



Euro Observational Research Programme:

Atrial Fibrillation Ablation Pilot Registry

Elena Arbelo¹, Gerhard Hindriks², Aldo Maggioni³, John Morgan⁴, Luigi Tavazzi⁵, Panos Vardas⁶,
Josep Brugada (chairperson)¹

¹Department of Cardiology, Thorax Institute, Hospital Clinic de Barcelona, Universidad de Barcelona, Barcelona, Spain
²Heart Center, University of Leipzig, Leipzig, Germany
³Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy
⁴Department of Cardiology, Wessex Cardiothoracic Unit, Southampton University Hospital, Southampton, United Kingdom
⁵Department of Cardiology, Policlinico S. Matteo, IRCCS, Pavia, Italy
⁶Department of Cardiology, Heraklion University Hospital, Crete, Greece

www.escardio.org

EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry

Belgium	Czech Republic	Germany	Denmark	Spain	France	Greece	Italy	Netherlands	Poland
100	100	168	100	126	319	95	202	100	100

Number of locked patients 1410

Number of locked patients performing Ablation procedure 1391

www.escardio.org

EURObservational Research Programme

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
- ↓
- Cardiac tamponade following transeptal puncture 7 pts
 - Intracardiac thrombus 7 pts
 - Cerebrovascular event 1 pt
 - Other 1 pt

www.escardio.org

EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry
Baseline characteristics – 1/2

	All (n. 1410 pts)
Age (years), • median (IQR) • > 65 years, %	60 (52 – 66) 31.0
Females, %	27.9
Body Mass Index (kg/m ²) • median (IQR) • > 30 kg/m ² , %	27 (25 – 30) 25.8
SBP (mmHg), • median (IQR) • > 140 mmHg, %	130 (120 – 140) 20.1
Creatinine (mg/dL), median (IQR)	0.9 (0.8 – 1.1)

www.escardio.org

EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry
Baseline characteristics – 2/2

CHADS ₂ score	All (n. 1391 pts)	CHA ₂ DS ₂ -VASc score	All (n. 1391 pts)
0	587 (42.2%)	0	294 (21.1%)
1	98 (7.0%)	1	398 (28.6%)
2	501 (36.0%)	2	348 (25.0%)
3	172 (12.4%)	3	215 (15.5%)
4	28 (2.0%)	4	80 (5.8%)
5	5 (0.4%)	5	39 (2.8%)
		6	11 (0.8%)
		7	6 (0.4%)

www.escardio.org

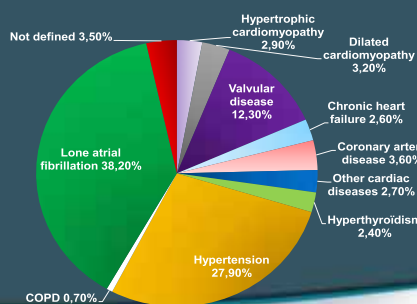
EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry
Risk factors

	All (n. 1391 pts)
Diabetes mellitus, %	8.3
Hypertension, %	50.0
Active smokers, %	11.4
Hypercholesterolemia, %	31.6

www.escardio.org

EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry
Underlying disorder

www.escardio.org

EURObservational Research Programme

Atrial Fibrillation Ablation Pilot Registry
Clinical history

	All (n. 1391 pts)
Previous peripheral/pulmonary embolism, %	1.9
Previous stroke/TIA, %	6.8
Peripheral vascular disease, %	2.0
PM, %	2.9
CRT, %	0.3
ICD, %	1.3

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Co-morbidities

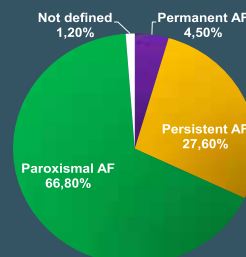
	All (n. 1391 pts)
Hyperthyroidism, %	3.2
Chronic kidney disease, %	1.8
COPD, %	3.2
Sleep apnea, %	4.3

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Characteristics of the AF – 1/2



www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Characteristics of the AF – 2/2

	All (n. 1391 pts)
HR (bpm), median (IQR)	100 (81 – 120)
Number of episodes in the last month, median (IQR)	2 (1 – 7)
Associated symptoms, %	85.8
Prior electrical cardioversions, %	40.0
Prior pharmacological cardioversions, %	29.3

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Symptoms during AF

	All (n. 1391 pts)
Palpitations, %	72.3
Syncope, %	3.8
Fatigue, %	41.8
Chest pain, %	10.4
Dizziness/Presyncope, %	13.7
Weakness, %	24.4
Dyspnea, %	37.6
No symptoms, %	13.1
Unknown, %	1.1

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Precipitating factors

	All (n. 1391 pts)
Thyreotoxicosis, %	1.8
Pulmonary infection, %	0.5
Heart failure, %	2.6
Surgical intervention, %	1.7
Physical exercise, %	5.5
Alcohol abuse, %	3.3
Sexual activity, %	1.8

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Ablation Procedure Indicators

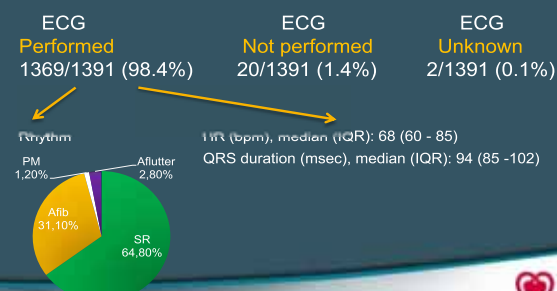
	All (n. 1391 pts)
Symptoms, %	89.7
Quality Of Life, %	73.4
Desire for drug-free lifestyle, %	34.9
Desire for sinus rhythm, %	39.6

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Investigations and procedures during the hospital stay – 1/4



www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Investigations and procedures during the hospital stay – 2/4

Countries where ECG was not performed

Countries	Number of centres	Number of patients
CZECH REPUBLIC	1	1
FRANCE	2	2
GERMANY	1	2
GREECE	2	6
ITALY	1	2
SPAIN	2	2
THE NETHERLANDS	2	5

www.escardio.org

EURObservational Research Programme





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 – 65)
- LA diameter (mm), median (IQR): 40 (32 – 54)



Atrial Fibrillation Ablation Pilot Registry Investigations and procedures during the hospital stay – 4/4

	All (n. 1391 pts)
Coronary angiography, %	3.0
Holter, %	23.7
Exercise test, %	3.2
EP study, %	13.9
Transesophageal echocardiography, %	67.2
CT scan	49.9
MRI scan	10.6



Atrial Fibrillation Ablation Pilot Registry Ablation Procedure Modality

	All (n. 1391 pts)
Non-irrigated radiofrequency, %	4.0
Radiofrequency with closed irrigation, %	2.2
Radiofrequency with open irrigation, %	77.8
Cryo, %	13.4
Duty-cycled radiofrequency energy, %	4.4
Laser balloon (endoscopic ablation system), %	0.8



Atrial Fibrillation Ablation Pilot Registry Ablation Procedure – 1/2

	All (n. 1391 pts)
Procedure duration (min), median (IQR)	180 (130 – 220)
Fluoroscopy total time (min), median (IQR)	26 (15 – 45)
General anesthetic during procedure, %	21.2
Transesophageal echocardiogram during procedure, %	10.5



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 – 1/2

No 1282/1391 (92.2%) **Yes** 107/1391 (7.7%) **Unknown** 2/1391 (0.1%)

	Yes (n. 107 pts)
CV, %	43.0
General, %	5.6
GI, %	0.9
Neuro, %	8.4
Peripheral/vascular, %	16.8
Pulmonary, %	7.5
Other, %	28.0



Atrial Fibrillation Ablation Pilot Registry Adverse Events – 2/2

Description – 1/3

Cardiovascular (n. 46 pts)

Cardiac Arrest	1
Bradycardia requiring Pacemaker	3
Endocarditis	1
Myocardial infarction	1
Pericarditis	17
Cardiac perforation	11
No AF, atypical atrial flutter	4
Other	12

General (n. 6 pts)

Allergic Reaction	4
Sepsis	2



Atrial Fibrillation Ablation Pilot Registry Adverse Events – 2/2

Description – 2/3

GI (n. 1 pt)

Esophageal Ulceration	1
-----------------------	---

Neuro (n. 9 pts)

Phrenic Nerve Damage	2
Stroke	4
TIA	4

Pulmonary (n. 8 pts)

Hemothorax	3
Pleural Effusion	2
Pneumothorax	1





Atrial Fibrillation Ablation Pilot Registry Adverse Events – 2/2

Description – 3/3

Peripheral/Vascular (n. 18 pts)

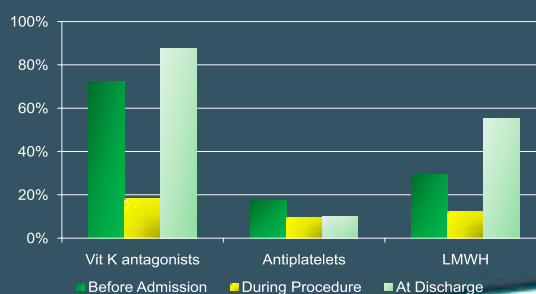
A-V Fistula	6
Bleeding requiring transfusion	1
Hematoma requiring evacuation or transfusion	4
Peripheral thromboembolic event	1
Pseudo aneurysm	6

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Medications: antithrombotics (n. 1391)

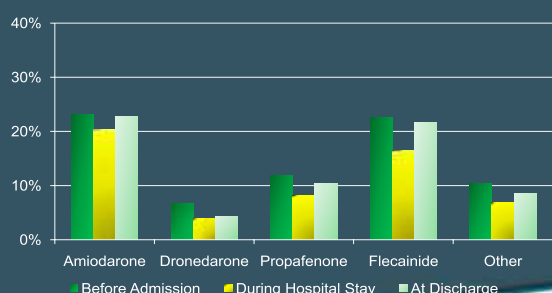


www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Medications: antiarrhythmics (n. 1391)

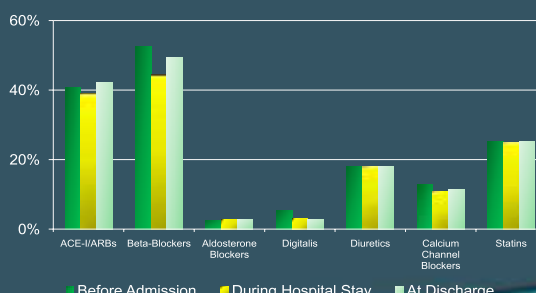


www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Medications: other CV (n.1391)

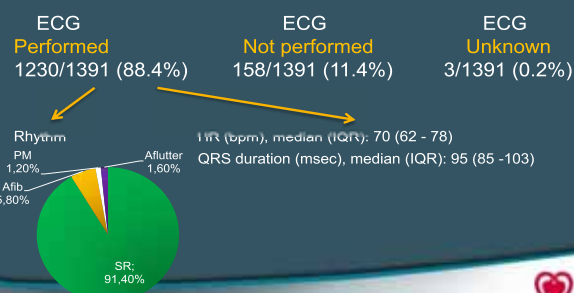


www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry ECG at discharge



www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Discharge

	All (n. 1391 pts)
Length of stay (days), median (IQR)	3 (2 - 4)
Cardiac death not procedure related	1
Events not related to AF, %	2.9
• CV, %	36.6
• Non CV, %	63.4

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Description of death

- Woman born on 02/08/1940
- Hypertrophic cardiomyopathy
- PM
- Hypertension
- Lung cancer radical operation in 1996
- Paroxysmal AF
- Ablation procedure on 01/04/2011
- Procedure duration = 95 min
- Acute success YES
- Cardiovascular AEs (cardiac arrest & endocarditis)

www.escardio.org

EURObservational Research Programme



Atrial Fibrillation Ablation Pilot Registry Conclusions

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 data-set 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 of 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.

www.escardio.org

EURObservational Research Programme





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

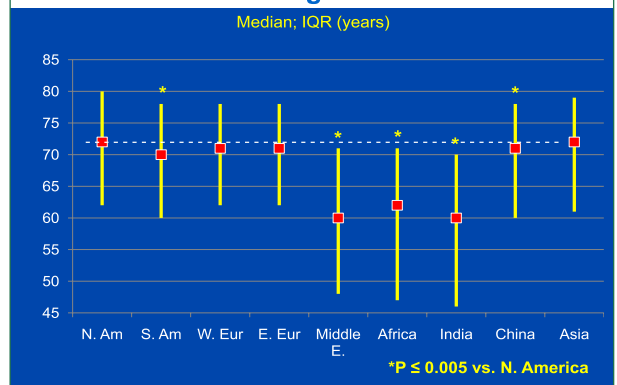
47 countries; 163 sites; 15,174 patients



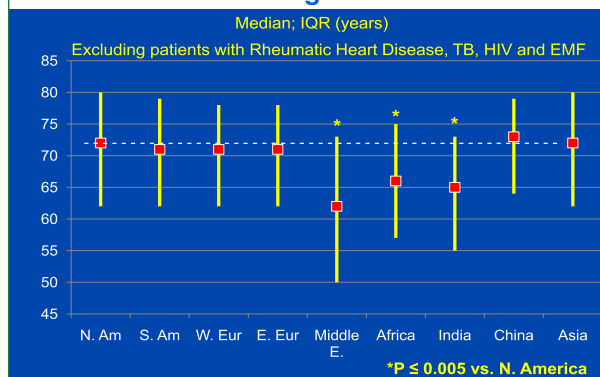
Patient Characteristics

- **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: 26%
 - Permanent AF: 40%

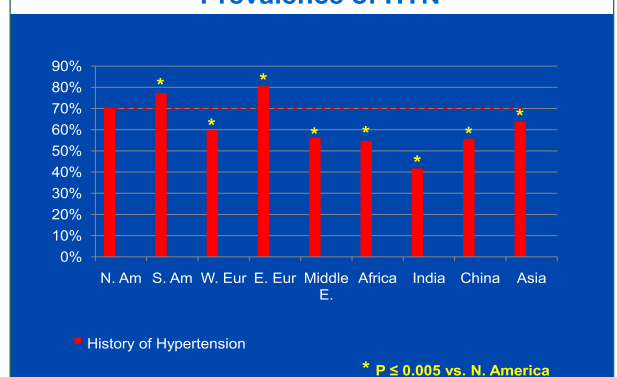
Age



Age

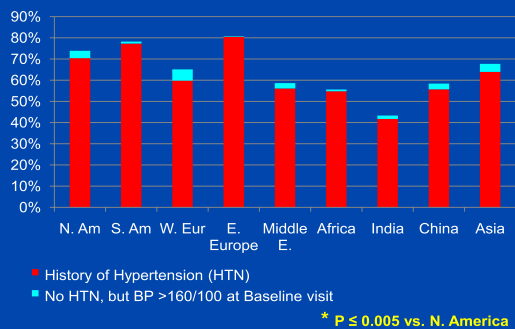


Prevalence of HTN

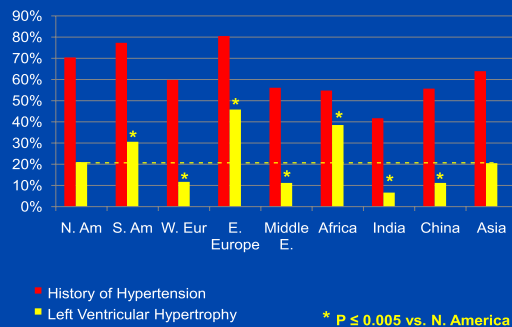




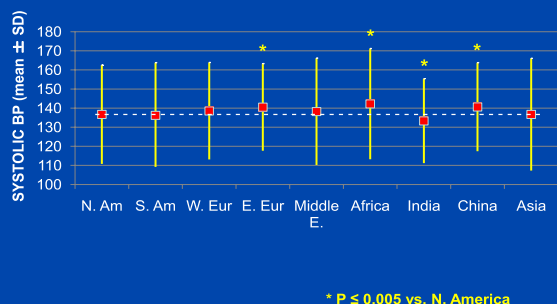
Patients with HTN and patients without history of HTN, but BP >160/100 at baseline



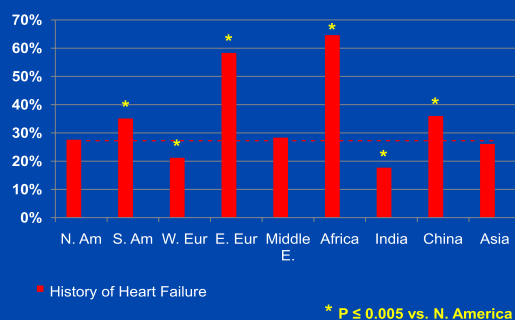
Patients with HTN: Proportion with LVH



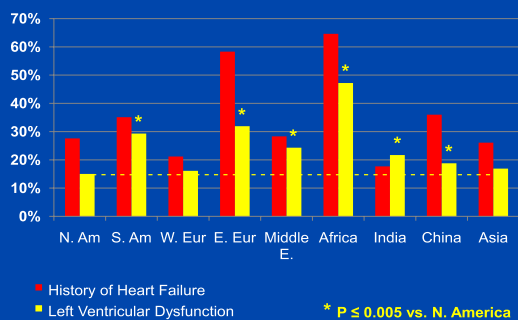
Patients with HTN: Systolic BP



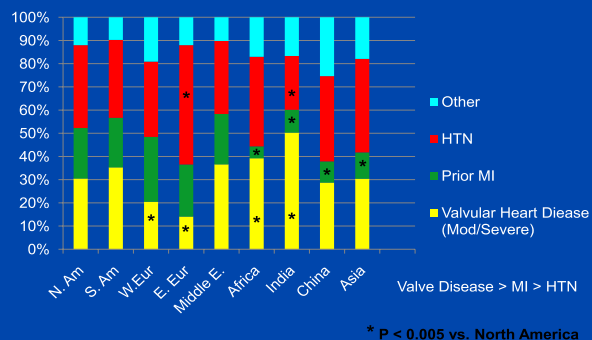
Heart Failure



Heart Failure and Systolic LV Dysfunction

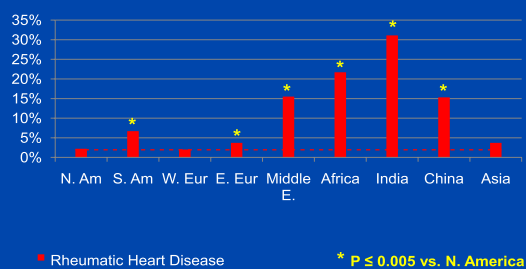


Primary Etiology of Heart Failure

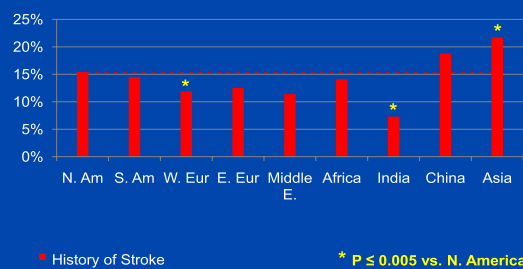


Prevalence of Rheumatic Heart Disease

N = 1760 patients



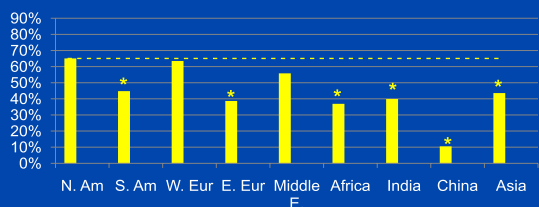
History of Stroke





Oral Anticoagulant Use: CHADS₂ ≥ 2

Patients with a Prior History of AF

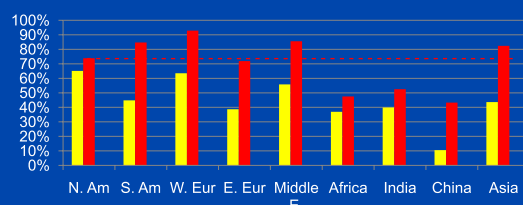


■ OAC Use CHADS₂ ≥ 2

* P ≤ 0.005 vs. N. America

Oral Anticoagulant Use: CHADS₂ ≥ 2 and Rheumatic

Patients with a Prior History of AF



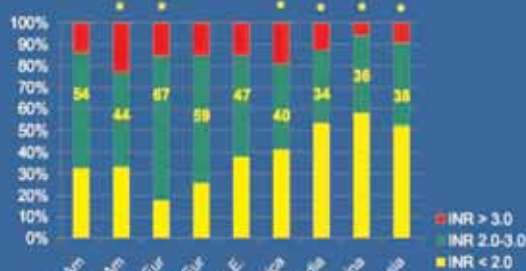
■ OAC Use Rheumatic

■ 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

• Steering committee

- J. Healey, S. Connolly, S. Yusuf (Canada); J. Oldgren, L. Wallentin (Sweden); M. Ezekowitz, A. Parekh (USA); A. Avezum (Brazil); P. Jansky (Czech Republic); P. Commerford (South Africa); J. Zhu, Lisheng Liu (China); P. Pais, A. Sigamani (India);

• Study Coordination

- A. Grinvalds, E. Themeles (Canada)
- Population Health Research Institute (Canada); Dante Pazzanese (Brazil); St. John's Research Institute (India); Fuwai Hospital (China)

• Study Sponsor

- Boehringer-Ingelheim: P. Reilly, J. Varrone



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

Imperial College
London



EUROACTION PLUS

Aim

The aim was to determine in high medical risk smokers 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

Imperial College
London



EUROACTION + Intensive Smoking Cessation with Varenicline



UK



Netherlands



Italy



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

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

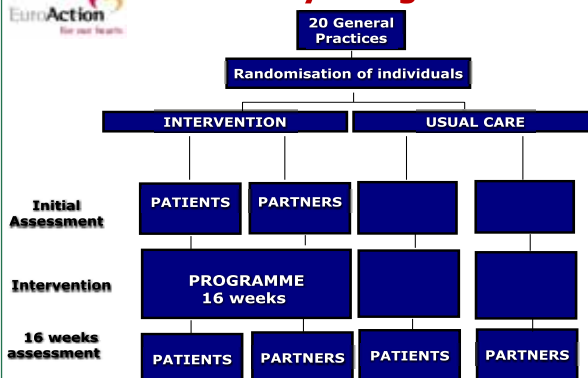
Study Population (2)

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

- i) Newly identified high multifactorial risk individuals: CVD risk equal or greater than 5% over 10 years according to the HeartScore risk estimation system
- ii) Are under treatment with antihypertensive and/or lipid-lowering therapies
- iii) Diagnosed with diabetes mellitus

Study Design

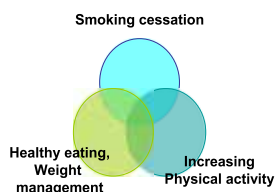


The EUROACTION PLUS preventive cardiology programme



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:

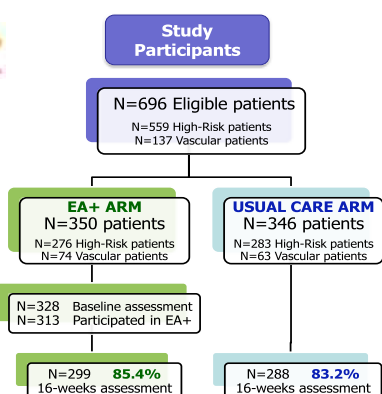
- Diet/ nutrition (Food Habit Questionnaire, Mediterranean Diet Score)
- Physical activity (7-day PAR, Pedometer, Chester step test, DASI physical activity questionnaire)
- Overweight/ obesity (body mass index (BMI), waist circumference)



Secondary Outcomes

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

- Blood pressure
- Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, calculated low-density lipoprotein (LDL) cholesterol
- Diabetes (known/new, fasting and random plasma glucose, glycated haemoglobin (Hb A1c) in patients with diabetes)
- Cardioprotective drug therapies
- Health Related Quality of Life (EQ-5D and EQ-VAS)



Distribution of patient characteristics

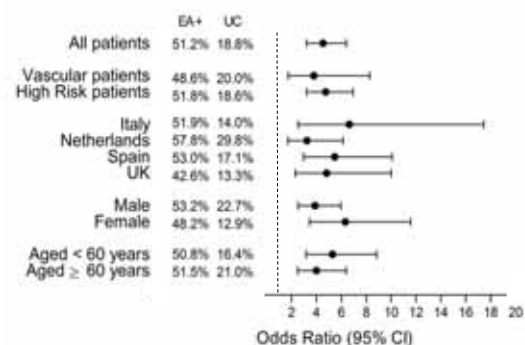
	Usual Care N=346	EuroAction+ N=350
Mean age	60.4 yrs	59.6 yrs
Aged < 60 years	47.6%	51.1%
Women	39.6%	41.1%
Vascular patient	18.2%	21.1%
Low education*	26.6%	25.3%
Not employed**	43.5%	44.0%
Centre		
Italy	15.3%	14.9%
Netherlands	25.4%	24.3%
Spain	32.7%	34.0%
UK	26.6%	26.9%

*primary school or less; **unemployed, house person or retired

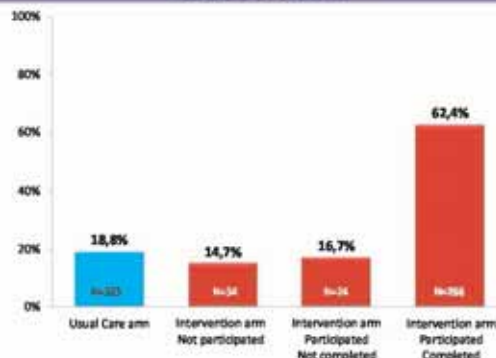
Smoking abstinence for last 7 days confirmed by breath CO <10ppm PRIMARY ENDPOINT



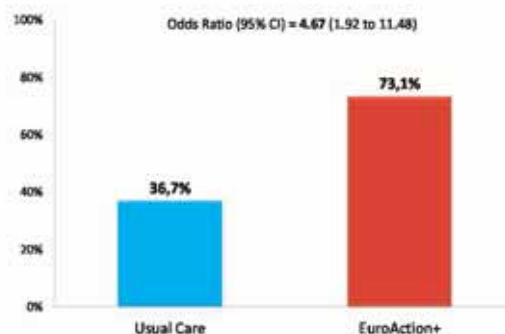
Smoking abstinence for last 7 days confirmed by breath CO <10 ppm PRIMARY ENDPOINT

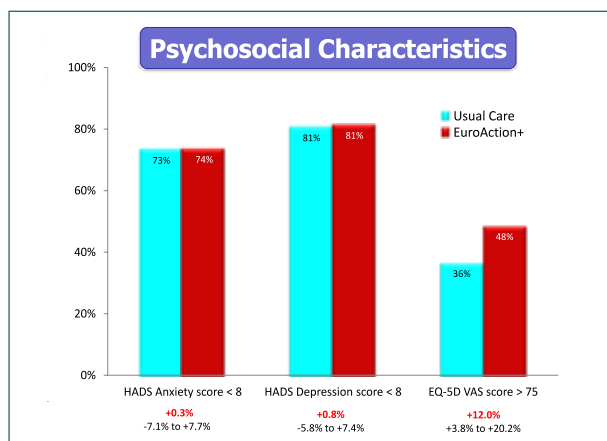
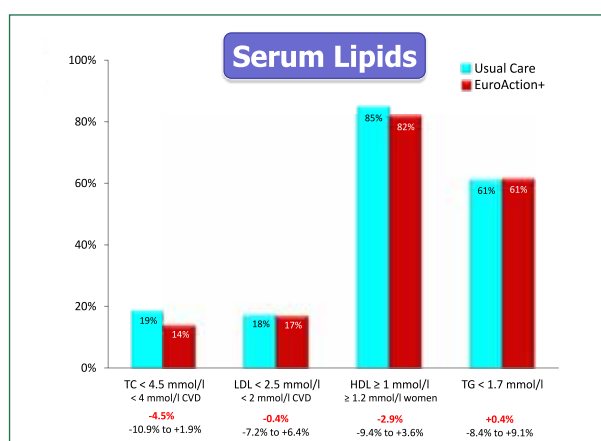
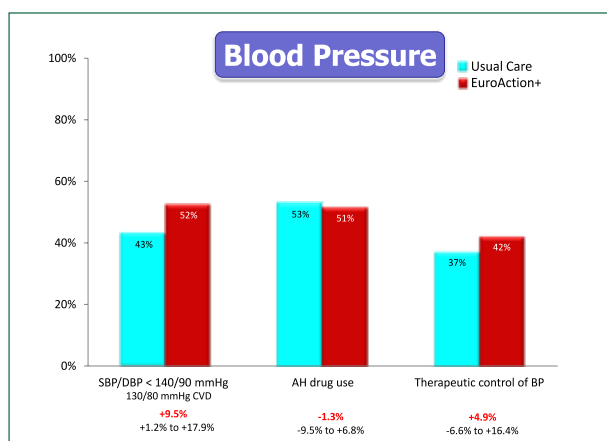
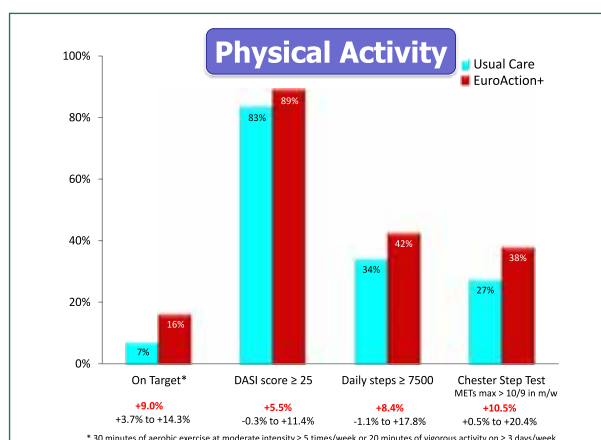
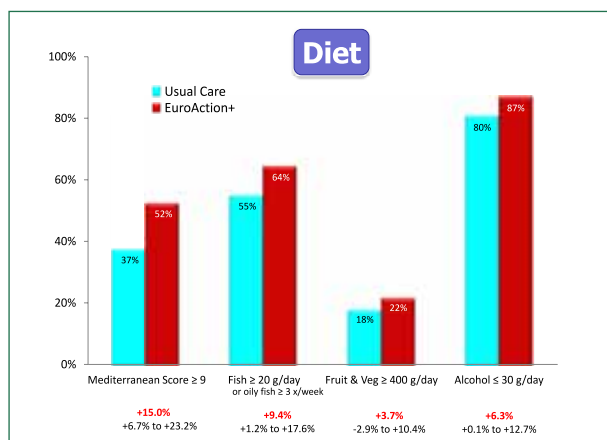


Smoking abstinence for last 7 days confirmed by breath CO <10 ppm PRIMARY ENDPOINT



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





Co-ordinating and Data Management Centre

Cardiovascular Medicine, International Centre for Circulatory Health,
National Heart and Lung Institute,
Imperial College London, UK

Professor David Wood (Professor of Cardiovascular Medicine), **Dr Kornelia Kotseva** (Senior Clinical Research Fellow), **Catriona Jennings** (Research Nurse Co-ordinator); **Alison Mead** & **Dr Anne Majumdar** (Dietetic specialist input); **Jennifer Jones** & **Shauna Raugust** (Physical activity input); **Raunaque Hasnat**, **Ahmadur Rahman** (Data Managers); **Magda Kudyba**, **Agnieszka Adamska** (Administrative Assistants)

Statistical Centre

Department of Public Health, Ghent University, Ghent, Belgium
Professor Dirk De Bacquer

National Coordinators and Teams

Italy
Professor Silvio Brusaferro
Professor Paolo Fioretti

The Netherlands
Professor Arno Hoes
Dr Monika Hollander & Dr Frans Rutten

Spain
Professor Jose de Velasco
Dr Jorge Navarro

United Kingdom
Professor David Wood
Dr Jonathan Morrell

Imperial College London

Smoking Cessation Specialist Advisors

Professor Serena Tonstad
Professor Peter Hajek
Ronnie Troughton

Imperial College London



EUROASPIRE III: modelling the clinical and cost-effectiveness of optimizing cardiovascular prevention in patients with established coronary heart disease in Europe

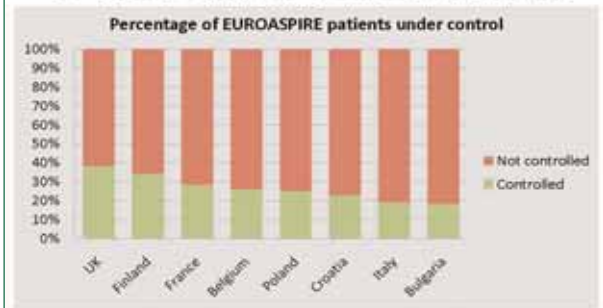
Delphine De Smedt (Ghent University, BE)
Lieven Annemans (Ghent University, BE)
Guy De Backer (Ghent University, BE)
Dirk De Bacquer (Ghent University, BE)
Kornelia Kotseva (Imperial College)
David Wood (Imperial College)

ESC PARIS, August 2011
Clinical Registry Highlight I
HL030

Study funded by EACPR



1. The reality of EUROASPIRE III



Controlled = Cholesterol and BP on target, non smoking

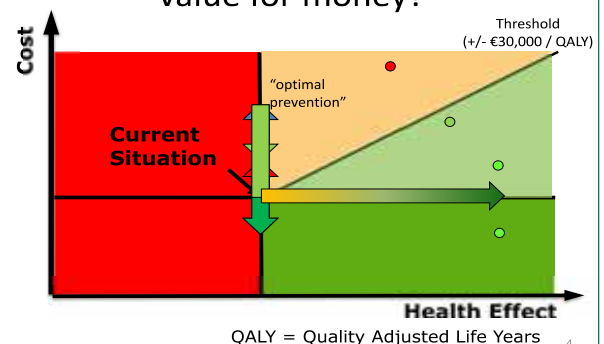
Source: own analysis based on EUROASPIRE III

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

Source: Graham I. et al: European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the ESC and other societies on cardiovascular disease prevention in clinical practice. Eur J Cardiovasc Prev Rehabil 2007, 14(Suppl 2):E1-40.

3. Will optimizing prevention be value for money?

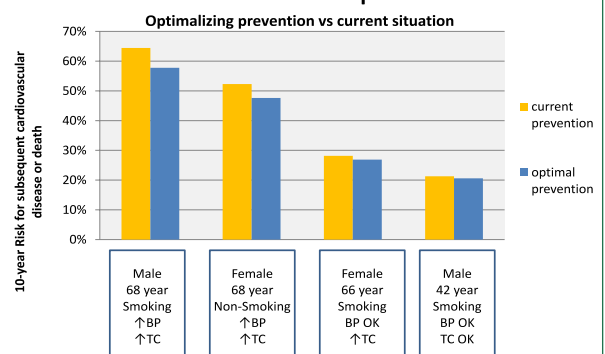


4. Methodology: five steps

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

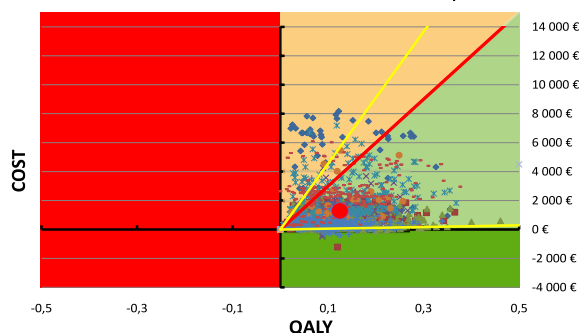
5

Some examples



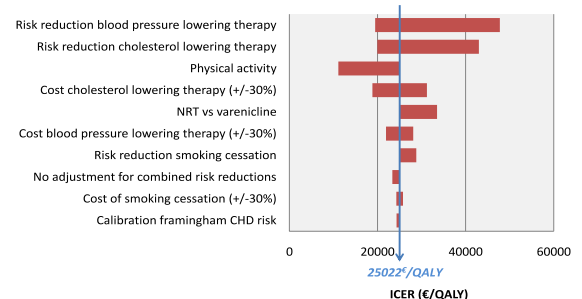
5. Results

5.1. Overall cost-effectiveness: €16000/QALY



5. Results

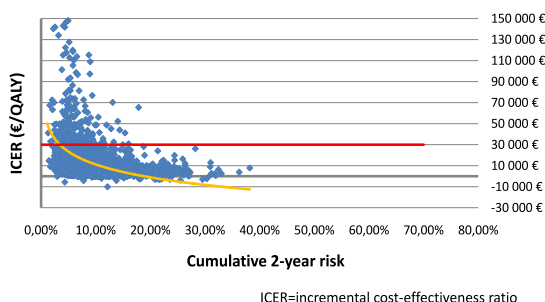
5.2. Uncertainty surrounding the results-UK example





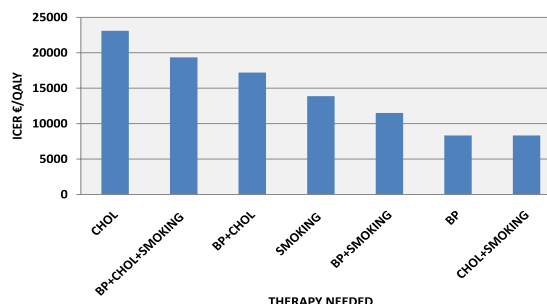
5. Results

5.3. Cost-effectiveness in function of risk status



5. Results

5.3. Cost-effectiveness in function of prevention 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 for 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. Loirat², A. Desplanques-Leperre², G. Derumeaux³, JF Thebaut³, 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

Disclosures

F Schiele reports receiving grant supports paid to his institution and travel support for scientific meetings from Astra Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Medtronic, Pfizer, Sanofi, Servier, Takeda.

G Derumeaux reports receiving grant supports paid to her institution from Astra Zeneca, Actelion, Bayer, Brahms, General Electric, Medtronic, Pfizer, Servier, Toshiba, Trophos, and travel support for scientific meetings from Actelion, Astra Zeneca, Boehringer Ingelheim, Medtronic, Pfizer, Sanofi, Servier.

F. Capuano, P. Loirat, J. Thebaut, A. Desplanques-Leperre, and C. Gardel have no conflict of interest to report.

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

¹ Ross *New Engl J Med* 2010;362:1110

² Canto *New Engl J Med* 2000;342:1573

³ Casale *J Am Coll Cardiol* 1998;32:885

⁴ West *Eur Heart J* 2011;32:706

⁵ Spertus *J Am Coll Cardiol* 2010;56:1767

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 analyses**: 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

Appropriate Prescription = prescription in absence of CI or non prescription in case of documented CI

- **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 heart failure
- **Assessment of LVEF and ACEI (or ARB)** in patients with LVEF<0.40
 - CI= Intolerance or hypotension
- **Statins** regardless of cholesterol level
 - CI= Intolerance

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 ORs for individual and composite QIs

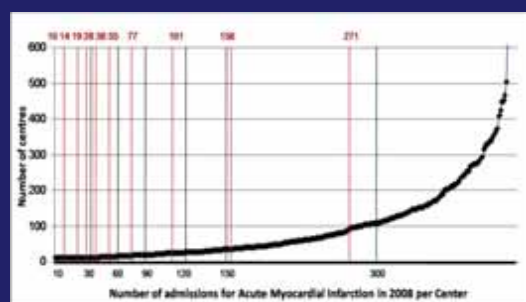
Temporal trend:

- Using 2008, 2009 and 2010 campaigns. Limited to centers who participated in all 3 campaigns
- Adjusted OR for Composite QI, by Volume class (±90 patients/year) and by year.

46 390 patient records

	2008 (12mo) 18159 records 598 centers	2009 (6mo) 12837 records 330 centers	2010 (9mo) 15394 records 359 centers
<10 records 759 (1.7%)	377 (3.7%) 186 centers	40 (0.3%) 7 centers	42 (0.3%) 5 centers
10-30 records 6628 (14.3%)	2486 (13.7%) 136 centers	2060 (16.3%) 120 centers	2082 (12.8%) 113 centers
>30 records 39003 (84.0%)	14996 (82.6%) 276 centers	10737 (83.0%) 203 centers	13270 (81.3%) 241 centers
3 years >10 39776 (85.1%)	14644 (80.6%) 291 centers	11638 (83.0%) 291 centers	13494 (87.7%) 291 centers

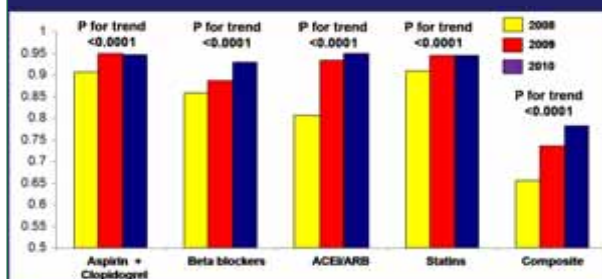
Center Volume distribution



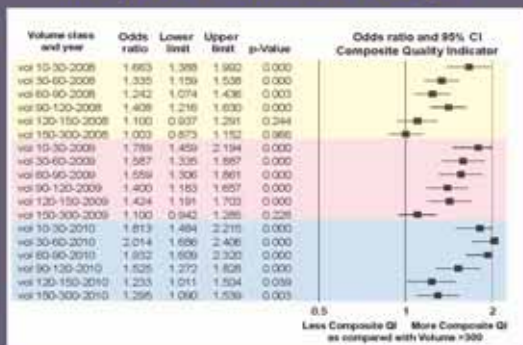
QI rates in Centers with >10 records in 2008

		2008	2009	2010
Aspirin and clopidogrel	CI to aspirin	804	289	347
	CI to clopidogrel	1628	816	963
	QI (%)	16151(88.9)	12178(94.9)	14583(94.7)
Beta Blockers	Absolute CI to betablockers	1672	918	1219
	Relative CI to betablockers	2047	130	616
	QI (%)	15465(85.2)	11392(88.7)	14326(93.1)
ACEI	LVEF assessment	15393	11410	13878
	LVEF< 40	3223	2332	2772
	CI to ACEI	396	269	327
	QI (%)	2685(80.8)	1909(93.4)	2301(94.8)
Statins	CI to statins	1121	624	736
	QI (%)	18159(89.2)	12837(94.4)	15394(94.6)
Composite QI		11398(62.8)	9486(73.9)	12101(78.6)

Temporal trends in QI rates

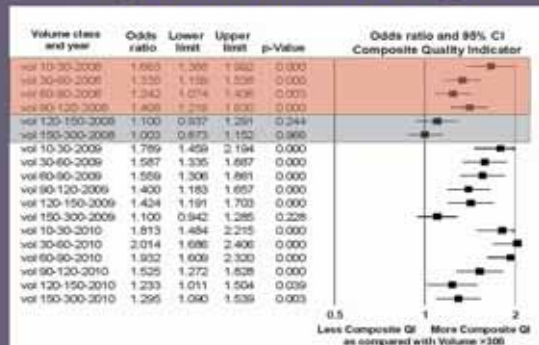


Impact of Volume on QIs



OR adjusted for age and gender

Impact of Volume on QIs



OR adjusted for age and gender



Temporal interaction Volume-QI

Quality Indicators	Odds ratio	Lower limit	Upper limit	p-Value	Odds ratio and 95% CI Failure of Quality Indicators
Aspirin-clopidogrel, 2008	1.523	1.353	1.714	0.000	P=0.15 for interaction
Aspirin-clopidogrel, 2009	1.404	1.180	1.671	0.000	
Aspirin-clopidogrel, 2010	1.494	1.276	1.749	0.000	
Betablockers, 2008	1.042	0.945	1.149	0.409	P=0.016 for interaction
Betablockers, 2009	1.338	1.165	1.537	0.000	
Betablockers, 2010	1.338	1.165	1.537	0.000	
ACEI/ARB, 2008	1.048	0.854	1.286	0.654	P=0.001 for interaction
ACEI/ARB, 2009	1.852	1.292	2.655	0.001	
ACEI/ARB, 2010	1.723	1.179	2.518	0.005	
Statins, 2008	1.340	1.189	1.510	0.000	P=0.85 for interaction
Statins, 2009	1.561	1.320	1.846	0.000	
Statins, 2010	1.563	1.337	1.827	0.000	
Composite, 2008	1.192	1.108	1.282	0.000	P<0.001 for interaction
Composite, 2009	1.337	1.221	1.464	0.000	
Composite, 2010	1.478	1.355	1.612	0.000	

0.5 1 2
More High Volume More in Low Volume

OR adjusted for age and gender

Discussion

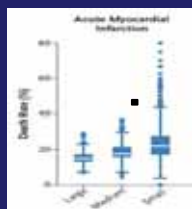
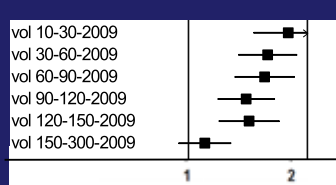
➤ **The strong points** of our study are the robust methodology, the use of a composite measure and the repeated evaluations over three consecutive years (over 46,000 admissions evaluated)

Spertus J Am Coll Cardiol 2010;56:1767

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.



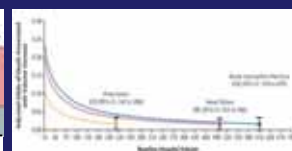
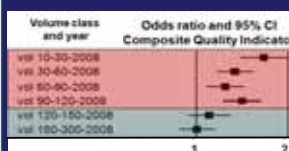
Ross New Engl J Med 2010;362:1110

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



Ross New Engl J Med 2010;362:1110

Discussion

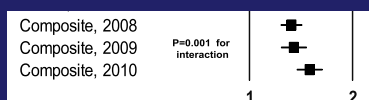
➤ **The strong points** of our study are the robust methodology, the use of a composite measure and the repeated evaluations over three consecutive years (over 46,000 admissions evaluated).

➤ **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

➤ **Magnitude of the effect**: 10 to 15% absolute between high and low volume (the impact of volume on mortality at 30 days after AMI, which was approximately 1 to 4%).

➤ **Persistent** (increased) volume-QI relation over time.



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

➤ **Magnitude of the effect**: 10 to 15% absolute between high and low volume (the impact of volume on mortality at 30 days after AMI, which was approximately 1 to 4%).

➤ **Persistent** (increased) volume-QI relation over time.

➤ **Heterogeneous quality of care** between the volume categories : physician experience has a greater impact than the centre volume

Halm Ann Intern Med 2002;137(6):511-20

West Eur Heart J 2011;32:706

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 ?



ARISTOTLE

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.

Duke Clinical Research Institute

UCR

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,

Duke Clinical Research Institute

UCR

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.

Duke Clinical Research Institute

UCR

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors

- Age ≥ 75 years
- Prior stroke, TIA or SE
- HF or LVEF $\leq 40\%$
- Diabetes mellitus
- Hypertension

Randomize
double blind,
double dummy
(n = 18,201)

Exclusion

- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus
thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

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

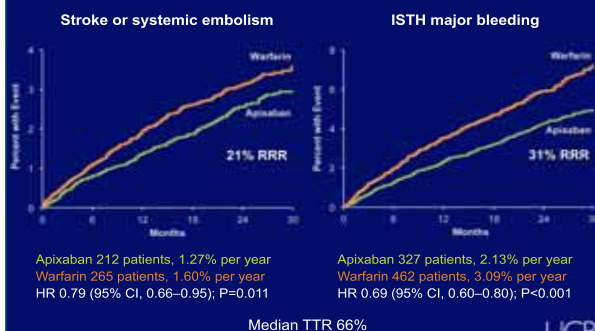
Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for
primary outcome, major bleeding, death

Duke Clinical Research Institute

UCR

ARISTOTLE Main Trial Results

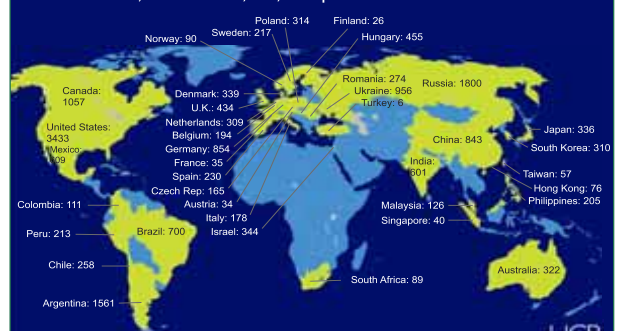


Duke Clinical Research Institute

UCR

Enrollment

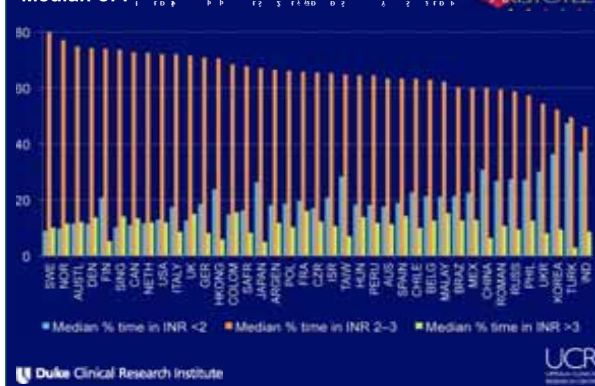
39 countries, 1034 sites, 18,201 patients



Duke Clinical Research Institute

UCR

Median of P



Duke Clinical Research Institute

UCR

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.

