ICPOEP 2016

Cardiovascular and metabolic diseases research

Disclosure

I’m a full-time employee of SERVIER

Servier introduction

- 1954: Dr Jacques Servier started activites with 9 people
- 1955: first 2 drugs launched (1 anti-hypertensive and 1 anti-diabetic)
- 1960: first research center
- 2001: International Center for Therapeutic Research in China
- 2014: Servier International Research Foundation

Servier guiding principles

The most obvious principle is the discovery of innovative drugs to enable physicians to bring relief to patients, to treat and cure them.

Just as importantly, we want our research to contribute to the progress of medicine. Research to us is at least as vital as being an industry.

Our third principle is all the more crucial as it is too often overlooked: it is that every person working for us should find fulfillment through and in what he or she does.

60 years of research in Cardiovascular & Diabetes

- Introduction
- Key programs in cardiovascular diseases
- Key programs in Metabolism
- Few perspectives for the future

60 years of research in Cardiovascular & Diabetes

- **Introduction**
- Key programs in cardiovascular diseases
- Key programs in Metabolism
- Few perspectives for the future

Cardiovascular diseases

•CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause

•An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke

WHO: Cardiovascular diseases (CVDs),Fact sheet
Reviewed September 2016

14 November 1891

WDD : World Diabetes Day

- One of the first diseases described in an Egyptian manuscript 1500 BC
- 1910: discovery of Insulin
- 1921: extraction of Insulin from dog's pancreas by Banting and Best
- 1923: Nobel Prize for Banting and Macleod
  Starting of commercialisation of Insulin by Eli Lilly

Charles Best and Frederick Banting in 1924

Diabetes epidemy…

*193 million people with diabetes are undiagnosed

60 years of research in Cardiovascular & Diabetes

- Introduction
- **Cardiovascular key programs**
- Metabolism Key programs
- Few perspectives for the future

Cardiovascular key programs

Continuous innovation
in the understanding and management
of cardiovascular disease

Cardiovascular drugs development

- Last 15 years: **> 200 clinical studies** from phase 1 to morbi-mortality trials

- **9 morbi-mortality trials**

• PROGRESS (perindopril + indapamide)	n= 6,000
• EUROPA (perindopril)	n = 12,000
• PERFORM (development discontinued)	n= 19,000
• ADVANCE (gliclazide + perindopril + indap)	n= 11,000
• HYVET (indapamide +/-perindopril)	n= 3,800
• BEAUTIFUL (ivabradine)	n = 11,000
• SHIFT (ivabradine)	n= 6,500
• SIGNIFY (ivabradine)	n= 19,100
• ATPCI (trimetazidine - on going)	n= 5,500

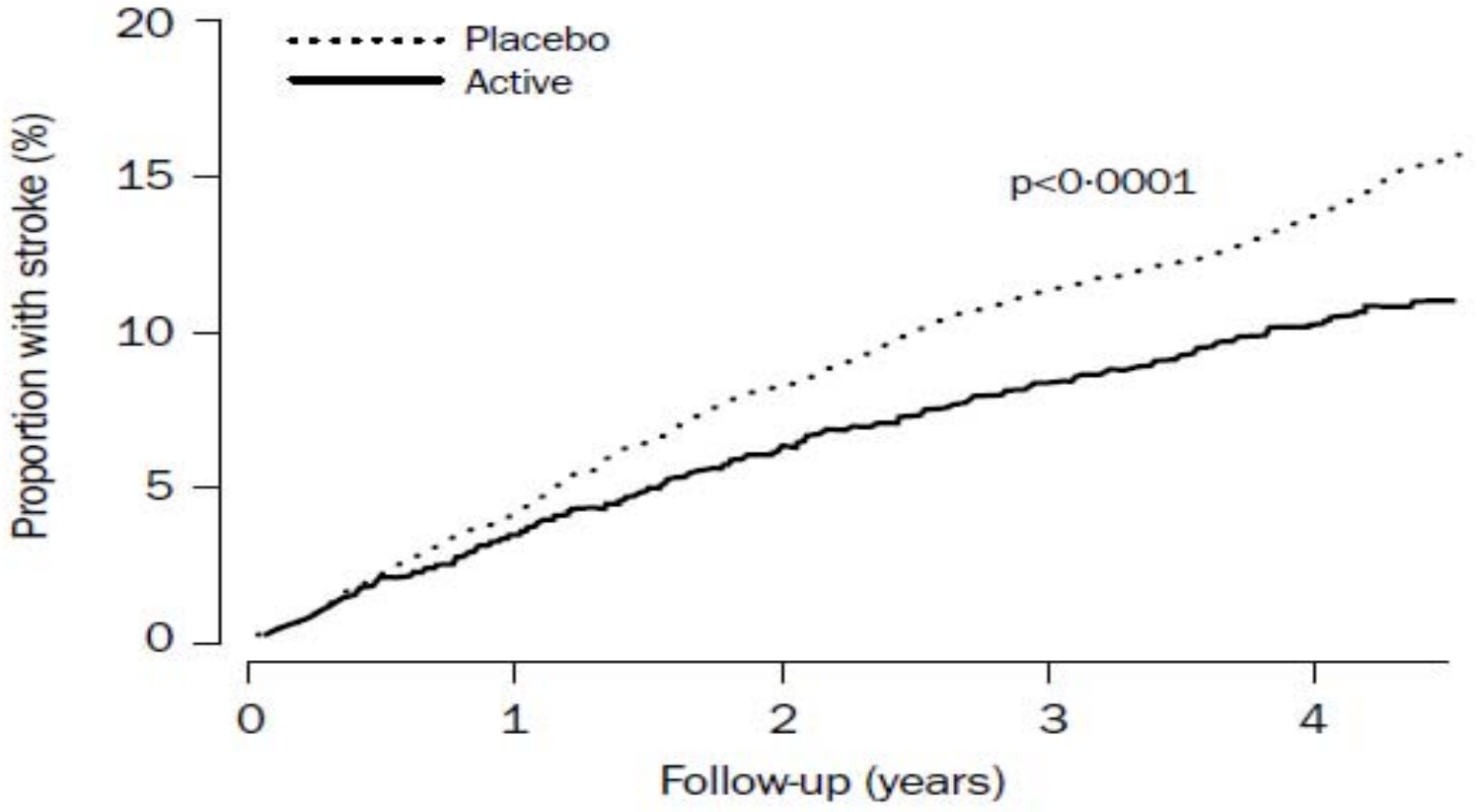
Secondary prevention of stroke

PROGRESS
PERINDOPRIL PROTECTION AGAINST RECURRENT STROKE STUDY

Double-blind randomized perindopril + indapamide vs placebo

> 6 000 patients with history of stroke or TIA / 172 centers

43 % reduction of stroke



Lancet, 2001 Sept 29; 358 (9287) : 1033-41

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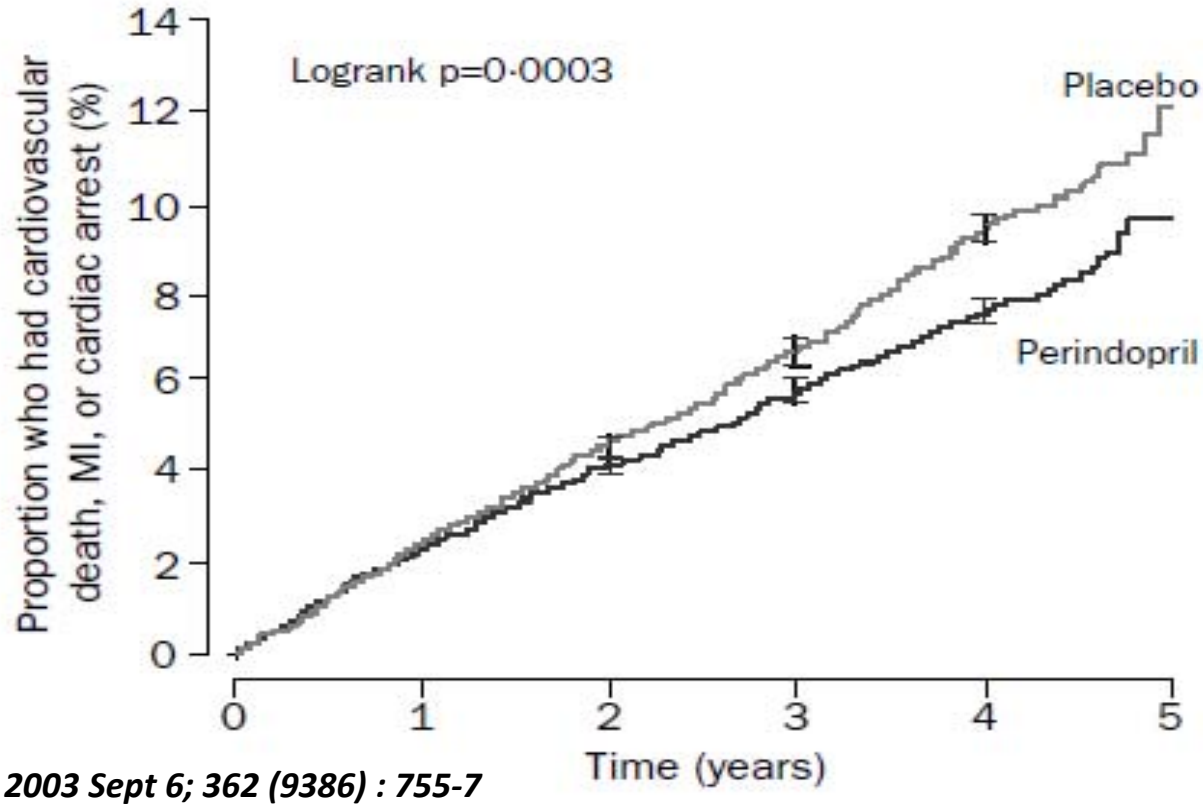
Secondary prevention Stable CAD

