Comments on the CURE and ACTIVE Genetics
ESC, Stockholm
Oct 29th, 2010

Robert M Califf MD
Vice Chancellor for Clinical Research
Duke University

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Strengths of Study

- Robust placebo controlled design of studies: Allows view of placebo event rates as well as View of differential treatment effect understanding interactions between baseline characteristics and treatment effect is difficult
- 2 disease states: Acute coronary syndromes Atrial fibrillation
- Independent academic analysis

Possible Interpretation

- Multiple studies in acute ACS with high PCI rates seem to show relationship between loss of function and outcomes
- These 2 studies show no definitive relationship between alleles and outcomes or treatment effect—both are dealing with “chronic phase”
- Perhaps genotype matters in acute phase with high rate of PCI, but not during the chronic phase

Industry Relationships and Conflict of Interest

- I have multiple industry grants and contracts to do clinical research and consulting related to that research. A complete up to date list is kept at www.dcri.org/research/coi.jsp
- These include research and consulting grants and contracts with companies with an interest in antiplatelet agents including Bayer, Sanofi, Lilly, Astra Zeneca, Novartis

Pharmacogenetics: A mysterious science by which marketing expect to increase profits while reducing the scope for drugs.

- Pharmacogenetics: A cutting-edge science that will start delivering miracle cures the year after next.
- PK Senn

Fundamental Findings

- No relationship between alleles and placebo event rates
- Alleles are NOT associated with reversal of treatment effect
- Gain of function carrier state MAY be associated with exaggerated treatment effect in ACS, however
- Only 2/15 interactions nominally significant
- No relationship with loss of function carrier state
- No relationship in atrial fibrillation treatment

Pharmacogenetics in Practice

- Genes can be found that alter the response to drugs, including CV drugs
- RNA, proteins and metabolites can be found in patterns that provide pharmacokinetic estimates of clinical outcomes
- Almost always these pharmacogenetic do not provide a deterministic predictor of outcome
- Usually they take one probability distribution of prespecified outcomes and divide the distribution into 2 or more overlapping distributions
- In a rational world, the issue of whether its worth using a genomic test is not different than any other predictive test
- Since more easily measurable patient descriptors (e.g age, GCS) and response measure (BP, LDL, SBP) also refine probability distributions, the use of pharmacogenetic testing is a competitive effectiveness issue
3-Year Interim Results of the Percutaneous MONARC™ System for the Treatment of Functional Mitral Regurgitation

**EVOLUTION I Study**

- Prospective, multi-center feasibility study
- Primary objective of the study is to evaluate the acute safety (30d, 90d) of the MONARC system in treating functional mitral regurgitation in heart failure patients
- Secondary objective of the study is reduction in MR by at least one grade at 90 days

**The Edwards MONARC System**

**Procedural Success**

- Device implanted n=50 (82%)
  - Procedural Time: 94 ± 58 min
- Device not implanted n=7 (12%)
  - Tortuous Anatomy
  - Size Outside of Offered Range

**Potential conflicts of interest**

**Inclusion / Exclusion Criteria**

**INCLUSION**

- Functional mitral valve regurgitation: dilated or ischemic cardiomyopathy
- MR grade 2+ to 4+ on a scale of 4+
- Coronary Sinus Dimensions:
  - Target Area is ≥ 14 cm and ≤ 18 cm in length.
  - Distal section of target area: the AV is ≥ 3 mm in diameter

**EXCLUSION**

- Organic mitral regurgitation
- Ischemia requiring cardiac revascularization within 3 months prior to or planned after the implant procedure
- Implantable cardiac defibrillator (ICD) or pacing leads within the coronary sinus
- Ejection Fraction < 25%
- Moderate to severe mitral annulus calcification

**Population: 72 Patients Enrolled**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male Gender</th>
<th>70+/- 10 years (57-90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Gender</td>
<td>Overall</td>
<td>72 %</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Overall</td>
<td>68%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>CABG</td>
<td>57%</td>
</tr>
<tr>
<td>CABG</td>
<td>PICA</td>
<td>47%</td>
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<tr>
<td>PICA</td>
<td>NYHA</td>
<td>40%</td>
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<tr>
<td>NYHA</td>
<td>CLASS I</td>
<td>4%</td>
</tr>
<tr>
<td>CLASS II</td>
<td>CLASS III</td>
<td>42%</td>
</tr>
<tr>
<td>CLASS IV</td>
<td>CLASS V</td>
<td>50%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>CLASS VI</td>
<td>4%</td>
</tr>
</tbody>
</table>

**Study Population at 3 Years**

- Subjects Enrolled, n=72
- Not implanted, n=13
- Expired, n=16
- Study End, n=4
- Missing Baseline TTE, n=1
- MRI/Implant, n=1
- Image Not Calibrated, n=1

TTE included in Analysis n=32, matched patients
**Cumulative Safety**

Device Migration, Death, MI, Device Embolization, Cardiac Tamponade, Coronary Sinus Thrombosis, or Pulmonary Embolism.

**Long Term Follow Up to 3 years:**

NYHA Class

<table>
<thead>
<tr>
<th>NYHA Class Population Distribution (n=12, matched patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-procedure</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Class IV</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class I</td>
</tr>
</tbody>
</table>

% of patients

- Pre-Pro 3 Year 2 Year
- Mean: 3.14 3.77
- Median: 2 2

**Artery compression**

Compression of a marginal branch seen in 10 pts. 3 pts had a clinical event.
One was successfully stented, one case resolved itself, and one died at day 651.

**Cumulative Safety**

- Pre-procedure: 3.14
- 3 Year: 3.77
- Median: 2

- Majority of subjects in Class I or II

**EVOLUTION I** Learning

- Implantation in the coronary sinus is feasible, easy and reproducible
- 3 year data with the MONARC system shows:
  - At 36-months, 64% of patients are event-free
  - Encouraging 36-months results compared to baseline
  - MR reduction
  - Clinical functional NYHA class reduction
- Developed understanding of potential compression risk to adjacent arteries

**Conclusions**

- EVOLUTION I solely designed as a safety study
  - Small 3-year sample size
  - No control group
  - Limited insight in quantifying clinical benefit
- EVOLUTION II underway:
  - Designed with the learning from EVOLUTION I, the largest single study with longest term follow-up of CS devices
  - With a prospective control group
  - MR and Hemodynamic responses
  - Clinical Outcomes: NYHA, 6MWT, QoL

**ISAR-TEST-4: Two-year results**

Comments from Jean Marco, FESC

**ISAR-TEST-4:** Two-year results

**Method**

One biodegradable polymer (BP) DES vs Two permanent polymer (PP) DES (Cypher & Xience)

Non-inferiority trial: \( \Delta \leq 3\% \)

1st EP: Composite of clinical events
Sample size calculation of 2600 patients
ISAR-TEST-4: Two-year results

Results

- **Efficiency [TVR]**
  - @ one year: 8.8% vs 9.4%
  - @ two years: 11.0% vs 11.7%
  - Loss: 2.2% vs 2.3% (NS)

- **Safety**
  - Cardiac death/MI related to TV
    - @ one year: 6.3% vs 6.2%
    - @ two years: 7.1% vs 7.3%
  - Lesion: 0.8% vs 1.0% (NS)
  - Acute Thrombosis:
    - @ one year: 1.0% vs 1.5%
    - @ two years: 1.1% vs 1.7% (NS)

Conclusion

- Primary composite endpoint
  - Δ: 1%

- Biodegradable Polymer (Yucon): non-inferior to the two permanent polymers (Cypher-Xience)

- Longer FU is needed

- Not possible to extend this conclusion to
  - others DES with PP
  - others DES with PP

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ISAR-TEST-4: Two-year results

Limitations

- Two permanent polymers
  - Cypher vs XIence

- Late inflammatory response related to polymer (intima)
  - Cypher but not with XIence

- Cardiac death/MI related to target vessel/TLR @ 1 year
  - Cypher: 15.2%
  - XIence: 13.6% (NS)
  - Δ: not available at 2 years

- Longer FU is needed

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Financial disclosure

- I, Robert A. Byrne, have nothing to disclose

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ISAR-TEST-4

Biodegradable Polymer Versus Permanent Polymer DES: Two-Year Outcomes from a Large-Scale Randomized Trial


Deutsches Herzzentrum & T. Med. Klinik rechts der Isar Technische Universität München Germany

Late Adverse Events with DES

- In comparison with bare metal stenting, DES therapy is associated with a small excess of late events occurring more than one year after intervention

Delayed Arterial Healing

- The pathological substrate underlying these events is delayed arterial healing and inflammatory response to DES permanent polymer coatings seems to play a central role
Delayed Arterial Healing

- Biodegradable polymer stent coatings offer potential to improve arterial healing and decrease late adverse events

Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial

- Robert A. Byrne, Adrian Kantor, Sebastian Rubner, Steffen Momburg, K. Anette Birkholzer, Karl-Ludwig Langlois, Stefan Schuler, Jörgen Pacht, Maximilian Furer, Matthias Szypert, Albert Schöng, and Silvinda Mohill

ISAR-TEST-4

Two-year Outcomes

ISAR-TEST-4 Trial

- Biodegradable polymer (BP) DES
  - sirolimus-eluting (Yakura/POC China)
  vs.
- Permanent polymer (PP) DES
  - sirolimus-eluting (Cypher)
  - everolimus-eluting (Xience)

ISAR-TEST-4 - Primary Endpoint

Cardiac death, TV-related MI or TLR at 12 months

Δ = -0.9%

ISAR-TEST-4 Study Design

Primary Endpoint: cardiac death, MI related to the target vessel or TLR at 12 months

Inclusion Criteria:
- Ischemic symptoms or evidence of myocardial ischemia and presence of >30% stenosis in native coronary arteries

Exclusion Criteria:
- Target lesion in left main stem
- In-stent restenosis lesion

Baseline clinical characteristics

- Age, years
- Male, %
- Hypertension, %
- Diabetes, %
- Current smoker, %
- Hyperlpedemia, %
- Prior bypass surgery, %
- Prior MI, %

- BP-DES n=1299
- PP-DES n=1304

- Clinical presentation, %
  - acute MI
  - unstable angina
  - stable angina

- Multivessel disease, %
- Multivessel PCI, %
- LV ejection fraction, %
Conclusion

- In the setting of a real world randomized trial, BP-DES and PP-DES are associated with similar clinical outcomes out to 2 years.

- Although the concept behind biodegradable polymer DES is intuitively attractive, the hypothesized late performance advantage of these devices remains unproven at least out to 2 years.

DISCUSSION

MULTI STRATEGY: 3 year follow-up of the comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction

Patrick W. Serruyts, MD, Ph.D.
Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

29th August 2010
14:25-18:10

Background

- There is limited data on the comparison between Abciximab vs. Tirofiban at high bolus dose (HBB: 25 μg/kg over 3 min).
  - 4 RCTs have so far contrasted these two drugs in 719 pts undergoing PCI of whom less than 300 were recruited in the setting of STEMI.

- The use of DES in the setting of STEMI is currently discouraged due to partially conflicting results on efficacy from MC-RCTs and safety concerns from registries.

Study Primary Endpoints

Power Analysis

With 600 pts randomized and type I error set @2.5%

<table>
<thead>
<tr>
<th>Assumed event rates</th>
<th>Endpoints</th>
<th>Test</th>
<th>Abciximab</th>
<th>Tirofiban</th>
<th>SES</th>
<th>BMS</th>
<th>5</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STR</td>
<td>1.30%</td>
<td>85%</td>
<td>85%</td>
<td></td>
<td></td>
<td>9%</td>
<td>&gt;85%</td>
</tr>
<tr>
<td></td>
<td>MACE Sup.</td>
<td>16%</td>
<td>27%</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At the time of his fellowship in Rotterdam, Dr. Vaiglmiñigl was already designing mentally this trial based on the concept of a maybe less effective IIb/IIIa combined with an expensive and effective DES vs. a IIb/IIIa considered more effective than others but more expensive combined with a cheap BMS.

Study Primary Endpoints

Pharmacology Arm

- Non-inferiority based
  - ≥50% ≤ ST segment elevation resolution within 90’ after last balloon inflation @ tt-EKG

Stent Arm

- Superiority based
  - Cumulative rate of MACE, defined as overall death, Reinfarction or TVR within 8 months

Summary

- Tirofiban enables non-inferior STR within 90’ after intervention and similar outcomes at 8 months than Abciximab

- The MACE rate was approximately halved by the use of SES compared to BMS
General considerations on the relevance of the report

The study was performed with the high bolus of tirofiban (25 μg/kg over 3 minutes).

Although the MULTISTRATEGY trial has been designed some years ago, it is still contemporary from that point of view.

The risk of long-term follow-up is that a concept which seemed revolutionary and a major question mark at the time of the design, may look somewhat more futile at the time of medium long-term follow-up report.

Strong points of the study

- Small difference between the number of patients assessed for the eligibility and the number of patients randomized.
- Small deviation between the number of patients “per protocol” and “intention to treat”.
- Excellent clinical follow-up (patients lost at follow-up range between 1 and 3 per cohort).
- Appropriate long-term and balanced treatment in the four arms.
- Idea of checking the P2Y12 inhibition remains unclear why in the first year between DES and BMS arms, but not tirofiban arms. The duration of the use is a confounding factor in the small study.

Strength and weakness of multifactorial analysis

- The efficacy of DES on BMS in terms of TVR reduction is overwhelming and superseded the potential subtle differences in IIb/IIIa.
- AMI related to TVR (more frequent in BMS) but not related to definite stent thrombosis (potentially more frequent in DES) is a complex confounding factor in the interpretation of the possible difference or absence of difference between the two IIb/IIIa at medium and long-term follow-up.

Financial ground for the War

Three different GP IIb/IIIa inhibitors approved for use: abciximab (Eli Lilly & Company, Indianapolis, Indiana), eptifibatide (Schering-Plough, Kenilworth, New Jersey), and tirofiban (Medtronic, Winnipeg, Canada). The fierce competition among the companies that make and market these drugs, fighting for their share of the billion-dollar market, has kept the issue of the comparative effectiveness of the GP IIb/IIIa inhibitors in the spotlight. The economic differences in the price among the 3 agents make the comparative effectiveness and relative costs of these drugs important in this era of health care reform. The average wholesale price of abciximab is $1,856.00 (for a 12-h infusion) and of eptifibatide is $1,121.81 and tirofiban is $711.72 (for 18-h infusion) for a 30-kg patient with normal renal function (Merchant C, personal communication, June 2010).”

Many argue about whether price ought to be a strong consideration when 2 competing therapies differ in efficacy and safety. If, however, 2 treatments are similar in efficacy and safety, price is a very important, perhaps the most important, consideration.

Based on the 30-day outcomes of patients undergoing primary PCI in recent trials, a trial comparing 2 GP IIb/IIIa agents would need to enroll more than 10,000 patients to show noninferiority of 2 agents if any small but clinically significant margin of noninferiority were used. Such a trial would be so expensive that it is very unlikely one will ever be performed.”
Conclusions

What are the physicians going to do, given the uncertainty about how the 3 GP IIB/IIIA inhibitor drugs compared with one another? No definitive answer can be provided.

- Some physicians will continue to choose the most studied agents, rejecting underpowered trials as inconclusive (which they are).
- Others are comfortable choosing a promising but less studied agent.
- Still others will choose the cheapest agent.
- Still others (unfortunately) choose the agent whose salespeople are most effective, friendly or attractive.

In this era of constrained health care dollars, physicians ought to have all of the evidence they need to make the most informed decisions for their patients.

The investigators of the MULTI STRATEGY trial are to be congratulated for contributing to the existing body of evidence.

Background

- The data comparing Tirofiban at high dose bolus (HDB: 25 µg/kg over 3 min) to Abciximab is largely confined to 30-day outcomes. The value of abciximab over placebo has been shown to accrue over time.

- The long-term DES safety profile in patients with STEMI remains uncertain as only a limited number of controlled data exists beyond 2 years.

MULTISTRATEGY P.I.s and Sites

G Campo Ferrao
G Percoco Lopasti
M Anselmi Ferrao
L Bolognese Arzio
S Colangelo Tonino
N de Cesare Gropgia
A Rodriguez 8. de la Riva
M Ferrario Villa
R Moreno Madrid
T Piva Accornero
I Sheiban Timisoara
G Pasquetto Venedig
F Prati Rome
M Nazzaro Rome
J Fernandez Madrid
J Mieres Tenerife


Potential Conflicts of interest

Speaker’s bureau: Iroko, Chiesi, Eli Lilly, MEDCO, Cordis, Medtronic, Abbott

Advisory Board: Iroko, Chiesi, Eli Lilly, MEDCO, Medtronic

Research grant: Iroko, Merck, Eli Lilly, Medtronic

MULTISTRATEGY Design

All-comer STEMI Patients

Aspirin + Clopidogrel + UFH

Before Articular Sheath Insertion

1:1

Tirofiban

Abciximab

SES

BMS

Ses

BMS

Clinical FU only @ 1, 4, 8 mos,
1yr and 3 years

Primary Endpoint

≥50% ST segment resolution

P<0.001 for non-inferiority at ITT and PP Analysis

100
80
60
40
20
0

83.6%
85.3%

H0: 85%

[Statistical analysis: t=6.35, P<0.01]
Impact of CYP2C19 and ABCB1 single nucleotide polymorphisms (SNPs) on outcomes with ticagrelor and clopidogrel in acute coronary syndromes

A PLATO genetic substudy

K-M estimate of the primary endpoint in relation to any CYP2C19 LOF allele

What is known, what is not known

What are the consequences?

Routine determination of SNPs?
- which single SNP is important for the individual patient?
- point-of-care assays are not available
- genetic profiling is frequently not refunded

Should we tailor clopidogrel treatment (dosage) or the use of other new ADP receptor blockers (prasugrel, ticagrelor) based on genetic profiling?
- studies are ongoing, but not as such; these trials are more targeted for pharmacodynamics
- for clinical outcome

Should we use more potent agents than clopidogrel in medium- to high risk patients (STEMI, high risk NSTE-1MI, stent thrombosis) without genetic profiling?
- no known influence of SNPs on pharmacodynamics of prasugrel
- ticagrelor has different pharmacokinetics and is not affected
Summary

Certain SNPs (CYP2C19) play a role for low response to clopidogrel by influencing pharmacokinetics (metabolism), pharmacodynamics (platelet function testing) as well as clinical outcome.

Genetic disorders explain only a part of “clopidogrel resistance.”

Based on the current data and missing outcome results of prospective intervention trials, genetic profiling should not be recommended for routine use at present but will remain of increased scientific interest.

The use of more efficient antiplatelet agents, especially in patients with a medium-to-high risk profile for thrombotic complications after STEMI, NSTE PCI, prior stent thrombosis, has been shown to be effective and safe and makes genetic profiling less important.

PLATO

Impact of CYP2C19 and ABCB1 SNPs on outcomes with ticagrelor versus clopidogrel in acute coronary syndromes: a PLATO genetic substudy

Lars Wallentin, Siegfried James, Robert T Storey, Mark Armstrong, Bryan Baron, Jay Horner, Stefan Husted, Hagi Kaul, Giacomo Steg, Richard Becker for the PLATO investigators

PLATO study design

NSTEMI (moderate-to-high risk) STEMI (primary PCI)

Clopidogrel: if pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance (add additional 100 mg w/p PCI)

Ticagrelor: 180 mg loading dose, then 90 mg bid maintenance (add additional 90 mg w/p PCI)

6–12 month exposure

Primary endpoint: CV death + MI + stroke

Primary safety endpoint: Total major bleeding

Objectives of the genetic subsyudy

- Primary
  - Investigate if CYP2C19 and/or ABCB1 polymorphisms influence primary efficacy outcome when comparing treatments with ticagrelor versus clopidogrel in PLATO

- Secondary
  - Explore the role of the CYP2C19 and ABCB1 polymorphisms regarding other efficacy and safety outcomes both between and within the ticagrelor and clopidogrel arms in PLATO

Background:

Genetic variability of P2Y12 inhibitor response

- CYP2C19 and ABCB1 are main genetic determinants of clopidogrel PK/PD variability

- CYP2C19 gene is polymorphic in populations, affecting enzyme activity
  - CYP2C19*2: ~17% Europeans (WT allele) 15% Asians
  - CYP2C19*3: ~1% Asians

- Recent data indicate that CYP2C19 LOF carriers have more clinical events

- FDA warning about poor metabolisers of clopidogrel (March 2010)

- No known genetic regulation of ticagrelor PK/PD or response

Methodology:

Genetic analysis

- 10,285 patients in the PLATO study provided samples for DNA analysis.
  - Genotyping: 7 CYP2C19 LOF alleles and 1 GOF allele, ABCB1 SNP
  - 96,000 genotypes (2 weeks)

Statistical analysis

- Data-guided decision as to appropriate genotype groupings within each arm for each outcome

- Assessment of impact of genotype on outcomes for each drug

- Application of these and literature precedent (any versus no LOF allele) groupings to between-arms analysis

- Compare outcomes between ticagrelor and clopidogrel groups
Safety outcomes in relation to CYP2C19 LOF alleles

Conclusions

In a broad, global population with ACS:

- ticagrelor vs clopidogrel superior for prevention of CV death, MI and stroke regardless of CYP2C19 and ABCB1 genotype
- ticagrelor vs clopidogrel benefits on ischemic events appear earlier in carriers of any CYP2C19 LOF allele
- ticagrelor vs clopidogrel bleeding comparisons are unaffected by CYP2C19 and ABCB1 genotypes
- with clopidogrel, carriers of CYP2C19 LOF alleles have higher ischemic event rates, but not later, after start of treatment
- with clopidogrel, carriers of CYP2C19 GOF alleles have higher bleeding rates
- with ticagrelor, no variation in rates of ischemic or bleeding events in relation to CYP2C19 or ABCB1 genotype

Implications

Ticagrelor is a more efficacious treatment for acute coronary syndromes than is clopidogrel, irrespective of CYP2C19 and ABCB1 polymorphisms.

Use of ticagrelor instead of clopidogrel eliminates the need for presently recommended genetic testing at the end of antiplatelet treatment.
Development of a Risk Score for TAVI

C-Statistics
- A measure how well a clinical prediction can correctly rank-order pts by risk.
- A model that accurately discriminates pts 85% of the time have a C-statistic of 0.85
- A complete random statistic would be 0.50

C-Statistics
- <0.6 no clinical value
- 0.6 - 0.7 limited value
- 0.7 - 0.8 modest value
- >0.8 adequate for clinical utility

Multivariate Analysis (TF)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-Value</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class IV</td>
<td>0.0007</td>
<td>1.948</td>
<td>1.203</td>
</tr>
<tr>
<td>Renal insufficiency / failure</td>
<td>&lt;0.0001</td>
<td>2.382</td>
<td>1.553</td>
</tr>
<tr>
<td>Hyperlipidemia / cholesterolemia</td>
<td>0.6293</td>
<td>0.602</td>
<td>0.382</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>0.8317</td>
<td>0.622</td>
<td>0.403</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.6009</td>
<td>2.206</td>
<td>1.399</td>
</tr>
<tr>
<td>Mitral valveoplasty</td>
<td>0.6040</td>
<td>2.237</td>
<td>1.950</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>0.6073</td>
<td>6.176</td>
<td>1.555</td>
</tr>
</tbody>
</table>

C Statistic = 0.8452

1-year Mortality by EuroSCORE

Fried Frailty Index
- Weight loss
- Grip strength
- Exhaustion
- Walk time, 15 feet
- Low activity
- >40 lb in last year
- Lowest 20% by gender/BMI
- Self-report
- Lowest 20% by gender/height
- Males <363 kcal/week
- Females <270 kcal/week

Fragility = 3 criteria

Frailty
- Slowness / Weakness
- Poor endurance / exhaustion
- Reduced physical activity
- Unintentional weight loss
Columbia Frailty Index

- Serum albumin
- Modified Physical Performance Test
- Grip strength
- Katz Index of Activities
- >19 lbs in last year
- Standing static balance
- Chair rise
- Lift a book
- Jacket on and off
- Pick up a pen
- Turn 360°
- 50 ft wall test
- Dynamometer

Conflict of Interest
Olaf Wendler
Has received speaker and/or advisory board fees from:
Edwards Lifesciences
Medtronic
St Jude Medical
Has received unrestricted research grants from:
Edwards Lifesciences

Background
- TAVI is an interventional/surgical option to treat high risk patients with AS.
- Currently the perioperative and long-term risk of TAVI is unclear.
- The SOURCE Registry describes outcome in a consecutive group of patients treated during the first year of commercialisation of the Edwards SAPIEN™ bioprosthesis.
- This data can be used to develop a risk score.

