Present and future options in the pharmacological treatment of heart failure

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ELSEVIER

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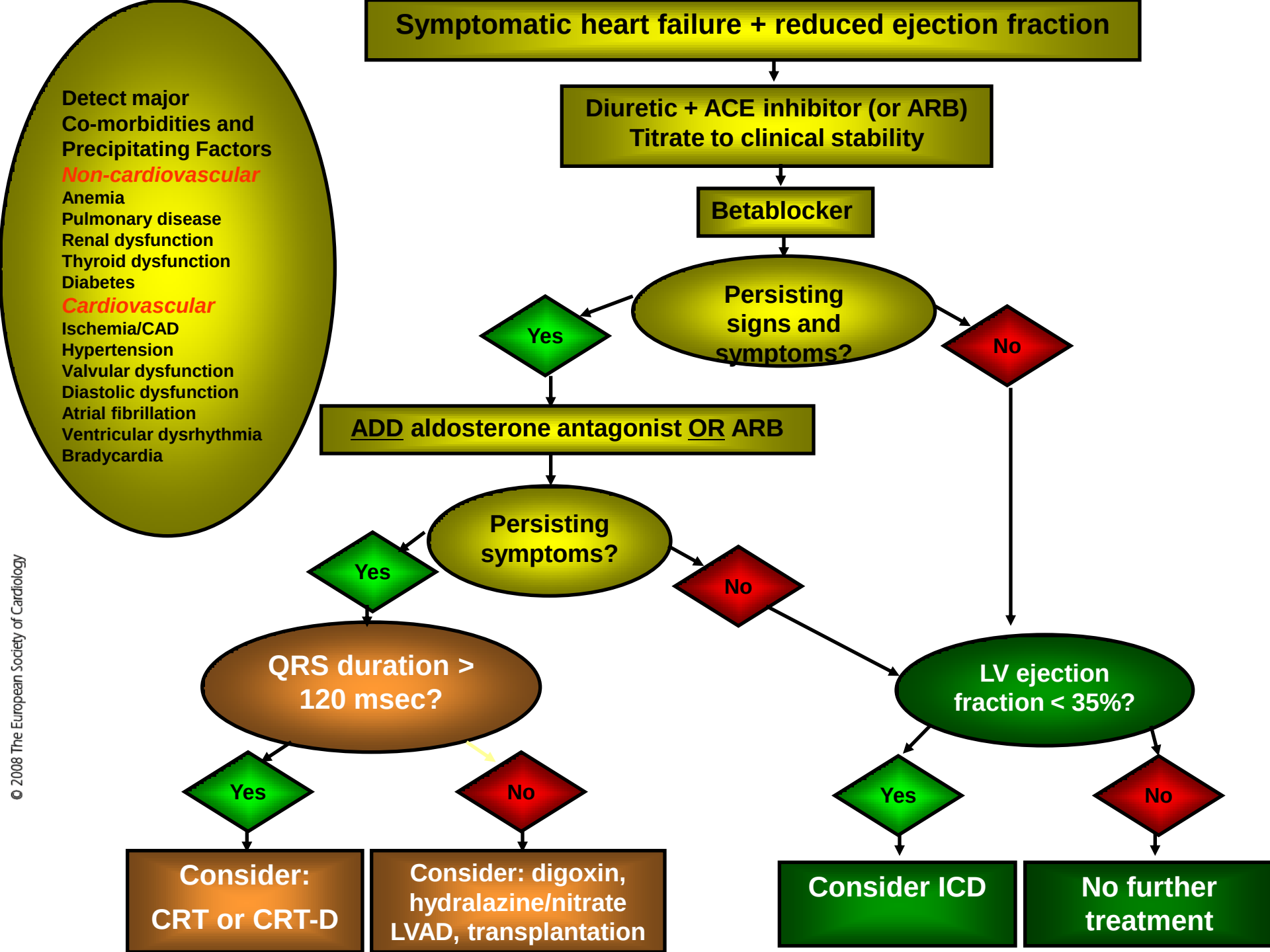
The European Journal of Heart Failure

www.elsevier.com/locate/ejheart

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008☆,☆☆

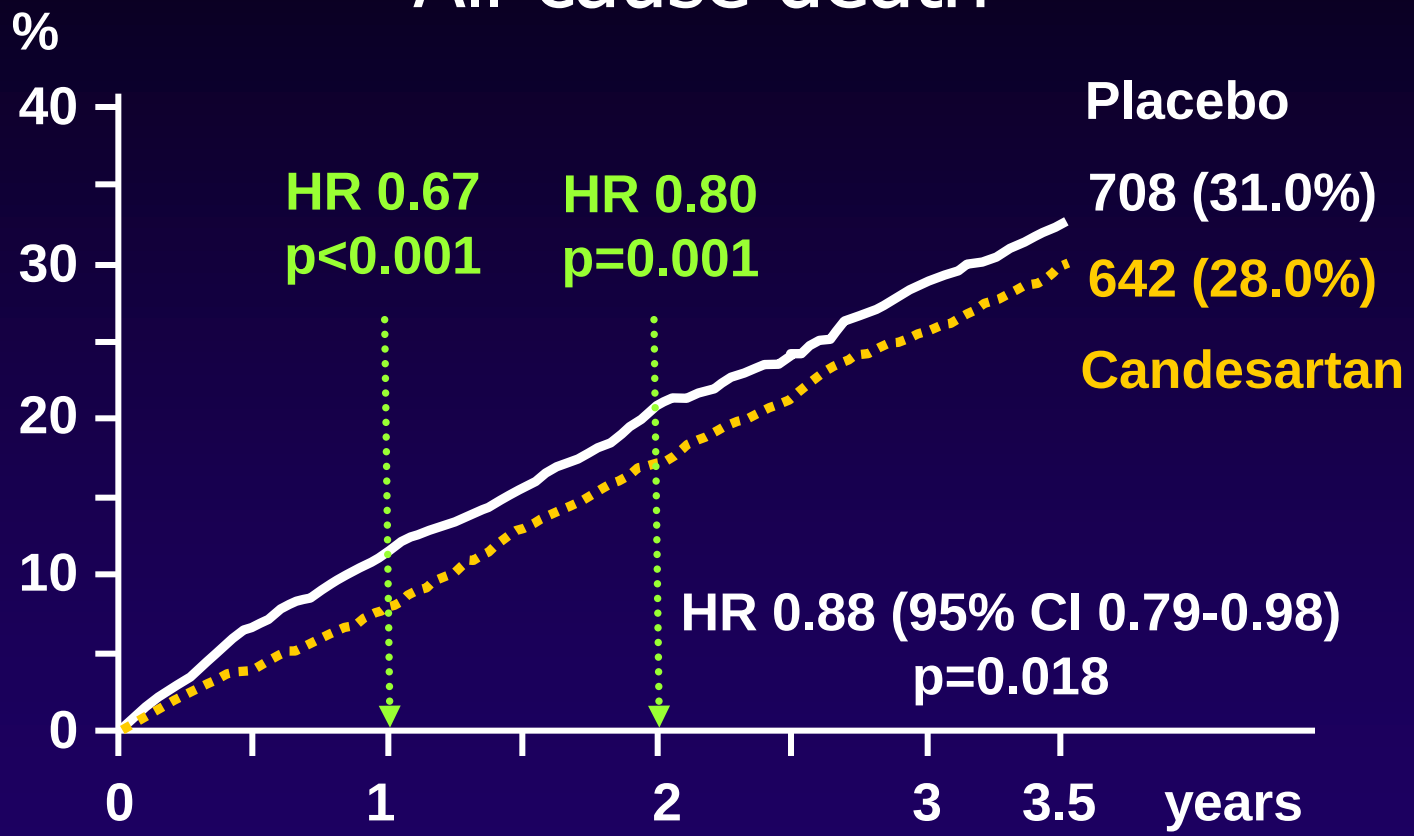
The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM)

Authors/Task Force Members: Kenneth Dickstein (Chairperson) (Norway)*, Alain Cohen-Solal (France), Gerasimos Filippatos (Greece), John J.V. McMurray (UK), Piotr Ponikowski (Poland), Philip Alexander Poole-Wilson (UK), Anna Strömberg (Sweden), Dirk J. van Veldhuisen (The Netherlands), Dan Atar (Norway), Arno W. Hoes (The Netherlands), Andre Keren (Israel), Alexandre Mebazaa (France), Markku Nieminen (Finland), Silvia Giuliana Priori (Italy), Karl Swedberg (Sweden)



CHARM - Low EF (Alternative and Added)

All-cause death



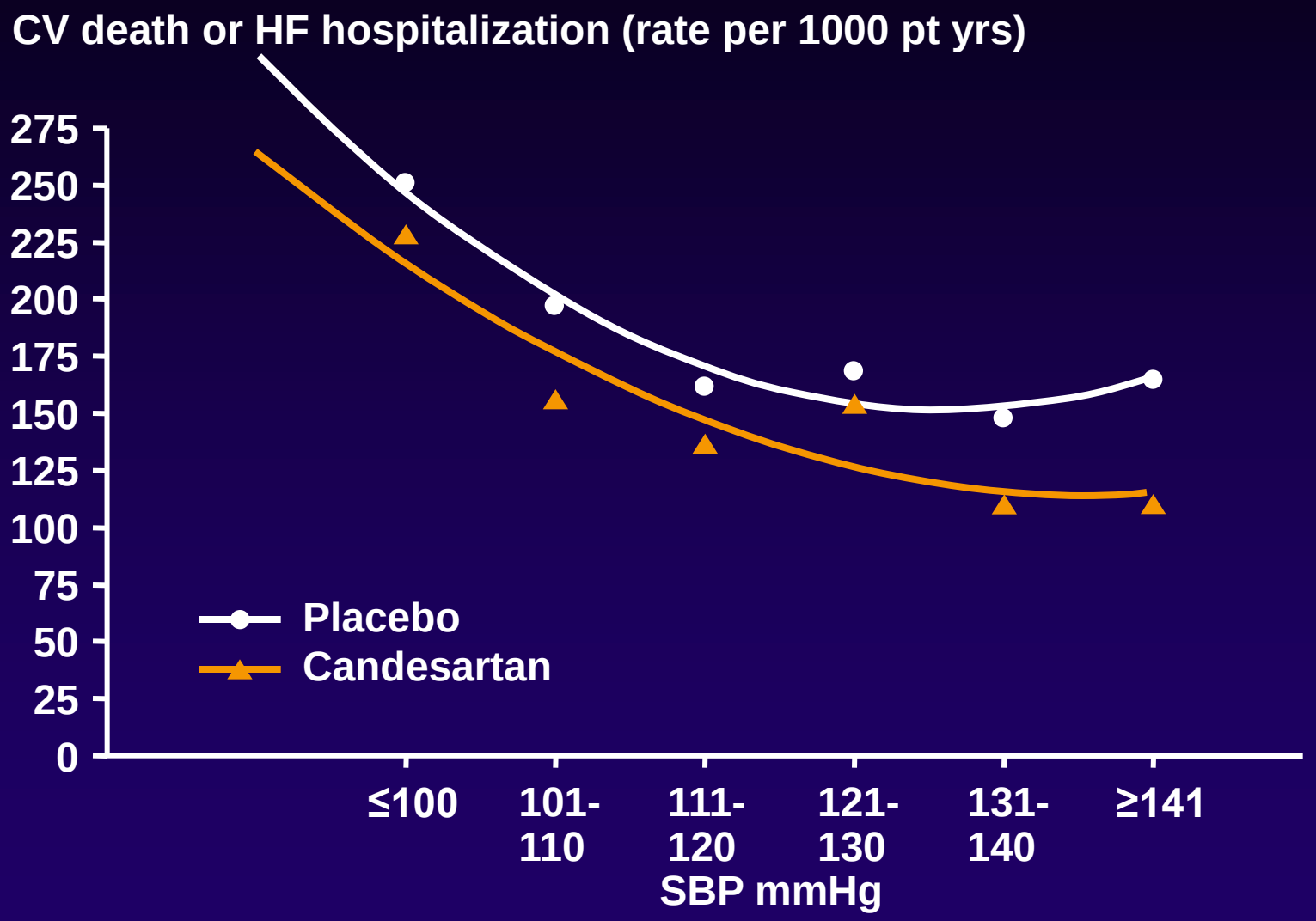
Number at risk

Candesartan	2289	2105	1894	1382
Placebo	2287	2023	1811	1333

Young et al. Circulation 2004

CHARM

Effect of candesartan compared to placebo on the risk of CV death or HF hospitalization by baseline systolic blood pressure



Meredith et al. JACC 2008

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary
Search

List Results | Refine Search | Results by Topic | Results on Map | Search Details

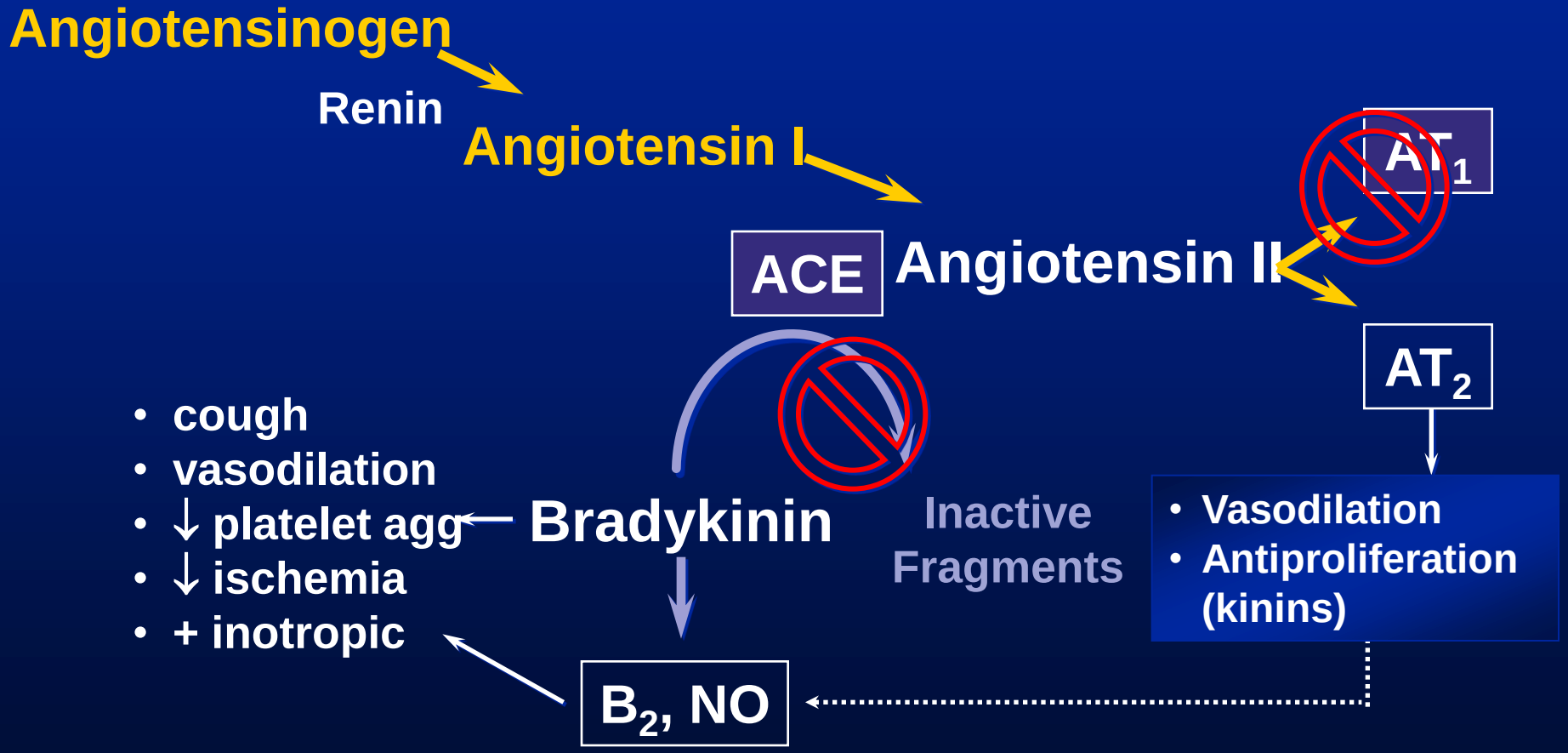
Found 940 studies with search of: heart failure | Open Studies

