39, 0.47)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>3254</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.01 (0.96, 1.06)</td>
<td>1.02 (0.97, 1.07)</td>
<td>0.62 (0.49, 0.76)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8994</td>
<td>0.99 (0.95, 1.03)</td>
<td>1.00 (0.96, 1.05)</td>
<td>0.99 (0.95, 1.03)</td>
<td>0.53 (0.29, 0.77)</td>
</tr>
<tr>
<td>Male</td>
<td>9368</td>
<td>1.01 (0.97, 1.05)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.01 (0.97, 1.05)</td>
<td>0.72 (0.42, 0.96)</td>
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<tr>
<td>10-Year CV Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 years</td>
<td>1689</td>
<td>0.99 (0.95, 1.03)</td>
<td>1.00 (0.96, 1.05)</td>
<td>0.99 (0.95, 1.03)</td>
<td>0.48 (0.41, 0.55)</td>
</tr>
<tr>
<td>≥15 years</td>
<td>2410</td>
<td>1.02 (0.97, 1.07)</td>
<td>1.01 (0.96, 1.06)</td>
<td>1.02 (0.97, 1.07)</td>
<td>0.21 (0.11, 0.32)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-anginal Pain</td>
<td>1447</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>0.48 (0.19, 0.69)</td>
</tr>
<tr>
<td>Possible Angina</td>
<td>2582</td>
<td>1.01 (0.96, 1.06)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.01 (0.96, 1.06)</td>
<td>0.92 (0.47, 0.98)</td>
</tr>
<tr>
<td>Prior CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>3770</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>0.63 (0.32, 0.92)</td>
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<tr>
<td>Yes</td>
<td>3788</td>
<td>1.01 (0.96, 1.06)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.01 (0.96, 1.06)</td>
<td>0.79 (0.57, 0.99)</td>
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<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>3702</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>1.00 (0.95, 1.05)</td>
<td>0.36 (0.20, 0.58)</td>
</tr>
<tr>
<td>Yes</td>
<td>444</td>
<td>1.01 (0.96, 1.06)</td>
<td>1.01 (0.96, 1.05)</td>
<td>1.01 (0.96, 1.06)</td>
<td>0.80 (0.40, 0.94)</td>
</tr>
</tbody>
</table>

*N Engl J Med* 2018; on line
Prognosis in Stable Coronary Artery Disease

CT Coronary Angiography

Anatomic Testing

Functional Testing

>50% of MIs had non-obstructive disease

>50% of MIs had a normal functional test

CT Coronary Angiography
High-risk Plaque

P value = .01

Ferencik et al. JAMA Cardiol. 2018;3:144-152.
Prognosis in Stable Coronary Artery Disease

CT Coronary Angiography

Anatomic Testing

Functional Testing

>50% of MIs had non-obstructive disease

>50% of MIs had a normal functional test

Gadolinium-Free Cardiac MR Stress T1-Mapping to Distinguish Epicardial From Microvascular Coronary Disease

Alexander Liu, MBBS, Rohan S. Wijesurendra, MB, BCHIR, Joanna M. Liu, MBBS, Andreas Greiser, PhD, Michael Jerosch-Herold, PhD, John C. Forfar, MD, PhD, Keith M. Channon, MD, Stefan K. Piechnik, DSc, PhD, MScEE, Stefan Neubauer, MD, Rajesh K. Kharbanda, MBChB, PhD, Vanessa M. Ferreira, MD, DPhil

JACC 2018;71:957

Stress T1 mapping accurately detected and differentiated between epicardial CAD and microvascular dysfunction, without the need for radiation.
Stress T1 mapping for the assessment of epicardial microvascular CAD

- Stress ΔT1 > 4.0%: Likely no obstructive epicardial CAD or microvascular dysfunction
- Stress ΔT1 1.5 - 4.0%: Likely microvascular dysfunction
- Stress ΔT1 < 1.5%: Likely obstructive epicardial CAD

Obstructive Epicardial CAD
FFR < 0.8
Microvascular Dysfunction
FFR ≥ 0.8
IMR ≥ 25U
Non-Obstructive Coronaries
FFR ≥ 0.8
IMR < 25U

FFR = fractional flow reserve
IMR = index of microvascular resistance
Non Invasive Imaging in Stable IHD
The Need for NEW Comparative Imaging Trials

Exciting advances are occurring faster than evidence can accumulate and are increasing health care costs.

A joint effort by all stakeholders, including cardiologists, radiologists, nuclear imaging scientists, professional societies, policy makers, and industry partners, is required.