Development of a Risk Score for Transcatheter Aortic Valve Implantation: 1-year Outcomes from over 1,000 Patients in the SOURCE Registry
Olaf Wendler, Gerhard Schymik, Thomas Wothke, Dominique Himbert, Thierry Lefèvre, Hendrik Treede, Holger Egggebrecht, Paolo Rubino, Tassan Michev, Martyn Thomas on behalf of the SOURCE Investigators

30 source estimates commercial launch
1/30 patients
data
523 patients

SOURCE Registry – Cohort 1 (1/07 – 01/09)
Excluded
2 centres / 65 patients
Unable to maintain Ethics approval
Unable to increase administrative support
One mortality patient due to unitch error

Included
32 centres (835 patients)
The SOURCE Registry has:
- 100% procedure data
- 99.5% 30 day data
- 98% 1-year follow-up
- All consecutively enrolled

Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>TF (n=463)</th>
<th>TA (n=330)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>81.7</td>
<td>80.4</td>
<td>0.022</td>
</tr>
<tr>
<td>Female</td>
<td>50.1%</td>
<td>58.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>24.6%</td>
<td>29.0%</td>
<td>NS</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>25.0%</td>
<td>32.9%</td>
<td>0.016</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>25.8</td>
<td>29.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>36.8%</td>
<td>29.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid Artery Stenosis (&gt;50%)</td>
<td>7.1%</td>
<td>17.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of CABD</td>
<td>47.2%</td>
<td>55.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Percutaneous Aorta</td>
<td>4.5%</td>
<td>11.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>17.0%</td>
<td>27.0%</td>
<td>0.003</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>12.8%</td>
<td>32.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Thirty-Day Results of the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry

EuroSCORE

Circulation (2010; 122:62-69)
Multivariate Analysis (TA)

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scaled Log EuroSCORE (%/10)</td>
<td>&lt;0.0001</td>
<td>1.200</td>
<td>1.088, 1.311</td>
</tr>
<tr>
<td>Renal insufficiency / failure</td>
<td>0.0047</td>
<td>1.592</td>
<td>1.154, 2.197</td>
</tr>
<tr>
<td>Coronary artery sten. (&gt;50%)</td>
<td>0.0014</td>
<td>0.454</td>
<td>0.290, 0.737</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.0005</td>
<td>3.154</td>
<td>1.646, 6.043</td>
</tr>
<tr>
<td>Other</td>
<td>0.0345</td>
<td>1.489</td>
<td>1.029, 2.163</td>
</tr>
</tbody>
</table>

C-Statistic = 0.8674

Multivariate Analysis (TF)

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class IV</td>
<td>0.0067</td>
<td>1.948</td>
<td>1.203, 3.153</td>
</tr>
<tr>
<td>Renal insufficiency / failure</td>
<td>&gt;0.0001</td>
<td>2.352</td>
<td>1.553, 3.605</td>
</tr>
<tr>
<td>Hyperlipidemia / cholesterolemia</td>
<td>0.0239</td>
<td>0.602</td>
<td>0.382, 0.950</td>
</tr>
<tr>
<td>Systemic Hypertension</td>
<td>0.0317</td>
<td>0.622</td>
<td>0.403, 0.959</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.0009</td>
<td>2.268</td>
<td>1.559, 3.677</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>0.0040</td>
<td>2.837</td>
<td>1.556, 3.496</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>0.0073</td>
<td>5.178</td>
<td>1.558, 17.208</td>
</tr>
</tbody>
</table>

C-Statistic = 0.6632

1-year Mortality by EuroSCORE

Challenges – TAVI Risk Score

- Risk score to predict 1-year mortality has never been created for cardiac surgical patients. (30d, in-hospital, 1 year?)
- Definitions of data fields not specific enough.
- Missing variables are not always able to identify.
- High number of causes of death which are not covered by preoperative risk factors.
- Are there preoperative variables which have not been looked at so far? (Frailty?)

Causes of Death

The EuroSCORE as an Example

- Risk score to predict 30 day mortality after cardiac surgery.
- Nearly 20,000 consecutive patients.
- 128 hospitals in 8 European countries.
- 97 risk factors assessed in all patients.
- Most important, reliable and objective risk factors used to prepare a scoring system.


Conclusions

- 1-Year survival after TAVI is comparable with reported surgical results for high risk patients*.
- In low risk patients (EuroSCORE<20) 1-year survival is equivalent between TA and TF.
- Although individual risk factors for 1-year mortality could be identified, creating of a risk score remains impossible at present.
- Certain risk factors to predict 1-year outcome are currently not assessed in the SOURCE Registry.


Future Options to Develop a Risk Score

- Increase patient numbers
- Complete and consecutive datasets
- Modifications in SOURCE XT
  - Geographical expansion
  - Clinical Event Adjudication Committee (VARC guidelines)
  - Screening analysis
  - Broader scope for trend analysis
  - Frailty score
  - Substudies (imaging, ECHO)

“Strong commitment from participating centres!”
ACS in Africa, Middle East, and Latin America
The ACCESS Registry

Discussant:
José López-Sendón
Hospital Universitario La Paz, Madrid, Spain

Conflict of interest:
• I will not discuss off-label use and/or investigational use in my presentation
• Consultant for: Boehringer, Lilly, Menarini, Servier
• Research support from: Bayer, EMS, Boehringer, GS, Medtronic, Lilly, Menarini, Roche, Sanofi-Aventis, Servier

Demographics and Risk Factors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>20%</td>
</tr>
<tr>
<td>Age ≥ 70y</td>
<td>21%</td>
</tr>
<tr>
<td>Smokers</td>
<td>40%</td>
</tr>
<tr>
<td>Overweight</td>
<td>42%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>22%</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>4%</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>42%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30%</td>
</tr>
<tr>
<td>PCI / CABG</td>
<td>18%</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCESS 1 year</th>
<th>EHS, GRACE, Berlin, RISK-HIA, MASCARA, other Before Hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>7.3%</td>
<td>4% - 6.6%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2%</td>
<td>1% - 2%</td>
</tr>
<tr>
<td>MI Infarction</td>
<td>3%</td>
<td>3% - 5%</td>
</tr>
<tr>
<td>MACE</td>
<td>11%</td>
<td>10% - 14%</td>
</tr>
<tr>
<td>MACE + Re-hospital.</td>
<td>17%</td>
<td>Re-hospitalization may be &gt; 15%</td>
</tr>
</tbody>
</table>

Conclusions

• Important information
• Medical treatment according to guidelines
• Low rate of reperfusion therapy in STEMI
• Fibrinolysis as 1st choice
• Very good outcomes
• Future opportunities for improvement and collaboration

Registry of Acute Coronary Syndromes

• Extraordinary collaborative effort
• Latin America, Middle East, North and South Africa
• 10,000 patients, 1 year follow-up
• Practical interest:
  • Demographic data, treatment strategies and outcomes not well known in many of the participant countries

Treatments (hospital)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ACCESS</th>
<th>EHS, GRACE, BERLIN, RISK-HIA, MASCARA, other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>93%</td>
<td>94% - 95%</td>
</tr>
<tr>
<td>Statin</td>
<td>90%</td>
<td>85% - 90%</td>
</tr>
<tr>
<td>Betablocker</td>
<td>73%</td>
<td>70% - 90%</td>
</tr>
<tr>
<td>Thrombolide (H disch)</td>
<td>81%</td>
<td>70% - 85%</td>
</tr>
<tr>
<td>ACE-i</td>
<td>63%</td>
<td>65-80% &gt; 80% if LVEF &lt; 40</td>
</tr>
</tbody>
</table>

STEMI

<table>
<thead>
<tr>
<th>Component</th>
<th>ACCESS</th>
<th>EHS, GRACE, BERLIN, RISK-HIA, MASCARA, other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PCI</td>
<td>25%</td>
<td>65% - 90%</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>39%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>No reperfusion treatment</td>
<td>0%</td>
<td>&lt; 30%</td>
</tr>
</tbody>
</table>

Limitations

• Selection of sites / patients?
• Diagnostic criteria less restrictive
• Quality controls?
• Follow-up reliable?
Acute coronary syndromes (ACS) in Africa, Middle East, and Latin America: The ACCESS registry

Dr. Necia ANTEPARA (Venezuela), Dr. Alvarez ESCOBAR (Colombia), Pr. Samir ALAM (Lebanon), Pr. Alain LEIZOROVICZ (France), Dr. Carlos MARTINEZ (Mexico), Pr. José NICOLAU (Brazil), Pr. Mohamed SOHBY (Egypt)

Funding & disclosures

- The ACCESS registry is sponsored by sanofi-aventis, Paris, France

ACCESS: background

- The burden of cardiovascular diseases is predicted to escalate in developing countries.

Study aim

- To investigate the descriptive epidemiology, practice patterns, and primary outcomes of patients hospitalized with an acute coronary syndrome (ACS) in countries in Latin America, the Middle East, and North and South Africa.

ACCESS: study population

- Patients (age ≥21 years) admitted alive to hospital with:
  - ischemic symptoms of ACS within 24 hours of presentation, and
  - At least 1 of the following:
    - ECG changes: transient ST↑ or STE≤1 mm, new T-wave inversion ≤1 mm, pseudonormalization of previously inverted T waves, new Q-waves, new R-wave S wave in lead V1, or new left bundle branch block;
    - Documentation of coronary artery disease
    - Elevated troponin or CK-MB concentration
    - Data at baseline, discharge and at 6: 1 mo., 12±1mo. Follow up.

ACCESS: endpoints

12-months from hospitalization

- Primary endpoint: all-cause death
- Secondary endpoints:
  - cardiovascular death
  - cardiovascular death & non-fatal MI
  - non-fatal stroke
  - non-fatal MI
  - CV death, stroke, or MI & rehospitalization for ischemic events
  - bleeding episodes

ACCESS: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall ACS</th>
<th>NSTE ACS</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>74</td>
<td>67</td>
<td>66</td>
</tr>
<tr>
<td>Age ≥70 years, n</td>
<td>21</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Medicohistory of CVD</td>
<td>65</td>
<td>58</td>
<td>31</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>CVA</td>
<td>3.5</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>32</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>PKD</td>
<td>4.6</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>PCI</td>
<td>13</td>
<td>17</td>
<td>7.3</td>
</tr>
<tr>
<td>CABG</td>
<td>5.1</td>
<td>4.4</td>
<td>1.3</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>4.2</td>
<td>4.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.4</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>
ACCESS: cause of death

- In this multinational, observational study of ACS patients, use of evidence-based pharmacological therapies for ACS was quite high, but reperfusion rates for STEMI (40%) were disappointingly low.
- These findings suggest opportunities to reduce further the risk of long-term ischaemic events in ACS patients in developing countries.

Main factors* associated with 12-month death (n=8788)

- Cardiac arrest: 0.6 (0.3, 1.3)  
- Cardiogenic shock: 5.4 (1.3, 20.3)  
- Stroke/TIA: 2.2 (1.8, 2.7)  
- Age >70 years: 2.2 (1.8, 2.7)

*Four strongest independent factors among 17

Background

- Post-Pericardiotomy Syndrome (PPS) is a relatively common complication of cardiac surgery
- Colchicine is recommended for treatment of acute (class IIA) and of recurrent pericarditis (class I) 
- A prospective randomized preliminary trial for primary prevention of PPS using Colchicine showed an encouraging trend toward significance

References:

- Matos R et al, Eur Heart J 2004;25:587;
- Fonteuno Y et al. JACC 2002;21:791
Main Results

- The 2 randomized groups of patients were well balanced
- All 360 patients received the allocated medications
- No patient was lost to follow-up, all were included in analysis

Main Results

- 85% of PPS events occurred within 30 days
- No severe adverse events recorded
- There was a statistically nonsignificant trend toward more gastrointestinal side effects and more drug withdrawals in the treated group

Importance of the Study

- COPPS is the first large scale, double-blind, randomized trial to test the efficacy of Colchicine in prevention of PPS
- COPPS was a carefully performed trial in which Colchicine proved an effective and safe treatment modality: it halved the risk of developing PPS without major side effects
- These results support the use of low dose Colchicine for prevention of PPS in the type of patients included in the COPPS trial

Background

- The Post-Pericardiotomy Syndrome (PPS) is a relatively common complication following cardiac surgery (10-40% of patients).
- No drug definitively proven to be efficacious for the prevention.
- NSAID, corticosteroids, colchicine use reported for treatment in anecdotal reports.

Funding

- The COPPS trial is an independent study founded and performed within the Italian National Healthcare System.
- The research protocol was approved by the relevant institutional review boards or ethics committees.
- All human participants gave written informed consent.
- The steering committee designed and oversaw the trial and had the final decision on the contents of the manuscript.
- All data were received, checked, and analyzed independently at the Coordinating Centre at the Cardiology Dept, Maria Vittoria Hospital, Torino, Italy following blinded adjudication of clinical events and side effects.
- Acradia Ltd provided supply of drug/placebo as an unrestricted grant.

Colchicine for the Prevention of Postpericardiotomy Syndrome

Yaron Imielinski, Joseph Sherman, Kiran Mahalab, Dan Alvarado, Yaron Bar-Eli, Alex Sager, Ernst Zvonro, Gideon Sahu, Anna Kunt Schneider, Taly Schachter, Bernard A. Volle, Yehuda Adler

Prospective, double-blind design.
- 165 patients; colchicine 1.5mg/day for 1 month
- 52/163 (31%) excluded (complications, intolerance, non-compliance)
- PPS at 3 months (placebo vs. colchicine; 14/84 vs. 5/47; p = NS)

References


ESC Congress 2010
28 Aug 2010 - 01 Sep 2010, Stockholm - Sweden

COChlincine for the Prevention of the Post-Pericardiotomy Syndrome. The COPPS trial:
A multicenter, randomized, double-blind, placebo-controlled trial

Presenter: Massimo Imazio, MD, FESC
On behalf of the COPPS Investigators
Cardiology Dept, Maria Vittoria Hospital, Torino, Italy
Methods

Rationale and design of the COPPS trial: a randomised, placebo-controlled, multicentre study on the use of colchicine for the primary prevention of postpericardiotomy syndrome

Massimo Imazio, Enrico Cecchi, Brasile D’Ambrosio, Alessandro Cingolani, Lucilla Coda, Alde Ghiso, Daniele Demaria, Salvatore Ierna and Rita Trinchero, on behalf of the COPPS Investigators

Methods: Colchicine seems to be well tolerated and effective in the treatment and prevention of pericarditis. A preliminary clinical trial has shown that colchicine may be considered not only for the treatment of postpericardiotomy syndrome (PPS), but also for the primary prevention. Implications: The COPPS trial will evaluate the use of colchicine for the primary prevention of PPS. This study will also provide important information on the frequency, clinical presentation, and prognosis of this syndrome in clinical practice. (Guideline Notes 2004-08-14) © 2007 Italian Federation of Cardiology

Inclusion/Exclusion Criteria

Inclusion criteria
- Candidate for cardiac surgery
- Age ≥ 18 years
- Informed consent

Exclusion criteria
- Known severe liver disease or current transaminases >1.5 times the upper normal limit
- Current serum creatinine >2.5 mg/dl
- Known myopathy or elevated baseline preoperative creatinine kinase
- Known blood dyscrasia or gastrointestinal disease
- Pregnant and lactating women
- Women of childbearing potential not protected by a contraceptive method
- Known hypersensitivity to colchicine
- Current treatment with colchicine for any indications
- Unfavorable short-term outlook for any cause

Results (I): Baseline data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=100)</th>
<th>Colchicine (N=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG surgery type (%)</td>
<td>77 (42.8%)</td>
<td>92 (51.1%)</td>
<td>0.14</td>
</tr>
<tr>
<td>VA/other surgery</td>
<td>55 (30.8%)</td>
<td>51 (28.3%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Aortic surgery</td>
<td>8 (4.0%)</td>
<td>4 (2.2%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Combined surgery</td>
<td>37 (20.0%)</td>
<td>35 (16.7%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.6%)</td>
<td>3 (1.5%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

CABG* Coronary Artery By-Pass Grafting

Results (II): Study end points

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=100)</th>
<th>Colchicine (N=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint: PPS at 12 months (%)</td>
<td>10 (21.1%)</td>
<td>14 (13.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Fever beyond 1st postoperative week</td>
<td>7 (13.9%)</td>
<td>6 (13.3%)</td>
<td>0.982</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>23 (12.2%)</td>
<td>7 (7.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Friction rub</td>
<td>15 (15.0%)</td>
<td>5 (5.1%)</td>
<td>0.006</td>
</tr>
<tr>
<td>New or worsening pericardial effusion</td>
<td>20 (20.0%)</td>
<td>22 (21.2%)</td>
<td>0.990</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>16.5</td>
<td>20.2</td>
<td>0.282</td>
</tr>
</tbody>
</table>

COPPS trial: Main results

NNT=8

Study Hypothesis: PPS rate of 22.0% and 11.1% between the two treatment arms (placebo and colchicine) with a power of 85% using a 2-sided p>0.05 level test. Analyses were performed by intention to treat.
Conclusions

- Colchicine is safe and efficacious in the primary prevention of the PPS and its related complications.

- In the COPPS trial colchicine halves the risk of the PPS (colchicine vs. placebo=9% vs. 21%, p=0.002; NNT= 8) following cardiac surgery.

Disclosures

- Research grants: Astra-Zeneca, Merck, Novartis, Pfizer, sanofi-aventis, Servier, The MedCo

- Fees for giving lectures and/or consulting:
  - Astra-Zeneca, BMS, Boehringer-Ingelheim, GSK, Lilly, Menarini, MSD-Schering, Novartis, Novo, Pfizer, sanofi-aventis, Servier, The MedCo

Strengths of EHS ACS 3

- Participation of 138 motivated centres, in 21 countries, including patients according to a similar methodology during 2 years, making temporal comparisons possible.

- Large population (> 8,000 patients)

- Use of the CARDS data set: common definition of key clinical data.

- Detailed and prudent analysis of the data.
Limitations of EHS ACS 3

- Limited representativeness: these results should not let us think that the battle is over.
- EHS Snapshot 2009: 485 centres in 47 countries:
  - Lower rate of reperfusion: 70% vs 81%
  - Median time to reperfusion much longer:
    - ECG to pPCI: 115 min vs 45 min
    - ECG toysis: 50 min vs 15 min
  - Higher in-hospital mortality for STEMI: 8.5% vs 6.6%, with inequalities across regions (5% to 10%)

Unresolved issues
Reperfusion is key but is not the only determinant of improved outcomes

Evolution of 30-day mortality in 3 French surveys

Unresolved issues
Role of benchmarking

- Efficacy of benchmarking not demonstrated by such a study:
  - the GRACE registry did not observe such satisfactory results in terms of reperfusion delays
  - Improved management is observed outside benchmarking efforts

- There is a risk in setting strict objectives, particularly when there are financial incentives attached.
  - MINAP, 2009 report: aspirin 88% (many hospitals 99 to 100%), clopidogrel 94%, statins 97%, beta-blockers 93%, ACE-I 92%

  Many centres had prescription rates of 99% to 100%:
  - Is this reasonable?

Benchmarks:
a word of caution or “Don’t overdo it…”

- Medical exceptions to quality measures are usually appropriate:

  Recommended medications prescribed in 89% to 90% of patients

  94% of the medical exceptions for not prescribing a recommended medication were judged appropriate, and an additional 3% were judged debatable

Unresolved issues
Many AMI patients do not reach the hospital

- Decline in incidence of STEMI patients who are hospitalised (e.g. Kaiser Permanente Northern California database: -51% from 1996 to 2005)

- The challenge of out-of-hospital sudden death:
  - Often caused by acute ischemia on a mild plaque that ruptures and leads to complete coronary occlusion with profound arrhythmogenic ischemia.
  - Need to improve the management of out-of-hospital cardiac arrest

Conclusion

- EHS ACS 3 data show that improving outcomes of STEMI patients is still possible and that shortening time delays for reperfusion is achievable.

- Monitoring performance indexes may help in improving results, although it probably does not suffice.

- We should not think, however, that we should now rest on these satisfactory results.

- Other combats are still ahead, such as reducing the inequalities across countries, or fighting sudden ischemic death.
GRACE 5 Years

Freek W.A. Verhaegt

Clinical Implications:
- The late complications of ACS are poorly recognised and often underestimated.
- This is despite substantial progress in acute treatment of ACS, and secondary prevention.
- Risk scores can accurately predict long-term outcome and identify those with most to gain from novel strategies and therapies.

Other Large Registries

<table>
<thead>
<tr>
<th>registry</th>
<th>publication</th>
<th>n</th>
<th>fu</th>
<th>ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NITI</td>
<td>WJCI 1999;33:1253-1260</td>
<td>3,140</td>
<td>3 years</td>
<td>STEMI</td>
</tr>
<tr>
<td>CCP Medicare</td>
<td>JACC 2000;36:366-371</td>
<td>15,540</td>
<td>1 year</td>
<td>STEMI</td>
</tr>
<tr>
<td>RIKS-HIA</td>
<td>JAMA 2006;296:1768-1778</td>
<td>26,306</td>
<td>1 year</td>
<td>STEMI</td>
</tr>
</tbody>
</table>

DISCLOSURE

Freek W.A. Verhaegt received:
1. educational and departmental grants from Bayer AG, Roche, Boehringer-Ingelheim and Eli Lilly
2. speaker fees and honoraria for consultancy from Sanofi-Aventis, Bayer AG, Boehringer Ingelheim, Merck and Eli Lilly

SWOT Analysis of GRACE 5 Years

<table>
<thead>
<tr>
<th>strengths</th>
<th>weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>- very long follow-up</td>
<td>- only 6% (3,721/68,723) of GRACE population</td>
</tr>
<tr>
<td>- follow-up 99.4% complete</td>
<td>- only 2 of the 29 (7%) GRACE countries</td>
</tr>
<tr>
<td>- GRACE risk model validated for long-term</td>
<td></td>
</tr>
</tbody>
</table>

Advantages and Disadvantages of Trials and Registries

<table>
<thead>
<tr>
<th>advantage</th>
<th>disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>randomized trial</td>
<td>- equal baseline data</td>
</tr>
<tr>
<td></td>
<td>- selection bias</td>
</tr>
<tr>
<td></td>
<td>- not generalizable</td>
</tr>
<tr>
<td></td>
<td>- limited follow-up</td>
</tr>
<tr>
<td>registry</td>
<td>- real world</td>
</tr>
<tr>
<td></td>
<td>- follow-up “unlimited”</td>
</tr>
<tr>
<td></td>
<td>confounding bias</td>
</tr>
</tbody>
</table>

Verhaegt F.W.A. Circulation 2001;119:3047-3049
Clinical Implications:

- The late complications of ACS are poorly recognised and often underestimated.
- This is despite substantial progress in acute treatment of ACS, and secondary prevention.
- Risk scores can accurately predict long-term outcome and identify those with most to gain from novel strategies and therapies.

Thrombolysis vs Primary PCI in GRACE (70y+)

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis (n = 706)</th>
<th>Primary PCI (n = 365)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality (%)</td>
<td>112 (1.48)</td>
<td>49 (1.35)</td>
<td>.54</td>
</tr>
<tr>
<td>Re-infarction (%)</td>
<td>44 (3.7)</td>
<td>4 (1.1)</td>
<td>.0003</td>
</tr>
<tr>
<td>Death or reinfarction (%)</td>
<td>143 (1.87)</td>
<td>52 (1.43)</td>
<td>.07</td>
</tr>
<tr>
<td>Cardiogenic shock (%)</td>
<td>86 (1.6)</td>
<td>41 (1.3)</td>
<td>.89</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>45 (2.9)</td>
<td>31 (8.4)</td>
<td>.09</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>21 (2.4)</td>
<td>4 (1.1)</td>
<td>.06</td>
</tr>
<tr>
<td>Length of stay in hospital (median, days) (%)</td>
<td>8</td>
<td>7</td>
<td>.005</td>
</tr>
</tbody>
</table>

What We also Would Like to See (1):

1. Data from the whole GRACE registry, not only UK and Belgium
2. Long term comparison between ACS treatments:
   - PCI vs lysis
   - surgery vs PCI
   - early invasive vs selective invasive strategies
   - etc.

What We also Would Like to See (2):

3. Comparisons between countries and/or continants within GRACE
4. Possibly, comparisons between registries:
   - GRACE vs CRUSADE
   - GRACE vs RISK-HIA
   - GRACE vs REACH

Underestimated and Under-recognised:
The Late Consequences of Acute Coronary Syndrome (GRACE UK-Belgian Study).