Include studies that are not seeking new volunteers

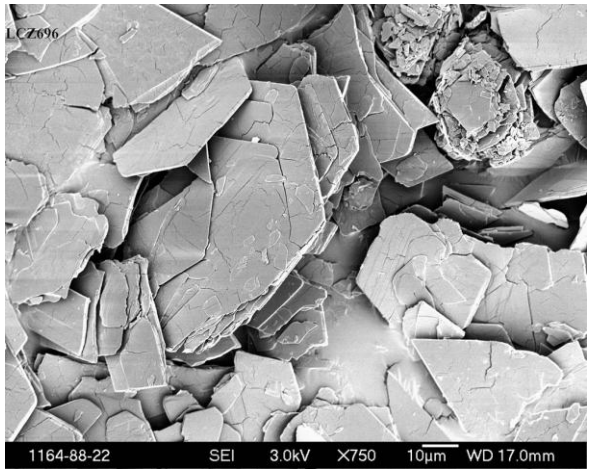
Display Options

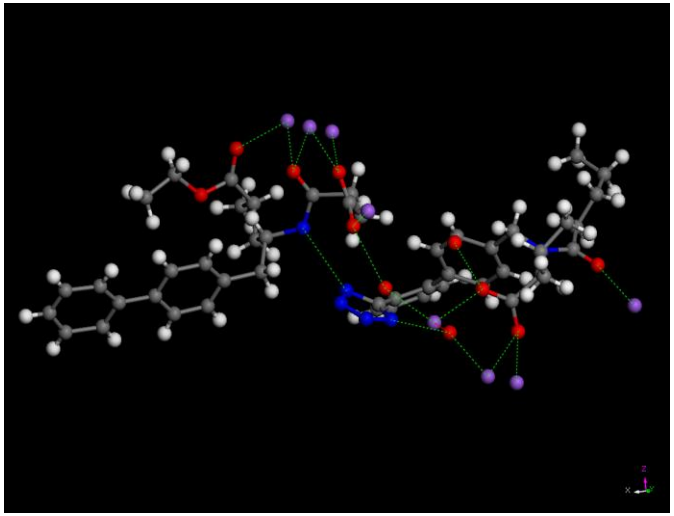
Rank	Status	Study
1	Recruiting	A Comparison Of Outcomes In Patients In New York Heart Association (NYHA) Class II Heart Failure When Treated With Eplerenone Or Placebo In Addition To Standard Heart Failure Medicines Condition: Heart Failure Interventions: Drug: Eplerenone; Drug: Placebo
2	Recruiting	Effects of Remote Patient Monitoring on Heart Failure Management Condition: Heart Failure Intervention: Device: heart failure remote patient monitoring system
3	Recruiting	Peripheral Venous Oxygen Saturation and Biomarkers to Estimate Cardiac Output and Filling Pressures in Heart Failure Condition: Congestive Heart Failure Intervention: Other: Standard of care therapy for severe decompensated heart failure
4	Recruiting	A Prospective, Open-labeled Trial in Patients With Systolic Heart Failure to Evaluate Bisoprolol Treatment for the Effects on Surrogate Markers of Heart Failure in Korea Condition: Heart Failure, Congestive Intervention: Drug: Bisoprolol
5	Recruiting	Cognitive Impairment in Patients With Heart Failure Conditions: Heart Failure; Cognitive Impairment Intervention: Drug: diuretics, inotropica
6	Recruiting	Feasibility Study of an Integrated Diagnostic System to Manage Heart Failure Condition: Heart Failure Interventions: Other: Integrated diagnositic system; Other: Routine in office visits
7	Recruiting	Six Months Efficacy and Safety of Aliskiren Therapy on Top of Standard Therapy, on Morbidity and Mortality in Patients With Acute Decompensated Heart Failure Conditions: Acute Decompensated Heart Failure; Congestive Heart Failure Interventions: Drug: Aliskiren; Drug: Placebo
8	Not yet recruiting	Depression and Self-care in Heart Failure

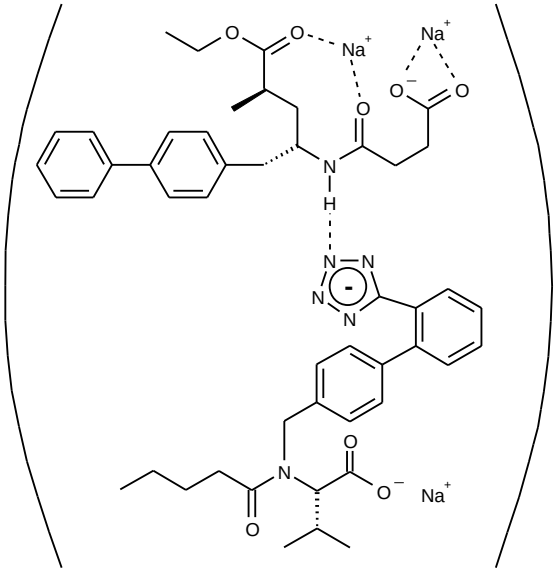
Renin-Angiotensin System



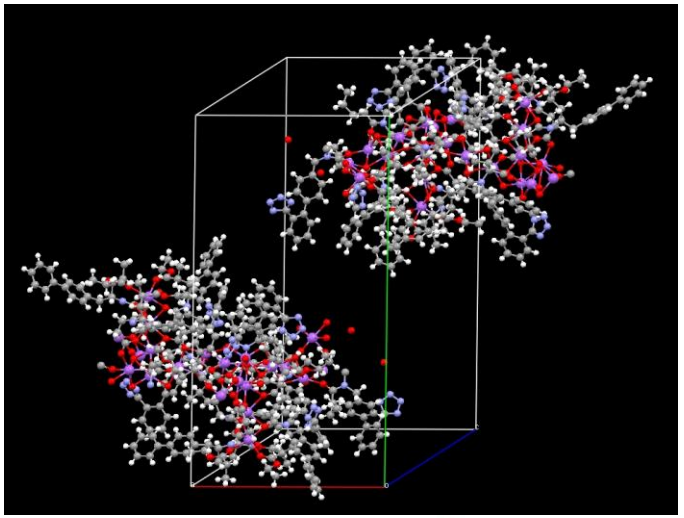
Angiotensin receptor blocker neprilysin inhibitor ARNI





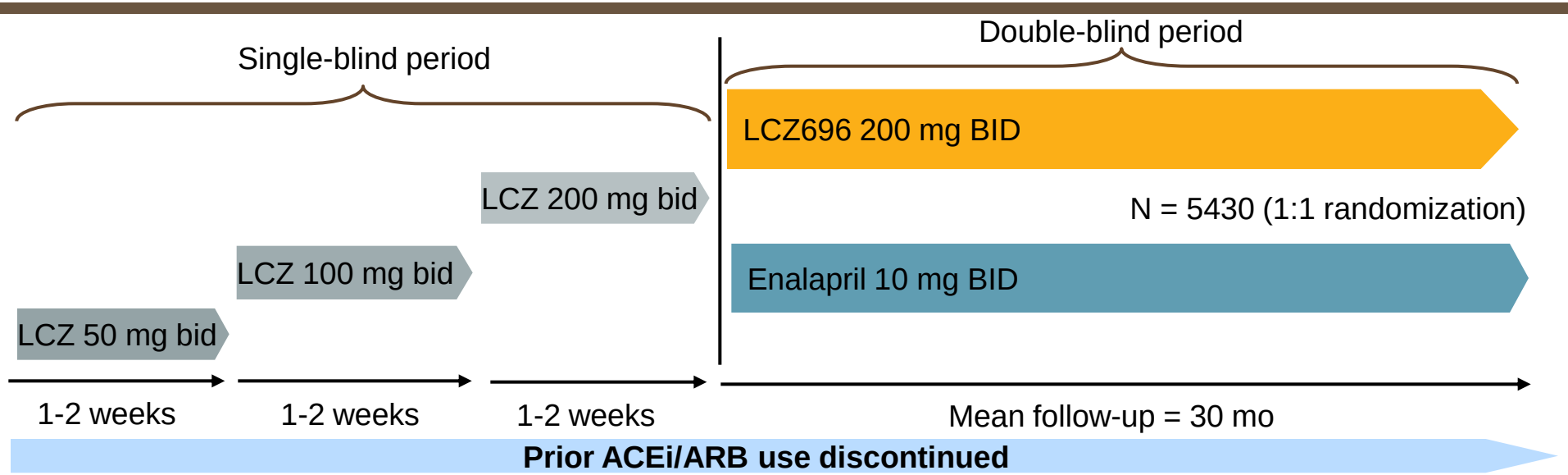


. 2.5 H_2O



NOVARTIS

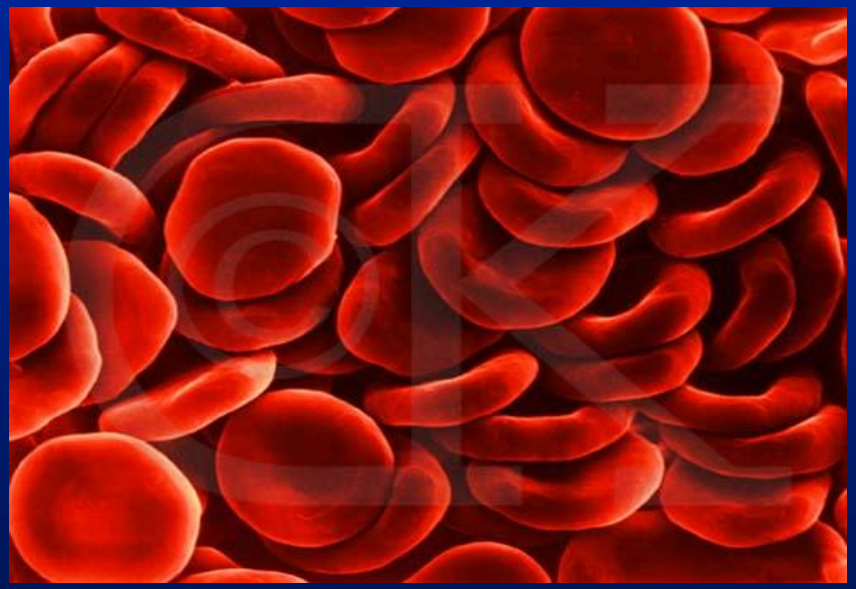
PARADIGM



Design	Randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety study
Primary objectives	Evaluate if LCZ696 is superior in delaying time to first occurrence of either **CV mortality or HF hospitalization** in CHF pts (NYHA Class II – IV) with reduced ejection fraction
Secondary objectives	▪ Clinical summary score (assessed by KCCQ) ▪ Clinical composite score (changes in NYHA and patient global assessment)
General overview	Patients will remain in the trial until either (1) the projected number of primary endpoint is reached, or (2) the trial is terminated prematurely at the recommendation of the DMC when pre-specified early-stopping criteria for efficacy or safety criteria are met
Duration	~39 mo (18 mo enrollment + 21 mo after LPFV); 1638 primary events expected

NOVARTIS

Treating anaemia in HF

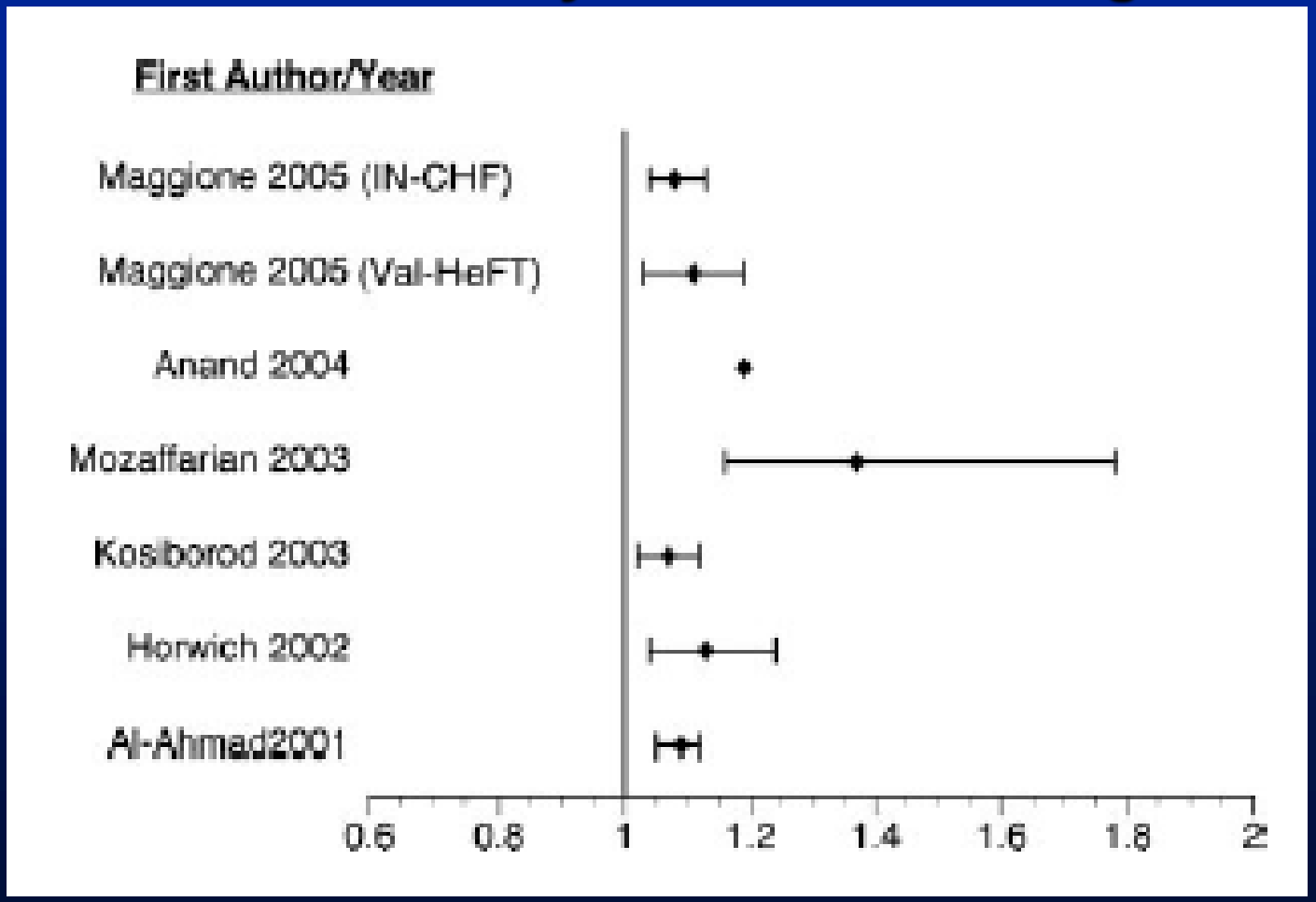


Treating anaemia in HF with an ESP?

Anemia and mortality

In CHF anemia is an independent predictor of increased mortality.

