What's new in cardiovascular medicine and lipid disorders

Select 74 Meeting, 11th January 2018, Bristol

Urs Widmer, Senior Medical Officer, SwissRe

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- Does PCI improve survival in **SIHD**?
- **Left main** interventions by PCI?
- Revascularization in **STEMI?**
- Chronic total occlusions (**CTOs**)?
- **Bioresorbable Scaffolds** (BRS)?

1. Coronary Interventions

Despite 40 years of coronary balloon angioplasty:

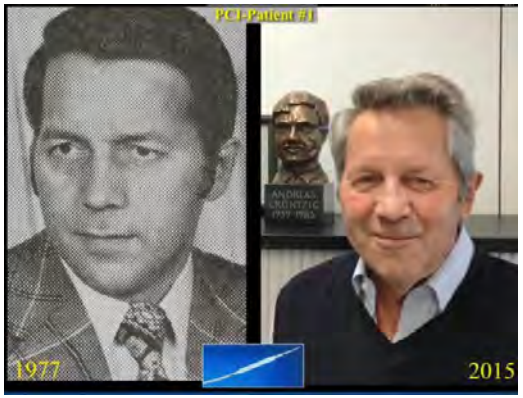
Many unanswered questions remain

The NEW ENGLAND JOURNAL of MEDICINE

Nonoperative Dilatation of Coronary-Artery Stenosis — Percutaneous Transluminal Coronary Angioplasty

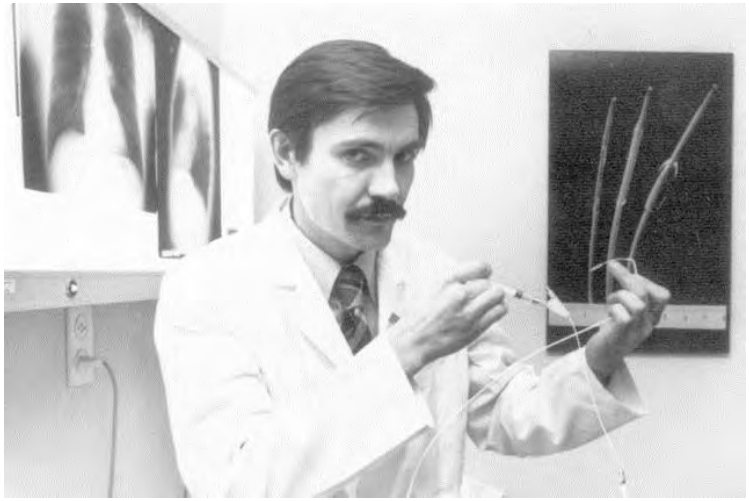
Andreas R. Grüntzig, M.D., Åke Senning, M.D., and Walter E. Siegenthaler, M.D.

N Engl J Med 1979; 301:61-68



First patient: Bachmann PTCA proximal LAD stenosis photographed in 1977 and recently in 2015

40 years



World's first balloon angioplasty at Zurich University Hospital 1977 by Andreas Grüntzig (later moved to Emory, Atlanta, USA)

Myocardial infarction – Nomenclature Consensus

REVIEW ARTICLE

Acute Myocardial Infarction

Jeffrey L. Anderson, M.D., and David A. Morrow, M.D.

ACUTE MYOCARDIAL INFARCTION WITH OR WITHOUT ST-SEGMENT ELEVATION (STEMI or non-STEMI) is a common cardiac emergency, with the potential for substantial morbidity and mortality. The management of acute myocardial infarction has improved dramatically over the past three decades and continues to evolve. This review focuses on the initial presentation and in-hospital management of type 1 acute myocardial infarction.

DEFINITION AND TYPES

Acute myocardial infarction is an event of myocardial necrosis caused by an unstable ischemic syndrome.[1] In practice, the disorder is diagnosed and assessed on the basis of clinical evaluation, the electrocardiogram (ECG), biochemical testing, invasive and noninvasive imaging, and pathological evaluation.

Acute myocardial infarction is classified on the basis of the presence or absence of ST-segment elevation on the ECG and is further classified into six types: infarction due to coronary atherothrombosis (type 1), infarction due to a supply–demand mismatch that is not the result of acute atherothrombosis (type 2), infarction causing sudden death without the opportunity for biomarker or ECG confirmation (type 3), infarction related to a percutaneous coronary intervention (PCI) (type 4a), infarction related to thrombosis of a coronary stent (type 4b), and infarction related to coronary-artery bypass grafting (CABG) (type 5).[1]

EPIDEMIOLOGIC FEATURES

The epidemiologic characteristics of acute myocardial infarction have changed dramatically over the past three to four decades (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Since 1987, the adjusted incidence rate of hospitalization for acute myocardial infarction or fatal coronary artery disease in the United States has declined by 4 to 5% per year.[2] Nevertheless, approximately 550,000 first episodes and 200,000 recurrent episodes of acute myocardial infarction occur annually.[2] Globally, ischemic heart disease has become the leading contributor to the burden of disease as assessed on the basis of disability-adjusted life-years.[3] Concurrently, the global burden of cardiovascular disease and acute myocardial infarction has shifted to low- and middle-income countries, where more than 80% of deaths from cardiovascular disease worldwide now occur.[3,4] Among 156,424 persons in 17 countries who were followed for an average of 4.1 years,[5] the risk-factor burden was directly related to income, with the highest burden of risk factors in high-income countries and the lowest burden in low-income countries. In contrast, an inverse relationship with income was noted for rates of acute myocardial infarction (1.92, 2.21, and 4.13 cases per 1000 person-years in high-, middle-, and low-income countries, respectively; P<0.001 for trend). Mitigation of the high burden of risk factors in higher-income countries was attributed to greater use of pre-

2053

The New England Journal of Medicine

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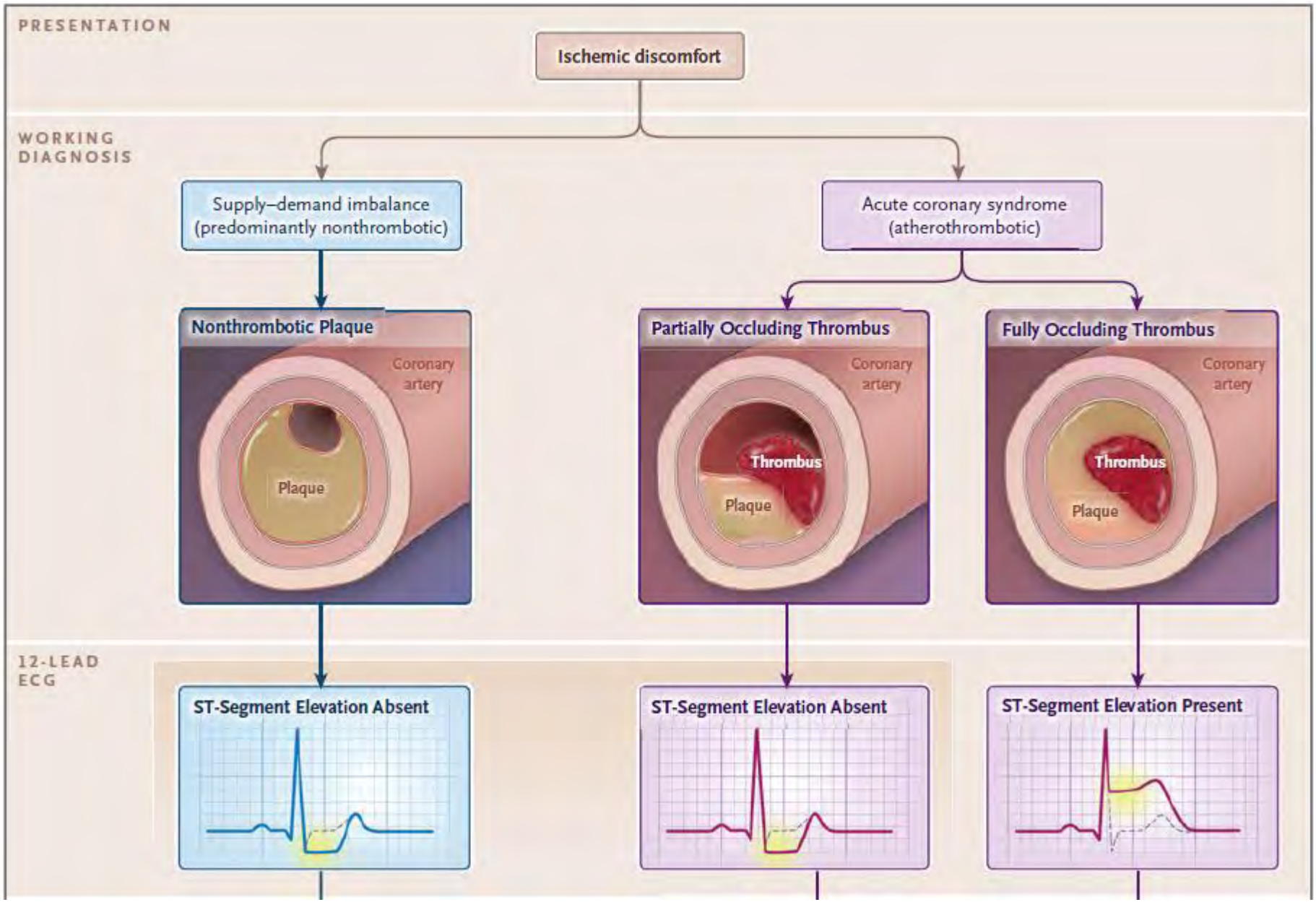
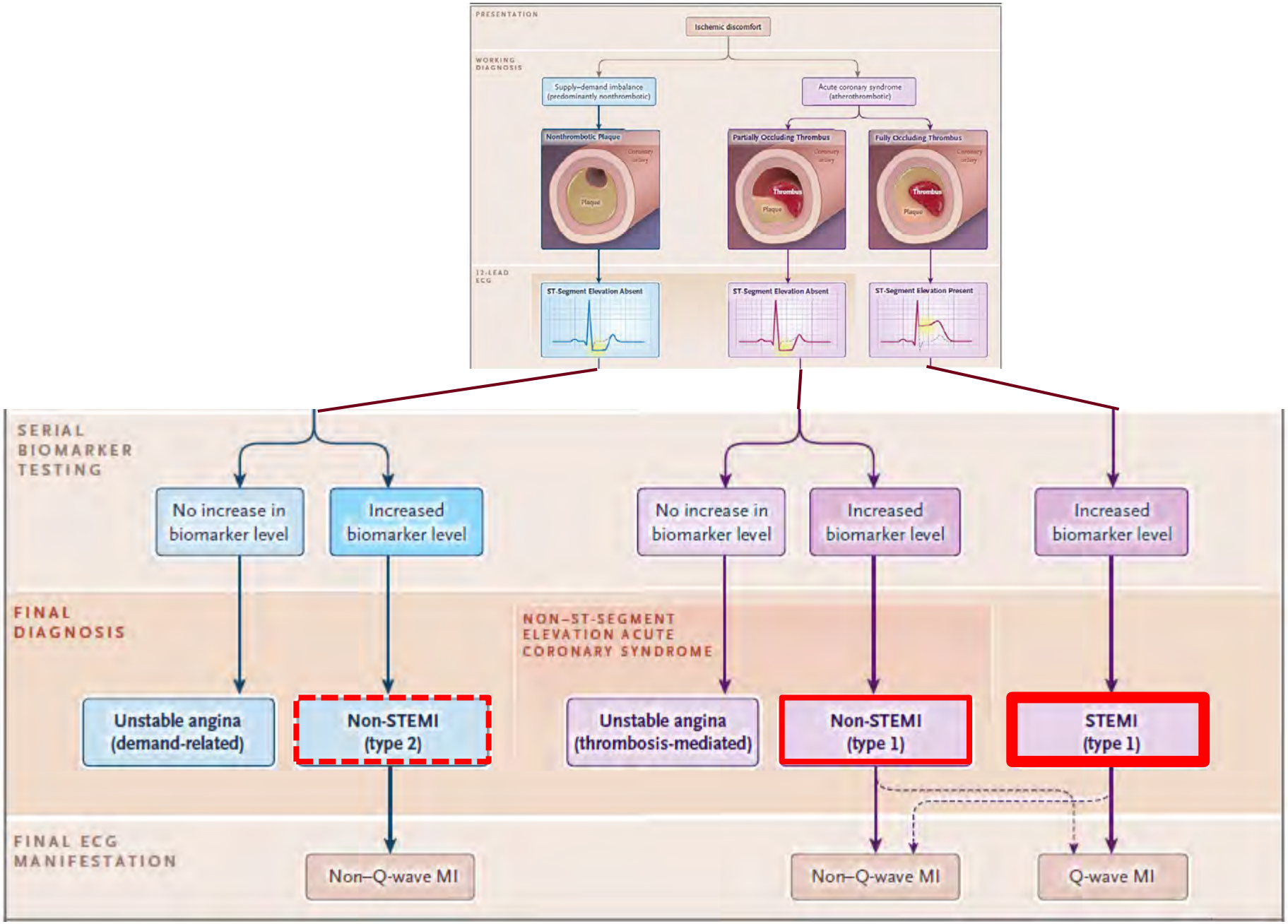
Rahul Patwari
8.7.2017