Keith A.A. Fox, Kathryn F Carruthers Donald R Dunbar, Catriona Graham, Jonathan R Manning, Herbert De Raedt, Ian Buyschoeert, Diether Lambrechts, Frans Van de Werf

Aims and Methods

- To define the long-term outcomes following ST Elevation and non-ST elevation ACS
- To determine whether the GRACE risk score predicts long-term risk of death, CV death and MI
- Prospective recruitment of patients presenting with ACS, audit, quality control and long-term follow-up
  - UK n= 2065, Belgium n= 1656
  - Individual patient follow-up and Record Linkage* with 99.8% successful linkage at 5 years (all except 4 patients)
**Outcomes at 5 years**

- **Myocardial Infarctions:**
  - 12.7% of patients one or more MI (24hrs to Sys)
- **Strokes:**
  - 7.7% of patients had one or more strokes
- **Revascularisations** (after initial hospital discharge):
  - 16.7% of patients had one or more revascularisation
- **Redmissions for suspected ACS:**
  - 53.6% of patients were re-admitted at least once

**GRACE risk score and outcomes**

<table>
<thead>
<tr>
<th>Event/Outcome</th>
<th>Death Low</th>
<th>Death Intermediate</th>
<th>Death High</th>
<th>Death MI Low</th>
<th>Death MI Intermediate</th>
<th>Death MI High</th>
<th>CV Death Low</th>
<th>CV Death Intermediate</th>
<th>CV Death High</th>
<th>Cardiovascular Death Low</th>
<th>CardiovascularDeath Intermediate</th>
<th>Cardiovascular Death High</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>43482</td>
<td>150726</td>
<td>524120</td>
<td>88445</td>
<td>80254</td>
<td>147547</td>
<td>8462</td>
<td>80734</td>
<td>8462</td>
<td>83482</td>
<td>80734</td>
<td>8462</td>
</tr>
<tr>
<td>Event (%)</td>
<td>1.300</td>
<td>2.496</td>
<td>10.981</td>
<td>1.131</td>
<td>3.108</td>
<td>3.108</td>
<td>2.496</td>
<td>1.131</td>
<td>3.108</td>
<td>1.300</td>
<td>2.496</td>
<td>1.131</td>
</tr>
<tr>
<td>Code Ratio</td>
<td>34.5</td>
<td>3.108</td>
<td>0.1601</td>
<td>0.676</td>
<td>3.751</td>
<td>3.751</td>
<td>3.108</td>
<td>0.676</td>
<td>3.751</td>
<td>3.108</td>
<td>3.108</td>
<td>0.676</td>
</tr>
<tr>
<td>Brier Score</td>
<td>0.050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
<td>0.0050</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**GRACE Risk Score: predictive accuracy**

- **Deaths (in-hospital)**
  - All deaths*: likelihood ratio 239, Wald 189, C statistic 0.88
  - CV deaths*: likelihood ratio 230, Wald 181, C statistic 0.88
- **Deaths (5 years)**
  - All deaths*: likelihood ratio 477, Wald 445, C statistic 0.77
  - CV deaths*: likelihood ratio 235, Wald 279, C statistic 0.75
- **CV Death or MI**
  - In-hospital*: likelihood ratio 219, Wald 85, C statistic 0.86
  - 5 years*: likelihood ratio 477, Wald 215, C statistic 0.68

*P values for all <0.0001
Survival according to GRACE Score (score for death in-hospital)

log-rank = 403.7, df=2, p<0.0001

No evidence of a difference [log-rank = 0.3597, df=1, p=0.56]

Survival according to ACS category

Conclusions:

- The late consequences of ACS are under-recognised:
  - Following STEMI presentation, 60% of all deaths to 5yrs occur after hospital discharge
  - Following Non-STEMI presentation 83% of deaths are after discharge
  - The greatest absolute late risk is among those with non-ST elevation ACS
  - This is despite high usage of guideline therapies and secondary prevention
  - The GRACE risk score has similar high predictive accuracy long-term (5 years and beyond) as at hospital discharge
  - The GRACE risk score predicts mortality, even among those surviving the first 6 months after ACS

Death or MI according to ACS category

log-rank = 104.6, df=2, p<0.0001

Landmark Analysis:

GRACE score and mortality after 6 months

log-rank = 104.6, df=2, p<0.0001

Clinical Implications:

- The late complications of ACS are poorly recognised and often underestimated.
- This is despite substantial progress in acute treatment of ACS, and secondary prevention.
- Risk scores can accurately predict long-term outcome and identify those with most to gain from novel strategies and therapies

Use and misuse of Registries

Prospective registries

- Framingham
- MONICA
- GRACE
- CRUSADE
- REACH

Advantages

- All corners – real world
- If longitudinal
  - natural hx of disease
  - incidence of new events
  - link between baseline factors and outcomes

Misuse not appropriate to investigate effect of interventions given potential selection bias and residual confounding

REACH Registry: Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis

DISCUSSION

Felicita Andreotti, Inst. Cardiology, Catholic Univ., Rome, I

No conflicts related to this task
VALUE of REACH

**COHORT**
- stable or stabilised outpatients
- array of CVD

**SIZE**
- > 34000 individuals

**TIMING**
- 4-year follow-up

**METHODS**
- prospective - audited centers
- hard endpoints - adjusted analyses
- analysis by pt hx and CV system

CV = cardiovascular; D = disease; pt hx = patient history

DRAWBACKS of REACH

**DEFINITIONS**
- events adjudicated locally
- carotid IMT same as 70% stenosis

**MIX**
- RFO group mixed with CVD patients

**GAPS**
- lack of emerging risk factors
- female representation low
- Africa missing

**SUMMING UP**
- conclusion on diabetes
- title not entirely clear

On Balance

The REACH Follow-up Registry data
- add novelty to our understanding of CVD, given
  - the type of cohort and length of follow-up
  - the analysis by patient history of ischaemia and by polyvascular / systemic involvement
- stimulate interventions in the higher-risk groups
- raise the issue of including a healthy control arm
- confirm the challenge of preventing CV death

REACH Registry: Comparative Determinants of 4-Year Cardiovascular Event Rates in Stable Outpatients at Risk of or With Atherothrombosis:

Final Follow-up From the International REACH Registry

DL Bhatt, KA Eagle, EM Chinnaiyan, AT Hirsch, S Goet, EM Mahoney, PW Wilson, MJ Alberts, R D’Agostino, CS Liu, J-L, Mas, J Röhrer, SC Smith, Jr, G Sackett, GF Coultart, JM Maisere, Ph G Stieg, on behalf of the REACH Registry Investigators

Disclosures


The REACH Registry is sponsored by: sanofi-aventis, Bristol-Myers Squibb, and the Waksman Foundation (Tokyo, Japan), and endorsed by the World Heart Federation.
Enrolment facts and figures
- 68,238 patients were enrolled between Dec 2003–Dec 2004 at 5,897 centres across 44 countries across the globe
- The initial follow-up period was 2 years, but enrolling centres were invited to participate in the extension of this project to a 4-year observation period
- Patients enrolled in the REACH Registry were stable outpatients (typically being treated in non-academic centres) with either:
  a. Established atherothrombotic disease with documented CAD, CVD, or PAD
  b. ≥ 3 risk factors for atherothrombotic disease
- Participation in REACH Registry: 4-year follow-up study
  - 45,227 patients enrolled at 3,647 centres in 29 countries provided outcomes data for this 4-year follow-up

Methods
- This analysis included all patients with 4-year outcomes data (n=45,227)
- Cumulative incidence rates reported were adjusted for age and gender
- Multivariable analysis used to identify determinants for CV events at 4 years
  - Variables tested: no. of disease, location of enrolment, prior ischemic event, additional variables identified by predictive model such as age, smoking, diabetes, cardiac failure, statin use
- Cumulative incidence for CV death, MI, or stroke were calculated using Kaplan-Meier approach

Demographics for patients eligible for 4-year follow-up

<table>
<thead>
<tr>
<th>Demographics</th>
<th>AI (n=34,343)</th>
<th>Ischemic event (n=1,297)</th>
<th>Stable atherothrombotic disease (n=1,182)</th>
<th>Risk factors (n=1,182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (n=34,343)</td>
<td>64.9±10.9</td>
<td>61.8±8.5</td>
<td>64.5±10.5</td>
<td>64.8±10.5</td>
</tr>
<tr>
<td>Men, %</td>
<td>55.5</td>
<td>57.0</td>
<td>56.5</td>
<td>56.2</td>
</tr>
<tr>
<td>Arteriothrombotic risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>81.0</td>
<td>79.1</td>
<td>80.3</td>
<td></td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>42.9</td>
<td>46.0</td>
<td>47.1</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>70.2</td>
<td>72.3</td>
<td>71.7</td>
<td></td>
</tr>
<tr>
<td>Obesity, kg/m²</td>
<td>27.4</td>
<td>24.5</td>
<td>25.7</td>
<td>26.1</td>
</tr>
<tr>
<td>Smoker at baseline, %</td>
<td>15.3</td>
<td>14.2</td>
<td>15.1</td>
<td>16.4</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>13.9</td>
<td>18.1</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>10.6</td>
<td>12.2</td>
<td>12.5</td>
<td>9.3</td>
</tr>
</tbody>
</table>

Baseline medical history in patients with 4-year outcomes data

<table>
<thead>
<tr>
<th>Vascular disease status</th>
<th>Risk factors</th>
<th>Prior ischemic event</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior ischemic event</td>
<td>No prior ischemic event</td>
<td>No prior ischemic event</td>
</tr>
<tr>
<td>Prior ischemic event</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prior ischemic event
- History of diabetes
- History of diabetes

4-year event rates according to single vs. polyvascular disease

<table>
<thead>
<tr>
<th>Prior ischemic event</th>
<th>Single vascular disease</th>
<th>Polyvascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior ischemic event</td>
<td>No prior ischemic event</td>
<td>No prior ischemic event</td>
</tr>
<tr>
<td></td>
<td>Single vascular disease</td>
<td>Polyvascular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key study populations and definitions
- Prior ischemic event: MI or stroke at baseline
- Stable atherothrombosis: Objectively confirmed, symptomatc, atherothrombotic disease without a prior ischemic event
- Risk factors only: Patients with ≥3 of the following risk factors for atherothrombotic disease:
  - Treated diabetes mellitus + diabetic nephropathy + ABI > 0.9 + asymptomatic carotid stenosis ≥ 70% + carotid IMT of ≥ 2 mm adjacent sites + SBP > 160 mmHg + hypercholesterolemia + current smoking + age > 55 years in men, age > 65 years in women
Limitations
- Complete follow-up of the initial cohort at 4 years could not be achieved due to some enrolment sites withdrawing
- Outcome events were not independently adjudicated
- Since REACH had specific enrolment criteria, we cannot rule out that selection bias could have affected some of the results

Conclusions (1)
- In patients with multiple risk factors for atherothrombosis or established atherothrombotic disease, four clinical criteria can be used to identify patients at increased risk for future CV events:
  - Polya vascular disease
  - Prior ischemic event
  - Prior ischemic event at any time
  - Diabetes
- CV event risk stratification among patients with established atherothrombosis enables the intensity of preventive treatments to be tailored to individual patient needs

Conclusions (2)
- While previous risk stratification tools have been developed for patients after an acute event, our analysis provides simple criteria for assessing risk for CV events in stable outpatients
- Our findings should help clinicians identify patients at very high-risk of MI, stroke, or cardiovascular death and adapt their treatment strategies accordingly
- The identification of high-risk populations may assist in the design of future clinical trials evaluating emerging treatment options in those requiring the most intensive preventive medications
Survival Benefit by 12 years registry-supported improvement of acute cardiac care in Sweden

Aims
To describe the adoption of new treatments & changes in short/long-term survival in Swedish patients admitted to the CCU with MI over a 12 year period (1995-2007)

Dr Susanna Price MD PhD FLSC

Background
RIKS-HIA
High quality registry, but:
- Net all admitted AMI patients admitted to CCU (2009)
- Diagnostic criteria for entry changed (2000)
- Comprehensiveness?

Guidelines
- 2005 Re-Fibrinolysis JME
- 2003 Management of chest pain
- 2001 STEMI management
- 2003 Estimation of cardiovascular risk
- 2004 Expert consensus on ICS inhibitors
- 2004 Expert consensus on beta blockers
- 2004 Consensus anti-platelet agents

Conclusion: increasing quality

SYSTEM
- Patient pathway
  - Pre-hospital care
  - Systems of care education
  - Protocols
  - QI programmes

PROCESS
- Performance indicators
  - Drug administration
  - Reperfusion
  - ACE-inhibitors
  - Cholesterol

OUTCOME
- Other outcome indicators
  - Complicators
  - Re-admission
  - Re-infraction
  - Functional status

Conclusion: increasing equality

- Equality vs equity (The concepts and principles of equity in health, Int J Health, 1992)
  - Equity vs equal access & quality, for equal need
  - Recognition of systematically disadvantaged groups
  - Requires need & risk assessment
  - Must be measured specifically to be meaningful

- "Inverse equity" hypothesis:
  - Public health interventions/programmes are more rapidly applied to groups of higher socioeconomic status
  - Leads initially to increased inequity despite the overall appearance of an improvement in performance indicators
  - Particularly relevant in rapidly changing fields where those with greatest need are in lowest socioeconomic group ("AMI")

Summary
- RIKS-HIA registry: high quality, showing increased prescription of guideline-related therapies/interventions, and a reduction in mortality over 12 year period
- Guidelines are not performance measures
- Rapidly changing practice & guidelines may increase inequity, despite improving overall quality
Survival benefits by 12 years registry supported improvement of acute cardiac care in Sweden - the RIKS-HIA 12 years study

Lars Wallentin1, René Swenne1, Johan Lindblad1, Tomas Jornberg1 for the SWEDHEART1 RIKS-HIA group
1 Uppsala Clinical Research Centre, Uppsala University Hospital, Uppsala, Sweden.

Introduction

- Over the last 15 years a series of randomized trials have documented the efficacy of several new treatments in patients with acute ST-elevation or non-ST-elevation MI.
- European and National guidelines have been developed to support the implementation of these treatments.
- Only limited information is available concerning the speed of implementation of these new treatment strategies and their impact on long term survival in real life health care.

Methods

- Consecutive patients admitted to a CCU and entered into RIKS-HIA register between 1996 and 2007 with a first time discharge diagnosis of myocardial infarction were included.
- To diagnose acute MI, the WHO criteria were used 1995-1996 and the ESC/AHA/ACCF criteria from 2001.
- More than 100 variables are prospectively registered: Risk factors, previous heart diseases, clinical presentation, received treatments, complications, in-hospital outcome.
- Mortality data were obtained by merging the RIKS-HIA database with the National Death Registry.
- Data quality was monitored in 2546 randomly selected records with 295030 measurement, with an agreement of 95%.
- All patients were informed about their participation and had the right to decline participation.

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1248</td>
<td>N = 2436</td>
<td>N = 2723</td>
<td>N = 2869</td>
<td>N = 2657</td>
<td>N = 2917</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.6 (70.7)</td>
<td>71.6 (70.1)</td>
<td>72.6 (71.0)</td>
<td>72.6 (71.0)</td>
<td>72.6 (71.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36%</td>
<td>36%</td>
<td>37%</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31%</td>
<td>32%</td>
<td>33%</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>22%</td>
<td>23%</td>
<td>23%</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>Previous disease at entry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>36%</td>
<td>39%</td>
<td>31%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>4%</td>
<td>9%</td>
<td>11%</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>5%</td>
<td>2%</td>
<td>8%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Medication at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>59%</td>
<td>61%</td>
<td>71%</td>
<td>80%</td>
<td>79%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>40%</td>
<td>41%</td>
<td>47%</td>
<td>53%</td>
<td>52%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7%</td>
<td>6%</td>
<td>9%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>34%</td>
<td>36%</td>
<td>38%</td>
<td>33%</td>
<td>32%</td>
</tr>
<tr>
<td>Treatment of STEMI - hospital level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 1596</td>
<td>N = 1390</td>
<td>N = 1395</td>
<td>N = 1679</td>
<td>N = 1854</td>
<td>N = 1615</td>
</tr>
<tr>
<td>Represtation and treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Represtation treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>57%</td>
<td>60%</td>
<td>60%</td>
<td>65%</td>
<td>66%</td>
</tr>
<tr>
<td>Other treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noprep PCI strep</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>14%</td>
<td>15%</td>
<td>14%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Revascularization</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Treatments at discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent</td>
<td>68%</td>
<td>71%</td>
<td>68%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Platelet</td>
<td>22%</td>
<td>22%</td>
<td>22%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Revascularization</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>ACE-inhibitor or ARB</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Time of stay (days)</td>
<td>6.5 (6.0)</td>
<td>6.4 (6.0)</td>
<td>6.4 (6.0)</td>
<td>6.5 (6.0)</td>
<td>6.5 (6.0)</td>
</tr>
</tbody>
</table>
In patients with myocardial infarction admitted for coronary care in Sweden registry supported implementation of new treatment guidelines has contributed to:
- increasing quality and equality of treatment
- more than halving 30 day mortality
- 1.7 – 2.6 years average gain in long-term survival
University of Oslo

Discussant:
Heart rate in heart failure: risk marker or risk factor?

SHIFT trial
by M. Böhm, S. Swedberg, M. Komajda, J. Borer, I. Ford, L. Tavazzi
European Society of Cardiology
Clinical Trial Update II
30.8.2010

Disclosure:
Member of the Data Monitoring Committee in the SIGNIFY trial

Patient characteristics:
The study is well balanced at baseline
High heart rate is characterized by:
- younger patients
- lower EF
- more smokers
- more diabetics
- reduced use of ACEI and BB
- increased use of diuretics and digitalis

Take home message
Heart rate in heart failure is
- a risk marker and a risk factor for CV death and HF hospitalizations
- a treatment target
- is effectively and safely reduced by ivabradine on top of a β-blocker

Major findings in the SHIFT trial:
- Mission accomplished!
- Primary endpoint reduced by 18% (p < 0.0001)
- Effect mainly driven by 26% reduction of HF events
- Relatively small but consistent effects on CV mortality (9%, p=0.128) and on all cause mortality (10%, p=0.092)
- Better effect on outcomes in patients with high baseline heart rates
- Patients who tolerated heart rate <60 b/min had the best outcome

Take home message
The SHIFT study shows:
- Consistent and reasonable effects on all endpoints
- Ivabradine well tolerated
- The major drivers of effects are HF hospitalisation (26%, p<0.001) heart failure death (26%, p<0.014)

Heart rate in heart failure: risk marker or risk factor?
A subanalysis of the SHIFT trial

M. Böhm, S. Swedberg, M. Komajda, J. Borer,
I. Ford, L. Tavazzi
on behalf of the SHIFT Investigators

Adverse events and limitations
- Result restricted to patients with β-blocker pretreatment and without atrial fibrillation
- Adverse events and withdrawals comparable between groups
- Ivabradine had slightly more asymptomatic and symptomatic bradycardia, and more visual symptoms, but not important reason for withdrawal
- Ivabradine generally better tolerated than β-blockers
- The slower the better -- but what is the lowest heart rate?
- J-curve not defined?

Disclosures
SHIFT Executive Committee members received fees, research grants, or both from Servier, as well as fees for speaking or consulting from other major cardiovascular pharmaceutical companies.
Heart rate and outcomes in HF: background

- Elevated resting heart rate is a marker of cardiovascular risk.
- Ivabradine slows the heart by selective If current inhibition and has no known cardiovascular effects other than heart rate reduction.
- SHIFT allows to further explore the prognostic importance and pathophysiological role of heart rate in heart failure.

- We hypothesized that heart rate is a risk factor for cardiovascular events, and tested the effect of isolated heart rate reduction with ivabradine on outcomes in a heart failure population.

Mean heart rate reduction

70% of patients on ivabradine 7.5 mg bid

Placebo

Ivabradine

Objective of current analysis

To determine whether heart rate at baseline and on heart rate-lowering treatment with ivabradine can predict outcomes in SHIFT patients with HF and systolic dysfunction.

Methods

- The relationship between risk and heart rate was tested in the placebo group divided by quintiles of baseline heart rate.
- Heart rate achieved at 28 days by ivabradine (end of titration) was related to subsequent outcomes.
- The effect of ivabradine on outcomes, adjusted for prognostic factors at baseline, was estimated by heart rate quintiles.
- Outcomes analyzed:
  - primary composite endpoint (cardiovascular death and HF hospitalisation)
  - secondary endpoints (all-cause/CHF death from HF, all-cause/CHF hospitalisation; composite of CV death, hospitalisation for HF or non-fatal MI).

Baseline characteristics in population divided by quintiles of heart rate

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 - 72</td>
<td>0.0001</td>
</tr>
<tr>
<td>72 - 75</td>
<td>0.0001</td>
</tr>
<tr>
<td>75 - 79</td>
<td>0.0001</td>
</tr>
<tr>
<td>79 - 83</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;83</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* P value for interaction (pre-planned test for categorical variables, Kruskal-Wallis for continuous variables)

Baseline characteristics in population divided by quintiles of heart rate

<table>
<thead>
<tr>
<th>Heart rate at baseline (bpm)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 12</td>
<td>0.0001</td>
</tr>
<tr>
<td>12 - 14</td>
<td>0.0001</td>
</tr>
<tr>
<td>14 - 15</td>
<td>0.0001</td>
</tr>
<tr>
<td>16 - 17</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;17</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* P value for interaction (pre-planned test for categorical variables, Kruskal-Wallis for continuous variables)
**Baseline heart rate is a predictor of endpoints on placebo**

- Patients with primary composite endpoint (%)
- Patients with cardiovascular death (%)

Primary composite endpoint risk increases by 3% per 10 bpm increase, and by 10% per 30 bpm increase.

**Distribution of patients by classes of heart rate achieved at D28**

**Placebo**

- Heart rate achieved at day 28 (bpm)

**Ivabradine**

- Heart rate achieved at day 28 (bpm)

*Data accrue patients reaching primary composite endpoint in the first 354 days.

**Treatment effect is explained by heart rate reduction**

**After adjustment for change in heart rate at 28 days:**

HR 0.95, 0.85 – 1.06, p = 0.352

**Effect of ivabradine vs placebo according to heart rate at baseline (whole population)**

- HR and 95% CI for first hospital admission for heart failure
- HR and 95% CI for cardiovascular death

**Conclusion**

- Our results indicate that in heart failure patients in sinus rhythm and heart rate ≥70 bpm, there is a positive continuous relationship between baseline heart rate and increased risk.
- The risk is modified and significantly decreased by ivabradine, and the effect is related to heart rate at baseline and heart rate achieved at 28 days.
- Patients with lowest heart rates on treatment with ivabradine have the best outcomes.
Clinical implications

- Elevated heart rate is a risk factor in HF
- Heart rate is an important target for therapy in HF
- Shifting patients to lower heart rate profiles with ivabradine reduces CV events
- Lower heart rates at baseline and lower heart rates achieved on treatment are associated with better outcomes, with incremental benefit by achieving heart rate ≤50 bpm when tolerated

Available now online from Lancet

Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial

www.lancet.com  published online August 26, 2010
DOI: 10.1016/S0140-6736(10)61259-7

Thank You!

M. Böhm
Innere Medizin II (Kardiologie / Angiologie / Internistische Intensivmedizin)
Universitätsklinikum des Saarlandes
Homburg/Saar, Germany

CARE-HF Long-Term Follow-Up
Presented by Prof. J.G.F. Cleland, Univ. of Hull, UK

ESC Congress 2010
Stockholm, Sweden
Hot Line Session, September 1, 2010

Ole-A. Breithardt, Discussant
Medizinische Klinik 2 - Universitätsklinikum Erlangen

No conflicts of interest

Hot Line Session CARE-HF LTFU
Discussion

- Randomized controlled clinical trials have well established the role of CRT for selected heart failure patients with cardiac dyssynchrony (identified by ECG criteria)
- Follow-up Duration of the key trials is limited:
  - MIRACLE-CRT (2002) = 6 months
  - COMPANION (2004) = 16 months
  - CARE-HF Pim Study (2005) = 24 months
  - CARE-HF Extension (2006) = 37 months
  - MADIT-CRT (2005) = 33 months
- CARE-HF LTFU: minimum FU Duration 5.5 years
  - ≥72 months

Hot Line Session CARE-HF LTFU
Limitations

- CARE-HF LTFU is not a “true controlled trial”, but presents “registry data” of patients previously implanted within a controlled trial
- New information about the long-term effect of “delayed” CRT implantation
- More patients from the control group had died before start of LTFU
  - possible selection bias (“healthier” control group?)
- How do the clinical characteristics of the two patient groups compare at LTFU study entry?
  - Data not presented

Hot Line Session CARE-HF LTFU
Survival

- Survival curves diverge initially (main study)... 
- proceed parallel between 3–6 years (day 1000-2000)...
  - (presumably hypothesis control group)
- ...and seem to converge during longer follow-up (?)
Hot Line Session CARE-HF LTFU
Effect of „delayed“ CRT Implantation

- > 99% of patients initially assigned to the „control“ group (medical therapy) had received a CRT-D device at the time of LTFU entry (time of re-consent)
- Early survival benefit of CRT-P cannot be compensated by delayed CRT-D implantation (identical risk factors for early mortality)
- How did the time of CRT implantation in the control group affect survival?
- What is the frequency of CRT-D in the late implanted „control“ group?

Hot Line Session CARE-HF LTFU
Summary
- CARE-HF LTFU provides data on the longest follow-up information from a randomized, controlled trial population
- Results confirm the long-term benefits of CRT-P (without revascularization backup)
- The available data suggest that the initial survival benefit of CRT-P can not be compensated by delayed CRT-D implantation

CONGRATULATIONS FOR THE VERY LONG FOLLOW UP DATA!

DISCUSSANT
Effect of valsartan in Japanese hypertensive patients with coronary artery disease: Results from the JIKEI Heart Study
Aldo Pietro Maggioni, MD, FESC
ANMICO Research Center
Firenze, Italy

Disclosures:
APM was a member of the Steering Committee of the Val-HeFT and VALIANT trials
Further, APM received honoraria for lectures from Novartis

Rationale, aim and main results of this subanalysis of the JIKEI trial

- **Rationale:** The risk of cardiac events in hypertensive patients with CAD is higher than in those without CAD
- **Aim:** To demonstrate that valsartan can decrease the occurrence of major CV events, with respect to standard treatment, in the subgroup of patients with a history of CAD more than in those without CAD
- **Main results:** Valsartan significantly reduced the incidence of the primary end-point (but specifically angina pectoris and congestive HF) in the high risk patients with CAD which may be attributed in part to the improvements of myocardial remodeling

Primary end-point

- The primary endpoint was a composite of CV mortality and morbidity
- Components of the endpoint included:
  - hospital admissions for stroke or TIA
  - myocardial infarction
  - admission for congestive heart failure
  - admission because of angina pectoris
  - dissecting aneurysm of the aorta
  - doubling of serum creatinine, or transition to dialysis
- The first of those events to arise in any specific patient was noted as the primary event

Some strengths

- Randomized trial conducted in Japan
- More than 3,000 patients, 1,036 of whom with a documented CAD
- Low mean dose of valsartan (76 mg daily) but in the range for Japanese people (40-80 mg daily)
- Electrocardiography and echocardiography were performed in all patients at baseline, 1 and 3 years after randomization
**Relevant weaknesses**

- Prospective randomised open-blinded-label endpoint (PROBE) design with a long list of hard and soft endpoints
- No effects on all hard endpoints (stroke, AMI, death)
- Favorable effect just on softer endpoints
- Post-hoc subgroup analysis
- No p-value for interaction available

**Conclusions**

- The JIKEI investigators are to be congratulated for this trial conducted in more than 3000 Japanese patients
- However, the data presented here cannot fully support the conclusions of the authors
- For this reason, the results of this subanalysis cannot be extrapolated to general practice

---

**Effect of valsartan in Japanese hypertensive patients with coronary artery disease: Results from the JIKEI Heart Study**


**AIM**

The risk of cardiac events in hypertensive patients with coronary artery disease (CAD) was higher than in those without CAD. We here report the result of a sub-analysis of a large-scale trial [JIKEI HEART Study (JHS)] which demonstrated that the addition of the angiotensin II receptor blocker (ARB) valsartan to standard cardiovascular treatments significantly reduced the primary composite endpoint of cardiovascular complications as compared with conventional treatments without ARB in Japanese patients.