Duke Clinical Research Institute

UCR



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=xx).
- The center's TTR was calculated as the median of individual TTRs during the whole study among its 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.

Duke Clinical Research Institute



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 drug), and warfarin naïve/experienced status.

Duke Clinical Research Institute



Baseline Characteristics and Centers' TTR

Center TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	P-value
Number of patients	4538	4535	4533	4538	
TTR with warfarin	50.7	62.5	69.3	76.7	
Warfarin naïve	57.4%	50.3%	35.4%	28.4%	<0.0001
Age (years, median)	68.0	69.0	71.0	72.0	<0.0001
Male	61.8%	61.8%	65.4%	70.1%	<0.0001
Weight (kg, median)	76.3	81.0	83.3	87.0	<0.0001
CHADS2 Score Mean	2.2	2.2	2.1	2.0	<0.0001
CHADS2 Score 3-6	32.6%	31.1%	30.0%	27.0%	<0.0001
Age > 75 yr	24.0%	28.1%	33.1%	39.5%	<0.0001
Prior stroke	13.4%	12.0%	11.5%	9.8%	<0.0001
Heart failure	41.8%	36.5%	27.2%	16.4%	<0.0001
Diabetes mellitus	23.8%	23.9%	25.1%	27.0%	0.0011
Hypertension	86.2%	89.8%	88.1%	85.7%	<0.0001
Prior MI	12.6%	15.3%	13.0%	15.9%	<0.0001

Duke Clinical Research Institute



Baseline Co-medication in Relation to Centers' TTR

Center TTR	<58.0	58.0–65.7	65.7–72.2	≥72.2	P-value
Randomized	4538	4535	4533	4538	
Aspirin	31.2%	35.2%	29.3%	28.2%	<0.0001
ARB	24.0%	21.5%	23.6%	26.5%	<0.0001
ACE I/ARB	70.6%	74.7%	70.2%	69.3%	<0.0001
Beta-blocker	60.3%	63.9%	64.5%	65.9%	<0.0001
Amiodarone	14.7%	13.9%	11.1%	5.8%	<0.0001
Digoxin	36.5%	33.9%	30.9%	28.1%	<0.0001
Lipid Lowering	34.0%	41.2%	47.2%	59.2%	<0.0001

Duke Clinical Research Institute



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

Center TTR (%)	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
< 58.0	70	1.75	88	2.28	0.77 (0.56, 1.06)	0.29
58.0–65.7	54	1.30	68	1.81	0.60 (0.56, 1.15)	
65.7–72.2	51	1.21	60	1.55	0.79 (0.54, 1.13)	
> 72.2	36	0.83	44	1.02	0.81 (0.52, 1.26)	

Duke Clinical Research Institute



Death and Composite Efficacy in Relation to Centers' TTR

Center cTTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
Mortality						0.39
< 58.0	163	3.95	191	4.75	0.83 (0.68, 1.03)	
58.0–65.7	158	3.71	177	4.10	0.91 (0.73, 1.12)	
65.7–72.2	147	3.44	174	4.07	0.84 (0.68, 1.05)	
> 72.2	133	3.03	127	2.91	1.04 (0.82, 1.33)	
Composite Efficacy*						0.27
< 58.0	212	5.31	254	6.57	0.81 (0.67, 0.97)	
58.0–65.7	212	5.12	231	5.50	0.93 (0.77, 1.12)	
65.7–72.2	202	4.83	236	5.66	0.85 (0.71, 1.03)	
> 72.2	180	4.18	185	4.33	0.96 (0.79, 1.18)	

* Composite Efficacy is a composite of stroke, systemic embolism, death and myocardial infarction.

Duke Clinical Research Institute



Bleeding in Relation to Centers' TTR

Center TTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	Events	Rate/100 person yrs	Events	Rate/100 person yrs		
Major bleeding						0.10
< 58.0	64	1.75	115	3.34	0.53 (0.39, 0.72)	
58.0–65.7	61	1.60	102	2.68	0.60 (0.43, 0.82)	
65.7–72.2	103	2.68	109	2.89	0.93 (0.71, 1.21)	
> 72.2	98	2.49	136	3.46	0.72 (0.55, 0.93)	
Major and clinically relevant bleeding						0.005
< 58.0	115	3.19	207	6.13	0.53 (0.42, 0.66)	
58.0–65.7	125	3.32	195	5.24	0.64 (0.51, 0.80)	
65.7–72.2	179	4.75	220	5.99	0.79 (0.65, 0.97)	
> 72.2	191	4.96	255	6.68	0.74 (0.62, 0.90)	

Duke Clinical Research Institute



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

Center TTR	Apixaban		Warfarin		HR (95% CI)	Adjusted Interaction P
	E	Rate/100 person yrs	E	Rate/100 person yrs		
Hemorrhagic stroke						0.5058
< 58.0	14	0.35	26	0.66	0.52 (0.27, 1.00)	
58.0–65.7	9	0.22	26	0.61	0.35 (0.16, 0.75)	
65.7–72.2	13	0.31	18	0.43	0.72 (0.35, 1.47)	
> 72.2	4	0.09	8	0.18	0.50 (0.15, 1.66)	
Net clinical benefit *						0.1060
< 58.0	250	7.00	326	9.74	0.73 (0.61, 0.86)	
58.0–65.7	255	6.86	294	7.95	0.86 (0.73, 1.02)	
65.7–72.2	278	7.44	308	8.40	0.89 (0.75, 1.04)	
> 72.2	255	6.58	285	7.41	0.89 (0.75, 1.05)	

* Net clinical benefit is a composite of stroke, systemic embolism, death and myocardial infarction.

Duke Clinical Research Institute





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.

Duke Clinical Research Institute

ARISTOTLE
UCL

ascot-11
Cardiac Outcomes Trial

The Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA):
11 Year Mortality Follow-up in the UK

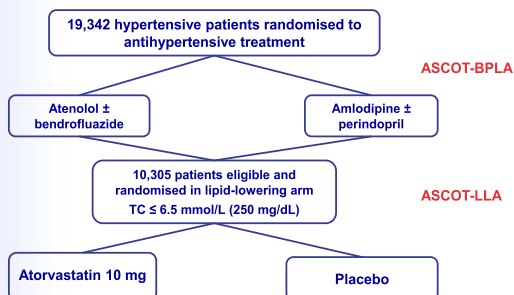
Peter S. Sever*, Choon L. Chang, Ajay Gupta, Andrew Whitehouse and Neil R. Poulter
on behalf of the ASCOT Investigators
*Imperial College London, UK

Presenter Disclosure Information

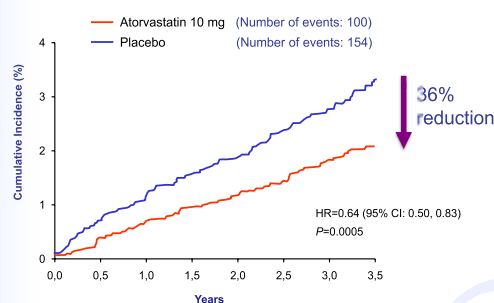
ASCOT-LLA: 11 year mortality follow-up in the UK

- 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

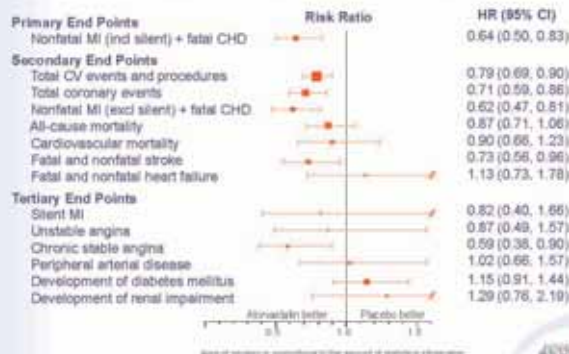
ASCOT Study Design



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



ASCOT-LLA: Effects of Atorvastatin and Placebo on End Points



ASCOT-LLA-Extension

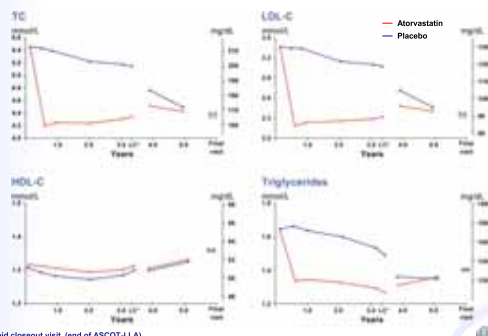
- Early closure of ASCOT-LLA
 - Median follow-up 3.3 years
 - Atorvastatin versus placebo:
 - 36% reduction in the primary endpoint
 - 27% reduction in stroke
- ASCOT-LLA-extension
 - Offering atorvastatin 10 mg daily to all patients in LLA
 - Continued for a further 2.2 years until the closure of ASCOT-BPLA
- Statin usage

	Atorvastatin (n=4978)		Placebo (n=4916)	
	Atorvastatin	Other statins	Atorvastatin	Other statins
End of ASCOT-LLA	4113 (82.6)	54 (1.1)	415 (8.4)	220 (4.5)
End of ASCOT-BPLA*	3122 (62.7)	200 (4.0)	2752 (56.0)	337 (6.9)

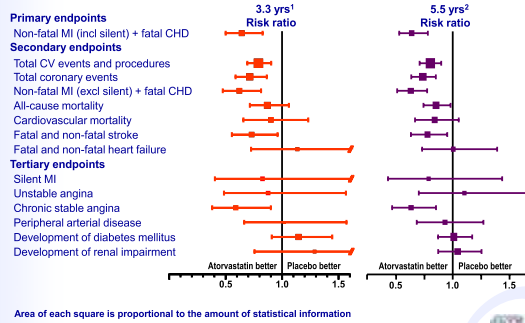
Values are n (%)
*Also the end of LLA-extension



Lipids Levels During ASCOT-LLA and LLA-Extension



ASCOT-LLA endpoints at the end of the trial (3.3 yrs) and at the end of BPLA (5.5 yrs)



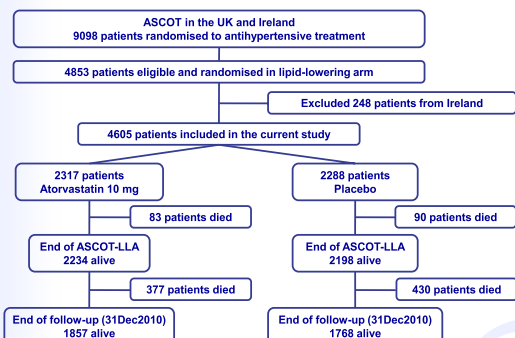
ASCOT-LLA: 11 Year Mortality Follow-up

- 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 diseases)
 - Infection/respiratory combined
- The cut-off date was 31st December 2010 (inclusive)

Statistical Methods

- Patients
 - All patients in the intention-to-treat population who were alive at the end of ASCOT-BPLA (also the end of LLA-extension)
- Cox regression analysis
 - Two randomised 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 smokers, ethnicity, randomised 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 trial period (in- or post-trial)
 - Atorvastatin and randomised blood pressure treatment
 - Whether the atorvastatin effects 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

ASCOT-LLA 11 Year Mortality: Study Profile



Effect of Atorvastatin on Mortality and Causes of Death – 1

Cause of Death	LLA				P value	Total Follow-up				P value
	Placebo N (%)	Atorvastatin Rate ^a	N (%)	Rate ^a	HR (95% CI) ^b	Placebo N (%)	Atorvastatin Rate ^a	N (%)	Rate ^a	HR (95% CI) ^b
All-cause	80 (3.8)	1.26	83 (3.6)	1.16	0.92 (0.66, 1.24)	520 (22.7)	2.24	490 (19.8)	1.94	0.86 (0.76, 0.98)
CV	38 (1.8)	0.51	30 (1.3)	0.43	0.83 (0.54, 1.28)	187 (7.3)	0.73	184 (8.0)	0.86	0.89 (0.72, 1.11)
Non-CV	44 (2.0)	0.77	53 (2.3)	0.75	0.96 (0.67, 1.44)	353 (15.4)	1.52	306 (12.2)	1.26	0.85 (0.73, 0.98)

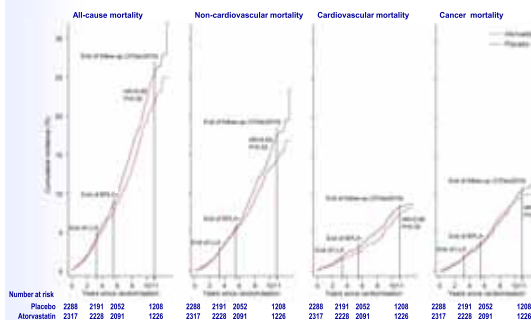
^aPer 100 person-years
^bUnadjusted hazard ratios (HR) (95% confidence interval [CI]) of atorvastatin effect on mortality and causes of death during ASCOT-LLA and total follow-up period

Effect of Atorvastatin on Mortality and Causes of Death – 2

Cause of Death	LLA				P value	Total Follow-up				P value
	Placebo N (%)	Atorvastatin Rate ^a	N (%)	Rate ^a	HR (95% CI) ^b	Placebo N (%)	Atorvastatin Rate ^a	N (%)	Rate ^a	HR (95% CI) ^b
Cancer	37 (1.6)	0.55	39 (1.7)	0.56	1.05 (0.67, 1.65)	212 (9.3)	0.82	201 (8.7)	0.85	0.92 (0.78, 1.12)
Infection/Respiratory	8 (0.3)	0.08	5 (0.2)	0.04	0.51 (0.12, 2.04)	38 (1.6)	0.24	37 (1.6)	0.18	0.74 (0.42, 0.97)
Infection	3 (0.1)	0.04	1 (0.0)	0.01	0.34 (0.04, 3.28)	37 (1.6)	0.16	25 (1.1)	0.10	0.60 (0.36, 1.02)
Respiratory	5 (0.2)	0.04	2 (0.1)	0.03	0.68 (0.11, 4.07)	19 (0.8)	0.08	14 (0.6)	0.06	0.72 (0.38, 1.44)

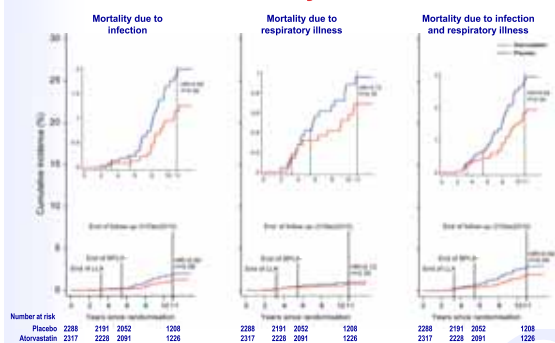
^aPer 100 person-years
^bUnadjusted hazard ratios (HR) (95% confidence interval [CI]) of atorvastatin effect on mortality and causes of death during ASCOT-LLA and total follow-up period

Cumulative Incidence by Cause of Death – 1





Cumulative Incidence by Cause of Death – 2



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

Adjusted Effect of Atorvastatin on Mortality and Causes of Death

Cause of death	LLA		Post-LLA		Total Follow-up	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
All-cause	0.93 (0.89, 1.26)	0.64	0.85 (0.74, 0.98)	0.02	0.88 (0.79, 0.98)	0.02
CV	0.88 (0.82, 1.36)	0.61	0.91 (0.72, 1.17)	0.47	0.90 (0.72, 1.12)	0.36
Non-CV	0.99 (0.65, 1.44)	0.94	0.62 (0.49, 0.87)	0.02	0.84 (0.72, 0.98)	0.03
Cancer	1.05 (0.67, 1.64)	0.84	0.69 (0.72, 1.10)	0.38	0.92 (0.79, 1.11)	0.37
Infection/Respiratory	0.51 (0.13, 2.05)	0.35	0.65 (0.42, 1.01)	0.06	0.64 (0.42, 0.97)	0.04
Infectious	0.33 (0.03, 3.16)	0.33	0.61 (0.36, 1.08)	0.07	0.58 (0.35, 0.98)	0.04
Respiratory	0.73 (0.12, 4.38)	0.73	0.75 (0.58, 1.00)	0.46	0.75 (0.57, 1.00)	0.42

*Participants who died during LLA period were excluded
Adjusted for age, sex, body mass index, systolic blood pressure, total cholesterol, diabetes, current smokers, ethnicity, randomised blood pressure treatment and completion educational age

Statins on Infection

- Experimental studies¹ show statins:
 - Modulate neutrophil function
 - Reduce pro-inflammatory cytokine release
 - Improve vascular function
 - Are anti-thrombotic and
 - Improve outcome from pneumonia and sepsis
- Observational studies have shown prior statin use reduces mortality from sepsis and community acquired pneumonia²
- A review and meta-analysis² of randomised trials and cohort studies found that:
 - In 9 cohorts addressing the role of statins in treating infection, the pooled effect estimate was 0.55 (95% CI: 0.36, 0.83) in favour of statin
 - In cohort studies investigating the prevention of infection in patients with vascular disease, the pooled effect estimate was 0.57 (95% CI: 0.43, 0.75) in favour of statin use
- A recent editorial³
 - Urged caution in their interpretation, on account of the fact that observational, retrospective and meta-analytical studies cannot eliminate the possibility of confounding bias
 - highlighted the need for formal prospective randomized controlled trials to be conducted

1. Chalmers JD, et al. *Resp Med*. 2010;104:1081-1091.
2. Tiegehe IM, et al. *Arch Intern Med*. 2009;169:1658-1667.
3. Chopra V and Flanders SA. *BMJ*. 2011;342:d1907

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

	Placebo (n=2198)	Atorvastatin (n=2234)	P value
Male, n (%)	1923 (87.5)	1948 (87.1)	0.70
Age (Years)	64.30 (8.21)	64.31 (8.10)	0.99
Age <60 years	1534 (69.8)	1560 (69.8)	0.98
White, n (%)	1939 (88.2)	1974 (88.4)	0.95
Current Smokers, n (%)	589 (26.8)	585 (26.2)	0.57
Alcohol (units/week)	11.17 (14.44)	10.82 (13.41)	0.41
SBP (mmHg)	162.18 (17.84)	162.00 (17.32)	0.74
DBP (mmHg)	92.75 (9.51)	92.41 (9.85)	0.24
BMI (kg/m ²)	28.89 (4.60)	28.87 (4.85)	0.92
Total Cholesterol (mmol/L)	5.49 (0.81)	5.48 (0.81)	0.66
LDL-C (mmol/L)	3.46 (0.75)	3.45 (0.74)	0.65
HDL-C (mmol/L)	1.29 (0.35)	1.30 (0.35)	0.50
Triglycerides (mmol/L)	1.66 (0.88)	1.64 (0.91)	0.32
Glucose (mmol/L)	6.34 (2.30)	6.22 (2.15)	0.08
Creatinine (mmol/L)	100.45 (16.89)	100.25 (17.12)	0.65
Stroke/TIA, n (%)	224 (10.2)	226 (10.1)	0.93
Diabetes, n (%)	641 (29.2)	632 (28.3)	0.52
LVH, n (%)	590 (27.3)	595 (26.6)	0.91
Peripheral vascular disease, n (%)	140 (6.4)	154 (6.9)	0.48
Other CV diseases, n (%)	55 (2.5)	63 (2.8)	0.51
Number of risk factors	3.72 (0.89)	3.69 (0.90)	0.31
Amlodipine, n (%)	1107 (50.4)	1108 (49.5)	0.57
Previous lipid-lowering drug, n (%)	21 (1.0)	28 (1.3)	0.34
Aspirin use, n (%)	490 (22.3)	511 (22.9)	0.64
Previous anti-BP drugs, n (%)	177 (8.1)	194 (8.7)	0.71
≥ 1	2021 (91.9)	2040 (91.3)	

Values are mean (SD) or n (%)

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 - 66yrs** (range 40-82)
 - expected lifelong therapy: **15-25 yrs** up to > 40 yrs
- ✓ ASCOT-LLA-UK offers some answers but raises also more questions

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

Trial	Follow-up	RR/HR	95% CI	p
4S	10 yr	0.85	0.74,0.97	.016
WOSCOPS	14,7 yr	0.88	0.79,0.98	.03
ASCOT-LLA UK	11 yr	0.86	0.76,0.98	.02

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 pharmaco-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 : 201= 0.85/100py
 - Placebo : 212= 0.92/100py HR 0.92 (CI 0.76,1.12)

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

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)

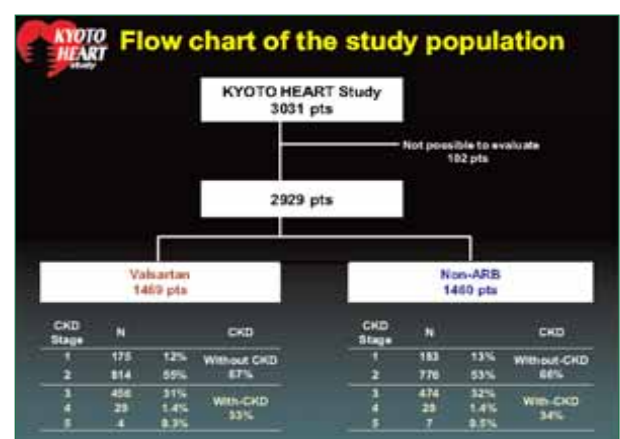
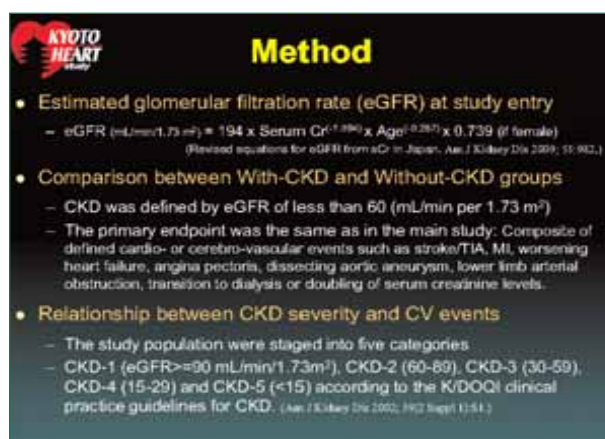
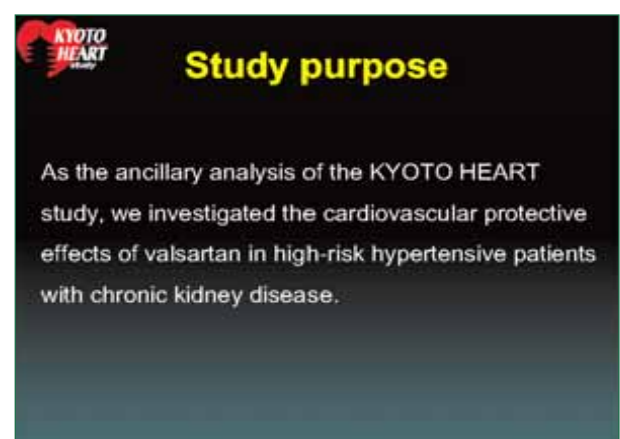
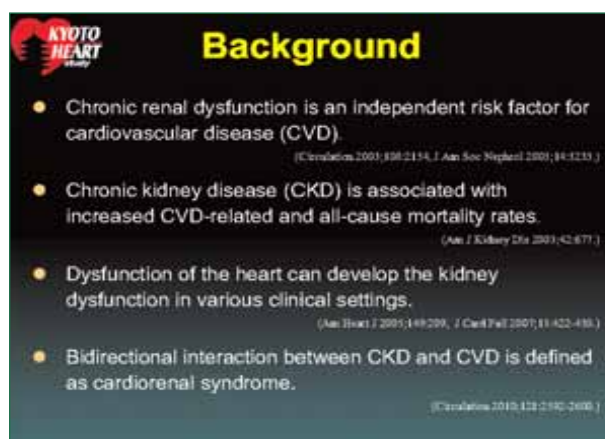
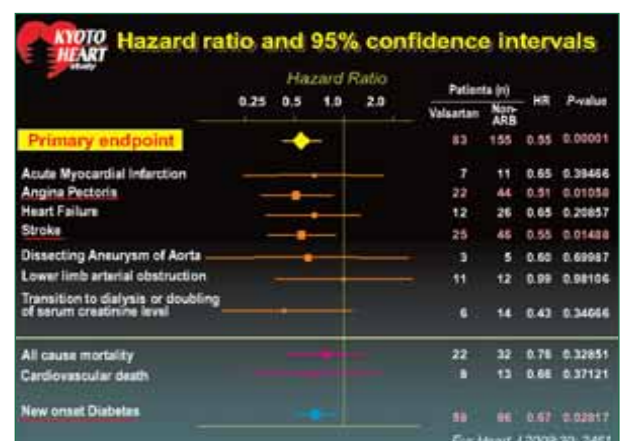
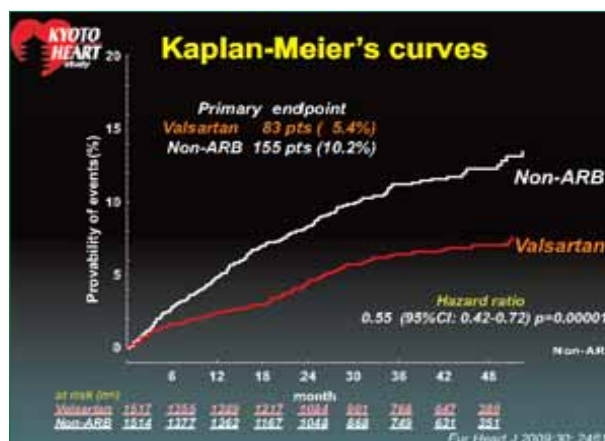
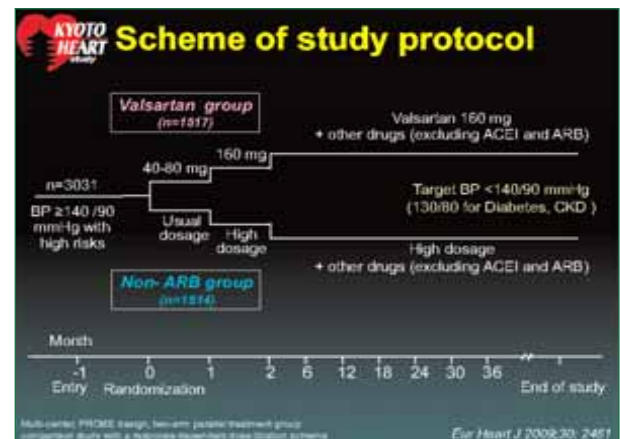
Cardiovascular protective effects of valsartan in high-risk hypertensive patients with chronic kidney disease: updated analysis of KYOTO HEART Study



Sawada T, Koide M, Shiraishi J, Yamada H, Matsubara H
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.





Baseline characteristics

	With-CKD			Without-CKD		
	Valsartan 480	Non-ARB 501	ALL 981	Valsartan 989	Non-ARB 959	ALL 1948
Age (years)*	70 ± 10	70 ± 10	70 ± 10	63.9 ± 11.1	63.8 ± 11	63.8 ± 11
Gender (men/women)	273 / 207	276 / 225	549 / 432	563 / 426	561 / 398	1124 / 824
Blood pressure (mmHg)						
Systole	158 ± 15	158 ± 15	158 ± 15	157 ± 14	156 ± 13	156 ± 14
Diastole	88 ± 12	87 ± 12	87 ± 12	89 ± 11	88 ± 11	89 ± 11
Heart rate (beats/min)	71 ± 19	72 ± 15	71 ± 17	70 ± 17	70 ± 17	70 ± 17
Body-mass index (kg/m ²)	25 ± 3.5	24 ± 3.9	24 ± 3.7	24.5 ± 3.7	24.7 ± 3.8	24.6 ± 3.8
LDL-cholesterol (mg/dL)	123 ± 32	123 ± 31	123 ± 31	122 ± 53	123 ± 31	122 ± 43
HDL-cholesterol (mg/dL)	54 ± 15	54 ± 16	54 ± 16	56 ± 15	55 ± 15	55 ± 15
Triglyceride (mg/dL)	151 ± 82	152 ± 86	152 ± 84	149 ± 102	154 ± 97	151 ± 99
HbA1c(%)	6.3 ± 3.7	6.1 ± 1.3	6.2 ± 2.7	6.0 ± 1.4	6.0 ± 1.2	6.0 ± 1.3
Fasting plasma glucose (mg/dL)	124 ± 49	122 ± 44	123 ± 47	121 ± 45	122 ± 46	121 ± 46
Serum creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
eGFR (mL/min/1.73m ²)**	48 ± 9	48 ± 10	48 ± 9	78 ± 15	79 ± 16	78 ± 16
Sodium (mEq/L)	144 ± 16	142 ± 14	143 ± 14	141 ± 6	146 ± 11	144 ± 8
Potassium (mEq/L)	4.3 ± 0.4	4.3 ± 1.0	4.3 ± 0.8	4.6 ± 1.0	4.3 ± 2.5	4.5 ± 0.8
Risk factor						
Obesity	189 (39%)	179 (36%)	368 (38%)	382 (39%)	384 (40%)	766 (39%)
Dyslipidemia	349 (73%)	378 (75%)	727 (74%)	687 (69%)	669 (70%)	1356 (70%)
Diabetes	124 (26%)	148 (30%)	272 (28%)	260 (26%)	241 (25%)	501 (26%)
Current smoker	87 (18%)	87 (17%)	174 (18%)	244 (25%)	232 (24%)	476 (24%)
Ischemic heart disease**	143 (30%)	152 (30%)	295 (30%)	200 (20%)	182 (19%)	382 (20%)
Cerebrovascular disease	19 (4%)	26 (5%)	45 (5%)	39 (4%)	37 (4%)	76 (4%)
LVH on ECG	129 (27%)	141 (28%)	270 (28%)	266 (27%)	259 (27%)	525 (27%)
Congestive heart failure**	35 (7%)	67 (13%)	102 (10%)	45 (5%)	36 (4%)	81 (4%)

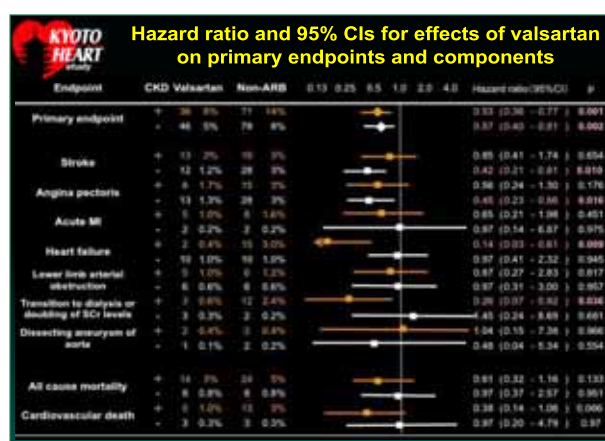
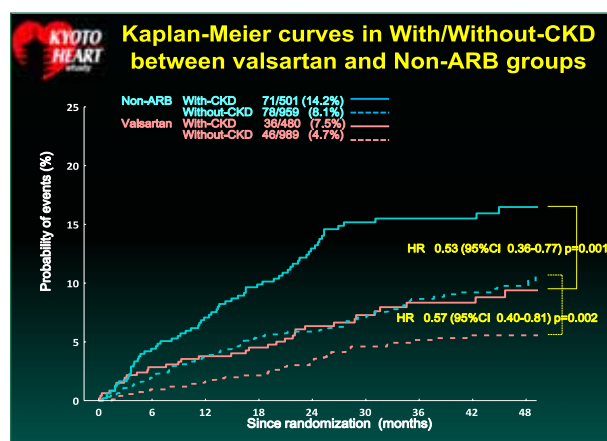
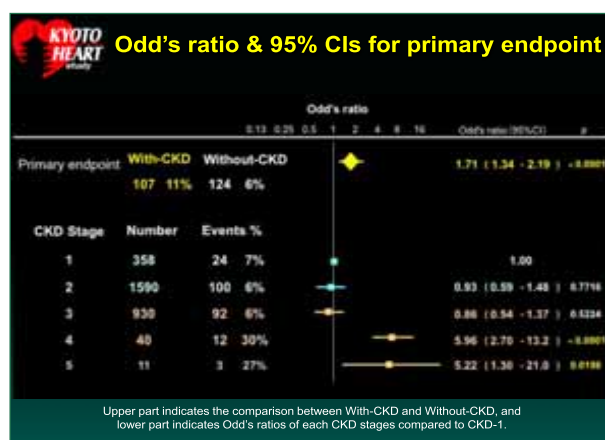
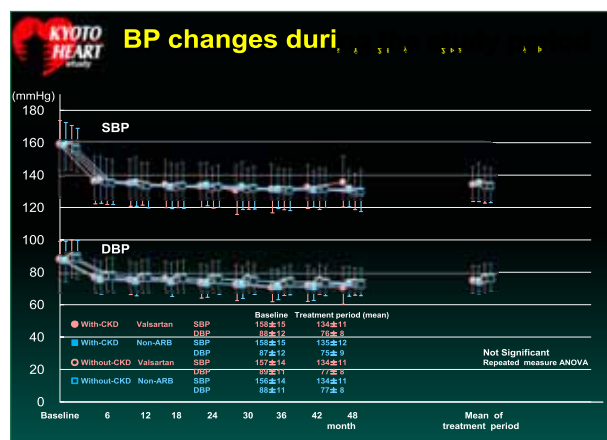
Data are mean ± SD or number (%), p* < 0.05 and p** < 0.01 compared between With-CKD vs Without-CKD.



Baseline medications at the entry

	With-CKD			Without-CKD		
	Valsartan 480	Non-ARB 501	ALL 981	Valsartan 989	Non-ARB 959	ALL 1948
Calcium-channel blocker	265 (55%)	297 (59%)	562 (57%)	542 (55%)	503 (52%)	1045 (54%)
ACE inhibitor**	100 (21%)	123 (25%)	223 (23%)	177 (18%)	171 (18%)	348 (18%)
β-blocker**	99 (21%)	106 (21%)	205 (21%)	157 (16%)	161 (17%)	318 (16%)
α-blocker	19 (4%)	19 (4%)	38 (4%)	25 (3%)	28 (3%)	53 (3%)
Thiazide	14 (3%)	19 (4%)	33 (3%)	38 (4%)	25 (3%)	63 (3%)
Other diuretics	38 (8%)	53 (11%)	91 (9%)	33 (3%)	28 (3%)	61 (3%)
Anti-aldosterone agent	15 (3%)	15 (3%)	30 (3%)	15 (2%)	10 (1%)	25 (1%)
Antiarrhythmic drugs	15 (3%)	29 (6%)	44 (4%)	31 (3%)	26 (3%)	57 (3%)
Nicorandil	31 (6%)	20 (4%)	51 (5%)	33 (3%)	31 (3%)	64 (3%)
Anti-coagulating agent	35 (7%)	45 (9%)	80 (8%)	51 (5%)	57 (6%)	108 (6%)
Anti-platelet agent**	149 (31%)	161 (32%)	310 (32%)	238 (24%)	245 (26%)	483 (25%)
Nitroglycerine or ISDN	53 (11%)	58 (12%)	111 (11%)	76 (8%)	65 (7%)	141 (7%)
Digoxin	11 (2%)	20 (4%)	31 (3%)	20 (2%)	21 (2%)	41 (2%)
Statin	150 (31%)	182 (36%)	332 (34%)	324 (33%)	303 (32%)	627 (32%)
Fibrate	14 (3%)	14 (3%)	28 (3%)	21 (2%)	16 (2%)	37 (2%)
Other lipid modulating drugs	18 (4%)	12 (2%)	30 (3%)	25 (3%)	17 (2%)	42 (2%)
Oral hypoglycemic agent(SU)	44 (9%)	55 (11%)	99 (10%)	122 (12%)	113 (12%)	235 (12%)
Other hypoglycemic agent	46 (10%)	50 (10%)	96 (10%)	92 (9%)	89 (9%)	181 (9%)
Insulin	13 (3%)	24 (5%)	37 (4%)	25 (3%)	15 (2%)	40 (2%)

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.

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 undersize 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.

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.



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 27%
 - CHF 16%
- 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 22%
 - 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

**Comments 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
life style characteristics
(„healthy adherer phenomenon“)



Objectives of ONTARGET

Patients:

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

Questions:

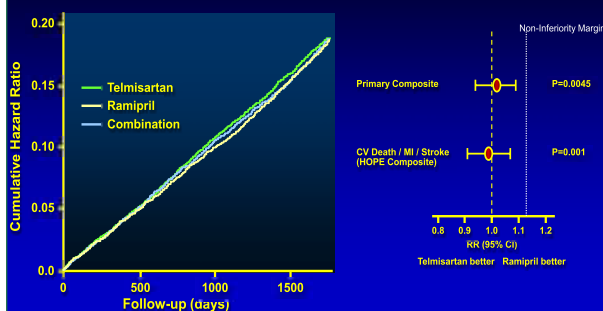
- 1.Is telmisartan “non-inferior” to ramipril?
- 2.Is the combination superior to ramipril?

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

ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial, Am Heart J 148: 52-61, 2004

Primary Outcome Telmisartan vs. Ramipril vs. Combination



ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial, N Engl J Med 358: 1547-1559, 2008

Objective of Current Analysis

- Identification of patient characteristics for nonadherence
- Effect of nonadherence on outcomes
- Effect of CV-outcomes on adherence

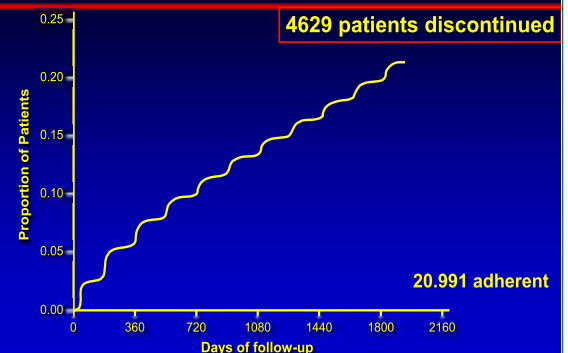
Definitions and Methods

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
- $p < 0.01$

Permanent Stop of Study Medication Continuously Increased Over Time



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

Variable	Pr > ChiSq	HR	95% CI
Age, linear	<0.0001	1.035	(1.030 – 1.039)
Female vs Male	<0.0001	1.200	(1.117 – 1.289)
Black vs White	0.0009	1.302	(1.115 – 1.521)
Asian vs White	<0.0001	0.569	(0.511 – 0.639)
Other vs White	<0.0001	0.645	(0.574 – 0.726)
Activity 2-6/week vs ≤ 1/week	<0.0001	0.863	(0.804 – 0.927)
Every day vs ≤ 1/week	<0.0001	0.806	(0.750 – 0.865)
Smoking Current vs Never	0.0005	1.193	(1.080 – 1.316)
Smoking Formerly vs Never	0.0026	1.113	(1.038 – 1.192)
Stroke / TIA	0.0013	1.128	(0.974 – 1.128)
History of diabetes	<0.0001	1.223	(0.927 – 1.104)
Episodes of depression	<0.0001	1.111	(0.867 – 1.036)

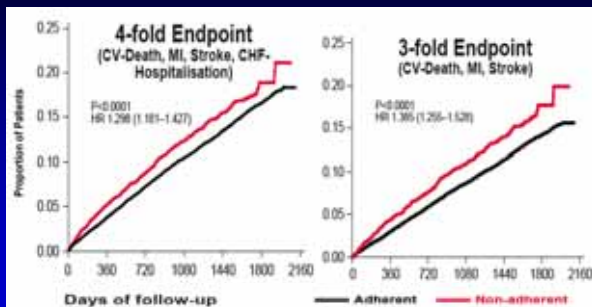
➡ Age, Gender, Ethnicity, Physical Activity, Smoking, Diabetes, neuro-psychiatric disorders

Distribution of Premature Permanent Discontinuations of Study Medication - By Time

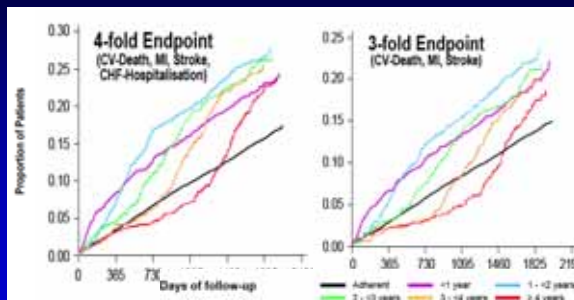
Permanent discontinuation	Frequency	Percent	Cumulative Frequency	Cumulative Percent
< 6 weeks	354	7.7	354	7.7
6w - < 6 months	585	12.6	939	20.3
6m - < 1 year	619	13.4	1558	33.7
1y - < 2 years	1038	22.4	2596	56.1
2y - < 3 years	785	17.0	3381	73.0
3y - < 4 years	613	13.2	3994	86.3
≥ 4 years	635	13.7	4629	100.0



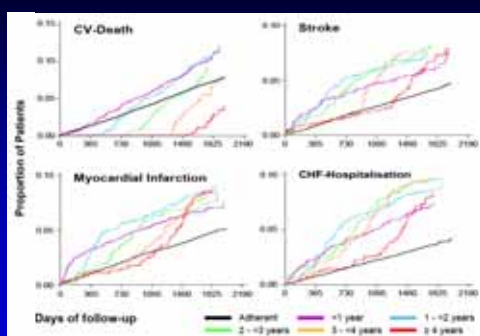
Nonadherence Increases Overall Event Rates



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



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

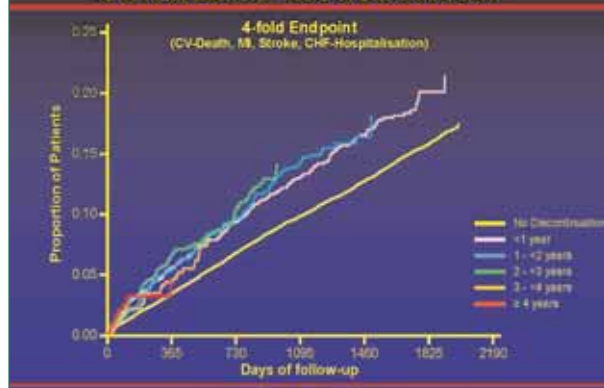


Cox Model with Time-Dependent Covariate

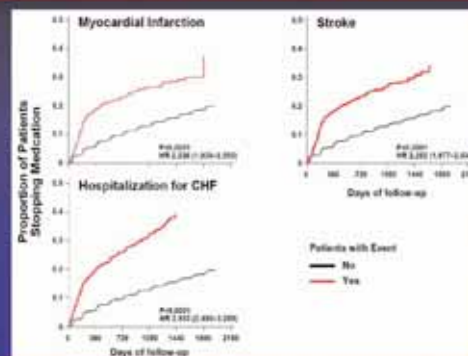


Time-dependent (HR for being off medication)	p	Hazard Ratio (CI)
4-fold endpoint	<0.0001	1.298 (1.181 – 1.427)
3-fold endpoint	<0.0001	1.385 (1.255 – 1.528)
CV death	<0.0001	2.050 (1.824 – 2.303)
MI	0.6568	1.043 (0.888 – 1.256)
Stroke	0.5171	1.066 (0.879 – 1.293)
CHF Hospitalisation	<0.0001	1.464 (1.228 – 1.745)

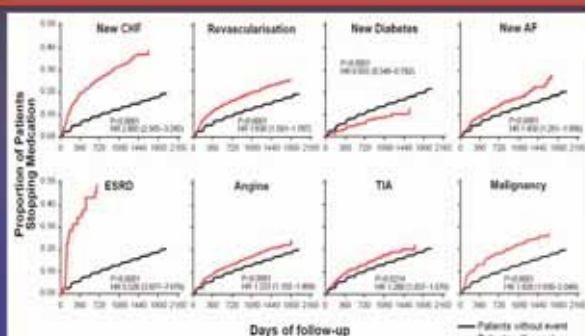
Rate of Rise of Event Rates after Stop of Study Medication is Similar Between Years of Discontinuation



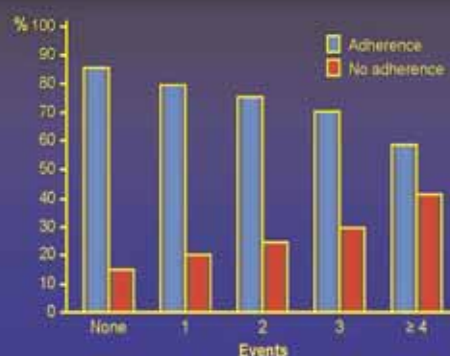
Risk for Discontinuation of Medication is Increased After Nonfatal Primary Event



Risk for Discontinuation of Medication is Increased After Nonfatal Other Events

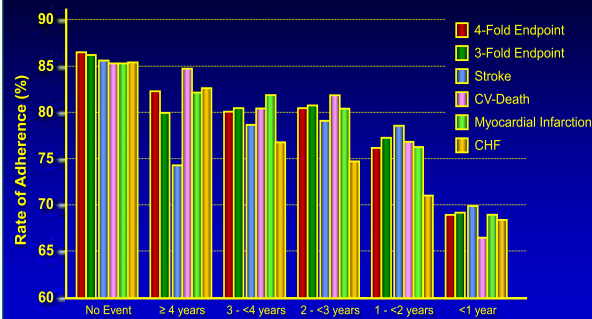


Number of Events Increases Nonadherence





Patients with an Early Event Have Worse Mean Adherence Rates

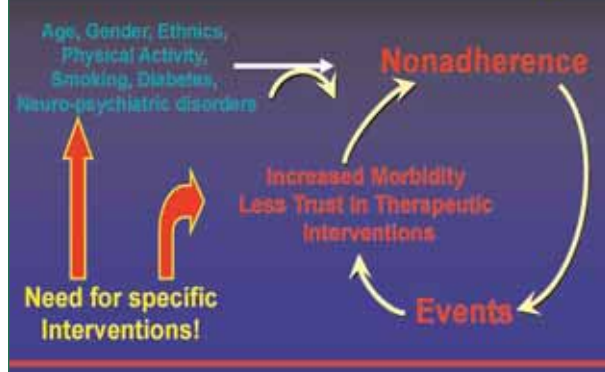


Conclusions:



- 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!

Concept: Nonadherence-Event Vicious Cycle



BOLESTI SRČANIH ZALISTAKA

Jure Mirat
Vedran Ćorić
i suradnici



ISBN: 978-953-167-244-3

Rujan 2011.

Izdavač: Nakladni zavod Globus

Cijena: 350 kn



Medication adherence and outcomes in high-risk cardiovascular patients in the ONTARGET trial

Discussant

Luigi Tavazzi, MD
GVM Care and Research
Cotignola (IT)

Paris - ESC Congress 2011
August 28th

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

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

The effects of non-adherence are difficult to disentangle

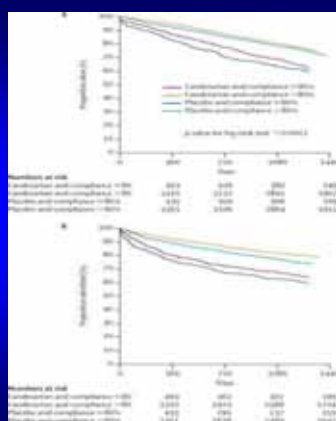
- Analysis of "placebo populations"
- Analyses of populations of "neutral" randomized controlled trials

Adherence to PLACEBO was associated to IMPROVED SURVIVAL in:

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

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%

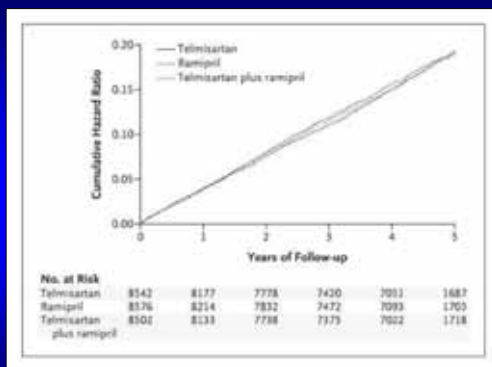


CHARM programme
Placebo group:
adherence effects
on mortality (panel A)
HF Hospitalization
(panel B)

Granger BB, et al. Lancet 2005;366:2005-11

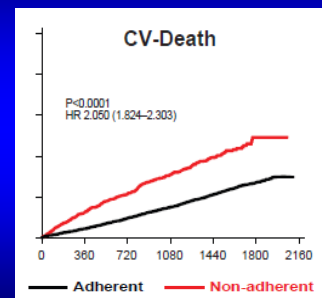
The effects of non-adherence are difficult to disentangle

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



ONTARGET investigators: NEJM 358(15):1547-1559, April 10, 2008

ONTARGET trial Effect of Adherence on Mortality



Non-adherence : new information from ONTARGET analyses

- Profile of non-adherer
- Impact of time discontinuation on events (modelling 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

Non-adherence : new information from ONTARGET analyses

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

Impact of time discontinuation on events

- An increase in events occurred rapidly after stopping treatment

Non-adherence : new information from ONTARGET analyses

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

Impact of ev

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

Impact of re on event rates

- Therapeutic drug monitoring (TDM) is the measurement of drug concentrations in blood or plasma to ensure that the drug concentration is within the therapeutic range and to avoid adverse events or for other reasons

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

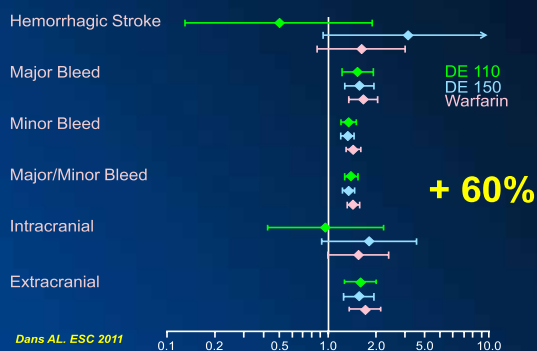
Dear First Woman Catholic, Amsterdam

DISCLOSURES FOR FREEK W.A. VERHEUGT

Research support/ principal investigator	Bayer HealthCare, Boehringer Ingelheim, Eli Lilly and Company, and Roche
Consultant	Bayer (the Netherlands), Eli Lilly and Company, and Merck & Co., Inc.
Speakers' bureau	Eli Lilly and Company and Merck & Co., Inc.
Honoraria	Bayer (the Netherlands), Eli Lilly and Company, and Merck & Co., Inc.
Scientific advisory board	AstraZeneca

One Year Women's Confab, Australia

Antiplatelet vs. No antiplatelet: Bleeding

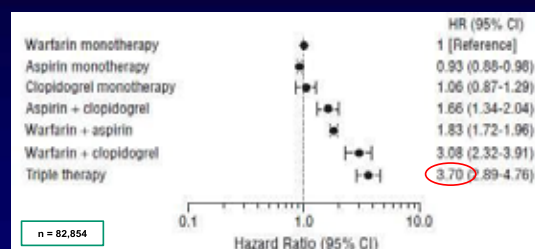


Dans AL. ESC 2011

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

Source 1: *Source 101* P.O. Box 1000, New York, NY 10001. Source 2: *Source 201* P.O. Box 2000, New York, NY 10001. Source 3: *Source 301* P.O. Box 3000, New York, NY 10001. Source 4: *Source 401* P.O. Box 4000, New York, NY 10001. Source 5: *Source 501* P.O. Box 5000, New York, NY 10001. Source 6: *Source 601* P.O. Box 6000, New York, NY 10001. Source 7: *Source 701* P.O. Box 7000, New York, NY 10001. Source 8: *Source 801* P.O. Box 8000, New York, NY 10001. Source 9: *Source 901* P.O. Box 9000, New York, NY 10001. Source 10: *Source 1001* P.O. Box 1000, New York, NY 10001.

