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

Robert M Califf MD
Vice Chancellor for Clinical Research
Duke University

Duke Translational Medicine Institute

Industry Relationships and Conflict of Interest

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

DTMI Transforming Medicine

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

BMJ 2003

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

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

PK Senn

DTMI Transforming Medicine

Strengths of Study

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

DTMI Transforming Medicine

Fundamental Findings

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

DTMI Transforming Medicine

Possible Interpretation

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

DTMI Transforming Medicine

Pharmacogenetics in Practice

- Genes can be found that alter the response to drugs, including CV drugs
- RNA, proteins and metabolites can be found in patterns that provide probabalistic estimates of clinical outcomes
- Almost always these genes/genomics do not provide a deterministic prediction of outcome
  - Instead they take one probability distribution of predicted outcomes and divide the distribution into 2 or more overlapping distributions
- In a rational world, the issue of whether its worth using a genomic test is not different than any other predictive test
- Since more easily measurable patient descriptors (eg age, CrCl) and response measure (INR, LDL, BP) also refine probability distributions, the use of pharmacogenomic testing is a comparative effectiveness issue

DTMI Transforming Medicine

3-Year Interim Results of the Percutaneous MONARC™ System for the Treatment of Functional Mitral Regurgitation

EVOLUTION I Study
Clinical EValuation Of the Edwards Lifesciences PercUTaneous Mitral AnnulOplasty System for the treatment of Mitral RegurgitatioN

Jan Harnek MD PhD FESC
Lund University Sweden

Investigators: Jan Harnek, John Webb, Karl-Heinz Kuck, Carsten Tschoepe, Christopher Buller, Stefan James, Christiane Tiefenbacher, Alec Vahanian

Potential conflicts of interest

Speaker's name: Jan Harnek MD PhD FESC

I have the following potential conflicts of interest to report:

Research contracts: Medtronic
Consulting: Edwards Lifesciences, Abbott Vascular, Cordis, Medtronic

EVOLUTION I Study

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

Inclusion / Exclusion Criteria

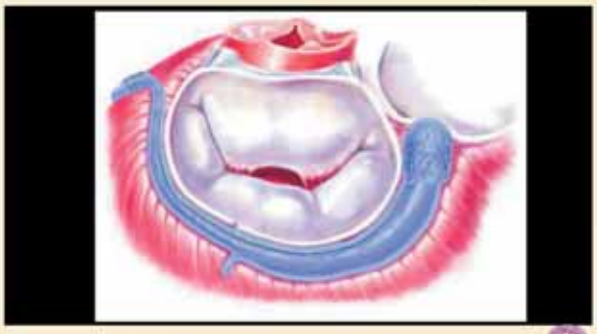
INCLUSION

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

EXCLUSION

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

The Edwards MONARC System



Population: 72 Patients Enrolled

Age		70 +/- 10 years (37-90)
Male Gender		72 %
Coronary artery disease	Overall	68%
	Myocardial infarction	57%
	CABG	47%
	PTCA	40%
NYHA	CLASS I	4%
	CLASS II	42%
	CLASS III	50%
	CLASS IV	4%
Congestive Heart Failure		57 %

Procedural Success

Patients Enrolled n = 72

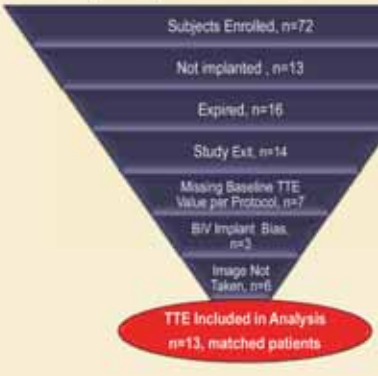
Device implanted n=59 (82%)

- Procedural Time: 84 ± 58 min

Device not implanted n=13 (18%)

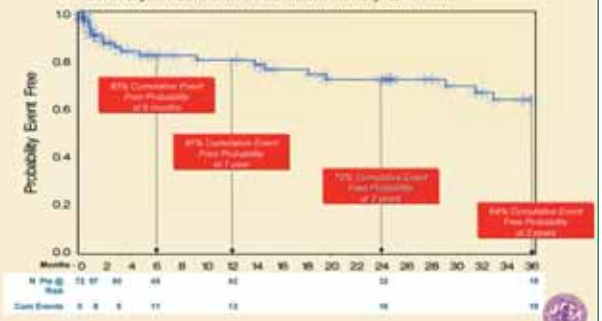
- Tortuous Anatomy
- Size Outside of Offered Range

Study Population at 3 Years



Cumulative Safety

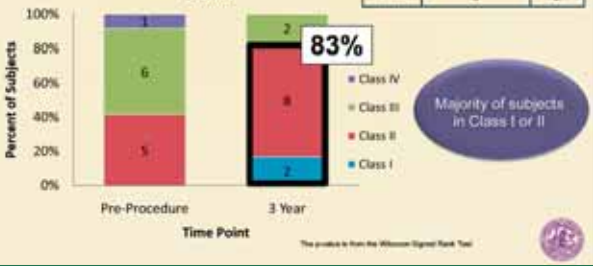
Device Migration, Death, MI, Device Embolization, Cardiac Tamponade Coronary Sinus Thrombosis or Pulmonary Embolism



Long Term Follow Up to 3 years: NYHA Class

NYHA Class Population Distribution
3 Year Data (n=12, matched patients)
p=0.0547

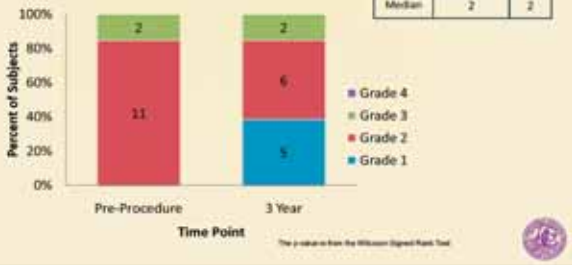
	Pre-procedure	3 Year
Mean	2.7	2
Median	3	2



Long Term Follow Up to 3 years: MR Severity

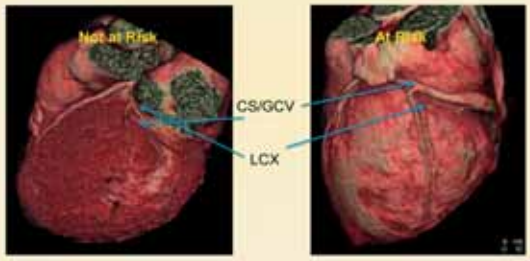
MR Grade Population Distribution
3 Year Data (n=13, matched patients)
p=0.1875

	Pre-procedure	3 Year
Mean	2.15	1.77
Median	2	2



Artery compression

Compression of a marginal branch seen in10 pts, 3 pts had a clinical event. One was succesfully stented, one case resolved itself, and one died at day 551



44% of pts in EVOLUTION I

56% of pts in EVOLUTION I

EVOLUTION I Learning

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

Conclusions

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

ISAR-TEST-4: Two-year results

Comments from Jean Marco, FESC

ISAR-TEST-4: Two-year results Method

One biodegradable polymer (BP) DES

vs

Two permanent polymer (PP) DES

(Cypher & Xience)

Non-inferiority trial : **Δ= 3%**

I° EP: Composite of clinical events

Sample size calculation of 2600 patients

ISAR-TEST-4: Two-year results
Results

- Efficacy (TLR)
  - @ one year : 8.8% vs 9.4%
  - @ two year : 11.0% vs 11.7%
  - Loss = 2.2% vs 2.3 % (NS)
- Safety
  - Cardiac death/MI related to TV
    - @ one year: 6.3% vs 6.2%
    - @ two year: 7.1% vs 7.2%
    - Loss= 0.8% % vs 1.0% % (NS)
  - Stent thrombosis :
    - @ one year: 1.0% vs 1.5%
    - @ two year : 1.1% vs 1.7% (NS)

Byrne et al EHJ 2009

ISAR-TEST-4: Two-year results
Limitations

- Two Permanent polymers
  - Cypher ≠ Xience
- Late inflammatory response related to polymer (autopsy)
  - Cypher but not with Xience
- Cardiac death/MI related to target vessel/TLR@ 1 year
  - Cypher: 15.2%
  - Xience: 13.6% (NS)
  - Δ : not available at 2 years ?

Longer FU: needed

ISAR-TEST-4: Two-year results
Conclusion

- Primary composite endpoint
  - Δ= 1%
  - Biodegradable Polymer DE(Yucon)= non-inferior to the two Permanent Polymer(Cypher-Xience)

Longer FU is needed

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

ISAR-TEST-4
Biodegradable Polymer Versus Permanent Polymer DES: Two-Year Outcomes from a Large-Scale Randomized Trial

R.A. Byrne, A. Kastrati, K. Tiroch, S. Massberg, A. Wieczorek, K-L. Laugwitz, S. Schulz, J. Pache, M. Fusaro, M. Seyfarth, A. Schömig, J. Mehilli

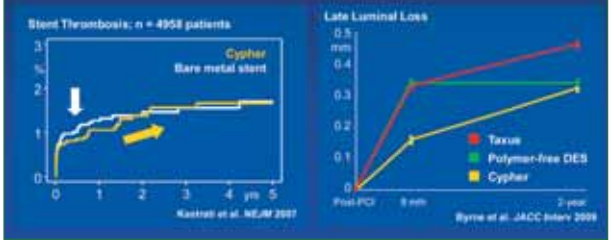
Deutsches Herzzentrum & 1. Med. Klinik rechts der Isar
Technische Universität Munich Germany

Financial disclosure

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

Late Adverse Events with DES

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



Delayed Arterial Healing

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

Delayed Arterial Healing

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

ISAR-TEST-4 Trial

Biodegradable polymer (BP) DES
– sirolimus-eluting (Yukon PC Choice)

vs.

Permanent polymer (PP) DES
– sirolimus-eluting (Cypher)
– everolimus-eluting (Xience)

ISAR Stent Project

Sirolimus-eluting
Biodegradable polymer
Microporous thin-strut (87 µm)
316L stainless steel

Byrne et al. *EHJ* 2009

ISAR-TEST-4 - Primary Endpoint -

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

ISAR-TEST-4

Two-year Outcomes

ISAR-TEST-4 Study Design

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

Inclusion Criteria:
ischemic symptoms or evidence of myocardial ischemia *and* presence of ≥50% stenosis in native coronary arteries

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

2603 patients enrolled at two centres in Munich, Germany

BP-DES n = 1299	PP-DES n = 1304
Angiographic follow-up at 6-8 mos (78%) 2 years (73%)	Angiographic follow-up at 6-8 mos (78%) 2 years (69%)
Clinical follow-up at 2 years (94.8%)	Clinical follow-up at 2 years (94.9%)

Baseline clinical characteristics

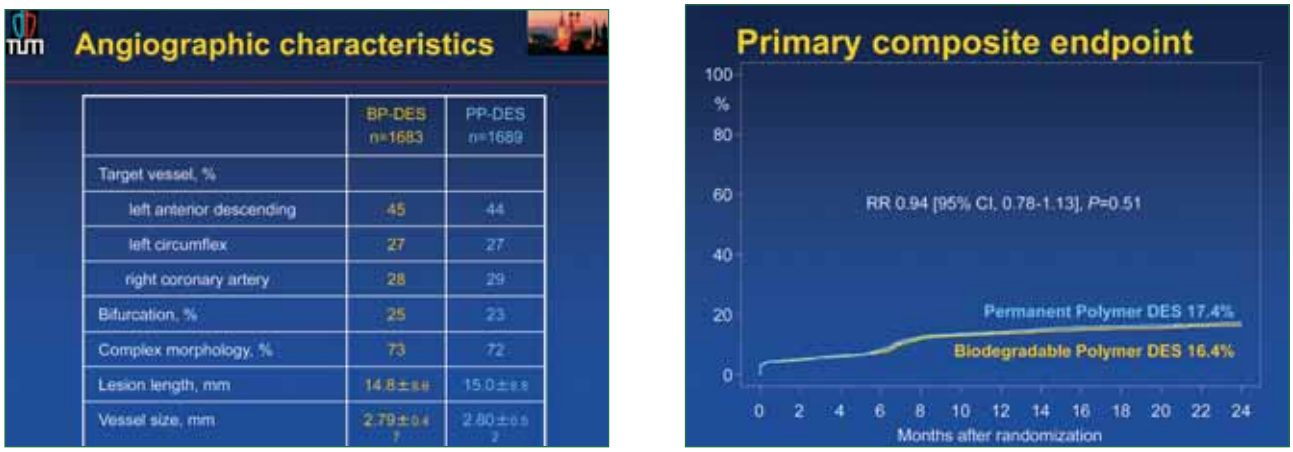
	BP-DES n=1299	PP-DES n=1304
Age, years	66.7±10.7	66.8±11.1
Male, %	75	77
Art. hypertension, %	69	68
Diabetes, %	29	29
Current smoker, %	16	17
Hyperlipidemia, %	67	65
Prior bypass surgery, %	10	10
Prior MI, %	29	29

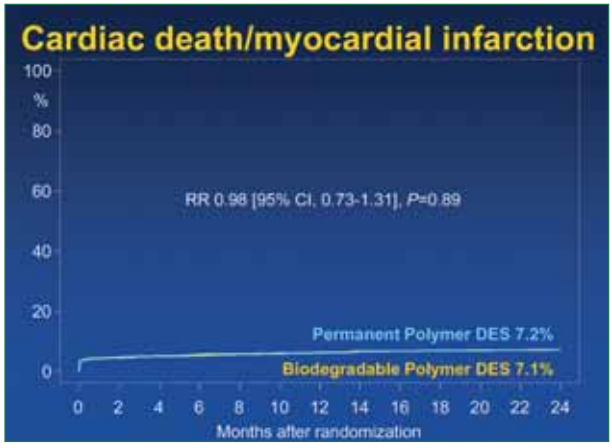
Baseline clinical characteristics

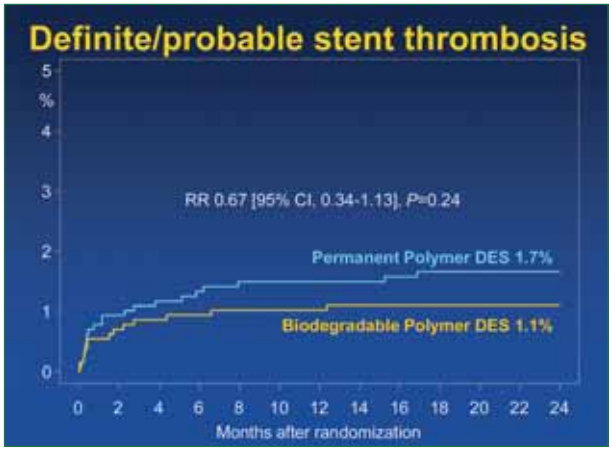
	BP-DES n=1299	PP-DES n=1304
Clinical presentation, %		
acute MI	13	11
unstable angina	29	29
stable angina	58	60
Multivessel disease, %	87	86
Multilesion PCI, %	29	26
LV ejection fraction, %	53.1±11.8	53.6±11.3

Angiographic characteristics

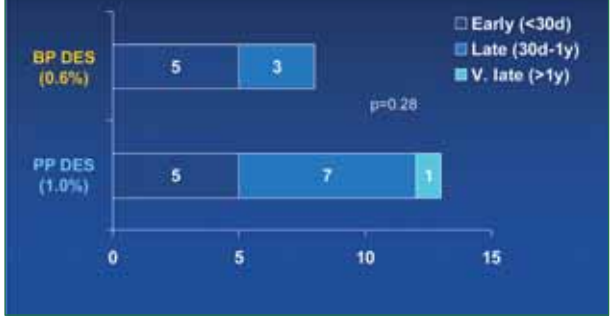
	BP-DES n=1683	PP-DES n=1689
Target vessel, %		
left anterior descending	45	44
left circumflex	27	27
right coronary artery	28	29
Bifurcation, %	25	23
Complex morphology, %	73	72
Lesion length, mm	14.8±8.8	15.0±8.8
Vessel size, mm	2.79±0.4 7	2.80±0.5 2

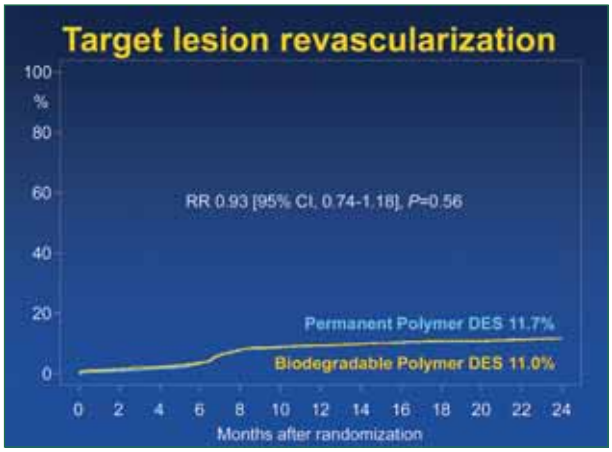




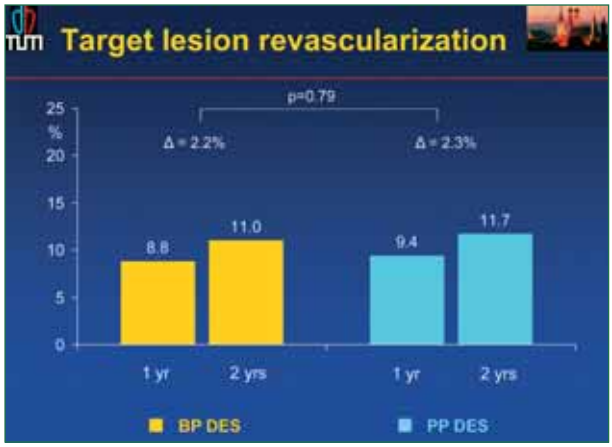


Definite Stent Thrombosis

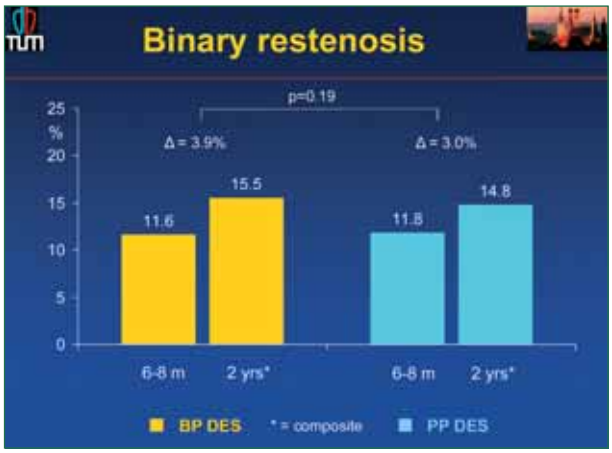




Target lesion revascularization



Binary restenosis



Conclusion

- In the setting of a real world randomized trial **BP-DES** and **PP-DES** are associated with similar clinical outcomes out to 2 years
- Although the concept behind **biodegradable polymer DES** is intuitively attractive, the hypothesised late performance advantage of these devices remains unproven at least out to 2 years

Thank You

ISAR-TEST-4 Trial

Deutsches Herzzentrum, Munich. Germany

DISCUSSION

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

Patrick W. Serruys, MD, PhD.

Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

29th, August, 2010
14:25-14:30

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

Background

- There is limited data on the comparison between Abciximab vs. Tirofiban at high bolus dose (HDB: 25 μg/kg over 3 min)
  - 4 RCTs have so far contrasted these two drugs in 719 pts undergoing PCI of whom less than 300 were recruited in the setting of STEMI [1,2]
- The use of DES in the setting of STEMI is currently discouraged due to partially conflicting results on efficacy from MC-RCTs [3,4] and safety concerns from registries [5,6]

1: Valgimigli et al. JAMA 2005; 2: Stenzl et al. Am J Cardiol 2004; 3: Spaulding et al. NEJM 2006
4: Laarman et al. NEJM 2006; 5: Spertus et al. Circulation 2006; Steg PG et al. ESC 2007

Study Primary Endpoints

Pharmacology Arm

Non-inferiority basis

≥50% Σ ST segment elevation resolution within 90' after last balloon inflation @ tt-EKG

Stent Arm

Superiority basis

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

Valgimigli et al. Am Heart J. 2007 Jul;154(1):39-45

Study Primary Endpoints Power Analysis

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

		Assumed event rates					
Endpoint	Test	Abciximab	Tirofiban	SES	BMS	δ	Power
≥Σ50% STR	N-Inf.	85%	85%	–	–	9%*	>85%
MACE	Sup.	–	–	16%	27%	–	80%

MACE rate at 9 months in the LEADERS trial (SES arm all comers-ACS 55.7%) 10.5%

*: ~50% of previously reported Δ ≥Σ50% STR between Abciximab vs. placebo in the ACE trial (Antoniucci et al. J Am Coll Cardiol 2003)

Summary

Our study provides evidence that in a broad population of largely unselected patients undergoing angioplasty for ST-elevation myocardial infarction:

- Tirofiban enables non-inferior STR within 90' after intervention and similar outcomes at 8 months than Abciximab
- The MACE rate was approximately halved by the use of SES compared to BMS

General considerations on the relevance of the report

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

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

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

Strong points of the study

- ✓ Small difference between the number of patients assessed for the eligibility and the number of patients randomized.
- ✓ Small deviation between the number of patients "per protocol" and "intention to treat".
- ✓ Excellent clinical follow-up (patients lost at follow-up range between 1 and 3 per cohort).
- ✓ Appropriate long-term and balanced treatment in the four arms.
- ✓ Idea of checking the P2Y12 inhibition

remains unclear why in the first year between DES and BMS arms, but not tirofiban arms. The duration of the us is a confounding factor in the anal study.

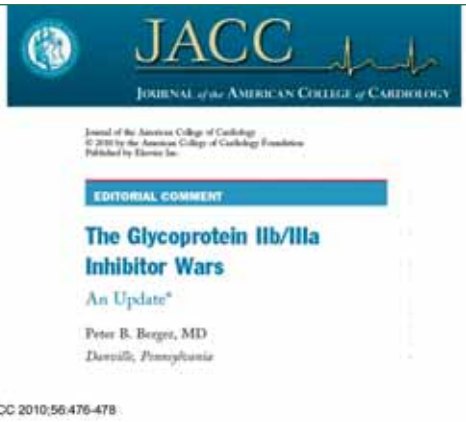
Did the authors hypothesize that an early difference in ST-resolution (with impact on peri-procedural re-infarction and acute stent thrombosis, acute mortality, etc) could substantially affect the long-term results up to the point that the drug-effect would supersede the difference between the two stent?

Strength and weakness of multifactorial analysis

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

✓ Personally, I do not like the yin/yang character of the hypothesis of this trial

A theoretically and borderline more effective IIb/IIIa would compensate for a fundamentally less effective BMS.


JACC
JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

EDITORIAL COMMENT

The Glycoprotein IIb/IIIa Inhibitor Wars

An Update*

Peter B. Berger, MD

Danville, Pennsylvania

JACC 2010;56:476-478

Financial ground for the War

" There exist 3 different GP IIb/IIIa inhibitors approved for use: abciximab (Eli Lilly & Company, Indianapolis, Indiana), eptifibatide (Schering-Plough, Kenilworth, New Jersey), and tirofiban (Medicure, Winnipeg, Canada). The fierce competition among the companies that make and market these drugs, fighting for their share of the billion-dollar market, has kept the issue of the comparative effectiveness of the GP IIb/IIIa inhibitors in the spotlight. The enormous differences in the price among the 3 agents make the comparative effectiveness and relative costs of these drugs important in this era of health care reform. The average wholesale price of abciximab is $1,836.90 (for a 12-h infusion) and of eptifibatide is $1,121.81 and tirofiban is $711.72 (for 18-h infusions) for an 80-kg patient with normal renal function (Merchant G, personal communication, June 2010)."

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

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

Conclusions

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

✓Some physicians will continue to choose the most studied agents, rejecting undersized trials as inconclusive (which they are).

✓Others are comfortable choosing a promising but less studied agent.

✓Still others will choose the cheapest agent.

✓Still others (unfortunately) choose the agent whose sales-people are most effective, friendly or attractive.

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

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

3-year Follow-up of the MULTIcentre evaluation of Single high-dose bolus TiRofiban versus Abciximab with sirolimus eluting sTEnt or bare metal stent in acute myocardial infarction studY

MULTISTRATEGY

ClinicalTrials.gov number: NCT00229515

M. Valgimigli, MD, PhD, FESC
On behalf of Multistrategy Investigators

Potential Conflicts of interest

Speaker's bureau:	Iroko, Chiesi, Eli Lilly, MEDCO, Cordis, Medtronic, Abbott
Advisory Board:	Iroko, Chiesi, Eli Lilly, MEDCO, Medotronic,
Research grant:	Iroko, Merck, Eli Lilly, Medtronic

Background

- The data comparing Tirofiban at high dose bolus (HDB: 25 μg/kg over 3 min) to Abciximab is largely confined to 30-day Outcomes[1]. The value of abciximab over placebo has been show to accrue over time[2]
- The long-term DES safety profile in patients with STEMI remains uncertain as only a limited number of controlled data exists beyond 2 years[2-7].

MULTISTRATEGY Design

All-comer STEMI Patients
Aspirin + Clopidogrel + UFH
Before Arterial Sheath Insertion

1:1

Tirofiban* — Abciximab

1:1 — 1:1

SES — BMS — SES — BMS

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

*: given as a bolus of 25 μg/kg, followed by an 18-24 hour infusion at 0.15 μg/kg/min

MULTISTRATEGY P.I.s and Sites

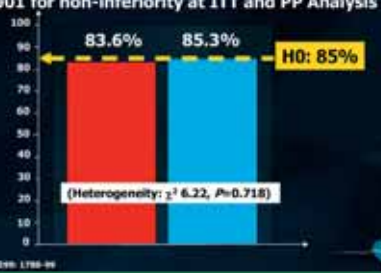
G Campo	Ferrara	R Moreno	Madrid
G Percoco	Lagosanto	T Piva	Ancona
M Anselmi	Verona	I Sheiban	Torino
L Bolognese	Arezzo	G Pasquetto	Mirano
S Colangelo	Torino	F Prati	Rome
N de Cesare	Zingonia	M Nazzaro	Rome
A Rodriguez	B. Aires	J Fernández	Huelva
M Ferrario	Pavia	J Mieres	B Aires

Recruitment: October 2004-April 2007

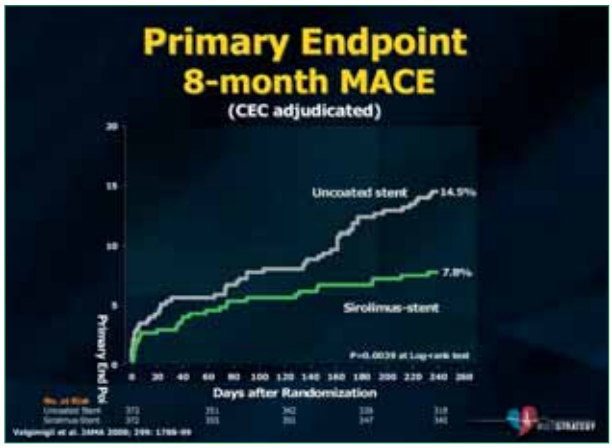
Primary Endpoint
≥50% Σ ST segment resolution

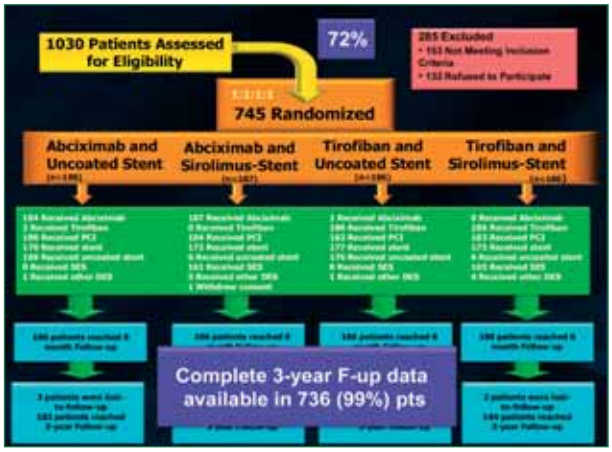
Abciximab — Tirofiban

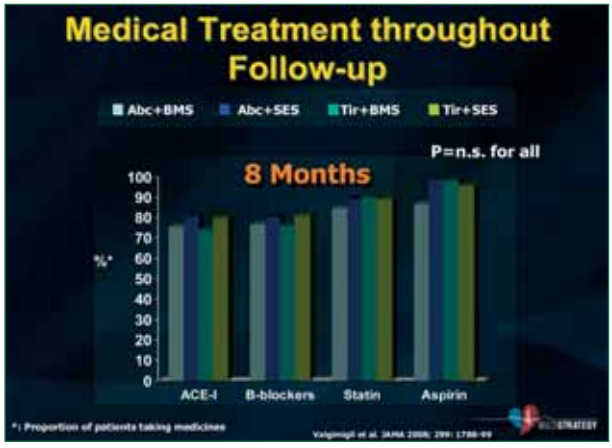
P<0.001 for non-inferiority at ITT and PP Analysis

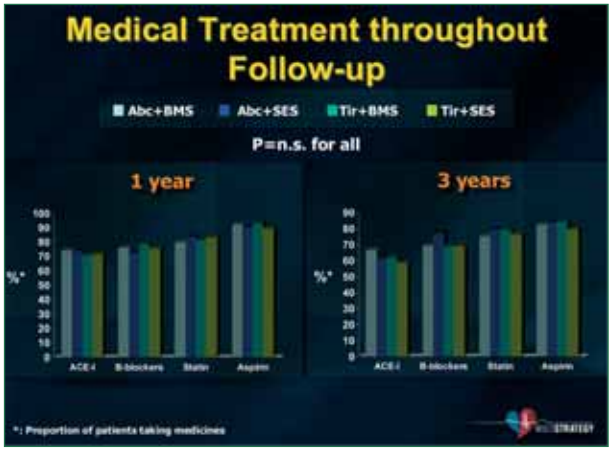


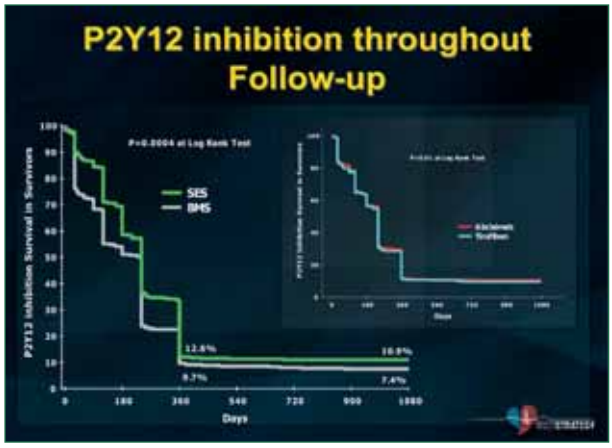
Valgimigli et al. JAMA 2008; 299: 1788-99


Primary Endpoint
8-month MACE
(CEC adjudicated)
Uncoated stent
14.5%
7.8%
Sirolimus-stent
P=0.0039 at Log-rank test
Primary End Pts
Days after Randomization


1030 Patients Assessed for Eligibility
72%
285 Excluded
745 Randomized
Abciximab and Uncoated Stent
Abciximab and Sirolimus-Stent
Tirofiban and Uncoated Stent
Tirofiban and Sirolimus-Stent
Complete 3-year F-up data available in 736 (99%) pts


Medical Treatment throughout Follow-up
Abc+BMS
Abc+SES
Tir+BMS
Tir+SES
P=n.s. for all
8 Months
%*
ACE-I
B-blockers
Statin
Aspirin
*: Proportion of patients taking medicines

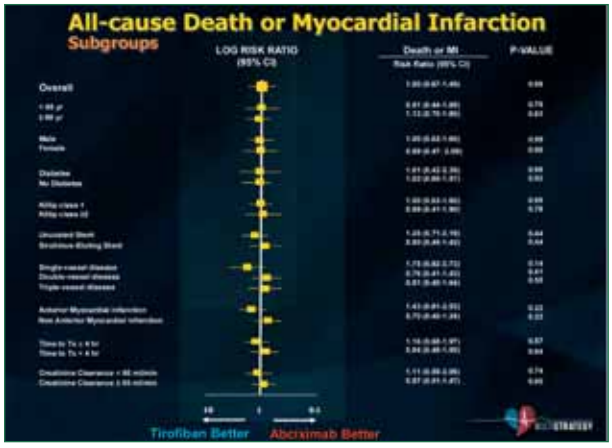

Medical Treatment throughout Follow-up
Abc+BMS
Abc+SES
Tir+BMS
Tir+SES
P=n.s. for all
1 year
3 years
%*
ACE-I
B-blockers
Statin
Aspirin
*: Proportion of patients taking medicines


P2Y12 inhibition throughout Follow-up
P=0.0004 at Log Rank Test
SES
BMS
P2Y12 inhibition Survival in Survivors
12.8%
10.9%
9.7%
7.4%
Days


3-year Outcomes
All-cause Death
Abciximab
Tirofiban
P=0.56
Probability of Death
7.8%
6.7%
Days

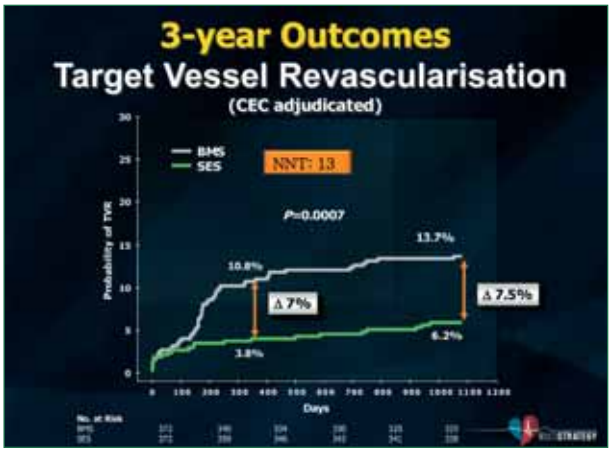

3-year Outcomes
CV-Death
(CEC adjudicated)
Abciximab
Tirofiban
p=0.33
Probability of CV Death
6.5%
4.8%
Days

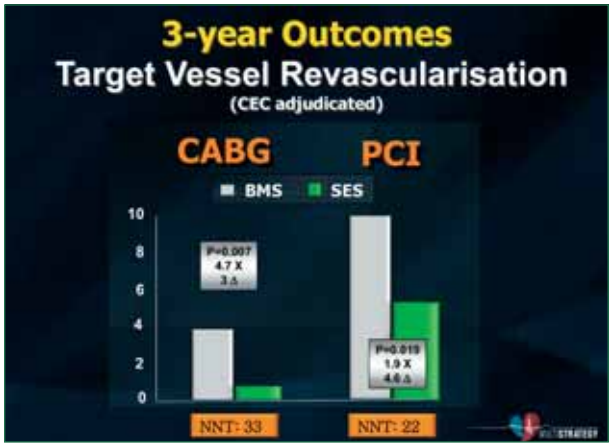

3-year Outcomes
All-cause Death or MI
(CEC adjudicated)
Abciximab
Tirofiban
Probability of Death or non fatal MI
12.8%
12.9%
P=0.99
Days


All-cause Death or Myocardial Infarction
Subgroups
LOG RISK RATIO (95% CI)
Death or MI
P-VALUE
Overall
Tirofiban Better
Abciximab Better


3-year Outcomes
All-cause Death
BMS
SES
P=0.79
7.5%
7.0%
Probability of Death
Days

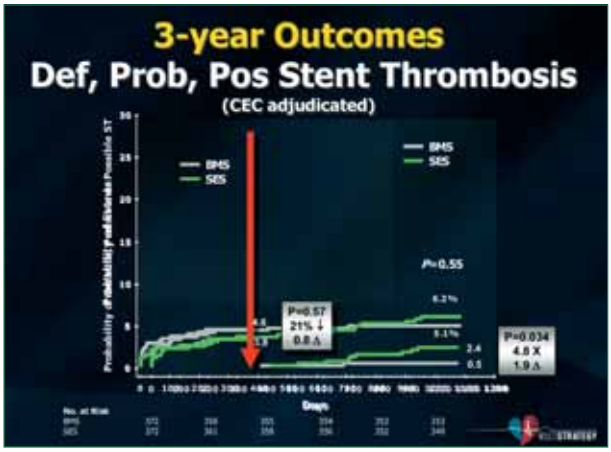

3-year Outcomes
All-cause Death or MI
(CEC adjudicated)
BMS
SES
P=0.83
13.3%
13.6%
Probability of Death or non fatal MI
Days


3-year Outcomes
Target Vessel Revascularisation
(CEC adjudicated)
BMS
SES
NNT: 13
P=0.0007
13.7%
10.8%
Δ 7%
Δ 7.5%
6.2%
3.8%
Probability of TVR
Days


3-year Outcomes
Target Vessel Revascularisation
(CEC adjudicated)
CABG
PCI
BMS
SES
P=0.007
4.7 X
3 Δ
P=0.019
1.9 X
4.6 Δ
NNT: 33
NNT: 22

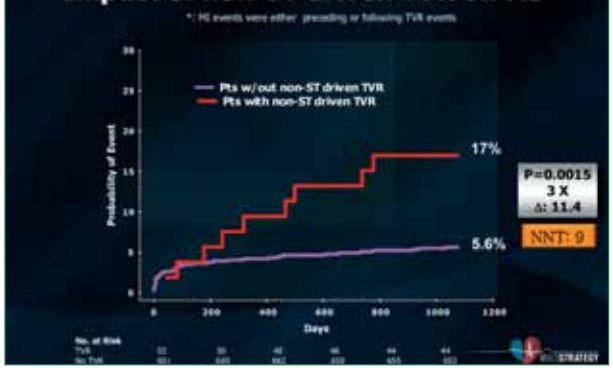

3-year Outcomes
Death-MI-TVR
(CEC adjudicated)
BMS
SES
22.3%
13.9%
P=0.026
Probability of MACE
Days


3-year Outcomes
Stent Thrombosis
(CEC adjudicated)
Definite
Probable
Possible
SES
3.5
4.0
6.2
P>0.99
P=0.71
P=0.55
BMS
3.5
4.6
5.1


3-year Outcomes
Def, Prob, Pos Stent Thrombosis
(CEC adjudicated)
BMS
SES
P=0.55
6.2%
5.1%
2.4
0.5
P=0.57
21% ↓
0.8 Δ
P=0.034
4.6 X
1.9 Δ
Days

3-year Outcomes

Impact of non-ST driven TVR on MI*



Summary

Our study provides evidence that in a broad population of largely unselected patients undergoing angioplasty for ST-elevation myocardial infarction followed-up for 3 years:

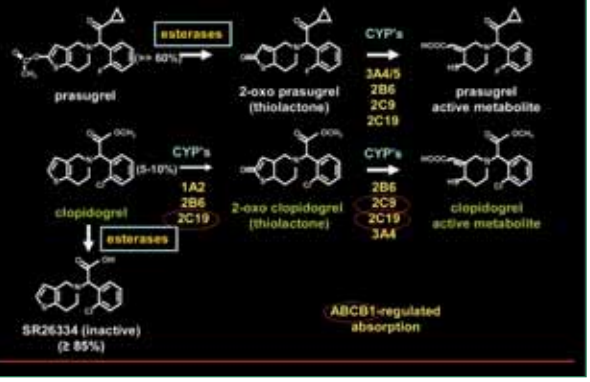
- Tirofiban is associated to similar long-term outcomes compared to abciximab
- Sirolimus-stent implantation displays sustained efficacy in reducing target vessel revascularization with no difference in death, repeat MI or overall stent thrombosis

Impact of CYP2C19 and ABCB1 single nucleotide polymorphisms (SNPs) on outcomes with ticagrelor and clopidogrel in acute coronary syndromes

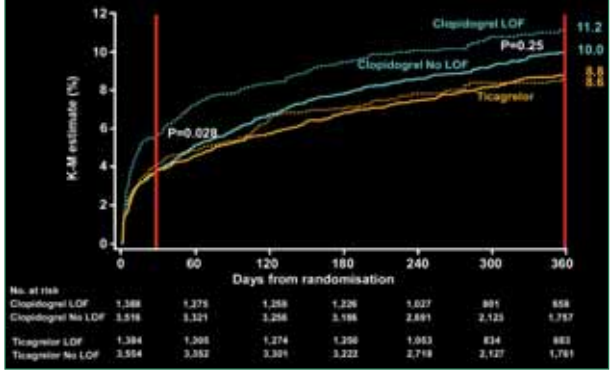
A PLATO genetic substudy

Discussant
Kurt Huber
3rd Med Dept, Cardiology & Emergency Medicine
Wilhelminenhospital, Vienna, Austria

Clopidogrel and prasugrel: formation of the active metabolite



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



Studies demonstrating influence of CYP 450 SNPs on clopidogrel metabolism and clinical outcome

Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Buttner HJ, Neumann F: Cytochrome P450 2C19 681G>A ploymorphism and high on clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol 2008;51:1925-1934.

Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS: Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-362.

Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, Siegbahn A, Walker JR, Wallentin L, Winters KJ, Close SL: Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744-1752.

Harmsze A, Van Werkum J, ten Berg J, Zwart B, Bouman H, Breet N, van 't Hoff A, Ruven H, Hackeng C, Klungel O, de Boer A, Deneer V: CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis - a case-control study. Eur Heart J 2010.

What is known, what is not known

CYP2C19 polymorphisms account for only approximately 12% of variability in clopidogrel platelet response
Shuldiner et al. JAMA 2009

The positive predictive value of CYP2C19 loss-of function polymorphisms for cardiovascular events in patients with ACS undergoing PCI is low, approximately 12% to 20%
Shuldiner et al. JAMA 2009, Mega et al. Circulation 2009

Retrospective analyses, meta-analyses

No prospective RCT combining genetic profiling with individual treatment

It is unknown, whether a specific genetic polymorphism is capable of influencing outcome for the individual patient

What are the consequences ?

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

Should we tailor clopidgrel treatment (dosage) or the use of other new ADP receptor blockers (prasugrel, ticagrelor) based on genetic profiling?
- studies are ongoing, but most of these trials investigate for pharmacodynamics (SPICE (2 trials), ACCEL-2C19, ACCELAMI2C19, ACCEL2C19, GeCCO, PAPI-2) and not for clinical outcome

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

Summary

Certain SNPs (CYP 2 C19) play a role for low-response to clopidogrel by influencing pharmacokinetics (metabolism), pharmacodynamics (platelet function testing) as well as clinical outcome

Genetic disorders explain only a part of „clopidogrel resistance"

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

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

PLATO

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

Lars Wallentin, Stefan James, Robert F Storey, Martin Armstrong, Bryan Barratt, Jay Horrow, Steen Husted, Hugo Katus, Gabriel Steg, Richard Becker for the PLATO investigators

Background: Genetic variability of $P2Y_{12}$ inhibitor response

PLATO

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

- CYP2C19 gene is polymorphic in populations, affecting enzyme activity
  - Caucasians: 72% EMs (WT/WT); 25% IMs (WT/LOF); ~2–3% PMs (LOF/LOF)
- Recent data indicate that CYP2C19 'LOF carriers' have more clinical events
- FDA warning about poor metabolisers of clopidogrel (March 2010)
- No known genetic regulation of ticagrelor PK/PD or response

PLATO study design

PLATO

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomized within 24 hours of index event
(N=18,624)

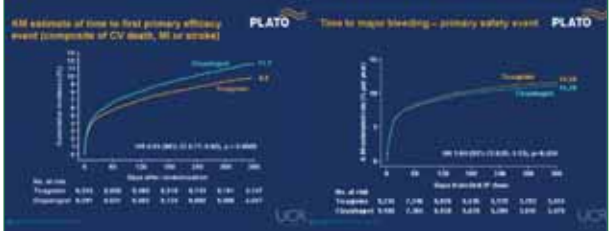
Clopidogrel	Ticagrelor
If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance; (additional 300 mg allowed pre PCI)	180 mg loading dose, then 90 mg bid maintenance; (additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + stroke
Primary safety endpoint: Total major bleeding

Background: Primary outcomes of the main PLATO trial

PLATO



Ticagrelor vs clopidogrel
- Less CV death, MI, stroke
- Less stent thrombosis

Ticagrelor vs clopidogrel
- Similar total major bleeding
- More non-CABG-related bleeding

Objectives of the genetic substudy

PLATO

- Primary
  - Investigate if CYP2C19 and/or ABCB1 polymorphisms influence primary efficacy outcome when comparing treatments with ticagrelor versus clopidogrel in PLATO
- Secondary
  - Explore the role of the CYP2C19 and ABCB1 polymorphisms regarding other efficacy and safety outcomes both between and within the ticagrelor and clopidogrel arms in PLATO

Methodology

PLATO

- Genetic analysis
  - 10,285 patients in the PLATO study provided samples for DNA analysis at randomization
  - Genotyping: 7 CYP2C19 LOF alleles and 1 GOF allele; ABCB1 SNP
  - ~95,000 genotypes (2 weeks)
- Statistical analysis
  - Data-guided decision as to appropriate genotype groupings within each arm for each outcome
  - Assessment of impact of genotype on outcomes for each drug
  - Application of these and literature precedent (any versus no LOF allele) groupings to between-arms analysis
  - Compare outcomes between ticagrelor and clopidogrel groups

Selected baseline characteristics

PLATO

Characteristic	Ticagrelor n=5,137	Clopidogrel n=5,148
Age, mean (SD)	62.5 (11)	62.5 (11)
Age ≥75 years	769 (15%)	839 (16%)
Female	1,577 (31%)	1,577 (31%)
Caucasian	5,057 (98%)	5,058 (98%)
Weight, mean kg (SD)	81.9 (15)	81.8 (16)
Body mass index ≥30 kg/m²	1,560 (30%)	1,520 (30%)
Habitual smoker	1,796 (35%)	1,829 (36%)
Diabetes mellitus	1,177 (23%)	1,189 (23%)
PPI use (at randomization)	2,154 (42%)	2,083 (40%)
Statin use (at randomization)	4,079 (79%)	4,059 (79%)
Aspirin use (at randomization)	4,962 (97%)	4,946 (96%)
Open-label clopidogrel	2467 (48%)	2,488 (48%)
Planned invasive treatment	3,403 (66%)	3,379 (66%)
Troponin positive	4,149 (81%)	4,199 (82%)

Predicted CYP2C19 phenotype and genotype by treatment

PLATO

	Ticagrelor n=5,137 (%)	Clopidogrel n=5,148 (%)
CYP2C19 predicted phenotype, n (%)		
Extensive metaboliser (*1/*1)	1,849 (36%)	1,862 (36%)
Intermediate metaboliser (*2/*2–*8)	894 (17%)	935 (18%)
Poor metaboliser (*2–*8/*2–*8)	121 (2%)	125 (2%)
Poor/rapid het metaboliser (*2–*8/*17)	369 (7%)	328 (6%)
Rapid het metaboliser (*1/*17)	1,437 (28%)	1,386 (27%)
Ultra rapid metaboliser (*17/*17)	268 (5%)	268 (5%)
CYP2C19 LOF category, n (%)		
No LOF	3,554 (72%)	3,516 (72%)
Any LOF	1,384 (28%)	1,388 (28%)

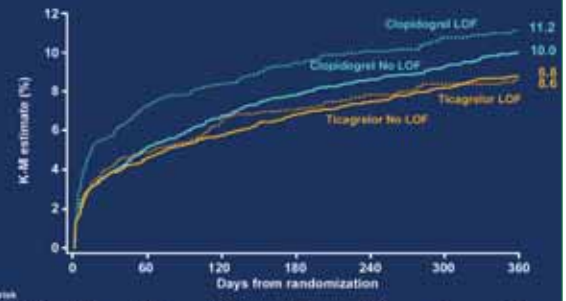
ABCB1 genotype by treatment

PLATO

ABCB1 predicted phenotype	Ticagrelor n=5,137 (%)	Clopidogrel n=5,148 (%)
High expression (C/C)	1,167 (22.7%)	1,195 (23.2%)
Intermediate expression (C/T)	2,570 (50.0%)	2,518 (48.9%)
Low expression (T/T)	1,349 (26.3%)	1,386 (26.9%)

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

PLATO



No. at risk							
Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	891	458
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757
Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	483
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

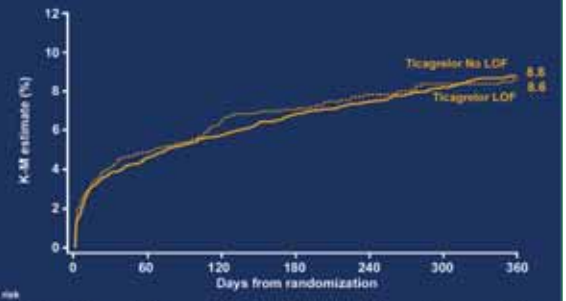
Efficacy outcomes in relation to CYP2C19 genetics

PLATO

Type of event	Ticagrelor Events (n)	Ticagrelor K-M %	Clopidogrel Events (n)	Clopidogrel K-M %	HR (95% CI)	Interaction p value
CV death + MI + stroke						
Any CYP2C19 LOF	115	8.6	149	11.2	0.77 (0.60, 0.99)	0.40
No CYP2C19 LOF	296	8.8	332	10.0	0.86 (0.74, 1.01)	
CV death + MI						
Any CYP2C19 LOF	102	7.7	138	10.4	0.73 (0.57, 0.93)	0.30
No CYP2C19 LOF	273	8.0	305	9.2	0.86 (0.73, 1.01)	
Definite stent thrombosis						
Any CYP2C19 LOF	15	1.6	21	2.3	0.71 (0.36, 1.37)	
No CYP2C19 LOF	22	1.0	35	1.5	0.62 (0.36, 1.05)	

Primary endpoint in the ticagrelor group in relation to any CYP2C19 LOF allele (K-M estimate)

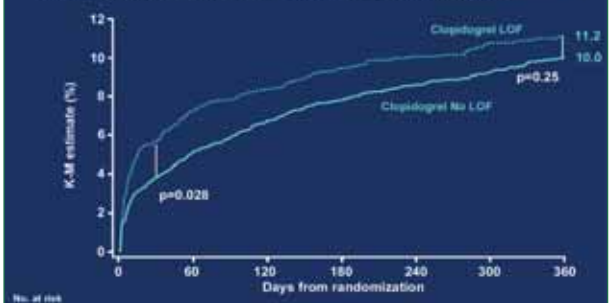
PLATO



No. at risk							
Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	483
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

Primary endpoint in the clopidogrel group in relation to any CYP2C19 LOF allele (K-M estimate)

PLATO

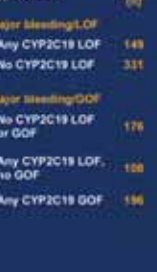


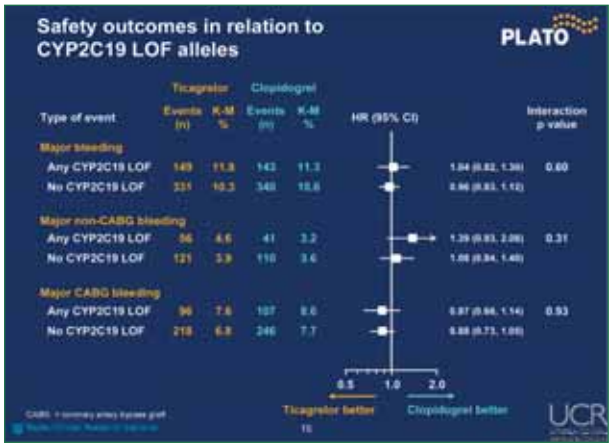
No. at risk							
Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	891	458
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757

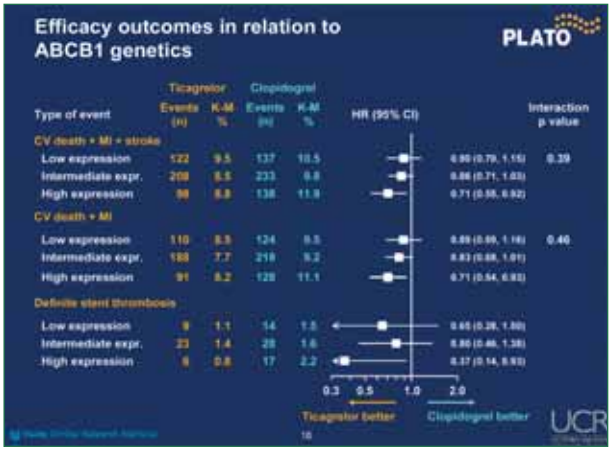
Safety outcomes in relation to CYP2C19 GOF allele

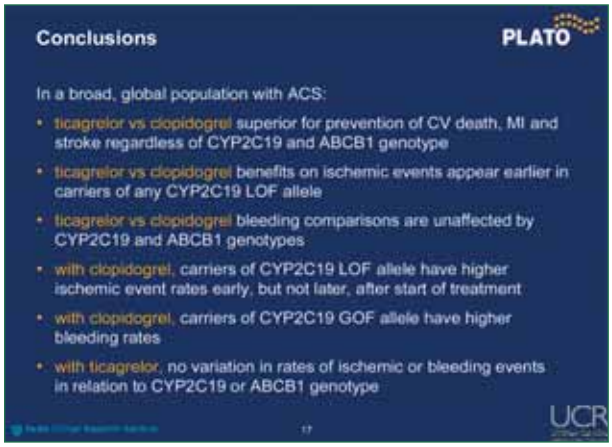
PLATO

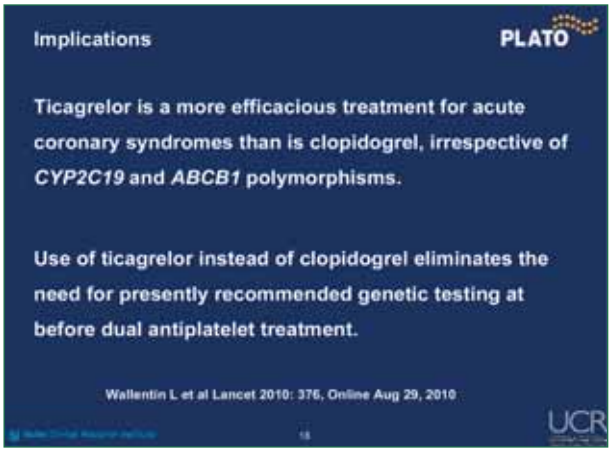
Type of event	Ticagrelor Events (n)	Ticagrelor K-M %	Clopidogrel Events (n)	Clopidogrel K-M %	HR (95% CI)	Interaction p value
Major bleeding/LOF						
Any CYP2C19 LOF	149	11.8	143	11.3	1.04 (0.82, 1.30)	0.60
No CYP2C19 LOF	331	10.3	340	10.6	0.96 (0.83, 1.12)	
Major bleeding/GOF						
No CYP2C19 LOF or GOF	176	10.5	161	9.5	1.12 (0.90, 1.38)	0.19
Any CYP2C19 LOF, no GOF	108	11.8	108	11.1	1.03 (0.79, 1.34)	
Any CYP2C19 GOF	156	10.5	214	11.9	0.86 (0.71, 1.05)	











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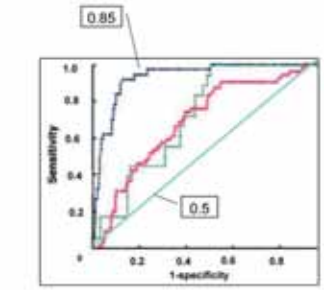
Development of a Risk Score for TAVI

Gerhard Schuler
Herzzentrum Leipzig

C-Statistics

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

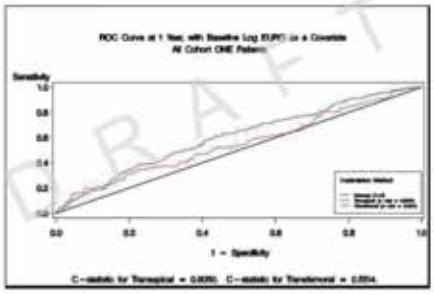
C-Statistic



C-Statistics

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

1-year Mortality by EuroSCORE



Multivariate Analysis (TF)