The evidence base must be improved in order to evaluate the comparative cost effectiveness of imaging-based decision making on outcomes, quality of life, cost-effectiveness, and downstream resource utilization.

Optimized Test Effectiveness Strategy

- Prognostic Utility
- Symptom Benefit
- Diagnostic Selectivity

Shaw LJ, JACC 2010
Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

CONCLUSIONS

In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years. (Funded by the National Heart, Lung, and Blood Institute; PROMISE ClinicalTrials.gov number, NCT01174550.)
• Patients were more likely to undergo cardiac catheterization after computed tomography angiography than after SPECT or PET after normal/nonobstructive and mildly abnormal study findings.
• Post-imaging use of cardiac catheterization and medical therapy increase in proportion to the degree of abnormal study results, the frequency of catheterization
Limitations of CCT ➔ especially false positive results

Severe calcification (Ca-Score >800)

In-Stent restenosis

Native vessels after CABG

Arrhythmia / High BMI ➔ low SNR
The “COURAGE” Trial → Obstructive CAD
Removing obstructive CAD does not impact on prognosis

Boden et al. NEJM 2007
Competency in Patient Care and Procedural Skills: In stable patients undergoing initial evaluation for suspected CAD, coronary CTA was associated with more frequent use of statins, aspirin, and invasive coronary procedures, and higher costs than functional testing. Patients undergoing coronary CTA faced a lower risk of subsequent MI but a similar risk of all-cause mortality compared with those evaluated by functional tests.

Translational Outlook: Further studies of the downstream consequences of initial noninvasive testing modalities for stable patients with suspected CAD are needed to appreciate the relative value of various diagnostic and management strategies.

CTA benefits

CTA drawbacks
Radiation dose

INVASIVE PROCEDURES

CT

NUCLEAR CARDIAC IMAGING

Annual Background Radiation (U.S.)
Chest X-Ray
Diagnostic Cardiac Catheterization
Percutaneous Coronary Intervention
Cardiac CT, Retrospective ECG-Gating
Cardiac CT, Prospective ECG-Triggering
CT Pulmonary Angiography
CT Thoracoabdominal Aorta
Dual Isotope $^{201}$Tl/$^{99m}$Tc
Rest-Stress $^{99m}$Tc
Rest $^{201}$Tl
Low-Dose $^{99m}$Tc Stress
$^{18}$F-FDG-PET

Effective Dose (mSv)

SCOT- Heart: 4,1 mSv
„Heidelberg“: 2,7 mSv
German CT-Registry: 3,6 mSv

Circulation. 2014; 129: 1341-1345
CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial

SCOT-HEART Investigators* 

Summary

Background The benefit of CT coronary angiography (CTCA) in patients presenting with stable chest pain has not been systematically studied. We aimed to assess the effect of CTCA on the diagnosis, management, and outcome of patients referred to the cardiology clinic with suspected angina due to coronary heart disease.

Methods In this prospective open-label, parallel-group, multicentre trial, we recruited patients aged 18–75 years referred for the assessment of suspected angina due to coronary heart disease from 12 cardiology chest pain clinics across Scotland. We randomly assigned (1:1) participants to standard care plus CTCA or standard care alone. Randomisation was done with a web-based service to ensure allocation concealment. The primary endpoint was certainty of the diagnosis of angina secondary to coronary heart disease at 6 weeks. All analyses were intention-to-treat, and patients were analysed in the group they were allocated to, irrespective of compliance with scanning. This study is registered with ClinicalTrials.gov, number NCT01149590.

Findings Between Nov 18, 2010, and Sept 24, 2014, we randomly assigned 4146 (42%) of 9849 patients who had been referred for assessment of suspected angina due to coronary heart disease. 47% of participants had a baseline clinic diagnosis of coronary heart disease and 36% had angina due to coronary heart disease. At 6 weeks, CTCA reclassified the diagnosis of coronary heart disease in 558 (27%) patients and the diagnosis of angina due to coronary heart disease in 481 (23%) patients (standard care 22% [1%] and 23 [1%]; p=0.0001). Although both the certainty (relative risk [RR] 2.56, 95% CI 2.33–2.79; p=0.0001) and frequency of coronary heart disease increased (1.09, 1.02–1.17; p=0.0172), the certainty increased (1.79, 1.62–1.96; p=0.0001) and frequency seemed to decrease (0.93, 0.85–1.02; p=0.1289) for the diagnosis of angina due to coronary heart disease. This changed planned investigations (15% vs 1%; p=0.0001) and treatments (23% vs 5%; p=0.0001) but did not affect 6-week symptom severity or subsequent admittances to hospital for chest pain. After 1–7 years, CTCA was associated with a 38% reduction in fatal and non-fatal myocardial infarction (26 vs 42, HR 0.62, 95% CI 0.38–1.01; p=0.0527), but this was not significant.