EUROPA
EUROPEAN TRIAL ON REDUCTION OF CARDIAC EVENTS WITH PERINDOPRIL IN STABLE CORONARY ARTERY DISEASE

Double-blind randomized perindopril vs placebo on top of recommended therapy
> 12 000 patients / 24 countries

20 % reduction in relative risk on primary endpoint (CV death, MI, cardiac arrest)

Perindopril 8 mg od prevents one CV death, non fatal MI or cardiac arrest among every 50 patients with coronary disease treated for 4 years



Lancet, 2003 Sept 6; 362 (9386) : 755-7

Hypertension in very elderly

HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

3845 very elderly (aged 80 or more) hypertensive patients

11 countries

Double-blind, natrilix SR vs placebo

SERVIER

Hypertension in very elderly

HYVET
HYPERTENSION IN THE VERY ELDERLY TRIAL

At 2 years:

MBP decr

Natrilix SF

- **21% for**
- **39% for**
- **30% for**
- **64% for**
- **34% for**

failure (p<

This means that one death would be avoided for every 40 patients treated with indapamide SR ±perindopril therapy for 2 years.

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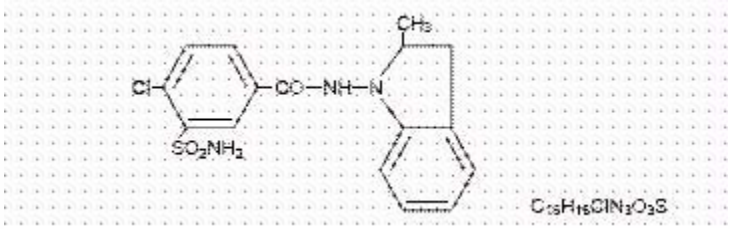
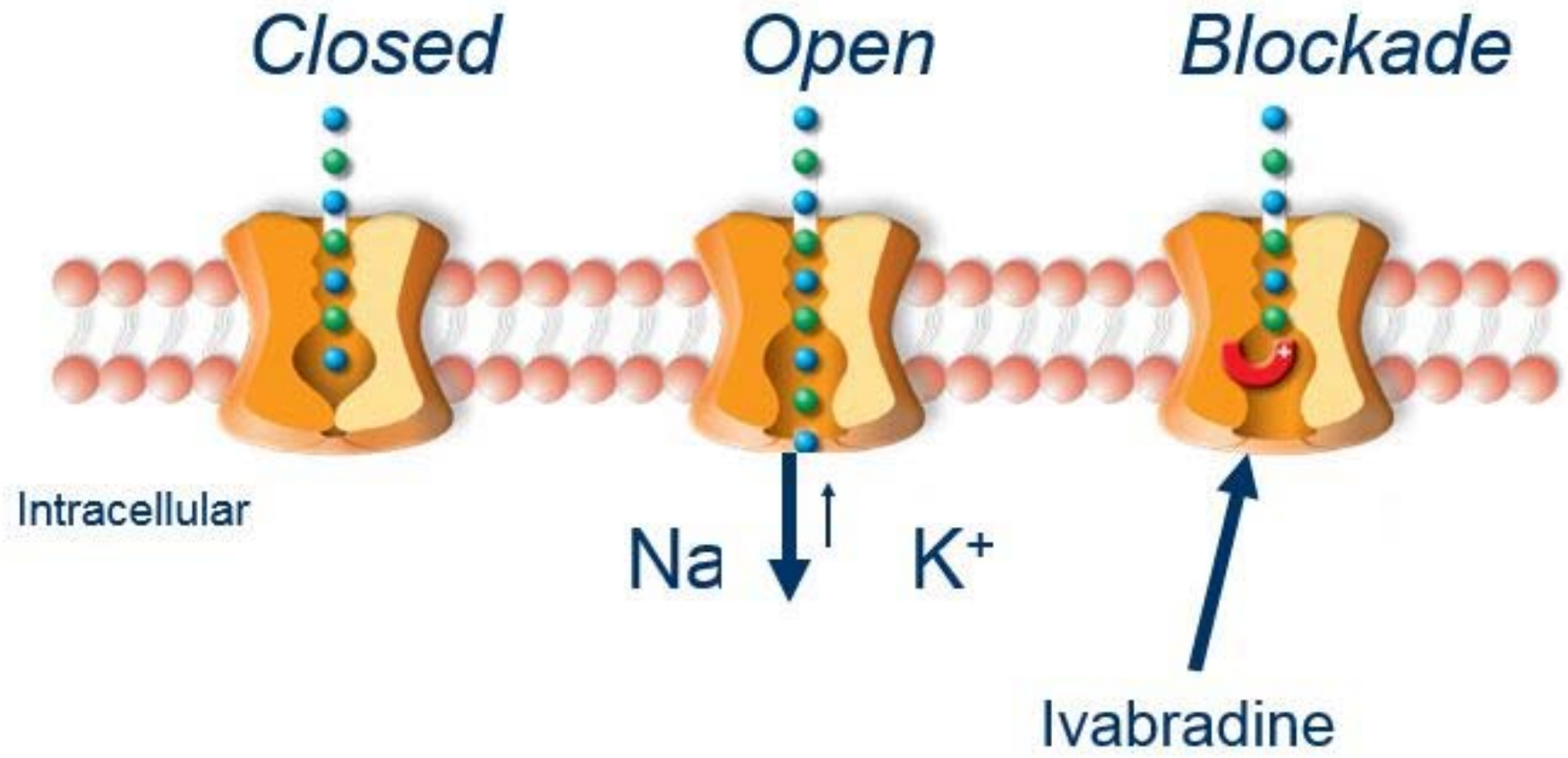
Indapamide