Analysis of Maximum Likelihood Estimates

Parameter	P-Value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
NYHA Class IV	0.0067	1.948	1.203	3.153
Renal insufficiency / failure	<0.0001	2.382	1.553	3.656
Hyperlipidemia / cholesterolemia	0.0293	0.602	0.382	0.950
Systemic Hypertension	0.0317	0.622	0.403	0.959
Smoking	0.0009	2.268	1.399	3.677
Mitral valvuloplasty	0.0040	8.237	1.956	34.690
Coagulopathy	0.0073	5.178	1.558	17.208

C Statistic = 0.6852

Frailty

- Slowness / Weakness
- Poor endurance / exhaustion
- Reduced physical activity
- unintentional weight loss

Fried Frailty Index

- Weight loss
- Grip strength
- Exhaustion
- Walk time, 15 feet
- Low activity

- >10 lb in last year
- Lowest 20% by gender/BMI
- Self-report
- Lowest 20% by gender/height
- Males <383 kcal/week
- Females <270 kcal/week

Frailty: ≥ 3 criteria

Fried LP, et al. J Gerontol A Biol Sci Med Sci 2001;56:M146-M157

Columbia Frailty Index

• Serum albumin	• >10 lb in last year
• Modified Physical Performance Test	• Standing static balance • Chair rise • Lift a book • Jacket on and off • Pick up a penny • Turn 360° • 50 ft walk test
• Grip strength	• Dynamometer
• Katz Index of Activities	0/1

Conflict of Interest
Olaf Wendler

Has received speaker and/or advisory board fees from:

Edwards Lifesciences

Medtronic

St Jude Medical

Has received unrestricted research grants from:

Edwards Lifesciences

Development of a Risk Score for Transcatheter Aortic Valve Implantation:
1-year Outcomes from over 1,000 Patients in the SOURCE Registry

Olaf Wendler, Gerhard Schymik, Thomas Walther, Dominique Himbert, Thierry Lefèvre, Hendrik Treede, Holger Eggebrecht, Paolo Rubino, Iassen Michev, Martyn Thomas
on behalf of the SOURCE investigators

Background

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

SOURCE Registry – Cohort I (11/07 – 01/09)

34 Centres Initially Participating in Commercial Launch
1123 patients

Excluded
2 Centres / 85 patients
- Unable to obtain Ethics approval
- Unable to secure administrative support
- One missing patient due to admin. error

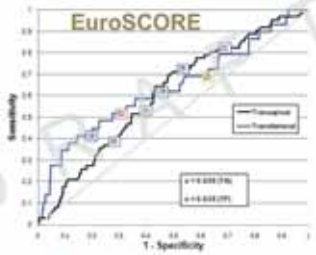
Included
32 centres
1038 patients

The SOURCE Registry has:
- 100% procedure data
- 99.9% 30 day data
- 98% 1-year follow-up
- All consecutively enrolled

Demographic Data

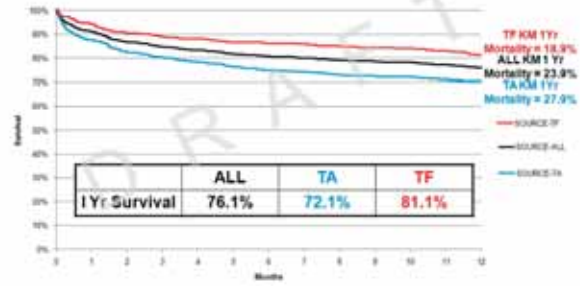
	TF (n=463)	TA (n=575)	P-Value
Age (yrs)	81.7	80.7	0.022
Female	55.1%	55.8%	NS
Pulmonary Disease	24.6%	29.9%	NS
Renal Dysfunction	25.5%	32.5%	0.016
Logistic EuroSCORE	25.8	29.0	0.007
Peripheral Vascular Disease	10.6%	20.0%	<0.001
Carotid Artery Stenosis (>50%)	7.1%	17.2%	<0.001
Incidence of CAD	47.5%	55.1%	0.020
Porcelain Aorta	4.5%	11.3%	0.001
Prior CABG	17.5%	27.0%	0.003
Mitral valve disease	15.8%	32.0%	<0.001

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



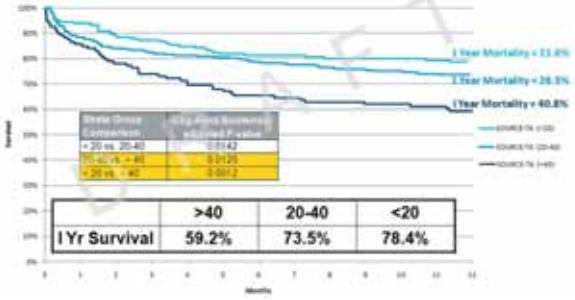
Circulation (2010; 122:62-69)

1- Year Survival (Kaplan-Meier)



	ALL	TA	TF
I Yr Survival	76.1%	72.1%	81.1%

TA – Survival 1-year (EuroSCORE)



	>40	20-40	<20
I Yr Survival	59.2%	73.5%	78.4%

TF – Survival 1-year (EuroSCORE)

	>40	20-40	<20
I Yr Survival	72.5%	83.5%	80.9%

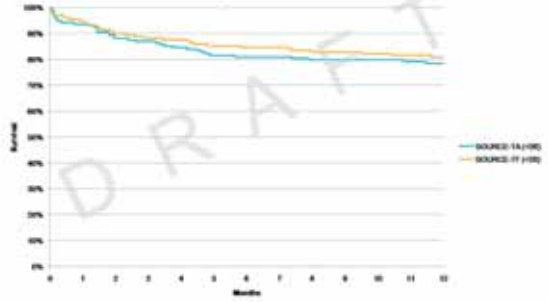
TF – TAVI: ES <20 vs 20-40

Baseline Demographics and Risk Factors

	TF: ES <20 (n=170)	TF: ES 20–40 (n=225)	P-Value
Age (Years)	79.8	82.7	<0.0001
Female	23.5%	32.4%	NS
NYHA Class III or IV	**29.4%**	**45.3%**	**0.0139**
Coronary Artery Disease	**17.2%**	**28.6%**	**0.0415**
Cardiomyopathy	**0.0%**	**1.8%**	**0.0211**
Congestive Heart Failure	**9.1%**	**20.3%**	**0.0018**
Carotid Artery Stenosis (over 50%)	**1.3%**	**5.8%**	**0.0051**
Porcelain Aorta	**2.8%**	**1.3%**	**0.0408**
Renal Insufficiency/Failure	**7.1%**	**15.2%**	**0.0199**
CABG	**3.8%**	**11.7%**	**0.0018**

TA vs TF in Patients with ES <20

1- year Survival



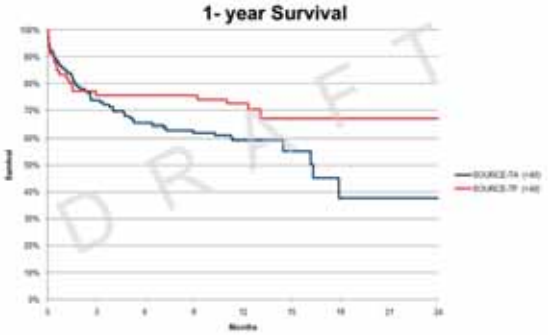
TA vs TF in Patients with ES <20

Baseline Demographics and Risk Factors

	TA: ES <20 (n=170)	TF: ES <20 (n=170)	P-Value
Age (Years)	79.4	79.8	NS
Female	58.2%	54.7%	NS
Smoking	**30.6%**	**20.0%**	**0.0334**
Myocardial Infarction	**17.1%**	**8.2%**	**0.0214**
Carotid Artery Stenosis (over 50%)	**11.2%**	**2.9%**	**0.0049**
Porcelain Aorta	**15.9%**	**6.5%**	**0.0091**
Mitral Valve Disease	**25.9%**	**14.1%**	**0.0096**
Peripheral Vascular Disease (non carotid)	**19.4%**	**9.4%**	**0.0128**
CABG	**16.5%**	**8.8%**	**0.0492**

TA vs TF in Patients with ES >40

1- year Survival



TA vs TF in Patients with ES >40

Baseline Demographics and Risk Factors

	TA: ES >40 (n=119)	TF: ES >40 (n=66)	P-Value
Age (Years)	82.0±6.3	83.1±5.3	NS
Female	42.9%	48.5%	NS
Peripheral Vascular Disease	**44.5%**	**13.6%**	**<0.0001**
Diabetes	**19.7%**	**34.5%**	**0.0427**
Carotid Artery Stenosis	**28.6%**	**7.6%**	**0.0006**
Mitral Valve Disease	**42.9%**	**22.7%**	**0.0066**
Tricuspid Valve Disease	**34.5%**	**12.1%**	**0.0009**
Pulmonary Disease	**44.5%**	**29.0%**	**0.0412**
CABG	**51.3%**	**30.3%**	**0.0083**
Prior Pacemaker	**20.2%**	**6.1%**	**0.0101**
CHF	**24.4%**	**44.0%**	**0.0080**

Multivariate Analysis (TA)

Analysis of Maximum Likelihood Estimates				
Parameter	P-Value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Scaled Log EuroSCORE (%/10)	<0.0001	1.200	1.098	1.311
Renal insufficiency / failure	0.0047	1.592	1.154	2.197
Carotid artery sten. (>50%)	0.0014	0.454	0.280	0.737
Liver disease	0.0005	3.154	1.646	6.043
Other	0.0345	1.489	1.029	2.153

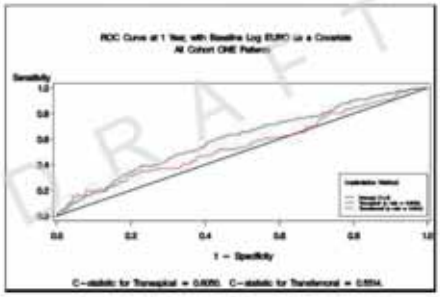
C Statistic = 0.6538

Multivariate Analysis (TF)

Analysis of Maximum Likelihood Estimates				
Parameter	P-Value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
NYHA Class IV	0.0067	1.948	1.203	3.153
Renal insufficiency / failure	<0.0001	2.382	1.553	3.656
Hyperlipidemia / cholesterolemia	0.0293	0.602	0.382	0.950
Systemic Hypertension	0.0317	0.622	0.403	0.959
Smoking	0.0009	2.268	1.399	3.677
Mitral valvuloplasty	0.0040	8.237	1.956	34.690
Coagulopathy	0.0073	5.178	1.558	17.208

C Statistic = 0.6852

1-year Mortality by EuroSCORE



Causes of Death

Other * = Arrhythmia, cardiac arrest
Pulmonary** = Respiratory Failure, Pulmonary Embolism and Pneumonia
Other*** = Sepsis, vascular access related, major bleeding, infection, suicide, and multiple organ failure

Challenges – TAVI Risk Score

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

The EuroSCORE as an Example

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

(Roques et al. Eur J Cardio-Thorac Surg 1999)

Conclusions

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

* Leontyev, S., et al., *Aortic valve replacement in octogenarians: utility of risk stratification with EuroSCORE.* Ann Thorac Surg, 2009. **87(5): p. 1440-5.**

Future Options to Develop a Risk Score

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

"Strong commitment from participating centres!"

ACS in Africa, Middle East, and Latin America
The ACCESS Registry

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

Conflict of interest:

- I will not discuss off label use and/or investigational use in my presentation
- Consultant for: Boeringher, Lilly, Menarini, Servier
- Research support from: Bayer, BMS, Boeringher, GKS, Medtronic, Lilly, Menarini, Roche, Sanophy-Aventis, Servier

ACCESS Registry

Registry of Acute Coronary Syndromes

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

ACCESS Registry

Demographics and Risk Factors

	ACCESS
Women	26%
Age ≥ 70y	21%
Smokers	40%
Overweight	43%
Previous MI	22%
Previous Stroke	4%
Dyslipemia	42%
Hypertension	57%
Diabetes	**36%**
PCI / CABG	18%

ACCESS Registry

Treatments (hospital)

	ACCESS	EHS, GRACE, BERLIN, RISK-HIA, MASCARA, other
ASA	93%	94% - 95%
Statin	90%	85% - 90%
Betablocker	78%	70% - 90%
Thyenopiridine (H disch)	81%	70% - 85%
ACE-i	68%	65-80% - >90% if LVEF < 40
STEMI		
Primary PCI	**26%**	65% - 90%
Thrombolysis	39%	< 20%
No reperfusion treatment	**60%**	< 30%

ACCESS Registry

Outcomes

	ACCESS 1 year	EHS, GRACE, Berlin, RISK-HIA, MASCARA, other Before Hospital discharge
Mortality	7,3%	4% - 6,6%
Stroke	2%	1% - 2%
M Infarction	3%	3% - 5%
MACE	11%	10% - 14%
MACE+ Re-hospital.	17%	Re-hospitalization may be > 15%

ACCESS Registry

Limitations

- Selection of sites / patients?
- Diagnostic criteria less restrictive
- Quality controls?
- Follow-up reliable?

ACCESS Registry

Conclusions

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

Acute coronary syndromes (ACS) in Africa, Middle East, and Latin America: The ACCESS registry

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

Funding & disclosures

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

ACCESS: background

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

Study aim

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

ACCESS: study design

- Prospective, observational, multinational registry in patients hospitalized for an ACS (Jan 2007- Jan 2008).
- Patients enrolled at 134 sites in 19 countries in
  - Latin America: Argentina, Brazil, Colombia, Dominican Republic, Ecuador, Guatemala, Mexico, Venezuela
  - Middle East: Egypt, Iran, Jordan, Kuwait, Lebanon, Saudi Arabia, United Arab Emirates
  - North Africa: Algeria, Morocco, Tunisia
  - South Africa

ACCESS: study population

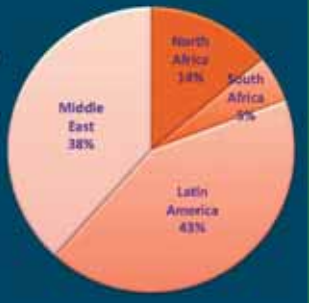
- Patients (age ≥21 years) admitted alive to hospital with:
  - ischaemic symptoms of ACS within 24 hours of presentation, and
  - At least 1 of the following:
    - ECG changes: transient ST↑ or ST↓ ≥1 mm, new T-wave inversion ≥1 mm, pseudonormalization of previously inverted T waves, new Q-waves, new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

ACCESS: endpoints 12-months from hospitalization

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

ACCESS: results

- 9732 ACS patients with 1-year follow-up
- Discharge diagnoses:
  - STEMI 45%
  - NSTE ACS 52%
    - NSTEMI 24%
    - Unstable angina 28%



ACCESS: baseline characteristics

	Overall ACS (n=12,068)	NSTE ACS (n=6320)	STEMI (n=5411)
Men, n (%)	74	67	81
Age ≥70 years	21	24	18
Medical history, n (%)			
Angina	45	58	31
Myocardial infarction	22	26	18
CHF	5.5	6.8	3.9
Family history of CVD	32	34	29
PAD	4.6	5.5	3.5
PCI	13	17	7.1
CABG	5.1	8.4	1.3
TIA/stroke	4.2	4.7	3.6
Bleeding	1.4	1.4	1.5

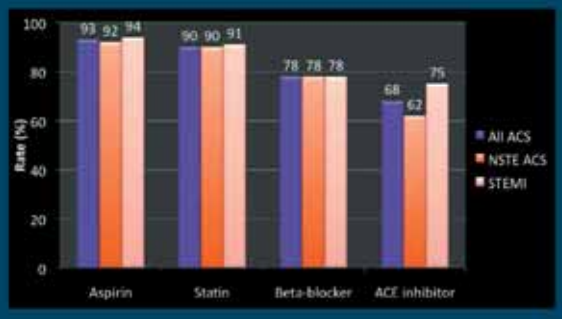
ACCESS: risk factors

	Overall ACS (n=12,068)	NSTE ACS (n=6320)	STEMI (n=5411)
Diabetes	36	38	33
Hypertension	57	65	47
Treated	84	87	78
Dyslipidemia	42	49	33
Treated	59	65	50
Overweight (BMI, 25–<30 kg/m²)	43	43	44
Class I obesity (BMI, 30–<35 kg/m²)	21	22	20
Class II obesity (BMI, ≥35 kg/m²)	7.4	8.5	6.1
Abdominal obesity	77	79	74
Current smoker	41	34	49
Alcohol misuse	3.4	2.8	4.1

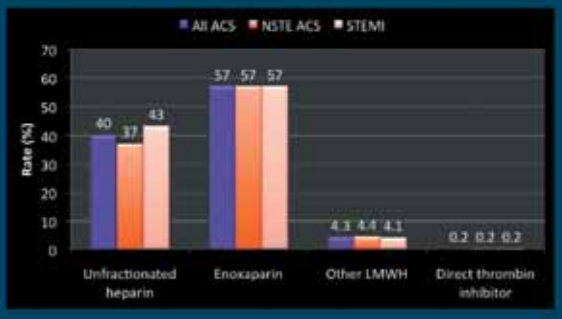
ACCESS: laboratory data

	Overall ACS (n=12,068)	NSTE ACS (n=6320)	STEMI (n=5411)
Serum creatinine (umol/L)	88 [77, 108]	88 [76, 108]	88 [79, 108]
Total cholesterol (mmol/L)	5.0 [4.1, 5.9]	4.9 [4.1, 5.9]	5.0 [4.2, 5.9]
Low-density lipoprotein (mmol/L)	3.1 [2.3, 3.8]	3.1 [2.3, 3.8]	3.0 [2.4, 3.8]
Haemoglobin (mmol/L)	8.7 [7.4, 9.3]	8.5 [7.4, 9.3]	8.7 [8.1, 9.6]
Left-ventricular ejection fraction (%)	52 [44, 60]	55 [45, 61]	50 [40, 57]
At least 1 elevated cardiac biomarker	6177 (53)	NSTEMI: 1851 (83) UA: 830 (25)	3496 (65)

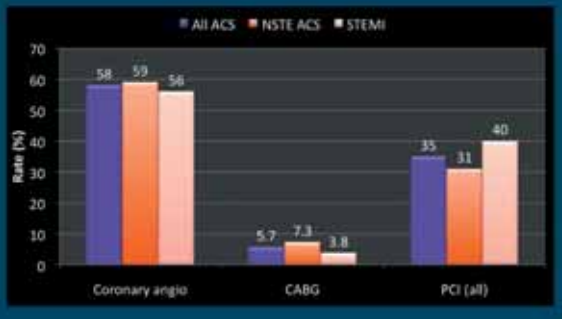
ACCESS: in-hospital medications



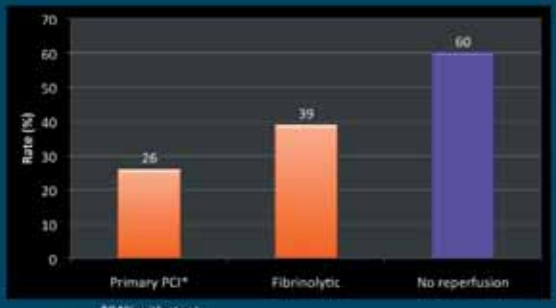
ACCESS: in-hospital antithrombotic therapy



ACCESS: in-hospital interventions



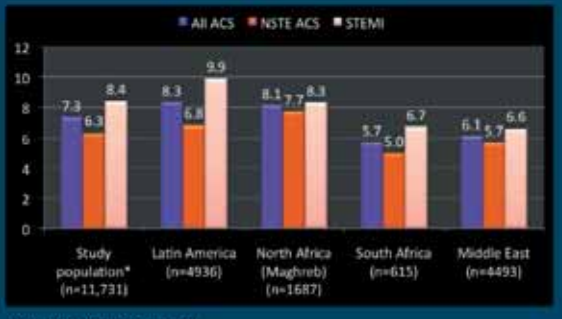
ACCESS: reperfusion in STEMI



*94% with stent;
39% with drug-eluting stent

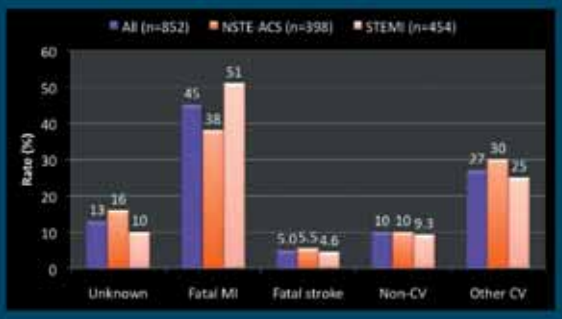
ACCESS: medications at discharge

ACCESS: death at 12 months

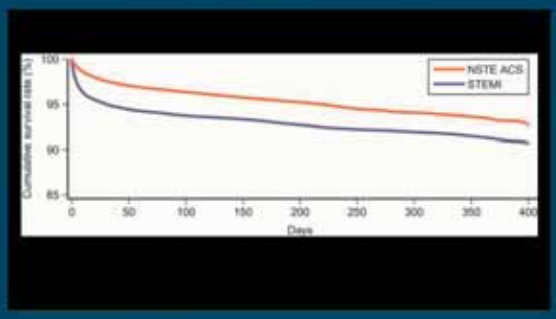


*P<0.05 for NSTE ACS vs STEMI

ACCESS: cause of death

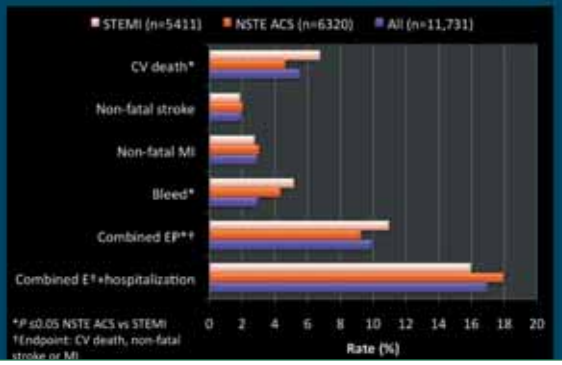


ACCESS: Survival curves



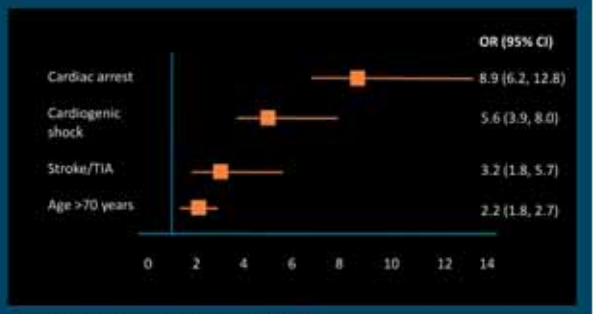
NSTE ACS vs STEMI *P* <0.0001

ACCESS: 12-month events



*P ≤0.05 NSTE ACS vs STEMI
†Endpoint: CV death, non-fatal stroke or MI

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



*Four strongest independent factors among 17

ACCESS: conclusions

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

Acknowledgements

Special acknowledgments to all doctors who participated in the ACESS registry from allover the World.

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

COPPS Trial
Massimo Imazio, MD
Torino, Italy

Discussant
Andre Keren, MD
Hadassah University Hospital, Jerusalem, Israel

1

Background

- **Post-Pericardiotomy Syndrome (PPS) is a relatively common complication of cadiac surgery**
- **Colchicine is recommended for treatment of acute (class IIA) and of recurrent pericarditis (class I)[1]**
- **A prospective randomized preliminary trial for *primary prevention* of PPS using Colchicine showed an encouraging trend toward significance[2]**

[1] Maisch B et al. Eur Heart J 2004;25:587; [2] Finkelstein Y et al. Herz 2002;27:791

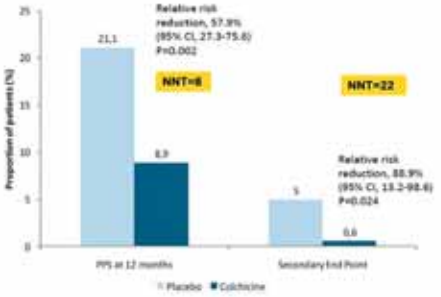
2

Main Results

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

3

Main Results



4

Main Results

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

5

Importance of the Study

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

6

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

COlchicine for the Prevention of the Post-Pericardiotomy Syndrome. The COPPS trial:

A multicenter, randomized, double-blind, placebo-controlled trial

Presenter: Massimo Imazio, MD, FESC
On behalf of the COPPS Investigators

Cardiology Dpt. Maria Vittoria Hospital, Torino, Italy

Funding

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

Background

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

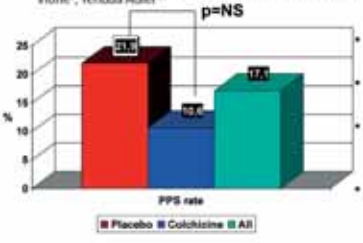
Finkelstein Y, Adler Y et al. Herz. 2002;27:791-4

Herz Original Article

Herz. 2002;27:791-4

Colchicine for the Prevention of Postpericardiotomy Syndrome

Yaron Finkelstein[1], Joseph Shemesh[2], Kerem Mahlab[2], Dan Abramov[2], Yaron Bar-El[2], Alex Sagie[2], Erez Sharoni[2], Gideon Sahar[3], Aram Kurt Smolinsky[4], Taly Schechter[1], Bernard A. Vidne[1], Yehuda Adler[1]



- Prospective, double-blind design.
- 163 patients; colchicine 1.5mg/day for 1 month
- 52/163 (31%) excluded (complications, intolerance, non-compliance)
- PPS at 3 months (placebo vs. colchicine: 14/64 vs.5/47; p= NS)

Methods

Research trial protocol

FIC

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

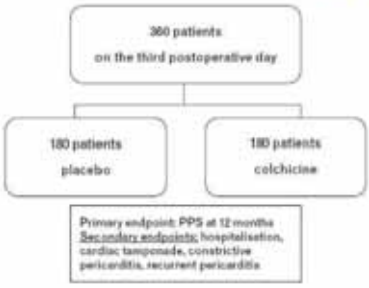
Massimo Imazio, Enrico Cecchi, Brunella Demichelis, Alessandra Chinaglia, Luisella Coda, Aldo Ghisio, Daniela Demarie, Salvatore Ierna and Rita Trinchero, on behalf of the COPPS Investigators

Rationale Colchicine seems to be well tolerated and effective in the treatment and prevention of pericarditis. A preliminary clinical trial has shown that colchicine may be considered not only for the treatment of postpericardiotomy syndrome (PPS), but also for its primary prevention.

Implications The COPPS trial will evaluate the use of colchicine for the primary prevention of PPS. This study will also provide important information on the frequency, clinical presentation, and prognosis of this syndrome in clinical practice. *J Cardiovasc Med* 8:1044–1048 © 2007 Italian Federation of Cardiology.

Imazio M, Trinchero R. et al. JCM 2007;8:1044-8

Trial design



Study Hypothesis: PPS rate of 22.0% and 11.0% between the two treatment arms (placebo and colchicine) with a power of 80% using a 2-sided p=0.05 level test. Analyses were performed by intention to treat.

Colchicine/Placebo: 1.0 mg BID for 1 day then 0.5mg BID for 1 month (Pts >= 70Kg)
0.5 mg BID for 1 day then 0.5mg for 1 month (Pts<70Kg)

Inclusion/Exclusion Criteria

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

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

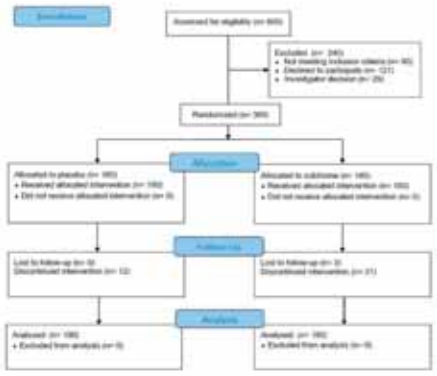
Diagnostic criteria for the PPS

Fever lasting beyond the first postoperative week without evidence of systemic or focal infection
Pleuritic chest pain
Friction rub
Pleural effusion
New or worsening pericardial effusion

The diagnosis will be based on the presence of at least two criteria.

Finkelstein Y, Adler Y et al. Herz. 2002;27:791-4
Imazio M, Trinchero R. et al. JCM 2007;8:1044-8

CONSORT 2010 Flow Diagram of the COPPS trial



Results (I): Baseline data

Characteristic	Placebo (N=180)	Colchicine (N=180)	P
Cardiac surgery type (%)			
CABG	77 (42.8%)	92 (51.1%)	0.141
Valvular surgery	55 (30.6%)	51 (28.3%)	0.717
Aorta surgery	8 (4.4%)	4 (2.2%)	0.382
Combined surgery	37 (20.6%)	30 (16.7%)	0.415
Other	3 (1.6%)	3 (1.9%)	0.674

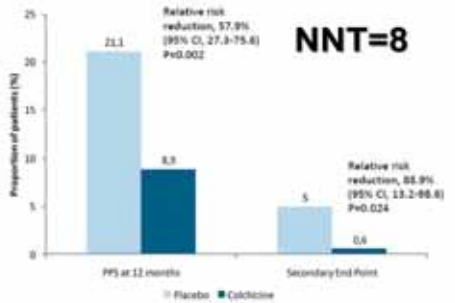
CABG= Coronary Artery By-Pass Grafting.

Results (II): Study end points

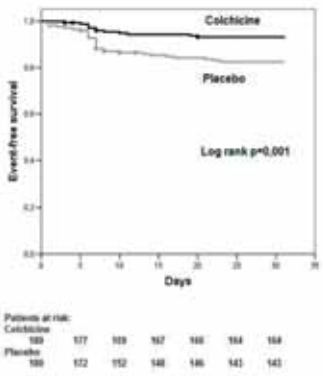
Event	Placebo (N=180)	Colchicine (N=180)	P
Primary end point: PPS at 12 months (%)	38 (21.1%)	16 (8.9%)	0.002
Fever beyond 1st postoperative week*	7 (3.9%)	6 (3.3%)	0.982
Pleuritic chest pain	23 (12.8%)	7 (3.9%)	0.004
Friction rub	15 (8.3%)	5 (2.7%)	0.036
Pleural Effusion	46 (25.6%)	22 (12.2%)	0.002
New or worsening pericardial effusion	41 (22.8%)	23 (12.8%)	0.019
Mean follow-up (months)	18.5	20.2	0.252

submitted

COPPS trial: Main results



submitted



PPS event-free survival

Safety: Side effects and drug withdrawal

Event	Placebo (N=180)	Colchicine (N=180)	p
Side effects (%):	9 (5.0%)	16 (8.9%)	0.212
Severe side effects	0 (0.0%)	0 (0.0%)	
Other side effects	9 (5.0%)	16 (8.9%)	0.212
Gastrointestinal	8 (4.4%)	16 (8.9%)	0.133
Alopecia	0 (0.0%)	0 (0.0%)	
Anorexia	0 (0.0%)	0 (0.0%)	
Hepatoxicity	0 (0.0%)	0 (0.0%)	
Myotoxicity	1 (0.6%)	0 (0.0%)	0.039
Bone marrow toxicity	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	0 (0.0%)	
Drug withdrawal (%):			
Overall	12 (6.7%)	21 (11.7%)	0.145
Related to side effects	9 (5.0%)	16 (8.9%)	0.212
Patient or Medical decision	3 (1.7%)	5 (2.8%)	0.728

Conclusions

- Colchicine is safe and efficacious in the primary prevention of the PPS and its related complications.
- In the COPPS trial colchicine halves the risk of the PPS (colchicine vs. placebo= 9% vs. 21%, p=0.002; NNT= 8) following cardiac surgery.

COPPS Steering Commitee, Recruiting centres and investigators

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).

COPPS recruiting centres and investigators:

Cardiology Dpt, Maria Vittoria Hospital, Torino, Italy (Coordinating Centre; investigators: M.Imazio, A. Chinaglia, B. Demichelis, D. Forno, S. Ierna),

Ospedali Riuniti, Bergamo, Italy (investigators: A. Brucato, S. Maestroni, C. Simon, D. Cumetti, P. Ferrazzi),

Cardiac Surgery, Ospedale Mauriziano, Torino, Italy (investigators: M.E. Rovere, E. Zingarelli, F. Sansone),

Ospedale Niguarda, Milano, Italy (investigators: A. Gandino, A. Barosi, D. Patrini, E. Vitali),

Department of Cardiology, San Maurizio Regional Hospital, Bolzano, Italy (R. Cemin),

Ospedale degli Infermi, Rivoli, Italy (S. Ferrua, M.R. Conte).

Euro Heart Survey 3

Nicolas DANCHIN, MD, FESC
Hôpital Européen Georges Pompidou, Paris France

Disclosures

- Research grants: Astra-Zeneca, Merck, Novartis, Pfizer, sanofi-aventis, Servier, The MedCo
- Fees for giving lectures and/or consulting:

  Astra-Zeneca, BMS, Boehringer-Ingelheim, GSK, Lilly, Menarini, MSD-Schering, Novartis, Novo, Pfizer, sanofi-aventis, Servier, The MedCo

EHS ACS 3: an optimistic message

- Over a 2-year period of time:
  - Improved rate of reperfusion, with increased use of primary PCI:
    77% to 81% *(52% to 64%)*
  - Improved time delays to reperfusion
    20 to 15 min (lysis)
    60 to 45 min (pPCI)
  - Decreased in-hospital mortality:
    8.1% to 6.6%

Strengths of EHS ACS 3

- Participation of 138 motivated centres, in 21 countries, including patients according to a similar methodology during 2 years, making temporal comparisons possible.
- Large population (≈ 8,000 patients)
- Use of the CARDS data set: common definition of key clinical data.
- Detailed and prudent analysis of the data.

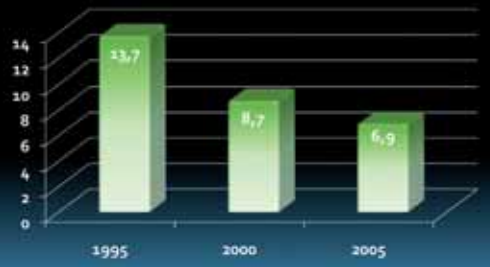
Limitations of EHS ACS 3

- Limited representativeness: these results should not let us think that the battle is over.
- EHS Snapshot 2009: 485 centres in 47 countries:
  - Lower rate of reperfusion 70% vs 81%
  - Median time to reperfusion much longer:
    - ECG to pPCI: 115 min vs 45 min
    - ECG to lysis: 50 min vs 15 min
  - Higher in-hospital mortality for STEMI: 8.5% vs 6.6%, with inequalities across regions (3% to 10%)

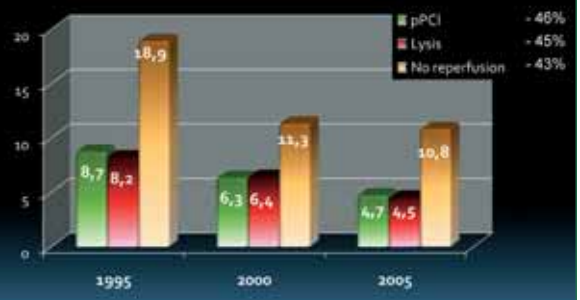
Unresolved issues

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

Evolution of 30-day mortality in 3 French surveys



Thirty-day mortality in 3 French surveys



Unresolved issues

Role of benchmarking

- Efficacy of benchmarking not demonstrated by such a study:
  - the GRACE registry did not observe such satisfactory results in terms of reperfusion delays
  - Improved management is observed outside benchmarking efforts
- There is a risk in setting strict objectives, particularly when there are financial incentives attached.
  - MINAP 2009 report: aspirin 98% (many hospitals 99 to 100), clopidogrel 94%, statins 97%, beta-blockers 93%, ACE-I 92%

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

Benchmarking:

a word of caution or "Don't overdo it…"

- Medical exceptions to quality measures are usually appropriate:

Recommended medications prescribed in 85% to 90% of patients

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

Unresolved issues

Many AMI patients do not reach the hospital

- Decline in incidence of STEMI patients who are hospitalised (e.g. Kaiser Permanente Northern California database: -51% from 1999 to 2008)
- The challenge of out-of-hospital sudden death:
  - often caused by acute ischemia on a mild plaque that ruptures and leads to complete coronary occlusion with profound, arrhythmogenic, ischemia.
  - need to improve the management of out-of-hospital cardiac arrest

Conclusion

- EHS ACS 3 data show that improving outcomes of STEMI patients is still possible and that shortening time delays for reperfusion is achievable.
- Monitoring performance indexes may help in improving results, although it probably does not suffice.
- We should not think, however, that we should now rest on these satisfactory results.
- Other combats are still ahead, such as reducing the inequalities across countries, or fighting sudden ischemic death.

GRACE 5 Years

Freek W.A. Verheugt

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

olvg

DISCLOSURE

Freek W.A. Verheugt received:

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

olvg

Clinical Implications:

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

SWOT Analysis of GRACE 5 Years

strengths	- very long follow-up - follow-up 99.4 % complete - GRACE risk model validated for long-term
weaknesses	- only 6% (3,721/60,723) of GRACE population - only 2 of the 29 (7%) GRACE countries

olvg

Other Large Registries

registry	publication	n	f/u	ACS
MITI	NEJM 1996;335:1253-1260	3,145	3 years	STEMI
CCP Medicare	JACC 2000;36:366-374	15,940	1 year	STEMI
RIKS-HIA	JAMA 2006;296:1749-1756	26,205	1 year	STEMI

olvg

Advantages and Disadvantages of Trials and Registries

	advantage	disadvantages
randomized trial	- equal baseline data	- selection bias - not generalizible - limited follow-up
registry	- real world - follow-up "unlimited"	- confounding bias

Verheugt FWA. Circulation 2009;119:3047-3049

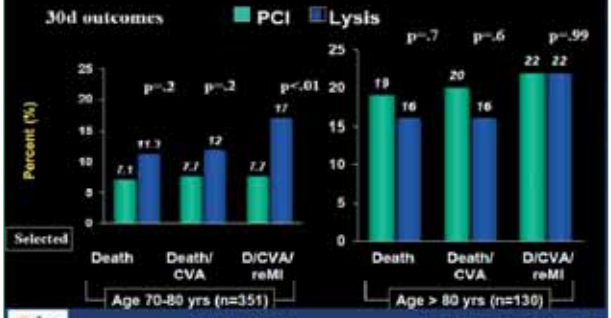
olvg

Clinical Implications:

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

Senior PAMI: A Randomized Trial Comparing PCI to Lysis in the Elderly

n=474/530 (pain to lysis 3 1/2 hrs, pain to 1st balloon 4 hrs)



Courtesy AM Ross

Thrombolysis vs Primary PCI in GRACE (70y+)

	Thrombolysis (n = 769)	Primary PCI (n = 365)	P
All-cause mortality (%)	113 (14.8)	49 (13.5)	.56
Reinfarction (%)	44 (5.7)	4 (1.1)	.0003
Death or reinfarction (%)	143 (18.7)	52 (14.3)	.07
Cardiogenic shock (%)	88 (11.6)	41 (11.3)	.89
Major bleeding (%)	45 (5.9)	31 (8.6)	.09
Stroke (%)	21 (2.8)	4 (1.1)	.08
Length of stay in hospital (median, days) (%)	8	7	.005

Mehta RH. Am Heart J 2004;147:253-259

What We also Would Like to See (1):

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

What We also Would Like to See (2):

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

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

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

Disclosures: Funding support from British Heart Foundation (Centre of Excellence Award) Chief Scientist Grant award (KAAF, KFC, DRD).
Original GRACE multinational project supported by Sanofi Aventis

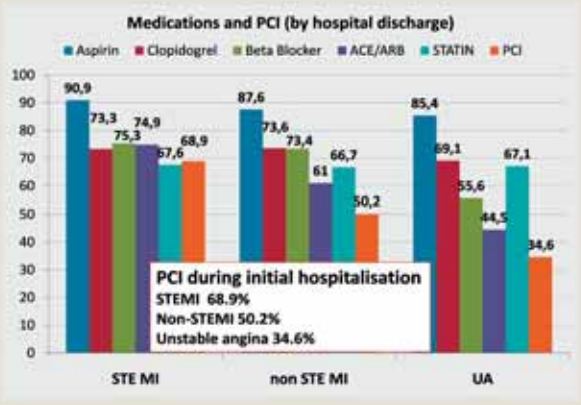
Aims and Methods

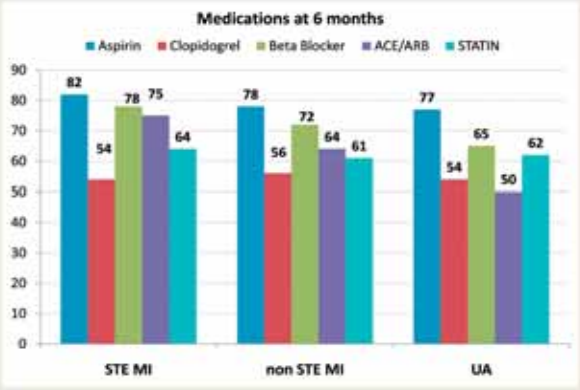
- To define the long-term outcomes following ST Elevation and non-ST elevation ACS
- To determine whether the GRACE risk score predicts long-term risk of death, CV death and MI
- Prospective recruitment of patients presenting with ACS, audit, quality control and long-term follow-up
  - UK n= 2065, Belgium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

Demographic Information and Prior History (%)

	Mean age yrs	Male %	Prior Angina %	Prior MI %	Prior PCI %	Prior Hypertension %	Prior Diabetes %	Prior TIA/Stroke %	Current Smoker %
STEMI n=1403	63	73	23	19	5	33	10	6	42
Non-STEMI n=1107	67	74	47	32	8	47	17	9	33
UA n=850	66	65	79	48	30	51	17	12	24

Non ACS cardiac discharge diagnosis n=135, non-cardiac n=163



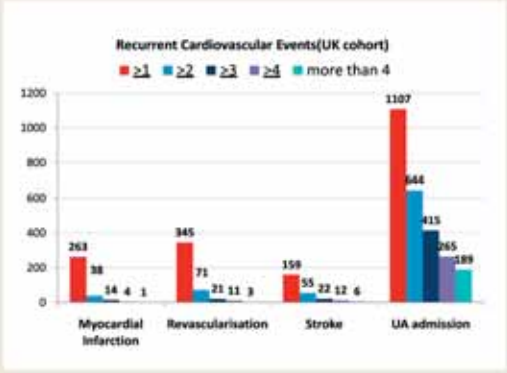


Outcomes at 5 years (death)

- **Deaths**: similar proportion of each category of ACS died by 5 yrs
  - STE MI 269/1403 (19%)
  - Non STE MI 262/1107 (22%)
  - Unstable angina 148/850 (17%)
- Most deaths were after initial hospital discharge:
  - STE MI 66%, Non-STE MI 83%, UA 95%

Outcomes at 5 years

- **Myocardial Infarctions**:
  - 12.7% of patients one or more MI (24hrs to 5yrs)
- **Strokes**:
  - 7.7% of patients had one or more strokes
- **Revascularisations** (after initial hospital discharge)
  - 16.7% of patients had one or more revascularisation
- **Readmissions for suspected ACS**:
  - 53.6% of patients were re-admitted at least once



GRACE risk score and outcomes

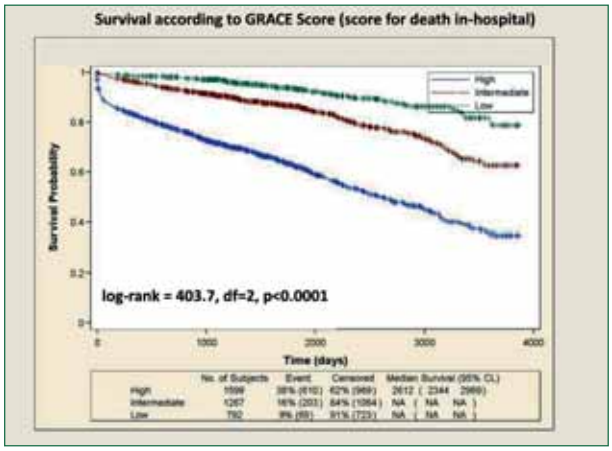
GRACE risk categories as in ESC Guidelines (Eur Heart J 2007: 28, 1598-1660)

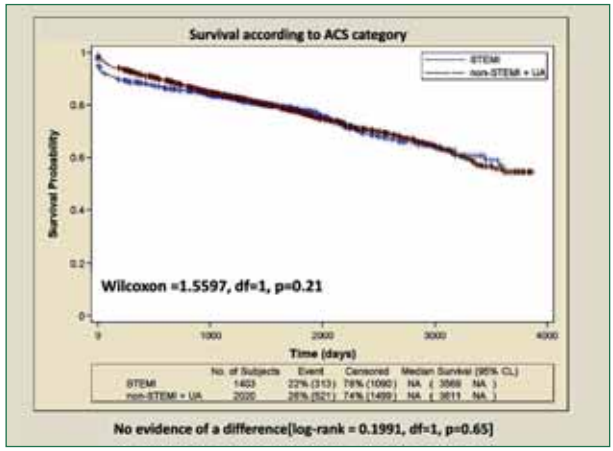
		N events/subjects (%)	Odds Ratio	95% CI	p-value
All Death	Low	43/462 (9.3)	1.000		
	Intermediate	150/736 (20.4)	2.494	(1.738, 3.580)	<0.0001
	High	524/1030 (50.9)	10.091	(7.205, 14.132)	<0.0001
All Death/MI	Low	99/446 (22.2)	1.000		
	Intermediate	80/328 (24.4)	1.131	(0.807, 1.583)	0.4747
	High	747/1547 (47.0)	3.108	(2.433, 3.969)	<0.0001
Cardiovascular Death	Low	32/462 (6.9)	1.000		
	Intermediate	107/736 (14.5)	2.286	(1.512, 3.456)	<0.0001
	High	379/1030 (36.8)	7.823	(5.346, 11.449)	<0.0001

GRACE Risk Score: predictive accuracy

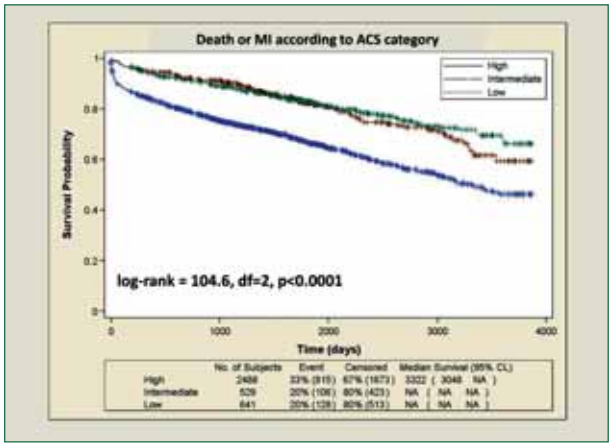
- **Deaths (in-hospital)**
  - All deaths*: likelihood ratio 239, Wald 189, C statistic 0.88
  - CV deaths*: likelihood ratio 230, Wald 181, C statistic 0.88
- **Deaths (5 years)**
  - All deaths*: likelihood ratio 477, Wald 445, C statistic 0.77
  - CV deaths*: likelihood ratio 235, Wald 279, C statistic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

***P* values for all <0.0001

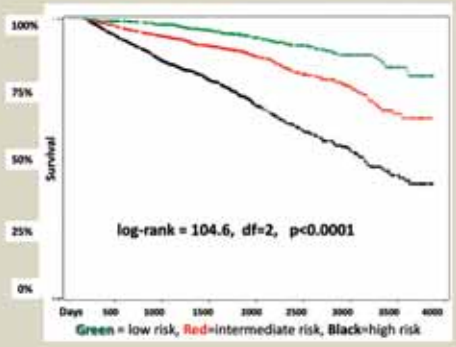




No evidence of a difference[log-rank = 0.1991, df=1, p=0.65]



Landmark Analysis: GRACE score and mortality after 6 months



Conclusions:

- The late consequences of ACS are under-recognised:
  - Following STEMI presentation, 66% of all deaths to 5yrs occur after hospital discharge
  - Following Non-STEMI presentation 83% of deaths are after discharge
  - Following UA presentation 95% of deaths are after discharge
- The greatest absolute late risk is among those with non-ST elevation ACS
- This is despite high usage of guideline therapies and secondary prevention
- The GRACE risk score has similar high predictive accuracy long-term (5 years and beyond) as at hospital discharge
- The GRACE risk score predicts mortality, even among those surviving the first 6 months after ACS

Clinical Implications:

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

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

DISCUSSION

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

No conflicts related to this talk

Use and misuse of Registries

Prospective registries

- Framingham
- MONICA
- GRACE
- CRUSADE
- ➢ REACH

Advantages

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

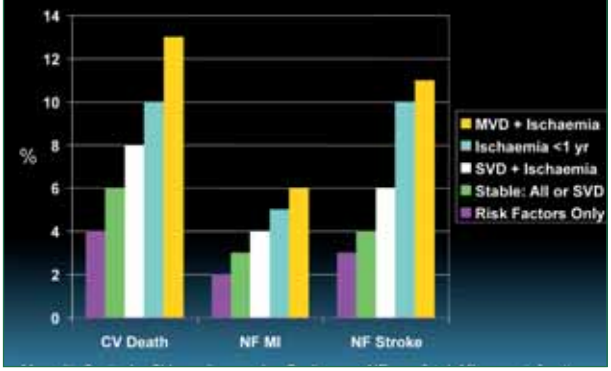
Misuse not appropriate to investigate effect of interventions given potential selection bias and residual confounding

VALUE of REACH

COHORT	▪ stable or stabilised outpatients ▪ array of CVD
SIZE	▪ > 34000 individuals
TIMING	▪ 4-year follow-up
METHODS	▪ prospective - audited centers ▪ hard endpoints – adjusted analyses ▪ analysis by pt hx and CV system

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

Events in REACH at 4 yrs

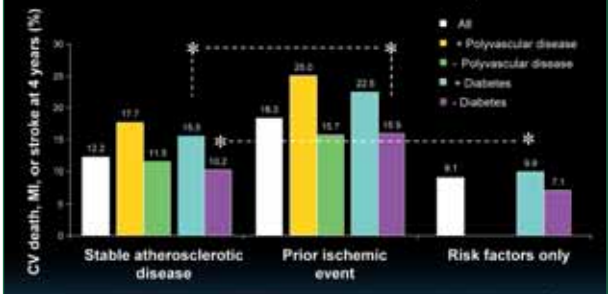


DRAWBACKS of REACH

DEFINITIONS	▪ events adjudicated locally ▪ carotid IMT same as 70% stenosis
MIX	▪ RFO group mixed with CVD patients
GAPS	▪ lack of emerging risk factos ▪ female representation low ▪ Africa missing
SUMMING UP	▪ conclusion on diabetes ▪ title not entirely clear

RFO=risk factors only, CVD=cardiovascular disease, IMT=intimal medial thickening

Diabetes and Events at 4 yrs



Not entirely in agreement with «Diabetes increased the risk of CV events in all but to a lesser extent than polyvascular disease or established atherosclerosis»

On Balance

The REACH Follow-up Registry data

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

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

Final Follow-up From the International REACH Registry

DL Bhatt, KA Eagle, EM Ohman, AT Hirsch, S Goto, EM Mahoney, PWF Wilson, MJ Alberts, R D'Agostino, C-S Liau, J-L Mas, J Röther, SC Smith, Jr, G Salette, CF Contant, JM Massaro, Ph G Steg, on behalf of the REACH Registry Investigators

Disclosures

- Presenter disclosures: Research grants – AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Heartscape, sanofi-aventis, The Medicines Company.

The REACH Registry is sponsored by: sanofi-aventis, Bristol-Myers Squibb, and the Waksman Foundation (Tokyo, Japan), and endorsed by the World Heart Federation.

Enrolment facts and figures

- 68,236 patients were enrolled between Dec 2003–Dec 2004 at 5,587 centres across 44 countries across the globe
- The initial follow-up period was 2 years, but enrolling centres were invited to participate in the extension of this project to a 4-year observation period
- Patients enrolled in the REACH Registry were stable outpatients (typically being treated in non-academic centers) with either:
  a. Established atherothrombotic disease with documented CAD, CVD, or PAD
  b. ≥ 3 risk factors for atherothrombotic disease

CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

Participation in REACH Registry: 4-year follow-up study

- 45,227 patients enrolled at 3,647 centres in 29 countries provided outcomes data for this 4-year follow-up

Methods

- This analysis included all patients with 4-year outcomes data (n=45,227)
- Cumulative incidence rates reported were adjusted for age and gender
- Multivariable analysis used to identify determinants for CV events at 4 years
  - Variables tested: no. of disease locations at enrolment, prior ischemic event, additional variables identified by predictive model[1] such as age, smoking, diabetes, cardiac failure, statin use
- Cumulative incidence for CV death, MI, or stroke were calculated using Kaplan-Meier approach

[1] Wilson PWF et al. JACC 2007; 49 suppl A: 39A.