Interpretation In patients with suspected angina due to coronary heart disease, CTCA clarifies the diagnosis, enables targeting of interventions, and might reduce the future risk of myocardial infarction.

Funding The Chief Scientist Office of the Scottish Government Health and Social Care Directorates [CZH/4/588] funded the trial with supplementary awards from Edinburgh and Lothian’s Health Foundation Trust and the Heart Diseases Research Fund.

Published Online
March 15, 2015
https://doi.org/10.1016/S0140-6736(15)60235-4

See Online Comment
http://dx.doi.org/10.1016/S0140-6736(15)64453-9

*Members listed at end of report.
RCT of Anatomic versus Functional Diagnostic Testing for Suspected Coronary Artery Disease

Symptoms suspicious for significant CAD Requiring non-emergent noninvasive testing

1:1 Randomization — 10,000 patients
Stratified by site and intended functional test

Anatomic strategy
- 64+ slice CTA

Functional strategy
- Exercise ECG or exercise imaging
- Pharmacologic stress imaging

Tests read locally; Results immediately available
Subsequent testing/management by site care team, per guidelines

Minimum follow-up 12 months

Douglas P. NEJM 2015; 372:1291
Conclusions

In patients presenting with suspected angina due to coronary heart disease, the addition of computed tomography coronary angiography

- Clarified the diagnosis: 1 in 4
- Increased the diagnosis of CHD but appears to reduce the diagnosis of angina due to CHD
- Altered subsequent investigations: 1 in 6 with more appropriate invasive coronary angiography
- Changed treatments: 1 in 4
- Appears to increase coronary revascularisation and halve fatal and non-fatal myocardial infarction
PET-Magnetic Resonance Imaging
Plaque Rupture and Thrombus Imaging

Axial | 2 Chamber | Short axis

PET-CTCA

MRCA

-F-MRCA

[Images of medical imaging showing different views of the heart and arrows indicating specific areas]
Future directions

PRE18FFIR
Prediction of Recurrent Events with 18F-Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction

PRE18FFIR - Heart attacks are caused by a blood clot which stops blood flowing to part of the heart muscle. The blood clots form in areas of blood vessels (arteries) that are damaged (inflamed) by a build-up of small fatty lumps (plaques). The fatty lumps can break and cause blood to stick to the wall of the blood vessel. It appears that this process can also occur without causing any symptoms and may put patients at increased risk of heart attacks in the future. It has also been shown that patients with a heart attack often have more than one damaged plaque. Previous research has shown a specialised scanning technique known as PET (positron emission tomography) using a tracer called 18F-sodium fluoride can identify these damaged plaques in patients with a recent heart attack. The aim of this study is to confirm whether this tracer can be used to identify patients who are at risk of having a heart attack or other heart problems in the future.

Chief Investigator: Professor David Newby

Number and location of participating sites (by region/ country): Multicentre study with 6 UK centres based in Aberdeen, Edinburgh, Manchester, Oxford, Leeds and Birmingham.

EudraCT number: 2014-004021-41

The Clinical Trials gov number is NCT02278211.

Funder: Wellcome Trust

Start and End date of grant award: Jan 2015 – Dec 2019
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<table>
<thead>
<tr>
<th></th>
<th>SCOT-HEART Trial</th>
<th>PROMISE Trial</th>
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<tbody>
<tr>
<td>Country</td>
<td>UK</td>
<td>North America</td>
</tr>
<tr>
<td>Sample Size</td>
<td>4,146</td>
<td>10,003</td>
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<tr>
<td>Comparators</td>
<td>CCTA + Standard of Care versus Standard of Care</td>
<td>CCTA versus Functional Stress test</td>
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<tr>
<td>Trial Design</td>
<td>Open-Label</td>
<td>Open-Label</td>
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<tr>
<td>Recruiting Centres</td>
<td>12</td>
<td>193</td>
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<tr>
<td>Length of Follow Up</td>
<td>20 months</td>
<td>25 months</td>
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<tr>
<td>Primary Endpoint</td>
<td>Certainty of diagnosis of angina due to coronary heart disease</td>
<td>Death, non-fatal MI, hospitalization for unstable angina, major procedural complications (anaphylaxis, bleeding and renal failure)</td>
</tr>
</tbody>
</table>

*Lancet* 2015;385:2383-2391  
Short-term Effects of CTCA

Clinical Outcomes

The SCOT-HEART Trial

CHD death or non-fatal myocardial infarction
HR 0.62 (95% CI, 0.38-1.01), P=0.053