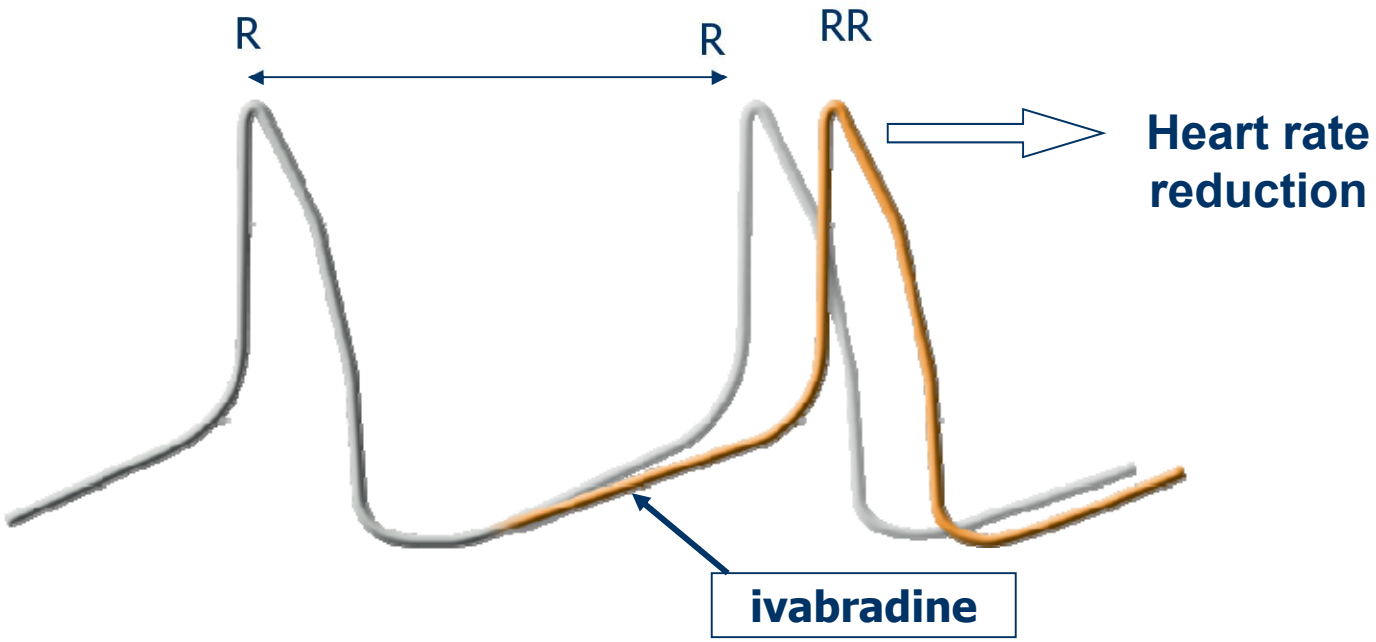
Indapamide is an oral antihypertensive/diuretic. Its molecule contains both a polar sulfamoyl chlorobenzamide moiety and a lipid-soluble methylindoline moiety. It differs chemically from the thiazides in that it does not possess the thiazide ring system and contains only one sulfonamide group. The chemical name of Indapamide is 4-Chloro- N-(2-methyl-1-indolinyl)-3-Sulfamoylbenzamide, and its molecular weight is 365.84. The compound is a weak acid, pKa=8.8, and is soluble in aqueous solutions of strong bases. It is a white to yellow-white crystalline (tetragonal) powder, and has the following structural formula:



Indapamide is the first of a new class of antihypertensive/diuretics, **the indolines.**



Ivabradine



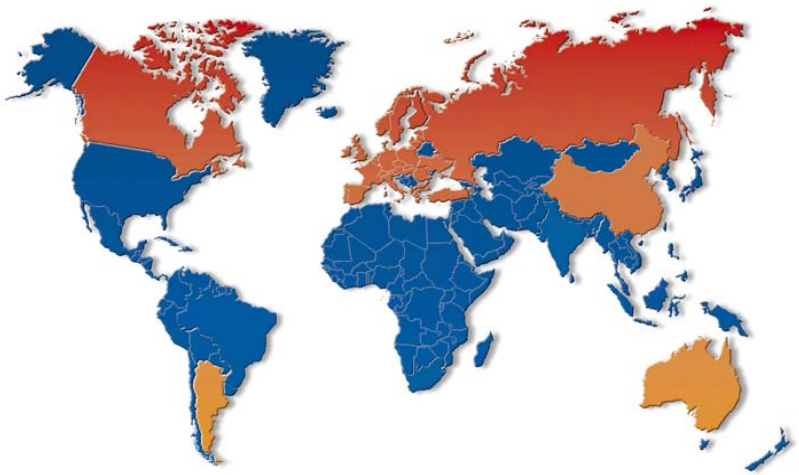
Ivabradine slows heart rate by decreasing the velocity of diastolic depolarization (ie, by reducing the 'steepness' of the I_f current slope of diastolic depolarization) in sinus node cells

→ **pure HR reduction without vasodilating or negative inotropic effects**

Bucchi A, et al. *J Gen Physiol.* 2002;120:1-15.

Cardiovascular prevention

MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction



- Beautiful was the first trial assessing the cardiovascular prevention benefits of a pure heart rate lowering agent beyond current preventive treatment
- Double-blind randomized, 10,917 patients with stable CAD in 33 countries

BEAUTIFUL

Inclusion criteria

- Male or female
- Nondiabetic ≥55 years, diabetic ≥18 years
- Documented coronary artery disease
- Sinus rhythm and resting heart rate ≥60 bpm
- Documented left ventricular systolic dysfunction (<40%)
- Clinically stable for 3 months with regards to angina or heart failure symptoms or both
- Therapeutically stable for 1 month (appropriate or stable doses of conventional medications)

K. Fox et al. *Am Heart J.* 2006;152:860-866.

Cardiovascular prevention

Ivabradine reduces all coronary events in coronary patients with HR ≥70 bpm

Predefined end point	Hazard ratio	Risk reduction	*P* value
Fatal MI	0.69	31%	0.114
Fatal and nonfatal MI	0.64	36%	0.001
Fatal and nonfatal MI or unstable angina	0.78	22%	0.023
Fatal and nonfatal MI, unstable angina, or revascularization	0.77	23%	0.009
Coronary revascularization	0.70	30%	0.016

Fox K et al. *Lancet.* 2008;372:807-816.

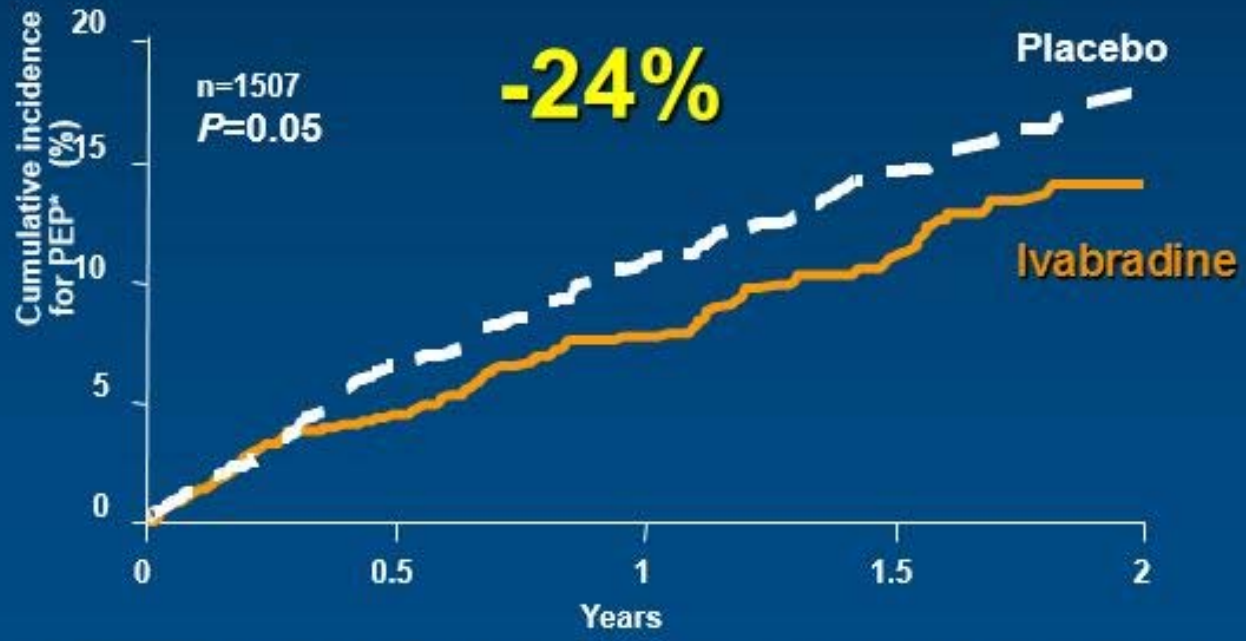
Cardiovascular prevention

BEAUTIFUL

Ivabradine reduces primary end point in angina patients

New results in angina patients

Primary end point(PEP) : CV death + hospitalization for HF or MI

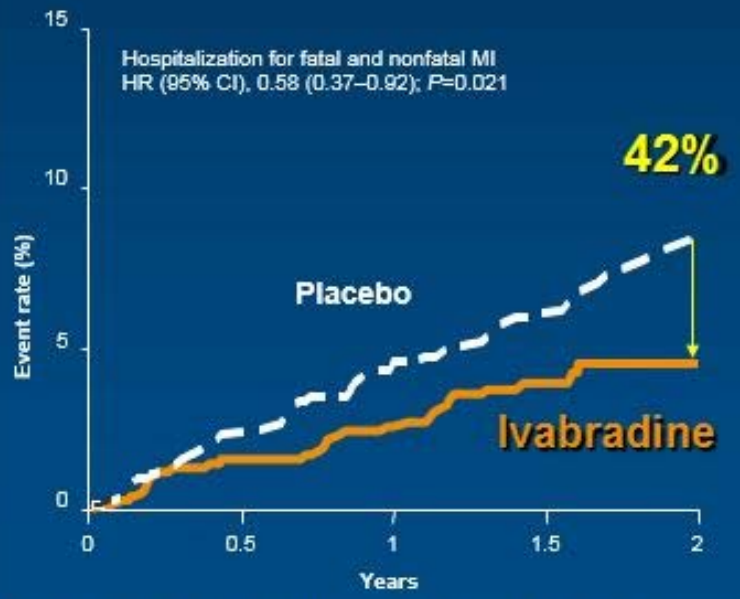


Fox K, Ford I, et al; BEAUTIFUL Investigators. Effect of ivabradine on cardiovascular outcomes in patients with stable coronary artery diseaseand left-ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur heart Jour On line.

