Atrial Fibrillation Ablation Pilot Registry

### Reasons why Ablation Procedure was not performed

- Complications not related to procedure: 3 pts
- Complications related to procedure: 16 pts

#### Baseline characteristics – 1/2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=1,459 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>60 (52–68)</td>
</tr>
<tr>
<td>Females, %</td>
<td>31.0</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²), &gt; 30 kg/m², %</td>
<td>25.8</td>
</tr>
<tr>
<td>SBP (mmHg), median (IQR)</td>
<td>130 (120–140)</td>
</tr>
<tr>
<td>Creatinine (mg/dL), median (IQR)</td>
<td>0.9 (0.8–1.1)</td>
</tr>
</tbody>
</table>

#### Risk factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>All (n=1,351 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, %</td>
<td>8.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>50.0</td>
</tr>
<tr>
<td>Active smokers, %</td>
<td>11.4</td>
</tr>
<tr>
<td>Hypocholesterolemia, %</td>
<td>31.6</td>
</tr>
</tbody>
</table>

#### Baseline characteristics – 2/2

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>All (n=1,381 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc score</td>
<td>All (n=1,381 pts)</td>
</tr>
<tr>
<td>0</td>
<td>587 (42.2%)</td>
</tr>
<tr>
<td>1</td>
<td>98 (7.0%)</td>
</tr>
<tr>
<td>2</td>
<td>501 (36.0%)</td>
</tr>
<tr>
<td>3</td>
<td>172 (12.4%)</td>
</tr>
<tr>
<td>4</td>
<td>28 (2.0%)</td>
</tr>
<tr>
<td>5</td>
<td>5 (0.4%)</td>
</tr>
</tbody>
</table>

### Underlying disorder

- Hypertension and diabetes: 2.6%
- Not defined: 3.5%
- Venous stenosis: 19.3%
- Isolated coronary artery disease: 4.0%
- Hypertrophic cardiomyopathy: 2.6%
- Chronic heart failure: 3.6%
- Chronic atrial fibrillation: 2.0%
- Other cardiac disease: 2.7%
- Hypertension: 7.4%

### Clinical history

<table>
<thead>
<tr>
<th>Event</th>
<th>All (n=1,391 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous peripheral/pulmonary embolism, %</td>
<td>1.9</td>
</tr>
<tr>
<td>Previous stroke/TIA, %</td>
<td>6.6</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>2.0</td>
</tr>
<tr>
<td>PM, %</td>
<td>2.9</td>
</tr>
<tr>
<td>CRT, %</td>
<td>0.3</td>
</tr>
<tr>
<td>ICD, %</td>
<td>1.3</td>
</tr>
</tbody>
</table>
Atrial Fibrillation Ablation Pilot Registry

Investigations and procedures during the hospital stay – 3/4

Transthoracic Echocardiography

Performed 804/1391 (57.8%)
Not performed 572/1391 (41.1%)
Unknown 15/1391 (1.1%)

- EF (%), median (IQR): 60 (55 – 66)
- LA diameter (mm), median (IQR): 40 (32 – 54)

Atrial Fibrillation Ablation Pilot Registry

Ablation Procedure Modality

<table>
<thead>
<tr>
<th>Procedure Modality</th>
<th>All (n=1391 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-irrigated radiofrequency, %</td>
<td>4.0</td>
</tr>
<tr>
<td>Radiofrequency with closed irrigation, %</td>
<td>2.2</td>
</tr>
<tr>
<td>Radiofrequency with open irrigation, %</td>
<td>77.8</td>
</tr>
<tr>
<td>Cryo, %</td>
<td>13.4</td>
</tr>
<tr>
<td>Duty-cycled radiofrequency energy, %</td>
<td>4.4</td>
</tr>
<tr>
<td>Laser balloon (endoablation system), %</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Atrial Fibrillation Ablation Pilot Registry

Ablation Procedure – 2/2

Acute Success

Yes 978/1391 (70.3%)
No 182/1391 (13.1%)
Unknown 231/1391 (16.6%)

- AF → SR during ablation, %: 31.1
- Non-inducibility of AF, %: 27.7

Atrial Fibrillation Ablation Pilot Registry

Adverse Events – 2/2

Cardiovascular (n=46 pts)
- Cardiac Arrest: 1
- Bradiyrdia requiring Pacing: 3
- Endocarditis: 1
- Myocardial infarction: 1
- Pericarditis: 17
- Cardiac perforation: 11
- No AF, atrial flutter: 4
- Other: 12

- General (n=6 pts)
- Allergic Reaction: 4
- Sepsis: 2

Atrial Fibrillation Ablation Pilot Registry

Adverse Events – 3/3

<table>
<thead>
<tr>
<th>Event</th>
<th>Yes (n=1391 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV, %</td>
<td>45.0</td>
</tr>
<tr>
<td>General, %</td>
<td>5.6</td>
</tr>
<tr>
<td>GI, %</td>
<td>0.9</td>
</tr>
<tr>
<td>Neuro, %</td>
<td>8.4</td>
</tr>
<tr>
<td>Peripheral vascular, %</td>
<td>10.8</td>
</tr>
<tr>
<td>Pulmonary, %</td>
<td>7.6</td>
</tr>
<tr>
<td>Other, %</td>
<td>28.0</td>
</tr>
</tbody>
</table>

Atrial Fibrillation Ablation Pilot Registry

Adverse Events – 2/3

- GI (n=1 pts)
  - Esophageal Ulceration: 1
- Neuro (n=9 pts)
  - Phrenic Nerve Damage: 2
  - Stroke: 4
  - TA: 4
- Pulmonary (n=8 pts)
  - Hemithorax: 9
  - Pleural Effusion: 2
  - Pneumothorax: 1

2011;6(9-10):148.
Atrial Fibrillation Ablation Pilot Registry

**Adverse Events – 2/2**

Description – 3/3

- Peripheral/Vascular (n. 18 pts)
  - A-V Fistula: 6
  - Bleeding requiring transfusion: 1
  - Hematoma requiring evacuation or transfusion: 4
  - Peripheral thromboembolic event: 1
  - Proximal aneurysm: 6

---

**Medications: antithrombotics (n. 1391)**

![Graph showing antithrombotics use](image1)

**Medications: antiarrhythmics (n. 1391)**

![Graph showing antiarrhythmics use](image2)

---

**ECG at discharge**

<table>
<thead>
<tr>
<th>ECG Performed</th>
<th>ECG Not performed</th>
<th>ECG Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1230/1391 (88.4%)</td>
<td>158/1391 (11.4%)</td>
<td>3/1391 (0.2%)</td>
</tr>
</tbody>
</table>

RR interval, mean: 697 (62 - 78)
QRS duration (msed): median (CI): 95 (85 - 105)

---

**Discharge**

<table>
<thead>
<tr>
<th>All (n. 1391 pts)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days), median (IQR)</td>
<td>3 (2 - 4)</td>
</tr>
<tr>
<td>Cardiac death not procedure related</td>
<td>1</td>
</tr>
<tr>
<td>Event not related to AF, %</td>
<td>2.9</td>
</tr>
<tr>
<td>CV, %</td>
<td>36.6</td>
</tr>
<tr>
<td>Non-CV, %</td>
<td>63.4</td>
</tr>
</tbody>
</table>

---

**Conclusion**

The Atrial Fibrillation Ablation Pilot Study provides relevant information with regards to the current clinical practice across Europe. These data may prove useful when designing management strategies of patients suffering from atrial fibrillation.

This Pilot Experience also provided invaluable information for the refinement of the database for its implementation in a long term Atrial Fibrillation Ablation pan-European Registry. Evaluation of the results at the 12-month follow-up will give us more insight on real-life outcomes of the ablation of atrial fibrillation. Finally, further analyses by geographical areas may contribute by identifying local or more generalized needs in relation to this procedure.
Global Variation in the Etiology and Management of Atrial Fibrillation: Baseline Results from a Global Atrial Fibrillation Registry

Background
- Current understanding of AF comes largely from studies conducted in North America and Europe
- It is not known how different the etiology and treatment of AF are between regions of the world
- The goals of this registry are to measure differences between regions of the world in the:
  - Predisposing conditions for AF
  - Treatment of AF
    - focus on BP management and anticoagulation

Study Methods
- Prospective registry, all continents
  - Diverse city sizes and practice settings
- Atrial fibrillation or atrial flutter
  - Primary or secondary diagnosis
  - Presenting to an emergency department
- Enrolled between January 2008 and April 2011
- Data obtained from clinical record
- Reference population North America
- Prevalence of risk factors adjusted for age

Patient Characteristics
- Arrhythmia
  - Atrial fibrillation: 98%; Atrial flutter: 2%
- Reason for ER visit
  - AF primary diagnosis: 44%; Secondary: 56%
- History of AF
  - First episode: 30%; Prior history: 70%
- Pattern of AF
  - Paroxysmal AF: 34%
  - Persistent AF: 28%
  - Permanent AF: 40%

Age
- Median; IQR (years)

Prevalence of HTN
- History of hypertension
- *P < 0.005 vs. N. America

*P < 0.005 vs. N. America
**Oral Anticoagulant Use: CHADS2 ≥ 2**

Patients with a Prior History of AF

*OAC Use CHADS2 ≥ 2

*P ≤ 0.005 vs. N. America

**Oral Anticoagulant Use: CHADS2 ≥ 2 and Rheumatic**

Patients with a Prior History of AF

*OAC Use Rheumatic

*OAC Use CHADS2 ≥ 2

*P ≤ 0.005 vs. N. America

**INR Control by Region**

Based on three most recent INR values (%)

*P ≤ 0.005 vs. N. America

**Conclusions**

- Presentation, etiology and treatment of AF vary greatly between geographic regions.
- Hypertension is the most common predisposing condition for AF worldwide, but
  - Rheumatic heart disease is a major cause in India, Africa, the Middle East and China.
- Oral anticoagulant use is low and INR control is poor
  - Very wide regional variation.
- The results of trials focused on AF patients and treatment strategies typical of N. America and W. Europe may not apply to patients elsewhere.

**Acknowledgements**

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  - J. Healey, S. Connolly, S. Yacoub (Canada); J. O’Gorman, L. Wallentin (Sweden); M. Gerasimts, A. Parekh (USA); A. Anuzis (Brazil); P. Järvelä (Czech Republic); P. Commia (South Africa); J. Zhu, Lisheng Liu (China); P. Pais, A. Sgambari (India);
- **Study Coordination**
  - A. Grinwald, E. Theranies (Canada)
  - Population Health Research Institute (Canada); Dante Pazzanese (Brazil); St. John’s Research Institute (India); Fuwai Hospital (China)
- **Study Sponsor**
  - Boehringer-Ingelheim; P. Ralli, J. Varone

---

**EUROACTION preventive cardiology programme plus intensive smoking cessation with Varenicline**

Professor David Wood,

Imperial College London, United Kingdom

ESC Congress, Paris, France

August 28th to 31st 2011

---

**EUROACTION PLUS**

**Aim**

The aim was to determine if a nurse-led, family based preventive cardiology programme (EUROACTION), with an intensive smoking intervention including optional use of Varenicline, could achieve greater smoking abstinence and improved lifestyle and risk factor control in vascular patients, people at high risk of developing atherosclerotic disease, and the partners of both, in everyday clinical practice.
**EUROACTION + Intensive Smoking Cessation with Varenicline**

- **UK**
- **Italy**
- **Netherlands**
- **Spain**

**Study Population (1)**

Vascular patients and partners

Patients with a new or recurrent diagnosis of coronary or other atherosclerotic disease (see below), and who are continuing to smoke, 18 years of age or older, but less than 80 years.

- Acute myocardial infarction (STEMI or NSTEMI)
- Unstable angina
- Stable angina pectoris
- Elective revascularisation: coronary artery bypass graft (CABG), percutaneous transluminal angioplasty (PTCA)
- Stroke
- Transient ischaemic attack (TIA)
- Peripheral vascular disease (PVD)

**Study Population (2)**

High vascular risk people and partners

- Men and women, 50 years of age or older, but less than 80 years, who are smokers and either
  - Newly identified high multifactorial risk individuals: CVD risk equal or greater than 5% over 10 years according to the HeartScore risk estimation system
  - Are under treatment with antihypertensive and/or lipid-lowering therapies
  - Diagnosed with diabetes mellitus

**The EUROACTION PLUS preventive cardiology programme**

A nurse-led multidisciplinary family-based programme for vascular patients, high-risk individuals and their partners

- Focus on smoking cessation
- Optional Varenicline to assist quit attempts
- Comprehensive lifestyle and risk factor management

**Smoking Cessation Management**

**Varenicline**

Start: 1 week before the patient’s chosen quit date

**Titration:**
- 0.5 mg: days 1 to 3
- 0.5 mg twice per day: days 4 to 7
- 1 mg twice per day: trough week 12

**Target quit date:** Within 4 weeks of starting Varenicline

**Statistical Analysis**

Intention to treat analysis based on all people having a 16-week assessment

**Outcome Measures**

- **Primary Endpoint**
  - 7-day point (period) prevalence of non-smoking validated by breath CO (< 10 ppm) at 16 weeks
Secondary Outcomes

Proportions of patients achieving European and national lifestyle, risk factors and therapeutic targets for cardiovascular disease prevention:

- Diet/nutrition (Food Habit Questionnaire, Mediterranean Diet Score)
- Physical activity (7-day PAR, Pedometer, Chester step test, DASE physical activity questionnaire)
- Overweight/obesity (body mass index (BMI), waist circumference)

**Study Participants**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Eligible patients</th>
<th>n=596</th>
<th>High-risk patients</th>
<th>n=396</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA+ ARM</td>
<td>N=350</td>
<td>350</td>
<td>350</td>
<td>High-risk patients</td>
<td>288</td>
</tr>
<tr>
<td>Usual Care Arm</td>
<td>N=346</td>
<td>346</td>
<td>346</td>
<td>High-risk patients</td>
<td>288</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>EA+ ARM</th>
<th>Usual Care Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N=313</td>
<td>N=313</td>
</tr>
<tr>
<td>12 weeks</td>
<td>N=278</td>
<td>N=270</td>
</tr>
</tbody>
</table>

**Distribution of patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual Care N=346</th>
<th>EuroAction+ N=350</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>60.4 yrs</td>
<td>59.6 yrs</td>
</tr>
<tr>
<td>Aged &lt; 60 years</td>
<td>47.6%</td>
<td>51.1%</td>
</tr>
<tr>
<td>Women</td>
<td>39.6%</td>
<td>41.1%</td>
</tr>
<tr>
<td>Vascular patient</td>
<td>38.2%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Low education*</td>
<td>26.6%</td>
<td>25.3%</td>
</tr>
<tr>
<td>Not employed*</td>
<td>41.5%</td>
<td>44.0%</td>
</tr>
<tr>
<td>Centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>15.3%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>25.4%</td>
<td>24.3%</td>
</tr>
<tr>
<td>Spain</td>
<td>32.7%</td>
<td>34.0%</td>
</tr>
<tr>
<td>UK</td>
<td>26.6%</td>
<td>26.9%</td>
</tr>
</tbody>
</table>

*primary care or high, **comprehensive, high-risk population included

**Smoking abstinence for last 7 days confirmed by breath CO <10ppm PRIMARY ENDPOINT**

<table>
<thead>
<tr>
<th>Group</th>
<th>Usual Care</th>
<th>18.3%</th>
<th>EuroAction+</th>
<th>31.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Smoking abstinence for last 7 days confirmed by breath CO <10 ppm PRIMARY ENDPOINT**

<table>
<thead>
<tr>
<th>Group</th>
<th>Usual Care</th>
<th>18.8%</th>
<th>EuroAction+</th>
<th>36.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Smoking abstinence for last 7 days confirmed by breath CO <10 ppm PRIMARY ENDPOINT IN PARTNERS (n=108)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Usual Care</th>
<th>36.7%</th>
<th>EuroAction+</th>
<th>79.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EUROASPIRE III: modelling the clinical and cost-effectiveness of optimizing cardiovascular prevention in patients with established coronary heart disease in Europe

2. What can we do about it?
- SMOKING
  - Install optimal smoking cessation (Varenicline + counseling)
- CHOLESTEROL
  - Improve compliance + Optimize statin dose/choice
- BLOOD PRESSURE
  - Improve compliance + Install combination therapy
- PHYSICAL ACTIVITY AND HEALTHY FOOD
  - Implement programmes

4. Methodology: five steps
1. Simulating current risk for stroke; re-CHD; CHF over 10 years
   - Based on profiles of 2196 patients in 8 countries
   - Using Framingham equations, adjusted for recent EU event rates
2. Cost of interventions to reduce risk
   - Based on local data
   - Depending on patient prevention status
3. Relative Risk (RR) associated with interventions
   - Based on RCTs and meta-analyses
   - Corrected for combinations of interventions
4. Cost of events
   - Based on local data
5. QALY loss with events
   - Based on published literature

5.1. Overall cost-effectiveness: €16000/QALY

3. Will optimizing prevention be value for money?

5.2. Uncertainty surrounding the results-UK example
5. Results

5.3. Cost-effectiveness in function of risk status

![Graph showing cost-effectiveness in function of risk status]

6. Conclusions and recommendations

- First individualized assessment of the cost-effectiveness of prevention in established disease
- Based on raw EUROASPIRE III data in 8 countries (+/- 2200 patients)
- In general COST-EFFECTIVE result
- Results are sensitive to the impact of intensified BP and cholesterol management. Need for improved meta-analyses.
- Only in a minority of patients cost-effectiveness of intensifying prevention cannot be justified
- CHOL control less cost-effective, possibly due to the fact that many patients (59% of those not at target) are close to target
- Our results emphasize the need for risk estimation in established disease.

Hospital Case Volume and Appropriate Prescription at Hospital Discharge After Acute Myocardial Infarction. A Nationwide Assessment

F. Schiele1, F. Capuano2, P. Loirat3, A. Desplanques-Leperre2, G. Derumeaux3, JF Thébaut2, C. Gardel2

(1) French Society of Cardiology, Paris, France
(2) Haute Autorité de Santé, Saint Denis, France
(3) National College of French Cardiologists, Paris, France

Volume-Quality of Care

- Association between hospital case volume and mortality has been demonstrated in various medical conditions1
- Acute STEMI: Hospital Volume and 30 day mortality explained by (1) Hospital equipment2, (2) Cardiologist on site3, (3) Use of Primary PCI and time to reperfusion4
- Quality of Care can be measured using Outcomes (mortality) or using Quality Indicators (variables specifically designed for this purpose)5. Compared to Outcomes, QI are less multifactorial
- The relation between Hospital Volume and QIs is not clearly determined

Aim of the study: to assess the relation between Hospital Volume and Quality Indicators at discharge after AMI

Methods (1): Design

- National Authority for Health (Haute Autorité de Santé, HAS) has defined specific QIs to evaluate management of AMI, benchmark performance and follow the evolution of AMI management nationwide from the initial onset of symptoms until 1 year after discharge
- Periods of analysis: Three campaigns to measure QIs for AMI have been implemented to date in 2008, 2009 and 2010, throughout the whole country, and in all 635 centres admitting patients for chest pain.
- Center Volume: number of patients with final diagnosis of acute MI in 2008. Centers with <10 records were excluded.
- Patient record selection: random selection of up to 80 patient charts with discharge diagnosis of acute MI (ICD10).
- Data recording by independent team after specific training in completion of the CRF
Methods (2): QIs at discharge

- **Aspirin + Clopidogrel**: CI = allergy, haemorrhagic process, uncontrolled gastric ulcer, pregnancy or lactation
- **Beta-blockers**: absolute or relative CI
  - Absolute CI: uncontrolled heart failure, shock, bradycardia, severe COPD, hypersensitivity
  - Relative CI: COPD, diabetes, asthma, AV block
- **Assessment of LVEF and ACEI (or ARB)** in patients with LVEF < 0.40
  - **CI**: Intolerance or hypotension
  - **Statin** regardless of cholesterol level
  - **CI**: Intolerance

**46,390 patient records**

<table>
<thead>
<tr>
<th>Number of records</th>
<th>2008 (1200)</th>
<th>2009 (8600)</th>
<th>2010 (9000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 records</td>
<td>769 (1.7%)</td>
<td>968 (2.1%)</td>
<td>1643 (1.8%)</td>
</tr>
<tr>
<td>10-30 records</td>
<td>6382 (14.9%)</td>
<td>7982 (17.4%)</td>
<td>8830 (9.8%)</td>
</tr>
<tr>
<td>&gt;30 records</td>
<td>39903 (94.1%)</td>
<td>36032 (79.7%)</td>
<td>42317 (49.4%)</td>
</tr>
<tr>
<td>3 years &gt;10</td>
<td>14464 (38.9%)</td>
<td>11638 (38.3%)</td>
<td>13464 (87.7%)</td>
</tr>
</tbody>
</table>

**Center Volume distribution**

<table>
<thead>
<tr>
<th>Volume class and year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite CI and year</td>
<td>11.68</td>
<td>11.68</td>
<td>11.68</td>
</tr>
<tr>
<td>Composite CI and year</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Methods (3): Statistical analysis**

- **Centre Volume**:
  - > 7 categories: 10-30; 31-60; 61-90; 91-120; 121-150; 150-300; > 300 admissions for AMI per year
- **Individual and Composite QIs**
  - Composite indicator: aggregate of the 4 BASI (all or none strategy = 1 if all PM score 1, 0 if at least one QI scores 0)
  - Centers with >30 records: mean (95% CI) for each QI
- **Volume-QI relation**:
  - Age- and gender-adjusted QIs for individual and composite QIs
- **Temporal trend**:
  - Using 2008, 2009 and 2010 campaigns. Limited to centers who participated in all 3 campaigns
  - Adjusted OR for Composite QIs by Volume class (<90 patients/year) and by year.

**QI rates in Centers with >10 records in 2008**

<table>
<thead>
<tr>
<th>QI</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and</td>
<td>904</td>
<td>903</td>
<td>903</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>18112 (81.9%)</td>
<td>17979 (81.5%)</td>
<td>14528 (79.6%)</td>
</tr>
<tr>
<td>Esterase</td>
<td>908</td>
<td>916</td>
<td>1219</td>
</tr>
<tr>
<td>Blockers</td>
<td>1672</td>
<td>130</td>
<td>810</td>
</tr>
<tr>
<td>LVEF assessment</td>
<td>15793</td>
<td>14827</td>
<td>13426</td>
</tr>
<tr>
<td>ACEI</td>
<td>306</td>
<td>323</td>
<td>272</td>
</tr>
<tr>
<td>Statins</td>
<td>1212</td>
<td>624</td>
<td>738</td>
</tr>
<tr>
<td>Composite CI</td>
<td>11586 (89.4%)</td>
<td>12397 (84.4%)</td>
<td>15336 (64.8%)</td>
</tr>
</tbody>
</table>

**Impact of Volume on QIs**

- **Aspirin + Clopidogrel**
- **Beta blockers**
- **ACEI/ARB**
- **Statins**
- **Composite CI**
**Temporal Interaction Volume-QI**

<table>
<thead>
<tr>
<th>Quality Indicators</th>
<th>Odd ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis, 2009</td>
<td>1.533</td>
<td>1.303</td>
<td>1.774</td>
<td>0.090</td>
</tr>
<tr>
<td>Aspergillosis, 2009</td>
<td>1.404</td>
<td>1.160</td>
<td>1.671</td>
<td>0.090</td>
</tr>
<tr>
<td>Aspergillosis, 2010</td>
<td>1.494</td>
<td>1.270</td>
<td>1.749</td>
<td>0.090</td>
</tr>
<tr>
<td>Bacillus, 2009</td>
<td>1.102</td>
<td>0.945</td>
<td>1.262</td>
<td>0.420</td>
</tr>
<tr>
<td>Bacillus, 2010</td>
<td>1.338</td>
<td>1.165</td>
<td>1.539</td>
<td>0.000</td>
</tr>
<tr>
<td>Bacillus, 2010</td>
<td>1.338</td>
<td>1.165</td>
<td>1.539</td>
<td>0.000</td>
</tr>
<tr>
<td>C. difficile, 2009</td>
<td>1.048</td>
<td>0.884</td>
<td>1.286</td>
<td>0.654</td>
</tr>
<tr>
<td>C. difficile, 2009</td>
<td>1.952</td>
<td>1.720</td>
<td>2.205</td>
<td>0.000</td>
</tr>
<tr>
<td>C. difficile, 2010</td>
<td>1.723</td>
<td>1.529</td>
<td>1.957</td>
<td>0.000</td>
</tr>
<tr>
<td>C. difficile, 2010</td>
<td>1.641</td>
<td>1.302</td>
<td>1.984</td>
<td>0.000</td>
</tr>
<tr>
<td>C. difficile, 2010</td>
<td>1.563</td>
<td>1.337</td>
<td>1.827</td>
<td>0.000</td>
</tr>
<tr>
<td>Composite, 2008</td>
<td>1.952</td>
<td>1.006</td>
<td>3.822</td>
<td>0.000</td>
</tr>
<tr>
<td>Composite, 2009</td>
<td>1.337</td>
<td>1.221</td>
<td>1.464</td>
<td>0.000</td>
</tr>
<tr>
<td>Composite, 2010</td>
<td>1.416</td>
<td>1.203</td>
<td>1.612</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Discussion**

- **The strong points** of our study are the robust methodology, the use of a composite measure and the repeated evaluations over three consecutive years (over 46,000 admissions evaluated).
- **Extend the relation** Volume-Mortality: the difference in mortality between centres is truly related to the quality of care.
- **Threshold of 90-120 patients/year**: no effect above this volume.