Key study populations and definitions

- Prior ischemic event: MI or stroke at baseline
- Stable atherosclerosis: Objectively confirmed, symptomatic, atherosclerotic disease without a prior ischemic event
- Risk factors only: Patients with ≥3 of the following risk factors for atherothrombotic disease:

Treated diabetes mellitus • diabetic nephropathy • ABI <0.9 • asymptomatic carotid stenosis ≥70% • carotid IMT of ≥2 adjacent sites • SBP ≥150 mmHg • hypercholesterolaemia • current smoking • age ≥65 years in men, age ≥70 years in women[1]

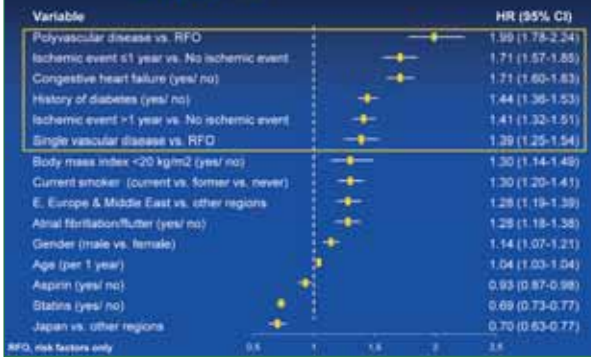
ABI, ankle-brachial index; IMT, intima media thickness; SBP, systolic blood pressure

Demographics for patients eligible for 4-year follow-up

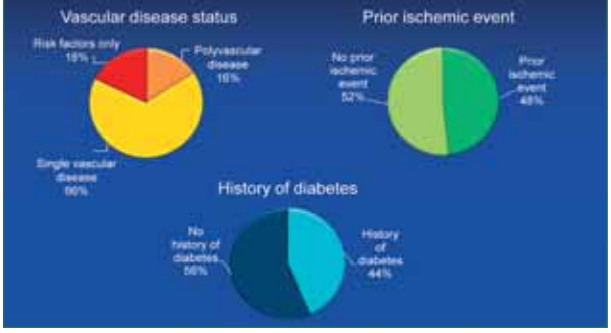
Patient characteristics	All (n=34,436)	Ischemic event (n=17,013)	Stable atherosclerotic disease (n=11,602)	Risk factors only (n=5,821)
Demographics				
Mean age ± SD	68.4 ± 9.9	67.6 ± 10.1	68.9 ± 9.8	69.4 ± 9.5
Men, %	65.5	70.9	65.3	50.2
Atherothrombotic risk factors				
Hypertension, %	81.0	79.1	79.8	89.3
Diabetes, %	42.9	36.0	37.3	74.4
Hypercholesterolemia, %	70.2	67.3	69.5	79.7
Obesity, ≥ 30 kg/m²	27.9	24.9	26.7	39.1
Smoker at baseline, %	15.2	14.2	15.1	18.4
Heart failure, %	13.9	18.1	11.9	5.8
Atrial fibrillation, %	10.6	12.0	10.5	6.3

SD, standard deviation

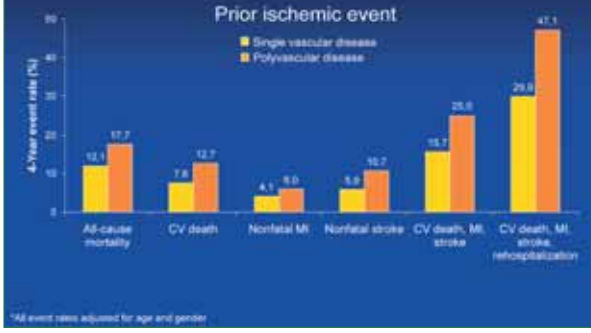
Multivariable predictors of CV events



Baseline medical history in patients with 4-year outcomes data

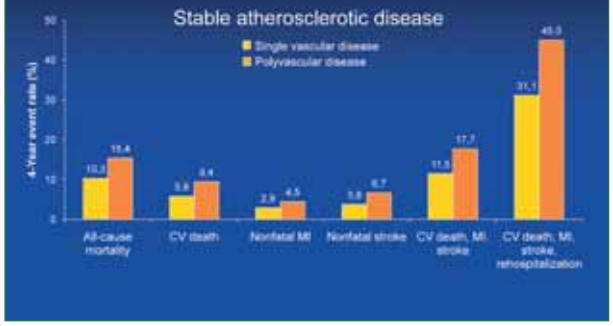


4-year event rates according to single vs. polyvascular disease

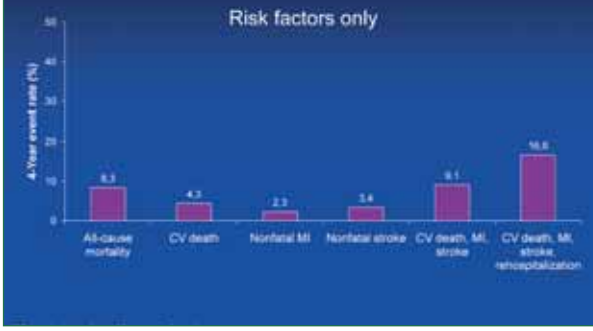


*All event rates adjusted for age and gender

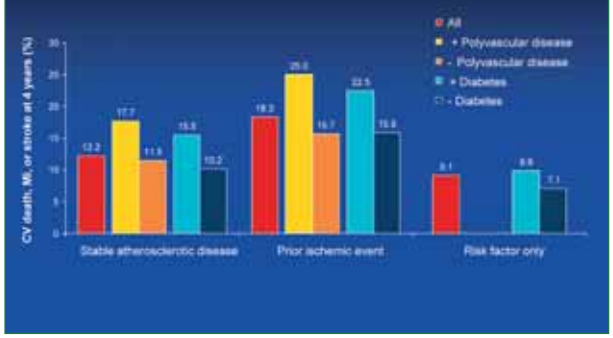
4-year event rates according to single vs. polyvascular disease



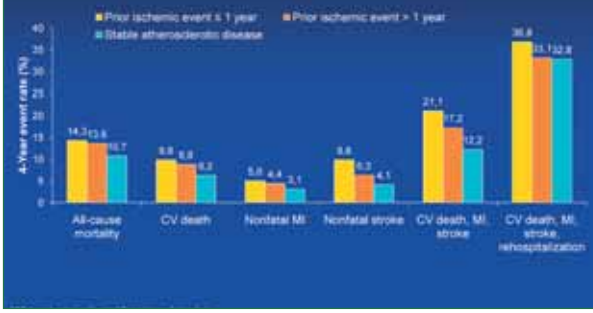
4-year event rates in patients with risk factors only at baseline



Impact of polyvascular disease and diabetes on CV events at 4 years



Comparative impact of ischemic event timing on 4-year event rates



Limitations

- Complete follow-up of the initial cohort at 4 years could not be achieved due to some enrolment sites withdrawing
- Outcome events were not independently adjudicated
- Since REACH had specific enrollment criteria, we cannot rule out that selection bias could have affected some of the results

Summary of key results

- Risk continuum for future CV events:

Patients with prior ischemic events at baseline » Patients with stable atherosclerosis at baseline » Patients with risk factors only

- Polyvascular disease was the strongest independent predictor of future CV events
- In patients with a prior ischemic events, an event ≤1 year prior to enrolment was a stronger predictor for CV events (vs. >1 year)
- Diabetes increased the risk of CV events in all populations but to a lesser extent than polyvascular disease or established atherosclerosis

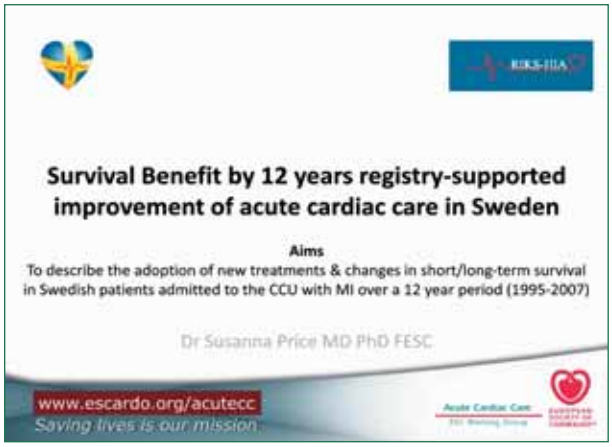
Conclusions (1)

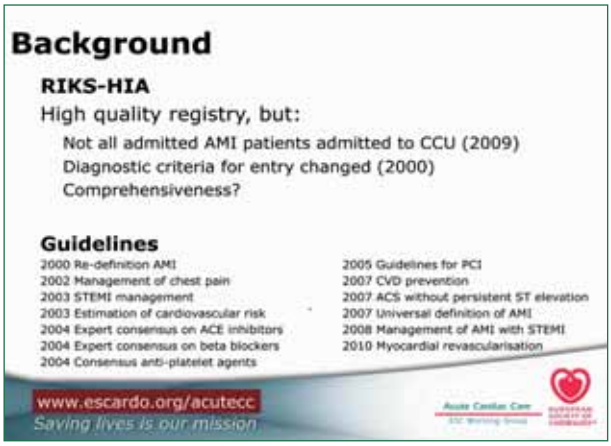
- In patients with multiple risk factors for atherothrombosis or established atherothrombotic disease, four clinical criteria can be used to identify patients at increased risk for future CV events:
  - Polyvascular disease
  - Recent ischemic event
  - Prior ischemic event at any time
  - Diabetes
-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

Conclusions (2)

- While previous risk stratification tools have been developed for patients after an acute event,[1-3] our analysis provides simple criteria for assessing risk for CV events in stable outpatients
- Our findings should help clinicians identify patients at very high-risk of MI, stroke, or cardiovascular death and adapt their treatment strategies accordingly
- The identification of high-risk populations may assist in the design of future clinical trials evaluating emerging treatment options in those requiring the most intensive preventive medications


REACH
REGISTRY
Thank you to all those who participated
in the REACH Registry
A complete list of the REACH Registry investigators is
published in JAMA 2006; 295: 180-189.


RIKS-HIA
Survival Benefit by 12 years registry-supported improvement of acute cardiac care in Sweden
Aims
To describe the adoption of new treatments & changes in short/long-term survival in Swedish patients admitted to the CCU with MI over a 12 year period (1995-2007)
Dr Susanna Price MD PhD FESC
www.escardo.org/acutecc
Saving lives is our mission


Background
RIKS-HIA
High quality registry, but:
Not all admitted AMI patients admitted to CCU (2009)
Diagnostic criteria for entry changed (2000)
Comprehensiveness?
Guidelines
2000 Re-definition AMI
2002 Management of chest pain
2003 STEMI management
2003 Estimation of cardiovascular risk
2004 Expert consensus on ACE inhibitors
2004 Expert consensus on beta blockers
2004 Consensus anti-platelet agents
2005 Guidelines for PCI
2007 CVD prevention
2007 ACS without persistent ST elevation
2007 Universal definition of AMI
2008 Management of AMI with STEMI
2010 Myocardial revascularisation
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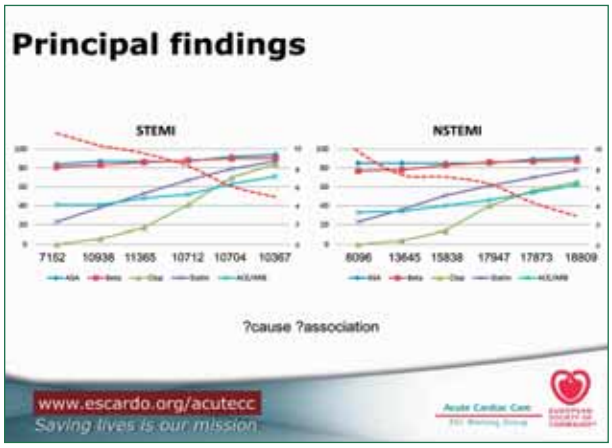
Principal findings
STEMI
NSTEMI
7152 10938 11365 10712 10704 10367
6096 13645 15838 17947 17873 18809
?cause ?association
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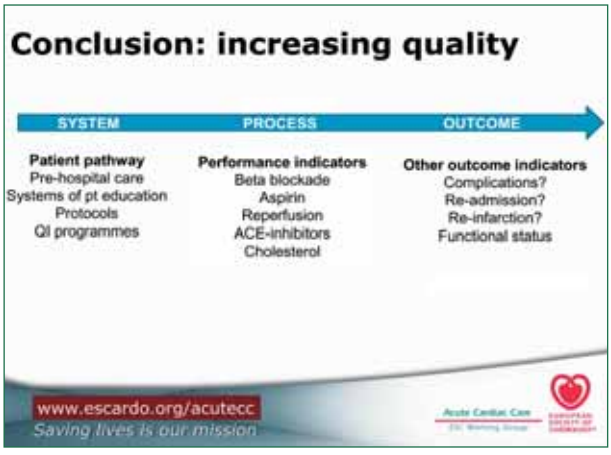
Conclusion: increasing quality
SYSTEM
PROCESS
OUTCOME
Patient pathway
Pre-hospital care
Systems of pt education
Protocols
QI programmes
Performance indicators
Beta blockade
Aspirin
Reperfusion
ACE-inhibitors
Cholesterol
Other outcome indicators
Complications?
Re-admission?
Re-infarction?
Functional status
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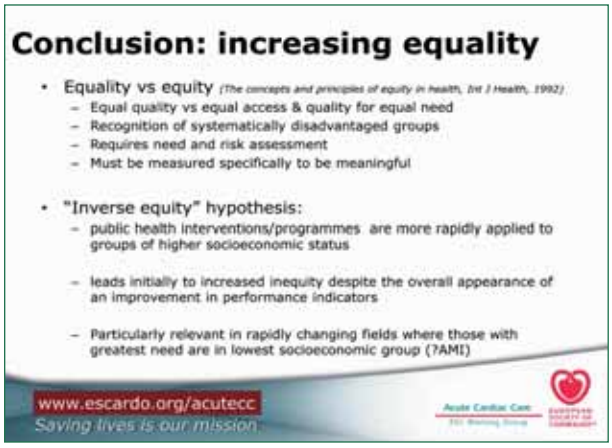
Conclusion: increasing equality
Equality vs equity (The concepts and principles of equity in health, Int J Health, 1992)
Equal quality vs equal access & quality for equal need
Recognition of systematically disadvantaged groups
Requires need and risk assessment
Must be measured specifically to be meaningful
"Inverse equity" hypothesis:
public health interventions/programmes are more rapidly applied to groups of higher socioeconomic status
leads initially to increased inequity despite the overall appearance of an improvement in performance indicators
Particularly relevant in rapidly changing fields where those with greatest need are in lowest socioeconomic group (?AMI)
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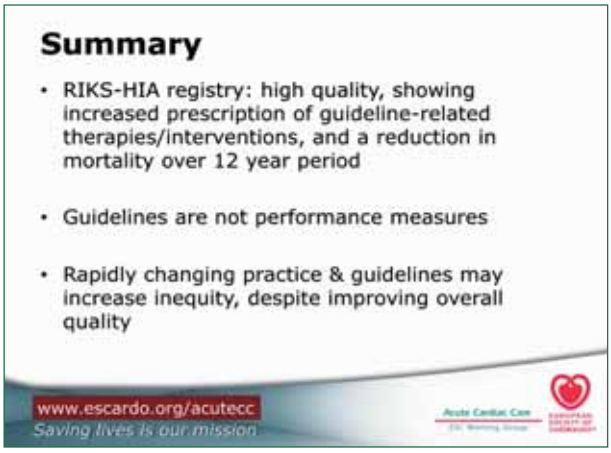

Summary
RIKS-HIA registry: high quality, showing increased prescription of guideline-related therapies/interventions, and a reduction in mortality over 12 year period
Guidelines are not performance measures
Rapidly changing practice & guidelines may increase inequity, despite improving overall quality
www.escardo.org/acutecc
Saving lives is our mission

Survival benefits by 12 years registry supported improvement of acute cardiac care in Sweden

- the RIKS-HIA 12 years study

Lars Wallentin[1], Bodil Svennblad[1], Johan Lindbäck[1], Tomas Jernberg[2] for the SWEDEHEART / RIKS-HIA group

1 Uppsala Clinical Research Centre, Uppsala.
2 Karolinska University Hospital, Stockholm.
Sweden.

Introduction

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

Introduction

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

Introduction

RIKS-HIA

- A National registry for acute coronary care since 1995
- All Swedish centers (74)
- Covers the whole acute care process for all patients admitted to a coronary care unit in Sweden.

Aim

To describe the adoption of new treatments and the development of short- and long-term survival in MI patients admitted to a CCU in a whole country consecutively over a 12 year period.

Methods

- Consecutive patients admitted to a CCU and entered into RIKS-HIA register between 1996 and 2007 with a first time discharge diagnosis of myocardial infarction were included.
- To diagnose acute MI, the WHO-criteria were used 1995-2000 and the ESC/ACC/AHA-criteria from 2001.
- More than 100 variables are prospectively registered: Risk factors, previous heart diseases, clinical presentation, received treatments, complications, in-hospital outcome.
- Mortality data were obtained by merging the RIKS-HIA database with the National Death Registry.
- Data quality was monitored in 5446 random records with 299,530 measurement, with an agreement of 95%.
- All patients were informed about their participation and had the right to decline participation.

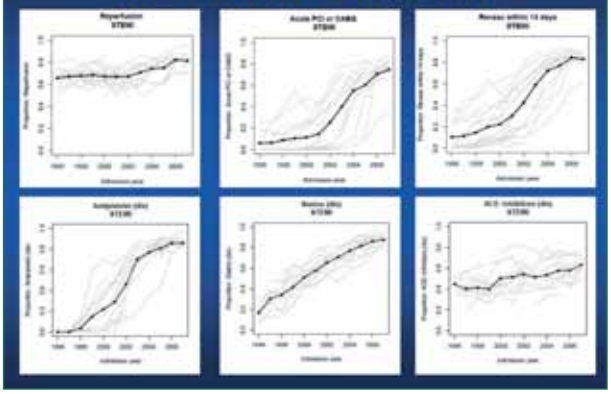
Baseline characteristics

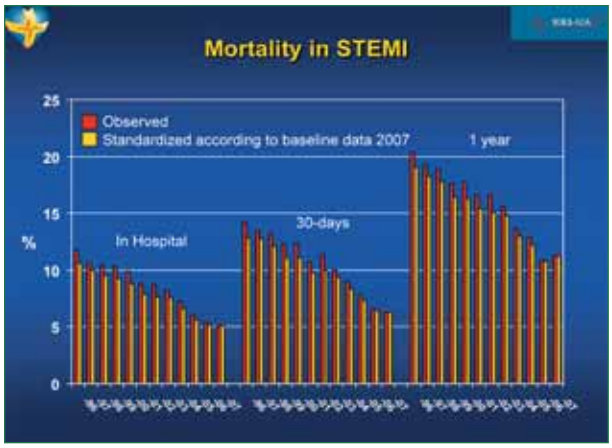
	1996-1997 N = 15248	1998-1999 N = 24583	2000-2001 N = 27203	2002-2003 N = 28659	2004-2005 N = 28577	2006-2007 N = 29176
Age	72(63-79)	73(62-79)	73(62-80)	73(63-80)	73(62-80)	73(62-80)
Gender - Women	35%	36%	37%	37%	37%	36%
Diabetes	20%	21%	22%	22%	22%	22%
Hypertension	31%	32%	34%	37%	40%	44%
Current smoker	23%	23%	23%	24%	24%	24%
Previous disease at entry						
- Myocardial infarction	25%	24%	22%	21%	18%	18%
- Heart failure	10%	10%	11%	11%	9%	9%
- Stroke	10%	10%	11%	11%	11%	10%
- Peripheral artery disease	5%	5%	5%	5%	5%	5%
- Renal failure	1%	1%	2%	2%	2%	2%
Medication at entry						
- Aspirin	33%	35%	36%	37%	35%	34%
- Beta-blocker	30%	32%	34%	35%	35%	34%
- Clopidogrel	0%	0%	1%	3%	5%	4%
- Statin	6%	9%	13%	16%	18%	21%
- ACE-inhibitor or ARB	13%	14%	16%	19%	22%	26%

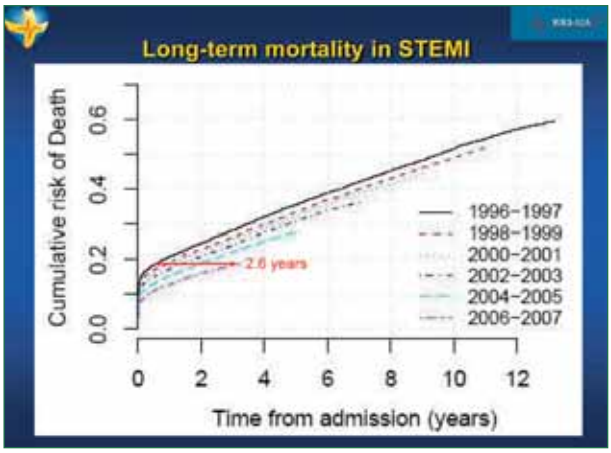
Treatment of STEMI

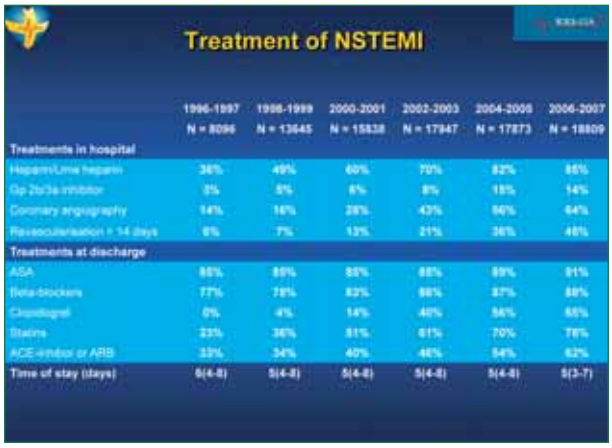
	1996-1997 N = 7152	1998-1999 N = 10938	2000-2001 N = 11365	2002-2003 N = 10712	2004-2005 N = 10704	2006-2007 N = 10367
Reperfusion treatment						
Reperfusion treatment	67%	68%	68%	69%	70%	78%
Acute PCI	4%	6%	9%	19%	44%	65%
Other treatments						
IV Gp 2b/3a inhibitor	6%	8%	11%	19%	44%	56%
Coronary angiography	12%	18%	31%	49%	71%	85%
Revasc within 14 days	8%	13%	22%	37%	63%	78%
Treatments at discharge						
ASA	84%	87%	87%	87%	92%	94%
Beta-blockers	81%	83%	86%	88%	90%	90%
Clopidogrel	0%	5%	17%	41%	70%	84%
Statin	23%	39%	53%	67%	78%	87%
ACE-inhibitor or ARB	41%	41%	48%	52%	63%	71%
Time of stay (days)	6(5-9)	6(4-8)	5(4-8)	5(4-7)	5(4-7)	3(4-6)

Treatment of STEMI - hospital level

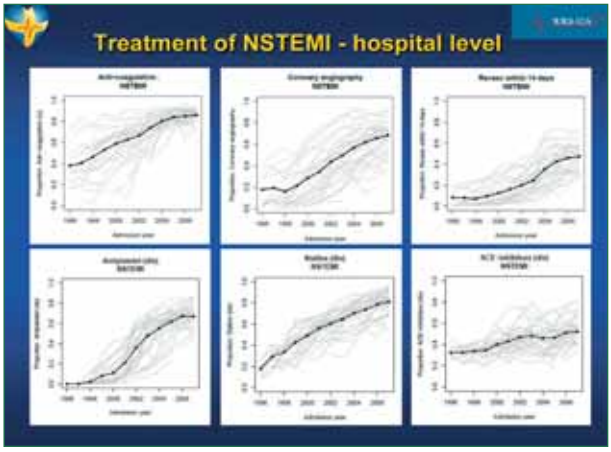


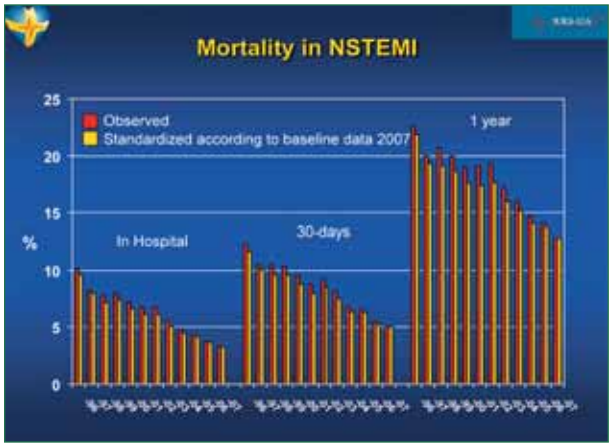


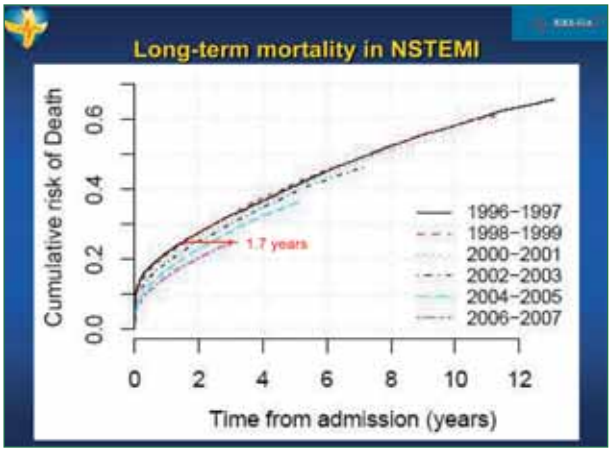




	1996-1997 N = 8096	1998-1999 N = 13645	2000-2001 N = 15838	2002-2003 N = 17947	2004-2005 N = 17873	2006-2007 N = 18809
Treatments in hospital						
Heparin/Lmw heparin	36%	49%	60%	70%	82%	86%
Gp 2b/3a inhibitor	5%	6%	8%	8%	15%	14%
Coronary angiography	14%	16%	28%	43%	56%	64%
Revascularisation < 14 days	6%	7%	13%	21%	36%	46%
Treatments at discharge						
ASA	85%	85%	85%	88%	89%	91%
Beta-blockers	77%	78%	82%	86%	87%	88%
Clopidogrel	0%	4%	14%	40%	56%	65%
Statins	23%	36%	51%	61%	70%	78%
ACE-inhibitor or ARB	33%	34%	40%	46%	54%	62%
Time of stay (days)	5(4-8)	5(4-8)	5(4-8)	5(4-8)	5(4-8)	5(3-7)







University of Oslo

Discussant:

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

SHIFT trial

by

M. Bøhm, Swedberg K, Komajda M, Borer J, Ford I, Tavazzi L

European Society of Cardiology Clinical Trial Update II

30.8.2010

Major findings in the SHIFT trial :

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

Kjekshus J. ESC 30.08.2010

Patient characteristics:

The study is well balanced at baseline
High heart rate is characterized by:

- younger patients
- lower EF
- more smokers
- more diabetics
- reduced use of ACEI and BB
- increased use of diuretics and digitalis

Adverse events and limitations

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

Kjekshus J. ESC 30.08.2010

Take home message

Heart rate in heart failure is

- a risk marker and a risk factor for CV death and HF hospitalizations
- a treatment target
- is effectively and safely reduced by ivabradine on top of a β-blocker

Take home message

The SHIFT study shows:

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

SHIFT

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

A subanalysis of the SHIFT trial

M. Böhm, K. Swedberg, M. Komajda, J. Borer, I. Ford, L. Tavazzi

on behalf of the SHIFT Investigators

SHIFT

Disclosures

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

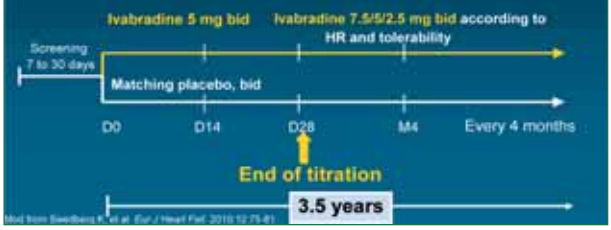
Heart rate and outcomes in HF: background

- Elevated resting heart rate is a marker of cardiovascular risk
- Ivabradine slows the heart by selective I_f current inhibition and has no known cardiovascular effects other than heart rate reduction
- SHIFT allows to further explore the prognostic importance and pathophysiological role of heart rate in heart failure
- We hypothesised that heart rate is a risk factor for cardiovascular events, and tested the effect of isolated heart rate reduction with ivabradine on outcomes in a heart failure population

Study design

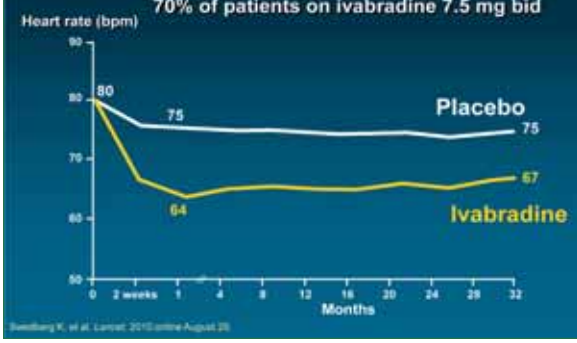
Double-blind, placebo-controlled multinational study, 6505 patients
median study duration: 22.9 months

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

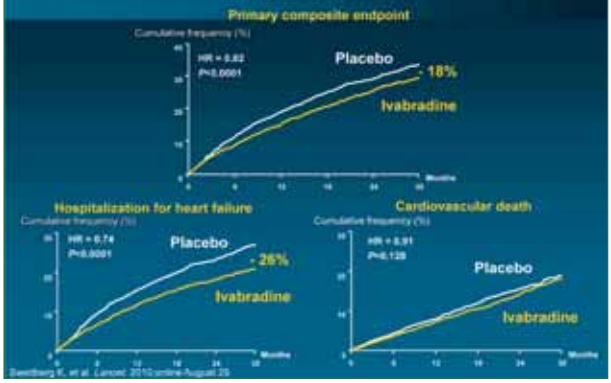


Mean heart rate reduction

70% of patients on ivabradine 7.5 mg bid



Ivabradine effect on outcomes



Objective of current analysis

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

Methods

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

Baseline characteristics in population divided by quintiles of heart rate

	Heart rate at baseline (bpm)					P value*
	70 - <72	72 - <75	75 - <80	80 - <87	≥87	
Heart rate (bpm)	70	73	77	82	96	-
Age (years)	63	61	60	60	58	<0.0001
Caucasian (%)	89	92	89	87	86	0.0009
Smoking (%)	15	14	16	18	23	<0.0001
Ischaemic cause of HF (%)	74	71	68	67	61	<0.0001
NYHA class III/IV (%)	48	48	47	52	61	<0.0001
Hypertension (%)	69	70	66	66	62	0.0007
Diabetes (%)	26	30	30	32	33	0.008

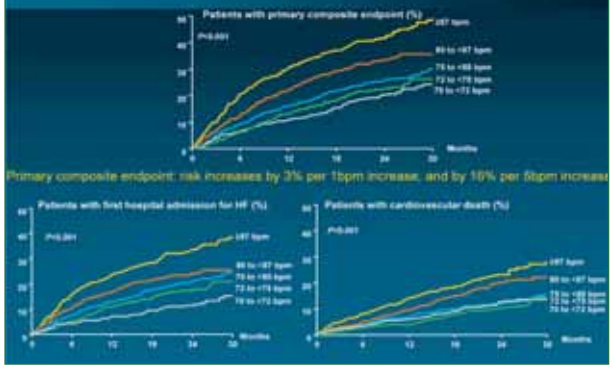
*p value for interaction (chi-squared test for categorical variables, Kruskal-Wallis test for continuous variables)

Baseline characteristics in population divided by quintiles of heart rate

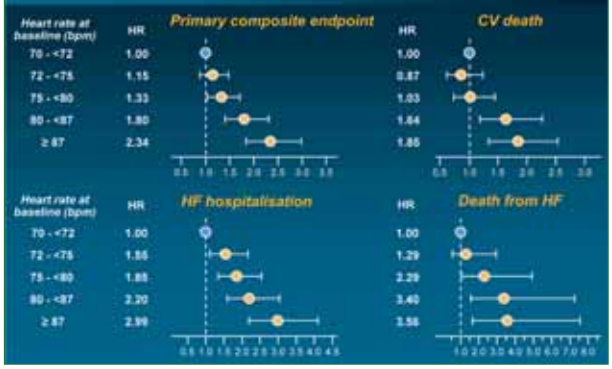
	Heart rate at baseline (bpm)					P value*
	70 - <72	72 - <75	75 - <80	80 - <87	≥ 87	
SBP (mm Hg), mean	122	122	122	122	120	0.006
DBP (mm Hg), mean	75	76	76	76	76	0.027
LVEF (%), mean	30	30	29	29	28	<0.0001
Beta-blockers (%)	93	92	92	88	82	<0.0001
ACE inhibitors (%)	81	81	81	76	75	0.0001
Diuretics (%)	82	82	82	85	86	0.004
Aldosterone antagonists (%)	56	59	59	61	65	0.0001
Cardiac glycosides (%)	18	18	21	23	28	<0.0001

*p value for interaction (chi-squared test for categorical variables, Kruskal-Wallis test for continuous variables)

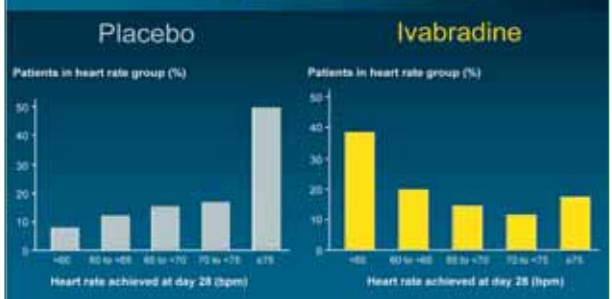
Baseline heart rate is a predictor of endpoints on placebo



Relative risk of primary composite endpoint in the placebo group divided by quintiles of heart rate

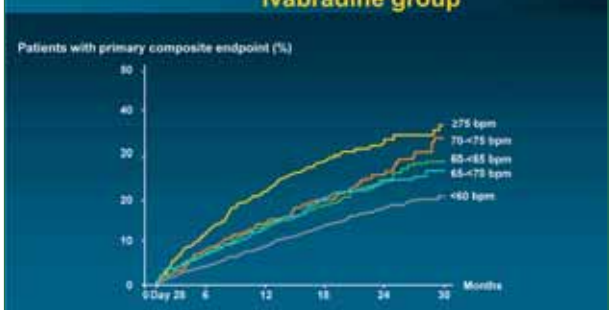


Distribution of patients by classes of heart rate achieved at D28*



*Data exclude patients reaching primary composite endpoint in the first 28 days

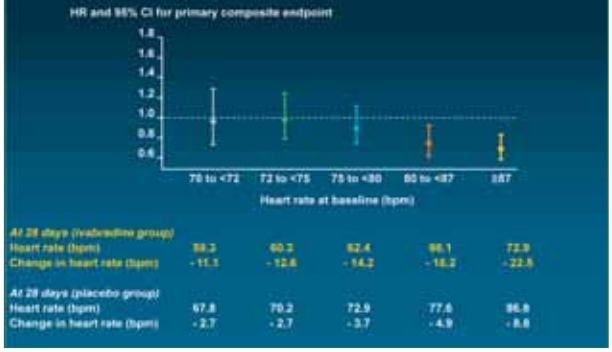
Primary composite endpoint according to heart rate achieved at D28* in the ivabradine group



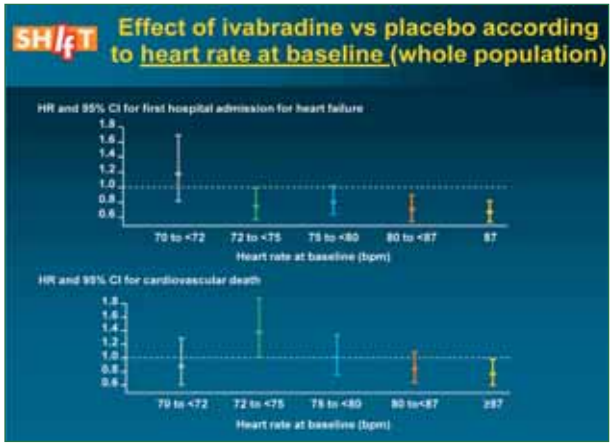
Treatment effect is explained by heart rate reduction

After adjustment for change in heart rate at 28 days:
HR 0.95, 0.85 – 1.06, p = 0.352

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



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



Conclusion

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

SHIFT Clinical implications

- Elevated heart rate is a risk factor in HF
- Heart rate is an important target for therapy in HF
- Shifting patients to lower heart rate profiles with ivabradine reduces CV events
- Lower heart rates at baseline and lower heart rates achieved on treatment are associated with better outcomes, with incremental benefit by achieving heart rate ≤60 bpm when tolerated

SHIFT Available now online from *Lancet*

10tl5226
Articles
LB

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

http://www.lancet.com published online August 29, 2010
DOI:10.1016/S0140-6736(10)61259-7

Thank You!

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CARE-HF Long-Term Follow-Up

Presented by Prof. J.G.F. Cleland, Univ. of Hull, UK

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

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

No conflicts of interest

Universitätsklinikum Erlangen

Hot Line Session CARE-HF LTFU
Discussion

- Randomized controlled clinical trials have well established the role of CRT for selected heart failure patients with cardiac dyssynchrony (identified by ECG criteria)
- Follow-up Duration of the key trials is limited:
  - MIRACLE-CRT (2002) ~6 months
  - Companion (2004) ~16 months
  - CARE-HF Main Study (2005) 29 months
  - CARE-HF Extension (2006) 37 months
  - MADIT-CRT (2009) ~28 months
- CARE-HF LTFU: minimum FU Duration 6.5 years!

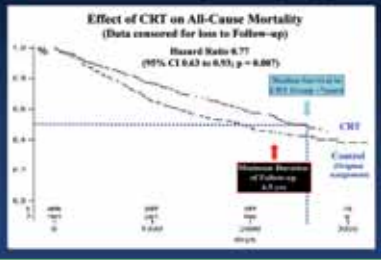
→ >72 months!

Hot Line Session CARE-HF LTFU
Limitations

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

Hot Line Session CARE-HF LTFU
Survival

- Survival curves diverge initially (main study)...
- ...proceed parallel between 3-6 years (day 1000-2000)...
  (cross over phase in control group)
- ...and seem to converge during longer follow-up (?)



Hot Line Session CARE-HF LTFU
Effect of „delayed" CRT Implantation

- > 90% of patients initially assigned to the „control" group (medical therapy) had received a CRT(-D) device at the time of LTFU entry (time of re-consent)
- Early survival benefit of CRT-P cannot be compensated by delayed CRT-P/-D implantation
  Identifiable risk factors for early mortality?
- How did the time of CRT implantation in the control group affect survival?
- What is the frequency of CRT-D in the late implanted „control group"?

Hot Line Session CARE-HF LTFU
Summary

- CARE-HF LTFU provides to date the longest follow-up information from a randomized, controlled trial population
- Results confirm the long-term benefits of CRT-P (without defibrillator backup!)
- The available data suggests that the initial survival benefit of CRT-P can not be compensated by delayed CRT(-D) implantation

CONGRATULATIONS FOR THE VERY LONG FOLLOW UP DATA!

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

Aldo Pietro Maggioni, MD, FESC
ANMCO Research Center
Firenze, Italy

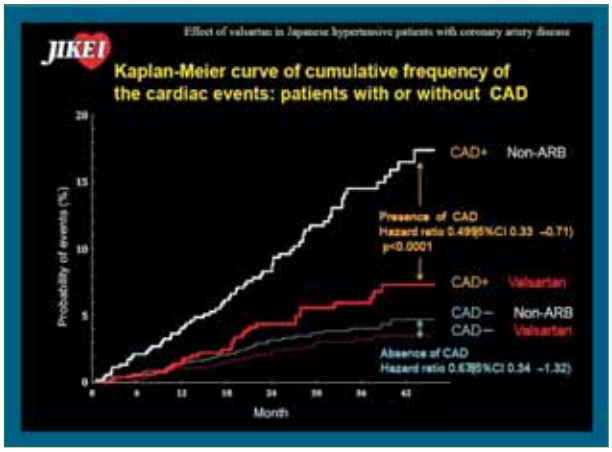
Disclosures:
APM was a member of the Steering Committee of the Val-HeFT and VALIANT trials
Further, APM received honoraria for lectures from Novartis


Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

Summary

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

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



Primary end-point

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

Some strenghts

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

Relevant weaknesses

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

Conclusions

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

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

JIKEI

Mitsuyuki Shimizu1, Hiroshi Yoshida, 2, Katsunori Ikewaki 3, Ikuo Taniguchi 1, Michihiro Yoshimura 1, Björn Dahlöf 4, Seibu Mochizuki 1, for the Jikei Heart Study group

1 Division of Cardiology
2 Department of Laboratory Medicine, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan
3 Division of Anti-Aging, Department of Internal Medicine, National Defense Medical College, Saitama, Japan
4 Institute of Medicine, Department of Emergency and Cardiovascular Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden

Conflict of interest

JIKEI

The JIKEI HEART study was "investigator driven study".

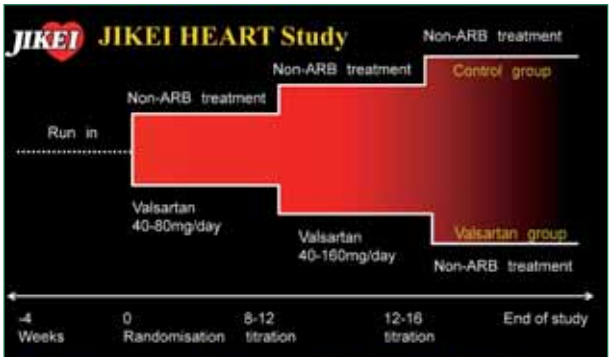
The JIKEI HEART study was funded by Jikei University School of Medicine.

The sponsor had no role in the collection, analysis and interpretation of data, in writing of the manuscript, or in the decision to submit the paper for publication.

AIM

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

JIKEI HEART Study

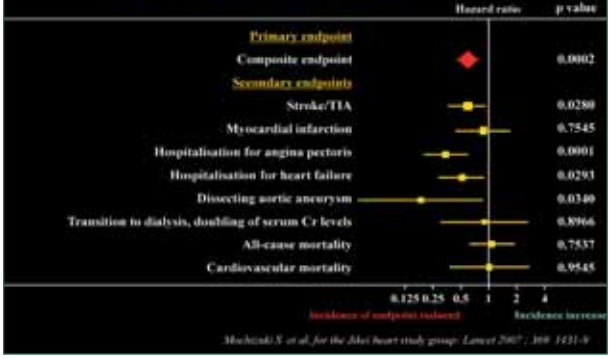


Schematic of study protocol with treatment phases

Doses of valsartan were given once daily.
Both groups given conventional non-ARB treatment.
PROBE method

JIKEI HEART Study

Effect of treatment on endpoints



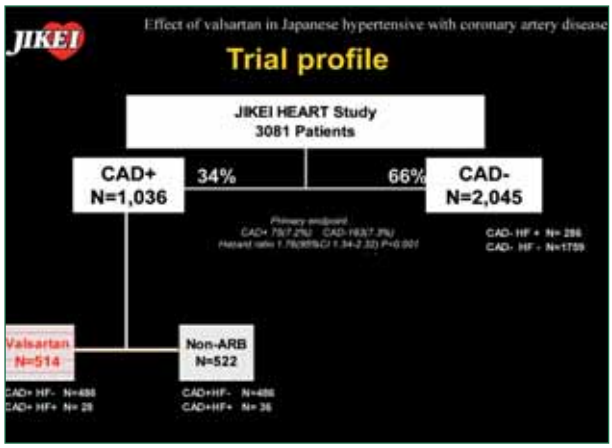
Mochizuki S et al, for the Jikei heart study group: Lancet 2007; 369: 1431-9

Methods

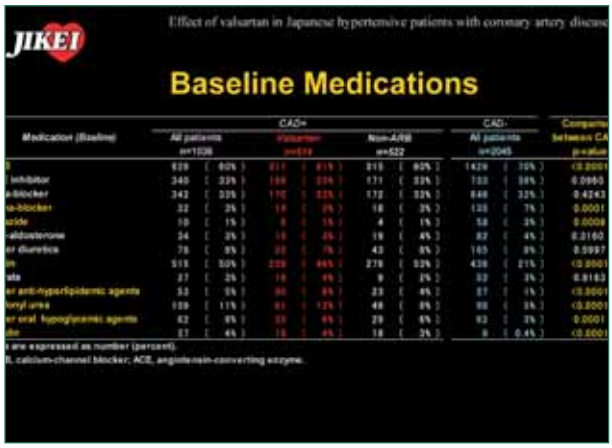
One thousand thirty six CAD patients in the JHS were subjected to this study.

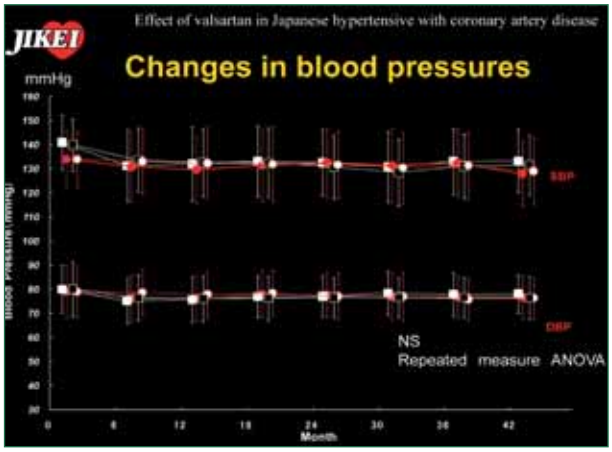
We assessed the following endpoints such as myocardial infarction, angina pectoris and congestive heart failure between valsartan group and non-ARB group.

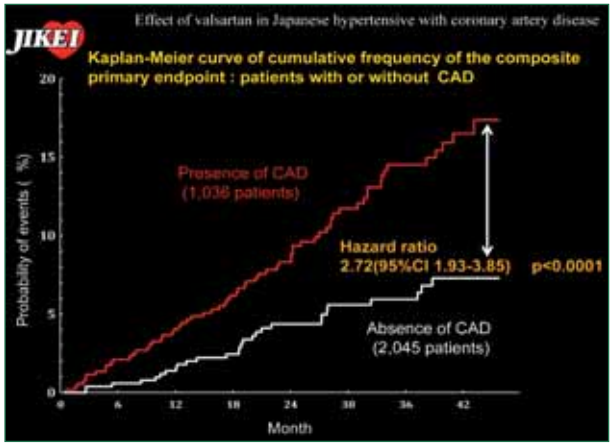
Electrocardiography and echocardiography were performed at baseline, 1 and 3 years after randomization.

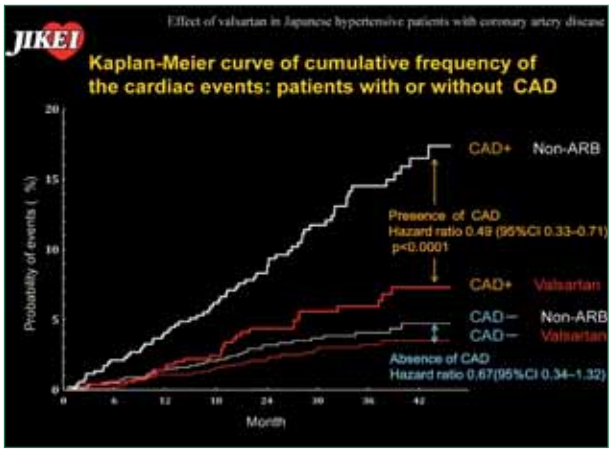

JIKEI
Effect of valsartan in Japanese hypertensive with coronary artery disease
Trial profile
JIKEI HEART Study
3081 Patients
CAD+
N=1,036
34%
66%
CAD-
N=2,045
Primary endpoint
CAD+ 79/7.2%/ CAD- 163/7.3%/
Hazard ratio 1.78(95%CI 1.34-2.33) P<0.001
CAD- HF + N= 286
CAD- HF - N=1759
Valsartan
N=514
Non-ARB
N=522
CAD+ HF- N=488
CAD+ HF+ N= 28
CAD+HF- N=486
CAD+HF+ N= 36

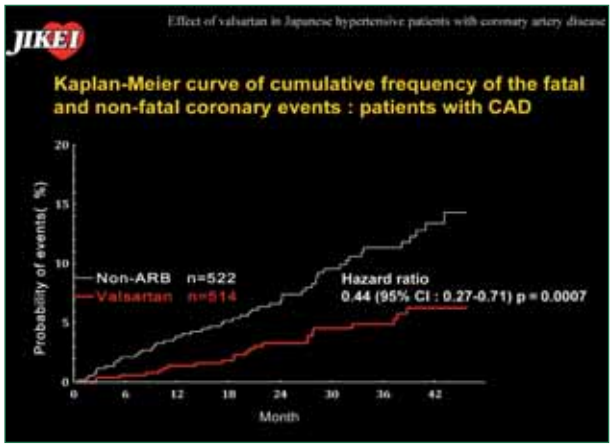

JIKEI
Effect of valsartan in Japanese hypertensive patients with coronary artery disease
Baseline Characteristics

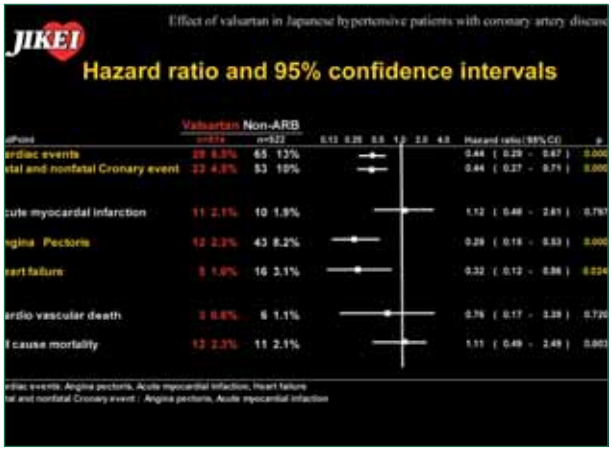

JIKEI
Effect of valsartan in Japanese hypertensive patients with coronary artery disease
Baseline Medications

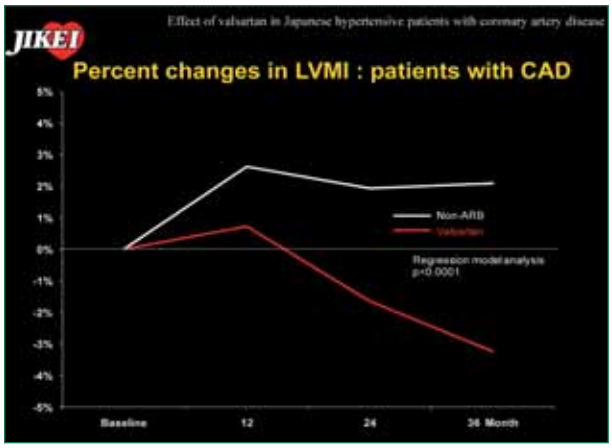

JIKEI
Effect of valsartan in Japanese hypertensive with coronary artery disease
Changes in blood pressures
mmHg
SBP
DBP
NS
Repeated measure ANOVA
Month

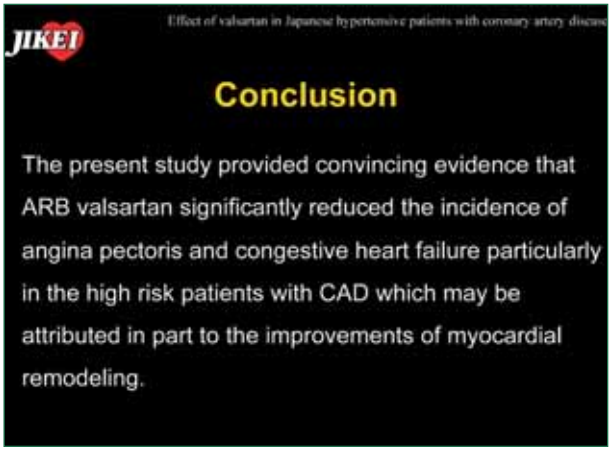

JIKEI
Effect of valsartan in Japanese hypertensive with coronary artery disease
Kaplan-Meier curve of cumulative frequency of the composite primary endpoint : patients with or without CAD
Probability of events (%)
Presence of CAD
(1,036 patients)
Hazard ratio
2.72(95%CI 1.93-3.85)
p<0.0001
Absence of CAD
(2,045 patients)
Month


JIKEI
Effect of valsartan in Japanese hypertensive patients with coronary artery disease
Kaplan-Meier curve of cumulative frequency of the cardiac events: patients with or without CAD
Probability of events (%)
CAD+ Non-ARB
Presence of CAD
Hazard ratio 0.49 (95%CI 0.33-0.71)
p<0.0001
CAD+ Valsartan
CAD− Non-ARB
CAD− Valsartan
Absence of CAD
Hazard ratio 0.67(95%CI 0.34-1.32)
Month


JIKEI
Effect of valsartan in Japanese hypertensive patients with coronary artery disease
Kaplan-Meier curve of cumulative frequency of the fatal and non-fatal coronary events : patients with CAD
Probability of events(%)
Non-ARB n=522
Valsartan n=514
Hazard ratio
0.44 (95% CI : 0.27-0.71) p = 0.0007
Month


JIKEI
Effect of valsartan in Japanese hypertensive patients with coronary artery disease
Hazard ratio and 95% confidence intervals





Editorial comment

Kyoto Heart Study, updated ancillary analyses.

Stéphane LAURENT, MD, PhD
Pharmacology Department and PARCC / INSERM U970
Hôpital Européen Georges Pompidou,
Université Paris Descartes, Assistance Publique-Hôpitaux de Paris

Inserm

PARIS DESCARTES

1. Effects of valsartan on primary and secondary prevention

A valsartan add-on treatment is more effective than a non-ARB regimen for preventing CV events* in uncontrolled hypertensive patients with high CV risk…

New finding

…both in secondary prevention, i.e. patients with previous CV events (CHD, stroke, CHF)
HR 0.63 [0.44-0.89], p=0.0088
…and in primary prevention
HR 0.44 [0.29-0.68], p=0.0002

* Primary end-point: A composite of CV events such as stroke/TIA, MI, worsening HF, angina, dissecting aortic aneurysm, lower limb arterial obstruction, transition to dialysis or doubling of serum creatinine levels

Analysis

In patient with previous CV events, as well as in those without, the benefit can be attributed to valsartan, because of

- **a similar reduction in brachial BP in "valsartan add-on" or "non-ARB" arms**
- **a similar level of CV risk at baseline in both arms**
- **similar baseline medications at baseline in both arms**

1. Effects of valsartan on primary and secondary prevention

Strengths

- **An issue rarely analysed, a prespecified analysis**
- **Large number of patients in both primary (n=2116) and secondary (n=915) prevention groups**
- **Similar number of patients in both arms (valsartan add-on and non-ARB) for primary (1065/1051) and secondary (452/463) prevention**
- **Primary end-point: Incidence of CV events close to that expected (10.2% vs 12% in 3 yrs FU) and high enough both in primary (n=102 in 3 yrs FU) and secondary preventions (n=146)**

Limitations

- **PROBE design (like in CASE-J, HIJ-CREATE, and JIKEI studies)**
- **Secondary prevention group: ACEI, given to 29% patients at baseline, had to be stopped in both arms, thus non-ARB patients had no RAS blockers, despite previous CHD or CHF, which are preferred indications (ESH-ESC Guidelines 2007)**
  - **→ increased CV risk in non-ARB?**
  - **→ valsartan ? ARB? or RAS blocker?**

1. Effects of valsartan on primary and secondary prevention

Clinical implications :

- **Major results for the Japanese/Asian population**
- **A large population is concerned**
  - **primary prevention: 1/2 to 2/3 of hypertensive patients are at high CV risk, despite no previous CV disease**
  - **uncontrolled hypertension: 2/3 of treated hypertensive patients are still not controlled (among those who are aware of HT and treated)**

→ In those patients, adding valsartan to previous treatment is more effective than a non-ARB regimen for preventing CV events

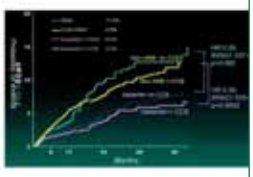
Remaining issues:

- **Mechanism of the BP-independent protective effect of valsartan ?**
  similar brachial BP ⇲ but higher central BP ⇲ ? (Boutouyrie et al. Hypertension 2010)
- **Protective effect of valsartan? or an ARB? or a RAS blocker?**
- **Extrapolation from an Japanese/Asian population to Western populations?**

2. Combination therapy with valsartan and CCB

Authors' conclusion

"Combination with valsartan+CCB showed lower primary events than non-ARB+CCB"



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

Limitations

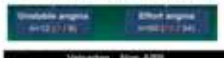
- **Prespecified analysis?**
  (Sawada T et al. J Human Hypertens 2009)
- **Indication bias for CCB?**

3. Stroke and angina prevention by valsartan

Authors' conclusions

Stroke: "Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs 36) but not bleeding."

Angina: "Valsartan was significantly effective for prevention of effort angina but not for unstable angina"



Preferred sentence: Angina prevention by Valsartan was rather due to inhibition of effort angina (16 vs 34) than unstable angina

Important limitation

Small number of events → undersized statistical power

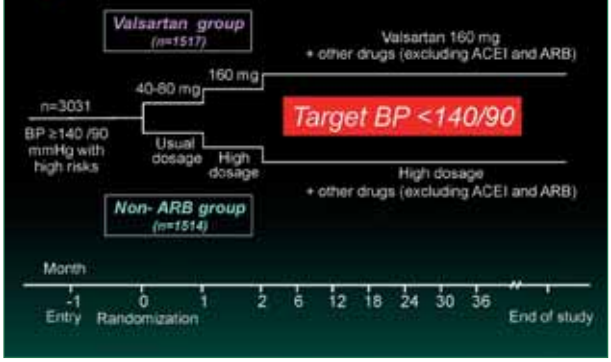
KYOTO HEART Study: Effect of Valsartan on cardiovascular outcomes in patients with high-risk hypertension: updated ancillary analyses

H.Matsubara, T.Sawada, H. Yamada, S. Kimura, J. Shiraishi
Kyoto Prefectural University of Medicine, Kyoto, Japan

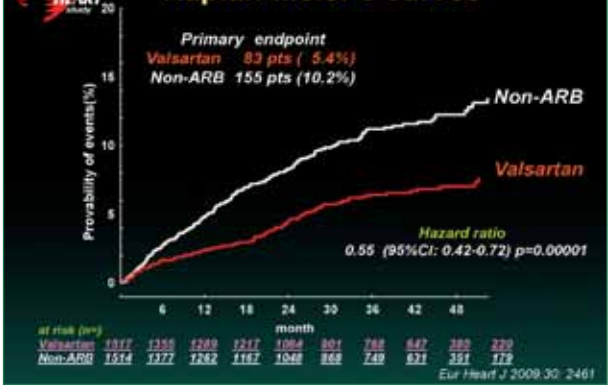
Conflict of Interest

- 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.