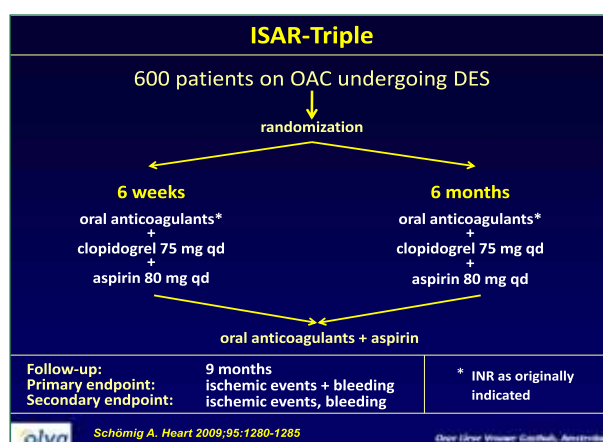
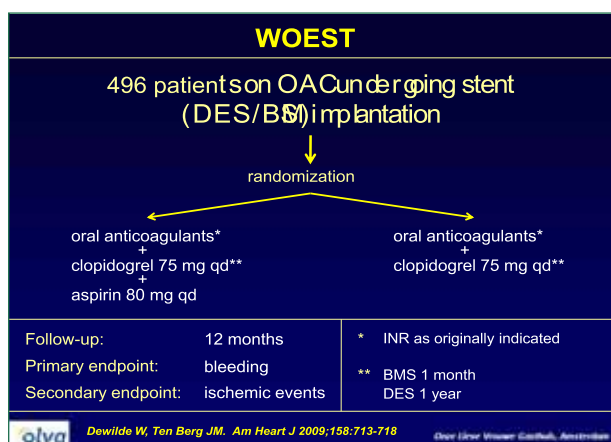
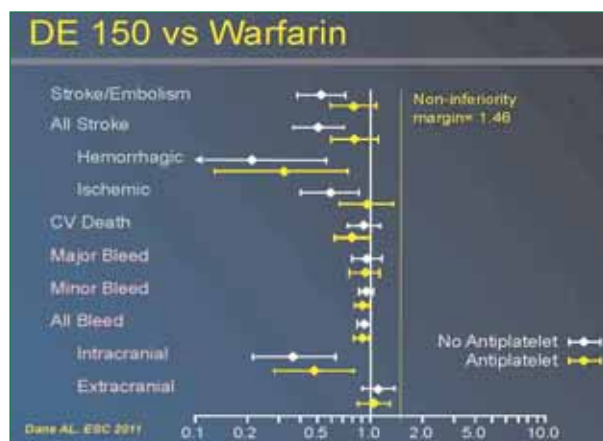
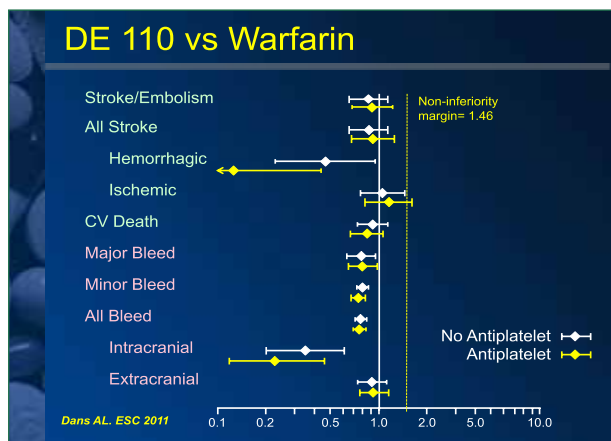
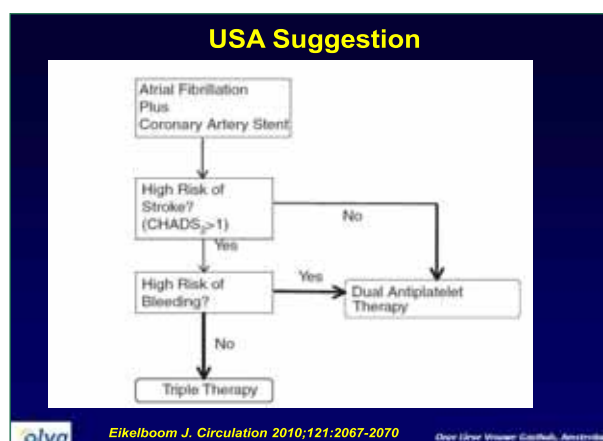
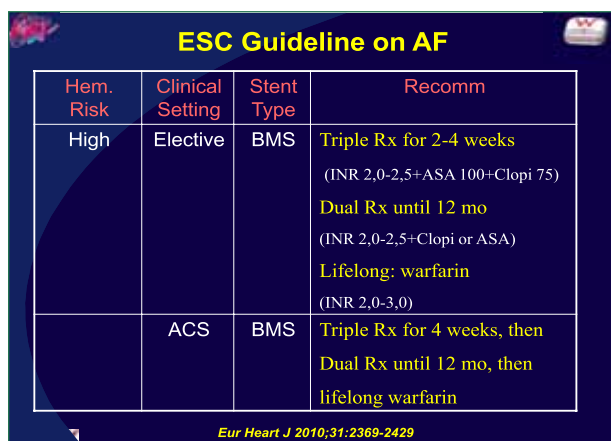
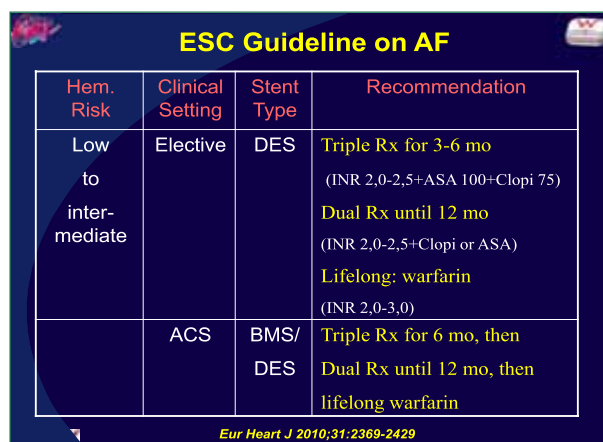
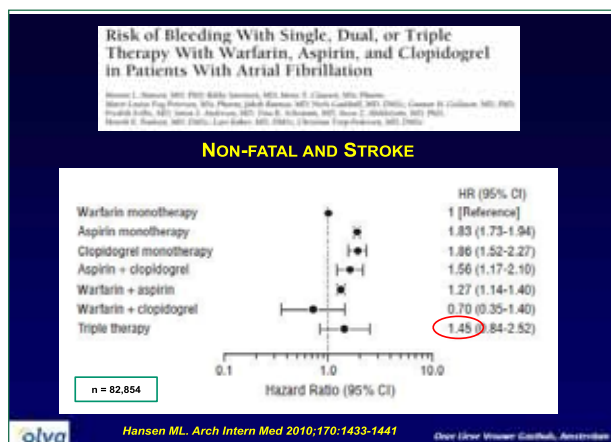
NON-FATAL AND FATAL BLEEDING



n = 82,854

Hansen ML. Arch Intern Med 2010;170:1433-1441

Open House Museum Catalogue, Australia





MUSICA-2

300 patients with AF (CHADS₂ ≤ 2) on OAC undergoing stenting

randomization

6 months

oral anticoagulants*

clopidogrel 75 mg qd

+ aspirin 100 mg qd

6 months

clopidogrel 75 mg qd

+ aspirin 300 mg qd

Follow-up:
Primary endpoint:
Secondary endpoint:

12 months
ischemic events + death
major and minor bleeding

* INR as originally
indicated



clinicaltrials.gov NCT01141153

Oliver H. Wagner, Götting, Amsterdam

NOVEL ANTICOAGULANTS AND DUAL ANTIPLATELET THERAPY

Conclusions-1

1. In RE-LY 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



Oliver H. Wagner, Götting, Amsterdam

NOVEL ANTICOAGULANTS AND DUAL ANTIPLATELET THERAPY

Conclusions-2

4. Low dose dabigatran seems a good candidate for patients with AF in the need of antiplatelet therapy (e.g. stenting and/or ACS), **but** this has to be confirmed in a new randomized trial against warfarin. However, it is unlikely, that such a trial will be done



Oliver H. Wagner, Götting, Amsterdam

ARISTOTLE

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

Duke Clinical Research Institute



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, Otsuka, Pfizer, sanofi-aventis, and The Medicines Company

Duke Clinical Research Institute



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.

Duke Clinical Research Institute



Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors

- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind,
double dummy
(n = 18,201)

Major exclusion criteria

- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

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

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Duke Clinical Research Institute





Enrollment

18,201 patients, 1034 sites, 39 countries



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

Objectives and Statistics

To control the overall type I error, a pre-specified hierarchical sequential testing was performed.

- The primary outcome (stroke or systemic embolism) for non-inferiority (upper limit of 95% CI < 1.38 and upper limit of 99% CI < 1.44)
- If met, then the primary outcome was tested for superiority
- If met, then major bleeding was tested for superiority
- If met, then all-cause mortality was tested for superiority

Methods

- The primary analyses were performed using Cox proportional hazards modeling with warfarin-naïve 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

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (25 th , 75 th %ile)	70 (63, 76)	70 (63, 76)
Women, %	35	35
Region, %		
North America	25	25
Latin America	19	19
Europe	40	40
Asia/Pacific	16	16
Warfarin naïve, %	43	43
CHADS ₂ score, mean (+/- SD)	2.1 (+/- 1.1)	2.1 (+/- 1.1)
≤ 1, %	34	34
2, %	36	36
≥ 3, %	30	30

Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	35	36
Diabetes	25	25
Hypertension	87	88
Renal function (Cr _{CL} , ml/min), %		
Normal (>80)	41	41
Mild impairment (>50 – 80)	42	42
Moderate impairment (>30 – 50)	15	15
Severe impairment (≤ 30)	1.5	1.5

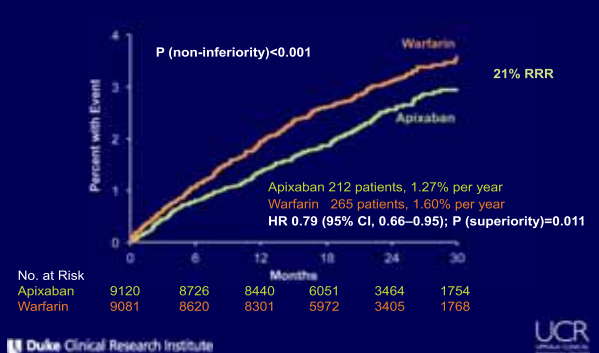
Trial Metrics

- Patients enrolled from December 2006 to April 2010
- Median duration of follow-up 1.8 years
- Drug discontinuation in 25.3% of apixaban and 27.5% of warfarin patients (p=0.001)
- Vital status at the end of the trial was missing in 380 (2.1%) patients
 - Withdrawal of consent in 92 patients in apixaban and 107 patients in warfarin groups
 - Loss to follow-up in 35 apixaban and 34 warfarin patients
- Median (and mean) times in therapeutic INR range among warfarin-treated patients were 66.0 (and 62.2)% calculated for each patient by the Rosendaal* method (excluding first 7 days and study drug interruptions)

*Rosendaal FR et al. Thromb Haemostasis 1993;69:236–39.

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



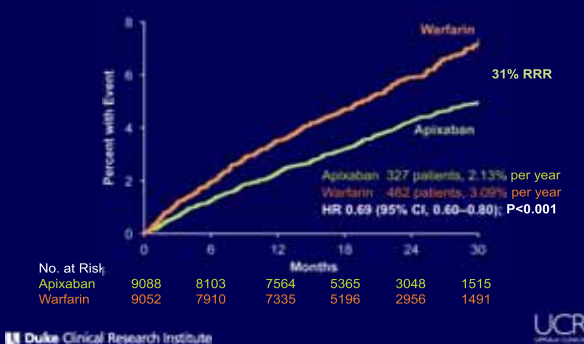


Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

* Part of sequential testing sequence preserving the overall type I error
Duke Clinical Research Institute

Major Bleeding ISTH definition

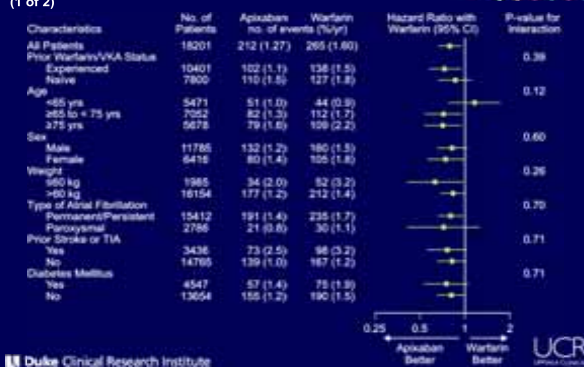


Bleeding Outcomes

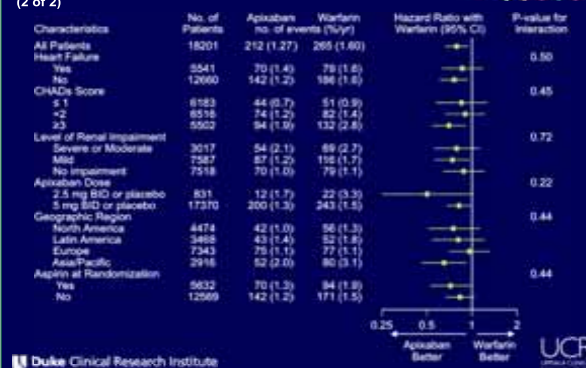
Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
GUSTO severe bleeding	0.52	1.13	0.46 (0.35, 0.60)	<0.001
TIMI major bleeding	0.96	1.69	0.57 (0.46, 0.70)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

* Part of sequential testing sequence preserving the overall type I error
Duke Clinical Research Institute

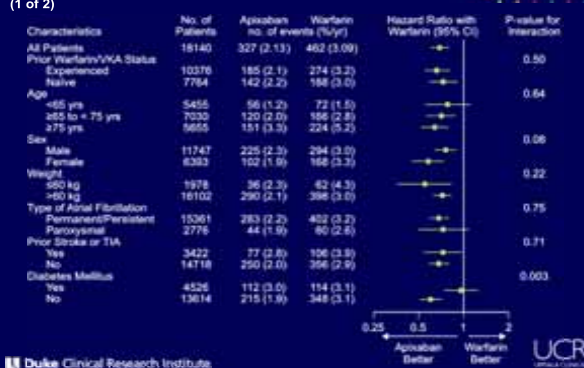
Subgroups for Stroke and Systemic Embolism (1 of 2)



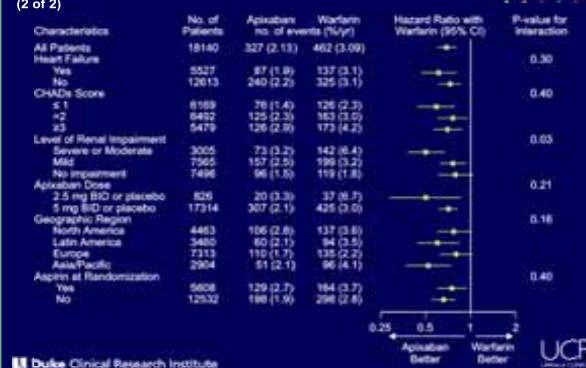
Subgroups for Stroke and Systemic Embolism (2 of 2)



Subgroups for Major Bleeding (1 of 2)



Subgroups for Major Bleeding (2 of 2)



Adverse Events and Liver Function Tests

N (%)	Apixaban (N=9088)	Warfarin (N=9052)
Total patients with an adverse event	7406 (81.5)	7521 (83.1)
Total patients with a serious adverse event	3182 (35.0)	3302 (36.5)
Serious adverse events reported in ≥ 1% of patients in either treatment group		
Atrial fibrillation	301 (3.3)	287 (3.2)
Pneumonia	202 (2.2)	231 (2.6)
Discontinuations due to an adverse event	688 (7.6)	758 (8.4)
ALT or AST > 3X ULN and total bilirubin > 2X ULN	30/ 8788 (0.3)	31/ 8756 (0.4)
ALT elevation		
> 3X ULN	100/ 8790 (1.1)	89/ 8759 (1.0)
> 5X ULN	45/ 8790 (0.5)	47/ 8759 (0.5)
> 10X ULN	16/ 8790 (0.2)	20/ 8759 (0.2)
> 20X ULN	8/ 8790 (<0.1)	12/ 8759 (0.1)

Duke Clinical Research Institute



Factors Influencing Physician Use of Anticoagulation in Atrial Fibrillation

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

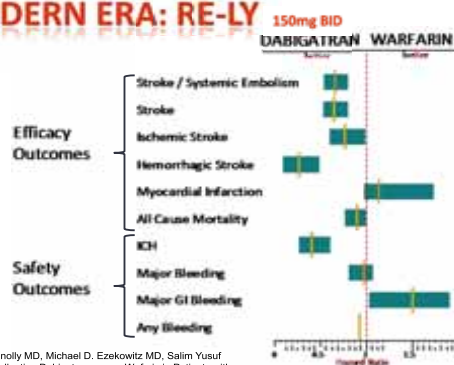
The decision to use warfarin in NVAF is driven by **perceived risks** (intracerebral bleeds)

Gross CP, Vogel EW, Dhondt AJ, Marple CB, Edwards RA, Hauch O, Demers EA, Ezekowitz MD. Factors Influencing Physician Use of Anticoagulation in Atrial Fibrillation. Submitted to *Clinical Therapeutics* 2009;36:No.8.

MODERN ERA

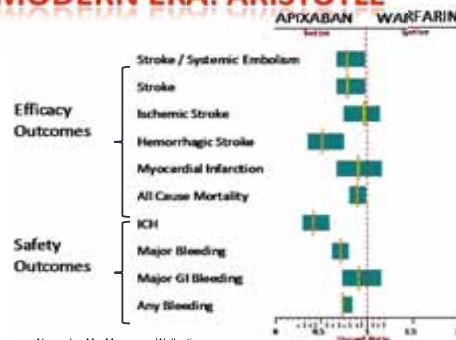
Characteristic	OPEN LABEL	BLINDED	
	RELY	ARISTOTLE	SPINAF
Randomized	18113	18201	538
Mean Age (yrs)	71	70	67
Male (%)	64	65	100
CHADS ₂ Score (mean)	2.1	2.1	~1.8
0-1 (%)	32	34	
2 (%)	35	35.8	
3+ (%)	33	30.2	
Prior Stroke/TIA/SE (%)	20	19	12
Prior MI (%)	16.8	14.2	21
CHF (%)	32	35.5	30
Baseline ASA (%)	39	38.5	
VKA-Naive (%)	50	36	
Mean Follow-Up (yrs)	2.0	1.8	1.7
Lost to Follow-Up (%)	0.1	0.4	0.3
Permanent Withdrawal (%)	19	22.7	13

MODERN ERA: RE-LY



Stuart Connolly MD, Michael D. Ezekowitz MD, Salim Yusuf MD, ... Wallentin. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *NEJM* 2009, 361:6 & *NEJM* 2010, 363

MODERN ERA: ARISTOTLE



Granger, Alexander, MacMurray, ... Wallentin, *NEJM* 2011

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



COLchicine for Recurrent Pericarditis (CORP): a multicenter, double-blind randomized controlled trial.

Presenter: Massimo Imazio, MD, FESC
on behalf of the CORP Investigators



Cardiology Dpt. Maria Vittoria Hospital,
ASLTO2, Torino, Italy



Disclosure: None

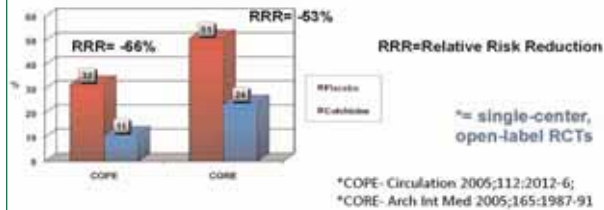
Role of the Funding Source:

- 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 Dpt, Maria Vittoria Hospital, Torino, Italy) following blinded adjudication of clinical events and side effects.
- Acarpia 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*.



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).

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).

Inclusion criteria

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

Criteria for recurrent pericarditis:

Recurrent pericarditis: Previous history of acute pericarditis (definite diagnosis) plus recurrent pain and at least one of the following criteria:

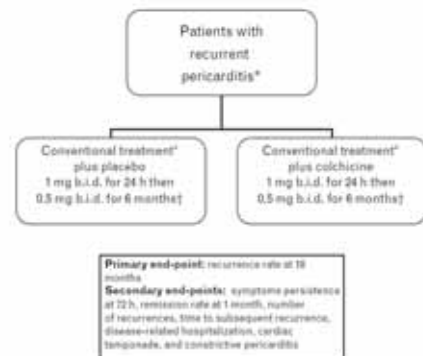
1. Fever
2. Pericardial friction rub
3. Electrocardiographic changes
4. New or worsening pericardial effusion
5. Elevations in the white blood cell count, erythrocyte sedimentation rate or C-reactive protein

J Cardiovasc Med 2007; 8: 830-4

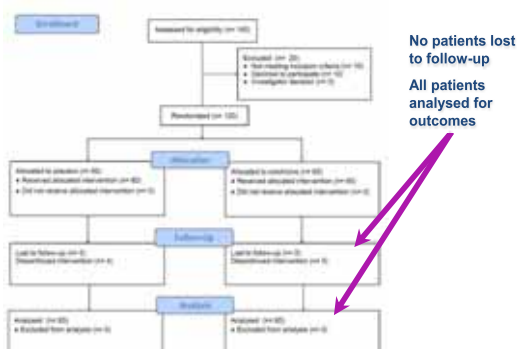
Exclusion criteria

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 $221 \mu\text{mol/L}$ (2.5 mg/dl);
5. Known myopathy or current serum creatine kinase above the upper normal limit;
6. Known blood dyscrasias 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 indications.

Intervention and End-points



CONSORT Flow Diagram of the CORP trial



Baseline features

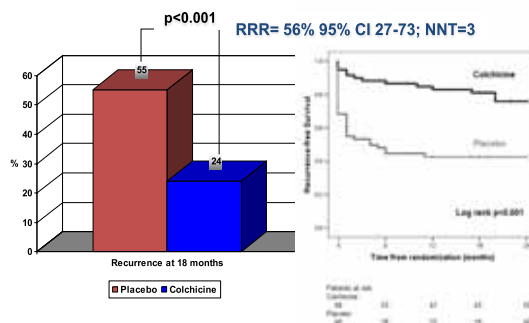
Characteristic	Placebo (n=60)	Colchicine (n=60)
Mean age (years)	47.3 (14.4)	47.9 (15.4)
Male sex	29 (48%)	34 (43%)
Smoke	25 (42%)	26 (56%)
Diabetes mellitus	1 (2%)	2 (3%)
COPD (Chronic Obstructive Pulmonary Disease)	2 (3%)	2 (3%)
Hypothyroidism	1 (2%)	2 (3%)
Previous idiopathic etiology	48 (80%)	50 (83%)
Previous corticosteroids use	6 (10%)	5 (8%)
Previous cardiac surgery	4 (7%)	3 (5%)
Time from first attack (months)	6.1 (4.9)	6.8 (4.0)
Pericardial Effusion	35 (58%)	36 (60%)
Ejection Fraction (%)	58 (4.2)	58 (6.2)
C-reactive protein elevation	54 (90%)	57 (95%)



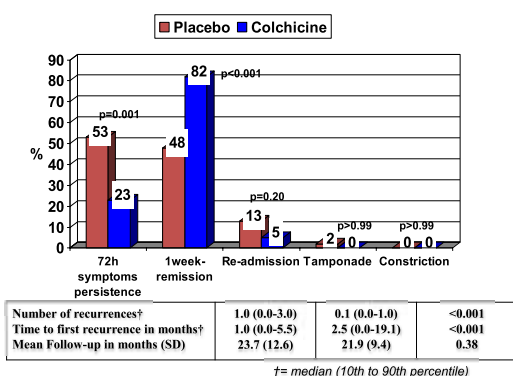
Concomitant therapies for recurrent pericarditis (adjunct to placebo/colchicine)

Characteristic	Placebo (n=60)	Colchicine (n=60)
Mean age (years)	47.3 (14.4)	47.9 (15.4)
Male sex	29 (48%)	34 (43%)
Fever	19 (32%)	18 (30%)
Pericarditic chest pain	60 (100%)	60 (100%)
Pericardial rub	13 (22%)	12 (20%)
Pericardial Effusion	35 (58%)	36 (60%)
Concomitant anti-inflammatory therapy: Aspirin or Ibuprofen	55 (92%)	56 (93%)
Prednisone	5 (8%)	4 (7%)

Primary end point: Recurrence rate at 18 months



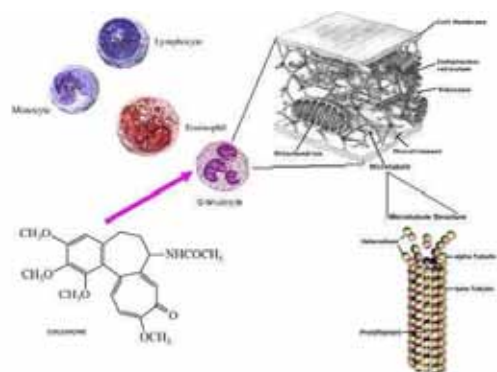
Secondary end points



Safety and Drug Withdrawal

Characteristic	Placebo (n=60)	Colchicine (n=60)
Overall side effects	4 (7%)	4 (7%)
Gastrointestinal intolerance	3 (5%)	4 (7%)
Hepatotoxicity	1 (2%)	0 (0%)
Myotoxicity	0 (0%)	0 (0%)
Alopecia	0 (0%)	0 (0%)
Other	0 (0%)	0 (0%)
Severe side effects	0 (0%)	0 (0%)
Drug withdrawal	4 (7%)	5 (8%)
- Physician decision	4 (7%)	4 (7%)
- Patient decision	0 (0%)	1 (2%)

How colchicine works...

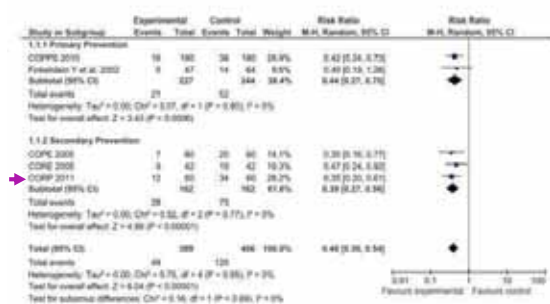


Comparison of study results with other published work

Study	Year	Design	Pts	Median time to relapse (days)	Adjusted	Follow up (months)	Recurrence Rate (%)
Guindo J	1990	NR	9	1.0	Yes	10-54	0/9 (0%)
Adler Y	1994	NR	8	1.0	Yes	18-34	0/8 (0%)
Millaire A	1994	NR	19	1.0	No	32-44	4/19 (21%)
Adler Y	1998	NR	51	1.0	Yes	6-128	7/51 (14%)
Imazio M	2005	NR	35	1.0	Yes	48-108	3/35 (9%)
CORE	2005	ROL	84	0.5-1.0	Yes	8-44	24 vs. 51% RRR=53%

NR= not randomised, ROL= randomised, open label; RRR=relative risk reduction

Meta-analysis of published trials



Limitations

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 multiple)

Only adults (may not apply to paediatric populations)

Bacterial and neoplastic etiologies were excluded

Patients with transaminases elevation, or severe liver disease, elevated creatinine, and patients with myopathy, blood dyscrasias or gastrointestinal disease were excluded

Women who are pregnant, lactating, or women of childbearing potential without sufficient contraceptive protection were excluded.



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

Acknowledgments

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.
- Co-chairman and Principal Investigator: Massimo Imazio, MD, Torino, Italy.
- Nucleus Members of the Study Group on "Heart and Infectious diseases" of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO).

Safety and Clinical events Committee:

- Yehuda Adler, MD (Coordinator), Tel Hashomer, Israel, Ralph Shabetai, MD, San Diego, USA, David H Spodick, MD, Worcester, USA.

CORP recruiting centres and investigators:

- Cardiology Dpt, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M. Imazio, D. Forno, S. Ferro, R. Belli), Ospedali Riuniti, Bergamo, Italy (investigators: A. Brucato, S. Maestroni, D. Cumetti), Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin), Ospedale SS Annunziata, Savigliano, Italy (S. Ferrua, A. Bassignana, B. Doronzo).



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

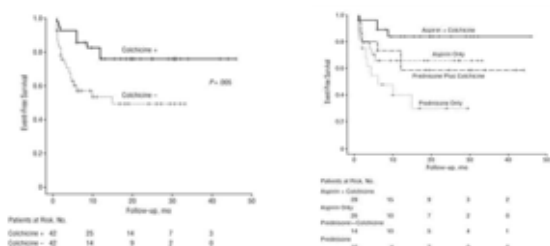
Background

- **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 as First-Choice Therapy for Recurrent Pericarditis

Results of the CORE (Colchicine for REcurrent pericarditis) Trial

Massimo Imazio, MD, Marco Boffa, MD, Enrico Cusi, MD, Daniela D'Amico, MD, Franco Fumari, MD, Mauro Moroni, MD, Aldo Ghisla, MD, Riccardo Belli, MD, Rita Trinchero, MD



Imazio M et al. Arch Intern Med 2011;171:184-191

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 4 weeks*
- Proton pump inhibitor in all

+/-

Colchicine doses

- loading: 1.0-2.0 mg/day for 1 day
- maintenance: 0.5-1.0 mg/day for 6 months

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

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

	CORE*	CORP#
No of pts	84	120
Initial episode		
- Corticoid Rx	30 (35%)	11(9%)
- Autoimmune	14 (17%)	22(18%)
After recurrence		
- Corticoid Rx	30 (35%)	9 (8%)
- Pericardial effusion	53 (63%)	71 (59%)

*Imazio M et al. Arch Intern Med 2005;165:1987-1991; # Imazio M et al. Arch Intern Med 2011;

The Recurrence Rate of Pericarditis

RRR	-53%	-56%
NNT	4	3
p	0.022	0.001



Predictors of a second
recurrence (multivariate
analysis)

Corticoid Rx
Colchicine -
protective

Pericardial effusion
Colchicine -
protective



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 28, 2011

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

Thomas F. Lüscher, et al. on behalf of the dal-VESEL investigators

Disclosures

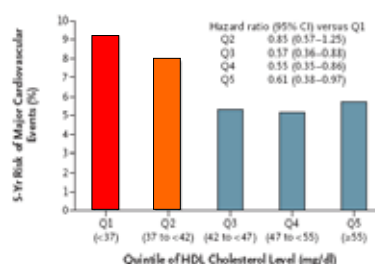
- The presenting author has received:
 - Research grants from Pfizer, Eli Lilly and Merck
 - Consultancy or lecture fees from CSL, Merck, Pfizer and F. Hoffmann-La Roche Ltd
- The dal-VESEL study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland

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 patients¹⁻³
- However, despite optimal statin use, significant risk remains⁴
- 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

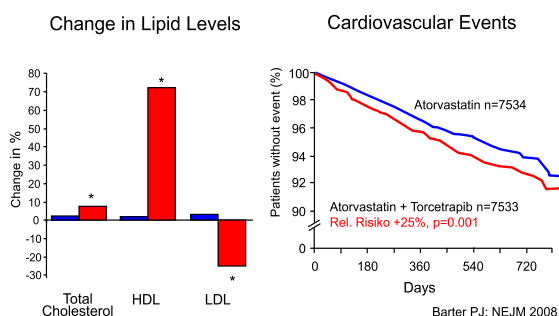
1. Sharrett AR et al. *Circulation*. 2001;104:1108-1113
2. Law MR et al. *BMJ*. 2003;326:1423
3. Baigent C et al. *Lancet*. 2005;366:1267-1278
4. Barter P et al. *N Engl J Med*. 2007;357:1301-1310

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

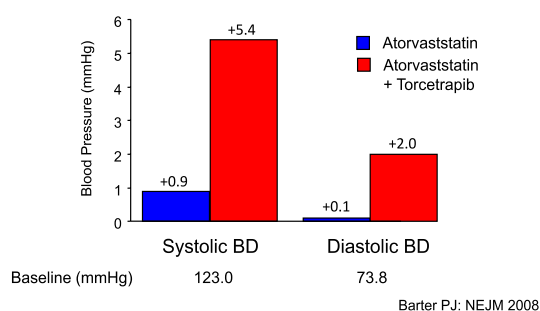


Barter P et al., *N Engl J Med* 2007; 357: 1301-10

Torcatrapib in Highrisk Patients - ILLUMINATE

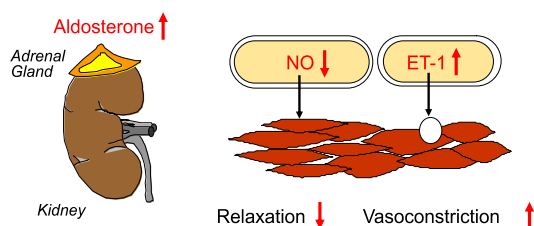


Torcatrapib and Blood Pressure - ILLUMINATE





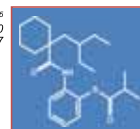
Mechanisms of Endothelial Dysfunction and Hypertension with Torcetrapib



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 torcetrapib²⁻⁴

dalcetrapib⁵
Molecular weight: 389.60
Lipophilicity: cLogP ~7



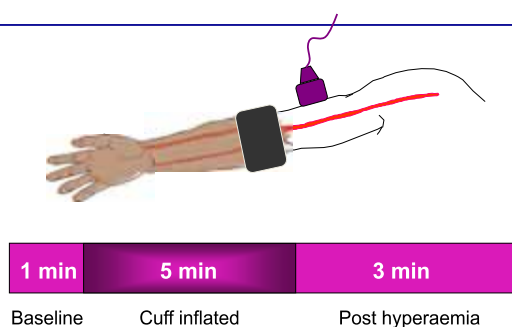
1. Nissen EJ et al. J Lipid Res 2010;51:3443-3454
2. Stein EA et al. Am J Cardiol 2009;104:62-91
3. Stroes ESG et al. Br J Pharmacol 2009;158:1763-1770
4. Stein EA et al. Eur Heart J 2010;31:460-468
5. <http://www.ama-assn.org/ama/upload/mm/365/dalcetrapib.doc>

dal-VESSEL – Concept of the trial

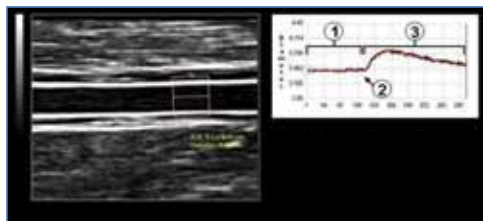
- The current study, dal-VESSEL, was designed to further investigate the safety of dalcetrapib and aimed to rule out any adverse effects of dalcetrapib on endothelial function and blood pressure^{1,2}
- To facilitate this, flow mediated dilatation (FMD) was to be used to provide an assessment of endothelial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

1. <http://clinicaltrials.gov/ct2/show/NCT00655538>. Accessed August 2011
2. Kastelein JJ et al. Curr Med Res Opin. 2011;27:141-150

dal-Vessel – Flow-mediated Dilation (FMD)



B-mode Ultrasound of Brachial Artery FMD

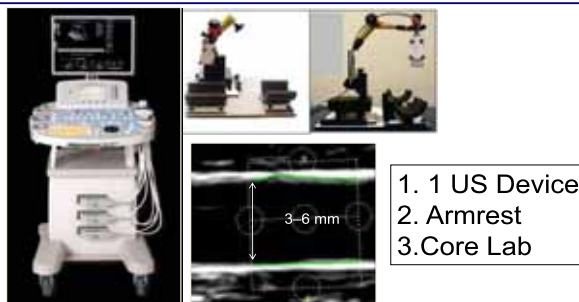


From Kastelein JJ et al. Curr Med Res Opin. 2011;27:141-50.

- Baseline diameter period
- Cuff release
- Post-ischaemia period



Standardization of Flow-mediated Dilation



- 1 US Device
2. Armrest
3. Core Lab

Standardization of Flow-mediated Dilation

Lectures

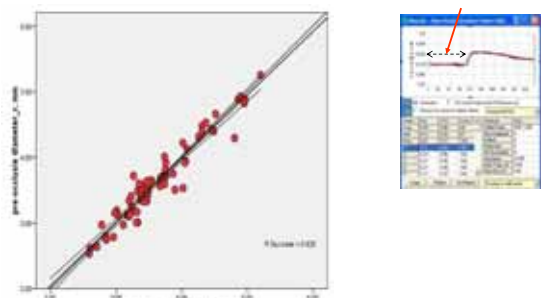
Practical Courses



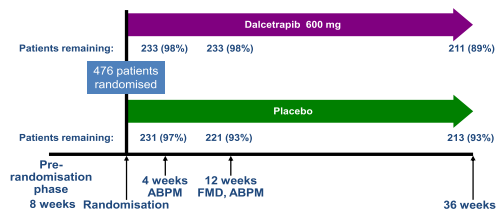
1. Central Training Courses for Sonographers
2. Certification Process
3. Blinded Analysis in Core Lab by expert Readers



dal-Vessel – Reproducibility of FMD



dal-Vessel - Study design



- Double-blind randomised, placebo-controlled, parallel-group multicentre FMD/ABPM study in patients with CHD or CHD-risk equivalent¹

Patients with CHD or CHD-risk equivalent and HDL-C <50 mg/dL (<1.29 mmol/L), with background therapy to manage CV risk factors. Follow-up at 4, 12 and 36 weeks.
Primary endpoints: FMD at 12 weeks; ABPM at 4 weeks
Additional assessments: FMD at 36 weeks; ABPM at 12 and 36 weeks

¹Kastelein JJ et al. Curr Med Res Opin 2011; 27:141-150

dal-Vessel - Endpoints

- 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 – Patient Flow



Figure 1. Screening, Randomisation and Follow-up of Study Subjects

dal-Vessel – Baseline characteristics

Characteristic*	Placebo (n=234)	Dalcetrapib (n=232)
Age, years	61.9 ± 7.92	62.3 ± 7.05
Male sex, n (%)	211 (90)	211 (91)
Body-mass index	28.7 ± 4.4	29.6 ± 4.8
Medical history of, n (%)		
Coronary heart disease	155 (66)	147 (63)
Symptomatic carotid artery disease	18 (8)	16 (7)
Peripheral arterial disease	16 (7)	24 (10)
Abdominal aortic aneurysm	5 (2)	6 (3)
Type II diabetes	102 (44)	108 (47)
Hypertension	175 (75)	171 (74)
Smoker, n (%)		
Ever	191 (82)	181 (78)
Current	57 (24)	65 (28)
Statin use*, n (%)	228 (97)	223 (94)

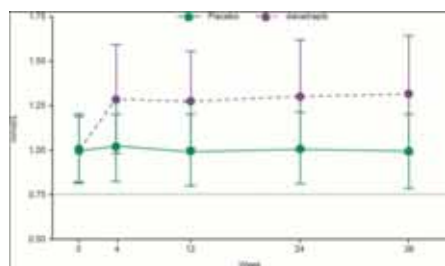
*All data reported as mean (SD); *patients with at least one treatment, multiple occurrences of the same treatment in one individual counted only once

dal-Vessel – Baseline lipids

Characteristic*	Placebo (n=234)	Dalcetrapib (n=232)
Total cholesterol, mmol/L [†]	3.802 ± 0.563	3.945 ± 0.665
HDL-C, mmol/L [†]	0.995 ± 0.185	1.013 ± 0.190
LDL-C, mmol/L [†]	2.051 ± 0.457	2.108 ± 0.553
Triglycerides, mmol/L [‡]	1.654 ± 0.733	1.819 ± 0.916
apoA-I mmol/L	1.333 ± 0.189	1.347 ± 0.178
apoB mmol/L	0.874 ± 0.170	0.895 ± 0.185

*All data reported as mean (SD); [†]to convert to mg/dL, multiply by 38.6; [‡]to convert to mg/dL, multiply by 88.5

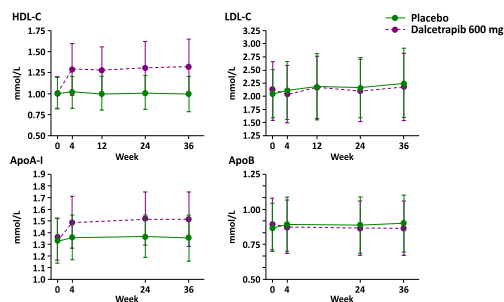
dal-Vessel – HDL-C levels increased with dalcetrapib over 36 weeks



HDL-C % change from baseline:

*wk4 placebo 2.73 ± 1.27, dalcetrapib 27.50 ± 1.28 p<0.0001
*wk36 placebo -0.14 ± 1.42, dalcetrapib 30.70 ± 1.45, p<0.0001

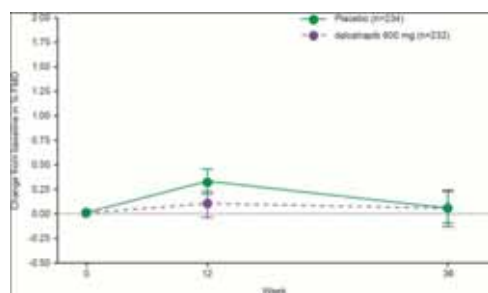
dal-Vessel – Lipids over 36 weeks



Data presented as absolute values at each timepoint, mean ± SD; placebo n=211 and dalcetrapib n=207 for HDL-C and LDL-C; placebo n=209 and dalcetrapib n=206 for ApoA-I and ApoB

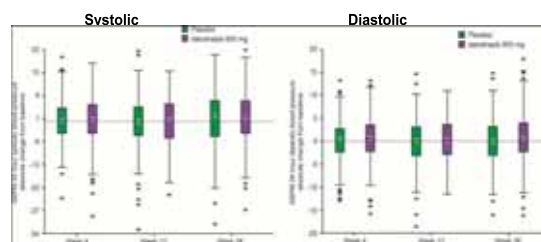


Baseline FMD exhibited no significant change with dalcetrapib over 36 weeks



Data reported as least squares mean (SE) absolute change from baseline in %FMD at weeks 12 and 36

dal-Vessel - ABPM was unchanged with dalcetrapib over 36 weeks



Data are box-whisker plots ± 1.5 *interquartile range

dal-Vessel – Change in biomarkers

Biomarker	Placebo (LSM [SE] % change)	Dalcetrapib (LSM [SE] % change)	Placebo-corrected change (LSM [95% CI])
hs-CRP	171.2 (90.2)	49.0 (91.7)	-122.2 (-358, 114), p=0.31
IL6	67.8 (15.8)	41.8 (16.1)	-26.0 (-67.3, 15.3), p=0.22
sP-selectin	0.2 (1.5)	-1.8 (1.6)	-2.1 (-6.1, 2.0), p=0.32
sE-selectin	6.1 (1.9)	6.0 (2.0)	-0.1 (-5.1, 4.9), p=0.98
Soluble intracellular adhesion molecule	2.0 (0.9)	1.1 (1.0)	-0.96 (-3.4, 1.5), p=0.44
Soluble vascular adhesion molecule	1.9 (0.8)	3.6 (0.8)	1.7 (-0.3, 3.8), p=0.09
Lipoprotein-associated phospholipasesA2*	5.8 (3.3)	23.2 (3.3)	17.4 (8.8, 26.1), p<0.0001
Matrix-metalloproteinase-3	3.4 (2.1)	3.5 (2.1)	0.0 (-5.4, 5.5), p=0.99
Matrix-metalloproteinase-9	20.4 (10.8)	28.1 (11.0)	7.8 (-20.4, 35.9), p=0.59
Myeloperoxidase	36.4 (18.1)	13.2 (18.4)	-23.1 (-70.2, 23.9), p=0.33
Tissue plasminogen activator	15.9 (5.5)	8.9 (5.6)	-7.0 (-21.3, 7.3), p=0.34
Plasminogen activator inhibitor 1-activity	14.7 (3.5)	16.9 (3.6)	2.2 (-7.1, 11.4), p=0.64
Plasminogen activator activity 1-antigen	42.5 (7.6)	38.8 (7.7)	-3.7 (-23.5, 16.0), p=0.71

*Lp-LPAA2 includes mass for both LDL and HDL

dal-Vessel – Safety parameters

Adverse Events (AEs)	Placebo (n=236)	Dalcetrapib (n=236)
Patients with at least one AE, n (%)	160 (68)	170 (72)
Total number of AEs, n	483	437
Patients with at least one:		
Clinical adverse AE leading to discontinuation, n (%)	9 (4)	11 (5)
Serious AE, n (%)	14 (6)	12 (5)
Drug-related serious AE, n (%)	2 (1)	1 (<1)
AE leading to death, n (%)	0 (0)	0 (0)
Most common AEs, n (%)		
Nasopharyngitis	42 (18)	38 (16)
Influenza	15 (6)	9 (4)
Diarrhoea	26 (11)	27 (11)
Back pain	16 (7)	8 (3)
Headache	13 (6)	10 (4)

dal-Vessel – Adjudicated CV events*

Adjudicated Cardiovascular Events, n	Placebo	Dalcetrapib
Major CV event†		
Death from coronary heart disease	1	0
Non-fatal myocardial infarction	3	2
Hospitalisation for acute coronary syndrome	1	0
Resuscitated cardiac arrest	0	0
Stroke	0	0
Subtotal	5	2
Other adjudicated events		
Revascularisation	7	9

*Adjudicated by an independent Clinical Endpoint Committee; a patient can have more than one event
†As defined by dal-OUTCOMES study protocol

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 (MRI 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**
Author (Zahi A. Fayad) present 3.30–4.30 pm

dal-Vessel – Conclusions

- Dalcetrapib reduced CETP activity, increased Apo A1 and elevated HDL-C levels by 31% without affecting LDL or ApoB100.
- Dalcetrapib did not cause endothelial dysfunction, but also did not improve it.
- In contrast to torcetrapib, dalcetrapib did not have an effect on ABPM, 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.