**Conclusion**

- Analysis of QIs at discharge demonstrates the existence of a relation between volume and quality of care, whereby centres with the highest volume perform better on quality measures than centres with lower volumes.
- Above a threshold of approximately 90-120 AMI admissions per year, an increase in volume of activity no longer appears to affect quality of treatment at discharge.
- Temporal analysis over 3 consecutive years confirms this relation and shows that it persists despite improvement in quality indicators between 2008 and 2010.
- Is it time for the ESC to define Quality Indicators and to recommend assessment of the QI in Cardiovascular Situations?
Efficacy and Safety of Apixaban Compared with Warfarin at Different Levels of INR Control for Stroke Prevention in Atrial Fibrillation

Presented by Lars Wallentin, Uppsala Clinical Research Center, Uppsala University, Sweden for the ARISTOTLE investigators.

**Background**
- Warfarin effectively prevents stroke in atrial fibrillation.
- Warfarin has a narrow therapeutic range at INR 2.0–3.0 and needs regular laboratory-guided dose adjustments as dose response is influenced by age, body weight, genetics, food, and other medications.
- Patient time in therapeutic range (TTR) varies widely between individuals, sites, and countries, and this affects outcomes.
- The quality of patients’ INR control at the center or country level may interact with the treatment effects when comparing new antithrombotic treatments with warfarin.

**ARISTOTLE Main Trial Results**

- **Stroke or Systemic Embolism**
  - Apixaban 2/12 patients, 1.27% per year
  - Warfarin: 15 (1.5% per year)
  - HR 0.72 (95% CI: 0.66–0.79) (P<0.001)

- **1STH Major Bleeding**
  - Apixaban 1/77 patients, 2.13% per year
  - Warfarin: 15 (2.2% per year)
  - HR 0.92 (95% CI: 0.83–1.05) (P=0.20)

**Disclosures for Lars Wallentin**

Institutional research grants from:
- BMS, Pfizer, Boehringer-Ingelheim, Astra-Zeneca, GSK, Roche, Merck-Schering-Plough

Advisory board or consultancy for:
- Portola, CSL Behring, Evolva, Athera, Regado.

**Atrial Fibrillation with at Least One Additional Risk Factor for Stroke**

- Randomized, double-blind, placebo-controlled
- Enrollment: n = 18,201
- Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)
- Warfarin (target INR 2-3)

Wartfarin/placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

**Enrollment**
- 39 countries, 1,034 sites, 18,201 patients

**Objectives**

What is the influence of centers’ quality of INR control, as estimated in their warfarin-treated patients, on the effects of apixaban compared with warfarin on major outcome events (pre-specified analysis)?

**Pre-specified outcomes**
- Stroke or systemic embolism: primary efficacy outcome
- Mortality
- Composite of stroke, systemic embolism, and myocardial infarction
- Major bleeding: primary safety outcome
- Composite of major and clinically relevant non-major bleeding

**Post-hoc explored outcomes**
- Hemorrhagic stroke
- Net clinical benefit, i.e., the composite of stroke, systemic embolism, myocardial infarction, death and major bleeding.
**Methods**

- Individual TTR during the trial was calculated for each warfarin treated patient by the Rosendaal method excluding the first 7 days after randomization and warfarin treatment interruptions until 2 days after the last dose of warfarin (patients with less than two INR levels were excluded, n=951).
- The center’s TTR was calculated as the median of individual TTRs during the whole study among their warfarin patients.
- The center’s TTR was assigned as a proxy for centers’ quality of INR control for all its patients (assigned to either warfarin or apixaban).
- The interquartile cut-off limits for centers’ TTR were identified to keep the patient numbers within each quartile approximately balanced.

**Baseline Characteristics and Centers’ TTR**

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>&lt;58.0</th>
<th>58.0-65.7</th>
<th>65.7-72.2</th>
<th>&gt;72.2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>4381</td>
<td>4035</td>
<td>4933</td>
<td>4936</td>
<td></td>
</tr>
<tr>
<td>TTR with warfarin</td>
<td>82.7</td>
<td>62.5</td>
<td>69.3</td>
<td>76.7</td>
<td></td>
</tr>
<tr>
<td>INR Failure rate</td>
<td>57.4%</td>
<td>50.2%</td>
<td>35.4%</td>
<td>28.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (years, median)</td>
<td>80.0</td>
<td>80.0</td>
<td>71.0</td>
<td>72.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Weight (kg, median)</td>
<td>89.3</td>
<td>81.0</td>
<td>83.3</td>
<td>81.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHADS2 Score Mean</td>
<td>2.2</td>
<td>2.2</td>
<td>2.1</td>
<td>2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CHADS2 Score 3/4</td>
<td>32.4%</td>
<td>31.5%</td>
<td>30.2%</td>
<td>27.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &gt; 75 yr</td>
<td>24.0%</td>
<td>23.1%</td>
<td>23.3%</td>
<td>20.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>13.4%</td>
<td>12.0%</td>
<td>11.5%</td>
<td>9.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>41.8%</td>
<td>39.6%</td>
<td>27.2%</td>
<td>16.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23.8%</td>
<td>23.9%</td>
<td>25.1%</td>
<td>27.0%</td>
<td>0.0011</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60.2%</td>
<td>61.9%</td>
<td>65.6%</td>
<td>66.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17.0%</td>
<td>15.9%</td>
<td>13.0%</td>
<td>15.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Baseline Co-medication in Relation to Centers’ TTR**

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>&lt;58.0</th>
<th>58.0-65.7</th>
<th>65.7-72.2</th>
<th>&gt;72.2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant</td>
<td>40.8%</td>
<td>40.3%</td>
<td>45.7%</td>
<td>45.8%</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>31.6%</td>
<td>36.2%</td>
<td>29.3%</td>
<td>25.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ARB</td>
<td>26.0%</td>
<td>21.3%</td>
<td>23.6%</td>
<td>24.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACE</td>
<td>70.6%</td>
<td>67.7%</td>
<td>71.0%</td>
<td>63.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>60.3%</td>
<td>63.9%</td>
<td>64.1%</td>
<td>65.9%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>14.7%</td>
<td>13.1%</td>
<td>11.1%</td>
<td>5.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>36.5%</td>
<td>33.9%</td>
<td>30.9%</td>
<td>28.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid Lowering</td>
<td>34.0%</td>
<td>41.2%</td>
<td>47.2%</td>
<td>59.2%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Stroke and Systemic Embolism (primary outcome) in Relation to Centers’ TTR**

<table>
<thead>
<tr>
<th>Center TTR (%)</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>17.5</td>
<td>15</td>
<td>0.10</td>
</tr>
<tr>
<td>50</td>
<td>15.0</td>
<td>12</td>
<td>0.0005</td>
</tr>
<tr>
<td>65.7-72.2</td>
<td>2.0</td>
<td>1.0</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

**Bleeding in Relation to Centers’ TTR**

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>Major bleeds</th>
<th>&lt;5.0</th>
<th>5.0-10.0</th>
<th>10.1-15.0</th>
<th>15.1-20.0</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>64</td>
<td>1.5</td>
<td>1.8</td>
<td>2.6</td>
<td>3.3</td>
<td>0.0005</td>
</tr>
<tr>
<td>Non-major bleed</td>
<td>13</td>
<td>3.1</td>
<td>3.2</td>
<td>2.1</td>
<td>3.6</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

**Hemorrhagic Stroke and Net Clinical Benefit in Relation to Quartiles of Centers’ TTR**

<table>
<thead>
<tr>
<th>Center TTR</th>
<th>&lt;58.0</th>
<th>58.0-65.7</th>
<th>65.7-72.2</th>
<th>&gt;72.2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic stroke</td>
<td>14</td>
<td>26</td>
<td>14</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>200</td>
<td>325</td>
<td>264</td>
<td>236</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

**Statistics**

- Outcomes were compared across the four groups defined by the quartiles of centers’ TTR as pre-specified.
- Hazard ratios and their 95% confidence intervals are presented.
- Tests for interactions between centers’ TTR and randomized treatment effects were evaluated by multivariable Cox regression analyses using the patients assigned center TTR value as a continuous variable.
- Interactions were adjusted for baseline variables potentially influencing both TTR and outcome: age, sex, body weight, CHADS2 score, prior stroke, diabetes mellitus, hypertension, heart failure, baseline medications (aspirin, digoxin, amiodarone, lipid lowering drugs), and warfarin naïve/experienced status.
Conclusion

- The benefits of apixaban over warfarin in preventing stroke, reducing bleeding and improving survival appear consistent regardless of centers’ quality of INR control.
- Therefore, in patients with atrial fibrillation, apixaban is a more effective and safer treatment than warfarin across a wide range of warfarin management.

Presenter Disclosure Information

ASCOT-LLA: 11 year mortality follow-up in the UK

- P. S. Sever and N. R. Poulter have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure lowering or lipid-lowering drugs, including Pfizer for ASCOT

ASCOT Study Design

19,342 hypertensive patients randomised to antihypertensive treatment

- Atorvastatin 10 mg
- Placebo

ASCOT-LLA Primary End Point: Nonfatal MI and Fatal CHD

- 18,305 patients eligible and randomised in lipid-lowering arm TCD 6.6 mmol/L (250 mg/dL)

ASCOT-LLA-Extension

- Early closure of ASCOT-LLA
  - Median follow-up 3.3 years
  - Atorvastatin versus placebo:
    - 38% reduction in the primary endpoint
    - 27% reduction in stroke
- ASCOT-LLA-extension
  - Ongoing atorvastatin 10 mg daily to all patients in LLA
  - Continued for a further 2.2 years until the closure of ASCOT-BPLA

- Statin usage

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=1018)</th>
<th>Placebo (n=1017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD (mmol/L)</td>
<td>41.5 (5.0)</td>
<td>41.5 (5.0)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>54 (11.0)</td>
<td>54 (11.0)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>151 (30.9)</td>
<td>151 (30.9)</td>
</tr>
</tbody>
</table>

*At baseline (35).
ASCOT-LLA: 11 Year Mortality Follow-up
- Post-trial mortality data were collected every 2-3 months in the UK.
- For the current analysis:
  - The primary causes of death were defined as death from:
    - Any cause
    - Cardiovascular (CV) or non-CV disease
    - Cancer
  - Additional post-hoc outcomes included are death from:
    - Infection (infectious or parasitic diseases)
    - Respiratory illness (disease of the respiratory system including pneumonia, chronic obstructive pulmonary disease and acute respiratory distress syndrome)
    - Infection/respiratory combined
  - The cut-off date was 31st December 2010 (inclusive)

ASCOT-LLA 11 Year Mortality: Study Profile
- 5646 patients randomized to antihypertensive treatment
- 4653 patients eligible and randomized in lipid-lowering arm
- 465 patients included in the current study

Effect of Atorvastatin on Mortality and Causes of Death – 1

Statistical Methods
- Patients
  - All patients in the intention-to-treat population who were alive at the end of ASCOT-LLA were classified as either atorvastatin or placebo users.
- Cox regression analysis
  - Two randomized treatment groups (i.e., atorvastatin and placebo) were compared for each mortality outcome.
  - Analyses were unadjusted and adjusted for prespecified baseline risk factors including age, sex, systolic blood pressure, body mass index, total cholesterol, diabetes, current smoker, atrial fibrillation, random blood pressure treatment and age at completion of education. Hazard ratios (HR) were estimated.
  - The assumption of proportionality was tested using Schoenfeld residuals.
- Tests for interactions were performed for:
  - Atorvastatin treatment and time period (no, yes, or both)
  - Atorvastatin and randomized blood pressure treatment
  - Whether the atorvastatin effect differed between subgroups such as age, sex, ethnic or diabetes status.
- Statistical tests were 2-sided and a P-value of <0.05 was considered to be of statistical significance.

Effect of Atorvastatin on Mortality and Causes of Death – 2

Cumulative Incidence by Cause of Death – 1

Original Reference (2011, 6(9-10):163.)
Summary

- A median 11 years after the initial randomisation for ASCOT, and approximately 8 years after the closure of the LLA, all-cause mortality remained significantly lower in those originally assigned atorvastatin.
- Among the UK participants of ASCOT-LLA who were initially randomised to atorvastatin 10 mg therapy:
  - CV deaths were fewer, but the difference was not significant.
  - Non-CV deaths were significantly fewer, attributed to a reduction in deaths caused by infection and respiratory illness.

Conclusions

- Long-term benefits on all-cause mortality were observed among the UK participants of ASCOT-LLA who were originally assigned atorvastatin.
- No definitive explanation has been established for the hypothesised legacy effects of atorvastatin therapy on non-CV death reduction.

Characteristics of Surviving Patients at the End of UK-ASCOT-LLA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60-64</td>
<td>65-69</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20-24</td>
<td>25-29</td>
<td>0.034</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120-140</td>
<td>140-160</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80-90</td>
<td>90-100</td>
<td>0.017</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>30-40</td>
<td>40-50</td>
<td>0.009</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>10-20</td>
<td>20-30</td>
<td>0.015</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10-20</td>
<td>20-30</td>
<td>0.003</td>
</tr>
<tr>
<td>Current user of statins</td>
<td>5-10</td>
<td>10-20</td>
<td>0.001</td>
</tr>
<tr>
<td>Current user of other lipid-lowering drugs</td>
<td>5-10</td>
<td>10-20</td>
<td>0.002</td>
</tr>
<tr>
<td>Current user of antiplatelet agents</td>
<td>5-10</td>
<td>10-20</td>
<td>0.004</td>
</tr>
</tbody>
</table>

The Anglo-Scandinavian Cardiac Outcomes Trial: 11 year mortality follow-up of the Lipid-Lowering Arm in the UK

Discussant
Guy De Backer
Ghent University
Ghent - Belgium

Clinical Trial Update Session, ESC Annual Congress 2011, Paris, France
No Conflict of Interest

Long term follow-up of participants from statin trials

- Prevention of CVD is a lifelong challenge
- Long term safety
- Carry-over effects
- Unexpected findings
**Prevention of CVD: a lifelong challenge**

- If statins are needed to control dyslipidaemia for the prevention of CVD, a lifelong approach is needed.
- This requires the assurance of long term safety particularly when applied in primary prevention.
- Placebo-controlled statin trials in primary prevention (n=10).
  - Median follow-up: 4.8 yrs (range 1.9-5.5).
  - Mean age range: 55 - 66 yrs (range 40-62).
  - Expected lifelong therapy: 15-25 yrs up to >40 yrs.
- ASCOT-LLA-UK offers some answers but raises also more questions.

**Long Term Safety – Statins and Cancer**

- **Background:**
  - Animal models: statins and cancer in rodents.
  - Conflicting results in single trials.
  - Competition between CV and CA deaths in the long run when CV deaths are partially prevented by statins.
- **Reassuring:**
  - Results from pharma-surveillance, meta-analyses, large propensity-matched pairs.
  - Long term follow-up post-trial in 4S, WOSCOPS.
  - ASCOT-LLA-UK: 11 yr incidence of CA deaths:
    - Atorva: 20.1 / 0.85/100py.
    - Placebo: 21.2 / 0.92/100py. HR 0.92 (CI 0.76,1.12).

**Interpretation of unexpected findings in clinical trials**

- Results from retrospective analyses of outcome measures that were not planned a priori can occur by chance only.
- Remember ISIS-II: subgroup analysis of patients by astrological sign showing that aspirin was effective in mortality reduction for all patients except those born under the signs of Gemini and Libra.
- Subgroup analysis in clinical trials: « fun to look at – but don’t believe them » (P. Sleight)

**Differences in Total Mortality between the groups originally assigned to statin or placebo during long term follow-up**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up</th>
<th>RR/HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>10 yr</td>
<td>0.85</td>
<td>0.74,0.97</td>
<td>.016</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>14.7 yr</td>
<td>0.88</td>
<td>0.79,0.96</td>
<td>.03</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>11 yr</td>
<td>0.86</td>
<td>0.76,0.98</td>
<td>.02</td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Carry-over effects?**

- Short term (2yr) post-statin trial follow-up provides convincing evidence that withdrawal from statin therapy is followed by sustained treatment benefit (4S, LIPID, ALERT, ASCOT-LLA).
- Do carry-over effects persist over longer term period?
  - WOSCOPS: ongoing reduction in risk of major coronary events.
  - 4S: no ongoing benefits ascribed to lipid lowering therapy in the majority of patients in both groups.
  - ASCOT-LLA-UK: carry over effects on non-CVD mortality.

**Cardiovascular protective effects of valsartan in high-risk hypertensive patients with chronic kidney disease: updated analysis of KYOTO HEART Study**

- 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.
**Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risk: KYOTO HEART Study**

Takahiro Sawada, Hiroyuki Yamaura, Yobu Daitoh, and Hiroshi Matsumura

For the KYOTO HEART Study Group

**Scheme of study protocol**

- **Valsartan group**
  - Valsartan 169 mg + other drugs (including A2C1 and ARB)
  - DP ≤ 140/90 mmHg with high risk
  - Usual dosage
  - High dosage

- **Non-ARB group**
  - Valsartan 169 mg + other drugs (excluding A2C1 and ARB)

**Kaplan-Meier’s curves**

**Primary endpoint**
- Valsartan 85 pts (4.4%) non-ARB 165 pts (16.2%)

**Background**

- Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD).
- Chronic kidney disease (CKD) is associated with increased CVD-related and all-cause mortality rates.
- Dysfunction of the heart can develop the kidney dysfunction in various clinical settings.
- Bidirectional interaction between CKD and CVD is defined as cardio-renal syndrome.

**Method**

- Estimated glomerular filtration rate (eGFR) at study entry
  - eGFR (ml/min/1.73 m²) = 194 x Serum Cr (mg/dL) x Age (if female) / 0.799
  - Where: Cr = Serum creatinine
  - Serum creatinine in mg/dL: 130–150, 150–200, 200–250, 250–300, >300
- Comparison between With-CKD and Without-CKD groups
  - CKD was defined by eGFR of less than 60 ml/min per 1.73 m².
  - The primary endpoint was the same as in the main study: Composite of defined cardio- or cerebro-vascular events such as stroke/TIA, MI, worsening heart failure, angina pectoris, post-myocardial infarction, lower limb arterial obstruction, transient or diastolic or systolic of serum creatinine values.
- Relationship between CKD severity and CV events
  - The study population was staged into five categories.

**Study purpose**

As the ancillary analysis of the KYOTO HEART study, we investigated the cardiovascular protective effects of valsartan in high-risk hypertensive patients with chronic kidney disease.

**Flow chart of the study population**

KYOTO HEART Study 301 pts

- Not possible to evaluate: 152 pts

- 249 pts

Valsartan 140 pts

Non-ARB 1493 pts
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>With-CKD</th>
<th>Without-CKD</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With-CKD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>70 ± 10</td>
<td>70 ± 10</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>273 / 207</td>
<td>276 / 225</td>
<td>549 / 432</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>158 ± 15</td>
<td>158 ± 15</td>
<td>158 ± 15</td>
</tr>
<tr>
<td>Diastolic</td>
<td>88 ± 12</td>
<td>87 ± 12</td>
<td>87 ± 12</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71 ± 19</td>
<td>72 ± 15</td>
<td>71 ± 17</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>25 ± 3.5</td>
<td>24 ± 3.0</td>
<td>24 ± 3.7</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>123 ± 32</td>
<td>123 ± 31</td>
<td>123 ± 31</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>54 ± 15</td>
<td>54 ± 15</td>
<td>54 ± 16</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>151 ± 82</td>
<td>152 ± 86</td>
<td>152 ± 84</td>
</tr>
<tr>
<td>HbA1c(%)</td>
<td>6.3 ± 3.7</td>
<td>6.1 ± 3.3</td>
<td>6.2 ± 2.7</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>124 ± 49</td>
<td>122 ± 44</td>
<td>123 ± 47</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)**</td>
<td>48 ± 10</td>
<td>46 ± 10</td>
<td>48 ± 10</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>144 ± 16</td>
<td>142 ± 14</td>
<td>143 ± 14</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 1.0</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>189 (39%)</td>
<td>179 (36%)</td>
<td>368 (38%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>349 (73%)</td>
<td>378 (75%)</td>
<td>727 (74%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>124 (26%)</td>
<td>148 (30%)</td>
<td>272 (28%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>87 (18%)</td>
<td>87 (17%)</td>
<td>174 (18%)</td>
</tr>
<tr>
<td>Ischemic heart disease**</td>
<td>143 (30%)</td>
<td>152 (30%)</td>
<td>295 (30%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>19 (4%)</td>
<td>26 (5%)</td>
<td>45 (5%)</td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>129 (27%)</td>
<td>141 (28%)</td>
<td>270 (28%)</td>
</tr>
<tr>
<td>Conceive heart failure**</td>
<td>35 (7%)</td>
<td>67 (13%)</td>
<td>102 (10%)</td>
</tr>
</tbody>
</table>

Data are mean±SD or number(%), p<0.05 and p**<0.01 compared between With-CKD vs Without-CKD.

### Baseline medications at the entry

<table>
<thead>
<tr>
<th></th>
<th>With-CKD</th>
<th>Without-CKD</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With-CKD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>265 (55%)</td>
<td>297 (59%)</td>
<td>562 (57%)</td>
</tr>
<tr>
<td>ACE inhibitor**</td>
<td>100 (21%)</td>
<td>123 (26%)</td>
<td>223 (23%)</td>
</tr>
<tr>
<td>β-blocker**</td>
<td>99 (21%)</td>
<td>106 (21%)</td>
<td>205 (21%)</td>
</tr>
<tr>
<td>σ-blocker**</td>
<td>19 (4%)</td>
<td>19 (4%)</td>
<td>38 (4%)</td>
</tr>
<tr>
<td>Thiazide</td>
<td>14 (3%)</td>
<td>19 (4%)</td>
<td>33 (3%)</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>38 (8%)</td>
<td>53 (11%)</td>
<td>91 (9%)</td>
</tr>
<tr>
<td>Anti-aldosterone agent</td>
<td>15 (3%)</td>
<td>15 (3%)</td>
<td>30 (3%)</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>15 (3%)</td>
<td>29 (6%)</td>
<td>44 (4%)</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>31 (6%)</td>
<td>20 (4%)</td>
<td>51 (5%)</td>
</tr>
<tr>
<td>Anti-coagulating agent</td>
<td>35 (7%)</td>
<td>45 (9%)</td>
<td>80 (8%)</td>
</tr>
<tr>
<td>Anti-platelet agent**</td>
<td>149 (31%)</td>
<td>161 (32%)</td>
<td>310 (32%)</td>
</tr>
<tr>
<td>Nitroglycerine or ISDN</td>
<td>53 (11%)</td>
<td>58 (12%)</td>
<td>111 (11%)</td>
</tr>
<tr>
<td>Dioxin</td>
<td>11 (2%)</td>
<td>20 (4%)</td>
<td>31 (3%)</td>
</tr>
<tr>
<td>Statin</td>
<td>150 (31%)</td>
<td>182 (36%)</td>
<td>332 (34%)</td>
</tr>
<tr>
<td>Fibrarte</td>
<td>14 (3%)</td>
<td>14 (3%)</td>
<td>28 (3%)</td>
</tr>
<tr>
<td>Other lipid modifying drugs</td>
<td>18 (4%)</td>
<td>12 (2%)</td>
<td>30 (3%)</td>
</tr>
<tr>
<td>Oral hypoglycemic agent (SU)</td>
<td>44 (9%)</td>
<td>55 (11%)</td>
<td>99 (10%)</td>
</tr>
<tr>
<td>Other hypoglycemic agent</td>
<td>46 (10%)</td>
<td>50 (10%)</td>
<td>96 (10%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>13 (3%)</td>
<td>24 (5%)</td>
<td>37 (4%)</td>
</tr>
</tbody>
</table>

Data are number(%), p**<0.01 compared between With-CKD vs Without-CKD.
Summary

- Hypertensive patients with CKD had significantly higher CV events than patients without CKD.
- Severity of CKD stage is closely related to the CV event incidence in patients with high-risk hypertension.
- Valsartan add-on treatment is more efficient than non-ARB treatment in high-risk hypertensive patients irrespective of CKD, although there was no significant difference in BP reduction levels among these regimens.
- Valsartan add-on regimen provides beneficial effects, especially in the prevention of heart failure and renovascular events in With-CKD and stroke and angina pectoris in Without-CKD.

Conclusion

- The ancillary analysis from the KYOTO HEART Study showed that CKD was significantly associated with CV events in high-risk hypertension, and the event rate stepped up according to CKD stages.
- Valsartan add-on regimen for high-risk hypertension is more efficient for CV event prevention not only for the patients with CKD but also without CKD.

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 underestimate the statistical power.
- Patient numbers in CKD stages are not equally distributed in the study. Most of CKD-5 were excluded because valsartan is a contra-indication in patients with Cr > 3.0mg/dL.
- 102 patients who could not provide Cr data at the entry were excluded from the ancillary analysis.
- 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.
Comment on:
Cardiovascular Protective Effects of
Valsartan in High-risk Hypertensive
 Patients with Chronic Kidney Disease:
Updated Analysis of KYOTO HEART Study
Josep Redon, MD, PhD, FAHA
Scientific Director

Comment 1:
Data confirmatory of previous studies
- CKD increases cardiovascular risk
  - eGFR <60 ml/min/1.73 m²
    - 1.71 (1.34 – 2.19) p<0.0001
  - Risk increases below 45 ml/min/1.73 m²
- Valsartan-based treatment reduce the risk to develop type 2 diabetes
  - New onset type 2 diabetes
    - 0.67 (0.50 – 0.90) p<0.03

Comment 2:
Limitations of the main study
- Soft endpoints with large impact in the main outcome
  - Angina 2.7%
  - CHF 15%
- Prospective Randomized Open Blinded End-point (PROBE) design

Comment 3:
Limitations of the subgroup study (I)
- Subgroups were not randomized and may not have been comparable in terms of baseline characteristics
  - CHF (V 7% vs n-ARB 13%)
  - Diabetes (V 26% vs n-ARB 30%)
- The numbers of patients (981) and outcome events in the subgroup was small (107), resulting in low statistical power

Comment 3:
Limitations of the subgroup study (II)
- Soft endpoints with large impact in the main outcome
  - Angina 2.2%
  - CHF 16% (the only non-renal significant)
- The renal outcome, doubling SCR or dialysis was achieved with few numbers
  - (V 0.6% 3 patients vs non-ARB 2.4% 12 patients)
- Results were reported without adjustment for multiple comparisons

Comment 4 and 5
General issues
- Can accept that the results are BP-independent in the absence of 24-hour ABPM?
- Can the results (stroke reduction in non-CKD) be generalized to other ethnic groups?