Scheme of study protocol

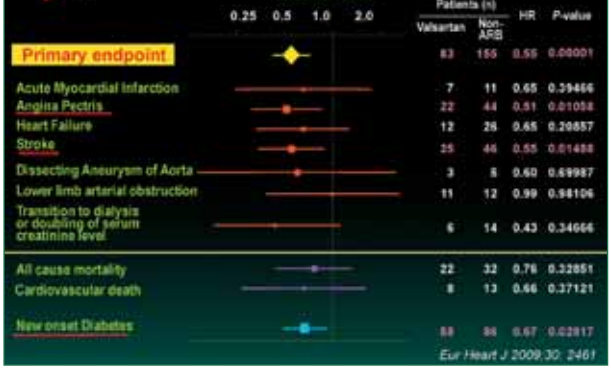


Kaplan-Meier's curves



Eur Heart J 2009;30: 2461

Hazard ratio and 95% confidence intervals



Eur Heart J 2009;30: 2461

Study purpose

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

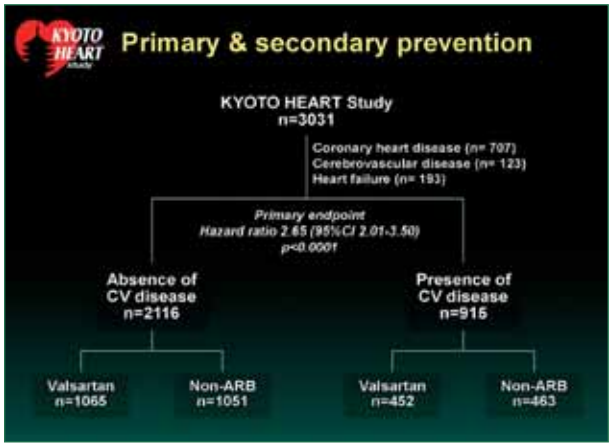
1) Effects of valsartan on primary and secondary prevention
2) Combination therapy with calcium channel blockers (CCB)
3) Additional analysis of angina & stroke events

Method-1

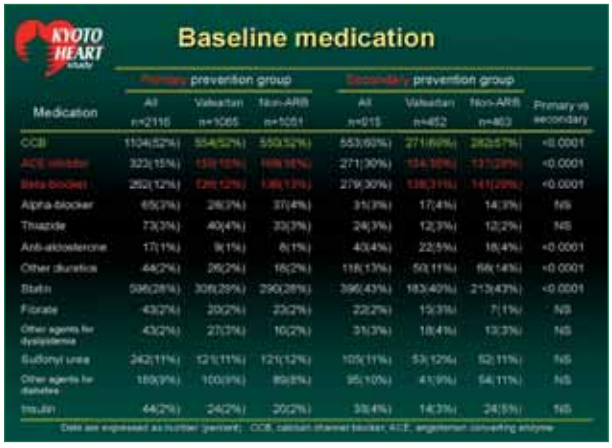
- Primary & secondary prevention
  - The population was divided into two groups according to the presence of previous CV events at the entry.
  - Primary endpoint: the same as in the main study.
    A composite of CV events such as stroke/TIA, MI, worsening HF, angina, dissecting aortic aneurysm, lower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

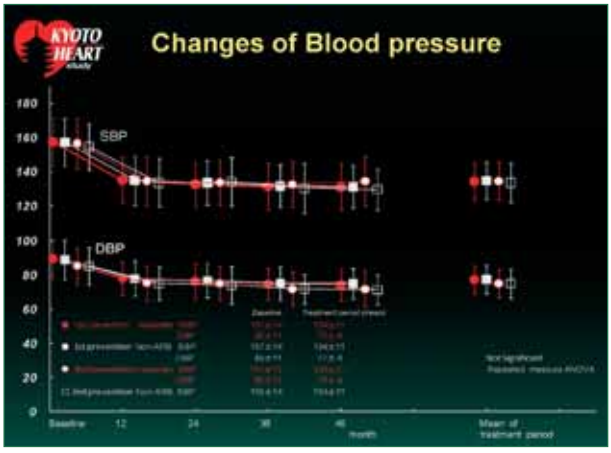
Method-2

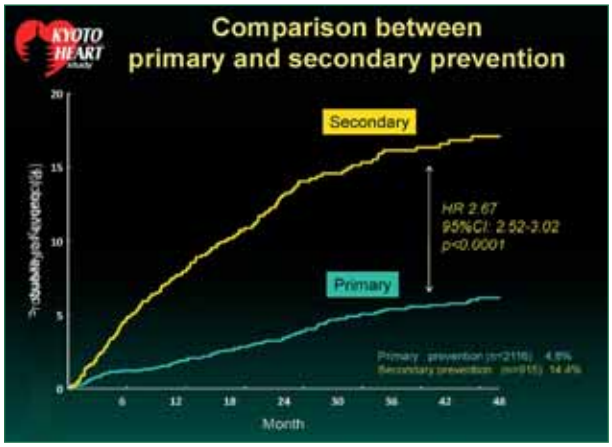
- Additional analysis of angina pectoris
  - Diagnosis of angina pectoris
    - hospital admission, ECG changes with chest syndrome, with CAG finding (>75% organic stenosis).
  - Angina events were classified into effort angina or unstable angina according to the clinical record file.
    - Guidelines on the management of stable angina pectoris. (Eur Heart J 2006;27:1341).
    - ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction—executive summary. 2007 Aug 14. 75.

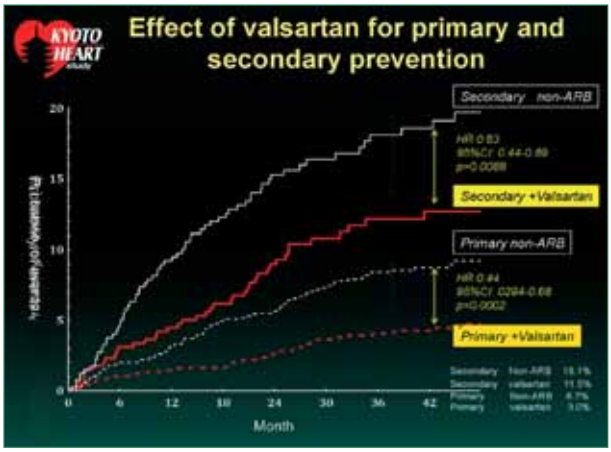

KYOTO HEART study
Primary & secondary prevention
KYOTO HEART Study
n=3031
Coronary heart disease (n= 707)
Cerebrovascular disease (n= 123)
Heart failure (n= 193)
Primary endpoint
Hazard ratio 2.65 (95%CI 2.01-3.50)
p<0.0001
Absence of CV disease n=2116
Presence of CV disease n=915
Valsartan n=1065
Non-ARB n=1051
Valsartan n=452
Non-ARB n=463

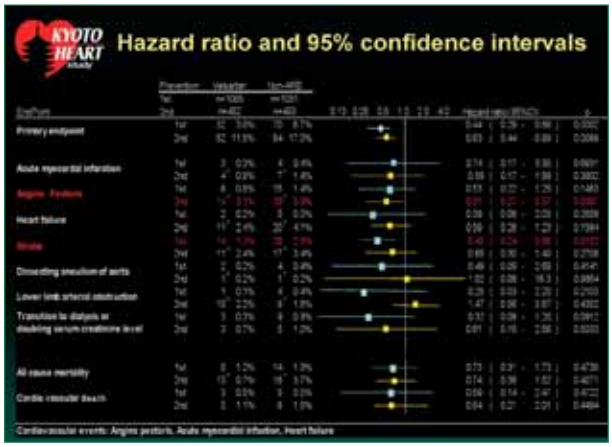

KYOTO HEART study
Baseline characteristics
Primary prevention group
Secondary prevention group
Medication
All
Valsartan
Non-ARB
Primary vs secondary
Age (years)
Gender (M/F)
SBP (mmHg)
DBP (mmHg)
Heart rate (/min)
BMI (kg/m²)
Risk factors
Smoking
Diabetes
Dyslipidemia
Obesity
LVH
CVD
CHD
Heart Failure

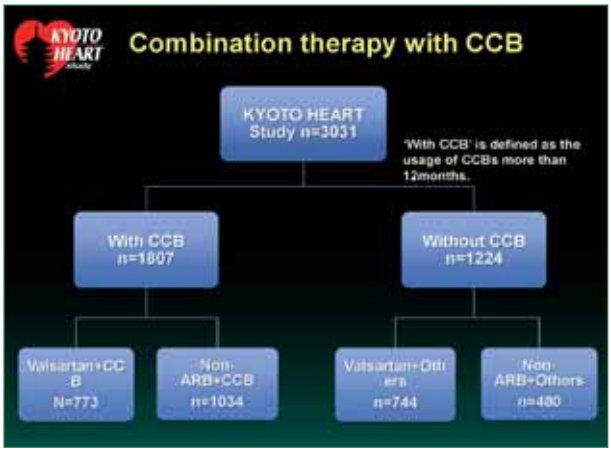

KYOTO HEART study
Baseline medication
Primary prevention group
Secondary prevention group
Medication
All
Valsartan
Non-ARB
Primary vs secondary
CCB
ACE inhibitor
Beta-blocker
Alpha-blocker
Thiazide
Anti-aldosterone
Other diuretics
Statin
Fibrate
Other agents for dyslipidemia
Sulfonyl urea
Other agents for diabetes
Insulin


KYOTO HEART study
Changes of Blood pressure
SBP
DBP
mmHg
month
Baseline
Mean of treatment period


KYOTO HEART study
Comparison between primary and secondary prevention
Secondary
Primary
HR 2.67
95%CI: 2.52-3.02
p<0.0001
Month


KYOTO HEART study
Effect of valsartan for primary and secondary prevention
Secondary non-ARB
Secondary +Valsartan
Primary non-ARB
Primary +Valsartan
HR 0.83
p=0.0088
HR 0.44
p<0.0001
Month


KYOTO HEART study
Hazard ratio and 95% confidence intervals
Primary endpoint
Acute myocardial infarction
Angina Pectoris
Heart failure
Stroke
Dissecting aneurism of aorta
Lower limb arterial obstruction
Transition to dialysis or doubling serum creatinine level
All cause mortality
Cardio vascular death
Cardiovascular events: Angina pectoris, Acute myocardial infarction, Heart failure

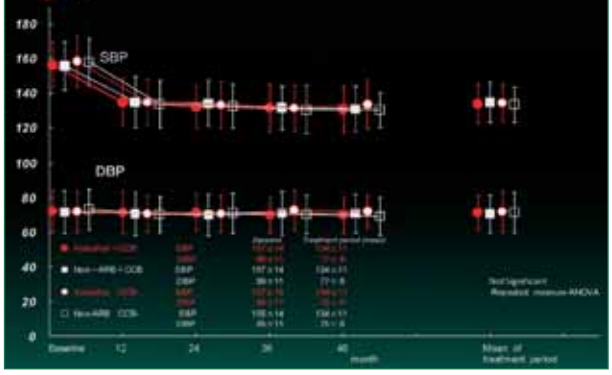

KYOTO HEART study
Combination therapy with CCB
KYOTO HEART Study n=3031
'With CCB' is defined as the usage of CCBs more than 12months.
With CCB n=1807
Without CCB n=1224
Valsartan+CCB N=773
Non-ARB+CCB n=1034
Valsartan+Others n=744
Non-ARB+Others n=480

Baseline characteristics

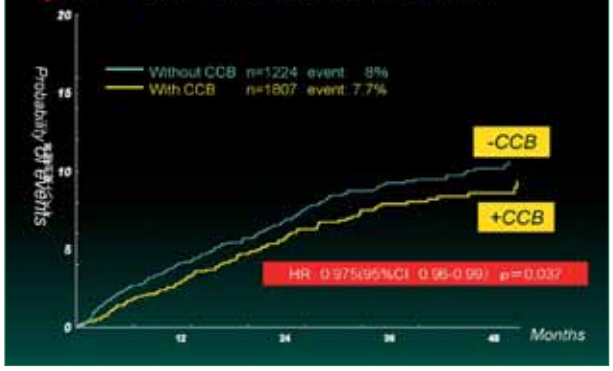
Medication	Valsartan+CCB n=773	Valsartan+others n=744	non-ARB+CCB n=1034	non-ARB+others n=480	
Age (years)	67+/-11	65+/-12	67+/-11	67+/-11	NS
Gender (M/F)	415/358	446/298	583/451	284/196	NS
SBP (mmHg)	156+/-14	159+/-15	156+/-14	156+/-14	NS
DBP (mmHg)	87+/-11	90+/-12	87+/-11	90+/-12	NS
Heart rate (/min)	70+/-17	69+/-18	71+/-15	70+/-18	NS
BMI (kg/m²)	25+/-4	25+/-4	25+/-4	24+/-4	NS
Risk factors					
Smoking	154(20%)	187(25%)	219(21%)	113(24%)	NS
Diabetes	210(27%)	191(26%)	282(27%)	124(26%)	NS
Dyslipidemia	556(72%)	509(68%)	734(71%)	345(72%)	NS
Obesity	327(42%)	266(36%)	415(40%)	169(35%)	NS
CVD	32(4%)	26(3%)	50(5%)	15(3%)	NS
CHD	201(26%)	154(21%)	255(25%)	97(20%)	NS
Heart Failure	37(5%)	47(6%)	79(8%)	30(6%)	NS

CVD, cerebrovascular disease; CHD, coronary heart disease

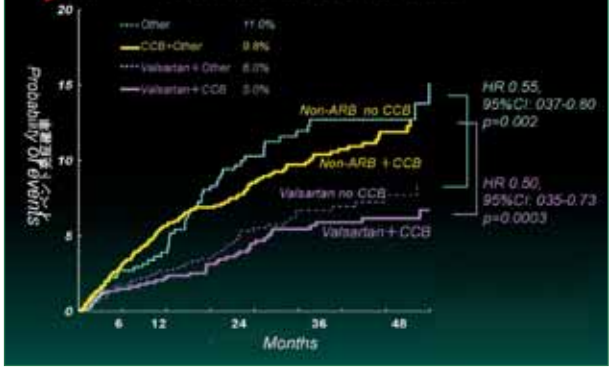
Changes of Blood pressure



Comparison between With CCB and Without CCB



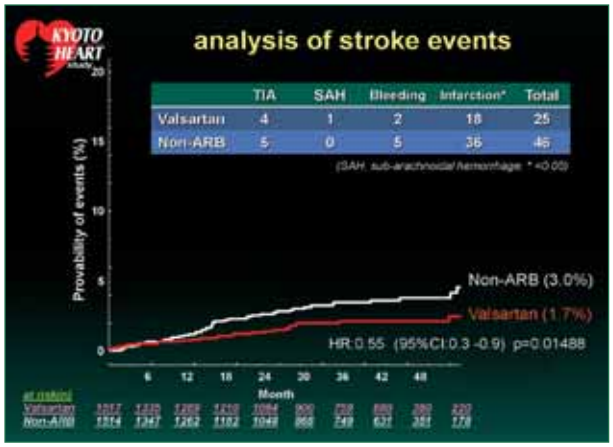
Combination therapy With valsartan and CCB



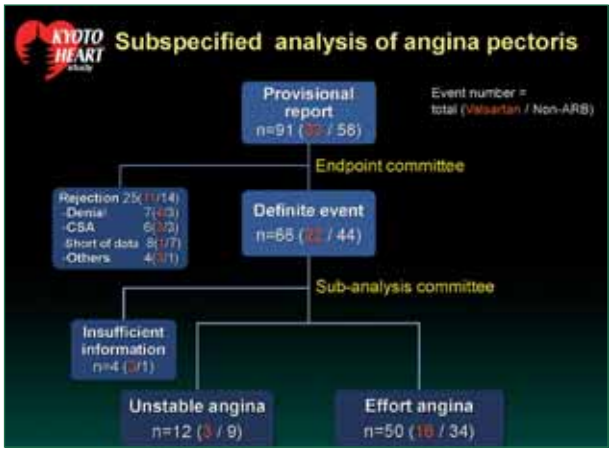
analysis of stroke events

	TIA	SAH	Bleeding	Infarction*	Total
Valsartan	4	1	2	18	25
Non-ARB	5	0	5	36	46

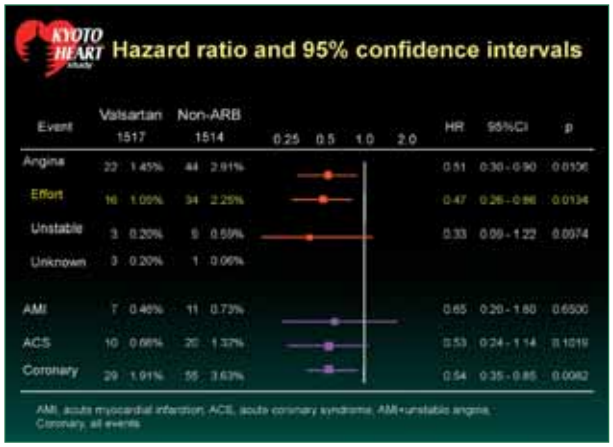
(SAH: sub-arachnoidal hemorrhage; * =0.05)



Subspecified analysis of angina pectoris



Hazard ratio and 95% confidence intervals



AMI, acute myocardial infarction; ACS, acute coronary syndrome; AMI+unstable angina; Coronary, all events

Summary

- Valsartan was more effective for both primary prevention (3.0% vs 6.7%) and secondary prevention (11.5% vs 18.1%), in which primary stroke and secondary AP events are significantly inhibited, respectively.
- Combination with Valsartan+CCB showed lower primary events than non-ARB+CCB (5.0% vs 9.8%)
- Stroke prevention by Valsartan was mainly due to inhibition of cerebral infarction (18 vs 36) but not bleeding.
- Valsartan was significantly effective for prevention of effort angina (1.1% vs 2.3%), but not for unstable angina (0.20% vs 0.59%, p=0.10).

Limitations

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

Study organization

Executive committee
Hiroaki Matsubara (Chair), Kyoto Prefectural University of Medicine (KPUM)
Björn Dahlöf, Sahlgrenska University Hospital/ Östra, Göteborg, Sweden
Steering committee: Takahisa Sawada (Main Steering Committee), Tomosaburo Takahashi, Hiroyuki Yamada, KPUM
Endpoint committee: Jitsuo Higaki, Ehime University Graduate School of Medicine; Shokei Kim-Mitsuyama, Kumamoto University School of Medicine; Toshihiro Ichiki, Kyushu University School of Medicine
Safety committee: Masafumi Kitakaze, National Cardiovascular Center; Tetsuro Sugiura, Kochi University School of Medicine; Hiromi Rakugi, Osaka University School of Medicine
Sub-analysis committee for angina pectoris
Hiroyuki Yamada, Takeshi Nakamura, Takahisa Sawada, KPUM
Data and safety monitoring board: Katsumi Yagi, Louis Pasteur Center for Medical Research; Keiichi Kanda, Chouhei Sakakura, KPUM
Statistical analysis organization
Katsumi Yagi, Louis Pasteur Center for Medical Research
Data monitoring board: Marika Miki, Sachiko Toyoda, KPUM

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

[1]Cheuk-Man Yu, [1]Joseph Yat-Sun Chan, [1]Fang Fang, [1,2]Qing Zhang, [3]Omar Razali, [1]Gabriel Wai-Kwok Yip, [3]Hussin Azlan, [4]Hamish Chi-Kin Chan, [1,5]Jeffrey Wing-Hong Fung

[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 Cardiology, West China Hospital, Sichuan University, China
[3] Department of Cardiology, National Heart Institute, Kuala Lumpur, Malaysia
[4] Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong
[5] Department of Medicine, North District Hospital, Hong Kong

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

Presenter Disclosure Information

- *< Cheuk-Man, YU >*
- *<Result of the 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

Background

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

PACE

Background

Biventricular (BiV) pacing
- Preserve myocardial performance better than RVA pacing in the presence of atrioventricular block and normal systolic function
  - in animal model &
  - in acute hemodynamic studies in patients with LV ejection fraction >40%

Picture from Boston Scientific

PACE

Background

- The recently published Pacing to Avoid Cardiac Enlargement (PACE) study is a
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PA

Background

Dyssynchrony

Synchrony

PACE

Hypothesis & Study Design

Pre-specified analysis in the PACE study to determine whether pacing-induced systolic dyssynchrony is the major determinant of deterioration of ejection fraction and LV remodelling at 12 months.

This will provide important insights for determination of patient groups who might benefit most from BiV pacing

PACE

Patients

Inclusion criteria

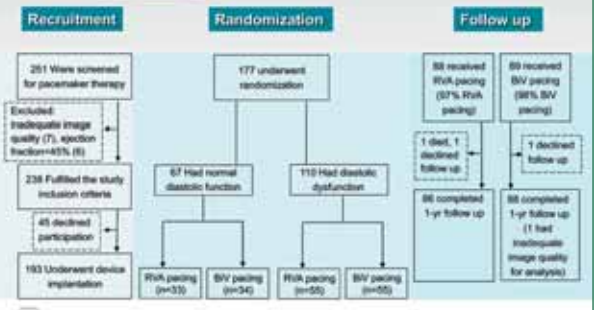
- Patients with normal LV ejection fraction (≥45%) who had standard pacing indications (advanced AV block in 59%, sinus-node dysfunction in 41%)

Exclusion criteria

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

PACE

Study flowchart

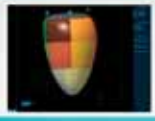


PACE

Echocardiography

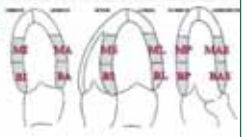
LV volumes and ejection fraction

- Real-time 3-dimensional echocardiography (iE33, Philips) performed in 90% of the patients
- Biplane Simpson's method was used in the others
- Follow-up : baseline and 12 months



LV systolic dyssynchrony

- Tissue Doppler imaging (TDI) to assess LV systolic dyssynchrony at 1 month (Vivid 7, GE)
- Systolic Dyssynchrony Index assessed with 12- LV segmental model (Ts-SD or Yu's index, JASE 2008;21:191-213.), a cutoff value >33ms defined significant dyssynchrony



PACE

Study End-points

Primary End-points

- LV ejection fraction at 12 months
- LV end-systolic volume at 12 months

Pre-specified secondary end-point

- Early occurrence of systolic dyssynchrony at 1 month (>33ms)

Definition of significant deterioration of LV systolic function

- Reduction of LV ejection fraction ≥5% at 12 months

PACE

Baseline Characteristics

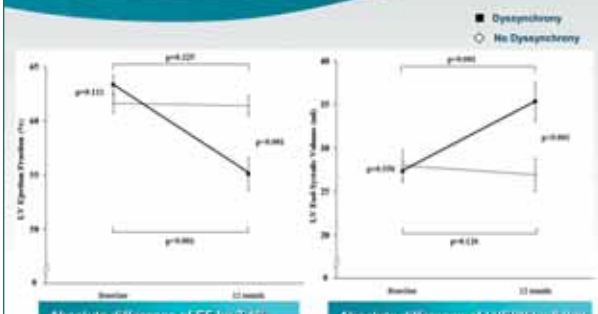
Variables	Dyssynchrony Group (>33ms) (n=59)	No Dyssynchrony Group (<33ms) (n=118)	P value
Patient's characteristics			
Age – years	70±11	68±12	0.168
Male sex – no. (%)	30 (51)	66 (56)	0.315
Body-mass index, kg/m²	24.1±3.8	24.3±5.8	0.937
Systolic blood pressure – mmHg	146±23	145±23	0.876
Diastolic blood pressure – mmHg	69±13	72±12	0.231
Heart rate – bpm	57±16	59±18	0.593
QRS duration – ms	111±30	104±27	0.139
Indication for pacing – no. (%)			
Advanced atrioventricular block	36 (61)	68 (58)	0.395
Sinus node dysfunction	23 (39)	50 (42)	
Medical history – no. (%)			
Hypertension	40 (68)	77 (65)	0.436
Diabetes mellitus	13 (22)	36 (27)	0.156
Coronary heart disease	14 (24)	25 (21)	0.419
Heart failure	10 (17)	12 (10)	0.148

Results

- Systolic dyssynchrony at 1 month (Dyssynchrony Group) occurred in 52% (n=46) of patients with RVA pacing, but only 15% (n=13) with BiV pacing (p<0.001)
- The Dyssynchrony Group had significantly lower LV ejection fraction with an absolute difference of 7.1% (p<0.001)
- LV end-systolic volume increased significantly in the Dyssynchrony Group with a relative difference of 30.7% (p<0.001)
- Reduction of ejection fraction ≥5% occurred in 67% (39 out of 58) of patients in the Dyssynchrony Group, but only in 18% (21 out of 115) in the No Dyssynchrony Group (p<0.001)

PACE

Comparison of Primary End-points

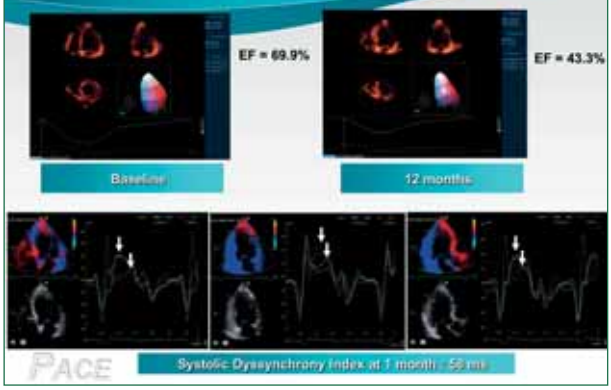


Absolute difference of EF by 7.1%

Absolute difference of LVESV by 6.3ml

PACE

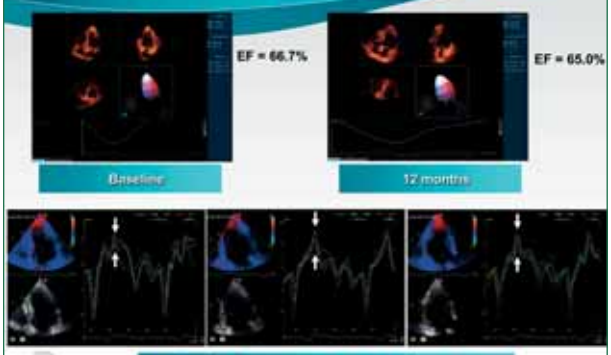
RVA pacing, Dyssynchrony at 1 month



PACE

Systolic Dyssynchrony Index at 1 month : 58 ms

BiV pacing, No Dyssynchrony at 1 month



PACE

Systolic Dyssynchrony Index at 1 month : 11 ms

Predictors of significant reduction in LV ejection fraction at 12-month

	Univariate		Multivariate	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, year	1.000 (0.972-1.029)	0.988	0.988 (0.949-1.028)	0.542
Gender	0.960 (0.512-1.800)	0.898	0.860 (0.387-1.908)	0.710
QRS duration at baseline, ms	1.010 (0.999-1.021)	0.062	1.008 (0.995-1.022)	0.236
Pre-existing diastolic dysfunction	1.184 (0.617-2.271)	0.611	1.417 (0.585-3.434)	0.440
Pre-existing hypertension	0.722 (0.375-1.391)	0.330	0.799 (0.333- 1.916)	0.615
Pre-existing diabetes mellitus	0.616 (0.296-1.282)	0.195	0.668 (0.264-1.692)	0.395
Pre-existing coronary heart disease	0.715 (0.326-1.566)	0.402	0.729 (0.271-1.957)	0.530
Systolic dyssynchrony at 1 month	5.187 (4.453-18.554)	<0.001	7.081 (3.164-15.848)	<0.001
RV pacing mode	4.119 (2.095-8.110)	<0.001	2.373 (1.079-5.264)	0.033

PACE

Discussion

Major findings in the study

- Systolic dyssynchrony was the main pathophysiological mechanism of detrimental effect of RVA pacing on LV function
- Majority of patients developing early systolic dyssynchrony after pacing are attributable to RVA pacing
- Patients with early systolic dyssynchrony had a seven-fold risk of significant reduction of LV ejection fraction at 12 months regardless of pacing mode
- RVA pacing exerts additional deleterious effect on LV function – mechanisms ?
- BiV pacing mode protect patients from adverse outcome and dramatically reduce the occurrence of systolic dyssynchrony

PACE

Discussion

Clinical implications

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

PACE

ALPHA OMEGA: Effect of low doses of n-3 fatty acids on cardiovascular diseases in post-MI patients. Editorial Comment

Luigi Tavazzi
GVM Care&Research, Cotignola, IT
Discussant

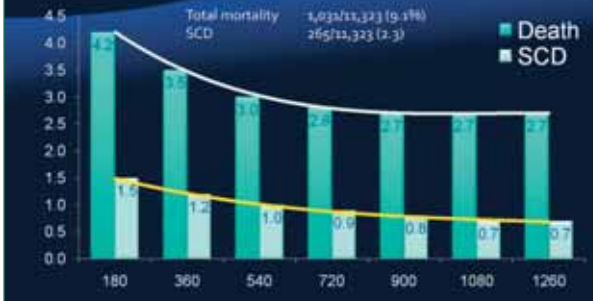
Why neutral results?

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

Assumptions

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

GISSI-Prevenzione trial (1999)

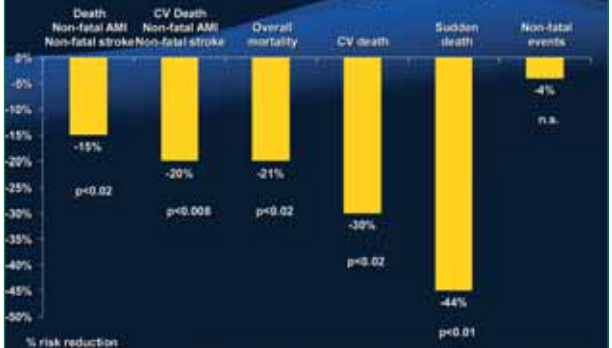


- During the course of the study the Steering Committee approved an increase in sample size from 4,000 to 4,837 subjects and an extended duration of intervention from 36 to 40 months.
- In 2009 the original primary endpoint of "fatal CHD" was replaced by "major CV events" (including all fatal/non-fatal CV events and therapeutic interventions)

Why neutral results?

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

Effect of n-3 PUFA treatment in GISSI-Prevenzione (11.323 post-MI pts)



(GISSI-Prevenzione Investigators, Lancet 1999; 354:447)

Why neutral results?

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

Methods

- Subjects were identified by hospital cardiologists, physically examined at enrollment by trained research nurses, and followed up by research staff through telephone interviews at 12 and 24 months (only)
- Non-fatal cardiovascular events were self-reported and verified *(if known)* against hospital records *(if available)*, otherwise they were not considered

ALPHA OMEGA:

Effect of low doses of n-3 fatty acids on cardiovascular diseases in post-MI patients

Daan Kromhout, MPH PhD

for the Alpha Omega Trial Group

Wageningen University, Division of Human Nutrition, The Netherlands

ESC, Stockholm, 29 August 2010

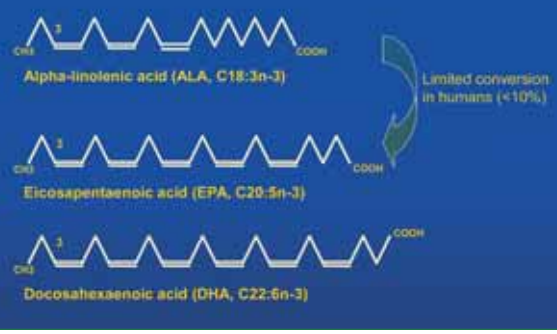
GRANTS

- Netherlands Heart Foundation, The Hague, The Netherlands
- National Institutes of Health, Bethesda MD, U.S.A.
- Unilever, Vlaardingen, The Netherlands
- Presenter disclosure: no conflicts of interest

TRIAL CONDUCT

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

N-3 FATTY ACIDS



HYPOTHESES

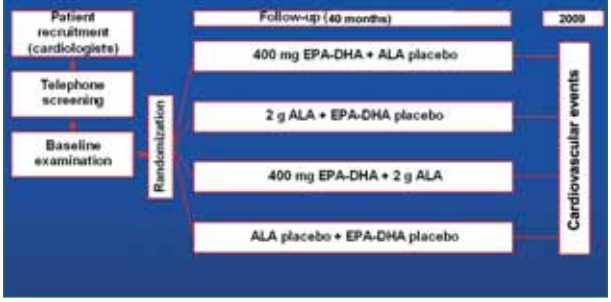
N-3 fatty acids reduce the risk of:

- major cardiovascular events
- fatal coronary heart disease
- ventricular arrhythmia-related events

PATIENT CHARACTERISTICS

	EPA+DHA and ALA n=1212	EPA+DHA n=1192	ALA n=1197	Placebo n=1236
Age, y	69 ± 6	69 ± 6	69 ± 6	69 ± 6
Men, %	78	78	78	79
Time since MI, y	4.2 ± 3.1	4.3 ± 3.2	4.4 ± 3.3	4.3 ± 3.3
Diabetes mellitus, %	20	22	22	20
Cardiovascular medication, %				
Antithrombotic agents	96	96	96	96
BP lowering drugs	90	91	88	89
Lipid lowering drugs	87	85	86	85
Antiarrhythmic drugs	3	3	3	3
Systolic blood pressure, mmHg	141 ± 22	142 ± 22	141 ± 21	142 ± 22
Serum total cholesterol, mmol/l	4.7 ± 1.0	4.8 ± 1.0	4.7 ± 1.0	4.8 ± 1.0
Body mass index, kg/m²	27.6 ± 4.0	27.7 ± 3.7	27.6 ± 3.8	27.6 ± 3.9
Current smoker, %	15	17	17	18

DESIGN ALPHA OMEGA TRIAL



TRIAL MARGARINES

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

Daily doses of n-3 fatty acids in the 4 groups:

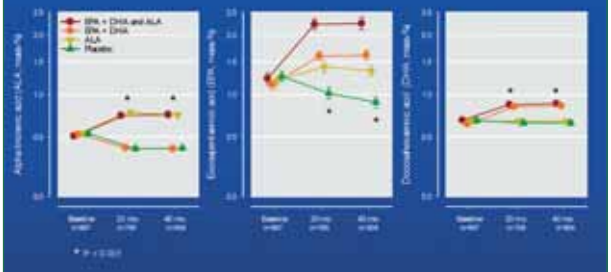
I: 400 mg EPA+DHA
II: 2 g ALA
III: 400 mg EPA+DHA and 2 g ALA
IV: 0 mg EPA+DHA, 0 mg ALA

PARTICIPATING CENTERS

Centers are listed at www.alphaomegatrial.com

COMPLIANCE

Change in plasma n-3 fatty acids during the trial



ENDPOINTS

Primary outcome

Major cardiovascular events: fatal and non-fatal cardiovascular events and cardiac interventions (PCI, CABG)

Secondary outcomes

Incidence of cardiovascular diseases

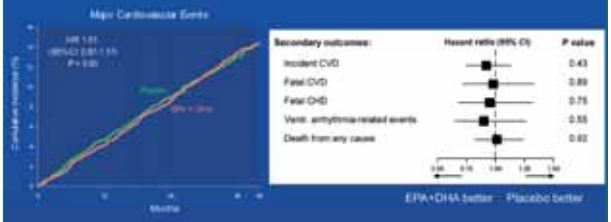
Fatal cardiovascular diseases

Fatal coronary heart disease

Ventricular arrhythmia-related events: sudden death, cardiac arrest and placement of implantable cardioverter-defibrillator

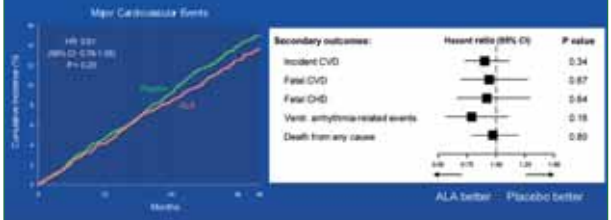
Death from any cause

EPA+DHA AND ENDPOINTS



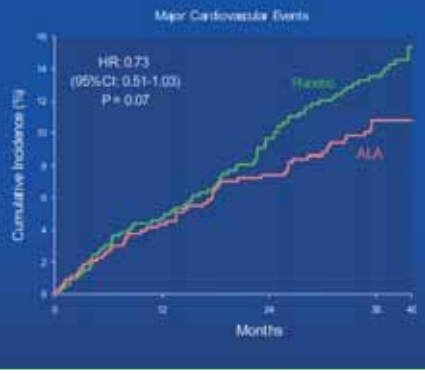
Findings were similar in men and women

ALA AND ENDPOINTS



Findings differed between men and women

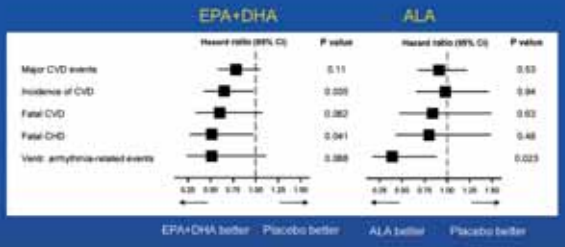
RESULTS IN WOMEN



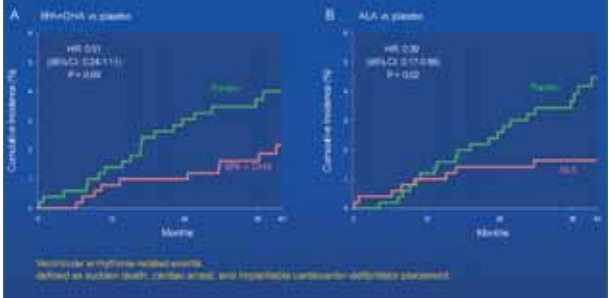
Post-hoc analysis

Patients with diabetes (n=1,014) had 30% higher risk of major cardiovascular events than non-diabetics (n=3,823)

RESULTS IN DIABETIC PATIENTS



VENTRICULAR ARRHYTHMIA-RELATED EVENTS IN DIABETIC PATIENTS



CONCLUSIONS

- In the total patient population, low doses of n-3 fatty acids were not related to major cardiovascular events
- In ***women***, ALA reduced major cardiovascular events borderline significantly
- In ***diabetic patients***, n-3 fatty acids reduced ventricular arrhythmia-related events (exploratory analysis)

IMPLICATIONS

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

Predicted and observed cases in the Alpha Omega Trial

- Predicted fatal CHD cases based on trials in the 1990's n=360
- Observed fatal cases in the Alpha Omega Trial:
  - Coronary heart disease n=138
  - Cardiovascular diseases n=162

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

Drug treatment	DART	GISSI-P	OMEGA	AOT
Antiplatelet (%)	10.2	87.9	95.0	97.6
Cholesterol-lowering (%)	NA	28.6	94.0	85.0
ACEI/ARB (%)	NA	40.9	83.0	56.4
BP-lowering	NA	NA	NA	89.7
CVD risk reduction (%)	31.0	17.7	No diff	No diff

NA: not available

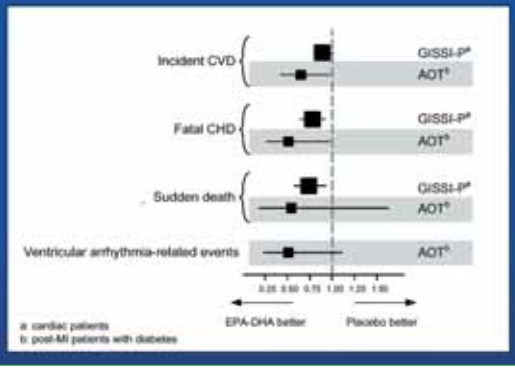
Adapted from Saravanan et al Lancet 2010;375:540-50

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

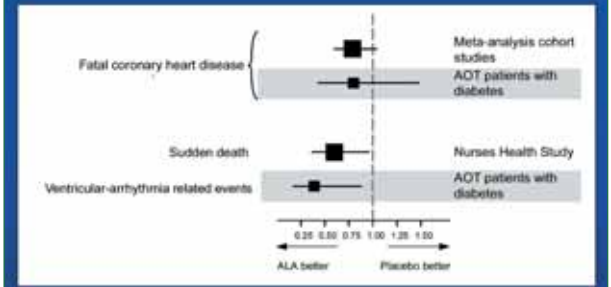
Fish consumption (servings/week)	Increase of stenosis Mean ± SEM
< 2	4.54 ± 1.37
≥ 2	-0.06 ± 1.59
P-value	0.003

Erkkilä et al Am J Clin Nutr 2004;80:626-32

RESULTS EPA-DHA IN GISSI-P AND AOT



RESULTS FOR ALA



PEARL-HF: A Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose Study to Evaluate the Effects of RLY5016 in Heart Failure Patients:

Authors (Disclosures):

Bertram Pitt, MD (Relypsa*; AstraZeneca; Medtronic; Bayer; Boehringer Ingelheim; Merck; Bayer; Novartis; Takeda; AstraZeneca; GE Healthcare; Forest Labs; Novartis; Abbott; BG Medicine; Pfizer*), **I-Zu Huang, MD** (Relypsa*; Anthera*), **Stefan Anker, MD, PhD** (Relypsa), **Dalal Bushinsky, MD** (Relypsa*; Amgen; Cytochroma; Genzyme), **Dalane Kitzman, MD** (Relypsa*; BMS/Lantheus Medical Imaging; Abbott; Boston Scientific; Emiyaxe; Gilead; Medtronic; Novartis), **Faiez Zannad, MD, PhD** (Relypsa; Abbott; AstraZeneca; Boehringer Ingelheim; Boston Scientific; Daiichi Sankyo; Medtronic; Merck; Novartis; Otsuka; Pfizer; Resmed; Servier; Takeda;)

*steak options

Hyperkalemia – Risks

"2.4 % mortality within 1 day of occurrence of hyperkalemia (K ≥ 5.5 mEq/L) (5900 deaths in 245,000 VA patient database within one day of serum blood draw)."*

2 Key Risk Factors

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

*Einhorn et al., 169 (ed 12) Arch Intern. Med. 1106 (June 22, 2009)

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

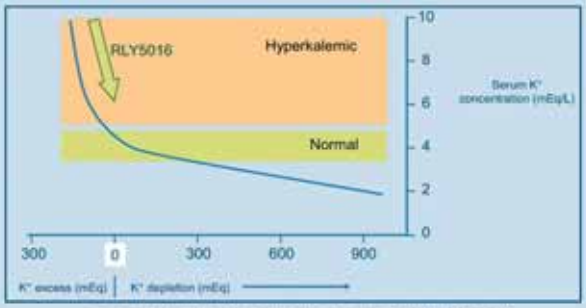
RLY5016	Property	Kayexalate
Non absorbed, well tolerated	Safety	Colonic Necrosis (black box warning) GI side effects
Spheres of uniform size/free flowing beads	Design/API	Irregular, sharp edges and fines/clay-like
No Na^+	Counterion	Na^+ loaded
Twice Kayexalate	Binding *in vitro*	Low binding
4 clinical studies with proven K^+ binding	Data/Dev Path	Grandfathered-in
Lower dose, non-gritty/neutral taste sachet (QD possible)	Dosing/ Compliance	Gritty, bad taste, up to 60 g TID

Site of Action for RLY5016

RLY5016 is designed to bind potassium in the colon, where the concentration of potassium is highest

Data sources:
1. Wong, G. and A. Mahaffey-Sibson (1985). "The electrolyte content of faeces." Proc R Soc Med 78(12): 1007-1008.
2. Forshaw, J. S. and T. W. Lockner (1985). "Some constituents and osmolality of gastric and small-intestinal fluids after eating." Am J Dig Dis 17(7): 669-681.
3. Relypsa data

Reduction In Total Potassium Excess Rapidly Normalizes Serum K^+



Brown, R. S. (1984). "Potassium homeostasis and clinical implications." Am J Med. 77(5A): 3-10.

Potassium Binding by RLY5016 and Effects on Serum K

- A 30 g/day dose of RLY5016 provides ~25 mEq/day extra excretion of potassium

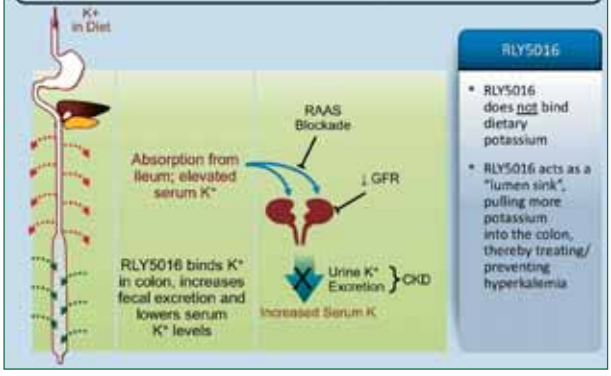
Initial Serum K Value (mEq/L)	Ending Serum K Value (mEq/L)
6.5	5.5
6.0	5.4
5.5	4.9
5.0	4.5
4.5	4.1
4.0	3.8
3.5	3.4

25 mEq/d additional potassium removal has more of an effect at higher serum K values than at lower serum K values*

*Assumption from the Brown/Hollis graph of serum K vs. TBK fecal potassium excretion is maximal.

Brown, R. S. Potassium homeostasis and clinical implications. Am J Med. 77(5A): 3-10 (1984) and Hollis, H. "Disorders of potassium balance" in Renal Dysfunction: Mechanisms Involved in Fluid and Solute Imbalance, pp. 99-111, Little, Brown and Company (1973).

RLY5016 Mechanism of Action: Reduction of Serum Potassium in Hyperkalemia



RLY5016

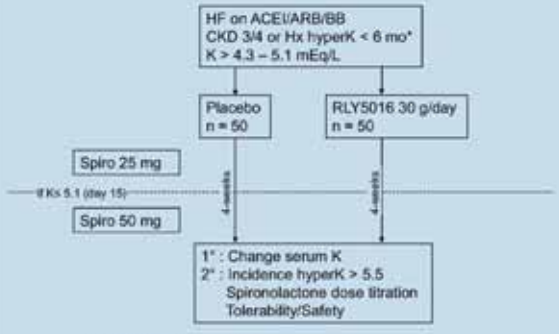
- RLY5016 does not bind dietary potassium
- RLY5016 acts as a "lumen sink", pulling more potassium into the colon, thereby treating/ preventing hyperkalemia

RLY5016 Drug Interaction Information

- RLY5016 is a cation-binder, so it may potentially inhibit the absorption of positively-charged drugs
- 18 drug interaction studies have been conducted with RLY5016 in rats (no human data is available)
  - The bioavailability of valsartan and rosiglitazone was reduced by 30%
  - No change in bioavailability was observed for:

• Enalapril	• Losartan	• Digoxin	• Spironolactone
• Quinapril	• Irbesartan	• Warfarin	• Eplerenone
• Lisinopril	• Metoprolol	• Glipizide	• Furosemide
• Ramipril	• Verapamil	•Atorvastatin	• Trimethoprim

PEARL-HF Study Design



PEARL-HF: Demographics

Parameter	RLY5016 30 g/day (n = 55)	Placebo (n = 49)	P value
Age (yrs)	68.3 ± 8.6	69.2 ± 10.5	0.940
Gender Male Female	 53% 47%	 69% 31%	0.108
BMI (kg/m²)	28.4 ± 5.5	27.0 ± 4.3	0.145
HF Duration (yrs)	4.5 ± 4.8	4.1 ± 3.4	0.581
Ejection Fraction (%)	39.6 ± 11.7	41.2 ± 11.8	0.561
NYHA Class I II III IV	 4% 53% 44% 0%	 2% 57% 41% 0%	0.936
eGFR (Cockroft-Gault)	64.1 mL/min	78.1 mL/mon	0.360
Diabetes Yes No	 27% 73%	 37% 63%	0.309

PEARL-HF: Baseline Medications

Drug	RLY5016 30 g/day (n = 55)	Placebo (n = 49)	P-value
No RAAS inhibitors or β-blockers*	0 (0%)	2 (4%)	NS
ACE, ARB, or BB only	13 (24%)	9 (18%)	NS
ACE or ARB + β-blocker	40 (73%)	37 (76%)	NS
ACE inhibitor + ARB + β-blocker	2 (4%)	1 (2%)	NS
Diuretics (Total) Thiazide** Loop** Indapamide**	41 (75%) 10 (18%) 32 (58%) 4 (7%)	36 (73%) 6 (12%) 27 (55%) 5 (10%)	NS NS NS NS

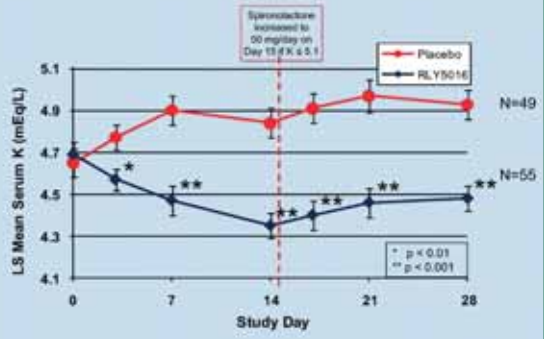
*Patients qualified under criteria 1B (discontinuation of RAAS inhibitor or β-blocker due to hyperkalemia)
NS = Not statistically significant at 0.10 level

PEARL-HF Primary Efficacy Endpoint: Change from BL in Serum K (N=104)

Serum K (mEq/L)	RLY5016 30 g/day (n = 55)	Placebo (n = 49)	P value
Baseline	4.69 ± 0.06	4.65 ± 0.07	0.664
Endpoint (LOCF)	4.48 ± 0.07	4.93 ± 0.07	<0.001
Change from Baseline	-0.22 ± 0.07	0.23 ± 0.07	<0.001
Difference RLY5016 vs Placebo	-0.45 ± 0.09		<0.001

All serum potassium values are least squares (LS) mean with standard errors (SE) of LS mean

PEARL-HF Primary Efficacy Endpoint: Change from BL in Serum K (LOCF) by Study Visit



PEARL-HF Efficacy: Proportion of Patients Able to Increase Spironolactone Dose to 50 mg/day

	RLY5016 30 g/day (n = 55)	Placebo (n = 49)	P value
Patients able to up-titrate spiro dose	50 (91%)	36 (74%)	0.019

PEARL-HF Efficacy: Change from BL in Serum K by GFR

GFR (mL/min)	N RLY/PBO	Difference in change in serum K (mEq/L)	P value
< 45	7/9	0.56	0.056
< 60	15/13	0.52	0.031
≥ 60	40/36	0.35	0.001
All patients (GFR = 81 ± 33)	**55/49**	**0.45**	**<0.001**

GFR (central lab values)

PEARL-HF: Proportion of Patients with Serum K > 5.5 mEq/L by eGFR

PEARL-HF: AE Summary

	RLY5016 30 g/day (n = 56)	Placebo (n = 49)	p-value
Number of patients with at least 1 AE	30 (54%)	15 (31%)	0.019
Number of patients with at least 1 GI AE	12 (21%)	3 (6%)	0.028
Number of patients with SAEs*	2 (4%)	2 (4%)	NS
Number of patients who died	0 (0%)	1 (2%)	NS
Number of patients who discontinued the study due to AE	4 (7%)	3 (6%)	NS

* No SAEs assessed drug-related by the investigators

PEARL-HF: GI AEs (most common)

Number of patients reporting

GI Adverse Events	RLY5016 30 g/day (n = 56)	Placebo (n = 49)
Flatulence*	4 (7%)	0 (0%)
Diarrhea*	3 (5%)	1 (2%)
Constipation*	3 (5%)	0 (0%)
Vomiting*	2 (4%)	0 (0%)

All reported GI adverse events were mild to moderate in severity, except for one case of flatulence

*p-value=NS

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

GFR (mL/min)	RLY5016 30 g/day	Placebo	P value
< 45	0/7 (0%)	0/9 (0%)	NA
< 60	3/15 (20%)	0/13 (0%)	0.088
≥ 60	0/40 (0%)	0/36 (0%)	NA
All patients (GFR = 81 ± 33)	3/55 (6%)	0/49 (0%)	0.094

GFR (central lab values)

Conclusions

- The incidence of hyperkalemia (K > 5.5 mEq/L) is relatively high in patients with HF/CKD receiving standard therapy and an AA (39%-56%).
- RLY5016 30 g/d is effective in preventing hyperkalemia in HF patients with a history of hyperkalemia and HF/CKD and is relatively well tolerated with only minor GI side effects.
- Patients with HF and a history of hyperkalemia without CKD should be rechallenged with guideline recommended doses of RAAS blockers before abandoning their use.
- Future studies will be necessary to determine the optimal RLY5016 dosing regimen to prevent hyperkalemia and avoid hypokalemia in patients with HF/CKD as well as to evaluate the efficacy and safety of RLY5016 to treat hyperkalemia once it occurs.

A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction

Adriaan A. Voors, Anne M.S. Belonje, Felix Zijlstra, Hans L. Hillege, Stefan D. Anker, Riemer H.J.A. Slart, René A. Tio, Arnoud van 't Hof, J. Wouter Jukema, Hans Otto J. Peels, José P. S. Henriques, Jurriën M. ten Berg, Jeroen Vos, Wiek H. van Gilst, Dirk J. van Veldhuisen, on behalf of the HEBE III investigators

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Disclosures

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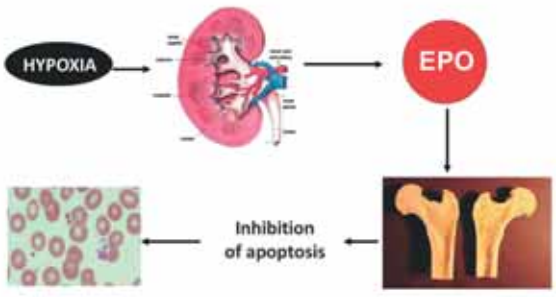
Classical Effect EPO: hematopoiesis



Experimental studies: cardioprotection with EPO

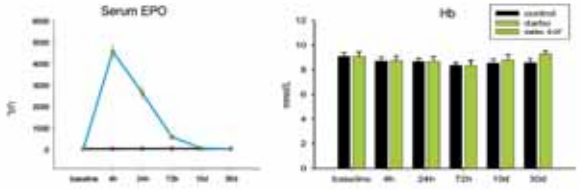
	Animal	Model	Outcome
Calvillo 2003	Rat	I/R: 30 min/7d	reduction of cardiomyocyte loss; improvement of LV function
Lipsic 2004	Rat	I/R: 40 min/1d	reduced infarct size
Parsa 2004	Rabbit	I/R: 30 min/3d	reduced infarct size ; improvement of LV function
Bullard 2005	Rat	I/R: 40 min/1d	reduced infarct size
Hirata 2005	Dog	I/R: 60 min/6h	reduced infarct size

	Animal	Model	Outcome
Parsa 2003	Rabbit	3d FU	improvement of LV function
Moon 2005	Rat	8w FU	reduced infarct size ; improvement of LV function
vd Meer 2005	Rat	9w FU	reduced infarct size improvement of LV function

Lipsic et al. JACC 2006

EPO in AMI: safety (pilot study)

In a first safety and feasibility study, a single high dose bolus of EPO (60.000 IU) in patients with a first ST-elevation myocardial infarction, resulted in a 200-fold increase in serum EPO levels, without hypertension, thrombotic, or other adverse events.