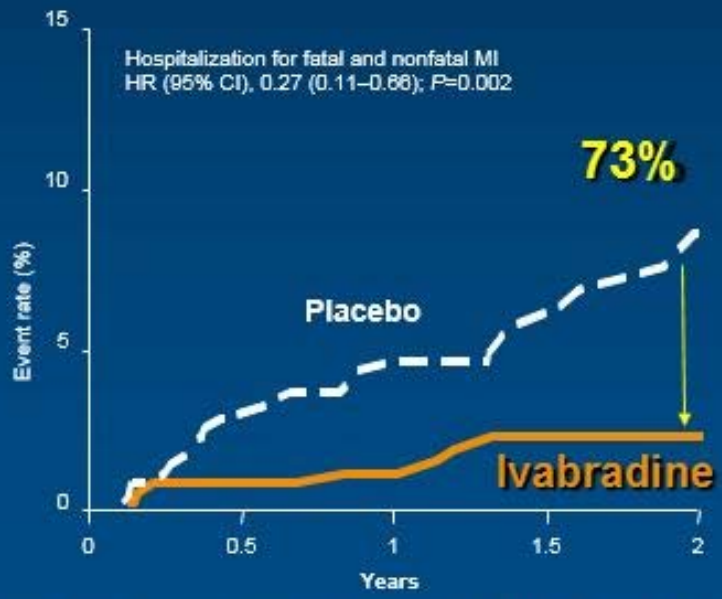
Ivabradine reduces myocardial infarction in patients with angina

New results in angina patients

All patients with angina



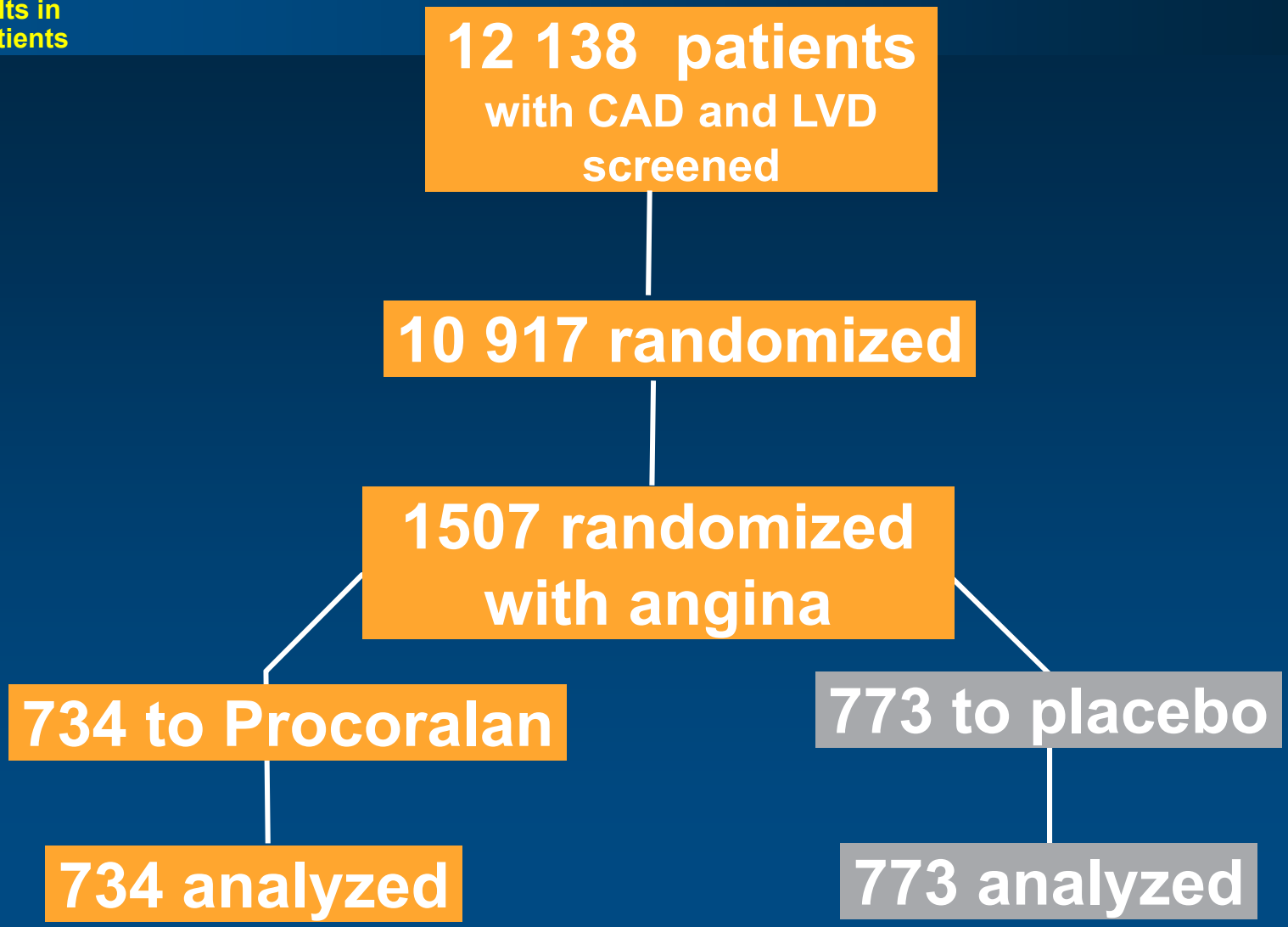
Patients with angina and heart rate ≥70 bpm



Fox K, Ford I, et al; BEAUTIFUL Investigators. Effect of ivabradine on cardiovascular outcomes in patients with stable coronary artery diseaseand left-ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur heart Jour On line.

