Starting Drugs in Heart Failure: Which ones, how fast in in what order?

Professor Thomas F. Lüscher, MD, FRCP
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www.tomluescher.ch

Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

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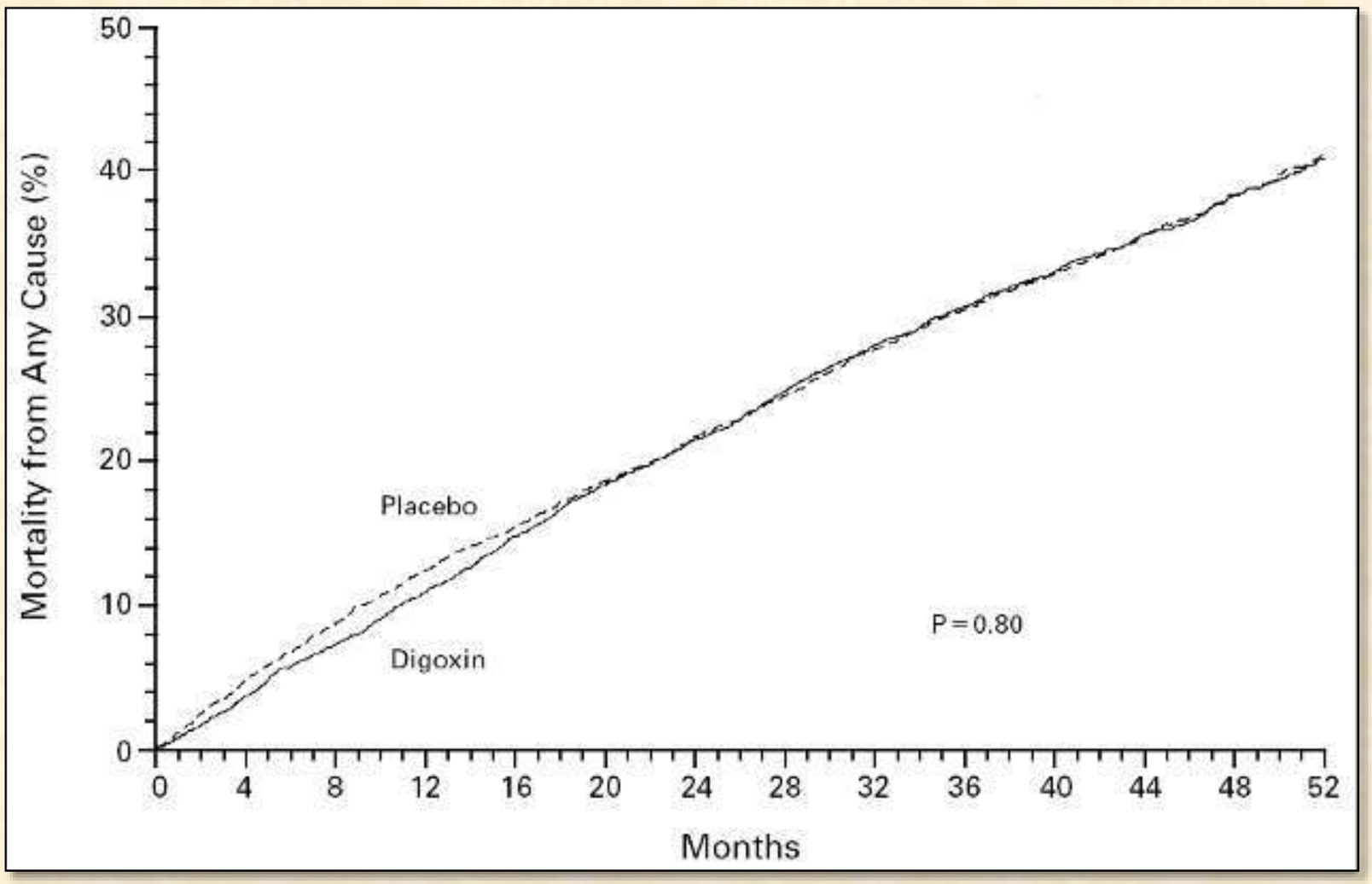
Normal Heart