https://www.youtube.com/watch?v=HuLNgGytkgQ


PRESENTATION
Ischemic discomfort
WORKING DIAGNOSIS
Supply–demand imbalance (predominantly nonthrombotic)
Acute coronary syndrome (atherothrombotic)
Nonthrombotic Plaque
Coronary artery
Plaque
Partially Occluding Thrombus
Coronary artery
Thrombus
Plaque
Fully Occluding Thrombus
Coronary artery
Thrombus
Plaque
12-LEAD ECG
ST-Segment Elevation Absent
ST-Segment Elevation Absent
ST-Segment Elevation Present


PRESENTATION
Ischemic discomfort
WORKING DIAGNOSIS
Supply–demand imbalance (predominantly nonthrombotic)
Acute coronary syndrome (atherothrombotic)
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Partially Occluding Thrombus
Fully Occluding Thrombus
Thrombus
Plaque
12-LEAD ECG
ST-Segment Elevation Absent
ST-Segment Elevation Absent
ST-Segment Elevation Present
SERIAL BIOMARKER TESTING
No increase in biomarker level
Increased biomarker level
No increase in biomarker level
Increased biomarker level
Increased biomarker level
FINAL DIAGNOSIS
NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME
Unstable angina (demand-related)
Non-STEMI (type 2)
Unstable angina (thrombosis-mediated)
Non-STEMI (type 1)
STEMI (type 1)
FINAL ECG MANIFESTATION
Non–Q-wave MI
Non–Q-wave MI
Q-wave MI

Functional assessment of CAD: Fractional flow reserve (FFR)

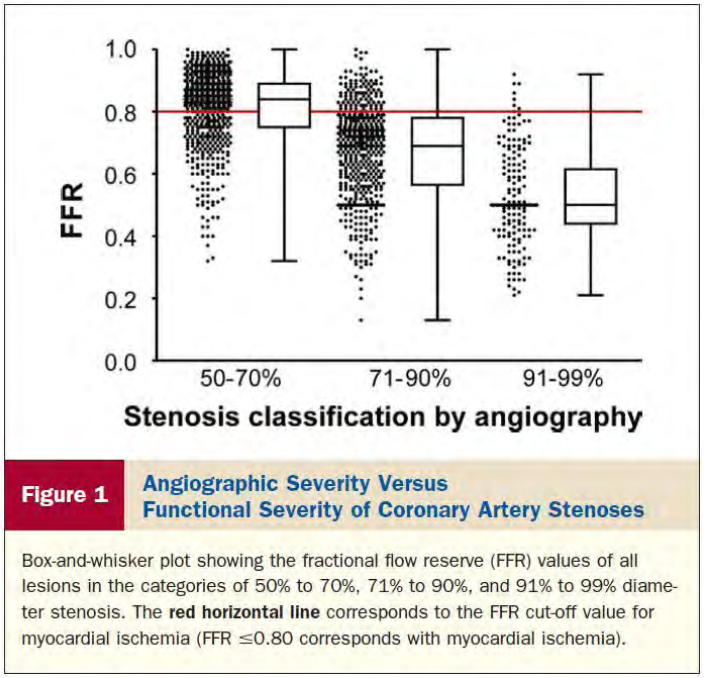
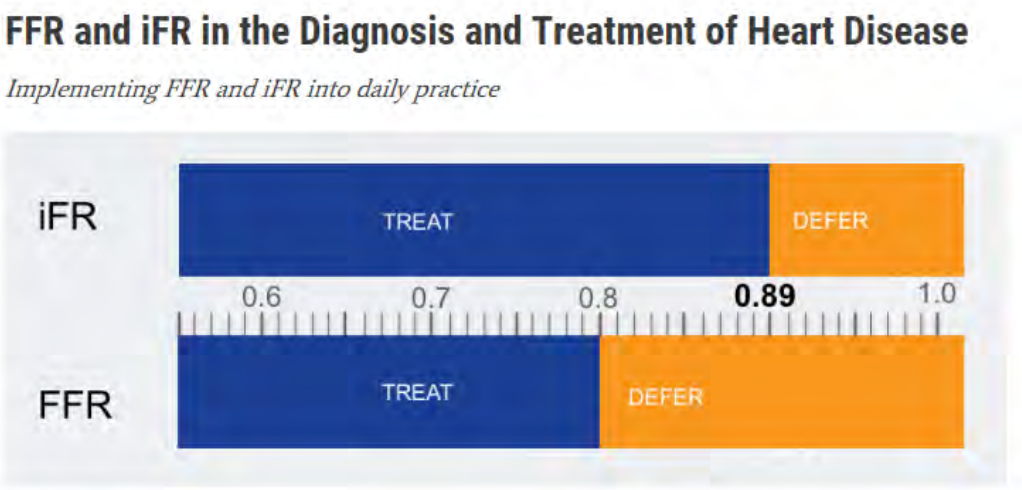


Figure 1 **Angiographic Severity Versus Functional Severity of Coronary Artery Stenoses**

Box-and-whisker plot showing the fractional flow reserve (FFR) values of all lesions in the categories of 50% to 70%, 71% to 90%, and 91% to 99% diameter stenosis. The **red horizontal line** corresponds to the FFR cut-off value for myocardial ischemia (FFR ≤0.80 corresponds with myocardial ischemia).

NEJMvideo Quick Take: FFR
https://www.youtube.com/watch?v=EPWa19jD7QQ

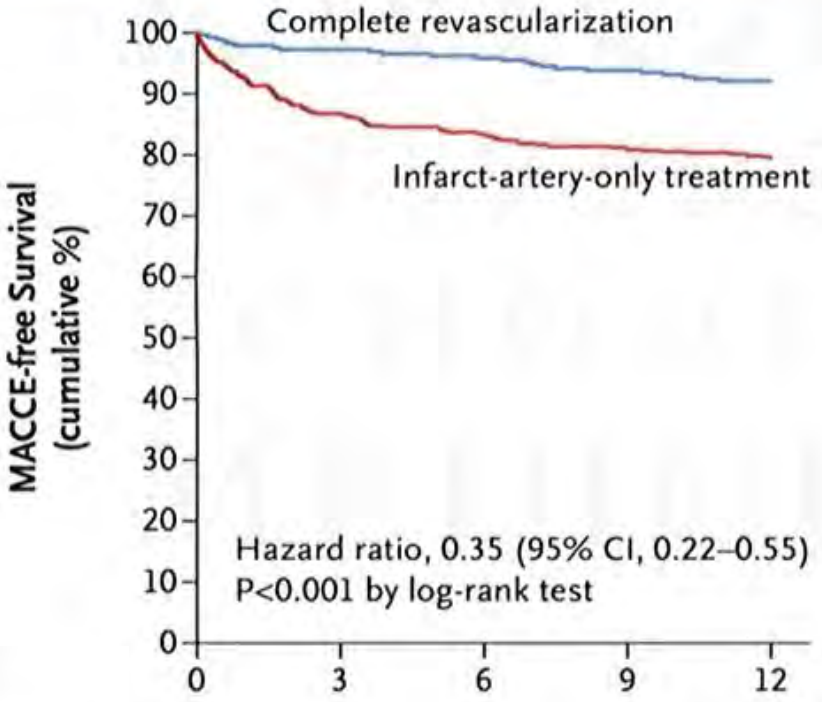


Countless studies indicating the weakness of the angiogram, far too many operators still rely on it for treatment guidance elimination of unnecessary treatments and reduction in readmissions
Unfortunately, many interventional cardiologists are still making final decisions to stent a vessel based on angiographic results without taking into consideration physiologic parameters

https://www.dicardiology.com/article/ffr-and-ifr-diagnosis-and-treatment-heart-disease

Fractional Flow Reserve–Guided Multivessel Angioplasty in Myocardial Infarction

MACCE denotes the composite of all-cause mortality, nonfatal myocardial infarction, any revascularization, and cerebrovascular events.