Acknowledgments: Participating Centres

- Switzerland: University Hospital Zürich, George Noll; CardioCentro Ticino, Lugano, Tiziano Mocetti
- Italy: Università degli Studi di Pisa, Pisa, Stefano Taddei
- Germany: Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Stephan Fichtlscherer; Klinikum der Johannes Gutenberg-Universität Mainz, Mainz, Thomas Münzel
- Austria: Universitäres Lehrkrankenhaus Feldkirch, Feldkirch, Heinz Drexler
- France: Hôpital Européen Georges Pompidou, Paris, Alain Simon
- Netherlands: Academic Medical Center, Amsterdam, Mieke D. Trip; Westfries Gasthuis Hoor, Hoor, Dick C.G. Basart; UMC Utrecht, Utrecht, Frank L.J. Visseren; Oosterschelde Ziekenhuis, Goes, A.H. Liem; Andromed b.v. Rotterdam, Rotterdam, Wouter van Kempen; Andromed Breda BV, Jan Jonker, Vicdan Kose; Andromed Eindhoven Bianca Lokhorst; Andromed Leiden Irma Agous; Andromed Oost Velp, Jacqueline Hoogendijk; Andromed Noord Groningen, Jeroen Tiebes; Andromed Oost Velp, Jacqueline Hoogendijk and Andromed Zoetermeer, Lenie de Schipper



Vascular Effects and Safety of Dalcetrapib in Patients with, or at Risk of CHD: the dal-VESSEL Randomised Clinical Trial

Discussant: Keith AA Fox
University and Royal Infirmary of
Edinburgh

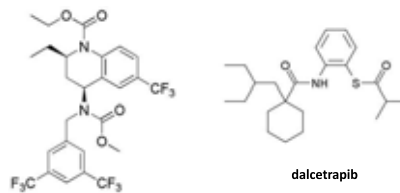
No conflicts with respect to any aspect of this presentation

dal -VESSEL (phase IIb trial)

- dal-VESSEL 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.

Cholesterol Ester Transport Inhibitors

cholesteryl ester transfer protein (CETP), normally transfers cholesterol from HDL cholesterol to very low density or low density lipoproteins (VLDL or LDL).

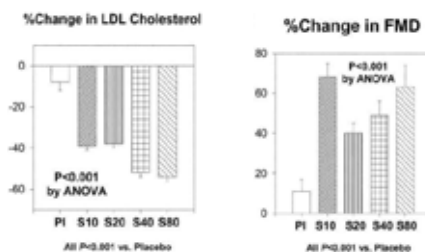


Torcetrapib

dalcetrapib

- *61% increase in HDL cholesterol, 20% decrease in LDL cholesterol. **4.6mm increase in blood pressure**, IVUS: no significant decrease in the progression of coronary atherosclerosis. NEJM 2007; 356:1304-1316
- *Phase 3 trial stopped: increase in deaths among patients taking torcetrapib and atorvastatin versus taking atorvastatin alone

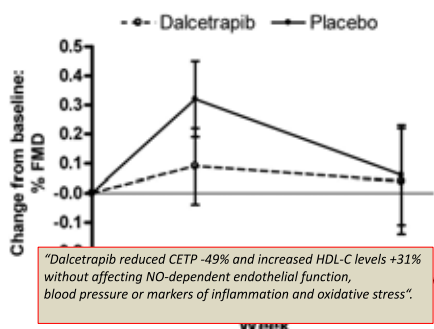
Flow mediated dilatation: What changes are seen with statins?



Simvastatin 10mg, 20mg, 40mg, 80mg

Koh et al, 2007

dal-Vessel-Trial – Flow-mediated Dilatation



"Dalcetrapib reduced CETP -49% and increased HDL-C levels +31% without affecting NO-dependent endothelial function, blood pressure or markers of inflammation and oxidative stress".

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; $P=0.253$).

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-OUTCOMES trial (NCT00658515) will show whether dalcetrapib improves outcomes.



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 Groenewold, Stefan Gräber*, Michael Böhm, Ulrich Laufs

Klinik für Innere Medizin III (Kardiologie, Angiologie und 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, Daiichi-Sankyo, Essex, MSD Sharp & Dohme, Novartis, Roche, Sanofi, Servier, Trommsdorff

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

ClinicalTrials.gov number: NCT00628524

The Homburg Cream and Sugar Study (HCS)
BACKGROUND

- Risk prediction by **fasting serum triglycerides** in patients at high cardiovascular risk remains uncertain.
- **Postprandial triglycerides** may be risk modifiers in secondary prevention.
- Postprandial triglycerides and **glucose tolerance** have not been assessed simultaneously in a prospective study in high risk patients.

Chapman MJ et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011;32:1345-61

Miller M et al. Triglycerides and cardiovascular disease: a scientific statement from the American heart association. *Circulation* 2011;123:2292-333

BACKGROUND
Postprandial increase of triglycerides

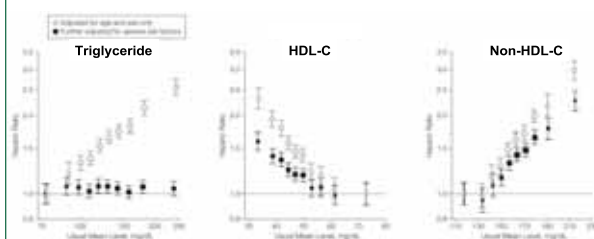


Factors affecting serum concentrations of TG-rich lipoproteins:

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

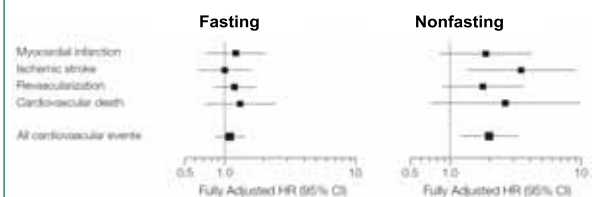
68 studies in 302 430 participants without prior history of CVD



The Emerging Risk Factors Collaboration.
JAMA 2009;302:1993-2000

Association of nonfasting triglyceride levels
with cardiovascular events in healthy individuals

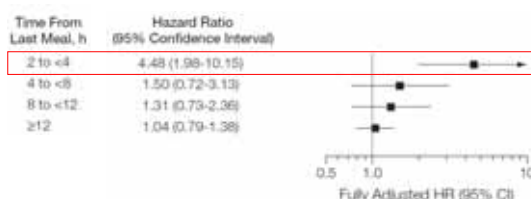
N=26.509 Women's Health Study (20.118 fasting, 6.391 nonfasting), 11.4 years



Bansal S et al., Women's Health Study, *JAMA* 2007;298(3):309-16
Nordestgaard BG et al., Copenhagen City Heart Study, *JAMA* 2007;298(3):299-308

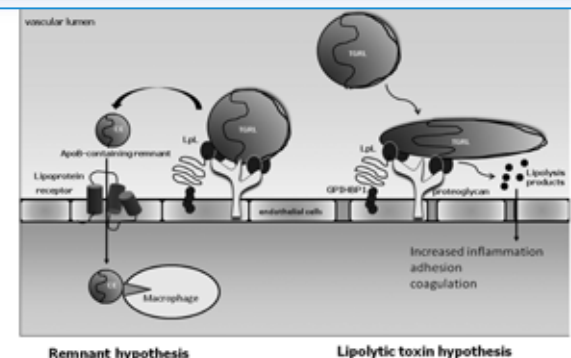
Association of nonfasting triglyceride levels
with cardiovascular events in healthy individuals

N=26.509 Women's Health Study (20.118 fasting, 6.391 nonfasting), 11.4 years



Bansal S et al., Women's Health Study, *JAMA* 2007;298(3):309-16

BACKGROUND - PATHOPHYSIOLOGY
Atherogenicity of triglyceride-rich lipoproteins



Goldberg IJ et al., *ATVB* 2011;31:1716-25

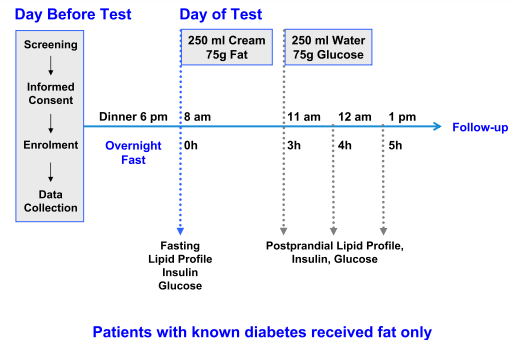


The Homburg Cream and Sugar Study (HCS) AIMS

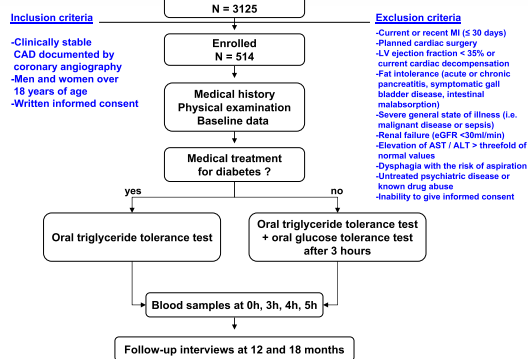
To determine whether characterization of postprandial triglyceride kinetics may

- improve the prediction of cardiovascular events
- in addition to the assessment of glucose tolerance and traditional risk factors
- in patients with coronary artery disease.

The Homburg Cream and Sugar Study (HCS) SEQUENTIAL METABOLIC TEST PROTOCOL



The Homburg C



The Homburg C

18 months follow-up

Primary outcome:
composite of cardiovascular death and cardiovascular hospitalization

Definition of cardiovascular hospitalization:
unstable angina and myocardial infarction, unplanned symptom-induced coronary angiography, heart failure, ischemic stroke, transitory ischemic attack, vascular disease requiring revascularization, cardiac arrhythmia requiring cardiopulmonary resuscitation, unplanned cardiac device implantation

The Homburg C

N	514	
Age (years)	66.4±10.1	
Male	82.9 %	
Clinical characteristics		
Smoking (active) (%)	18.9	
Alcohol >3x / week (%)	23.9	
Positive family history (%)	31.7	
Arterial hypertension (%)	92.9	
Systolic BP (mmHg)	126.7±15.8	
Diastolic BP (mmHg)	74.6±9.2	
LV ejection fraction (%)	64.0±12.9	
Heart rate (min-1)	66.7±9.1	
Body mass index (kg/m2)	28.9±4.2	
Waist circumference (cm)	103.6±11.4	
Waist-to-hip-ratio	1.00±0.1	
Metabolic characterisation		
Normal glucose tolerance (%)	24.5	
Impaired glucose tolerance (%)	29.2	
Diabetes mellitus (%)	46.3	
Metabolic syndrome (%)	53.7	
Fasting glucose (mg/dl)	120.7±27.4	
HOMA index (mg/dl*μIU/ml)	3.54±5.2	
HbA1c (%)	6.17±1.1	
Total cholesterol (mg/dl)	173.0±38.8	
HDL cholesterol (mg/dl)	44.8±13.8	
LDL cholesterol (mg/dl)	105.1±33.9	
Medication (%)		
Platelet inhibitors	97.3	
ACE-I / ARB	95.5	
Beta-blockers	93.5	
Diuretics	43.9	
Statins	94.6	

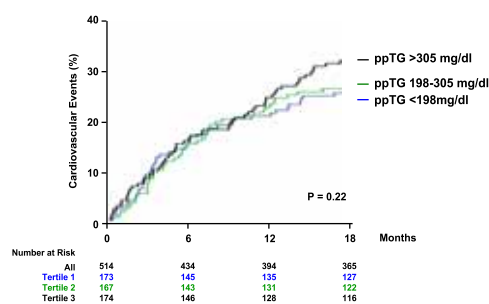
The Homburg C

N	514	
Age (years)	66.4±10.1	
Male	82.9 %	
Clinical characteristics		
Smoking (active) (%)	18.9	
Alcohol >3x / week (%)	23.9	
Positive family history (%)	31.7	
Arterial hypertension (%)	92.9	
Systolic BP (mmHg)	126.7±15.8	
Diastolic BP (mmHg)	74.6±9.2	
LV ejection fraction (%)	64.0±12.9	
Heart rate (min-1)	66.7±9.1	
Body mass index (kg/m2)	28.9±4.2	
Waist circumference (cm)	103.6±11.4	
Waist-to-hip-ratio	1.00±0.1	
Metabolic characterisation		
Normal glucose tolerance (%)	24.5	
Impaired glucose tolerance (%)	29.2	
Diabetes mellitus (%)	46.3	
Metabolic syndrome (%)	53.7	
Fasting glucose (mg/dl)	120.7±27.4	
HOMA index (mg/dl*μIU/ml)	3.54±5.2	
HbA1c (%)	6.17±1.1	
Total cholesterol (mg/dl)	173.0±38.8	
HDL cholesterol (mg/dl)	44.8±13.8	
LDL cholesterol (mg/dl)	105.1±33.9	
Medication (%)		
Platelet inhibitors	97.3	
ACE-I / ARB	95.5	
Beta-blockers	93.5	
Diuretics	43.9	
Statins	94.6	

HCS - OUTCOMES

Postprandial triglycerides do not predict outcome

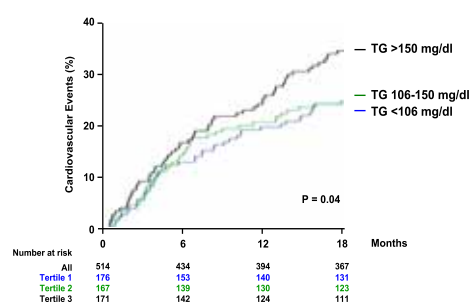
Kaplan-Meier plots of primary outcome events (cardiovascular death and cardiovascular hospitalization) in the total cohort up to 18 months stratified by tertiles of maximal postprandial triglyceride serum concentrations



HCS - OUTCOMES

Increased number of events in patients with fasting TG >150mg/dl

Kaplan-Meier plots of primary outcome events (cardiovascular death and cardiovascular hospitalization) in the total cohort up to 18 months stratified by fasting triglyceride tertiles

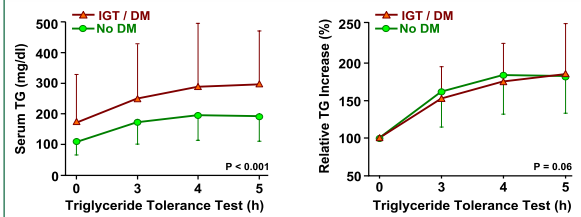


**HCS - OUTCOMES****Fasting, but not postprandial TG predict outcome in total cohort**

cumulative primary endpoints and TG tertiles in total cohort, n=514

	Tertile 1 number (rate)	Tertile 2 number (rate)	Tertile 3 number (rate)	P-value
Fasting triglycerides	58 (33.0)	56 (33.5)	93 (54.4)	0.01*
Postprandial TG maximum	68 (39.3)	57 (34.1)	82 (47.1)	0.30
Absolute triglyceride increase	66 (38.2)	75 (44.4)	66 (38.4)	0.70
Area under the curve	53 (31.0)	71 (41.8)	83 (48.0)	0.12
Incremental area under the curve	69 (40.8)	69 (40.8)	69 (39.2)	0.98
Relative triglyceride increase	64 (37.4)	67 (40.6)	76 (42.7)	0.80

*significance is lost in multivariable analysis, e.g. by including age and gender or HDL-C

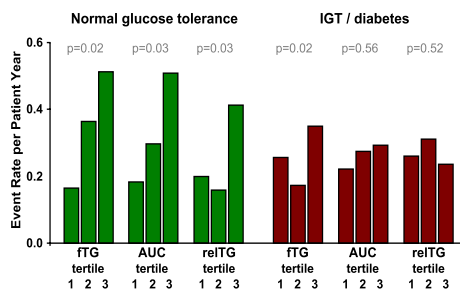
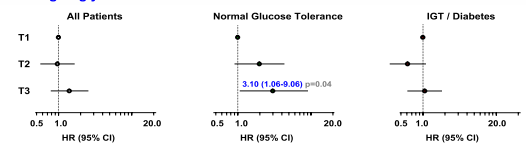
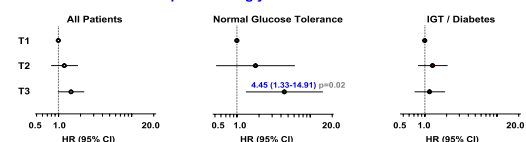
HCS - Metabolism**Postprandial triglyceride kinetics and glucose tolerance**

	All	No DM	IGT / DM	P-Value
Fasting Triglycerides (mg/dl)	156.1±140.7	108.1±42.0	171.8±157.1	<0.001
Absolute TG increase (mg/dl)	134.2±99.5	103.6±62.7	144.1±107.0	<0.001
Area Under the Curve (mg/dl)	1082±722.1	788.3±306.5	1177±789.7	<0.001
Relative TG Increase (%)	195.4±58.2	200.3±55.5	194.4±59.0	0.15

Laufs et al., ESC Hotline Abstract 28. 08. 2011

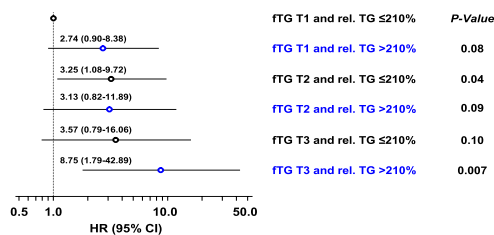
HCS: Postprandial TG predict outcomes only in patients with normal glucose tolerance

cumulative primary endpoints and TG tertiles

**HCS: Fasting and postprandial TG independently predict outcomes in patients with normal glucose tolerance****Fasting Triglycerides****Relative Increase of Postprandial Triglycerides**

Multivariable Cox regression model adjusted for age, gender, waist-to-hip ratio, blood pressure, smoking, diabetes, metabolic syndrome, HOMA index, HDL-C, LDL-C, regular alcohol intake, statins, beta-blockers.

Laufs et al., ESC Hotline Abstract 28. 08. 2011

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

Multivariable Cox regression model adjusted for age, gender, waist-to-hip ratio, blood pressure, smoking, diabetes, metabolic syndrome, HOMA index, HDL-C, LDL-C, regular alcohol intake, statins, beta-blockers.

Laufs et al., ESC Hotline Abstract 28. 08. 2011

The Homburg Cream and Sugar Study (HCS) in patients with normal glucose tolerance

cumulative primary endpoints and TG tertiles

- 5 h test protocol
- 95% on statin
- no genetic testing
- predominantly caucasian ethnicity

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:

Fasting and postprandial TG are elevated but do not independently predict CV outcomes.

Patients with CAD + normal glucose metabolism:

Both fasting and - with superior risk prediction - 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

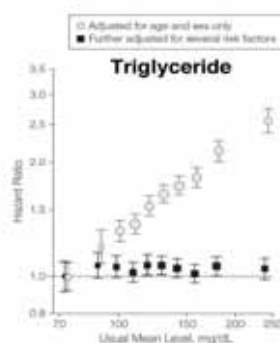
Discussant: Philip Barter
The Heart Research Institute
Sydney, Australia

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

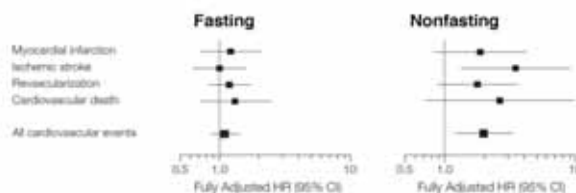


The Emerging Risk Factors Collaboration.
JAMA 2009;302:1993-2000

Fasting and non-fasting TG levels and coronary risk

Women's Health Study

N=26,509 Women's Health Study (20,118 fasting, 6,391 nonfasting), 11.4 years



Bansal S et al., Women's Health Study, JAMA 2007;298(3):309-16

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

Duality of In

None to declare with regards this presentation

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.

Aims

- To document the use of proven secondary prevention medications in the community in high, mid 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.

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.

Countries in PURE



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.

Key Characteristics of Eligible vs Enrolled

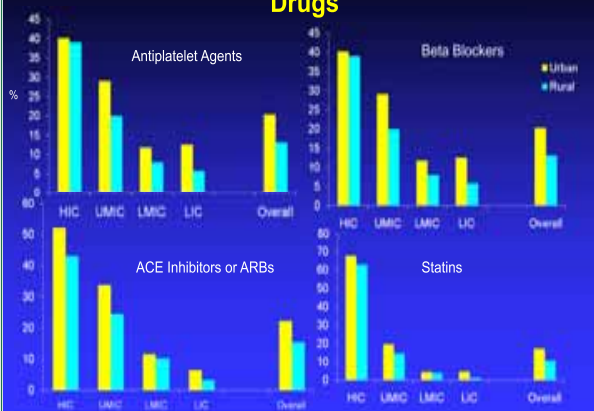
	Eligible	Enrolled
No.	197,332	153,662
Mean age (years)	50.2	50.7
% Females	53.0	55.6
% Current Smokers	22.1	21.2
% Low education	41.7	42.3
% H/O Hypertension	13.3	14.7
% H/O Diabetes	5.2	5.3
% H/O Stroke	1.2	1.3
% H/O CHD	3.5	3.9
% H/O Cancer	1.3	1.2



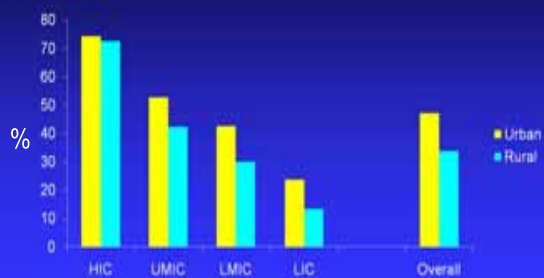
Use of K

	CHD	Stroke
No.	5650	2292
	%	
Antiplatelets	25.8	24.3
Beta-blockers	20.4	9.4
ACE-I/ARB	20.0	18.6
Diuretics	13.6	15.2
CCB	13.3	14.4
BP lowering	43.0	40.0
Statins	16.7	9.0

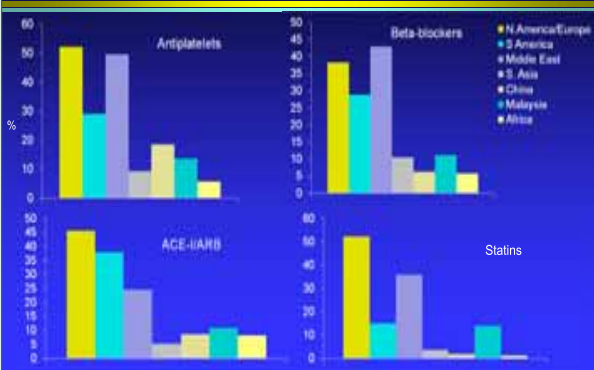
Drugs



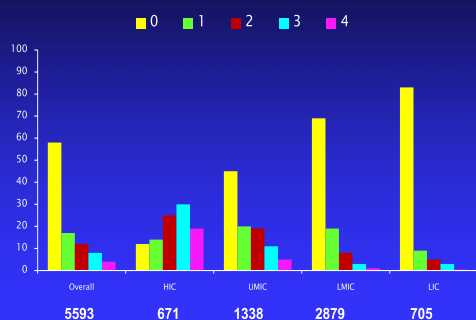
BP Lowering D



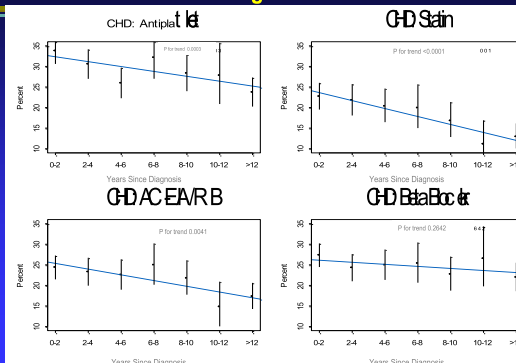
Drugs by Re



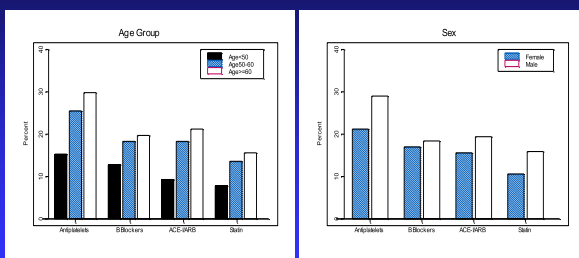
% receiving proven medications in CAD (154,000 people from 17 countries:PURE)



Medications by the Number of Years since Diagnosis

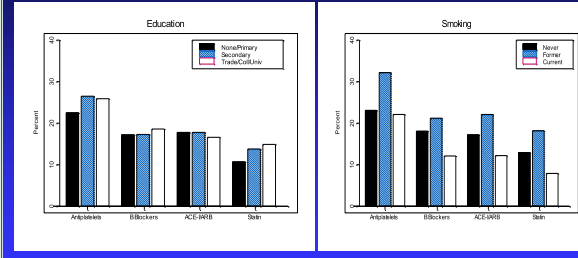


Medication in those with CHD or Stroke* Age and Sex



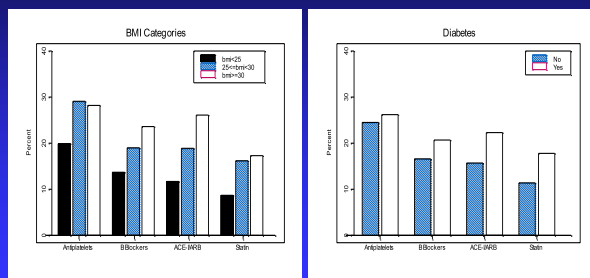
*Age, sex, mutual adjustment

Medication in those with CHD or Stroke Education & Smoking*



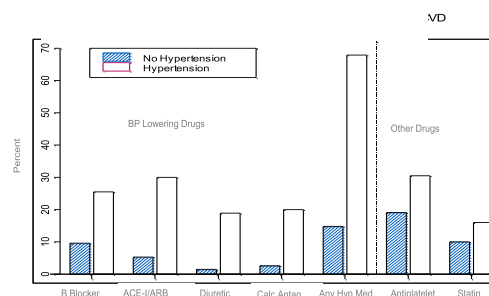
*Age, sex adjusted

Medication in those with CHD or Stroke BMI and Diabetes*

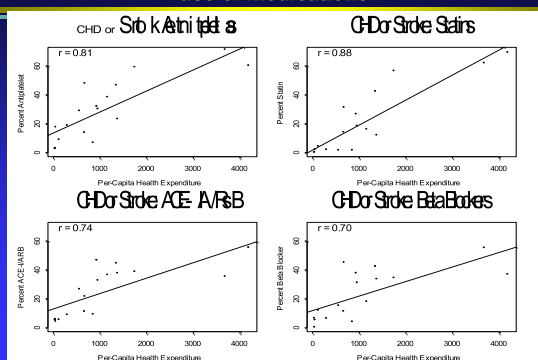


*Age, sex adjusted

Drug Use by



Per-Capita Health Expenditure vs Percentage the use of medications



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

Medication	Between Country Variance (%)	Within Country Variance (%)
Antiplatelet	60.0	40.0
Beta-blocker	59.8	41.2
ACE-I/ARB	54.8	45.2
Statin	79.4	20.6
Any one of the above	68.4	31.6

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.

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.

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

Julian Yano, *Self-Regulation, Class & Class: Scientific Management, Class Struggles, and the Rise of Capitalist Management in Argentina*, *Journal of Latin American Studies*, 39 (2007), 1, 101–22.
 María Victoria Rodríguez, *El trabajo en la Argentina: una historia social del trabajo*, Buenos Aires: Trilce, 2006, 200 pp., \$12.000.
 María Victoria Rodríguez, *El trabajo en la Argentina: una historia social del trabajo*, Buenos Aires: Trilce, 2006, 200 pp., \$12.000.
 María Victoria Rodríguez, *El trabajo en la Argentina: una historia social del trabajo*, Buenos Aires: Trilce, 2006, 200 pp., \$12.000.



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

The context: causes of deaths

Low-income and lower-middle income countries

In the World



Anderson GF et al. N Engl J Med 2007;356:209-211

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)**

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)

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

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 (i.e: HIV)
 - 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 than 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?

Boggon R¹, Van Staa T¹, Timmis A², Hemingway H³, Ray KK⁴, Begg A⁵, Emmas C⁶, Fox KAA⁷

GPRD¹, Barts and the London School of Medicine and Dentistry², Department of Epidemiology & Public Health University College London³, Cardiac and Vascular Sciences St George's University of London⁴, Medical Science University of Dundee⁵, AstraZeneca⁶, Centre for Cardiovascular Science and Royal Infirmary Edinburgh⁷

Funding: AstraZeneca

Disclosures

- **RB and TvS** - GPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare products Regulatory Agency (MHRA). GPRD has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl), includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health.
- **AT** is a committee member of the National Institute of Cardiac Outcomes Research (NICOR) which received funding from AstraZeneca for sharing MINAP data used in this study
- **HH** is a committee member of NICOR and is funded by the UK National Institute for Health Research (RP-PG-0407-10314; <http://www.nihr.ac.uk>) and the Wellcome Trust (086091/Z/08/Z) for research linking MINAP to primary care and investigator led cohorts.
- **KKR** has received honoraria for lectures and consulting from Lilly/ Daiichi and AstraZeneca
- **AB** has received advisory, consultancy and lecture fees from AstraZeneca and fees or travel grants from are Takeda, Menarini, Servier, MSD, Solvay, Pfizer and Roche
- **CE** is a full-time employee of AstraZeneca the manufacturer of ticagrelor
- **KAAF** and members of his group have received grant or honoraria funding from: Bayer, J&J, Lilly & AstraZeneca

DAP Clopidogrel and Aspirin

ESC Guideline 2008

- NSTEMI and STEMI: Clopidogrel 12 months whether or not stenting

AHA Guideline 2007

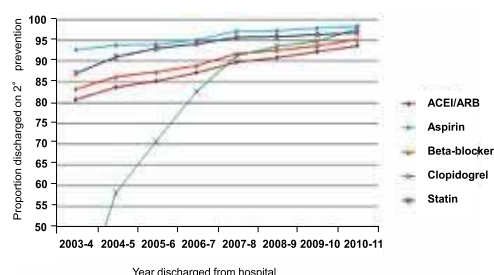
- NSTEMI: Clopidogrel 4 weeks (1A), up to 1 year (1B) - whether or not BM stenting. 6 months DE stenting
- STEMI: Clopidogrel 1-3 months whether or not BM stenting. 6 months DE stenting

NICE Guideline 2007

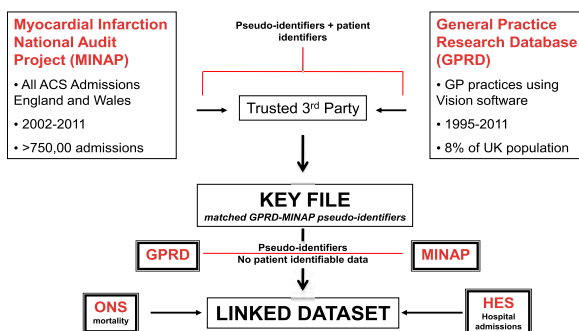
- NSTEMI: Continue clopidogrel treatment for 12 months
- STEMI: Continue clopidogrel for 4 weeks (currently being updated)

MINAP registry data: 2^o prevention

deaths, contraindicated and patient refused are all excluded



Linking electronic patient records



Patients in linked MINAP-GPRD dataset

Linked Dataset 23,740

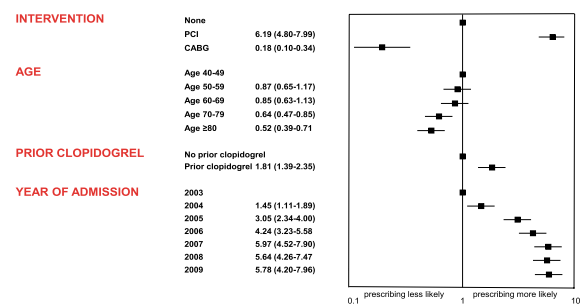
NSTEMI/STEMI 7,543

Aged ≥40, discharged from hospital to home after 2003

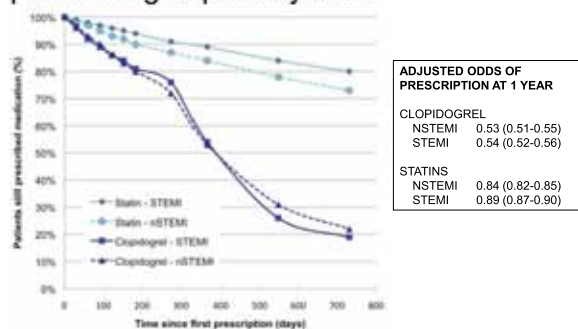
Clopidogrel prescription in 1^o care within 3 months of AMI 4,650

Characteristics associated with 1^o care clopidogrel prescribing within 3 months

adjusted for gender, alcohol, diabetes, smoking, BMI, SES, history of angina/MI, prior aspirin or 1^o care, prior hospitalisations, geographical region



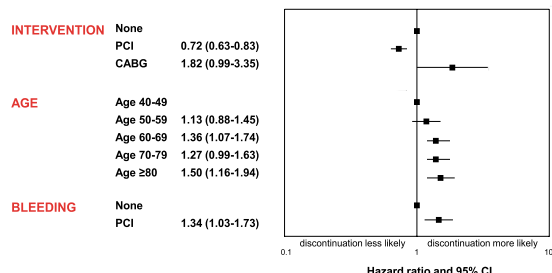
Discontinuation of clopidogrel and statin prescribing in primary care





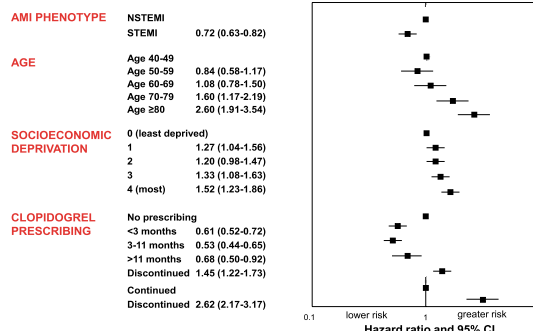
Characteristics associated with discontinuation of 1st care clopidogrel prescribing within 1 year

adjusted for age, gender, discharge diagnosis, socioeconomic status, medical history of angina/MI, calendar year and geographical region



Characteristics associated with death or MI in first year after discharge

adjusted for age, gender, discharge diagnosis, socioeconomic status, medical history of angina/MI, calendar year and geographical region



Rates of death in first year after discharge

	Clopidogrel prescribed in 1st 3 months	
	Yes	No
ALL	18.15 (16.83-19.58)	36.69 (34.14-39.41)
NSTEMI	22.42 (20.54-24.48)	48.42 (44.43-52.76)
STEMI	11.69 (10.07-13.57)	23.55 (20.67-26.83)

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) discordance between statin and clopidogrel discontinuation
 - b) All outcome data adjusted for prior coronary events and hospitalisations

Summary

In patients with acute myocardial infarction discharged home from hospital

- Failure to prescribe clopidogrel in first 3 months is associated with 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 older patients and those with bleeding complications

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



European CRT Survey 1 Year Follow-up Results

Nigussie Bogale
Stavanger University Hospital, Norway
On behalf of the SC, NC and the investigators

Disclosures

Some authors have received grants or honoraria from the device companies in EUCOMED (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical).



The Scientific Committee

Kenneth Dickstein (HFA Coordinator)
Silvia Priori (EHRA Coordinator)
Angelo Auricchio
Nigussie Bogale
Josep Brugada
John GF Cleland
Geneviève Derumeaux
Anselm Gitt
Daniel Gras
Michel Komajda
Cecilia Linde
John Morgan
Dirk J van Veldhuisen

National Coordinators 13 countries

Austria Friedrich Fruhwald, Bernhard Strohmer
Belgium Marc Goethals, Johan Vijgen
France Jean Noel Trochu, Daniel Gras
Germany Michael Kindermann, Christoph Stellbrink
Ireland Ken McDonnald, David Keane
Israel Tuvia Ben Gal, Michael Glikson
Italy Marco Metra, Maurizio Gasparini
Netherlands Alexander Maass, Luc Jordaens, Marco Alings
Norway Alf Inge Larsen, Svein Færevstrand
Spain Juan Delgado, Luis Mont
Sweden Hans Persson, Fredrik Gadler
Switzerland Hans Peter Brunner-La Rocca, Stefan Osswald
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)

Methodology

- Inclusion criteria: *successful* CRT implantations
- All implanting centres in the 13 countries were invited
- Patient recruitment Nov. 2008 – June 2009
- Data entered into an eCRF at implantation and follow-up
- Data collection and management: Institut für Herzinfarktforschung in Ludwigshafen, Germany

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

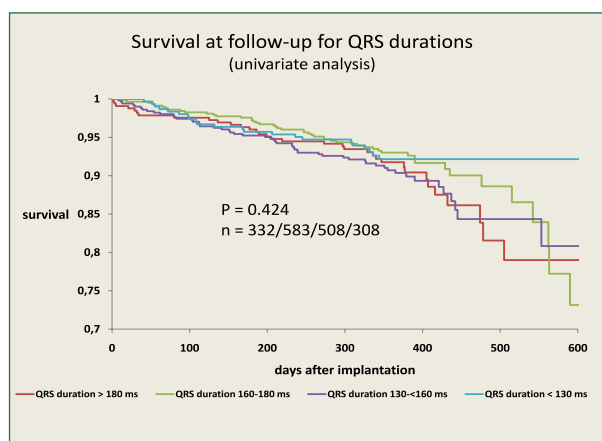
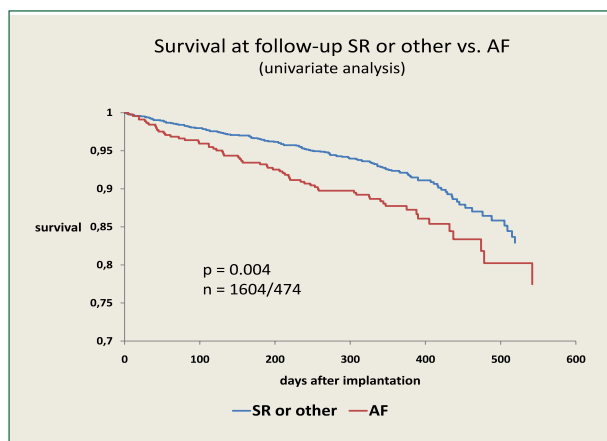
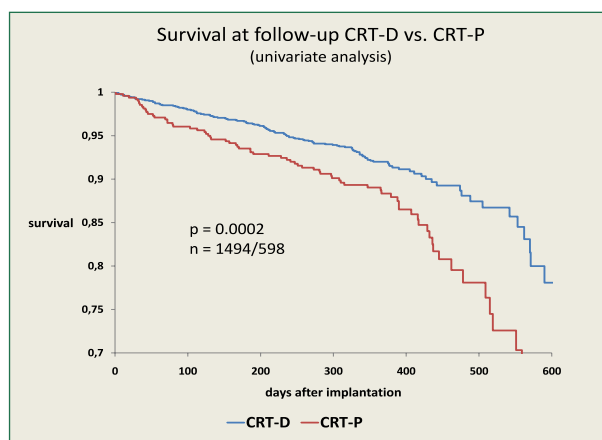
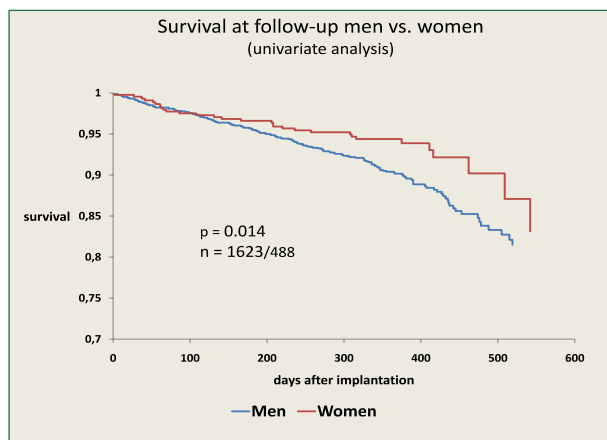
- 2438 patients included
- Follow-up data acquired from 2111 patients (87 %)
 - 207 patients died (9.8 %)
 - 346 patients (16.4 %) hospitalized (CV)
 - 501 patients (23.7 %) died or were hospitalized (CV)

Survival at 1 year follow-up (univariate analysis)

	Dead	Alive	p-value
Patients (n, %)	207 (9.8)	1904 (90.2)	
Demographics			
Age (yr and med.)	71 (65-76)	70 (62-76)	< 0.01
Age > 75	71 (34)	575 (30)	0.22
Women	32 (16)	456 (24)	< 0.01
HF aetiology			
Ischaemic	118 (61)	888 (50)	< 0.01
Non-ischaemic	53 (28)	725 (41)	< 0.001
Other	22 (11)	157 (9)	0.25
Past medical hist.			
HF hosp. last year	119 (69)	914 (54)	< 0.001
Diabetes mellitus	78 (45)	479 (28)	< 0.0001
Chronic lung disease	48 (28)	265 (16)	< 0.0001
NYHA func. class			
I	3 (2)	27 (2)	0.91
II	21 (11)	364 (21)	< 0.01
III	119 (65)	1251 (71)	0.09
IV	41 (22)	127 (7)	< 0.0001
LVEF %	24 ± 7	27 ± 8	< 0.0001
Rhythm			
Sinus	133 (65)	1391 (74)	< 0.01
Atrial fibrillation	64 (31)	410 (22)	< 0.01

CV hospitalization at 1 year follow-up (univariate analysis)

	CV hospitalization	No CV hospitalization	p-value
Patients (n, %)	346 (16.4)	1443 (68.1)	
Demographics			
Age (yr and med.)	69 (61-75)	70 (62-76)	0.32
Age > 75	100 (29)	446 (31)	0.50
Women	68 (20)	363 (25)	< 0.05
HF aetiology			
Ischaemic	170 (53)	702 (52)	0.51
Non-ischaemic	126 (40)	503 (41)	0.77
Other	17 (5)	88 (7)	0.46
Past medical hist.			
HF hosp. last year	215 (63)	764 (53)	< 0.01
Diabetes mellitus	106 (31)	409 (28)	0.38
Chronic lung disease	67 (20)	230 (16)	0.12
NYHA func. class			
I	2 (1)	22 (2)	0.17
II	48 (14)	316 (22)	< 0.001
III	243 (72)	969 (69)	0.24
IV	45 (13)	105 (7)	< 0.001
LVEF %	26 ± 8	27 ± 8	< 0.05
Rhythm			
Sinus	220 (65)	1063 (74)	< 0.001
Atrial fibrillation	106 (31)	305 (21)	< 0.001



Selected variables for CRT-D and CRT-P recipients

	CRT-D	CRT-P	P-value
Age (yrs, median)	68 (61-74)	75 (68-80)	< 0.0001
Age ≥ 75	396 (23)	337 (52)	< 0.0001
Women	363 (21)	194 (30)	< 0.0001
RBBB	120 (7)	34(5)	0.10
QRS duration (msec)			
< 130	269 (18)	75 (8)	0.37
130- < 160	450 (30)	137 (30)	0.82
160-180	493 (33)	155 (33)	0.86
>180	277 (19)	95 (21)	0.35
Previous VF/sustained VT	295 (20)	15 (2)	< 0.0001

Selected variables for atrial fibrillation and sinus rhythm or other

	Atrial fibrillation	Sinus rhy. or other	P-value
Age (yrs, median)	71 (65-77)	69 (61-76)	< 0.0001
Women	112 (21)	441 (25)	0.06
RBBB	50 (9)	104 (6)	< 0.01
QRS duration (msec)			
< 130	82 (22)	261 (16)	< 0.05
130 - < 160	107 (28)	481 (31)	0.38
160-180	111 (29)	538 (34)	<0.05
>180	80 (21)	294 (19)	0.44
Device type			
CRT-D	338 (62)	1340 (75)	< 0.0001
CRT-P	207 (38)	442 (25)	< 0.0001

Selected variables for ischaemic and non-ischaemic aetiology

	Ischaemic	Non-ischaemic	P-value
Age (yrs, median)	71 (65-77)	68 (60-75)	< 0.0001
Women	168 (15)	339 (32)	< 0.0001
QRS duration (msec)			
< 130	188 (20)	132 (16)	< 0.01
130 - < 160	282 (30)	241 (28)	0.23
160-180	286 (31)	304 (36)	< 0.01
>180	175 (19)	172 (20)	0.44
Device type			
CRT-D	842 (77)	671 (63)	< 0.0001
CRT-P	251 (23)	391 (37)	< 0.0001

Factors associated with death (multivariate analysis)

Variables	OR	95 %-CI	p-values
NYHA III-IV	1.91	(1.16-3.17)	0.0116
Atrial fibrillation	1.81	(1.24-2.66)	0.0022
Ischaemic aetiology	1.75	(1.20-2.54)	0.0034
Device type: CRT-P	1.65	(1.11-2.44)	0.0130
Age groups	1.05	(0.80-1.38)	0.7211
QRS durations	0.96	(0.81-1.14)	0.0831
Women	0.63	(0.39-1.02)	0.0589



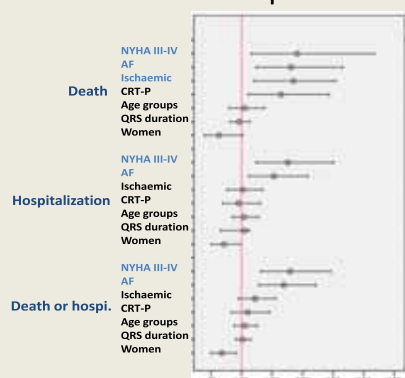
Factors associated with CV hospitalization (multivariate analysis)

Variables	OR	95 %-CI	p-values
NYHA III-IV	1.76	(1.24-2.51)	0.0017
Atrial fibrillation	1.53	(1.12-2.09)	0.0073
Ischaemic aetiology	1.02	(0.77-1.34)	0.9102
Device type: CRT-P	0.95	(0.69-1.31)	0.7645
Age groups	1.04	(0.85-1.28)	0.6750
QRS durations	1.05	(0.92-1.19)	0.5094
Women	0.71	(0.51-1.00)	0.0476

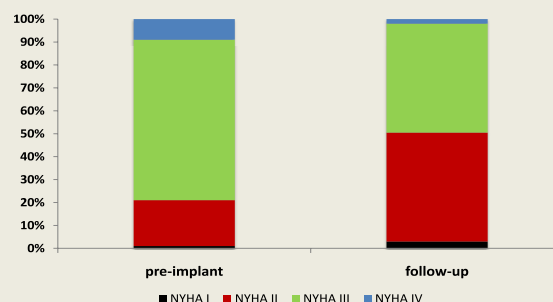
Factors associated with death or CV hospitalization (multivariate analysis)

Variables	OR	95 %-CI	p-values
NYHA III-IV	1.80	(1.32-2.46)	0.0002
Atrial fibrillation	1.69	(1.28-2.22)	0.0002
Ischaemic aetiology	1.23	(0.95-1.56)	0.1196
Device type: CRT-P	1.10	(0.83-1.46)	0.4989
Age groups	1.05	(0.88-1.26)	0.5874
QRS durations	1.02	(0.91-1.15)	0.7188
Women	0.68	(0.50-0.92)	0.0134

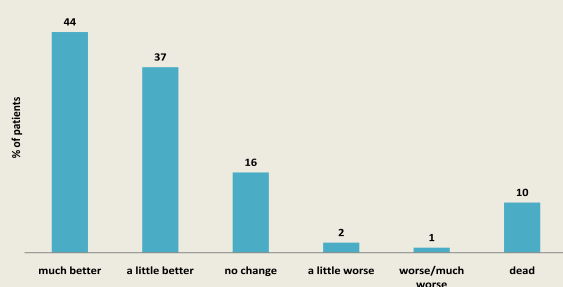
Forest-plot of OR



NYHA functional class shift pre-implantation to follow up



Patient Self- Reported Global Assessment



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

	(n, %)
Device related complications	170 (10.3)
Lead displacement	55 (3.3)
Lead malfunction	13 (0.8)
Device related arrhythmias	18 (1.1)
Phrenic nerve stimulation	51 (3.1)
Device replacement	6 (0.4)
Infection	27 (1.6)

Comparison with RCT's

	COMPANION	CARE-HF	REVERSE	MADIT-CRT	RAFT	CRT Survey
No of patients (CRT-P/CRT-D)	1212	409	419	1089	894	2438
control groups	308	404	191	731	904	0
Mean follow-up (mo)	14.8-16.5	37.4	12	28.8	40	12
Baseline characteristics (%)						
Mean age (years)	67	66	62	65	66	68
Men	67	74	79	75	83	76
Ischaemic heart disease	55	38	55	55	67	51
Atrial fibrillation	0	0	0	0	13	23
Previous device	0	0	0	0	NA	28
Ventric. paced rhythm	0	0	0	0	8	18
RBBB	10	0	10	13	9	6
QRS duration (ms)	160	165	153	65 % > 150	158	160
Mean LVEF	22	24.8	27	24	23	26
NYHA class						
I/II	0	0	100	100	80	22
III/IV	100	100	0	0	20	78
Outcomes						
Mortality during follow-up	246 (20.3)	101 (24.7)	9 (2.2)	74 (6.8)	186 (20.8)	207 (9.8)
Death or hospitaliz. for HF	449 (37.1)	118 (28.9)	26 (6.2)	187 (17.2)	297 (33.2)	501 (23.7)

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
 - unsuccessful attempts



Conclusions

- 81 % of patients report symptom improvement (self-assessed)
- Over all survival is more than 90 %
- Benefits of CRT observed in RCT,s 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

