5 Important Trials in Ischemic Heart Disease in the Last Year

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Conflicts and disclosures – none
The NEW ENGLAND JOURNAL of MEDICINE

December 8, 2016

Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

EXCEL results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PCI</th>
<th>CABG</th>
<th>Non Inferior</th>
<th>Superior</th>
</tr>
</thead>
</table>
| **Primary:**  
Death, CVA or MI  
- 3 years | 15.4% | 14.7% | Yes | No |
| **Secondary:**  
Death, CVA or MI  
- 30 days | 4.9% | 7.9% | Yes | Yes |
| Death, CVA, MI or revascularization  
- 3 years | 23.1% | 19.1% | Yes | No |

Stone GW: NEJM 2016
EXCEL – noteworthy observations

Largest ULMCA trial

Best 2G DES – ST in 0.7%

Optimal surgical procedures
  Arterial conduits, off pump etc

30% had diabetes mellitus

Large periprocedural MI counted for PCI and CABG

SYNTAX Score not discriminatory
Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial

Timo Mäkilä, Niels R Holm, Mitchell Lindsay, Mark S Spence, Andrejs Erglis, Ian B A Menown, Thor Trovik, Markku Eskola, Hannu Romppanen, Thomas Keller, Jan Ravikilde, Lisette O Jensen, Gintaras Kalinauskas, Rikard B A Linder, Markku Pentikainen, Anders Hervold, Adrian Banning, Azfar Zaman, James Cotton, Erlend Eriksen, Sulev Margus, Henrik T Sørensen, Per H Nielsen, Matti Niemelä, Kari Kervinen, Jens F Lassen, Michael Maeng, Keith Oldroyd, Geoff Berg, Simon J Walsh, Colm G Hanratty, Indulis Kumsars, Peteris Stradins, Terje K Steigen, Ole Fröbert, Alastair NJ Graham, Petter C Endresen, Matthias Corbascio, Olli Kajander, Uday Trivedi, Juha Hartikainen, Vesa Anttila, David Hildick-Smith, Leif Thuesen, Evald H Christiansen, for the NOBLE study investigators
# NOBLE results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PCI</th>
<th>CABG</th>
<th>Non Inferior</th>
<th>Inferior</th>
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<tbody>
<tr>
<td><strong>Primary:</strong> Death, CVA, MI, revascularization - 3 years</td>
<td>29%</td>
<td>19%</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Death*</td>
<td>12%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>7%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>16%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA*</td>
<td>5%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST or symptomatic graft occlusion*</td>
<td>3%</td>
<td>4%</td>
<td></td>
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* P = NS

Makikallio T: Lancet 2016
# NOBLE results

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Makikallio T: Lancet 2016

* P = NS
NOBLE – noteworthy observations

Composite EP included repeat revascularization
Primary endpoint timing changed (event rate low)
1G DES in 11%; BES 89% with ST in 3%
Optimal CABG techniques – not quite?
No routine check for periprocedural MI
Perplexing stroke rate in PCI – play of chance?
SYNTAX Score not discriminatory
2 Good Options for uLMCA Revascularization

- Improved immediate and long term PCI results
- Longer follow-up required …
  - trade-off of fewer early for more later events with PCI?
- Challenges CABG as default revascularization option

“…majority of patients with unprotected left main coronary artery disease….can now be managed equally well by means of two strategies of revascularization if carried out by expert, experienced teams…” (Braunwald E)*

*Editorial by Braunwald E: NEJM 2016
Current practice and guidelines

CABG preferred over PCI

PCI class IB in Europe

PCI class IIA in USA
Bioresorbable Scaffolds versus Metallic Stents in Routine PCI

Joanna J. Wykrzykowska, M.D., Ph.D., Robin P. Kraak, M.D., Sjoerd H. Hofma, M.D., Ph.D., Rene J. van der Schaaf, M.D., Ph.D., E. Karin Arkenbout, M.D., Ph.D., Alexander J. Ijsselmuiden, M.D., Ph.D., Joëlle Elias, M.D., Ivo M. van Dongen, M.D., Ruben Y. G. Tijssen, M.D.

