University of Glasgow | Institute of Cardiovascular & Medical Sciences

British Heart Foundation

Angina with no obstructive CAD: new directions in diagnosis and management

Prof. Colin Berry

Golden Jubilee National Hospital

University of Glasgow, UK.

COVADIS Steering Committee,

Barcelona, 30 August 2017

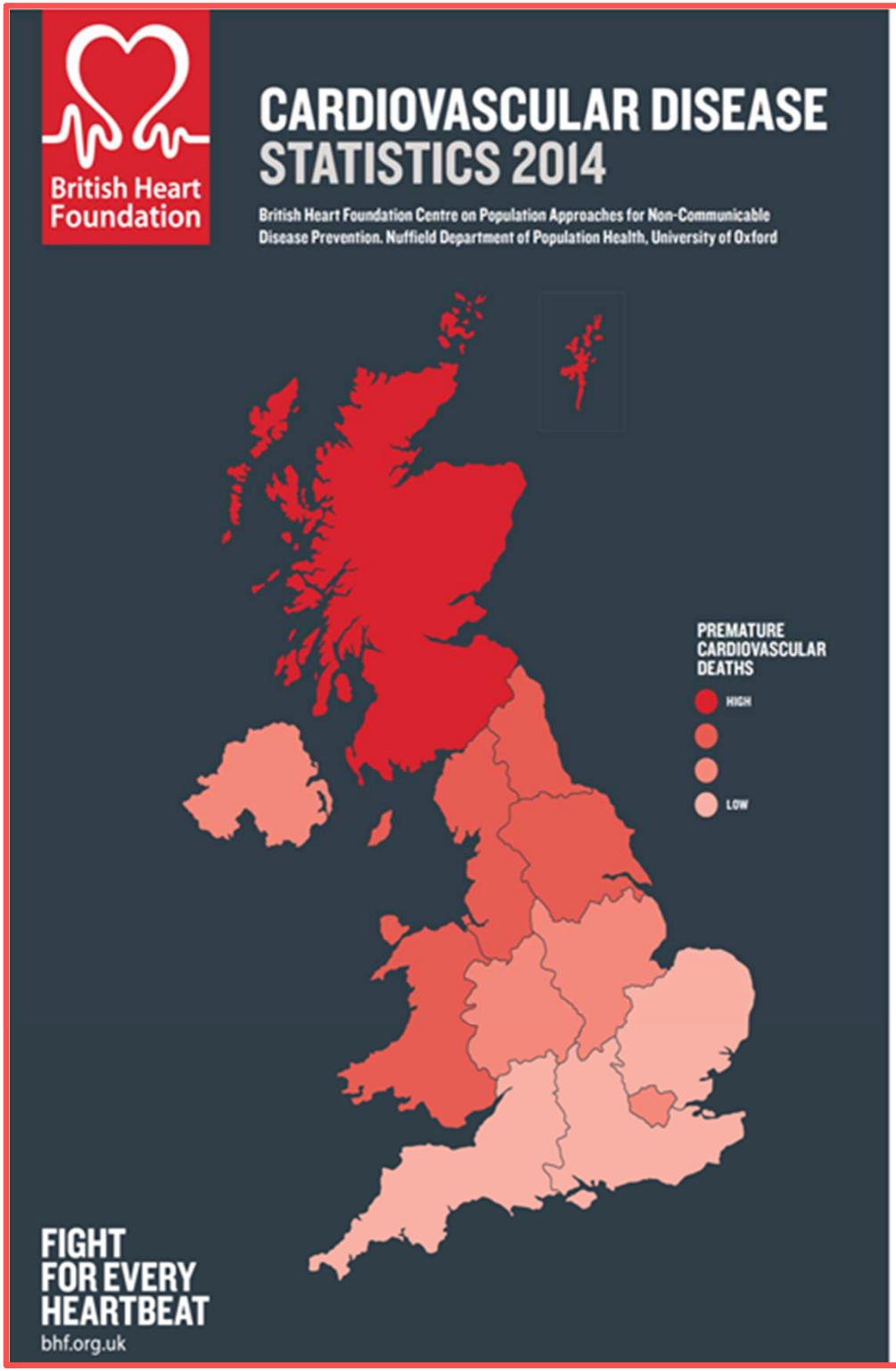
Introduction

Thank you for the invitation.

Acknowledgement - COVADIS Steering Committee members & their seminal research.

Vision

Close the gap in evidence for coronary function tests by undertaking randomised controlled trials in patients with chest pain but no obstructive CAD.



Chest pain clinic attendances

650,000 – 1.3 million

Angina: 2013/2014

In-patient episodes

Men - 71,435

Women - 47,653

Angina prevalence, UK

3.9% men, 2.5% women

3.2% overall, 53 million

>2 million people with angina

>1 in 3, microvascular disease = 600,000 +

Angina drug prescriptions

55,051 (15% of all, 370,000)

Angiograms (2014)

247,363

NHS CHD costs - £954 million

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NHS SCOTLAND

British Heart Foundation

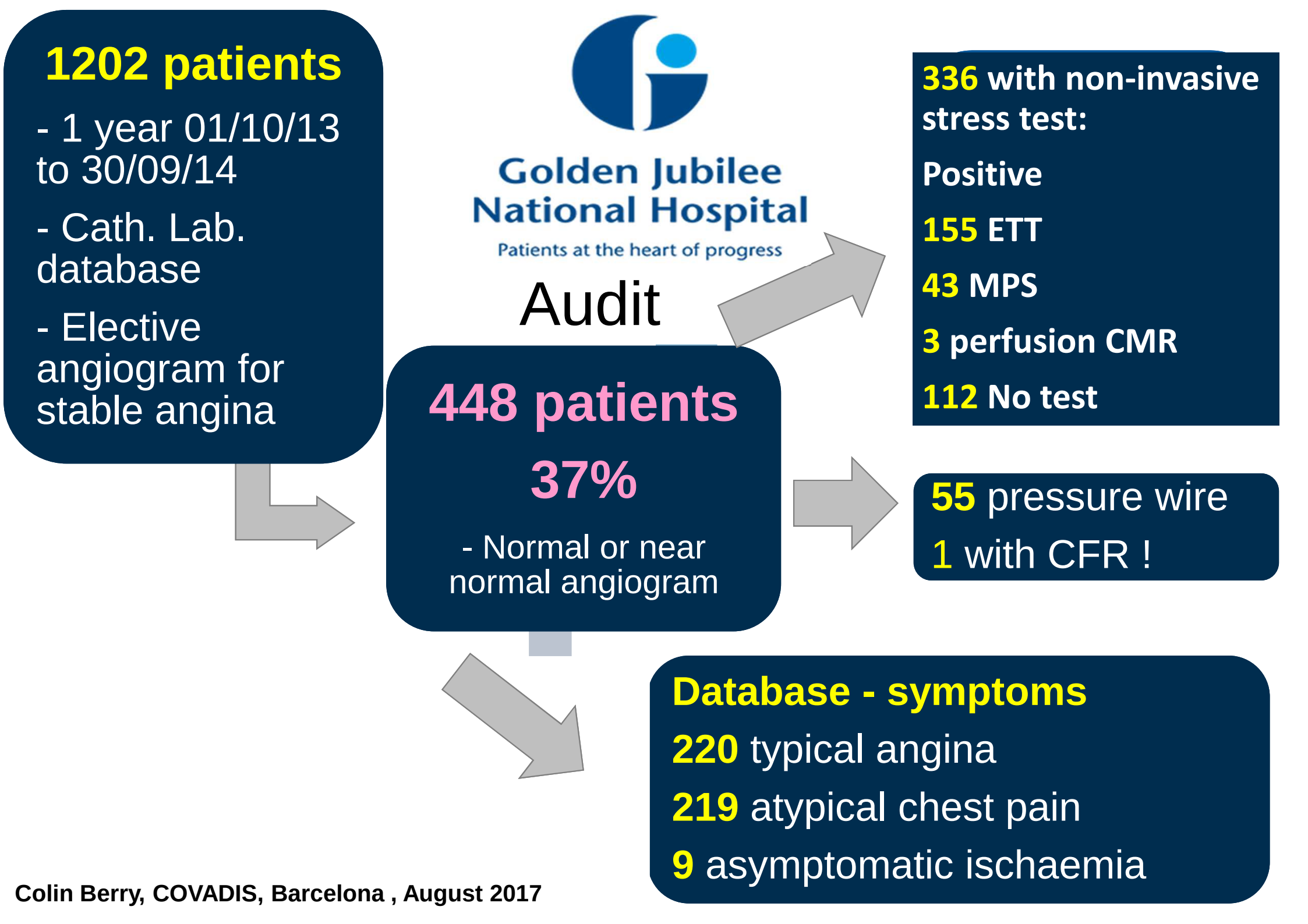
Golden Jubilee National Hospital, Glasgow