1. ESC Congress 2011 Paris	2. ESC Congress 2011 Paris
3. ESC Congress 2011 Paris	4. ESC Congress 2011 Paris
5. ESC Congress 2011 Paris	6. ESC Congress 2011 Paris
7. ESC Congress 2011 Paris	8. ESC Congress 2011 Paris
9. ESC Congress 2011 Paris	10. ESC Congress 2011 Paris
11. ESC Congress 2011 Paris	12. ESC Congress 2011 Paris
13. ESC Congress 2011 Paris	14. ESC Congress 2011 Paris
15. ESC Congress 2011 Paris	16. ESC Congress 2011 Paris
17. ESC Congress 2011 Paris	18. ESC Congress 2011 Paris
19. ESC Congress 2011 Paris	20. ESC Congress 2011 Paris
21. ESC Congress 2011 Paris	22. ESC Congress 2011 Paris
23. ESC Congress 2011 Paris	24. ESC Congress 2011 Paris
25. ESC Congress 2011 Paris	26. ESC Congress 2011 Paris
27. ESC Congress 2011 Paris	28. ESC Congress 2011 Paris
29. ESC Congress 2011 Paris	30. ESC Congress 2011 Paris
31. ESC Congress 2011 Paris	32. ESC Congress 2011 Paris
33. ESC Congress 2011 Paris	34. ESC Congress 2011 Paris
35. ESC Congress 2011 Paris	36. ESC Congress 2011 Paris
37. ESC Congress 2011 Paris	38. ESC Congress 2011 Paris
39. ESC Congress 2011 Paris	40. ESC Congress 2011 Paris
41. ESC Congress 2011 Paris	42. ESC Congress 2011 Paris
43. ESC Congress 2011 Paris	44. ESC Congress 2011 Paris
45. ESC Congress 2011 Paris	46. ESC Congress 2011 Paris
47. ESC Congress 2011 Paris	48. ESC Congress 2011 Paris
49. ESC Congress 2011 Paris	50. ESC Congress 2011 Paris
51. ESC Congress 2011 Paris	52. ESC Congress 2011 Paris
53. ESC Congress 2011 Paris	54. ESC Congress 2011 Paris
55. ESC Congress 2011 Paris	56. ESC Congress 2011 Paris
57. ESC Congress 2011 Paris	58. ESC Congress 2011 Paris
59. ESC Congress 2011 Paris	60. ESC Congress 2011 Paris
61. ESC Congress 2011 Paris	62. ESC Congress 2011 Paris
63. ESC Congress 2011 Paris	64. ESC Congress 2011 Paris
65. ESC Congress 2011 Paris	66. ESC Congress 2011 Paris
67. ESC Congress 2011 Paris	68. ESC Congress 2011 Paris
69. ESC Congress 2011 Paris	70. ESC Congress 2011 Paris
71. ESC Congress 2011 Paris	72. ESC Congress 2011 Paris
73. ESC Congress 2011 Paris	74. ESC Congress 2011 Paris
75. ESC Congress 2011 Paris	76. ESC Congress 2011 Paris
77. ESC Congress 2011 Paris	78. ESC Congress 2011 Paris
79. ESC Congress 2011 Paris	80. ESC Congress 2011 Paris
81. ESC Congress 2011 Paris	82. ESC Congress 2011 Paris
83. ESC Congress 2011 Paris	84. ESC Congress 2011 Paris
85. ESC Congress 2011 Paris	86. ESC Congress 2011 Paris
87. ESC Congress 2011 Paris	88. ESC Congress 2011 Paris
89. ESC Congress 2011 Paris	90. ESC Congress 2011 Paris
91. ESC Congress 2011 Paris	92. ESC Congress 2011 Paris
93. ESC Congress 2011 Paris	94. ESC Congress 2011 Paris
95. ESC Congress 2011 Paris	96. ESC Congress 2011 Paris
97. ESC Congress 2011 Paris	98. ESC Congress 2011 Paris
99. ESC Congress 2011 Paris	100. ESC Congress 2011 Paris



ESC Congress 2011 Paris

Early aggressive versus initially conservative strategy in elderly patients with non-ST-elevation acute coronary syndrome: the Italian Elderly ACS randomised trial

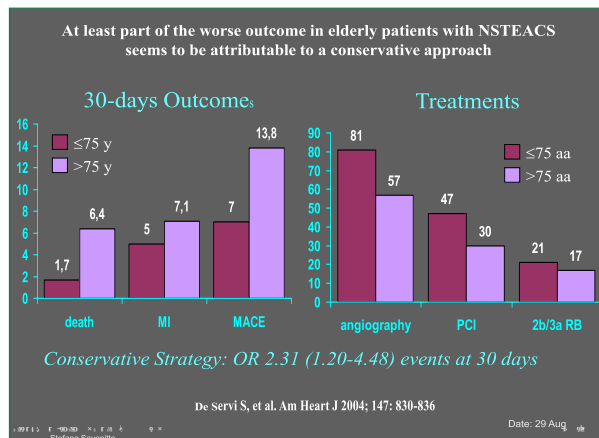
(ClinicalTrials.gov ID: NCT00510185)

Stefano Savonitto, Ernesto Murena, Roberto Antonicelli, Claudio Cavallini, Anna Sonia Petronio, Alice Sacco, Giuseppe Steffenino, Nuccia Morici, Maria Cristina Jori and Stefano De Servi

On behalf of the Italian Elderly ACS Study Investigators



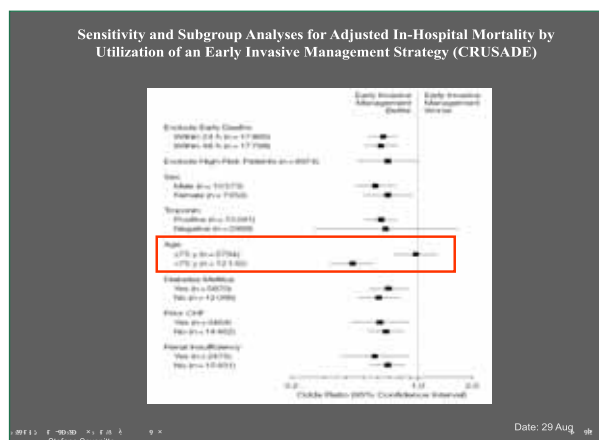
Federazione Italiana di Cardiologia

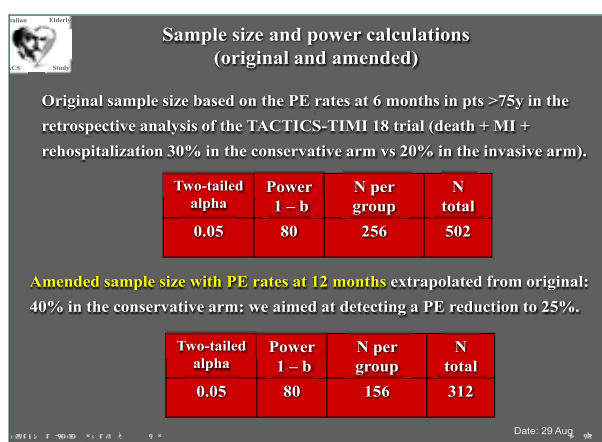
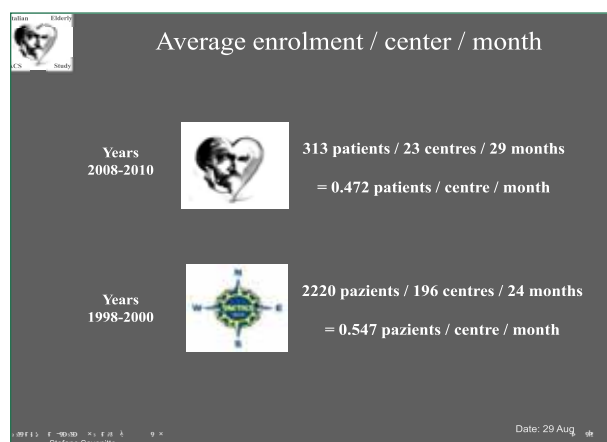
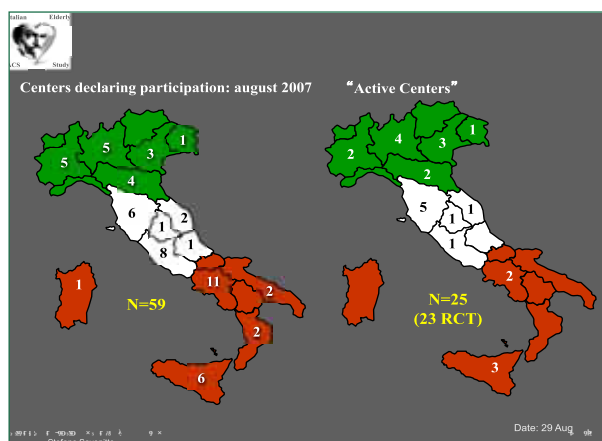
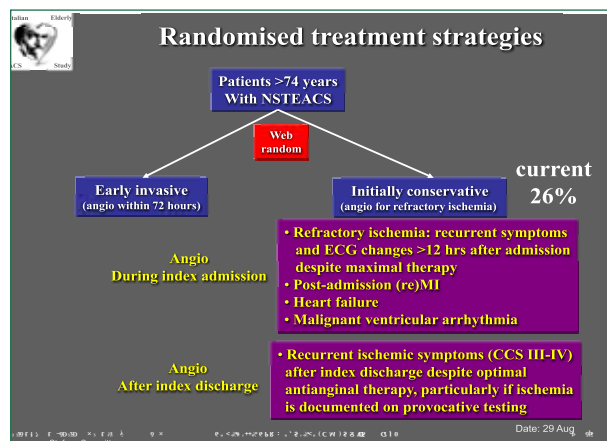
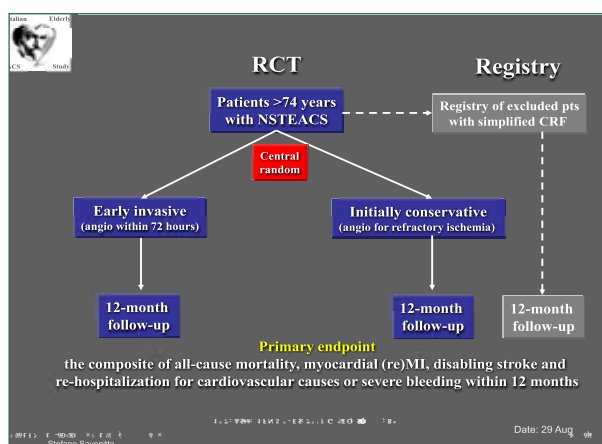
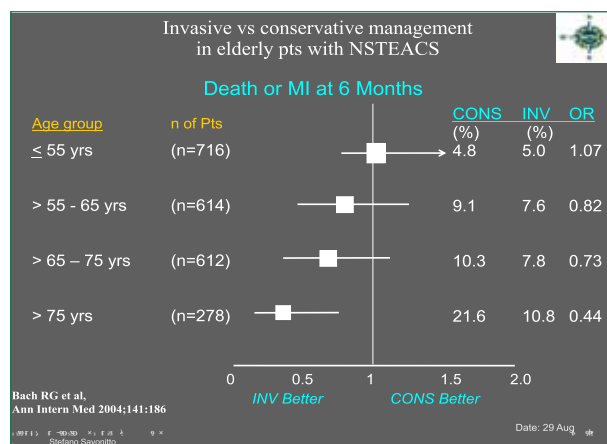
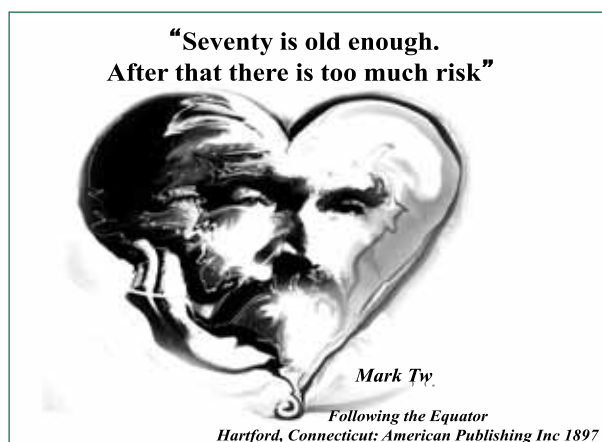
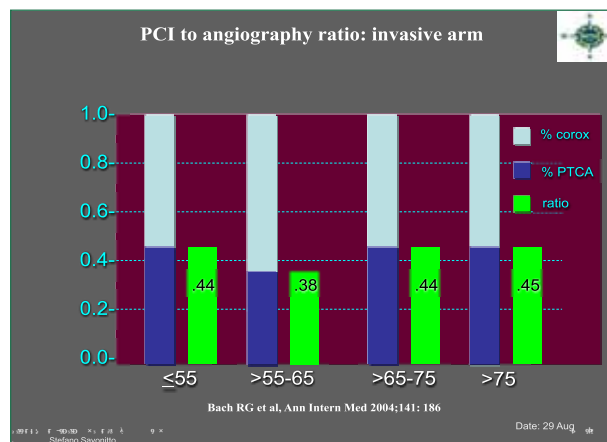


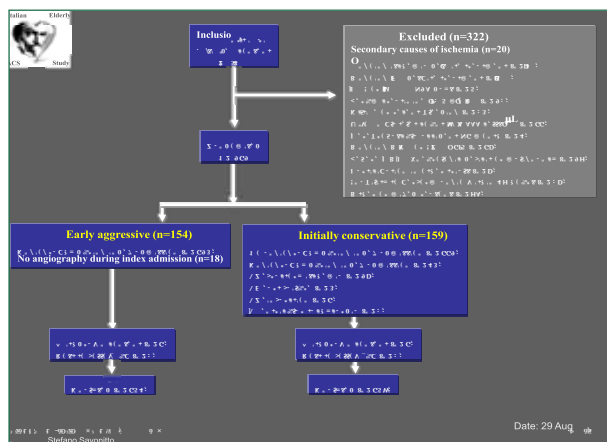
Elderly patients are under-represented in RCTs of early invasive treatment in NSTEMI/ACS

Trial	Average age	% pts ≥75y	Outcome
TIMI IIIIB	59	3	Benefit only >65 y
VANQWISH	61	8	No difference
FRISC II	65	19 (mean 76y)	Benefit only >65 y
RITA 3	63	12	Not reported by age
TACTICS	62	12.5	39% RR >65 56% RR >75
ICTUS	61	13 (max 80y)	Trend towards > benefit >65y

Date: 29 Aug







Baseline characteristics (1)

	Early aggressive (n=154)	Initially conservative (n=159)
Age (yrs)	81.8	81.8
Female (%)	51	49
Hypertension (%)	92	85
Diabetes (%)	38	41
Prior stroke (%)	7.5	9.7
eGFR	51 (S.D. 18)	54 (S.D. 20)
≥moderate mitral valve insuff (%)	20	25
Prior MI (%)	28	34
Prior HF (%)	10	9

Date: 29 Aug

Baseline characteristics (2)

	Early aggressive (n=154)	Initially conservative (n=159)
Prior CABG (%)	11	7.6
Prior PCI (%)	11	20
Chronic angina (%)	25	18
Mean Ejection fraction (%)	49	48
Mean TRS	4.3	4.3
Sinus rhythm (%)	84	87
A fibrillation (%)	15	12
Ischemic ECG (%)	61	67
Elevated Tn (%)	62	60

Date: 29 Aug

Cardiac procedures during index admission and at follow-up

	Early Aggressive (n=154)		Initially Conservative (n=159)	
	Index admission	Within one year	Index admission	Within one year
Angio (%)	88		29	
PCI (%)	50	51	23	29
CABG (%)	5.8	7	0.6	2.5
Any revasc (%)	55 → 58		23 → 31	

Date: 29 Aug

Myocardial revascularization procedures during index admission

	Early Aggressive (n=154)	Initially Conservative (n=159)
Coronary angiography performed	136 (88)	46 (29)
Time from random (hrs)	24 (IQR 15-46)	67 (IQR 24-113)
PCI immediate	65 (48)	32 (71)
PCI delayed	13 (9.6)	4 (8.9)
Radial access	55 (70)	28 (78)
Coronary stenting	73 (96)	34 (97)
BMS/DES (%)	46/54	44/56
Procedural success	74 (97)	35 (100)
CABG	9 (5.8)	1 (0.6)
Surgical success	9 (100)	1 (100)

Date: 29 Aug

Antithrombotic treatments during index admission

	Early Aggressive (n=154)	Initially Conservative (n=159)
Aspirin	95	99
Ticlopidine	4.6	1.9
Clopidogrel	90	92
Unfractionated heparin	25	24
Enoxaparin	64	59
GPIIb/IIIa inhibitor	17	6
Bivalirudin	3.8	1.3
Fondaparinux	8.5	8.5

Date: 29 Aug

Therapy at discharge

	Early Aggressive (n=154)	Initially Conservative (n=159)
Aspirin	88	94
Ticlopidine	2.6	1.9
Clopidogrel	69	83
Betablockers	58	60
ACE inhibitors / ARB	77	85
Calcium antagonists	29	29
nitrates	54	623
statines	77	84
diuretics	51	53

Date: 29 Aug

Adverse clinical events during index hospitalization

	Early Aggressive (n=154)	Initially Conservative (n=159)	p
Death	N (%) 8 (5.2)	5 (3.1)	
Myocardial infarction	3 (1.9)	5 (3.1)	
Severe recurrent ischemia	1 (0.6)	15 (9.4)	0.0004
Heart failure	11 (7.1)	4 (2.5)	0.06
Cardiac arrhythmia	3 (1.9)	3 (1.9)	
Any stroke / Disabling stroke	N 2 / 0	1 / 0	
TIMI major bleeding	0	1 (0.6)	
CABG-related bleeding/transfusion	4 (2.6)	0	
Infection/sepsis	2 (1.3)	1 (0.6)	

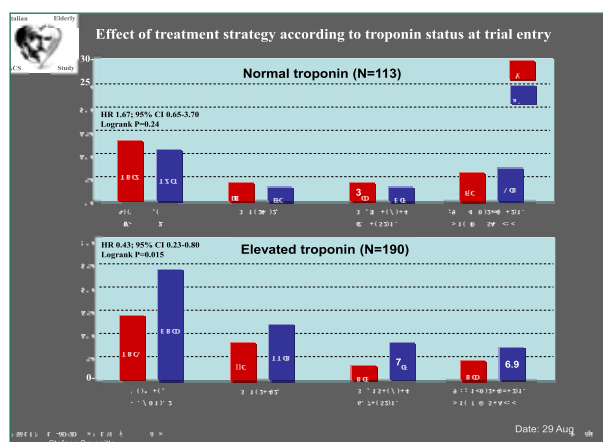
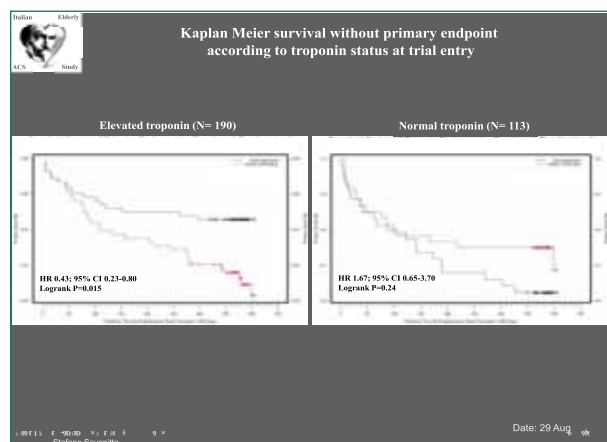
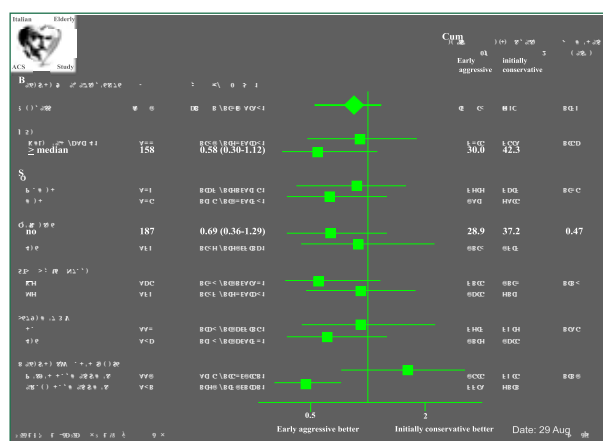
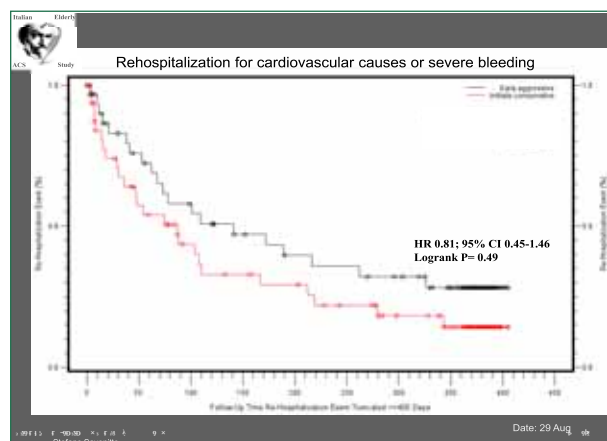
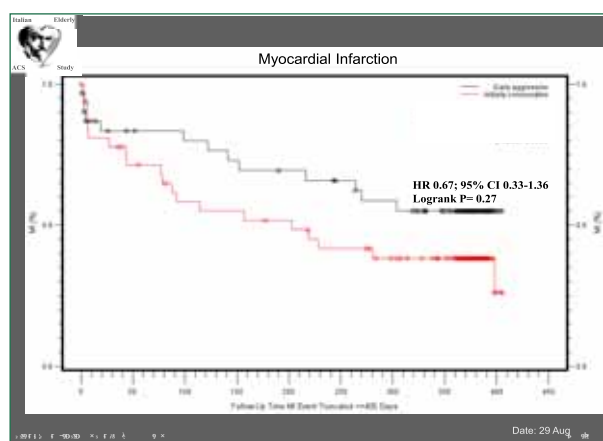
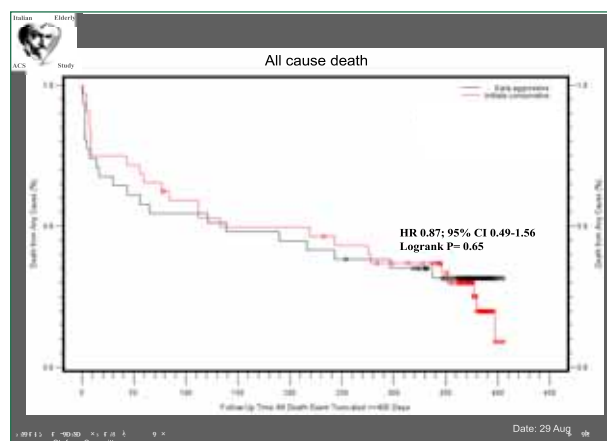
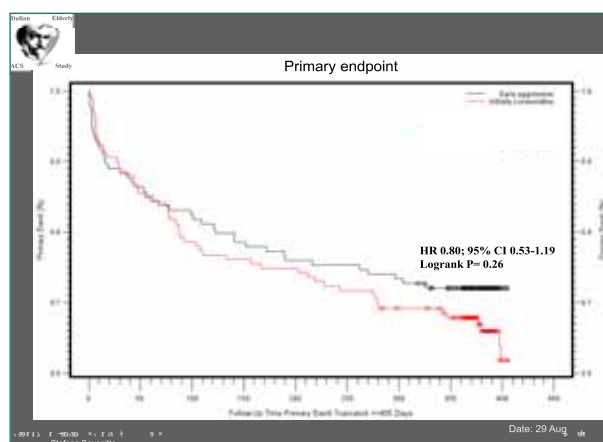
Date: 29 Aug



Cumulative rate of the primary endpoint and its components

Outcome	Early Aggressive (n=154)	Initially Conservative (n=159)	HR (95% CI)	Logrank P
Primary EP	43 (27.9)	55 (34.6)	0.80 (0.53-1.19)	0.26
Death				
CV	19 (12.3)	22 (13.8)	0.87 (0.49-1.56)	0.65
non CV	3 (2.0)	4 (2.5)		
Myocardial Infarction	11 (7.1)	17 (10.7)	0.67 (0.33-1.36)	0.27
Rehospitalization for CV causes or severe bleeding	18 (11.7)	22 (13.8)	0.81 (0.45-1.46)	0.49

Date: 29 Aug





Conclusions

(with the caveat of a subgroup analysis of an underpowered trial)

In elderly patients with NSTEMACS 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.

Stefano Savonitto

Date: 29 Aug

Why does the implantable cardioverter-defibrillator not improve mortality early after myocardial infarction?
Insights from the IRIS trial
Discussant
C. Leclercq
Service de Cardiologie
Centre Cardio-Pneumologique
Rennes, France

Presenter Disclosure Information

Christophe Leclercq, MD, PhD

FINANCIAL DISCLOSURE:

Research Grants: Boston Scientific, Medtronic, Sorin Group, St. Jude Medical,

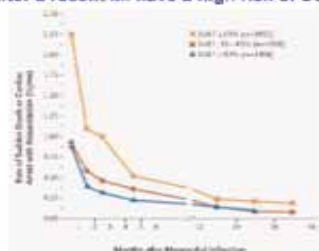
Consulting / Advisory board: Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Sorin Group

Lectures: Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Sorin Group, GE

Stock Options: None; Salary Support: None; Speaker Bureau: None

Rationale of the problem?

- Current guidelines for ICD implantation for primary prevention exclude patients with recent myocardial infarction, i.e. within the first 40 days (ESC, ACC, AHA and HRS guidelines).
- Patients after a recent MI have a high risk of SCD



Solomon. N Engl J Med 2005; 352: 2581

Is an ICD implantation early after MI effective to reduce mortality?

- DINAMIT trial : (LVEF $\leq$ 35% and cardiac autonomic dysfunction)
- IRIS trial: (LVEF $\leq$ 40% and HR > 90 bpm and /or NSVT)

➤ Decrease in SCD offsets by an increase in non SCD

	ICD		Control		Cox Model Results		
	# of events	Rate (%/year)	# of events	Rate (%/year)	Hazard Ratio	95% CI	p-value (two-sided)
Death from any cause							
DINAMIT	82/211	7.5	58/242	6.9	1.08	0.76 – 1.33	0.69
IRIS	116/445	7.9	117/453	7.6	1.04	0.81 – 1.35	0.15
Arrhythmic Death							
DINAMIT	12/111	1.5	23/242	3.5	0.42	0.22 – 0.83	0.008
IRIS	27/445	2.03	60/453	4.4	0.55	0.31 – 1.00	0.048
Non-Arrhythmic Death							
DINAMIT	50/211	6.1	23/242	3.5	1.75	1.11 – 2.76	0.016
IRIS	68/445	5.1	39/453	2.8	1.92	1.29 – 2.84	0.001

Summary of the 2011 IRIS results

- ✓ ICD reduces SCD only within the 2 first years
- ✓ Higher NSCD mortality with ICD especially after 3 years
- ✓ Age, multivessel disease, wide QRS, NYHA %, 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 patientsand these patients were excluded because of the divergence of the results with the other populations....???
- ✓ RV pacing increase mortality (lack of data in IRIS trial)
- ✓ Appropriate therapies were associated with an increase in mortality especially non SCD (MADIT, SCD-HeFT, COMPANION... and DINAMIT)

Role of appropriate therapies

- Secondary analysis of the DINAMIT trial using a competitive-risks analysis and an adjusted time-dependant 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 B-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%

Dorian. Circulation 2010; 122: 2645-52



Complexity of the problem

- Ventricular arrhythmias may enhance cardiac deterioration and increase risk of death
- An intercurrent 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 Bradycardia Patients with Preserved Systolic Function: Two-year Results of PACE

¹Cheuk-Man Yu, ¹Fang Fang, ^{1,2}Jeffrey Wing-Hong Fung, ³Qing Zhang, ⁴Omar Razali, ⁵Gabriel Wei-Kwok Yip, ⁶Hussain Azlan, ⁷Harish Chi-Kin Chan, ¹Joseph Yat-Sun Chan



¹ Institute of Vascular Medicine & Division of Cardiology, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong.
² Department of Medicine, North District Hospital, Hong Kong.
³ Department of Cardiology, West China Hospital, Sichuan University, China
⁴ Department of Cardiology, National Heart Institute, Kuala Lumpur, Malaysia
⁵ Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong



Presenter Disclosure Information

- PI and presenting author : Cheuk-Man YU
 - "Biventricular Pacing is Superior to Right Ventricular Pacing in Bradycardia Patients with Preserved Systolic Function: Two-year Results of Pacing to Avoid Cardiac Enlargement (PACE) Trial"
- FINANCIAL DISCLOSURE:
- Consulting fees from Philips; lecture fees from GE, St. Jude Medical, Philips, Medtronic, and Boston Scientific; and research grants from Sanofi-Aventis, Hong Kong and Philips.
- This study was supported by a research grant from Medtronic Inc.

UNLABELED/UNAPPROVED USES DISCLOSURE: None

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, H. Azlan; National Heart Institute

Echocardiographic Core Laboratory:

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

Clinical Event Committee:

- W. Chan, 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:

- Alice Ho Miu Ling Nethersole Hospital, Hong Kong – H.C.K. Chan, W.L. Chan; Prince of Wales Hospital, The Chinese University of Hong Kong – J.Y.S. Chan, C.M. Yu, G.W.K. Yip, A.K.Y. Chan; G.C.P. Chan; National Heart Institute, Kuala Lumpur – O. Razali, H. Azlan, K.H. Lam; North District Hospital, Hong Kong – J.W.H. Fung, K.H. Yiu

PACE

Background

Right ventricular apical (RVA) pacing

- Non-physiological Pacing leads to dyssynchronous contraction
- Exerts deleterious effect with a 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

PACE

It is a bad plan that cannot be altered

— Pubilius Syrus



PACE

Background

Biventricular (BiV) pacing

- Attenuation the dyssynchronous contraction
- Preserve left ventricular function
- Avoid the left ventricular remodeling



Picture from Medtronic

PACE



PACE study

The Result of PACE study at 1-Year



Extended Follow-Up : Rationale

- In long-term cohort studies the percentage of patients with LV dilatation and impaired LV ejection fraction (LVEF) was significantly higher than in short-term follow up studies
- To date, there are no data from randomized trial on whether the deleterious effect of RVA pacing and the protective effect of BIV pacing persist with time

Patients Selection

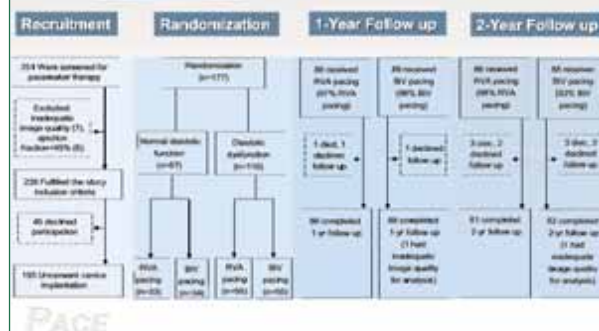
Inclusion criteria

- Patients with normal LV ejection fraction ($\geq 45\%$)
- With standard pacing indications

Exclusion criteria

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

Study flowchart



Assessment

Echocardiography

- Real-time 3-dimensional echocardiography (IE33 & Q-Lab 7.0, Phillips, Andover, MA)
- LV volumes and ejection fraction, dyssynchrony index
- Off-line analysis blinded to treatment and clinical data
- Inter-intra-observer variability: 3.9 & 4.2% (ejection fraction), 6.7 & 6.5% (LV volume)

Clinical status

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

Time point

- * Baseline, 1 month, 3, 6, 9, 12, 18 and 24 months

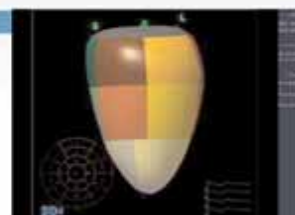
Study End-points

Co-Primary End-points

- LV ejection fraction
- LV end-systolic volume

Secondary End-points

- LV end-diastolic volume
- 6-min hall walk distance
- Quality of life scores



Echocardiography

LV systolic dyssynchrony

- Tissue Doppler Imaging (TDI) to assess LV systolic dyssynchrony at baseline, 1-year and 2-year follow-up (Vivid 7, GE)
- Systolic Dyssynchrony Index assessed with 12- LV segmental motion (Ts-SD or Yu's Index, JASE 2008;21:191-213.), a cutoff value >33ms defined significant dyssynchrony



Statistical Analysis

Statistical analysis on end-points at 2-year

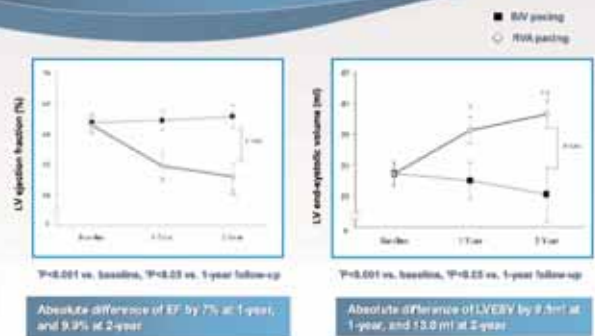
- Intention-to-treat : patients with ≥ 3 months follow up were included
- For drop outs : analyzed by last-observation-carried-forward principle
- Repeat measurement analysis : difference in end-point among time intervals of baseline, first and second year
- General Liner Model : potential interaction of clinical factors on primary end-points



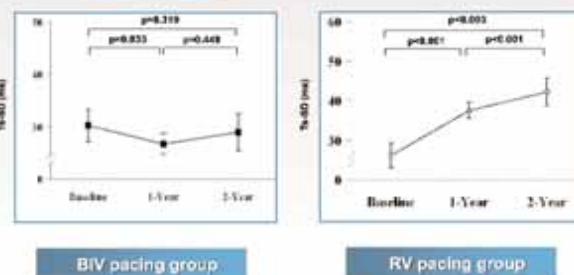
Baseline Characteristics

Parameters	RVA pacing (n=88)	BIV pacing (n=88)	P value
Age - years	68:11	69:11	0.76
Male sex - no. (%)	49 (56)	47 (53)	0.70
Systolic blood pressure - mmHg	143:22	140:24	0.14
Diastolic blood pressure - mmHg	89:12	73:12	0.01
Heart rate - bpm	89:16	89:17	0.99
QRS duration - ms	107:30	107:27	0.99
Left ventricular ejection fraction - %	61.5:6.8	61.9:6.7	0.86
Indication for pacing - no. (%)			0.24
Advanced atrioventricular block	35 (40)	49 (56)	
Sinus node dysfunction	33 (37)	49 (56)	
Medical history - no. (%)			
Hypertension	59 (67)	62 (70)	0.24
Diabetes mellitus	26 (29)	33 (38)	0.70
Coronary heart disease	20 (23)	19 (21)	0.71
Heart failure	12 (14)	10 (11)	0.63
Chronic renal failure	4 (5)	2 (2)	0.44

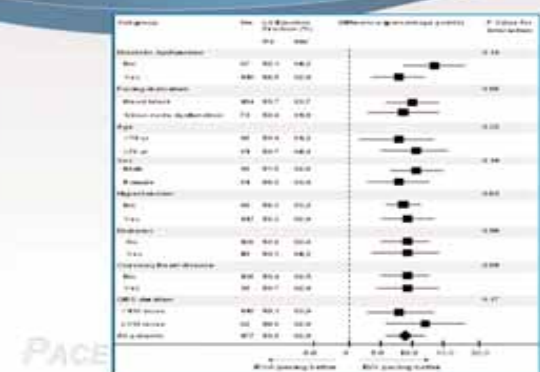
Comparison of Primary End-points



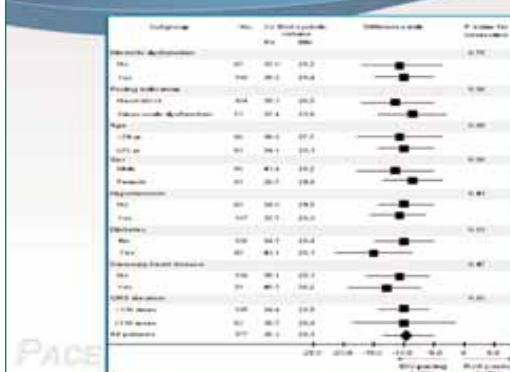
Comparison of Systolic Dyssynchrony



Subgroup Analysis - LV Ejection Fraction



Subgroup Analysis - LV End-Systolic Volume



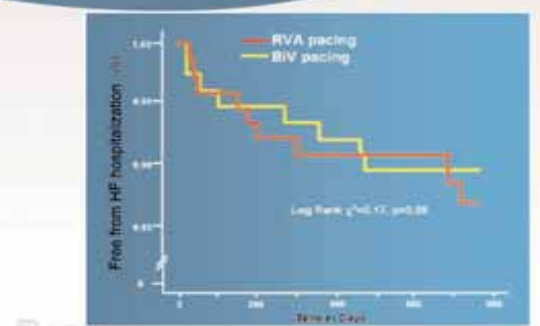
Comparison of Secondary End-points

Parameters	Baseline	RVA pacing	BIV pacing	P value
Stroke risk - no. (%)				
Baseline	100/100	100/100	100/100	0.99
1 Year	100/100	100/100	100/100	0.99
2 Year	100/100	100/100	100/100	0.99
Stroke risk - no. (%)				
Baseline	100/100	100/100	100/100	0.99
1 Year	100/100	100/100	100/100	0.99
2 Year	100/100	100/100	100/100	0.99
Stroke risk - no. (%)				
Baseline	100/100	100/100	100/100	0.99
1 Year	100/100	100/100	100/100	0.99
2 Year	100/100	100/100	100/100	0.99
Stroke risk - no. (%)				
Baseline	100/100	100/100	100/100	0.99
1 Year	100/100	100/100	100/100	0.99
2 Year	100/100	100/100	100/100	0.99

Comparison of Secondary End-points

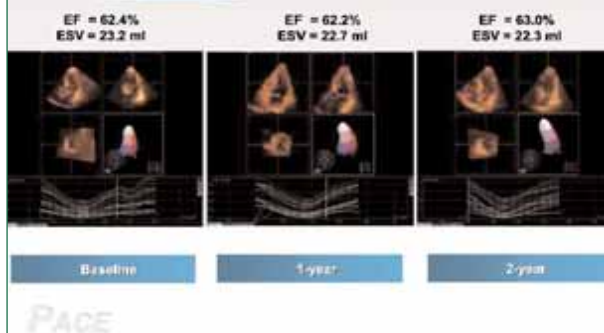
Parameters	Baseline	RVA pacing	BIV pacing	P value
SF-36 score				
Physical function	Baseline	40.00	40.00	0.99
1 Year	40.00	40.00	40.00	0.99
2 Year	40.00	40.00	40.00	0.99
Role limitation	Baseline	40.00	40.00	0.99
1 Year	40.00	40.00	40.00	0.99
2 Year	40.00	40.00	40.00	0.99
Role limitation	Baseline	40.00	40.00	0.99
1 Year	40.00	40.00	40.00	0.99
2 Year	40.00	40.00	40.00	0.99
Role limitation	Baseline	40.00	40.00	0.99
1 Year	40.00	40.00	40.00	0.99
2 Year	40.00	40.00	40.00	0.99

Heart failure hospitalization

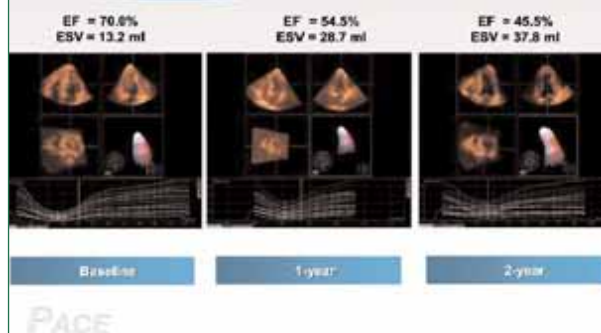




BIV pacing, preservation of LV function and remodeling



RVA pacing, progression of LV function and remodeling



Discussion

Major findings in the study

- The extended 2-year follow up : deleterious 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 LVESV 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 increase in LVESV corresponds to the increase in Dyssynchrony Index (DI) in the RVA pacing group. DI 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 protects 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

PACE 2 year follow up results : Now available online in "European Heart Journal"

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

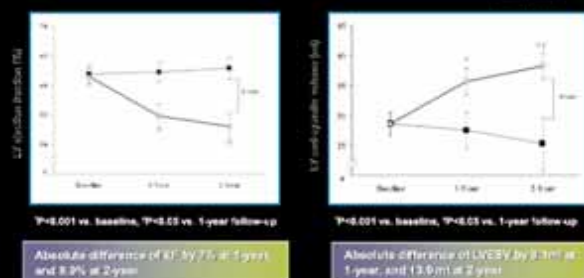


- The 2-year follow-up in the Pacing to Avoid Cardiac Enlargement (PACE) trial confirms that chronic RV pacing in patients with bradycardia and preserved LV function leads to sustained and progressive deterioration of LVEF and increases in LV volumes.
- This adverse remodelling process was prevented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

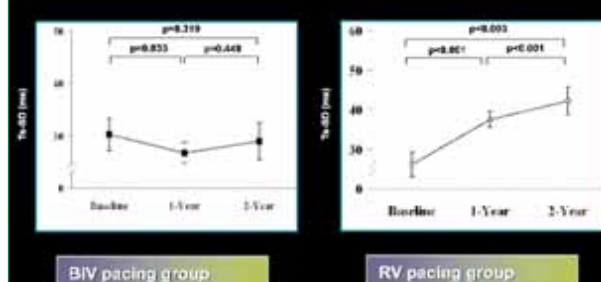
Adverse Remodelling

- 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 intra-ventricular dyssynchrony.

Primary End-points



Systolic Dyssynchrony





Recommendations in patients with heart failure and a concomitant class I pacemaker indication			
Recommendations	Patient Population	Class	Level
CRT-P/CRT-D* is recommended to reduce morbidity	NYHA function class III/IV LVEF≤35%, QRS ≥120 ms	I	B
CRT-P/CRT-D* should be considered to reduce morbidity	NYHA function class III/IV LVEF≤35%, QRS<120 ms	IIa	C
CRT-P/CRT-D* may be considered to reduce morbidity	NYHA function class II LVEF≤35%, QRS<120 ms	IIb	C

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

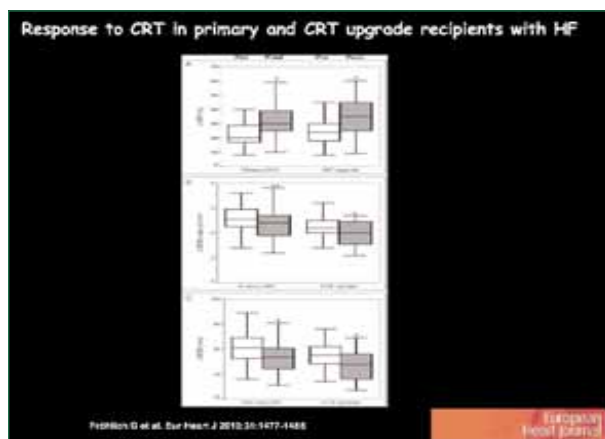
Eur Heart J. 2010 Nov;31(21):2677-87
Eur J Heart Fail. 2010 Nov;12(11):1143-52
Europace. 2010 Nov;12(11):1526-36

CRT-P/CRT-D in patients with heart failure and a conventional pacemaker indication

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

Eur Heart J. 2010 Nov;31(21):2677-87
Eur J Heart Fail. 2010 Nov;12(11):1143-52
Europace. 2010 Nov;12(11):1526-36

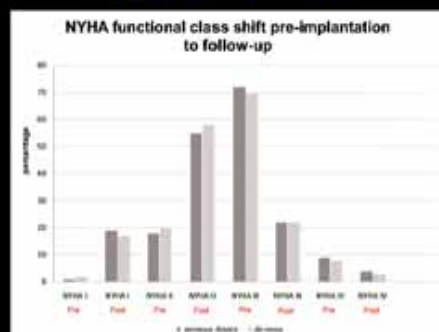


The European CRT Survey: Upgrades from a PPM or ICD to a CRT-P or CRT-D

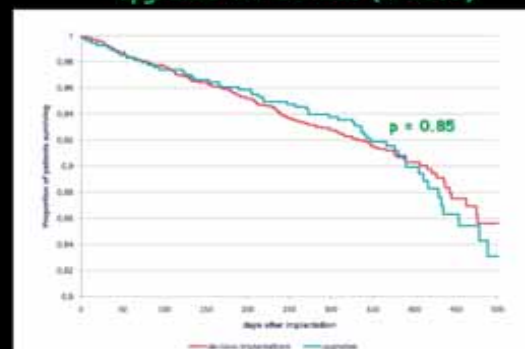
- 2367 patients in this analysis
- 1675 de-novo implantations
- 692 upgrades

Eur J Heart Fail 2011

NYHA Change upgrade vs. de-novo



Survival: upgrades vs. de novo (n=2367)



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

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 not 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...

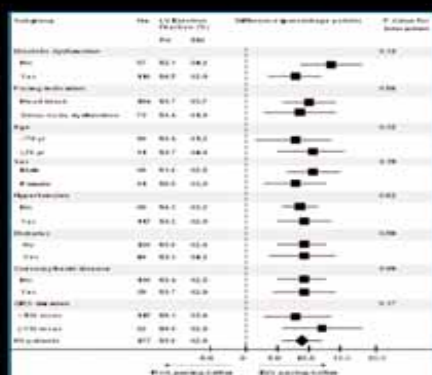
BACKUP

It is encouraging when research results are consistent with our understanding of the operative mechanisms, especially when there is a direct potential impact on clinical practice.

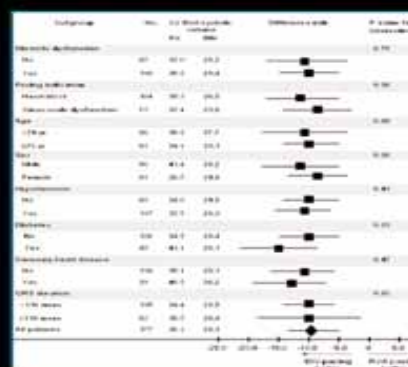
Baseline Characteristics EF, QRS, indication

Parameters	RVA pacing (n=86)	BIV pacing (n=89)	P value
Male sex - no. (%)	49 (56)	47 (53)	0.70
Diastolic blood pressure - mmHg	69/12	73/12	0.01
QRS duration - ms	107/30	107/27	0.98
Indication for pacing - no. (%)			0.24
Sinus node dysfunction	33 (37)	43 (48)	
Hypertension	55 (62)	62 (70)	0.24
Coronary heart disease	20 (23)	19 (21)	0.71
Chronic renal failure	4 (5)	2 (2)	0.44

Subgroup Analysis - LV Ejection Fraction



Subgroup Analysis - LV End-Systolic Volume





Comparison of Secondary End-points

Parameters	RVA pacing	BiV pacing	P value
6-min hall walk - meter			
Baseline	339:92	342:99	0.88
24-month	363:117	361:165	0.79
12-month	76.7:22.5	71.8:17.8	0.25
SF-36 score			
12-month	67:22	71:27	0.85
Role physical [†]			
Baseline	39:44	43:45	0.58
24-month	64:43	60:43	0.24
12-month	72:28	77:28	0.24

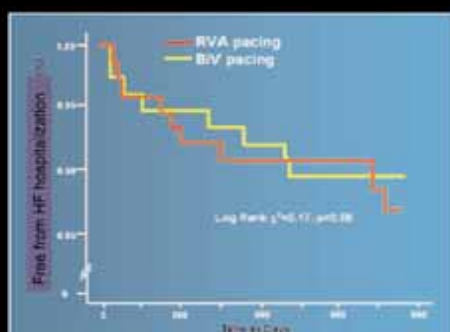
[†]P<0.05 among different time interval

Comparison of Secondary End-points

Parameters	RVA pacing	BiV pacing	P value
General health			
Baseline	433:3	482:3	0.08
24-month	445:4	485:4	0.26
12-month	78:18	77:20	0.67
Role - emotional			
Baseline	88:43	89:43	0.26
12-month	87:42	71:29	0.83
24-month	88:42	71:39	0.68
12-month	80:38	80:38	0.73
Vitality			
Baseline	67:24	64:22	0.08
24-month	84:24	86:21	0.48

[†]P<0.05 among different time interval

Heart failure hospitalization



Pre-implantation Data

Demographics	
Age (years)	70 (62-78)
Age ≥ 75 (%)	31
Females (%)	27
Heart failure aetiology (%)	
Ischaemic	51
Past History (%)	
Prior device (PPM, ICD)	28
Prior device (PPM, ICD)	28
ECG	
Atrial fibrillation (%)	23
QRS complex	
Paced rhythm (%)	19
QRS duration (msec)	157 ± 32
QRS duration < 120 ms (%)	9
QRS duration 120 – 129 ms (%)	10
QRS duration ≥ 150 ms (%)	82

Comparison with RCTs

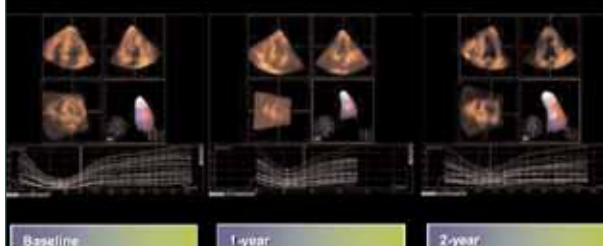
	COMPANION	CARE-HF	REVERSE	CRT Survey
Number of patients	1213	409	418	2439
CRT-P (%)	51	100	18	27
CRT-D (%)	49	NA	82	72
Previous device	0*	0*	0*	26
Women (%)	33	27	22	24
Ischaemic heart disease (%)	55	38	56	51
NYHA class III (%)	86	84	0	70
LV ejection fraction (%)	22	26	27	26
LV diastolic diameter (mm)	67	72	69	66
QRS (ms)	169	165	153	160
Atrial fibrillation (%)	0*	0*	0*	23
Diuretics (%)	95	99	91	88
ARB/ACEi (%)	89	85	96	91
Beta-blockers (%)	68	72	96	85
Aldosterone antagonists (%)	54	56	NA	46

* Previous device implantation and atrial fibrillation were exclusion criteria.