Increased risk of death by decrease of Hb 1 g/dl



Tang and Katz, Circulation 2006

Clinical characteristics associated with increased risk of anemia in HF

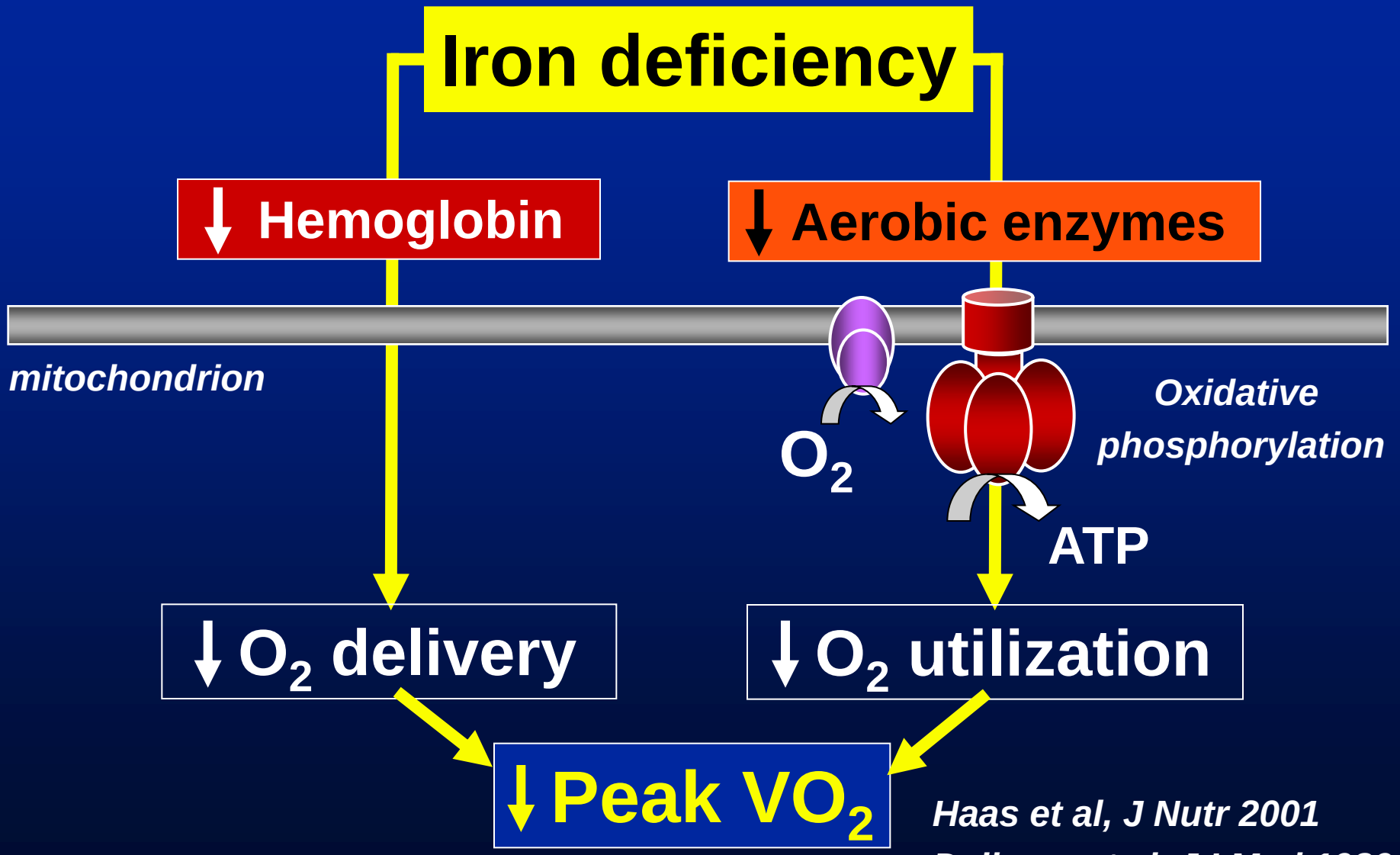
- Advanced age
- Female gender
- Chronic renal disease
- Severity of heart failure
- Acute (vs chronic) settings
- Other co-morbidities
- Decreased BMI
- Use of ACE-inhibitors

Tang and Katz, Circulation 2006

Treatment Options for Anaemia in CHF

- Blood transfusions
  - Demetri GD et al. Br J Cancer 2001
- Erythropoietic agents in combination with intravenous (iv) iron therapy or with Vit B12/Folate
  - Silverberg D et al. J Am Coll Cardiol 2000 + 2001
  - Mancini DM et al., Circulation 2003
- Iron (oral or iv)
  - FAIR-HF

Iron, peak VO_2 & energy production



Haas et al, J Nutr 2001

Dallman et al, J I Med 1989

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

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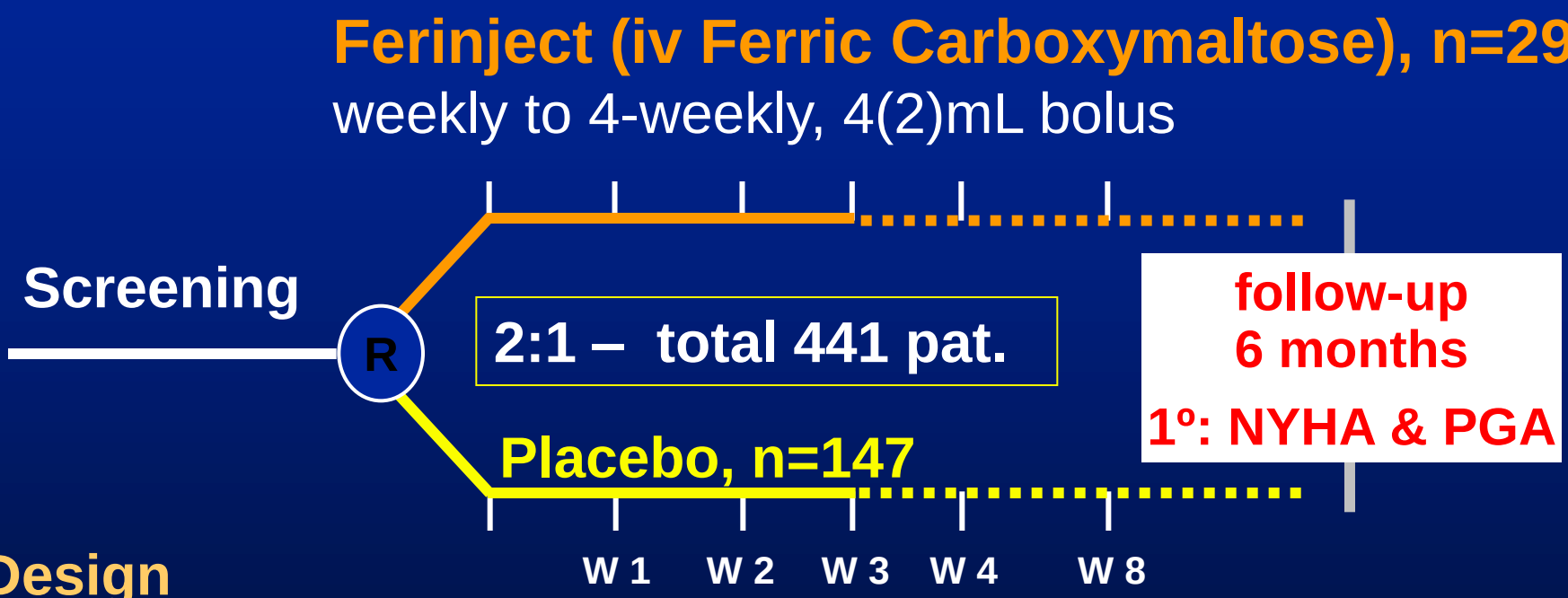
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†

Study Design FAIR-HF

Ferinject ® (iv iron) vs Placebo in addition to standard therapy in CHF patienten with iron defficiency

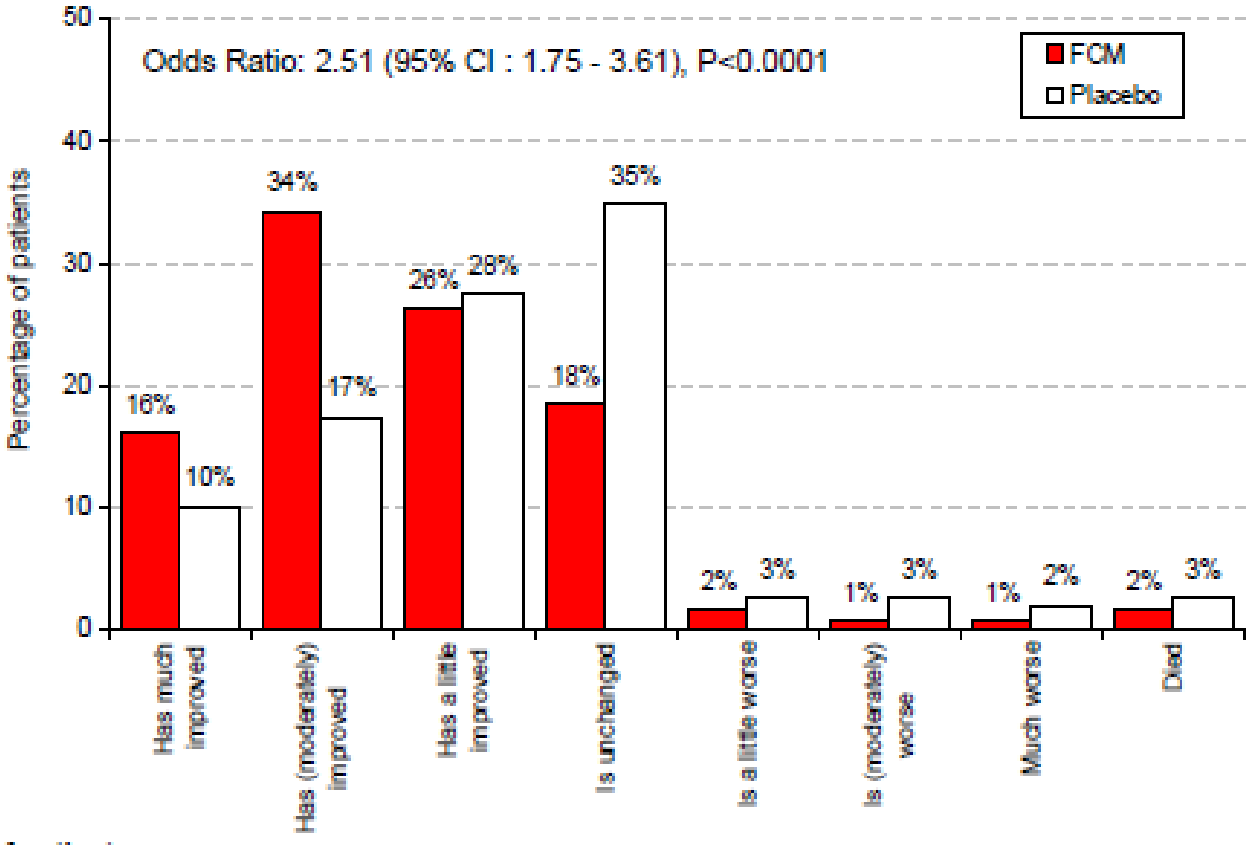


Design

- Multi-center, double-blind, randomized
- **Exec. Committee:** P. Poole-Wilson (chair), SD Anker (co-chair), P. Ponikowski, T. Lüscher, R. Willenheimer, H. Drexler, G. Filippatos, K. Dickstein
- **Inclusion:** functional ID & Hb 9.5–13.5 & LVEF ≤40% (II) or ≤45% (III)
- **Treatment stop:** Hb>16 or ferritin >600 or TSAT>50%

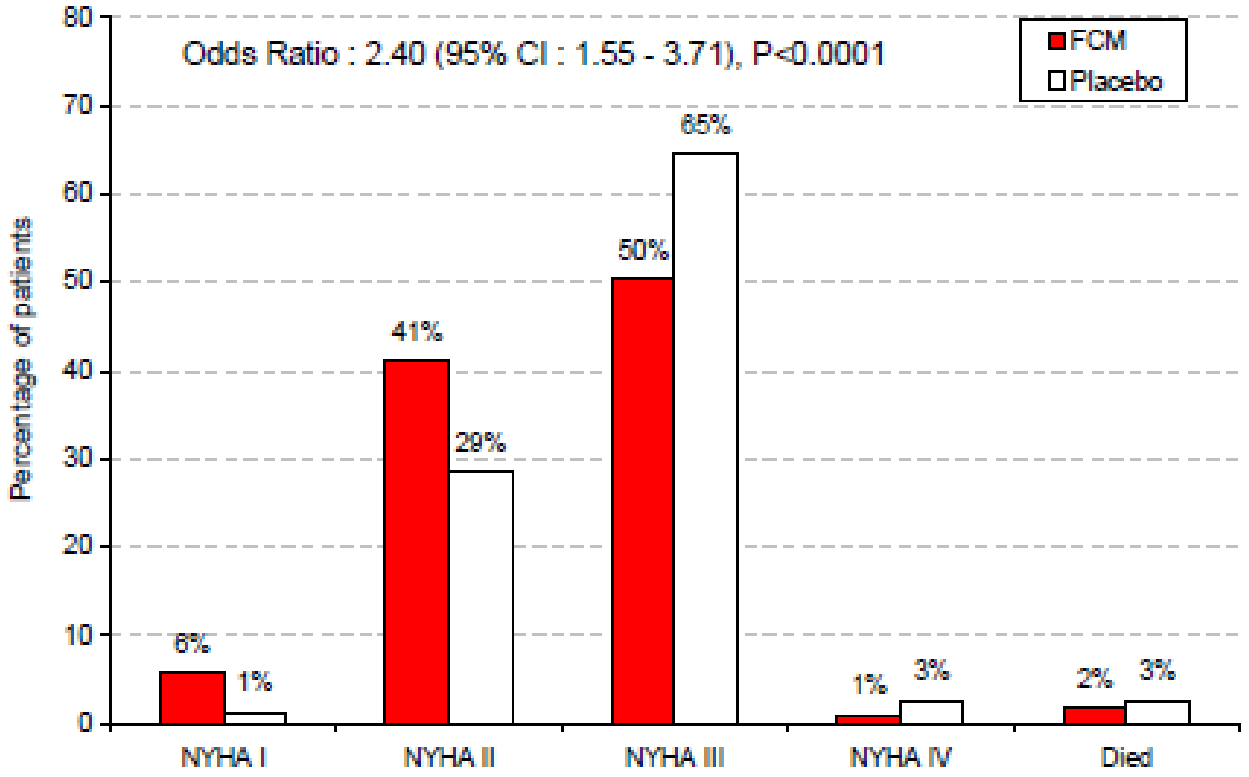
Primary Endpoint:
Patient Global Assessment at Week 24

- FCM improved self-reported PGA scores at week 24
- Odds ratio: 2.51 (95% CI 1.75,3.61), P<0.0001



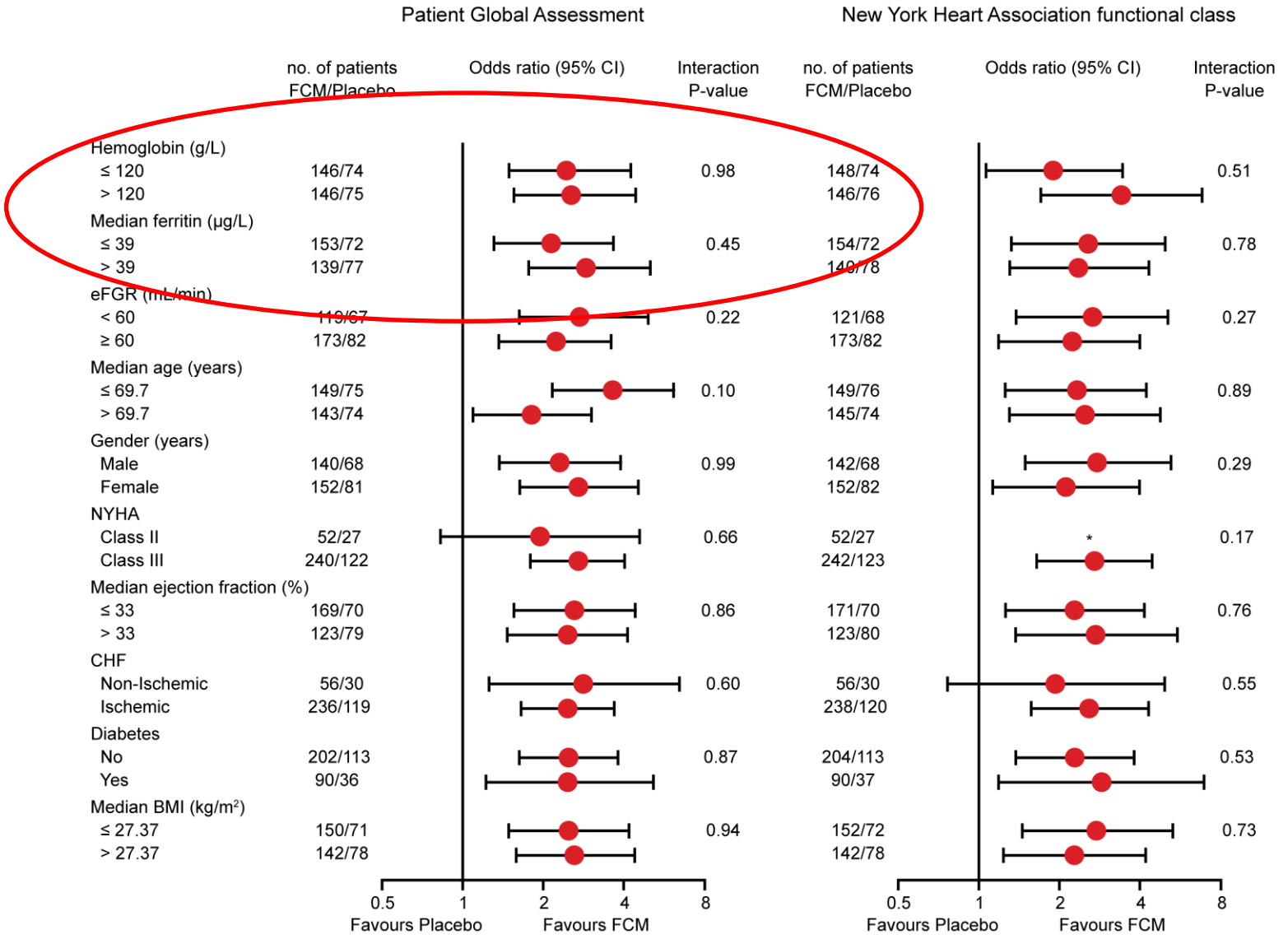
Primary Endpoint:
NYHA Functional Class at Week 24