Largest cardiothoracic centre in UK

770 STEMI, 2600 NSTEMI, 1200 elective angiograms, pa

National Services for heart & lung disease

Electronic case record linkage for life-long follow-up



Colin Berry, COVADIS, Barcelona , August 2017

Visit to Dr Bill and Francis Fulton

Braemar, Scotland
July 17th, 2010

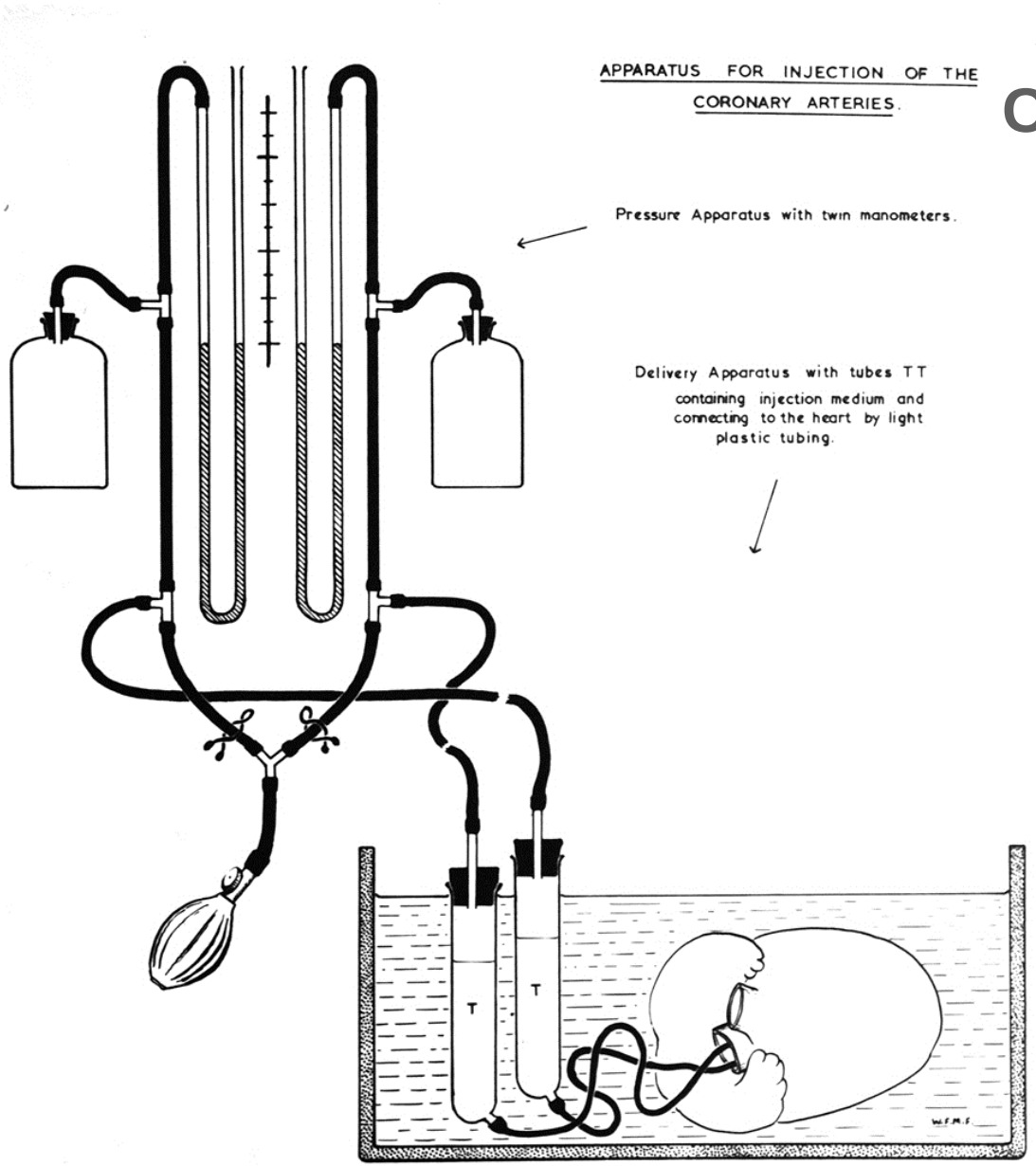
Colin Berry, COVADIS, Barcelona , August 2017

William and Francis Fulton, Braemar, Scotland, July 2010

William Fulton, MD

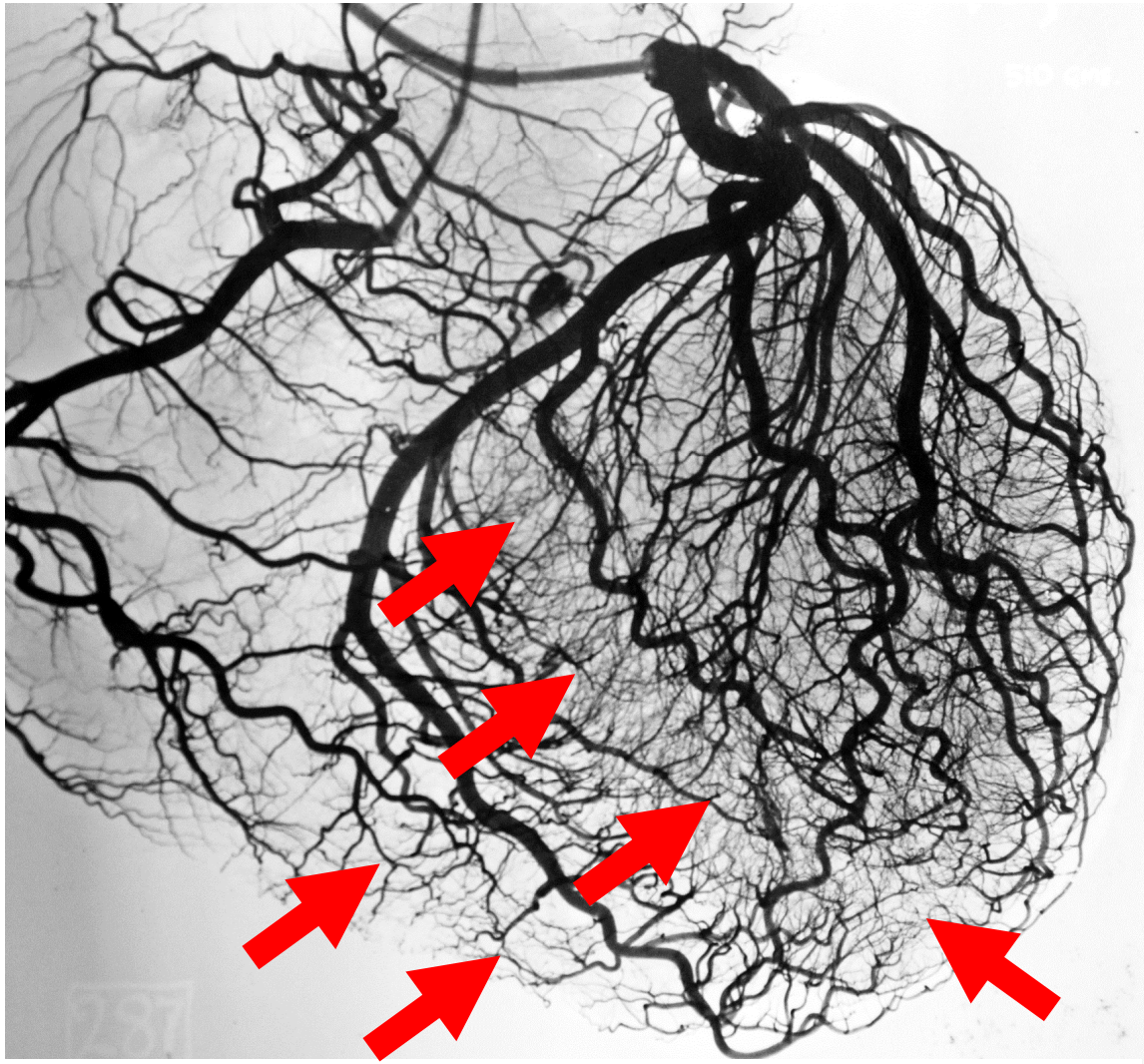
William Fulton MD, University of Glasgow. July 2010

Intact perfused human heart



Reproduced with permission William Fulton .MD Thesis, 1963.