HFrEF after STEMI in the LAD Territory

The First Drug was for Heart Failure

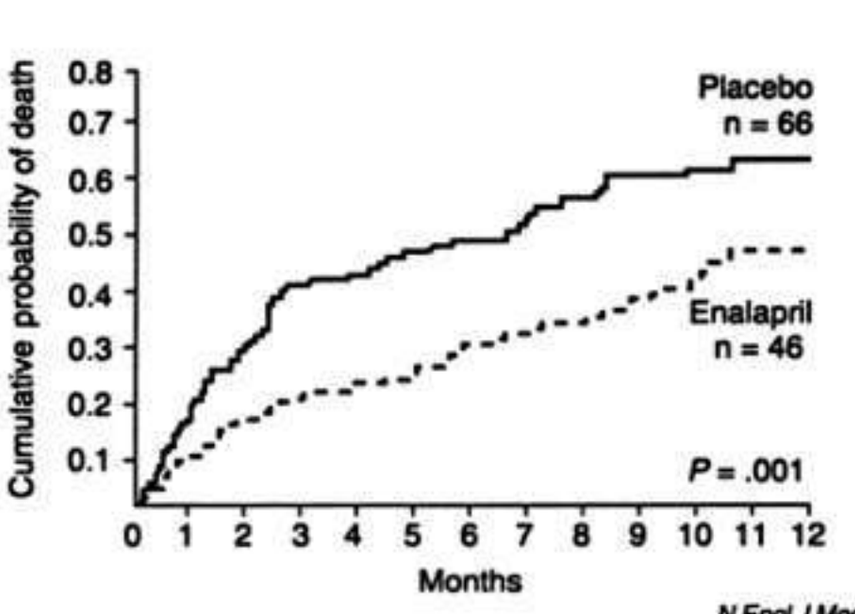
Cardiac glycosides (cardenolides)

- Sir William Withering, 1785(English botanist and physician)
- Purple foxglove plant (*Digitalis purpurea*)



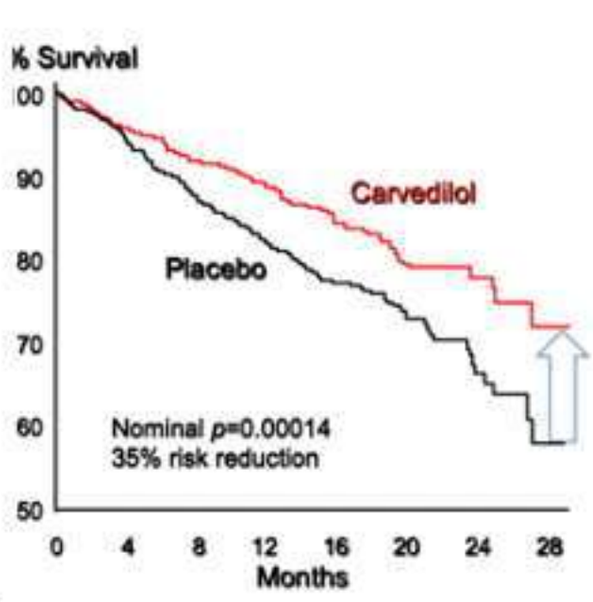
Lumping or the Seminal Trials: Heart Failure is HFrEF