Medication Adherence and Outcomes in High Risk Cardiovascular Patients in the ONTARGET Trial
M. Böhm, H. Schumacher, U. Laufs, P. Sleight, R. Schmieder, T. Unger, K. Koon, S. Yusuf on behalf of the ONTARGET-Investigators

Disclosures
Authors were members of the ONTARGET Steering Committee and received honoraria and research grants from Boehringer Ingelheim as well as fees from other major cardiovascular pharmaceutical companies
Background

Nonadherence to medications
- is a problem in high risk patients
- associated with multidrug treatment
- related to outcomes in several conditions
  - Hypertension
  - Hyperlipidemia
  - CAD
  - CHF
- Associated with health related lifestyle characteristics ("healthy adherer phenomenon")

Objectives of ONTARGET

Patients:
CV high risk patients after MI, Stroke, PAD, or DM + 2RF

Questions:
1. Is telmisartan "non-inferior" to ramipril?
2. Is the combination superior to ramipril?

Outcome:
1. Primary: CV death, MI, stroke, CHF hosp
2. Key secondary: CV death, MI, stroke (HOPE trial outcome)
3. Single Components of the primary

Definitions and Methods

Nonadherence: Complete and Permanent Discontinuation of All Study Medications

Statistical Analysis:
- differences tested by Chi-square (categorical) or Student's t-test (continuous)
- Cox proportional hazard model
- nonadherence as time-dependent covariate
- multiple regression
- p<0.01

Cox Regression on Time to Permanent Stop of Study Medication (Non-Adherence, adjusted)

Variable | P > Chi Sq | HR | 95% CI
--- | --- | --- | ---
Age, linear | <0.0001 | 1.035 | (1.030 - 1.039)
Female vs Male | <0.0001 | 1.230 | (1.117 - 1.351)
Black vs White | <0.0001 | 1.102 | (1.115 - 1.251)
Asian vs White | <0.0001 | 1.059 | (1.051 - 1.063)
Other vs White | <0.0001 | 1.045 | (1.034 - 1.056)
Activity 2 days/week vs 1 week | <0.0001 | 0.893 | (0.889 - 0.907)
Every day vs 2 weeks | <0.0001 | 0.806 | (0.792 - 0.821)
Smoking Current vs Never | 0.0005 | 1.193 | (1.098 - 1.304)
Smoking Former vs Never | 0.0026 | 1.113 | (1.028 - 1.203)
Stroke/TA | 0.0013 | 1.128 | (0.974 - 1.298)
History of diabetes | 0.0001 | 1.222 | (1.127 - 1.314)
Episodes of depression | 0.0001 | 1.311 | (1.286 - 1.336)

Permanent Stop of Study Medication Continuously Increased Over Time

Distribution of Premature Permanent Discontinuations of Study Medication - By Time

<table>
<thead>
<tr>
<th>Permanent discontinuation</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative Frequency</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 weeks</td>
<td>354</td>
<td>7.7</td>
<td>354</td>
<td>7.7</td>
</tr>
<tr>
<td>6w - &lt; 6 months</td>
<td>585</td>
<td>12.6</td>
<td>939</td>
<td>20.3</td>
</tr>
<tr>
<td>6m - &lt; 1 year</td>
<td>619</td>
<td>13.4</td>
<td>1558</td>
<td>33.7</td>
</tr>
<tr>
<td>1y - &lt; 2 years</td>
<td>1938</td>
<td>22.4</td>
<td>3296</td>
<td>56.1</td>
</tr>
<tr>
<td>2y - &lt; 4 years</td>
<td>785</td>
<td>17.0</td>
<td>4081</td>
<td>73.3</td>
</tr>
<tr>
<td>4y - &lt; 4 years</td>
<td>613</td>
<td>13.2</td>
<td>4894</td>
<td>86.5</td>
</tr>
<tr>
<td>4 yrs+</td>
<td>613</td>
<td>13.2</td>
<td>4894</td>
<td>86.5</td>
</tr>
</tbody>
</table>
Nonadherence Increases Overall Event Rates

4-fold Endpoint (CV-Death, MI Stroke, Heart Failure, Hospitalization)

3-fold Endpoint (CV-Death, MI Stroke)

Rapid Increase of Events by Year After Permanent Discontinuation of Study Medication

4-fold Endpoint (CV-Death, MI Stroke, CHF-Hospitalization)

3-fold Endpoint (CV-Death, MI Stroke)

Cox Model with Time-Dependent Covariates

Time-dependent (HR for being off medication)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>3-year HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-fold endpoint</td>
<td>1.29 (1.84–1.47)</td>
</tr>
<tr>
<td>3-fold endpoint</td>
<td>1.28 (1.25–1.32)</td>
</tr>
<tr>
<td>CV death</td>
<td>2.05 (1.63–2.50)</td>
</tr>
<tr>
<td>MI</td>
<td>1.04 (0.99–1.09)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.08 (0.87–1.30)</td>
</tr>
<tr>
<td>CHF Hospitalization</td>
<td>1.46 (1.27–1.74)</td>
</tr>
</tbody>
</table>

Risk for Discontinuation of Medication is Increased After Nonfatal Primary Event

Rapid Increase of Events by Year After Permanent Discontinuation of Study Medication

Risk for Discontinuation of Medication is Increased After Nonfatal Other Events

Number of Events Increases Nonsadherence
Conclusions:

- Ageing, females, ethnics, low physical activity, smoking, diabetes, neuro-psychiatric disorders are predictors of nonadherence.
- Becoming nonadherent rapidly increases events.
- The event itself reduces adherence leading into a vicious cycle.
Medication adherence and outcomes in high-risk cardiovascular patients in the ONTARGET trial

Discussant

Luigi Tavazzi, MD
GVM Care and Research
Cattolica (CT)
Paris - ESC Congress 2011
August 28th

How can non-adherence influence outcome?

- Non adherer cannot benefit from the treatment effect
- Non-adherence may be an indicator of worse outcome unrelated to the treatment

Adherence to PLACEBO was associated to IMPROVED SURVIVAL in:

- Coronary Drug Project (CDP)
- Beta Blocker in Heart Attack trial
- CHARM programme

Non-adherence is common and risky

- Reported in all chronic diseases including very symptomatic or fatal diseases, such as asthma, tuberculosis, epilepsy, leprosy and all cardiovascular diseases.
- In the real world no more than 50% of patients adhere to long-term therapy
- Is associated with poor outcome in patients with all chronic cardiovascular diseases

The effects of non-adherence are difficult to disentangle

- Analysis of "placebo populations"
- Analyses of populations of "neutral" randomized controlled trials

Adherence* effect on mortality in CHARM (Cox model with adherence as time dependent covariate)

- Candesartan group (n 3709)
  HR (95% CI): 0.66 (0.55 - 0.81)
- Placebo group (n 3703)
  HR (95% CI): 0.64 (0.53 - 0.78)
  * Adherence: >80%

The effects of non-adherence are difficult to disentangle

- Analysis of "placebo populations"
- Analyses of populations of "neutral" randomized controlled trials: pooling of randomized groups

Non-adherence: new information from ONTARGET analyses

- Profile of non-adherer
- Impact of time discontinuation on events (modeling non-adherence as time dependent covariate)
- Impact of reasons for discontinuation on event rates
- Impact of events on adherence

Profile of non-adherer

- Old, female, less formal education, physically inactive, smoker, often with neurological and cardiovascular disorders, diabetes

Impact of time discontinuation on events

- An increase in events occurred rapidly after stopping treatment

Impact of event

- After an event adherence worsened and, in parallel, CV
- So the patients entered a vicious risk of further CV outcomes
Non-adherence: new information from ONTARGET analyses

- Profile of non-adherence
- Impact of time discontinuation on events (modeling non-adherence as time dependent covariate)
- Impact of events on adherence
- Impact of reasons for discontinuation on event rates

In conclusion (1)

- The finding that in several RCTs adherence to even placebo was strongly related to outcome suggests that adherent behaviour "itself" is associated with outcome.

In conclusion (2)

- This is related in part to a poorer health profile of non-adherers.
- Conversely, adherence is a surrogate for healthier behaviours, better self-management, compliance to recommended therapy and behaviours that favourably affect outcome.

The Antiplatelet Sub-study of RE-LY

Discussion

Freek W.A. Verheugt

Department of Cardiology, Onze Lieve Vrouwe Gasthuis
Amsterdam, The Netherlands

Antiplatelet vs. No antiplatelet: Bleeding

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic Stroke</td>
<td></td>
</tr>
<tr>
<td>Major Bleed</td>
<td></td>
</tr>
<tr>
<td>Minor Bleed</td>
<td></td>
</tr>
<tr>
<td>Major/Minor Bleed</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td></td>
</tr>
<tr>
<td>Extracranial</td>
<td></td>
</tr>
</tbody>
</table>

In press: 13 DE 150 Warfarin + 60%

Risk of Bleeding With Single, Dual or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Non-fatal and Fatal Bleeding

<table>
<thead>
<tr>
<th>Therapy</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin monotherapy</td>
<td></td>
</tr>
<tr>
<td>Aspirin monotherapy</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel monotherapy</td>
<td></td>
</tr>
<tr>
<td>Aspirin + Clopidogrel</td>
<td></td>
</tr>
<tr>
<td>Warfarin + aspirin</td>
<td></td>
</tr>
<tr>
<td>Warfarin + clopidogrel</td>
<td></td>
</tr>
<tr>
<td>Triple therapy</td>
<td></td>
</tr>
</tbody>
</table>

Risk Ratio (95% CI)
**MUSICA-2**

300 patients with AF (CHADS, 2) on OAC undergoing stenting

randomization

6 months
oral anticoagulants *
dobutagrel 75 mg qd
apirin 100 mg qd

6 months
dobutagrel 75 mg qd
napirin 300 mg qd

Follow-up:
Primary endpoint: 12 months
Secondary endpoint: 6 months

* INR as originally indicated

**NOVEL ANTICOAGULANTS AND DUAL ANTIPLATELET THERAPY**

Conclusions-1

1. In RELY triple therapy (OAC, ASA and clopidogrel) increases major bleeding by 60% irrespective the anticoagulant used

2. The ischemic AND bleeding benefit of dabigatran over warfarin is maintained with antiplatelet therapy

3. The lowest rate of ICH in this study is seen with low dose dabigatran, which is even lower than with warfarin without antiplatelets

---

**ARISTOTELE**

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Results of the ARISTOTLE Trial

Presented on behalf of the ARISTOTLE Investigators and Committees

Sponsored by Bristol-Myers Squibb and Pfizer

**Background**

- Warfarin is very effective at preventing stroke in patients with atrial fibrillation
- Warfarin has several limitations, including drug and food interactions, a narrow therapeutic range, need for anticoagulation monitoring, and bleeding
- Apixaban is a novel oral factor Xa inhibitor with rapid absorption, a half life of about 12 hours, and 25% renal elimination
- Apixaban has been shown to reduce stroke and systemic embolism by 55% compared with aspirin in patients with atrial fibrillation and not suitable for warfarin

---

**Atrial Fibrillation with at Least One Additional Risk Factor for Stroke**

- Major exclusion criteria
  - Severe renal insufficiency
  - Need for aspirin plus thromboprophylaxis
- Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)
- Warfarin (INR 2-3)

---

**Disclosures for Christopher Granger**

Institutional research grants from:
Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, AstraZeneca, Astellas Pharma, GlaxoSmithKline, Medtronic Foundation, Merck & Co., Sanofi Aventis, and The Medicines Company

Advisory board or consultancy for:
AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-La Roche, Novartis Pharmaceutical Company, Bristol-Myers Squibb, sanofi aventis, and The Medicines Company
**Objectives**

**Primary objective**
- To determine whether apixaban is non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

**Primary safety outcome**
- Major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.

**Key secondary objectives**
- Superiority to warfarin for the primary outcome
- Superiority to warfarin for mortality

**Methods**
- The primary analyses were performed using Cox proportional hazards modeling with warfarin-naive status and world region (North America, South America, Europe, Asia/Pacific) as strata.
- Efficacy analyses included all randomized patients (intention-to-treat) and included all events from randomization until the efficacy cutoff date (predefined as January 30, 2011).
- Bleeding analyses were “on treatment” including all randomized patients who received at least 1 dose of study drug and all events from initial receipt until 2 days after the last dose of study drug.

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apixaban (n=9120)</th>
<th>Warfarin (n=9001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (25%, 75%, %ile)</td>
<td>70 (63, 76)</td>
<td>70 (63, 76)</td>
</tr>
<tr>
<td>Women, %</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Region, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Latin America</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Europe</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Warfarin naive, %</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>CHADS2 score, mean (+/- SD)</td>
<td>2.1 (+/-1.1)</td>
<td>2.1 (+/-1.1)</td>
</tr>
<tr>
<td>≤ 1, %</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>2, %</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>≥ 3, %</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

**Primary Outcome**

Stroke (ischemic or hemorrhagic) or systemic embolism

- Apixaban 2.32 patients, 1.27% per year
- Warfarin 2.62 patients, 2.34% per year
- HR 0.97 (95% CI, 0.68-1.38), P=0.83

*Republished with permission from Thromb Haemost 2011;6(9-10):178.*
### Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=2033)</th>
<th>Warfarin (N=2051)</th>
<th>HR (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism (4%)</td>
<td>1.27</td>
<td>1.05</td>
<td>0.79 (0.65, 0.95) 0.011</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.16</td>
<td>1.05</td>
<td>0.79 (0.65, 0.95) 0.012</td>
</tr>
<tr>
<td>Ischemic or uncertain</td>
<td>0.87</td>
<td>1.05</td>
<td>0.92 (0.74, 1.13) 0.42</td>
</tr>
<tr>
<td>Any death</td>
<td>1.94</td>
<td>1.05</td>
<td>0.84 (0.41, 1.77) &lt;0.0001</td>
</tr>
<tr>
<td>Systemic embolism (4%)</td>
<td>0.09</td>
<td>1.29</td>
<td>0.87 (0.64, 1.22) 0.20</td>
</tr>
<tr>
<td>All-cause death (5%)</td>
<td>1.52</td>
<td>1.05</td>
<td>0.89 (0.60, 0.99) 0.047</td>
</tr>
<tr>
<td>Stroke, SE, or all-cause death</td>
<td>4.45</td>
<td>3.04</td>
<td>0.89 (0.81, 0.98) 0.019</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53</td>
<td>2.61</td>
<td>0.98 (0.86, 1.17) 0.37</td>
</tr>
</tbody>
</table>

* Part of sequential testing sequence preserving the overall type I error

---

### Major Bleeding

#### ISTH definition

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=2033)</th>
<th>Warfarin (N=2051)</th>
<th>HR (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>1981</td>
<td>2021</td>
<td>0.97 (0.93, 1.01) 0.27</td>
</tr>
<tr>
<td>Bleeding rate of events (%)</td>
<td>21.15</td>
<td>24.20</td>
<td>0.80 (0.76, 0.86) &lt;0.0001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>2.31</td>
<td>3.69</td>
<td>0.68 (0.54, 0.86) &lt;0.0001</td>
</tr>
<tr>
<td>Intestinal bleeding</td>
<td>0.33</td>
<td>0.40</td>
<td>0.82 (0.65, 1.04) 0.14</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.76</td>
<td>0.66</td>
<td>0.89 (0.76, 1.05) 0.13</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>4.07</td>
<td>6.01</td>
<td>0.68 (0.61, 0.75) &lt;0.0001</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>0.52</td>
<td>1.13</td>
<td>0.46 (0.35, 0.60) &lt;0.0001</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>16.1</td>
<td>25.5</td>
<td>0.67 (0.64, 0.71) &lt;0.0001</td>
</tr>
</tbody>
</table>

* Part of sequential testing sequence preserving the overall type I error

---

### Subgroups for Stroke and Systemic Embolism

#### (1 of 2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
<th>Apixaban (%)</th>
<th>Warfarin (%)</th>
<th>Hazard Ratio</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>541</td>
<td>79 (6.3)</td>
<td>79 (8.0)</td>
<td>0.98</td>
<td>0.63</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>1009</td>
<td>142 (2.3)</td>
<td>166 (2.1)</td>
<td>1.00</td>
<td>0.40</td>
</tr>
<tr>
<td>LVEF ≤ 30%</td>
<td>2013</td>
<td>22 (1.1)</td>
<td>36 (2.1)</td>
<td>0.87</td>
<td>0.12</td>
</tr>
<tr>
<td>High-intensity oral anticoagulant use</td>
<td>1531</td>
<td>153 (2.0)</td>
<td>156 (2.5)</td>
<td>0.92</td>
<td>0.22</td>
</tr>
<tr>
<td>Time ≥ 90 days post-PCI</td>
<td>1738</td>
<td>130 (2.0)</td>
<td>183 (2.5)</td>
<td>0.71</td>
<td>0.44</td>
</tr>
<tr>
<td>Asia/Latin America</td>
<td>466</td>
<td>67 (1.3)</td>
<td>53 (1.1)</td>
<td>1.26</td>
<td>0.33</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1535</td>
<td>193 (2.0)</td>
<td>246 (2.4)</td>
<td>0.82</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1589</td>
<td>176 (2.0)</td>
<td>291 (2.5)</td>
<td>0.83</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* Duke Clinical Research Institute

### Subgroups for Major Bleeding

#### (1 of 2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients</th>
<th>Apixaban (%)</th>
<th>Warfarin (%)</th>
<th>Hazard Ratio</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>1510</td>
<td>130 (2.1)</td>
<td>187 (2.5)</td>
<td>0.81</td>
<td>0.10</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>1000</td>
<td>168 (2.0)</td>
<td>196 (2.5)</td>
<td>0.95</td>
<td>0.57</td>
</tr>
<tr>
<td>LVEF ≤ 30%</td>
<td>1515</td>
<td>21 (1.5)</td>
<td>29 (2.0)</td>
<td>0.86</td>
<td>0.31</td>
</tr>
<tr>
<td>High-intensity oral anticoagulant use</td>
<td>1459</td>
<td>145 (2.0)</td>
<td>236 (2.2)</td>
<td>0.83</td>
<td>0.23</td>
</tr>
<tr>
<td>Time ≥ 90 days post-PCI</td>
<td>1731</td>
<td>118 (2.0)</td>
<td>166 (2.6)</td>
<td>0.80</td>
<td>0.14</td>
</tr>
<tr>
<td>Asia/Latin America</td>
<td>466</td>
<td>70 (1.5)</td>
<td>84 (1.6)</td>
<td>0.83</td>
<td>0.64</td>
</tr>
</tbody>
</table>

* Duke Clinical Research Institute

### Adverse Events and Liver Function Tests

#### (1 of 2)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ≥ 2X ULN</td>
<td>414</td>
<td>162 (41.0)</td>
<td>149 (41.5)</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>AST ≥ 2X ULN</td>
<td>414</td>
<td>162 (41.0)</td>
<td>149 (41.5)</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>Total bilirubin ≥ 2X ULN</td>
<td>414</td>
<td>162 (41.0)</td>
<td>149 (41.5)</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>Total bilirubin ≥ 3X ULN</td>
<td>414</td>
<td>162 (41.0)</td>
<td>149 (41.5)</td>
<td>1.00</td>
<td>0.94</td>
</tr>
<tr>
<td>Total bilirubin ≥ 4X ULN</td>
<td>414</td>
<td>162 (41.0)</td>
<td>149 (41.5)</td>
<td>1.00</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* Duke Clinical Research Institute
Apixaban versus warfarin (over 1.8 years) prevented

- 6 Strokes
- 15 Major bleeds
- 8 Deaths
per 1000 patients treated.

Summary

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% (p<0.01)
- Reduces major bleeding by 31% (p<0.001)
- Reduces mortality by 11% (p<0.047)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability.

Conclusion

In patients with atrial fibrillation, apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality.

The full article is now available online at www.nejm.org

Response to Aristotle

Michael D. Ezekowitz
MBChB  DPhil  FACC  FAHA  FRCP  MA  FESC
Professor, Thomas Jefferson Medical School

Open Label

<table>
<thead>
<tr>
<th>Study</th>
<th>A (AFSAK)</th>
<th>B (BAAK)</th>
<th>C (SPA)</th>
<th>D (SPAFA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>27</td>
<td>15</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect</td>
<td>811</td>
<td>922</td>
<td>908</td>
<td>972</td>
</tr>
</tbody>
</table>

Warfarin better
Warfarin worse
Risk Reduction

DISCLOSURES
Consultant: Alexion Therapeutics, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Glaxo, Merck, Merix, Omron-Modit, Portola
Research, Portola, Sanoﬁ-‐Aventis, St Jude Medical
Johnson & Johnson
Grants: Alexion Therapeutics, AstraZeneca, BMS, Boehringer Ingelheim, Daiichi Sankyo, Portola
CDR: P-‐00, Executive Committee Engage AF,
Lead Investigator: Srinivasan
Factors Influencing Physician Use of Anticoagulation in Atrial Fibrillation

Physicians more influenced by events induced (bleeds) than those prevented (strokes)

The decision to use warfarin in NVAF is driven by perceived risks (intracerebral bleeds)


MODERN ERA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RELY</th>
<th>ARISTOTLE</th>
<th>SPINAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>1/113</td>
<td>1/12/1</td>
<td>1/30</td>
</tr>
<tr>
<td>Mean Age (yrs)</td>
<td>71</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Male (%)</td>
<td>64</td>
<td>66</td>
<td>100</td>
</tr>
<tr>
<td>CHADS2 Score (mean)</td>
<td>2.1</td>
<td>2.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>0 - 1 (%)</td>
<td>32</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>2 - 6 (%)</td>
<td>56</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Prior Stroke/TA /TE (%)</td>
<td>20</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>16.8</td>
<td>14.2</td>
<td>21</td>
</tr>
<tr>
<td>CRF (%)</td>
<td>32</td>
<td>35.5</td>
<td>36</td>
</tr>
<tr>
<td>Baseline ATRA (%)</td>
<td>39</td>
<td>39.6</td>
<td></td>
</tr>
<tr>
<td>VFA-VNT (%)</td>
<td>50</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>Mean Follow-Up (yrs)</td>
<td>2.0</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Lost to Follow-Up (%)</td>
<td>0.1</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Permanent Withdrawal (%)</td>
<td>19</td>
<td>22.7</td>
<td>12</td>
</tr>
</tbody>
</table>

MODERN ERA: RE-LY

MODERN ERA: ARISTOTLE

NEW DAWN

- Millions of patients world wide with AF will benefit from significant stroke reduction
- Superiority of Dabigatran and Apixaban inspite of different mechanism of action / renal excretion and metabolism
- Challenge: Translating Clinical Trials into practice must minimize temporary and permanent discontinuation

Disclosure: None

Role of the Funding Source:

- Independent study founded and performed within the Italian National Healthcare System.
- Approval by the relevant institutional ethical review boards, written informed consent by participants.
- The steering committee designed and oversaw the trial.
- All data were received, checked, and analyzed independently at the Coordinating Centre (Cardiology Dept, Maria Vittoria Hospital, Torino, Italy) following blinded adjudication of clinical events and side effects.
- Acapria Lda (Madeira, Portugal) provided supply of drug/placebo as unrestricted grant.
Background

I. Recurrences are reported in 30% of patients (range 10-50%) after pericarditis;
II. Colchicine is a promising drug for pericarditis treatment and prevention according to non-randomised studies, and COPE-CORE trials.

Study design and setting

- **Design:** Prospective, randomized, double-blind, placebo-controlled, multicenter trial;
- **Setting:** 4 general hospital in North of Italy-urban areas (Torino, Bergamo, Bolzano, Savigliano-Cuneo);
- **Patients:** 120 patients with a first recurrence of pericarditis (sample size to detect a difference 50 vs 25% in recurrence rate between placebo and colchicine with a power of 80% using a 2-sided p=0.05 level test).

Exclusion criteria

1. First attack of acute pericarditis or second or subsequent recurrence;
2. Tuberculous, neoplastic or purulent etiologies;
3. Known severe liver disease or current transaminases >1.5 times the upper normal limit;
4. Current serum creatinine above 221 μmol/L (2.5 mg/dL);
5. Known myopathy or current serum creatine kinase above the upper normal limit;
6. Known blood dyscrasia or gastrointestinal disease;
7. Pregnant and lactating women (in whom colchicine is considered contraindicated);
8. Women of childbearing potential not protected by a contraception method;
9. Known hypersensitivity to colchicine;
10. Current or previous treatment with colchicine for any indication.

CONSORT Flow Diagram of the CORP trial

No patients lost to follow-up. All patients analysed for outcomes.

Objective

- To evaluate the efficacy and safety of colchicine for the secondary prevention of pericarditis (recurrence prevention);
- Specific condition to test: first recurrence of pericarditis (reported recurrence rate: 50% according to CORE study).