3D stereo-arteriography resolves: Collateral connections vs. 2D overlap

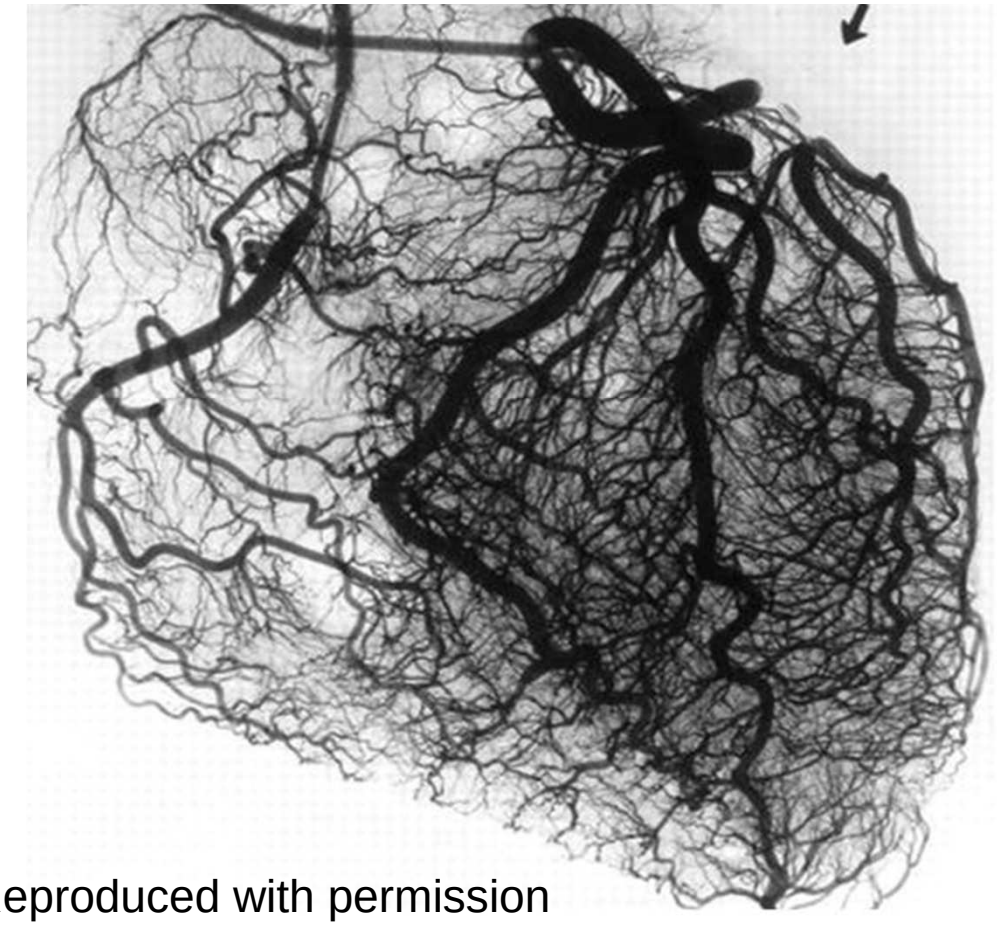


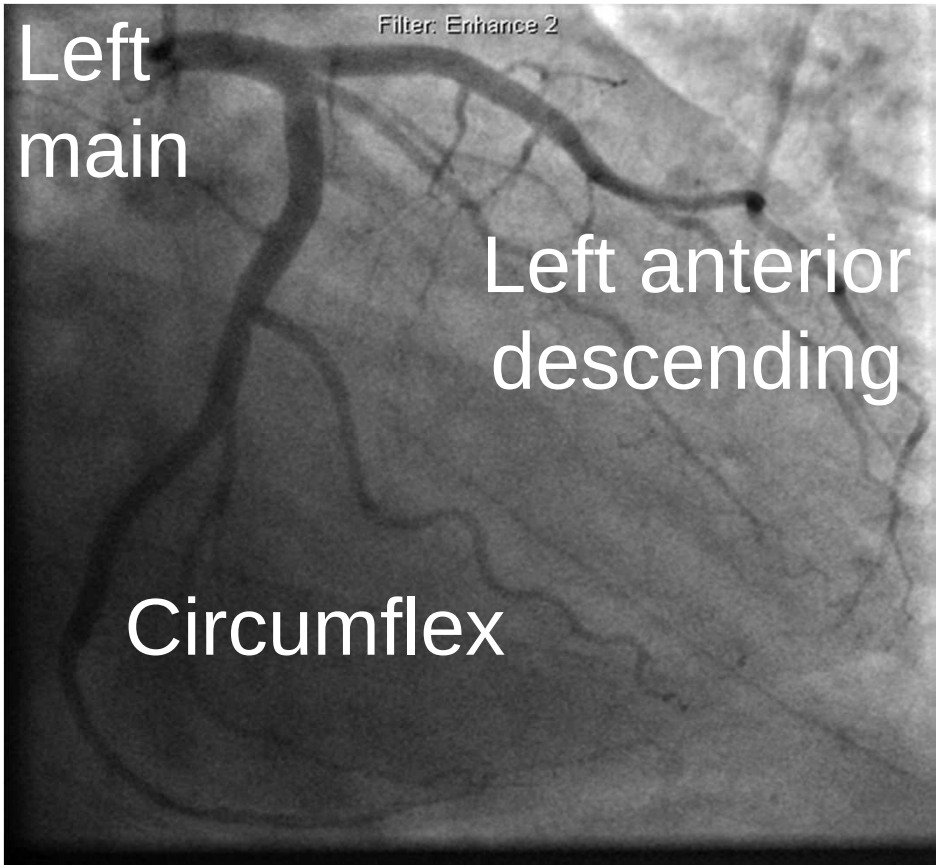
Adult, 'normal' coronary arteries

The human coronary microcirculation

- Stereo-arteriogram
- Coronary angiogram

30 µm **Resolution** **300 µm +**





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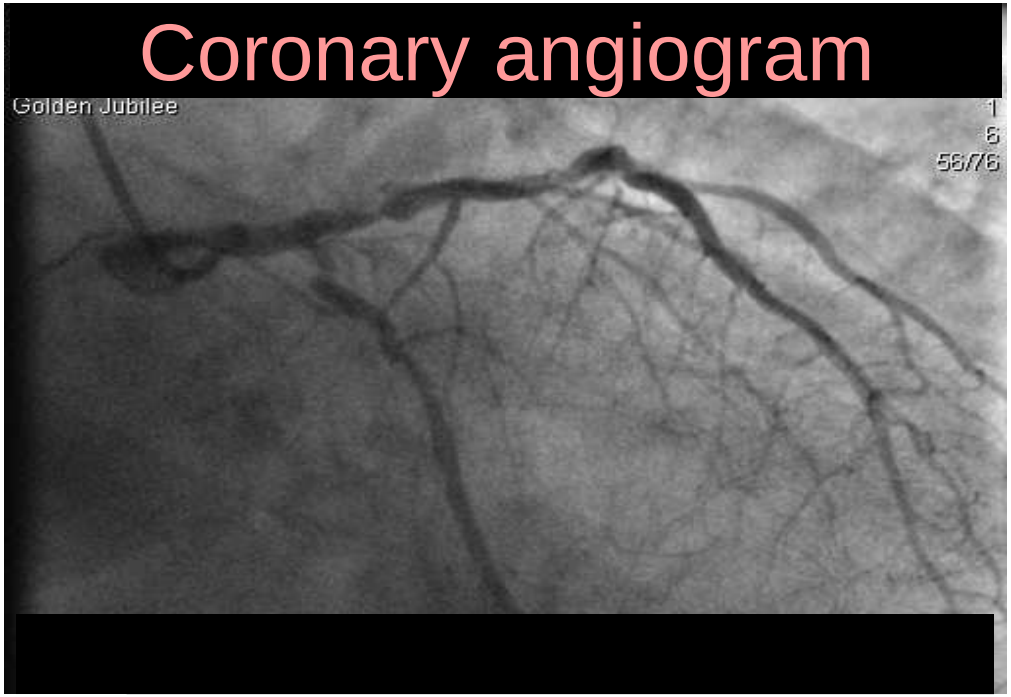
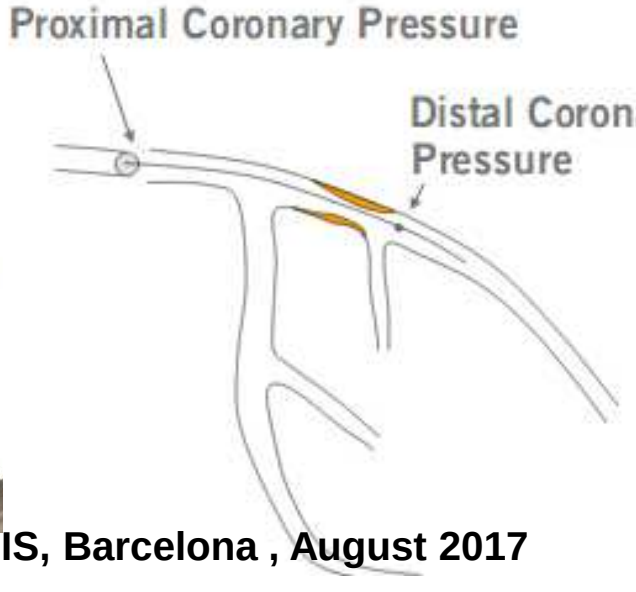
University of Glasgow, William Fulton MD, 1963.

Clinical conundrums in daily practice



Diagnostic wire to assess flow-limitation



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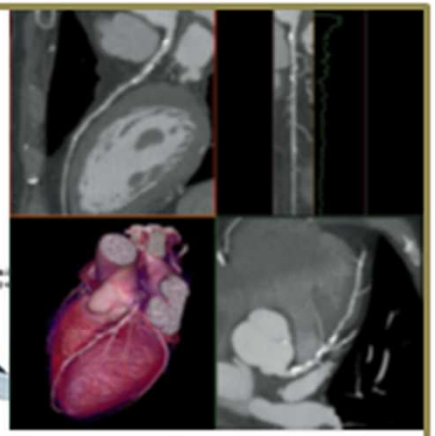
Standard care pathways

Outpatient clinic

Medical assessment

Exercise test

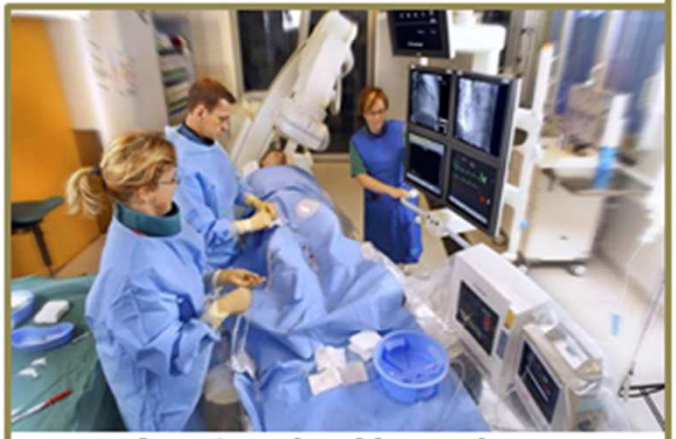


Anatomical imaging

Cardiac CT scan

NICE-95 Update
Nov. 2016

Catheter Laboratory



Anatomical imaging

Coronary angiogram

No tests of small vessel function

Diagnostic Group

Undifferentiated chest pain

Non cardiac, 2 in 5
No diagnosis, 2 in 5

Non-obstructive disease or normal, 2 in 3

1 in 3 - 5

Obstructive disease
>70% narrowed artery, 2 in 3

Non-obstructive or normal, 1 in 3

Small vessel disease unknown or uncertain

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Negative coronary angiogram in a patient with angina?