BiV pacing, preservation of LV function and remodeling



RVA pacing, progression of LV function and remodeling





SHIfT

Systolic Heart failure treatment with the *if* inhibitor Ivabradine Trial

Effects of heart rate reduction with ivabradine on left ventricular remodeling and function: results of the SHIFT echocardiography substudy

JC Tardif, E O'Meara, M Komajda, M Böhm, JS Borer, I Ford, L Tavazzi, K Swedberg
on behalf of the SHIFT Investigators

SHIfT

Disclosures

- All authors have received fees, research grants, or both from Servier.
- The study was supported by Servier, France.

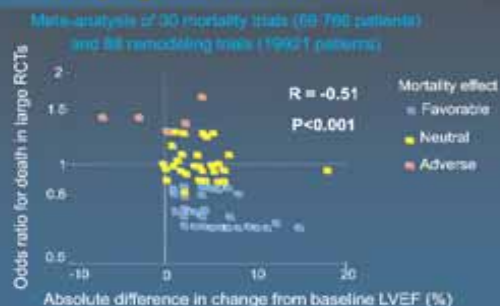


SHIfT

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.

Relationship between drug/device effects on LVEF and prognosis in heart failure



Kramer DG et al. J Am Coll Cardiol 2010;56:392-406

SHIfT

Background

- SHIFT is a randomised, double-blind, placebo-controlled, multinational trial in 6505 pts with chronic HF, LVEF $\leq 35\%$, sinus rhythm and heart rate (HR) ≥ 70 bpm.
- Patients were randomly allocated to ivabradine 5 mg bid or placebo and the dosage could be adjusted to 7.5 mg or 2.5 mg bid depending on HR and tolerability.
- HR lowering with ivabradine led to an 18% reduction in the primary endpoint of CV death/HF hospitalization ($P < 0.0001$).

Swedberg K et al. Lancet. 2010;376:875-885

SHIfT

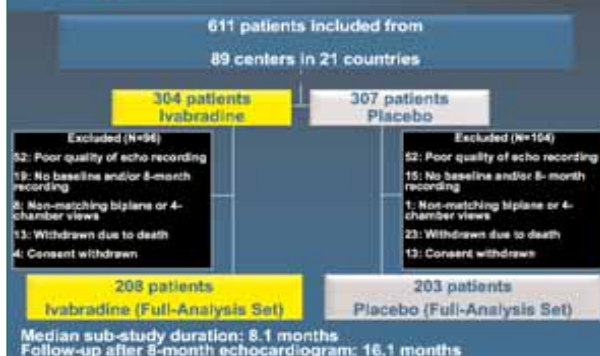
Objective of the pre-specified echocardiography sub-study

To evaluate the effects of the *if* inhibitor ivabradine on LV remodeling and function:

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

SHIfT

Sub-study population



SHIfT

Baseline characteristics

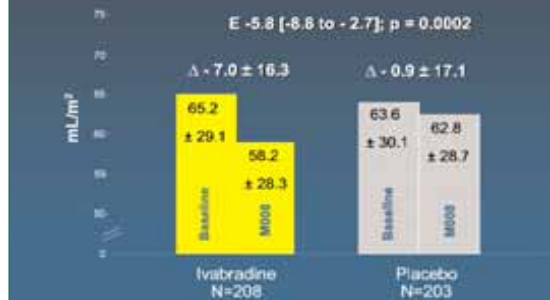
	Ivabradine N=304	Placebo N=307
Mean age, years	60	59
Male, %	80	82
Mean BMI, kg/m ²	28	28
Mean HF duration, years	4	4
HF ischaemic cause, %	67	65
NYHA class II, %	48	46
NYHA class III, %	51	53
Mean LVEF, %	32	32
Mean HR, bpm	78	79
Mean systolic BP, mm Hg	121	119
Mean diastolic BP, mm Hg	75	75



SH/fT Baseline background treatment

	Ivabradine N=304	Placebo N=307
Beta-blocker, %	92	92
ACE inhibitor, %	80	83
ARB, %	17	12
Diuretic (excluding antialdo), %	87	87
Aldosterone antagonist, %	74	71
Digitalis, %	27	32
Devices, %	3	4

SH/fT Primary endpoint: change in LVESVI from baseline to 8 months



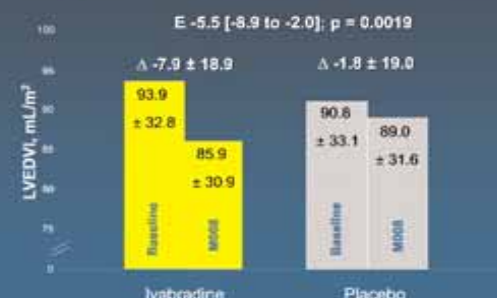
LVESVI: Left ventricular end-systolic volume index

SH/fT Relative change in LVESVI from baseline to 8 months



LVESVI: Left ventricular end-systolic volume index

SH/fT Secondary endpoint: change in LVEDVI from baseline to 8 months

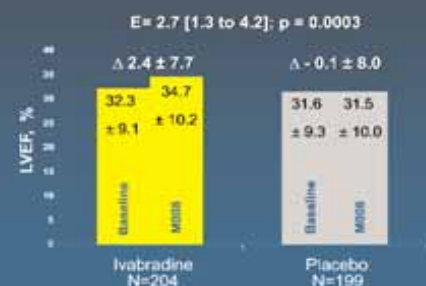


LVEDVI: Left ventricular end-diastolic volume index

SH/fT Changes in LVESV and LVEDV from baseline to 8 months

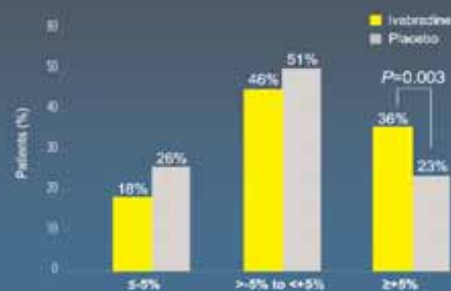
	Baseline	MS - baseline	E, 95% CI	P value
LVESV, mL				
Ivabradine (N=208)	123.8 ± 55.6	-13.0 ± 31.6	-11.2 [-17.1 to -5.4]	<0.001
Placebo (N=203)	122.2 ± 59.8	-1.3 ± 32.8		
LVEDV, mL				
Ivabradine (N=204)	178.4 ± 63.4	-14.7 ± 36.4	-10.9 [-17.6 to -4.2]	0.0014
Placebo (N=199)	174.7 ± 67.6	-2.9 ± 36.8		

SH/fT Secondary endpoint: change in LVEF from baseline to 8 months



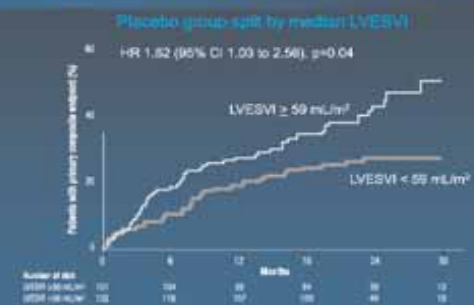
LVEF: Left ventricular ejection fraction

SH/fT Absolute change in LVEF from baseline to 8 months



LVEF: Left ventricular ejection fraction

SH/fT LVESVI and the risk of the SHIFT primary composite endpoint



LVESVI: Left ventricular end-systolic volume index



SHIFT

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 $\geq$ 70 bpm, in sinus rhythm and predominantly 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

SHIFT

Conclusions

- Ivabradine reverses left ventricular remodeling 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

SHIFT

Available now online
European Heart Journal



European Heart Journal
doi:10.1093/eurheartj/ehk311

FASTTRACK
ESC CLINICAL TRIAL UPDATE

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

Jean-Claude Tardif¹*, Eileen O'Meara¹, Michel Komajda², Michael Böhm³, Jeffrey S. Borer⁴, Ian Ford⁵, Luigi Tavazzi⁶, and Karl Swedberg⁷, 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*



Discussant
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

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

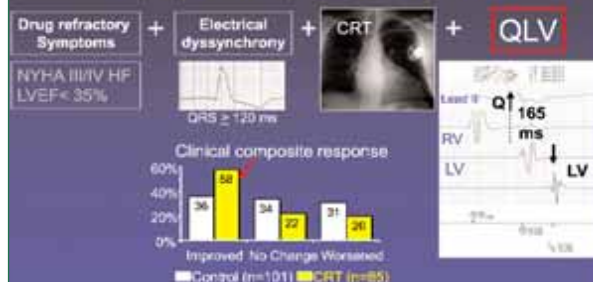
to areas of viability

to area of latest activation by QLV

→ The SMART AV substudy

Rationale for SMART AV substudy

The question – will addition of



Improve the response rate to CRT treatment >60% ?



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)

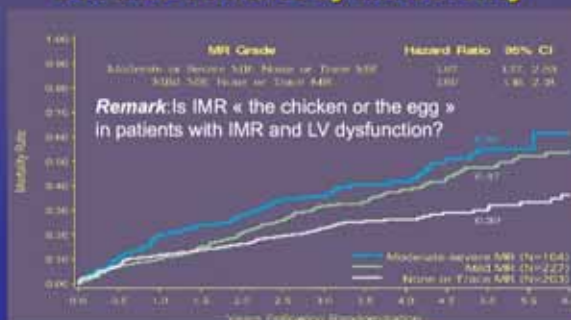
Remarks :

Limitations in the assessment of severity of MR (absence of Corelab, integrative quantification ?)

Mitral regurgitation? ☐ None or trace ☐ Mild (1-24%) ☐ Moderate (25-49%) ☐ Severe (50-74%) ☐ Not assessed

Merging moderate and severe MR is unusual

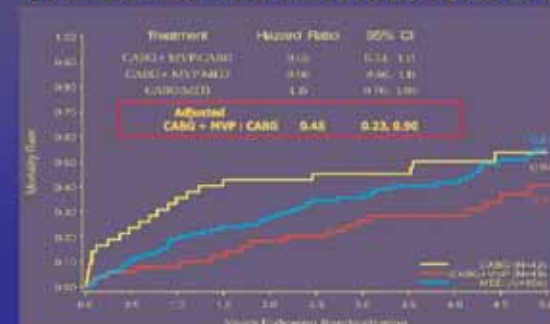
All-Cause Mortality Estimates for 534 MED Patients by MR Severity



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

- 91Pts, 49 underwent MVR
- Patients who underwent MVR had :
More pre op. PCI, worse LVEF, larger LVESVI,
More complicated post operative outcome
BUT
only 2% operative mortality

All-Cause Mortality Estimates for 195 Patients with Moderate/Severe MR



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



ESC/EACTS GUIDELINES



Combined CABG and:	Class ^a	Level ^b
Mitral valve surgery is indicated in patients with a primary indication for CABG and <u>severe</u> ischaemic mitral regurgitation and EF >30%.	I	C
Mitral valve surgery should be considered in patients with a primary indication for CABG and <u>moderate</u> ischaemic mitral regurgitation provided valve repair is feasible, and performed by experienced operators.	IIa	C

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

Hiroki Shiomi, Junichi Tazaki, Takeshi Morimoto,
Yutaka Furukawa, and Takeshi Kimura,

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

Department of Cardiology, Graduate School of Medicine, Kyoto University

Pharmaceuticals and Medical Devices Agency (PMDA)

Research Institute for Production Development



CREDO-KYOTO PCI/CABG Registry Cohort-2

Funding Source

Pharmaceuticals and Medical Devices Agency in Japan

Disclosures

Hiroki Shiomi: Nothing to disclose

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.

The SYNTAX trial 3-year Results

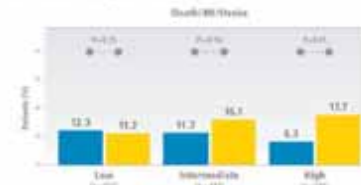


A.P.Kappetein et al. Eur Heart J. 2011

Background

- The SYNTAX trial also suggested that PCI was associated with higher risk for Death/MI/Stroke in patients with intermediate or high SYNTAX Score, but not in those with low SYNTAX Score.
- However, the limitation of this observation in the SYNTAX trial was apparent lack of statistical power in evaluating this endpoint.

The SYNTAX trial 3-year Results



Friedrich W. Mohr et al. TCT 2010

CREDO-KYOTO PCI / CABG Registry Cohort-2

PCI arm total 13087 patients

CABG arm total 2176 patients

- 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

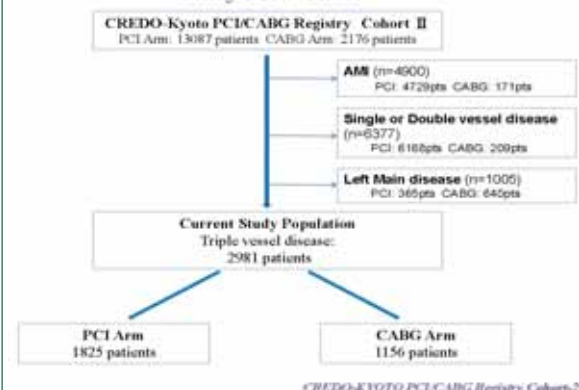
CREDO-Kyoto PCI/CABG Registry Cohort-2 Participating 26 centers and Investigators:

Centers	Investigators
Kansai Densetsu Hospital	Katsuhiko Ishii
Kishiwada City Hospital	Mitsuo Matsuda
Kyoto University Hospital	Takashi Kimura
Nara Hospital, Nara University School of Medicine	Manabu Shimizu
Kansai University Hospital	Hiroshi Ogawa
Koto Memorial Hospital	Tomoyuki Murakami
Mitsubishi Kyoto Hospital	Shoji Miki
Shimada Municipal Hospital	Takashi Aoyama
Shiga University of Medical Science Hospital	Mitsuo Horie
Kagoshima University Medical and Dental Hospital	Chunsei Teri
Juntendo University Shizuoka Hospital	Satoru Sawa
Kakano Memorial Hospital	Masahiko Nakagawa
Kobe City Medical Center General Hospital	Toru Kato
Nishi-Kobe Medical Center	Hiroshi Kato
	Masahiko Ohtsuka
	Mitsuo Hara
	Yutaka Furukawa
	Yukihisa Okada
	Hiroshi Iizawa

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

Centers	Investigators
Shizuoka General Hospital	Osamu Doi
Shizuoka City Shizuoka Hospital	Akiteru Takizawa
Kanagawa Central Hospital	Kazuki Miyabe
Osaka Red Cross Hospital	Masaru Tanaka
Torii Hospital	Yoshihisa Nakagawa
Shimada Hospital	Masaru Takahashi
Japanese Red Cross Society Wakayama Medical Center	Takashi Tanaka
Hamaoka Hospital	Masaki Aoki
Hamaoka Hospital	Masaki Takahashi
Matsuyama City Hospital	Ryosuke Tanaka
Fukuoka University Hospital	Jung-Dae Lee
Hyogo Prefectural Amagasaki Hospital	Yoshiaki Takahashi
Kitano Hospital	Ryosuke Nishida

Study Flow Chart



CREDO-KYOTO PCI/CABG Registry Cohort-2



CREDO-KYOTO PCI/CABG Registry Cohort-2

Primary Outcome Measure

- Composite of Death, MI and Stroke

Secondary Outcome Measures

- Death
- Cardiac Death
- MI
- Stroke
- Any Coronary Revascularization

Baseline Characteristics

	PCI	CABG	p value
Number of patients	1825	1156	
Age (years)	69.7±10.0	68.0±8.9	<.001
Age ≥ 75 years	642 (35%)	305 (26%)	<.001
Male	1295 (71%)	846 (73%)	.59
BMI	23.8±3.8	23.5±3.3	.005
Acute coronary syndrome	182 (10%)	96 (8.3%)	.32
Hypertension	1534 (83%)	972 (84%)	.01
Diabetes mellitus	911 (50%)	644 (56%)	.002
no insulin therapy	252 (14%)	216 (19%)	<.001
Current smoking	462 (25%)	280 (24%)	.50
Heart failure	378 (21%)	356 (31%)	.35

Baseline Characteristics

	PCI	CABG	p value
Number of patients	1825	1156	
Ejection fraction <= 40%	190 (12%)	362 (31%)	.07
Prior myocardial infarction	345 (19%)	297 (25%)	<.001
Prior stroke (symptomatic)	292 (16%)	173 (15%)	.45
Peripheral vascular disease	211 (12%)	101 (8.7%)	.32
eGFR < 30, without hemodialysis	103 (5.6%)	101 (8.7%)	.001
Hemodialysis	99 (5.4%)	75 (6.5%)	.21
Anemia (Hb <11.0g/dl)	284 (16%)	219 (19%)	.02
COPD	60 (3.3%)	25 (2.2%)	.07
Malignancy	152 (8.3%)	119 (10%)	.84

Procedural Characteristics

	PCI	CABG	p value
Number of target lesions or anastomoses	2.05±0.99	1.44±1.05	<.001
Target of proximal LAD	1171 (64%)	1120 (97%)	<.001
Target of CTO	416 (23%)	564 (49%)	<.001
Target of bifurcation	701 (38%)	—	—
Emergency procedure	104 (5.7%)	37 (3.2%)	.002
Total number of stents	2.81±1.66	—	—
Total stent length (mm)	62.0±40.0	—	—
Stent use	1775 (97%)	—	—
DES use	1328 (73%)	—	—
ITA use	—	1131 (98%)	—
Off pump	—	727 (63%)	—

Primary Outcome Measure: Death/MI/Stroke



CREDO-KYOTO PCI/CABG Registry Cohort-2

All-cause Death



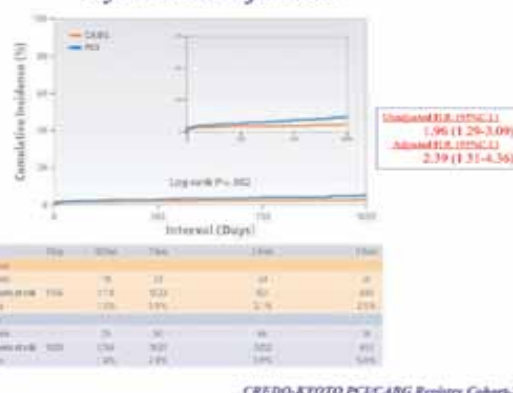
CREDO-KYOTO PCI/CABG Registry Cohort-2

Cardiac Death

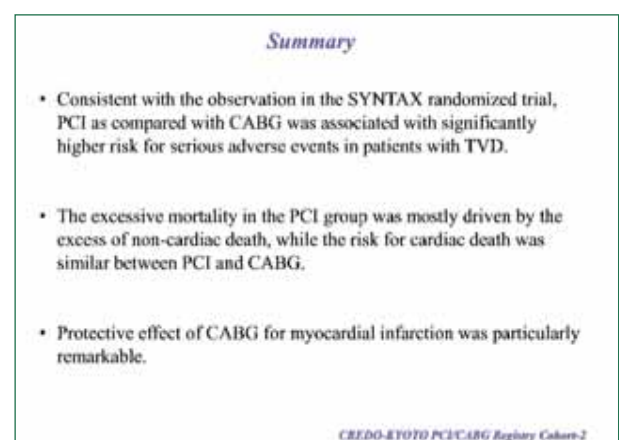
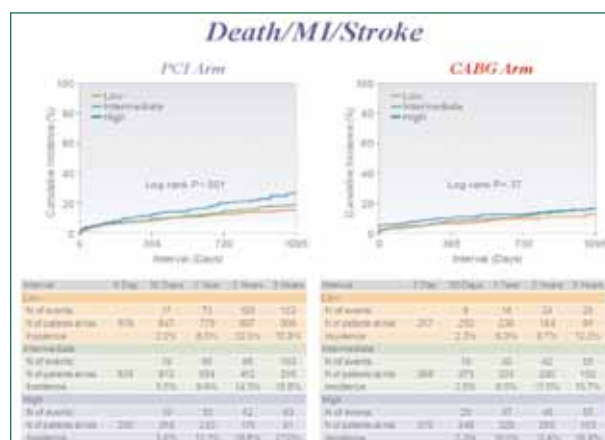
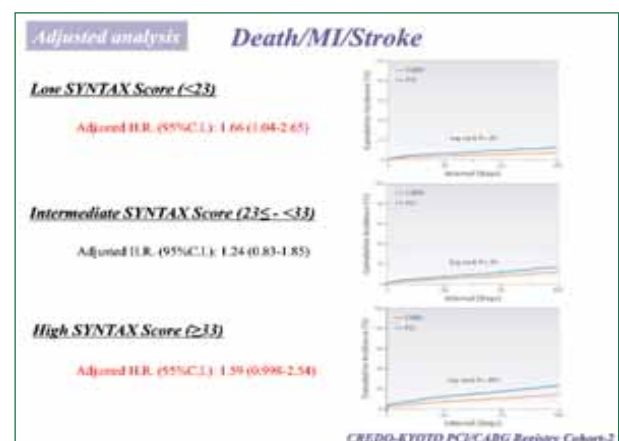
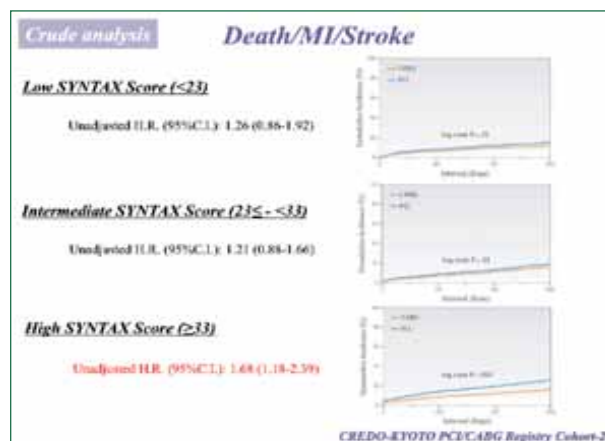
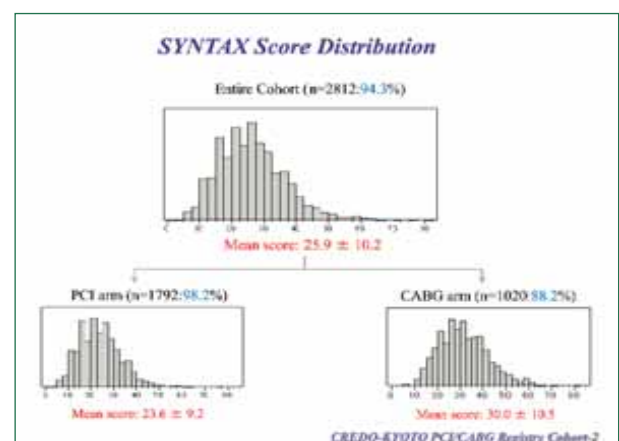
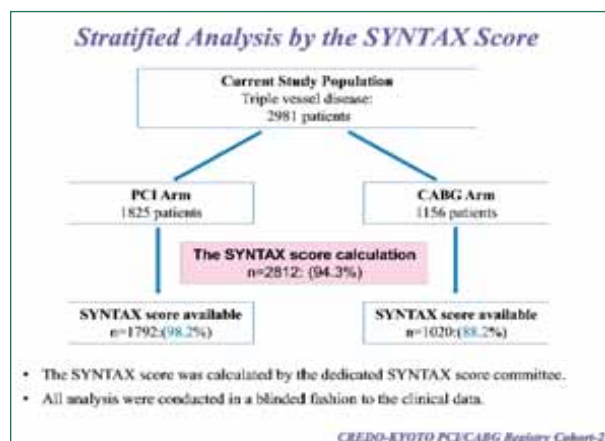
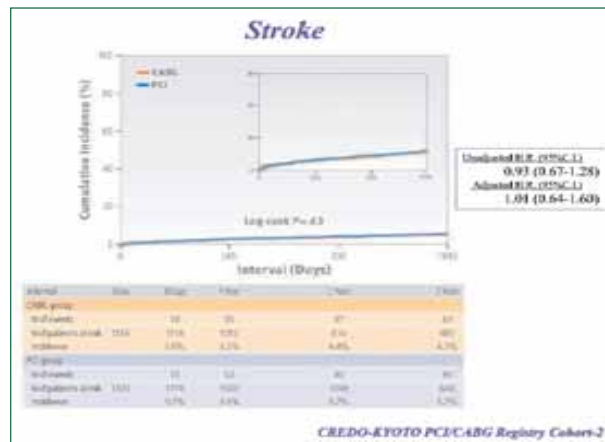


CREDO-KYOTO PCI/CABG Registry Cohort-2

Myocardial Infarction



CREDO-KYOTO PCI/CABG Registry Cohort-2





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 tertiles.
- 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.

CREDO-XYOTO PCI/CABG Registry Cohort-2

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.

CREDO-XYOTO PCI/CABG Registry Cohort-2



University Lille 2
Droit et Santé

Safety and Effectiveness of ICD Follow-up using Remote Monitoring

ECOST Study

Salem Kacet, Laurence Guédon-Moreau
On behalf of the ECOST Study Investigators



Disclosure

- Research grants, Advisory board, conferences fees from:
 - Biotronik, Boston Scientific, Medtronic, Saint Jude Medical, Sorin Group
 - Bayer, Boehringer-Ingelheim
 - Meda, Sanofi-Aventis
- ECOST Study is supported by grants from Biotronik SE & Co KG



Background

- The implant rate for ICD in the prevention of Sudden Cardiac Death has reached in 2010 an average of
 - ~250 per million population in Europe
 - ~675 per million population in USA
- HRS/EHRA 2008 expert consensus on the monitoring of CIEDs points out:
 - The potential of remote ICD follow-up to increase patient safety and convenience
 - The need of proofs with clinical studies
- Remote follow-up of ICDs (TRUST) has been demonstrated to reduce the number of in person device F.U. without increasing death, strokes and ICD related AE requiring surgical interventions
- Global cardiovascular safety of Remote follow-up remains uncertain



Home Monitoring system

- HM allows the **transmission of diagnostic data** from the ICD to the physician by:
 - Communication by a radiofrequency transmitter circuitry integrated in the ICD
 - Acceptance and transfer data from the ICD to a service center using a telephone landline via the Cardiomessenger®
 - Data reception by the service center and generation of a cardiologic report accessible online by the physician via a secure Internet access
 - Potential alerts to the physician of clinical or technical events



Primary Hypothesis

- We hypothesized that ICD follow-up with Home Monitoring would be **safe** and **cost-effective** when compared with standard ambulatory follow-up
- Safety was defined as **Major Adverse Events (MAE)** including:
 - Death from any cause
 - Major cardiovascular adverse event
 - Major device-related adverse event
- **Adverse Event(AE)** was defined as major if:
 - Fatal or life-threatening
 - Prompts or prolongs a hospitalization
 - Causes major or permanent disability or injury
 - Requires an intervention to prevent permanent impairment or damage



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
 - 5% significance level
 - Sample size requirement of 400 patients
- Randomized controlled trial**
Randomization on a 1:1 basis to:
 - Remote Monitoring Follow-up
 - Vs.
 - In-Person Follow-up

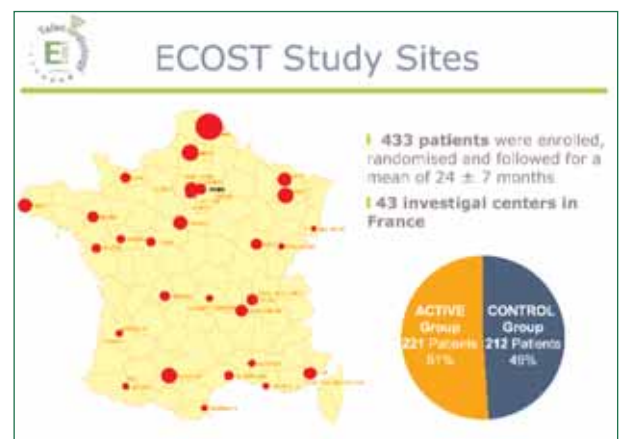
Inclusion / Exclusion Criteria

Key Inclusion criteria:

- Indication for single or dual chamber ICD (without CRT)

Key Exclusion criteria:

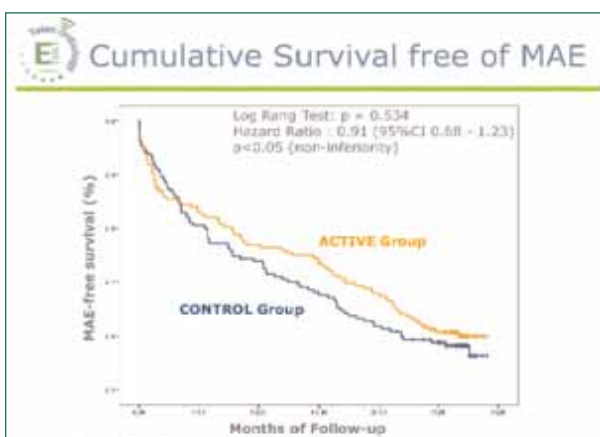
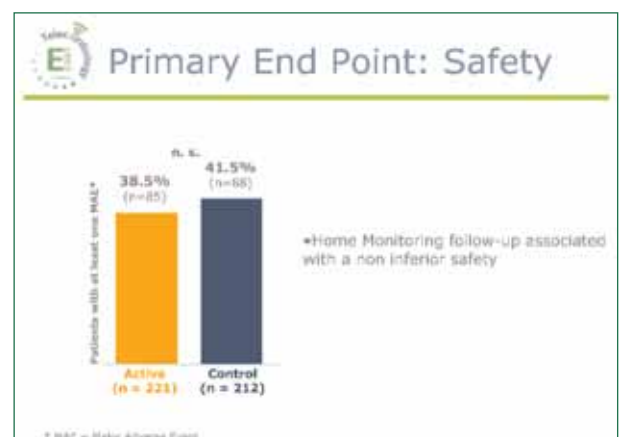
- NYHA class IV
- Pregnant woman or woman who plan to become pregnant during the trial
- Patient whose medical situation is not stable
- Presence of any disease, other than patient's cardiac disease, associated with reduced likelihood of survival for the duration of the trial, e.g. cancer, uremia (urea > 70mg/dl or creatinine > 3mg/dl), liver failure, etc.
- Age < 18 years
- Patient unable to handle Home Monitoring system correctly
- The patient is not willing and able to comply with the protocol
- Change of residence expected during study
- Participation in another clinical study
- Patient unwilling to sign the consent for participation



Population: Baseline Characteristics

Non significant difference

	ACTIVE	CONTROL
Number of patients	221	212
Age	62.0 ± 13.0	61.2 ± 12.9
Gender (male) (%)	67.3	69.2
LVF (%)	34.7 ± 13.0	36.1 ± 13.8
NYHA (%) I / II / III	27 / 63 / 8	25 / 61 / 12
History of SVT (%)	17	14
Technical success, first insertion attempt (%)	65 / 35	67 / 33
Primary prevention (%)	53.8	53.3
Dual chamber implants (%)	27.1	33.5
Past respiration (%)	84.2	85.3



Primary End Point by Component

Procedure implant related MAE

Non significant difference

	ACTIVE (n=221)	CONTROL (n=212)
Hematoma	2	1
Infection	4	2
Venous thrombosis	0	2
Pneumothorax	3	0
Lead dislodgment (< 1 month)	5	1
VV Induction: test failure	1	3
Other	0	2
TOTAL	15 MAE (14 pts: 6.3%)	11 MAE (11 pts: 5.3%)



Primary End Point by Component

Cardiovascular MAE

Non significant difference

	ACTIVE (n=221)		CONTROL (n=212)	
	Events	Patients	Events	Patients
Ventricular arrhythmia without shock	10	8	4	4
Ventricular arrhythmia with shock	10	9	5	5
Electrical storm	15	11	17	12
Myocardial infarction	0	0	1	1
Supra-ventricular arrhythmia	6	5	1	1
Stroke	7	4	0	0
Heart failure	40	25	61	32
Acute coronary syndrome	6	6	12	10
Other	1	1	6	6
TOTAL	95 MAE (59 pts: 26.7%)		107 MAE (63 pts: 29.7%)	

Primary End Point by Component

Device related MAE

Non significant difference

	ACTIVE (n=221)		CONTROL (n=212)	
	Events	Patients	Events	Patients
Inappropriate shock	3	2	6	6
- related to SVT	1	1	1	1
- related to T-wave oversensing	1	1	5	4
- related to lead dysfunction	1	1	0	0
Lead dysfunction without shock	5	5	1	1
Other	3	3	4	4
TOTAL	13 MAE (12 pts: 5.4%)		17 MAE (14 pts: 6.6%)	

Primary End Point by Component

- Death occurred in 20 (9.0%) patients in the active group and 20 (9.4%) patients in the control group.
- No significant difference between groups

Deaths

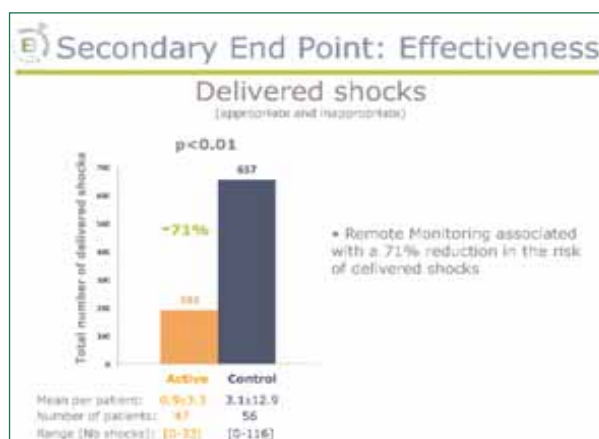
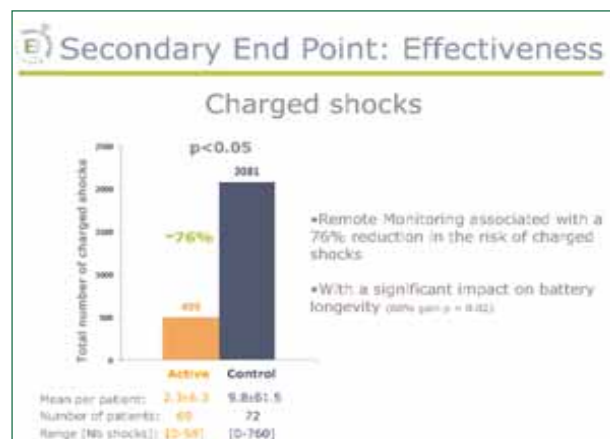
	ACTIVE (n=221)	CONTROL (n=212)
Stroke	1	0
Heart failure	7	8
Infarction	0	1
Arrhythmia	3	1
Non cardiac	7	8
Unknown	2	2
TOTAL	20 (9.0%)	20 (9.4%)

Secondary End Point: Effectiveness

Inappropriate Shocks (IS)

- Remote Monitoring associated with a 52% reduction in the number of patients with inappropriate shocks and with a 72% reduction in the risk of IS related hospitalizations

	ACTIVE (n=221)	CONTROL (n=212)	P value
Number of patients with ≥ 1 IS	11 (5.0%)	22 (10.4%)	0.03
Number of IS delivered	28	283	
Mean per patient	2.5 $\pm$ 2.2	12.9 $\pm$ 25.2	0.05
Range	[1-8]	[1-87]	
Number of patients hospitalized	3	11	0.02



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 FU of ICD recipients

Steering Committee – S. Kacet (Chairman), L. Guédon-Moreau, N. Canot

Endpoint Adjudication Committee – J. Clémenty, D. Lacroix, N. Sadoul

Electrogram Analysis Core Laboratory – L. Guédon-Moreau, X. Laroche

Study Coordinator – S. Fauquembergue

Funding Source – Biotronik SE & Co. KG

Statistical Analysis Group – X. Bry, A. Gannoun

ECOST investigators – S. Abbey, E. Aliot, W. Amara, D. Babuty, H. Bader, M. Belhameche, H. Benkemoun, J.P. Bernis, G. Bertaux, O. Bizeau, J.J. Blanc, P. Blanc, D. Bleinc, P. Bordachar, M. Boursier, S. Boveda, F. Briand, F. Brigadeau, J.P. Camous, A. Chapelet, S. Cheggour, P. Chenevez, P. Chevalier, X. Copie, P. Couderc, A. Da Costa, J.M. Davy, J.C. Deharo, N. Delarche, M. Delay, A. Duparc, J.M. Dupuis, P. Durand, N. Elbaz, D. Flammang, R. Frank, J. Graux, A. Gressard, L. Guédon-Moreau, J.S. Hermida, D. Klug, C. Kouakam, A. Kowsar, D. Lamaison, L. Larouchi, G. Lascault, A. Leenhardt, J. Levy, P. Mabo, H. Mansour, J. Mansourati, C. Marquié, C.J. Mariotti, C. Moïni, J.L. Pasquie, O. Paziand, O. Piot, H. Poty, M. Salvador, P. Sbragia, P. Scanu, O. Thomas







Discussant-ECOST

JC Daubert Rennes, France

Disclosure 2008-2011

Medical device	Sponsor	Consultant	Total compensation
ICD			
Implanted Defibrillator	+	+	+
Medtronic	+	+	+
St. Jude Medical	+	+	+
Heart group	+	+	+
Drug companies			
Amgen	+	+	+
Novartis	+	+	+
Roche	+	+	+
Pfizer	+	+	+
Novartis	+	+	+



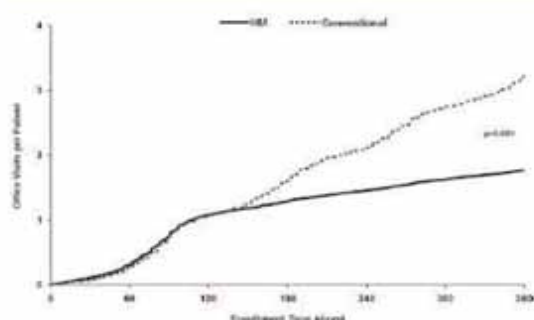
Remote Monitoring of ICD Patients

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 36d (P=0.002)
- **CONNECT (N=1997 pts)**
Time from clinical event to clinical decision.
Reduced from 22d to 4.6 d (P<0.001)
Length of CV hospital stay: 3.3d vs 4.0d (P=0.002)

N Charras et al. Circulation 2010; 122: 325-332
GH Crossley et al. JACC 2011; 57: 1181-1189

TRUST Trial: Primary Objective



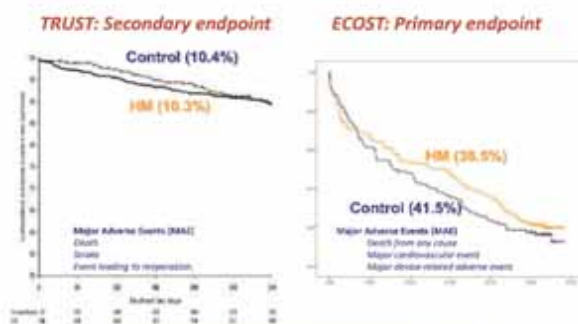
N Charras et al. Circulation 2010; 122: 325-332

ECOST and EVATEL

First randomised trials with robust clinical EP

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

Clinical safety of Home Monitoring



Hypothesis of non-inferiority validated in ECOST

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

Differences between studies?

	ECOST	EVATEL
Sponsor	Industry	Institutional/Gov.
Nb systems tested	1 (HM)	All available
Nb patients	433	1501
F/u duration (mo)	Mean=27	12
Baseline characteristics		
Secondary prevention	47%	35%
1-st implant	85%	100%

ECOST and EVATEL

Concordent 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'

Bertram Pitt, M.D., John J.V. McMurray, M.D., Henry Krum, M.B., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Karl Swedberg, M.D., Ph.D., Harry Shi, M.S., John Vincent, M.B., Ph.D., Stuart J Pocock, Ph.D. and Faez Zannad, M.D., Ph.D. for the EMPHASIS-HF Committees and Investigators

ClinicalTrials.gov: NCT00221516

* Eplerenone is a MII/Potassium-ATPase Inhibitor. And Statin Study is Heart Failure.

EMPHASIS HF

Disclosure Information

- Faez Zannad: Grants/contracts, consultant (moderate)
- John J.V. McMurray: Grants/contracts, consultant (moderate)
- Henry Krum: Grants/Contracts, consultant (moderate)
- Dirk J. Van Veldhuisen: Grants/Contracts, consultant (moderate)
- Karl Swedberg: Grants/Contracts, consultant (moderate)
- Harry Shi: Pfizer employee
- John Vincent: Pfizer employee
- Stuart J Pocock: Grants/Contracts, consultant (moderate)
- Bertram Pitt: Grants/Contracts, consultant (moderate)

EMPHASIS-HF was funded by Pfizer Inc. All analyses were performed or replicated independently at the London School of Hygiene and Tropical Medicine (Tim Collier). Eplerenone is approved for treating heart failure after myocardial infarction in 72 countries.

EMPHASIS HF

Disclosure Information

- Faez Zannad: Grants/contracts, consultant (moderate)
- John J.V. McMurray: Grants/contracts, consultant (moderate)
- Henry Krum: Grants/Contracts, consultant (moderate)
- Dirk J. Van Veldhuisen: Grants/Contracts, consultant (moderate)
- Karl Swedberg: Grants/Contracts, consultant (moderate)
- Harry Shi: Pfizer employee
- John Vincent: Pfizer employee
- Stuart J Pocock: Grants/Contracts, consultant (moderate)
- Bertram Pitt: Grants/Contracts, consultant (moderate)

EMPHASIS-HF was funded by Pfizer Inc. All analyses were performed or replicated independently at the London School of Hygiene and Tropical Medicine (Tim Collier). Eplerenone is approved for treating heart failure after myocardial infarction in 72 countries.