Inclusion criteria

1. Definite diagnosis of recurrent pericarditis (first recurrence);
2. Age ≥18 years;
3. Informed consent.

Criteria for recurrent pericarditis:

<table>
<thead>
<tr>
<th>Recurrent pericarditis</th>
<th>Previous history of acute pericarditis (definite diagnosis plus recurrent pain and at least one of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. New Pericardial fluid</td>
</tr>
<tr>
<td></td>
<td>2. Pericardial friction</td>
</tr>
<tr>
<td></td>
<td>3. Electrocardiographic alterations</td>
</tr>
<tr>
<td></td>
<td>4. New or worsening pericarditis effusion</td>
</tr>
<tr>
<td></td>
<td>5. Edema in the white blood cell count, pericardial tamponade, or constrictive pericarditis</td>
</tr>
</tbody>
</table>

Baseline features

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=60)</th>
<th>Colchicine (n=60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>47.3 (14.4)</td>
<td>47.9 (15.4)</td>
</tr>
<tr>
<td>Male %</td>
<td>59 (68%)</td>
<td>34 (64%)</td>
</tr>
<tr>
<td>Smoke %</td>
<td>25 (42%)</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus%</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>COPD %</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Hypothyroid %</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Previous idiopathic etiology %</td>
<td>48 (80%)</td>
<td>50 (88%)</td>
</tr>
<tr>
<td>Previous cardiovascular %</td>
<td>9 (15%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Previous pericarditis %</td>
<td>4 (7%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Time from first attack (months)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>35 (80%)</td>
<td>36 (80%)</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>58 (42%)</td>
<td>58 (42%)</td>
</tr>
<tr>
<td>C-reactive protein elevation</td>
<td>54 (90%)</td>
<td>57 (95%)</td>
</tr>
</tbody>
</table>
Concomitant therapies for recurrent pericarditis (adjunct to placebo/colchicine)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=68)</th>
<th>Colchicine (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>72.3 (14.4)</td>
<td>47.9 (15.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (68%)</td>
<td>34 (50%)</td>
</tr>
<tr>
<td>Fever</td>
<td>19 (32%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>Pericardial chest pain</td>
<td>60 (86%)</td>
<td>60 (86%)</td>
</tr>
<tr>
<td>Pericardial rub</td>
<td>13 (22%)</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Pericardial Effusion</td>
<td>35 (53%)</td>
<td>36 (60%)</td>
</tr>
</tbody>
</table>

Concomitant anti-inflammatory therapy: Aspirin or Ibuprofen
- Placebo: 55 (82%)
- Colchicine: 56 (83%)

Secondary end points

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=68)</th>
<th>Colchicine (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall side effects</td>
<td>4 (7%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Gastrointestinal intolerance</td>
<td>3 (8%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Myocardial steal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe side effects</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Drug withdrawal</td>
<td>4 (7%)</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

Safety and Drug Withdrawal

Comparison of study results with other published work

Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Total (n)</th>
<th>RCT</th>
<th>Duration (weeks)</th>
<th>Adjunct</th>
<th>Follow-up on events</th>
<th>ACE inhibitor (mg)</th>
<th>Tension dose (mg)</th>
<th>Dropout rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>Yes</td>
<td>12</td>
<td>Yes</td>
<td>0-100</td>
<td>Yes</td>
<td>0.5</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Our findings might not be generalizable to other settings or other patient populations

- Colchicine is not registered for the prevention of pericarditis in North America or Europe and its use as such is off-label
- Our limited sample size might have precluded the identification of certain adverse effects
- Only first recurrence of pericarditis (not multi-site)
- Only adults (may not apply to pediatric populations)
- Bacterial and neoplastic etiologies were excluded
- Patients with transaminase elevation, or severe liver disease, elevated creatinine, and patients with myopathy, blood dyscrasia or gastrointestinal disease were excluded
- Women who are pregnant, lactating, or women of childbearing potential without sufficient contraceptive protection were excluded

Imazio M et al. submitted
Conclusions

Following an initial episode of recurrent pericarditis, colchicine, as adjunct to empiric anti-inflammatory therapy, appears to be an in-expensive and safe means

- to hasten symptoms resolution,
- improve remission rates by 1 week,
- reduce further recurrences during follow-up.

Full paper published online today on the ANNALS OF INTERNAL MEDICINE

Acknowledgements

The most important acknowledgement is to the participants in the study and to the physicians, nurses, ethical committees, and administrative staff in hospitals who assisted with its conduct.

Steering Committee:
- Chairman: Rita Trinchero, MD, Torino, Italy.
- Cochairman and Principal Investigator: Massimo Imazio, MD, Torino, Italy.
- Acute Members of the Study Group on “Heart and Infectious diseases” of the Assoazione Nazionale Medici Cardiologi Ospedalieri (ANMCO).

Safety and Clinical events Committee:
- Yuhasz Adler, MD (Coordinator), Tel Hashomer, Israel; Ralph Shabschied, MD, San Diego, USA; David H Spodick, MD, Worcester, USA.

COPD recruiting centres and investigators:
- Cardiology Dept, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M. Imazio, D. Ferrero, S. Ferrero, A. Belli); Ospedale Rivoli, Bergamo, Italy (Investigators: A. Bruno, S. Mancini, D. Cometti), Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (G. Caminiti). Ospedale SS Annunziata, Savigliano, Italy; S. Ferrero, A. Balighiana, R. Donofrio.

Background

- Recurrence is a most troublesome and frequent complication of acute pericarditis and up to 50% of those with a first relapse experience a second one.

- Colchicine was effective in secondary prevention of recurrent pericarditis in the open label, single center, randomized CORE trial.

Colchicine for Recurrent Pericarditis (the CORP trial), by Imazio M et al.

Discussant: Andre Keren MD, FESC, FACC
Hadassah Hebrew University Hospital
Jerusalem, Israel

No Disclosures

Colchicine as First-Choice Therapy for Recurrent Pericarditis

Results of the CORE (Colchicine for Recurrent Pericarditis) Trial

Massimo Imazio, MD; Marco Robbi, MD; Enrico Cardi, MD; Serena DeMauro, MD; Francesco Ponti, MD; Marco Merlo, MD; Marco Chiesa, MD; Recursive Ads, MD; Marco Tardelli, MD

Not only the dose, but also the frequency of steroid use differed in the two trials

<table>
<thead>
<tr>
<th></th>
<th>CORE*</th>
<th>CORP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>84</td>
<td>120</td>
</tr>
<tr>
<td>Initial episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Corticoid Rx</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>- Autimmune</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>After recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Corticoid Rx</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>- Pericardial effusion</td>
<td>53 (63%)</td>
<td>71 (59%)</td>
</tr>
</tbody>
</table>

Therapy of Recurrent Pericarditis in the CORP trial

- ASPIRIN 800-1000 mg or IBUPROFEN 600mg TID

- 7-10 days & 3-4 weeks tapering

- Prednisone 0.2-0.5 mg/kg/day for 4 weeks*

- Proton pump inhibitor in all

Colchicine doses

- Loading: 1.0-2.0 mg/kg/day for 1 day
- Maintenance: 0.5-1.0 mg/kg/day for 6 months

* Prednisone in the CORE trial 1.0-1.5mg/kg/day for 4 weeks

The Recurrence Rate of Pericarditis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRR</td>
<td>-33%</td>
<td>-36%</td>
</tr>
<tr>
<td>NNT</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>p</td>
<td>0.022</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CORP TRIAL – Clinical Importance

- Well designed and carefully performed, first double-blind, multicenter randomized placebo-controlled trial which evaluated the efficacy of Colchicine for prevention of recurrent episodes of pericarditis
- The results strongly support the use of low-dose Colchicine as a safe, well-tolerated and effective “first line” adjuvant to standard treatment in patients with recurrent pericarditis
- The high safety and tolerability profile of the drug might have been influenced both by the low doses employed and by the careful selection of patients enrolled in the study

European Society of Cardiology
Paris, France, August 30, 2011

Vascular Effects and Safety of Dalteparin in Patients with or at Risk of Coronary Heart Disease – the dal-VESSEL Randomised Clinical Trial


Dal-Vessel: Background

- Lowering of low-density lipoprotein cholesterol (LDL-C) through statin use is a highly effective method of improving cardiovascular outcome in a broad range of patients,
- However, despite optimal statin use, significant risk remains,
- Agents that act on cholesteryl ester transfer protein (CETP) activity to raise high-density lipoprotein cholesterol (HDL-C) levels are currently being investigated as a new therapeutic option

Torcetrapib in High Risk Patients - ILLUMINATE

Disclosures

- The presenting author has received:
  - Research grants from Pfizer, Eli Lilly and Merck
  - Consultancy or lecture fees from CSL, Merck, Pfizer and F. Hoffmann-La Roche Ltd
- The dal-VESSEL study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland

Torcetrapib and Blood Pressure - ILLUMINATE

Barter PJ, NEJM 2008

Reduced HDL Cholesterol is associated with increased cardiovascular risk – despite intense statin therapy

Barter PJ, NEJM 2008

Torcetrapib in High Risk Patients - ILLUMINATE

Change in Lipid Levels

Cardiovascular Events
Mechanisms of Endothelial Dysfunction and Hypertension with Torcetrapib

**dal-Vessel - Dalcetrapib**
- Dalcetrapib acts on CETP activity, decreasing CETP activity and increasing HDL-C by up to 36%.\(^1\)\(^2\)
- To date, dalcetrapib has not exhibited any of the off-target effects associated with the CETP inhibitor torcetrapib.\(^2\)\(^4\)

**dal-VESSEL - Concept of the trial**
- The current study, dal-VESSEL, was designed to further investigate the safety of dalcetrapib and aimed to rule out any adverse effects of dalcetrapib on endothelial function and blood pressure.\(^1\)\(^2\)
- To facilitate this, flow mediated dilation (FMD) was to be used to provide an assessment of endothelial function.
- Blood pressure was to be assessed by ambulatory blood pressure monitoring (ABPM).

**B-mode Ultrasound of Brachial Artery FMD**

**Standardization of Flow-mediated Dilation**
- 1. US Device
- 2. Armrest
- 3. Core Lab

**Standardization of Flow-mediated Dilation**
- Lectures
- Practical Courses
  1. Central Training Courses for Sonographers
  2. Certification Process
  3. Blinded Analysis in Core Lab by expert Readers
**dal-Vessel** - Reproducibility of FMD

**dal-Vessel - Study design**

- Primary endpoints:
  - Change from baseline of FMD of the right brachial artery after 5 min of cuff occlusion at 12 weeks
  - 24-hour ABPM at week 4
- Secondary endpoints:
  - Change from baseline of FMD after 36 weeks
  - Change in ABPM after 12 and 36 weeks
  - Changes in lipids
  - Standard safety parameters

**dal-Vessel - Endpoints**

**dal-Vessel - Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=234)</th>
<th>Dalteparin (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.93 ± 9.92</td>
<td>62.2 ± 6.6</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>121 (52)</td>
<td>121 (96)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.7 ± 0.64</td>
<td>29.6 ± 2.48</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.8 ± 1.85</td>
<td>21.6 ± 1.93</td>
</tr>
<tr>
<td>Glycemic control</td>
<td>116 (96)</td>
<td>104 (94)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (16)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>36 (15)</td>
<td>31 (13)</td>
</tr>
<tr>
<td>Acute renal disease</td>
<td>5 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>100 (43)</td>
<td>100 (40)</td>
</tr>
</tbody>
</table>

**dal-Vessel - Baseline lipids**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=234)</th>
<th>Dalteparin (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.90 ± 0.54</td>
<td>3.91 ± 0.55</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.09 ± 0.15</td>
<td>1.10 ± 0.16</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.61 ± 0.61</td>
<td>2.63 ± 0.63</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.64 ± 0.73</td>
<td>1.64 ± 0.73</td>
</tr>
<tr>
<td>apo A-I (mg/L)</td>
<td>1.33 ± 0.18</td>
<td>1.37 ± 0.18</td>
</tr>
<tr>
<td>apo B (mg/L)</td>
<td>0.82 ± 0.17</td>
<td>0.89 ± 0.16</td>
</tr>
</tbody>
</table>

**dal-Vessel - HDL-C levels increased with dalteparin over 36 weeks**

**dal-Vessel - Lipids over 36 weeks**

- Data presented as absolute change at each timepoint, mean ± SEM; placebo n=23 and dalteparin n=125 for HDL-C and LDL-C; placebo n=23 and dalteparin n=125 for apo A-I and apo B.
Baseline FMD exhibited no significant change with dalcetrapib over 36 weeks.

dal-Vessel – Change in biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline</th>
<th>Column 1 (p=0.01)</th>
<th>Column 2 (p=0.001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-P</td>
<td>94.5 (4.2)</td>
<td>93.5 (4.2)</td>
<td>86.5 (4.2)</td>
</tr>
<tr>
<td>HDL</td>
<td>45.5 (4.2)</td>
<td>45.5 (4.2)</td>
<td>45.5 (4.2)</td>
</tr>
<tr>
<td>TG</td>
<td>182 (4.2)</td>
<td>182 (4.2)</td>
<td>182 (4.2)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.5 (4.2)</td>
<td>0.5 (4.2)</td>
<td>0.5 (4.2)</td>
</tr>
<tr>
<td>TSH</td>
<td>4.6 (4.2)</td>
<td>4.6 (4.2)</td>
<td>4.6 (4.2)</td>
</tr>
</tbody>
</table>

dal-Vessel – Safety parameters

<table>
<thead>
<tr>
<th>Adverse Events (n)</th>
<th>Placebo (n=1246)</th>
<th>Dalce...t (n=1246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>14 (11.2%)</td>
<td>14 (11.2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (11.2%)</td>
<td>14 (11.2%)</td>
</tr>
</tbody>
</table>

Results from dal-PLAQUE

- The results from dal-PLAQUE also provide reassurance regarding the safety of dalcetrapib.
- dal-PLAQUE was a multicentre study using non-invasive simultaneous multimodality imaging (MRA and PET/CT) to assess structural and inflammatory indices of atherosclerosis.
- MRI results: significant reduction in total vessel area with dalcetrapib versus placebo after 24 months; the wall area was numerically reduced versus placebo.
- PET/CT results: no evidence of a pro-inflammatory effect of dalcetrapib.
- Sunday, August 28, 2–6 pm; Poster Zone C

Acknowledgments: Participating Centres

- Switzerland: Universitaet Hospital Zürich, George Noll, CardioCentro Ticino, Lugano, Tiziano Miccoli
- Italy: Universita degli Studi di Perugia, Stefano Tadini
- Germany: Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt/Main, Stephan Pichlmeier, Klinikum der Johann-Wolfgang-Universität Mainz, Malin, Thomas Misura
- Austria: Universitätsklinikum Salzburg, Felix Eberlein, Heinrich Dresel
- France: Hopital Saint-Louis, Georges Pomposelli, Paris, Jean-Philippe Zuber

dal-Vessel – Conclusions

- Dalcetrapib reduced CETP activity, increased Apo A1 and elevated HDL-C levels by 31% without affecting LDL or ApoB.
- Dalcetrapib did not cause endothelial dysfunction, but also did not improve it.
- In contrast to torcetrapib, dalcetrapib did not have an effect on APBM, providing further reassurance regarding the safety of the compound.
- This trial also demonstrates the feasibility of using FMD to test the influence of novel cardiovascular compounds on the biology of the vessel wall and endothelial function in particular.
Vascular Effects and Safety of Dalcetrapib in Patients with, or at Risk of CHD: the dal-VESEL Randomised Clinical Trial

Discussant: Keith AA Fox
University and Royal Infirmary of Edinburgh

No conflicts with respect to any aspect of this presentation

dal-VESEL (phase IIb trial)

- dal-VESEL randomised, double-blind, placebo-controlled study in patients with CHD or CHD risk equivalents.
- 476 patients with HDL-C levels <50 mg/dL; dalcetrapib 600 mg/day or placebo in addition to their existing treatments.
  - Primary efficacy endpoint is change in brachial flow mediated dilatation after 12 weeks.
  - Primary safety endpoint was 24-hour ambulatory blood pressure.
- Flow Mediated Dilatation is a marker of endothelial dysfunction and associated with atherosclerosis.

dal-Vessel-Trial – Flow-mediated Dilatation

![Graph showing flow-mediated dilatation change over time for Dalcetrapib and Placebo]

- Dalcetrapib reduced CETP by 49% and increased HDL-C levels by 31% without affecting NO-dependent endothelial function.
- Blood pressure and markers of inflammation and oxidative stress.

dal-Vessel-Trial

- The first multicentre trial demonstrating the feasibility of using FMD to evaluate risk markers using novel CV compounds.
- Dalcetrapib reduced CETP activity by 49% and increased HDL-C levels by 31%.
- No significant effect on NO-dependent endothelial function, blood pressure or markers of inflammation and oxidative stress.
- The dal-OCTIMES trial (NCT01658515) will show whether dalcetrapib improves outcomes.

Cholesterol Ester Transport Inhibitors

- Cholesterol ester transfer protein (CETP) normally transfers cholesterol from HDL (cholesterol in very low density lipoproteins (VLDL or LDL).

Flow mediated dilatation: What changes are seen with statins?

![Graph showing % change in LDL cholesterol and FMD over time for different treatment groups]

- Dalcetrapib reduced CETP by 49% and increased HDL-C levels by 31% without affecting NO-dependent endothelial function.

Blood pressure changes at 4 weeks

- Mean SBP dalcetrapib (128 mmHg) placebo (125 mmHg).
- Difference vs placebo 0.65 mmHg, 95% CI -0.68, 1.99; P=0.337.
- “The primary safety endpoint was therefore met with respect to SBP”.
- At 12 weeks (difference vs placebo 1.21 mmHg, 95% CI -0.15, 2.58; P=0.081).
- At 36 weeks (difference vs placebo 0.90 mmHg, 95% CI -0.65, 2.45; P=0.253).
The Homburg Cream and Sugar Study (HCS):
Prospective evaluation of postprandial triglycerides and cardiovascular events in patients with coronary artery disease

Christian Werner, Anja Filmer, Marco Fritsch, Stephanie Groenswold, Stefan Gräber*, Michael Böhme, Ulrich Laufs

Klinik für Innere Medizin III (Kardiologie, Angiologie und Internistische Intensivmedizin)
Institut für Medizinische Biometrie, Epidemiologie und Medizinische Informatik,
Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

Disclosures:
U. Laufs has received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Dalich-Sankyo, Essex, MSD Sharp & Dohme, Novartis, Roche, Sanofi, Servier, Tournadour

The study was funded by the Deutsche Stiftung für Herzforschung and the Universität des Saarlandes (HOMFOR)

ClinicalTrials.gov number: NCT00625534

BACKGROUND
Postprandial increase of triglycerides
Factors affecting serum concentrations of TG-rich lipoproteins:
time of food intake
composition of food
glucose metabolism, insulin
lipid metabolism, HDL-C
medication
comorbidities
genetic predisposition

Fasting triglycerides, HDL-C, non-HDL-C
and hazard ratios for coronary heart disease
68 studies in 302 430 participants without prior history of CVD

The Emerging Risk Factors Collaboration
JAMA 2009;302:1603-2006

Association of nonfasting triglyceride levels
with cardiovascular events in healthy individuals
N=26,993 Women’s Health Study (26,918 fasting, 6,391 nonfasting), 11.4 years

Bansal S et al., Women’s Health Study, JAMA 2007;298(3):391-16

BACKGROUND - PATHOPHYSIOLOGY
Atherogenicity of triglyceride-rich lipoproteins

Remnant hypothesis
Lipolytic toxin hypothesis
Geoffroy Li et al., ATVB 2011;31:1716-20
HCS - OUTCOMES
Fasting, but not postprandial TG predict outcome in total cohort

<table>
<thead>
<tr>
<th>TG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>0.01</td>
</tr>
<tr>
<td>Postprandial</td>
<td>0.31</td>
</tr>
</tbody>
</table>

HCS - Metabolism
Postprandial triglyceride kinetics and glucose tolerance

HCS: Postprandial TG predict outcomes only in patients with normal glucose tolerance

HCS: Fasting and postprandial TG independently predict outcomes in patients with normal glucose tolerance

HCS: Triglycerides predict CV events in CAD patients with normal glucose tolerance – discrimination by postprandial TG kinetics

<table>
<thead>
<tr>
<th>TG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>0.00</td>
</tr>
<tr>
<td>Postprandial</td>
<td>0.04</td>
</tr>
</tbody>
</table>

The Homburg Cream and Sugar Study (HCS) SUMMARY

- Combined testing of postprandial glucose and triglyceride tolerance is feasible in clinical practice.
- Postprandial TG do not predict CV outcomes in the total cohort of patients with CAD on statin treatment.
- Subgroup analyses:
  - Patients with CAD = IGT / diabetes: Postprandial TG are elevated but not independently predict CV outcomes.
  - Patients with CAD = normal glucose metabolism: Both fasting and -postprandial TG are independent markers for CV outcomes.

The Homburg Cream and Sugar Study (HCS) CONCLUSION

Fasting and postprandial triglyceride concentrations independently predict cardiovascular events in patients with coronary artery disease and normal glucose tolerance.

Thank you
**The Homburg Cream and Sugar Study**

*Discussant: Philip Barter*

*The Heart Research Institute*

*Sydney, Australia*

---

**Philip Barter Disclosures**

Received honorariums for lectures, consultancies or membership of advisory boards from:

AstraZeneca, CSL, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis

---

**Fasting TG levels and coronary risk**


**Main Findings of Current Study**

After adjustment for other factors, neither the fasting nor postprandial TG level predicted CV outcomes in the total cohort.

However, both fasting and postprandial TG levels predicted CV outcomes in those with normal glucose tolerance but not in those with IGT/diabetes.

---

**Limitations and weaknesses**

The relatively small sample size, relatively short follow-up and a consequent small number of CV events limits the conclusions that can be drawn.

The composite endpoint was rather “soft”.

In addition, there is no indication of the mechanism responsible for what, if real, is a very interesting finding.

---

**Strength of this study**

This is the first study designed to assess whether glucose metabolic status impacts on the ability of TG levels to predict cardiovascular risk.

The results are provocative and, if real, have potentially important clinical implications.
Secondary prevention medications for CVD in 628 communities from 17 high, middle and low income countries

The Prospective Urban Rural Epidemiologic (PURE) study

Salim Yusuf on behalf of the PURE investigators

Background

- Antiplatelet drugs, betablockers, ACE-I/ARBs and statins reduce MI, stroke and death in CHD; and these interventions and BP lowering reduces stroke after a cerebro-vascular event.
- Most studies regarding the use of these drugs are hospital based or among patients followed by physicians, but not from the community.
- Little information from low and middle income countries, where >80% of global CVD occurs.

Design of PURE

- Unbiased population sample from 628 urban and rural communities in 17 countries involving >390,000 people (154,000 are >35 to 70 yrs; surveyed in 2003-2010.
- Documentation of the characteristics of the community, the household and individual (lifestyles, conditions, and drug use).
- Long term follow-up ongoing.

Classification of countries

Based on World Bank classifications at the beginning of the study (2003 – 2007):

- **HIC:** Canada, Sweden & UAE.
- **UMIC:** Argentina, Brasil, Chile, Poland, Turkey, S Africa, Malaysia.
- **LMIC:** Colombia, Iran, China.
- **LIC:** India, Bangladesh, Pakistan, Zimbabwe.

Duality of In

None to declare with regards this presentation

Aims

- To document the use of primary and secondary prevention medications in the community in high, middle and low income countries.
- To describe the variations in drug use by societal (economic level of countries and urban vs rural) and individual (gender, age, SES, other conditions) factors.

Countries in PURE

Key Characteristics of Eligible vs Enrolled

<table>
<thead>
<tr>
<th>No.</th>
<th>Eligible</th>
<th>Enrolled</th>
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</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>50.2</td>
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<tr>
<td>% Females</td>
<td>53.0</td>
<td>55.6</td>
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<tr>
<td>% Current Smokers</td>
<td>22.1</td>
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<tr>
<td>% Low education</td>
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<td>42.3</td>
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<tr>
<td>% Hypertension</td>
<td>13.3</td>
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<tr>
<td>% Diabetes</td>
<td>5.2</td>
<td>5.3</td>
</tr>
<tr>
<td>% Stroke</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>% CHD</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>% Cancer</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Medication in those with CHD or Stroke
BMI and Diabetes*

*Age, sex adjusted

Per-Capita Health Expenditure vs Percentage the use of medications

Country (between country) & individual level (within country) variances

Conclusions

- Substantial underutilization of proven, inexpensive secondary prevention medications in the community worldwide, but the gap is worse in MIC & LIC.
- Less use of medications in rural compared to urban communities, especially in LIC and MIC, in young, females, less educated, smokers, non-obese, & non-DM individuals.

Lancet, August 28, 2011

Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey

Conclusions

- Marked differences in use of BB, ACE-I/ARB, diuretics & CCB in those with hypertension + CVD vs those without hypertension & CVD: Do physicians treat risk factors rather than risk?
- Inter-country variability twice as large as between subject variability: national policies & structured health systems are more important.