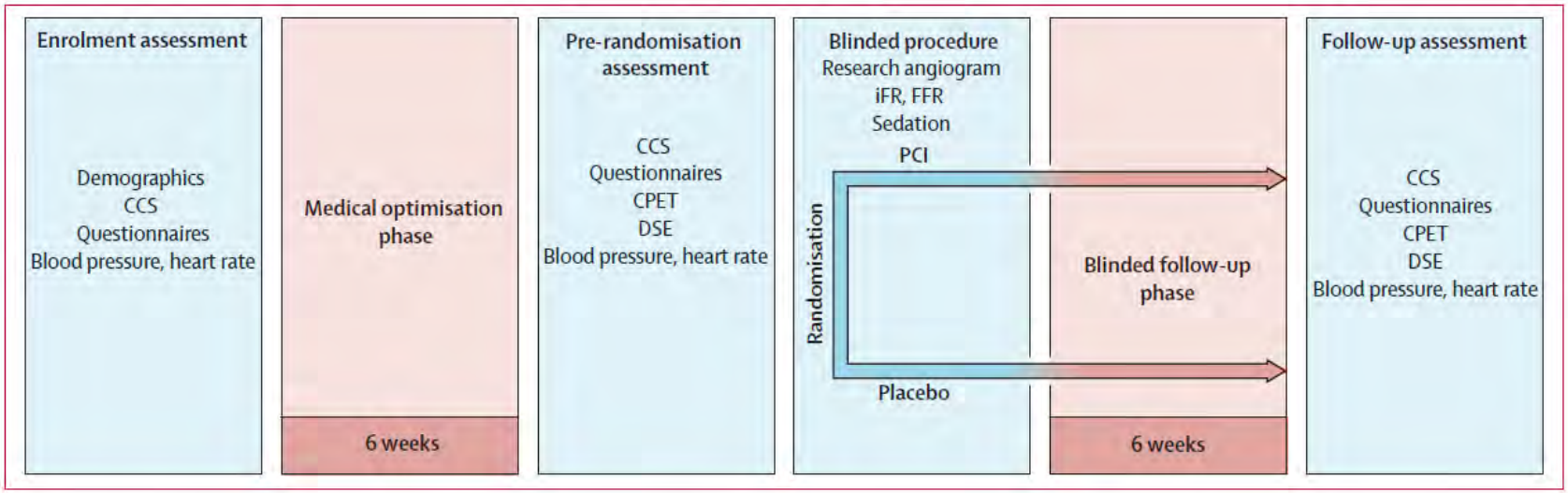
N Engl J Med 2017;376:1234-44.

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

*Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators**

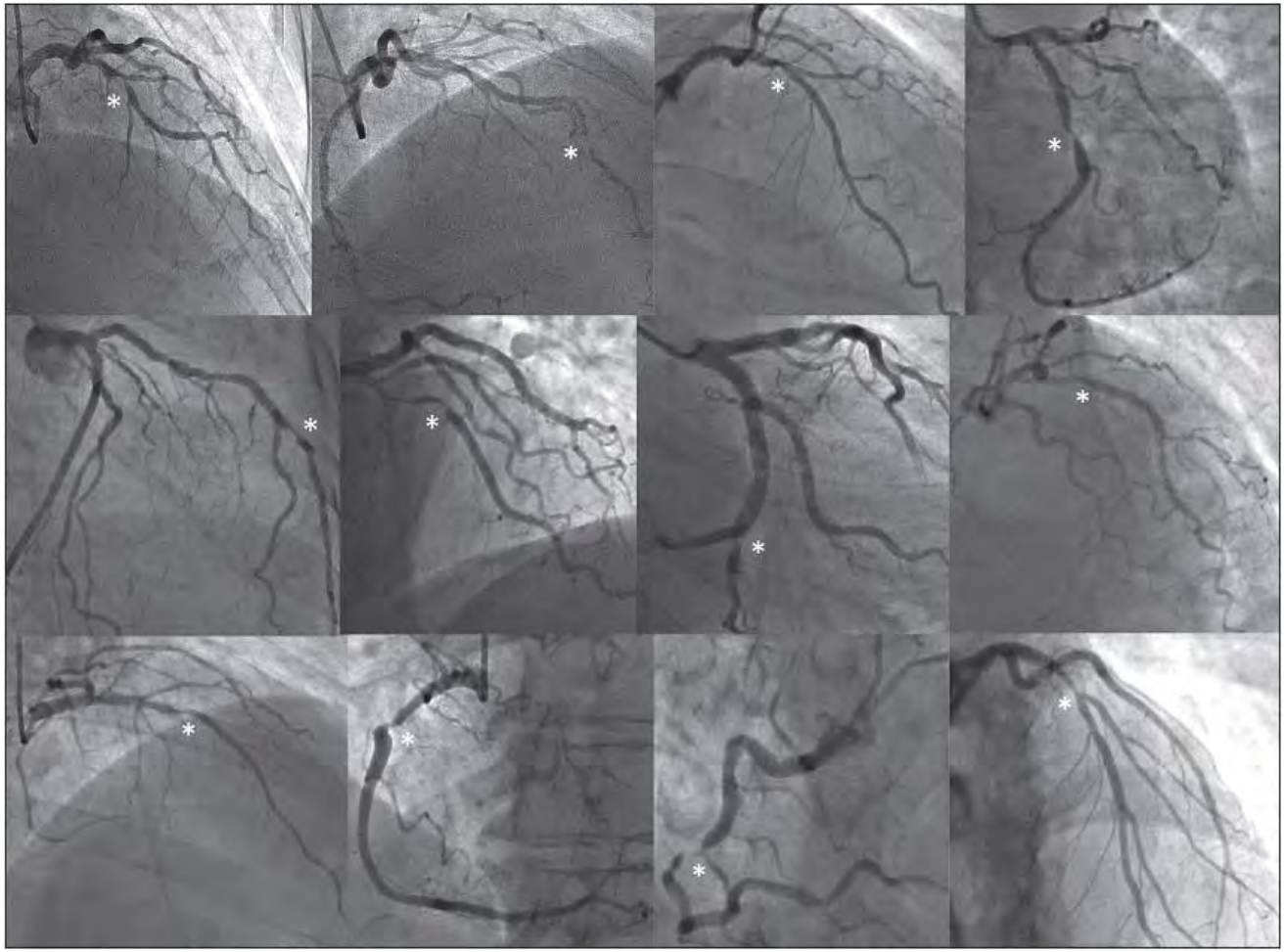
ORBITA: World's first Sham-Controlled PCI Trial 2017 (from UK)

ORBITA remains, by far, one of the most controversial and heatedly debated studies in a long time.



CCS=Canadian Cardiovascular Society angina severity grading. CPET=cardiopulmonary exercise testing. DSE=dobutamine stress echocardiography. iFR=instantaneous wave-free ratio. FFR=fractional flow reserve. PCI=percutaneous coronary intervention.

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial



Coronary angiograms of the first 12 consecutively randomised patients
The target vessel is marked with an asterisk.

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

	PCI	Placebo
Exercise time (s)		
Patients assessed	104	90
Pre-randomisation	528·0 (178·7)	490·0 (195·0)
Follow-up	556·3 (178·7)	501·8 (190·9)
Increment (pre-randomisation to follow-up)	28·4 (95% CI 11·6 to 45·1)	11·8 (95% CI −7·8 to 31·3)
Difference in increment between groups	16·6 (95% CI −8·9 to 42·0)	..
p value	0·200	

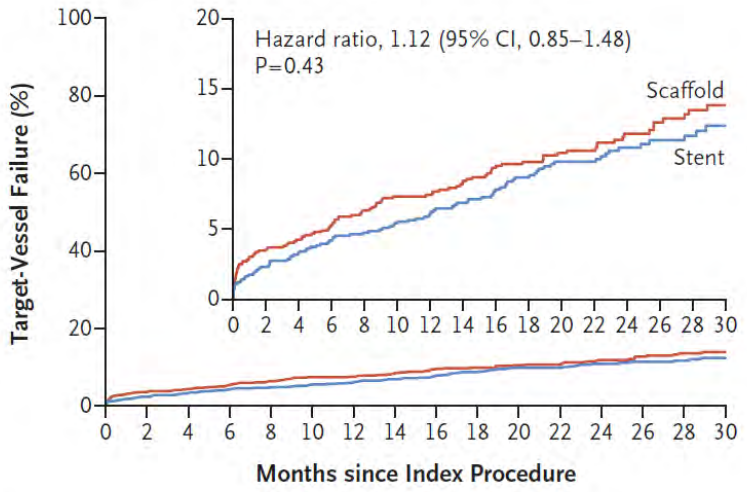
Does PCI Improve Survival in SIHD?

- Average RCT outcomes will not help very much.
- Trials, large enough to drill down to many subsets are needed.
- New trials of low ischemic risk should compare PCI with OMT.
- The ongoing ISCHEMIA trial is looking at higher risk patients with selection based on physiology (large ischemic burden on nuclear scan).
- Trials with selection based on anatomy (invasive angiography or CTA) are also needed.
- Sham-control RCTs should also be considered in the U.S.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 15, 2017 VOL. 376 NO. 24