√ True negative

Alternative non-cardiac chest pain

False negative

Angina microvascular, spasm

False positive non-invasive test

i.e. artefact, mis-diagnosis

Test failure

True obstructive CAD, *mis-diagnosis*

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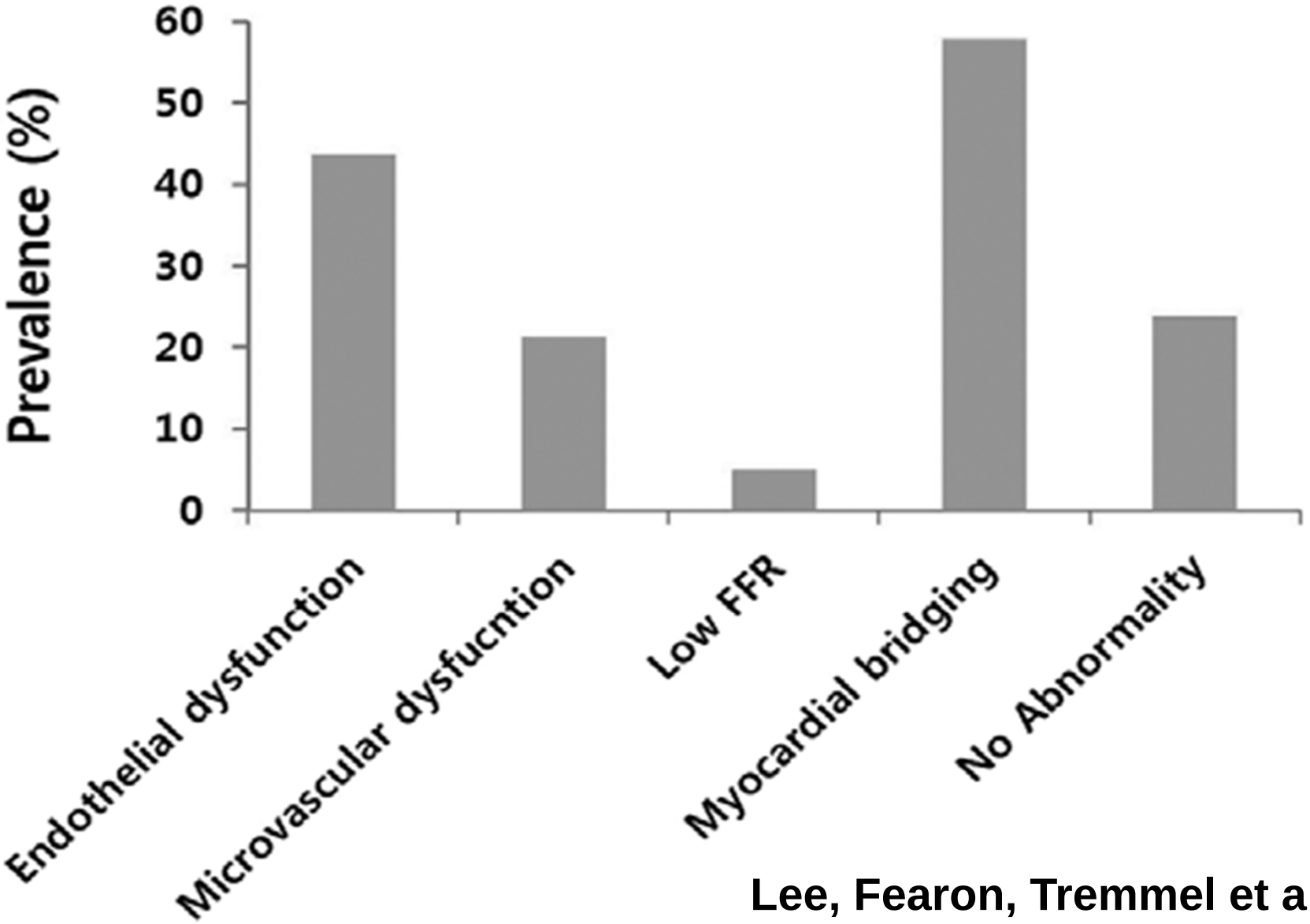
Abnormalities of coronary function are common
Case series, Stanford Medical Centre

Angina, negative angiogram, n = 139



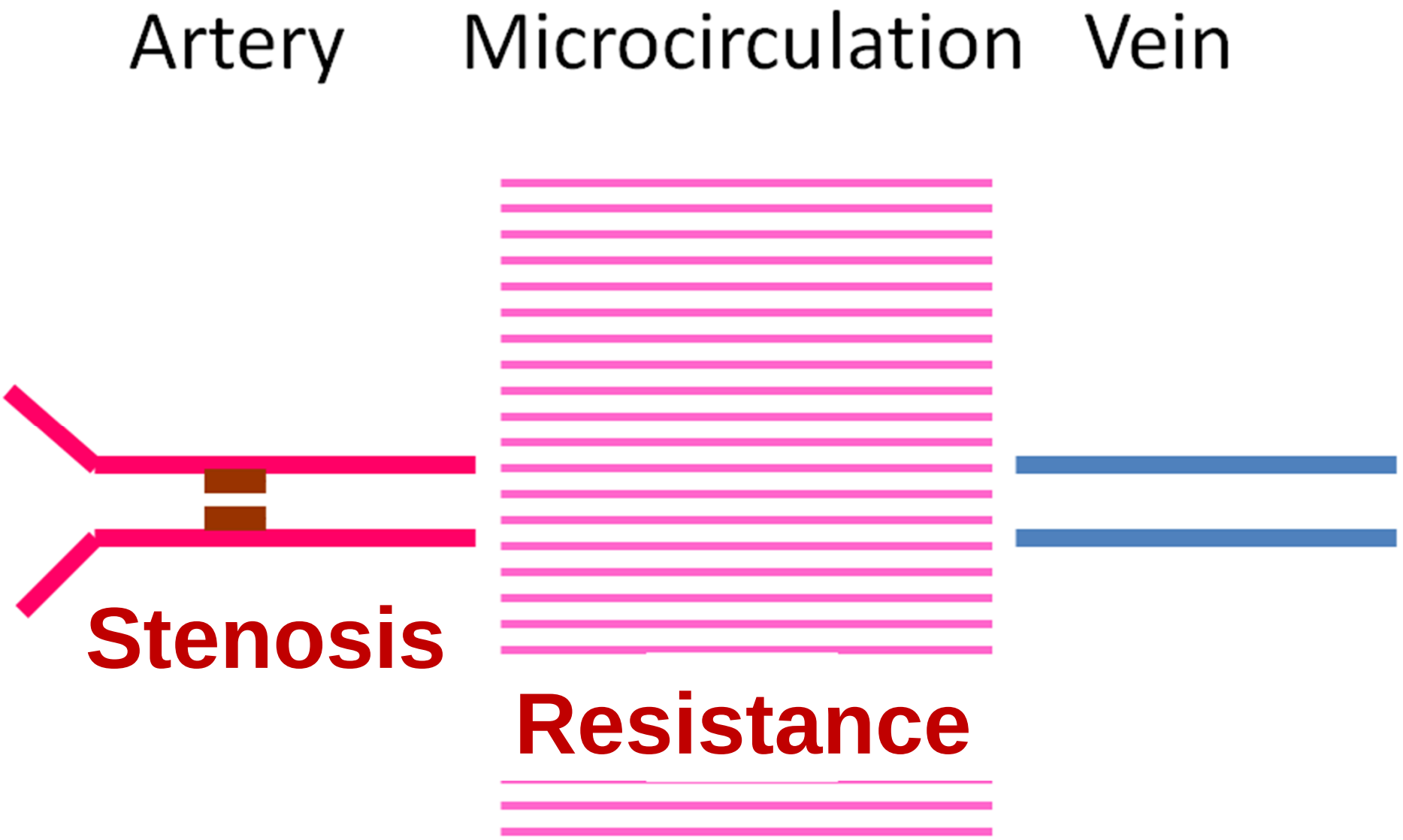
Endothelial dysfunction
61 (44%)

IMR ≥ 25
29 (21%)

CFR < 2.0
9 (7%)

NAD
32 (23%)

Lee, Fearon, Tremmel et al. Circulation 2015



Coronary artery circulation

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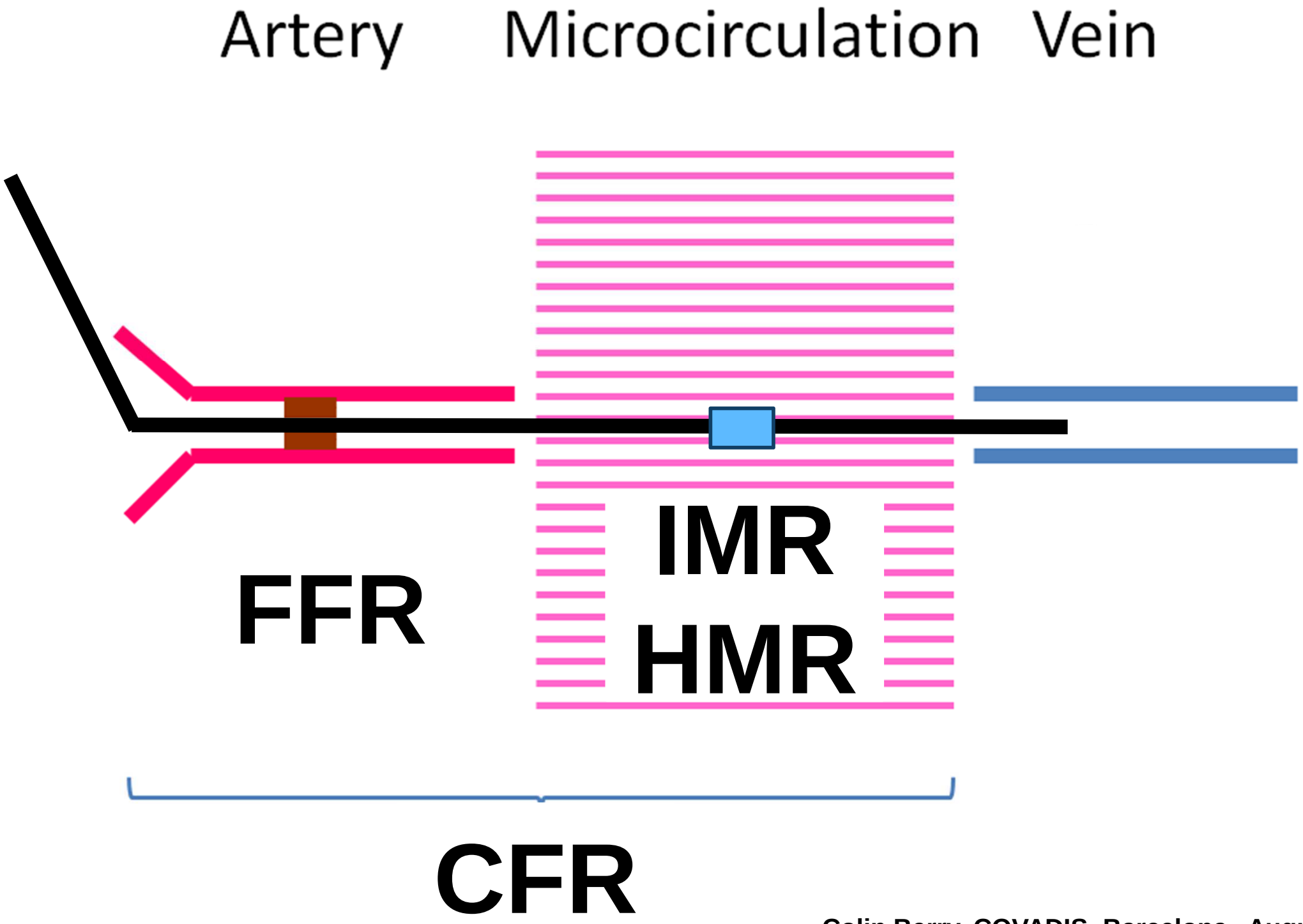