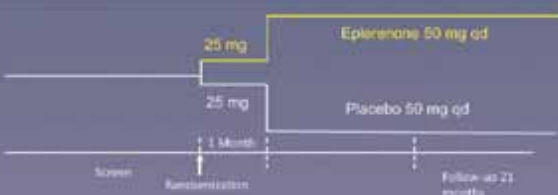
EMPHASIS HF

Inclusion Criteria

- Inclusion
 - > 55 years of age
 - NYHA functional class II
 - Ejection fraction $\leq 30\%$ (or, if between 31% and 35%, QRS > 130 msec)
 - Treated with the recommended or maximally tolerated dose of ACE inhibitor (or an ARB or both) and a beta-blocker (unless contraindicated)
 - Within 6 months of hospitalization for a cardiovascular reason (or, if no such hospitalization: BNP ≥ 250 pg/ml or NT-pro-BNP ≥ 500 pg/ml (males) or 750 pg/ml (females))
- Exclusion
 - Serum potassium > 5.0 mmol/L
 - eGFR < 30 ml/min/1.73 m²
 - Need for a potassium-sparing diuretic
 - Any other significant comorbid condition

EMPHASIS HF

Study Design



- Primary endpoint: CV death or hospitalization for HF

EMPHASIS HF

Baseline Therapy

Characteristic - n (%)	Eplerenone (N=1364)	Placebo (N=1373)
ACEi or ARB or both	1282 (94.0)	1275 (92.9)
Beta-blocker	1181 (86.6)	1193 (86.9)
Diuretic	1150 (84.3)	1176 (85.7)
ICD	178 (13.0)	184 (13.4)
CRT-P	38 (2.8)	22 (1.6)
CRT-D	74 (5.4)	99 (7.2)
Digitalis glycosides	363 (26.6)	377 (27.5)
Antiarrhythmic drug	196 (14.4)	192 (14.0)
Antithrombotic drug	1205 (88.3)	1214 (88.4)

EMPHASIS HF

Results on Key Clinical Endpoints

Outcome	Eplerenone (N=1364)	Placebo (N=1373)	Hazard Ratio (95% CI)	P Value
CV death or HF hospitalization* (Primary Endpoint) (%)	249 (18.2)	356 (25.9)	0.63 (0.54-0.74)	<0.0001
Deaths from any cause* (%)	171 (12.5)	213 (15.5)	0.76 (0.62-0.93)	0.008
Hospitalization from any cause* (%)	438 (31.8)	491 (35.8)	0.77 (0.67-0.88)	<0.0001
Cardiovascular death* (%)	147 (10.8)	185 (13.5)	0.76 (0.61-0.94)	0.01
Hospitalization for HF* (%)	164 (12.0)	253 (18.4)	0.58 (0.47-0.70)	<0.0001

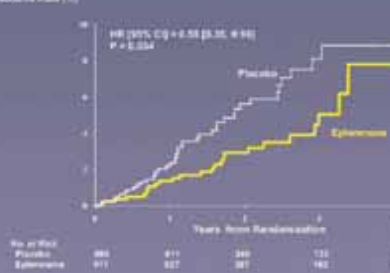
* N=1364 and N=1373

All results are adjusted for important baseline characteristics. (Randomized analysis: number under results)

EMPHASIS HF

New Onset Atrial Fibrillation/Flutter (AFF)

New Onset AFF Cumulative Rate (%)



Swedish J. H. ESC J HF 2011

EMPHASIS HF



Safety Results: Serum Potassium and Renal Function

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	158/1336 (11.8)	96/1340 (7.2)	<0.001
Serum K ⁺ >6.0 mmol/l	33/1336 (2.5)	25/1340 (1.9)	0.29
Hyperkalemia leading to treatment discontinuation	15/1360 (1.1)	12/1373 (0.9)	0.57
Hospitalization for hyperkalemia	4/1360 (0.3)	3/1373 (0.2)	0.85
Serum K ⁺ <3.5 mmol/l	100/1336 (7.5)	148/1340 (11.0)	0.002
Hospitalization for worsening renal failure	9/1360 (0.7)	8/1373 (0.6)	0.95

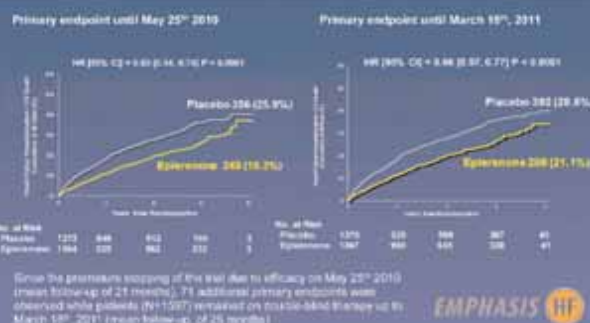
EMPHASIS HF

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

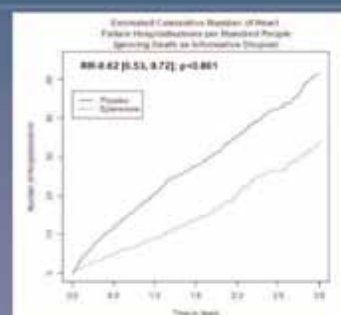
EMPHASIS HF

Primary Endpoints: CV death or HF hospitalization



EMPHASIS HF

Repeat hospitalization for Heart Failure



Rate Ratio (95% CI) of hospitalization rates for heart failure

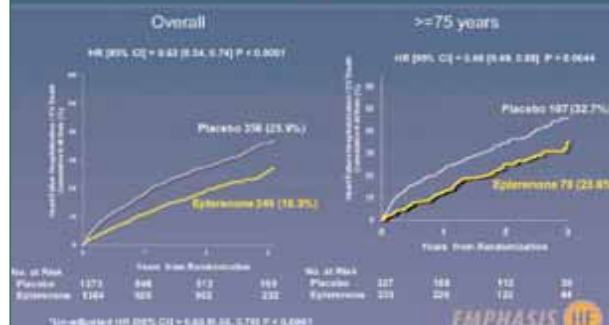
EMPHASIS HF

High Risk Sub Groups

- Age >75 years
- Diabetes Mellitus
- eGFR < 60 ml/min/1.73 m²
- LVEF <30%
- Systolic blood pressure <123 mmHg

EMPHASIS HF

CV Death or HF Hospitalization



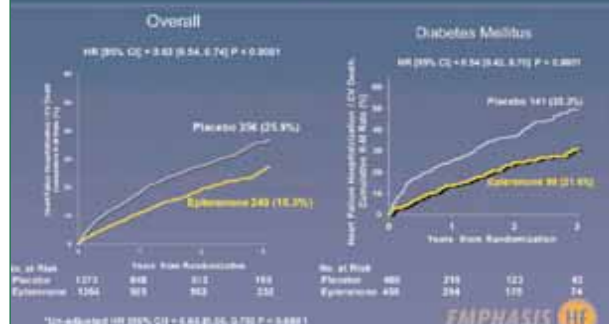
EMPHASIS HF

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

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	40/322 (12.4)	24/318 (8.0)	0.02
Serum K ⁺ >6.0 mmol/l	7/322 (2.2)	4/318 (1.3)	0.55
Hyperkalemia leading to treatment discontinuation	3/330 (0.9)	3/327 (0.9)	1.00
Hospitalization for hyperkalemia	1/330 (0.3)	1/327 (0.3)	0.98
Serum K ⁺ <3.5 mmol/l	22/322 (6.8)	34/318 (10.7)	0.09
Hospitalization for worsening renal function	5/330 (1.5)	3/327 (0.9)	0.52

EMPHASIS HF

CV Death or HF Hospitalization



EMPHASIS HF

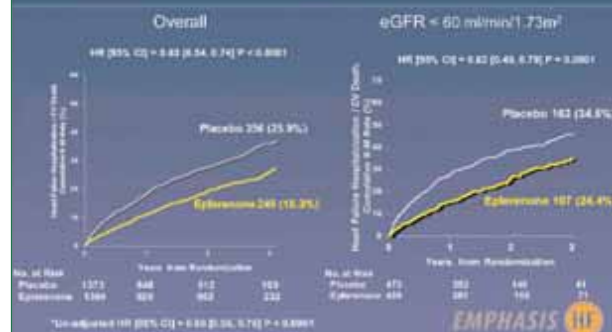


Safety Results: Serum Potassium and Renal Function in Patients with Diabetes Mellitus

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	63/447 (14.1)	33/387 (8.5)	0.01
Serum K ⁺ >6.0 mmol/l	17/447 (3.8)	8/387 (2.1)	0.16
Hyperkalemia leading to treatment discontinuation	9/459 (2.0)	3/400 (0.8)	0.15
Hospitalization for hyperkalemia	4/459 (0.9)	2/400 (0.5)	0.55
Serum K ⁺ <3.5 mmol/l	31/447 (6.9)	46/387 (11.9)	0.016
Hospitalization for worsening renal function	5/459 (1.1)	7/400 (1.8)	0.39

EMPHASIS HF

CV Death or HF Hospitalization



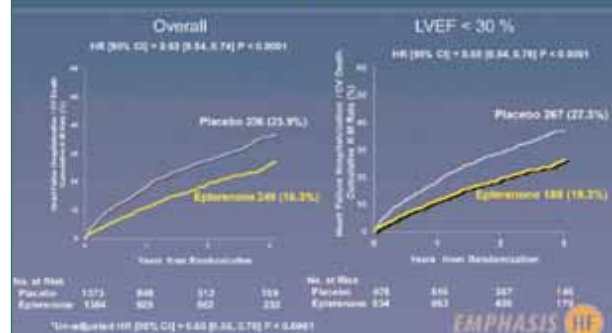
EMPHASIS HF

Safety Results: Serum Potassium and Renal Function - eGFR<60 ml/min/1.73m²

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	70/422 (16.6)	43/461 (9.3)	0.002
Serum K ⁺ >6.0 mmol/l	8/422 (1.9)	15/461 (3.3)	0.29
Hyperkalemia leading to treatment discontinuation	5/439 (1.1)	10/473 (2.1)	0.30
Hospitalization for hyperkalemia	1/439 (0.2)	2/473 (0.4)	0.57
Serum K ⁺ <3.5 mmol/l	26/422 (6.2)	46/461 (10.0)	0.048
Hospitalization for worsening renal function	5/439 (1.1)	6/473 (1.7)	0.32

EMPHASIS HF

CV Death or HF Hospitalization



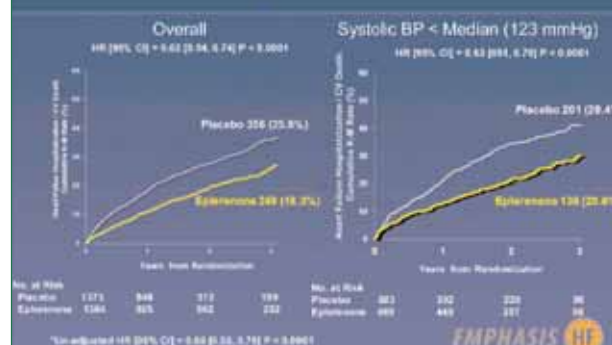
EMPHASIS HF

Safety Results: Serum Potassium and Renal Function in Patients with a LVEF<30%

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	100/926 (11.5)	75/961 (7.8)	0.008
Serum K ⁺ >6.0 mmol/l	18/926 (2.1)	21/961 (2.2)	0.87
Hyperkalemia leading to treatment discontinuation	7/934 (0.7)	10/978 (1.0)	0.47
Hospitalization for hyperkalemia	2/934 (0.2)	2/978 (0.2)	1.00
Serum K ⁺ <3.5 mmol/l	76/926 (8.2)	120/961 (12.5)	0.003
Hospitalization for worsening renal function	4/934 (0.4)	6/978 (0.6)	0.52

EMPHASIS HF

CV Death or Hospitalization



EMPHASIS HF

Safety Results: Serum Potassium and Renal Function in Patients with a Systolic BP <Median (123 mmHg)

Outcome	Eplerenone	Placebo	p-value
Serum K ⁺ >5.5 mmol/l	72/558 (10.9)	48/560 (7.3)	0.02
Serum K ⁺ >6.0 mmol/l	14/558 (2.1)	16/560 (2.4)	0.85
Hyperkalemia leading to treatment discontinuation	8/569 (1.2)	5/563 (0.7)	0.42
Hospitalization for hyperkalemia	2/569 (0.3)	2/563 (0.3)	0.99
Serum K ⁺ <3.5 mmol/l	51/558 (7.8)	77/560 (11.7)	0.02
Hospitalization for worsening renal function	3/569 (0.4)	5/563 (0.7)	0.44

EMPHASIS HF

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 after the premature stopping of enrollment 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

EMPHASIS HF



EMPHASIS-HF: 2737 patients in 29 countries, 278 Investigators



EMPHASIS HF

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 Deharo, Salem Kacet,
Eric Bellissant, Jean-Claude Daubert

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

EVATEL

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

Background

- Implantable cardioverter defibrillator (ICD) has been shown to be effective to reduce mortality in selected patients.
- The expanding 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.

EVATEL

Aims of the study

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

EVATEL

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

EVATEL

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

EVATEL



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%

E V A T E L

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

E V A T E L

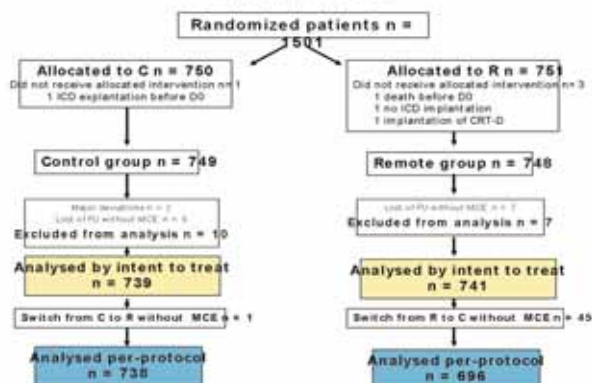
Sample size

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

Sample size : 1600 patients

E V A T E L

Flow chart



ICD manufacturers and types

		Control n = 750	Remote n = 749*
Manufacturer	Biotronik	315 (42.0%)	360 (41.1%)
	Boston-Guidant	40 (5.3%)	35 (4.7%)
	Medtronic	229 (30.5%)	237 (31.6%)
	St Jude Medical	166 (22.1%)	169 (22.6%)
	Other	100 (13.3%)	108 (14.5%)
Type	Single chamber	503 (67.1%)	488 (65.2%)
	Dual chamber	247 (32.9%)	261 (34.8%)

*all implanted devices

E V A T E L

Reasons for switch

	Control n = 1	Remote n = 55
Phone network not compatible with remote transmission to use correctly the transmission system	—	32 (58.2%)
Patient wish	1 (100.0%)	4 (7.3%)
Patient condition requiring conventional close follow-up	—	2 (3.6%)
Unknown	—	1 (1.8%)
Other	—	10 (18.2%)

Data are numbers of patients (percentages)

E V A T E L

Population Characteristics (1)

	Control n = 750	Remote n = 751	p value
Gender, male	628 (83.7%)	646 (86.0%)	0.2168
Age, years	59±13	60±13	0.1654
ICD indication			
Primary prevention	481 (64.1%)	489 (65.1%)	0.6656
Secondary prevention	269 (35.9%)	261 (34.8%)	
Documented ventricular arrhythmia	373 (49.7%)	355 (47.3%)	0.3397
Ventricular fibrillation	101 (13.5%)	81 (10.8%)	0.1116
Atrial arrhythmia	142 (18.9%)	179 (23.8%)	0.0206

Continuous variables are means SD. Categorical variables are numbers of patients (percentages)

E V A T E L

Population Characteristics (2)

	Control n = 750	Remote n = 751	p value
Underlying disease			0.0673
Structural heart disease	681 (90.9%)	700 (93.5%)	
Electrical disease	68 (9.1%)	49 (6.5%)	
Structural heart disease etiologies			
Ischemic cardiomyopathy	467 (62.3%)	479 (64.0%)	
Non-ischemic cardiomyopathy	133 (17.8%)	138 (18.4%)	
NYHA class			0.2051
I	262 (35.7%)	231 (31.4%)	
II	370 (50.5%)	394 (53.5%)	
III	101 (13.8%)	111 (15.1%)	
LVEF < 35%	412 (56.4%)	436 (59.6%)	0.2144
≥ 35%	318 (43.6%)	295 (40.4%)	
Heart failure hospitalisation (within 1 year before inclusion)	141 (18.9%)	179 (23.8%)	0.0185
Chronic associated diseases			
Arterial hypertension	384 (51.2%)	310 (41.3%)	0.1832
Diabetes	154 (20.5%)	163 (21.7%)	0.5784
Chronic respiratory disease	90 (12.1%)	113 (15.0%)	0.2698
Chronic renal failure	41 (5.5%)	50 (6.7%)	0.3336



Primary endpoint (1)

(Death/ CV hospitalisation/ ineffective or inappropriate therapy)

Intent to treat analysis (N=1480) – Non-inferiority hypothesis

	Control n = 738	Remote n = 741	Difference (Rate) 95% CI
Number of patients with at least 1 MCE	210 (28.4%)	214 (28.9%)	0.5 [-4.1 to 5.1]
95% CI	[25.2 to 31.7]	[26.8 to 32.1]	

p = 0.0101

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

	Control n = 738	Remote n = 696	Difference (Rate) 95% CI
Number of patients with at least 1 MCE	210 (28.5%)	210 (30.2%)	1.7 [-5.0 to 8.4]
95% CI	[25.7 to 31.7]	[26.8 to 33.6]	

p = 0.0026

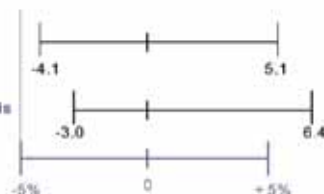
EVATEL

Primary endpoint (2)

Intent to treat analysis

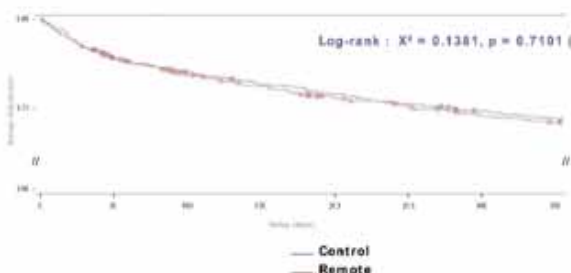
Per-protocol analysis

Non-inferiority margin



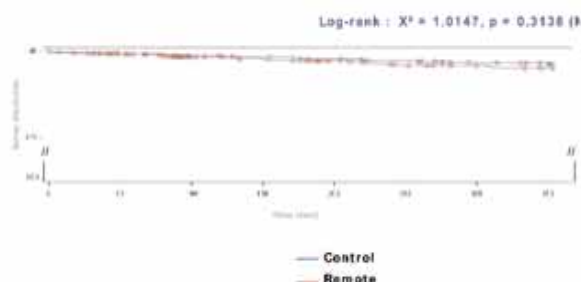
EVATEL

Time to the first major cardiovascular



EVATEL

Time to death



EVATEL

Secondary endpoints

	Control n = 738	Remote n = 696	p value
Hospitalization for a cardiovascular event	152 (20.6%)	172 (24.7%)	0.0625
Inappropriate or ineffective therapy	66 (8.1%)	38 (5.5%)	0.0452
Ineffective therapy	5 (0.7%)	6 (0.9%)	0.6889
Inappropriate therapy	55 (7.5%)	33 (4.7%)	0.0325

Data are numbers of patients (percentages)

EVATEL

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

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.

EVATEL

Thanks to all investigation centres

Dr Alain AMIEL, CHU Poitiers
Pr Frédéric ANSELME, CHU Rouen
Dr Claude BARNAY, CH Aix en Provence
Pr Jean-Jacques BLANC, CHU Brest
Dr Patrick BLANC, CHU Limoges
Dr Florent BRIAND, CHU Besançon
Pr Jean Pierre CAMOUS, CHU Nice
Pr Michel CHAUVIN, CHU Strasbourg
Pr Philippe CHEVALIER, HC Lyon
Pr Jacques CLEMENTY, CHU Bordeaux
Pr Pierre COSNAY, CHU Tours
Pr Antoine DA COSTA, CHU St Etienne
Pr Jean-Marc DAVY, CHU Montpellier
Pr Jean-Claude DEHARO, APH Marseille
Dr Jean-Marc DUPUIS, CHU Angers
Dr Nathalie ELBAZ, APH Paris
Dr Robert FRANK, Dr Françoise LUCET, APH Paris
Dr Laurence GUEDON-MOREAU, CHU Lille
Dr Gabriel LAURENT, CHU Dijon
Pr Antoine LEENHARDT, APH Paris
Pr Jean-Yves LE HEUZEV, APH Paris
Pr Hervé LE MAREC, CHU Nantes
Dr Yacoub SALUDAS, CHU Clermont-Ferrand
Pr Patrick MESSNER PELLENC, CHU Nîmes
Pr Damien METZ, CHU Reims
Pr Nicolas SADDUL, CHU Nancy
Dr Michèle SALVADOR-MAZENO, CHU Toulouse
Dr Patrice SCARU, CHU Caen

EVATEL



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



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

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

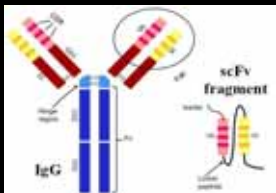
➤ Coating of MB with antibodies directed against clot epitopes



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

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

Single-Chain Antibody (scFv)

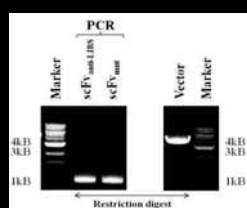
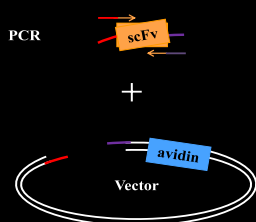
- Small recombinant antibody fragment
 - Non-immunogenic
 - Easy to modify
- 
- scFv_{anti-LIBS} (targets activated platelets)
 - Ligand Induced Binding Site on activated GPIIb/IIIa
 - scFv_{mut} (non-targeting)

Aims

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

Generation of biotinylated scFvs

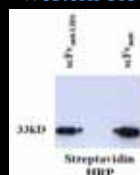
- Molecular Biology
 - Genetic fusion of the scFv with avidin
 - Production of biotin-labelled scFv in bacteria
 - Purification of biotinylated scFv



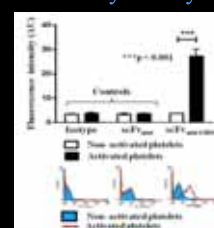
Functionality of scFv Constructs

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

Western blot

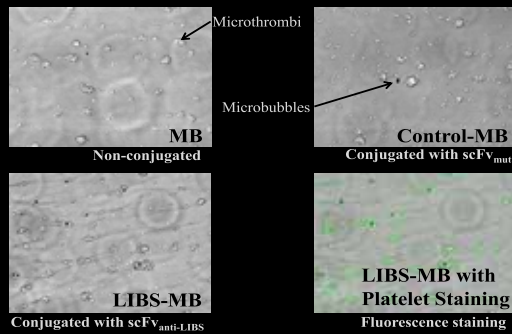


Flow cytometry

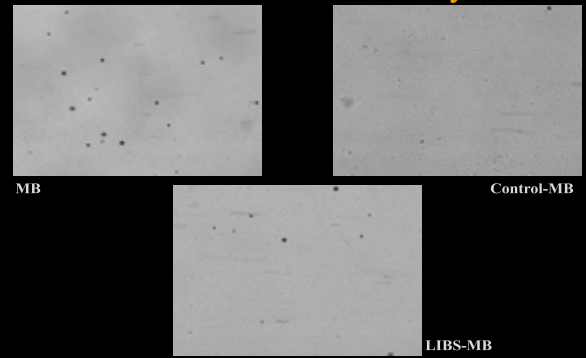




Targeting of Microbubbles to Microthrombi

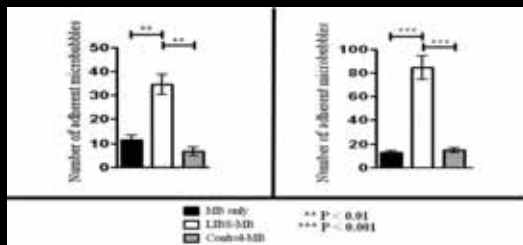


Adhesion of Microbubbles on Activated Platelet Monolayers



Strong Adhesion on Microthrombi as well as on a Platelet Monolayer

- Platelet microthrombi
- Monolayer of activated platelets



Aims

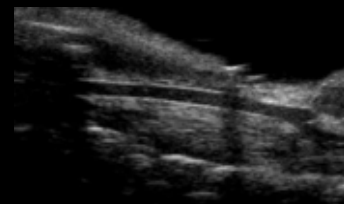
- Targeting microbubbles to activated platelets and thrombi by conjugation to scFv
- Identifying thrombi *in vivo* via non-invasive ultrasound based molecular imaging using targeted microbubbles

High Resolution Ultrasound Imaging

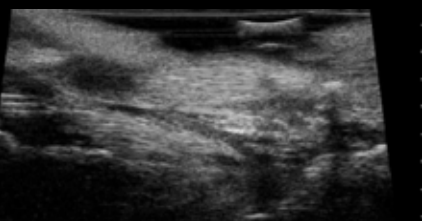


- High frequency small animal ultrasound scanner
- 40 MHz transducer
- Carotid artery of a mouse
 - Small diameter of 300 to 400 μ m
 - Ferric chloride injury
 - Platelet-rich but non-occlusive thrombus

Injection of Microbubbles in Carotid Artery

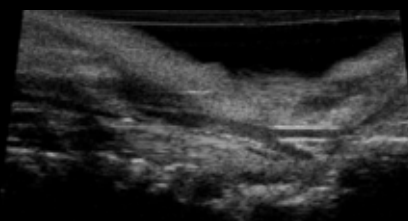


Minimal Attachment of MB



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

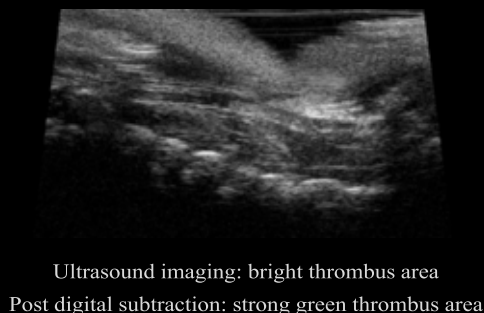
Minimal Attachment of Control-MB



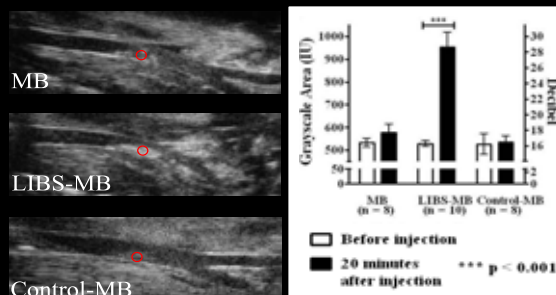
Ultrasound imaging: vaguely distinguishable thrombus
Post digital subtraction: only non-specific movement artifacts



Strong Attachment with LIBS-MB



Detection of Thrombi

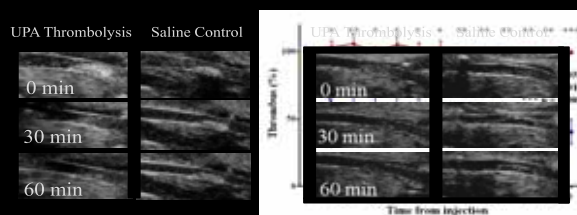


Aims

- 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)

Monitoring of Thrombolysis

- LIBS-MB
- No microbubbles



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

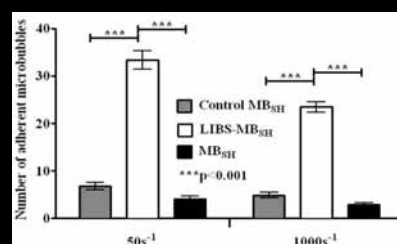
- Development into a promising diagnostic tool for clinical use for early detection of thrombi
 - Carotid artery (prevention of stroke)
 - Cardiac chambers (therapeutic implications)
 - Coronary artery (early and rapid diagnosis of MI)

Acknowledgements

- Xiaowei Wang, BS
- Ingo Ahrens, MD
- Christoph Hagemeyer, PhD
- Jia Fu, MD
- Ephraem Leitner, BS
- 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

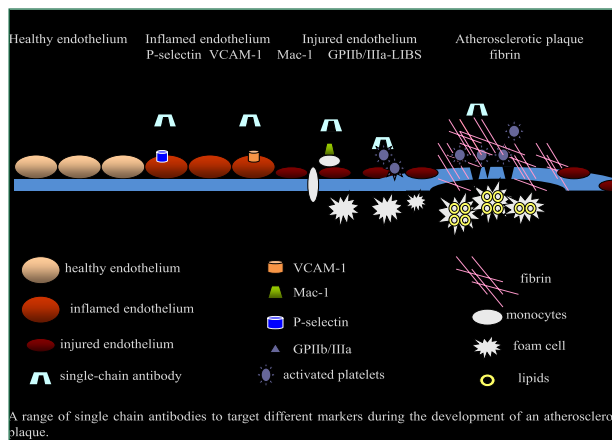
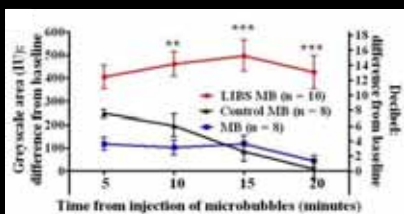
Biocompatible conjugation

- Sortase A + GGG-maleimide + MB_{SH}

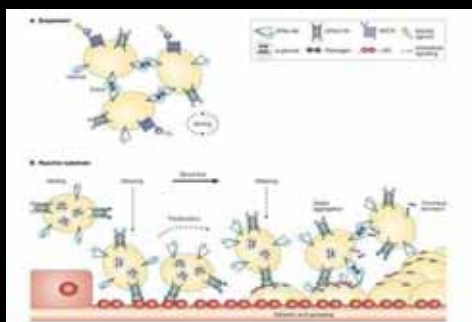




Timeline post MBs injection



Platelet Aggregation



Jackson & Schoenwaelder, Nat Rev Drug Discov 2003

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



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

Anna Fusco, Gaetano Santulli, Daniela Sorriento, Ersilia Cipolletta, Corrado Garbi, Gerald W. Dorn, Bruno Trimarco, Antonio Feliciello, Guido Iaccarino



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

BACKGROUND

- GRK2 belongs to a family of seven serine/threonine protein kinases, each encoded by a single gene, that specifically phosphorylates 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 master energy production and expenditure

Bibliography:

J. Inglese, et al. *J Biol Chem* 268, 23735-23738 (1993)
C. Ribas, et al. *Biochim Biophys Acta* 1768, 913-922 (2007)
E. Cipolletta, et al. *Cardiovasc Res* 84, 407-415 (2009)

2

BACKGROUND

- Mitochondria play an important role in cell energy production
- The mitochondria functional state varies dramatically depending on the functional and metabolic state of the cell
- Post transduction modification of mitochondrial proteins and in particular protein phosphorylation appears to be an important mechanism of mitochondrial function

Bibliography:

G. Benard, et al. *Biochim Biophys Acta* 1797, 698-709 (2010)
Valeria G. Antico Arciuch, et al. *Advanced Drug Delivery Reviews* 61, 1234-1249 (2009)
Olga Martins de Brito, et al. *Mitochondrion* 9, 222-226 (2009)

3

AIM

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



4



MATERIALS AND METHODS

In vitro sup:

• Cell culture:

- HEK-293
- HEK-293 transfected with pcDNA3.1 encoding for GRK2 (GRK2-HEK)
- Primary culture cells from floxed GRK2 gene (GRK2^{fl}) mice, infected with AdCRE, 10⁷ pfu/ml (GRK2^{fl}EC)

- Assay for oxidative ATP synthesis
- Subcellular fractionation by Percoll gradient and western blotting
- Immunogold
- Immunofluorescence
- Overlay assay
- Kinase assay
- Immunoprecipitation
- Quantitative analysis of mitochondrial nucleic acids
- Cytofluorimetry
- Cell culture hypoxia

In vivo study:

- Homozygous GRK2^{fl} mice
- Intramuscular injection of AdCRE, 10⁹ pfu/ml (GRK2^{fl}EC)
- Ischemia
- Assay for oxidative ATP synthesis

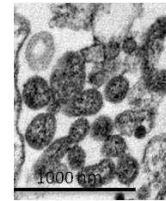
5



ELECTRON MICROSCOPY

In Vitro Study:

HEK-293 cells



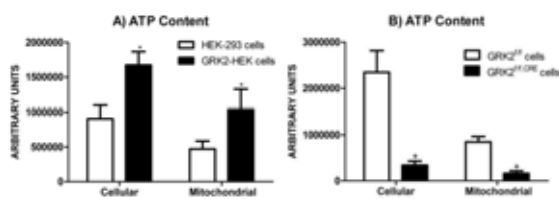
Mitochondria extracts preparation by 30% Percoll gradient

6



GRK2 increases oxidative ATP synthesis

In Vitro Sup

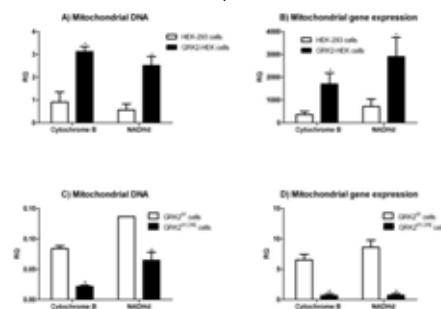


7



GRK2 increases mitochondrial biogenesis

In Vitro Sup



8

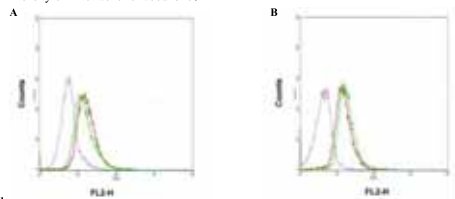


GRK2 increases mitochondrial biogenesis

In Vitro Study

GRK2 overexpression in HEK293 cells induces a rightward shift in the emission profile of mitotracker, which increased by a 36%.

In GRK2^{fl}EC cells, we observe a leftward shift compared to GRK2^{fl} cells, accounting for a decrease of emission intensity of mitotracker of about 31%



Legend:

A: Intensity of fluorescence emission in HEK-293 (green) and GRK2-HEK (red) cells and mitotracker unstained control cells (purple) under FACS analysis.

B: Intensity of fluorescence emission in GRK2^{fl} (green) and GRK2^{fl}EC (red) cells and mitotracker unstained control cells (purple) under FACS analysis.

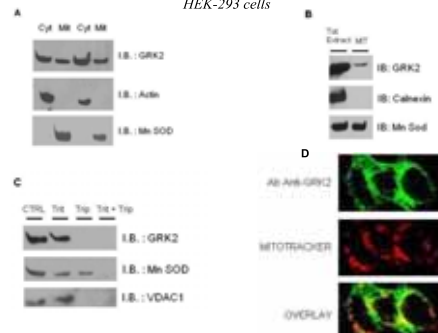
9



GRK2 is located in mitochondria

In Vitro Sup

HEK-293 cells



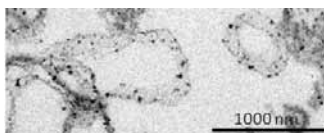
10



GRK2 is located in mitochondria

In Vitro Study:

HEK-293 cells



Immunogold on mitochondria extracts using anti-GRK2 antibody

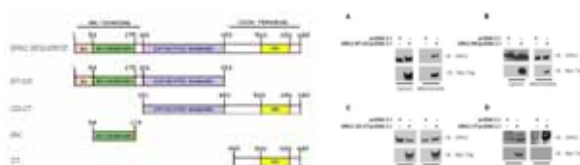
11

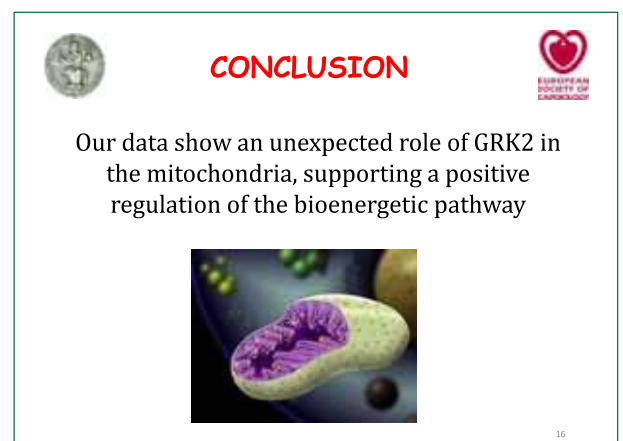
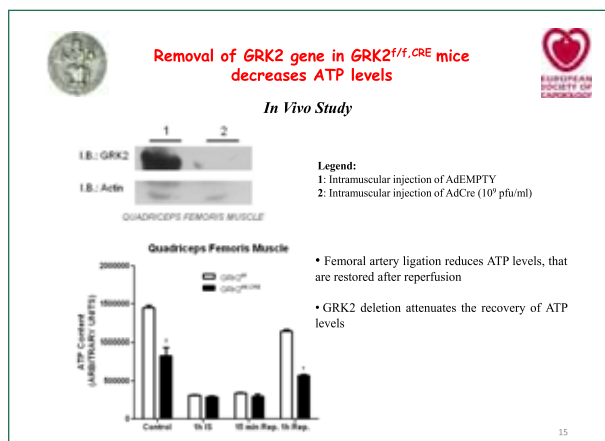
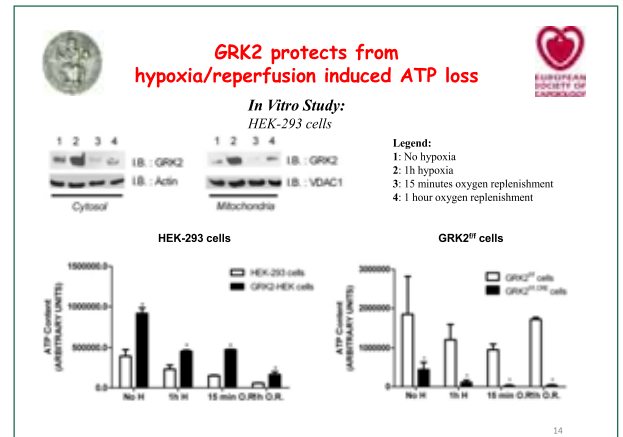
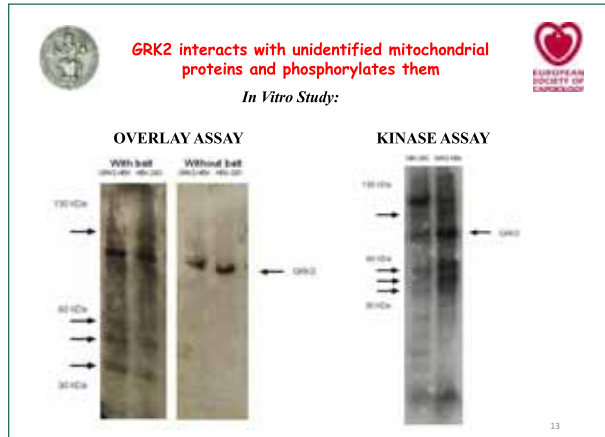


Two regions of GRK2 possess ability for mitochondrial localization

In Vitro Sup

HEK-293 cells





EMORY UNIVERSITY SCHOOL OF MEDICINE

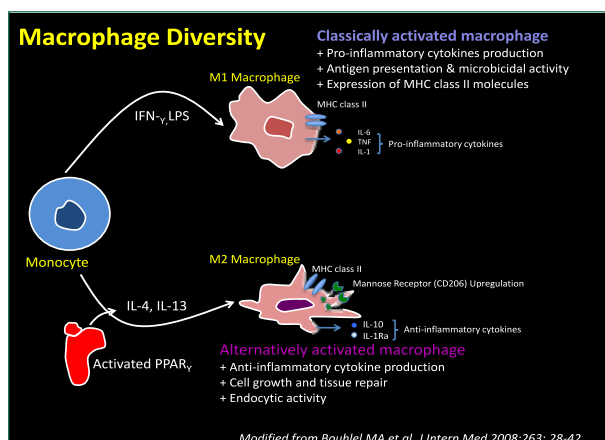
Hemoglobin Directs Macrophage Differentiation and Prevents Foam Cell Formation in Human Atherosclerotic Plaques

Aloke V. Finn MD, Masataka Nakano MD, Rohini Polavarapu, BA, Vinit Karmali, MA, Omar Saeed, MD, XiaoQing Zhao, PhD, Saami Yazdani, PhD, Fumiyuki Otsuka, MD, Talina Davis, Anwer Habib, MD, Jagat Narula, MD, PhD, Frank D. Kolodgie PhD, Renu Virmani MD.

ALOKE FINN, MD
EMORY UNIVERSITY SCHOOL OF MEDICINE
ESC 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



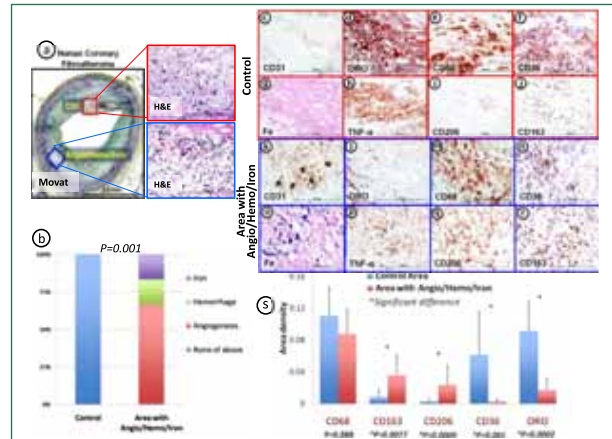
Macrophage Diversity

- Some data support the presence of IL-4 induced M2 macrophages in human atherosclerosis (Bouhrel 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

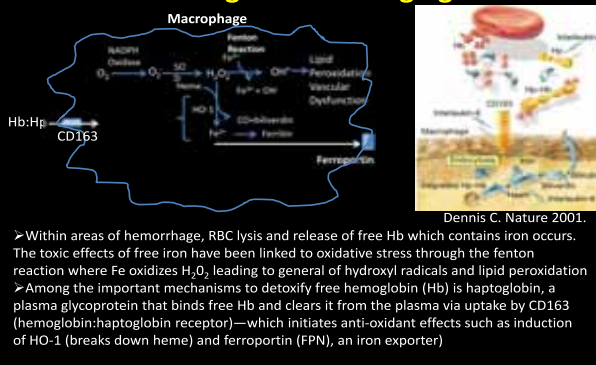


Methods

- 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

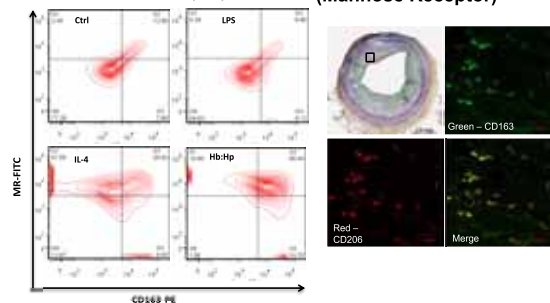


Macrophages are Important Cells For Hemoglobin Scavenging

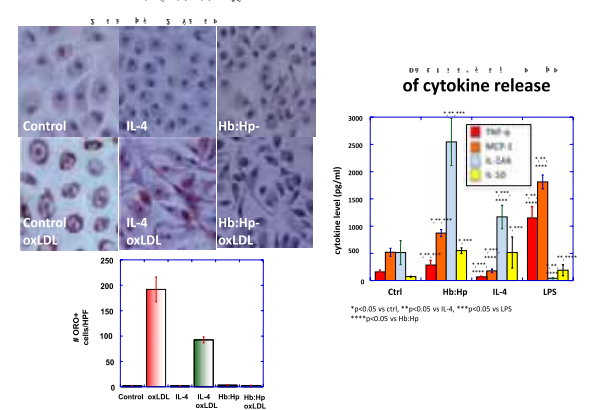


Hp:Hb Ingestion by Monocytes Leads to Distinct Mac Phenotype We Have Termed M(Hb)

Human Plaque M(Hb) Macrophages Express Both CD163 and CD206 (Mannose Receptor)



M(Hb) are p



Macrophage Differentiation and Cholesterol Uptake: Live Cell Imaging

Control Macs IL-4 M2 M(Hb)



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

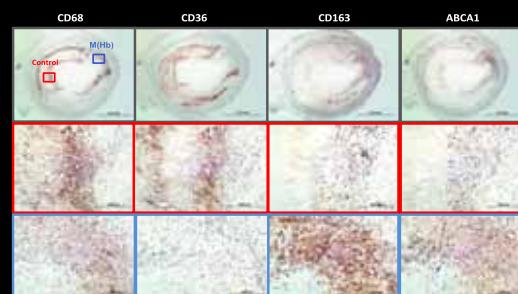
Receptors involved in Lipid Uptake

Scavenger Receptor	Fold Versus Control (normalized to 1)	P value
SR-A1		0.006
SR-A2	0.15±0.16	0.009
CD36	0.09±0.04	0.004
SR-B1	0.54±0.32	0.03

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

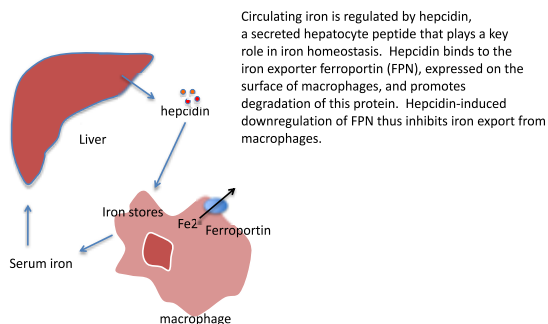
ABC Transporter	Fold Versus Control (normalized to 1)	P value
ABCA1	4.18±2.99	0.03
ABCG1	29.92±31.98	0.03

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

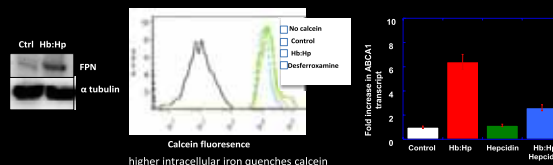




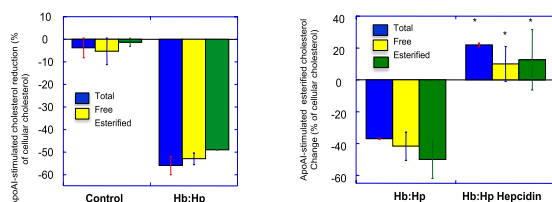
Iron Metabolism



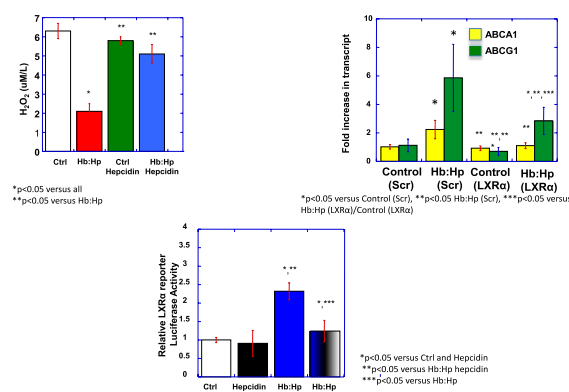
What is the mechanism of ABC transporter expression? Could it be ROS mediated and related to iron handling?



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



Reduction of ROS Mediates LXRA Activation of ABC Transporters in M(Hb)



Findings

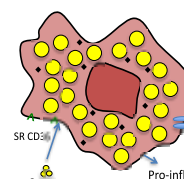
- Hemorrhage and release of free Hb determines macrophages differentiation into a distinct subtype we have termed M(Hb)

Macrophage Type	M1	M2	M(Hb)
Stimulus	LPS, IFN γ	IL-4/IL-13	Hb
Marker	↓MR ↓CD163	↑MR ↓CD163	↑MR ↑CD163
Foam Cell Formation	Yes	Yes	No
Intracellular iron	↑	↓	↓
ROS	↑	↓	↓

M(Hb) in Human Atherosclerosis

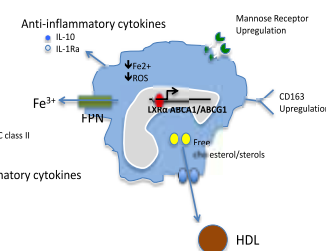
Foamy Macrophage

Stimulus: oxLDL
+ Cytokine production – pro-inflammatory
+ MHC class II expression
↑ Lipid uptake
↑ Reactive Oxygen Species (ROS)



M(Hb) Macrophage

Stimulus: Hb:Hp
+ Cytokine production – anti-inflammatory
↓ Lipid uptake
↑ cholesterol efflux
↓ Intracellular iron and ROS



Therapeutics: Can Manipulation of Macrophage Intracellular Iron Reduce Foam Cell Formation and Lesion Progression?

- Iron Hypothesis-theorized that iron depletion protects against atherosclerosis
- Initially presented as an explanation for sex differences in CV disease and increase in disease after menopause in women
- Our data demonstrate that lowering intracellular iron decreases ROS which increases ABC transporter expression
- This may in part explain how modulations in macrophage iron control cholesterol efflux proteins

Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet*. 1981;1(8233):1293-1294.

Conclusion

- We have demonstrated a novel non-lipid driven macrophage phenotype driven by monocyte ingestion of Hb:Hp
- 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

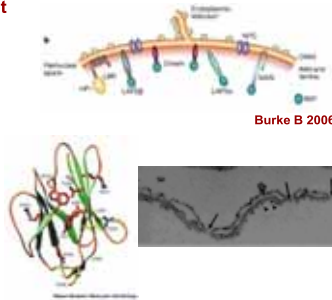
Dilated Cardiomyopathy

- 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 DCMP (~10%) (van Berio JH et al 2005)

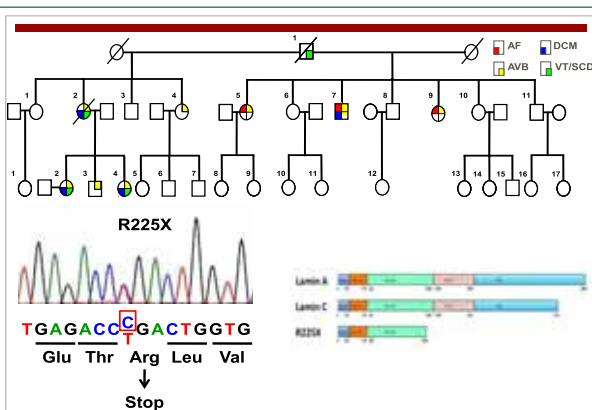
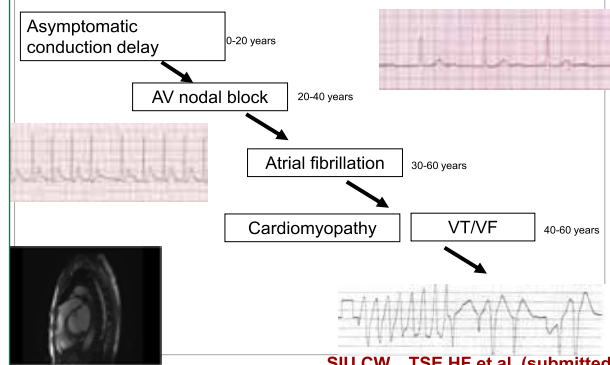
Locus	Gene
1p1-q21	Lamin A/C
1q32	Troponin I
1q42-q43	α -Actinin
2q31	Titin
2q35	Desmin
3p21	Troponin C
3p22-p25	SCN5A
5q33	δ -Sarcoglycan
6q22.1	Phospholamban
10q22-q23	Metavinculin
11p11	Myosin-binding protein-C
11p15	Cardiac muscle LIM protein
12p12	SUR2A
12q22	Thymopietin
14q12	β -Myosin heavy chain
15q14	Cardiac actin
15q22	α -Tropomyosin
17q12	Telethonin
19q13	Troponin I

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

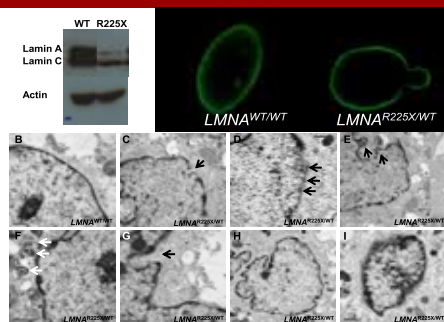


DCM with conduction abnormalities

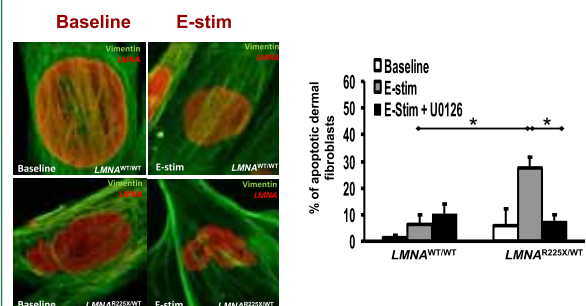


- What is the pathogenic link between the genotype and clinical phenotype?
- What is the mechanism(s) for organ specific phenotypes?