**JIKEI HEART Study**

### Method

One thousand thirty-six CAD patients in the JHS were subjected to this study.

We assessed the following endpoints such as myocardial infarction, angina pectoris and congestive heart failure between valsartan group and non-ARB group.

Electrocardiography and echocardiography were performed at baseline, 1 and 3 years after randomization.

---

**Effect of valsartan on endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>0.6062</td>
<td>0.0926</td>
</tr>
<tr>
<td>Mortality endpoint</td>
<td>0.4729</td>
<td>0.0745</td>
</tr>
<tr>
<td>Non-cancer death</td>
<td>0.3903</td>
<td>0.0493</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
<td>0.5605</td>
<td>0.0990</td>
</tr>
<tr>
<td>Hospitalization for death</td>
<td>0.3548</td>
<td>0.0358</td>
</tr>
<tr>
<td>Transition to chronic phase</td>
<td>0.8794</td>
<td>0.1367</td>
</tr>
<tr>
<td>Total mortality</td>
<td>0.7853</td>
<td>0.1705</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.9545</td>
<td>0.3104</td>
</tr>
</tbody>
</table>

Methods: In-study JIKEI Heart study group. Lett Jpn Cardiovasc Dis 2010; 48: 123-39

**Schematic of study protocol with treatment phases**

- Run in
- Non-ARB treatment
- Non-ARB treatment
- Valtsartan 40-60mg/d
- Valtsartan 40-60mg/d
- Non-ARB treatment
- End of study

**Conflict of interest**

The JIKEI HEART study was “investigator driven study”. The JIKEI HEART study was funded by Jikei University School of Medicine.

The sponsor had no role in the collection, analysis and interpretation of data, in writing of the manuscript, or in the decision to submit the paper for publication.
1. Effects of valsartan on primary and secondary prevention

**Strengths**
- An issue rarely analysed, a prespecified analysis
- Large number of patients in both primary (n=2116) and secondary (n=615) prevention groups
- Similar number of patients in both arms (valsartan add-on and non-ARB) for primary (10/510/101) and secondary (40/46/463) prevention
- Primary end-point: Incidence of CV events close to that expected (10.3% vs 12% in 3 yrs F1) and high enough both in primary (n=102 in 3 yrs F1) and secondary prevention (n=144)

**Limitations**
- PROS study (like in CAD-C, IN-CREATE, and JIKEI studies)
- Secondary prevention group: ACEI given to 29% patients at baseline, had to be stopped in both arms, thus non-ARB patients had no RAS blockers, despite previous CHD or CHF, which are preferred indications (ESH-ESC Guidelines 2007)
  - Increased CV risk in non-ARB?
  - Valsartan? ARB? or RAS blocker?

2. Combination therapy with valsartan and CCB

**Authors’ conclusion**
“Combination with valsartan+CCB showed lower primary events than non-ARB+CCB”

Preferred sentence: Valsartan add-on treatment lowered the incidence of CV events, whether patients received in addition CCB or not

**Limitations**
- Prespecified analysis?
- Indication bias for CCB?

3. Stroke and angina prevention by valsartan

**Authors’ conclusions**
- Stroke: “Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs 36) but not bleeding.”

**Angina**: “Valsartan was significantly effective for prevention of effort angina but not for unstable angina”

**Preferred sentence**: Angina prevention by Valsartan was rather due to inhibition of effort angina (16 vs 14) than unstable angina

**Important limitation**
- Small number of events ➔ underpowered statistical power

---

**Conclusion**

The present study provided convincing evidence that ARB valsartan significantly reduced the incidence of angina pectoris and congestive heart failure particularly in the high risk patients with CAD which may be attributed in part to the improvements of myocardial remodeling.
**KYOTO HEART Study: Effect of Valsartan on cardiovascular outcomes in patients with high-risk hypertension: updated ancillary analyses**

Kyoto Prefectural University of Medicine, Kyoto, Japan

### Conflict of Interest

- The study was funded by Kyoto Prefectural University School of Medicine.  
- The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Kaplan-Meier's curves

- **Primary endpoint**  
  - Valsartan
  - Non-ARB
- **Secondary endpoint**  
  - Non-ARB

### Study purpose

As the ancillary analysis of the KYOTO HEART study, we investigated:

1. Effects of valsartan on primary and secondary prevention
2. Combination therapy with calcium channel blockers (CCB)
3. Additional analysis of angina & stroke events

### Method-1

- **Primary & secondary prevention**  
  - The population was divided into two groups according to the presence of previous CV events at the entry.  
  - Primary endpoint: the same as in the main study.  
  - Secondary endpoint: new onset of HF, angina, dissecting aortic aneurysm, lower limb arterial obstruction, transition to dialysis or doubling of serum creatinine level
- **Combination therapy with CCB**  
  - The population was divided into two groups based on the usage of CCBs.  
  - Primary endpoint: the same as in the main study.
- **Additional analysis of stroke**  
  - Stroke were classified into bleeding and infarction

### Method-2

- **Additional analysis of angina pectoris**  
  - Diagnosis of angina pectoris  
    - hospital admission, ECG changes with chest pain, Q-wave MI, worsening HF, angina, dissecting aortic aneurysm, lower limb arterial obstruction, transition to dialysis or doubling of serum creatinine level  
  - Angina events were classified into effort angina or unstable angina according to the clinical record file.  
Baseline characteristics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Valsartan (n=112)</th>
<th>Non-ARB (n=104)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67±11</td>
<td>66±14</td>
<td>0.679</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>41/71</td>
<td>38/66</td>
<td>0.106</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>155±14</td>
<td>156±14</td>
<td>0.679</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87±11</td>
<td>85±12</td>
<td>0.380</td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>75±12</td>
<td>77±12</td>
<td>0.380</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24±4</td>
<td>25±4</td>
<td>0.958</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94±13</td>
<td>95±14</td>
<td>0.679</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>210±40</td>
<td>210±27</td>
<td>0.679</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53±16</td>
<td>53±34</td>
<td>0.679</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>178±78</td>
<td>178±22</td>
<td>0.679</td>
</tr>
<tr>
<td>CVD</td>
<td>30.4%</td>
<td>30.4%</td>
<td>NS</td>
</tr>
<tr>
<td>CHD</td>
<td>13.2%</td>
<td>13.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Changes of Blood pressure

Comparison between With CCB and Without CCB

Analysis of stroke events

Subspecified analysis of angina pectoris

Hazard ratio and 95% confidence intervals

Summary

- Valsartan was more effective for both primary prevention (3.0% vs. 6.7%) and secondary prevention (11.5% vs. 18.1%), in which primary stroke and secondary AP events are significantly inhibited, respectively.
- Combination with Valsartan+CCB showed lower primary events than non-ARB+CCB (5.0% vs. 9.8%).
- Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs. 26) but not bleeding.
- Valsartan was significantly effective for prevention of effort angina (1.1% vs. 2.3%), but not for unstable angina (0.20% vs. 0.59%, p=0.10).
Limitations

- The study is a post-hoc analysis. The differences of patient characteristics in the groups cannot be completely excluded, and lower sample volume in each sub-groups might underscore the statistical power.
- Since the main study was performed in the PROBE design, we could not exclude possible bias in event reporting, particularly for softer endpoints such as angina and TIA.
- However, all coronary culprit lesions were ascertained by coronary angiography and cerebrovascular events were diagnosed by CT and/or MRI, while the investigators were kept blinded to the diagnostic criteria for softer endpoints which had been determined by the endpoint committee.

Impact of Pacing-Induced Systolic Dyssynchrony on the Development of Left Ventricular Remodeling in Patients with Bradycardia and Normal Systolic Function: Analysis from the PACE Study

Chuek-Man Yu, Joseph Yen-San Chan, Fung Peng, Qing Zhang, Omar Rezaie, Gabriel Wee-Kwek Yip, Moosa Amin, Hanish Chi-Kin Chan, Jeffrey Wai-Hong Fung

Presenter Disclosure Information

- Chuek-Man, Yu
- <Role of the Pacing to Avoid Cardiac Enlargement (PACE) Trial>

Financial Disclosure:

Consulting fees from Philips; lecture fees from GE, St. Jude Medical, Phillips, Medtronic, and Boston Scientific; and research grants from Sanofi-Aventis, Hong Kong and Philips.

This study was supported by a research grant from Medronic Inc.

Unlabeled/Unapproved Uses Disclosure: None

Background

Biventricular apical (BVA) pacing

- The commonest location for ventricular lead placement in the pacing management
- Exerts deleterious effect on left ventricular (LV) systolic function and adverse clinical outcomes in patients with:
  - standard pacing indications
  - cardioverter defibrillator therapy
- Need to explore new pacing site or pacing mode

Epicardial Invasive Pacing in Patients with Bradycardia and Normal Ejection Fraction

Chuek Man Yu, MD, FACC, Joseph Yen-San Chan, FACC, MD, Qing Zhang, MD, PhD, Moosa Amin, MD, Gabriel Wee-Kwek Yip, MD, FACC, Hanish Chi-Kin Chan, FACC, Jeffrey Wai-Hong Fung, MD, FACC
Background

- Dysynchrony
- Synchrony

Hypothesis & Study Design

Pre-specified analysis in the PACE study to determine whether pacing-induced systolic dysynchrony is the major determinant of deterioration of ejection fraction and LV remodeling at 12 months. This will provide important insights for determination of patient groups who might benefit most from BIV pacing.

Patients

Inclusion criteria:
- Patients with normal LV ejection fraction (>45%) who had standard pacing indications (advanced AV block in 59%, sinus-node dysfunction in 41%)

Exclusion criteria:
- Persistent atrial fibrillation
- Acute coronary syndrome
- Percutaneous coronary intervention or CABG <3 months
- Life expectancy of <6 months
- Heart transplant recipients
- Pregnant women

Echocardiography

- LV volumes and ejection fraction
  - Real-time 3-dimensional echocardiography (iE33, Philips) performed in 96% of the patients
  - Biplane Simpson’s method was used in the others
  - Follow-up: baseline and 12 months
- LV systolic dysynchrony
  - Tissue Doppler imaging (TDI) to assess LV systolic dysynchrony at 1 month (Vivid 7, GE)
  - Systolic Asynchrony Index (SAI) introduced at 12th World Congress on Cardiac Pacing, 1 year

Baseline Characteristics

- Variables
  - Systolic Dysfunction Group: 200 patients
  - Non-Dys synchrony Group: 195 patients
  - P value

- Variables
  - LV ejection fraction at 12 months
  - LV end-systolic volume at 12 months
  - Pre-specified secondary endpoint
    - Early occurrence of systolic dysynchrony at 1 month (<33ms)
    - Definition of significant deterioration of LV systolic function
      - Reduction of LV ejection fraction 20% at 12 months

Study End-points

- Primary End-points
  - LV ejection fraction at 12 months
  - LV end-systolic volume at 12 months

- Pre-specified secondary endpoint
  - Early occurrence of systolic dysynchrony at 1 month (<33ms)
  - Definition of significant deterioration of LV systolic function
    - Reduction of LV ejection fraction 20% at 12 months

Results

- Systolic dysynchrony at 1 month (Dysynchrony Group) occurred in 52% (n=48) of patients with RVA pacing, but only 15% (n=13) with BIV pacing (p<0.001)
- The Dysynchrony Group had significantly lower LV ejection fraction with an absolute difference of 7.1% (p<0.001)
- LV end-systolic volume increased significantly in the Dysynchrony Group with a relative difference of 30.7% (p<0.001)
- Reduction of ejection fraction 25% occurred in 67% (39 out of 58) of patients in the Dysynchrony Group, but only in 16% (21 out of 115) in the No Dys synchrony Group (p<0.001)
Discussion

Major findings in the study:
- Systolic dysynchrony was the main pathophysiological mechanism of detrimental effect of RVA pacing on LV function.
- Majority of patients developing early systolic dysynchrony after pacing are attributable to RVA pacing.
- Patients with early systolic dysynchrony had a seven-fold risk of significant reduction of LV ejection fraction at 12 months regardless of pacing mode.
- RVA pacing exerts additional deleterious effect on LV function – mechanisms?
- BIV pacing mode protects patients from adverse outcome and dramatically reduces the occurrence of systolic dysynchrony.

Clinical implications:
- BIV pacing prevents early development of systolic dysynchrony.
- Systolic dysynchrony might be the most important contributing factor for the detrimental effect of pacing on ejection fraction and LV remodeling.
- Early dysynchrony only present in about half of patients received RVA pacing.
- The use of echocardiographic technique to screen for the early occurrence of dysynchrony may play a role in triaging patient with preserved systolic function to receive BIV pacing as the treatment of bradycardia.

ALPHA OMEGA: Effect of low doses of n-3 fatty acids on cardiovascular diseases in post-MI patients.
Editorial Comment
Luigi Tavazzi
GVM Care & Research, Cologno, Italy
Discussant

DART
GISSI-Prevenzione
JELIS
GISSI-HF
Why neutral results?

- Was the hypothesis sound enough?
- Low n-3 PUFA dose?
- How large is large enough?
- Optimistic expectations of benefit?
- Were the components of the composite primary endpoint specific enough for the specific mechanisms of action of n-3 PUFA?
- Too pragmatic study conduct?

Assumptions

- Incidence of CHD mortality of 4% per year in patients aged 60 to 80, enrolled 3.7 years (median) after MI
- 25% risk of CHD mortality reduction for EPA+DHA and 20% for ALA over 3 years (2 ways analysis)

During the course of the study the Steering Committee approved an increase in sample size from 4,000 to 4,837 subjects and an extended duration of intervention from 36 to 40 months.

In 2009 the original primary endpoint of “fatal CHD” was replaced by “major CV events” (including all fatal/non-fatal CV events and therapeutic interventions)

Effect of n-3 PUFA treatment in GISSI-Prevenzione (11,323 post-MI pts)

Methods

- Subjects were identified by hospital cardiologists, physically examined at enrollment by trained research nurses, and followed up by research staff through telephone interviews at 12 and 24 months (only)
- Non-fatal cardiovascular events were self-reported and verified (if known) against hospital records (if available), otherwise they were not considered
ALPHA OMEGA:
Effect of low doses of n-3 fatty acids on cardiovascular diseases in post-MI patients

Daan Kromhout, MPH PhD
for the Alpha Omega Trial Group
Wageningen University, Division of Human Nutrition
The Netherlands

TRIAL CONDUCT

• Investigator-initiated study
• Study design, conduct and reporting are solely those of the Alpha Omega Trial Group
• Data-analysis by independent statistician

N-3 FATTY ACIDS

- alpha-linolenic acid (ALA, C18:3n-3)
- eicosapentanoic acid (EPA, C20:5n-3)
- docosahexanoic acid (DHA, C22:6n-3)

LIMITED CONVERSION IN HUMANS (+10%)

HYPOTHESES

N-3 fatty acids reduce the risk of:
• major cardiovascular events
• fatal coronary heart disease
• ventricular arrhythmia-related events

PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>EPA/DHA and ALA</th>
<th>EHA/DHA</th>
<th>ALA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72(19)</td>
<td>72(19)</td>
<td>71(19)</td>
<td>71(19)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>7.42±1.3</td>
<td>7.33±1.5</td>
<td>7.33±1.3</td>
<td>7.34±1.3</td>
</tr>
<tr>
<td>Baseline median, %</td>
<td>56 (56)</td>
<td>56 (56)</td>
<td>56 (56)</td>
<td>56 (56)</td>
</tr>
<tr>
<td>Antiplatelet medication</td>
<td>68</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>65</td>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Antiarhythmic drugs</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>142±22</td>
<td>143±22</td>
<td>148±21</td>
<td>142±22</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>87±10</td>
<td>86±10</td>
<td>87±10</td>
<td>87±10</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.8±4.0</td>
<td>27.7±3.7</td>
<td>27.9±3.0</td>
<td>27.9±3.2</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

DESIGN ALPHA OMEGA TRIAL

- Patient recruitment
- Telephone screening
- Baseline examination
- Randomization
- Follow-up (4 times monthly)
- Cardiac events

- 400 mg EPA-DHA + ALA placebo
- 2 g ALA + EPA-DHA placebo
- 400 mg EPA-DHA + 2 g ALA
- ALA placebo + EPA-DHA placebo

TRIAL MARGARINES

Use of trial margarine on bread 20 grams per day ~ 3-4 slices of bread

Daily doses of n-3 fatty acids in the 4 groups:
I: 400 mg EPA+DHA
II: 2 g ALA
III: 400 mg EPA+DHA and 2 g ALA
IV: 0 mg EPA+DHA, 0 mg ALA
PARTICIPATING CENTERS
Centers are listed at www.aspacomegatrial.com

ENDPOINTS
Primary outcome
Major cardiovascular events: fatal and non-fatal cardiovascular events and cardiac interventions (PCI, CABG).

Secondary outcomes
Incidence of cardiovascular diseases
Fatal cardiovascular diseases
Fatal coronary heart disease
Ventricular arrhythmia-related events: sudden death, cardiac arrest, and placement of implantable cardioverter-defibrillator.
Death from any cause

COMPLIANCE
Change in plasma n-3 fatty acids during the trial

EPA+DHA AND ENDPOINTS
Findings were similar in men and women

ALA AND ENDPOINTS
Findings differed between men and women

ALPHA ANALYSIS
Patients with diabetes (n=1,014) had 30% higher risk of major cardiovascular events than non-diabetics (n=3,623)

RESULTS IN WOMEN

RESULTS IN DIABETIC PATIENTS
IMPLICATIONS

- Major cardiovascular events cannot be prevented by low doses of n-3 fatty acids in stable, well-treated post-MI patients
- ALA may prevent major cardiovascular events in women, which needs confirmation
- Whether n-3 fatty acids prevent ventricular arrhythmia-related events in post-MI patients with comorbid diabetes warrants further study

Comparison of drug therapy and CVD mortality in clinical trials with EPA + DHA

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>DART</th>
<th>GISSI-P</th>
<th>OMEGA</th>
<th>AOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>16.2</td>
<td>87.6</td>
<td>95.0</td>
<td>97.6</td>
</tr>
<tr>
<td>Displeased/lowering (%)</td>
<td>NA</td>
<td>23.6</td>
<td>94.0</td>
<td>95.5</td>
</tr>
<tr>
<td>ACEI/ARB (%)</td>
<td>NA</td>
<td>43.9</td>
<td>63.0</td>
<td>69.4</td>
</tr>
<tr>
<td>BP-lowering (%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>89.7</td>
</tr>
<tr>
<td>CVD risk reduction (%)</td>
<td>31.0</td>
<td>17.7</td>
<td>No dif</td>
<td>No dif</td>
</tr>
</tbody>
</table>

NA = not available
Adapted from: Szauter et al. Lancet 2010; 375: 540-50

RESULTS EPA-DHA IN GISSI-P AND AOT

3-year increase in stenosis to fish consumption in post-menopausal women with CAD and diabetes

<table>
<thead>
<tr>
<th>Fish consumption (servings/week)</th>
<th>Increase of stenosis (Mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>0.54 ± 1.37</td>
</tr>
<tr>
<td>≥ 2</td>
<td>0.00 ± 1.98</td>
</tr>
</tbody>
</table>

P-value: 0.003

RESULTS FOR ALA

- In total patient population, low doses of n-3 fatty acids were not related to major cardiovascular events
- In women, ALA reduced major cardiovascular events borderline significantly
- In diabetic patients, n-3 fatty acids reduced ventricular arrhythmia-related events (exploratory analysis)
PEARL-HF: A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose Study to Evaluate the Effects of RLY5016 in Heart Failure Patients:

- Authors: [List of authors]

RLY5016: A Novel, Non-Absorbed, Polymeric Potassium Binder with Advanced Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Layvaskate</th>
<th>Layvaskate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-aromatized, well-tolerated</td>
<td>Safety</td>
<td>Colors/Recesses (black, low warning)</td>
</tr>
<tr>
<td>Spheres of uniform surface; floating tablet</td>
<td>Design &amp; A1</td>
<td>Irregular, sharp edges and flowability issues</td>
</tr>
<tr>
<td>No Na⁺</td>
<td>Counterion</td>
<td>Na⁺ loaded</td>
</tr>
<tr>
<td>Twice Layvaskate</td>
<td>Binding in vitro</td>
<td>Low binding</td>
</tr>
<tr>
<td>4 clinical studies with proven &quot;K⁺&quot; binding</td>
<td>Data/Peer Path</td>
<td>Granulated-in</td>
</tr>
<tr>
<td>Lower dose, non-gut-neutral taste tablet (CDI process)</td>
<td>Dosing/Compliance</td>
<td>Grilly, backgrade, up to 60 g TID</td>
</tr>
</tbody>
</table>

Reduction in Total Potassium Excess Rapidly Normalizes Serum K⁺

- [Graph showing reduction in total potassium and normalization of serum K⁺]

RLY5016 Mechanism of Action: Reduction of Serum Potassium in Hyperkalemia

- RLY5016 acts as a "lumen sink": drawing more potassium into the colon, thereby treating/preventing hyperkalemia

RLY5016 Drug Interaction Information

- RLY5016 is a cation-binder, so it may potentially inhibit the absorption of positively-charged drugs.
- 18 drug interaction studies have been conducted with RLY5016 in rats (no human data is available):
  - The bioavailability of valsartan and reserpine was reduced by 50%.
  - No change in bioavailability was observed for:
    - Enalapril
    - Lisinopril
    - Losartan
    - Quinapril
    - Ramipril
    - Ticlopidine

Hyperkalemia – Risks

- Chronic kidney disease (CKD)
- RAAS inhibitors that block renal handling of potassium

Potassium Binding by RLY5016 and Effects on Serum K⁺

- A 50 mg/day dose of RLY5016 provides ~30 mEq/day extra excretion of potassium

Site of Action for RLY5016

- RLY5016 is designed to bind potassium in the colon, where the concentration of potassium is highest.
PEARL-HF: AE Summary

<table>
<thead>
<tr>
<th>RLY5016 30 mg/day (n = 56)</th>
<th>Placebo (n = 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least 1 AE</td>
<td>30 (54%)</td>
<td>15 (21%)</td>
</tr>
<tr>
<td>Number of patients with at least 1 GI AE</td>
<td>12 (21%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Number of patients with SAEs*</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Number of patients who died</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Number of patients who discontinued the study due to AE</td>
<td>4 (7%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>
* No SAEs assessed drug-related by the investigators

PEARL-HF Efficacy: Proportion of Patients with Serum K < 3.5 at any Study Visit (by GFR)

<table>
<thead>
<tr>
<th>GFR (mL/min)</th>
<th>RLY5016 30 mg/day</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 45</td>
<td>0/7 (0%)</td>
<td>0/9 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>3/15 (20%)</td>
<td>0/13 (0%)</td>
<td>0.008</td>
</tr>
<tr>
<td>≥ 60</td>
<td>0/10 (0%)</td>
<td>0/6 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>All patients</td>
<td>3/25 (6%)</td>
<td>0/19 (0%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusions

- The incidence of hyperkalemia (K > 5.5 mEq/L) is relatively low in patients with HF and CKD receiving standard therapy and an ACE (39%-50%).
- RLY5016 30 mg is effective in preventing hyperkalemia in HF patients with a history of hyperkalemia and HF and CKD and is relatively well tolerated with only minor GI adverse effects.
- Patients with HF and a history of hyperkalemia without CKD should be rechallenged with gaseous sodium extended-release doses of PRAA blocks before abandoning their use.
- Future studies will be necessary to determine the optimal RLY5016 dosing regimen to prevent hyperkalemia and avoid hypokalemia in patients with HF and CKD as well as to evaluate the efficacy and safety of RLY5016 in these hyperkalemia once it occurs.

Disclosures

- SDA received consultancy fees and honoraria for speaking at Amgen Inc., Vifor Pharma, BUMHMS AG and consultancy fees from Nanosphere. DWF received consultancy fees from Amgen Inc.
- The study was funded by the Interuniversity Cardiology Institute of the Netherlands (ICIN).
- Additional unrestricted grants were received from Janssen-Glaxo, Tilburg, and the Netherlands, and B.R.A.H.M.S. AG, Henningdorf, Germany.

A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction


Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands; Applied Cardiovascular Research, Department of Cardiology, Churgh, Campus Vichico Klinikum, Berlin, Germany; Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, The Netherlands; Isla Clinic, Zwolle, the Netherlands; Isla University Medical Center, Isla, the Netherlands; Medical Center Alkmaar, Alkmaar, the Netherlands; Academic Medical Center, Amsterdam, the Netherlands; St. Antonius Hospital, Vlaarweg, the Netherlands; Amphia Hospital, Breda, the Netherlands.

Classical Effect EPO: hematopoiesis

[Diagram showing the effect of EPO on hematopoiesis]
EPO in AMI: safety (pilot study)

In a first safety and feasibility study, a single high dose of EPO (40,000 IU) in patients with a first ST-elevation myocardial infarction, resulted in a 200% increase in serum EPO levels, without hypertension, thrombosis, or other adverse events.