The large global gap in use of proven, inexpensive and safe strategies that could be readily dealt with that can benefit millions of individuals each year.
**Discussant**
Low use of secondary prevention medications for cardiovascular disease in the community in 17 high, middle and low income countries (the PURE Study)

Aldo Pietro Maggioni, MD
ANMCO Research Center
Firenze, Italy

**Disclosures:** none

**Most important findings of the PURE study**

- Medications for secondary prevention
  - underused everywhere, and even more in poorer countries
  - higher use in urban compared to rural areas (more evident in low income countries)
- Use of all drugs higher in patients with hypertension
  - risk factors per se (i.e., hypertension) more considered by doctors than level of patient risk
- Use of proven medications substantially lower in women and in younger patients
- In any case, the economic status of a country is more relevant (2/3 of the variations) than individual factors (only 1/3)

**Few limitations**

- An analysis comparing different health systems (i.e., drugs completely or partially reimbursed or no reimbursement at all) could explain differences, irrespective of the economical status
- Dosages of treatments are not available, but they could be important in different ethnicities

**Relevant strenghts**

- Large very representative setting
  - 154,000 individuals from 600 urban and rural communities in 17 high, middle and low income countries with any level of development and socio-cultural characteristics of 5 continents
- Data collection in the community and not, as usual, in a hospital setting and just by cardiologists
- Information on a large number of females (more than 50% of the population)

**Perspectives**

- Very important, essential point of reference for further research
  - Need to improve the knowledge, with ad-hoc designed studies for specific countries on
    - reasons of under-treatment
    - relationships between rate of use of preventive drugs and occurrence of further CV events
    - impact of different NHS on secondary prevention strategies irrespective of country economical status
  - Need to improve the access to prevention
    - stronger collaborations between cardiologists/GPs and, specifically in low-income countries, also with nurses and non-physician health operators (e.g., HV)
    - widespread diffusion of EB drugs, as generics but even better as essential WHO drugs available at no cost (polypill?)

**Conclusions**

- PURE is a perfect example on how observational research can effectively contribute to the incorporation of EB treatments in clinical practice
- A real improvement of global CV health could be likely obtained through
  - preventive strategies focused on the well known risk factors (INTERHEART, INTERSTROKE etc), including life-style changes
  - socio-political strategies focused to increase the use of preventive drugs
  - more then through the identification of new sophisticated predictive biomarkers or modest refinements of the pharmacological properties of existing classes of drugs
IS CLOPIDOGREL DISCONTINUATION FOLLOWING ACUTE CORONARY SYNDROME HOSPITALISATION ASSOCIATED WITH A HIGHER RISK OF DEATH AND MYOCARDIAL INFARCTION?

Boggs R1, Van Staas T, Timms A1, Hemingway H1, Ray KK2, Begg A1, Emmas C1, Fox KAA1

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2. Department of Public Health, University of Oxford, Oxford, UK

Funding: AstraZeneca

DAP Clopidogrel and Aspirin

ESC Guideline 2008
- NSTEMI and STEMI: Clopidogrel 12 months whether or not starting

AHA Guideline 2007
- NSTEMI: Clopidogrel 4 weeks (1A), up to 1 year (1B) - whether or not BMS starting, 6 months DE starting
- STEMI: Clopidogrel 1-3 months whether or not BMS starting, 6 months DE starting

NICE Guideline 2007
- NSTEMI: Continue clopidogrel treatment for 12 months
- STEMI: Continue clopidogrel for 4 weeks (currently being updated)

MINAP registry data: 2° prevention

Patients in linked MINAP-GPRD dataset

Linked Dataset

NSTEMI/STEMI

Clopodigrel prescription in 1° care within 3 months of AMI

Characteristics associated with 1° care clopidogrel prescribing within 3 months

Discontinuation of clopidogrel and statin prescribing in primary care

Disclosures
- R.B. and T.G. - GPRD is owned by the UK Department of Health, and operated within the Medicines and Healthcare products Regulatory Agency (MHRA). GPRD has received funding from the National Institute for Health Research (NIHR) Biomedical Research Centre at the University of Sheffield and the NIHR Sheffield Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the UK Department of Health.
- R.B. is a member of the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care for the North West Coast (NIHR CLAHRC NW). The views expressed are those of the authors and not necessarily those of the NIHR.
- K.M. has received fees for lectures and consultancy from Lilly (UK) and AstaZeneca.
- A.H. has received advisory compensation and travel from AstaZeneca and Novartis.
- C.E. is a HCP employee of AstaZeneca and hence is a manufacturer representative.
Characteristics associated with discontinuation of 1st care clopidogrel prescribing within 1 year

TABLE

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<th>Age</th>
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<td>1.34 (1.09-1.67)</td>
</tr>
<tr>
<td>CABG</td>
<td>1.62 (0.90-3.36)</td>
<td>1.30 (1.11-1.54)</td>
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AGE

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<th>Age</th>
<th>Odds Ratio</th>
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<td>60-64</td>
<td>1.13 (0.81-1.58)</td>
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<tr>
<td>65-69</td>
<td>1.56 (1.37-1.74)</td>
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<td>70-79</td>
<td>1.27 (0.99-1.63)</td>
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<tr>
<td>80+</td>
<td>1.50 (1.16-1.94)</td>
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Bleeding

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<thead>
<tr>
<th>PCI</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.34 (1.09-1.67)</td>
</tr>
<tr>
<td>PCI</td>
<td>1.34 (1.09-1.67)</td>
</tr>
</tbody>
</table>

In patients with acute myocardial infarction discharged home from hospital

- Failure to prescribe clopidogrel in first 3 months is associated approximately twice the rate of death or recurrent AMI in the first year.
- Discontinuation of clopidogrel prescription in the first year is associated with >200% the hazard of death or recurrent AMI compared with patients who do not discontinue clopidogrel.
- Discontinuation trajectory of clopidogrel steeper than statins in first year.
- Discontinuation of clopidogrel more common in old or patients and those with bleeding complications.

Unanswered question

Why do patients who are never prescribed clopidogrel in first 3 months after NSTEMI/STEMI or who discontinue treatment in the first year have higher event rates?

- More prone to thrombotic events due to heightened platelet activation?
  - Consistent with data from RCTs and platelet function studies.
- Healthy user bias - sicker patients tend to stop taking treatment?
  - Consistent with increased bleeding risk and older age of patients who discontinued treatment, but
  a) discontinued at stage of clopidogrel discontinuation
  b) All outcome data adjusted for prior coronary events and hospitalisations.

Conclusion

In patients with acute myocardial infarction discharged home from hospital

- Linking primary care and hospital based registries is feasible and provides unique insights into ongoing management after discharge and its relation to outcomes.
- Discontinuation of clopidogrel prescription in the first year is common, particularly in older patients, and is associated with adverse outcomes.
- The mechanism of this association needs clarification.
- Strategies to promote appropriate use of secondary prevention treatment in this high risk group of patients are required.

Disclosures

Some authors have received grants or honoraria from the device companies in EUROMED (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical).
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Switzerland Hans Peter Brunner-Le Roux, Stefan Osvald
United Kingdom Ian Squire, John Morgan

Objectives

To evaluate contemporary European practice related to CRT implantations with regard to:

- Clinical characteristics
- Diagnostic criteria
- Implantation routines and techniques
- Adverse experience
- In-hospital course

A follow-up visit at 1 year (9-15 months)

Baseline findings

- Cohort similar to RCT’s
- However, the Survey provides data on 4 important populations not included in RCTs: elderly
  AF
  narrow QRS
  upgrades from a previous device

Follow-up

- 2438 patients included
- Follow-up data acquired from 2111 patients (87%)
  - 207 patients died (9.8%)
  - 346 patients (16.4%) hospitalized (CV)
  - 501 patients (23.7%) died or were hospitalized (CV)

Survival at 1 year follow-up

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<tr>
<th>Trait</th>
<th>All</th>
<th>P-value</th>
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<tr>
<td>Patients (n, %)</td>
<td>229 (99)</td>
<td>0.012</td>
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<tr>
<td>Demographics</td>
<td>73 (64.4)</td>
<td>76 (65.6)</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>71 (62.6)</td>
<td>74 (66.2)</td>
</tr>
<tr>
<td>AF and drug available</td>
<td>74 (65.6)</td>
<td>73 (64.4)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>72 (65.6)</td>
<td>75 (64.4)</td>
</tr>
<tr>
<td>Other</td>
<td>76 (66.2)</td>
<td>74 (65.6)</td>
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<tr>
<td>Total number of patients</td>
<td>73 (65.6)</td>
<td>75 (65.6)</td>
</tr>
<tr>
<td>Cotreatment and use of Amiodarone</td>
<td>74 (66.2)</td>
<td>74 (65.6)</td>
</tr>
<tr>
<td>Use of other drugs</td>
<td>74 (65.6)</td>
<td>74 (65.6)</td>
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<td>NYHA Class I/II</td>
<td>74 (66.2)</td>
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CV hospitalization at 1 year follow-up

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<tr>
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<td>75 (64.4)</td>
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<tr>
<td>Other</td>
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<td>74 (65.6)</td>
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<tr>
<td>NYHA Class V</td>
<td>74 (66.2)</td>
<td>74 (65.6)</td>
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</table>
Survival at follow-up men vs. women (univariate analysis)

![Graph showing survival at follow-up men vs. women.]

Survival at follow-up CRT-D vs. CRT-P (univariate analysis)

![Graph showing survival at follow-up CRT-D vs. CRT-P.]

Survival at follow-up SR or other vs. AF (univariate analysis)

![Graph showing survival at follow-up SR or other vs. AF.]

Survival at follow-up for QRS durations (univariate analysis)

![Graph showing survival at follow-up for QRS durations.]

Selected variables for CRT-D and CRT-P recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>CRT-D</th>
<th>CRT-P</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (yrs, median)</td>
<td>68 (61-74)</td>
<td>75 (68-80)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>396 (23)</td>
<td>337 (52)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RBBB</td>
<td>363 (21)</td>
<td>194 (30)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130</td>
<td>269 (18)</td>
<td>75 (8)</td>
<td>0.37</td>
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<tr>
<td>130 - 160</td>
<td>450 (30)</td>
<td>137 (30)</td>
<td>0.82</td>
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<tr>
<td>160-180</td>
<td>493 (33)</td>
<td>155 (33)</td>
<td>0.86</td>
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<tr>
<td>&gt;180</td>
<td>277 (19)</td>
<td>95 (21)</td>
<td>0.35</td>
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<tr>
<td>Previous VT/sustained VT</td>
<td>295 (20)</td>
<td>15 (2)</td>
<td>&lt; 0.0001</td>
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Selected variables for atrial fibrillation and sinus rhythm or other

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<th>Atrial fibrillation</th>
<th>Sinus rhy. or other</th>
<th>P-value</th>
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<tbody>
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<td>Age (yrs, median)</td>
<td>71 (65-77)</td>
<td>69 (61-76)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>112 (21)</td>
<td>44 (23)</td>
<td>0.06</td>
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<tr>
<td>RBBB</td>
<td>50 (9)</td>
<td>104 (6)</td>
<td>&lt; 0.01</td>
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<tr>
<td>QRS duration (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130</td>
<td>82 (22)</td>
<td>261 (16)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>130 - 160</td>
<td>107 (28)</td>
<td>486 (31)</td>
<td>0.38</td>
</tr>
<tr>
<td>160-180</td>
<td>111 (29)</td>
<td>538 (34)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt;180</td>
<td>80 (20)</td>
<td>294 (19)</td>
<td>0.44</td>
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Device type

<table>
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<tr>
<th>CRT-D</th>
<th>CRT-P</th>
</tr>
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<tbody>
<tr>
<td>338 (62)</td>
<td>340 (75)</td>
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Factors associated with death (multivariate analysis)

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<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
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<tr>
<td>NYHA III-IV</td>
<td>1.91</td>
<td>(1.16-3.37)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.81</td>
<td>(1.24-2.66)</td>
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<td>Ischaemic aetiology</td>
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<td>(1.32-2.34)</td>
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<td>1.65</td>
<td>(1.17-2.44)</td>
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<tr>
<td>Age groups</td>
<td>1.05</td>
<td>(0.88-1.29)</td>
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<tr>
<td>QRS durations</td>
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<tr>
<td>Women</td>
<td>0.63</td>
<td>(0.39-1.02)</td>
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Selected variables for ischaemic and non-ischaemic aetiology

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<th>Non-ischaemic</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (yrs, median)</td>
<td>71 (65-77)</td>
<td>68 (60-75)</td>
</tr>
<tr>
<td>Women</td>
<td>168 (15)</td>
<td>3.39 (2.2)</td>
</tr>
<tr>
<td>QRS duration (msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130</td>
<td>188 (20)</td>
<td>1.32 (1.6)</td>
</tr>
<tr>
<td>130 - 160</td>
<td>282 (30)</td>
<td>1.21 (2.8)</td>
</tr>
<tr>
<td>160-180</td>
<td>286 (31)</td>
<td>3.04 (6.6)</td>
</tr>
<tr>
<td>&gt;180</td>
<td>175 (19)</td>
<td>1.72 (2.0)</td>
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Device type

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<td>6.71 (6.3)</td>
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<tr>
<td>251 (23)</td>
<td>3.91 (3.7)</td>
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Factors associated with CV hospitalization (multivariate analysis)

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p-values</th>
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<tbody>
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<td>NYHA III-IV</td>
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<td>0.0017</td>
</tr>
<tr>
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<td>(1.12-2.09)</td>
<td>0.0073</td>
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<td>Ischemic etiology</td>
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<td>(0.77-3.44)</td>
<td>0.3028</td>
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<tr>
<td>Device type: CRT-D</td>
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<td>(0.69-1.31)</td>
<td>0.7945</td>
</tr>
<tr>
<td>Age groups</td>
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<td>0.6750</td>
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<tr>
<td>QRS duration</td>
<td>1.05</td>
<td>(0.82-1.38)</td>
<td>0.5384</td>
</tr>
<tr>
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<td>0.71</td>
<td>(0.51-1.03)</td>
<td>0.0476</td>
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Factors associated with death or CV hospitalization (multivariate analysis)

<table>
<thead>
<tr>
<th>Variables</th>
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<td>Ischemic etiology</td>
<td>1.23</td>
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<tr>
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<td>QRS duration</td>
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<tr>
<td>Women</td>
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<td>(0.50-0.90)</td>
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**Forest-plot of OR**

**Patient Self- Reported Global Assessment**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Number</th>
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<tbody>
<tr>
<td>Much better</td>
<td>44</td>
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<tr>
<td>A little better</td>
<td>27</td>
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<tr>
<td>No change</td>
<td>16</td>
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<tr>
<td>A little worse</td>
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<td>Worse/bad</td>
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**Comparison with RCT’s**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>COMPARISON</th>
<th>COMPARISON</th>
<th>COMPARISON</th>
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<th>COMPARISON</th>
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<tr>
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<td>1.78</td>
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<tr>
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<td>0.00</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
<tr>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
<td>QRS duration (ms)</td>
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<td>143.0</td>
<td>143.0</td>
<td>143.0</td>
<td>143.0</td>
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<tr>
<td>Mean ECG</td>
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<td>22.8</td>
<td>22.8</td>
<td>22.8</td>
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<td>1.79</td>
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<td>1.79</td>
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<tr>
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<td>0.50</td>
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<tr>
<td>Age (years)</td>
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<td>65.7</td>
<td>65.7</td>
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</tr>
<tr>
<td>Previous device</td>
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<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
<td>1.79</td>
</tr>
</tbody>
</table>

**NYHA functional class shift pre-implantation to follow up**

<table>
<thead>
<tr>
<th>Class</th>
<th>Pre-implant</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>NYHA II</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Device related complications during 1 year (9-15 months)**

<table>
<thead>
<tr>
<th>Complication</th>
<th>(n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device related complications</td>
<td>170    (10.3)</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>55     (3.3)</td>
</tr>
<tr>
<td>Lead malfunction</td>
<td>13     (0.8)</td>
</tr>
<tr>
<td>Device related arrhythmias</td>
<td>18     (1.1)</td>
</tr>
<tr>
<td>Phrenic nerve stimulation</td>
<td>51     (3.1)</td>
</tr>
<tr>
<td>Device replacement</td>
<td>6      (0.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>27     (1.6)</td>
</tr>
</tbody>
</table>

**Limitations**

- Selection bias - consecutive successful inclusions
- Investigator bias
- Centre participation was voluntary
- Variation regarding number of patients/centres
- Short length of follow-up
- 87% follow-up
- No information on patients—screened but not implanted—unsatisfactory attempts
Conclusions

- 81% of patients report symptom improvement (self-assessed)
- Over all survival is more than 90%
- Benefits of CRT observed in RCTs can be replicated in routine clinical practice
- Further randomized trials are needed in patients with AF and narrow QRS durations

Acknowledgements

- Heart Failure Association of the ESC
- European Heart Rhythm Association of the ESC
- Stavanger University Hospital, Norway
- EUcomed
- Roche Diagnostics Ltd.
- The ESC web department
- Tessa Baak, Florian Schulz, Claus Jünger, Morten Aarflot

List of c.

...
“Seventy is old enough. After that there is too much risk”

Mark Ty

Following the Equator
Harford, Connecticut: American Publishing Inc 1897
Cumulative rate of the primary endpoint and its components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Death Aggressive (n=193)</th>
<th>Initially Conservative (n=193)</th>
<th>HR (95% CI)</th>
<th>Logrank P</th>
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</thead>
<tbody>
<tr>
<td>Primary EF</td>
<td>41 (21.9)</td>
<td>55 (28.6)</td>
<td>0.80 (0.53-1.19)</td>
<td>0.26</td>
</tr>
<tr>
<td>Death CV, non-CV</td>
<td>19 (12.3)</td>
<td>16 (10.4)</td>
<td>1.04 (0.69-1.56)</td>
<td>0.65</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>11 (7.1)</td>
<td>17 (10.7)</td>
<td>0.70 (0.53-1.16)</td>
<td>0.27</td>
</tr>
<tr>
<td>Rehospitalization for CV, non-CV bleeding</td>
<td>18 (11.7)</td>
<td>22 (13.6)</td>
<td>0.81 (0.55-1.16)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

**All cause death**

**Myocardial infarction**

**Rehospitalization for cardiovascular causes or severe bleeding**

Kaplan Meier survival without primary endpoint according to troponin status at trial entry

Effect of treatment strategy according to troponin status at trial entry

Normal troponin (N=115)

Elevated troponin (N=10)

Date: 20 Aug.
Conclusions

In elderly patients with NSTE-ACS and no emergency indication for coronary angiography, a systematic early aggressive approach confers significant benefits only in those with elevated troponin levels on admission.

Coronary revascularization using preferentially the radial approach and a moderate use of i.v. antithrombotic agents is extremely safe in patients who don’t have severe renal dysfunction or recent bleeding.

Why does the implantable cardioverter-defibrillator not improve mortality early after myocardial infarction? Insights from the IRIS trial

Discusant
C. Leclercq
Service de Cardiologie
Centre Cardio-Pneumologique
Rennes, France

Rationale of the problem?

- Current guidelines for ICD implantation for primary prevention exclude patients with recent myocardial infarction, i.e. within the first 48 days (ESC, ACC, AHA and HRS guidelines).
- Patients after a recent MI have a high risk of SCD

Summary of the 2011 IRIS results

✓ ICD reduces SCD only within the 2 first years
✓ Higher MCS mortality with ICD especially after 3 years
✓ Age, multi-vessel disease, wide QRS, NYHA IV, low LVEF and non optimal medical treatment are independent predictors of mortality. (MADIT, SCD-Heft, and DINAMIT)
✓ No efficacy of ICD to reduce SCD in patients without reperfusion but only 91 patients …and these patients were excluded because of the divergence of the results with the other populations…???
✓ RV pacing increase mortality (back of data in IRIS trial)
✓ Appropriate therapies were associated with an increase in mortality especially non SCD (MADIT, SCD-Heft, COMPANION…, and DINAMIT)

Presenter Disclosure Information

Christophe Leclercq, MD, PhD

FINANCIAL DISCLOSURE:
Research Grants: Boston Scientific, Medtronic, Sorin Group, St. Jude Medical,
Consulting/Advisory board: Boston Scientific, Biostere, Medtronic, St. Jude Medical, Sorin Group
Lectures: Boston Scientific, Biostere, Medtronic, St. Jude Medical, Sorin Group, GE
Stock Options: None; Salary Support: None; Speaker Bureau: None

Role of appropriate therapies

• Secondary analysis of the DINAMIT trial using a competitive-risk analysis and an adjusted time-dependent analysis
• 3 groups: no ICD; ICD without appropriate ICD therapy (AT) and ICD with AT
• Patients with AT had a > 2-fold increase in all cause mortality especially in non arrhythmic mortality
  - Same LVEF, same acute reperfusion rate for the 3 groups but less PTCA in the AT group
  - Patients with AT had more MI before the index infarct, more NSVT, more HF before randomization and less 3-blocker.
  - More intercurrent clinical events after randomization
  - UA or MI: 32% versus 16% (No AT) and 23% (control)
  - New HF: 44% versus 21 and 26%
Complexity of the problem

- Ventricular arrhythmias may enhance cardiac deterioration and increase risk of death
- An inurceunt cardiac event may cause VA
- Therapy (shocks) may directly or indirectly increase mortality (importance of the programming of ATP)

- So why does not the ICD early implanted after MI reduce total mortality; so far no answer....
- No evidence to support changes in the guidelines

Biventricular Pacing Superior to Right Ventricular Pacing in Brachyarrhythmia Patients with Preserved Systolic Function: Two-year Results of PACE


Pace study

Steering Committee:
- C.M. Yu, G.W.K. Yip, Q. Zhang, J.Y.S. Chan, The Chinese University of Hong Kong; J.W.H. Fung, North District Hospital; O. Razali, National Heart Institute

Electrophysiology Core Laboratory:
- G.W.K. Yip, C.M. Yu, Q. Zhang, F. Fang, The Chinese University of Hong Kong

Clinical Event Committee:
- W. Chen, A. Chan, The Chinese University of Hong Kong; W.L. Chan, Alice Ho Miu Ling Nethersole Hospital

Other investigators and institutions that participated in the PACE study:

Background

Right ventricular apical (RVA) pacing

- Non-physiologica1 pacing leads to dysynchronous contraction
- Exerts deleterious effect with high RVA pacing on:
  - Left ventricular systolic & diastolic function
  - LV adverse structural remodeling
  - Adverse clinical outcomes
- Solution: reduction of the pacing percentage to minimize the harmful impact
- Impossible for those with high degree of heart block

Biventricular (BIV) pacing

- Attenuation the dysynchronous contraction
- Preserve left ventricular function
- Avoid the left ventricular remodeling
**Biventricular Pacing in Patients with Bradyarrhythmia and Normal Ejection Fraction**

**Patients Selection**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with normal LV ejection fraction (≥ 40%)</td>
<td>Persistent atrial fibrillation</td>
</tr>
<tr>
<td>With standard pacing indications</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td></td>
<td>Percutaneous coronary intervention or CABG &lt; 6 months</td>
</tr>
<tr>
<td></td>
<td>Life expectancy of &lt; 6 months</td>
</tr>
<tr>
<td></td>
<td>Heart transplant recipients</td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
</tr>
</tbody>
</table>

**Assessment**

- **Echocardiography**
  - Real-time 3-dimensional echocardiography (IE33 & G-Lab 7.0, Philips, Andover, MA)
  - LV volumes and ejection fraction: dyssynchrony index
  - Off-line analysis blinded to treatment and clinical data
  - Intra- and inter- observer variability: 3.6 ± 4.3% (ejection fraction), 1.7 ± 0.9% (LV volume)

- **Clinical data**
  - Blinded to treatment and echocardiographic data
  - 6-min walk distance
  - Quality of life scores (SF-36 health survey questionnaires)

- **Time point**
  - Baseline, 1 month, 6, 9, 12, 18 and 24 months

**Study End-points**

- **Co-Primary End-points**
  - LV ejection fraction
  - LV end-systolic volume

- **Secondary End-points**
  - LV end-diastolic volume
  - 6-min walk distance
  - Quality of life scores

**Statistical Analysis**

- Statistical analysis of end points at 2-year
  - Intention-to-treat: patients with >3 months follow up were included
  - For drop outs: analyzed by last-observation-carried-forward principle
  - Repeat measurement analysis: differences in end-point among time intervals of baseline, first and second year
  - General Liner Model: potential interaction of clinical factors on primary end-points
**BIV pacing, preservation of LV function and remodeling**

- EF = 62.4%
- ESV = 31.2 ml

**RVA pacing, progression of LV function and remodeling**

- EF = 76.9%
- ESV = 11.2 ml

**Discussion**

**Major findings in the study**

- The extended 2-year follow-up: deterministic effect of a high percentage of RVA pacing on LV function and adverse remodelling observed after 1st year continued to progress in a 2nd year.
- Reduction in LVEF and increase in LVEF in the RVA pacing group were more dramatic at 1st year, a smaller amplitude but significant worsening was observed at 2nd year.
- The change in LVEF and LVEF corresponds to the increase in Dyssynchrony Index (DyI) in the RVA pacing group. DyI only increased in the RVA group, but was unchanged in the BIV group.
- The PACE study was the first randomized study to show BIV pacing prevents against the adverse effects of RVA pacing on LV structure and function, and the current extended follow up demonstrates that the protective effect persists for 2 years.

**Adverse Remodelling**

- A maladaptive process involving structural, haemodynamic, histopathological, and genetic changes.
- If progressive, leads to further deterioration of LV function, LV dilatation, and eventually the typical symptoms of heart failure.
- RV pacing results in substantial widening of the QRS complex and induces both inter- and intraventricular dyssynchrony.

**Primary End-points**

- BIV pacing
- RVA pacing

**Systolic Dyssynchrony**

- 3IV pacing group
- RV pacing group

**PACE 2 year follow up results:** Now available online in “European Heart Journal”

Chan JYS ... Yu CM. Eur Heart J 2011

- The 2-year follow-up in the Pacing to Avoid Cardiac Enlargement (PACE) trial confirms that chronic RV pacing in patients with bradycardia and preserved LV function leads to sustained and progressive deterioration of LVEF and increases in LV volumes.