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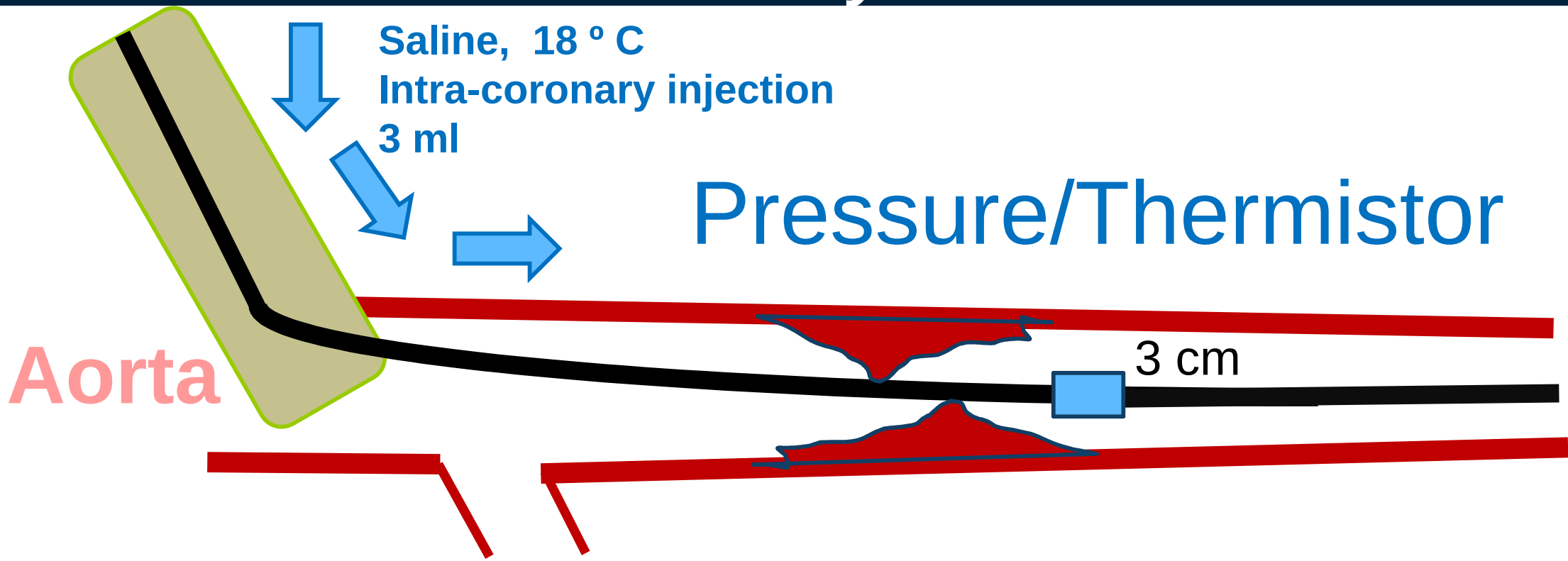
CFR
IMR
Microvascular function assessed by thermodilution



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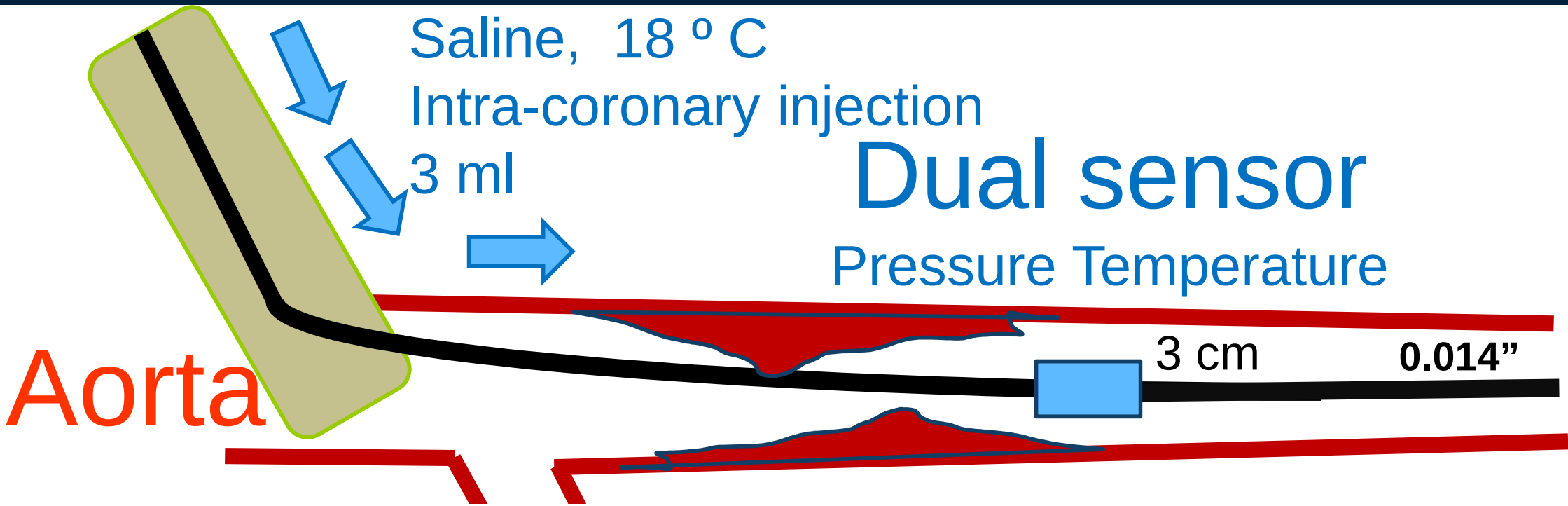
METHODS: Direct measurement of coronary microvascular function in acute MI patients



Coronary flow reserve, CFR

= Tmn rest / Tmn hyperaemia

Index of microvascular resistance, IMR

= Distal coronary pressure x mean transit time during hyperaemia

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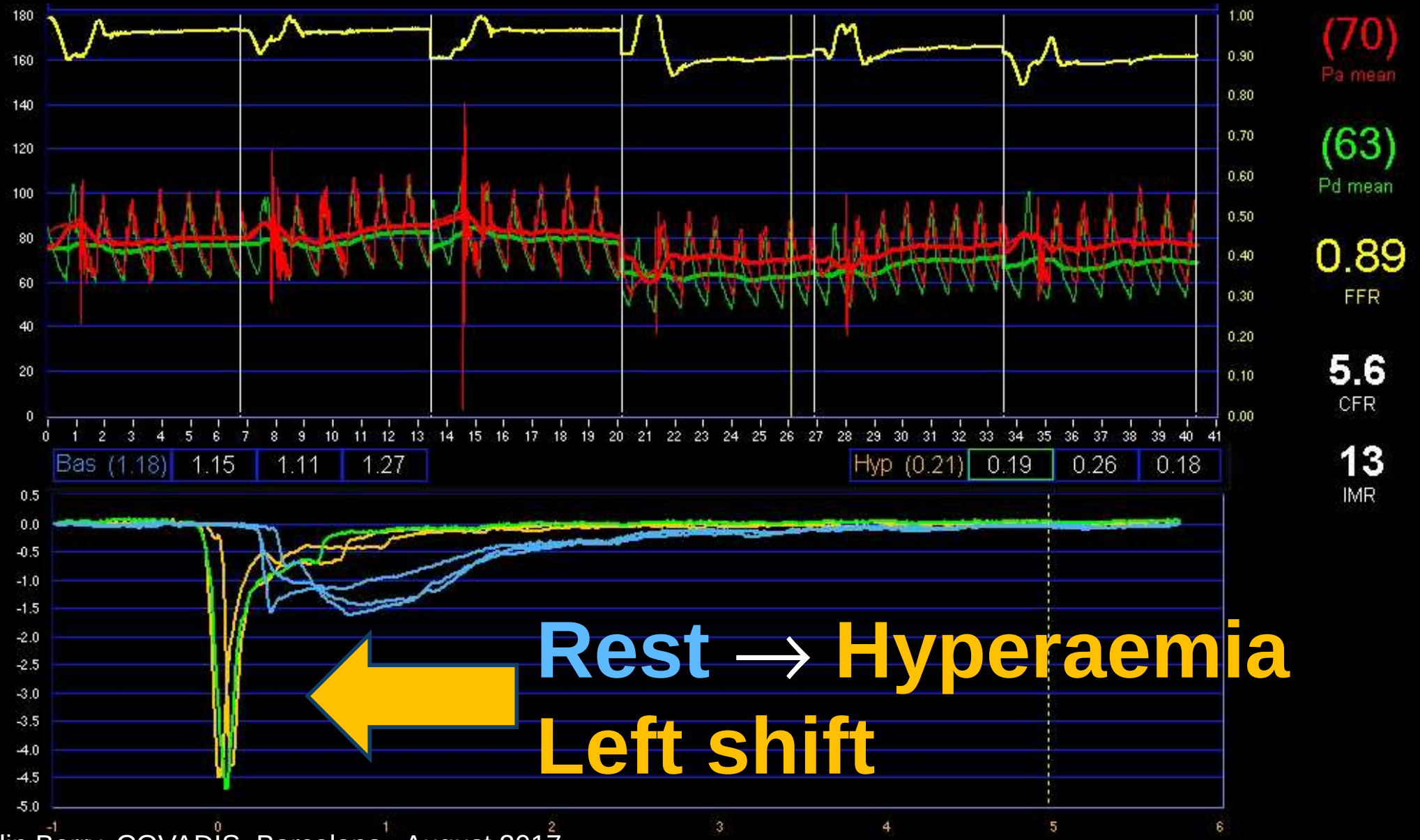
Coronary thermodilution