- FCM improved NYHA functional class at week 24
- Odds ratio: 2.40 (95% CI 1.55,3.71), P<0.0001*



*adjusted for baseline

•Secondary Endpoints: PGA & NYHA Class in Predefined Subgroups



Treatment Options for Anaemia in CHF

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  - Silverberg D et al. J Am Coll Cardiol 2000 + 2001
  - Mancini DM et al., Circulation 2003
- Iron (oral or iv)
  - FAIR-HF
- Erythropoietic agents alone (iron permitted)
  - RED-HF

RED-HF Trial: Hypothesis and Study Design

Hypothesis:

Treatment of anemia with darbepoetin alfa in subjects with symptomatic left ventricular systolic dysfunction and anemia decreases the risk of all-cause mortality or hospital admission for worsening HF

Study Population

- Hemoglobin 9 to 12 g/dL
- LVEF ≤ 35%
- NYHA Class II to IV

Darbepoetin alfa group (target hemoglobin 13.0 to 14.5 g/dL)
N = 1200

1:1 randomization

Placebo group
N = 1200

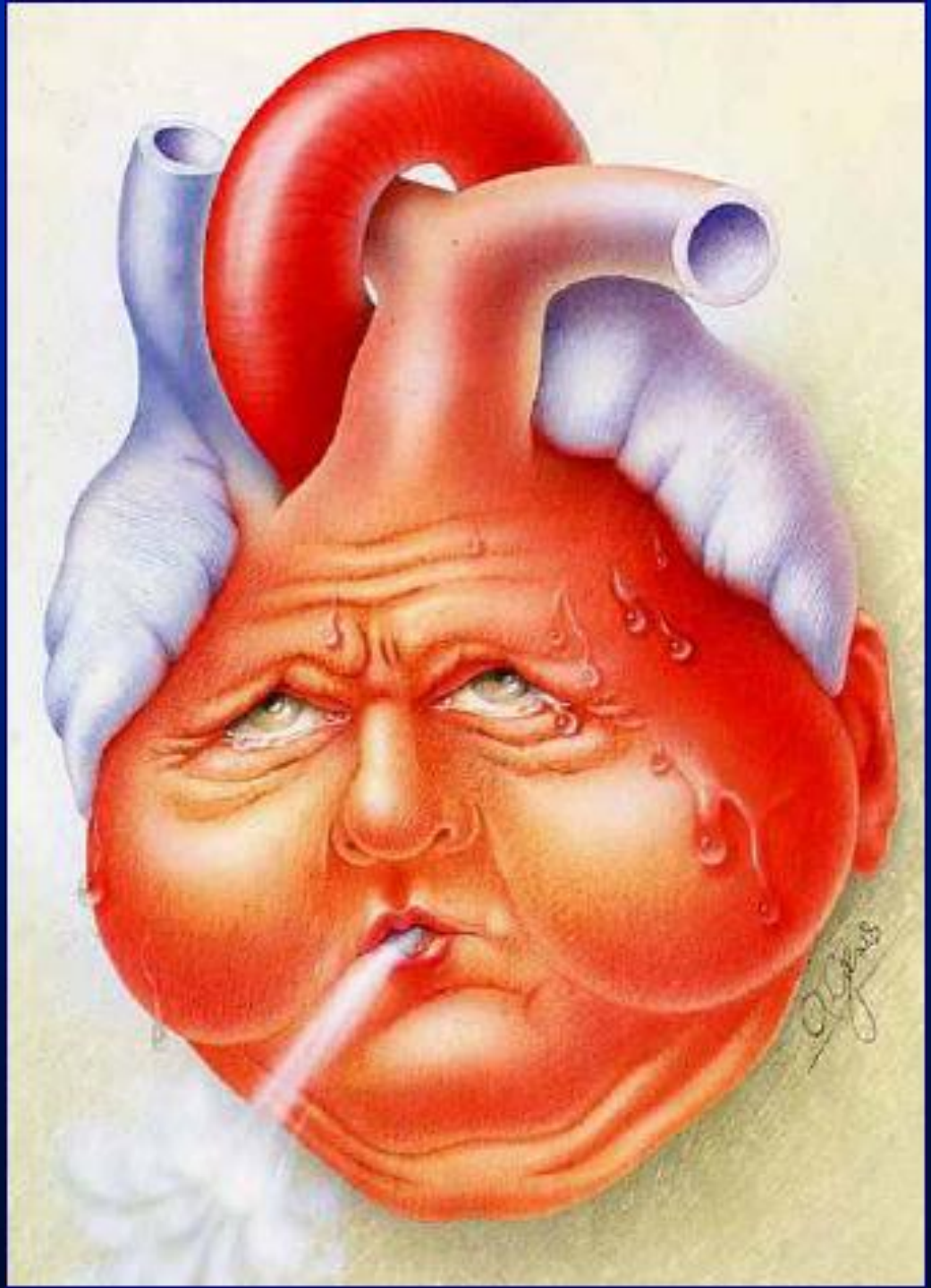
Timelines

Approximately 620 global sites

RED-HF Trial is Now ~ 68% Enrolled

Region	Screened	SF Rate	Enrolled
Australia	42	55%	19
Canada	82	59%	33
Europe	2138	61%	814
India	529	58%	203
Latin America	569	62%	205
United States	1204	57%	501
	4564	**60%**	**1775**

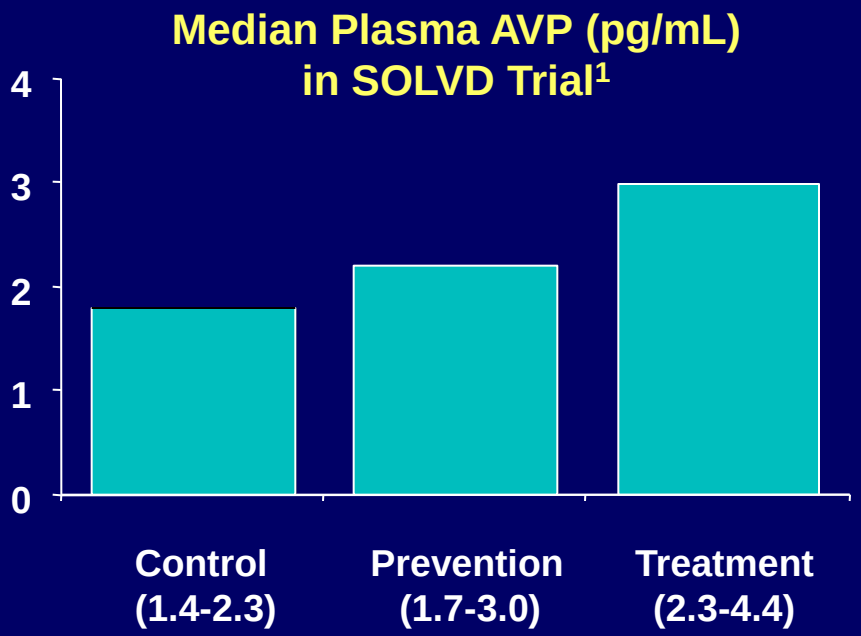
As of April 9, 2010

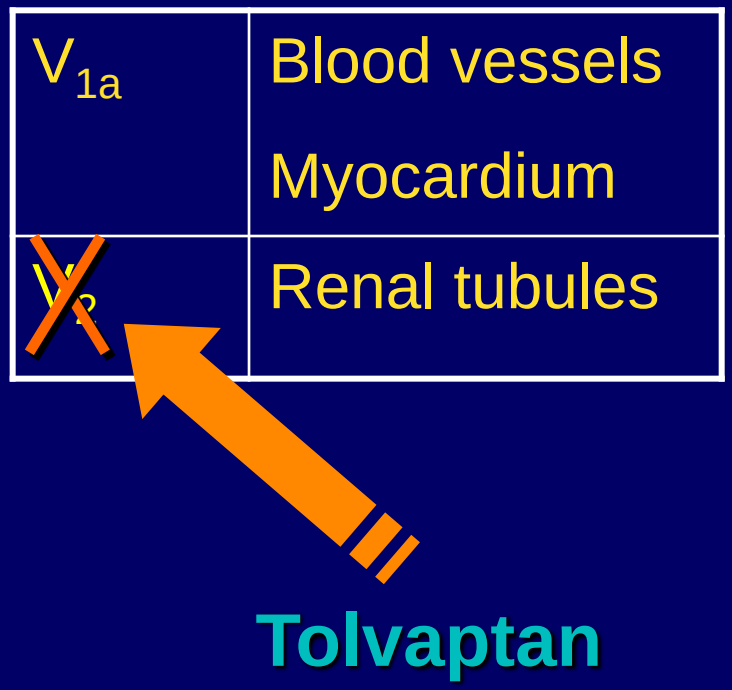


Diuretics and heart failure

- Diuretics are mainstay of therapy for acute heart failure (given to > 90% of pts in ADHERE)
- Relieve symptoms of dyspnea and edema in most patients
- Associated with variety of problems:
  - Electrolyte abnormalities
  - Activation of RAAS and SNS
  - Diuretic resistance
  - Increased mortality?

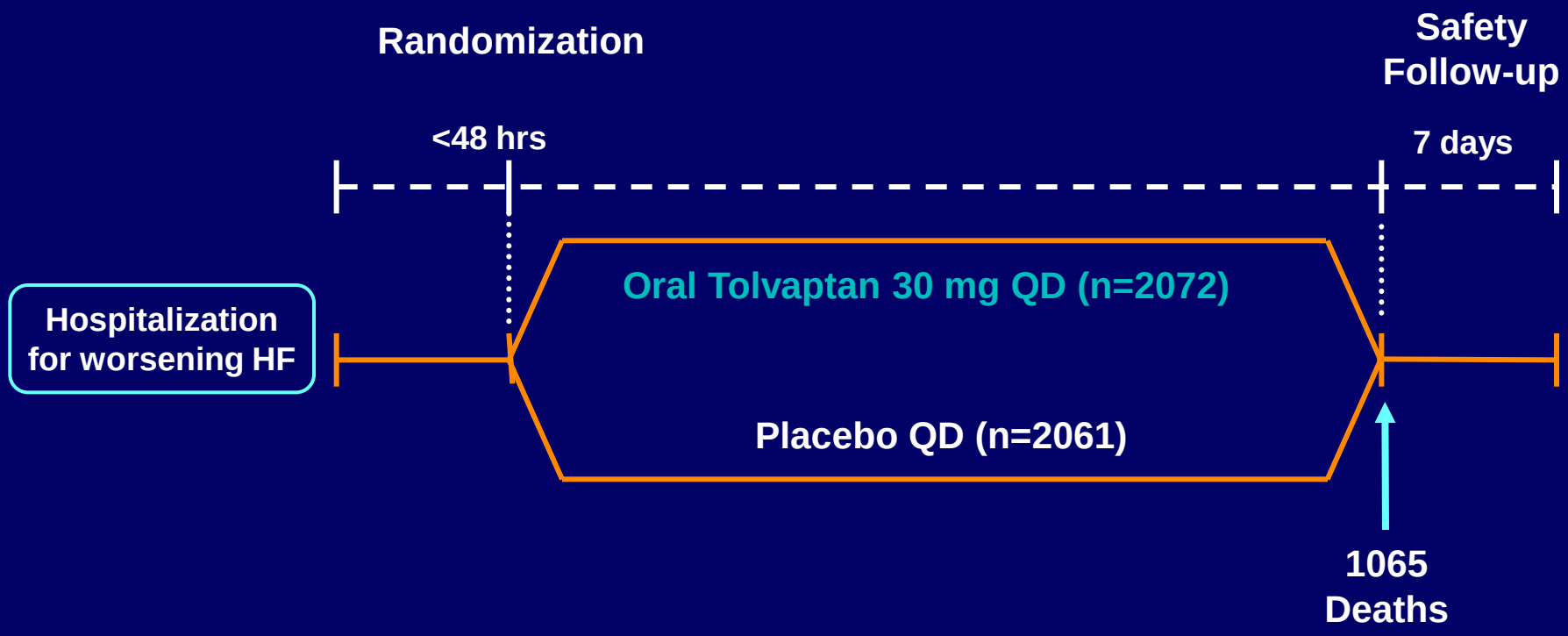
Arginine Vasopressin





Francis et al. *Circulation* 1990;82:1724-1729.

Combined Outcome Trial Design

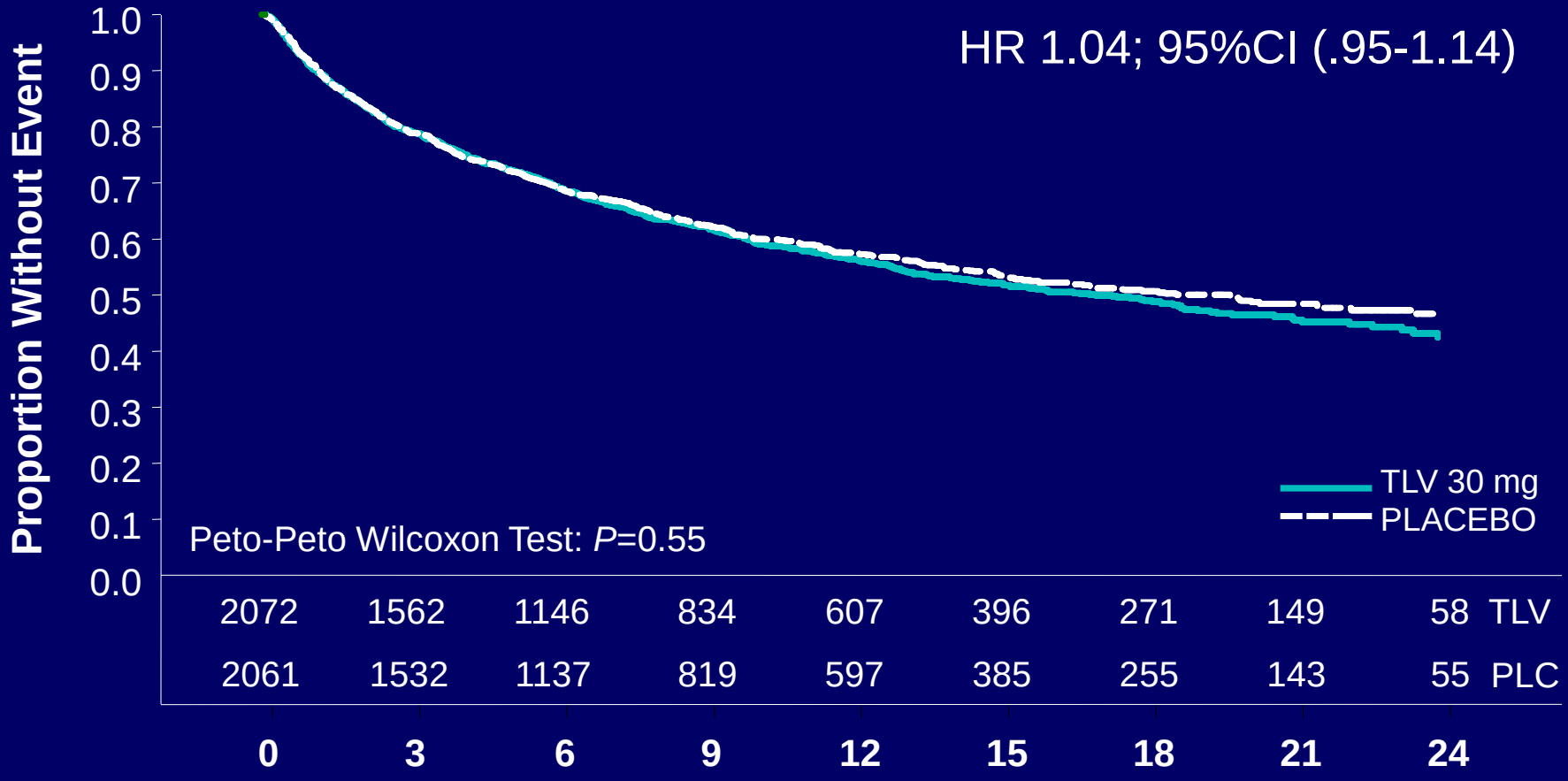


Dual Primary Endpoints:

- **Improvement / non-inferiority in All-cause Mortality**
- **Improvement in CV death or HF hospitalization**

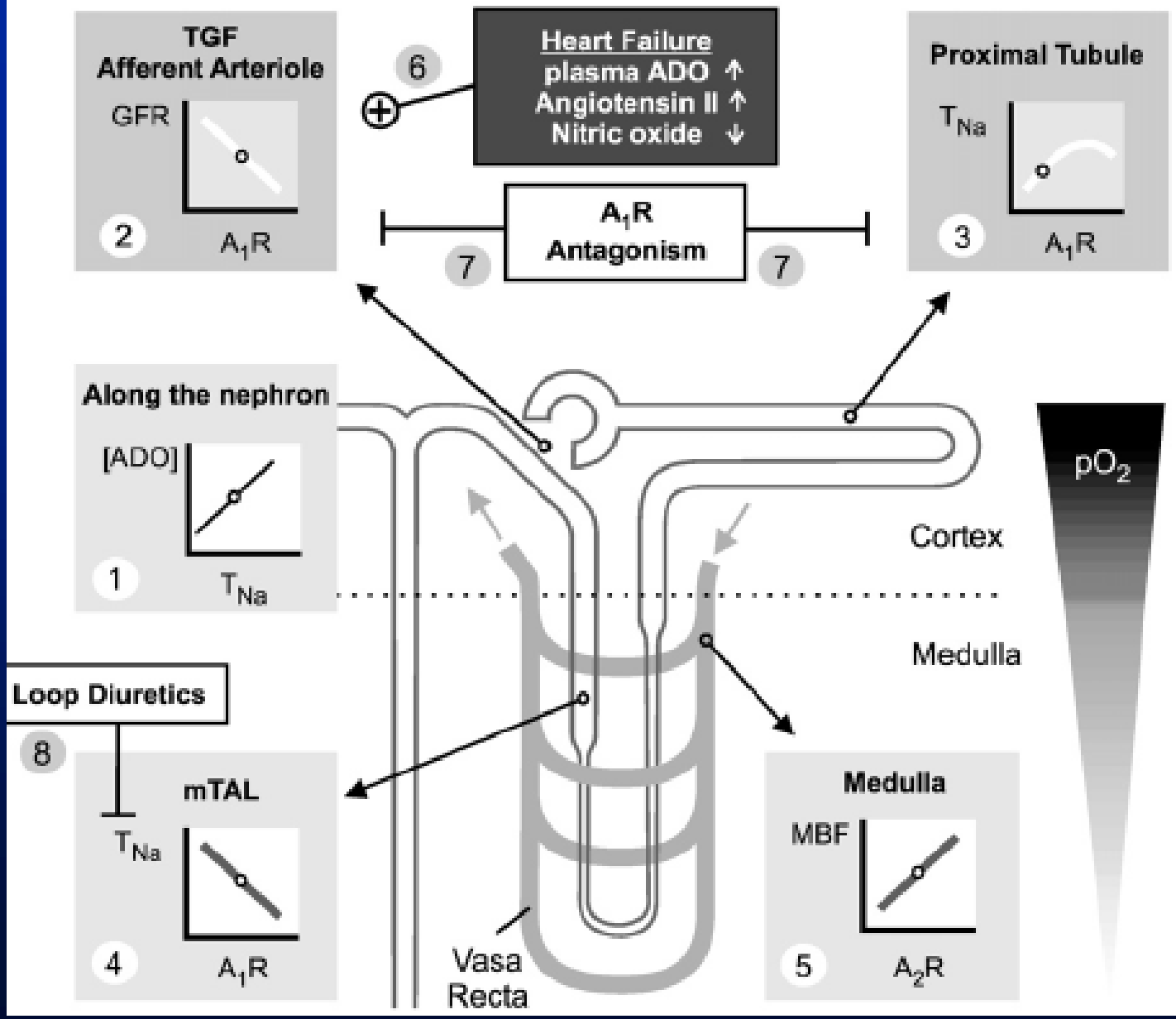
Gheorghiade, et al. *J Card Fail.* 2005;11:260-269.

CV Mortality or HF Hospitalization



Konstam et al JAMA 2007

EVEREST


TGF
Afferent Arteriole
GFR
2
A_1R
6
Heart Failure
plasma ADO ↑
Angiotensin II ↑
Nitric oxide ↓
A_1R
Antagonism
7
7
Proximal Tubule
T_{Na}
3
A_1R
Along the nephron
[ADO]
1
T_{Na}
Cortex
Medulla
pO_2
Loop Diuretics
8
mTAL
T_{Na}
4
A_1R
Vasa
Recta
Medulla
MBF
5
A_2R

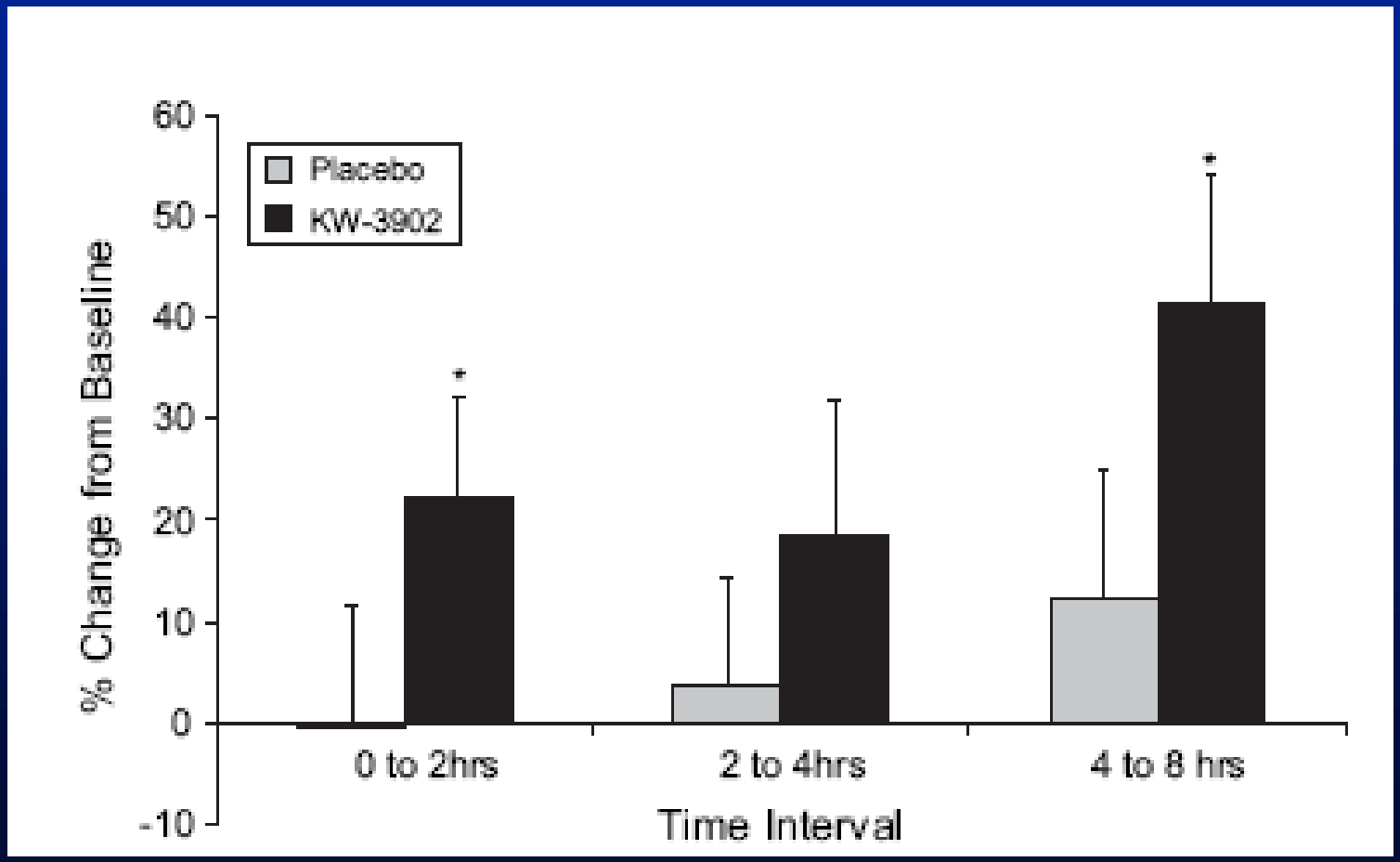
Journal of Cardiac Failure Vol. 13 No. 8 2007

The Effect of KW-3902, an Adenosine A_1 Receptor Antagonist, on Renal Function and Renal Plasma Flow in Ambulatory Patients With Heart Failure and Renal Impairment

HOWARD C. DITTRICH, MD,[1] DINESH K. GUPTA, MD,[2] TERRENCE C. HACK, MD,[3] THOMAS DOWLING, PhD,[4] JANICE CALLAHAN, PhD,[5] AND SCOTT THOMSON, MD[6]

San Diego, California; Tullahoma, Tennessee; Ayer, Massachusetts; Baltimore, Maryland

- **32 CHF patients randomized XO, placebo/KW-3902**



MERCK

News Release

FOR IMMEDIATE RELEASE

Media Contacts: Ronald Rogers (908) 423- 6449

Mary Elizabeth Blake (267) 305-5550

Investor Contacts: Eva Boratto (908) 423-5185

Carol Ferguson (908) 423-4465

Rolofylline Did Not Demonstrate Efficacy for Acute Heart Failure in Clinical Trial

WHITEHOUSE STATION, N.J., June 5, 2009 – Merck & Co., Inc. today said that preliminary results for the pivotal Phase III study of rolofylline (MK-7418), the Company's investigational medicine for the treatment of acute heart failure, show that rolofylline did not meet the primary or secondary efficacy endpoints. While Merck will continue to analyze the data with outside experts, the Company will not file applications for regulatory approval this year. The results from this study will be presented at a medical meeting later this year.

PROTECT

Table 1: Effects on Primary 3 Category Ordered Endpoint

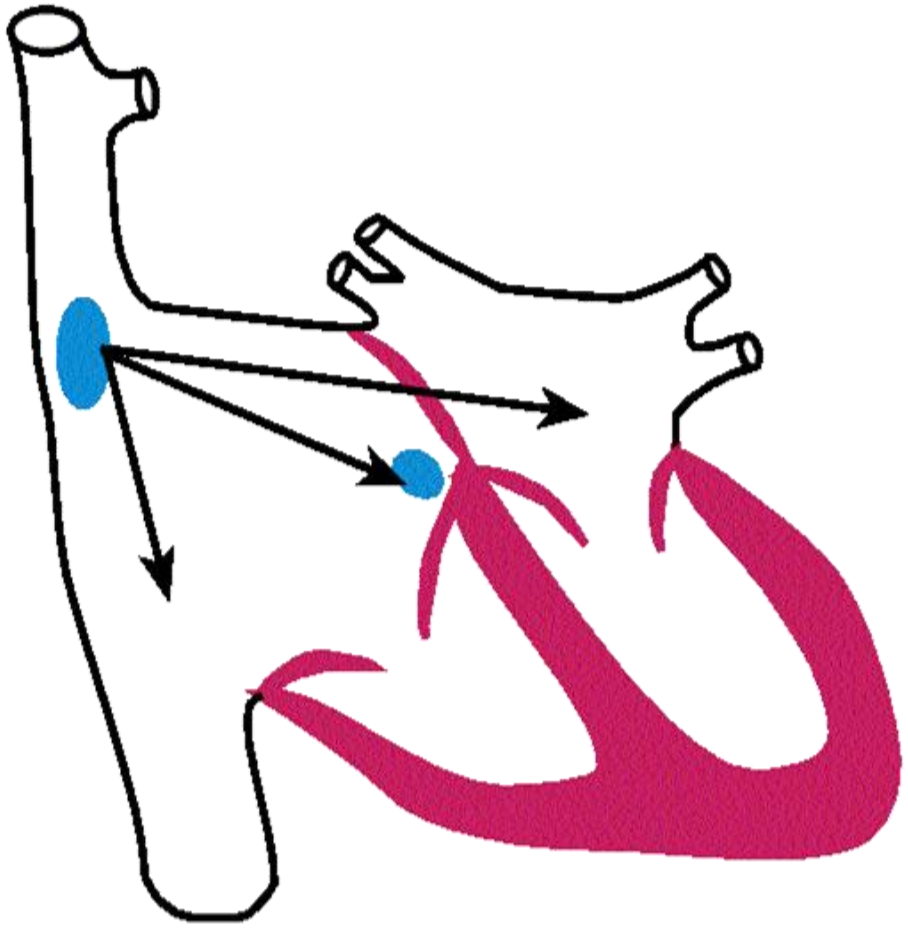
	Rolofylline 30 mg N = 1356	Placebo N = 677
Success, % (n)	40.6 (551)	36.0 (244)
Unchanged, % (n)	37.5 (509)	44.2 (299)
Failure, % (n)	21.8 (296)	19.8 (134)

Table 2: Dyspnea Improvement and Failure Criteria

	Rolofylline 30 mg N=1356	Placebo N= 677
Moderate or marked dyspnea improvement at both 24 and 48 hours, % (n)	51.2 (694)	44.5 (301)
Components of treatment failure % (n)		
- Death / Day 7	1.7% (23)	2.1% (14)
- HF readmission /Day 7	0.4% (5)	0.6% (4)
- Worsening HF Day 7/discharge	9.1% (123)	9.7% (66)
- Persistent renal impairment	12.7% (172)	11.1% (75)
- SCr ↑ ≥0.3 mg/dL (Day 7 and Day 14)	12.3% (167)	10.6% (72)
- Initiation of hemofiltration	0.4% (6)	0.9% (6)

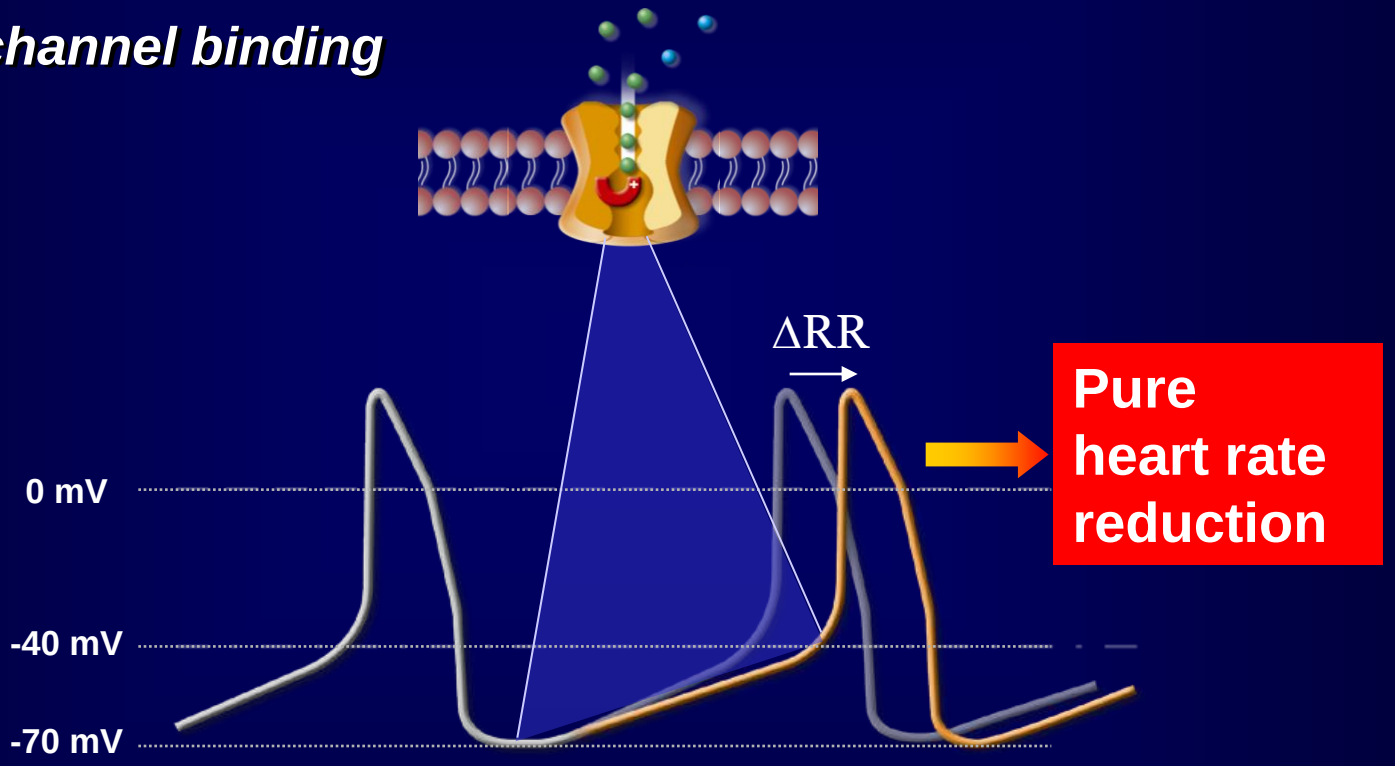
Metra et al ESC Congress Hot Line 2009

Sinus node inhibition



Selective I_f current inhibition

Specific f-channel binding



Ivabradine inhibits the I_f current, which slows diastolic depolarization slope

DiFrancesco D, Camm AJ. *Drugs.* 2004.