Bioresorbable Scaffolds versus Metallic Stents in Routine PCI



No. at Risk						
Scaffold	924	870	776	594	385	196
Stent	921	873	792	599	388	188

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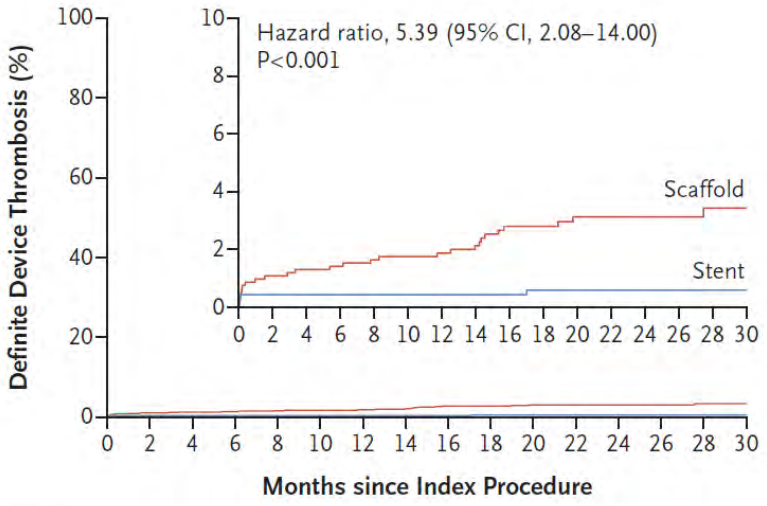
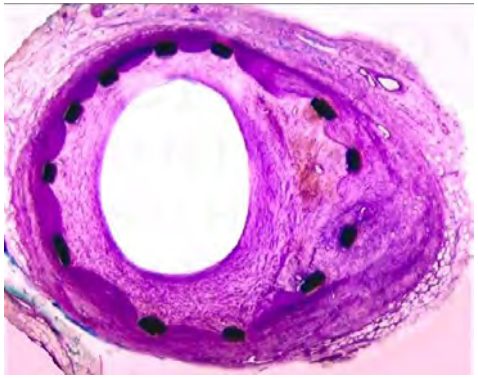
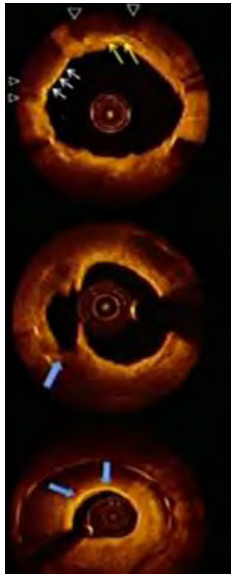


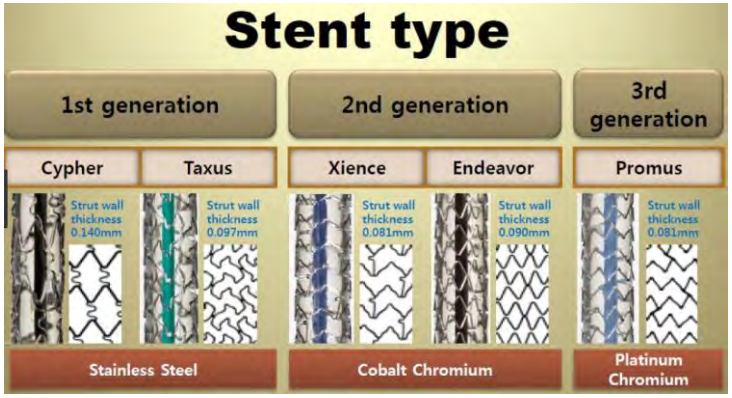
No. at Risk						
Scaffold	924	898	812	632	416	211
Stent	921	903	828	635	421	207

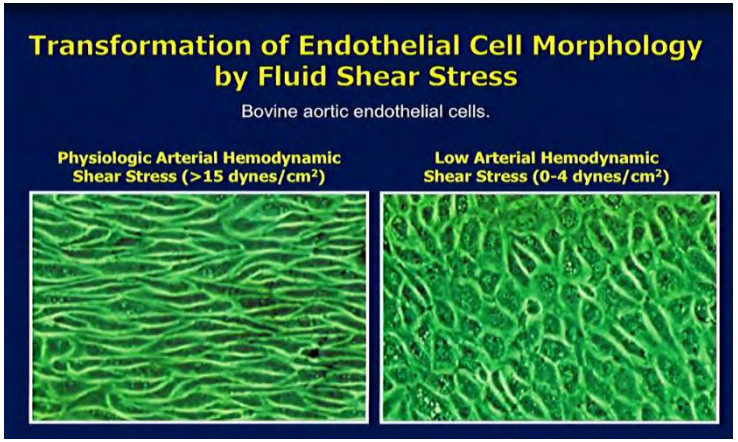
N Engl J Med 2017;376:2319-28.

Stent Design

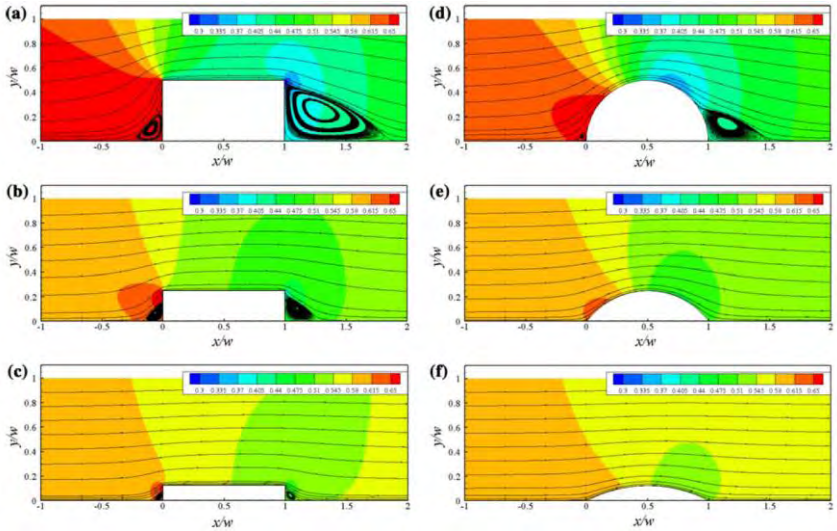








Hemodynamically Driven Stent Strut Design



Annals of Biomedical Engineering, Vol. 37, No. 8, August 2009 pp. 1483–1494

EDITORIAL COMMENT

Can the Vanishing Stent Reappear?

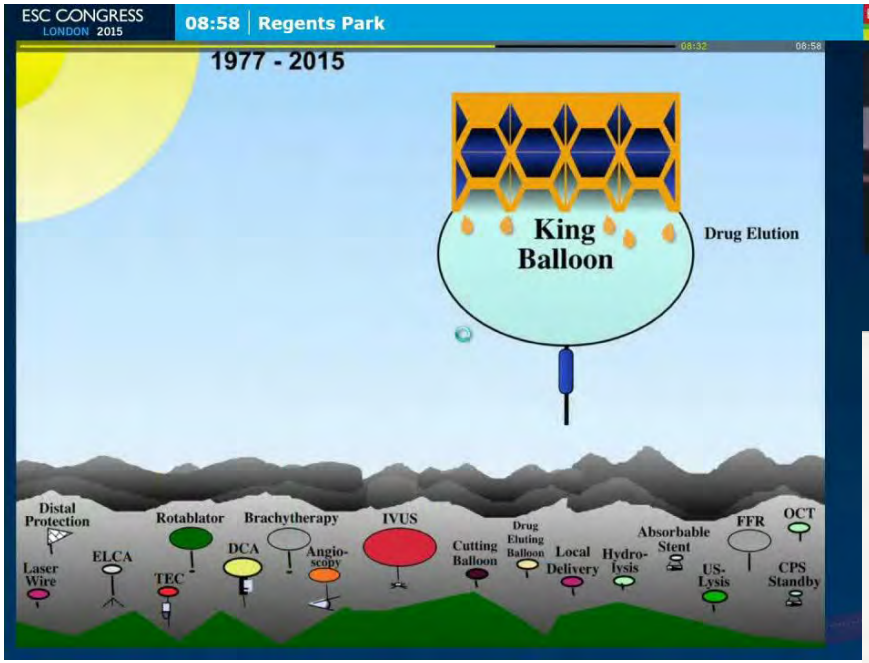
Fix the Technique, or Fix the Device?*

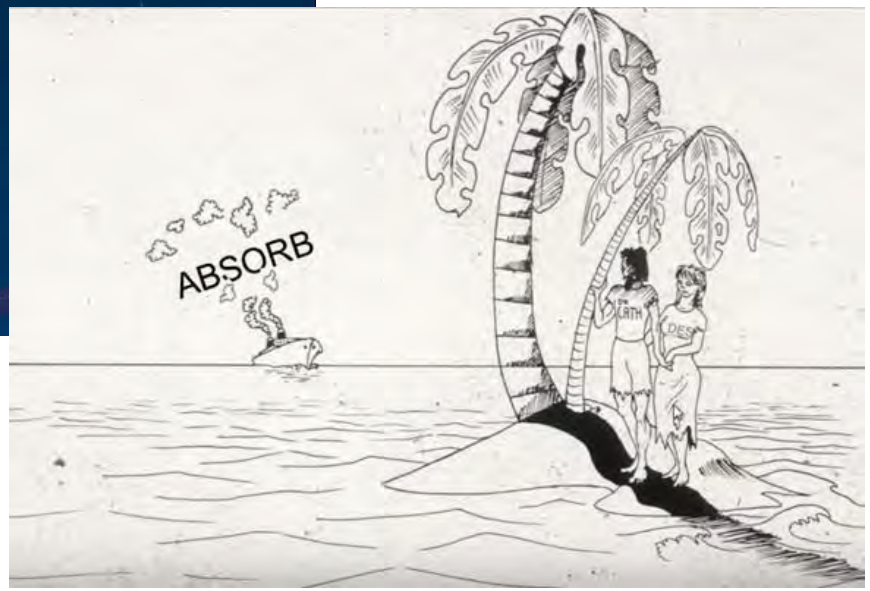
Spencer B. King III, MD, Bill D. Gogas, MD, PhD

© JACC

"For the time being, although the ABSORBing scaffold has vanished, we believe that improved disappearing technologies will eventually reappear; whether they will be competitive with current and future coronary stents remains questionable."

Bernhard Meier's Review (ESC 2015, London)





ESC TV 2015 - ESC Andreas Grüntzig Lecture on Interventional Cardiology (Session 763)

European Society of Cardiology
Ajoutée le 2 sept. 2015

Patent foramen ovale (PFO) device closure for prevention of recurrent ischemic stroke

PFO

"Please Figure Out," or Now "Potentially Figured Out?"*

Barry A. Love, MD,[a] Hans-Christoph Diener, MD, PhD[b]

three recent randomized trials, RESPECT extended follow-up [36], REDUCE [37], and CLOSE [38]

RESPECT Saver JL et al. Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke. N Engl J Med. 2017;377(11):1022.

REDUCE Søndergaard L, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. N Engl J Med. 2017;377(11):1033.