Methods

- Inclusion Criteria:
  - Successful primary PCI (TIMI 2/3) for a first AMI, diagnosed by:
    - Sustained chest pain
    - ST depression > 0.2 mV in 2 or more leads
    - New left bundle branch block
    - TIMI flow 0-1 before primary PCI on diagnostic coronary angiography

- Key Exclusion Criteria:
  - Previous AMI
  - Hemoglobin levels > 17 g/dL before PCI
  - Anticipated additional revascularization within 6 wk
  - Atrial fibrillation
  - Cardiogenic shock
  - End stage renal failure
  - Malignant hypertension
  - Previous treatment with RhEPO

Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Total cohort</th>
<th>EPO</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) *</td>
<td>63.3 ± 11.1</td>
<td>60.8 ± 10.9</td>
<td>63.0 ± 11.3</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77.9</td>
<td>79.7</td>
<td>79.9</td>
</tr>
<tr>
<td>Wt (kg/m²) *</td>
<td>27.1 ± 4.2</td>
<td>27.4 ± 4.3</td>
<td>27.5 ± 4.0</td>
</tr>
<tr>
<td>History of hypertension *</td>
<td>18 (29.0)</td>
<td>21 (32.1)</td>
<td>17 (27.2)</td>
</tr>
<tr>
<td>Diabetes *</td>
<td>17 (27.5)</td>
<td>20 (30.4)</td>
<td>15 (23.0)</td>
</tr>
<tr>
<td>History of revascularization *</td>
<td>29 (49.0)</td>
<td>23 (34.3)</td>
<td>23 (34.4)</td>
</tr>
<tr>
<td>Current smoker *</td>
<td>13 (22.7)</td>
<td>16 (24.2)</td>
<td>12 (18.2)</td>
</tr>
<tr>
<td>Family history of CAD *</td>
<td>30 (50.0)</td>
<td>32 (48.5)</td>
<td>28 (42.4)</td>
</tr>
<tr>
<td>History of revascularization *</td>
<td>10 (16.9)</td>
<td>9 (13.5)</td>
<td>9 (13.5)</td>
</tr>
<tr>
<td>EF (LVEF) *</td>
<td>42 ± 5.7</td>
<td>42 ± 5.7</td>
<td>42 ± 5.7</td>
</tr>
<tr>
<td>LVEF (LVEF) *</td>
<td>42 ± 5.7</td>
<td>42 ± 5.7</td>
<td>42 ± 5.7</td>
</tr>
<tr>
<td>Stroke *</td>
<td>7.6 ± 3.4</td>
<td>7.6 ± 3.4</td>
<td>7.6 ± 3.4</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204 ± 40.8</td>
<td>196 ± 40.6</td>
<td>194 ± 40.4</td>
</tr>
</tbody>
</table>

Baseline Endpoint

After a mean of 6.5 (±2.0) weeks, planar radionuclide ventriculography was obtained in 448 patients (89%). Mean (SD) VEF was 0.51 (0.10) in the EPO group and 0.52 (0.11) in the control group (p=0.41).
Secondary Endpoint: 
Enzymatic infarct size

<table>
<thead>
<tr>
<th></th>
<th>EPO</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=263</td>
<td></td>
<td>N=266</td>
<td></td>
</tr>
<tr>
<td>Peak CK IU/l</td>
<td>1754</td>
<td>1262</td>
<td>0.203</td>
</tr>
<tr>
<td>(95% CI 625-2175)</td>
<td></td>
<td>(512-1976)</td>
<td></td>
</tr>
<tr>
<td>AKI (3x normal)</td>
<td>51.0</td>
<td>51.5</td>
<td>0.458</td>
</tr>
<tr>
<td>(95% CI 33.9-70.5)</td>
<td></td>
<td>(33.9-70.5)</td>
<td></td>
</tr>
<tr>
<td>Peak CKMB IU/l</td>
<td>314</td>
<td>337</td>
<td>0.955</td>
</tr>
<tr>
<td>(95% CI 16.9-460)</td>
<td></td>
<td>(14.1-420)</td>
<td></td>
</tr>
<tr>
<td>Peak Troponin T (ng/l)</td>
<td>4.00</td>
<td>4.00</td>
<td>0.644</td>
</tr>
<tr>
<td>(95% CI 3.30-4.35)</td>
<td></td>
<td>(3.30-4.35)</td>
<td></td>
</tr>
</tbody>
</table>

Secondary Endpoint: 
Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>EPO</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=263</td>
<td></td>
<td>N=266</td>
<td></td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>8</td>
<td>19</td>
<td>0.032</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1</td>
<td>2</td>
<td>0.649</td>
</tr>
<tr>
<td>Emergency re-PCI for In-hospital Thrombolysis/Infarction</td>
<td>2</td>
<td>7</td>
<td>0.288</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>0.205</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>7</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Major Adverse Cardiovascular Events were defined as: cardiovascular death, n-myocardial infarction, re-PCI, or coronary artery bypass graft, stroke, and clear symptoms of heart failure.

Time to first major adverse cardiovascular event

Subgroup analysis: 
changes in NT-proBNP

In a subgroup of 134 patients, NT-proBNP was available at baseline and follow-up.
Median (IQR) NT-proBNP increased from (165 (63-300)) to (306 (139-485)) pg/ml in the EPO group and from (265 (46-465)) to (758 (121-390)) pg/ml in the control group (p=0.036). In the control group (p=0.036).

Safety

- 49 Serious Adverse Events (SAEs) were reported in 40 control patients, and 33 SAEs were reported in 29 EPO patients.
- EPO was well tolerated and there were no reports of malignant hypertension, seizure, or deep vein thrombosis. Only one pulmonary embolism was reported in the control group and none in the EPO group.
- Changes in haemoglobin between baseline and 24 hours were available in 201 patients. Mean drop in haemoglobin (SD) was 0.52 (1.19) g/dl in the EPO group and 0.53 (1.02) g/dl in the control group (p=0.86).
- Similarly, there were no differences in the change in haematocrit (p=0.73), haematocrit (p=0.75) or platelet count (p=0.37) between both groups.

Conclusions

- A single high dose of EPO after a successful PCI for a first ST-elevation myocardial infarction did not improve LVEF after six weeks (primary endpoint).
- In addition, no significant reduction in enzymatic infarct size was observed (secondary endpoint).
- EPO reduced pre-defined major adverse cardiovascular events (secondary endpoint).
- A single high dose of EPO in non-anemic STEMI patients was safe and well tolerated.
- A large phase III clinical trial powered to detect a reduction in predefined hard clinical endpoints should be performed before EPO can be routinely used in this setting.

Acknowledgements

- Data Safety Monitoring Board: Prof. Dr. J.J. Tijssen, department of Cardiology, Academic Medical Centre Amsterdam, the Netherlands and M. van den Brand, MD, Erasmus Medical Centre Rotterdam, the Netherlands.
- Endpoint committee: B.J. de Smelt, MD, and A.J. van den Heuvel, MD, University Medical Center Groningen, the Netherlands.
- Statistical Support: N. Verhaar, PhD, Trial Coordination Center, University Medical Centre Groningen, the Netherlands.
- Netherlands Heart Foundation: Prof. Voors and Prof. van Velthuisen are clinical established investigators of the Netherlands Heart Foundation (E71-317 and 2000/13) and Dr. Belonje is supported by the Netherlands Heart Foundation (grant 200/17/20).

Online Publication

The results of this study are now published online in the European Heart Journal.
HEBE II: A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction

Discussant

Piotr Ponikowski, MD, PhD, FESC
Medical University, Centre for Heart Disease
Clinical Military Hospital
Wroclaw, Poland

What have cardiologists learned about EPO?

- EPO – not just an erythropoietic hormone, but rather a local, tissue-protective cytokine against ischemic injury
  - EPOR – myocardium, blood vessels, brain, liver, ...
  - EPO interacts with EPOR
    - apoptotic, promotion of survival and growth
    - anti-inflammatory processes
    - neovascularization (EPCs, VEGF)
  - Animal models of AMI: infarct size, improves contractility & hemodynamics, anti-remodeling – not related to hematopoiesis

Questions and hopes for the future

1. Selection of the end-points and patients
   a. Is LVEF sensitive enough?

2. Selection of the end-points and patients
   a. Is LVEF sensitive enough?
   b. Is 6-week follow-up period long enough?
   c. Would patients with more impaired LVEF benefit?

Beneficial effects of EPO in AMI: does clinical evidence support experimental data?

HEBE II results

Primary endpoint - neutral

Secondary endpoints – promising signal

LVEF 6 weeks after primary PCI

Questions and hopes for the future

1. Selection of the end-points and patients
   a. Is LVEF sensitive enough?
   b. Is 6-week follow-up period long enough?
   c. Would patients with more impaired LVEF benefit?
**Questions and hopes for the future**

1. Selection of the end-points and patients
   a. Is LVEF sensitive enough?
   b. Is 6-week follow-up period long enough?
   c. Would patients with more impaired LVEF benefit?

2. Safety and dosage of EPO therapy
   a. How to maximize “pure” pleiotropic EPO-effects?
   b. Lessons learned from neurology

**Lessons learned from neurology**

- Based on an analysis of total intent-to-treat and per-protocol populations only, this is a negative trial that also raises safety concerns, particularly in patients receiving systemic thrombolysis

**EPO in AMI: what is the evidence today?**

<table>
<thead>
<tr>
<th>Study, author</th>
<th>Population &amp; design</th>
<th>End-points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ljuščec E et al, 2006</td>
<td>80±2, 2.3% of patients died</td>
<td>EPOs mobilization at 72h LVEF (6 months) – rs</td>
</tr>
<tr>
<td>Bimbrik A et al, 2009</td>
<td>48±2, 24% of patients died</td>
<td>Intact size (Cx/MRI) – cm</td>
</tr>
<tr>
<td>Tarassow M et al, 2010</td>
<td>80±1, 2% of patients died</td>
<td>Intact size (CBR) – %</td>
</tr>
<tr>
<td>REVIVAL-2</td>
<td>80±1, 3.8% of patients died</td>
<td>LVEF (6 months) – rs</td>
</tr>
<tr>
<td>ACC 2009</td>
<td>80±1, 2.2% of patients died</td>
<td>LVESV, LVEDV – rs</td>
</tr>
</tbody>
</table>

**Hyperkalaemia in HF**

- How common?
  - In RALES, 13% to 21% of patients had K+ > 5.5 mmol/L.
  - In RALES 2%, had severe hyperkalaemia (> 6 mmol/L).
  - In EPHESUS 5.8% to 6.8% of patients had K+ > 6 mmol/L.
  - In unselected patients in clinical trials 15% to 30%.

- Risk markers
  - Age > 70 years or older
  - Renal impairment (Creatinine > 104 mmol/L) increases in up to 40% of patients with HF.
  - Intensive care unit stay and previous cardiac surgery.
  - Intensive care unit stay and previous cardiac surgery.

- Treatments with eustatics, RAAS-inhibitors, beta blockers, digoxin

- Non-HF medications on renal function
  - NSAIDs, heparins, diuretics, Insulin, gentamicin, vancomycin etc.

- Dietary
  - Salt substitutes, K supplements, bananas and other fruits.

**Plasma K+, TBK+ and VT**

- Dargie HJ et al BMJ 1974; 4: 316

**PEARL-HF**

- Double blind randomised parallel group RCT
  - Placebo controlled
  - Background Rx with RAAS and β blockers
  - Challenged with spironolactone 25 – 50 mg/day
  - Majority, 58% overall, had mild HF (NYHA II/III)
  - No patients in NYHA IV
  - LVEF was 40% overall, +/- 12%
  - Preserved and impaired LV EF and Fraction
  - CKD 3 and 4 (eGFR 30-59 and 15-29 ml/min)
  - Mean eGFR 64 and 78 ml/min in Reo and Pbc;
  - CKD 2/3
  - Diabetes in 73% and 63% in Reo/Pbc p=NS

**Impact of RALES**

- Jazrawi DN et al NEJM 1994; 543-51
**The K^+ Continuum**
- the twin ‘perils’ of hyper and hypokalaemia

- Total body K^+ = 3300 mmol
- Only 2% (60-70 mmol) in blood
- Small bi-directional shifts can cause hyper or hypokalaemia
- Insulin, aldosterone, angiotensin and adrenergic activity promote cellular uptake
- HF and its treatment affect serum

*Brown RS, American Journal of Medicine 2004;117:3-10*

**PEARL-HF**
- summary and conclusions

- Carefully designed placebo controlled RCT
  - performed by experienced investigators
- Trial demographics appropriate for age (68 yrs)
  - Relative risk HF for ARA
  - With relatively mild CKD (80 ml/min)
- Relypsa lowers K and prevents hyperkalaemia
  - Very high incidence of hyperkalaemia (>5.5 mmol/L)
  - 19-39% on placebo vs 6-7% on Relypsa
- Longer term risks and benefits analyses required
  - Future studies should target higher risk patients in large trials
  - Older, more severe HF and renal dysfunction
- Will we need a mortality trial?

**DISCLOSURES**

*Research grants:*
NLHBI, Covetins, Novartis

*Consultant/Advisory Board:*
Angen, ARCA, Boston Scientific, Covetins, CVRx, Medtronic, Paracor, Sanofi-avantis

**RATIONALE OF THE SHIFT STUDY**

High heart rate is strongly related with mortality in the general population and in patients with CAD and Heart Failure. In placebo group of patients studied in BEAUTIFUL Trail, with LV dysfunction EF <40%, 84% receiving beta-blockers, those with HR >median 70 bpm or HR <70 bpm:

**CARDIOVASCULAR DEATH**
- In patients with HR >70 bpm, compared to placebo
  - 16.3% in the risk of PEP, CV mortality and Hospitalization for HF
  - 20% in the risk of Hospitalization for HF
- 9% in the risk of CV mortality (p=0.002)
- 10% in the risk of all-cause mortality (p=0.002)
- Improvement in NYHA class, patient and physician global assessment
- Greater benefit was seen in patients HR >77 bpm, independent of BB dose
- Hypokalaemia had no serious adverse effects

**Majour Findings of SHIFT**

**A Beautiful Study**

In patients with HF, EF <35%, in SR, and baseline resting HR >70 bpm, 50% on BB, 90% AECI, 10% aldosterone blockers, use of hydralazine was associated with:

- 9 bpm in HR compared to placebo
- 18% in the risk of PEP, CV mortality, and Hospitalization for HF
- 20% in the risk of Hospitalization for HF
- 9% in the risk of CV mortality (p=0.002)
- 10% in the risk of all-cause mortality (p=0.002)
- Improvement in NYHA class, patient and physician global assessment
- Greater benefit was seen in patients HR >77 bpm, independent of BB dose
- Hydralazine had no serious adverse effects

**Was the background dose of beta-blocker used in SHIFT optimal?**

- Only 29% of patients were prescribed target dose of BB by the investigators, despite being encouraged to comply with the guidelines and up-titrate BB to the highest dose possible, 55% received at least 50% target dose
- In BB HF trials, higher % patients reached target dose: 39% in CIBIS II, 43% in CIBIS III, 64% in MERIT-HF, and 68% in COPERNICUS
- BB doses used in recent drug and device trials are not published
- In clinical practice much lower doses of BB are used

<table>
<thead>
<tr>
<th>HF Registries</th>
<th>Target dose reached (%)</th>
<th>% &gt; 50% target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBIS II (USA, 2004)</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>UK MARITIME (UK, 2009)</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Bata Heart Survey (2010)</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Impact Rhythm (France, 2009)</td>
<td>23</td>
<td>54</td>
</tr>
<tr>
<td>IMPROVE HF (USA, 2010)</td>
<td>17</td>
<td>-</td>
</tr>
</tbody>
</table>

**Could use of higher BB dose have changed the outcomes?**

Meta-regression of 23 beta-blocker HF trials involving 39,309 patients

Mortality benefit related to magnitude of HR reduction and not to the dose of BB:
- Pooled Mortality HR 0.70 (24%) for an average Heart Rate Reduction 12 bpm
CONCLUSIONS

- SHIFT confirms the importance of heart rate in the pathophysiology of HF and supports the concept that reduction in HR contributes significantly to beneficial outcomes in patients with HF.

- In patients with systolic HF in SR with HR >70 bpm, receiving usual clinical care and are unable to tolerate higher doses of BB, the addition of the pure HR reducing agent ivabradine is likely to improve HF outcomes.

Disclosures

SHIFT Executive Committee members received fees, research grants, or both from Servier, as well as fees for speaking or consulting from other major cardiovascular pharmaceutical companies.

Resting heart rate and mortality in HF post MI patients

The DIAMOND study: 1518 patients with HF post MI, 10 years follow up.
Primary objective

To evaluate whether the I\textsubscript{f} inhibitor ivabradine improves cardiovascular outcomes in patients with
1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction ≤35%
3. Heart rate ≥70 bpm and
4. Recommended therapy

Inclusion criteria

- ≥18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate ≥70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤12 months

Study endpoints

Primary composite endpoint
- Cardiovascular death
- Hospitalisation for worsening heart failure

Other endpoints
- All-cause / CV / HF death
- All-cause / CV / HF hospitalisation
- Composite of CV death, hospitalisation for HF or non-fatal MI
- NYHA class / Patient & Physician Global Assessment

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Iivabradine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>60.7</td>
<td>60.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Ischaemic aetiology, %</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>NYHA II, %</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>NYHA III/IV, %</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>67</td>
<td>66</td>
</tr>
</tbody>
</table>

7411 screened
6558 randomized
3268 to Iivabradine
3264 to placebo

3241 analysed
3264 analysed
2 lost to follow-up
1 lost to follow-up

Median study duration: 22.9 months; maximum: 41.7 months
**Effect of ivabradine on outcomes**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>0.82</td>
<td>[0.73, 0.91]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.90</td>
<td>[0.82, 1.04]</td>
<td>0.003</td>
</tr>
<tr>
<td>Death from HF</td>
<td>0.74</td>
<td>[0.62, 0.89]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospitalisation for any cause</td>
<td>0.09</td>
<td>[0.02, 0.39]</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hospitalisation for CV reason</td>
<td>0.15</td>
<td>[0.08, 0.29]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV death/hospitalisation for HF</td>
<td>0.82</td>
<td>[0.74, 0.90]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Patients with at least 50% BB target dose (n=3181)**

<table>
<thead>
<tr>
<th></th>
<th>Nitrate</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>0.33</td>
<td>0.40</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.17</td>
<td>0.17</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalisation for worsening HF</td>
<td>0.21</td>
<td>0.20</td>
<td>0.021</td>
</tr>
</tbody>
</table>

**Incidence of selected adverse events (N = 6492)**

<table>
<thead>
<tr>
<th>Patients with an event</th>
<th>Ibivradine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>44% (1460)</td>
<td>46% (1595)</td>
<td>0.025</td>
</tr>
<tr>
<td>All adverse events</td>
<td>75% (2421)</td>
<td>74% (2432)</td>
<td>0.303</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21% (688)</td>
<td>29% (931)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>5% (159)</td>
<td>1% (32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>6% (186)</td>
<td>1% (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9% (306)</td>
<td>5% (161)</td>
<td>0.012</td>
</tr>
<tr>
<td>Phrenic</td>
<td>1% (4)</td>
<td>1% (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1% (7)</td>
<td>&lt;1% (7)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

**Incidence of serious adverse events**

<table>
<thead>
<tr>
<th>Patients with an event</th>
<th>Ibivradine</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All serious adverse events</td>
<td>45% (2405)</td>
<td>49% (2455)</td>
<td>0.023</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20% (602)</td>
<td>30% (901)</td>
<td>0.001</td>
</tr>
<tr>
<td>General disorders, administration conditions</td>
<td>3% (95)</td>
<td>8% (264)</td>
<td>0.617</td>
</tr>
<tr>
<td>Infection and infarctions</td>
<td>7% (119)</td>
<td>7% (236)</td>
<td>0.351</td>
</tr>
<tr>
<td>Respiratory, thoracic, cardiac disorders</td>
<td>3% (107)</td>
<td>4% (142)</td>
<td>0.347</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>3% (95)</td>
<td>4% (135)</td>
<td>0.137</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>3% (95)</td>
<td>3% (135)</td>
<td>0.312</td>
</tr>
<tr>
<td>Neoplastic benign, malignant and unspecified</td>
<td>2% (66)</td>
<td>2% (67)</td>
<td>0.554</td>
</tr>
<tr>
<td>Mental and neurotic disorders</td>
<td>2% (66)</td>
<td>1% (43)</td>
<td>0.018</td>
</tr>
<tr>
<td>Reproductive disorders</td>
<td>1% (3)</td>
<td>1% (23)</td>
<td>0.273</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1% (3)</td>
<td>&lt;1% (3)</td>
<td>0.374</td>
</tr>
</tbody>
</table>

**Conclusion**

- Heart failure with systolic dysfunction and elevated heart rate is associated with poor outcomes (primary composite endpoint in the placebo group is 16%/year)
- Ivabradine reduced CV mortality or heart failure hospitalisation by 18% (p<0.0001). The absolute risk reduction was 4.2%
- This beneficial effect was mainly driven by a favourable effect on HF death/hospitalisation (NNT 26%)
- Overall, treatment with ivabradine was safe and well tolerated
Clinical implications

- The addition of ivabradine to recommended therapy significantly reduces death and hospitalisations related to heart failure in patients with heart rate ≥70 bpm

- The NNT for 1 year to prevent...
  - One primary endpoint is 26
  - One hospitalisation for heart failure is 27

Are the BEAUTIFUL and the SHIFT populations similar?

<table>
<thead>
<tr>
<th>Baseline population</th>
<th>BEAUTIFUL</th>
<th>SHIFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>83/17</td>
<td>77/23</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>NYHA (%)</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>62</td>
<td>49</td>
</tr>
<tr>
<td>NYHA III (%)</td>
<td>23</td>
<td>51</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>32</td>
<td>29</td>
</tr>
</tbody>
</table>

SHIFT versus BEAUTIFUL (HR ≥70 bpm): effect of ivabradine
Do HF patients frequently have heart rate ≥70 bpm?

Heart rate in European surveys: beta-blocker therapy

Are HF patients with heart rate ≥70 bpm at elevated CV risk?

YES

High CV risk despite recommended therapy:
PEP in the placebo group was 18% / year

Annual risk of mortality in placebo group in HF trials

Annual risk of HF death in major HF trials
The acute and long-term effect of intracoronary stem cell transplantation in 191 patients with chronic heart failure.

A new STAR in the cardiovascular stem cell therapy sky

The regeneration capability of the mammalian heart can be enhanced by transfer of embryonic or adult stem cells (repair, tissue reconstruction).

Premature experience in >1600 pts with acute or chronic infarction
- Enormous heterogeneity
- Substantial safety profile
- Mixed improvement in LV function and remodeling
- Mechanisms of benefit poorly understood (clinical setting?)
- Transdifferentiation into cardiac cells
- Qualifying effect
- Paracrine effect

The STAR-Heart Study

INSIGHTS INTO STEM CELL MECHANISMS OF BENEFIT

- The transdifferentiation into cardiomyocytes of 69 × 12³ BMCs is not enough to improve LV function in large healed infarctions
- The observed benefit suggests paracrine activation of resident cells

CONCLUSIONS

The results of the STAR-heart study suggest that intracoronary transfer of BMCs safely improves left ventricular performance and clinical outcomes of patients with chronic symptomatic left ventricular dysfunction due to healed infarction.

The amount of cells transferred is not enough to improve LV performance through a pure regenerative mechanism (transdifferentiation). This test supports scaffolding effect and paracrine activation as predominant mechanisms of benefit.

Randomized, double-blinded, mechanistic clinical trials with imaging surrogates are warranted to confirm these results and to compare different cells and different methods of delivery.
Table 1. Baseline Characteristics of the Patients with Ischemic Heart Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline cell therapy</th>
<th>Control group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1 ± 11.3</td>
<td>65.5 ± 12.1</td>
<td>= NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55.7</td>
<td>58.3</td>
<td>= NS</td>
</tr>
<tr>
<td>House (%)</td>
<td>44.3</td>
<td>41.7</td>
<td>= NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130.1 ± 18.2</td>
<td>130.4 ± 19.0</td>
<td>= NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.0 ± 4.2</td>
<td>28.4 ± 4.8</td>
<td>= NS</td>
</tr>
<tr>
<td>Intake of ischemic coronary artery revascularization procedures</td>
<td>10.0 ± 3.2</td>
<td>10.2 ± 3.3</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 2. Hemodynamics of the Left Ventricle

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline/Pot Cell Therapy</th>
<th>Chronic Heart Failure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV (ml)</td>
<td>150.0 ± 40.0</td>
<td>180.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>= NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>25.0 ± 10.0</td>
<td>25.5 ± 10.5</td>
<td>= NS</td>
</tr>
<tr>
<td>Interact (%)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 3. Quantitative Ventriculography

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline/Pot cell therapy</th>
<th>Chronic Heart Failure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV (ml)</td>
<td>150.0 ± 40.0</td>
<td>180.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>= NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>25.0 ± 10.0</td>
<td>25.5 ± 10.5</td>
<td>= NS</td>
</tr>
<tr>
<td>Interact (%)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 4. Contractility of the left ventricle

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline-Pot cell therapy</th>
<th>Chronic Heart Failure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/sAR (c)</td>
<td>150.0 ± 40.0</td>
<td>180.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>= NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>25.0 ± 10.0</td>
<td>25.5 ± 10.5</td>
<td>= NS</td>
</tr>
<tr>
<td>Interact (%)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 5. Arrhythmogenic indexes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline/Pot cell therapy</th>
<th>Chronic Heart Failure</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate variability (ms)**</td>
<td>30 ± 16.0</td>
<td>30 ± 16.0</td>
<td>= NS</td>
</tr>
<tr>
<td>LV morphology (ms)**</td>
<td>30 ± 16.0</td>
<td>30 ± 16.0</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 6. Quantitative ventriculography before, and 1, 2, and 6 months after BMC therapy comparison to control group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMG group</th>
<th>Control group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESV (ml)</td>
<td>150.0 ± 40.0</td>
<td>180.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>= NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>25.0 ± 10.0</td>
<td>25.5 ± 10.5</td>
<td>= NS</td>
</tr>
<tr>
<td>Interact (%)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>= NS</td>
</tr>
</tbody>
</table>

Table 7. NYHA class and LVEF before, and 1, 2, and 6 months after BMC therapy in comparison to control group

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>BMG group</th>
<th>Control group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>123.0 ± 45.0</td>
<td>283.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>II</td>
<td>53.0 ± 36.0</td>
<td>283.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>III</td>
<td>30.0 ± 36.0</td>
<td>283.0 ± 50.0</td>
<td>= NS</td>
</tr>
<tr>
<td>IV</td>
<td>10.0 ± 10.0</td>
<td>283.0 ± 50.0</td>
<td>= NS</td>
</tr>
</tbody>
</table>

** p < 0.05 vs. baseline (Bonferroni alpha correction). ** p < 0.05 vs. baseline.
Figure 1: A total of n=391 patients with reduced LVEF due to ischemic heart disease were enrolled in this prospective study. All patients had myocardial infarction and the time interval between the infarct and admission to our clinic was 8.5±3.2 years. BMC therapy has been proposed to all patients with reduced LVEF due to ischemic cardiomyopathy. Patients who refused the BMC treatment and accepted to undergo all procedures identical to the BMC group acted as control group. Coronary angiography, bpline left ventriculography, ECG at rest, spiroergometry, right heart catheterization and measurements of late potentials (LP) of short-term heart rate variability (HRV) and of 24-h Holter ECG were performed. The therapeutic follow-up was evaluated at 3, 12 and 60 months after the treatment.