BEAUTIFUL

Population

≥ 55 years or diabetics > 18years

Documented CAD

LV Ejection Fraction < 40%

HR ≥ 60 bpm

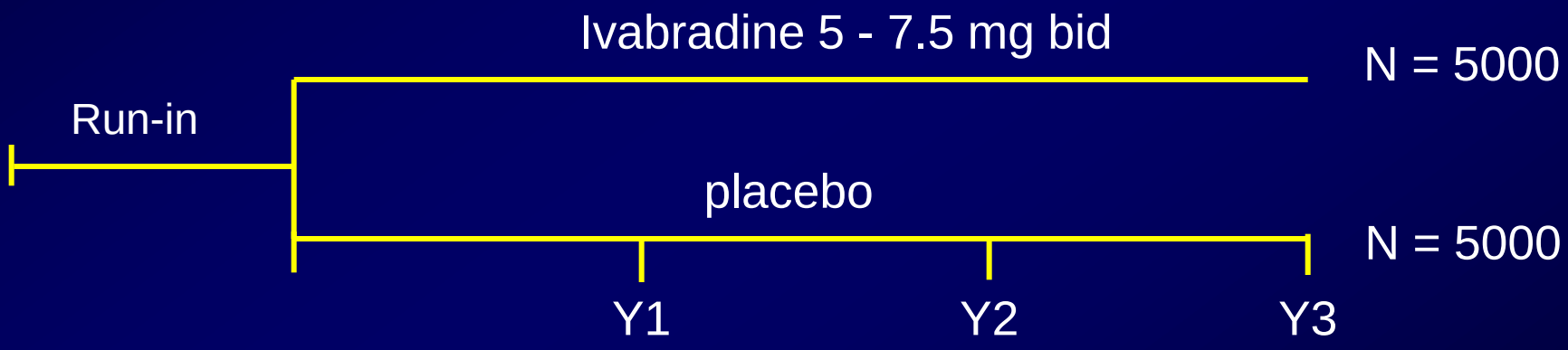
Methods

Events 11%, n=950, RRR: 19%

Power: 90%; alpha bilateral 5%

Mean follow-up: 2.25 years

850 centers in 33 countries



Combined primary endpoint

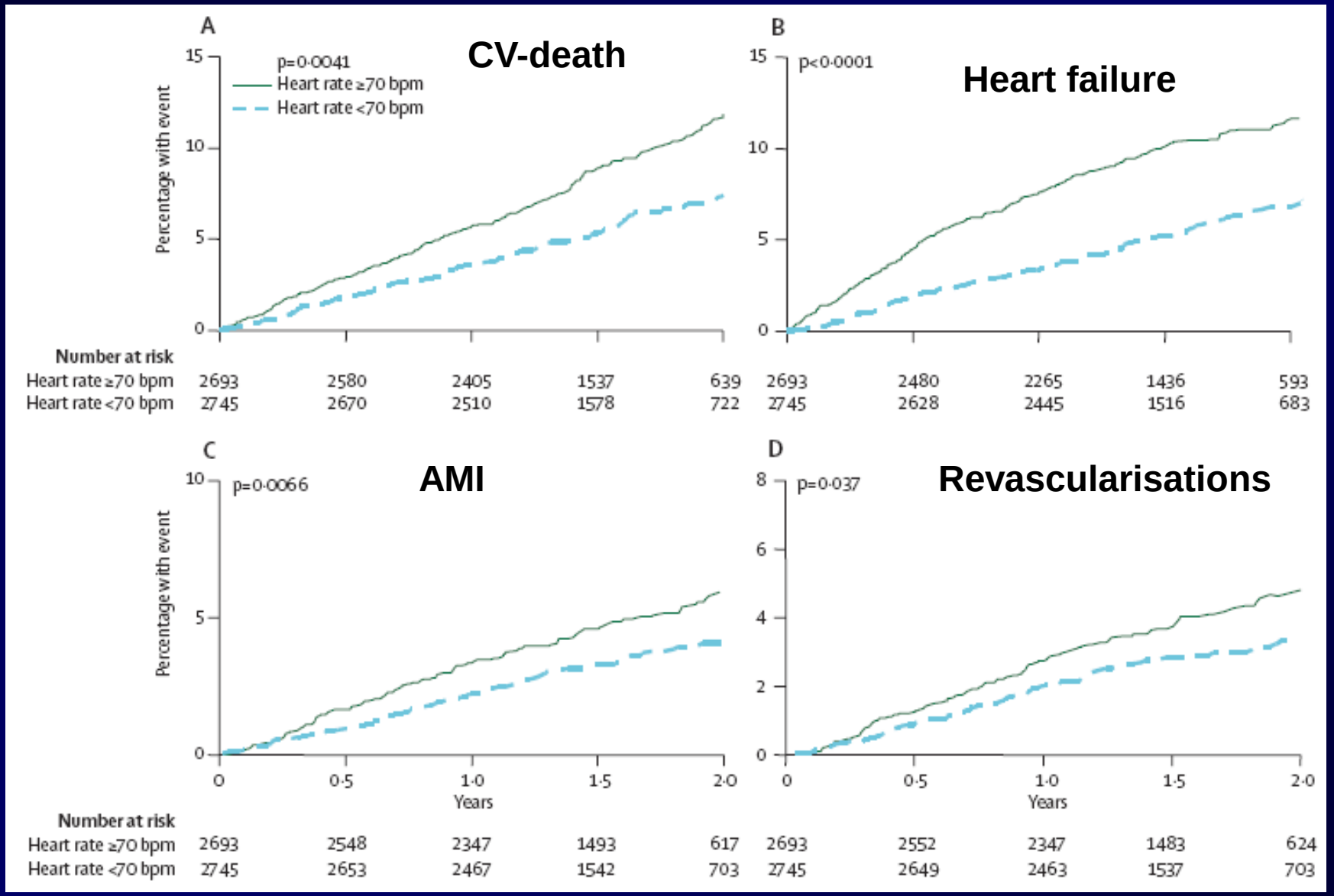
Cardiovascular death

Hospitalisation for acute myocardial infarction (MI)

Hospitalisation for new onset or worsening heart failure (HF)

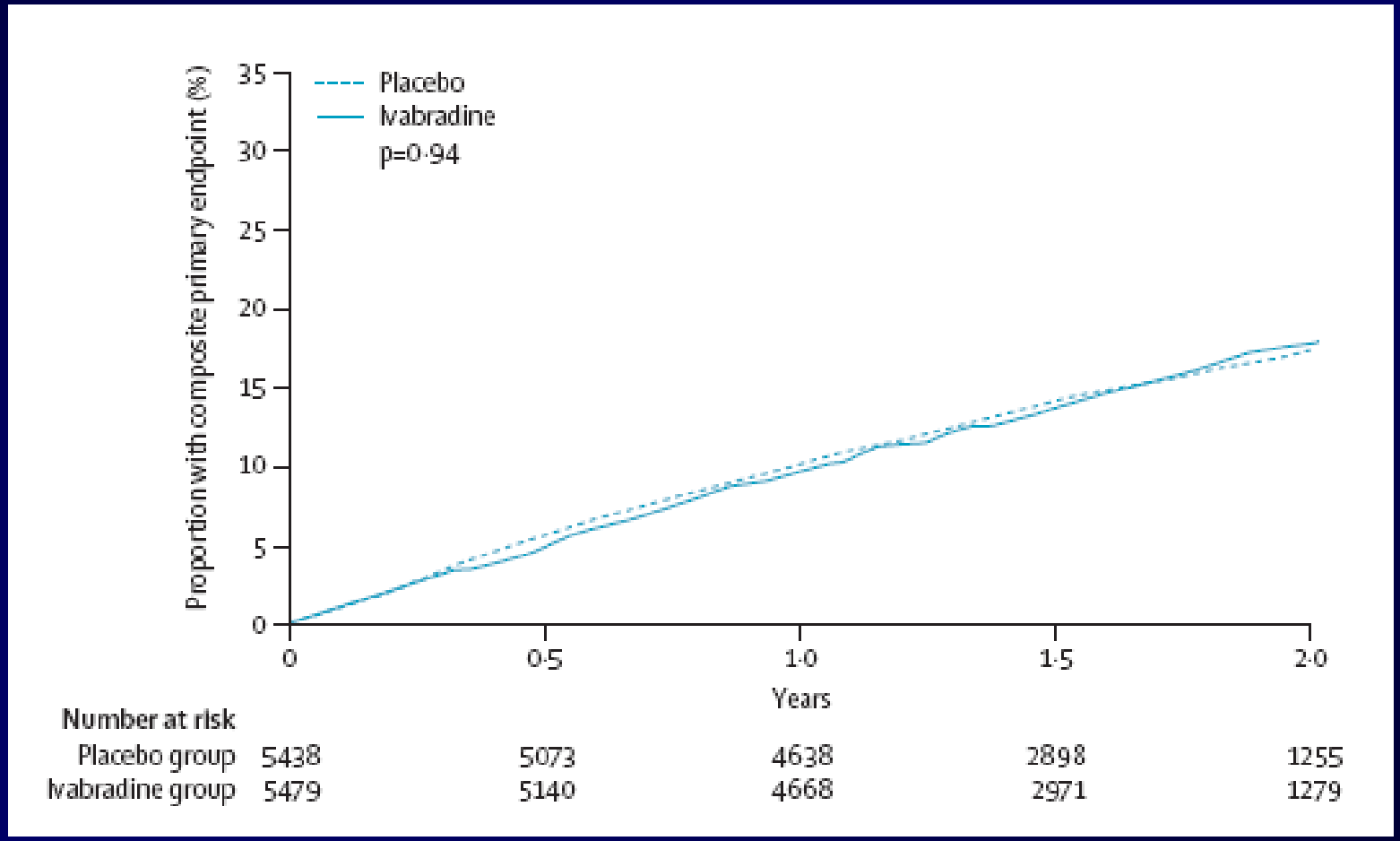
SERVIER

Heart rate

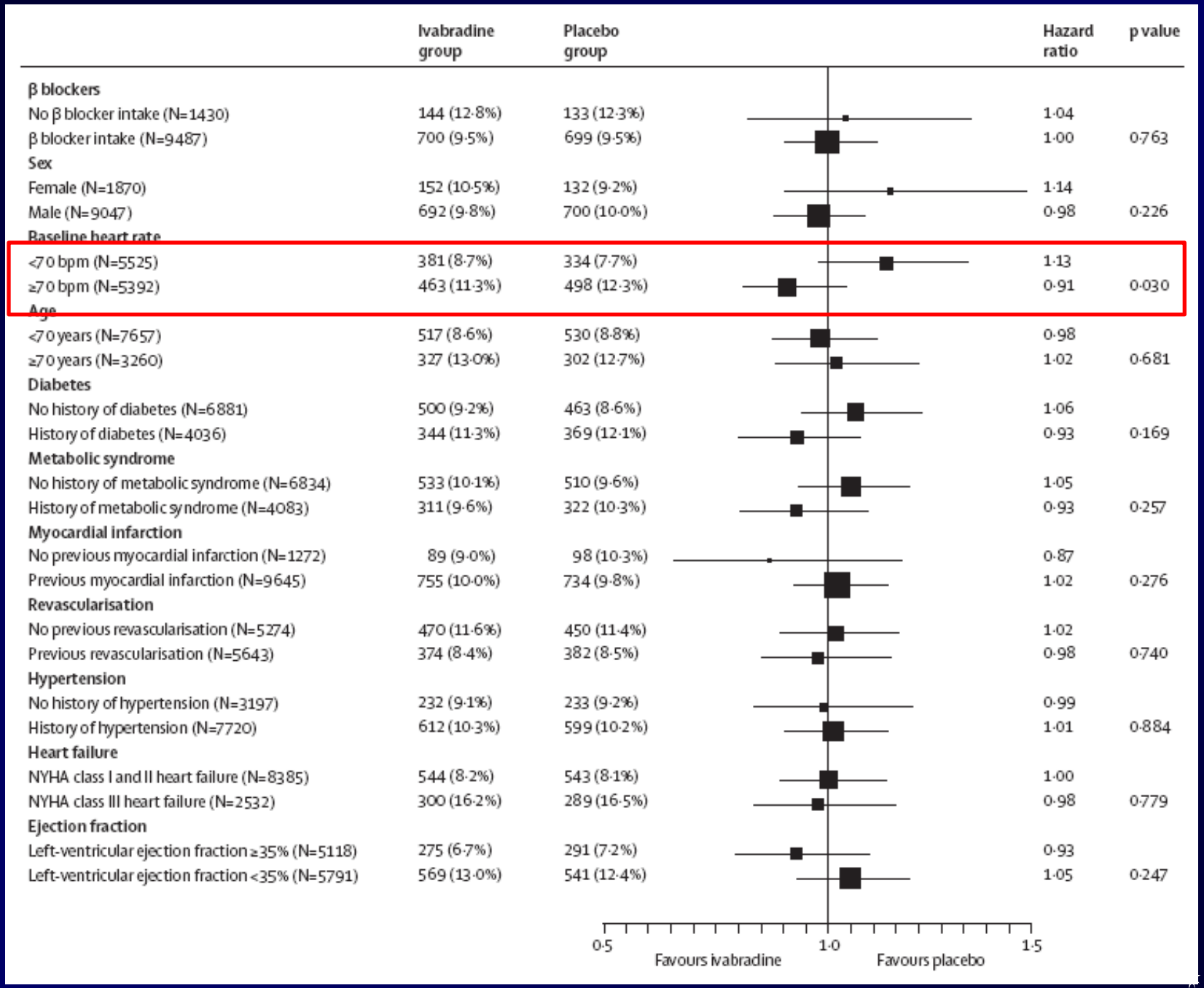


Fox et al Lancet 2008

Primary outcome
CV-death or hospitalisation for AMI or heart failure



Fox et al Lancet 2008


Ivabradine group
Placebo group
Hazard ratio
p value
β blockers
No β blocker intake (N=1430) 144 (12·8%) 133 (12·3%) 1·04
β blocker intake (N=9487) 700 (9·5%) 699 (9·5%) 1·00 0·763
Sex
Female (N=1870) 152 (10·5%) 132 (9·2%) 1·14
Male (N=9047) 692 (9·8%) 700 (10·0%) 0·98 0·226
Baseline heart rate
<70 bpm (N=5525) 381 (8·7%) 334 (7·7%) 1·13
≥70 bpm (N=5392) 463 (11·3%) 498 (12·3%) 0·91 0·030
Age
<70 years (N=7657) 517 (8·6%) 530 (8·8%) 0·98
≥70 years (N=3260) 327 (13·0%) 302 (12·7%) 1·02 0·681
Diabetes
No history of diabetes (N=6881) 500 (9·2%) 463 (8·6%) 1·06
History of diabetes (N=4036) 344 (11·3%) 369 (12·1%) 0·93 0·169
Metabolic syndrome
No history of metabolic syndrome (N=6834) 533 (10·1%) 510 (9·6%) 1·05
History of metabolic syndrome (N=4083) 311 (9·6%) 322 (10·3%) 0·93 0·257
Myocardial infarction
No previous myocardial infarction (N=1272) 89 (9·0%) 98 (10·3%) 0·87
Previous myocardial infarction (N=9645) 755 (10·0%) 734 (9·8%) 1·02 0·276
Revascularisation
No previous revascularisation (N=5274) 470 (11·6%) 450 (11·4%) 1·02
Previous revascularisation (N=5643) 374 (8·4%) 382 (8·5%) 0·98 0·740
Hypertension
No history of hypertension (N=3197) 232 (9·1%) 233 (9·2%) 0·99
History of hypertension (N=7720) 612 (10·3%) 599 (10·2%) 1·01 0·884
Heart failure
NYHA class I and II heart failure (N=8385) 544 (8·2%) 543 (8·1%) 1·00
NYHA class III heart failure (N=2532) 300 (16·2%) 289 (16·5%) 0·98 0·779
Ejection fraction
Left-ventricular ejection fraction ≥35% (N=5118) 275 (6·7%) 291 (7·2%) 0·93
Left-ventricular ejection fraction <35% (N=5791) 569 (13·0%) 541 (12·4%) 1·05 0·247
0·5
1·0
1·5
Favours ivabradine
Favours placebo