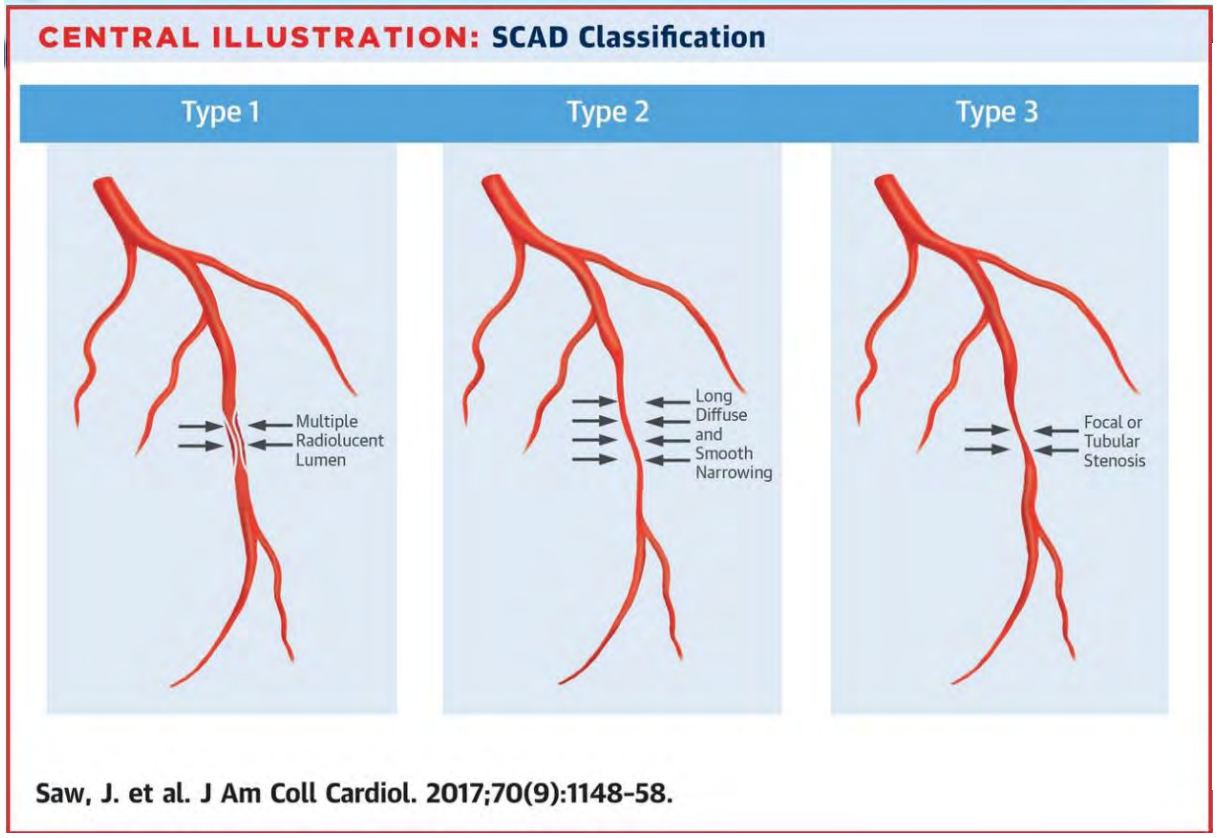
CLOSE Mas JL et al. Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke. N Engl J Med. 2017;377(11):1011.

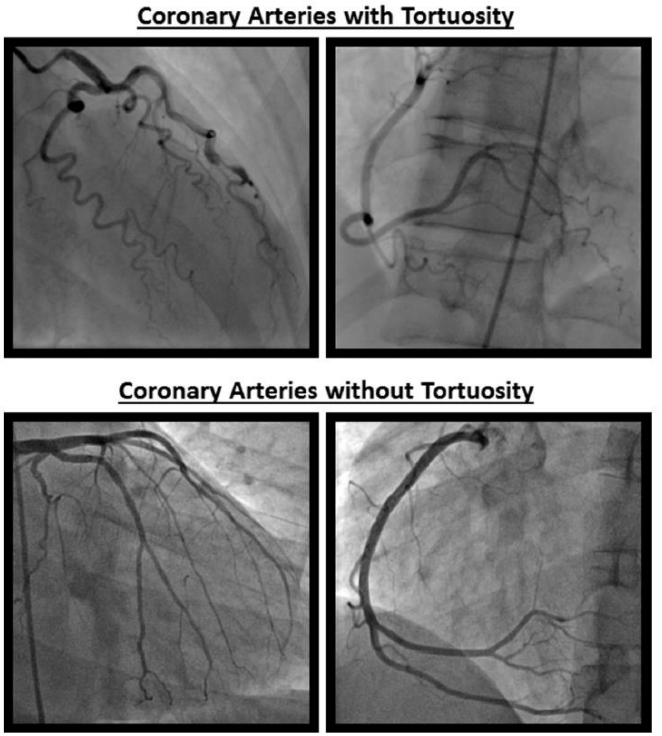
http://dx.doi.org/10.1016/j.jacc.2015.12.022

2. Unusual causes
for coronary artery stenosis/obstruction

- Spontaneous Coronary Artery Dissection
- Myocardial bridging
- Air embolism
- Congenital anomaly of coronary arteries

Spontaneous Coronary Artery Dissection (SCAD)





3. CVD Biomarkers

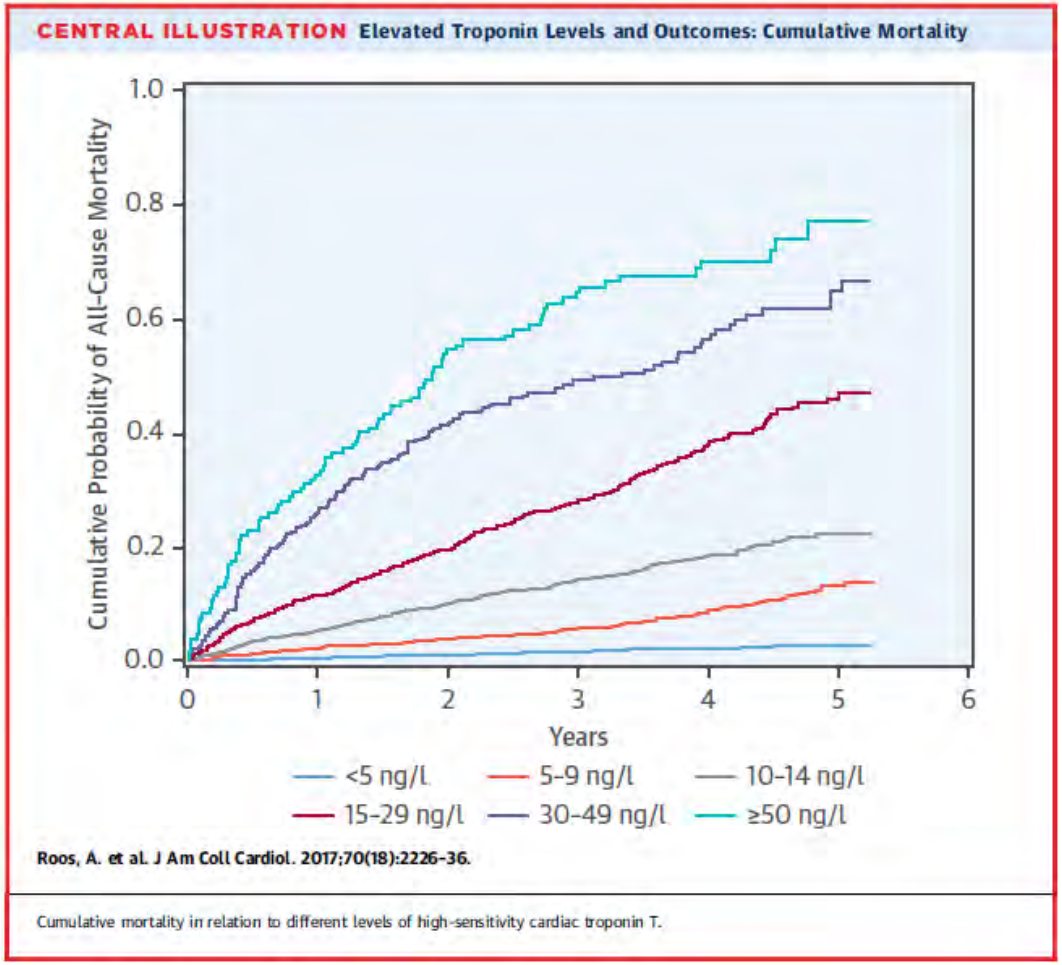
- Troponin (hs-cTnT)
- NT-proBNP

Balloons over Clifton Suspension Bridge. Photograph: courtesy of Business Interiors.

Stable High-Sensitivity Cardiac Troponin T Levels and Outcomes in Patients With Chest Pain

Patients (N=22,589)>25 years of age with chest pain and hs-cTnT analyzed concurrently in the emergency department of Karolinska University Hospital, Stockholm, Sweden from 2011 to 2014

Andreas Roos, MD,[a,b] Nadia Bandstein, MD, PhD,[a,b] Magnus Lundbäck, MD, PhD,[c,d] Ola Hammarsten, MD, PhD,[e] Rickard Ljung, MD, PhD,[f] Martin J. Holzmann, MD, PhD[a,b]



J AmColl Cardiol 2017;70:2226–36)

High sensitivity cardiac troponin test results in the general population?