Normal microvascular function



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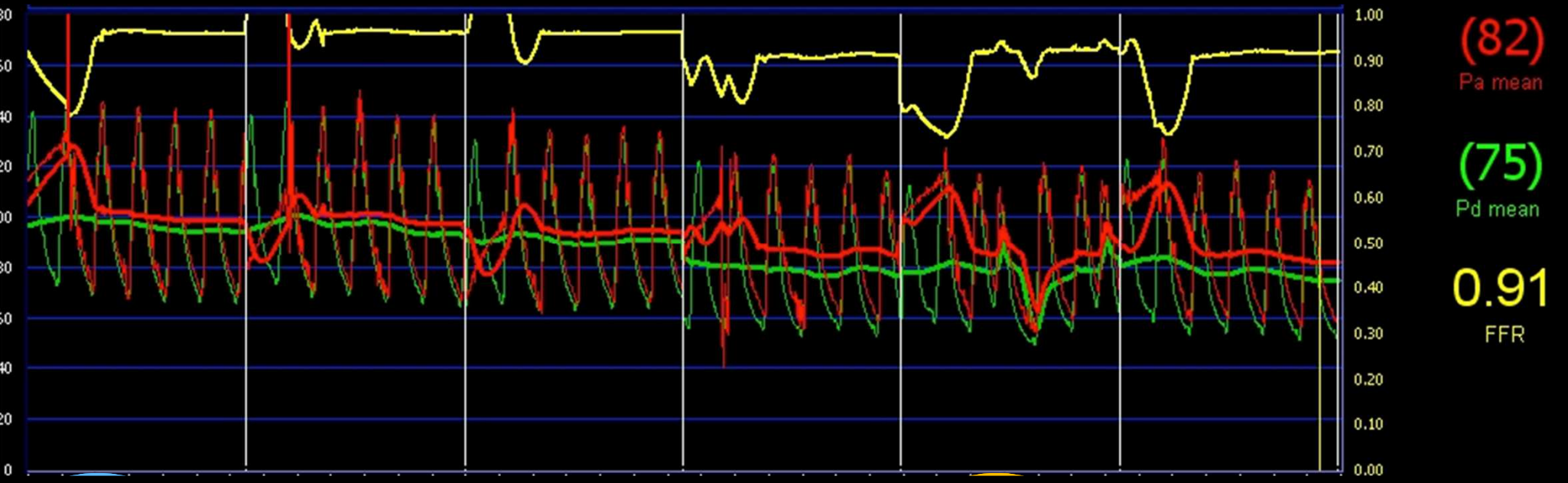
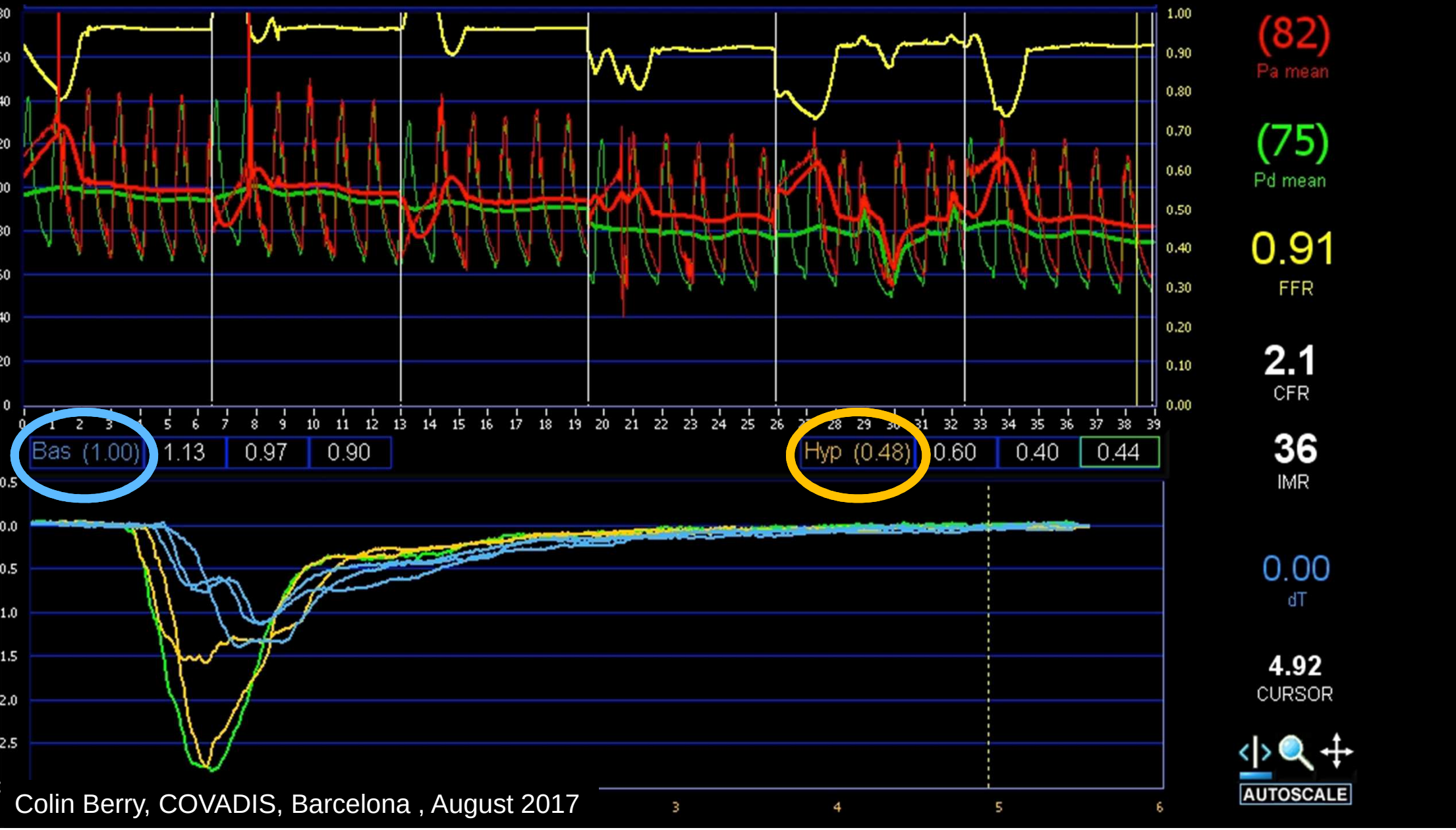
Invasive diagnostic testing of coronary artery function



Invasive diagnostic testing of coronary artery function



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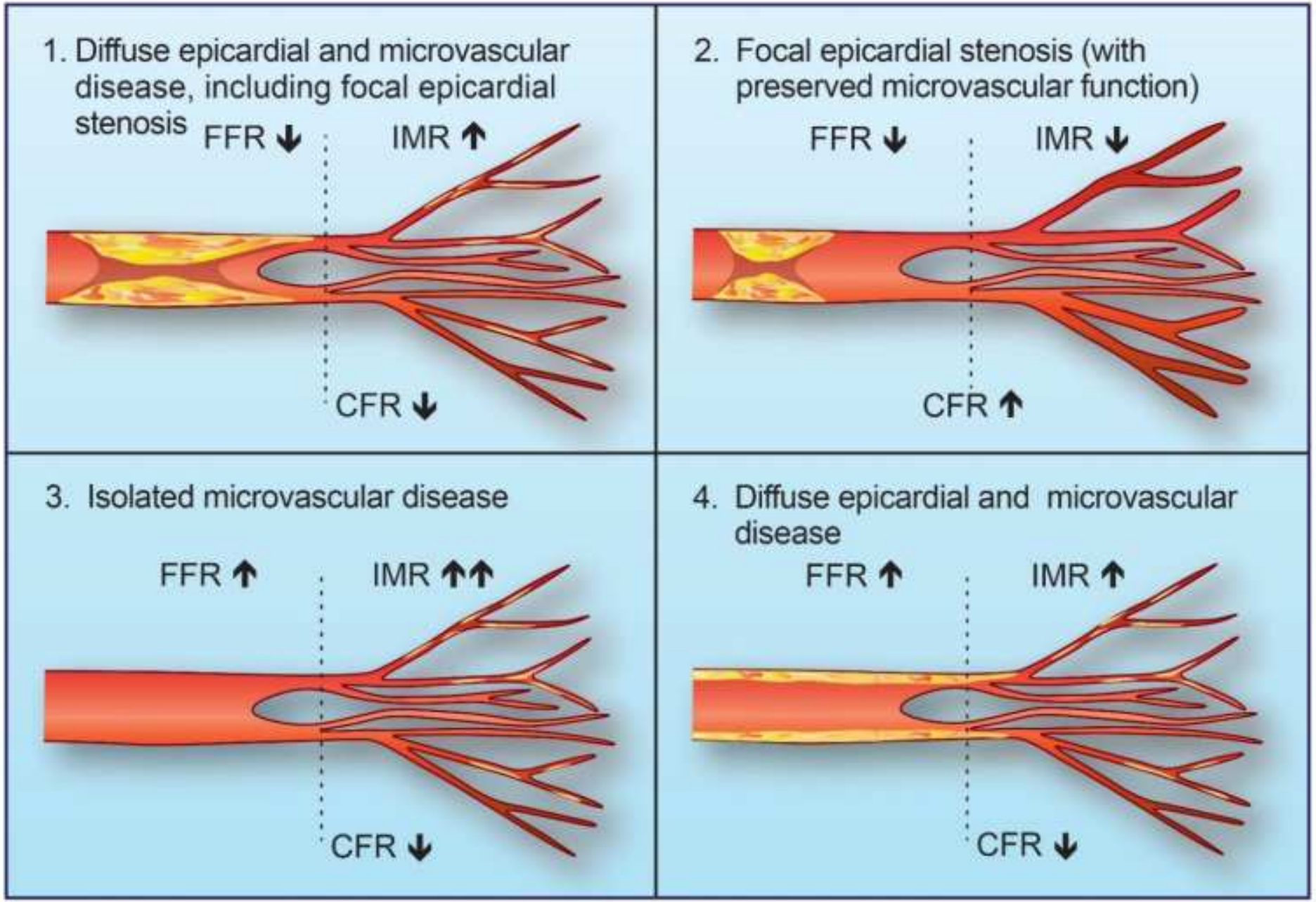
Diagnosis of coronary endotypes