CONSENSUS TRIAL
(ENALAPRIL vs. Placebo)
NYHA IV

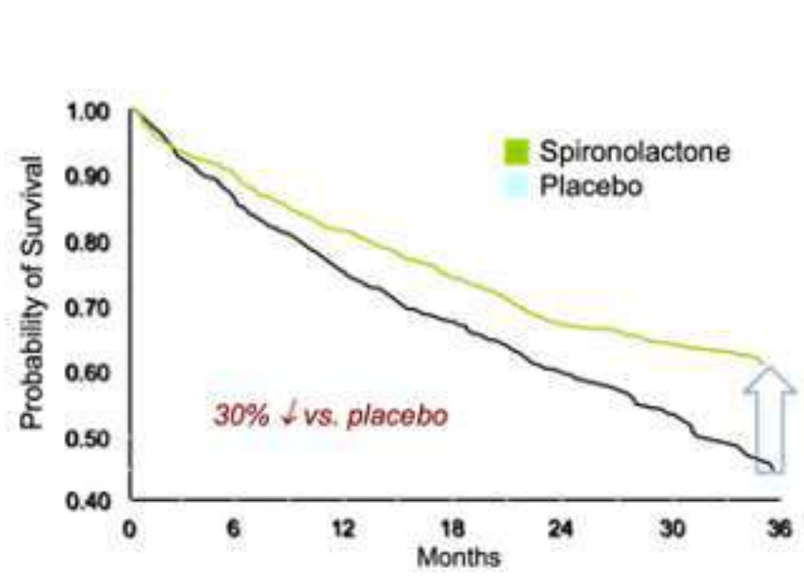


N Engl J Med. 1987

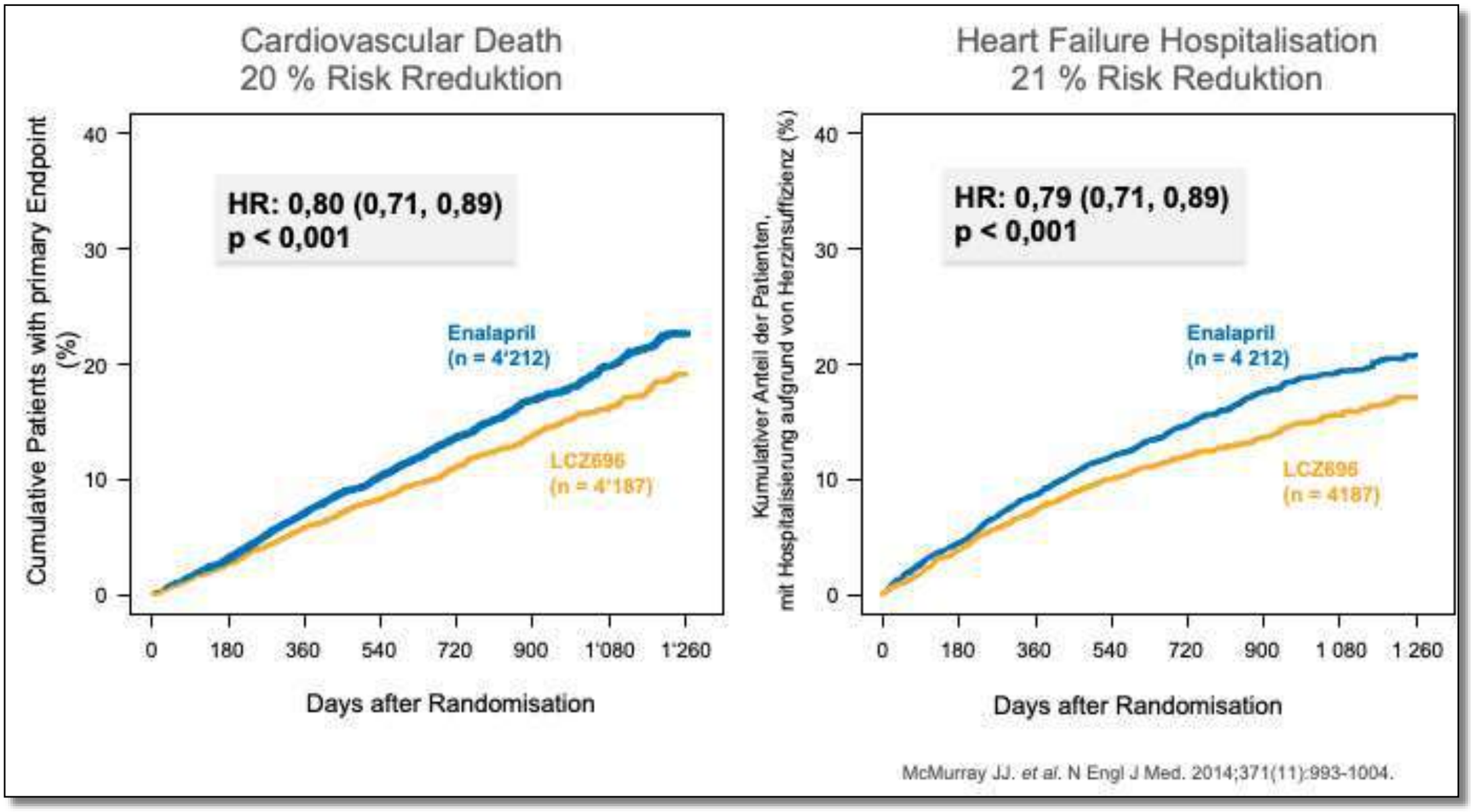
COPERNICUS TRIAL
(Carvedilol vs. Placebo)
LVEF <35%