High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants

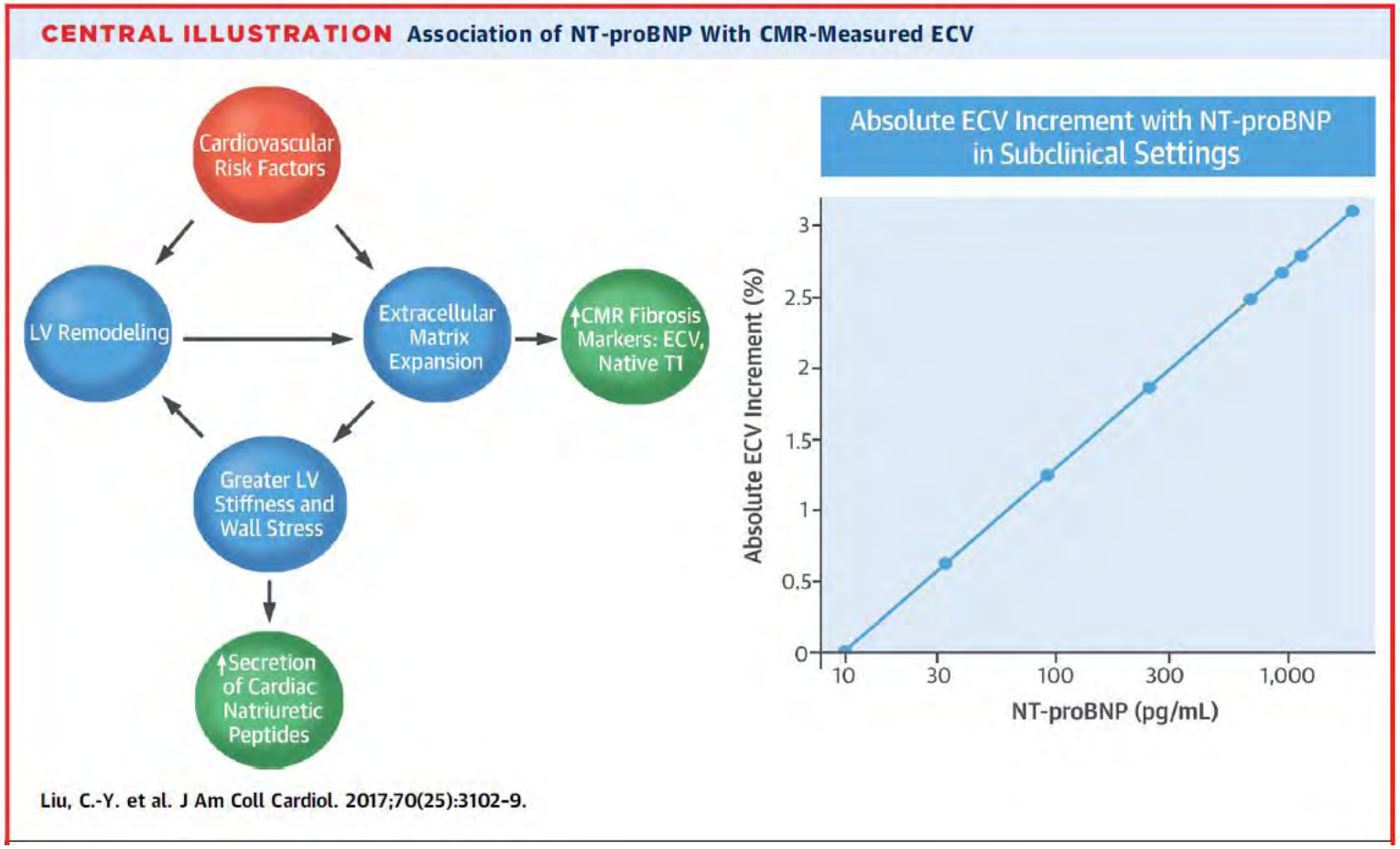
Peter Willeit, MD, MPHIL, PHD,[a,b] Paul Welsh, PHD,[c] Jonathan D.W. Evans, MBCHB,[b,d] Lena Tschiderer, DIPL-ING, BSC,[a] Charles Boachie, BSC,[c] J. Wouter Jukema, MD, PHD,[e] Ian Ford, PHD,[f] Stella Trompet, PHD,[g] David J. Stott, MD,[c] Patricia M. Kearney, MD, PHD,[h] Simon P. Mooijaart, MD, PHD,[g] Stefan Kiechl, MD,[a] Emanuele Di Angelantonio, MD, MSC, PHD,[b,i,j,k] Naveed Sattar, MD, PHD[c]

In the general population, high cardiac troponin concentration within the normal range is associated with increased CVD risk. This association is independent of conventional risk factors, strongest for fatal CVD, and applies to both CHD and stroke.

J Am Coll Cardiol. 2017;70(5):558.

NT-proBNP as predictor of diffuse fibrosis in heart failure?

1,334 participants (52% white, 23% black, 11% Chinese, 14% Hispanic, and 52% men with a mean age of 67.6 years) at 6 sites had both serum NT-proBNP measurements and CMR with T1 mapping of indices of fibrosis at 1.5 T.



J Am Coll Cardiol. 2017;70(25):3102–9.

NT-proBNP as predictor of diffuse fibrosis in heart failure?

NT-proBNP and Myocardial Fibrosis

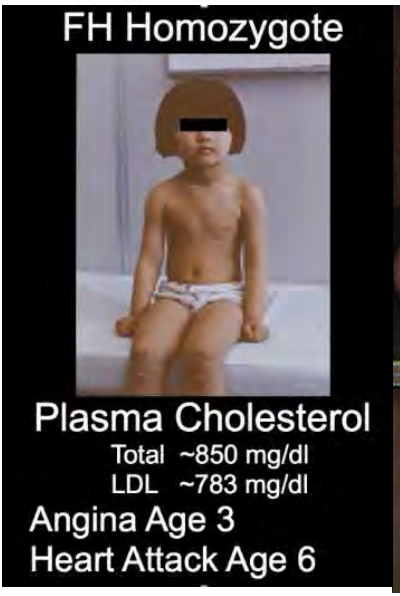
The Invisible Link Between Health and Disease*

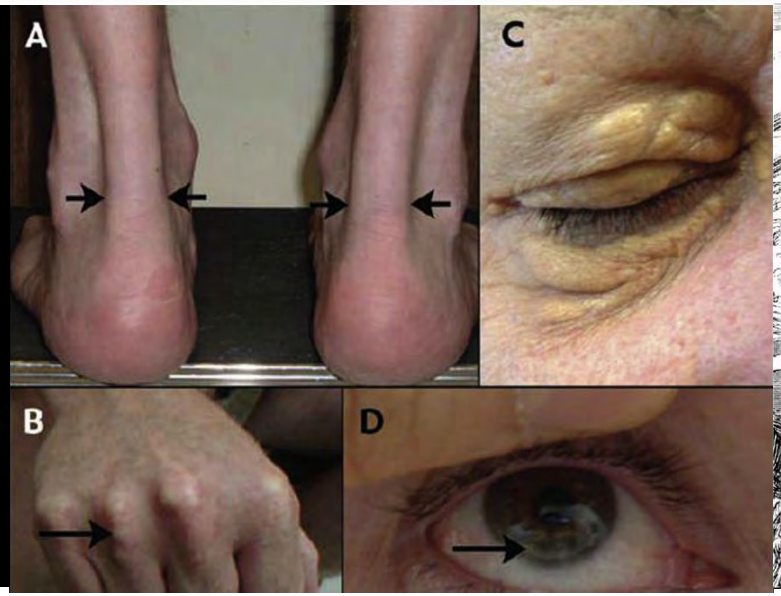
Ana G. Almeida, MD, PhD

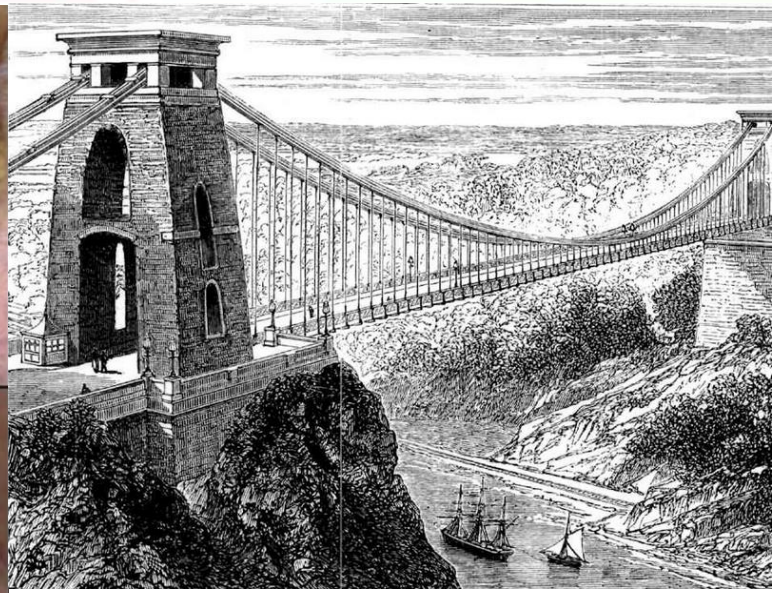
- Natriuretic peptides discovered in the 1980s
- Myocardial stretch signal is the key stimulant for BNP synthesis
- In the normal state, the cardiac production and plasma concentrations of BNP and NT-proBNP are very low but are readily increased with appropriate stimulus
- NT-proBNP and BNP are established as powerful biomarkers for heart failure diagnosis and prognosis, identifying high-risk patients
- Liu et al. examined the relationship of NT-proBNP and diffuse myocardial fibrosis in a community-based study from the MESA (Multi-Ethnic Study of Atherosclerosis) study, using a cardiac magnetic resonance T1 mapping technique (accepted as a surrogate marker of diffuse fibrosis)

https://doi.org/10.1016/j.jacc.2017.11.010

4. CVD risk factors Lipidology



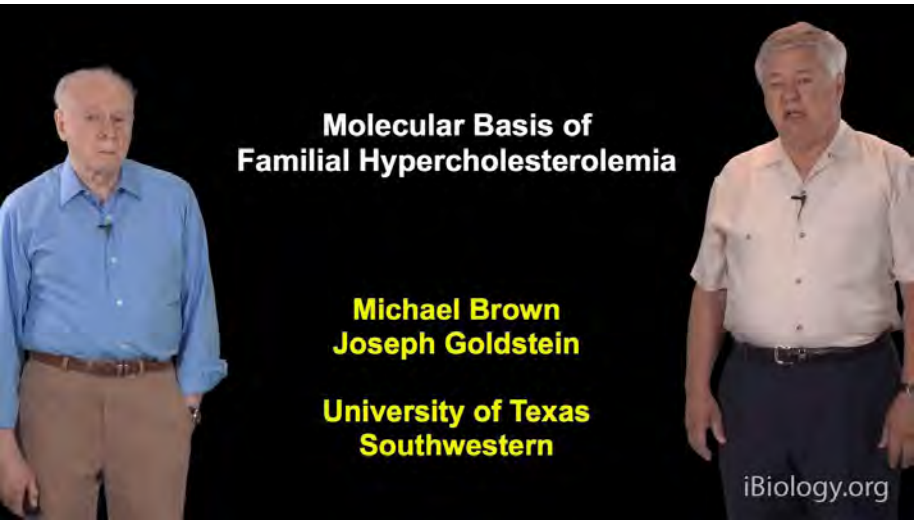




What causes Familial Hypercholesterolemia?

PCSK9 and PCSK9 Inhibitors

Gene of rare effect: A mutation that gives people rock-bottom cholesterol levels has led geneticists to what could be the next blockbuster heart drug.