- This adverse remodelling process was prevented by pacing with cardiac resynchronization.
**Recommendations in patients with heart failure and a concomitant class I pacemaker indication**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Patient Population</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P/CRT-D*</td>
<td>NYHA functional class III/IV, LVEF &lt;30%, QRS width ≥120 ms</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>CRT-P/CRT-D*</td>
<td>NYHA functional class III, LVEF &lt;30%</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>CRT-P/CRT-D*</td>
<td>NYHA functional class I/II, LVEF &lt;50%, QRS width ≥120 ms</td>
<td>IIIb</td>
<td>D</td>
</tr>
</tbody>
</table>

* Reasonable expectation of survival with good functional status for >1 year for CRT-D. Patient with a secondary prevention indication for an ICD should receive a CRT-D.

---

**Key points:**

- In patients with a conventional indication for pacing, NYHA III/IV symptoms, LVEF ≤35%, QRS width ≥120 ms, a CRT-P/CRT-D is indicated.
- RV pacing will induce dyssynchrony.
- Chronic RV pacing in patients with LV dysfunction should be avoided.
- CRT may permit adequate up-titration of beta-blocker treatment.

---

**Response to CRT in primary and CRT upgrade recipients with HF**

- **NYHA Change**
  - **upgrade vs. de-novo**

- The CRT Survey suggests that there are no clinically important differences in demographics, procedural details, outcomes or complication rates between upgrades and de-novo procedures to CRT.

---

**The European CRT Survey: Upgrades from a PPM or ICD to a CRT-P or CRT-D**

- **2367 patients in this analysis**
- **1675 de-novo implantations**
- **692 upgrades**

---

**Survival:**

- **Upgrades vs. de novo (n=2367)**

---

**Issues**

- No between-group difference on 6 minute walk distance or the quality-of-life tool (SF-36 score). However, these patients did not have notably symptomatic HF or reduced EF.
- RV pacing in patients with sinus node dysfunction without AV block is not required and may have resulted in avoidable adverse remodelling in these patients.
**Issues**

- There is some non-trivial, added morbidity associated with CRT implantation as compared with RV pacing, especially with inexperienced operators.

- What amount of benefit would justify the modest increased risk at implantation as well as the increased costs of a device with shorter longevity?

**Clinical Implications**

- What type of device will you implant in your next patient with bradycardia, expectation of pacemaker dependency and a preserved EF?

- Will you only upgrade to a CRT when there is evidence of adverse remodelling on RV pacing?

- What about patients with HF and preserved EF (HFPEF)-requiring a pacemaker?

**Today's EHJ publications**

"Biventricular pacing is superior to right ventricular pacing in bradycardia patients with preserved systolic function: 2-year results of the PACE trial"
Chan et al., Eur Heart J doi:10.1093/eurheartj/ehr336

"Chronic right ventricular pacing, adverse remodelling, and CRT: an ounce of prevention?"
Dickstein Eur Heart J doi:10.1093/eurheartj/ehr337

**Bottom Line**

- Will CRT in patients with bradycardia and preserved systolic function translate into prevention of meaningful adverse endpoints such as survival or hospitalization for HF?

- If so, it becomes a good investment. Benjamin Franklin put it well: "An ounce of prevention is worth a pound of cure."

- In this case, it’s about 2 ounces...

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RV pacing (no.)</th>
<th>RV pacing (no.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex – no. (%)</td>
<td>49 (94)</td>
<td>48 (96)</td>
<td>0.70</td>
</tr>
<tr>
<td>Systolic blood pressure – mean</td>
<td>120 (13)</td>
<td>120 (13)</td>
<td>0.06</td>
</tr>
<tr>
<td>CRT indication – min</td>
<td>107 (12)</td>
<td>107 (12)</td>
<td>0.98</td>
</tr>
<tr>
<td>Indication for pacing – no. (%)</td>
<td>53 (10)</td>
<td>53 (10)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean mode diastolic</td>
<td>50 (9)</td>
<td>50 (9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (10)</td>
<td>62 (12)</td>
<td>0.24</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>24 (48)</td>
<td>13 (26)</td>
<td>0.71</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

**Subgroup Analysis – LV Ejection Fraction**

**Subgroup Analysis – LV End-Systolic Volume**
Comparison of Secondary End-points

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RVA pacing</th>
<th>BIV pacing</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event free RVR</td>
<td>Baseline</td>
<td>122/122</td>
<td>122/122</td>
</tr>
<tr>
<td>Event free RVR</td>
<td>1 month</td>
<td>122/122</td>
<td>122/122</td>
</tr>
<tr>
<td>Event free RVR</td>
<td>12 months</td>
<td>122/122</td>
<td>122/122</td>
</tr>
<tr>
<td>BP ≥ 90 mmHg</td>
<td>Baseline</td>
<td>66/122</td>
<td>66/122</td>
</tr>
<tr>
<td>BP ≥ 90 mmHg</td>
<td>1 month</td>
<td>66/122</td>
<td>66/122</td>
</tr>
<tr>
<td>BP ≥ 90 mmHg</td>
<td>12 months</td>
<td>66/122</td>
<td>66/122</td>
</tr>
</tbody>
</table>

Heart failure hospitalization

Comparison with RCTs

<table>
<thead>
<tr>
<th>Previous device</th>
<th>CARE-HF</th>
<th>REVERSE</th>
<th>CRT Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motion (%)</td>
<td>22</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>LV systolic function (%)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>LV diastolic diameter (mm)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aldosterone antagonists (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pre-implantation Data

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 (%)</td>
<td>31</td>
</tr>
<tr>
<td>Heart failure etiology (%)</td>
<td>51</td>
</tr>
<tr>
<td>Past stroke (%)</td>
<td>7</td>
</tr>
<tr>
<td>Prior device (PPM, ICD)</td>
<td>28</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>24</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>23</td>
</tr>
<tr>
<td>QRS complex</td>
<td>24</td>
</tr>
<tr>
<td>Pwave (% of patients)</td>
<td>19</td>
</tr>
<tr>
<td>QRS duration (%)</td>
<td>10</td>
</tr>
</tbody>
</table>

BIV pacing, preservation of LV function and remodeling

*Previous device implantation and atrial fibrillation were exclusion criteria.
**Background**

- Cardiac remodeling is central to the pathophysiology of heart failure (HF) and is a prognostic factor in patients with HF.
- Left ventricular (LV) enlargement and reduced ejection fraction are powerful predictors of outcomes in heart failure.
- Therapeutic effects of drugs and devices on LV remodeling are associated with their longer-term effects on mortality.
- It is therefore relevant to evaluate the impact of HF therapies on cardiac remodeling.

**Objective of the pre-specified echocardiography sub-study**

To evaluate the effects of the β-blocker ivabradine on LV remodeling and function:

- **Primary endpoint**: the change in the LV end-systolic volume index (LVESV) from baseline to 8 months.
- **Secondary endpoints**: changes during the same interval in:
  - LV end-diastolic volume index (LVEDVI)
  - LV end-systolic, and diastolic volumes (LVESV, LVEDV)
  - LV ejection fraction (LVEF).

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ivabradine N=304</th>
<th>Placebo N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Male, %</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Mean HF duration, years</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HF ischemic cause, %</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>NYHA class II, %</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Mean LVEF, %</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Mean HR, bpm</td>
<td>75</td>
<td>79</td>
</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>121</td>
<td>119</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>


**Limitations**

- Analysis not designed to clarify the time-course of treatment effects and could not evaluate the acute effect of ivabradine.
- The beta-blocker dosage was similar to other recently published data but higher doses can affect LVEF.
- Data recorded in patients with HR ≥ 70 bpm, in sinus rhythm and predominance in men, which may limit generalisation.
- One third of patients were excluded from the analysis; usually for reasons related to the quality or collection of recordings.

**Conclusions**

- Ivabradine reverses left ventricular remodelling in patients with heart failure and LV systolic dysfunction.
- Marked reductions of LV volumes.
- Significant improvement of LVEF.
- These results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy.

**Available now online**

**European Heart Journal**

**Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function results from the SHIFT echocardiography substudy**

Jean-Claude Thriel*, Eline O'Meara†, Michel Komajda†, Michael Böhm‡, Jeffrey S. Buenø, Ian Ford, Luigi Tavazzi*, and Karl Swedberg†, on behalf of the SHIFT Investigators.

---

**The Role of Ventricular Electrical Delay to Predict Left Ventricular Remodeling With Cardiac Resynchronization Therapy**

*a SMART AV substudy*

By M Gold et al

Discusant

Cecilia Linde

Karolinska University Hospital

Stockholm

**Declaration of potential conflicts of interest**

- Research grants
  - The Swedish Heart-Lung Foundation, Medtronic
- Principal Investigator
  - REVERSE
- Member of DSMB
  - Biopace

**Rationale for SMART AV substudy**

**The question – will addition of**

Drug refractory symptoms +

Electrical dyssynchrony +

CRT +

QLV

Improve the response rate to CRT treatment >60%?

**Efforts to enhance response to CRT**

**Patient selection**

Mechanical dyssynchrony failed in PROSPECT

QRS width & LBBB

**Optimization of CRT**

failed in SMART AV

**Tailoring of LV lead position**

to areas of latest activation by QLV

→ The SMART AV substudy
Results: CRT Response at 6 months by QLV Quantiles in 426/968 pts w/NYHA III/IV HF, LVEF 20%, QRS 151 ms

Highest vs lowest Q increased LVEF response from 39 to 68%
IMR in Candidates for CABG and Low EF

Findings:
- Moderate and severe IMR are frequent (18%) in patients with low EF, considered for CABG.
- Patients with significant IMR have worse presenting characteristics (higher NYHA class III/IV, lower LVEF, larger LVESV, higher estimated operative risk).

Remarks:
- Limitations in the assessment of severity of MR (absence of Coats, integrative quantification?).

Merging moderate and severe MR is unusual.

Patients with Moderate/Severe MR undergoing CABG+/- MVR

- 91 Pts. 49 underwent MVR.
- Patients who underwent MVR had:
  - More pre-op, PCI, worse LVEF, larger LVESV, and NYHA class.
  - More complicated post-operative outcome.
  - Burr only 2% operative mortality.

Patients with Moderate/Severe MR undergoing CABG+/- MVR

Remarks:
- Decision of MVR left to the operator.
- Possibility of heterogeneity in repair techniques.
- Limitations in design: No RCT, no Multivariate analysis.
- Lack of information on residual MR, re-hospitalisations.

What is Needed to Improve the Evidence on Usefulness of MVR in Ischemic MR?

- Dedicated RCT.
- Improvement of pre-operative evaluation.
  - Comprehensive quantification of MR at rest and dynamic.
  - Identification of predictors of recurrence of MR.
  - Myocardial viability.
- Evaluation of techniques.
  - Annuloplasty, including dynamic components.
  - LV « remodelling ».
  - Percutaneous techniques.
Comparison of Three-year Outcome after PCI and CABG in Triple Vessel Coronary Artery Disease
Stratified analysis by the SYNTAX Score

CREDO-Kyoto PCI/CABG Registry Cohort-2

Hiroshi Shiono, Junichi Tsuzuki, Takeshi Morimatsu, Tsukasa Funakawa, and Takeshi Kimura

on behalf of the CREDO Kyot PCI/CABG registry cohort-2 investigators.

Department of Cardiology, Graduate School of Medicine, Kyushu University
Pharmaceuticals and Medical Devices Agency (PMDA)
Research Institute for Production of Development

Background

- Three-year results from the SYNTAX trial showed that excess risk of PCI relative to CABG was significant in terms of all-cause death and a composite of Death/MI/Stroke in the triple vessel disease subset.

CREDO-Kyoto PCI / CABG Registry Cohort-2

<table>
<thead>
<tr>
<th>PCI arm</th>
<th>total: 1301 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG arm</td>
<td>total: 2116 patients</td>
</tr>
</tbody>
</table>

- Consecutive Patients Undergoing First Coronary Revascularization
- During January, 2005 and December, 2007 after approval of DES in Japan
- Multi-center Registry among 26 centers in Japan

CREDO-Kyoto PCI/CABG Registry Cohort-2 Participating 26 centers and Investigators:

<table>
<thead>
<tr>
<th>Center</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaman General Hospital</td>
<td>Shintaro Ito</td>
</tr>
<tr>
<td>Kibunai City Hospital</td>
<td>Hideki Okuyama, Hideki Shimazu</td>
</tr>
<tr>
<td>Kyushu University Hospital</td>
<td>Takeshi Kimura, Tatsuya Akiyama, Akiko Hori</td>
</tr>
<tr>
<td>Nishin Hospital, Tohoku University School of Medicine</td>
<td>Masahiro Shimizu, Masao Ishibashi</td>
</tr>
<tr>
<td>Kagoshima University Hospital</td>
<td>Katsuo Takeshi, Hiroshi Takeda</td>
</tr>
<tr>
<td>Matsuyama General Hospital</td>
<td>Shigeru Kato, Wataru Kato</td>
</tr>
<tr>
<td>Shiga University of Medical Science</td>
<td>Toshinori Kimura, Hiroshi Takeda</td>
</tr>
<tr>
<td>Kanazawa University Medical and Pharmaceutical</td>
<td>Hiroshi Takeda</td>
</tr>
<tr>
<td>Saitama University Saitama Medical</td>
<td>Hiroshi Takeda</td>
</tr>
<tr>
<td>Kofu City General Hospital</td>
<td>Kenji Kato, Tatsuya Kaneko</td>
</tr>
<tr>
<td>Saitama Medical Center</td>
<td>Hiroshi Takeda, Hiroharu Tanaka</td>
</tr>
</tbody>
</table>

Study Flow Chart

CREDO-Kyoto PCI/CABG Registry Cohort II
PCI Arm: 1821 patients, CABG Arm: 2116 patients

AM (P=0.002)
PCI: 4/28 PCI, CABG: 10/1

Single or Double vessel disease (P=0.037)
PCI: 5/8 PCI, CABG: 20/20

Left Main disease (P=0.005)
PCI: 7/8 PCI, CABG: 40/2

Current Study Population
Triple vessel disease: 29/21 patients

P CI Arm: 13/21 patients
CABG Arm: 15/21 patients

CREDO-KyOTO PCI/CABG Registry Cohort-2

Funding Source
Pharmaceuticals and Medical Devices Agency in Japan

Disclosures
Hiroshi Shiono: Nothing to disclose

Friedrich W. Meier et al. ISCT 2010
Primary Outcome Measure
- Composite of Death, MI and Stroke

Secondary Outcome Measures
- Death
- Cardiac Death
- MI
- Stroke
- Any Coronary Revascularization

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>162</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68.7±0.9</td>
<td>68.0±0.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age &lt;= 75 years</td>
<td>44 (35%)</td>
<td>47 (35%)</td>
<td>.81</td>
</tr>
<tr>
<td>Male</td>
<td>129 (79%)</td>
<td>126 (80%)</td>
<td>.66</td>
</tr>
<tr>
<td>BMI</td>
<td>23.3±3.6</td>
<td>23.5±3.1</td>
<td>.005</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>14 (10%)</td>
<td>16 (10%)</td>
<td>.23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (11%)</td>
<td>17 (11%)</td>
<td>.61</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (15%)</td>
<td>34 (22%)</td>
<td>.032</td>
</tr>
<tr>
<td>on insulin therapy</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>40 (25%)</td>
<td>33 (21%)</td>
<td>.52</td>
</tr>
<tr>
<td>Heart failure</td>
<td>77 (48%)</td>
<td>74 (47%)</td>
<td>.5</td>
</tr>
</tbody>
</table>

Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of target lesion or anastomosis</td>
<td>2.05 (1.0-2.3)</td>
<td>1.44 (1.0-2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Target of proximal LAD</td>
<td>1.71 (1.0-2.7)</td>
<td>1.32 (0.9-2.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Target of CTO</td>
<td>1.16 (0.9-1.4)</td>
<td>1.02 (0.8-1.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Target of bifurcation</td>
<td>2.5 (1.3-4.1)</td>
<td>3.1 (1.2-3.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Emergency procedure</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>.41</td>
</tr>
<tr>
<td>Total number of stents</td>
<td>2.81 (1.4-5.2)</td>
<td>2.6 (1.2-5.3)</td>
<td>.28</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>3.4 (1.8-5.6)</td>
<td>3.1 (1.7-5.5)</td>
<td>.66</td>
</tr>
<tr>
<td>Silent use</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>.78</td>
</tr>
<tr>
<td>DES use</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>.55</td>
</tr>
<tr>
<td>IRA use</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>.55</td>
</tr>
<tr>
<td>Off pump</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (0.8-1.2)</td>
<td>.55</td>
</tr>
</tbody>
</table>

All-cause Death

Cardiac Death

Myocardial Infarction
Stratified Analysis by the SYNTAX Score

- The SYNTAX score was calculated by the dedicated SYNTAX score committee.
- All analysis were conducted in a blinded fashion to the clinical data.

SYNTAX Score Distribution

- The SYNTAX score calculation
  - PCI Arm: 1425 patients
  - CAGB Arm: 156 patients
  - SYNTAX score available:
    - PCI Arm: 1797 (97.9%)
    - CAGB Arm: 1184 (91.9%)
  - Mean score: PCI Arm: 23.9 ± 10.2
  - Mean score: CAGB Arm: 30.0 ± 12.3

Crate analysis

- Low SYNTAX Score (<23):
  - Unadjusted HR (95% CI): 1.26 (0.98-1.62)

- Intermediate SYNTAX Score (23 ≤ <33):
  - Unadjusted HR (95% CI): 1.31 (1.08-1.60)

- High SYNTAX Score (>33):
  - Unadjusted HR (95% CI): 1.48 (1.18-2.38)

Adjusted analysis

- Low SYNTAX Score (<23):
  - Adjusted HR (95% CI): 1.46 (1.04-2.05)

- Intermediate SYNTAX Score (23 ≤ <33):
  - Adjusted HR (95% CI): 1.24 (0.83-1.85)

- High SYNTAX Score (>33):
  - Adjusted HR (95% CI): 1.39 (0.998-2.54)

Summary

- Consistent with the observation in the SYNTAX randomized trial, PCI, as compared with CAGB, was associated with significantly higher risk for serious adverse events in patients with TVD.

- The excessive mortality in the PCI group was mostly driven by the excess of non-cardiac death, while the risk for cardiac death was similar between PCI and CAGB.

- Protective effect of CAGB for myocardial infarction was particularly remarkable.
**Summary**

- Clinical outcome after PCI was adversely influenced by the increasing SYNTAX scores, while outcome after CABG was not affected by complexity of coronary anatomy.

- Unadjusted risk for serious adverse events was not significantly different between PCI and CABG in the SYNTAX score low and intermediate sextiles.

- However, adjusted analysis suggested that PCI as compared with CABG was associated with significantly higher risk for serious adverse events even in patients with low SYNTAX score tertile.

**Conclusions**

- CABG would still remain the standard treatment option in patients with TVD, particularly when their SYNTAX scores are high.

- Use of PCI in patients with high SYNTAX score should be seriously discouraged unless the operative risk is prohibitively high.

- Selection of revascularization strategies in TVD patients with less complex coronary anatomy deserves further consideration.

**Safety and Effectiveness of ICD Follow-up using Remote Monitoring**

**ECOST Study**

Salene Yacoub, Lawrence Guellid-Moreau
On behalf of the ECOST Study Investigators

**Background**

- The implant rate for ICD in the prevention of Sudden Cardiac Death has reached 120,000 per year in Europe.
- The potential to reduce ICD follow-up to increase patient safety and convenience.
- The need for local clinical studies.
- Remote follow-up of ICDs (TRUST) has been demonstrated to reduce the number of inpatient device F/U, without increasing death, strokes and ICD related AE requiring surgical interventions.

**Home Monitoring system**

- HM allows the transmission of diagnostic data from the ICD to the physician by:
  - Communication by radiofrequency transmitting circuitry integrated in the ICD
  - Data reception by the service center and generation of a charting report accessible online by the physician via a secure internet access.

**Primary Hypothesis**

- We hypothesized that ICD follow-up with Home Monitoring would be safe and cost-effective when compared with standard ambulatory follow-up.

**Secondary Hypothesis**

- Objective: Evaluation of the effectiveness of Home Monitoring on:
  - Inappropriate therapies
  - Number of ICD charges

- Objective: Cost of Care in ICD recipients (not available)
Study Design

- Designed to detect the non-inferiority in the primary end point:
  - 80% power
  - 1% significance level
  - Sample size requirement of 450 patients

- Randomized controlled trial
  Randomization on a 1:1 basis to:
  - Remote Monitoring Follow-up
  - In-Person Follow-up

Inclusion / Exclusion Criteria

Key Inclusion criteria:
- Trivialization or episode of dual chamber ICD (without CRT)

Key Exclusion criteria:
- NYHA class IV
- Preexisting heart or worse who plans to become pregnant during the trial
- Patient whose renal function is in question
- Presence of any disease, other than patient’s cardiac disease, associated with reduced life expectancy for the duration of the trial, e.g., cancer, cancer (tumor >30cm/3 or otherwise >3in/dia), liver failure, etc.
- Age < 15 years
- Patient unable to handle home monitoring system correctly
- Patient is not willing and able to comply with the protocol
- Change in residence expected during study
- Participation in another clinical study
- Patient unwilling to sign the consent for participation.

Population: Baseline Characteristics

<table>
<thead>
<tr>
<th>Non significant difference</th>
<th>ACTIVE</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>221</td>
<td>212</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (13.9)</td>
<td>67 (12.5)</td>
</tr>
<tr>
<td>Gender (male) (%)</td>
<td>67.3</td>
<td>80.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>34.7 (13.0)</td>
<td>32.7 (13.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 (13.8)</td>
<td>23.0 (12.1)</td>
</tr>
<tr>
<td>History of 5%</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Asthma (current) (%)</td>
<td>15.8 (7.1)</td>
<td>67.3 (33)</td>
</tr>
<tr>
<td>Primary prevention (%)</td>
<td>83.8</td>
<td>83.3</td>
</tr>
<tr>
<td>Dual chamber devices (%)</td>
<td>27.1</td>
<td>51.5</td>
</tr>
<tr>
<td>Post myocardial (%)</td>
<td>84.2</td>
<td>80.3</td>
</tr>
</tbody>
</table>

Primary End Point: Safety

- Monitoring follow-up associated with a non-inferiority in safety

Cumulative Survival free of MAE

<table>
<thead>
<tr>
<th>Procedure implant related MAE</th>
<th>ACTIVE</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Seizure</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Local edema</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>VF induction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15 MAE</td>
<td>11 MAE</td>
</tr>
</tbody>
</table>

Primary End Point by Component
Primary End Point by Component

Cardiovascular MAE

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE (n=223)</th>
<th>CONTROL (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Patients</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Electrical storms</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Supraventricular arrhythmia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>95 MAE</strong>*</td>
<td><strong>107 MAE</strong>*</td>
</tr>
</tbody>
</table>

Primary End Point by Component

Device related MAE

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE (n=223)</th>
<th>CONTROL (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Patients</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>related to VT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>related to VT</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>related to CAD</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Local dysfunction</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>without shock</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20 MAE</strong>*</td>
<td><strong>34 MAE</strong>*</td>
</tr>
</tbody>
</table>

Primary End Point: Effectiveness

Deaths

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE (n=223)</th>
<th>CONTROL (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Non cardiac</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20 (9.4%)</strong></td>
<td><strong>20 (9.4%)</strong></td>
</tr>
</tbody>
</table>

Secondary End Point: Effectiveness

Inappropriate Shocks (IS)

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE (n=223)</th>
<th>CONTROL (n=223)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>11 (5.0%)</td>
<td>22 (10.4%)</td>
<td>0.63</td>
</tr>
<tr>
<td>with IS</td>
<td>28</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>Mean per patient</td>
<td>2.5±2.2</td>
<td>1.9±2.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-9</td>
<td>1-17</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>3</td>
<td>11</td>
<td>0.02</td>
</tr>
<tr>
<td>hospitalized</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary End Point: Effectiveness

Charged shocks

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>charged shocks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>per patient</td>
<td>2.3±1.5</td>
<td>1.8±1.5</td>
</tr>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>72</td>
</tr>
</tbody>
</table>

Conclusions

- Device management of patients with ICD using Home Monitoring® system with daily telemetry is safe.
- It is not inferior to conventional In-person follow-up.
- Remote follow-up is significantly associated with:
  - Reduction of 52% in the number of patients with inappropriate shocks.
- Remote Monitoring might soon set a new gold standard of care for the EU of ICD recipients.