Population

≥ 18 years

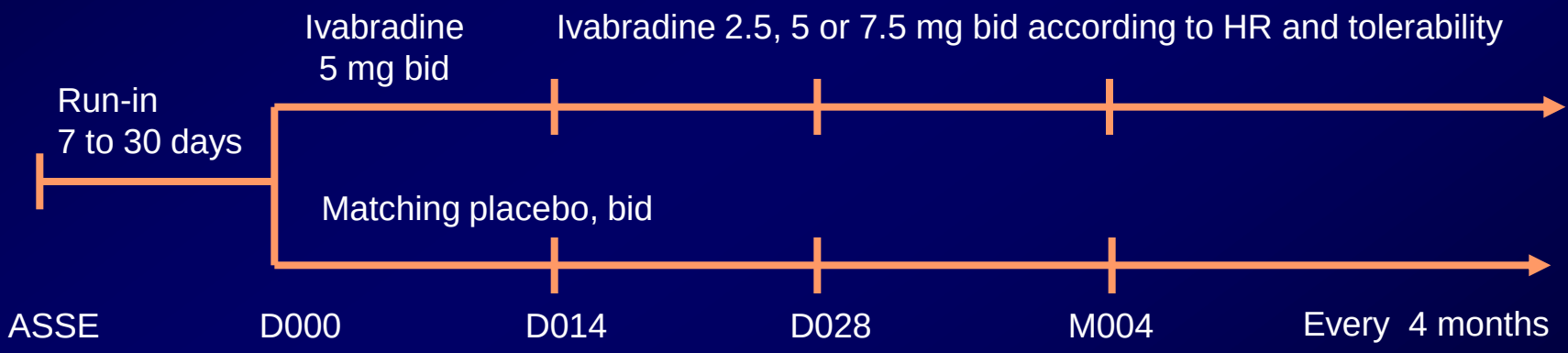
Symptomatic CHF, class II to IV NYHA

All etiologies of CHF

Documented hospital admission for worsening heart failure ≤ 12 months

LV systolic dysfunction (EF) ≤ 35%

HR ≥ 70 bpm



Composite primary endpoint

Cardiovascular death

Hospitalisation for worsening heart failure

BEAUTIFUL Implications of the results on SHIFT

- ✓ SHIFT is specifically designed for a severe HF population
- ✓ With a different study treatment schedule
- ✓ With different study population characteristics
- ✓ Different background treatment

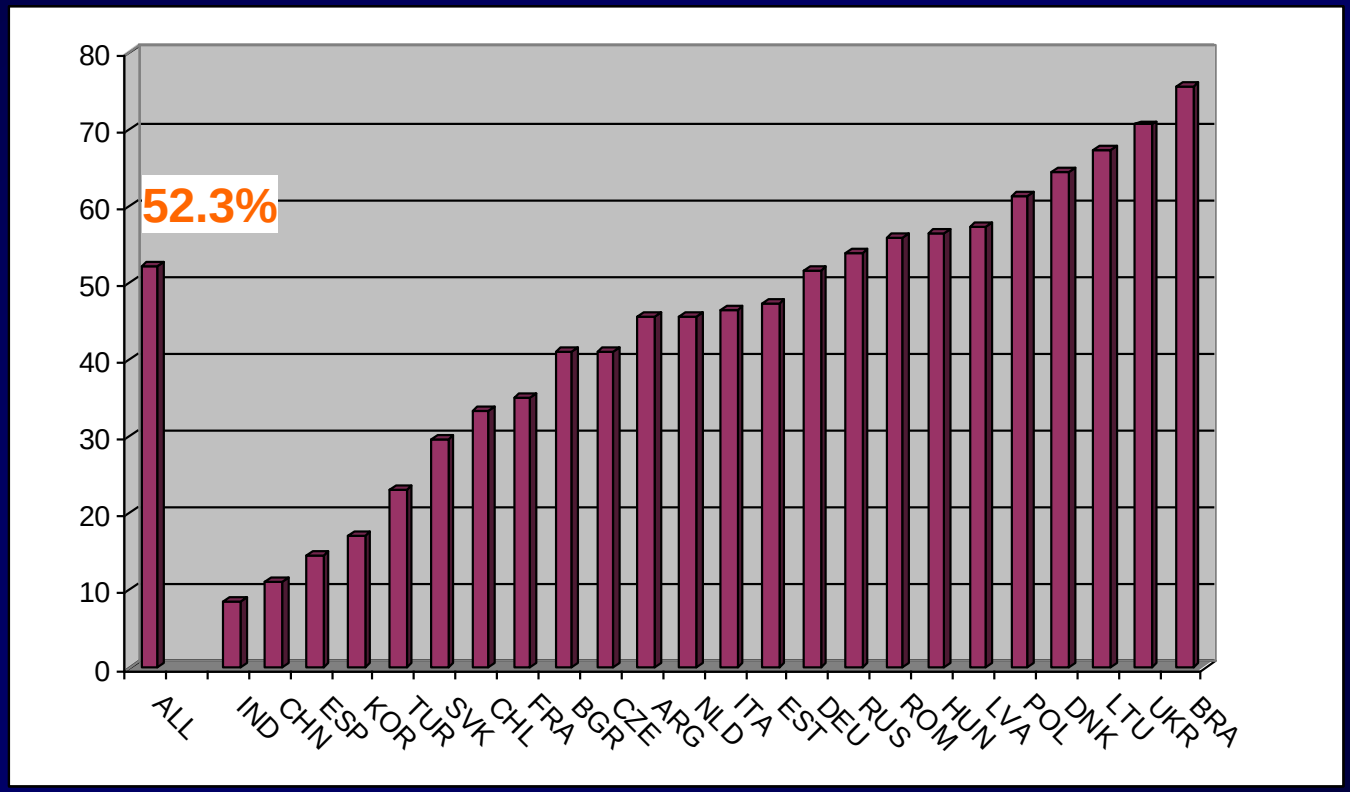
50% BB target daily dose

(RS = 5618 -03/10/08)

- ✓ Among patients treated with BB* (n=4911), 52.3 % receive at least 50% of the target daily dose

(*:Carvedilol, bisoprolol, nebivolol, metoprolol tartrate, metoprolol succinate;

393 (8.4%) patients with missing data)

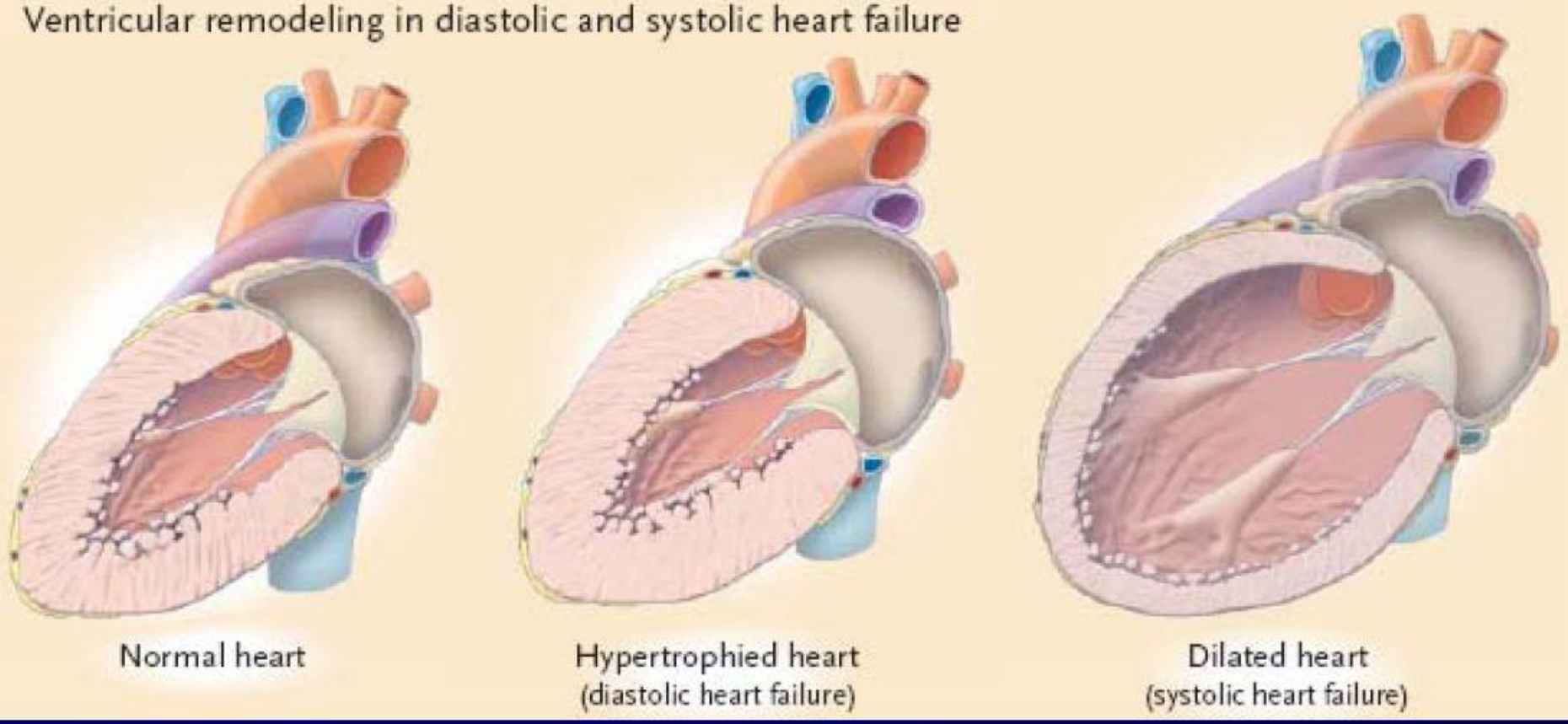


- ✓ Overall, 45.7% of all randomised patients (n=5618) receive at least 50% of the BB target daily dose

Study status

- ✓ **Study follow-up ended March 31 2010**
- ✓ **Presentation in a Hot Line session at ESC congress in Stockholm August 29**
- ✓ **Simultaneous publication in Lancet**

Ventricular remodeling in diastolic and systolic heart failure



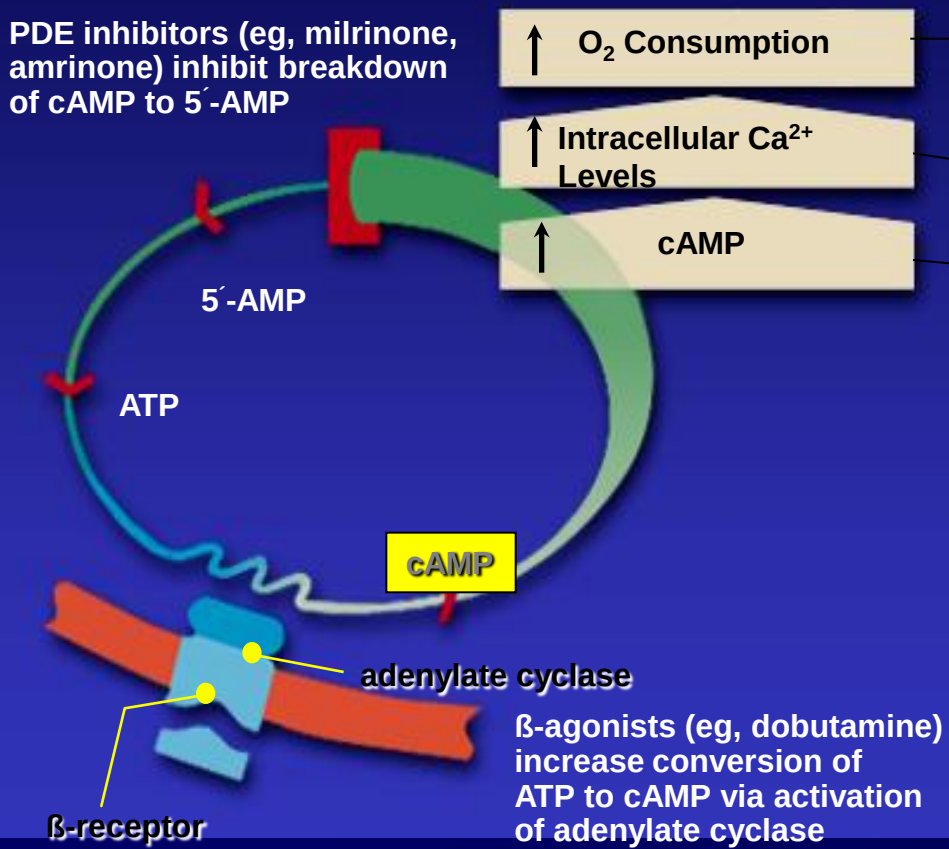
Normal heart

Hypertrophied heart
(diastolic heart failure)

Dilated heart
(systolic heart failure)

Mechanism of Action
Increasing contractility - selected mechanisms

PDE Inhibitors & β–Agonists

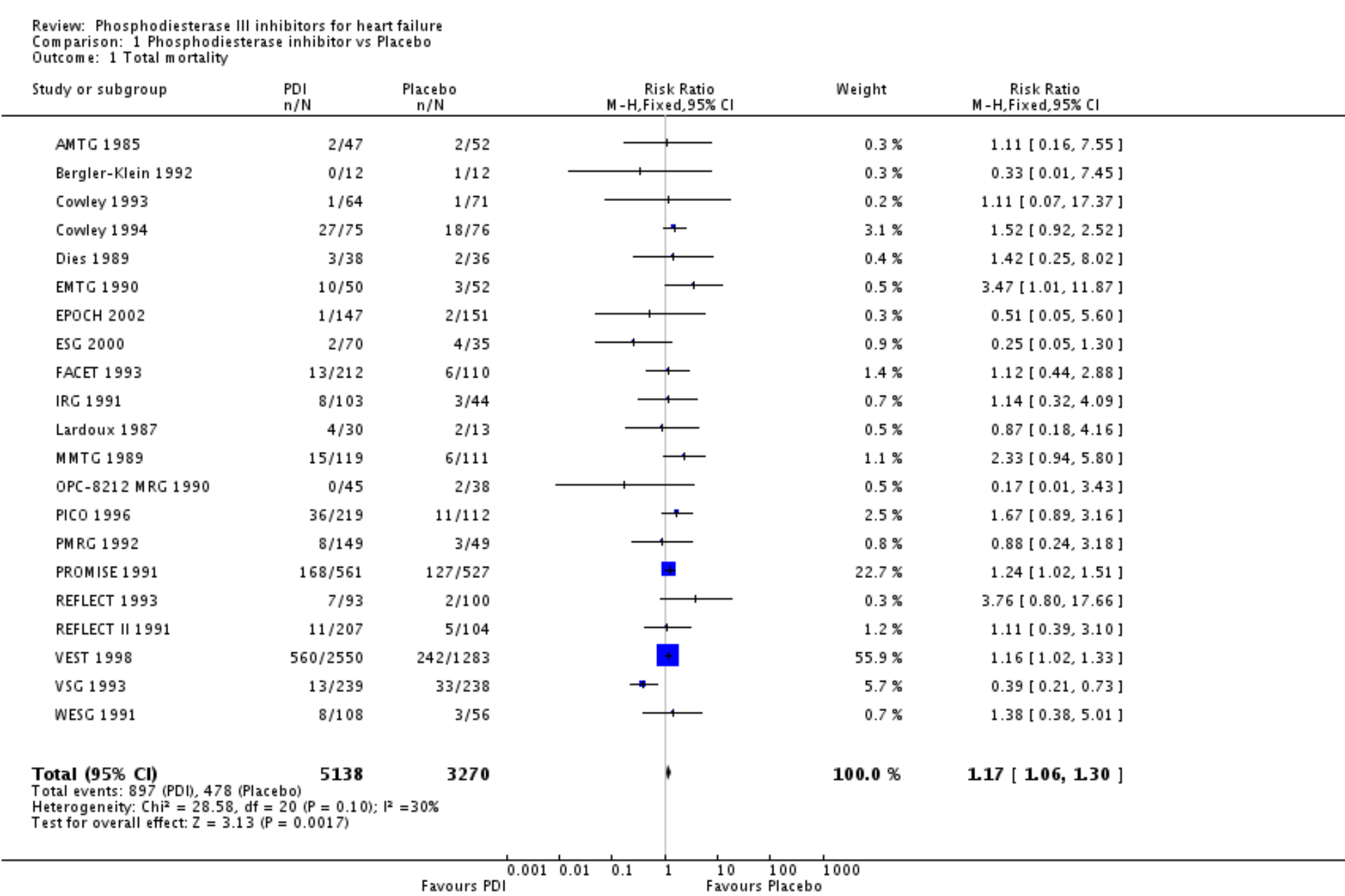


Levosimendan (Calcium Sensitiser)

- ✓ No significant increase in myocardial O_2 consumption
- ✓ No increase in intracellular Ca^{2+} levels
- ✓ Mechanism is not dependent on cAMP or β-receptors

- **Increases contractility by:**
  - **Increasing sensitivity of myofilaments to Ca^{2+}**
  - **Increasing *number & duration* of cross-bridge attachments**

Varró and Papp. *J Cardiovasc Pharmacol*.