Stent thrombosis almost 4x higher with Bioresorbable Scaffold versus Metallic EES

Wykrzkowska JJ: NEJM 2017
Primer on Coronary Stent Technology

Stent scaffold
  Co-Chromium (permanent)
  Poly (L-lactide) (bioreosorbable)

Polymer which elutes the active drug
  Durable or bioreosorbable

Polymer-free - passive

Antiproliferative drug
  e.g. everolimus
Bioresorbable Vascular Scaffold (BVS)

Stent scaffold  poly (L-lactide) (bioreabsorbable)
Polymer  bioresorbable
Eluted drug  everolimus
Failed to meet co-primary endpoints of superior vasomotor function and non-inferior late lumen loss compared to metallic EES (Xience)
ABSORB II
Device-Oriented Clinical Endpoints

Stent thrombosis:
ABSORB scaffold 3%
Xience stent 0%

HR (95% CI) 2.17 (1.01–4.69); log-rank P=0.0425

2-year results of ABSORB III

Abbott’s pivotal trial for US premarket approval

In 2015, 1-year results had shown non inferiority*

Results: Xience DES superior to BVS

Target vessel failure and MI

Numerically more cardiac death and TLR

Numerically more device thrombosis

*Ellis SG: NEJM 2015
## AIDA – Main results at 2 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Scaffold</th>
<th>Metallic EES</th>
<th>Non Inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong> Target vessel failure*</td>
<td>11.7%</td>
<td>10.7%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Safety:</strong> Definite device thrombosis</td>
<td>3.5%</td>
<td>0.9%</td>
<td>HR 3.87 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

*Cardiac death, target vessel MI, target vessel revascularization

Wykrzkowska JJ: NEJM 2017
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease


...canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering

Ridker PM: NEJM 2017
Inflammation and atherothrombosis

Role for inflammation well documented

Lack evidence demonstrating lower CV events by decreasing vascular inflammation, independent of lipid-lowering (statins)

Canakinumab:
- Human monoclonal Ab inhibits interleukin-1β
- Lowers interleukin-6 and CRP
- Does not lower LDL-C
CANTOS results
10,061 pts with prior MI and elevated hsCRP

<table>
<thead>
<tr>
<th>Endpoint (48 months)</th>
<th>Placebo</th>
<th>All doses</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong> MI, CV death or CVA</td>
<td>4.50%</td>
<td>3.95%</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Secondary:</strong> Primary + unstable angina leading to revascularization</td>
<td>5.13%</td>
<td>4.36%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Ridker PM: NEJM 2017
Shared decision making
Magnitude of treatment effect

Placebo

Canakinumab 150-mg dose

$200,000 per year
Proof of concept achieved but what are the clinical implications of CANTOS?

Modest effect but only by decreasing non fatal MI
Excess fatal infections and sepsis
Lower mortality from cancer
Cost in this population is prohibitive

“…cannot justify its routine use in patients with prior MI…”

Harrington RA: NEJM 2017
Oh no!
Now what?
Triple therapy?
Patients with AF who had PCI, risk of major bleeding was significantly lower with dual therapy (dabigatran and a P_2Y_{12} inhibitor) compared to triple therapy. Adverse ischemic events were similar.
2725 patients
AF (CHA$_2$DS$_2$-VASc 3.6)
PCI (DES >82%)

981 pts
Dabigatran 110-mg
P$_2$Y$_{12}$ inhibitor

"Dual 110-mg"

763 pts*
Dabigatran 150-mg
P$_2$Y$_{12}$ inhibitor

"Dual 150-mg"

981 pts
Warfarin, P$_2$Y$_{12}$ inhibitor and ASA

"Triple therapy"

*Excluded elderly pts outside USA

Cannon CP: NEJM 2017
RE-DUAL results at 14 months

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Dual 110-mg</th>
<th>Dual 150-mg</th>
<th>Triple therapy</th>
<th>Non inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary:</strong> Major bleeding</td>
<td>15.4%</td>
<td>20.2%</td>
<td>26.9%</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Efficacy:</strong> Composite</td>
<td>13.7%</td>
<td>13.4%</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>CVA</td>
<td>1.7%</td>
<td>1.2%</td>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Def stent thrombosis</td>
<td>1.5%</td>
<td>1.0%</td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>

Cannon CP: NEJM 2017
Commentary

Results consistent with 2 prior trials
Dropping ASA results in significant lower risk of major bleeding
No signal of increase in ischemic events
Strongly consider avoiding triple therapy in patients with AF who undergo PCI with DES
Majority were on clopidogrel, not ticagrelor
Ideal combination not known
bell.malcolm@mayo.edu