Figure 2: EF improves significantly in BMC group in comparison to the control group. The initial beneficial effect of BMC therapy, as evidenced by a significant improvement of EF after 3 months, was lasting after 12 and 60 months. The EF decreases in the control group.

Figure 3: Mortality of BMC group was significantly reduced in comparison to the control group.
Many cohort studies (>500)

Multiple IM grafting was associated with 18% reduction in death and cardiac events, caused by deterioration in all adverse endpoints and fewer stenting.

Bacterial IM grafting (BIMA)

- Reducing mortality
- Reducing cardiac death
- Reducing late cardiac events
  - Bilateral internal thoracic artery grafting paltry for the left coronary artery system best paltry
  - Prevent 1-45% of vein grafts failed between 12 and 18 months
- Reducing stroke
  - "No-touch" technique is considered effective for reducing stroke risk in patients with the atherosclerotic-endothelial occlusion.

Off pump and stroke

<table>
<thead>
<tr>
<th>ART SIMA</th>
<th>ART BIMA</th>
<th>SYNTAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off pump</td>
<td>40%</td>
<td>41.8%</td>
</tr>
<tr>
<td>CVA</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Advantages Saphenous grafts

- Accessibility, sufficient length, and ease of manipulation
- Optimising patency
  - Antiplatelet therapy
  - Statins
  - PTC therapy
  - No-touch technique
  - External stenting
  - Harvesting the saphenous vein after systemic heparinisation

Advantages BIMA

- More deep sternal wound infections
  - Euro Heart J 2004; 25; 1650-1655
  - More target vessels with mild stenosis, composite grafting resulted in a higher incidence of graft occlusion or stent sign due to flow competition
  - More advanced techniques: "no-touch" technique to reduce the risk of infection and stent in-situ.

Some Concerns in Randomised Trials

- Power
- Cross-overs
- Lost-to-follow up

Trials

Study protocol

Protocol for the Arterial Revascularisation Trial (ART): A randomised trial to compare survival following bilateral versus single internal mammary artery grafting in coronary revascularisation (EORTC 46555-22345)

David F Taggart, 1, Brescia (Italy), Antonia Gray, 2, Douglas C. Mayo, 3, Marc A. Bellic, 2, Keith Chambers 2 and the ART Investigators

The aim is to enrol at least 3000 patients (1500 in each arm) over 3 to 5 year recruitment period in 20 centres in the UK, Australia, Poland and Brazil (Table 1). As the intervention or the operation, compliance is likely to be 100% except in the unusual situation where the planned operation is not possible for technical reasons.
**Conclusion ART trial**

- Use of Bilateral Internal Mammary Artery Grafting is safe:
  - 30 day or 1 year mortality not increased
  - duration of post op stay not increased
  - risk of stroke, MI, revascularization not increased
- Use of BIMA is not always possible, even in experienced hands
  - In BIMA group 10.4% of patients did not receive allocated treatment versus 3.3% in CAVANA group.
- Stroke rate in CAVG reduced by off pump surgery?

---

**Background**

- CABG remains best therapy for severe CAD (SYNTAX trial)
- CABG is limited by eventual failure of vein grafts (50–75% by 10 years)
- 10 years after CABG on TMA L-risk: *Death (<1.6), MI (<1.4), stroke (<1.25), redo surgery (>2)*
- Patency rates of TMA ≥ 95% at 10 years (versus 25%–50%)
- Benefits persist into 2nd and 3rd decade of follow up

---

**The New England Journal of Medicine**

- Randomized Trial to Compare Bilateral Versus Single Internal Mammary Coronary Artery Bypass Grafting (CAVG):
  - One Year Results of the Arterial Revascularisation Trial (ART)

---

**Trial Simulation**

- Number of Simulations

---

**Original Design**

- Current Study

---
**Use of BIMA in Routine Clinical Practice**

- Uncommon
  - <10% of CABG patients in Europe
  - <5% of CABG patients in USA

- Potential reasons for NOT using BIMA
  - Technically more challenging
  - Adds to duration of operation
  - Increases early mortality
  - Increases early major morbidity
  - Increases risk of eternal wound breakdown

**Trial Design**

- Protocol published (Trials 2006; 7: 7)
- Funded: UK Medical Research Council (MRC) & British Heart Foundation (BHF)
- Sample size
  - 3000 patients
  - 5% in 10 year mortality (from 25% to 20%)
- 90% power. 5% alpha required 2938 patients
- Two-arm randomised trial
- Randomisation: 1:1 SIMA to BIMA
- Supplementary vein/artery grafts as required
- Patients: Off-CPB procedure
- Multi-centre (n=23 hospitals in 7 countries worldwide)

**ART Endpoints**

- Primary
  - Survival at 10 years

- Secondary
  - Cause specific & 30 day mortality
  - Need for re-intervention
  - Clincial events
  - Quality of Life (SF-36, Rose and EuroQol)
  - Cost effectiveness

- Sub groups
  - Diabetes
  - Age (<70 yrs vs >70 yrs)
  - On vs off pump
  - Radial artery vs vein grafts
  - Number of grafts
  - Impaired ventricular function

**ART Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SIMA (n=1554)</th>
<th>BIMA (n=1542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: years mean (± SD)</td>
<td>63.5 (1.4)</td>
<td>63.7 (1.7)</td>
</tr>
<tr>
<td>Male</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23.4%</td>
<td>24%</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>7.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>43.8%</td>
<td>40%</td>
</tr>
<tr>
<td>Prior revascularisation</td>
<td>16%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Prior CVA</td>
<td>3.1%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>7.6%</td>
<td>6.6%</td>
</tr>
</tbody>
</table>

**ART Outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SIMA (n=1552)</th>
<th>BIMA (n=1542)</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Mortality</td>
<td>1.2%</td>
<td>1.2%</td>
<td>0%</td>
</tr>
<tr>
<td>CVA</td>
<td>1.1%</td>
<td>1.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>MT</td>
<td>1.5%</td>
<td>1.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Revision</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Wound reconstruction</td>
<td>0.6%</td>
<td>1.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Mortality</td>
<td>2.3%</td>
<td>2.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>CVA</td>
<td>1.8%</td>
<td>1.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MT</td>
<td>2.0%</td>
<td>2.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Revision</td>
<td>1.3%</td>
<td>1.8%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
ART Summary and Conclusions

- ART is largest RCT in cardiac surgery comparing two operations.
  - Confirm feasibility of international multi-centre RCT.
- Shows that routine use of BIMA is feasible in CABG patients.
- Testimony to safety of contemporary CABG with 1 or 2 TIMA.
  - 30 day mortality 1.2%; 1 year mortality 2.5%.
- Use of BIMA does not increase.
  - 30 day or 1 year mortality.
  - Duration of post op stay.
  - Risk of stroke, MI, revascularization.
- Use of BIMA results in a slight increase in the risk of eternal wound reconstruction by 13%.
- ART is funded for 10 years to determine if BIMA reduce mortality and need for repeat revascularization (expected completion 2015)
- ART will also report on costs, cost-effectiveness & QoL measures.

ART Trial Steering and Data Monitoring Committees

**TRIAL STEERING COMMITTEE**

- Verma, Sanjay
  - Principal Investigator Dr. Sanjay Verma Oxford
- Ahmad, Shahid
  - Professor of Health Studies Oxford
- Choo, Kit
  - Professor of Cardiovascular Medicine Oxford
- Cullin, A
  - Professor of Cardiology Oxford
- Dave, John
  - Professor of Cardiac Surgery Oxford
- Feil, Bernd
  - Professor of Cardiology Berlin
- Farrow, J
  - Professor of Cardiology Oxford
- Fittler, Thomas
  - Professor of Cardiology Berlin
- Gold, Austin
  - Professor of Cardiology Oxford
- Papier, J
  - Professor of Cardiology Oxford
- Slatkin, M
  - Professor of Cardiology Oxford
- Thomas, T
  - Professor of Cardiology Oxford
- Voss, S
  - Professor of Medicine Oxford

**DATA MONITORING COMMITTEE**

- Zajac, J
  - Professor of Cardiology Oxford
- Pasierbiak, M
  - Professor of Cardiology Oxford
- Kostis, J
  - Professor of Cardiology Oxford
- Vynne, S
  - Professor of Medicine Oxford

ATOLL: An international, randomized trial comparing i.v. enoxaparin with i.v. unfractionated heparin in primary PCI for ST-elevation myocardial infarction

Harvey White
Green Lane Cardiovascular Service and Cardiovascular Research Unit
Auckland City Hospital, Auckland, New Zealand

ATOLL: Notable features

- No effect on TIMI 3 flow or ST resolution
- No effect on bleeding
- Main secondary ischemic endpoint (death, recurrent MI, UADS or urgent revascularization) reduced: 11.3% UFH vs 6.7% enoxaparin, p=0.04
- Trend for reduction in mortality; 0.35 UFH vs 3.3% enoxaparin, p=0.04. In absence of a reduction in infarct size, improved TIMI 3 flow or decreased bleeding, this probably occurred by chance.
- Non-specific endpoint of death, MI or revascularization reduced: 8.5% UFH vs 5.1% enoxaparin, p=0.04

ATOLL: Notable features

- Pro-hospital randomization in 70%, radial approach in 67.5%, high use of high dose clopidogrel >80%, IIb/IIIa antagonists 73.8%, and thrombectomy 39.2%
- Unusual primary endpoint of death, MI, procedural failure or non-CABG major bleeding. Negative for primary endpoint: RR 0.83, CI 0.88 - 1.01, p=0.07
- Underpowered statistically for a realistic 20% reduction in primary endpoint. Confidence limits include a 32% reduction to a 1% increase
- No ranking of secondary endpoints (Hochberg) or adjustment for multiple analyses

ATOLL: Things I would like to know

- Comparable endpoints to other primary PCI trials for ischemic endpoints and for bleeding: role of BARC definition
- I would like to see % of patients in Killip Class I
- Role of radial access (67.5%)
- Role of clopidogrel dosage >600mg (>60%)
- Role of IIb/IIIa antagonists (73.8%)
- Role of thrombectomy (39.2%)
- Role of extended SC injections of enoxaparin
- Effect of therapies on stent thrombosis
Conclusions

- The ATOLL investigators have performed an excellent trial on a background of high use of evidence-based therapies.
- The role of Ib/IIa antagonists in the setting of intensive oral antiplatelet therapy (e.g., clopidogrel 600mg, prasugrel or ticagrelor) is not well defined.
- The ATOLL investigators have shown that enoxaparin is safe and likely has a clinical relevant effect on ischemic endpoints for patients undergoing primary PCI.
- They have moved us closer to the goal of further improving the outcomes of patients suffering STEMI.

ATOLL
An international randomized study
comparing IV enoxaparin to UFH in primary PCI

G. Montalescot, M. Conen, P. Goldstein,
K. Huber, C. Polack, U. Zeymer, E. Viciut
for the ATOLL investigators

ATOLL: Apixaban in STEMI Patients in Primary PCI Trial
Comparing Enoxaparin to UFH in STEMI Patients

Intravenous 0.5 mg/kg Enoxaparin

Clinical experience

- Choass et al (elective PCI)
- Millor et al (ACS-PCI)
- Carremazan et al (elective PCI)
- STEPS E (elective PCI)
- PEGASUS-70 (ACS-PCI)
- SHYNA (primary PCI)
- TRITON (primary PCI)
- ENGERI et al (Primary PCI)

ATOLL Trial design

Randomization as early as possible (MCL +3)
Real life population (acute, cardiac arrest included)
No anticoagulation or no lytic before Rota
Similar antiplatelet therapy in both groups

STEMI → Primary PCI

ENOXAPARIN IV 0.5 mg/kg

with or without GP IIb/IIIa

30-day results

Trial organization

ACTION Study Group (Academic Research Organization, Paris):

- 1 coordinating center: Institute of Cardiology, Pitié-Salpêtrière Hospital, Paris
- 2 Data center: IRIS (International Research Information System), Pitié-Salpêtrière Hospital, Paris
- 4 international PAC: Perfusion Paris
- Funding: AP-HP and institutional research grant from Sanofi-Aventis Group

Steering Committee:
- G. Montalescot (Chair, France)
- M. Cohen (USA), P. Goldstein (France), W. Huber (Australia), C. Polack (USA), E. Viciut (France), U. Zeymer (Germany)

Data Safety Monitoring Board:
- A. Cohen (Chair, France), M. Guthier (France), A. Ott (Germany)

Clinical Event Committee:
- F. Philippe, P. Salcieri, F. Rocca, A. Bellman, O. Grouny

Treatments:
- Enoxaparin 0.5 mg/kg
- UFH IV
- UFH IV or SC

Clinical experience

- 1 mg SC
- 2.5 mg IV
Main objectives

- 1st EP:
  - All-cause mortality at 30
  - Complications of MI at 30 [associated cardiac arrest, recurrent MI/ACS, urgent revascularization, stroke, peripheral or pulmonary embolism]
  - Procedure failure [definite stent thrombosis, BPCI use of CLOT/IMA, Non-TIMI 3 flow after PCI, STE resolution < 50% after PCI]
- Main EP: All-cause mortality, Recurrent MI/ACS or Urgent revascularization at 30
- Main safety EP: Non-CABG major bleeding (STEEPLE definition) during hospitalization

Other objectives

- Death or complication of MI
- Death, re-MI or urgent revascularization
- Death; Death or resuscitated cardiac arrest
- Major or minor bleeding
- Transfusion

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>UFH (n=463)</th>
<th>Enoxaparin (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>58% (268)</td>
<td>59% (266)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>60 (15)</td>
<td>60 (15)</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>17% (80)</td>
<td>16% (74)</td>
</tr>
<tr>
<td>Pre-hospital revascularization</td>
<td>71% (329)</td>
<td>72% (324)</td>
</tr>
<tr>
<td>Current smoker, % (n)</td>
<td>48% (218)</td>
<td>44% (196)</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>52% (99)</td>
<td>55% (102)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>46% (217)</td>
<td>48% (220)</td>
</tr>
<tr>
<td>Prior myocardial infarction, % (n)</td>
<td>3% (14)</td>
<td>2% (13)</td>
</tr>
<tr>
<td>Prior stroke, % (n)</td>
<td>3% (16)</td>
<td>3% (12)</td>
</tr>
<tr>
<td>Shock and/or cardiac arrest before admission, % (n)</td>
<td>5% (24)</td>
<td>4% (17)</td>
</tr>
<tr>
<td>Time from symptom onset to randomization—mean (SD)</td>
<td>20.7±10</td>
<td>20.3±11</td>
</tr>
</tbody>
</table>

Primary Endpoint

Death, Complication of MI: Procedure Failure or Major Bleeding

Main Secondary Endpoint (ischemic)

Death, Recurrent MI/ACS or Urgent Revascularization

Procedure and study medications

<table>
<thead>
<tr>
<th></th>
<th>UFH (n=463)</th>
<th>Enoxaparin (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial artery access, % (n)</td>
<td>93% (430)</td>
<td>93% (430)</td>
</tr>
<tr>
<td>Other artery access, % (n)</td>
<td>24% (110)</td>
<td>21% (97)</td>
</tr>
<tr>
<td>Stent implanted (PCI patients), % (n)</td>
<td>94% (430)</td>
<td>94% (430)</td>
</tr>
<tr>
<td>Thrombectomy among PCI patients, % (n)</td>
<td>44% (192)</td>
<td>42% (194)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa before start of PCI, % (n)</td>
<td>77% (371)</td>
<td>71% (231)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>66% (304)</td>
<td>69% (303)</td>
</tr>
<tr>
<td>Eliptique</td>
<td>15% (56)</td>
<td>15% (56)</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>3% (11)</td>
<td>3% (11)</td>
</tr>
<tr>
<td>Medication before or during hospitalization — % (n)</td>
<td>95% (430)</td>
<td>95% (430)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>93% (427)</td>
<td>94% (427)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>93% (427)</td>
<td>94% (427)</td>
</tr>
<tr>
<td>&gt; 160 mg</td>
<td>77% (371)</td>
<td>77% (231)</td>
</tr>
<tr>
<td>160 mg or &lt; 300 mg</td>
<td>37% (131)</td>
<td>35% (114)</td>
</tr>
<tr>
<td>&lt; 300 mg</td>
<td>25% (115)</td>
<td>25% (131)</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>3% (21)</td>
<td>3% (21)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>73% (342)</td>
<td>72% (342)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>53% (245)</td>
<td>53% (245)</td>
</tr>
</tbody>
</table>
**Triple Ischemic Endpoint**

Death, re-MI or Urgent Revascularization

- Log-Rank Test: p = 0.04
- 30 day rate (%)
  - USF
  - ENOX
  - 8.5%
  - 5.1%

**Death finding → Chance finding?**

- REGISTRIES
- RANDOMIZED

**Main Safety Endpoint**

Non-CABG Major Bleeding (STEPPLE definition)

- % of patients
  - UFH
  - ENOX
  - P = NS

**All Safety Endpoints**

- % of patients
  - Major bleeding
  - Minor bleeding
  - Non-bleeding
  - Stroke
  - Death

- RRR = 32%
- P = 0.03

**Conclusions**

In this 1st pure head-to-head comparison between two anticoagulants in primary PCI, i.v. enoxaparin:

- Did not reduce procedural failure
- Reduced serious ischemic events, on top of intense antplatelet therapy
- Had a good safety profile, with a superior net clinical benefit
**E5555: Phase II data**

Fram Van de Werf, MD, PhD
Leuven, Belgium

**Cumulative death rates in 3721 GRACE ACS patients from UK and Belgium at ± 5 year**

- 15% after discharge
- 16% after 30 days
- 17% after 1 year

**Longer and better antithrombotic treatment after ACS**

- Prolonged anticoagulation (eg oral anti-Xa agents)
- Prolonged dual platelet inhibition with aspirin and a P2Y12 inhibitor (eg ticagrelor in PEGASUS study)
- Adding a third antplatelet agent inhibiting yet another pathway of platelet aggregation (eg thrombin receptor inhibitors, vorapaxar and E5555)

**Disclosures**

- I am a member of the executive committee of the TRACER trial (a phase III study with another PAR-1 antagonist, vorapaxar, in ACS patients)
- I am a member of the steering committee of the TRAP trial (Phase III study with vorapaxar in chronic CAD)

**Why is there a high late event rate after ACS?**

- Insufficient platelet inhibition and/or lack of anticoagulant therapy might be partly responsible .......among other causes

**The E5555 phase II data**

- are in line with those of the phase II studies with another thrombin receptor antagonist, vorapaxar:
  - no significant increase in clinically relevant bleeding complications
  - some evidence for a further reduction in ischemic events
But.....E5555 phase II studies

- relatively small
- liver dysfunction and QT prolongation are of concern

Conclusions

- Additional antiplatelet therapy with a thrombin receptor antagonist (PAR-1 inhibitor) looks promising
- Only the phase III studies can give the final answer!

Disclosure

Research grants from:
Pfizer, Sanofi-Aventis, Ono, Eisai, Otsuka, Sankyo, Daiichi, Takeda, Asteras, Kowa, AstraZeneca.

Honouraria from:
Sanofi-Aventis, Eisai, Otsuka, Daiichi-Sankyo, Schering-Plough.

Background

- Thrombin plays a critical role in the development and propagation of thrombus through both blood coagulation and platelet aggregation.
- E5555 is a novel oral Protease-Activated Receptor-1 (PAR-1) antagonist that binds selectively to PAR-1.
- In preclinical and Ph I studies in healthy volunteers, E5555 inhibited platelet aggregation induced by thrombin without affecting the blood coagulation, fibrinolysis system and bleeding time.

Study Populations

- **High risk CAD study**
  - Confirmed CAD defined as one of the following:
    - Post-ACS, MI or PCI (>1 wks), Post CABG (>12 wks),
    - AP with documented ischemia (ECG or image) or
    - Documented lesion occluding ≥75% of a coronary vessel
  - Other risk defined as one or more of the following:
    - Diabetes mellitus under Rx treatment, history of PAD or history of thrombo-embolic TIA or stroke >1 yr
- **ACS study**
  - UA and NSTEMI defined as
    - Ischemic chest pain ≥25 minute or
    - Symptoms requiring sublingual nitrate agent to reduce chest pain
  - Randomization within 24 hrs after onset

Study Design
**Demographic**

<table>
<thead>
<tr>
<th>Patients with ACS</th>
<th>Patients with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin 20 mg</td>
<td>Fluvastatin 80 mg</td>
</tr>
<tr>
<td>59.82% (n=181)</td>
<td>41.78% (n=109)</td>
</tr>
<tr>
<td>40.18% (n=125)</td>
<td>58.22% (n=167)</td>
</tr>
</tbody>
</table>

**CEC-Adjudicated TIMI Bleeds**

ACS up to 12 wks

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Active 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MAI</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Major</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

CAD up to 24 wks

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Active 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MAI</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Major</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**CEC-Adjudicated MACE by Category**

ACS up to 12 wks

<table>
<thead>
<tr>
<th>Placebo</th>
<th>All 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MI</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

CAD up to 24 wks

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Active 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>MI</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Overall Adverse Events (>10%)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

**Delta QTcF at LOCF from baseline**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>All 1 (n=180)</th>
<th>Active 5 (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

**Conclusion**

- E5555 showed a dose related trend to increased “nuisance” bleeding events, but did not increase clinically significant bleeding events in ACS and high risk CAD.
- E5555 added to standard antplatelet therapy indicated the potential for reduction of MACE in patients with ACS and high risk CAD populations.
- All doses tested achieved a significant level of IPA.
- Safety issues including liver function test and QTc should be addressed in future study.
- Thus, PAR-1 antagonism appears to be an attractive pathway for the treatment of atherothrombosis.

**Lecture fees and temporary advisory boards:**

- AstraZeneca
- Daichii-Sankyo
- Eli Lilly
- sanofi-aventis
- The Medicines Company

**INNOVATE PCI - ESC 2010**

Steen D. Kristensen, FESC
Department of Cardiology
Aarhus University Hospital Skejby
Denmark
**Targets for Platelet Inhibition**

- Aspirin
- Ticlopidine
- Clopidogrel
- Warfarin
- Heparin
- Glycoprotein IIb/IIIa inhibitors
- Thienopyridines

**Elinogrel: potential advantages**

- Immediate, high-level platelet inhibition with the i.v. formulation in the acute setting and a smooth transition to predictable oral platelet inhibition in the chronic setting.
- Reversible - surgery and in case of severe bleeding.

**INNOVATE PCI**

- Dose-finding
- Safety (bleeding and other side effects)
- Effect on platelet aggregation

**Elinogrel**

- Faster onset
- Stronger platelet inhibition

**Pharmacodynamic effect of Elinogrel vs. Clopidogrel**

- Day 30
- C (N=20)
- E100 (N=13)
- E150 (N=13)

**INNOVATE PCI**

- Dose-finding
- Safety (bleeding and other side effects)

**INNOVATE PCI**

- Dose-finding
- Safety (bleeding and other side effects)

- Randomized, double blind

- Power calculation

- Bleeding definition
INNOVATE PCI

- Dose-finding
- Safety (bleeding and other side effects)

Randomized, double blind
Power calculation
Bleeding definition
Effective PCI (46% clopidogrel)

INNOVATE PCI: bleeding

- No statistical significant difference

INNOVATE PCI: ischaemic endpoint

- No difference between clopidogrel and elinogrel

Bleeding at 24 hrs or d/c – TIMI Scale

Rates + 95% confidence intervals

Bleeding at 24h-120d – TIMI Scale

Rates + 95% confidence intervals

Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel N=226</th>
<th>Pooled Elinogrel 100 mg N=201</th>
<th>Pooled Elinogrel 156 mg N=207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>11.1%</td>
<td>14.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Drug d/c due to AE or SAE</td>
<td>5.1%</td>
<td>11.5%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.3%</td>
<td>15.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.5%</td>
<td>1.9%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>ALT/AST = 3x</td>
<td>1.2%</td>
<td>3.3%</td>
<td>4.0%</td>
</tr>
<tr>
<td>ALT/AST &gt; 5x</td>
<td>0.6%</td>
<td>2.3%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>
### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel N=208</th>
<th>Pooled Eliogrel 100 mg N=201</th>
<th>Pooled Eliogrel 150 mg N=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>11.1%</td>
<td>14.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Drug ex. due to AE or SAE</td>
<td>9.1%</td>
<td>11.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>15.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.5%</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>ALT/AST &gt; 3x</td>
<td>1.2%</td>
<td>3.3%</td>
<td>4.0%</td>
</tr>
<tr>
<td>ALT/AST &gt; 5x</td>
<td>0.9%</td>
<td>2.6%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

### INNOVATE PCI: conclusion
- Promising new P2Y12-inhibitor
- Phase III trials

**Congratulations to the investigators**

### Reversible P2Y12 inhibition
- Intravenous - fast
- No metabolism
- Surgery and and other intervention
- Easier to manage bleeding

### The variability in responsiveness to clopidogrel
- Is great with currently approved doses and may only to some extent be overcome with higher doses.
- Is related to increased clinical event rate.
- Is often caused by a inadequate generation of the active metabolite.
- May in part be genetically determined by reduced metabolizing function of CYP2C19.