Ford, Corcoran, Berry. EHJ 2017

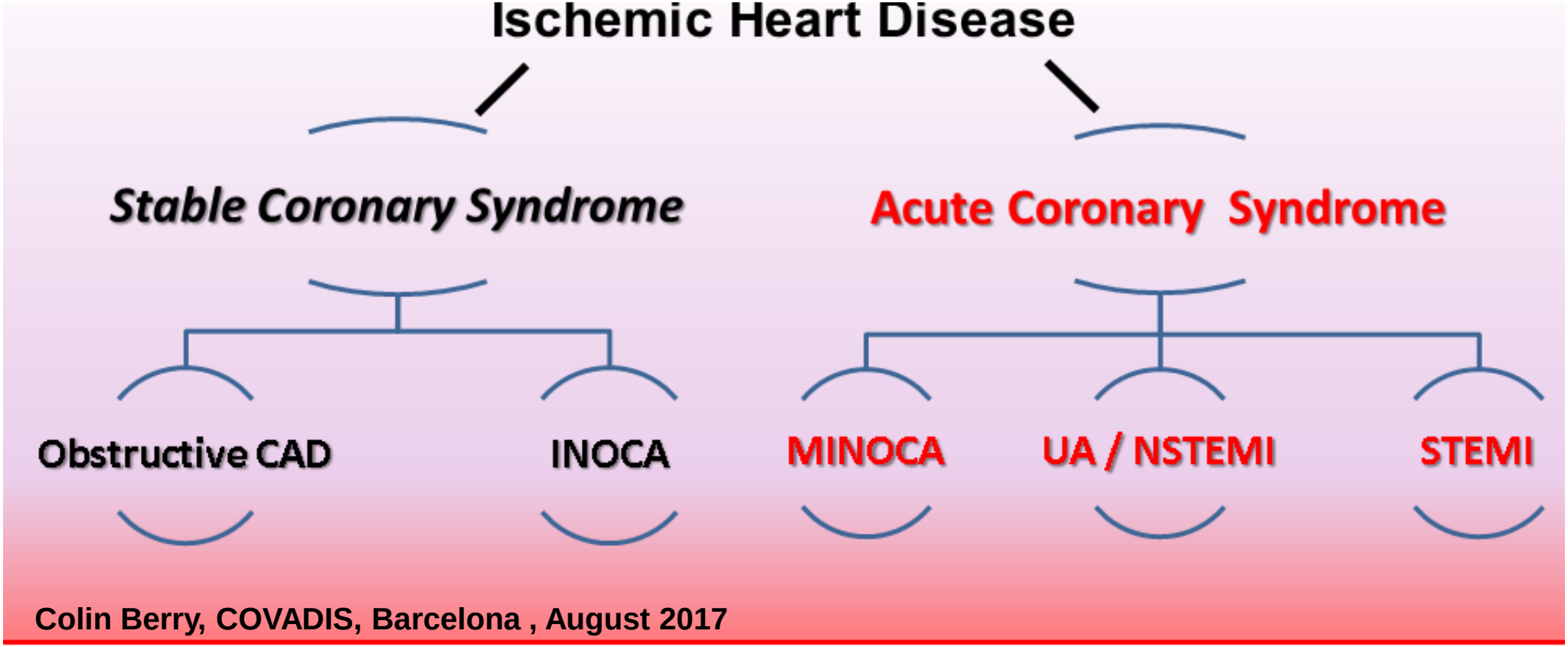
August 1, 2017

Colin Berry, Frame of reference article

Stable Coronary Syndromes

The Case for Consolidating the Nomenclature of Stable Ischemic Heart Disease

Circulation. 2017;136:00–00. DOI: 10.1161/CIRCULATIONAHA.117.028991



Aim

Close the gap in evidence for coronary function tests by undertaking randomised controlled trials in patients with chest pain but no obstructive CAD.