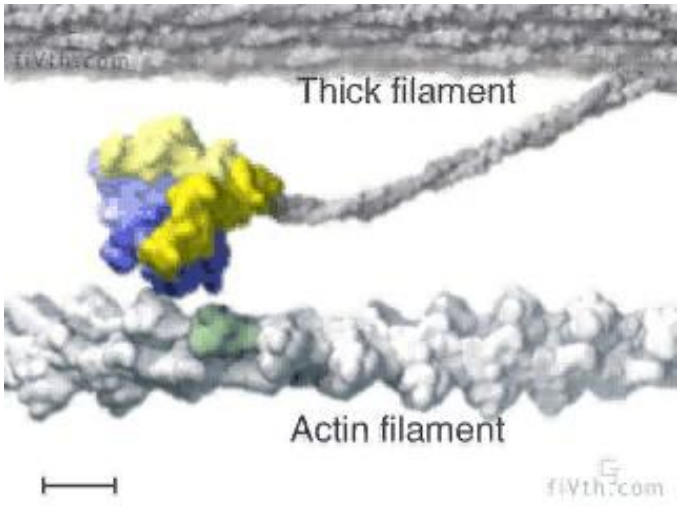


Amsallem E, et al. Phosphodiesterase III inhibitors for heart failure.

***Cochrane Database of Systematic Reviews* 2005**

Omecamtiv Mecarbil: A Cardiac Myosin Activator
Preclinical Profile

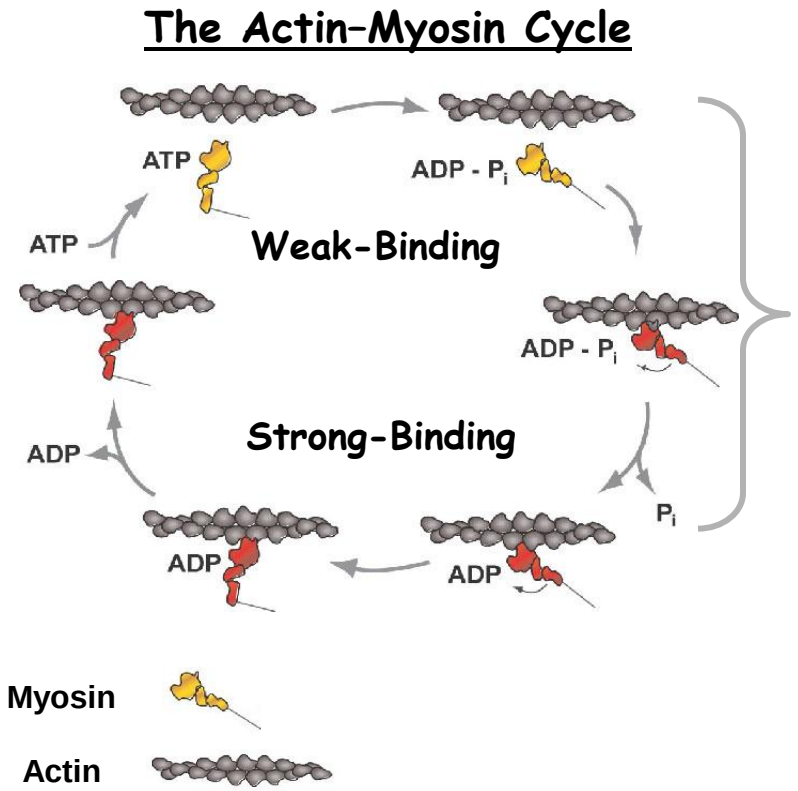
- Selective activator of cardiac myosin
- Prolongs duration of systole by
  - Increasing entry rate of myosin into force-producing state
  - Thus increasing overall number of active cross-bridges
- Increases stroke volume
- No change in dP/dt_{max}
- No increase in MVO_2



Vale and Milligan
Science Apr 2000

How Does a Cardiac Myosin Activator Work?

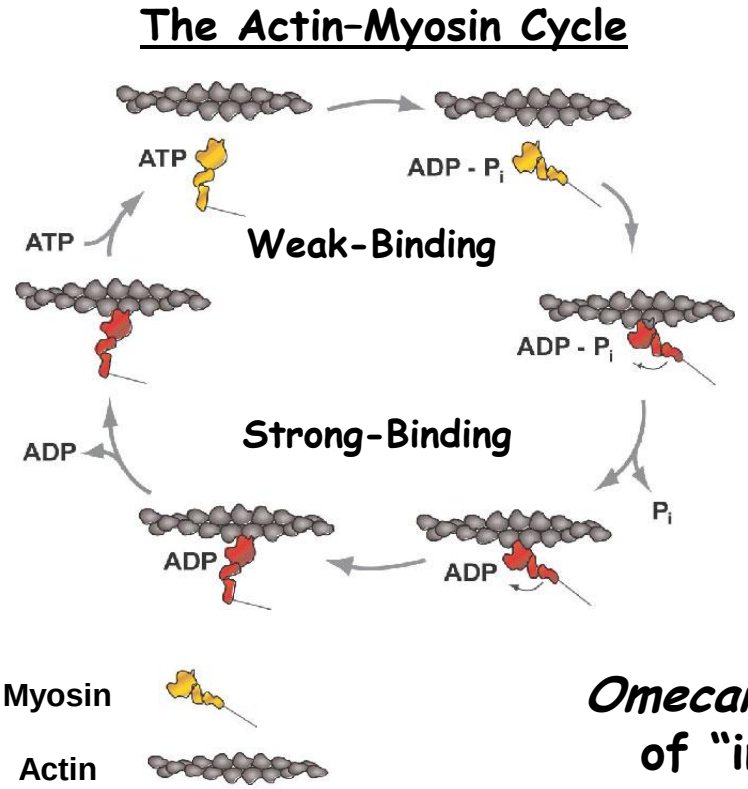
The Chemical and Mechanical Cycles are Linked



Weak Binding
to Strong Binding
Transition

How Does a Cardiac Myosin Activator Work?

The Chemical and Mechanical Cycles are Linked



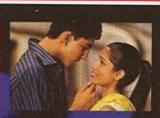
Omecamtiv mecarbil **increases the transition rate from weak to strong binding states**

Omecamtiv mecarbil **thus increases the number of "independent force generators" (myosin heads) interacting with the actin filament**

FEBRUARY 9, 2009

Why U.S. Banks Are Broken—And What to Do

After the Crash: Davos Debates the Road Ahead



The Oscar Race: How *Slumdog* Became Top Dog

TIME

Diabetes.
Heart Disease.
Parkinson's.

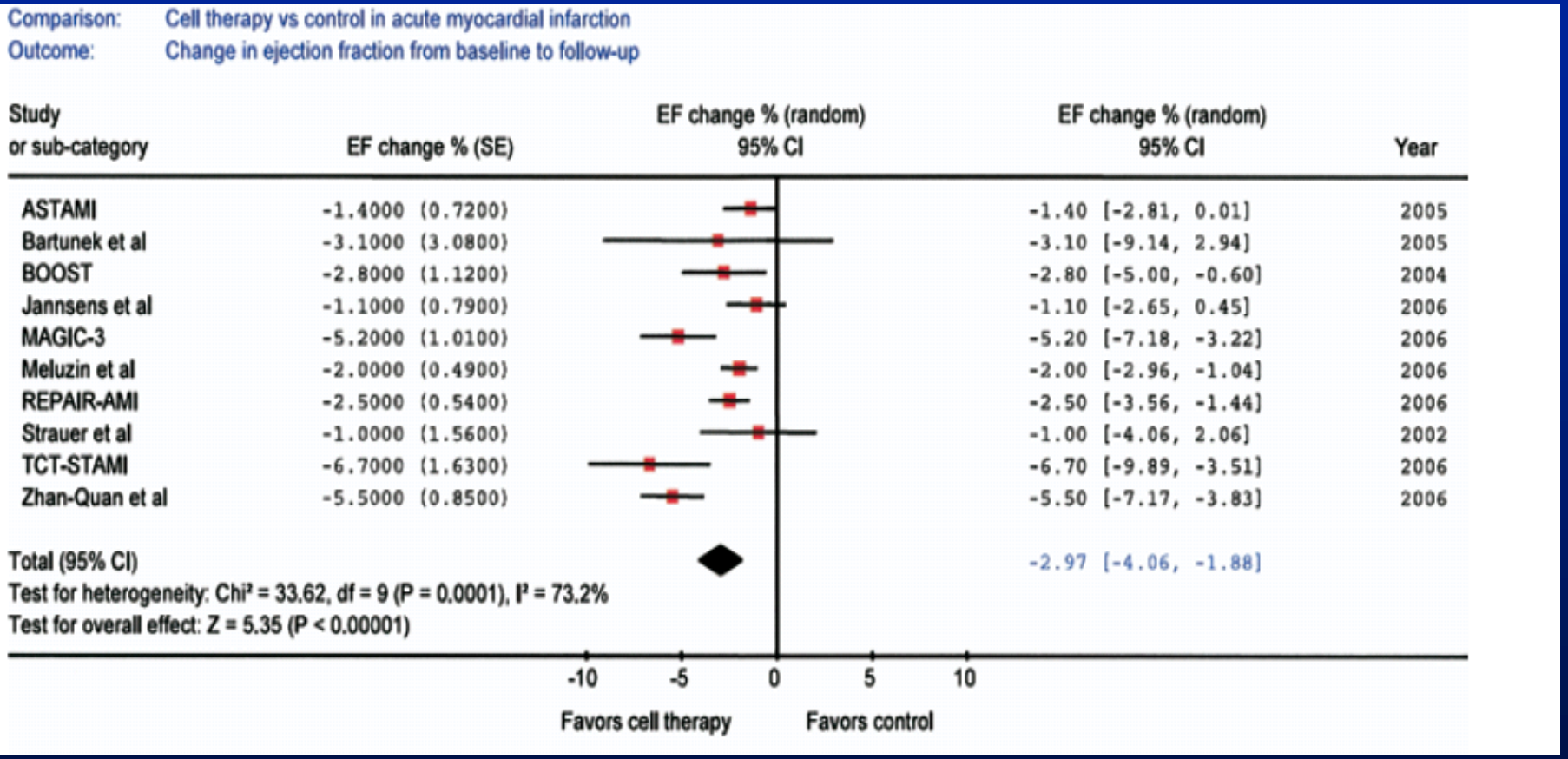
How the Coming Revolution in

STEM CELLS

Could Save Your Life

BY ALICE PARK

www.time.com



Lipinski et al. JACC 2007

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search

List Results | Refine Search | Results by Topic | Results on Map | Search Details

Found 8 studies with search of: "heart failure"AND "cell transplantation" | Open Studies | NIH Industry Other

Include studies that are not seeking new volunteers.

Rank	Status	Study
1	Recruiting	Combined CABG and Stem-Cell Transplantation for Heart Failure Conditions: Heart Failure; Myocardial Infarction; Coronary Artery Disease Interventions: Procedure: Coronary bypass operation; Procedure: Bone marrow aspiration (crista iliaca); Biological: Intramyocardial mesenchymal stem c Biological: Intramyocardial injection of autologous serum
2	Recruiting	Safety and Efficacy Study of Stem Cell Transplantation to Treat Dilated Cardiomyopathy Condition: Dilated Cardiomyopathy Interventions: Biological: CD34+ autologous stem cell transplantation; Drug: Bone Marrow Stimulation
3	Recruiting	The Transendocardial Autologous Cells (hMSC or hBMC) in Ischemic Heart Failure Trial (TAC-HFT) Conditions: Stem Cell Transplantation; Ventricular Dysfunction, Left Interventions: Biological: Autologous human mesenchymal cells (hMSCs); Biological: Autologous human bone marrow cells (hBMCs); Biological: Placeb
4	Recruiting	Progenitor Cell Therapy in Dilative Cardiomyopathy Conditions: Heart Failure, Congestive; Cardiomyopathy, Dilated; Stem Cell Transplantation Intervention: Procedure: intracoronary infusion of BMC
5	Recruiting	Bypass Surgery and CD133 Marrow Cell Injection for Treatment of Ischemic Heart Failure Conditions: Coronary Artery Disease With Need for Bypass Surgery; Myocardial Ischemia, Angina Pectoris; Congestive Heart Failure; Previous Myoc Intervention: Procedure: Intramyocardial injection of autologous CD133+ marrow cells
6	Recruiting	Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) Conditions: Stem Cell Transplantation; Ventricular Dysfunction, Left Interventions: Genetic: Lower dose mesenchymal stem cell (MSC) injection; Genetic: Placebo; Genetic: Higher dose MSC injection

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary

Search

List Results | Refine Search | Results by Topic | Results on Map | Search Details

Found 10 studies with search of: "heart failure" AND "cell transplantation" | Open Studies

Include studies that are not seeking new volunteers.

Display Options

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4	Recruiting	AutoLogous Human CArdiac-Derived Stem Cell to Treat Ischemic cArdiomyopathy (ALCADIA) Conditions: Congestive Heart Failure; Ischemic Cardiomyopathy; Ventricular Dysfunction Intervention: Biological: Autologous hCSC intramyocardial injection
5	Recruiting	The Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis Pilot Study (The POSEIDON-Pilot Study) Condition: Stem Cell Transplantation Interventions: Biological: Auto-hMSCs; Biological: Allo-hMSCs
6	Recruiting	Bypass Surgery and CD133 Marrow Cell Injection for Treatment of Ischemic Heart Failure Conditions: Coronary Artery Disease With Need for Bypass Surgery; Myocardial Ischemia, Angina Pectoris; Congestive Heart Failure; Previous Myocardial Infarction Intervention: Procedure: Intramyocardial injection of autologous CD133+ marrow cells
7	Recruiting	Cell Therapy in Myocardial Infarction Condition: Acute Myocardial Infarction Interventions: Procedure: Catheter based Stem cells delivery; Other: Autologous Bone Marrow Mononuclear Cells Transplantation

Celltransplantation

- Dose not clear
- Mode of administration not clear
- Target organ reception (homing) not clear
- Progenitor/stem cells function worse in CHF
- Longterm safety not clear
- No solution in sight for clinical applications

Examples of areas of ongoing trials

- Treatment of Depression
- Immunomodulation
- Devices
  - CRT
  - Rate control
  - Home monitoring

Conclusions

- Patients with heart failure are at high risk and they are generally undertreated
- Blockade of the neuroendocrine activation is the best treatment strategy and should be included in the background therapy in chronic heart failure
- New treatment options are needed
- Many ongoing trials
- The next 20 years looks as exciting as the previous years for further improvement