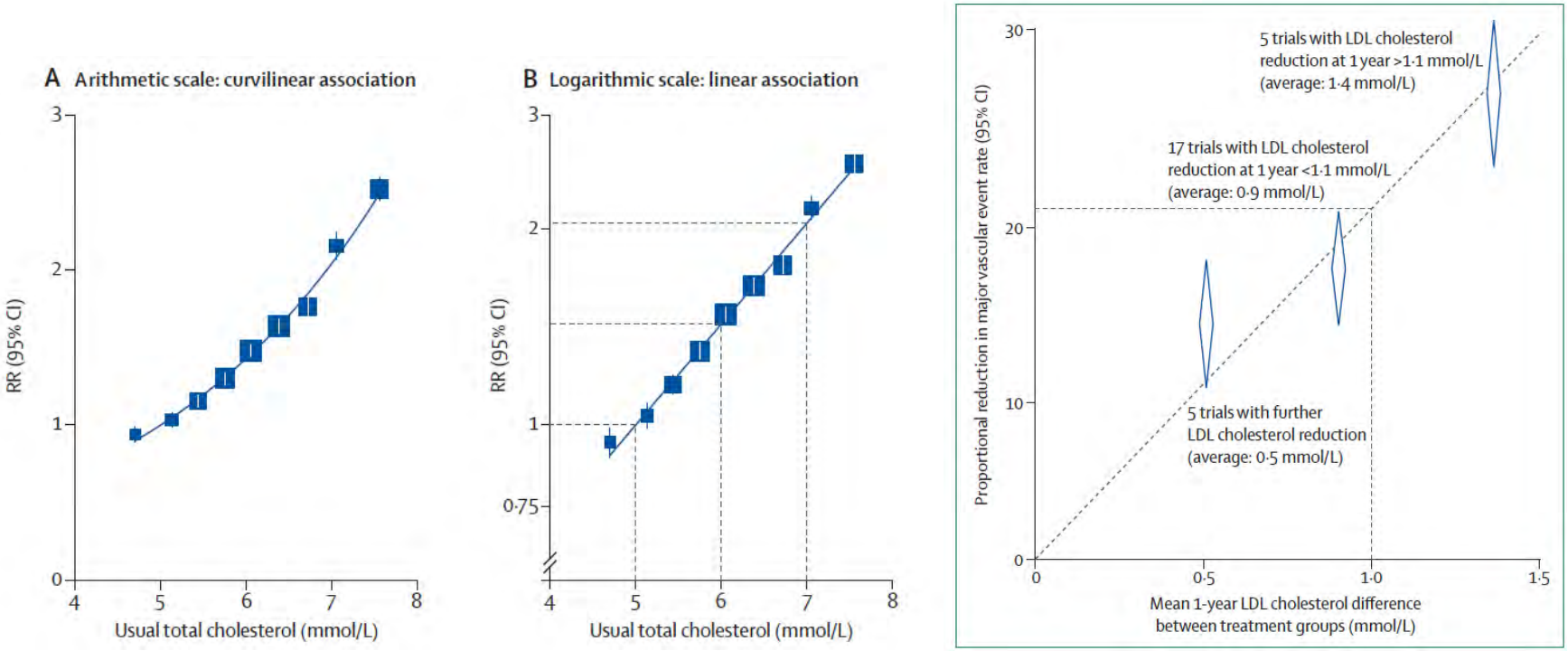
Michael Brown & Joseph Goldstein, UTSW

Helen Hobbs and **Jonathan Cohen**'s approach to heart-disease genetics yielded a target for drugs that could compete with statins, see **2016 Breakthrough Prize**

Stephen S. Hall, 152 | NATURE | VOL 496 | 11 APRIL 2013

Interpretation of the evidence for the efficacy and safety of statin therapy

Rory Collins, Christina Reith, Jonathan Emberson, Jane Armitage, Colin Baigent, Lisa Blackwell, Roger Blumenthal, John Danesh, George Davey Smith, David DeMets, Stephen Evans, Malcolm Law, Stephen MacMahon, Seth Martin, Bruce Neal, Neil Poulter, David Preiss, Paul Ridker, Ian Roberts, Anthony Rodgers, Peter Sandercock, Kenneth Schulz, Peter Sever, John Simes, Liam Smeeth, Nicholas Wald, Salim Yusuf, Richard Peto



Association of blood concentrations of total cholesterol with rates of coronary heart disease mortality.
Proportional major vascular event reductions versus absolute LDL cholesterol reductions in randomised trials of routine statin therapy versus no routine statin use and of more intensive versus less intensive regimens (CTT Collaboration)

THE LANCET

Statin awareness and reported muscle-related adverse events

Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

Ajay Gupta, David Thompson, Andrew Whitehouse, Tim Collier, Bjorn Dahlof, Neil Poulter, Rory Collins, Peter Sever, on behalf of the ASCOT Investigators

These analyses illustrate the so-called nocebo effect, with an excess rate of muscle-related AE reports only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded.
These results will help assure both physicians and patients that most AEs associated with statins are not causally related to use of the drug and should help counter the adverse effect on public health of exaggerated claims about statin-related side-effects.

"Like cholera, obesity may be a problem that cannot be solved by individual persons but that requires community action"

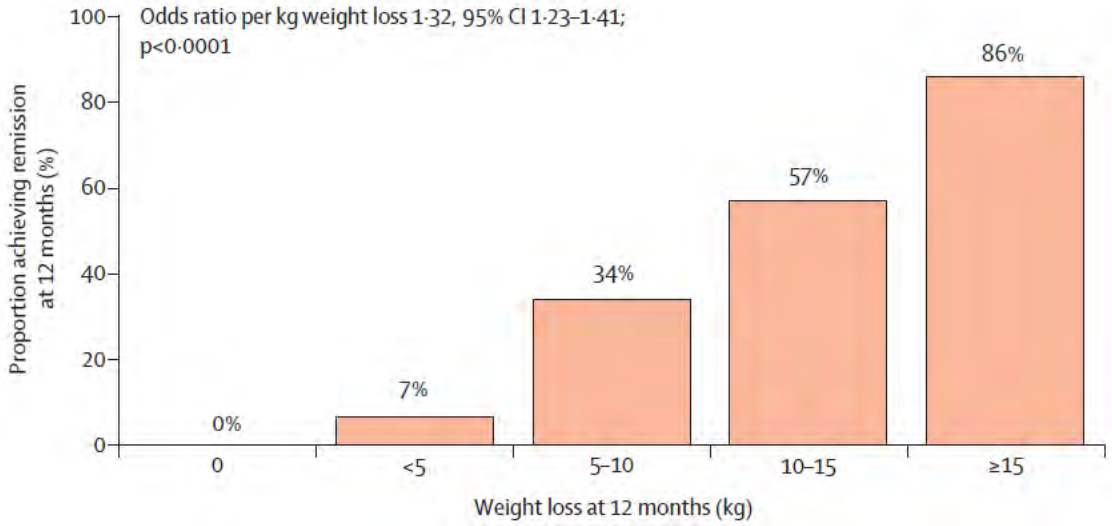
6. CVD risk factors Glucocentric view

NEJM 2009;360:859

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

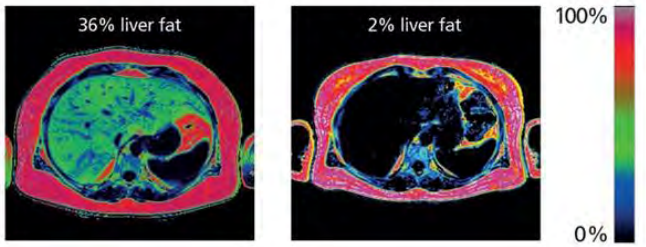
Michael EJ Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Remission of diabetes in relation to weight loss at 12 months



Professor **Roy Taylor** at Newcastle University (left) and Professor **Mike Lean** at the University of Glasgow (right) are leading the DIRECT study

Open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and the Tyneside region of England.
20–65 years old individuals who had been diagnosed with type 2 diabetes within the past 6 years, with a BMI 27–45 kg/m², and not on insulin.
149 participants per group comprised the intention-to-treat population.
At 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care.



An MRI scan of the liver - shows high levels of fat in green (left) and a big decrease in fat after a low-calorie diet (right)

The Lancet, December 5, 2017
http://dx.doi.org/10.1016/S0140-6736(17)33102-1

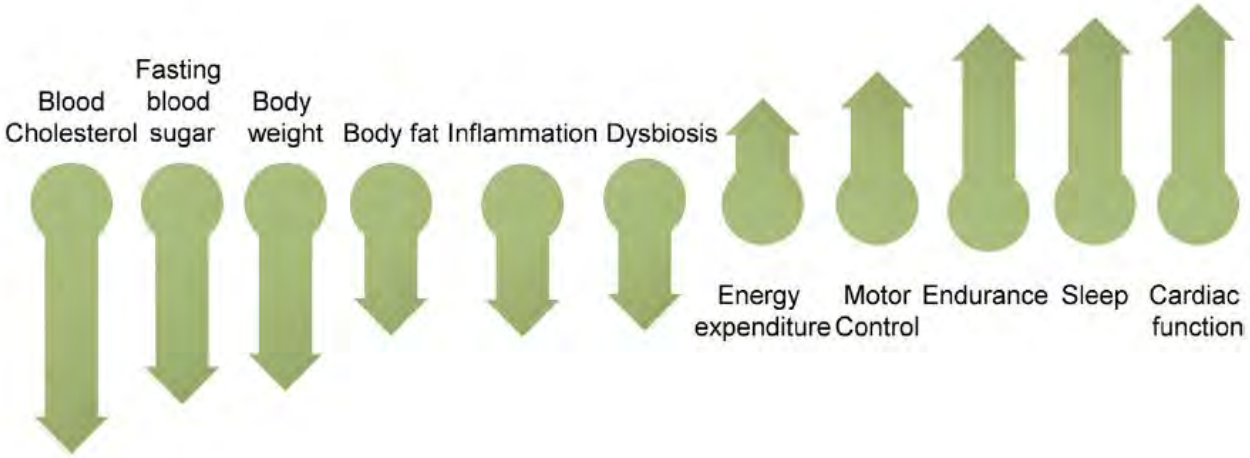
Fasting Mimicking Diet
includes autophagy induction