### Optimal P2Y12 inhibition
- Maybe switching between clopidogrel and cangrelor cause some problem
- Use the same drug iv plus orally could theoretically be a solution to the problem
A Randomized, Double-Blind, Active Controlled Trial to Evaluate Intravenous and Oral PRT060128 (elnogrel), a Selective and Reversible P2Y12 Receptor Inhibitor, vs Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions (INNOVATE-PCI)

Background

- Antiplatelet therapy is essential to reduce adverse events in patients with ischemic heart disease
- Recent clinical trials demonstrate that greater platelet inhibition is associated with improved ischemic outcomes, but increased major bleeding
- Reversible platelet inhibition may mitigate these risks and further improve outcomes
- Elnogrel is a novel potent platelet inhibitor that competitively and reversibly binds to the P2Y12 receptor and can be administered both intravenously and orally

INNOVATE-PCI Objectives

- Phase II study to evaluate the safety, clinical efficacy, and tolerability of IV and oral elnogrel in patients undergoing non-urgent PCI
- Examine a number of clinical and biological endpoints to understand how elnogrel dose relates to safety, clinical and biological efficacy, and tolerability
- Not statistically powered for any specific endpoint
- Obtain pharmacodynamic (PD) data for the IV and oral elnogrel doses in a subset of trial participants

Disclosures

- INNOVATE-PCI was supported by Portola Pharmaceuticals Inc.
- Sunil V. Rao, MD
  - Research funding: Portola, Novartis, Cordis Corporation, Glaxo Smith Kline
- This presentation discusses the unapproved use of elnogrel (PRT060128) in patients undergoing PCI

Properties of Elnogrel

- The only reversible and competitive P2Y12 receptor antagonist
- Direct-acting: no metabolic activation required
- Available for intravenous and oral administration, enabling acute and chronic use
- Immediate and maximal platelet inhibition achieved with IV
- Duration of action
  - Half-life: 12 hours
- No major CYP metabolism – low potential for drug-drug interactions (including PPIs)
- Balanced clearance: 50% renal; 50% hepatic (10% metabolized to pharmaceutically inactive metabolite)

Inclusion & Exclusion Criteria

**INCLUSION**

- Nonurgent PCI with ≥1 coronary lesion amenable to PCI

**EXCLUSION**

- **Bleeding risk**
  - A history of bleeding disorders, recent trauma or bleeding, or a history of bleeding within 30 days of index procedure
- **Concomitant therapies**
  - Clopidogrel loading dose within 7 days prior to PCI, thienopyridines, oral anticoagulants, fondaparinux
- **General**
  - Age > 75 yrs, weight < 55 kg, crcl < 45 cc/min, allergy to study drugs

Endpoints

- **Safety** – 24 hr or d/c & 10-day
- **TIMI bleeding** major, minor
- **Bleeding requiring medical attention**
- **Clinically relevant bleeding** major, minor, nuisance

Biomarker efficacy - periprocedural

- Any troponin** elevation at 24 hrs or d/c
- Troponin** elevation > 2 X LNL at 24 hrs or d/c

**Clinical efficacy**

- 24 hr or d/c death, MI, stroke, uTIVA, GP IIb/IIIa bailout, stent thrombosis
- 120-day death, MI, stroke, uTIVA, GP IIb/IIIa bailout, stent thrombosis
- 120-day death, MI, stroke, uTIVA, stent thrombosis

*Data from INNOVATE-PCI
Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clopidogrel 300 mg N=422</th>
<th>Pooled elinogrel 150 mg N=405</th>
<th>Pooled elinogrel 300 mg N=352</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>11.1%</td>
<td>9.3%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Drug dir due to AI or SAE</td>
<td>7.7%</td>
<td>7.5%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Dyspnea*</td>
<td>4.3%</td>
<td>5.4%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5%</td>
<td>1.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.5%</td>
<td>1.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>ACS/STEMI &gt; 5a</td>
<td>1.0%</td>
<td>0.0%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

* Dyspnea was generally mild, transient, and infrequently led to discontinuation
* Most cases occurred within first 6 days and were asymptomatic; all cases resolved, even when treatment was continued, for N=85 cases

Conclusions

- IV and oral elinogrel result in greater and more rapid antiplatelet effect than clopidogrel during both the acute and chronic phase of therapy
- No excess TIMI major or minor bleeding at both the 24-hour and 120-day time points
- Dose-dependent trend of increase in less severe bleedings (Bleeding Requiring Medical Attention), mostly occurring at the vascular access site in the peri-procedural period
- No significant differences in efficacy at 24 hrs or 120 days (trial not powered for efficacy)

INNOVATE-PCI Study Organization

- Study Chair: Robert A. Harrington MD
- Co-Principal Investigators: Sunil I. Kas MD, Robert H. W. MD
- Steering Committee: Uwe Zeymer MD, Janusz Kuchman MD, Kurt Huber MD, Deepak Bhurj MD, C. Michael Sibson MD, Mitja M stylish MD
- DCR: Gayla Paytet (project lead), Lisa Barden, Vhuza Thompson MPH (Stats), Gail E. Haffey MD (Stats)
- DMC: David J. Malville MD (chair), Eric Cohen MD, Paul Blanke MD, Bich T. G. (Stats)
- Study Sponsor (Portal): Matthew McCune MD, Daniel O'Neen MD, Deb Chapman, Sally Greenberg MD

Thank you to all innovative PCI investigators and study coordinators worldwide.

ISAR-REACT 3A

Comments

Christian W. Hamm
Koch Hill, Heart & Thorax Center
Bad Nauheim, Germany

No conflict to report with respect to this study.

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS)

W. Wijns, P. Kolh et al., in press
Facts: UFH during PCI

- Effect poorly predictable
- Dose empiric
- ACT control controversial
- Few controlled/randomized trials

Advice from Guidelines

ESC Guidelines 2010

Unfractionated heparin (UFH) is currently the gold standard antithrombotic medication:
70-100 IU/kg IV bolus without GPIIb-IIIa inhibitors, ...

Recommendation I - C

W. Wijns, P. Kolh et al, in press

Primary (Quadruple) Endpoint - Net clinical Outcome -

Good News

Anticoagulation during PCI 2010

- Less thrombogenic material (guide, wires, ...)
- Shorter procedures
- Less thrombogenic contrast media
- Adjunctive antiplatelet medication: clopidogrel

UFH Dose?

- ISAR-REACT 3A: 140 U/KG vs. 100 U/kg

- STEEPLE (2006) 70 – 100 U/kg
- Vainer et al. (1997) 5000 U
- Koch et al. (1997) 5000 U
- Kaluski et al. (2003) 2500 U
- Caussin et al. (2003) 3000 U

Take home message

- In elective PCI:

  Not more than 100 U / kg UFH
  Probably less!
Background

- Optimal dose of unfractionated heparin (UFH) during percutaneous coronary intervention (PCI) is not known.

- In the predecessor ISAR-REACT 3 trial a bolus dose of 140 U/kg UFH without activated clotting time (ACT) monitoring was compared with bivalirudin in biomarker negative patients undergoing PCI.

Kastrati et al, NEJM 2006

Aims of ISAR-REACT 3A:

To evaluate whether in biomarker negative patients undergoing PCI after pretreatment with 600 mg clopidogrel

(i) 100 U/kg UFH is superior to 140 U/kg UFH regarding net clinical outcome at 30 days

(ii) 100 U/kg UFH is at least non-inferior to bivalirudin regarding net clinical outcome at 30 days

Methods

- Prospective, multicenter, single-arm, open-label, historical control trial.

- 3 participating centers in Germany:
  Deutsches Herzzentrum Munich, Klinikum rechts der Isar, Munich, Horz-Zentrum Bad Kissingen.

- Same eligibility, inclusion and exclusion criteria and endpoints as in ISAR-REACT 3.

Treatment Regimen

Clopidogrel 600 mg at least 2 hours before PCI
Aspirin ≥325 mg orally or intravenously

Single bolus dose of 100 U/kg UFH without ACT guidance

Clopidogrel 75-150 mg/day until discharge (≤3 days)
75 mg/day thereafter
Aspirin 80-325 mg/day indefinitely
Primary (Quadruple) Endpoint at 30 Days

Composite rate of:
- Death
- Myocardial infarction (defined as CK-MB ≥2x upper limit normal)
- Urgent target vessel revascularization
- Major bleeding (according to the REPLACE-2 criteria, JAMA '03)

- Intracranial, intracardiac, or retroperitoneal bleeding, or
- Clinically overt bleeding resulting in a decrease in Hb>4 g/dL or
- Any decrease in Hb>4 g/dL, or
- Transfusion of ≥2 units of packed red blood cells or whole blood

Secondary (Triple) Endpoint at 30 Days

Composite rate of:
- Death
- Myocardial infarction
- Urgent target vessel revascularization

Sample Size Calculation

**Superiority hypothesis (100 vs. 140 U/kg UFH)**
- Incidence of the primary endpoint is ISAR-REACT 3 (historical control).
  - 8.7% in 140 U/kg UFH group
- Assumptions:
  - 20% relative reduction (2.2% in absolute) with lower UFH dose
  - Power 80%, 2-sided α-level of 0.05
- Calculated sample size: 2367 pts
to account for possible losses to follow-up; planned enrollment of 2500 pts

**Non-inferiority hypothesis (100 U/kg vs. Bivalirudin)**
- With 2500 patients the study had 74% power to check for non-inferiority of the lower UFH dose versus Bivalirudin
- Based on the incidence of 3.3% in the bivalirudin group of ISAR-REACT 3

Study Population

ISAR-REACT 3A (Aug 2008 - Feb 2010)
ISAR-REACT 3 (Sep 2006 - Jan 2009)

4570 Patients

2505 Pts
2281 Pts
2289 Pts

PCI

30-day Follow-up

Baseline Characteristics

<table>
<thead>
<tr>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>66 (30-94)</td>
<td>63 (30-74)</td>
</tr>
<tr>
<td>Women, %</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.4</td>
<td>27.2</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Hypercholesterol, %</td>
<td>71</td>
<td>79</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>History of CABG, %</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Stable angina, %</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.0 (0.67-1.5)</td>
<td>0.9 (0.56-1.3)</td>
</tr>
</tbody>
</table>

**P=0.05 for UFH 100 U/kg vs UFH 140 U/kg # P=0.05 for UFH 100 U/kg vs Bivalirudin

Angiographic Characteristics

<table>
<thead>
<tr>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction, %</td>
<td>58 (50-62)</td>
<td>60 (52-66)</td>
</tr>
<tr>
<td>Multivessel, %</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>Vessel treated, %</td>
<td>Left main</td>
<td>4</td>
</tr>
<tr>
<td>LAD</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>LCX</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>RCA</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>bypass graft</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>B2/C lesion, %</td>
<td>71</td>
<td>68</td>
</tr>
</tbody>
</table>

**P=0.05 for UFH 100 U/kg vs UFH 140 U/kg # P=0.05 for UFH 100 U/kg vs Bivalirudin

Procedural Characteristics

<table>
<thead>
<tr>
<th>UFH 100 U/kg</th>
<th>UFH 140 U/kg</th>
<th>Bivalirudin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DES</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>BMS</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>PTCA</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Final DS, %</td>
<td>11.3 (7.3-14.8)</td>
<td>10.8 (7.3-14.8)</td>
</tr>
</tbody>
</table>

**Primary (Quadruple) Endpoint - Net clinical Outcome**

- Cumulative incidence (%)

HR: 0.81; 95% CI: 0.87 - 1.00; P= 0.045
Adjusted HR: 0.75; 95% CI: 0.60 - 0.92; P = 0.007

140 U/kg UFH: 8.7%
100 U/kg UFH: 7.3%
**Major Ischemic Events**

![Graph showing ischemic events]

**Conclusion**

Using ISAR-REACT 3 treatment arms as control, ISAR-REACT 3A shows:

(I) In biomarker negative patients undergoing PCI a reduction in heparin dose from 140 to 100 U/kg provides net clinical benefit. The benefit was mostly driven by a reduction in bleeding.

(II) The lower UFH dose also provided non-inferior net clinical outcome compared with the bivalirudin group.

Available now online at *European Heart Journal*

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**Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization (LESSON-I study presented by S. Windecker)**

Comments by Petr Widimsky
Cardiocenter Vinohrady,
Charles University Prague, CZ

**DES (sirolimus or paclitaxel) vs. BMS: No mortality difference.**


**Summary of results: Besides the stent thrombosis difference, both stents had rather similar outcomes.**

*Stent design differences: Strut thickness (DES: 31 μm versus SES: 140 μm). Polymer coating (DES: 7.5 μm versus SES: 17.4 μm).*

**Sirolimus vs. Paclitaxel vs. BMS: More AMIs after paclitaxel stents.**


**DES „Premier League“**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Sirolimus</th>
<th>Zotarolimus</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>XXXXX</td>
<td>1:0</td>
<td>1:1</td>
<td>1:0</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0:1</td>
<td>XXXXX</td>
<td>1:1</td>
<td>1:0</td>
</tr>
<tr>
<td>Zotarolimus</td>
<td>1:1</td>
<td>1:1</td>
<td>XXXXX</td>
<td>1:1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0:1</td>
<td>0:1</td>
<td>1:1</td>
<td>XXXXX</td>
</tr>
</tbody>
</table>

Windecker’s study limitations

- Single center study
- Not randomized
- And mainly ..........

Major study limitation: historical controls.

- Most sirolimus patients were treated in 2004-5 vs. most everolimus in 2007-9.
- The knowledge (about the risk of stent thrombosis) and skills (how to prevent it by implantation technique) improved during this period.
- With historical controls, the authors should rigorously look whether the procedural techniques were comparable (inflation pressures, final real – not nominal – stent diameter, non-compliant / oversized balloons postdilatations, etc.)
- This information is missing

Remaining questions

- How important is the strut thickness?
- Are the results caused by drug difference or stent design / struts difference?
- Would there be any difference between everolimus and sirolimus if both drugs would be used with the same stent design?

Summary

- Despite the limitations, this academic study confirmed effectiveness and safety of „limus eluting“ stents.
- New generation DES showed better outcomes when compared with older generation DES.
LESSON I - Patient Background

- The newer generation everolimus-eluting stent (EES) is a thin strut, cobalt chromium stent and releases everolimus, a semisynthetic sirolimus analogue from a polyfluoropropylene mixture.
- Compared with paclitaxel-eluting stents, everolimus-eluting stents have been shown to significantly reduce:
  - the need for target lesion revascularization
  - the composite of cardiac death or MI
  - the rate of definite or probable stent thrombosis
- However, the therapeutic benefit of everolimus-eluting stents compared to otherimus-analogous - namely sirolimus-eluting stents - in terms of safety and efficacy remains to be established.

LESSON I - Patient Population

**Inclusion Criteria**
- All consecutive patients undergoing implantation of everolimus-eluting and sirolimus-eluting stents in patients with stable angina, silent ischemia, and acute coronary syndromes (UA, NSTEMI and STEMI).
- Diameter stenosis ≥ 80%.
- Number of lesions: no limitation.
- Number of vessels: no limitation.
- Lesion length: no limitation.
- Written informed consent.

**Exclusion Criteria**
- Patients with sirolimus-eluting stents implanted prior to April 2013 due to clopidogrel prescription of 3 instead of 12 months.
- Patients with sirolimus-eluting stents included into the SIRIUS trial in view of mandatory angiographic follow-up.

LESSON I - Sample Size Calculation

**Primary Endpoint**
- Composite of death, MI and TVR through 3 years.
- Relative risk assumption of 0.75 in favour of EES compared with GES based on:
  - Meta-analysis comparing EES vs. PES (RR=0.80).
  - Network meta-analysis comparing EES vs. PES (RR=0.80).
- Expected event rate = 18% @ median 9/4 1.5 years.
- 1430 matched patients → 90% power.

**Secondary Endpoints**
- Death, MI, TLR, TVR.
- Cardiac death or MI.
- Stent thrombosis according to ARC.

LESSON I - Antithrombotic Drug Regimen

**Pre or during procedure**
- Acetylsalicylic acid ≥ 100 mg.
- Clopidogrel 300-600 mg loading dose.
- Unfractionated heparin.
- Bypass of at least 6000 IU IV or 71 IA/kg.
- Glycoprotein IIb/IIIa antagonists.
- Operator discretion.

**Post procedure**
- Acetylsalicylic acid: 100 mg indefinitely.
- Clopidogrel 75 mg/d for 12 months.

<table>
<thead>
<tr>
<th>Eversolimus Stent</th>
<th>Sirolimus Stent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65±12 (EELS)</td>
<td>62±11 (SES)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>79 (EELS)</td>
<td>78 (SES)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27±5 (EELS)</td>
<td>27±4 (SES)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>18 (EELS)</td>
<td>18 (SES)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>80 (EELS)</td>
<td>54 (SES)</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>54 (EELS)</td>
<td>30 (SES)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>28 (EELS)</td>
<td>28 (SES)</td>
</tr>
<tr>
<td>Family History of CAD, %</td>
<td>29 (EELS)</td>
<td>27 (SES)</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>15 (EELS)</td>
<td>21 (SES)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>33 (EELS)</td>
<td>30 (SES)</td>
</tr>
</tbody>
</table>
LESSON I – Patient Characteristics
After Propensity Score Matching (N=2684)

<table>
<thead>
<tr>
<th>Everolimus Stent</th>
<th>Sirolimus Stent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1342 Patients</td>
<td>1342 Patients</td>
<td>0.62</td>
</tr>
<tr>
<td>Age</td>
<td>84 ± 12</td>
<td>84 ± 12</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>78 ± 4</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27 ± 1</td>
<td>27 ± 1</td>
</tr>
<tr>
<td>Diabetes mellitus,%</td>
<td>17 ± 3</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51 ± 2</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>30 ± 3</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>29 ± 3</td>
<td>27 ± 3</td>
</tr>
<tr>
<td>Family History of CVD, %</td>
<td>19 ± 2</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Stable angina</td>
<td>48 ± 5</td>
<td>45 ± 5</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>STEMI</td>
<td>30 ± 10</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>19 ± 10</td>
<td>20 ± 10</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2 ± 1</td>
<td>1 ± 1</td>
</tr>
</tbody>
</table>

LESSON I – Procedural Characteristics
After Propensity Score Matching (N=2684)

<table>
<thead>
<tr>
<th>Everolimus Stent</th>
<th>Sirolimus Stent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1342 Patients</td>
<td>1342 Patients</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multivessel treatment, %</td>
<td>24 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Number of vessels per patient</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Number of lesions per patient</td>
<td>1.8 ± 1.8</td>
<td>1.5 ± 1.7</td>
</tr>
<tr>
<td>1 lesion, %</td>
<td>52 ± 60</td>
<td>60 ± 60</td>
</tr>
<tr>
<td>2 lesions, %</td>
<td>29 ± 24</td>
<td>27 ± 24</td>
</tr>
<tr>
<td>3 lesions, %</td>
<td>13 ± 12</td>
<td>5 ± 5</td>
</tr>
<tr>
<td>4 lesions, %</td>
<td>6 ± 2</td>
<td>2 ± 2</td>
</tr>
<tr>
<td>Number of stents per patient</td>
<td>2.0 ± 1.1</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>2.9 ± 0.4</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>Stent length per patient (mm)</td>
<td>31.4 ± 16.4</td>
<td>32.7 ± 19.0</td>
</tr>
</tbody>
</table>

Lesson I – Primary Endpoint
Death, MI, or TVR @ 3 Years

Hazard Ratio = 0.83, 95% CI 0.64 – 1.00, P=0.056

Lesson I – Target Vessel Revascularization
After Propensity Score Matching (N=2684)

<table>
<thead>
<tr>
<th>Everolimus Stent</th>
<th>Sirolimus Stent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1342 Patients</td>
<td>1342 Patients</td>
<td>0.05</td>
</tr>
<tr>
<td>Acetylsalicylic Acid, %</td>
<td>98 ± 10</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>98 ± 50</td>
<td>96 ± 50</td>
</tr>
<tr>
<td>Oral Anticoagulation, %</td>
<td>1.4 ± 2.0</td>
<td>2.0 ± 2.0</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>64 ± 61</td>
<td>61 ± 61</td>
</tr>
<tr>
<td>ACE Inhibitor, %</td>
<td>53 ± 54</td>
<td>54 ± 54</td>
</tr>
<tr>
<td>AT II Inhibitor, %</td>
<td>14 ± 18</td>
<td>16 ± 16</td>
</tr>
<tr>
<td>Calcium Antagonist, %</td>
<td>8.8 ± 0.9</td>
<td>9.0 ± 0.9</td>
</tr>
<tr>
<td>Statin, %</td>
<td>83 ± 86</td>
<td>86 ± 86</td>
</tr>
<tr>
<td>Oral Antidiabetics, %</td>
<td>10 ± 10</td>
<td>10 ± 10</td>
</tr>
<tr>
<td>Insulin, %</td>
<td>6 ± 6</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>18 ± 19</td>
<td>19 ± 19</td>
</tr>
<tr>
<td>Proton Pump Inhibitor, %</td>
<td>20 ± 18</td>
<td>18 ± 18</td>
</tr>
</tbody>
</table>

Lesson I – All Cause Mortality @ 3 Years

Hazard Ratio = 0.92, 95% CI 0.88 – 1.25, P=0.59

Lesson I – Myocardial Infarction @ 3 Years

Hazard Ratio = 0.62, 95% CI 0.42 – 0.93, P=0.017
**LESSON 1 – Clinical Outcome @ 3 Years**

<table>
<thead>
<tr>
<th>Event</th>
<th>Everolimus Stent 1342 Patients</th>
<th>Sirolimus Stent 1342 Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.7%</td>
<td>4.5%</td>
<td>0.59</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>3.3%</td>
<td>4.4%</td>
<td>0.51</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.3%</td>
<td>5.0%</td>
<td>0.047</td>
</tr>
<tr>
<td>NOQMI</td>
<td>2.9%</td>
<td>3.1%</td>
<td>0.41</td>
</tr>
<tr>
<td>QWMI</td>
<td>0.5%</td>
<td>1.6%</td>
<td>0.10</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>6.8%</td>
<td>8.9%</td>
<td>0.330</td>
</tr>
<tr>
<td>Death or MI</td>
<td>9.3%</td>
<td>10.8%</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac death, MI or TVR</td>
<td>12.7%</td>
<td>16.2%</td>
<td>0.025</td>
</tr>
<tr>
<td>Death, MI, or TVR</td>
<td>14.9%</td>
<td>18.0%</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**LESSON 1 – Stent Thrombosis Through 3 Years**

<table>
<thead>
<tr>
<th>Event</th>
<th>Everolimus Stent 1342 Patients</th>
<th>Sirolimus Stent 1342 Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite Stent Thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0.3%</td>
<td>0.5%</td>
<td>0.72</td>
</tr>
<tr>
<td>Late</td>
<td>0.2%</td>
<td>0.4%</td>
<td>0.42</td>
</tr>
<tr>
<td>Very late</td>
<td>0%</td>
<td>0.7%</td>
<td>0.0027</td>
</tr>
<tr>
<td>Overall</td>
<td>0.5%</td>
<td>1.0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Definite or Probable Stent Thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>2.3%</td>
<td>3.1%</td>
<td>0.290</td>
</tr>
<tr>
<td>Late</td>
<td>0.2%</td>
<td>0.4%</td>
<td>0.42</td>
</tr>
<tr>
<td>Very late</td>
<td>0%</td>
<td>0.7%</td>
<td>0.0072</td>
</tr>
<tr>
<td>Overall</td>
<td>2.5%</td>
<td>4.0%</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**Lesson 1 – Definite Stent Thrombosis @ 3 Years**

**Limitations**

- Non-randomized observational study
  - Propensity score matching to minimize bias
- Patients treated with everolimus-eluting stents were more complex as compared to patients treated with sirolimus-eluting stents
  - Sensitivity analysis adjusted for potential confounders
  - showed mixed results
- Death, MI, or TVR: HR=0.78, 95% CI 0.63-0.97, P=0.029
- Sequential enrolment period for patients treated with sirolimus-eluting and everolimus-eluting stents
  - Treatment protocols and medication regimen at a single institution did not change significantly
  - Minimizes the potential of confounding by indication

**Conclusions**

- In this observational, propensity-score matched study, the use of everolimus-eluting stents was associated with a lower risk of myocardial infarction, target vessel revascularization, and stent thrombosis compared with sirolimus-eluting stents during long-term follow-up to three years
- Differences in rates of myocardial infarction were driven by a 70% lower risk of QWMI and were observed early and continued to increase during long-term follow-up
- The lower risk of myocardial infarction in favor of everolimus-eluting stents was explained at least in part by the lower risk of definite stent thrombosis
- These results require confirmation in large scale randomized clinical trials

**AVERROES**

**Editorial comment**

- Apixaban is a reversible inhibitor of factor Xa with a high oral bioavailability, rapid onset, and a half-life of ~12 hours → 2 daily doses
- No monitoring required
- Obs! Drugs metabolised by CYP 3A4
- AVERROES is a randomised, double-blind, event driven study with 5680 patients, estimated to give a 35% reduction in stroke or systemic embolism of apixaban vs ASA with at least 90% power and a 1-sided α = 0.025, assuming a stroke rate of 3.3/100 subject-years in ASA-treated patients.
**AVERROES** Editorial comment (cont)

- Study terminated after first protocolled interim analysis of efficacy, recommended by the DMC (4 SD).
- Baseline characteristics:
  - Age 70 years; Male = 60%; Diabetes = 20%; Prior stroke/TIA = 14%; CHF = 40%; Baseline ASA users = 75%; VKA "unsuitable" = 48%.
  - CHADS2 score 2.1 (mean), 0-1 = 35%, 2-3 = 35%, 3+ = 30%.