Steering Committee – S. Kacor (Chairman), L. Guédron-Moriceau, N. Canot
Endpoint Adjudication Committee – J. Clémenty, D. Lacroix, N. Scouet
Electrogram Analysis Core Laboratory – L. Guédron-Moriceau, X. Lechevère
Study Coordinator – S. Faurquiergue
Funding Source – Biotronik SE & Co. KG
Statistical Analysis Group – X. Bry, A. Gannec

Remote Monitoring of ICD Patients

Current clinical evidence from large scale RCT's: based on surrogate endpoints

- TRUST (N=1339 pts)
  Number of total in-office device evaluations
  Reduction by 45% without affecting safety
  Median time to evaluation: <2 vs 36 d (P<0.002)
- CONNECT (N=1997 pts)
  Time from clinical event to clinical decision
  Reduced from 22 to 4.6 d (P<0.001)
  Length of CV hospital stay: 3.36 vs 4.0d (P<0.002)

ECOST and EVATEL

First randomised trials with robust clinical Endpoints

- Nearly similar design, inclusion criteria and endpoints
- But, different objective:
  - Safety (MAE) > Efficiency in ECOST
  - Safety and efficiency (MCE) in EVATEL

ECOST and EVATEL

Global results

- ECOST: Home monitoring non-inferior to Standard care (In-clinic visits)
- EVATEL: Non-inferiority non validated;
  No significant difference between Telemonitoring and Standard care

ECOST and EVATEL

Concordant results:

As compared with Standard care
- Remote monitoring of ICD patients is clinically safe
- No clear evidence that RM can contribute to prevent major CV events (even if favorable trend in ECOST)
- Clear evidence that RM reduces the risk and number of inappropriate therapies: RRR=37-52%
- Significant reduction on charged shocks and total shocks with HM; possible impact on device longevity (ECOST)
- RM cost-effective? No clear response at that time
EMPHASIS-HF: The effect of eplerenone versus placebo on cardiovascular mortality or heart failure hospitalization in subjects with NYHA class II chronic systolic heart failure: An analysis of the high-risk groups

Barbara B. G., John J. McMurray, K.S. Henry Korn, M.A. B.P., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg M.D., Ph.D., Barry S. M., John Vincen M.B., B.Ch., Stuart J. Perko-Koosh, Ph.D., and Bertram Pitt, M.D., P.D. for the EMPHASIS-HF Committee and Investigators

Disclosure Information

- Fazel Zinnad
  - Grant/contracts, consultant (moderate)
- John J. McMurray
  - Grant/Contracts, consultant (moderate)
- Henry Korn
  - Grant/Contracts, consultant (moderate)
- Dirk J. Van Veldhuisen
  - Grant/Contracts, consultant (moderate)
- Karl Swedberg
  - Grant/Contracts, consultant (moderate)
- Barry S. M.
  - Pfizer, employee
- John Vincen
  - Pfizer, employee
- Stuart J. Perko-Koosh
  - Grant/Contracts, consultant (moderate)
- Bertram Pitt
  - Grant/Contracts, consultant (moderate)

EMPHASIS-HF was funded by Pfizer Inc. All analyses were performed or reported independently at the Cardiovascular Institute and Thoracic Medicine (CIMC). Eplerenone is approved for treating heart failure after revascularization or in NYHA class II.

Inclusion Criteria

- Includes:
  - Age ≥ 65 years of age
  - NYHA functional class II
  - Cardiac failure (including NYHA class I)
  - Treated with the recommended or maximally tolerated dose of ACE inhibitors or ARBs in both (at least 4 months of treatment).
  - Faber criteria for hospitalisation for a cardiac reason or if no such hospitalisation, BNP ≥ 250 pg/mL or NT-proBNP ≥ 1,000 pg/mL (male) or ≥ 500 pg/mL (female)

Exclusion:

- Serum potassium < 3.5 mmol/L
- eGFR < 30 ml/min/1.73m²
- Need for a potassium sparing diuretic

Study Design

- Primary endpoint: CV death or hospitalization for HF

Baseline Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>Eplerenone (N=1,189)</th>
<th>Placebo (N=1,175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age or AFB or birth</td>
<td>2202 (44.9)</td>
<td>1275 (92.3)</td>
<td></td>
</tr>
<tr>
<td>BLS blocker</td>
<td>1181 (66.6)</td>
<td>1190 (66.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>1153 (64.3)</td>
<td>1176 (65.7)</td>
<td></td>
</tr>
<tr>
<td>KDO</td>
<td>176 (14.9)</td>
<td>191 (16.4)</td>
<td></td>
</tr>
<tr>
<td>CRT-P</td>
<td>8 (0.7)</td>
<td>8 (0.7)</td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>7 (0.6)</td>
<td>6 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Digital glycosuria</td>
<td>263 (22.6)</td>
<td>371 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive drug</td>
<td>136 (14.4)</td>
<td>192 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulant drug</td>
<td>205 (16.0)</td>
<td>204 (16.0)</td>
<td></td>
</tr>
</tbody>
</table>

Results on Key Clinical Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone (N=1,189)</th>
<th>Placebo (N=1,175)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or HF hospitalisation (Primary Endpoint)</td>
<td>268 (14.3)</td>
<td>266 (13.8)</td>
<td>1.03 (0.84, 1.26)</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Death from any cause (%)</td>
<td>117 (12.6)</td>
<td>213 (18.1)</td>
<td>0.78 (0.42, 0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalisation from any cause (%)</td>
<td>438 (39.9)</td>
<td>491 (42.0)</td>
<td>0.77 (0.67, 0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death (%)</td>
<td>147 (15.0)</td>
<td>185 (15.5)</td>
<td>0.76 (0.58, 0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospitalisation for HF (%)</td>
<td>194 (16.9)</td>
<td>253 (21.4)</td>
<td>0.59 (0.47, 0.72)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

New Onset Atrial Fibrillation/Flutter (AFF)

- [Graph showing AFF incidence over time]
Safety Results: Serum Potassium and Renal Function

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K = 5.5 mmol/l</td>
<td>158 (12.6)</td>
<td>151 (12.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum K = 6.0 mmol/l</td>
<td>23 (2.4)</td>
<td>32 (3.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypokalemia leading to treatment discontinuation</td>
<td>15 (0.9)</td>
<td>17 (1.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospitalization for hypokalemia</td>
<td>170 (0.9)</td>
<td>171 (1.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum K = 3.5 mmol/l</td>
<td>100 (7.5)</td>
<td>148 (11.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hospitalization for worsening renal failure</td>
<td>5 (0.9)</td>
<td>8 (1.0)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

New Analyses of EMPHASIS-HF

1. Extension of double blind treatment from May 25 to March 18, 2011
2. Recurrent hospitalizations for heart failure (as opposed to time for first hospitalization)
3. Efficacy and safety of eplerenone in high-risk patients

Primary Endpoints: CV death or HF hospitalization

- Primary endpoint until May 20th, 2010
- Primary endpoint until March 15th, 2011

Repeat hospitalization for Heart Failure

CV Death or HF Hospitalization

High Risk Sub Groups

- Age >75 years
- Diabetes Mellitus
- eGFR <50 ml/min/1.73 m²
- LVEF <30%
- Systolic blood pressure <123 mmHg

Safety Results: Serum Potassium and Renal Function in Patients >75 years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K = 5.5 mmol/l</td>
<td>46 (22)</td>
<td>24 (12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum K = 6.0 mmol/l</td>
<td>1/102</td>
<td>4/188</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypokalemia leading to treatment discontinuation</td>
<td>3/330 (0.9)</td>
<td>3/327 (0.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hospitalization for hypokalemia</td>
<td>1/102 (0.3)</td>
<td>1/102 (0.3)</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum K = 3.5 mmol/l</td>
<td>22/222 (6.3)</td>
<td>34/188 (18.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospitalization for worsening renal function</td>
<td>5/222 (1.8)</td>
<td>3/327 (0.9)</td>
<td>0.92</td>
</tr>
</tbody>
</table>
Safety Results: Serum Potassium and Renal Function in Patients with Diabetes Mellitus

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eplerenone</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K&lt;3.5 mEq/l</td>
<td>63/487 (4.6)</td>
<td>33/587 (6.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum K&lt;3.0 mEq/l</td>
<td>17/447 (3.8)</td>
<td>8/267 (2.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertension leading to treatment discontinuation</td>
<td>5/469 (2.0)</td>
<td>5/469 (0.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hospitalization for hypokalemia</td>
<td>4/458 (0.9)</td>
<td>2/469 (0.8)</td>
<td>0.55</td>
</tr>
<tr>
<td>Serum K&gt;3.0 mEq/l</td>
<td>31/447 (7.0)</td>
<td>46/267 (17.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>Hospitalization for worsening renal function</td>
<td>5/459 (1.1)</td>
<td>7/469 (1.6)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Summary/Conclusions

- The efficacy and safety of eplerenone in addition to standard therapy in patients with systolic heart failure and mild symptoms was relatively consistent across a number of pre-specified, high-risk subgroups.

- The beneficial effect of eplerenone on the primary endpoint, all-cause mortality, was greater than 1 year after the pre-specified stopping of enrolment into the trial due to efficacy (mean follow-up 21 months) remained significant over an additional follow-up up-to 10 months (total of mean follow-up 25 months) on double-blind therapy.
EVATEL Study

Remote follow-up of patients implanted with an ICD: the prospective randomized EVATEL study

Philippe Mabo, Pascal Defaye, Nicolas Sadoul, Jean-Marc Davy, Jean-Claude Dehard, Saâlem Kacet, Eric Bellissant, Jean-Claude Daubert

Sponsor: Rennes University Hospital, France
Grant: French Ministry for Health

Background

- Implantable cardioverter defibrillator (ICD) has been shown to be effective to reduce mortality in selected patients.
- The expending indications of this therapy will have an impact on the follow-up (FU) strategy.
- Currently, regular in-office FU are scheduled every 3 months.
- In this context, remote device FU appears to be a promising technique, allowing to transmit information about the device status and delivered therapies, without the need for in-office visit.

Study design

- Randomized, prospective, open-label and multicentre French trial
- Two groups
  - Control (C): conventional in-office follow-up at the implant centre every 3 months
  - Remote follow-up (R): remote transmission to the implant centre every 3 months
- One year FU
- In-office visit at 6 weeks and 12 months for all patients

Disclosures

- Biotronik: research grants, consulting
- Boston Guidant: research grants, consulting
- Medtronic: research grants, consulting
- St Jude Medical: research grants, consulting
- Sorin Group: speaker, research grants, consulting

Aims of the study

- To evaluate safety and efficiency of ICD remote FU as compared to conventional in-office FU
- Cost-effectiveness evaluation

Selection criteria

- Inclusion criteria
  - Adults over 18 years
  - First implantation of a single or dual-chamber ICD
  - Primary or secondary prevention
  - ICD with data transmission features
  - Phone network compatible with remote transmission
  - Ability to correctly use the transmission system
  - Written informed consent
- Exclusion criteria
  - NYHA class IV
  - Life expectancy < 1 year
  - CRT-D indication
Primary endpoint

- Combined endpoint
- Rate of major cardiovascular events (MCE) occurring during the first year after ICD implantation
  - Death (all causes)
  - Hospitalization for a cardiovascular event
    - Ineffective therapy
    - Inappropriate therapy
- Evaluated on the 95% confidence interval of the MCE rate difference between the 2 groups with a non-inferiority margin of 5%.

Sample size

- Non-inferiority hypothesis
- Expected rate of MCE in the control group: 20%
- Non-inferiority margin: 5%
- Power: 80% - Risk: 5%

Sample size: 1600 patients

ICD manufacturers and types

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Control n = 750</th>
<th>Remote n = 745*</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Jude</td>
<td>235 (31.2%)</td>
<td>230 (31.7%)</td>
</tr>
<tr>
<td>Biotronik</td>
<td>60 (8.0%)</td>
<td>55 (7.6%)</td>
</tr>
<tr>
<td>Biotronik</td>
<td>223 (29.8%)</td>
<td>237 (31.5%)</td>
</tr>
<tr>
<td>McKesson</td>
<td>166 (22.1%)</td>
<td>169 (22.8%)</td>
</tr>
<tr>
<td>Medtronic</td>
<td>503 (67.1%)</td>
<td>498 (65.3%)</td>
</tr>
<tr>
<td>Dualechamber</td>
<td>267 (35.5%)</td>
<td>261 (34.8%)</td>
</tr>
</tbody>
</table>

*All implanted devices

Main secondary endpoints

- Time to onset of the first MCE
- One year survival distribution
- Rate of cardiovascular hospitalization
- Rate of ineffective or inappropriate ICD therapies
- Cost/effectiveness analysis

Flow chart

Allocated to Group n = 350
Control group n = 750
Remote group n = 745
Allocated to Group n = 750
Remote group n = 745
Excluded from analysis n = 10
Analysed by intent to treat n = 750
Analysed by intent to treat n = 750

Reasons for switch

<table>
<thead>
<tr>
<th></th>
<th>Control n = 1</th>
<th>Remote n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACS network</td>
<td>–</td>
<td>32 (62.3%)</td>
</tr>
<tr>
<td>Cannot be used</td>
<td>–</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>Correct the transmission system</td>
<td>–</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Patient wish</td>
<td>1 (100.0%)</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Patient condition requiring conventional close follow-up</td>
<td>–</td>
<td>3 (5.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>–</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>–</td>
<td>10 (19.2%)</td>
</tr>
</tbody>
</table>

Data on number of patients (percentages)

Population Characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>Control n = 750</th>
<th>Remote n = 751</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>628 (83.1%)</td>
<td>646 (86.0%)</td>
<td>0.2160</td>
</tr>
<tr>
<td>Age, years</td>
<td>59[12]</td>
<td>60[13]</td>
<td>0.1694</td>
</tr>
<tr>
<td>ICD indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>412 (54.5%)</td>
<td>430 (57.1%)</td>
<td>0.6458</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>169 (22.5%)</td>
<td>261 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>377 (35.7%)</td>
<td>395 (43.9%)</td>
<td>0.3397</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>101 (13.5%)</td>
<td>81 (10.5%)</td>
<td>0.1116</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>124 (16.5%)</td>
<td>178 (23.2%)</td>
<td>0.0206</td>
</tr>
</tbody>
</table>

Population Characteristics (2)

<table>
<thead>
<tr>
<th></th>
<th>Control n = 720</th>
<th>Remote n = 721</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>681 (96.5%)</td>
<td>68 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Electrical disease</td>
<td>497 (64.5%)</td>
<td>39 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>Structural heart disease etiologies</td>
<td>(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>497 (64.5%)</td>
<td>39 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>262 (35.1%)</td>
<td>231 (31.1%)</td>
<td>0.0519</td>
</tr>
<tr>
<td>II</td>
<td>262 (35.1%)</td>
<td>231 (31.1%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>100 (13.5%)</td>
<td>111 (15.1%)</td>
<td></td>
</tr>
<tr>
<td>LVF &lt;35%</td>
<td>412 (55.4%)</td>
<td>416 (55.4%)</td>
<td>0.2144</td>
</tr>
<tr>
<td>LVF &gt;35%</td>
<td>315 (41.6%)</td>
<td>295 (39.0%)</td>
<td></td>
</tr>
<tr>
<td>Heart failure hospitalization (within 5 year death)</td>
<td>141 (19.4%)</td>
<td>176 (23.9%)</td>
<td>0.0165</td>
</tr>
<tr>
<td>Chronic comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>270 (35.1%)</td>
<td>294 (39.5%)</td>
<td>0.1103</td>
</tr>
<tr>
<td>Diabetes</td>
<td>86 (11.5%)</td>
<td>113 (15.0%)</td>
<td>0.0505</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>14 (1.9%)</td>
<td>0.8505</td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>41 (5.5%)</td>
<td>50 (6.7%)</td>
<td>0.1336</td>
</tr>
</tbody>
</table>
Primary endpoint (1)
(Death/CV hospitalisation/ineffective or inappropriate therapy)

<table>
<thead>
<tr>
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<th>Control n = 738</th>
<th>Remote n = 741</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least 1 MACE</td>
<td>210 (28.4%)</td>
<td>218 (29.1%)</td>
<td>0.75 (0.11 to 1.39)</td>
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</table>

Per-protocol analysis (N=1434) – Non-Inferiority hypothesis

<table>
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<th>Remote n = 695</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with at least 1 MACE</td>
<td>210 (28.4%)</td>
<td>219 (30.1%)</td>
<td>1.70 (0.29 to 3.11)</td>
</tr>
</tbody>
</table>

Primary endpoint (2)

Intent to treat analysis

Per-protocol analysis

Non-inferiority margin

Time to death

Log-rank: 31.5, p = 0.0132

Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Control n = 738</th>
<th>Remote n = 695</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for a cardiovascular event</td>
<td>912 (12.6%)</td>
<td>172 (24.7%)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Inappropriate or ineffective therapy</td>
<td>60 (4.1%)</td>
<td>38 (5.5%)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Ineffective therapy</td>
<td>5 (0.7%)</td>
<td>6 (0.9%)</td>
<td>0.0038</td>
</tr>
<tr>
<td>Inappropriate therapy</td>
<td>55 (7.5%)</td>
<td>33 (4.7%)</td>
<td>0.0320</td>
</tr>
</tbody>
</table>

Data are numbers of patients (percentages)

Conclusions

• The non-inferiority hypothesis between the two groups was not validated.

• Nevertheless, a difference between groups on the primary endpoint has not been demonstrated.

• No difference in terms of survival.

• Significant reduction of inappropriate therapies in the remote group.

• ICD remote FU may be proposed as a safe alternative to in-office FU.

Study limitations

• Included population < calculated sample size
• Inclusion period limited to 2 years
• Some differences at baseline between the 2 groups with possibly sicker patients in the remote group
• Switches from remote to control group mainly due to phone network connexion
• Short follow-up

Thanks to all investigation centres

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Dr. Robert FRAK, Dr. François LECET, APH Poitiers
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Pr. Antoine LÉDÉAUX, APH Paris
Pr. Yves-Bernard LEVEZ, APH Poitiers
Pr. Nonton LE MARC, CHU Nantes
Pr. Alexandre BALZER, CHU Clermont-Ferrand
Pr. Patricia MEBIA, APH Poitiers
Pr. Cano NINET, CHU Nantes
Pr. Matthias SADDA, CHU Nancy
Pr. Christophe SALVADOR-MAJERIO, CHU Toulouse
Pr. Patricia SCARY, CHU Grenoble
Antibody-coupling and targeting of microbubbles to activated platelets allows molecular imaging of thrombosis and monitoring of success or failure of thrombolysis using non-invasive ultrasound.

K. Peter, X. Wang, C. Hagemeyer, J. Fu
E. Leitner, I. Ahrens
No disclosure

Targeted Ultrasound Microbubbles (MB)

- Ultrasound contrast = Echo enhancers
- Increase the backscatter by > 300 fold
- Gas-filled bubbles that are encapsulated by a biocompatible lipid or protein shell
- Targeting of bubbles towards clots

-Coating of MB with antibodies directed against clot epitopes

Single-Chain Antibody (scFv)

- Small recombinant antibody fragment
- Non-immunogenic
- Easy to modify

- scFv<sub>anti-LIBS</sub> (targets activated platelets)
  - Ligand Induced Binding Site on activated GPIIb/IIIa
- scFv<sub>mut</sub> (non-targeting)

Generation of biotinylated scFvs

- Molecular Biology
  - Genetic fusion of the scFv with avidin
  - Production of biotin-labelled scFv in bacteria
  - Purification of biotinylated scFv

Ultrasound Imaging of Thrombi

- Long sought-after (e.g. diagnosis of myocardial infarction)
  - Early and rapid diagnosis
    - Fast invasive or non-invasive therapy
    - Monitoring of success or failure of fibrinolytic therapy
  - Early decision towards an interventional approach

Overall, such a technical advance could substantially reduce morbidity and mortality of myocardial infarction

Activated GPIIb/IIIa: The Ideal Target for Molecular Imaging of Thrombi

- Platelets are the central component of clots
- Each platelet expresses ≈ 80,000 GPIIb/IIIa
- Absolutely specific for platelets
- Change in confirmation when activated
- Recombinant antibodies for specific targeting of activated GPIIb/IIIa receptors only

Aims

- Coupling of scFvs to microbubbles and targeting to activated platelets and thrombi

Functionality of scFv Constructs

- Successful biotinylation and purification of scFv
- Specificity for activated platelets

Western blot

Flow cytometry
Targeting of Microbubbles to Microthrombi

Strong Adhesion on Microthrombi as well as on a Platelet Monolayer

• Platelet microthrombi
• Monolayer of activated platelets

Aims

• Targeting microbubbles to activated platelets and thrombi by conjugation to scFv
• Identifying thrombi in vivo via non-invasive ultrasound based molecular imaging using targeted microbubbles

High Resolution Ultrasound Imaging

• High frequency small animal ultrasound scanner
• 40 MHz transducer
• Carotid artery of a mouse
  – Small diameter of 300 to 400 μm
  – Ferric chloride injury
  – Platelet-rich but non-occlusive thrombus

Injection of Microbubbles in Carotid Artery

Minimal Attachment of MB

Ultrasound imaging: vaguely distinguishable thrombus
Post digital subtraction: only non-specific movement artifacts

Minimal Attachment of Control-MB

Ultrasound imaging: vaguely distinguishable thrombus
Post digital subtraction: only non-specific movement artifacts
**Strong Attachment with LIBS-MB**

Ultrasound imaging: bright thrombus area

Post digital subtraction: strong green thrombus area

**Detection of Thrombi**

**Aims**

- Targeting microbubbles to activated platelets and thrombi by conjugation to scFv
- Identifying thrombi in vivo via non-invasive ultrasound based molecular imaging using targeted microbubbles
- Monitoring success or failure of thrombolysis with targeted microbubbles
  - Treatment (UPA) or Control (Saline)

**Conclusions**

- Targeted microbubbles bind specifically to activated platelets in vitro and in vivo thereby facilitating ultrasound molecular imaging of thrombi.

- Thrombus size and its reduction following pharmacological thrombolysis can be monitored in real-time, offering early diagnosis and monitoring of therapeutic thrombolysis.

**Future directions**

- Development into a promising diagnostic tool for clinical use for early detection of thrombi
  - Carotid artery (prevention of stroke)
  - Cardiac chambers (therapeutic implications)
  - Coronary artery (early and rapid diagnosis of MI)

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- Jan David Hohmann, BS
- Paul Armstrong, PhD

**Funding**

- Baker IDI Heart and Diabetes Institute
- Monash University
- National Health & Medical Research Council of Australia
- German Research Foundation

**Biocompatible conjugation**

- Sortase A + GGG-malamide + MB<sub>SH</sub>
**Background**

- GRK2 belongs to a family of seven transmembrane protein kinases, each encoded by a single gene, that specifically phosphorylate the activated form of GPCRs, mediating their desensitization.

- Recent studies demonstrate a novel role of GRK2 in controlling the cellular use of glucose and, more in general, the ability of the cell to maintain energy production and expenditure.

**AIM**

Verify the hypothesis that GRK2 might affect energy cellular production by interfering with mitochondrial function.

**Background**

- Mitochondria play an important role in cell energy production.

- The mitochondrial functional state varies dramatically depending on the functional and metabolic state of the cell.

- Post-translational modification of mitochondrial proteins, and in particular protein phosphorylation, appears to be an important mechanism of mitochondrial function.

---

**MITOCHONDRIAL LOCALIZATION UNVEILS A NOVEL ROLE FOR GRK2 IN THE REGULATION OF OXIDATIVE METABOLISM**

Arya Faico, Gaetano Santulli, Danilo Sorrento, Emilia Cipolletta, Carmela Garbi, Gerald W. Dorn, Bruno Trimbosio, Antonia Feliciello, Guido Iaccarino

Department of Clinical Medicine, Cardiovascular and Immunologic Sciences, "Federico II" University, Naples, Italy

---

**Timeline post MBs injection**

![Timeline post MBs injection](image)

**Platelet Aggregation**

![Platelet Aggregation](image)

**Antibody-coupling and targeting of microbubbles to activated platelets allows molecular imaging of thrombosis and monitoring of success or failure of thrombolysis using non-invasive ultrasound.**

K. Peter, X. Wang, C. Hagemeyer, J. Fu, E. Leitner, I. Ahrens

---

**Background**

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- Recent studies demonstrate a novel role of GRK2 in controlling the cellular use of glucose and, more in general, the ability of the cell to maintain energy production and expenditure.

**AIM**

Verify the hypothesis that GRK2 might affect energy cellular production by interfering with mitochondrial function.
MATERIALS AND METHODS

**In Vitro**

- Cell culture
  - HEK-293
  - HEK-293 transfected with pcDNA3.1 encoding for GRK2 (GRK2-HEK)
  - Primary culture cells from fetal GRK2 gene (GRK2-FF) were infected with
    - ΔC1, 10% plating GRK2-ΔC1
  - Assay for oxidative ATP synthesis
  - Subcellular fractionation by Nycodenz gradient and western blotting
  - Immunoprecipitation
  - Western blotting
  - Assay for oxidative ATP synthesis

**In vivo**

- Homogenate GRK2 mice
  - Intramuscular injection of AICAR (10% plating ΔC1 GRK2 mice)
  - In vivo
  - Assay for oxidative ATP synthesis

---

**GRK2 increases oxidative ATP synthesis**

**In Vitro**

![ATP Content](image)

**GRK2 increases mitochondrial biogenesis**

**In Vitro**

**GRK2 is located in mitochondria**

**In Vitro**

**Two regions of GRK2 possess ability for mitochondrial localization**

**In Vitro**

![Immunogold on mitochondria extracts using anti-GRK2 antibody](image)
**Hemoglobin Directs Macrophage Differentiation and Prevents Foam Cell Formation in Human Atherosclerotic Plaques**

Aloke V. Finn MD, Masataka Nakano MD, Rohini Polavarapu, BA, Venit Karranlal MA, Omar Saed, MD, XiaoQing Zhao, PhD, Soami Yazdani, PhD, Fumiyuki Otsuka, MD, Talina Davis, Awer Habib, MD, Jagat Narula, MD, PhD, Frank D. Koldoge PhD, Renu Virmani MD.

EMORY UNIVERSITY SCHOOL OF MEDICINE
BSC 2011 LATE BREAKING BASIC AND TRANSLATIONAL HOTLINE
PARIS, FRANCE
AUGUST 29, 2011

**Macrophage Diversity**

- Macrophages are the major inflammatory cells involved in the progression of atherosclerosis
- Macrophage infiltration into the arterial wall followed by uptake of oxidized LDL is marked by the formation of foam cells, a primary hallmark of atherosclerosis
- A newer concept is one of macrophage diversity—
  - Microenvironment drives these cells into morphologically and functionally distinct types

**Macrophage Diversity**

- Some data support the presence of IL-4 induced M2 macrophages in human atherosclerosis (Bourhel MA Cell Metabolism 2007)
- The M1/M2 concept is perhaps too black and white—there is more likely a spectrum of different macrophage subtypes
- Overall, little is known about the existence and function of different macrophage subtypes in human atherosclerosis
- We have previously shown that intraplaque hemorrhage is associated with necrotic core enlargement through the release of cholesterol from red cell membranes
- Here we examined the effects of hemorrhage on macrophage diversity and function in human atherosclerosis
**Methods**

- We used human atherosclerotic plaques to analyze macrophage differentiation in response to hemorrhage using traditional markers of M2 macrophages.
- We confirmed the effects of hemorrhage on macrophage differentiation in vitro using human monocytes and explored the mechanisms underlying this phenotype.