Dr. Roy Walford – Biosphere 2

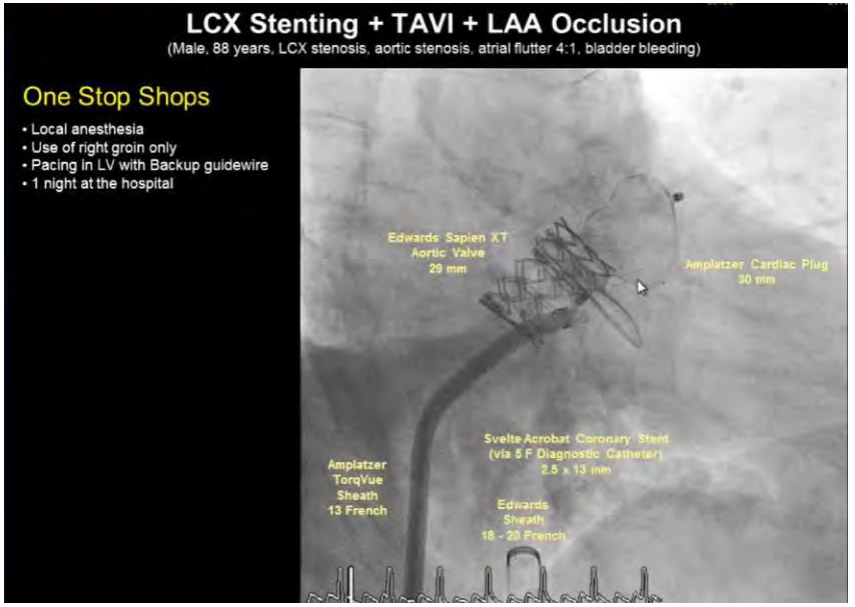
Calorie Restriction

HUMANS: Fasting Mimicking Diet (FMD)

5 days a month for 3 months

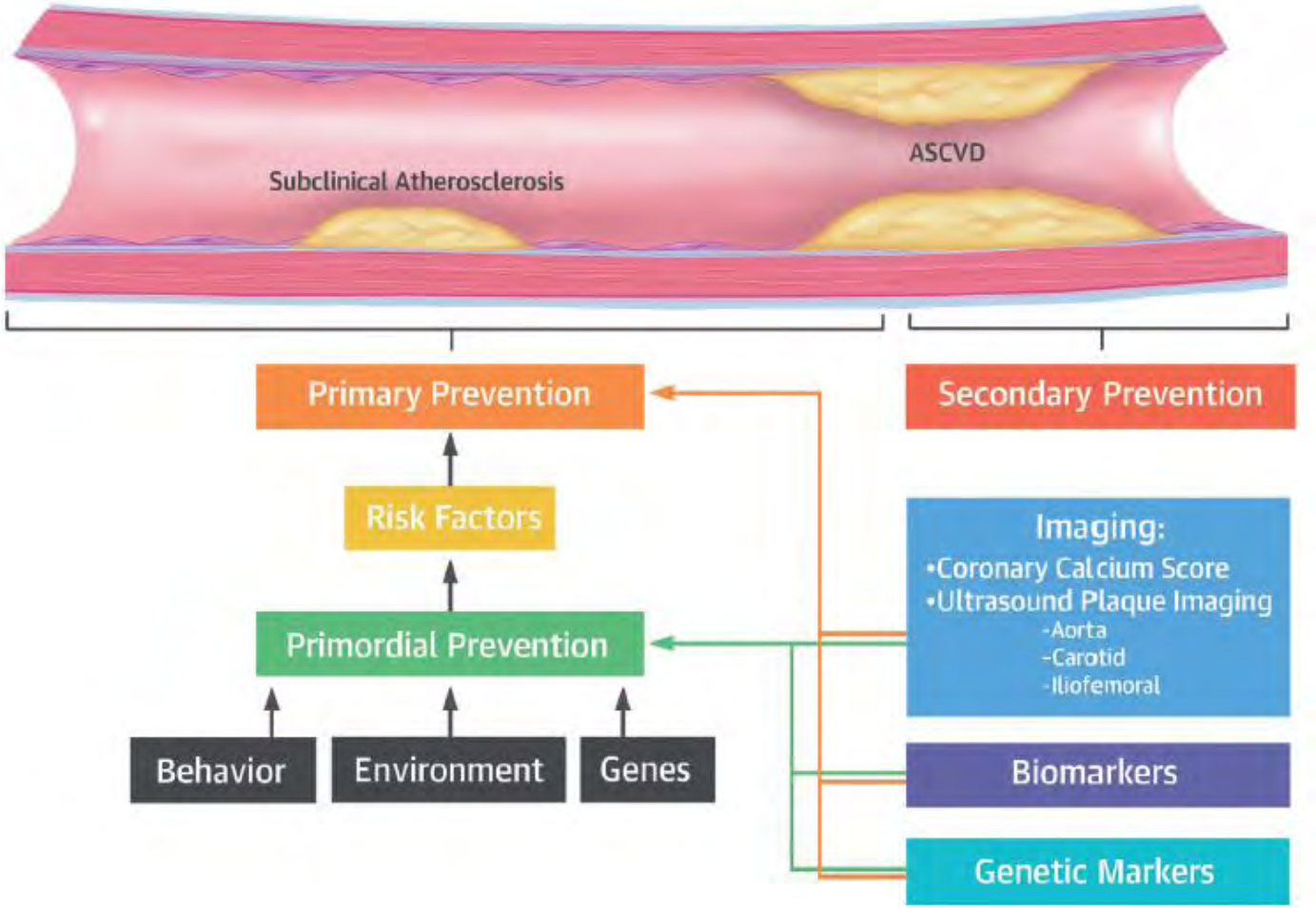


7. CVS risk assessment
Further developments



Primary Prevention of Atherosclerosis

Time to Take a Selfie?*

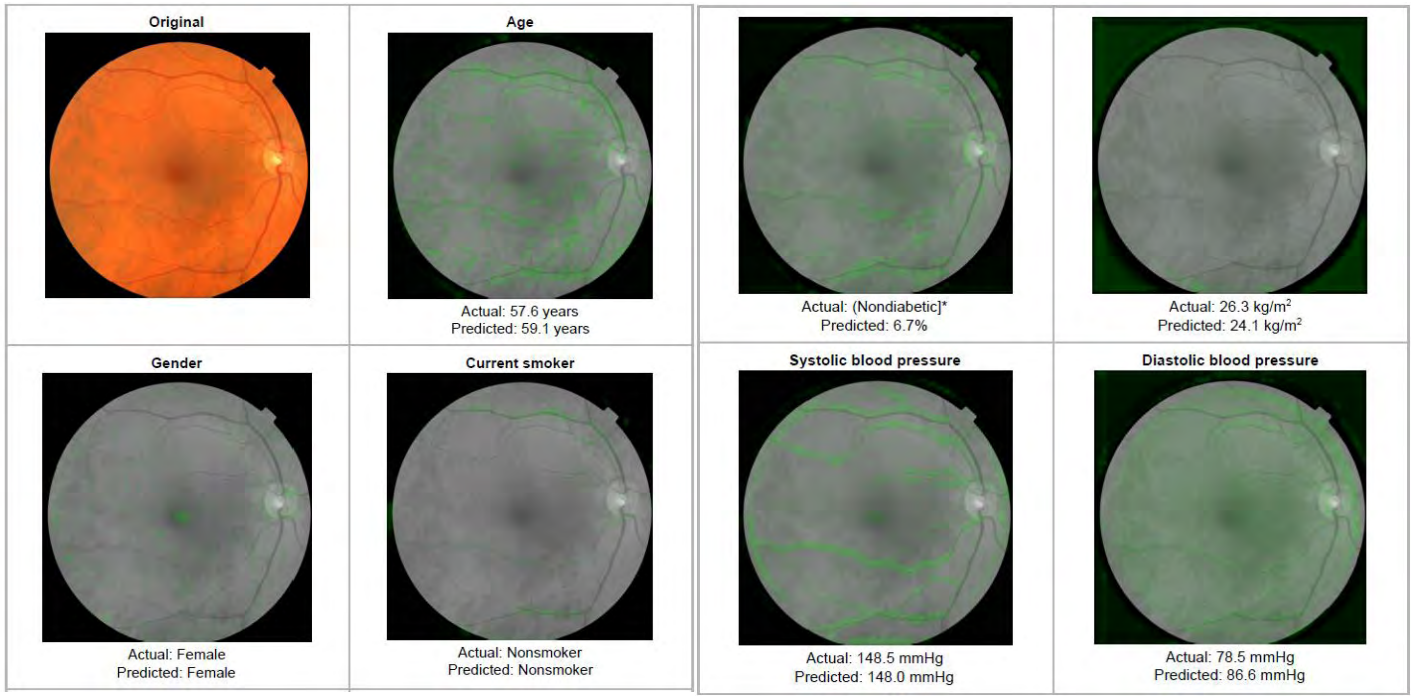


Prevention of ASCVD: A future framework for prevention of atherosclerotic cardiovascular disease (ASCVD), potentially incorporating imaging, biomarkers, and genetics.

https://doi.org/10.1016/j.jacc.2017.10.068

Predicting Cardiovascular Risk Factors from Retinal Fundus Photographs using Deep Learning

Ryan Poplin, Avinash V. Varadarajan, Katy Blumer, Yun Liu, Michael V. McConnell, Greg S. Corrado, Lily Peng, Dale R. Webster



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Deep learning was used to discover CVD risk factors from retinal fundus images. Using models trained on data from **284'335** patients, and validated on two independent datasets of **12'026** and **999** patients, we predict cardiovascular risk factors not previously thought to be present or quantifiable in retinal images, such as age, gender, smoking status, HbA1c, systolic blood pressure as well as major adverse cardiac events. Surprisingly, models used distinct aspects of the anatomy to generate predictions, such as optic disc or blood vessels.

https://arxiv.org/abs/1708.09843
Cite as: arXiv:1708.09843 [cs.CV] (or arXiv:1708.09843v2 [cs.CV] for this version)

Conclusion

- Fractional flow reserve (FFR)-guided PCI is best practice
- PCI + drug eluting stents (DES) are used, current bioresorbable scaffolds are to “clumsy” and have high rates of stent thrombosis
- ORBITA: UK pioneered the world’s first sham-controlled PCI Trial 2017 in stable, 1-vessel CAD
- hs-Troponin and NT-proBNP might become useful for long term prognosis
- Drugs targeting PCSK9 (via degradation of the LDL receptor) lower cholesterol effectively, but are expensive
- Screening by imaging for detecting subclinical atherosclerosis even in the absence of CVD risk factors might be used more often: “Time for a selfie”
- Type 2 Diabetes therapy paradigm change: T2D gets in remission after ±15 kg weight loss. Diets should be prescribed, not antidiabetic drugs! (Fasting mimicking diet, Low carbohydrate & high fat diet, low calorie diet)

Thank you!

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