**AVERROES** Editorial comment (cont)

**Conclusion**

- **AVERROES** is a "landmark study", with impressive design, conduction and results!
- The results from **AVERROES** will obviously have impact on guidelines in AF, and the use of ASA will probably be drastically reduced.
- The "patients unsuitable for VKA therapy" should be clearly defined
- With 2 daily oral doses of apixaban compliance will be a challenge, and surveillance studies should be planned.

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**DANPACE: The Danish multicenter randomised trial on AAIR versus DDDR pacing in sick sinus syndrome**

Jens Coeeds Nielles,
Aarhus University Hospital
on behalf of the DANPACE investigators

---

**Background**

- In patients with sick sinus syndrome (SSS) bradycardia can be treated with any pacemaker: AAIR, VVI, or DDDR.
- VVIR pacing increases atrial fibrillation as compared with physiological pacing (DDDR or AAIR), and VVIR pacing was associated with increased mortality as compared with AAIR pacing in one small trial.¹
- Ventricular pacing has been found to cause ventricular desynchronisation with lowering of LVEF and left atrial dilatation, resulting in heart failure and atrial fibrillation.

¹: Andersen HR et al., Lancet 1997

---

**DANPACE investigators**

**Standing Committee (numbers of patients included):**
- Benny EK Andersen (Chairman) and Jens Coeeds Nielles (co-chairman), Aarhus University Hospital, Skjellerup (137);
- You-Erik Brin-Thumshir, Gentofte Hospital (58);
- Per Fælstrøm, Hvidovre Hospital (16);
- Magne Mikkelsen, Copenhagen University Hospital (114);
- Thomas Nøstvedt, Aalborg Hospital (16);
- Morten Østerlund, Herning Hospital (76);
- Stine Pedersen, Falster Hospital (77);
- Magne Aslund, Kolding Hospital (71);
- Jørgen Viby Eriksen, Aalborg Hospital (70);
- Per Tvede Christiansen, Vejle Hospital (60);
- Lifschütz-Stensgaard, Hjørring Hospital (68);
- Jørgen Odder-Andersen, Østfold Hospital (50);
- Søren Hage, Rønne Hospitals (56);
- Jan Aarøye Bendtsen, Slagelse Hospital (16).

**From United Kingdom:**
- William G. Battrick (coordinating investigator), Sarah Brack, Guy's Hospital, London (8);
- Craig Berry, Aarhus Treningscenter, Aarhus Hospital, Aarhus (8);
- John Cole, Andrew Clark, Sarah Hurren, Castle Hill Hospital, Leeds (4).

**From Sweden:**
- Anna Nordqvist, Pernilla Andén, Mårten Norden, Confined Hospital, Linköping (12).
- Karin Boden, Göran Östensson, Göteborg University Hospital (11).

**From Canada:**
- Jeffrey J. Steady, Hamilton (8).

---

**Aim**

- To compare AAIR and DDDR pacing in SSS.
- Primary endpoint: Death from any cause.
- Secondary endpoints:
  - Paroxysmal atrial fibrillation (as planned follow-up)
  - Chronic atrial fibrillation
  - Stroke
  - Heart failure
  - Pacemaker reoperation
**Statistics**

- 1,300 patients.
- Followed for a mean 5.5 years.
- Identify a 6% difference in mortality.
- Power 80%, overall p = 0.05.
- Intention to treat.
- Two planned interim analyses after 1/3 and 2/3 of the expected number of deaths.

**Methods**

- Randomised controlled trial.
- **Inclusion criteria:**
  - Symptomatic bradycardia and documented sinus pauses ≥2 s or sinus bradycardia <40 bpm ≥1 minute whilst awake,
  - PR interval ≥0.22 s (age 18–70 years) or PR interval ≥0.26 s (age ≥70 years),
  - QRS width ≤0.12 s.
- **Exclusion criteria:**
  - AV Block,
  - Bundle branch block,
  - Persistent atrial fibrillation >12 months,
  - Atrial fibrillation with QRS rate >40 bpm for ≥1 min or pauses >3 s,
  - A positive test for catecholamine hypersensitivity.

**Pacemaker programming**

- Rate adaptive function was active
- Lower rate 60 bpm
- Upper rate 133 bpm
- DDDR:
  - Paced AV-interval = 23 ms
  - Sensed AV-interval = 300 ms.
  - Rate-adaptive shortening of the AV-interval.

**Randomisation and pacing mode**

- **First PM:**
  - AAR 660
  - DDOR 46
  - VVR 1
- **PM at last FU:**
  - AAR 585
  - DDOR 155
  - VVR 17

**Results**

- Follow-up 3.4±2.6 years
- No patients lost for follow-up
- **Pacing in the atrium:**
  - AAR group: 58±29%
  - DDOR group: 59±31%
  - P = 0.52
- **Pacing in the ventricle:**
  - DDOR group: 65±33%

**Survival**

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>No. at Risk</th>
<th>Single Lead Atrial Pacing</th>
<th>Dual Chamber Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1018</td>
<td>548</td>
<td>468</td>
</tr>
<tr>
<td>1</td>
<td>868</td>
<td>301</td>
<td>567</td>
</tr>
<tr>
<td>2</td>
<td>664</td>
<td>251</td>
<td>433</td>
</tr>
<tr>
<td>3</td>
<td>451</td>
<td>182</td>
<td>269</td>
</tr>
<tr>
<td>4</td>
<td>304</td>
<td>154</td>
<td>149</td>
</tr>
<tr>
<td>5</td>
<td>186</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>133</td>
<td>56</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>92</td>
<td>41</td>
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<td>8</td>
<td>63</td>
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<td>9</td>
<td>42</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

The p-value for survival is 0.53.

**Atrial fibrillation**

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>No. at Risk</th>
<th>Single Lead Atrial Pacing</th>
<th>Dual Chamber Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1018</td>
<td>548</td>
<td>468</td>
</tr>
<tr>
<td>1</td>
<td>868</td>
<td>301</td>
<td>567</td>
</tr>
<tr>
<td>2</td>
<td>664</td>
<td>251</td>
<td>433</td>
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<tr>
<td>3</td>
<td>451</td>
<td>182</td>
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<td>4</td>
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<td>5</td>
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<td>92</td>
<td>41</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

The p-value for atrial fibrillation is 0.024.
Heart failure

- NYHA class at last FU: $p=0.43$.
- Diuretics at last follow-up: $p=0.89$.
- Hospitalization for heart failure: $p=0.90$.

Conclusions

- No difference in survival between AAI and DDDR pacing in SSS.
- Risk of reoperation is doubled with AAI pacing.
- Paroxysmal atrial fibrillation is more common in AAI pacing.
- DDDR pacing with an AV interval of 220 ms is the preferred pacing mode for SSS.
- AAI pacing should no longer be used.

Clinical Outcomes – Multivariate analysis

<table>
<thead>
<tr>
<th></th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.94</td>
<td>0.71-1.24</td>
<td>0.52</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>1.21</td>
<td>1.01-1.42</td>
<td>0.049</td>
</tr>
<tr>
<td>Chronic AF</td>
<td>1.01</td>
<td>0.74-1.39</td>
<td>0.93</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.05</td>
<td>0.70-1.59</td>
<td>0.86</td>
</tr>
<tr>
<td>Reoperation</td>
<td>2.09</td>
<td>1.54-2.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Financial support

- Medtronic.
- St Jude Medical.
- Boston Scientific.
- EL Medical.
- PFEAR.
- The Danish Heart Foundation (10-04-878-A2954-22779).

Disclosures for Harald Darius

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- Employees: No relevant conflicts of interest to declare.
- Consultant: No relevant conflicts of interest to declare.
- Mass Stockholder: No relevant conflicts of interest to declare.
- Scientific Advisory Board: Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi-Aventis, The Medicines Company.
Primary efficacy outcome analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recurrence VTE (n=1,731)</th>
<th>Recurrence VTE + PE (n=1,718)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>36 (2.1%)</td>
<td>40 (2.3%)</td>
</tr>
<tr>
<td>Enoxaparin/VKA</td>
<td>51 (2.9%)</td>
<td>54 (3.1%)</td>
</tr>
</tbody>
</table>

Primary efficacy outcome: time to first event

Quality of SAG-WM 57.7% in target range?
Yes! 31st percentile associated with poor INR control.

Primary efficacy outcome: time to first event

EINSTEIN DVT: study design
Randomized, open-label, event-driven, non-intervention study
- 48 hours’ treatment with heparin/low-molecular-weight heparin permitted before study entry.
- 36 primary efficacy outcomes: treatment effect at 1 month.
- Treatment period: 5.8 months.

Primary efficacy outcome: time to first event

Primary efficacy outcome: time to first event

Conclusions
- Rivaroxaban was non-inferior to warfarin with a trend towards lower bleeding rates (all bleeding significant in the dose regimen chosen).
- Rivaroxaban is of borderline superior efficacy (not significant) without advantages in bleeding in the dose regimen chosen.
- Enoxaparin is a carefully designed and performed trial.
- Some data are still missing or need to be interpreted (waiting for publication) e.g. less efficacy past 6 mo.
- Rivaroxaban is of borderline superior efficacy (not significant) without advantages in bleeding in the dose regimen chosen.
- We are facing a new era of antithrombotic therapy for patients with DVT with some questions still to be answered e.g.
- Rivaroxaban/Enoxaparin superior to warfarin in the event of recurrent VTE
- Rivaroxaban non-inferior to warfarin in the event of recurrent VTE
- Rivaroxaban inferior to warfarin in the event of recurrent VTE
ESC Hotline Discussant: RESPONSE Trial
Christi Deason, PhD, RN, FESC
University of Manchester
Central Manchester Foundation Trust
Manchester, UK

RESPONSE Trial
- Multi-centre RCT
- Subjects primarily male and younger
- Modest intervention
  - Additional training: few days
  - 4 visits nurse-coordinated programme over 6 months
  - 93% attendance by patients
  - 93% follow-up at 1 year

Implications
- This type of intervention could be widely implemented
- Nurses well-suited to coordinate or lead secondary prevention programmes
- Most effective 'close' of intervention for sustained effect: not known
  - Components, intensity, duration
  - Titration based on individual characteristics (e.g., older with multiple co-morbidity conditions)

Context
- Nurse-led or nurse-coordinated secondary prevention programmes have been shown to be effective and feasible
  - EUROACTION (Wood, et al. 2007)
  - SCRP Trial (Hedell, et al. 1994)
  - Kaiser Permanente (Dehark, et al. 1994)
  - Nurse-led clinics in primary care (Monie, et al. 2003)

RESPONSE Findings
- Use of SCORE: controversial and intriguing
  - Intended for patients without CHD
  - Means of quantifying relative change in risk
  - 17% relative risk reduction (predicted 10-year mortality) at one year for intervention patients
- Individual and composite risk factor control favored intervention
  - Neither group improved BMI & waist circumference
  - Both decreased smoking rates (by self-report)

Background
- Secondary prevention may effectively prevent recurrent cardiovascular events.
- Guidelines have been issued by ESC, AHA/ACC
- A gap exists between these guidelines and clinical practice
- New, practical initiatives are needed to reduce this gap
Study design

Study goal:
- To quantify the impact of a nurse coordinated prevention program on risk factor levels in patients with a recent coronary event.

Population:
- Patients 18-80 years
- ACS within 8 weeks before inclusion

Main outcome:
- SCORE 10 year risk of mortality at 12 months after index event

Participating centers

- Breda: Armpa Zeerenaus
- Eindhoven: Medisch Spectrum Twente
- Does: Oostelijke Heelvdiensten
- Deventer: Devester Ziekenhuis
- Enschede: Catharina Ziekenhuis
- Heerlen: Arcus Medisch Centrum
- Nijmegen: St. Anthony Ziekenhuis
- Leeuwarden: Medisch Centrum Leeuwarden
- Hilversum: Tergooi Ziekenhuis
- Delft: Reine De Graaf Gasthuis

sponsored by an unrestricted grant from Abbott, the Netherlands.

Baseline characteristics

- Randomised treatment
  - Intervention (N=397)
  - Control (N=394)
- Age, years
  - Intervention: 57.5
  - Control: 57.2
  - P-value: 0.20
- Female
  - Intervention: 20%
  - Control: 21%
  - P-value: 0.001
- Diagnosis category at index event
  - ST-segment elevation myocardial infarction
    - Intervention: 50%
    - Control: 48%
    - P-value: 0.17
  - Non-ST-segment elevation myocardial infarction
    - Intervention: 33%
    - Control: 33%
    - P-value: 0.03
- Unstable Angina Pectoris
  - Intervention: 17%
  - Control: 19%
  - P-value: 0.06
- Previous vascular disease (prior to index event)
  - Intervention: 26%
  - Control: 27%
  - P-value: 0.05
- History of cardiovascular risk factors
  - Intervention: 59%
  - Control: 60%
  - P-value: 0.14
- Positive family history
  - Intervention: 14%
  - Control: 14%
  - P-value: 0.001
- History of diabetes mellitus
  - Intervention: 65%
  - Control: 71%
  - P-value: 0.001
- Hypertension
  - Intervention: 47%
  - Control: 43%
  - P-value: 0.001
- Ex-smoker
  - Intervention: 36%
  - Control: 39%
  - P-value: 0.001
- History of hypertension
  - Intervention: 36%
  - Control: 38%
  - P-value: 0.001

On target analysis

- Baseline intervention (N=397)
  - Systolic blood pressure
    - Intervention: 140 mmHg
    - Control: 141 mmHg
  - Diastolic blood pressure
    - Intervention: 89 mmHg
    - Control: 90 mmHg

- 12 months intervention (N=397)
  - Systolic blood pressure
    - Intervention: 130 mmHg
    - Control: 133 mmHg
  - Diastolic blood pressure
    - Intervention: 85 mmHg
    - Control: 87 mmHg

- Adjusted p-value: 0.001
**Medication use**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Intervention</th>
<th>Control</th>
<th>p value</th>
<th>Baseline</th>
<th>Intervention</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antithrombotic agents</td>
<td>18%</td>
<td>20%</td>
<td>0.002</td>
<td>88%</td>
<td>92%</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>64%</td>
<td>68%</td>
<td>0.015</td>
<td>6%</td>
<td>8%</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>27%</td>
<td>23%</td>
<td>0.009</td>
<td>13%</td>
<td>10%</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Centrally converting enzyme inhibitors</td>
<td>14%</td>
<td>14%</td>
<td>0.859</td>
<td>21%</td>
<td>24%</td>
<td>0.565</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>15%</td>
<td>15%</td>
<td>0.854</td>
<td>8%</td>
<td>7%</td>
<td>0.475</td>
<td></td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>0%</td>
<td>0%</td>
<td>1.000</td>
<td>0%</td>
<td>0%</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>

**Risk factor control**

- Poor: 0-2 factors on target
- Medium: 3-4 factors on target
- Good: 5-9 factors on target

**Conclusions**

- A nurse coordinated hospital based prevention program with up to 4 outpatient clinic visits in addition to usual care results in sustained lowering of cardiovascular risk in patients with coronary disease.
- The program was well attended, practical and can be readily implemented into daily practice.

**ESC Congress 2010**

Stockholm, Sweden 28 August - 1 September
Session: Science Hot Line
August 30, 2010 – 11:00-12:30
Stockholmsmässan
Room: Anka - Zone C

R. Medina, E. Montanaro, Y. Geng, R. de Caterina

"G. d'Arenzo" University – Chieti,
Texas Heart Institute and
University of Texas Medical School in Houston

**Hypothesis and Goal**

- Whether the hyperosmotic stress attainable by hyperglycemia in overt diabetes plays a role in plaque destabilization and microvascular dysfunction, remains unexplored.
- To test here the hypothesis that hyperosmotic stress plays a causal role in promoting inflammatory angiogenesis through the induction of putative "hyperosmotic stress proteins" such as COX-2 and the regulation of expression and activities of MMPs in micro- and macro-vascular endothelial cells exposed to high glucose.

**Hyperosmolarity induces COX-2 expression in endothelial cells exposed to high glucose**

1 day Incubations

- COX-2
- β-actin

2 days Incubations

- COX-2
- β-actin
Therefore

- Concentrations of glucose attainable in conditions of hyperglycemia induce COX-2 in human endothelial cells through an AQPI- and an NHE1-dependent hyperosmolar mechanism and, through this mechanism, promote angiogenesis.
- TonEBP/NFAT5 is involved in the hypertonic induction of COX-2 and MMP-9 and angiogenesis, since TonEBP/NFAT gene disruption was able to prevent the hypertonic induction of these genes and angiogenesis.
- Hypertonicity determines the nuclear accumulation of TonEBP/NFAT in endothelial cells, suggesting its role in the response to hypertonic stress.

Conclusions (i)

These observations indicate COX-2 and MMP-9 as putative "hypertonic stress proteins", placing COX-2 and MMP-9 genes among the genetic markers that might sensitize subgroups of diabetic patients to the effects of hyperglycemia, which, if expressed in vivo, might constitute a significant risk factor for diabetic complications such as proliferative retinopathy and plaque destabilization.

Conclusions (ii)

Correction of hyperosmolarity by downstream targeting osmosignaling pathway (TonEBP/NFAT5) might be a novel strategy, in addition to upstream targeting osmosensing structures (AQPI and NHE1) for the control of excessive angiogenesis as a consequence of diabetic hyperglycemia.
Testing hypothesis 1: Remote ischaemic preconditioning requires recruitment of sensory nerves sending information from the remote organ to the central nervous system.

Hypothetical "Remote Preconditioning Reflex"

Testing hypothesis 2: Remote ischaemic preconditioning requires vagal parasympathetic innervation of the heart.

CONCLUSIONS
1. Sensory denervation of the remote ischaemic tissue or removal of parasympathetic input to the heart both completely abolish cardioprotection induced by remote ischaemic preconditioning.
2. These data directly demonstrate the existence of a "remote preconditioning reflex", which involves sensory afferent pathway from the peripheral organ and parasympathetic vagal efferent outflow to the heart.
Proteomic analysis of smooth muscle cells derived from carotid plaque reveals differences between symptomatic and asymptomatic plaques.

Louise Full
Kennedy Institute of Rheumatology
Imperial College London, UK

Conflicts of Interest: None

1. Proteomic investigation into differences between plaque and medial SMC.
2. Comparison of atherosclerotic SMC from symptomatic and asymptomatic patients.

Mitochondrial proteins are decreased in Plaque SMC

ATP Synthase subunits
Adenylate Deaminase

Low mitochondrial protein expression in Plaque SMC compared to Aorta SMC.
2. Comparison of SMC from Symptomatic & Asymptomatic plaques

**SUMMARY & CONCLUSIONS**

1. Comparison of plaque & aortic SMC proteome

**ER DYSREGULATION**
- Increased expression of periloxin-6 in plaque SMC

**MITOCHONDRIAL DAMAGE**
- Decrease in mitochondrial proteins ATP synthesis subunits D2 involved in ATP synthesis
- Decrease in co-oxidation Dehydrogenase 2
- Proinflammatory mediators in the plaque contribute to this reduced protein expression

**ACKNOWLEDGEMENTS**

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Dr Robin Watt
Professor Avi He Daries
Tina Ray
Scott Strang
Amanda Cross
Najmeh Arotia
Joseph Shahnew

**Galectin-2 expression is dependent on the rs7291467 single nucleotide polymorphism and acts as an inhibitor of arteriogenesis**

AM van der Laan, SH Schmier, MR de Vries, JJ Konig, OL Volger, JO Fleiderer, AJNN Bastiaansen, JM Baggen, KT Koch, J Baan Jr, JP Herijgers, RJ van der Schaeff, MR Vis, RE Meul, TC van der Peuwe Klaas, PH Guisk, JJ Piek, AD Huerenpel and N van Royen

ESC
August 30th 2010

No conflict of interest or financial disclosures
Heterogenic response in patients

Coronary artery disease (n = 728)

Patient inclusion and exclusion criteria

Inclusion criteria:
- Chronic total coronary occlusion

Exclusion criteria:
- Previous myocardial infarction
- Cardiac surgery
- Depressed left ventricular function
- Diabetes mellitus
- Inflammatory or neoplastic disease.

Monocyte isolation procedure

Whole blood

CD14+ beads

Fluor gradient

MNC fraction

Monocyte negative isolation

Resident monocytes

Stimulated monocytes

Macrophage

Collateral flow index

Median: 0.07

Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CFI &lt; 0.37 (n = 40)</th>
<th>CFI &gt; 0.37 (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collateral flow index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 13.4</td>
<td>58 ± 8.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.7 (23.1 – 26.3)</td>
<td>24.7 (23.1 – 26.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>7</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of anginal symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3 months</td>
<td>7</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Whole genome transcriptome analysis (10 vs 10)

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<thead>
<tr>
<th></th>
<th>Unstimulated monocytes</th>
<th>Stimulated monocytes</th>
<th>Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intensity</td>
<td>t-value</td>
<td>Intensity</td>
</tr>
<tr>
<td>LIG4L2</td>
<td>0.002</td>
<td>2.1</td>
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</tr>
<tr>
<td>C1QA</td>
<td>0.025</td>
<td>1.4</td>
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</tr>
<tr>
<td>PHAC3</td>
<td>0.012</td>
<td>1.7</td>
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</tr>
<tr>
<td>RNF213</td>
<td>0.012</td>
<td>2.1</td>
<td>0.006</td>
</tr>
<tr>
<td>LRAP</td>
<td>0.007</td>
<td>1.7</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Galectin-2 mRNA expression

Galectin-2 mRNA expression is increased in patients with a low capacity of the collateral circulation ($n = 50$)

The association between the rs7291467 SNP and the collateral circulation

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Low CFI ($n = 25$)</th>
<th>High CFI ($n = 25$)</th>
<th>Total ($n = 50$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>9</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>CT</td>
<td>11</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>TT</td>
<td>5</td>
<td>6</td>
<td>14</td>
</tr>
</tbody>
</table>

Chi-square test for trend $P < 0.05$

Mechanisms of action?

- Monocyte function
- VSMC proliferation
- EC proliferation
- T-cell homeostasis

Galectin-2 is overexpressed in patients with a poor developed collateral circulation

In vivo, the exogenous application of galectin-2 inhibits arteriogenesis

Collectively, the data derived from this study point towards an important role of galectin-2 in collateral artery growth

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  - N. van Royen, MD, PhD
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  - O.L. Vos, PhD
  - J. Baggen

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  - M. de Vries
  - A.J.N.M. Baas, MD
Telomerase and Myocardin-A synergistically regulate expression of promyogenic transcription factors in mesenchymal stem cells of adult adipose tissue

Rosalinda Madonna, Raffaele De Caterina, James T Willerson, Yong-Jian Geng

University of Texas Health Science Center at Houston/Texas Heart Institute, Houston, TX, USA; University of Chieti, Italy

Telomeres comprise long tracts of double-stranded TTAGGG repeats that extend for 9 to 15 kb and their length is maintained by telomerase, a specialized ribonucleoprotein that prevents the natural ends of linear chromosomes from undergoing inappropriate repair.

Hypothesis and Goal

- We hypothesized that an interaction or synergy between Myoc-A and the catalytic subunit of telomerase, telomerase reverse transcriptase (TERT) may occur during the development of myogenic stem cells.
- The current study was designed to test expression of myogenic factors in mesenchymal stem cells (MSCs) with overexpression and interruption of McA and/or TERT functions.

TERT positive cells take little Dil-acLDL and express high levels of Myoc-A

Myocardin (MyoC): A co-transcription factor that controls expression of a cluster of genes critical for cardiovascular myogenesis

Multipotent Adult Stem Cells from Adipose Tissue Are Capable of Giving Rise to Mature Cardiovascular Cells


Experimental Strategy and Methods

- MSCs isolated and grown from murine abdominal adipose tissue by enzymatic digestion.
- TERT and Myoc-A cDNA cloned by PCR used to transduce over-expression of TERT and Myoc-A.
- Co-immunoprecipitation with anti-TERT and anti-Myoc-A in murine MSCs isolated from adult adipose tissues.
- Assessment of proliferation and differentiation in MSCs with expressed TERT and McA.
- MSCs treated with siRNA for TERT or Myoc-A for expression of the promyogenic transcription factors Oct-4, Nkx2.5 and MLC2v as determined by qRT-PCR.
**Conclusions**

- Co-expression of TERT and Myoc-A promotes myogenic development of MSCs from adult adipose tissue.
- TERT and Myoc-A promote expression of promyogenic nuclear factors by activating the SRF-containing promoters.
- TERT or Myoc-A siRNA treatment blocks partially activation of SRF via down-regulation of TERT and Myoc-A expression.
- TERT and Myoc-A may have a synergy in regulation of cardiovascular myogenic development, potentially important for cardiac regenerative medicine.