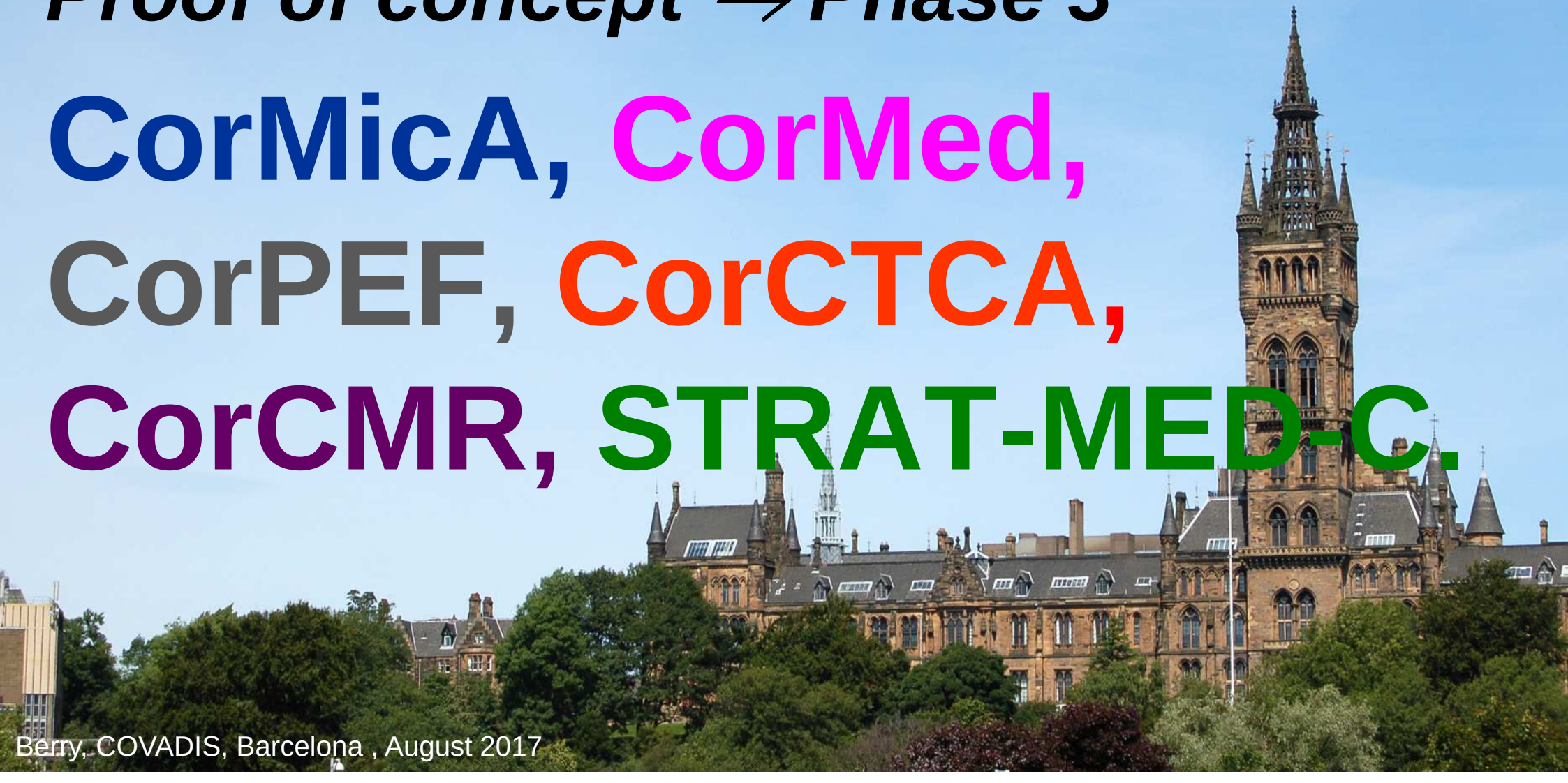
Clinical trials

Proof of concept → Phase 3

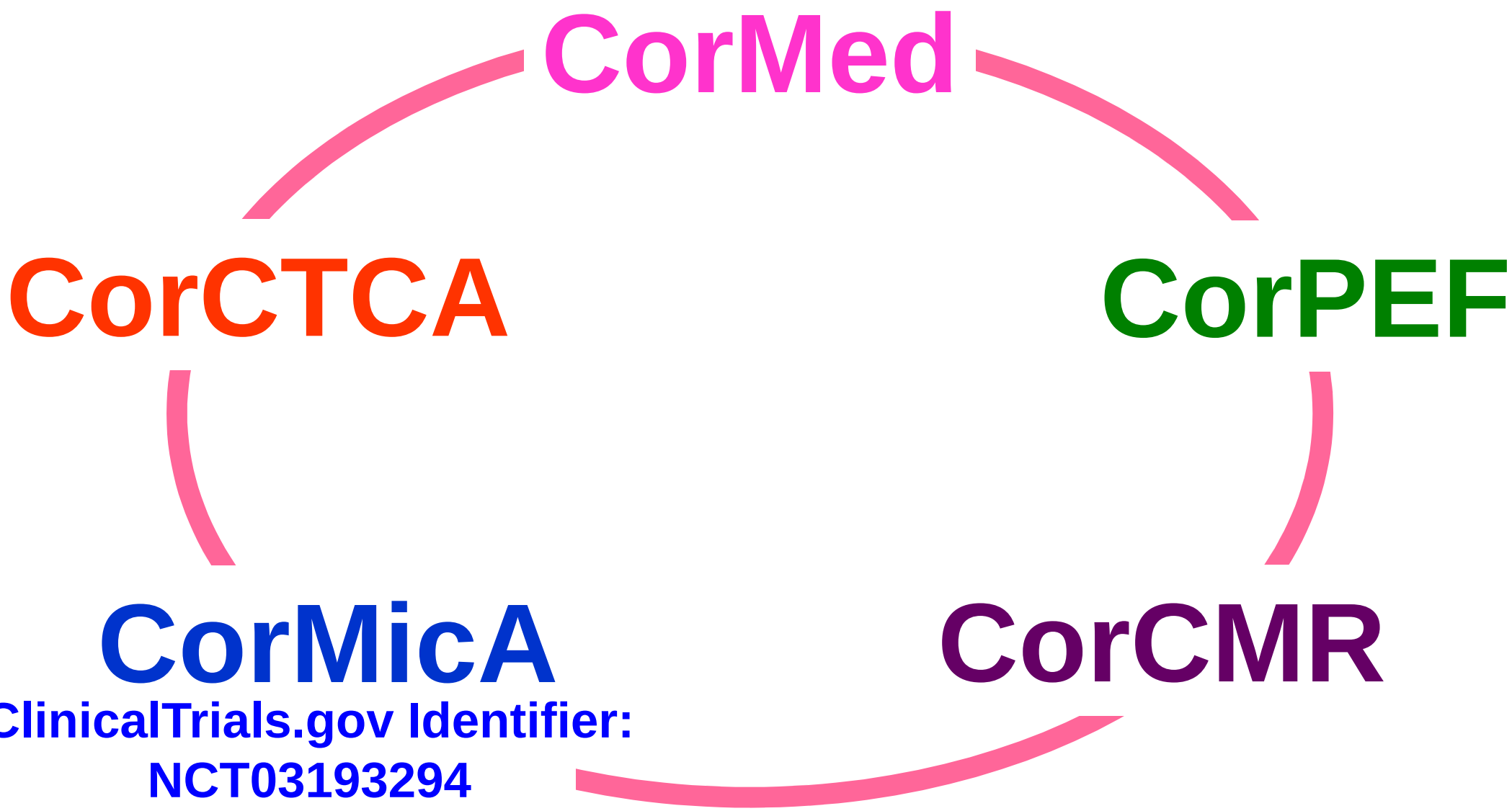
CorMicA, CorMed,

CorPEF, CorCTCA,

CorCMR, STRAT-MED-C.



CorFamily of randomised trials



ClinicalTrials.gov Identifier: NCT03193294

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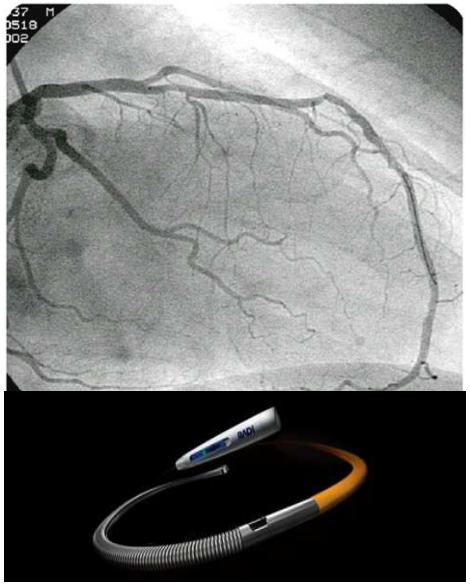
CorMed

Natural history study, life-long

Angiogram
± coronary function tests



MRI scan
Pixel-mapping of perfusion

1200 – 2460 patients

Started – August 2016; 10 year study
Dr. David Corcoran, Ness Orchard

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CorMicA

British Heart Foundation

Key questions

(1) Does a routine strategy of adjunctive tests of coronary function change the diagnosis and management?

(2) Does a treatment plan informed by endotype classification improve health and well being, compared to standard care without knowledge of coronary function.

Endotypes, n = 5

Obstructive CAD, MVA, VSA, both, none (other)

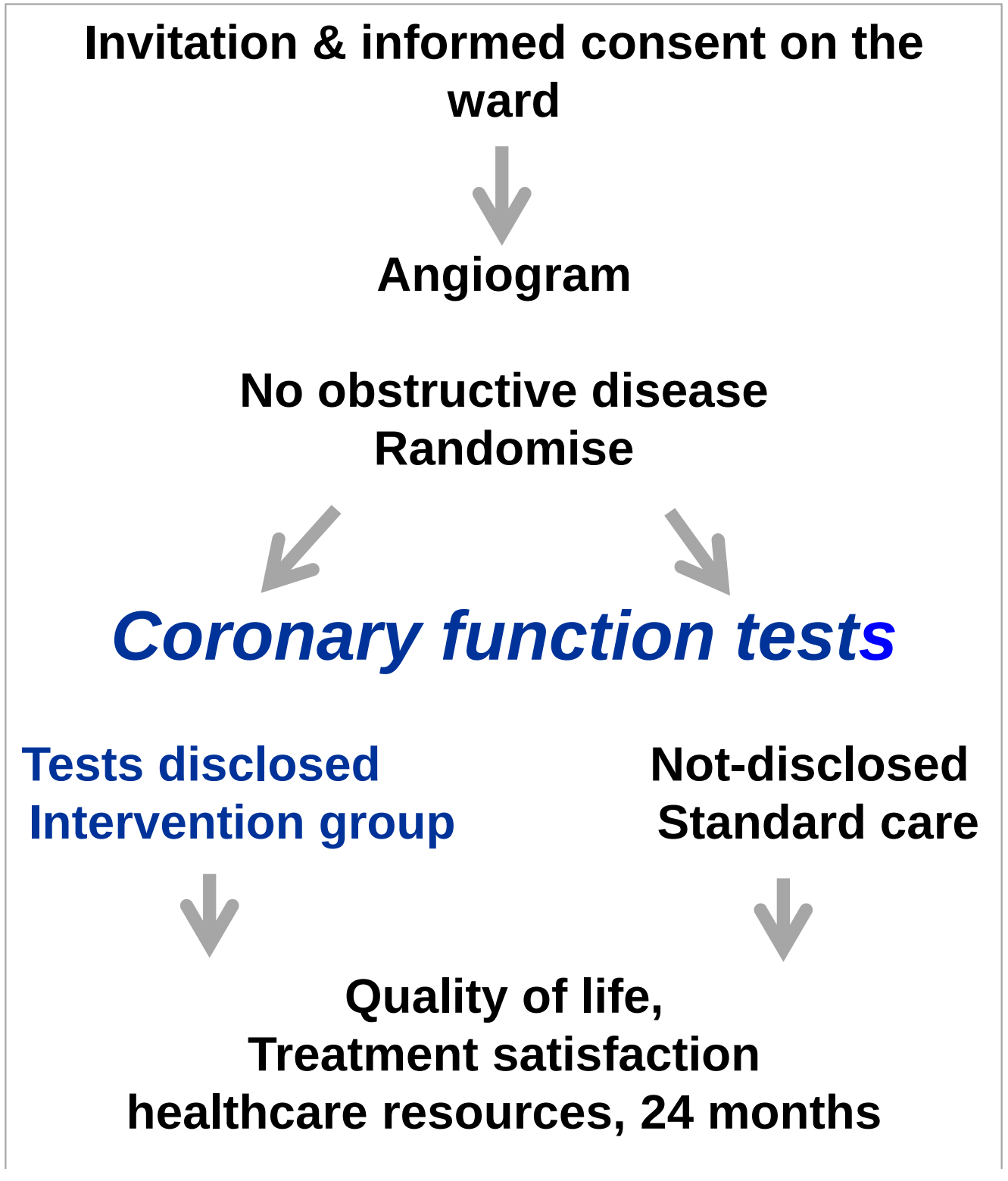
CorMicA

NCT03193294

Golden Jubilee hospital, Glasgow

Hairmyres Hospital

Tom Ford



N

Screen 500

Randomise 150

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VIA VERITAS VITA

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Mechanisms of disease

Peripheral Small Vessel Function in Patients with Coronary Microvascular Angina – a CorMicA Substudy

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Studies of intracellular signalling

Primary culture of vascular cells (VSMCs, fibroblasts)

ET-1 stimulation

+ / - ET-1 receptors antagonists

In collaboration with Prof Touyz's group

Activation of contractile signalling

Regulation of calcium homeostasis

Assessment of possible downstream effectors of ET-1 signalling (i.e oxidative stress)

Conclusions

1. Ischaemic heart disease persists as the major global cause of premature death and disability, notably in women.
2. Disorders of coronary vasomotion & microvascular disease are an unmet need.
3. Evidence gap from randomised trials
4. Proof of concept trials initiated √
5. Stratification of enotypes → Personalised medicine

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Ness Orchard

Rhian Touyz, Adam Harvey, Guto Montezano, Elizabeth Beattie, Laura McPherson

Clinical Colleagues

MRC Medical Research Council

Leading science for better health