Lipsic et al. Cardiovasc Drugs Ther 2006

Methods

- Prospective, multicenter, randomized open label trial with blinded endpoints (PROBE) in 529 first ST-elevation myocardial infarction patients
- Primary Endpoint: LVEF (radionuclide ventriculography) at 6 weeks after AMI
- Secondary Endpoints:
  - Enzymatic infarct size
  - Major Adverse Cardiovascular Events
- All endpoints were assessed in a blinded manner
- Major Adverse CV-events were adjudicated by an independent and blinded endpoint committee

Belonje et al. Am Heart J 2008

Methods

- **Inclusion Criteria:**

  Successful primary PCI (TIMI 2/3) for a first AMI, diagnosed by:
  - Suggestive Chest pain
  - Symptom onset <12 h before hospital admission or <24 h in case of ongoing ischemia
  - ECG with ST-T segment elevation >1 mV in 2 or more leads or newleft bundle branch block
  - TIMI flow 0/1 before primary PCI on diagnostic coronary angiography

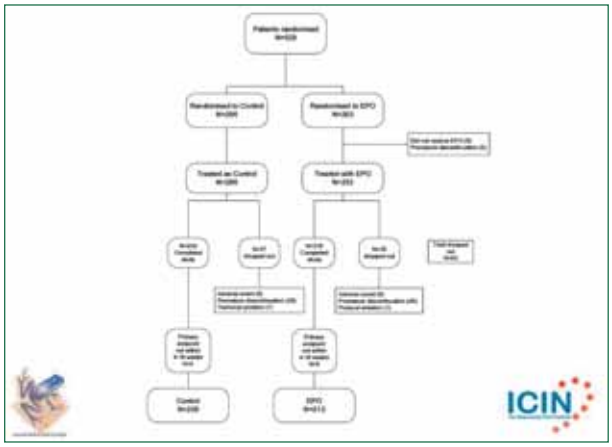
- **Key Exclusion Criteria:**
  - Previous AMI
  - Hemoglobin levels >17.1 g/dL before PCI
  - Anticipated additional revascularization within 6 wk
  - Atrial fibrillation
  - Cardiogenic shock
  - End stage renal failure
  - Malignant hypertension
  - Previous treatment with RhEPO

Belonje et al. Am Heart J 2008

Methods

- Patients with a successful PCI (TIMI 2/3) were randomized to receive either standard medical care alone, or in combination with a single bolus with 60,000 IU i.v. of Epoetin Alfa within 3 hours after PCI.
- To demonstrate 3% improvement of LVEF after EPO treatment, with a standard deviation of 11%, a power of 0.8 and a p-value < 0.05, 2-sided, 212 primary endpoints per group were needed. Estimated sample size ~528 patients.

Belonje et al. Am Heart J 2008



Baseline characteristics

	Total cohort N=529	EPO N=263	Control N=266
Age (yrs) *	60.9 ± 11.1	60.8 ± 10.9	61.0 ± 11.3
% Male	77.7	75.7	79.7
BMI (kg/m²) *	27.3 ± 4.2	27.4 ± 4.3	27.3 ± 4.0
History of Hyperlipidaemia †	98 (19.0)	53 (21.0)	45 (17.2)
Diabetes †	47 (9.1)	25 (9.9)	22 (8.4)
History of Hypertension †	174 (33.8)	84 (33.2)	90 (34.4)
Current smoker †	116 (22.7)	58 (23.2)	58 (22.2)
Fam history of CAD †	186 (36.1)	95 (37.3)	91 (34.7)
History of revascularisation †	13 (2.5)	5 (2.0)	8 (3.1)
Hb at baseline (g/dL) *	14.2 ± 1.37	14.0 ± 1.35	14.3 ± 1.29
Ht at baseline (L/L) *	0.41 ± 0.04	0.40 ± 0.04	0.41 ± 0.03
Serum Creatinine (mg/dL) §	0.86 (0.75-1.0)	0.85 (0.74-1.0)	0.87 (0.76-1.01)
Systolic BP (mmHg) *	128.5 ± 24.1	127.2 ± 24.9	129.7 ± 23.3
Diastolic BP (mmHg) *	76.8 ± 14.4	76.3 ± 15.0	77.3 ± 13.8
Heart rate (beats/min) *	74.5 ± 15.8	74.9 ± 15.5	74.2 ± 16.0

*mean±SD; †n (%); §median (IQR)

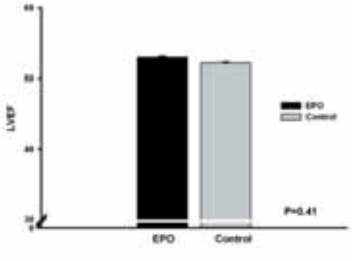
Baseline Characteristics

	Total cohort N=529	EPO N=263	Control N=266
Time from symptom onset to PCI (minutes) §	180 (120-270)	180 (126-288)	174 (120-251)
Platelet glycoprotein IIb/IIa inhibitor †	411 (77.7)	199 (75.7)	212 (79.7)
No. of diseased vessels †	348 (66.8)	170 (66.1)	178 (67.9)
1	131 (25.1)	65 (25.3)	65 (24.8)
2	42 (8.1)	22 (8.6)	19 (7.3)
3			
Infarct Related Artery †	209 (40.1)	105 (40.9)	104 (39.4)
LAD	226 (43.4)	112 (43.6)	114 (43.2)
RCA	85 (16.3)	40 (15.6)	45 (17.0)
RCx			
Medication at follow up †			
Aspirin	468 (94.6)	226 (93.8)	242 (95.3)
Oral anticoagulants	33 (6.7)	16 (6.6)	17 (6.7)
Clopidogrel	425 (85.9)	209 (86.7)	216 (85.0)
Beta-blockers	460 (92.9)	225 (93.4)	235 (92.5)
ACE-inhibitors	348 (70.3)	163 (67.6)	185 (72.8)
ARB	37 (7.5)	19 (7.9)	18 (7.1)
Statins	478 (96.6)	235 (97.5)	243 (95.7)

*mean±SD; †n (%); §median (IQR)

Primary Endpoint

After a mean of 6.5 (±2.0) weeks, planar radionuclide ventriculography was obtained in 448 patients (85%). Mean (±SD) LVEF was 0.53 (±0.10) in the EPO group and 0.52 (±0.11) in the control group (p=0.41)



Secondary Endpoint: enzymatic infarct size

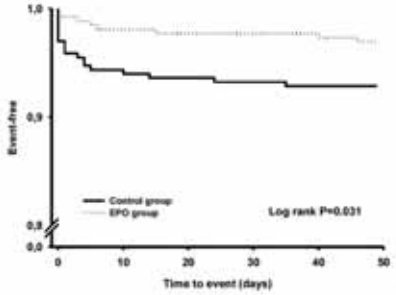
	EPO N=263	Control N=266	P-value
Peak CK (U/L)	1750 (895-2970)	1726 (967-3300)	0.293
AUC CK (U/L per 72h)	50,136 (28,212-76,664)	53,510 (33,973-90,486)	0.058
Peak CKMB (U/L)	214 (116-344)	219 (109-322)	0.955
AUC CKMB (U/L per 72h)	5622 (3487-8204)	5931 (3757-8801)	0.16
Peak Troponin T (µg/L)	4.30 (1.94-7.89)	5.90 (2.20-8.00)	0.564

Secondary Endpoint: Major Adverse Cardiovascular Events

	EPO N=263	Control N=266	P-value
All cardiovascular events	**8**	**19**	**0.032**
Cardiovascular death	1	2	0.569
Emergency re-PCI for	2	7	0.288
In-stent thrombosis/reinfarction	3	2	
Unstable angina			
Stroke	1	1	0.993
Heart failure	1	7	0.034

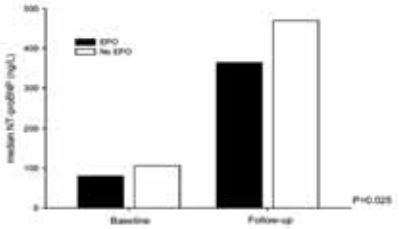
Major Adverse Cardiovascular Events were defined as cardiovascular death, re-myocardial infarction, re-PCI, or coronary artery bypass graft, stroke, and clear symptoms of heart failure.

Time to first major adverse cardiovascular event



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

Subgroup analysis: changes in NT-proBNP



In a subgroup of 234 patients, NT-proBNP was available at baseline and follow-up. Median (IQR) NT-proBNP increased from 81 (40-394) to 380 (198-853) pg/ml in the EPO group and from 106 (45-286) to 470 (217-1030) pg/ml in the control group (p for difference in change from baseline to 6 weeks=0.025)

Safety

- 49 Serious Adverse Events (SAE's) were reported in 40 control patients, and 33 SAE's were reported in 29 EPO patients.
- EPO was well tolerated and there were no reports of malignant hypertension, seizure, or deep vein thrombosis. Only one pulmonary embolism was reported in the control group and none in the EPO group.
- Changes in haemoglobin between baseline and 24 hours were available in 201 patients. Mean drop in haemoglobin (±SD) was 0.52 (±1.09) g/dL in the EPO group and 0.55 (±1.02) g/dL in the control group (p=0.86)
- Similarly, there were no difference in the change in haematocrit (p=0.73), leucocyte count (p=0.75) or platelet count (p=0.37) between both groups

Conclusions

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

Acknowledgements

- Data Safety Monitoring Board: Prof. Dr. J.G. Tijssen, department of Cardiology, Academic Medical Centre Amsterdam, the Netherlands and M. van den Brand, MD, Erasmus Medical Centre Rotterdam, the Netherlands.
- Endpoint committee: B.J. de Smet,MD, and A.F. van den Heuvel, MD, University Medical Center Groningen, the Netherlands.
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Nederlandse Hartstichting

Online Publication

The results of this study are now published online in the European Heart Journal

HEBE III: A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction

Discussant

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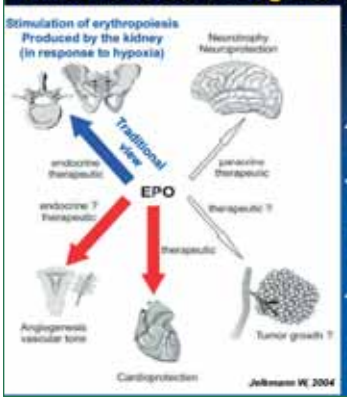
HEBE III: A Single Dose of Erythropoietin in ST-elevation Myocardial Infarction

Discussant

EPO's rescue mission in AMI: hopes and evidence

- Background
- The evidence for practicing cardiologists – HEBE III results
- Questions and hopes for the future

What have cardiologists learned about EPO?



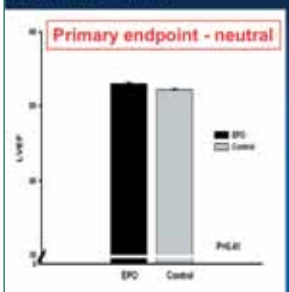
EPO – not just a erythropoietic hormone, but rather a local, tissue protective cytokine against ischemic injury

- EPOR – myocardium, blood vessels, brain, liver...
- EPO interacts with EPOR:
  (-) apoptosis, promotion of survival and growth
  (+) anti-inflammatory processes
  (+) neovascularization (EPCs, VEGF)
- Animal models of AMI:
  ↓ infarct size, improves contractility & hemodynamics, anti-remodeling cardioprotection – not related to haematopoiesis

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

HEBE III results

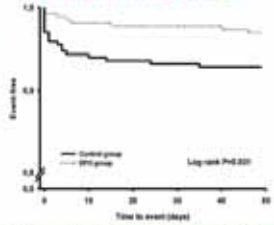
Primary endpoint - neutral



LVEF 6 weeks after primary PCI

Secondary endpoints – promising signal

- trend towards smaller infarct size (enzymatically)
- less cardiovascular events



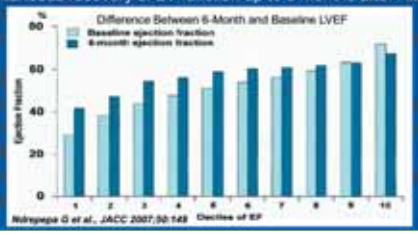
EPO well tolerated, favourable safety profile

Questions and hopes for the future

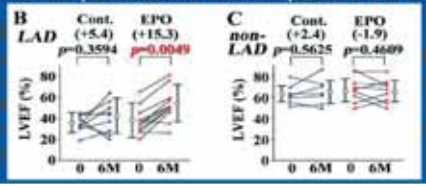
1. Selection of the end-points and patients

a. is LVEF sensitive enough ?
to detect potentially subtle beneficial EPO effects that may have occurred only during 6-week follow-up

b. is 6-week follow-up period long enough ?
spontaneous recovery of LV function up to 6 months after AMI



c. would patients with more impaired LVEF benefit ?



Ozawa T et al. Circ J 2010;74:1415

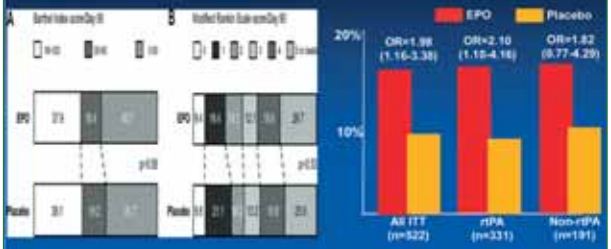
Questions and hopes for the future

1. **Selection of the end-points and patients**
   - **a. is LVEF sensitive enough ?**
     to detect potentially subtle beneficial EPO effects that may have occurred only during 6-week follow-up
   - **b. is 6-week follow-up period long enough ?**
     spontaneous recovery of LV function up to 6 months after AMI
     HF-related episodes occur later after AMI
   - **c. would patients with more impaired LVEF benefit ?**
2. **Safety and dosage of EPO therapy**
   - **a. how to maximize „pure" pleiotropic EPO-effects ?**
     avoid ↑Ht, ↑platelet activity, rise in BP, risk of thromboembolism
   - **b. lessons learned from neurology**
   - **c. repeated EPO doses to maintain salutary effects on infarcted myocardium**

Lessons learned from neurology German Multicenter EPO Stroke Trial

Results of main outcome parameters

90-day mortality



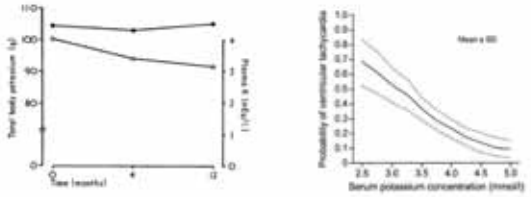
„Based on analysis of total intent-to-treat and per-protocol populations only, this is a negative trial that also raises safety concerns, particularly in patients receiving systemic thrombolysis"

Ehrenreich, H. et al. Stroke 2009;40:e647-e656

EPO in AMI: what is the evidence today ?

Study, author	Population & design	End-points
Lipsic E et al. 2006	N=22; 1st STEMI 300µg darbepoetin-α i.v.	↑ EPCs mobilization at 72h LVEF (4 months) – ns
Binbrek AS et al. 2009	N=236; STEMI EPO – 30000 IU i.v. before f-lysis	Infarct size (CKMB) - ns
Ferrario M et al. 2009	N=36; 1st STEMI with PCI; 3x EPO (placebo), 33000 IU; before PCI, 24h, 48h	Infarct size (CKMB) – ↓ 30% ↑CD34+ mobilization; PBC gene expression antiapoptotic, antiinflammatory, pro-angiogenic
REVIVAL-3 ACC 2009	N=138; STEMI with PCI, EF<50%; 3x EPO (Placebo), 33000IU; after PCI, 24h, 48h	LVEF (6 months) – ns LVESVI, LVEDVI – ns
EPO-AMI 2010	N=38; STEMI, successful PCI; EPO – 12000 IU i.v.	↑ LVEF / rEF (6 months) LAD-AMI: +15% vs +5%
Voors A et al. 2010	N=529; 1st STEMI, successful PCI EPO – 30000 IU, after PCI	LVEF (6 weeks) – ns infarct size (CK, CKMB) - ↓ CV events ↓

Plasma K^+,TBK^+ and VT



Dargie HJ et al BMJ 1974; 4: 316

Nordrehaug JE et al Circulation 1985; 71: 645

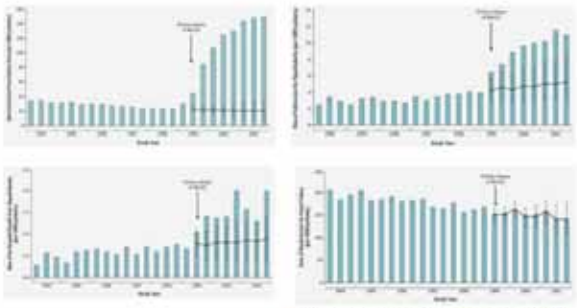
Hyperkalaemia in HF

- How common?
  - In RALES Pilot 13, 20 and 24% on 25, 50 and 75mg had K^+ > 5.5mmol/L
  - In RALES 2% had severe hyperkalaemia (</+ 6 mmol/L
  - In EPHESUS 5.5% and 3.9% on eplerenone and placebo had K^+ >/= 6 mmol
  - In unselected patients in clinical series 15% to 50%
- Risk Markers
  - 70 years or older
  - Renal impairment (CKD) occurs in up to 40% patients with HF
    - Intrinsic related to age, diabetes, renovascular disease, specific renal diseases
    - Reversible due to heart failure
    - Acidosis, a feature of severe acute HF
  - Treatment with Diuretics, RAAS inhibitors, beta blockers, digoxin
- Non HF medicines on renal function
  - NSAIDs, heparin, ciclosporin, trimethoprim, gentamicin, vancomycin etc
- Dietary
  - Salt substitutes, K supplements, bananas and other fruits

PEARL-HF - design

- Double blind randomised parallel group RCT
  - Placebo controlled
- Background Rx with RAAS and β blockers
  - Challenged with spironolactone 25 – 50 mg/day
- Majority, 58% overall, had mild HF% (NYHA I/II)
  - No patients in NYHA IV
- LVEF was 40% overall +/- 12%
  - preserved and impaired LV Ejection Fraction
- CKD 3 and 4 (eGFR 30-59 and 15-29 ml/min)
  - mean eGFR 84 and 78 ml/min in Rel and Pbo;
  - ? CKD 2/3
- Diabetes in 73% and 63% in Rel/Plb p=NS

Impact of RALES

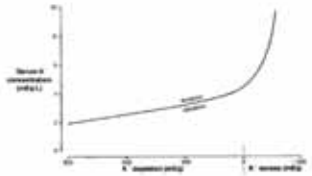


Juurlink DN et al NEJM 2004; 543-51

'The K+ Continuum'

- the twin 'perils' of *hyper* and *hypo*kalaemia

- Total body K^+ = 3500 mmol
- Only 2% (60 -70 mmol) in blood
- Small bi-directional shifts can cause hyper or hypokalaemia
- Insulin, alkalosis, aldosterone and adrenergic activity promote cellular uptake
- HF and its treatment affect serum



Brown RS American Journal of Medicine 2004;77:3-10

PEARL-HF

- summary and conclusions

- Carefully designed placebo controlled RCT
  - performed by experienced investigators
- Trial demographics appropriate for age (68 yrs)
  - Relatively mild HF for ARA
  - With relatively mild CKD (80ml/min)
- Relypsa lowers K and prevents hyperkalaemia
  - *very high incidence of hyperkalaemia (> 5.5 mmol/L)*
  - *19-56% on placebo v 0-7% on Relypsa*
- Longer term Risks and benefits analyses required
  - Future studies should target higher risk patients in large trials
  - Older, more severe HF and renal dysfunction
- Will we need a mortality trial?

SHIFT

Discussant

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DISCLOSURES

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Consultant / Advisory Board:

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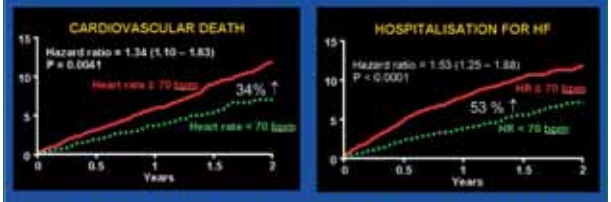
Rationale of the SHIFT Study

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



Lowering HR to reduce CV outcomes is an attractive hypothesis to test

Major Findings of SHIFT

A BEAUTIFUL Study

In patients with HF, EF < 35% in SR, and baseline resting HR > 70 bpm, 90% on BB, 90% ACEi, >60% aldosterone blockers, use of Ivabradine was associated with:

- – 9 bpm ↓ in HR compared to placebo
- 18% ↓ in the risk of PEP - CV mortality and Hospitalization for HF
- 26% ↓ in the risk of Hospitalization for HF
- 9% ↓ in the risk of CV mortality (p=ns)
- 10% ↓ in the risk of all-cause mortality (p=0.09)
- Improvement in NYHA class, patient and physician global assessment
- Greater benefit was seen in patients HR >77 bpm, independent of BB dose
- Ivabradine had no serious adverse effects

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

- Only 26% patients were prescribed target dose of BB by the investigators, despite being encouraged to comply with the guidelines and up-titrate BB to the highest dose possible. 55% received at least 50% target dose
- In BB HF trials, higher % patients reached target dose: 38% in CIBIS, 43% in CIBIS II, 64% in MERIT-HF and 65% in COPERNICUS
- BB doses used in recent drug and device trials are not published
- In clinical practice much lower doses of BB are used:

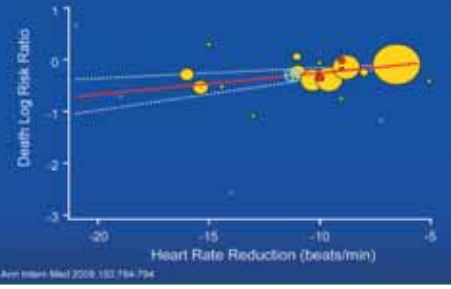
HF Registeries	Target dose reached (%)	% > 50% target dose
COHERE (USA, 2004)	44	-
VA NATIONAL (USA, 2009)	25	-
Euro Heart Survey (2005)	10	-
Impact Reco II (France, 2009)	23	54
IMPROVE HF (USA, 2010)	17	-

Could use of higher BB dose have changed the outcomes?

Meta-regression of 23 beta-blocker HF trials involving 19,209 patients

Mortality benefit related to magnitude of HR reduction and not to the dose of BB

Pooled Mortality HR 0.76 (24%↓) for an average Heart Rate Reduction 12 bpm



McAlister et al Ann Intern Med 2009;152:784-794

Could use of higher BB dose changed the outcomes?

- The reduction in mortality hazard with Ivabradine for an average 9-bpm decrease in HR is consistent with the prediction from the meta-analysis.
- In clinical trials higher doses of BB have not been shown reduce HR further. In SHIFT, higher dose of BB did not cause greater ↓ HR. ↓15.4 bpm in entire cohort vs ↓ 15.5 bpm those on > 50% target dose. Unlikely that use of higher BB doses in SHIFT would have caused a further ↓HR or altered the outcomes
- In real world clinicians are unable to ↑doses of BB to target levels because of actual or perceived side effects. Previous drug or device HF trials that led to the approval of specific therapies were done in patients receiving background therapy as prescribed by the investigators and no force titration was attempted. Hence SHIFT should be judged on the merits of its findings in the population studied

Which patients are likely to be candidates for Ivabradine?

- **Patients with A Fib unlikely to benefit:** ~ 25% HF patients will be excluded
- **Patients with resting HR > 70 bpm:** Data from recent HF trials and HF registries suggest that >50% patients have HR >70 bpm and ~ 40% have HR >77 bpm where most of the beneficial effects of ivabradine were seen
- **Use of devices was low** in SHIFT because of inclusion criteria and geography. These patients need not be excluded if they meet the other inclusion criteria and pacing rate are set appropriately low. Interaction between ivabradine and devices is unknown and needs to be studied.
- Approximately 40% of all HF patients with LV systolic dysfunction receiving standard of care HF therapies might benefit from the addition of ivabradine

CONCLUSIONS

- SHIFT confirms the importance of heart rate in the pathophysiology of HF and supports the concept that reduction in HR contributes significantly to beneficial outcomes in patients with HF
- In patients with systolic HF in SR with HR >70 bpm, receiving usual clinical care and are unable to tolerate higher doses of BB, the addition of the pure HR reducing agent ivabradine is likely to improve HF outcomes

SHIFT

Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial

Michel Komajda and Karl Swedberg
on behalf of the SHIFT Investigators

SHIFT Disclosures

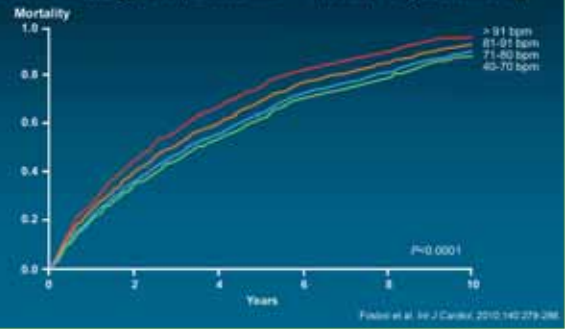
SHIFT Executive Committee members received fees, research grants, or both from Servier, as well as fees for speaking or consulting from other major cardiovascular pharmaceutical companies

SHIFT Background

- Elevated heart rate is associated with poor outcome in a number of cardiovascular conditions including heart failure
- Heart rate remains elevated in many heart failure patients despite treatment by beta-blockers
- Ivabradine is a novel heart rate-lowering agent acting by inhibiting the I_f current in the sino-atrial node
- We hypothesized that the addition of ivabradine to recommended therapy would be beneficial in heart failure patients with elevated heart rate

Resting heart rate and mortality in HF post MI patients

DIAMOND study; 1518 patients with HF post MI, 10 years follow up



Ivabradine: pure heart rate reduction

I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

SHIfT — Primary objective

To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction ≤35%
3. Heart rate ≥70 bpm and
4. Recommended therapy

SHIfT — Multinational study

6505 patients, 37 countries, 677 centres

SHIfT — Inclusion criteria

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

SHIfT — Study design

SHIfT — Study endpoints

Primary composite endpoint

- Cardiovascular death
- Hospitalisation for worsening heart failure

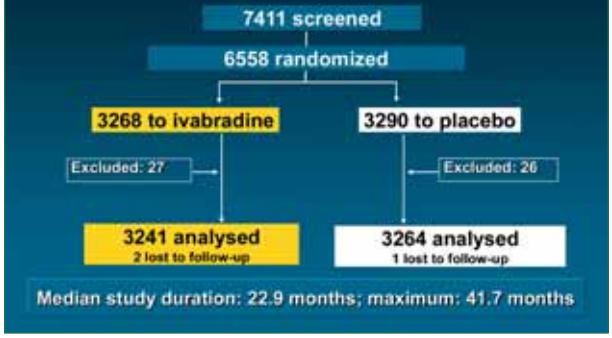
Other endpoints

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

In total population and in patients with at least 50% target dose of beta-blockers

Swedberg K, et al. Eur J Heart Fail. 2010;12:75-81.

SHIfT — Patients and follow-up



Median study duration: 22.9 months; maximum: 41.7 months

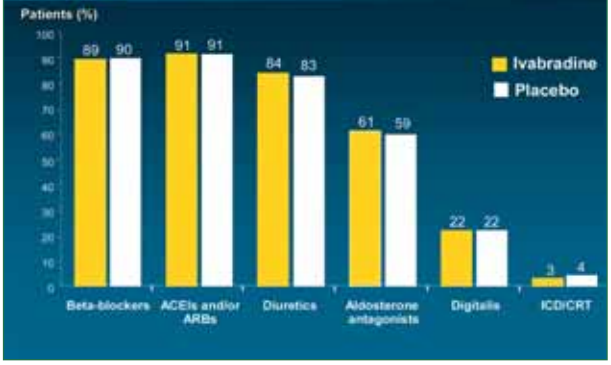
SHIfT — Baseline characteristics

	Ivabradine 3241	Placebo 3264
Mean age, y	60.7	60.1
Male, %	76	77
Ischaemic aetiology, %	68	67
NYHA II, %	49	49
NYHA III/IV, %	51	51
Previous MI, %	56	56
Diabetes, %	30	31
Hypertension, %	67	66

SHIFT Baseline characteristics

	Ivabradine	Placebo
	3241	3264
Mean heart rate, bpm	80	80
Mean LVEF, %	29	29
Mean SBP, mm Hg	122	121
Mean DBP, mm Hg	76	76
eGFR, mL/min/1.73 m²	75	75

SHIFT Chronic HF background treatment



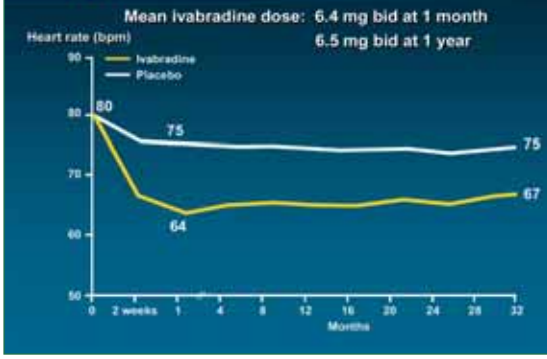
SHIFT Background beta-blocker treatment

SHIFT Background beta-blocker treatment

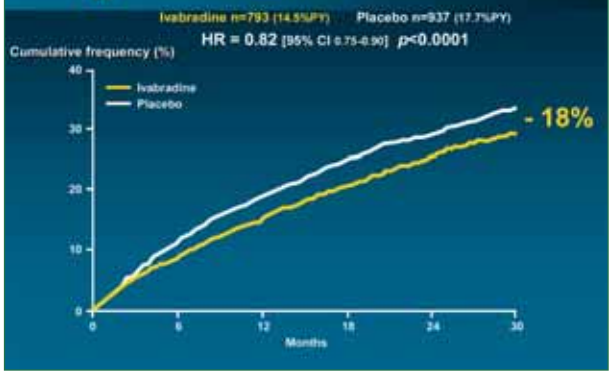
Main reasons for not prescribing BB, %	Ivabradine n=344	Placebo n=341
COPD	37	32
Hypotension	17	20
Asthma	10	11
Cardiac decomp.	7	9
Fatigue	5	6

Main reasons for not achieving BB target dose, %	Ivabradine n=2099	Placebo n=2126
Hypotension	44	45
Fatigue	32	32
Dyspnea	14	14
Dizziness	13	12
Bradycardia	6	6

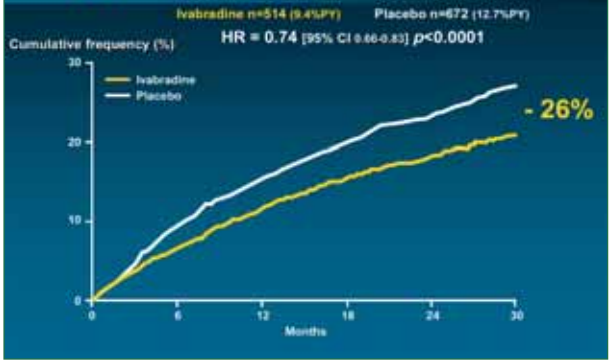
SHIFT Mean heart rate reduction



SHIFT Primary composite endpoint



SHIFT Hospitalisation for heart failure

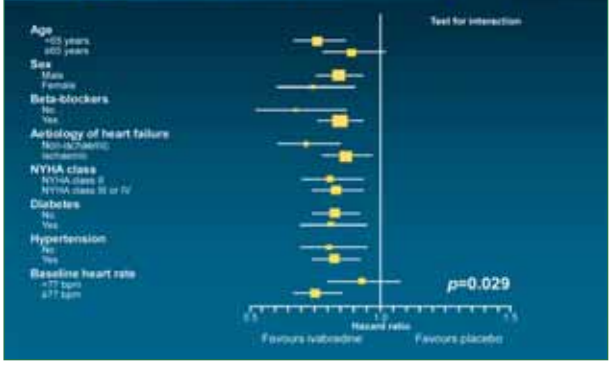


SHIFT Cardiovascular death

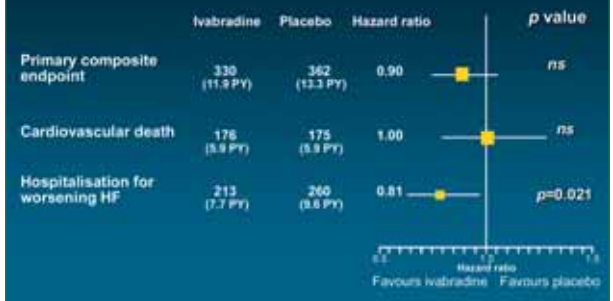
SHIFT Effect of ivabradine on outcomes

Endpoints	Hazard ratio	95% CI	p value
Primary composite endpoint	0.82	[0.75;0.90]	p<0.0001
All-cause death	0.90	[0.80;1.02]	p=0.092
Death from HF	0.74	[0.58;0.94]	p=0.014
Hospitalisation for any cause	0.89	[0.82;0.96]	p=0.003
Hospitalisation for CV reason	0.85	[0.78;0.92]	p=0.0002
CV death/hospitalisation for HF or non-fatal MI	0.82	[0.74;0.89]	p<0.0001

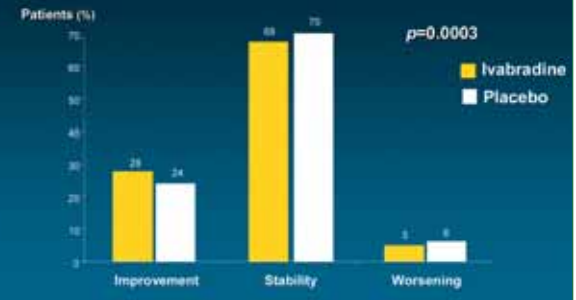
SHIFT Effect of ivabradine in prespecified subgroups



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



SHIFT NYHA class changes



SHIFT Incidence of selected adverse events (N = 6492)

	Patients with an event		
	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	p value
All serious adverse events	45% (1450)	48% (1553)	0.025
All adverse events	75% (2430)	74% (2423)	0.303
Heart failure	25% (804)	29% (937)	0.0005
Symptomatic bradycardia	5% (150)	1% (32)	<0.0001
Asymptomatic bradycardia	6% (194)	1% (48)	<0.0001
Atrial fibrillation	9% (308)	8% (251)	0.012
Phosphenes	3% (89)	1% (17)	<0.0001
Blurred vision	1% (37)	< 1% (7)	0.042

SHIFT Incidence of serious adverse events

	Patients with an event		
	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	p value
All serious adverse events	45% (1450)	49% (1553)	0.025
Cardiac disorders	28% (920)	30% (991)	0.091
General disorders, administration conditions	7% (240)	8% (254)	0.617
Infection and infestations	7% (216)	7% (238)	0.381
Respiratory, thoracic, mediastinal disorders	3% (107)	4% (122)	0.347
Surgical and medical procedures	3% (102)	4% (122)	0.197
Gastrointestinal disorders	3% (99)	3% (103)	0.342
Neoplasm benign, malignant and unspecified	2% (66)	2% (61)	0.534
Renal and urinary disorders	2% (51)	1% (47)	0.685
Hepatobiliary disorders	1% (29)	1% (39)	0.273
Eyes disorders	1% (16)	<1% (13)	0.374

SHIFT Treatment discontinuation

	Patients with an adverse event, leading to withdrawal		
	Ivabradine N=3232, % (n)	Placebo N=3260, % (n)	p value
All	14% (467)	13% (416)	0.051
Heart failure	2% (70)	3% (82)	0.367
Symptomatic bradycardia	1% (20)	<1% (5)	0.002
Asymptomatic bradycardia	1% (28)	<1% (5)	<0.0001
Atrial fibrillation	4% (130)	3% (113)	0.137
Phosphenes	<1% (7)	<1% (3)	0.224
Blurred vision	<1% (1)	<1% (1)	1.000

SHIFT Conclusion

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

SHIFT Clinical implications

- The addition of ivabradine to recommended therapy significantly reduces death and hospitalisations related to heart failure in patients with heart rate ≥70 bpm
- The NNT for 1 year to prevent …
  - ✓ One primary endpoint is 26
  - ✓ One hospitalisation for heart failure is 27

SHIFT

KEY Questions & Answers

Are the BEAUTIFUL and the SHIFT populations similar?

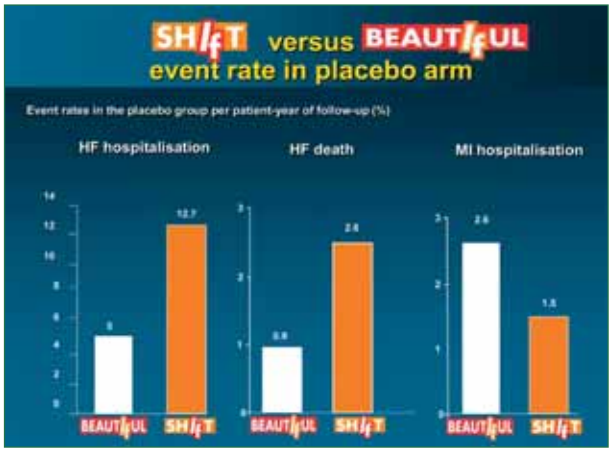
BEAUTIFUL versus SHIFT

	BEAUTIFUL	SHIFT
	Differences	
	All documented CAD	All documented CHF
LV ejection fraction	<40%	≤35%
NYHA	Classes I, II, & III	Classes II, III, & IV
Heart rate	>60 bpm	≥70 bpm
	Primary endpoint	
	CV death + hospitalisation for AMI + new onset/worsening HF	CV death + hospitalisation for worsening HF

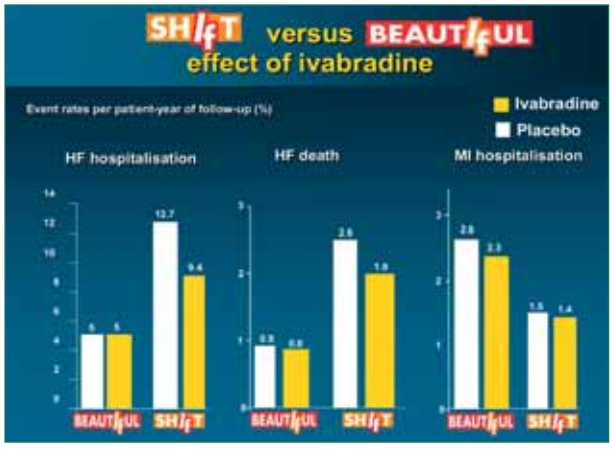
BEAUTIFUL versus SHIFT

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

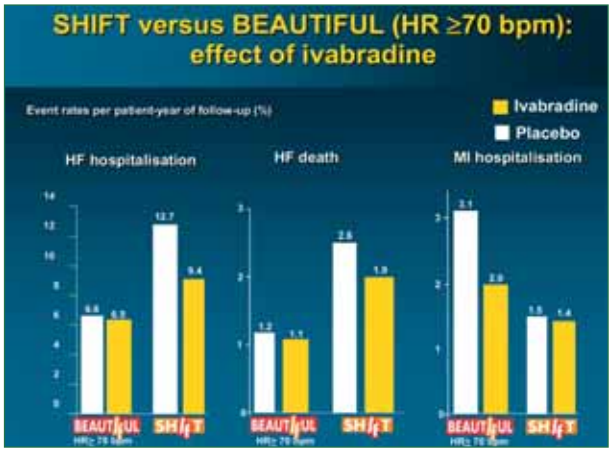
SHIFT versus BEAUTIFUL event rate in placebo arm



SHIFT versus BEAUTIFUL effect of ivabradine

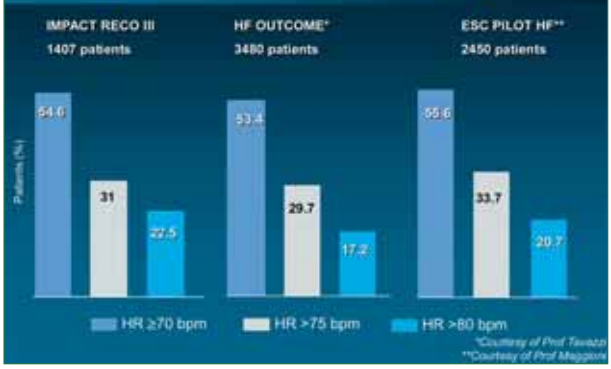


SHIFT versus BEAUTIFUL (HR ≥70 bpm): effect of ivabradine

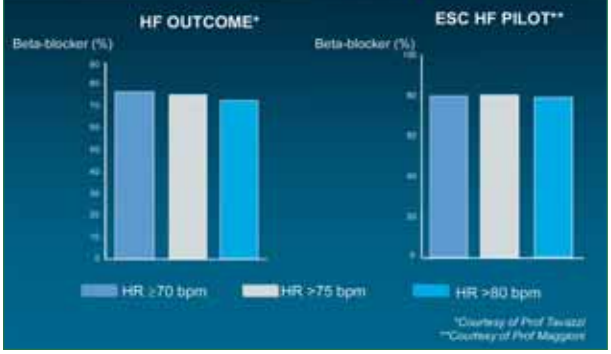


Do HF patients frequently have heart rate ≥70 bpm?

HF registries: more than 50% of patients have heart rate ≥70 bpm



Heart rate in European surveys: beta-blocker therapy



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

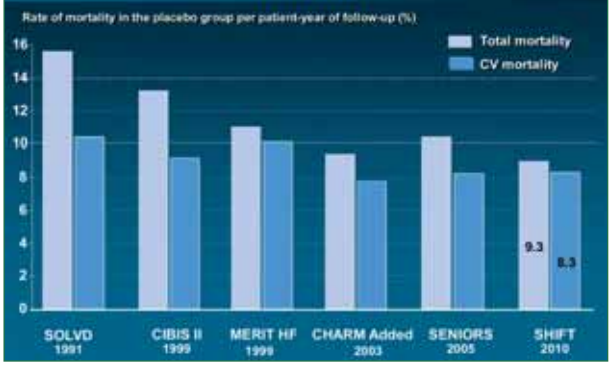
Are HF patients with heart rate ≥70 bpm at elevated CV risk?

YES

High CV risk despite recommended therapy:

PEP in the placebo group was 18% / year

Annual risk of mortality in placebo group in HF trials



Annual risk of HF death in major HF trials

ESC Congress 2010
28 August - 1 September
STOCKHOLMSMÄSSAN

The acute and long-term effect of intracoronary Stem cell Transplantation in 191 patients with chronic heART failure:

A new STAR in the cardiovascular stem cell therapy sky

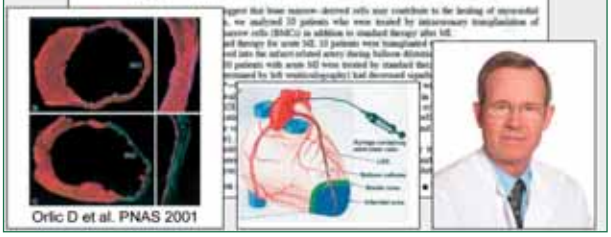
Francisco Fernández-Avilés
Department of Cardiology
Hospital General Universitario Gregorio Marañón
Complutense University of Madrid – School of Medicine
faviles@vercardiologia.es

Circulation 2002; 106: 1913 – 1918

Clinical Investigation and Reports

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD; Michael Brehm, MD; Tobias Zeus, MD; Matthias Kögler, MD; Anna Hernandez, PhD; Rüdiger V. Sorg, PhD; Gesine Kögler, PhD; Peter Wernet, MD



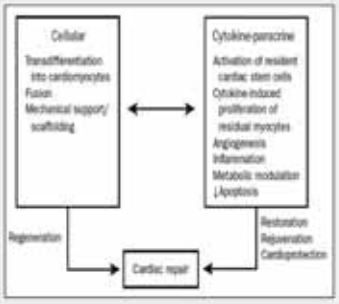
Orlic D et al. PNAS 2001

Stem cell therapy for heart repair
STATUS – 2010

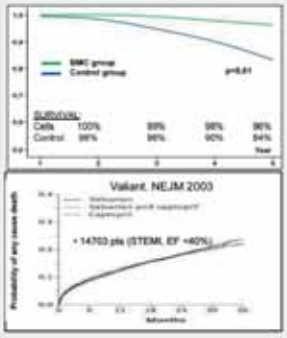
The regeneration capability of the mammalian heart can be enhanced by transfer of embryonic or adult stem cells (repair, total reconstruction)

Preliminary experience in >1500 pts with acute or chronic infarction
- Enormous heterogeneity
- Favourable safety profile
- Modest improvement in LV function and remodelling

Mechanisms of benefit poorly understood (clinical setting?)
- Transdifferentiation into cardiac cells
- Scaffolding effect
- Paracrine effect



The STAR-Heart Study
CONTRIBUTION



Largest trial comparing BMSCs vs conventional therapy in patients with heart failure due to healed infarction.

Longest follow-up

Simple and reproducible method of delivery

Comprehensive and precise assessment of physiologic parameters

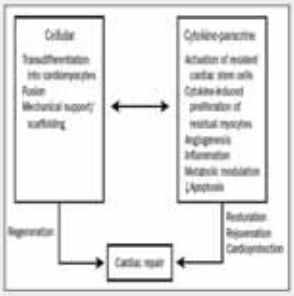
Excellent outcome with optimal therapy

Safe and positive effect of BMSc on LV performance, quality of life and clinical outcome

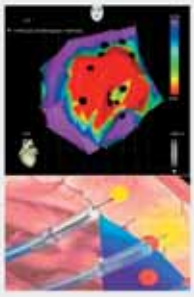
Insights into stem cell mechanisms of left ventricular benefit

The STAR-Heart Study
INSIGHTS INTO STEM CELL MECHANISMS OF BENEFIT

- The transdifferentiation into cardiomyocytes of 66 x 10^6 BMCs is not enough to improve LV function in large healed infarctions
- The observed benefit suggests scaffolding effect and/or paracrine activation of resident cells



The STAR-Heart Study
OPPORTUNITIES



Open label non-randomized study

Healed infarctions (no viability) assumed but not clearly documented

Surrogate endpoints elegantly managed but underpowered for clinical hard endpoints.

Intracoronary injection versus intramyocardial delivery (stable setting, chronic occlusion)

Limited amount of cells. Unnecessary in chronic patients
- Autologous expanded stem cells (MSCs from bone marrow or adipose tissue, IPSCs)
- Autologous adipose derived fresh MSCs
- Allogenic stem cells

CONCLUSIONS

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

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

Randomized, double-blinded, mechanistic clinical trials with imaging surrogates are warranted to confirm these results and to compare different cells and different methods of delivery

Table 1. Baseline Characteristics of the patients with ischemic heart failure

Characteristics	Stem cell group n=191	Control group n=200	P Value
Age	59±12	60±11	n.s.
BMI	30.1	30.2	n.s.
Sex (male %)	89.3	89.3	n.s.
EF (%)	29.4±12.7	36.1±13.8	n.s.
Number of injected cells (x10⁶)	6.6±3.3	-	-
Infarct related coronary artery RCA/LAD/RCX (%)	33.4/49.1/17.5	31.2/50.7/18.1	n.s.
Number of stenosd coronary arteries	1,71±0,72	1,7±0,69	n.s.
Medications:			
Aspirin (%)	100	100	n.s.
ACE-Inhibitor/AT2- Receptorantagonist (%)	88	89	n.s.
Diuretics (%)	80	81	n.s.
Digitalis (%)	41	42	n.s.
β-Blocker (%)	91	92	n.s.
Statins (%)	93	92	n.s.
Cardiovascular risk factors:			
Diabetes mellitus (%)	27	24	n.s.
Hyperlipoproteinemia (%)	58	54	n.s.
Smoking (%)	36	36	n.s.
Obesity (%)	62	67	n.s.
Arterial hypertension (%)	62	64	n.s.

Values are mean±SD or number of patients (%). BMI=body mass index, EF=ejection fraction, RCA=right coronary artery, RIVA=ramus interventricularis anterior, RCX=ramus circumflexus, ACE=angiotensin converting enzyme. Baseline characteristics of BMC group and control group. 191 patients underwent intracoronary BMC therapy. The control group consisted of 200 patients.

Table 2. Hemodynamics of the left ventricle

Parameter	Baseline/post cell therapy	Chronic heart failure	
		Cell therapy	Control
CI-rest (l/min x m²)	baseline	2,7±0.63	2,8±0.9
	post	3,3±0,6***	2,3±1,2
	Abs.	0,56±0,5	-0,45±0,8
VO_{2max} (ml/min)	baseline	1015±308	1546±190
	post	1681±527**	1539±180
	Abs.	158±365	-29,3±120
O_2-Pulse (ml/beat)	baseline	12,8±3,4	13,1±4
	post	13,6±3,4**	13±2
	Abs.	0,52±2,1	-0,9±1,2
Ergometry (Watt)	baseline	78,7±30	78±8
	post	90,7±33,8***	81±4
	Abs.	11,3±22,9	-15,2±8,7

Abs.=absolute difference to baseline, CI=cardiac index, PAP=pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, CPI=cardiac power index, VO2peak=peak oxygen uptake, O_2-Puls=oxygen pulse. Hemodynamics of the left ventricle before and after BMC therapy in patients with chronic ischemic cardiomyopathy in comparison to control group. 3 months after BMC therapy significant improvements of CI, PAP, PCWP, CPI, VO_{2peak},O_2-Pulse and exercise capacity were documented.

*** p<0,01 (pre/post), ** p<0,05 (pre/post), * p<0,1 (pre/post)

Table 3. Quantitative ventriculography

Parameter	Baseline/post cell therapy	Chronic heart failure	
		Cell therapy	Control
EDV (ml)	baseline	184±52	184±49
	post	174±49**	185±50
	Abs.	-9,9±33,3	2,9±32,1
ESV (ml)	baseline	128±53	118±43
	post	110±47***	120±43
	Abs.	-15,9±30,2	4,3±29,8**
EF (%)	baseline	29,4±12,7	36,1±13,8
	Post	38±13,3***	35,5±13,5
	Abs.	8,1±8,3	-0,5±2,1**
SVI (ml/m²)	baseline	33,1±11,2	32,5±11,2
	post	37,3±12***	32±10,9
	Abs.	4,45±10,4	-0,38±1,84
Infarct size (%)	baseline	28,1±17	27,9±16,9
	Post	24,9±16,4**	28,4±16,8
	Abs.	-4,5±9,8	1,8±11,1

Abs.=absolute difference to baseline, EDV=end-diastolic volume, ESV=end-systolic volume, SVI=stroke volume index. Quantitative analysis of the left ventricle before and after BMC therapy in patients with chronic ischemic cardiomyopathy in comparison with the control group. 3 months after BMC therapy a significant improvement of EDV, ESV, EF and SVI was seen. A significant decrease of the infarct size was documented.

*** p<0,01 (pre/post), ** p<0,05 (pre/post), * p<0,1 (pre/post)

Table 4. Contractility of the left ventricle

Parameter	Baseline/post cell therapy	Chronic heart failure	
		Cell therapy	Control
MNSER (vol./sec)	baseline	1,2±0,7	1,14±0,5
	post	1,31±0,6***	1,05±0,6
	Abs.	0,11±0,3	-0,09±0,3
Payst/ESV (mmHg/ml)	baseline	1,45±1	1,31±0,76
	Post	1,72±1,1 ***	1,28±0,73
	Abs.	0,29±0,8	-0,04±0,4
Global $T_{systolic}$ (10^{-3}*N*m²)	baseline	19,4±5,9	19,1±5,5
	Post	18,5±5,9*	19,2±5,5
	Abs.	-1,1±2,7	0,3±2,9
Global $T_{diastolic}$ (10^{-3}*N*m²)	baseline	5,1±2,3	5±1,9
	post	5,2±2,6	5,02±1,93
	Abs.	0,2±1,7	0,06±0,88

Abs.=absolute difference to baseline, MNSER=mean normalized systolic ejection rate, Payst/ESV=contractility index calculated by dividing LV systolic pressure (P_{systol}) by end-systolic volume. Contractility parameters of the left ventricle before and after BMC therapy in patients with chronic ischemic cardiomyopathy in comparison with the control group. Improvements of the MNSER and Payst/ESV were documented 3 months after BMC therapy.

*** p<0,01 (pre/post), ** p<0,05 (pre/post), * p<0,1 (pre/post)

Table 5. Arrhythmogenic indexes

Parameter	Baseline/post cell therapy	Chronic heart failure	
		Cell therapy	Control
Heart rate variability (HRV): SD of the RR-intervals (ms)	Baseline	31,7±19,2	34±15,2
	Post	37,2±23,2***	32,6±14,1
	Abs.	5,7±15,8	-2,67±9,8
Lown classification	baseline	2,49±1,5	2,31±1,6
	Post	1,96±1,6**	2,5±1,7
	Abs.	-0,46±1,1	0,2±1,1

Abs.=absolute difference to baseline. Arrhythmogenic indexes before and 3 months after BMC therapy. Significant improvements of HRV and Lown classification were documented.

*** p<0,01 (pre/post), ** p<0,05 (pre/post), * p<0,1 (pre/post)

Table 6: Quantitative ventriculography before, and 3, 12 and 60 months after BMC therapy comparison to control group

Parameter	mean/ Abs.	Chronic heart failure							
		BMC group				Control group			
		Baseline (before BMC therapy) n=191	After 3 Months n=191	After 12 months n=191	After 60 months n=184	Baseline n=200	After 3 Months n=200	After 12 months n=199	After 60 months n=188
EDV (ml)	mean	184±52	174±49*	174±39*	175±30*	184±49	185±50	187±37	180±42*
	Abs.	-	-9,9±33,3	-9,2±30,4	-9±27,6	-	2,9±32,1	2,2±30,2	4,9±28,1
ESV (ml)	mean	128±53	110±47**	112±43**	111±30**	118±43	120±43	123±40	132±46*
	Abs.	-	-15,9±30,2	-14,9±32,2	-14,4±26,7	-	4,3±29,8	4,8±31,2	9,9±26,7
EF (%)	mean	29,4±12,7	38±13,3**	37,8±13,4**	36,8±9**	36,1±13,8	35,5±13,5	34,8±12,6	32,3±12,3*
	Abs.	-	8,1±8,3	8,4±8,7	8,2±8,4	-	-0,5±2,1	-1,3±3,7	-0,5±8,9
SVI (ml/m²)	mean	33,1±11,2	37,3±12**	38,4±10,6**	38,1±7**	32,5±11,2	32±10,9	30,4±10,4*	28±9,7**
	Abs.	-	4,45±10,4	5,2±8,1	4,8±7,1	-	-0,38±9,1	-1,8±8,1	-3,9±7,5
Payst./ESV (mmHg/ml)	mean	1,45±1	1,7±1,1*	1,7±0,9*	1,67±0,4*	1,31±0,76	1,28±0,73	1,19±0,43*	1,1±0,44*
	Abs.	-	0,29±0,8	0,33±0,71	0,24±0,8	-	-0,04±0,4	-0,1±0,38	-0,1±0,4

Values are mean ± SD. Abs.=absolute difference to baseline, EDV=end-diastolic volume, ESV=end-systolic volume, SVI=stroke volume index. Payst/ESV=contractility index calculated by dividing LV systolic pressure (Payst.) by end-systolic volume. Payst./ESV and quantitative ventriculography over the course of time in treated patients in comparison to control group.

** p<0,0167 vs. baseline (bonferroni alpha correction), * p<0,05 vs. baseline

Table 7: NYHA class and late potentials before, and 3, 12 and 60 months after BMC therapy in comparison to control group

Parameter	mean/ Abs.	Chronic heart failure							
		BMC group				Control group			
		Baseline (before BMC therapy) n=191	After 3 Months n=191	After 12 months n=191	After 60 months n=184	Baseline n=200	After 3 Months n=200	After 12 months n=199	After 60 months n=188
NYHA (class)	mean	2,23±0,7	2,29±0,7**	2,1±0,7**	1,46±0,5**	2,06±0,8	2,3±0,5*	2,06±0,8*	2,1±0,4*
	Abs.	-	-0,9±0,4	-0,06±0,7	-1,2±0,66	-	0,3±0,4	0,46±0,7	0,6±0,67
LP (Number of arrears criteria)	mean	1,41±1,12	1,21±1,14**	1,11±1**	0,7±1**	1,43±1,3	1,41±1,1	1,5±1,1	2,5±0,8*
	Abs.	-	-0,36±0,87	-0,29±0,88	-0,5±0,91	-	-0,02±0,81	0,11±0,8	0,87±0,95

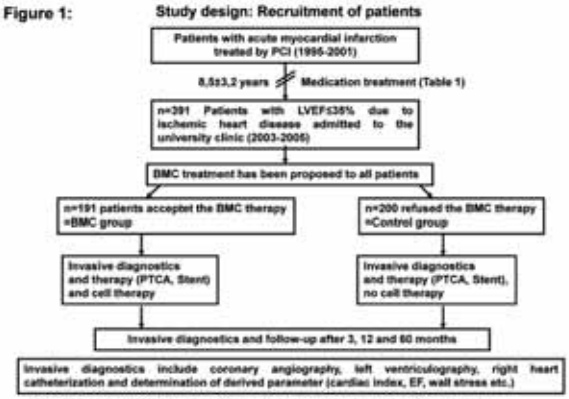
Values are mean ± SD. Abs.=absolute difference to baseline, LP=late potential, NYHA=New York Heart Association, NYHA class and late potential over the course of time in treated patients in comparison to control group.