Design and methodology

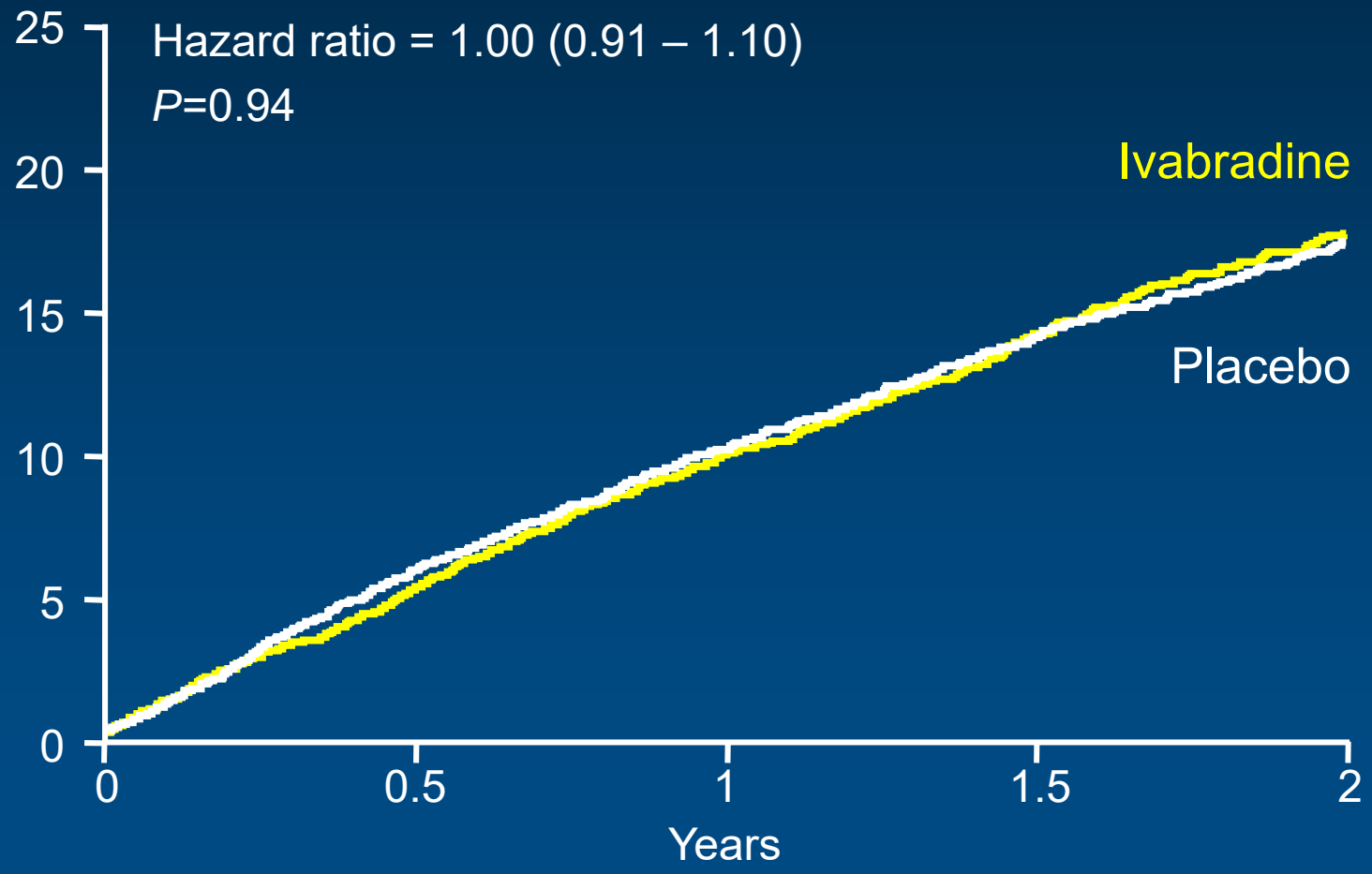
New results in angina patients



Fox K, Ford I, et al; BEAUTIFUL Investigators. Effect of ivabradine on cardiovascular outcomes in patients with stable coronary artery diseaseand left-ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Data on file.

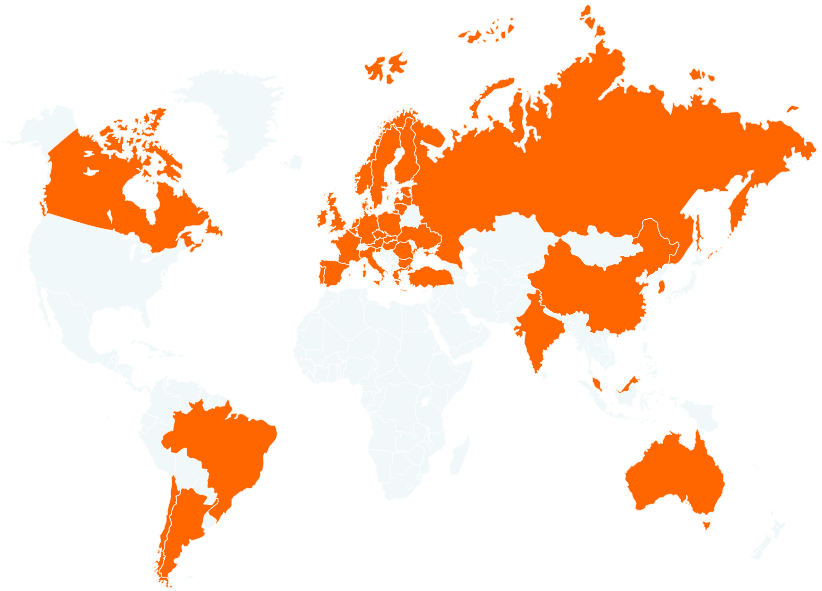
Effect of ivabradine on primary endpoint (Overall population)

% with primary composite end point of CV death, hospitalization for acute MI, or for new-onset or worsening heart failure



Fox K et al. *Lancet.* 2008;372:807-816.

Cardiovascular prevention



6505 patients

37 countries

677 centres

To evaluate whether the If 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 in sinus rhythm
4. Best recommended therapy

Ca

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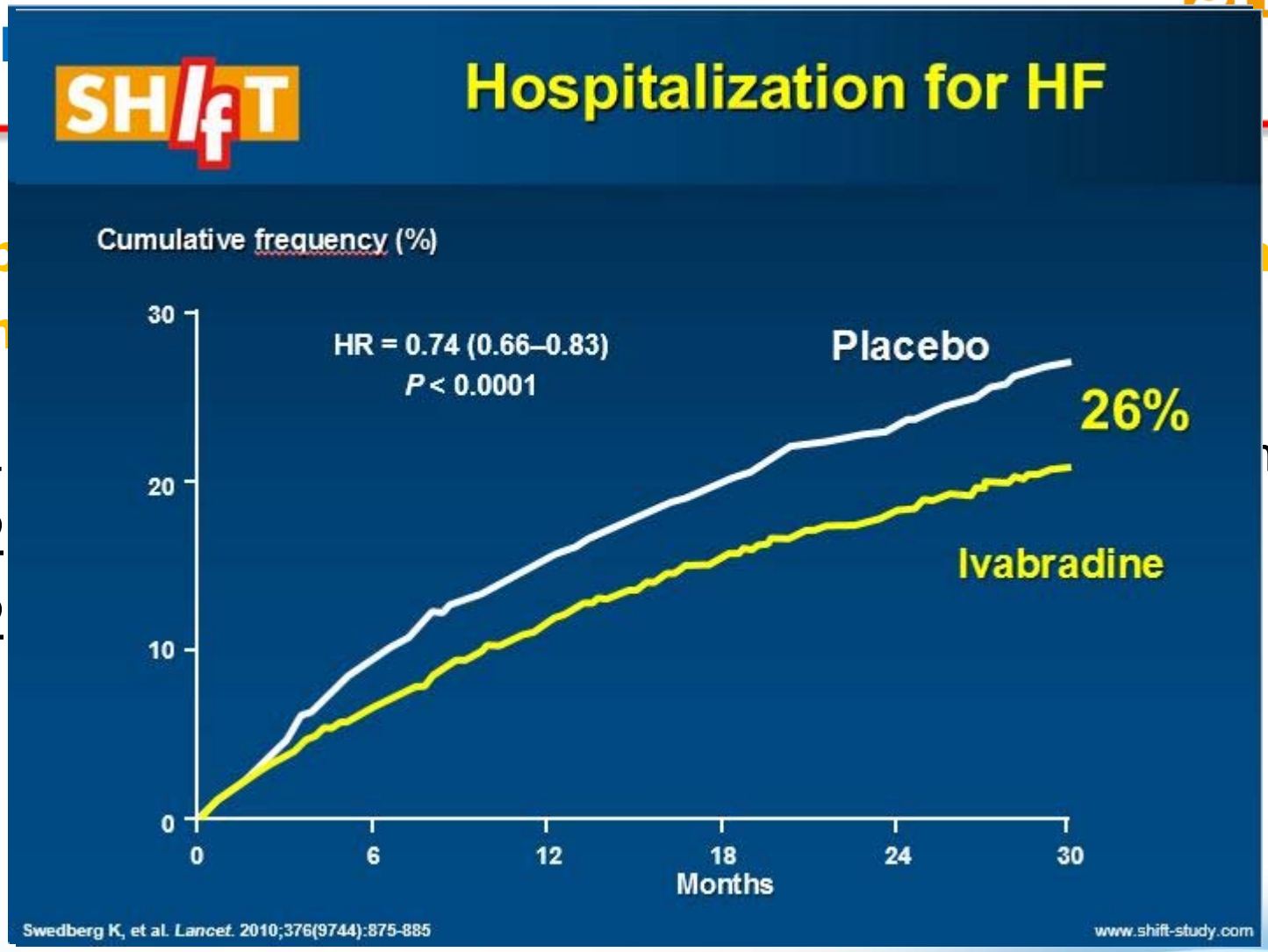

Cardiovascular prevention

19 102 STABLE CAD PATIENTS – 51 COUNTRIES – 1 139 CENTERS

SIGNIFY is assessing whether heart rate reduction using ivabradine improves cardiovascular mortality and morbidity in patients with stable CAD, without clinical heart failure

Conclusion

- Lowering heart rate with ivabradine in CAD patients without clinical heart failure does not reduce the risk of CV death or nonfatal MI
- In the subgroup of patients with angina (CCS class ≥II), there appeared to be an increase in CV death or nonfatal MI
- In the same subgroup there appeared to be improvement in symptoms and need for elective coronary revascularization

Ivabradine indications

Symptomatic treatment of **chronic stable angina pectoris** in coronary artery disease patients with normal sinus rhythm. PROCORALAN is indicated :

- in patients unable to tolerate or with a contra-indication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > *60 bpm*.