Morphological changes in Skin Fibroblasts

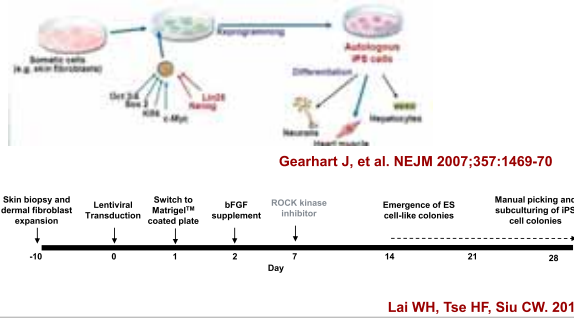


Culturing Skin Fibroblasts under Electrical Field

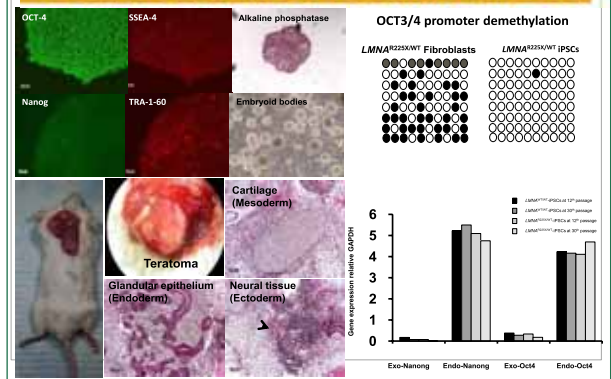




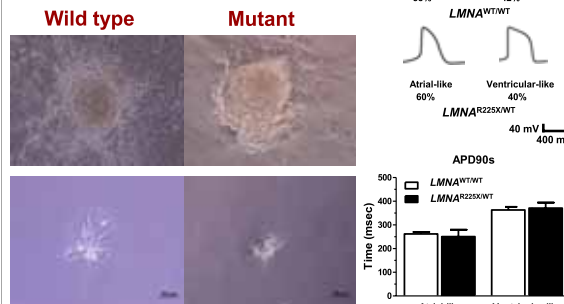
Induced Pluripotent Stem Cells (iPSCs)



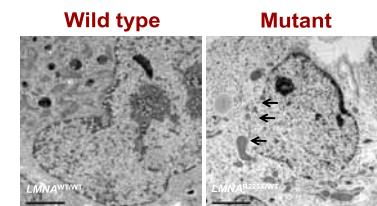
Characterization of LMNA iPSCs



Diseases-specific iPSC-CM

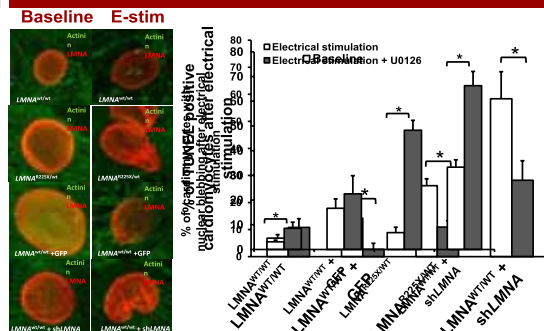


Electromicroscopy of Disease-specific iPSC-CMs



SIU CW, TSE HF et al. (submitted)

Effects of Electrical field to iPSC-CMs



Conclusions

- Lamin A/C mutation is the most common cause of familial DCM; however, mechanisms remain elusive
- Using human iPSC-technology, we show that
 - 1) Electrical stimulation results in nuclear morphological changes & accelerated apoptosis of LMNA^{R225X/WT} iPSC-CMs
 - 2) shLMNA treatment reproduces similar changes in wildtype iPSC-CMs, suggestive of halodisregulation
 - 3) MEK1/ERK1/2 signal pathway is involved

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

Acknowledgement

- PIs in HKU laboratory:
 - HF Tse
 - CW Siu
 - QZ Lian
- Collaborators
 - Alan Colman (Singapore)
- PDFs
 - Jenny Ho
 - KM Ng
 - YC Chan
- PhD students
 - YK Lee
- Technicians:
 - Kevin Lai
 - Karen Au
 - Virginia Lau

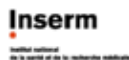


Critical role for STIM1 in cardiac hypertrophy

Presenter : Dr Jean-Sébastien Hulot, MD PhD

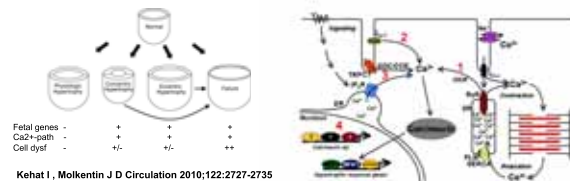
Associate Professor of Medicine, Cardiology
Cardiovascular Research Institute
Mount Sinai School of Medicine
New York - USA

Disclosure: None

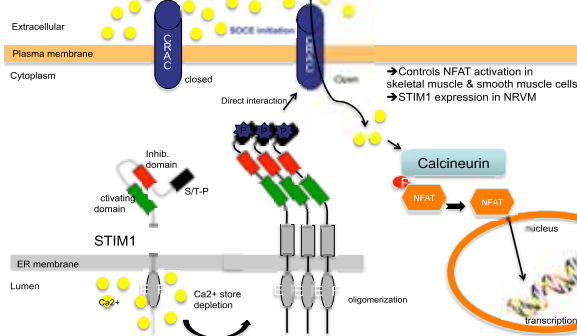


Calcium homeostasis & cardiac hypertrophy

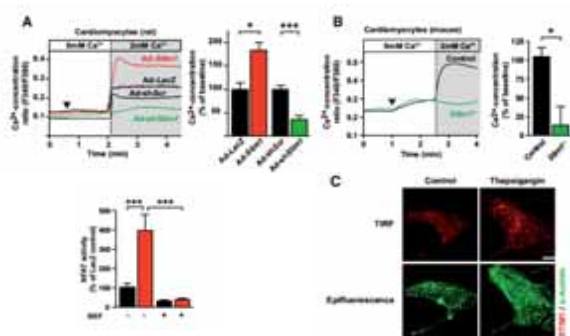
- Sustained pro-hypertrophic signaling within cardiomyocytes is detrimental and leads to failure.
- Pathological cardiac hypertrophy is typically characterized by the activation of Ca²⁺-dependent signaling pathways and re-expression of a fetal gene program.
- The mechanisms driving the Ca²⁺-dependent activation of Calcineurin/NFAT are unclear.



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

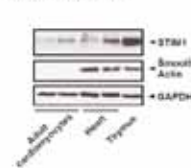


STIM1-dependent store-operated calcium entry in neonatal cardiomyocytes

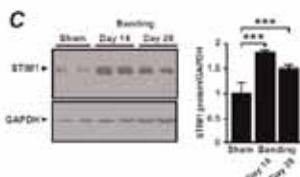


STIM1 is present in adult cardiomyocytes and is over-expressed during cardiac hypertrophy

STIM1 expression in the adult heart and in adult cardiomyocytes

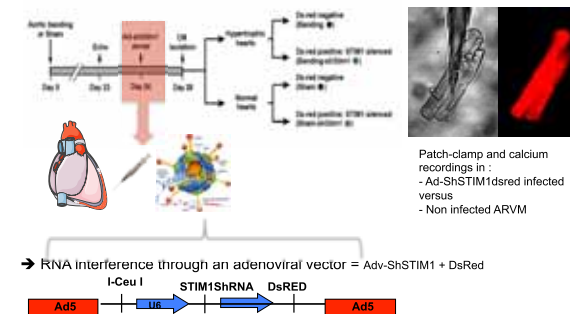


Pressure-overload hypertrophy



- STIM1 functionality in adult CM ?
- STIM1 -/- lethal after few days of life

Experimental strategy to modulate STIM1 in adult rat hearts

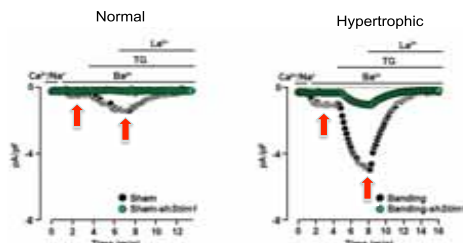


→ RNA interference through an adenoviral vector = Ad5-shSTIM1 + DsRed



Patch-clamp and calcium recordings in :
- Ad5-shSTIM1dsred infected versus
- Non infected ARVM

STIM1-dependent SOCE is present only in hypertrophic cardiomyocytes



- Induction of SOCE after store depletion (TG) higher in hypertrophic conditions
- STIM1 silencing reduces this current
- Before experimental store depletion, a current is recorded in hypertrophic cells while marginal in normal cells
- No store depletion in this model as assessed by caffeine application

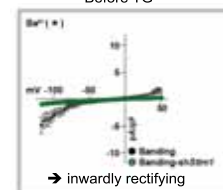
STIM1 controls two different currents in hypertrophic cardiomyocytes

I_{SOCE} characteristics

	Before TG	After TG
Ba ²⁺	→	→
Divalent Free	↑	↑
La ³⁺	↓	↓
SKF	↓	↓

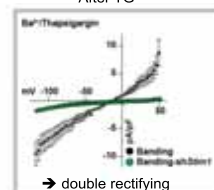
Current-Voltage (IV plot)

Before TG



→ inwardly rectifying

After TG

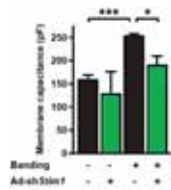


→ double rectifying

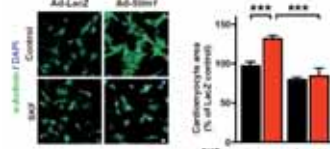


STIM1- dependent cation current does not affect excitation contraction coupling but the growth of isolated cardiomyocytes

Adult CM size estimated by membrane capacitance



Neonatal cell size after STIM1 manipulation

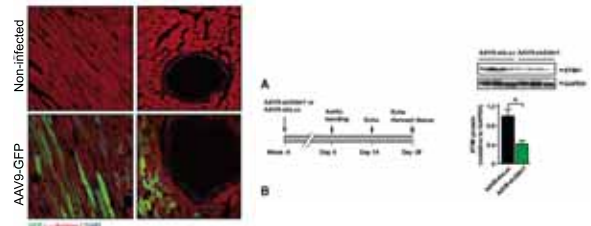


→ STIM1 silencing reciprocally prevents PE-induced NRVM hypertrophy

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

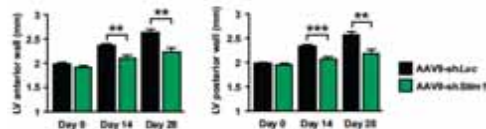
→ In vivo model of pressure-overload hypertrophy in rat :

- Sprague dawley 200 g rats
- Tail vein injection of 5x10¹¹ dsAAV9 shSTIM1 or ShLuci
- 60% on cardiomyocytes infected 3 weeks later
- No infection of interstitial or vascular cells
- No morphological or functional consequences following STIM1 silencing under physiological conditions

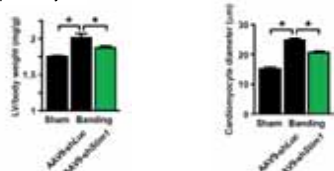


Adeno-associated virus-mediated silencing of STIM1 in vivo prevents cardiac hypertrophy (1)

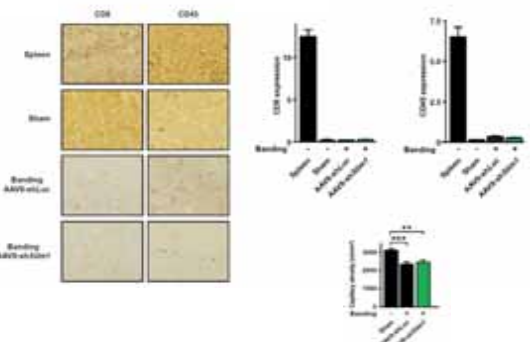
Echocardiography



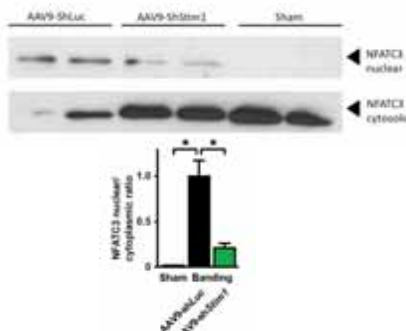
Morphometry



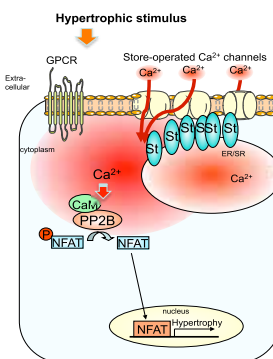
Adeno-associated virus-mediated silencing of STIM1 in vivo does not affect the inflammatory response nor the capillary density



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



CONCLUSIONS



- STIM1 expression and function reemerges in hypertrophied cardiomyocytes
- In this condition, STIM1 controls a cation current that
 - Occurs under native conditions (ie. in the absence of drug-induced calcium store depletion)
 - 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

Heart Failure

Critical Role for Stromal Interaction Molecule 1 in Cardiac Hypertrophy

Jean-Sebastien Hubot, MD, PhD; Jeremy Foucomet, PhD; Iderik Ramonnan, MSc; Antoine Chausse, MD; Flore Aubert, MD; Yasmine Saad, PhD; Sabine Merkle, PhD; Olivier Casella, PhD; Anne Ouillet, PhD; Morgan Dupuis, PhD; Laurence Hubot, PhD; Dongrak Jeong, PhD; Sika Mitrova, MSc; Jonathan Schmitt, MD; Arlette Bruns, PhD; Ludovic Bismuth, PhD; Yousuke Kubota, PhD; Bernhard Lippert, PhD; Sherrill Nussbaum, PhD; Alain Lacourpaille, PhD; Roger J. Hajos, MD; Anne-Marie Lippert, PhD; Stefan Engelhardt, MD, PhD (J. Intern. Med. 2011; 250: 1094-1104).

Key Words: cardiac • hypertrophy • cardiac • gene therapy • STIM1 protein •



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 Wenaweser, Joost Daemen, Bernhard Meier, Peter Jüni, 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 - Objective

To compare the safety of the unrestricted use of EES (XIENCE/PROMUS™) compared with early generation sirolimus-eluting (CYPHER™) (SES) and paclitaxel-eluting stents (TAXUS Express™) (PES) for coronary revascularization in a large, consecutively enrolled patient population during 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 $p < 0.10$ 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 - Clinical Trial Organization

Event Adjudication Committee

- Salvatore Brugaletta, MD, Barcelona, Spain
- Josep Lara Gomez, MD, Barcelona, Spain
- Gerrit Hellige, MD, Aarau, Switzerland
- Niklas Millauer, MD, Bern, Switzerland

Central Data Monitoring

- Clinical Trials Unit Bern, Switzerland

Independent Statistical Analysis

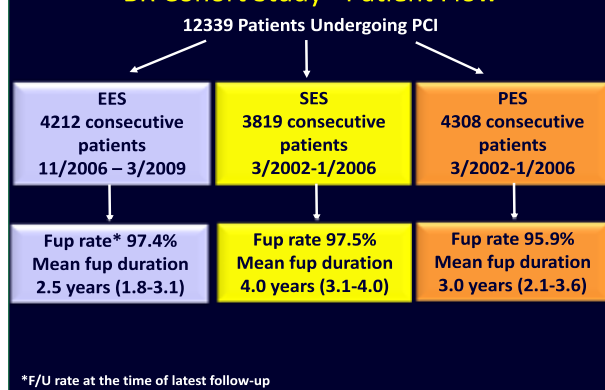
- Clinical Trials Unit Bern and Institute of Social and Preventive Medicine, P. Jüni, B. Kalesan

Funding

- Intramural grants of CTU Bern and a grant of the Swiss National Science Foundation.



BR Cohort Study - Patient Flow



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

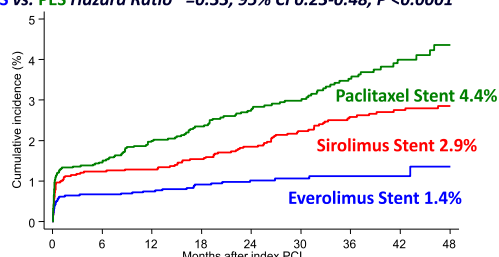
	EES	SES	PES	EES vs. SES	EES vs. PES
Total (n)	4212	3819	4308		
Age (%)	64±12	63±12	63±12	<0.0001	<0.0001
Sex (%)	73	75	74	0.11	0.35
BMI (%)	27±4	27±4	27±4	0.98	0.02
Hypertension (%)	57	52	41	<0.0001	<0.0001
Current smoking (%)	37	46	30	<0.0001	<0.0001
Dyslipidaemia (%)	54	55	46	0.54	<0.0001
Diabetes mellitus (%)	19	18	14	0.28	<0.0001
Renal failure (%)	11	12	12	0.46	0.81
LVEF <50%	34	27	25	<0.0001	<0.0001
ACS (%)	63	53	59	<0.0001	0.004
UA/NSTEMI (%)	42	57	45		
STEMI (%)	58	43	55		
Cardiogenic shock (%)	3	2	2	<0.0001	<0.0001

BR Cohort Study - Procedural Characteristics

	EES	SES	PES	EES vs. SES	EES vs. PES
Total (n)	4212	3819	4308		
Multivessel treatment (%)	16	17	19	0.29	0.003
No of vessels treated (n±SD)	1.2±0.4	1.2±0.4	1.2±0.4	0.21	0.66
No of lesions treated (n±SD)	1.8±1	1.5±0.7	1.4±0.7	<0.0001	<0.0001
1 lesion (%)	51	64	65		
2 lesion (%)	29	27	28		
3 lesion (%)	13	7	6		
>4 lesions (%)	7	1	1		
Left main (%)	4	2	4	<0.0001	0.08
Saphenous vein graft (%)	3	3	1	0.41	<0.0001
No of stents per patient (n±SD)	1.9±1.2	1.9±1.1	2.0±1.3	0.01	<0.0001
Average stent diameter (n±SD)	3.0±0.4	2.9±0.5	3.0±0.4	<0.0001	0.03
Total stent length (n±SD)	33±23	34±23	39±28	0.27	<0.0001
GP IIb/IIIa antagonist (n%)	21	19	18	0.03	<0.0001

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, $P < 0.0001$

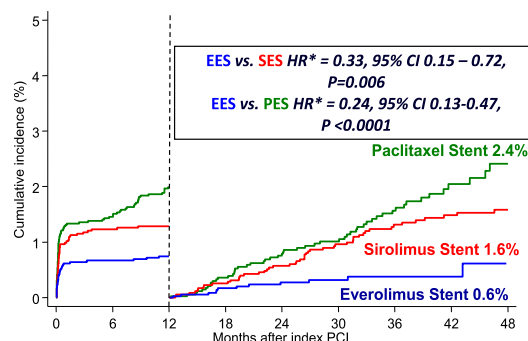


No. at risk	PES	4214	3916	3797	3176	2905	2344	1880	1077	686
	SES	3784	3617	3569	3499	3404	3080	2521	2118	1734
	EES	4135	3913	3793	3284	2604	1856	1041	514	208

*from Cox proportional hazards model

Very Late ST (1-4yrs)

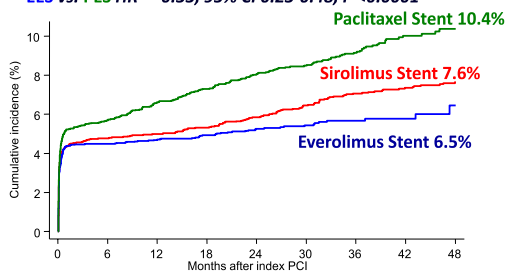
EES vs. SES HR* = 0.33, 95% CI 0.15 – 0.72, $P = 0.006$
EES vs. PES HR* = 0.24, 95% CI 0.13–0.47, $P < 0.0001$



*from Cox proportional hazards model

ARC Definite or Probable ST @ 4yrs

EES vs. SES HR* = 0.41, 95% CI 0.27–0.62, $P < 0.0001$
EES vs. PES HR* = 0.33, 95% CI 0.23–0.48, $P < 0.0001$

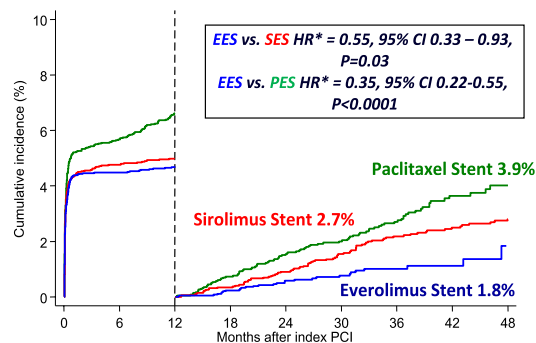


No. at risk	PES	4214	3859	3726	3106	2831	2274	1821	1034	660
	SES	3784	3649	3499	3428	3332	3010	2456	2061	1687
	EES	4135	3878	3753	3241	2666	1831	1025	505	203

*from Cox proportional hazards model

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

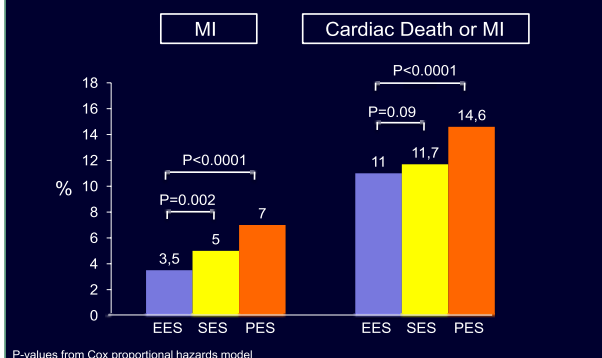
EES vs. SES HR* = 0.55, 95% CI 0.33 – 0.93, $P = 0.03$
EES vs. PES HR* = 0.35, 95% CI 0.22–0.55, $P < 0.0001$



*from Cox proportional hazards model



BR Cohort Study - Clinical Safety Outcome @4yrs



Association of Cardiac Death or MI With ARC Definite ST

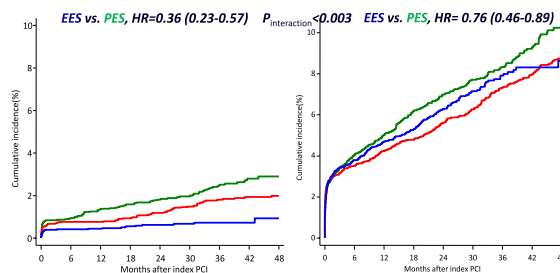
Cardiac Death or MI associated with ST

EES vs. SES, HR = 0.40 (0.20-0.81)

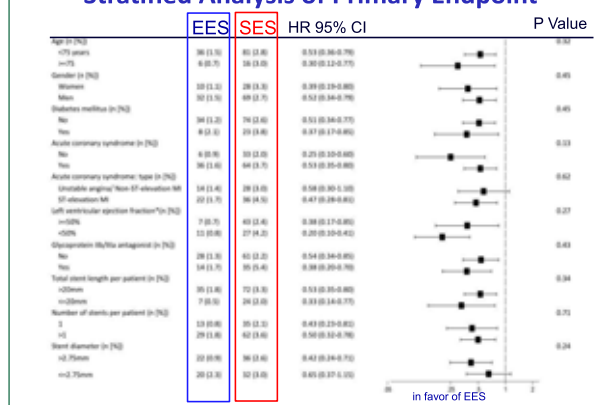
$P_{\text{interaction}} = 0.01$

Cardiac Death or MI not associated with ST

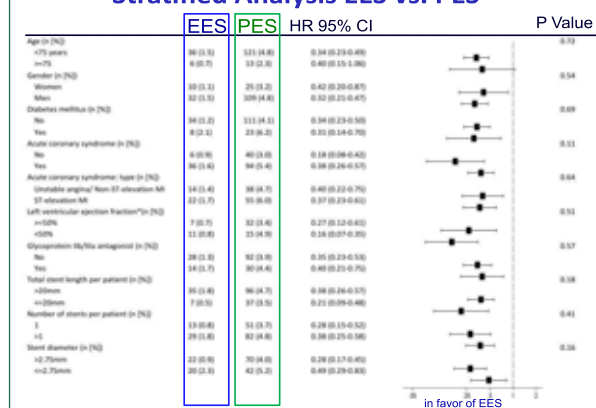
EES vs. SES, HR = 1.00 (0.84-1.20)



Stratified Analysis of Primary Endpoint



Stratified Analysis EES vs. PES



BR Cohort Study - Antiplatelet Therapy

	EES	SES	PES	EES vs. SES	EES vs. PES
At Discharge*					
ASA	4212	3819	4308	0.36	0.10
Clopidogrel	98.7	98.9	98.3	<0.001	0.17
DAPT	99.2	99.8	99.4	0.15	0.006
At Follow-up**					
Mean follow-up duration (yrs)	2.4	3.6	4.0		
Aspirin, %	93.2	87.1	86.9		
Clopidogrel, %	28.5	21.7	18.6		
DAPT, %	24.1	16.4	13.7		

*all patients, **only Bern data available

BR Cohort Study - Limitations

- Non-randomized observational study
 - analyses were adjusted for differences using inverse probability of treatment weighting (ITPW)
 - differences in favour of EES were large and consistent among subgroups
- Patients were enrolled sequentially and advances in implantation technique and prolongation of DAPT to one year may have favored EES
 - Study focused on very late ST
 - DAPT duration during last follow-up was comparable among all groups
 - Sequential enrollment reduces the risk of selection bias
 - EES patients were at higher risk

BR Cohort Study - Conclusions

- 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 a 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 VLST with the unrestricted use of EES overcomes the principal limitation of early generation DES and constitutes an important advance in DES safety.



EXAMINATION trial

The EXAMINATION (a clinical Evaluation of Xience-V stent in Acute Myocardial INfArcTION) trial:

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

EXAMINATION trial

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.

EXAMINATION trial

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 included¹.
- We conducted a RCT with an "all-comers" design with the aim to evaluate the performance of 2nd generation DES in the complex setting of STEMI and to provide data that may be generalizable to the real world population.

¹ De Boer SPM. Eur Heart J 2011; May 2011, ahead of print

EXAMINATION trial

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.

EXAMINATION trial (A Clinical Evaluation of Xience-V stent in Acute Myocardial INfArcTION)



12 centres - 3 countries



EXAMINATION trial

Participants (I)

PI: M Sabaté; Clinic Hospital, Barcelona, SP
Co-PI: PW Serruys; Erasmus MC; R'dam, NL

Steering Committee:

M Sabaté; PW Serruys; A Cequier; A Iñiguez; M Valgimigli; R Hdez-Antolín; GA van Es.

Promotor: Spanish Society of Cardiology

CRO: Cardialysis, R'dam, NL

Monitoring: J Toro (SP) S Cellini (I), C Morelli (I), R Schneijdenber (NL)

DSMB: I Ferreira (SP); B Garcia del Blanco (SP)

CEC: P Vrancks (B); E McFadden (UK); B Rensing (NL)

Statistics: Cardialysis, R'dam, NL

EXAMINATION trial

Participants (II)

Centres:

- Spain:

- H Prínceps d'Espanya, Barcelona; Dr. A Cequier
- H Sant Pau, Barcelona; Dr. A Serra
- H Clínic, Barcelona; Dr. M Sabaté
- H do Meixoeiro, Vigo; Dr. A Iñiguez
- H San Carlos, Madrid; Dr. R Hernández-Antolín
- H Univ Alicante; Alicante; Dr. V Mainar
- H Juan Canalejo; A Coruña; Dr. N Vázquez
- H Son Dureta; Palma de Mallorca; Dr. A Bethencourt

- Italy

- Univ H Ferrara- Dr. M Valgimigli
- Univ H Bolognini Seriate- Dr. M Tespili

- The Netherlands

- Erasmus MC, Rotterdam- Dr. PW Serruys
- Amphia Ziekenhuis, Breda- Dr. den Heijer

EXAMINATION trial

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.

EXAMINATION trial

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.

EXAMINATION trial

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.

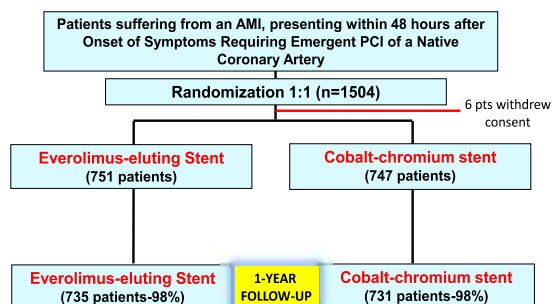
EXAMINATION trial

Statistical analysis:

- The overall sample size for the study of 1500 patients is based on the following assumptions:
 - A 2-sided type I error rate $\alpha = 0.05$
 - Randomization ratio is 1 (XIENCE V): 1 (Vision).
 - A statistical power of at least 86% to detect a (approximate 30%) 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.

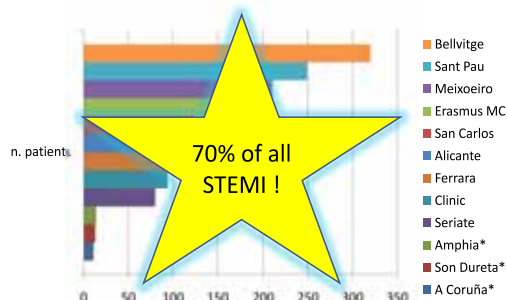
EXAMINATION trial

Study Design = All-comer RCT



EXAMINATION trial

Number of patients included per centre

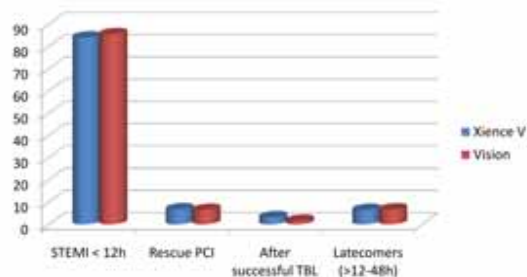


EXAMINATION trial

Baseline Characteristics	Xience V n=751	Vision n=747
Age, years	61 ± 12 (28-90)	62 ± 12 (27-95)
Male, %	84.4	81.7
Body mass index, Kg/m ²	27 ± 4	27 ± 4
Diabetes, %	18	16
Hypertension, %	46	50
Smoker, %	72	72
Dyslipidemia, %	47	40
Family History, %	18	16
Previous Myocardial Infarction, %	4.4	6.3
Previous PCI, %	3.9	4.3
Previous CABG, %	0.4	0.9
Previous stroke, %	1.6	2.5

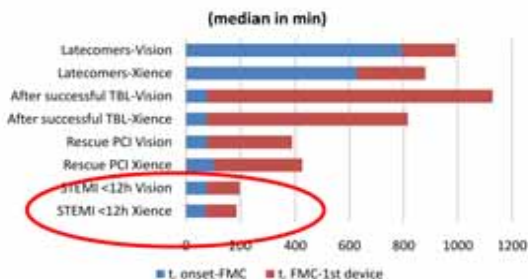
EXAMINATION trial

Clinical presentation





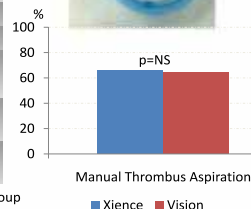
Ischemia time according to clinical presentation



Anatomical Characteristics	Xience V n=751	Vision n=747
Infarct-related artery:		
LAD, n (%)	379 (42)	343 (39)
RCA, n (%)	380 (42)	396 (45)
LCx, n (%)	130 (15)	132 (15)
Left Main, n (%)	6 (0.7)	4 (0.5)
SVG, n (%)	4 (0.4)	4 (0.5)
N. diseased vessels:		
One, n (%)	645 (86)	654 (88)
Two, n (%)	76 (10)	63 (8.4)
Three, n (%)	24 (3.2)	25 (3.4)
Ejection fraction, %; median [IQR]	52 [45-58]	51.5 [45-58]

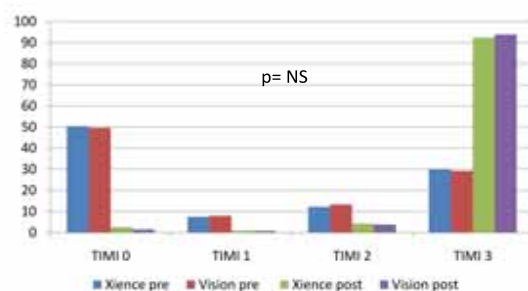
Procedural Aspects

Antithrombotic Therapy	Xience V n=751	Vision n=747
Unfractionated heparin, n (%)	597 (79.5)	587 (78.7)
LMWH, n (%)	62 (8.3)	71 (9.5)
Bivalirudin, n (%)	49 (6.5)	56 (7.5)
IIb/IIIa inh.* (99% reopro), n (%)	400 (53.3)	383 (51.2)
Aspirin, n (%)	692 (92.1)	691 (92.6)
Clopidogrel, n (%)	710 (94.5)	703 (94.2)



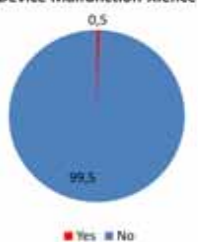
* 63% vs 60% when analysed within STEMI <12h group

Acute Results

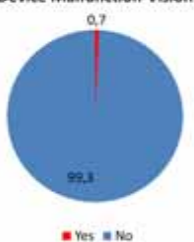


Acute performance

Device Malfunction-Xience

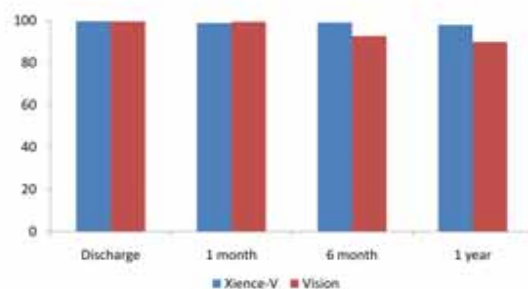


Device Malfunction-Vision



p = NS

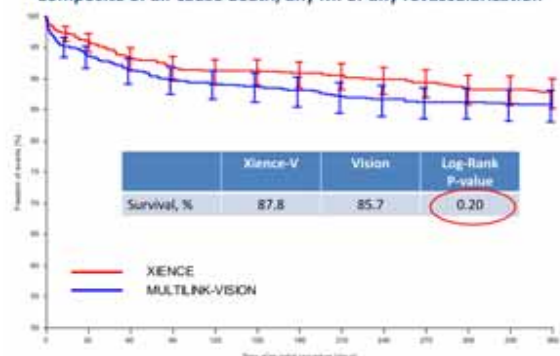
Dual Antiplatelet Regimen

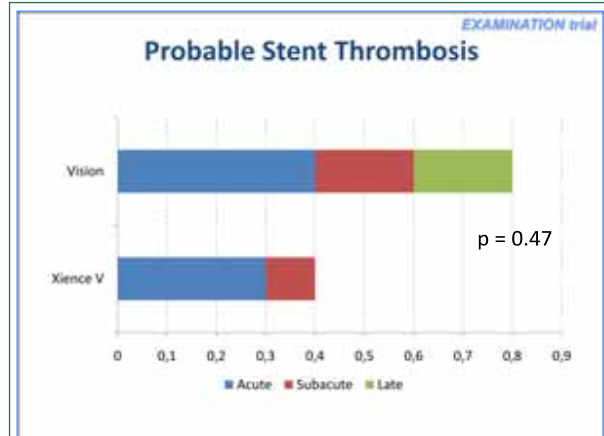
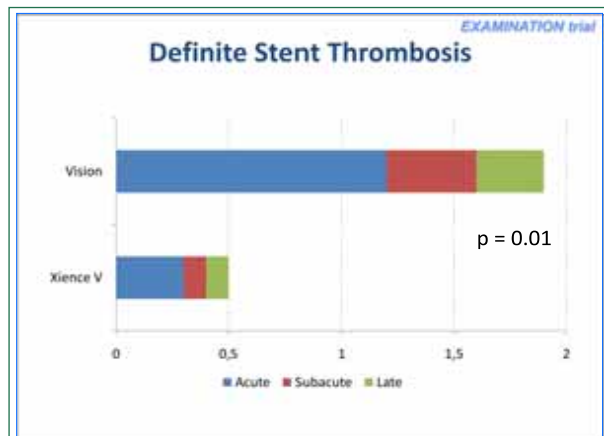
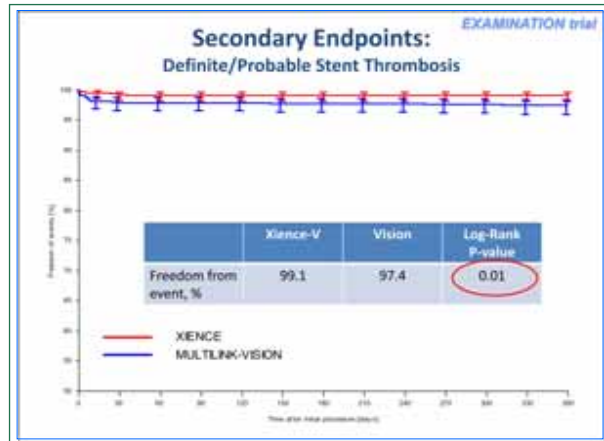
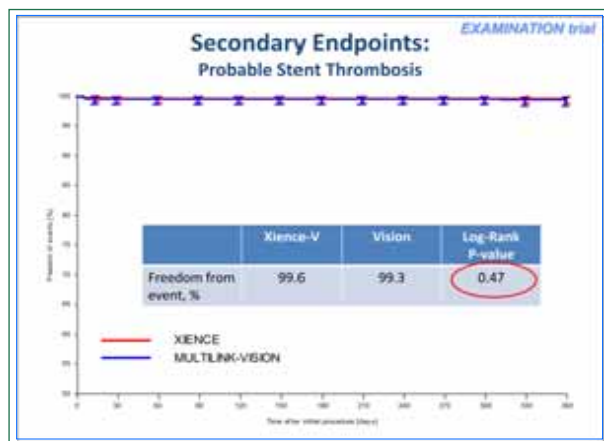
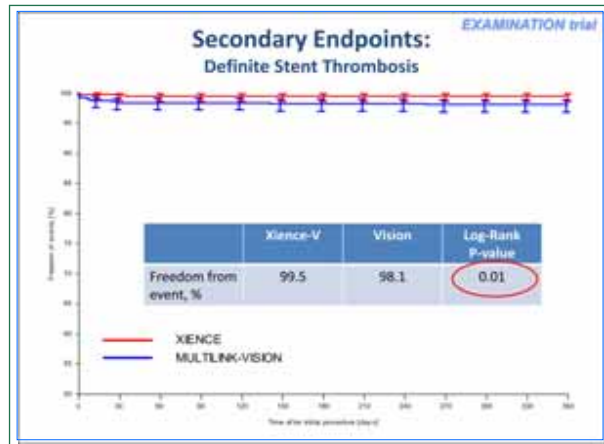
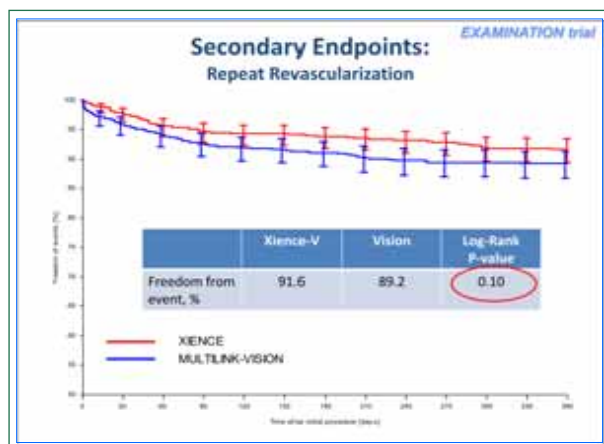
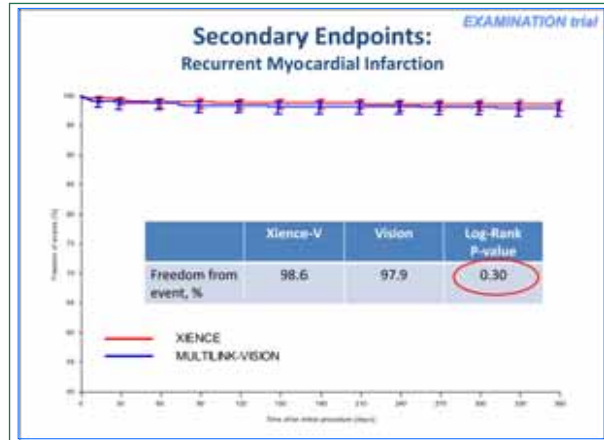
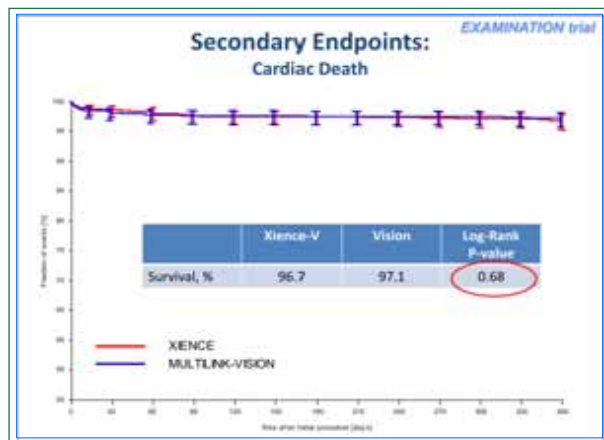


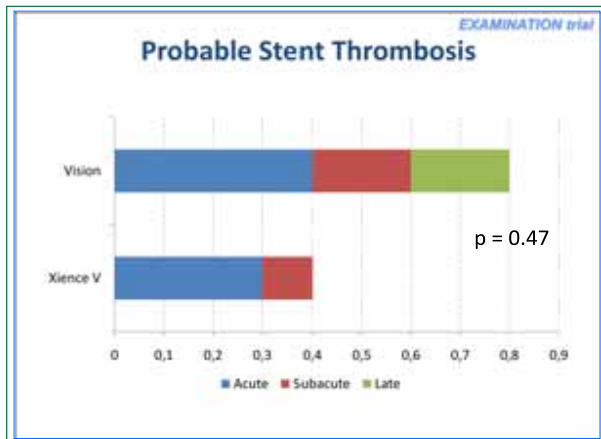
1-YEAR RESULTS

Primary Endpoint:

Composite of all-cause death, any MI or any revascularization







EXAMINATION trial

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



Conflicts of interest

- Lecture fees from AstraZeneca, Eli Lilly, The Medicines Company, Merck.

Oral Xa inhibitors

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

ACS: dual antiplatelet therapy

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

aspirin

clopidogrel



ACS: dual antiplatelet therapy

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

aspirin

clopidogrel

ticagrelor

prasugrel



Anticoagulation plus dual antiplatelet therapy in ACS

Sørensen R et al.,
Lancet 2009

APPRaise: apixaban

ATLAS ACS-TIMI 46:
rivaroxiban

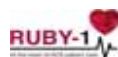


Photo: R De Caterina



Oral Xa inhibition in ACS: RUBY-1

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



RUBY-1

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

darexaban



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.

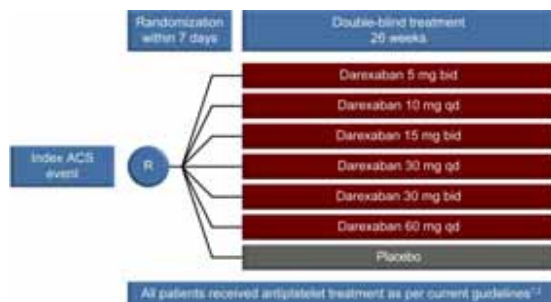


Selection of patients

- 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.



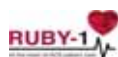
Dosing and design



ASA was used at a dose of 75–325 mg daily, as per local practice. The lower dose range of ASA (75–81 mg/day) was recommended, or clopidogrel 75 mg/day if ASA was contraindicated or not tolerated, or a combination of ASA 75–325 mg and clopidogrel 75 mg daily.

1. Braunholtz P, et al. For Heart J 2007;28:1339–1340
2. Anderson JL, et al. J Am Coll Cardiol 2007;50:1–157

R: randomization



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%**.



Darexaban: safety

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

No major side effects



Darexaban: safety

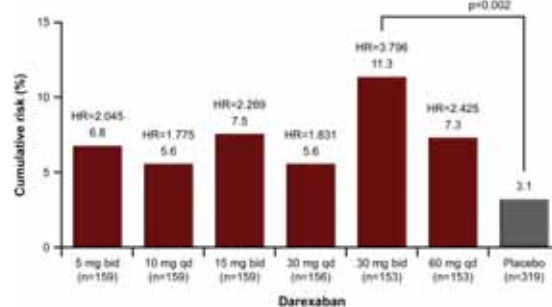
- 291 patients (23.1%) discontinued treatment early.
- Overall mean compliance to study drugs was 97.9%.

No major side effects

No toxicity



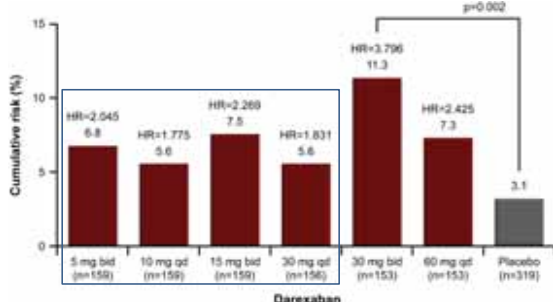
Primary Safety Endpoint: Major and CRNM Bleeding at 6 months

Dose-response relationship ($p=0.009$) for increased bleeding

Kaplan-Meier analysis of cumulative risk of major and CRNM bleeding events



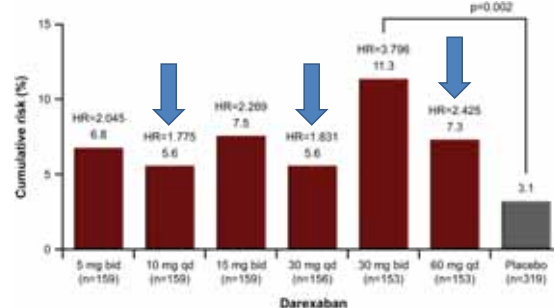
Primary Safety Endpoint: Major and CRNM Bleeding at 6 months

Dose-response relationship ($p=0.009$) for increased bleeding

Kaplan-Meier analysis of cumulative risk of major and CRNM bleeding events



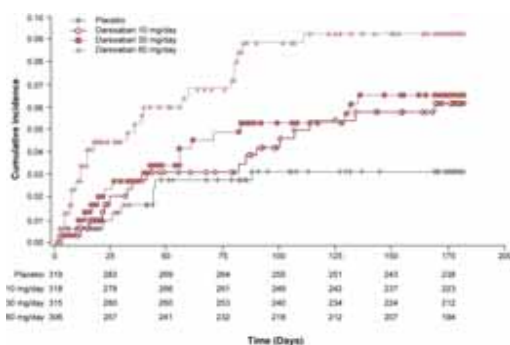
Primary Safety Endpoint: Major and CRNM Bleeding at 6 months

Dose-response relationship ($p=0.009$) for increased bleeding

Kaplan-Meier analysis of cumulative risk of major and CRNM bleeding events



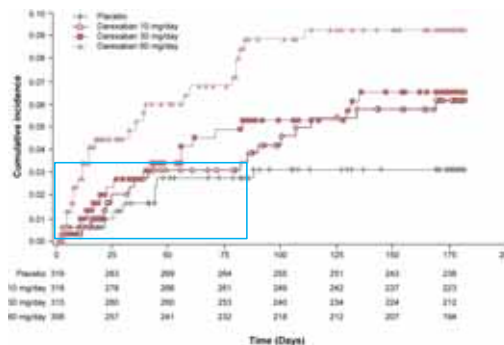
Cumulative Risk of Major and CRNM Bleeding for Darexaban Total Daily Doses at 6 Months



Cumulative incidences are calculated using Kaplan-Meier estimates and presented as relative to 1 (e.g. 0.06 represents 6%)



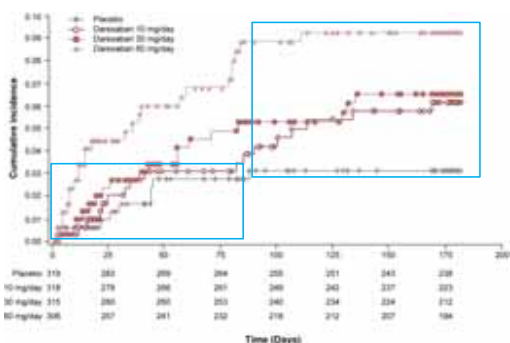
Cumulative Risk of Major and CRNM Bleeding for Darexaban Total Daily Doses at 6 Months



Cumulative incidences are calculated using Kaplan-Meier estimates and presented as relative to 1 (e.g. 0.06 represents 6%)



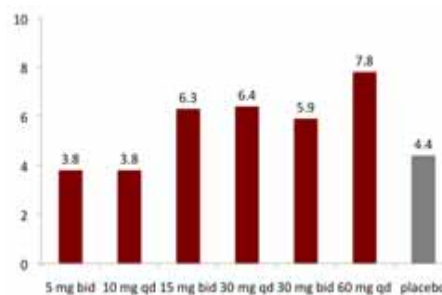
Cumulative Risk of Major and CRNM Bleeding for Darexaban Total Daily Doses at 6 Months



Cumulative incidences are calculated using Kaplan-Meier estimates and presented as relative to 1 (e.g. 0.06 represents 6%)



Main Secondary Endpoint: Composite Efficacy Outcome at 6 Months



Crude risk of all cause mortality, non-fatal myocardial infarction, non-fatal stroke and severe recurrent ischaemia



THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Santiago D. Lopez, M.D., Ph.D., Stefan James, M.D., Ph.D., Rishi Filani, M.S., Yashua Ho, M.D., Ph.D., Puneet Mahan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Gosselin, M.D., Frank W. Verheugt, M.D., Ph.D., Marcus Fisher, M.D., Kurt Huber, M.D., Danny Liew, M.D., Ph.D., Steven E. Harnt, M.D., Jose Lopez-Sendon, M.D., Ruffalo De Caterina, M.D., Feng-junshu, M.D., Harald Darius, M.D., Gregorio Vitoriano, M.D., Jan H. Cornel, M.D., Frank Gohlke, M.D., Don-Atar, M.D., Jose Luis Linares-Pardo, M.D., Malyet Khatib, M.D., Hiron-Ogawa, M.D., Ph.D., Peter Vals, M.D., Alexander Pothmann, M.D., Winold Buzjyn, M.D., Rafal Dziel, M.D., Henry White, M.D., Michael Rude, M.D., Margarita Gonzalez, Ph.D., Jack Lawrence, M.D., Robert B. Harrington, M.D., and Lars Wallentin, M.D., Ph.D., for the APELLAS-2 Investigators*

CONCLUSIONS

The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events.

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.

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.

Drug, dose, duration

Patients

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.

Drug, dose, duration

Patients