** p<0,0167 vs. baseline (bonferroni alpha correction), * p<0,05 vs. baseline

Figure 1:

A total of n=391 patients with reduced LVEF due to ischemic heart disease were enrolled into this prospective study. All patients had myocardial infarction and the time interval between the infarct and admission to our clinic was 8,5±3,2 years. BMC therapy has been proposed to all patients with reduced LVEF due to ischemic cardiomypathy. Patients who refused the BMC treatment and accepted to undergo all procedures identical to the BMC group acted as control group. Coronary angiography, biplane left ventriculography, ECG at rest, spiroergometry, right heart catheterization and measurements of late potentials (LP), of short-term heart rate variability (HRV) and of 24-h Holter ECG were performed. The therapeutic follow-up was evaluated 3, 12 and 60 months after the treatment.

Figure 1: Study design: Recruitment of patients



PCI= percutaneous coronary intervention, LVEF= left ventricular ejection fraction, BMC= bone marrow cell, PTCA= percutaneous transluminal coronary angioplasty

Figure 2:

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

Figure 2: Ejection fraction (EF) in the course of time in BMC group in comparison to control group

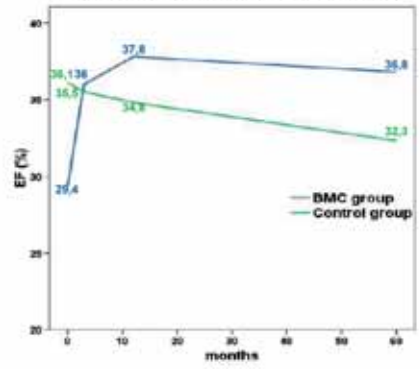
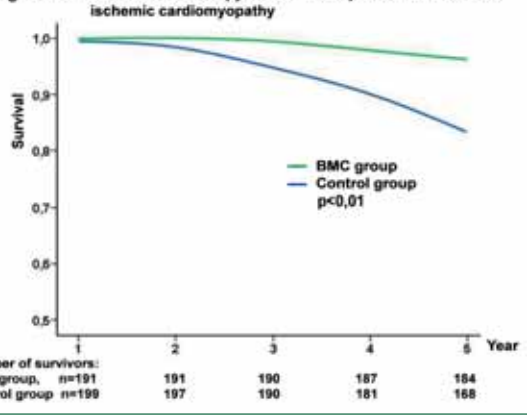


Figure 3:

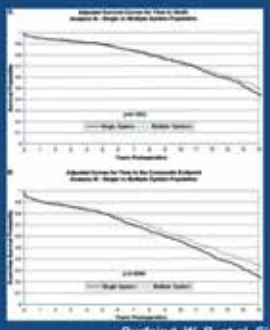
Mortality of BMC group was significantly reduced in comparison to the control group.

Figure 3: Effect of BMC therapy on survival in patients with chronic ischemic cardiomyopathy



Number of survivors:					
BMC group,	n=191	191	190	187	184
Control group	n=199	197	190	181	168

Many cohort studies (>500)



Multiple IMA grafting was associated with a 19.2% adjusted risk reduction in death and cardiac events, caused by decreases in all adverse end points and fewer reoperations

Burfeind, W. R. et al. Circulation 2004;110:II-27-II-35

Advantages BIMA

- Reducing mortality
- Reducing Cardiac death
- Reducing late cardiac events
  - Bilateral internal thoracic artery grafting patency for the left coronary artery system best patency
  - Prevent IV: 45% of vein grafts failed between 12 and 18 months
- Reducing stroke
  - "no-touch" technique is considered effective for reducing stroke risk in patients with the atherosclerotic ascending aorta

Off pump and stroke

	ART SIMA	ART BIMA	SYNTAX
Off pump	40%	41.8%	15%
CVA	1.8%	1.5%	2.2%

Concerns BIMA over SIMA

- More deep sternal wound infections
  - Sauge ER, Grab JD, O'Brien SM, et al. Use of both internal thoracic arteries in diabetic patients increases deep sternal wound infection. Ann Thorac Surg 2007;83:1302–7.
- In target vessels with mild stenosis, composite grafting resulted in a higher incidence of graft occlusion or string sign due to flow competition
  - Manabe S, Fukui T, Shimokawa T, et al. Increased graft occlusion or string sign in composite arterial grafting for mildly stenosed target vessels. The Annals of thoracic surgery. 2010;89(1):163–7.
- Usage in USA < 4%, Europe < 12%, SYNTAX 26%
  - Takata et al. 2009 - Prevalence and Variability of Internal Mammary Artery Graft Use in Contemporary Multivessel Coronary Artery

Advantages Saphenous grafts

- Accessibility, sufficient length, and ease of manipulation
- Optimising patency
  - Antiplatelet therapy
  - statins
  - gene therapy
  - no touch technique
  - external stenting
  - harvesting the saphenous vein after systemic heparinization

Some Concerns in Randomised Trials

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

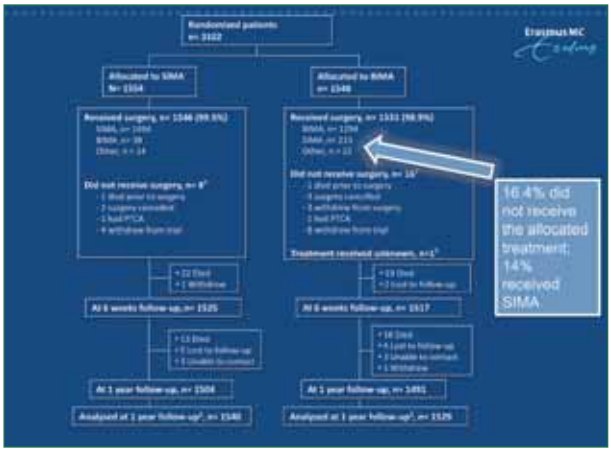
Trials

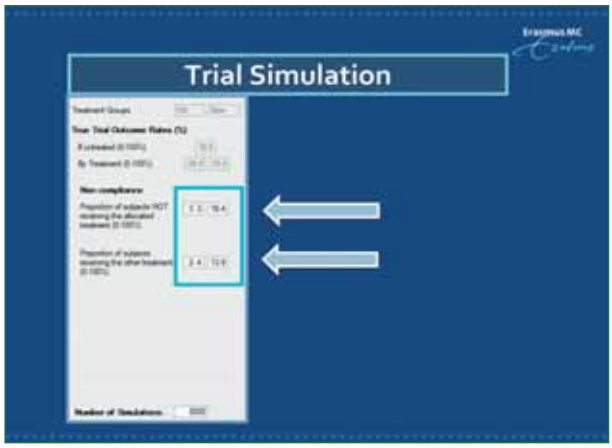
Study protocol — Open Access

Protocol for the Arterial Revascularisation Trial (ART). A randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]

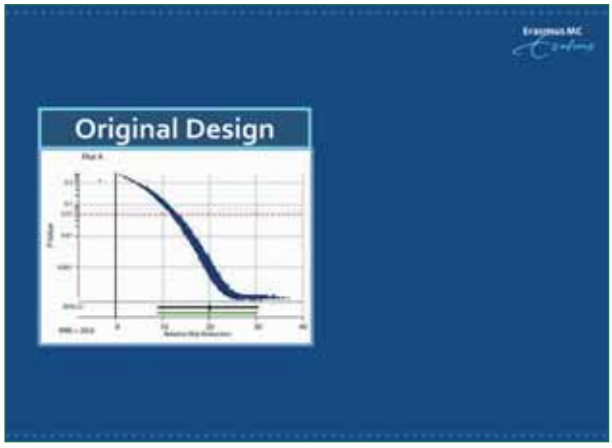
David P Taggart*[1], Belinda Lees[2], Alastair Gray[3], Douglas G Altman[4], Marcus Flather[2], Keith Channon[5] and the ART Investigators

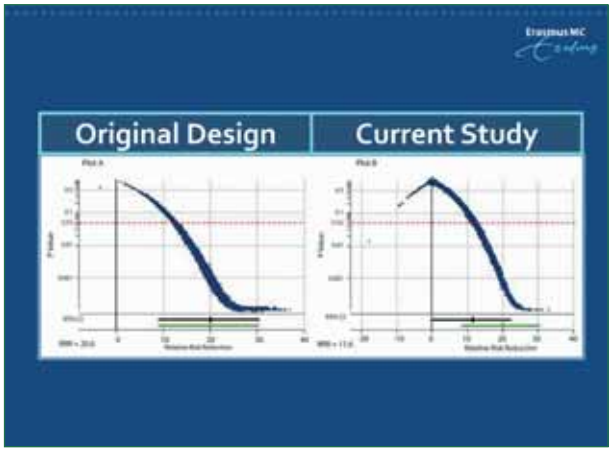
The aim is to enrol at least 3000 patients (1500 in each arm) over a 2 to 3 year recruitment period in 20 centres in the UK, Australia, Poland and Brazil (Table 3). As the intervention is the operation, compliance is likely to be 100% except in the unusual situation where the planned operation is not possible for technical reasons.

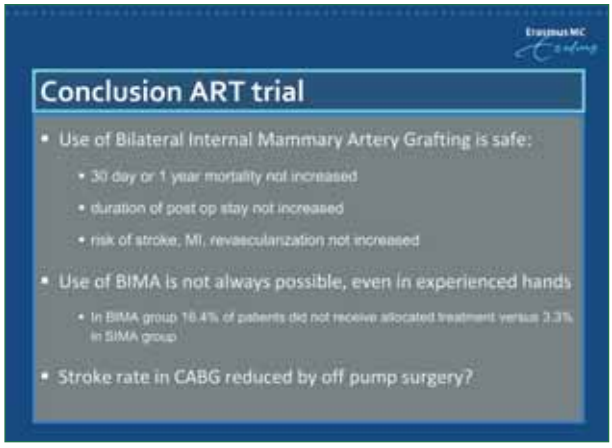


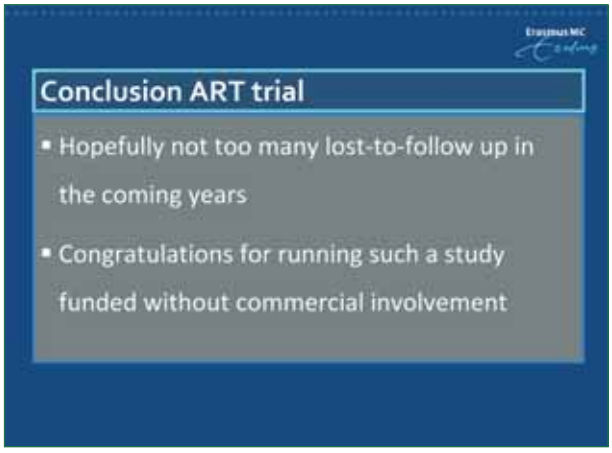

Trial Simulation


Trial Simulation

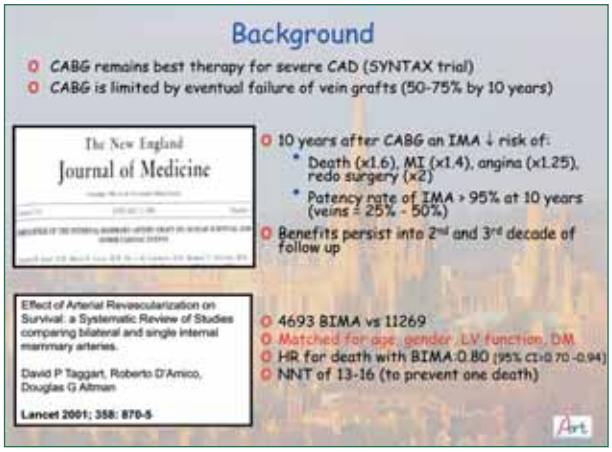

Original Design


Original Design
Current Study


Conclusion ART trial
Use of Bilateral Internal Mammary Artery Grafting is safe:
30 day or 1 year mortality not increased
duration of post op stay not increased
risk of stroke, MI, revascularization not increased
Use of BIMA is not always possible, even in experienced hands
In BIMA group 16.4% of patients did not receive allocated treatment versus 3.3% in SIMA group
Stroke rate in CABG reduced by off pump surgery?

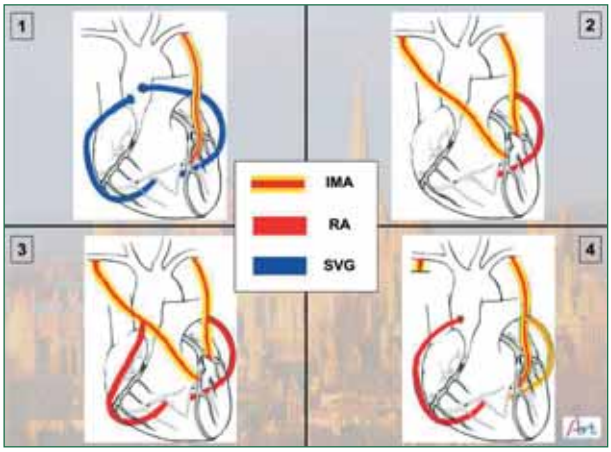

Conclusion ART trial
Hopefully not too many lost-to-follow up in the coming years
Congratulations for running such a study funded without commercial involvement


Arterial Revascularisation Trial
Randomized Trial to Compare Bilateral Versus Single Internal Mammary Coronary Artery Bypass Grafting (CABG): One Year Results of the Arterial Revascularisation Trial (ART)
DP Taggart, DG Altman, AM Gray, B Lees, F Nugara, LM Yu, H Campbell, M Flather, on behalf of the ART Investigators
ESC Hot Line 2010, Stockholm
On Line publication in EHJ
MRC


Background
CABG remains best therapy for severe CAD (SYNTAX trial)
CABG is limited by eventual failure of vein grafts (50-75% by 10 years)
The New England Journal of Medicine
10 years after CABG an IMA ↓ risk of:
Death (x1.6), MI (x1.4), angina (x1.25), redo surgery (x2)
Patency rate of IMA > 95% at 10 years (veins = 25% - 50%)
Benefits persist into 2nd and 3rd decade of follow up
Effect of Arterial Revascularization on Survival: a Systematic Review of Studies comparing bilateral and single internal mammary arteries.
David P Taggart, Roberto D'Amico, Douglas G Altman
Lancet 2001; 358: 870-5
4693 BIMA vs 11269
Matched for age, gender, LV function, DM
HR for death with BIMA:0.80 (95% CI:0.70 -0.94)
NNT of 13-16 (to prevent one death)

Use of BIMA in Routine Clinical Practice

- Uncommon
  - <10% of CABG patients in Europe
  - <5% of CABG patients in USA
- Potential reasons for NOT using BIMA
  - Technically more challenging
  - Adds to duration of operation
  - Increases early mortality
  - Increases early major morbidity
  - Increases risk of sternal wound breakdown

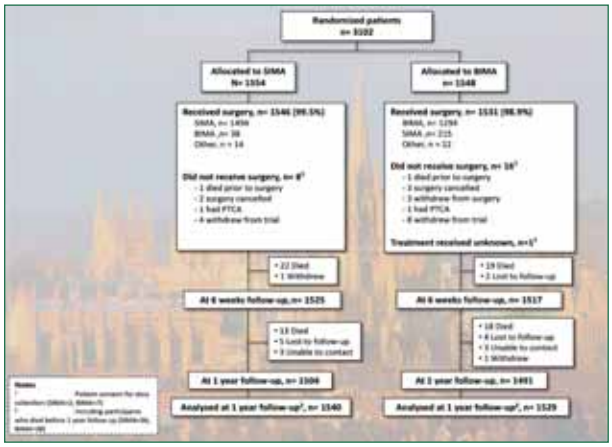


Trial Design

- Protocol published (*Trials 2006, 7:7*)
- Funded: UK Medical Research Council (MRC) & British Heart Foundation (BHF)
- Sample size
  - 3000 patients
  - 5% ↓ in 10 year mortality (from 25% to 20%)
  - 90% power, 5% alpha required 2928 patients
- Two arm randomised trial
  - Randomised 1:1 SIMA to BIMA
  - Supplementary vein/artery grafts as required
- On or Off-pump procedure
- Multi-centre (n=28 hospitals in 7 countries worldwide)

ART Endpoints

- Primary
  - Survival at 10 years
- Secondary
  - Cause specific & 30 day mortality
  - Need for re-intervention
  - Clinical events
  - Quality of Life (SF-36, Rose and EuroQol)
  - Cost effectiveness
- Sub-groups
  - Diabetes
  - Age (<70 yrs vs >70 yrs)
  - On vs off pump
  - Radial artery vs vein grafts
  - Number of grafts
  - Impaired ventricular function



ART Patient Characteristics

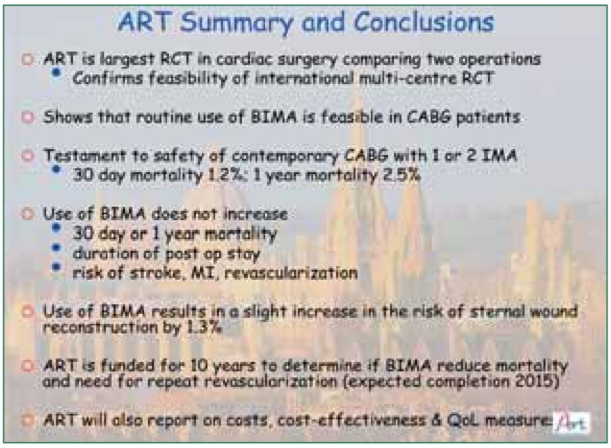
	SIMA (n=1554)	BIMA (n=1548)
Age: years mean (±SD)	63.5 (9.1)	63.7 (8.7)
Male	86%	85%
Diabetes	23.4%	24%
Urgent CABG	7.9%	7.6%
Prior myocardial infarction	43.8%	40%
Prior stenting	16%	15.6%
Prior CVA	3.1%	2.7%
Peripheral arterial disease	7.6%	6.6%

ART Surgery

		SIMA (n=1552)	BIMA (n=1542)	Δ
Off-Pump		40%	41.8%	
Grafts	1	0.7%	0.5%	
	2	17.7%	17.8%	
	3	48.5%	50.4%	
	4+	33.2%	31.3%	
Surgery length: mins mean (SD)		199 (58)	222 (61)	23 mins
Ventilation length: mins mean (SD)		863 (3293)	968 (3029)	105 mins
Duration ITU stay: hours mean (SD)		38 (106)	41 (94)	3 hours
Duration of post-op stay: days mean (SD)		7.5 (7.6)	8.0 (7.4)	0.5 days
Re-exploration for any cause		3.5%	4.3%	
Blood transfusion		12%	12%	
Intra Aortic Balloon Pump		3.7%	4.4%	
Renal support		4.4%	5.9%	

ART Outcomes

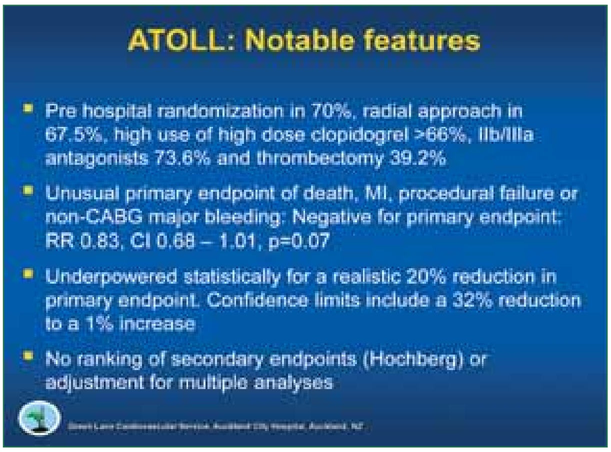
		SIMA (n=1552)	BIMA (n=1542)	Δ
30 days	All Mortality	1.2%	1.2%	
	CVA	1.2%	1.0%	
	MI	1.5%	1.4%	
	Revasc	0.4%	0.7%	
	Wound reconstruction	0.6%	1.9%	1.3%
1 year	All Mortality	2.3%	2.5%	
	CVA	1.8%	1.5%	
	MI	2.0%	2.0%	
	Revasc	1.3%	1.8%	

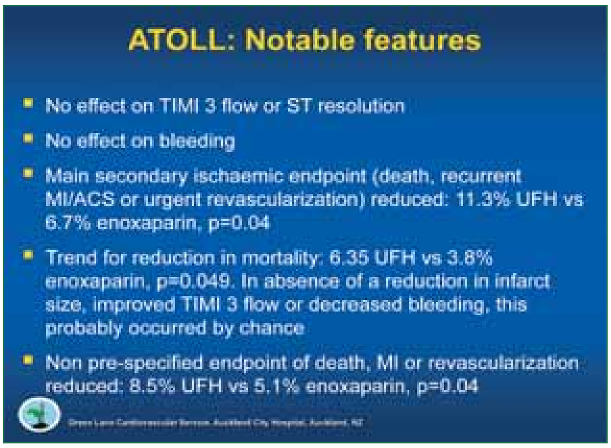

ART Summary and Conclusions
ART is largest RCT in cardiac surgery comparing two operations
Confirms feasibility of international multi-centre RCT
Shows that routine use of BIMA is feasible in CABG patients
Testament to safety of contemporary CABG with 1 or 2 IMA
30 day mortality 1.2%; 1 year mortality 2.5%
Use of BIMA does not increase
30 day or 1 year mortality
duration of post op stay
risk of stroke, MI, revascularization
Use of BIMA results in a slight increase in the risk of sternal wound reconstruction by 1.3%
ART is funded for 10 years to determine if BIMA reduce mortality and need for repeat revascularization (expected completion 2015)
ART will also report on costs, cost-effectiveness & QoL measure
Art

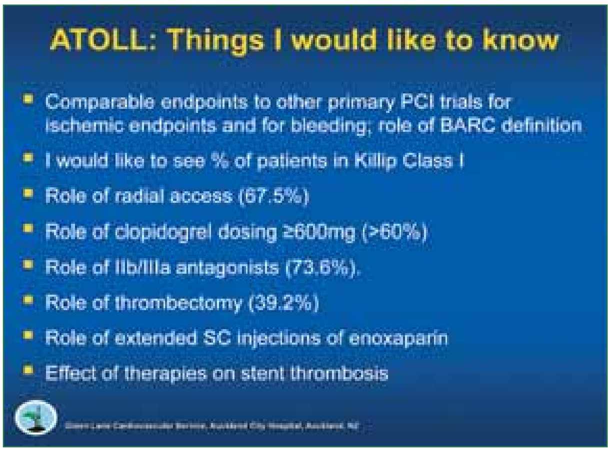

ART Participating Centres (n=28)
City
Hospital
Surgeons
Art

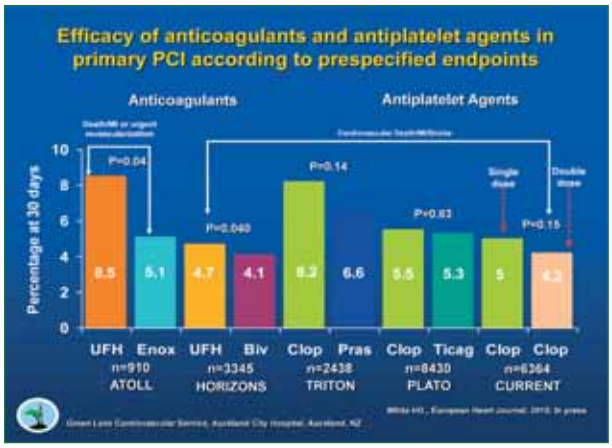

ART Trial Steering and Data Monitoring Committees
TRIAL STEERING COMMITTEE
Vermes, Geza Patient Lay Member Emeritus Professor of Hebrew Studies Oxford
Altman, Douglas Statistician Professor of Statistics in Medicine Oxford
Channon, Keith Cardiologist Professor of Cardiovascular Medicine Oxford
Collins, Rory Epidemiologist Professor of Epidemiology/Medicine Oxford
Dark, John Lead Surgeon Professor of Cardiac Surgery Newcastle
Farrell, Barbara Trials Advisor Co-Director, Resource Centre for Trials Oxford
Flather, Marcus Co-Principal Investigator Director, CTEU, Royal Brompton Hospital London
Gray, Alastair Health Economist Professor of Health Economics Oxford
Pepper, John Lead Surgeon Professor of Cardiac Surgery London
Sleight, Peter CHAIRMAN Emeritus Professor of Cardiovascular Me Oxford
Stables, Rod Cardiologist Consultant Cardiologist Liverpool
Taggart, David Principal Investigator Consultant Cardiac Surgeon Oxford
DATA MONITORING COMMITTEE
Julian, Desmond Cardiology Advisor Emeritus Professor of Cardiology London
Pocock, Stuart Statistician Professor of Statistics in Medicine London
Treasure, Tom Surgical Advisor Professor of Cardiothoracic Surgery London
Yusuf, Salim CHAIRMAN Professor of Medicine Hamilton,Ca
Art

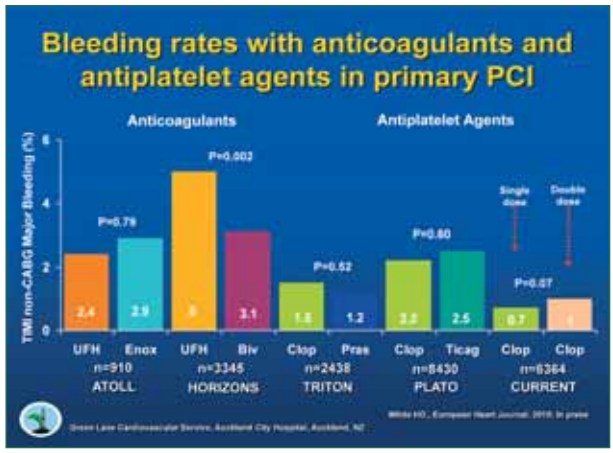

ATOLL: An international, randomized trial comparing i.v. enoxaparin with i.v. unfractionated heparin in primary PCI for ST-elevation myocardial infarction
Harvey White
Green Lane Cardiovascular Service and
Cardiovascular Research Unit
Auckland City Hospital; Auckland, New Zealand


ATOLL: Notable features
Pre hospital randomization in 70%, radial approach in 67.5%, high use of high dose clopidogrel >66%, IIb/IIIa antagonists 73.6% and thrombectomy 39.2%
Unusual primary endpoint of death, MI, procedural failure or non-CABG major bleeding: Negative for primary endpoint: RR 0.83, CI 0.68 – 1.01, p=0.07
Underpowered statistically for a realistic 20% reduction in primary endpoint. Confidence limits include a 32% reduction to a 1% increase
No ranking of secondary endpoints (Hochberg) or adjustment for multiple analyses


ATOLL: Notable features
No effect on TIMI 3 flow or ST resolution
No effect on bleeding
Main secondary ischaemic endpoint (death, recurrent MI/ACS or urgent revascularization) reduced: 11.3% UFH vs 6.7% enoxaparin, p=0.04
Trend for reduction in mortality: 6.35 UFH vs 3.8% enoxaparin, p=0.049. In absence of a reduction in infarct size, improved TIMI 3 flow or decreased bleeding, this probably occurred by chance
Non pre-specified endpoint of death, MI or revascularization reduced: 8.5% UFH vs 5.1% enoxaparin, p=0.04

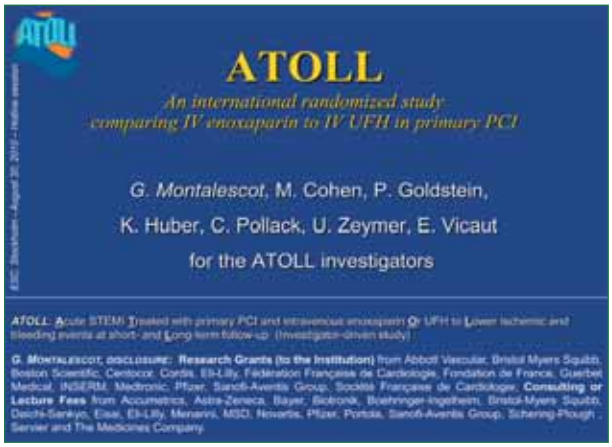

ATOLL: Things I would like to know
Comparable endpoints to other primary PCI trials for ischemic endpoints and for bleeding; role of BARC definition
I would like to see % of patients in Killip Class I
Role of radial access (67.5%)
Role of clopidogrel dosing ≥600mg (>60%)
Role of IIb/IIIa antagonists (73.6%).
Role of thrombectomy (39.2%)
Role of extended SC injections of enoxaparin
Effect of therapies on stent thrombosis

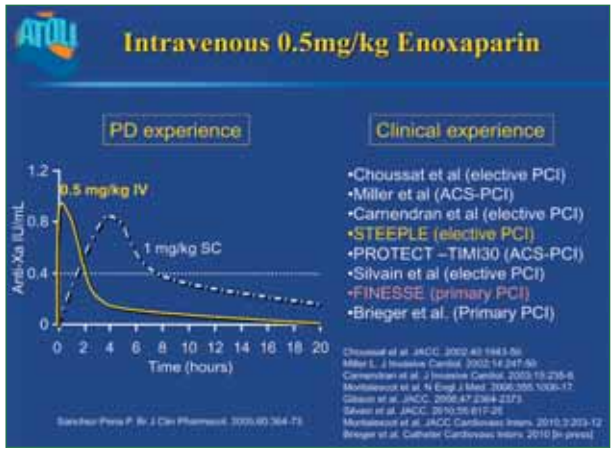


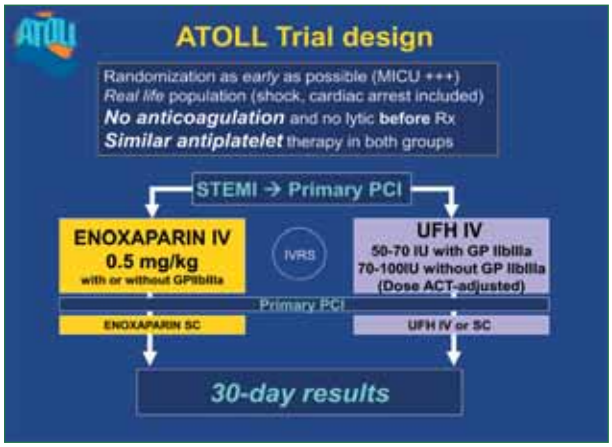


Conclusions

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







Main objectives

- 1° EP:
  - All-cause mortality at D30,
  - Complications of MI at D30 [resuscitated cardiac arrest, recurrent MI/ACS, urgent revascularization, stroke, peripheral or pulmonary embolism],
  - Procedure failure [definite stent thrombosis; B.O. use of GpIIB/IIIa; Non-TIMI 3 flow after PCI; ST resolution < 50% after PCI],
  - Non-CABG major bleeding during hospitalization
- Main 2° EP: All-cause mortality, Recurrent MI/ACS or Urgent revascularization at D30
- Main safety EP: Non-CABG major bleeding (STEEPLE definition) during hospitalization

Other objectives

Efficacy
- Death *or* complication of MI
- Death, re-MI *or* urgent revascularization
- Death; Death *or* resuscitated cardiac arrest

Safety
- Major *or* minor bleeding
- Transfusion

Net Benefit
- Death, complication of MI *or* Major bleeding

Statistics

- Study had a 80% statistical power to detect a difference between a group UFH proportion of 0.30 and a group enoxaparin proportion of 0.216 (RRR 28%, OR of 0.643) when the sample size in each group is 425.
- Sample size reassessment after 75% recruitment based on conditional power calculation (Addplan software).
- Analysis done on all randomized patients. Multiple imputation procedures for missing values done for sensitivity analysis of the main criteria (Proc MI SAS).
- Chisquare test for frequency comparisons and log-rank for survival analysis (SAS version 9.2).

Baseline characteristics

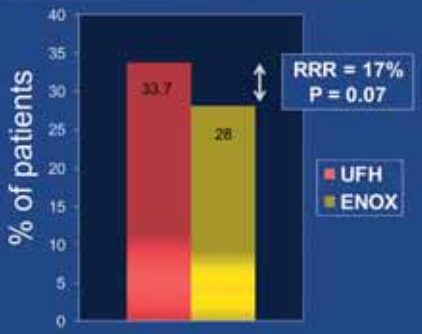
	UFH (n=460)	ENOXAPARIN (n=450)
Male sex	78% (359)	78% (353)
Age, median (Q1;Q3)	60 (52; 70)	59 (52; 71)
Age > 75	17% (80)	19% (85)
Pre-hospital randomization	71% (325)	70% (318)
Current smoker, % (n)	47% (218)	44% (199)
Diabetes, % (n)	15% (69)	14% (63)
Hypertension, % (n)	45% (207)	46% (205)
Hyperlipidemia, % (n)	40% (184)	40%(180)
Prior myocardial infarction, % (n)	10% (44)	6% (28)
Prior stroke, % (n)	2% (10)	3% (12)
Shock and/or cardiac arrest before sheath, % (n)	5% (24)	4% (17)
Time from symptom onset to randomization—hr, median (Q1;Q3)	2h19 (1h26; 4h37)	2h33 (1h29; 4h50)

Procedure and study medications

	UFH (n=460)	ENOXAPARIN (n=450)
Radial artery access, % (n)	66% (305)	69% (309)
Other artery access, % (n)	34% (155)	31% (141)
Stent implanted (among PCI patients) , % (n)	94% (366)	96% (364)
Thrombectomy (among PCI patients) , % (n)	44% (173)	48% (184)
Glycoprotein IIb/IIIa before start of PCI,% (n)	77% (357)	71% (313)
Abciximab	64% (295)	62% (277)
Eptifibatide	11% (54)	8% (34)
Tirofiban	2% (8)	0.4% (2)
Medications before/during hospitalization — % (n)		
Aspirin	94% (434)	96% (431)
Clopidogrel	93% (427)	94% (422)
≤ 300mg	37% (171)	37% (166)
> 300 and ≤ 600mg	37% (172)	39% (174)
> 600 and ≤ 900mg	25% (113)	22% (101)
> 900mg	1% (4)	2% (7)
Beta-blockers	84% (385)	88% (398)
ACE-inhibitors	72% (333)	75% (336)
Statins	83% (382)	87% (392)

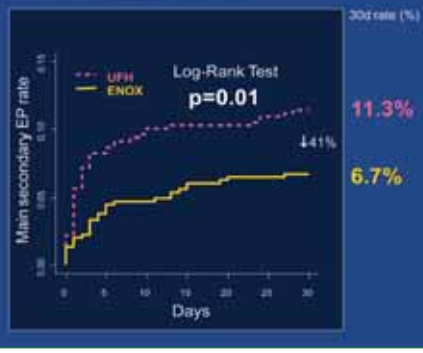
Primary Endpoint

Death, Complication of MI, Procedure Failure or Major Bleeding



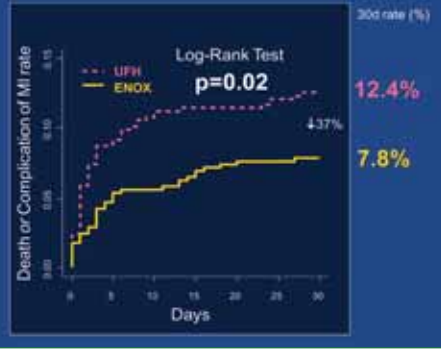
Main Secondary Endpoint (ischemic)

Death, Recurrent MI/ACS or Urgent Revascularization



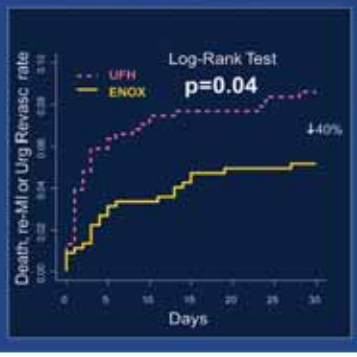
Death or Complication of MI

Death, resuscitated cardiac arrest, recurrent MI/ACS, Urg Revasc, stroke, peripheral or pulmonary embolism



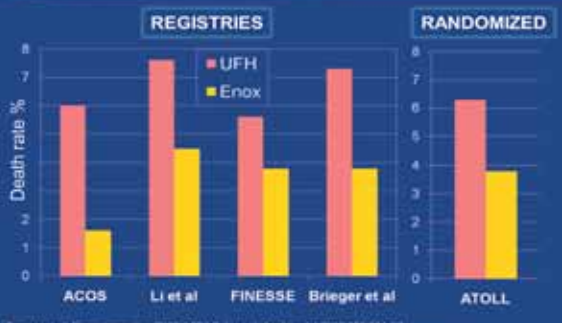
Triple Ischemic Endpoint

Death, re-MI or Urgent Revascularization



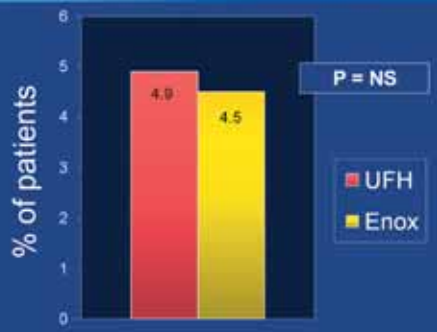
Death (any) — Death *or* resuscitated cardiac arrest

Death finding → Chance finding?

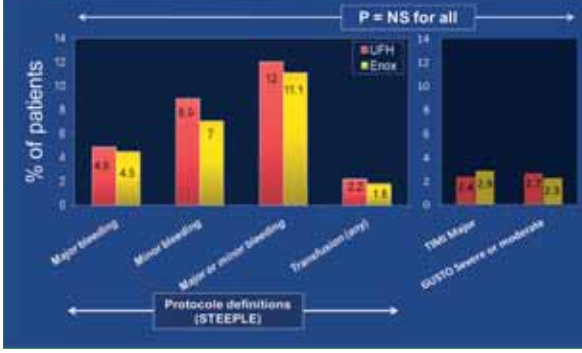


Main Safety Endpoint

Non-CABG Major Bleeding (STEEPLE definition)

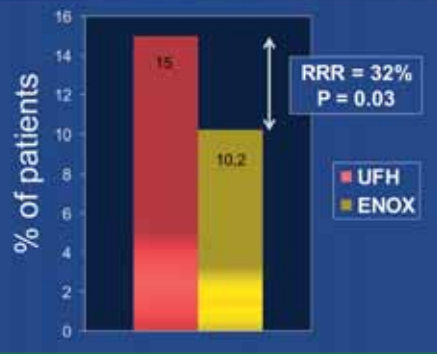


All Safety Endpoints



Death, Complication of MI or Major bleeding

Net clinical benefit



Study Limitations

- Not a pivotal registration trial → Independent trial led by the investigators
- Medium size trial → « Real life » population (>70% Rx in the field) and no prior anticoagulation
- Misses its primary EP, a mix of ischemic, safety and « classic » surrogate EP → Effective on hard ischemic EP
- Reflects practice in a limited number of countries → Contemporary study (>70% of GPIIbIIIa, >60% high dose clopidogrel, >66% radial)

Conclusions

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

- Did not reduce procedural failure
- Reduced serious ischemic events, on top of intense antiplatelet therapy
- Had a good safety profile, with a superior net clinical benefit

Special Thank to:

INVESTIGATORS – **Austria:** WR. Benzer, K. Huber, F. Leisch, F. Weidinger – **France:** F. Adnet, M. Angioi, B. Barberon, JF. Benezet, JL. Bonnet, J. Boschat, B. Boulanger, D. Carrie, T. Chouihed, P. Coste, Y. Cottin, H. Courcoux, C. Cuvier, N. Danchin, JL. Ducasse, F. Duclos, P. Ecollan, S. Elhadad, E. Filippi, M. Freysz, F. Funck, S. Gallula, B. Gelée, A. Greffet, P. Henry, A. Jacquemin, T. Joseph, JM. Lablanche, H. Lardoux, H. Le Breton, B. Lederman, A. Margenet, G. Mehu, O. Nallet, F. Paganelli, M. Pansieri, L. Payot, C. Pouges, E. Salengro, C. Spaulding, G. Steg, O. Stibbe, E. Teiger, M. Thicoipe, C. Thuaire, J. Treuil, O. Wittenberg, O. Wolf – **Germany:** D. Andresen, C. Axthelm, Fischer, E. Girth, E. Hauptmann, U. Zeymer – **USA:** M.Cohen, F. Shamoon

COMMITTEES – A Appaix-Bellemain, F Boccara, A Cohen, M. Cohen, M Cucherat, R Dumaine, A Gitt, P Goldstein, O Gourmay, K Huber, F Philippe, C Pollack, P Sabouret, A Samadi, E Vicaut, U Zeymer

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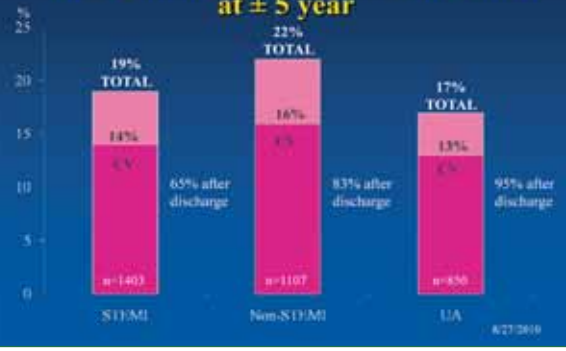
E5555 : Phase II data

Frans Van de Werf, MD, PhD
Leuven, Belgium

Disclosures

- I am a member of the executive committee of the TRACER trial (a phase III study with another PAR-1 antagonist ,vorapaxar , in ACS patients)
- I am a member of the steering committee of the TRA2P trial (Phase III study with vorapaxar in chronic CAD)

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



Why is there a high late event rate after ACS ?

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

Longer and better antithrombotic treatment after ACS

- Prolonged anticoagulation (eg oral anti-Xa agents)
- Prolonged dual platelet inhibition with aspirin and a P2Y12inhibitor (eg ticagrelor in PEGASUS study)
- Adding a third antiplatelet agent inhibiting yet another pathway of platelet aggregation (eg thrombin receptor inhibitors, vorapaxar and E5555)

The E5555 phase II data

- are in line with those of the phase II studies with another thrombin receptor antagonist , vorapaxar :

  → no significant increase in clinically relevant bleeding complications

  → some evidence for a further reduction in ischemic events

But…..E5555 phase II studies

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

Conclusions

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

Double-Blind, Placebo-Controlled Phase II Studies of E5555 in Japanese Patients with Acute Coronary Syndrome (ACS) and high risk Coronary Artery Disease (CAD)

Shinya Goto, Hisao Ogawa, Marcus D. Flather and Deepak L. Bhatt
on behalf of the J-LANCELOT investigators

Japanese - Lesson from Antagonizing the Cellular Effect of Thrombin

Disclosure

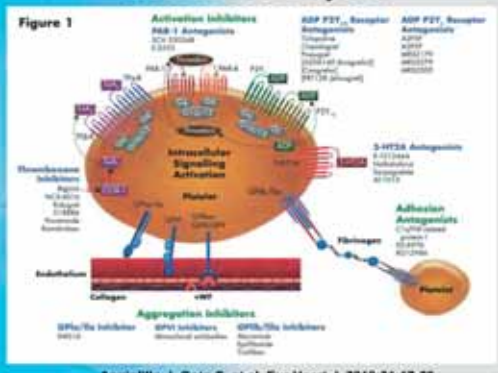
Research grants from ;
Pfizer, Sanofi-Aventi, Ono, Eisai, Otsuka, Sankyo, Daiichi, Takeda, Asteras, Kowa, Astra Zeneca.

Honoraria from ;
Sanofi-Aventis, Eisai, Otsuka, Daiichi-Sankyo, Schering-Plough.

Background

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

Platelet Receptor

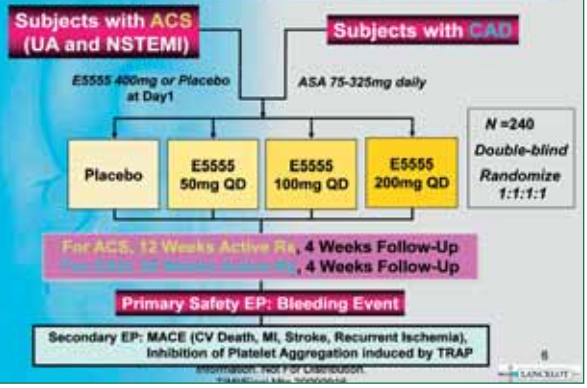


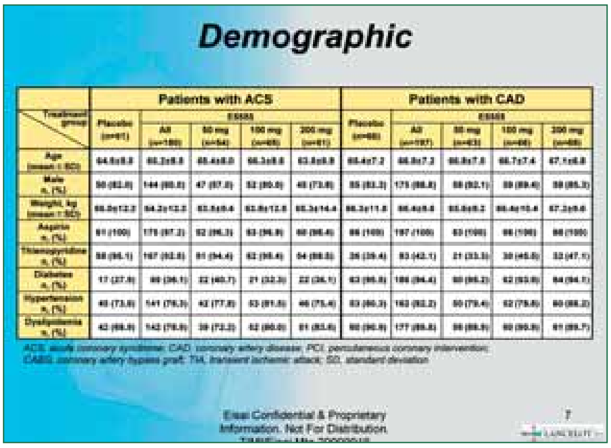
Angiolillo J, Goto S, et al. Eur Heart J 2010;31:17-28

Study Populations

- **High risk CAD study**
  - **Confirmed CAD defined as one of the following:**
    - Post ACS, MI or PCI (>4 wks), Post CABG (>12wks),
    - AP with documented ischemia (ECG or image) or
    - Documented lesion occluding ≥70% of a coronary vessel
  - **High risk defined as one or more of the following:**
    - Diabetes mellitus under Rx treatment, history of PAD or history of thrombo-embolic TIA or stroke >1 yr
- **ACS study**
  - **UA and NSTEMI defined as**
    - Ischemic chest pain ≥5 minute or
    - Symptoms requiring sublingual nitric acid agent to reduce chest pain
  - **Randomization within 24 hrs after onset**

Study Design




Demographic
Patients with ACS
Patients with CAD
ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; SD, standard deviation
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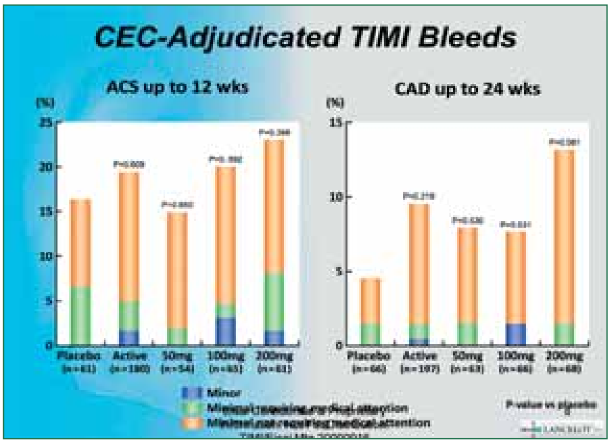
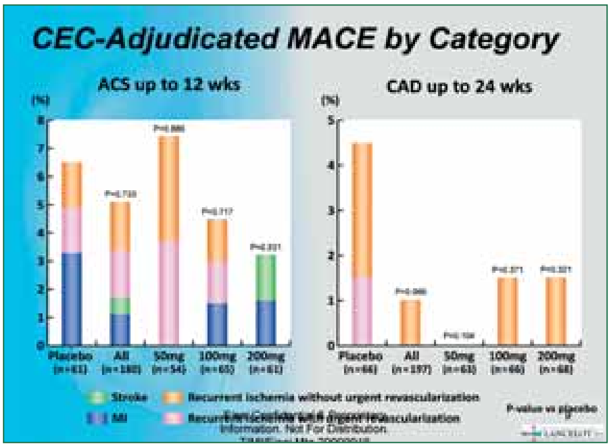
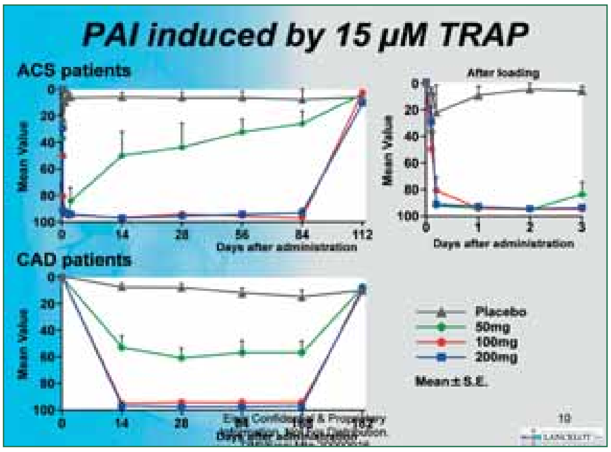
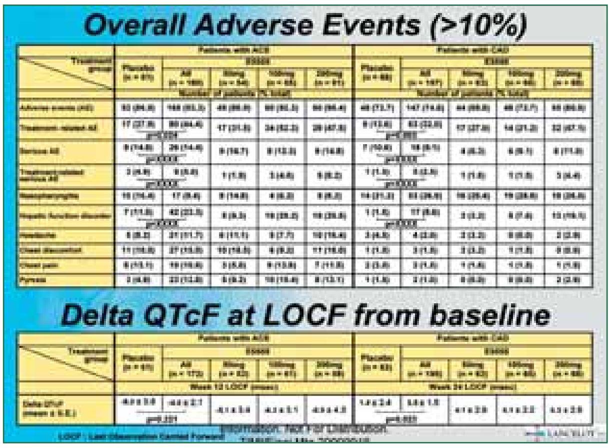
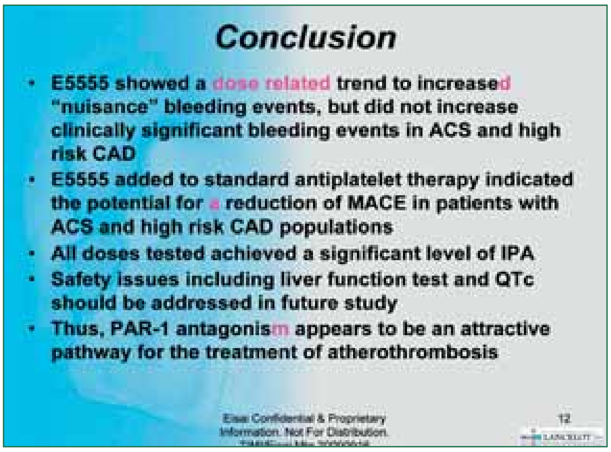

CEC-Adjudicated TIMI Bleeds
ACS up to 12 wks
CAD up to 24 wks
Placebo
Active
50mg
100mg
200mg
Minor
Minimal requiring medical attention
Minimal not requiring medical attention
P-value vs placebo


CEC-Adjudicated MACE by Category
ACS up to 12 wks
CAD up to 24 wks
Placebo
All
50mg
100mg
200mg
Stroke
MI
Recurrent ischemia without urgent revascularization
Recurrent ischemia with urgent revascularization
P-value vs placebo


PAI induced by 15 µM TRAP
ACS patients
CAD patients
After loading
Mean Value
Days after administration
Placebo
50mg
100mg
200mg
Mean ± S.E.
10


Overall Adverse Events (>10%)
Patients with ACS
Patients with CAD
Delta QTcF at LOCF from baseline
LOCF : Last Observation Carried Forward


Conclusion
E5555 showed a dose related trend to increased "nuisance" bleeding events, but did not increase clinically significant bleeding events in ACS and high risk CAD
E5555 added to standard antiplatelet therapy indicated the potential for a reduction of MACE in patients with ACS and high risk CAD populations
All doses tested achieved a significant level of IPA
Safety issues including liver function test and QTc should be addressed in future study
Thus, PAR-1 antagonism appears to be an attractive pathway for the treatment of atherothrombosis
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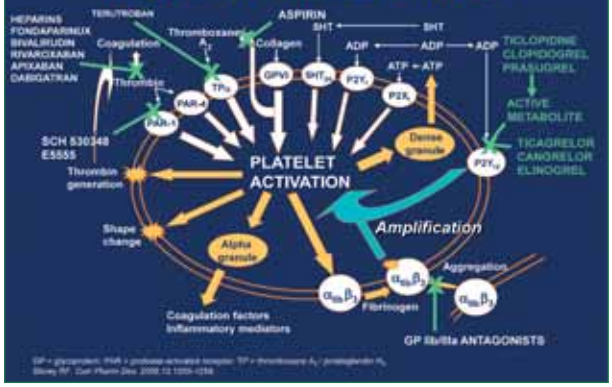
INNOVATE PCI - ESC 2010
Steen D. Kristensen, FESC
Department of Cardiology
Aarhus University Hospital Skejby
Denmark


Lecture fees and temporary advisory boards:
AstraZeneca
Daichii-Sankyo
Eli Lilly
sanofi-aventis
The Medicines Company

Targets for Platelet Inhibition



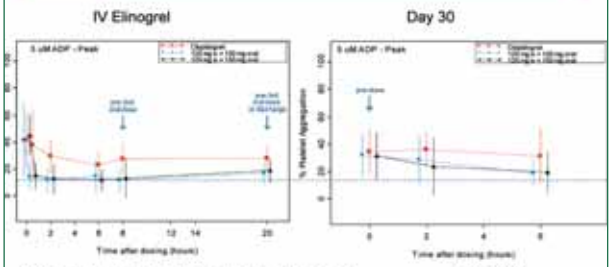
Elinogrel: potential advantages

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

INNOVATE PCI

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

Pharmacodynamic effect of Elinogrel vs. Clopidogrel



75% of pts represented above were on maintenance Clopidogrel

C (N=20)
E100 (N=13)
E150 (N=19)