PROCORALAN is indicated in **chronic heart failure** NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

Trimetazidine

It has been recently demonstrated that trimetazidine, known for years to be an effective antianginal agent, shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase.

By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation and leading to adenosine triphosphate production with lesser oxygen consumption.

Eur Heart J Supplements 2001; 3 (Suppl O): O12–O15)

Trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.

Cardiovascular prevention

ATPpci

The effic**A**cy and safety of **T**rimetazidine in **P**atients with angina pectoris having been treated by percutaneous **C**oronary **I**ntervention. ATPCI study An international, multicentre, randomised, double-blind, placebo-controlled study in patients treated for 2 to 4 years.

Study outcomes

- Required nb of events: 1363, N=5800
- Estimated mean follow-up: 36 months

Population

•<85 years old patients,

•with a single or multivessel CAD and having undergone PCI treating at least one stenosis, where the PCI was indicated because of stable angina or in the context of an ACS excluding STEMI

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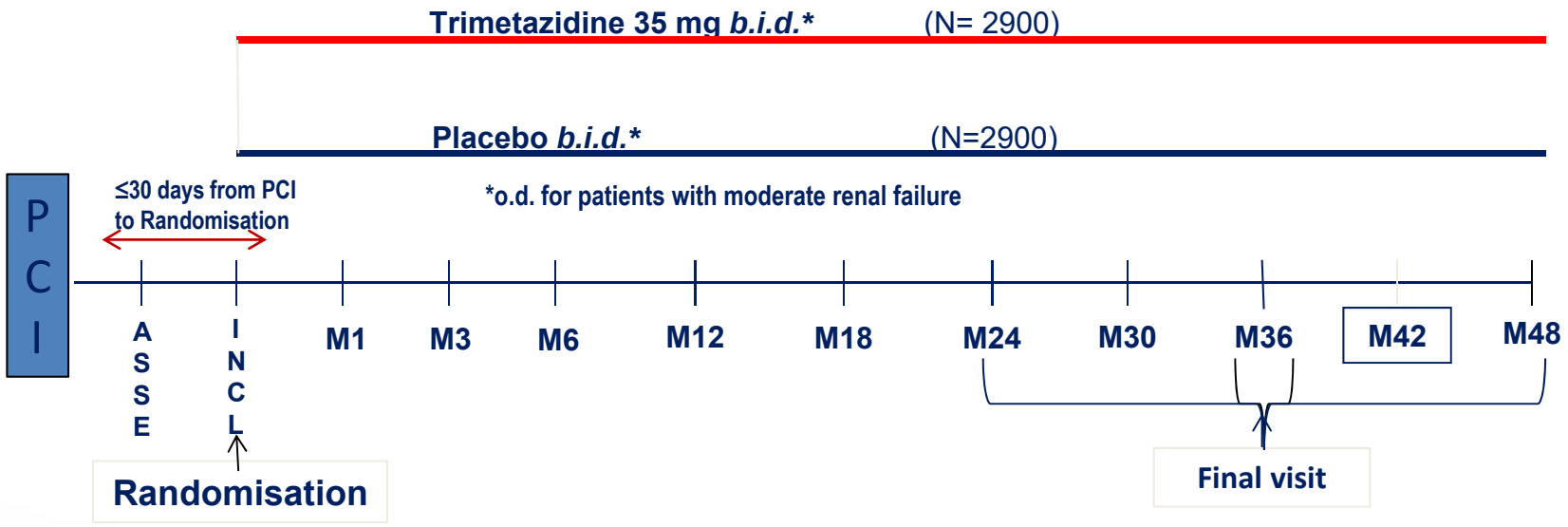
Cardiovascular prevention

ATPpci

27 countries, 384 centres, 5 800 patients



Primary end point = composite : *cardiac death, hospitalization for a cardiac event, recurrent or persistent angina leading to adding, switching or increasing the dose of one of the evidence-based antianginal therapy, recurrent or persistent angina leading to performing a coronary angiography. Adjudication committee.*

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60 years of research in Cardiovascular & Diabetes

- Introduction
- Key programs in cardiovascular diseases
- **Key programs in Metabolism**
- Few perspectives for the future

Diamicron (Gliclazide) 40 years of experience

1st scored modified release tablet in diabetology

Original licensed Process: hydrophilic matrix

Prevention CV & diabetes complications

A factorial randomised trial of blood pressure lowering and intensive glucose control for the prevention of vascular disease among 11 140 high risk patients with type 2 diabetes

213 collaborating centers in 20 countries from North America, Australasia and Europe

Perindopril + Indapamide vs placebo

- 18 % reduction in CV mortality,
- 21 % reduction in renal events

Intensive Glucose control (gliclazide-based) resulted in

- 21 % reduction in new or worsening nephropathy
- 65% reduction in end-stage kidney disease

ADVANCE

ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION

ADVANCE-ON

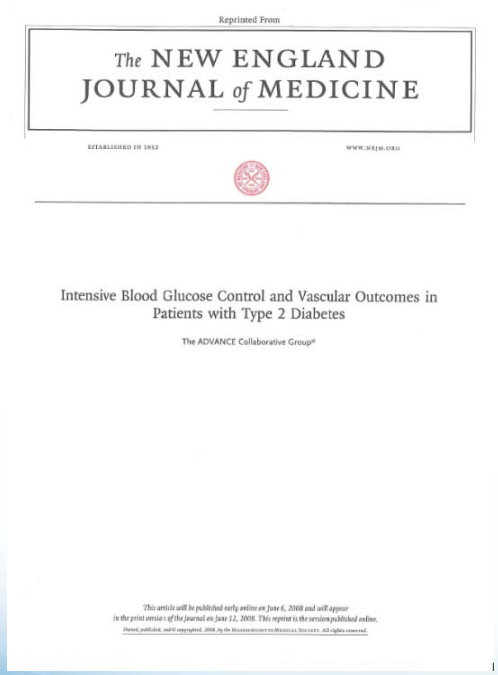
ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION POST-TRIAL OBSERVATIONAL STUDY

11 140 patients from 20 countries

A long term commitment in clinical research

5 years of intensive treatment (Diamicron MR 60)

5-year non interventional follow up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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 WWW.NEJM.ORG

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group*

This article will be published early online on June 6, 2008 and will appear in the print version of the Journal on June 12, 2008. This reprint is the version published online.

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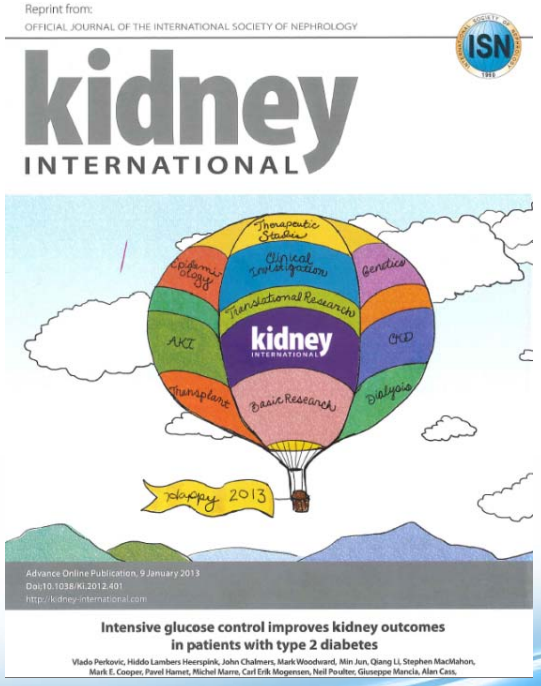

Reprint from:

OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

kidney INTERNATIONAL

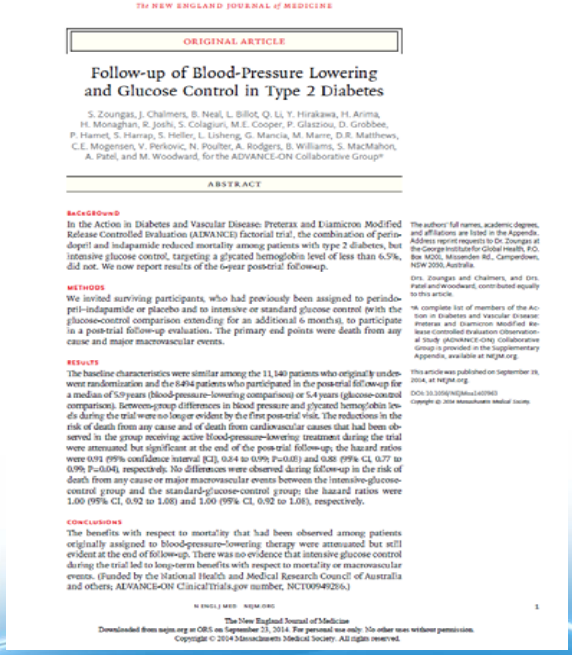
Advance Online Publication, 9 January 2013

Doi:10.1038/ki.2012.401

http://kidney-international.com

Intensive glucose control improves kidney outcomes in patients with type 2 diabetes

Vlado Perkovic, Hiddo Lambers Heerspink, John Chalmers, Mark Woodward, Min Jun, Qiang Li, Stephen MacMahon, Mark E. Cooper, Pavel Hamet, Michel Marre, Carl Erik Mogensen, Neil Poulter, Giuseppe Mancia, Alan Cass,


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

S. Zoungas, J. Chalmers, B. Neal, L. Billot, Q. Li, Y. Hirakawa, H. Arima, H. Monaghan, R. Joshi, S. Colagiuri, M.E. Cooper, P. Glasziou, D. Grobbee, P. Hamet, S. Harrap, S. Heller, L. Lisheng, G. Mancia, M. Marre, D.R. Matthews, C.E. Mogensen, V. Perkovic, N. Poulter, A. Rodgers, B. Williams, S. MacMahon, A. Patel, and M. Woodward, for the ADVANCE-ON Collaborative Group*

ABSTRACT

BACKGROUND

In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) factorial trial, the combination of perindopril and indapamide reduced mortality among patients with type 2 diabetes, but intensive glucose control, targeting a glycated hemoglobin level of less than 6.5%, did not. We now report results of the 6-year post-trial follow-up.

METHODS

We invited surviving participants, who had previously been assigned to perindopril–indapamide or placebo and to intensive or standard glucose control (with the glucose-control comparison extending for an additional 6 months), to participate in a post-trial follow-up evaluation. The primary end points were death from any cause and major macrovascular events.

RESULTS

The baseline characteristics were similar among the 11,140 patients who originally underwent randomization and the 8494 patients who participated in the post-trial follow-up for a median of 5.9 years (blood-pressure–lowering comparison) or 5.4 years (glucose-control comparison). Between-group differences in blood pressure and glycated hemoglobin levels during the trial were no longer evident by the first post-trial visit. The reductions in the risk of death from any cause and of death from cardiovascular causes that had been observed in the group receiving active blood-pressure–lowering treatment during the trial were attenuated but significant at the end of the post-trial follow-up, the hazard ratios were 0.91 (95% confidence interval [CI], 0.84 to 0.99; P=0.03) and 0.88 (95% CI, 0.77 to 0.99; P=0.04), respectively. No differences were observed during follow-up in the risk of death from any cause or major macrovascular events between the intensive-glucose-control group and the standard-glucose-control group; the hazard ratios were 1.00 (95% CI, 0.92 to 1.08) and 1.00 (95% CI, 0.92 to 1.08), respectively.

CONCLUSIONS

The benefits with respect to mortality that had been observed among patients originally assigned to blood-pressure–lowering therapy were attenuated but still evident at the end of follow-up. There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events. (Funded by the National Health and Medical Research Council of Australia and others; ADVANCE-ON ClinicalTrials.gov number, NCT00949286.)

The New England Journal of Medicine

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2008

More than **80** publications

2014

SERVIER

- Intensive glucose control in patients with type 2 DM resulted in:
  - 10% reduction in combined macro and microvascular events
  - 14% reduction in microvascular events
  - 21% reduction in new or worsening nephropathy
  - 65% reduction in end-stage kidney disease
  - No reduction in total mortality

Benefits appeared to be independent of initial HbA1c, and similar in all major subgroups

THE GEORGE INSTITUTE for Global Health

key programs

Cont
in the understanding and
of cardiovascular disease

2001 PROGRESS

2006
950 elderly patients with diastolic HF

perindopril in elderly people with chronic heart failure

ADVANCE

ATPCI

2017
10 000 post PCI patients expected

60 years of research in Cardiovascular & Diabetes

- Introduction
- Key programs in cardiovascular diseases
- Key programs in Metabolism
- **Few perspectives for the future**

Partnership with INTARCIA therapeutics
ITCA 650—Convergence of Technology and Medicine

1 TECHNOLOGY

- Previously-approved delivery system
- Proprietary stabilization formulation

–Maintains stability at temps ≈37°C

–Maintains stability for ≥ 12 months

+

MEDICINE: EXENATIDE 2

- Previously-approved GLP-1 therapeutic with demonstrated:

–Glycemic control

–Weight loss

–Safety

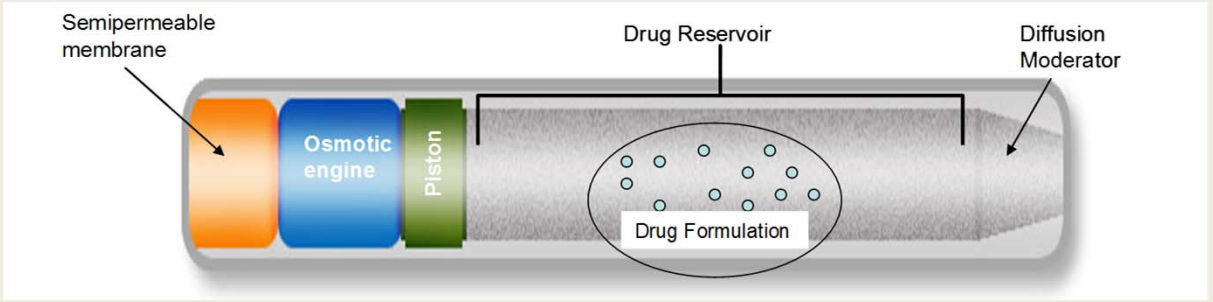
Intarcia

SERVIER

S95002 / ITCA 650

- Exenatide (GLP-1 agonist) mini-pump (for 3 months and 6 months)
- Type 2 diabetes treatment
- Phase III on going
- First Filing US and EU: 2017

Intarcia SERVIER



SERVIER

GLOBAL PHASE III PROGRAM

FREEDOM Global Phase III—Studying 5000+ Patients

Complete — **FREEDOM-1**

- Placebo-controlled trial
- HbA1c ≥7.5% to ≤10%
- 460 patients
- PE: Δ in HbA1c @ 9 mos

Presented at ADA and EASD 2015

Complete — **FREEDOM-1 HBL**

- Open-label substudy
- HbA1c >10% and ≤12%
- 60 patients
- PE: Δ in HbA1c @ 9 mos

Presented at ADA and EASD 2015

Complete — **FREEDOM-2**

- Head-to-head study
- 500+ patients
- HbA1c ≥7.5% to ≤10.5%
- PE: Δ in HbA1c @ 12 mos

