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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• Bioresorbable Scaffolds (BRS)?

1. Coronary Interventions
Despite 40 years of coronary balloon angioplasty:
Many unanswered questions remain
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

World’s first balloon angioplasty at Zurich University Hospital 1977 by Andreas Grüntzig (later moved to Emory, Atlanta, USA)
Myocardial infarction – Nomenclature Consensus

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

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.

- Complete revascularization
- Infarct-artery-only treatment

Hazard ratio, 0.35 (95% CI, 0.22–0.55)
P<0.001 by log-rank test

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

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Exercise time (s)</td>
<td>104</td>
<td>90</td>
</tr>
<tr>
<td>Patients assessed</td>
<td>528.0 (178.7)</td>
<td>490.0 (195.0)</td>
</tr>
<tr>
<td>Pre-randomisation</td>
<td>556.3 (178.7)</td>
<td>501.8 (190.9)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>28.4 (95% CI 11.6 to 45.1)</td>
<td>11.8 (95% CI -7.8 to 31.3)</td>
</tr>
<tr>
<td>Increment (pre-randomisation to follow-up)</td>
<td>16.6 (95% CI -8.9 to 42.0)</td>
<td></td>
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<tr>
<td>Difference in increment between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.200</td>
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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.
Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

Graph A: Hazard ratio, 1.12 (95% CI, 0.85–1.48) P=0.43

Graph B: Hazard ratio, 5.39 (95% CI, 2.08–14.00) P<0.001

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

Months since Index Procedure

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

“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)

https://www.youtube.com/watch?v=J_ZOs8bcj3w&t=1801s
Patent foramen ovale (PFO) device closure for prevention of recurrent ischemic stroke

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


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
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.
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.
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.

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)
4. CVD risk factors
Lipidology

FH Homozygote

Plasma Cholesterol
Total ~850 mg/dl
LDL ~783 mg/dl
Angina Age 3
Heart Attack Age 6
What causes Familial Hypercholesterolemia?

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


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


Remission of diabetes in relation to weight loss at 12 months

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)
Fasting Mimicking Diet includes autophagy induction

Calorie Restriction

Dr. Roy Walford – Biosphere 2

Baseline  Calorie Restricted  Re-fed

HUMANS: Fasting Mimicking Diet (FMD)
5 days a month for 3 months

The FMD

Blood
Cholesterol  Fasting
blood sugar  Body
weight  Body fat  Inflammation  Dysbiosis

Energy expenditure  Motor Endurance  Sleep  Cardiac function

Cell Metabolism 23, June 14, 2016
SELECT 74 Bristol  Jan 2018
7. CVS risk assessment
Further developments

http://www.telegraph.co.uk
Primary Prevention of Atherosclerosis

Time to Take a Selfie?*


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

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
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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