The promise Trial

Death or non-fatal myocardial infarction
HR 0.66 (95% CI, 0.44-1.00), P=0.049

Lancet 2015;385:2383-2391
Short-term Effects of CTCA

Invasive Coronary Angiography & Coronary Revascularisation

The SCOT-HEART Trial

The promise Trial

CT Coronary Angiography
Standard of Care

HR 1.20 (95% CI, 0.99-1.45), P=0.06

Frequency @ 90 Days (%)

Invasive Coronary Angiography

P<0.001

CTCA

Coronary Revascularisation

P<0.001

8.1
12.2
3.2
6.2

Lancet 2015;385:2383-2391

Invasive Coronary Angiography and Coronary Revascularisation

Hazard ratio 1.00
(95% CI, 0.88 to 1.13)
P = 0.993

Coronary Revascularisation

Hazard Ratio 1.07
(95% CI, 0.91 to 1.27)
P = 0.409

Follow up (years)

No. at Risk
Standard Care
CCTA

Follow up (years)

No. at Risk
Standard Care
CCTA

--- Standard Care Alone --- CTCA + Standard Care

N Engl J Med 2018; on line
Invasive Coronary Angiography and Coronary Revascularisation: Beyond One-Year (Post-hoc Analysis)

**Hazard ratio 0.70**
(95% CI, 0.52 to 0.95)  
P=0.022

**Hazard Ratio 0.59**
(95% CI, 0.38 to 0.90)  
P=0.015

---

- **No. at Risk**
  - Standard Care: 1874, 1439, 1416, 1291, 878
  - CCTA: 1854, 1419, 1405, 1255, 866

---

Follow up (years)

---

**N Engl J Med** 2018; on line
Rationale and design of the PERFECTION (comparison between stress cardiac computed tomography PERfusion versus Fractional flow rEserve measured by Computed Tomography angiography In the evaluation of suspected cOroNary artery disease) prospective study
$^{18}$F-Fluoride uptake indicating myocardial microcalcification

Marchesseau S et al.
J Nucl Cardiol 2017; epub
FFR Measured Noninvasively From Coronary CTA

Plaque Characteristics, CT Angio-FFR and Lesion-specific Ischaemia Added Integrative Information

Prospective International Multicenter Trial

252 patients (407 lesions) with suspected or known CAD (64-row CT) + IC Angio-FFR

CTA

CT-FFR

Functional Evaluation

FFR < 0.80

Stenosis Severity

CAD ≥ 50%

Plaque Characteristics

Gibbons et al. JACC Year in Cardiac Imaging 2013
Current clinical practice

How to improve the detection of coronary artery disease functionally significant with currently available techniques

• Invasive ICR + FFR

• Non-invasive CTA+SPECT
Limitations of CCT ➔ especially false positive results

Severe calcification (Ca-Score >800)

In-Stent restenosis

Native vessels after CABG

Arrhythmia / High BMI ➔ low SNR
Μέχρι πριν λίγο καιρό η γνώση της ανατομίας του στεφανιαίου δικτύου απατούσε την διενέργεια επεμβατικής στεφανιογραφίας και ως εκ τούτου οι ασθενείς που παραπέμπονταν είχαν ενδείξεις σοβαρής μορφής στεφανιαιας νόσου βασιζόμενη σε προγνωστικούς αλγόριθμους και κλινική συμπτωματολογία η ήταν προσεκτικά επιλεγμένοι επί τη βάση της θετικής έκβασης προηγηθείσας λειτουργικής μελέτης η η οποία καθόριζε τη βαρύτητα (gatekeeper) με τη μορφή ανεστραμμένης πυραμίδας. Με της ευρεία κλινική εφαρμογή της αναίμακτης αξονικής στεφανιογραφίας η ουδός αξιολόγησης της βαρύτητας της νόσου χαμήλωσε και άρχισε να περιλαμβάνει και ελαφρότερες μορφές νόσου η και ασυμπτωματικούς χωρίς να έχει προηγηθεί λειτουργική δοκιμασία. Η μορφή της αξιολόγησης άλλαξε και μετατράπηκε σε τραπεζοειδές λήγη του συμπτωματικού αριθμού παραπεμπόμενων για αξονική στεφανιογραφία δημιουργώντας μια μεταστροφή στην αντίληψη (paradigm shift) για τη χρήση των λειτουργικών δοκιμασιών από ήθομό έλεγχου σε καθοδηγητικό εργαλείο για την επιλογή επεμβατικής η συντηρητικής φαρμακευτικής θεραπείας.