Presented at ADA and EASD 2016

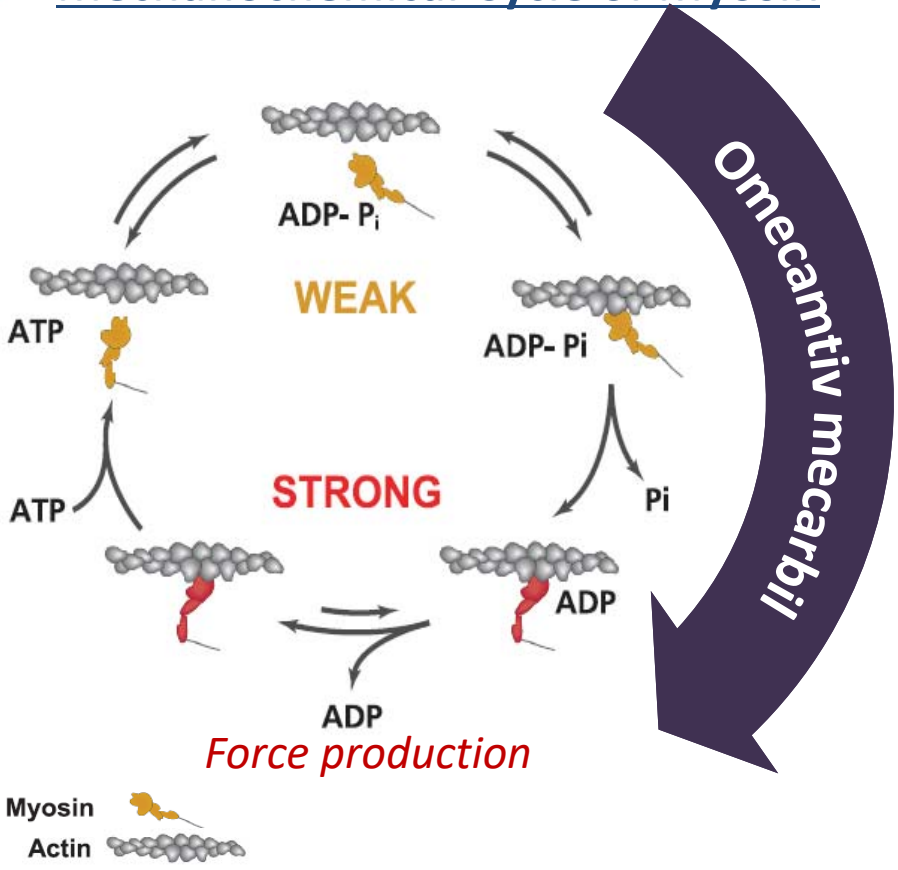
Fully Enrolled — **FREEDOM-CVO**

- Cardiovascular outcomes study
- 4156 patients
- Event-driven, noninferiority trial to support cardiovascular safety

Closeout Procedures Under Way

Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Malik FI, *et al.* *Science* 2011; 331:1439-43.

Omecamtiv mecarbil increases the entry rate of myosin into the tightly-bound, force-producing state with actin

"More hands pulling on the rope"

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

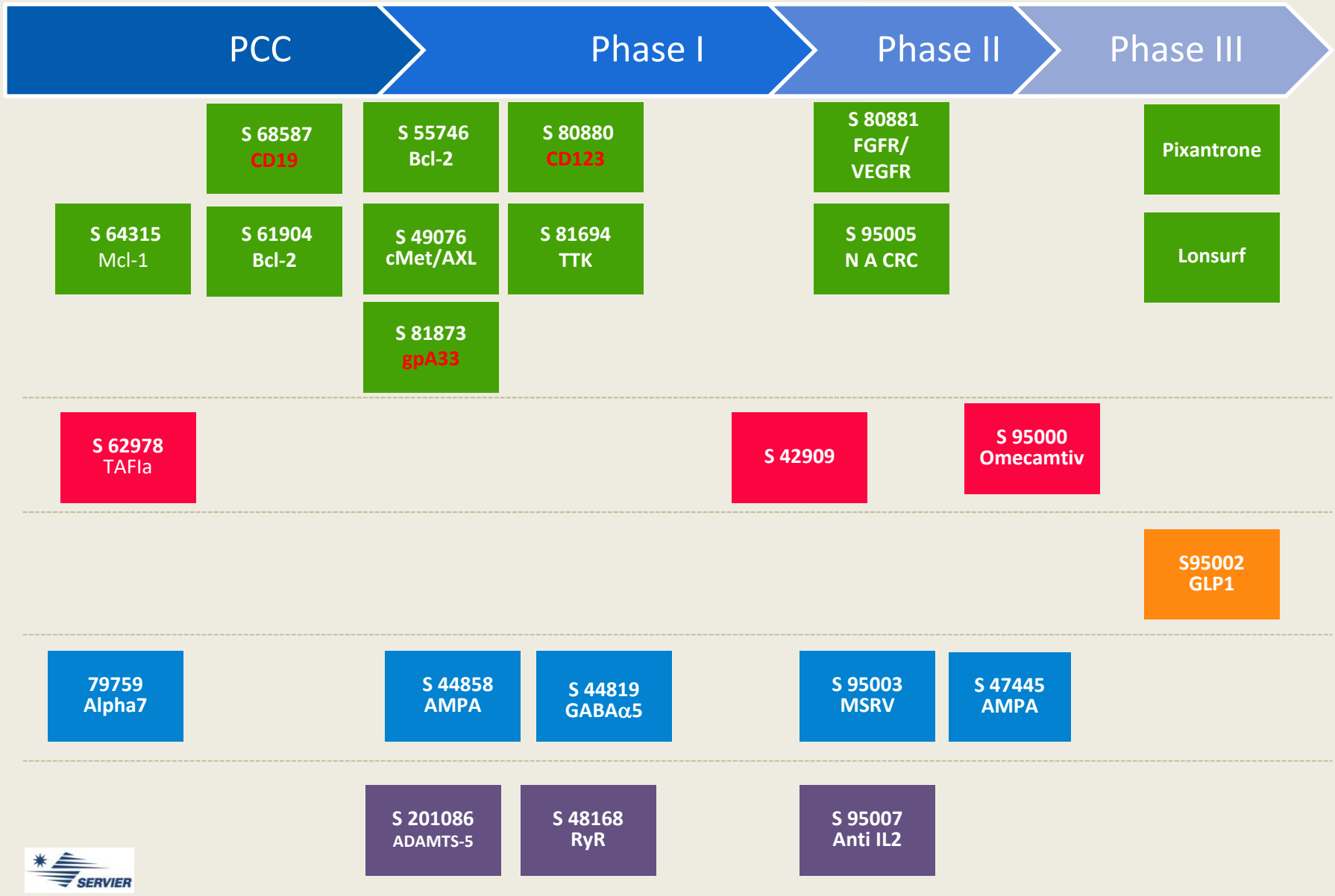
The decision to advance omecamtiv mecarbil into Phase 3 was based on positive results from COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure), a Phase 2 trial evaluating the treatment in patients with chronic heart failure, which were presented as a Late-Breaking Clinical Trial at the American Heart Association (AHA) Scientific Sessions in November 2015

TAFIa inhibitor

Since activated **T**hrombin-**A**ctivatable **F**ibrinolysis **I**nhibitor (TAFIa) was discovered in 1988, considerable interest has developed in the biological role of this enzyme, particularly in hemostasis and thrombotic diseases.

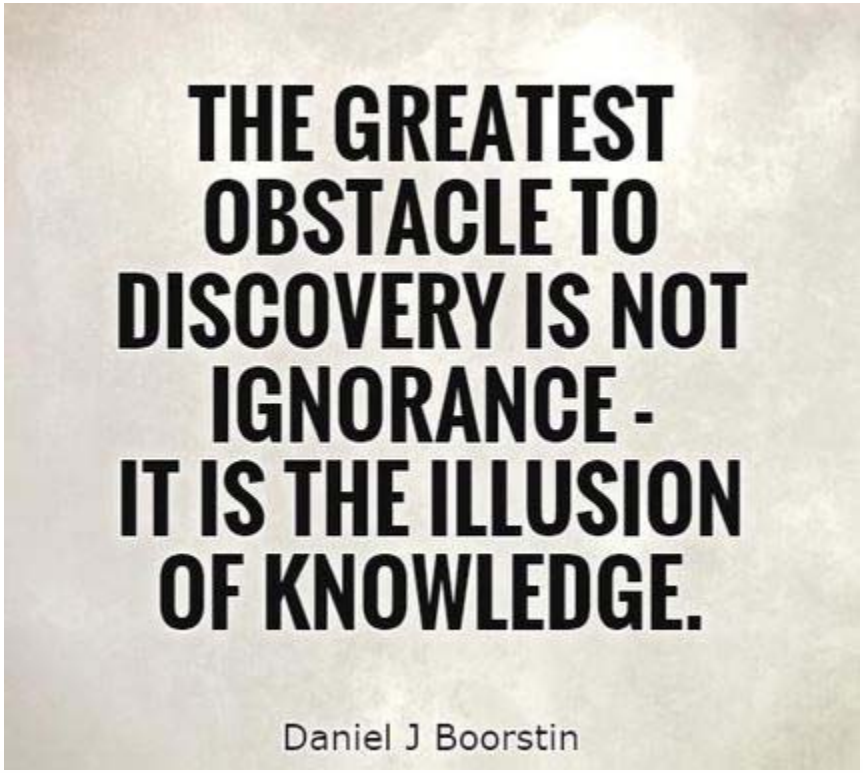
CARDIOLOGY METABOLISM ONCOLOGY NEUROPSYCHIATRY RHEUMATOLOGY

NMEs IN DEVELOPMENT



SERVIER

Thank you!



Our marketed portofolio
in the cardiovascular and metabolism fields