**Macrophages are Important Cells For Hemoglobin Scavenging**

Within areas of hemorrhage, RBC lysis and release of free Hb which contains iron occurs. The toxic effects of free hemoglobin are linked to oxidative stress through the Fenton reaction where Fe(II) oxides H2O2 leading to generation of hydroxyl radicals and lipid peroxidation. Among the important mechanisms to detoxify free hemoglobin (Hb) scavenging, a plasma glycoprotein that binds free Hb and carcinot from the plasma via uptake by CD353 (hemoglobin scavenging receptor) which initiates anti-oxidant effects such as induction of HO-1 (carnosine and catalase), an iron exporter.

**Macrophage Differentiation and Cholesterol Uptake: Live Cell Imaging**

Control Macs | IL-4 M2 | M(Hb)
---|---|---

**What is the Mechanism of Lipid Handing in M(Hb)?**

**Receptors involved in Lipid Uptake**

<table>
<thead>
<tr>
<th>Scavenger Receptor</th>
<th>Fold Versus Control (normalized to 1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR-A1</td>
<td>1.016 ± 0.16</td>
<td>0.006</td>
</tr>
<tr>
<td>SR-A2</td>
<td>1.020 ± 0.04</td>
<td>0.004</td>
</tr>
<tr>
<td>SR-B1</td>
<td>0.946 ± 0.32</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ATP Binding Cassette (ABC) Transporters involved in apo AI mediated cholesterol efflux to HDL (i.e. reverse cholesterol transport)

<table>
<thead>
<tr>
<th>ABC Transporter</th>
<th>Fold Versus Control (normalized to 1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCA1</td>
<td>4.18 ± 2.59</td>
<td>0.03</td>
</tr>
<tr>
<td>ABCG1</td>
<td>3.93 ± 3.84</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Understanding how M(Hb) Hande Lipid Receptors May Allow For the Development of Strategies to Prevent Foam Cell Formation**
Iron Metabolism

Circulating iron is regulated by hepatocyte growth factor (HGF), a secreted heparin-binding peptide that plays a key role in iron homeostasis. Hepatocyte growth factor (HGF) binds to the iron exporter ferroportin (FPN), expressed on the surface of hepatocytes, and promotes degradation of this protein. Hepatocyte growth factor (HGF) thus inhibits iron export from hepatocytes.

Intracellular Iron Affects ABC Transporter Expression and Cholesterol Efflux in M(Hb)

**Findings**

- Hemorrhage and release of free Hb determines macrophages differentiation into a distinct subtype we have termed M(Hb).

| Macrophage subtype | M(Hb) | M(Hb)
|-------------------|-------|-------|
| Maiv | M | M | M | M | M | M | M
| C3 | - | - | - | - | - | - | -
| Foam cell formation | - | - | - | - | - | - | -
| Intracellular iron | - | - | - | - | - | - | -
| ROS | - | - | - | - | - | - | -

**M(Hb) in Human Atherosclerosis**

**Foamy Macrophage**
- Stimulate M1
  - Cytokine production – pro-inflammatory
  - M1 macrophages
  - Pro-oxidant
  - Reactive Oxygen Species (ROS)

**M(Hb) Macrophage**
- Stimulate M2
  - Cytokine production – anti-inflammatory
  - M2 macrophages
  - Pro-resolving macrophages
  - Foam cell resolution and ROS

**Conclusion**

- We have demonstrated a novel non-lipid driven macrophage phenotype driven by monocyte ingestion of Hb/Hip.
- Hb, not IL-4, is an important stimulus for macrophage differentiation in human atherosclerosis.
- Iron metabolism through ROS plays an important role in macrophage lipid handling.
  - The exact mechanism by which lowering ROS increases ABC transporter expression requires further investigation.
  - Perhaps the iron hypothesis may in part be explained by its effects on macrophage lipid handling.
- Manipulation of macrophage intracellular iron may be of therapeutic value for prevention of CAD by increasing macrophage cholesterol efflux but awaits confirmatory data.
Modeling LMNA related DCM using Induced Pluripotent Stem Cells

Chung-Wah SIU, MD  
Department of Medicine  
The University of Hong Kong

Lamin (LMNA) A/C proteins

- Type V intermediate filament  
- Nuclear envelope: Communications between nucleus and cytoplasm  
- Encoded by LMNA  
- Lamin A and C are created by alternative splicing  
- Cell cycle regulation and differentiation  
- Apoptosis

Dilated Cardiomyopathy

- 60% cardiomyopathies  
- Heterogeneous diseases  
- Idiopathic DCM ~ 35%  
- Positive familial history in ~ 50% DCM pts  
- >90% autosomal dominant  
- LMNA is the most common identifiable form of familial DCM (~10%)  (van Beek JF et al 2005)

DCM with conduction abnormalities

- Asymptomatic conduction delay  
- AV nodal block  
- Atrial fibrillation  
- Cardiomyopathy  
- VT/VF

- What is the pathogenic link between the genotype and clinical phenotype?  
- What is the mechanism(s) for organ specific phenotypes?

Morphological changes in Skin Fibroblasts

Culturing Skin Fibroblasts under Electrical Field

Baseline  
E-stim

<table>
<thead>
<tr>
<th>% of area occupied</th>
<th>Obase</th>
<th>O-Estim</th>
<th>O-Estim + U0126</th>
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<tbody>
<tr>
<td>1</td>
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</table>

SIU CW., TSE HF et al. (submitted)
Induced Pluripotent Stem Cells (iPSCs)

Characterization of LMNA iPSCs

Disease-specific iPSC-CMs

Electromicroscopy of Disease-specific iPSC-CMs

Conclusions

Electromicroscopy of Disease-specific iPSC-CMs

Conclusions

Disease-specific iPSCs and its derivatives could provide new insights into the pathophysiology by permitting the analysis of a system that is close to that of humans.

Disease-specific iPSCs and its derivatives provide a platform for drug screening and testing.

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- QZ Lian
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- Jenny Ho
- KM Ng
- YC Chan
- PhD students
- YK Lee
- Technicians:
  - Kevin Lai
  - Karen Au
  - Virginia Lau

Collaborators
- Alan Colman (Singapore)
Critical role for STIM1 in cardiac hypertrophy

Presenter: Dr Jean-Sébastien Hulot, MD PhD
Associate Professor of Medicine, Cardiology
Cardiovascular Research Institute
Mount Sinai School of Medicine
New York - USA

Disclosure: None

Calcium homeostasis & cardiac hypertrophy
- Sustained pro-hypertrophic signaling within cardiomyocytes is detrimental and leads to failure.
- Pathological cardiac hypertrophy is typically characterized by the activation of Ca^2+-dependent signaling pathways and re-expression of a fetal gene program.
- The mechanisms driving the Ca^2+-dependent activation of calcineurin/NFAT are unclear.

The calcium sensor STIM1 promotes calcium entry and calcium-related signalling pathways in non-excitable cells

STIM1-dependent store-operated calcium entry in neonatal cardiomyocytes

STIM1 is present in adult cardiomyocytes and is over-expressed during cardiac hypertrophy

Experimental strategy to modulate STIM1 in adult rat hearts

STIM1-dependent SOCE is present only in hypertrophic cardiomyocytes

STIM1 controls two different currents in hypertrophic cardiomyocytes

i_{Ca} characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before TG</th>
<th>After TG</th>
</tr>
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<tbody>
<tr>
<td>Ba^{2+}</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>Ca^{2+}</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
<tr>
<td>La^{3+}</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
</tr>
<tr>
<td>Sr^{2+}</td>
<td>$\uparrow$</td>
<td>$\downarrow$</td>
</tr>
</tbody>
</table>

Current: Voltage (V pL) Before TG: Inwardly rectifying After TG: Double rectifying
**STIM1-dependent cation current does not affect excitation-contraction coupling but the growth of isolated cardiomyocytes**

- Adult CM size at identical membrane capacitance
- Neonatal cell size after STIM1 manipulation

⇒ STIM1 silencing reciprocally prevents PE-induced N/R/M hypertrrophy

**In vivo cardiac-targeted RNA interference against STIM1 using a recombinant AAV9 vector**

- In vivo model of pressure-overload hypertrophy
  - Sprague Dawley rats
  - Tissue injection of STIM1 or STIM1-ShRNA
  - 60% reduction in cardiomyocyte lifetime
  - No evidence of arrhythmia or cardiac failure

**Adeno-associated virus-mediated silencing of STIM1 in vivo prevents cardiac hypertrophy**

- Echocardiography
- Morphology

**Adeno-associated virus-mediated silencing of STIM1 in vivo does not affect the inflammatory response nor the capillary density**

**Nuclear translocation of NFAT is reduced in AAV9-shSTIM1 treated animals**

**CONCLUSIONS**

⇒ STIM1 expression and function are regulated in hypertrophied cardiomyocytes

- In this condition, STIM1 controls cation current
  - Occurs under native conditions
  - Promotes cardiomyocyte growth through activation of Ca2+-signaling pathways

⇒ STIM1 silencing prevents cardiomyocyte hypertrophy in vitro and in vivo

⇒ This may lead to the development of novel approaches to prevent cardiac dysfunction
Bern-Rotterdam Cohort Study

Newer generation everolimus-eluting stents eliminate the risk of very late stent thrombosis compared with early generation sirolimus-eluting and paclitaxel-eluting stents

Lorenz Räber, Michael Magro, Giulio G. Stefanini, Bindu Kalesan, Ron T. van Domburg, Yoshinobu Onuma, Peter Windecker, Joost Daemen, Bernhard Meier, Peter Jün, Patrick W. Serruys, Stephan Windecker

Department of Cardiology
Swiss Cardiovascular Center and Clinical Trials Unit Bern
Bern University Hospital, Switzerland
Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

BR Cohort Study - Background I

- Stent thrombosis (ST) is a rare but potentially devastating complication following coronary stent implantation and is associated with death or myocardial infarction in up to 90% of cases.
- Whereas early and late ST occur with similar frequency among patients treated with early generation drug-eluting stents (DES) and bare metal stents (BMS), very late ST is more common with early generation DES with an annual risk of up to 0.6% per year during long-term follow-up.

BR Cohort Study - Background II

- The newer generation everolimus-eluting stent (EES) is a thin strut, cobalt chromium stent and releases everolimus, a semisynthetic sirolimus analogue from an acrylic and fluoropolymer mixture.
- Whether the newer generation EES reduces the risk of very late ST as compared to early generation DES has not been investigated in an adequately powered study with sufficient long-term follow-up.

BR Cohort Study - Patient Population

Inclusion Criteria
- All consecutive patients treated with EES, SES, and PES at Bern University Hospital and the Thoraxcenter, Erasmus University Hospital in the setting of stable angina, silent ischemia, and acute coronary syndromes (UA, NSTEMI, STEMI)
- Diameter stenosis >50%
- Number of lesions: no limitation
- Number of vessels: no limitation
- Lesion length: no limitation

Exclusion Criteria
- Implantation of more than one stent type

BR Cohort Study - Endpoints

Primary Endpoint
- ARC definite ST

Secondary Endpoints
- ARC very late definite ST
- ARC definite or probable ST
- ARC very late definite or probable ST
- Cardiac Death
- Myocardial Infarction (MI)
- Cardiac Death or MI

BR Cohort Study - Statistical Analysis

- Propensity scores for receiving EES were estimated using a probit model including age, gender and pre-treatment variables associated with stent selection at ≥0.10 and used to derive inverse probability of treatment weights (ITPW).
- Comparisons between stents were performed using a Cox proportional hazards model, crude and adjusted by weighting using ITPW.
- Landmark analyses according to a pre-specified landmark point at 1 year (360 days) were used and hazard ratios and cumulative incidence rates were estimated separately for events up to one year, and beyond.
- Clinical events are expressed as counts and cumulative incidence rates per 100 patient years.
**BR Cohort Study - Patient Flow**

- EES
  - 4212 consecutive patients
  - Fup rate: 97.4%
  - Mean fup duration: 2.5 years (1.9-3.1)
- SES
  - 3819 consecutive patients
  - Fup rate: 97.5%
  - Mean fup duration: 4.0 years (3.1-4.0)
- PES
  - 4308 consecutive patients
  - Fup rate: 95.9%
  - Mean fup duration: 3.0 years (2.1-3.6)

*F/U rate at the time of latest follow-up

**BR Cohort Study - Antithrombotic Drug Regimen**

**Pre or during procedure**
- Acetylsalicylic acid: ≥ 100 mg
- Clopidogrel: 300-600 mg loading dose
- Unfractionated heparin
  - Bolus of at least 5000 IU i.v. or 70 IU/kg
- Glycoprotein IIb/IIIa antagonists
  - Operator discretion

**Post procedure**
- Acetylsalicylic acid: 100 mg/d indefinitely
- Clopidogrel 75 mg/d for 3-12 months

**BR Cohort Study - Patient Characteristics**

<table>
<thead>
<tr>
<th>Total (n)</th>
<th>EES</th>
<th>SES</th>
<th>PES</th>
<th>EES vs.</th>
<th>SES vs.</th>
<th>PES vs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (%)</td>
<td>64.2±2</td>
<td>63.5±2</td>
<td>63.3±2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sex (%)</td>
<td>73</td>
<td>75</td>
<td>74</td>
<td>0.11</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>BMI (%)</td>
<td>27.8±2</td>
<td>27.2±2</td>
<td>27.1±2</td>
<td>0.98</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>57</td>
<td>32</td>
<td>41</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>37</td>
<td>46</td>
<td>30</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic tension (%)</td>
<td>54</td>
<td>55</td>
<td>46</td>
<td>0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>19</td>
<td>18</td>
<td>14</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;50% (%)</td>
<td>34</td>
<td>27</td>
<td>25</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS (%)</td>
<td>63</td>
<td>53</td>
<td>59</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA/NSTEMI (%)</td>
<td>42</td>
<td>17</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>58</td>
<td>43</td>
<td>55</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiogenic shock (%)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint**

**ARC Definite ST @ 4 Years**

- EES vs. SES Hazard Ratio* = 0.41, 95% CI 0.27-0.62, P=0.0001
- EES vs. PES Hazard Ratio* = 0.33, 95% CI 0.23-0.48, P<0.0001

**Very Late ST (1-4yrs)**

- EES vs. SES Hazard Ratio* = 0.33, 95% CI 0.15 – 0.72, P=0.006
- EES vs. PES Hazard Ratio* = 0.24, 95% CI 0.13-0.47, P<0.0001

**ARC Definite or Probable ST @ 4yrs**

- EES vs. SES Hazard Ratio* = 0.41, 95% CI 0.27-0.62, P=0.0001
- EES vs. PES Hazard Ratio* = 0.33, 95% CI 0.23-0.48, P<0.0001

- Pacitaxel Stent 4.4%
- Sirolimus Stent 2.9%
- Everolimus Stent 1.4%

**ARC Definite or Probable Very Late ST (1-4yrs)**

- EES vs. SES Hazard Ratio* = 0.55, 95% CI 0.33 – 0.93, P=0.03
- EES vs. PES Hazard Ratio* = 0.35, 95% CI 0.22-0.55, P=0.0001

- Pacitaxel Stent 3.9%
- Sirolimus Stent 2.7%
- Everolimus Stent 1.8%
In this observational, prospective cohort study, the unrestricted use of a EES was associated with a lower risk of overall ARC definite and ARC definite or probable ST up to four years of follow-up.

The benefit in favor of EES was most pronounced during the very late period with a 71% and 77% reduced risk of definite ST compared with SES and PES, respectively, resulting in a nearby elimination of very late ST.

The reduced risk of VLIST with the unrestricted use of EES overcomes the principal limitation of early generation DES and constitutes an important advance in DES safety.
The EXAMINATION (a clinical Evaluation of Xience-V stent in Acute Myocardial Infarction) trial:

Manel Sabaté
Hospital Clinic, Barcelona
(On behalf of the Examination Investigators)

Background and Rationale (I)

- Acute coronary syndromes repeatedly appear as independent predictor of stent thrombosis in most of Clinical Registries. Although these registries reflect real world population, they may be subject to clinical bias.
- First generation drug-eluting stent (DES) have been evaluated in RCT in the setting of STEMI with (overall) positive results. However, most of these RCT lack of good generalizability of real world due to highly selected inclusion/exclusion criteria.
- Currently, no data exists regarding new generation DES in terms of safety and efficacy in this high risk group of patients with STEMI.

Background and Rationale (II)

- Recently, RCT with an “all-comers” design apply wide inclusion and few exclusion criteria that may result in a more representative sample of the target population.
- However, even in such design it is not expected that every consecutive patient will be enrolled. In a recent analysis from 2 all-comers RCT (Leaders and Resolute) only 48% of the total number of patients were actually included.
- We conducted a RCT with an “all-comers” design with the aim to evaluate the performance of second generation DES in the complex setting of STEMI and to provide data that may be generalizable to the real world population.

EXAMINATION TRIAL design

Multicentre, multinational, prospective, randomized, two-arm, single-blind, controlled trial

OBJECTIVE
To assess the safety and performance of the XIENCE™ V Everolimus Eluting Coronary Stent System vs. the cobalt chromium MULTI-LINK VISION® balloon expandable stent in the setting of primary percutaneous coronary intervention for treatment of patients presenting with ST-segment elevation myocardial infarction.

Participants (I)

PI: M Sabaté; Clinic Hospital, Barcelona, SP
Co-PI: PW Serruy; Erasmus MC: R’dam, NL
Steering Committee:
M Sabaté; PW Serruy; A Cequier; A Iríñez; M Vaigiglì; R Hdez-Antolin, GA van Es,
Promoter: Spanish Society of Cardiology
CRO: Cardialysis, R’dam, NL
Monitoring: J Toro (SP) S Cellini (I), C MorelI (I), R Schneijdenber (NL)
DBMA: I Ferrara (SP); R Garcia del Blanco (SP)
CEC: P Vanacck (B); E McFadden (UK); B Ransing (NL)
Statistics: Cardialysis, R’dam, NL

Participants (II)

Centres:
- Spain:
  - H Príncips d’Espanya, Barcelona; Dr. A Cequier
  - H Sant Pau, Barcelona; Dr. A Serra
  - H Clinic, Barcelona; Dr. M Sabaté
  - H de Mèxic, Vigo; Dr. A Iríñez
  - H San Carlos, Madrid; Dr. R Hénández-Antolin
  - H Univ Alcántara; Alicante; Dr. V Mainer
  - H Juan Canalejo; A Coruña; Dr. N Vázquez
  - H Son Dureta; Palma de Mallorca; Dr. A Bethencourt
- Italy:
  - Univ H Ferrara; Dr. M Vaigiglì
  - Univ H Bolognia Seriate; Dr. M Tespi
- The Netherlands:
  - Erasmus MC, Rotterdam; Dr. PW Serruy
  - Amphia Ziekenhuis, Breda; Dr. des Heijer

Disclosures

Investigator Initiated Trial: NCT00828087.
Unrestricted grant from Abbott to the Spanish Heart Foundation.
EXAMINATION TRIAL design

PRIMARY ENDPOINT
- Patient-oriented (ARC) primary endpoint at 1 year
  Composite endpoint of all-cause death, any myocardial infarction and any revascularization.

SECONDARY ENDPOINTS
- All-cause and cardiac mortality at 1 year and yearly up to 5 years.
- Recurrent MI at 1 year and yearly up to 5 years.
- TLR and TVR at 1 year and yearly up to 5 years.
- Stent thrombosis (ARC) at 1 year and yearly up to 5 years.
- Clinical device and procedure success.
- Major and minor bleeding at 1 year and yearly up to 5 years.

Exclusion criteria:
- Age < 18y
- Pregnancy
- Intolerance to aspirin, clopidogrel, everolimus, cobalt-chromium, heparin.
- Need of chronic treatment with anti vitamin K agents.
- STEMI secondary to stent thrombosis.
- Impossibility to obtain clinical follow-up.

Study Design = All-comer RCT

Patients suffering from an AMI, presenting within 48 hours after onset of Symptoms Requiring Emergent PCI of a Native Coronary Artery

Randomization 1:1 (n=1504)
5 pts withdraw consent

Everolimus-eluting Stent (761 patients)
Cobalt-chromium stent (747 patients)

Everolimus-eluting Stent (735 patients 98%)
1-YEAR FOLLOW-UP
Cobalt-chromium stent (731 patients 98%)

Inclusion criteria ("all-comer"):
- Patients presenting with STEMI within 48 h requiring emergent PCI:
  - STEMI < 12h ("primary PCI")
  - Rescue PCI
  - After successful thrombolysis
  - Latecomers (>12h-48h)
- Vessel size between 2.25-4.0 mm to allow the implantation of currently available stents.
- Informed consent.

Statistical analysis:
- The overall sample size for the study of 1,500 patients is based on the following assumptions:
  - A 2-sided type I error rate = 0.05
  - Randomization ratio = 1 (XIENCE V: 1 (Vision)).
  - A statistical power of at least 80% to detect a (approximate 10%) reduction in the rate of the primary endpoint at 1 year by the Xience V stent as compared to the Vision stent.
- The primary combined endpoint will be analyzed for the intent-to-treat population.
- Staged procedures that were indicated in the CRF at the time of the initial procedure, and are performed within one month of the initial procedure will not be counted as endpoints.

Number of patients included per centre

70% of all STEMI!

Clinical presentation

Cardiogenic shock: 1.3% Xience V vs. 3.1% Vision; p=NS
Secondary Endpoints: Cardiac Death

<table>
<thead>
<tr>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival, %</td>
<td>96.7</td>
<td>97.1</td>
</tr>
</tbody>
</table>

Secondary Endpoints: Recurrent Myocardial Infarction

<table>
<thead>
<tr>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from event, %</td>
<td>98.6</td>
<td>97.9</td>
</tr>
</tbody>
</table>

Secondary Endpoints: Repeat Revascularization

<table>
<thead>
<tr>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from event, %</td>
<td>91.6</td>
<td>89.2</td>
</tr>
</tbody>
</table>

Secondary Endpoints: Definite Stent Thrombosis

<table>
<thead>
<tr>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from event, %</td>
<td>99.5</td>
<td>98.1</td>
</tr>
</tbody>
</table>

Secondary Endpoints: Probable Stent Thrombosis

<table>
<thead>
<tr>
<th>Xience-V</th>
<th>Vision</th>
<th>Log-Rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from event, %</td>
<td>99.0</td>
<td>99.3</td>
</tr>
</tbody>
</table>

Definite Stent Thrombosis

Probable Stent Thrombosis

p = 0.01

p = 0.47
**Probable Stent Thrombosis**

<table>
<thead>
<tr>
<th>Vision</th>
<th>Xience V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.47 \]

**Conclusions**

- The use of Xience V stent in the setting of STEMI resulted in a numerically (not significantly) reduced primary endpoint at the expense of a trend in reduction the repeat revascularization rate.
- The significant reduction observed in the definite and definite/probable stent thrombosis rates suggest an excellent safety profile of the Xience V stent in this high risk patients presenting with STEMI.
- The results of this “all-comer” randomized controlled trial are highly representative of the real world population.

**The RUBY-1 trial**

Steen D. Kristensen, FESC
Aarhus
Denmark

**Oral Xa inhibitors**

- Promising results in the prevention and treatment of venous thromboembolism and in patients with atrial fibrillation.
- Acute Coronary Syndrome (ACS)?

**Conflicts of interest**


**ACS: dual antiplatelet therapy**

- ESC Guidelines: NSTEMI, STEMI, Myocardial Revascularization.
- 12 months of dual antiplatelet therapy.

**Anticoagulation plus dual antiplatelet therapy in ACS**

Sørensen R et al., Lancet 2009

APPRAISE: apixaban
ATLAS ACS-TIMI 46: rivaroxaban

**Photo**: R DeCaterina
Oral Xa inhibition in ACS: RUBY-1

- Drug
- Patients
- Dosing
- Duration/timing of treatment

Selection of patients

- 70% were ST-elevation MI patients.
- 75% of all patients underwent PCI prior to inclusion.
- Median age was 56 years and only about 20% were women.
- More than 96% of the patients were on dual antiplatelet therapy with aspirin and clopidogrel.

Dosing and design

RUBY-1

- Drug
- Patients
- Dosing
- Duration/timing of treatment

Darexaban: duration

- Overall mean exposure to study drug was 21.3 weeks

Darexaban: safety

- 291 patients (23.1%) discontinued treatment early.
- Overall mean compliance to study drugs was 97.9%.

Selection of patients

- Patients with active bleeding during the first days were excluded.
- Patient scheduled for invasive procedures with potential for bleeding within 60 days were excluded.
- Stroke/TIA (<12 months) excluded.

Darexaban: safety

- 291 patients (23.1%) discontinued treatment early.
- Overall mean compliance to study drugs was 97.9%.

No major side effects
Darexaban: safety

- 291 patients (23.1%) discontinued treatment early.
- Overall mean compliance to study drugs was 97.9%.

No major side effects
No toxicity
Conclusion

- RUBY-1 trial is a nicely conducted double-blinded phase II study.
- Darexaban is well tolerated.
- Darexaban caused a dose-related 2- to 4-fold increase in bleeding.
- Phase III trials in ACS are needed.