Elinogrel

- Faster onset
- Stronger platelet inhibition

INNOVATE PCI

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

Randomized, double blind

INNOVATE PCI

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

Randomized, double blind

Power calculation

INNOVATE PCI

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

Randomized, double blind

Power calculation

Bleeding definition

INNOVATE PCI

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

Randomized, double blind

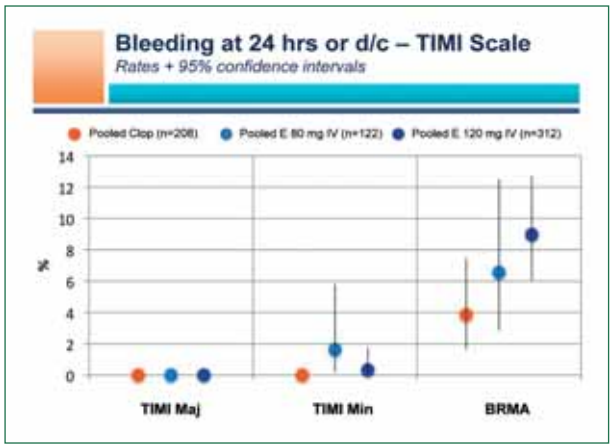
Power calculation

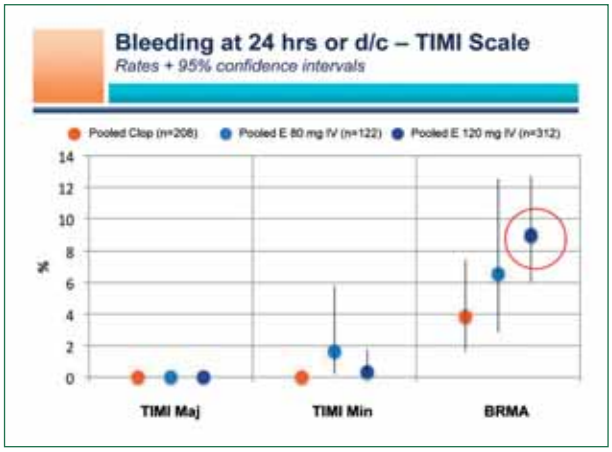
Bleeding definition

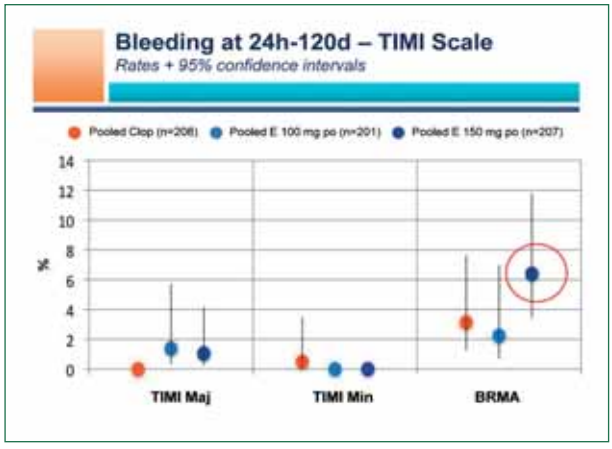
Elective PCI (46% clopidogrel)

INNOVATE PCI: bleeding

- No statistical significant difference







INNOVATE PCI: ischaemic endpoint

- No difference between clopidogrel and elinogrel

Adverse events

	Clopidogrel N=208	Pooled Elinogrel 100 mg N=201	Pooled Elinogrel 150 mg N=207
Any SAE	11.1%	14.9%	12.7%
Drug d/c due to AE or SAE	9.1%	11.5%	14.0%
Dyspnea	4.3%	15.4%	12.1%
Bradycardia	0.5%	1.0%	0.5%
Syncope	0.5%	1.5%	0.5%
ALT/AST > 3x	1.2%	3.3%	4.5%
ALT/AST > 5x	0.6%	2.0%	3.2%

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INNOVATE PCI: conclusion

- Promising new P2Y12-inhibitor
- Phase III trials

INNOVATE PCI: conclusion

- Promising new P2Y12-inhibitor
- Phase III trials

Congratulations to the investigators

BACK-UP

Reversible P2Y12 inhibition

- Intravenous - fast
- No metabolism
- Surgery and and other intervention
- Easier to manage bleeding

The variability in responsiveness to clopidogrel

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

Optimal P2Y12 inhibition

- Maybe switching between clopidogrel and cangrelor cause some problem
- Use the same drug iv plus orally could theoretically be a solution to the problem

A Randomized, Double-Blind, Active Controlled Trial to Evaluate Intravenous and Oral PRT060128 (elinogrel), a Selective and Reversible $P2Y_{12}$ Receptor Inhibitor, vs. Clopidogrel, as a Novel Antiplatelet Therapy in Patients Undergoing Non-urgent Percutaneous Coronary Interventions (INNOVATE-PCI)

INNOVATE-PCI

Disclosures

- INNOVATE-PCI was supported by Portola Pharmaceuticals Inc.
- Sunil V. Rao, MD
  - Research funding: Portola, Novartis, Cordis Corporation, Glaxo Smith Kline
  - Consultant: sanofi-aventis, Bristol Myers-Squibb, The Medicines Company, Astra Zeneca
- This presentation discusses the unapproved use of elinogrel (PRT060128) in patients undergoing PCI

Background

- Antiplatelet therapy is essential to reduce adverse events in patients with ischemic heart disease
- Recent clinical trials demonstrate that greater platelet inhibition is associated with improved ischemic outcomes, but increased major bleeding
- Reversible platelet inhibition may mitigate these risks and further improve outcomes
- Elinogrel is a novel potent platelet inhibitor that competitively and reversibly binds to the $P2Y_{12}$ receptor and can be administered both intravenously and orally

Properties of Elinogrel

- The only reversible and competitive $P2Y_{12}$ receptor antagonist
- Direct-acting: no metabolic activation required
- Available for intravenous and oral administration, enabling acute and chronic use
- Immediate and near maximal platelet inhibition achieved with IV
- Duration of action
  - Half-life: 12 hours
- No major CYP metabolism – low potential for drug-drug interactions (including PPIs)
- Balanced clearance: 50% renal; 50% hepatic (10% metabolized to pharmacologically inactive metabolite)

INNOVATE-PCI Objectives

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

Inclusion & Exclusion Criteria

INCLUSION

- Nonurgent PCI with ≥ 1 coronary lesion amenable to PCI

EXCLUSION

- Bleeding risk
  - Anemia/thrombocytopenia, recent trauma or bleeding, CVA or TIA within prior 5 years
- Concomitant therapies
  - Clopidogrel loading dose within 7 days prior to PCI, thrombolytics, oral anticoagulants, fondaparinux
- General
  - Age > 75 yrs, weight < 55 kg, CrCL < 45 cc/min, allergy to study drugs

Treatment Schema

	ACUTE PHASE Peri-PCI		CHRONIC PHASE Post-PCI	
ARM 1: clopidogrel	300-600mg Loading Dose	PCI	75 mg QD	n=200
ARM 2: elinogrel	80 mg IV Bolus+ 50mg PO	PCI	50 mg BID	n=200
ARM 3: elinogrel	80mg IV Bolus + 100mg PO	PCI	100 mg BID	n=200
ARM 4: elinogrel	80mg IV Bolus + 150mg PO	PCI	150 mg BID	n=200

- April 8, 2[illegible] DSMC recommended discontinuation of the 50 mg BID dose and increasing IV bolus dose to 120 mg as per protocol
- April 16, 2009: Chronic phase extended from 60 days to 120 days of treatment

Endpoints

Safety – 24-hr or d/c & 120-day

- TIMI bleeding: major, minor, bleeding requiring medical attention
- Clinically relevant bleeding: major, minor, nuisance

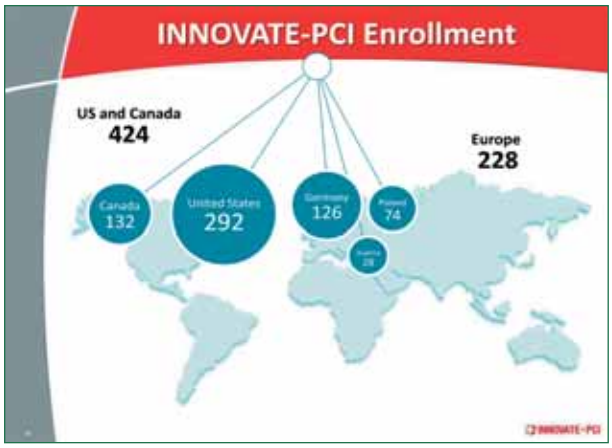
Biological efficacy - periprocedural

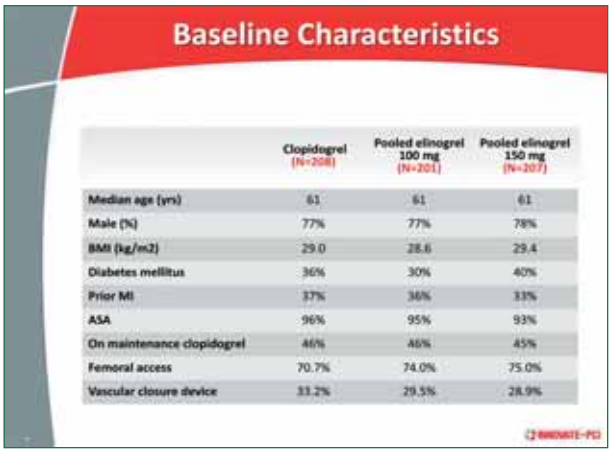
- Any Troponin* elevation at 24 hrs or d/c
- Troponin* elevation > 2 X ULN at 24 hrs or d/c

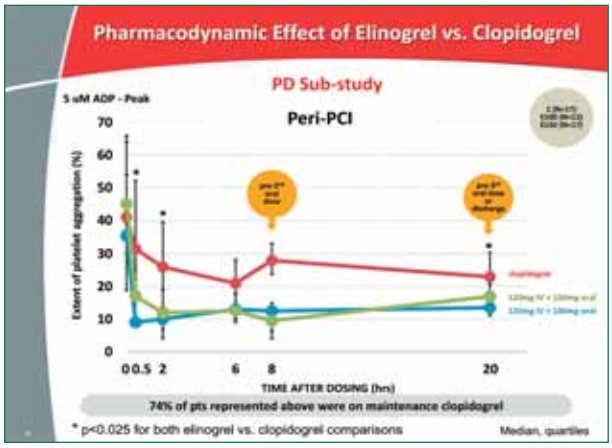
Clinical efficacy

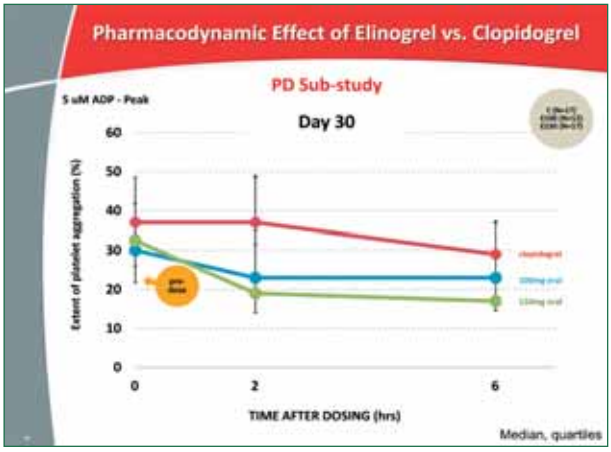
- 24-hr or d/c death, MI, stroke, uTVR, GP IIb/IIIa bailout, stent thrombosis
- 120-day death, MI, stroke, uTVR
- 120-day death, MI, stroke, uTVR, stent thrombosis

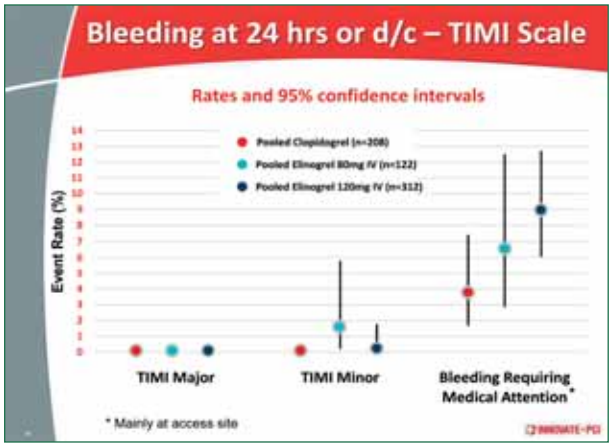
*Core lab troponin I

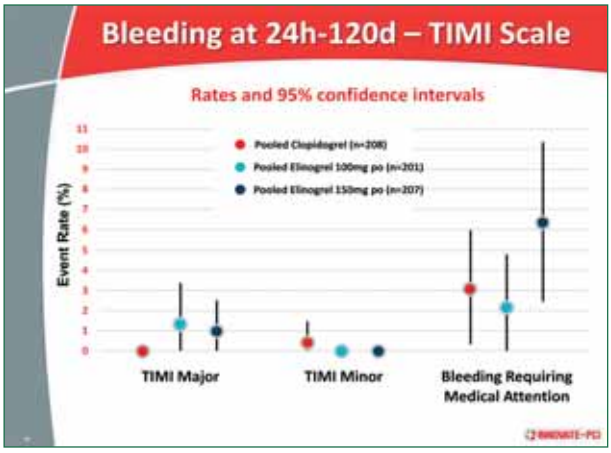

INNOVATE-PCI Enrollment
US and Canada
424
Europe
228
Canada
132
United States
292
Germany
126
Poland
74
France
28

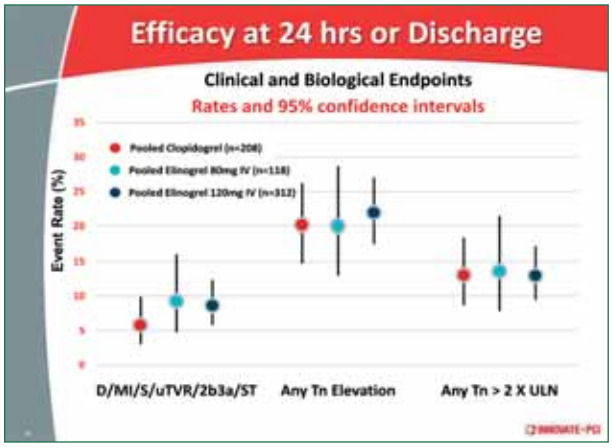

Baseline Characteristics
Clopidogrel (N=208)
Pooled elinogrel 100 mg (N=201)
Pooled elinogrel 150 mg (N=207)
Median age (yrs) 61 61 61
Male (%) 77% 77% 78%
BMI (kg/m2) 29.0 28.6 29.4
Diabetes mellitus 36% 30% 40%
Prior MI 37% 36% 33%
ASA 96% 95% 93%
On maintenance clopidogrel 46% 46% 45%
Femoral access 70.7% 74.0% 75.0%
Vascular closure device 33.2% 29.5% 28.9%

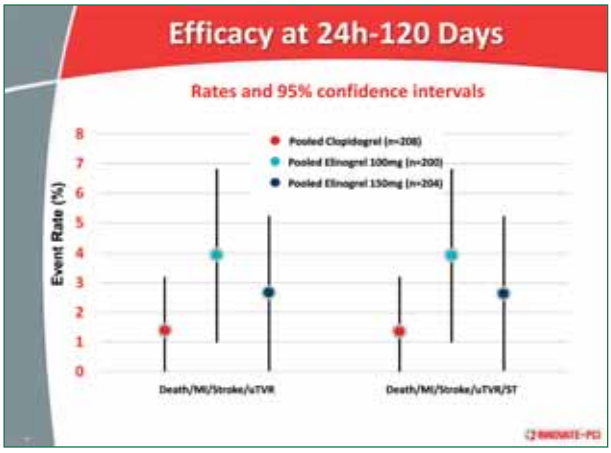

Pharmacodynamic Effect of Elinogrel vs. Clopidogrel
PD Sub-study
Peri-PCI
5 uM ADP - Peak
Extent of platelet aggregation (%)
TIME AFTER DOSING (hrs)
74% of pts represented above were on maintenance clopidogrel
* p<0.025 for both elinogrel vs. clopidogrel comparisons
Median, quartiles


Pharmacodynamic Effect of Elinogrel vs. Clopidogrel
PD Sub-study
Day 30
5 uM ADP - Peak
Extent of platelet aggregation (%)
TIME AFTER DOSING (hrs)
Median, quartiles


Bleeding at 24 hrs or d/c – TIMI Scale
Rates and 95% confidence intervals
Pooled Clopidogrel (n=208)
Pooled Elinogrel 80mg IV (n=122)
Pooled Elinogrel 120mg IV (n=312)
Event Rate (%)
TIMI Major
TIMI Minor
Bleeding Requiring Medical Attention*
* Mainly at access site


Bleeding at 24h-120d – TIMI Scale
Rates and 95% confidence intervals
Pooled Clopidogrel (n=208)
Pooled Elinogrel 100mg po (n=201)
Pooled Elinogrel 150mg po (n=207)
Event Rate (%)
TIMI Major
TIMI Minor
Bleeding Requiring Medical Attention


Efficacy at 24 hrs or Discharge
Clinical and Biological Endpoints
Rates and 95% confidence intervals
Pooled Clopidogrel (n=208)
Pooled Elinogrel 80mg IV (n=118)
Pooled Elinogrel 120mg IV (n=312)
Event Rate (%)
D/MI/S/uTVR/2b3a/ST
Any Tn Elevation
Any Tn > 2 X ULN


Efficacy at 24h-120 Days
Rates and 95% confidence intervals
Pooled Clopidogrel (n=208)
Pooled Elinogrel 100mg (n=200)
Pooled Elinogrel 150mg (n=204)
Event Rate (%)
Death/MI/Stroke/uTVR
Death/MI/Stroke/uTVR/ST

Adverse Events

	Clopidogrel N=208	Pooled elinogrel 100 mg N=201	Pooled elinogrel 150 mg N=207
Any SAE	11.1%	14.9%	12.6%
Drug d/c due to AE or SAE	7.2%	7.5%	10.1%
Dyspnea*	4.3%	15.4%	12.1%
Bradycardia	0.5%	1.0%	0.5%
Syncope	0.5%	1.5%	0.5%
ALT/AST > 3x^	1.0%	4.0%	4.8%
ALT/AST > 5x	0.5%	2.0%	3.4%

* Dyspnea was generally mild, transient, and infrequently led to discontinuation
^ Most cases occurred within first 60 days and were asymptomatic; All cases resolved, even when treatment was continued; No Hy's Law cases.

INNOVATE-PCI

Conclusions

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

INNOVATE-PCI

Conclusions (2)

- Adverse events similar between elinogrel and clopidogrel
  - Dyspnea more frequent in the elinogrel arms
    - Mild, transient, infrequently led to discontinuation
  - Excess in transaminase elevation cases in the elinogrel arms
    - Occurred early and were generally asymptomatic
    - All resolved even when treatment was continued
    - No Hy's Law cases
- INNOVATE PCI data support moving forward into Phase 3

INNOVATE-PCI

Phase 3 Chronic CHD Trial – Sponsored by Novartis

Patients with Prior MI
(~24,000 pts)
6-mos to 5 yrs post-index event
Background ASA

PLACEBO	ELINOGREL (low exposure dose)	ELINOGREL (high exposure dose)

Study is event driven,
expected mean duration is ~29 months

PRIMARY EFFICACY ENDPOINT:
CV Death, MI, Stroke

INNOVATE-PCI

INNOVATE-PCI Study Organization

Study chair	Robert A. Harrington MD
Co-Principal Investigators	Sunil V. Rao MD, Robert Welsh MD
Steering Committee	Uwe Zeymer MD, Janusz Kochman MD, Kurt Huber MD, Deepak Bhatt MD, C. Michael Gibson MD, Mina Madan MD
DCRI	Gayle Paynter (project lead), Lisa Berdan, Vivian Thompson MPH (Stats), Gail E. Hafley MS (Stats)
DSMC	David J. Moliterno MD (chair), Eric Cohen MD, Neal Kleiman MD, Butch Tsiatis PhD
Study sponsor (Portola)	Matthew McClure MD, Daniel Gretler MD, Deb Chapman, Sally Greenberg PhD

Thank you to all Innovate PCI investigators
and study coordinators worldwide

INNOVATE-PCI

ESC CONGRESS 2010
STOCKHOLM

ISAR-REACT 3A

Comments

Christian W. Hamm
Kerckhoff Heart & Thorax Center
Bad Nauheim Germany

No conflict to report with respect to this study

UNIVERSITÄT FRANKFURT AM MAIN

Guidelines on myocardial revascularization

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

Table 34 Antithrombotic treatment options in myocardial revascularization

Elective PCI				
Antiplatelet therapy		Class[a]	LoE[b]	Ref.[c]
	ASA	I	B	11
	Clopidogrel	I	A	11
	Clopidogrel – pretreatment with 300 mg loading dose 4–6 h before PCI (or 600 mg 2 h before)	I	C	—
	+ GPIIb–IIIa antagonists (bailout situation only)	IIa	C	—
Anticoagulation				
	UFH	I	C	—
	Enoxaparin	IIa	B	144

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

Facts: UFH during PCI

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

Advice from Guidelines

ESC Guidelines 2010

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

Recommendation I - C

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

ISAR-REACT 3A:

(Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment 3A)

A trial of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention

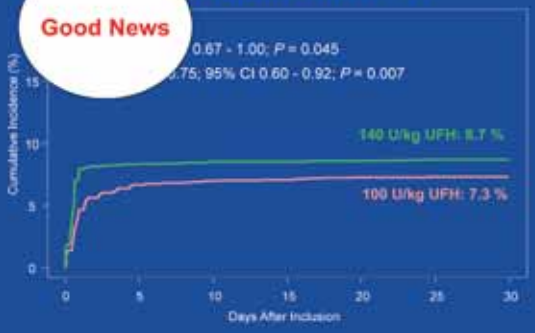
Primary (Quadruple) Endpoint

Net clinical Outcome -

Good News

0.67 - 1.00; *P* = 0.045

.75; 95% CI 0.60 - 0.92; *P* = 0.007



UFH Dose?

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

• STEEPLE (2006)	70 – 100 U/kg
• Vainer et al. (1997)	5000 U
• Koch et al. (1997)	5000 U
• Kaluski et al. (2000)	2500 U
• Caussin et al (2003)	3000 U

Anticoagulation during PCI 2010

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

Take home message

- **In elective PCI:**

Not more than 100 U / kg UFH

Probably less!

ClinicalTrials.gov Identifier NCT00735280

ISAR-REACT 3A:

Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment 3A)

A trial of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention

S. Schulz[1], J. Mehilli[1], FJ. Neumann[2], T. Schuster[3], S. Massberg[1], C. Valina[2], M. Seyfarth[1], J. Pache[1], KL. Laugwitz[4], HJ. Büttner[2], G. Ndrepepa[1], A. Schömig[1,4], A. Kastrati[1]

[1] Deutsches Herzzentrum Munich, [2] Herz-Zentrum Bad Krozingen, [3] Institut für Medizinische Statistik und Epidemiologie, Klinikum rechts der Isar, Munich [4] 1. Medizinische Klinik, Klinikum rechts der Isar, Munich, Germany

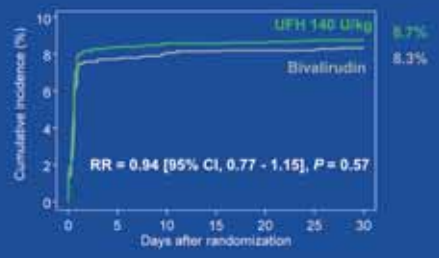
Background

- Optimal dose of unfractionated heparin (UFH) during percutaneous coronary intervention (PCI) is not known
- In the predecessor ISAR-REACT 3 trial a bolus dose of 140 U/kg UFH without activated clotting time (ACT) monitoring was compared with bivalirudin in biomarker negative patients undergoing PCI

Kastrati *et al*, NEJM 2008

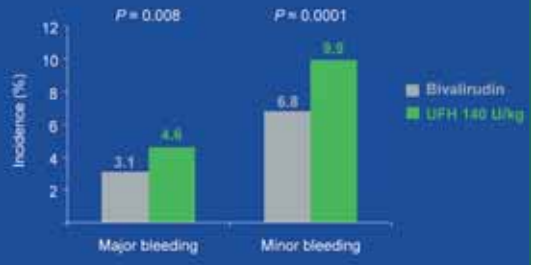
ISAR-REACT 3:

UFH 140 U/kg and Bivalirudin Provide Comparable Net Clinical Outcome (Death, MI, uTVR, Major Bleeding)



ISAR-REACT 3:

More Bleeding with 140 U/kg UFH



Aims of ISAR-REACT 3A:

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

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

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

Methods

- Prospective, multicenter, single-arm, open-label, historical control trial
- 3 participating centers in Germany:
  Deutsches Herzzentrum Munich, Klinikum rechts der Isar, Munich, Herz-Zentrum Bad Krozingen
- Same eligibility, inclusion and exclusion criteria and endpoints as in ISAR-REACT 3

Key Inclusion Criteria

- Patients older than 18 years of age undergoing PCI who were biomarker negative at study entry
- Clopidogrel loading ≥ 2 hrs prior to PCI

Key Exclusion Criteria

- Acute coronary syndromes with positive biomarkers or ST-segment elevation on ECG
- Cardiogenic shock
- Active bleeding, bleeding diathesis
- Impaired renal function (creatinine >3 mg/dl)

Treatment Regimen

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

single arm, open-label

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

Clopidogrel 75-150 mg/day until discharge (≤3 days)
75 mg/day thereafter

Aspirin 80-325 mg/day indefinitely

Primary (Quadruple) Endpoint at 30 Days

Composite rate of:

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

- Intracranial, intraocular, or retroperitoneal bleeding, or
- Clinically overt bleeding resulting in a decrease in Hb>3 g/dL, or
- Any decrease in Hb>4 g/dL, or
- Transfusion of ≥2 units of packed red blood cells or whole blood

Secondary (Triple) Endpoint at 30 Days

Composite rate of:

- Death
- Myocardial infarction
- Urgent target vessel revascularization

Sample Size Calculation

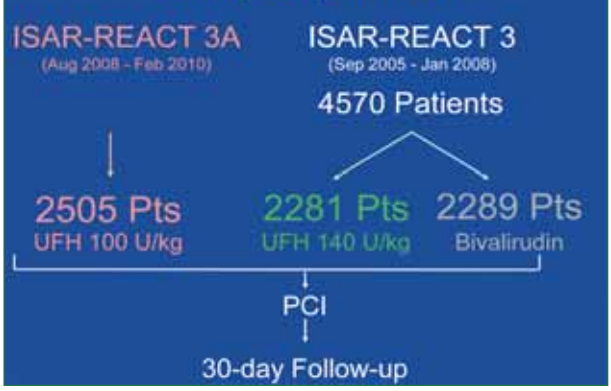
Superiority hypothesis (100 vs 140 U/kg UFH)

- Incidence of the primary endpoint in ISAR-REACT 3 (historical control):
  - 8.7% in 140 U/kg UFH group
- Assumptions:
  - 25% relative reduction (2.2% in absolute) with lower UFH dose
  - Power: 80%, 2-sided α-level of 0.05
- Calculated sample size: 2367 pts
  to account for possible losses to follow-up: planned enrolment of **2500** pts

Non-inferiority hypothesis (100 U/kg vs. Bivalirudin)

- With 2500 patients the study had 74% power to check for non-inferiority of the lower UFH dose versus bivalirudin,
  based on the incidence of 8.3% in the bivalirudin group of ISAR-REACT 3 and the following assumptions:
  - margin of non-inferiority of 1.8%
  - one sided α-value of 0.05

Study Population



Baseline Characteristics

	UFH 100 U/kg		UFH 140 U/kg	Bivalirudin
Age, yrs	68 [60-74]		68 [60-74]	68 [60-74]
Women, %	22		23	24
BMI, kg/m²	27.4	#	27.2	27.1
Diabetes, %	30	#	28	27
Hypertension, %	91	#	90	89
Current smoker, %	15		15	14
Hyperchol, %	71	*#	79	81
History of MI, %	34	*	30	32
History of CABG, %	14	*	11	12
Unstable angina, %	23	*#	18	18
Stable angina, %	77	*#	82	82
Creatinine, mg/dl	1.0 [0.8-1.1]	*#	0.9 [0.8-1.1]	0.9 [0.8-1.1]

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

Angiographic Characteristics

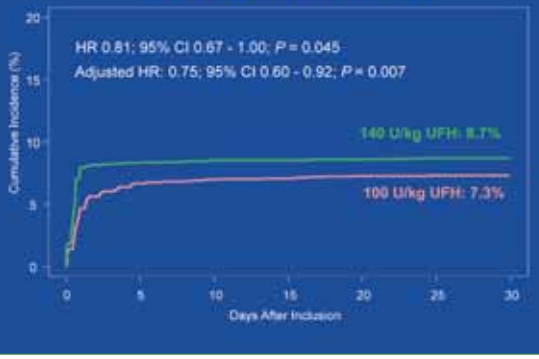
	UFH 100 U/kg		UFH 140 U/kg	Bivalirudin
Ejection fraction, %	58 [50-62]	*#	60 [52-65]	60 [52-65]
Multivessel, %	86	*#	80	80
Vessel treated, %				
Left main	4		3	4
LAD	38		39	41
LCX	27		26	25
RCA	28		30	28
bypass graft	2		2	2
B2/C lesion, %	71	*#	68	67

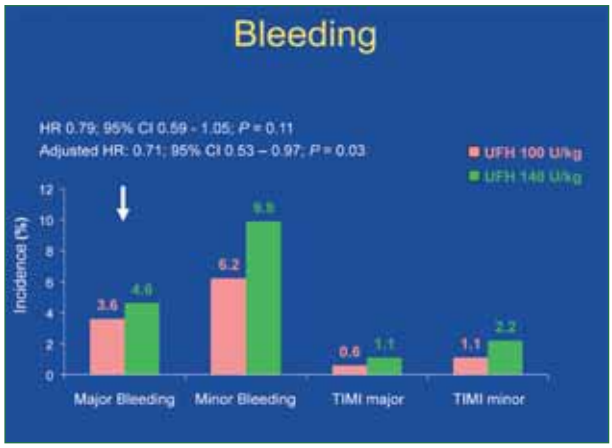
*P<0.05 for UFH 100 U/kg vs UFH 140 U/kg; # P<0.05 for UFH 100 U/kg vs Bivalirudin

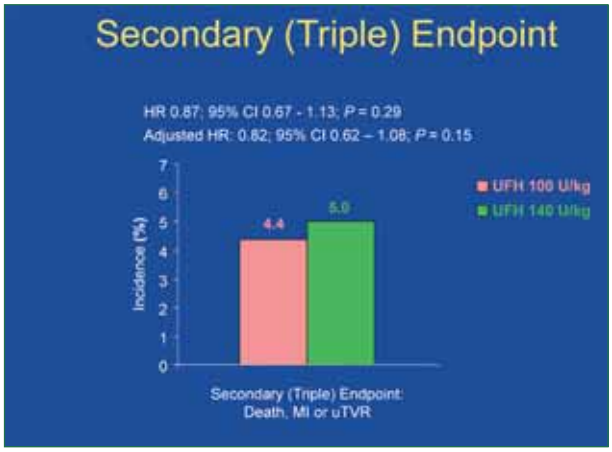
Procedural Characteristics

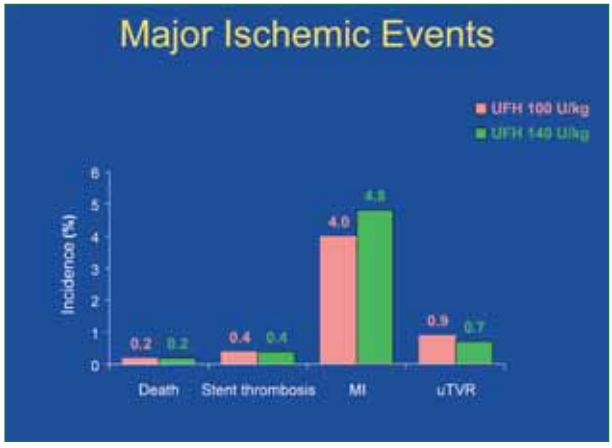
	UFH 100 U/kg		UFH 140 U/kg	Bivalirudin
Intervention, %		*#		
DES	91		87	88
BMS	2		6	5
PTCA	8		7	7
Max balloon pressure, atm	16 [13-18]	*#	15 [12-18]	15 [12-18]
Final DS, %	11.3 [7.8-16.0]	*#	10.8 [7.3-14.8]	10.9 [7.3-14.9]

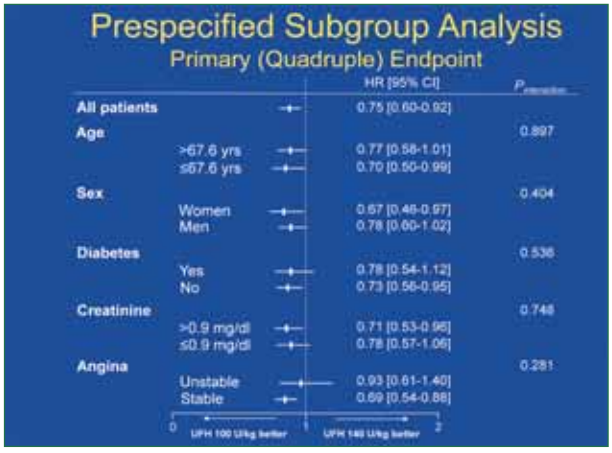
Primary (Quadruple) Endpoint - Net clinical Outcome -

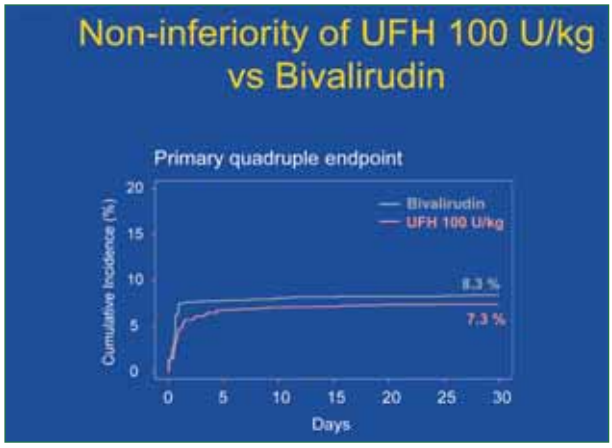


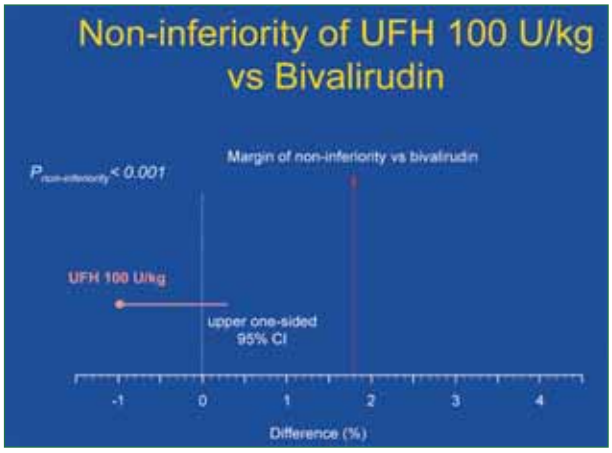

Bleeding
HR 0.79; 95% CI 0.59 - 1.05; P = 0.11
Adjusted HR: 0.71; 95% CI 0.53 – 0.97; P = 0.03
UFH 100 U/kg
UFH 140 U/kg
Incidence (%)
3.6
4.6
6.2
9.5
0.6
1.1
1.1
2.2
Major Bleeding
Minor Bleeding
TIMI major
TIMI minor

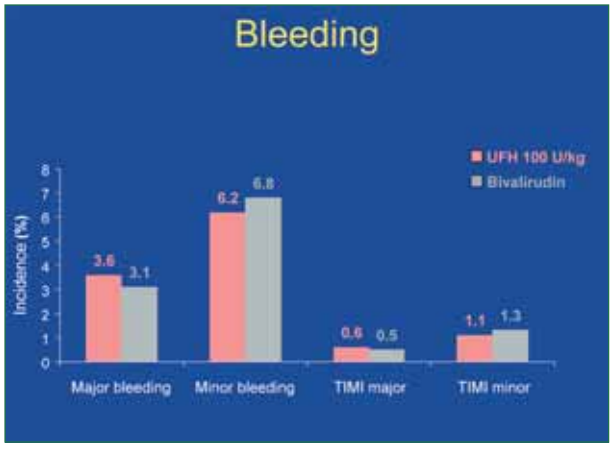

Secondary (Triple) Endpoint
HR 0.87; 95% CI 0.67 - 1.13; P = 0.29
Adjusted HR: 0.82; 95% CI 0.62 – 1.08; P = 0.15
UFH 100 U/kg
UFH 140 U/kg
Incidence (%)
4.4
5.0
Secondary (Triple) Endpoint:
Death, MI or uTVR

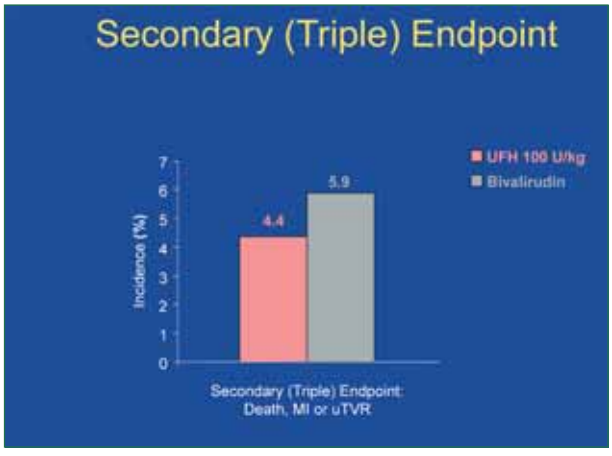

Major Ischemic Events
UFH 100 U/kg
UFH 140 U/kg
Incidence (%)
0.2
0.2
0.4
0.4
4.0
4.8
0.9
0.7
Death
Stent thrombosis
MI
uTVR


Prespecified Subgroup Analysis
Primary (Quadruple) Endpoint
HR [95% CI]
All patients
0.75 [0.60-0.92]
Age
0.897
>67.6 yrs
0.77 [0.58-1.01]
≤67.6 yrs
0.70 [0.50-0.99]
Sex
0.404
Women
0.67 [0.46-0.97]
Men
0.78 [0.60-1.02]
Diabetes
0.536
Yes
0.78 [0.54-1.12]
No
0.73 [0.56-0.95]
Creatinine
0.748
>0.9 mg/dl
0.71 [0.53-0.96]
≤0.9 mg/dl
0.78 [0.57-1.06]
Angina
0.281
Unstable
0.93 [0.61-1.40]
Stable
0.69 [0.54-0.88]
UFH 100 U/kg better
UFH 140 U/kg better

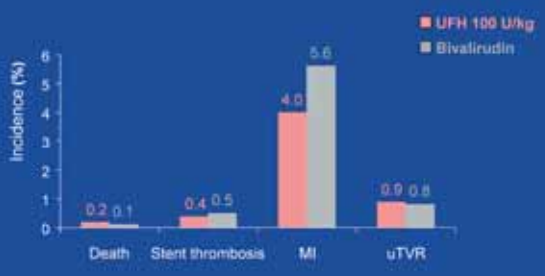

Non-inferiority of UFH 100 U/kg vs Bivalirudin
Primary quadruple endpoint
Bivalirudin
UFH 100 U/kg
Cumulative Incidence (%)
8.3 %
7.3 %
Days


Non-inferiority of UFH 100 U/kg vs Bivalirudin
Margin of non-inferiority vs bivalirudin
P non-inferiority < 0.001
UFH 100 U/kg
upper one-sided
95% CI
Difference (%)


Bleeding
UFH 100 U/kg
Bivalirudin
Incidence (%)
3.6
3.1
6.2
6.8
0.6
0.5
1.1
1.3
Major bleeding
Minor bleeding
TIMI major
TIMI minor


Secondary (Triple) Endpoint
UFH 100 U/kg
Bivalirudin
Incidence (%)
4.4
5.9
Secondary (Triple) Endpoint:
Death, MI or uTVR

Major Ischemic Events



Conclusion

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

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

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

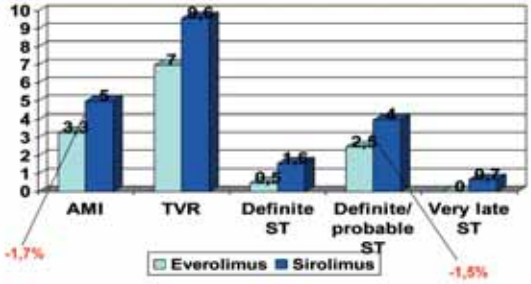
Available now online at ***European Heart Journal***

Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization

(LESSON-I study presented by S. Windecker)

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

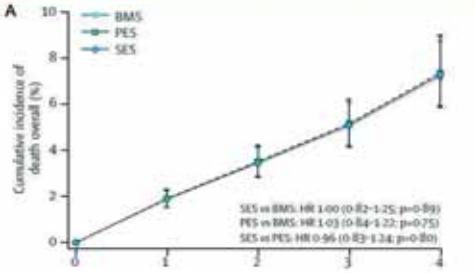
Summary of results: Besides the stent thrombosis difference, both stents had rather similar outcomes.



Stent design differences: Strut thickness (EES: 81 µm versus SES: 140 µm). Polymer coating (EES: 7.6 µm versus SES: 12.6 µm).

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

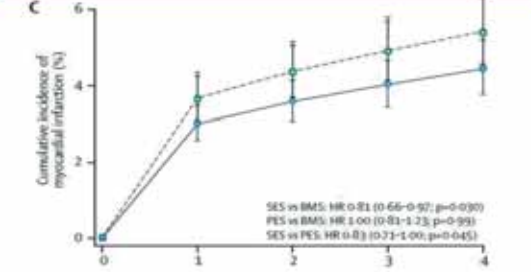
(Stettler C et al. Lancet 2007; 370: 937–48)



BMS	4921	309/4904	48/3340	31/2264	44/1875
PES	6331	138/6283	78/4263	32/2187	15/869
SES	6771	139/6730	72/4041	38/2340	24/10810

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

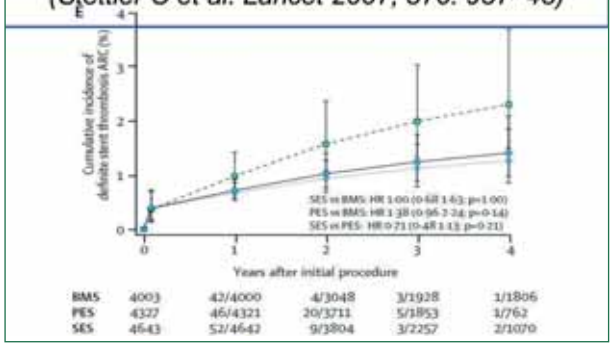
(Stettler C et al. Lancet 2007; 370: 937–48)



BMS	4891	210/4874	20/3174	17/2129	9/1745
PES	6300	249/6252	47/4057	15/2054	8/805
SES	6771	232/6730	25/3884	11/2236	7/1025

Sirolimus vs. Paclitaxel vs. BMS: AMI difference caused mainly by stent thrombosis.

(Stettler C et al. Lancet 2007; 370: 937–48)



DES „Premier League“

	Everolimus	Sirolimus	Zotarolimus	Paclitaxel
Everolimus	XXXXX	1:0 *(Windecker, ESC 2010)*	1:1 *(Serruys, NEJM 2010)*	1:0 *(Stone, NEJM 2010)*
Sirolimus	0:1	XXXXX	1:1 *(Rasmussen, Lancet 2010, Byrne, JACC 2010, Lee, Am J Cardiol 2009)*	1:0 *(Stettler, Lancet 2007)*
Zotarolimus	1:1	1:1	XXXXX	1:1 *(Leon, JACC 2010)*
Paclitaxel	0:1	0:1	1:1	XXXXX

How important are the differences between various DES ?

Everolimus – Sirolimus – Zotarolimus – Paclitaxel

If there are any significant differences, are they caused mainly by the:

- Drug ?
- Stent design (e.g. strut thickness) ?
- Polymer ?

Windecker's study limitations

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

Major study limitation: historical controls.

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

Remaining questions

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

Summary

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

LESSON - I

Long-term comparison of Everolimus-eluting and Sirolimus-eluting Stents for cOronary revascularizatioN

Lorenz Räber, Peter Jüni, Eveline Nüesch, Bindu Kalesan, Peter Wenaweser, Aris Moschovitis, Ahmed A. Khattab Maryam Bahlo, Mario Togni, Stéphane Cook, Rolf Vogel, Christian Seiler, Bernhard Meier and Stephan Windecker

Department of Cardiology
Swiss Cardiovascular Center and Clinical Trials Unit Bern
Bern University Hospital, Switzerland

LESSON I - Objective

- To compare the safety and efficacy of the unrestricted use of everolimus-eluting stents (XIENCE™) with sirolimus-eluting stents (CYPHER™) for coronary revascularization in a large, consecutively enrolled patient population followed up to 3 years in a propensity-score matched analysis.

LESSON I - Patient Background

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

LESSON I - Patient Population

Inclusion Criteria

All consecutive patients undergoing implantation of everolimus-eluting and sirolimus-eluting stents in patients with stable angina, silent ischemia, and acute coronary syndromes (UA, NSTEMI and STEMI)

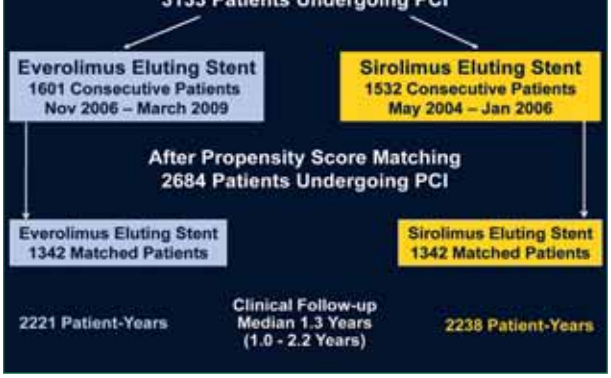
Diameter stenosis ≥ 50%
Number of lesions: no limitation
Number of vessels: no limitation
Lesion length: no limitation

Written informed consent

Exclusion Criteria

Patients with sirolimus-eluting stents implanted prior to April 2003 due to clopidogrel prescription of 3 instead of 12 months
Patients with sirolimus-eluting stents included into the SIRTAX trial in view of mandatory angiographic follow-up

LESSON I – Patient Flow



LESSON I - Sample Size Calculation

Primary Endpoint

- Composite of death, MI and TVR through 3 years
- Relative risk assumption of 0.75 in favour of EES compared with SES based on
  - Meta-analysis comparing EES vs PES (RR=0.60)
  - Network meta-analysis comparing SES vs PES (RR=0.80)
- Expected event rate = 18% @ median f/u 1.5 years
- 1400 matched patients ➡ 90% power

Secondary Endpoints

- Death, MI, TLR, TVR
- Cardiac death or MI
- Stent thrombosis according to ARC

LESSON I – Antithrombotic Drug Regimen

Pre or during procedure

Acetylsalicylic acid: ≥ 100 mg
Clopidogret: 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 12 months

LESSON I – Patient Characteristics

Before Propensity Score Matching (N=3133)

	Everolimus Stent 1601 Patients	Sirolimus Stent 1532 Patients	P
Age	65±12	63±11	<0.001
Male sex, %	76	78	0.16
Body mass index	27±5	27±4	0.66
Diabetes mellitus, %	18	18	0.76
Hypertension, %	60	54	<0.01
Hypercholesterolemia, %	54	50	0.02
Current smoking, %	28	32	0.01
Family History of CAD, %	29	27	0.30
Indication			<0.001
stable angina	44	45	
unstable angina	7	4	
NSTEMI	33	30	
STEMI	16	21	

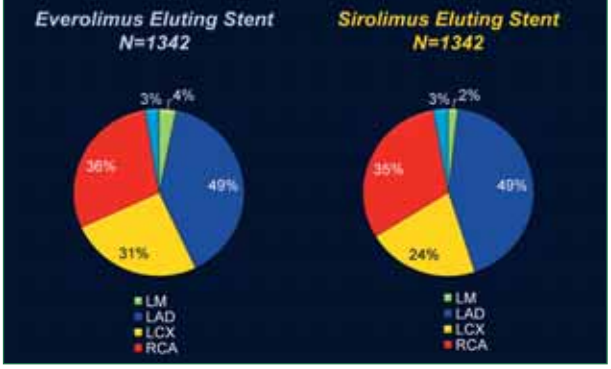
LESSON I – Patient Characteristics

After Propensity Score Matching (N=2684)

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Age	64±12	64±11	0.62
Male sex, %	78	78	0.72
Body mass index	27±5	27±4	0.72
Diabetes mellitus, %	17	18	0.72
Hypertension, %	56	55	0.94
Hypercholesterolemia, %	51	53	0.33
Current smoking, %	30	32	0.48
Family History of CAD, %	29	27	0.25
Indication			0.009
stable angina	48	45	
unstable angina	3	5	
NSTEMI	30	31	
STEMI	19	20	
Cardiogenic shock	2	1	0.08

LESSON I – Target Lesion Distribution

After Propensity Score Matching (N=2684)



LESSON I – Procedural Characteristics

After Propensity Score Matching (N=2684)

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Multivessel treatment, %	24	16	<0.001
Number of vessels per patient	1.3 ± 0.5	1.2 ± 0.4	<0.001
Number of lesions per patient	1.8 ± 1.0	1.5 ± 0.7	<0.001
1 lesion, %	52	63	
2 lesions, %	29	27	
3 lesions, %	13	9	
4 lesions, %	6	2	
Number of stents per patient	2.0 ± 1.1	1.8 ± 0.9	<0.001
Stent diameter (mm)	2.9 ± 0.4	2.9 ± 0.4	0.001
Stent length per patient (mm)	31.4 ± 19.4	32.7 ± 19.0	0.07

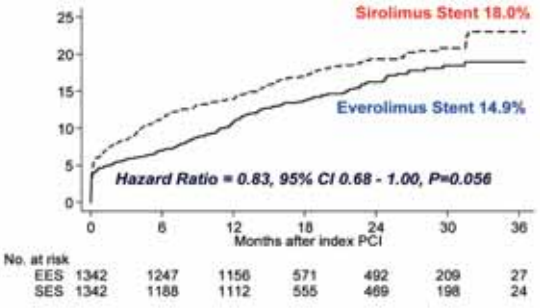
LESSON I – Medication at Discharge

After Propensity Score Matching (N=2684)

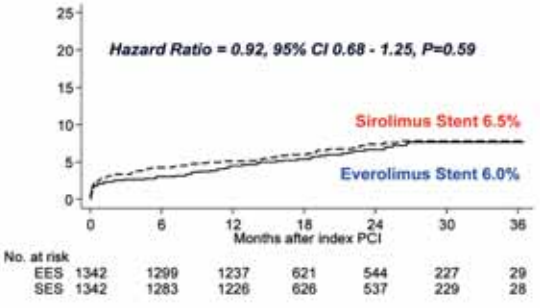
	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Acetylsalicylic Acid, %	98	97	0.06
Clopidogrel, %	98	96	0.07
Oral Anticoagulation, %	1.4	2.0	0.23
Betablocker, %	64	61	0.14
ACE Inhibitor, %	52	54	0.20
AT II Inhibitor, %	14	16	0.23
Calcium Antagonist, %	8.8	9.9	0.32
Statin, %	83	86	0.06
Oral Antidiabetics, %	10	10	0.84
Insulin, %	6.1	6.0	0.91
Diuretics, %	18	19	0.43
Proton Pump Inhibitor, %	20	19	0.33

Lesson I - Primary Endpoint

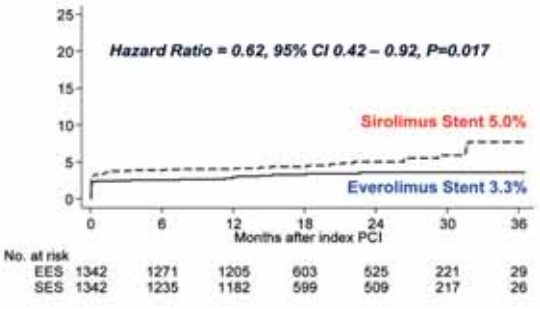
Death, MI, or TVR @ 3 Years



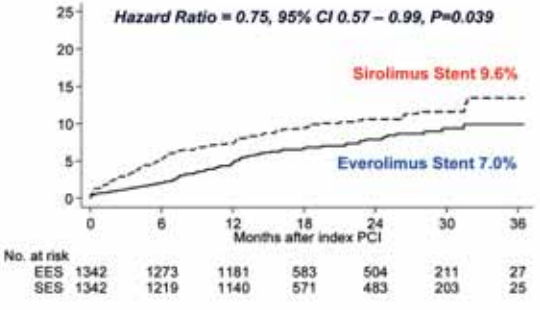
Lesson I – All Cause Mortality @ 3 Years



Lesson I – Myocardial Infarction @ 3 Years



Lesson I – Target Vessel Revascularization



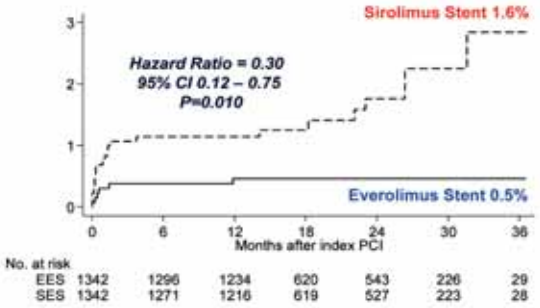
LESSON I – Clinical Outcome @ 3 Years

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Death	6.0%	6.5%	0.59
Cardiac death	3.9%	4.4%	0.51
Myocardial infarction	3.3%	5.0%	0.017
NQWMI	2.8%	3.1%	0.43
QWMI	0.5%	1.6%	0.010
Cardiac death or MI	6.8%	8.9%	0.030
Death or MI	8.9%	10.8%	0.08
Cardiac death, MI or TVR	12.7%	16.2%	0.025
Death, MI, or TVR	14.9%	18.0%	0.056

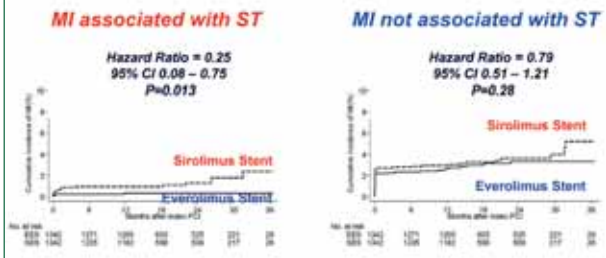
LESSON I - Stent Thrombosis Through 3 Years

	Everolimus Stent 1342 Patients	Sirolimus Stent 1342 Patients	P
Definite Stent Thrombosis			
Early	0.3%	0.8%	0.12
Late	0.2%	0.4%	0.42
Very late	0%	0.7%	0.007
Overall	0.5%	1.6%	0.010
Definite or Probable Stent Thrombosis			
Early	2.3%	3.1%	0.20
Late	0.2%	0.4%	0.42
Very late	0%	0.7%	0.007
Overall	2.5%	4.0%	0.041

Lesson I – Definite Stent Thrombosis @ 3 Years



Association of Myocardial Infarction With Definite Stent Thrombosis



Limitations

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

Conclusions

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

ESC Stockholm 31.08.10:

HOT LINE III – Cardiovascular disease and rhythm disturbances

AVERROES

Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes in patients with atrial fibrillation who have failed or are unsuitable for vitamin K antagonist treatment.

Discussant: Harald Arnesen
Center for Clinical Heart Research
Oslo University Hospital Ullevål
Oslo, Norway

ULLEVÅL University Hospital

Center for Clinical Heart Research, OUH, Ullevål

AVERROES"Editorial comment"

- Apixaban is a reversible inhibitor of f.Xa with a high oral bioavailability, rapid onset and a half-life of ~ 12 hours → 2 daily doses
- No monitoring required
- Obs! Drugs metabolised by CYP 3A4
- AVERROES is a randomised, double-blind, event driven study with 5600 patients, estimated to give a 35% reduction in stroke or systemic emboli of apixaban vs ASA with at least 90% power and a 1-sided α = 0.025, assuming a stroke rate of 3.3/100 subject-years in ASA-treated patients.

AVERROES"Editorial comment" (cont)

- Study terminated after first protocolled interim analysis of efficacy, recommended by the DMC (4 SD).
- Baseline characteristics:
  Age 70 years; Male ~60%; Diabetes ~20%; Prior stroke/TIA ~14%; CHF ~40%; Baseline ASA users ~75%; VKA "unsuitable" ~40%.

  CHADS2 score 2.1(mean), 0-1 ~35%, 2 ~35%,3+ ~30%.

AVERROES"Editorial comment" (cont)

- Primary outcomes.
- Stroke: Apixaban 48 = 1.7 %/year
  ASA 100 = 3.6 %/year RR 0.48, p<0.001
  NNT 53 /year
- Major bleeding: Apixaban 47 = 1.6 %/year
  ASA 40 = 1.4 %/year RR 1.18, p=0.45
  NNH 500 /year
- Intracranial bleeding: Apixaban 13 = 0.5 %/year
  ASA 11 = 0.4 %/year RR 1.19, p=0.43

AVERROES"Editorial comment" (cont)

Conclusion

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

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

Jens Cosedis Nielsen,
Aarhus University Hospital
on behalf of the DANPACE investigators

DANPACE investigators

Steering Committee (numbers of patients included):

- Henning Rud Andersen (chairman) and Jens Cosedis Nielsen (co-chairman), Aarhus University Hospital, Skejby (337);
- Poul-Erik Bloch-Thomsen, Gentofte Hospital (180);
- Søren Højberg, Bispebjerg Hospital (121);
- Mogens Møller, Odense University Hospital (114);
- Thomas Vesterlund, Aalborg Hospital (111);
- Dorthe Dalsgaard, Herning Hospital (108);
- Tonny Nielsen, Esbjerg Hospital (77);
- Mogens Aaklund, Kolding Hospital (72);
- Elsebeth Vilbeke Friis, Hadersley Hospital (70);
- Per Dahl Christensen, Viborg Hospital (56);
- Erik Hertel Simonsen, Hillerød Hospital (47);
- Ulrik Hedegaard Eriksen, Vejle Hospital (39);
- Gunnar Vagn Hagemann Jensen, Roskilde Hospital (28);
- Jesper Hastrup Svendsen, Rigshospitalet (24).

From United Kingdom:

- William D. Toff (UK coordinating investigator), J. Douglas Skehan, Kieran Brack, Glenfield Hospital, Leicester (8);
- Craig Barr, Andreas Tselios, Nicola Gordon, Russells Hall Hospital, Dudley (6);
- John Cleland, Andrew Clark, Sarah Hurren, Castle Hill Hospital, East Cottingham (3);
- David McEneaney, Andrew Moriarty, Anne Mackin, Craigavon Area Hospital, Craigavon (2);
- Arif Ahsan, Jane Burton, Ruth Oliver, Nottingham City Hospital (2),
- Barry Kneale, Lynda Huggins, Worthing Hospital (2).

From Canada:

- Jeffrey S. Healey, Hamilton (8).

Background

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

[1]: *Andersen HR et al., Lancet 1997*

Aim

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

Statistics

- 1,900 patients.
- Followed for in mean 5.5 years.
- Identify a 6% absolute difference in mortality.
- Power 80%, overall α=0.05.
- Intention to treat.

- Two planned interim analyses after 1/3 and 2/3 of the expected number of deaths.

Methods

- Randomised controlled trial.

- Inclusion criteria:
  - symptomatic bradycardia and documented sinus-pause >2s or sinus bradycardia <40bpm >1 minute whilst awake,
  - PR-interval ≤0.22s (age 18-70 years) or PR-interval ≤0.26s (age ≥70 years),
  - QRS width <0.12s.

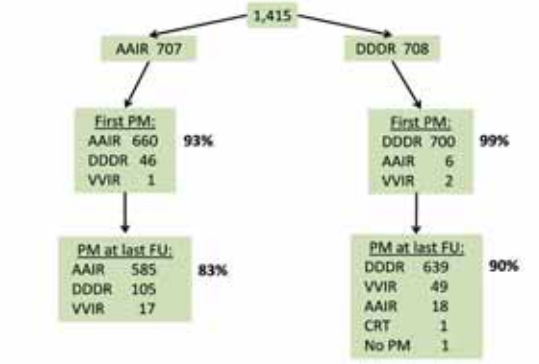
- Exclusion criteria:
  - AV block,
  - bundle branch block,
  - persistent atrial fibrillation >12 months,
  - atrial fibrillation with QRS rate <40 bpm for ≥1 min or pauses >3s,
  - a positive test for carotid sinus hypersensitivity.

Pacemaker programming

- Rate adaptive function was active
- Lower rate 60 bpm
- Upper rate 130 bpm

- DDDR:
  - Paced AV-interval ≤220 ms
  - Sensed AV-interval ≤200 ms.
  - Rate-adaptive shortening of the AV-interval.

Randomisation and pacing mode



Results

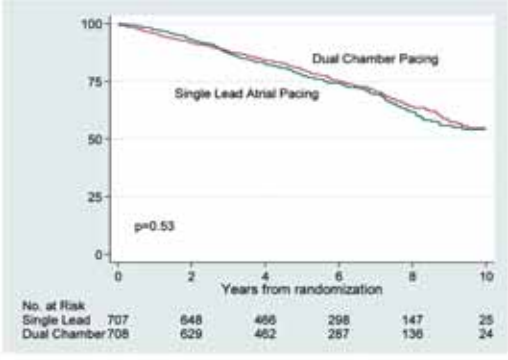
- Follow-up 5.4±2.6 years
- No patients lost for follow-up

- Pacing in the atrium:
  - AAIR group: 58±29%
  - DDDR group: 59±31%

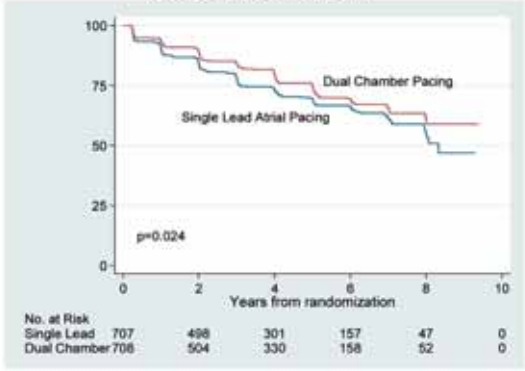
  P=0.52

- Pacing in the ventricle:
  - DDDR group: 65±33%

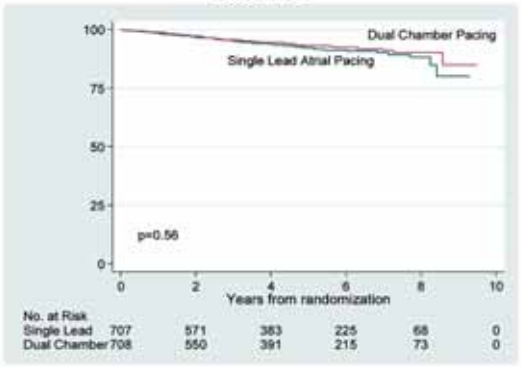
Survival



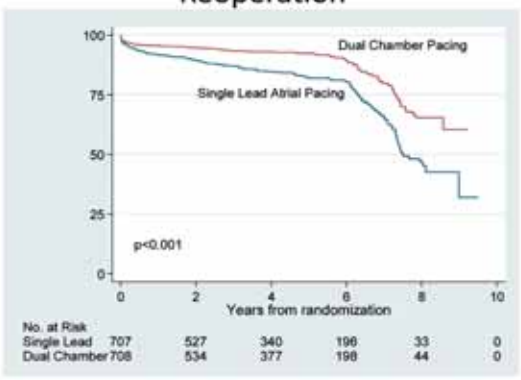
Atrial fibrillation



Stroke



Reoperation



Heart failure

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

Clinical Outcomes – Multivariate analysis

	Adjusted HR	95% CI	P-value
Death	0.94	0.77-1.14	0.52
Paroxysmal AF	1.24	1.01-1.52	0.042
Chronic AF	1.01	0.74-1.39	0.93
Stroke	1.05	0.70-1.59	0.80
Reoperation	2.00	1.54-2.61	<0.001

Conclusions

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

Financial support

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- Medtronic,
- St Jude Medical,
- Boston Scientific,
- Ela Medical,
- Pfizer,
- The Danish Heart Foundation (10-04-R78-A2954-22779).

Oral rivaroxaban versus standard therapy for the acute and continued treatment of symptomatic deep vein thrombosis. The EINSTEIN DVT study

Comments

Harald Darius, Berlin

Disclosures for Harald Darius

Research Support / P.I.	Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi-Aventis
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	Unfortunately, no conflicts of interest to declare
Speakers Bureau	Bayer HealthCare, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi-Aventis, The Medicines Company
Scientific Advisory Board	Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Sanofi-Aventis, The Medicines Company

EINSTEIN DVT: study design

Randomized, open-label, event-driven, non-inferiority study

- 48 hours' treatment with heparins/fondaparinux permitted before study entry
- 88 primary efficacy outcomes needed; non-inferiority margin 1.75; 90% power

Treatment period: 3, 6 or 12 months

Confirmed symptomatic DVT without symptomatic PE → N=3,449 → R

- Rivaroxaban 15 mg bid → Rivaroxaban 20 mg od
- Enoxaparin 1.0 mg/kg bid ≥5 days, followed by VKA; INR range 2–3

Day 1 Day 21

30-day observation period

N = 3,449	3429 safety population; 3096 per protocol population — 9.7% missing
Mean age	56 yrs
Creatinin Clearance < 50/min	7 %
Pretreatment LMWH/Fonda	73 and 71 %; (clinical convenience for outpatients = no pretreatment)
Statistics	very wide confidence margin for non-inferiority 1.75
Treatment regimen	3 wks 15 mg bid continued 20 mg od; Really necessary?

Primary efficacy outcome analysis

	Rivaroxaban (n=1,731) n (%)	Enoxaparin/VKA (n=1,718) n (%)
First symptomatic recurrent VTE	36 (2.1)	51 (3.0)
Recurrent DVT	14 (0.8)	25 (1.4)
Recurrent DVT + PE	1 (<0.1)	0 (0)
Non-fatal PE	20 (1.2)	18 (1.0)
Fatal PE/unexplained death where PE cannot be ruled out	4 (0.2)	6 (0.3)

0.44 0.68 1.04

0 1 1.75

Hazard ratio

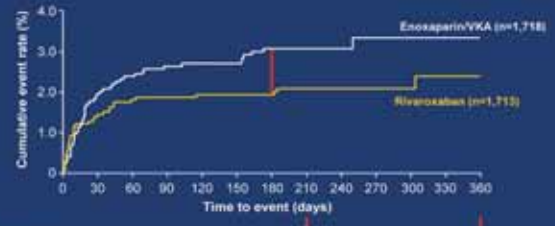
Rivaroxaban superior | Rivaroxaban non-inferior | Rivaroxaban inferior

p=0.076 for superiority (two-sided) *p*<0.0001 for non-inferiority (one-sided)

ITT population Results of the per protocol cohort ?

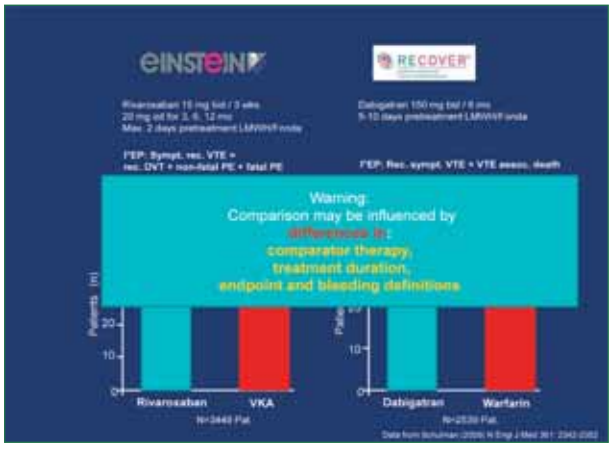
Primary efficacy outcome: time to first event

Quality of OAC: INR 57.7% in target range ?
Were PEP events associated with poor INR control ?



Number of subjects at risk

Rivaroxaban	1,731	1,668	1,648	1,621	1,424	1,412	1,220	400	369	363	345	309	266
Enox/VKA	1,718	1,616	1,581	1,553	1,368	1,356	1,186	380	362	337	325	297	264



Conclusions

- Einstein DVT is a carefully designed and performed trial
- Some data are still missing or need to be interpreted (waiting for publication) e.g. late efficacy past 6 mo
- Rivaroxaban is of borderline superior efficacy (net benefit significant) without advantages in bleeding in the dose regimen chosen
- Dabigatran was non inferior to warfarin but with a trend towards lower bleeding rates (all bleedings significant) in the dose regimen chosen
- We are facing a new era of antithrombotic therapy for patients with DVT with some questions still to be resolved e.g.
  - initial subcutaneous treatment necessary or
  - optimal duration of treatment or
  - treatment of elderly patients with reduced renal function or
  - performance of other F.Xa inhibitors or direct antithrombins in this indication

ESC Hotline Discussant: RESPONSE Trial

Christi Deaton, PhD, RN, FESC
University of Manchester
Central Manchester Foundation Trust
Manchester, UK

Context

- Nurse-led or nurse-coordinated secondary prevention programmes have been shown to be effective and feasible
  - EUROACTION (Wood, et al. 2007)
  - SCRIP Trial (Haskell, et al.1994)
  - Kaiser Permanente (DeBusk, et al. 1994)
  - Nurse-led clinics in primary care (Murchie, et al. 2003)

RESPONSE Trial

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

RESPONSE Findings

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

Implications

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

RESPONSE

Randomised Evaluation of Secondary Prevention by Outpatient Nurse SpEcialists.

On behalf of the RESPONSE studygroup:
Ron JG Peters, MD

Academic Medical Center
University of Amstedam
Amsterdam
The Netherlands

Background

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

Study design

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

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

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

Study design

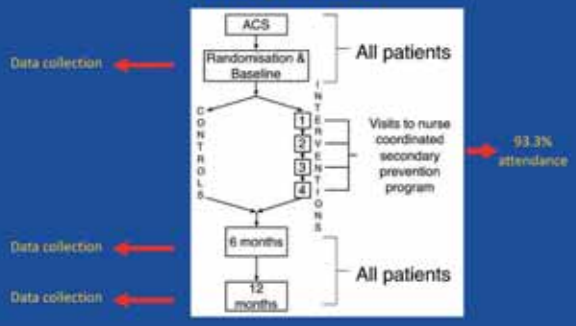
- Multicenter (n=11) randomised clinical trial in The Netherlands

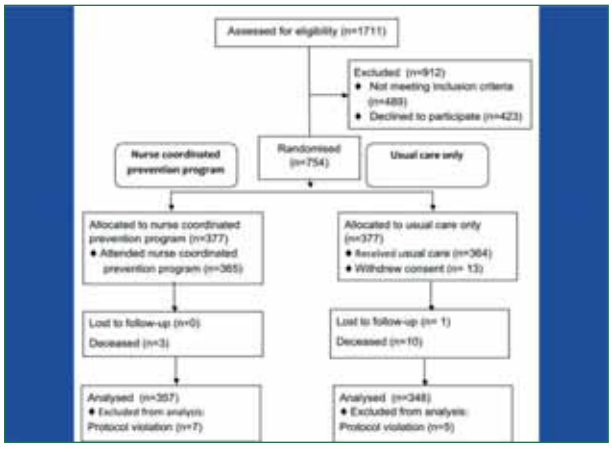
Participating centers

Breda	Amphia Ziekenhuis	Marco Alings, MD
Enschede	Medisch Spectrum Twente	Clemens von Birgelen, MD
Goes	Oosterscheldeziekenhuizen	Anho Liem, MD
Deventer	Deventer Ziekenhuis	Dirk Lok, MD
Eindhoven	Catharina Ziekenhuis	Jan-Melle van Dantzig, MD
Heerlen	Atrium Medisch Centrum	Hans Kragten, MD
Nieuwegein	St. Antonius Ziekenhuis	Wybren Jaarsma, MD
Leeuwarden	Medisch Centrum Leeuwarden	Kees-Jan de Vries, MD
Hilversum	Tergooiziekenhuizen	Paul de Milliano, MD
Delft	Reinier de Graaf Gasthuis	Adrie Withagen, MD

sponsored by an unrestricted grant from AstraZeneca, the Netherlands.

Study design

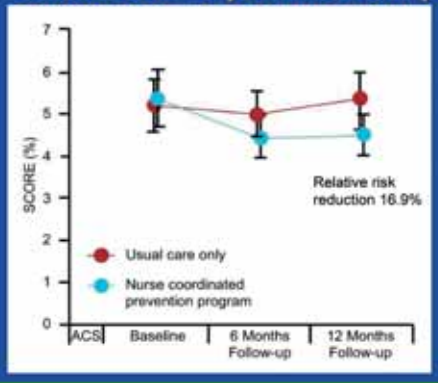




Baseline characteristics

	Randomised treatment	
	Intervention (N=357)	Control (N=348)
Age, years	57·5	57·7
Female	20%	21%
Diagnostic category at index event		
ST-segment elevation myocardial infarction	50%	48%
Non ST-segment elevation myocardial infarction	33%	33%
Unstable Angina Pectoris	17%	19%
Previous vascular disease (prior to index event)	26%	27%
History of cardiovascular risk factors		
Positive family history	59%	60%
History of diagnosed diabetes mellitus	14%	14%
History of dyslipidemia	69%	71%
Current smoking	47%	43%
Ex-smoker	36%	39%
History of hypertension	38%	35%

Calculated 10 year mortality



On target analysis

targets	Baseline Intervention (n=357)	Baseline Control (n=348)	p value	12 months Intervention (n=357)	12 months Control (n=348)	p value
Nurse targeted parameters						
Body mass index ≤25 kg/m2	23%	28%	0·121	20%	27%	0·048
Waist circumference men ≤94 cm, women ≤80 cm	20%	26%	0·049	22%	24%	0·47
Systolic blood pressure ≤140 mmHg	68%	73%	0·138	74%	61%	<0·001
LDL-cholesterol ≤2.5 mmol/L	67%	68%	0·871	73%	64%	0·013
Current smoker	47%	53%	0·289	23%	24%	0·859
Physical activity ≥30 min, ≥5 times per week	50%	51%	0·763	67%	54%	0·001
Alcohol consumption men ≤3 units per day, women ≤2 units per day	95%	93%	0·213	98%	96%	0·178
Vegetables ≥200 g per day	71%	66%	0·193	81%	71%	0·003
Fruit ≥2 pieces per day	80%	83%	0·248	94%	85%	<0·001

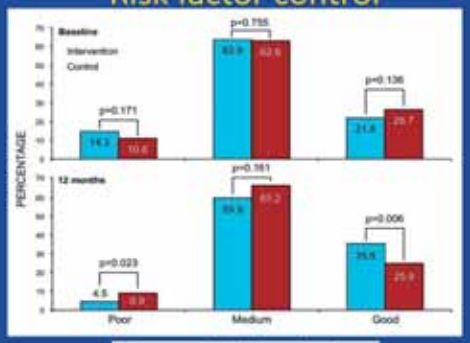
*Number of patients currently smoking, data presented at baseline measurements represents smoking status prior to index event.

Medication use

	Baseline Intervention (N=357)	Control (N=346)	p value	12 months Intervention (N=352)	Control (N=345)	p value
Any antithrombotic agent	99%	100%	0·624	98%	99%	0·773
Any lipidlowering agent	96%	97%	0·565	93%	94%	0·642
Beta blockers	90%	90%	1.000	76%	79%	0·470
Calcium channel blocker	17%	18%	0·921	22%	19%	0·345
Diuretics	14%	14%	1.000	22%	15%	0·030
Angiotensin-converting enzyme inhibitors	55%	48%	0·083	57%	46%	0·008
Angiotensin II receptor blockers	10%	8%	0·515	17%	16%	0·837
Alfa blockers	0%	1%	0·120	0%	1%	0·059

Antithrombotic agents are aspirinie, clopidogrel, dipyridamol or any oral anticoagulant.
Lipidlowering agents are statins or non-statin lipidlowering agents.

Risk factor control



Poor: 0-3 factors on target
Medium: 4-6 factors on target
Good: 7-9 factors on target

Conclusions

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

ESC Congress 2010

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

Hyperosmolarity caused by high levels of glucose and mannitol induces angiogenesis by activating the Tonicity-responsive cis-acting elements, aquaporin 1- and Na^+/H^+ exchanger 1 and COX-2 and MMPs in human endothelial cells

R. Madonna, E. Montebello, YJ. Geng, R. De Caterina

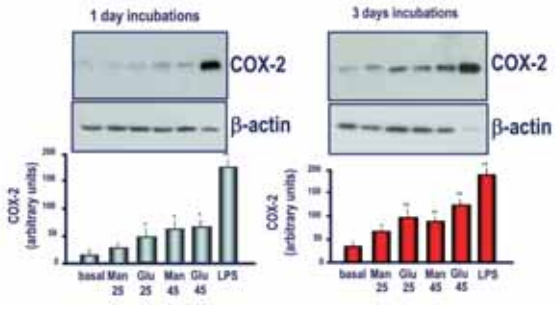
"G. d'Annunzio" University – Chieti,
Texas Heart Institute and
University of Texas Medical School in Houston

- In overt diabetes, hyperglycemia causes increased plasma osmolarity, which determines an osmotic efflux of water potentially promoting cellular adaptive responses, such as the expression of putative "hypertonicity stress genes and proteins".
- Aquaporins and sodium/hydrogen exchangers (AQP1 and NHE- 1 in endothelial cells) are membrane-associated proteins induced by hyperosmotic agents and mainly involved in the transmembrane transport of water driven by osmotic gradients (Guillaume Vial, 2008; Umenishi, 2003).
- Cycloxygenase (COX)-2 is an early gene product of inflammation (Dubois, 1998), with prominent pro-angiogenic effects, induced by hyperosmotic agents in the renal epithelial cells (Favale, 2009).
- COX-2 colocalizes with some matrix metalloproteinases (MMPs) in unstable plaques and plays an essential role in plaque destabilization and microvascular dysfunction, all characterized by excessive angiogenesis (Libby, 1995).

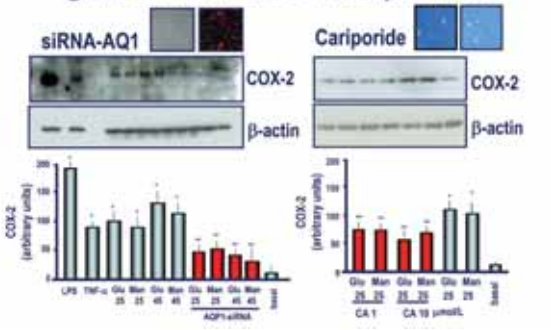
Hypothesis and Goal

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

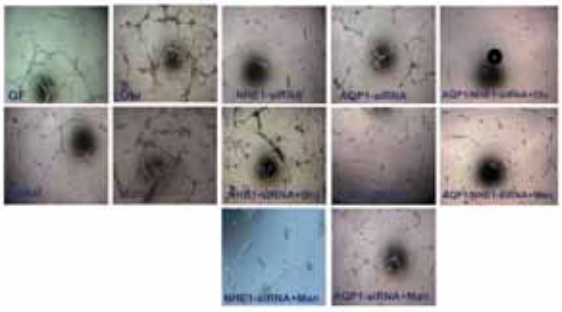
Hyperosmolarity induces COX-2 expression in endothelial cells exposed to high glucose



Targeted disruption of AQP1 gene expression and NHE-1 blockage prevent glucose-induced COX-2 expression



High glucose promotes angiogenesis via hyperosmolarity changes involving AQ1 and NHE-1



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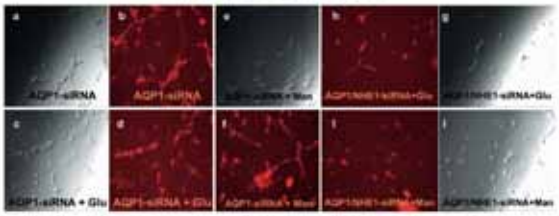

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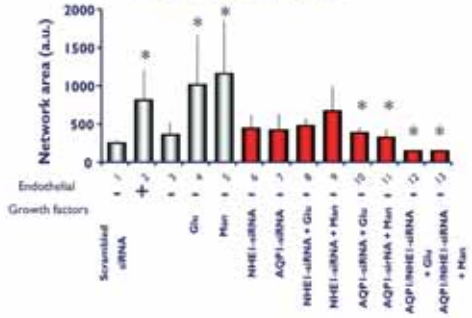
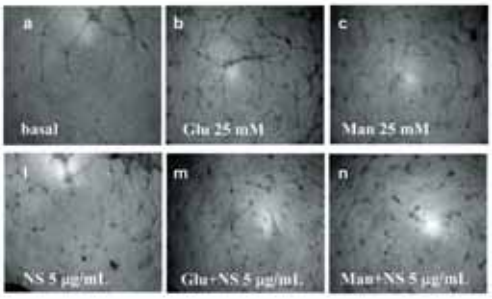
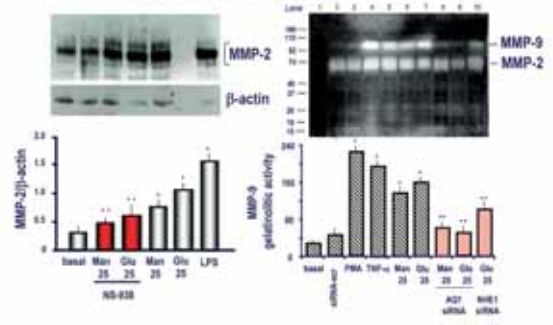


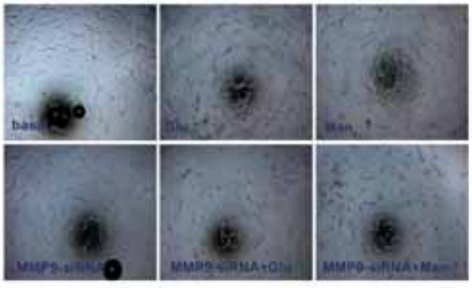
High glucose promotes angiogenesis through hyperosmolarity-induced expression of COX-2



Hyperosmolarity induces MMP-9 and MMP-2 activity in endothelial cells exposed to high glucose

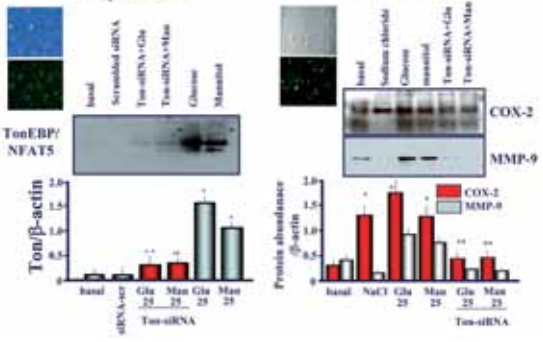


Targeted disruption of MMP-9 gene expression prevents hyperosmolarity-induced angiogenesis in endothelial cells exposed to high glucose

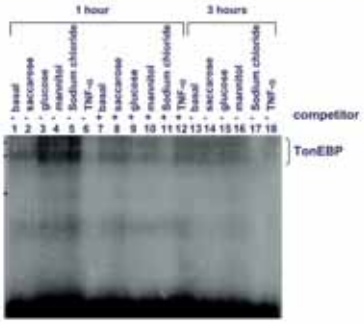


Hyperosmolarity induces TonEBP/NFAT5 expression

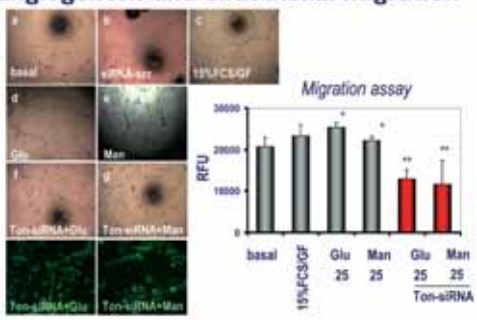
siRNA- Ton prevents Cox-2 and MMP-9 expression



TonEBP/NFAT5 is recruited to TonE binding sites in osmotically stressed endothelial cells



Targeted disruption of TonEBP/NFAT5 gene expression prevents glucose-induced angiogenesis and endothelial migration



Therefore

- Concentrations of glucose attainable in conditions of hyperglycemia induce COX-2 in human endothelial cells through an AQP1- and an NHE1-dependent hyperosmolar mechanism and, through this mechanism, promote angiogenesis.
- TonEBP/NFAT5 is involved in the hypertonic induction of COX-2 and MMP-9 and angiogenesis, since TonEBP/NFAT gene disruption was able to prevent the hypertonic induction of these genes and angiogenesis.
- Hypertonicity determines the nuclear accumulation of TonEBP/NFAT in endothelial cells, suggesting its role in the response to hypertonic stress.

Conclusions (i)

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

Conclusions (ii)

Correction of hyperosmolarity by *downstream* targeting osmosignaling pathway (TonEBP/NFAT5) might be a novel strategy, in addition to upstream targeting osmosensing structures (AQP1 and NHE1) for the control of excessive angiogenesis as a consequence of diabetic hyperglycemia.

Presenter:
Madonna Rosalinda, MD PhD Assistant Professor
Cardiovascular Biology and Atherosclerosis Research
University of Texas Houston Medical School,
and Texas Heart Institute, Houston, Texas, USA

UCL

"Remote preconditioning reflex"

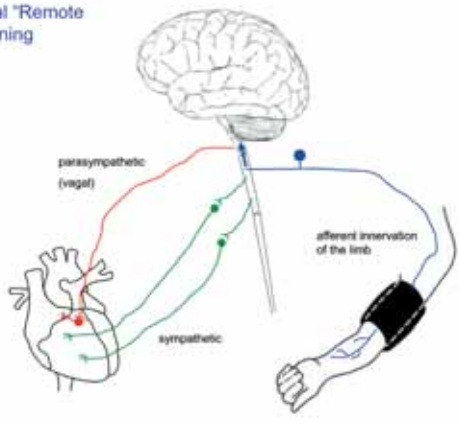
A neural pathway of cardioprotection during myocardial ischaemia and reperfusion induced by remote ischaemic preconditioning

by

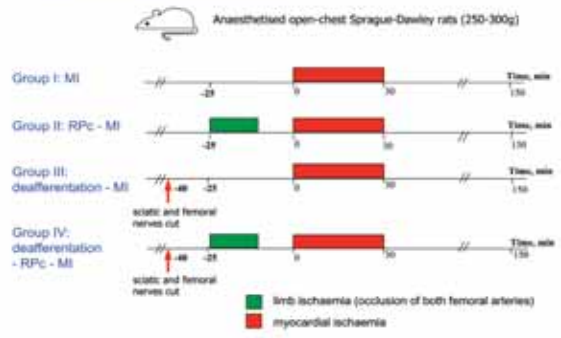
Andrey Gourine, Svetlana Mastitskaya, Michael P. Gilbey, Gareth L. Ackland, Alexander V. Gourine

wellcome trust

Hypothetical "Remote Preconditioning Reflex"



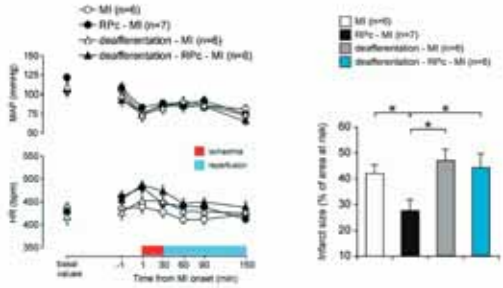
Testing Hypothesis 1: Remote ischaemic preconditioning requires recruitment of sensory nerves sending information from the remote organ to the central nervous system.



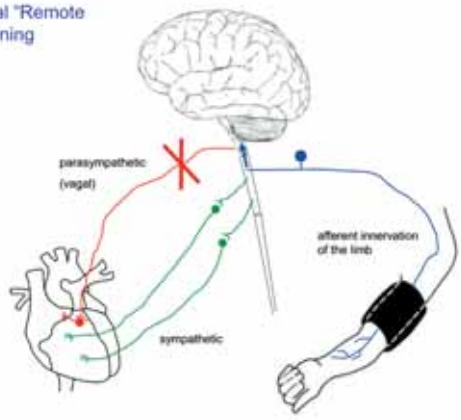
Testing Hypothesis 1: Remote ischaemic preconditioning requires recruitment of sensory nerves sending information from the remote organ to the central nervous system.

Arterial blood pressure and heart rate data

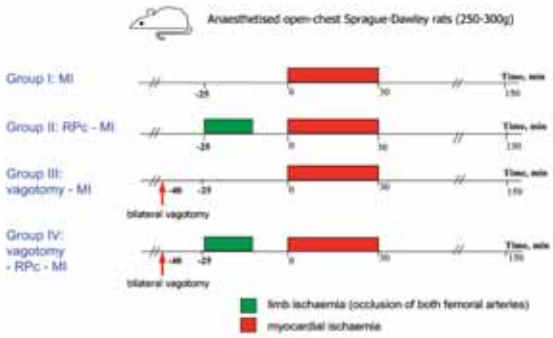
Infarct size data



Hypothetical "Remote Preconditioning Reflex"



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



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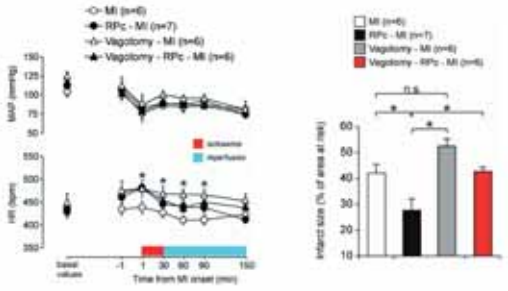
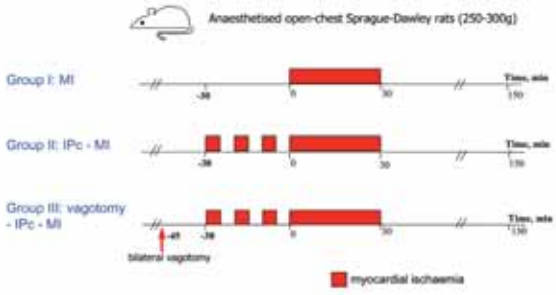
Arterial blood pressure and heart rate data

Infarct size data



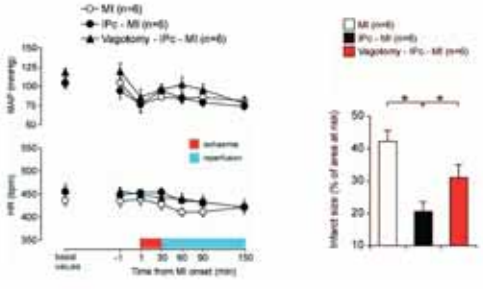
Role of vagal parasympathetic innervation of the heart in local preconditioning.



Role of vagal parasympathetic innervation of the heart in local preconditioning.

Arterial blood pressure and heart rate data

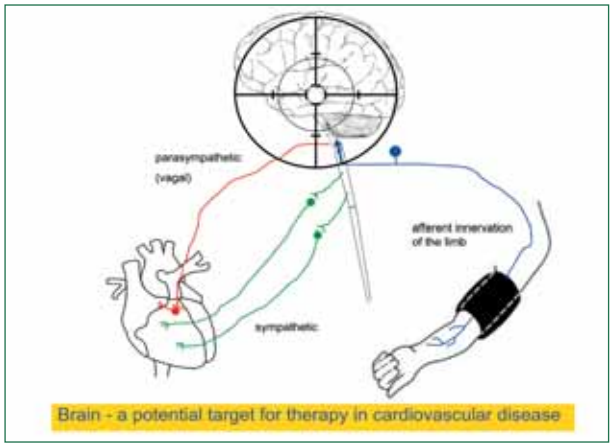
Infarct size data



CONCLUSIONS

1. Sensory denervation of the remote ischaemic tissue or removal of parasympathetic input to the heart both completely abolish cardioprotection induced by remote ischaemic preconditioning.

2. These data directly demonstrate the existence of a "remote preconditioning reflex", which involves sensory afferent pathway from the peripheral organ and parasympathetic vagal efferent outflow to the heart.



Brain - a potential target for therapy in cardiovascular disease

Imperial College London

Proteomic analysis of smooth muscle cells derived from carotid plaque reveals differences between symptomatic and asymptomatic plaques

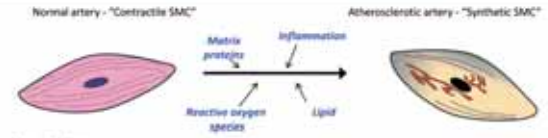
Louise Full

Kennedy Institute of Rheumatology
Imperial College London, UK

Conflicts of interest: none

Imperial College London

Smooth Muscle Cells in Atherosclerosis



- **Contraction of artery**
Express contractile proteins Smooth muscle alpha-actin & Smooth muscle myosin heavy chain (Chamley-Campbell, J et al (1979). Physiol Rev 59(1): 1-61.)

- **Formation of fibrous cap encasing lipid core**
- **Decrease** in contractile properties
- **Matrix synthesis, i.e. collagens I and III** (Chamley-Campbell, J., et al. (1979). Physiol Rev 59(1): 1-61.)
- **Senescence** (Gorenne, I., et al. (2006). Cardiovasc Res 72(1): 9-17.)
- **Apoptosis** (Clarke, M. C., et al. (2006). Nat Med 12(9): 1075-80.)

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

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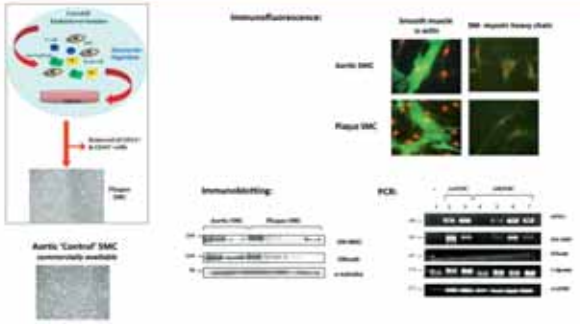
Isolation of Smooth Muscle Cells from carotid endarterectomy



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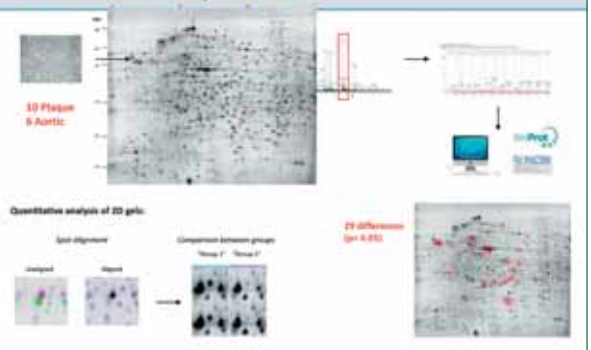
Proteomic analysis of SMC



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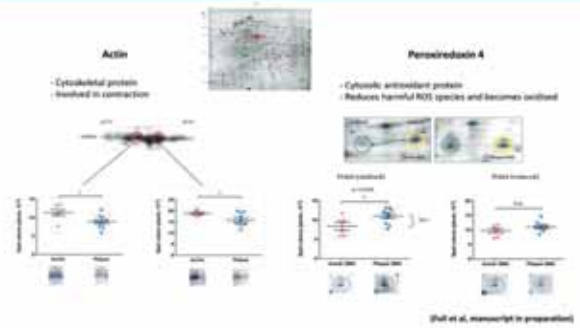
1. Proteomic Comparison of Plaque and Aortic SMC



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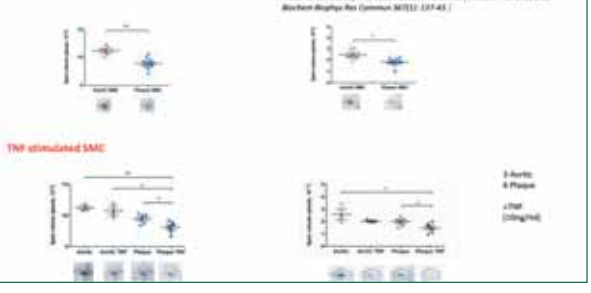
Mitochondrial proteins are decreased in Plaque SMC

ATP Synthase subunit beta
- Complex V (ATP Synthase) of electron transport chain
- Production of ATP

Aldehyde Dehydrogenase 2
- Elimination of reactive aldehydes such as 4-HNE and acetaldehyde
- Protective against oxidative damage
-ALDH2 deficiency increases oxidative stress (Wenzel, P. et al. (2008). Biochem Biophys Res Commun 367(1): 137-43.)



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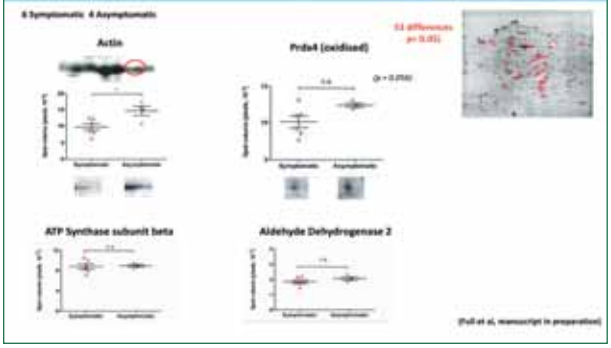
2. Comparison of SMC from Symptomatic & Asymptomatic plaques



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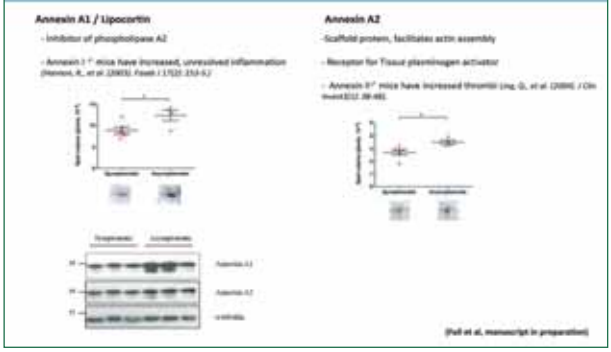
Annexins A1 and A2 are decreased in SMC from Symptomatic patients



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Summary & Conclusions

1. Comparison of plaque & aortic SMC proteome

OXIDATIVE STRESS:

Increase in oxidation of peroxiredoxin-4 in plaque SMC

MITOCHONDRIAL DAMAGE:

Decrease in mitochondrial proteins ATP Synthase subunit-β involved in ATP synthesis

Decrease in Aldehyde Dehydrogenase 2

Proinflammatory mediators in the plaque contribute to this reduced protein expression

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Summary & Conclusions

2. Comparison of SMC from Symptomatic & Asymptomatic plaques

No significant difference in oxidative stress or levels of mitochondrial proteins between SMC of different symptomatic status

Annexin A1:
Anti-inflammatory properties including inhibition of phospholipase A2, production of proinflammatory cytokines, inhibition of lymphocyte migration

Increased levels of Annexin A1 in Asymptomatic SMC suggest that SMC from asymptomatic patients have an ability to control a proinflammatory response

Annexin A2:
Receptor for tissue plasminogen activator – involved in fibrinolysis
Increased Annexin A2 in Asymptomatic SMC suggests an increase in anti-coagulent processes helping to prevent thrombotic complications.

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

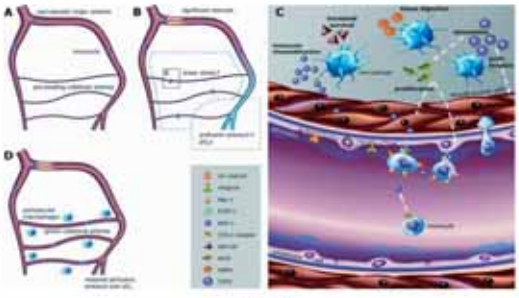
AM van der Laan, SH Schirmer, MR de Vries, JJ Koning, OL Volger, JO Fledderus, AJNM Bastiaansen, JM Baggen, KT Koch, J Baan Jr, JP Henriques, RJ van der Schaaf, MM Vis, RE Mebius, TC van der Pouw Kraan, PH Quax, JJ Piek, AJ Horrevoet and N van Royen

ESC

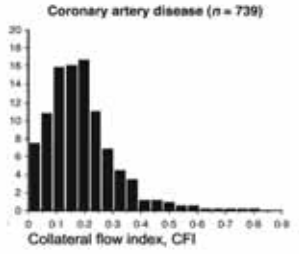
August 30th 2010

No conflict of interest or financial disclosures

Background



Heterogenic response in patients



Wustmann et al. Circulation 2003

Aim of the study

Bad arteriogenic responders

Good arteriogenic responders

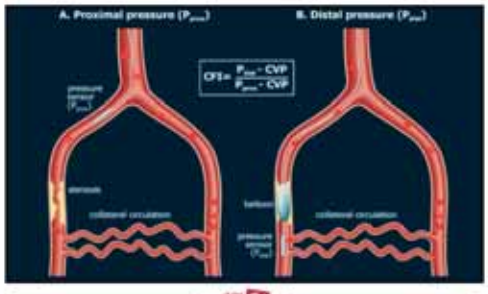
Finding monocytic targets that relate to the arteriogenic response

Patient inclusion and exclusion criteria

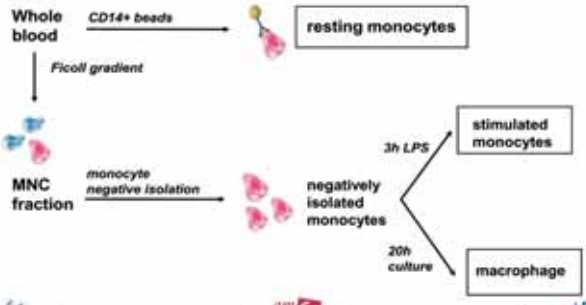
Inclusion criteria:
- chronic total coronary occlusion

Exclusion criteria:
- previous myocardial infarction
- cardiac surgery
- depressed left ventricular function
- diabetes mellitus
- inflammatory or neoplastic disease.

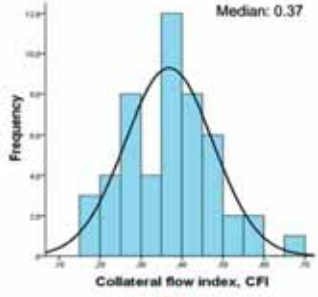
Assessment of the collateral flow index (CFI_p)



Monocyte isolation procedure



Collateral flow index



Patient characteristics

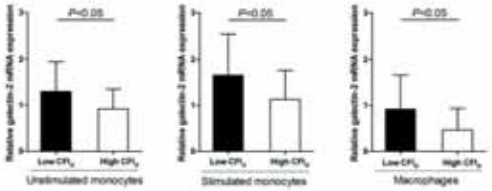
Characteristic	$CFI_p \leq 0.37$ (n = 10)	$CFI_p > 0.37$ (n = 10)	P-value
Collateral flow index$_p$	0.27 ± 0.06	0.47 ± 0.08	< 0.001
Age (years)	57.6 ± 13.4	58.0 ± 6.4	NS
Male gender	6	8	NS
Body mass index	24.7 [24.2 – 26.3]	27.0 [25.7 – 28.4]	NS
Coronary risk factors			
Hypertension	7	6	NS
Family history of CAD	7	4	NS
Hypercholesterolemia	4	6	NS
Current smoker	1	2	NS
Ex smoker	5	4	NS
Duration of anginal symptoms			
< 3 months	3	3	NS
≥ 3 months, < 1 year	5	5	NS
> 1 year	2	2	NS

Whole genome transcriptome analysis (10 vs 10)

	Unstimulated monocytes			Stimulated monocytes			Macrophages		
Gene symbol	Intensity	Fold-change	P-value	Intensity	Fold-change	P-value	Intensity	Fold-change	P-value
LGALS2	1014	2.0	0.002	296	1.6	0.004	550	2.8	0.001
C1QA	348	1.5	0.025	118	1.2	0.023	184	1.4	0.041
PHACS	583	1.5	0.012	157	1.4	0.007	234	1.7	0.002
RNF213	289	1.7	0.001	126	1.3	0.012	282	1.6	0.021
LRAP	361	-1.9	0.007	127	-1.3	0.026	217	-1.7	0.002

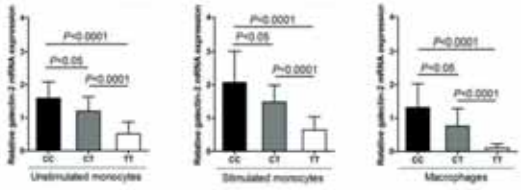
Galectin-2 mRNA expression

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



Galectin-2 mRNA expression and the rs7291467 SNP

Galectin-2 mRNA expression is associated with the rs7291467 SNP in intron 1 of the galectin-2 gene



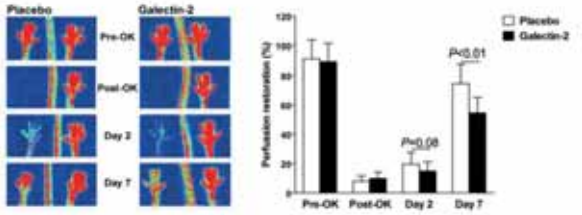
The association between the rs7291467 SNP and the collateral circulation

Genotype	Low CFI_p (n = 25)	High CFI_p (n = 25)	Total (n = 50)
CC	9	3	12
CT	11	13	24
TT	5	9	14

Chi-square test for trend $P < 0.05$

Experimental validation

Galectin-2 inhibits arteriogenesis in a murine hindlimb model



Mechanisms of action?

galectin-2 ⟞ **arteriogenesis**

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

Galectin-2 induces apoptosis of lamina propria T lymphocytes and ameliorates acute and chronic experimental colitis in mice

Galectin-2 Suppresses Contact Allergy by Inducing Apoptosis in Activated $CD8^+$ T Cells

Conclusions

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

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

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

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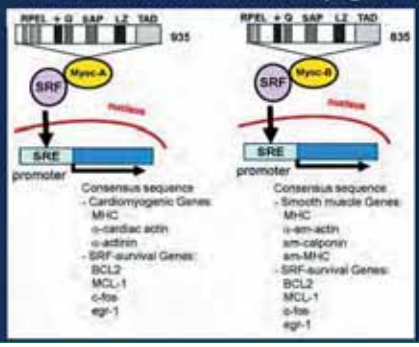
- A.J.N.M. Bastiaansen, MD

Telomerase and Myocardin-A synergistically regulates expression of promyogenic transcription factors in mesenchymal stem cells of adult adipose tissue

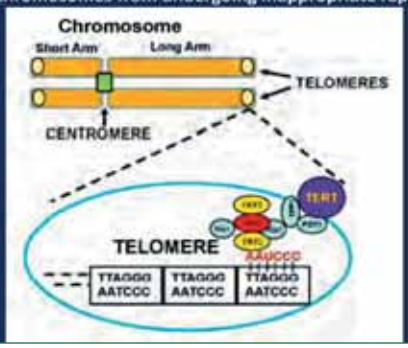
Rosalinda Madonna , Raffaele De Caterina, James T Willerson, Yong-Jian Geng

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

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



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



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

- **Madonna R, Willerson JT, Geng YJ.** Myocardin a enhances telomerase activities in adipose tissue mesenchymal cells and embryonic stem cells undergoing cardiovascular myogenic differentiation. **Stem Cells. 2008, 26(1):202-11.**
- **Léobon B, Roncalli J, Joffre C, et al.** Adipose-derived cardiomyogenic cells: in vitro expansion and functional improvement in a mouse model of myocardial infarction. **Cardiovasc Res. 2009 Sep 1;83(4):757-67.**
- **Planat-Bénard V, Menard C, André M, et al.** Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. **Circ Res. 2004 Feb 6;94(2):223-9.**

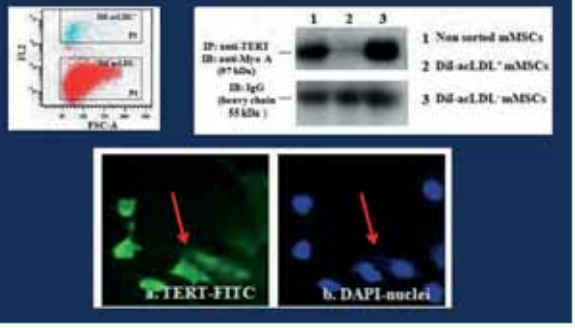
Hypothesis and Goal

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

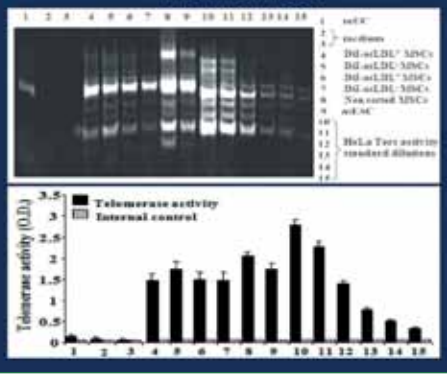
Experimental Strategy and Methods

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

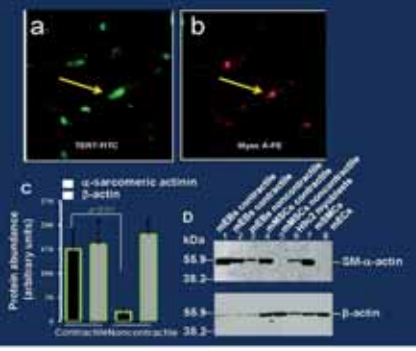
TERT positive cells take little DiI-acLDL and express high levels of Myoc-A



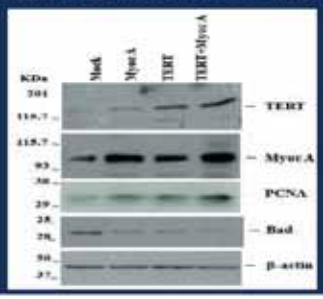
TERT activity in MyocA Immunoprecipitates in Murine MSCs



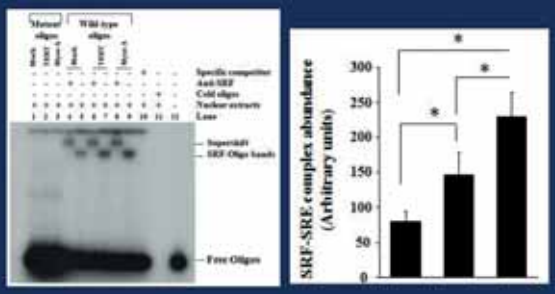
TERT/Myoc-A positive cells express cardiovascular biomarkers



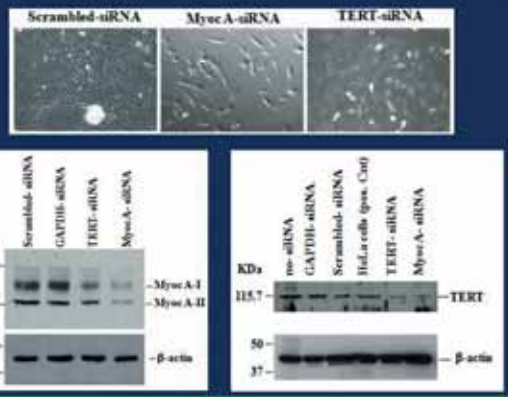
TERT and Myoc-A transduction Increases PCNA but Reduces Bad in MSCs



TERT and Myoc-A transduction Enhances SRF activity in MSCs



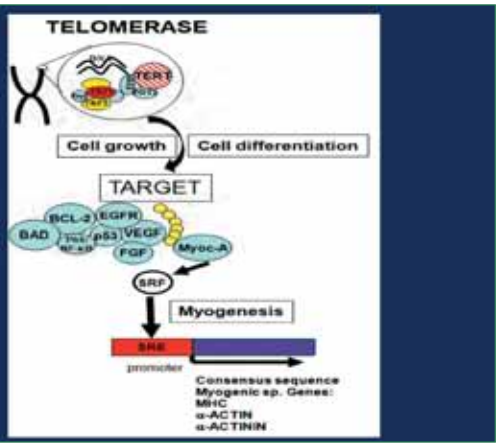
TERT/Myoc-A siRNAs suppress expression of TERT and Myoc-A in MSCs



Ratio	non - transfected	siRNA-scrambled	siRNA- McA	siRNA-TERT	siRNA-TERT+McA
Oct-4/18S rna	28.2±0.3	28.1±0.2	24.5±1.2*	25.9±0.1**	24.2±0.1†
Nkx2.5/18S rna	26.9±0.1	27.5±0.2	25.3±0.4**	25.3±0.3**	24.6±0.6†
MLC2v/18S rna	28.1±1.4	29.1±0.2	26.5±1.6	26.2±0.2**	25.1±0.9†
MEF2/GAPDH	70.3±13.1	72.9±10.2	21.3±8.2**	16.4±5.3**	10.3±2.5**

Conclusions

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



Presenter:
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