RALES TRIAL
(Spironolactone vs. Placebo)
LVEF < 35%



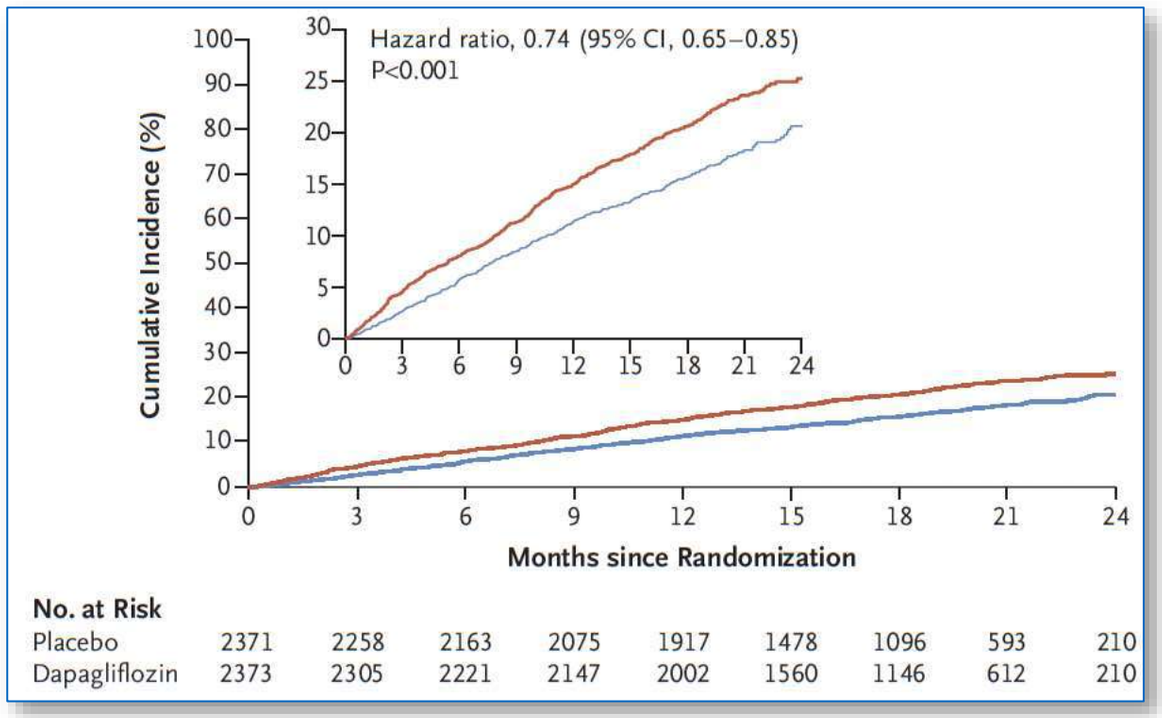
RAAS Inhibition in HFrEF: From ACE-I to ARNI



McMurray JJ. *et al*. N Engl J Med. 2014;371(11):993-1004.

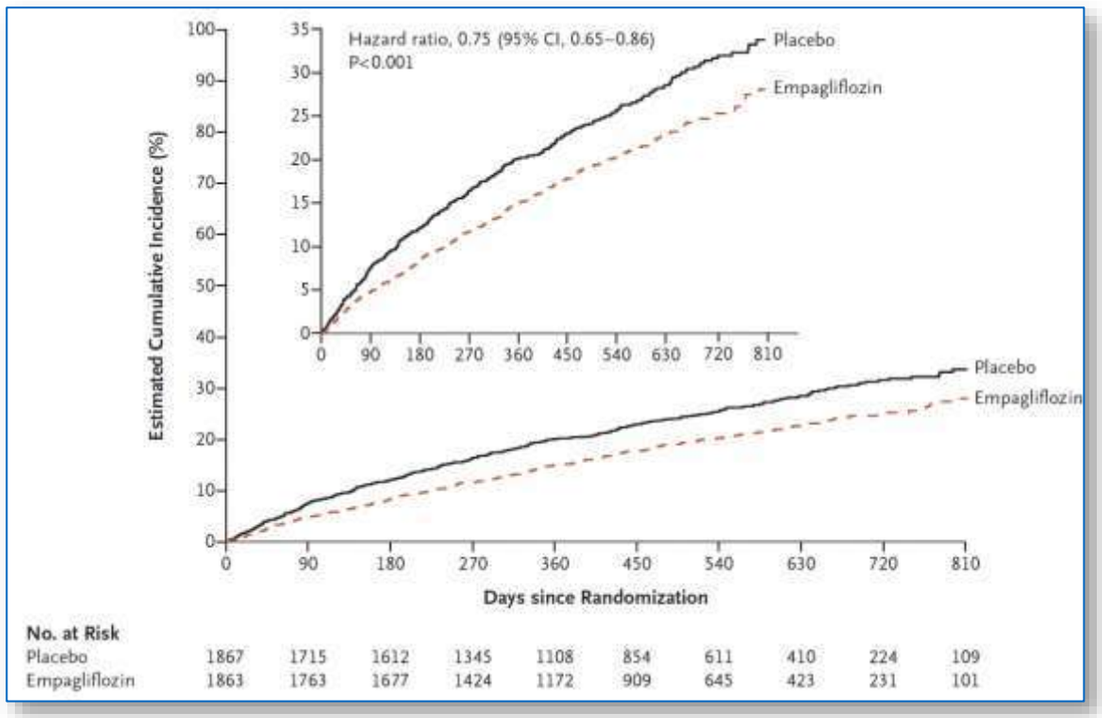
Sodium-Glucose Transport Inhibition in Heart Failure with reduced Ejection Fraction

Dapa-HF



N Engl J Med 2019;381:1995-2008.

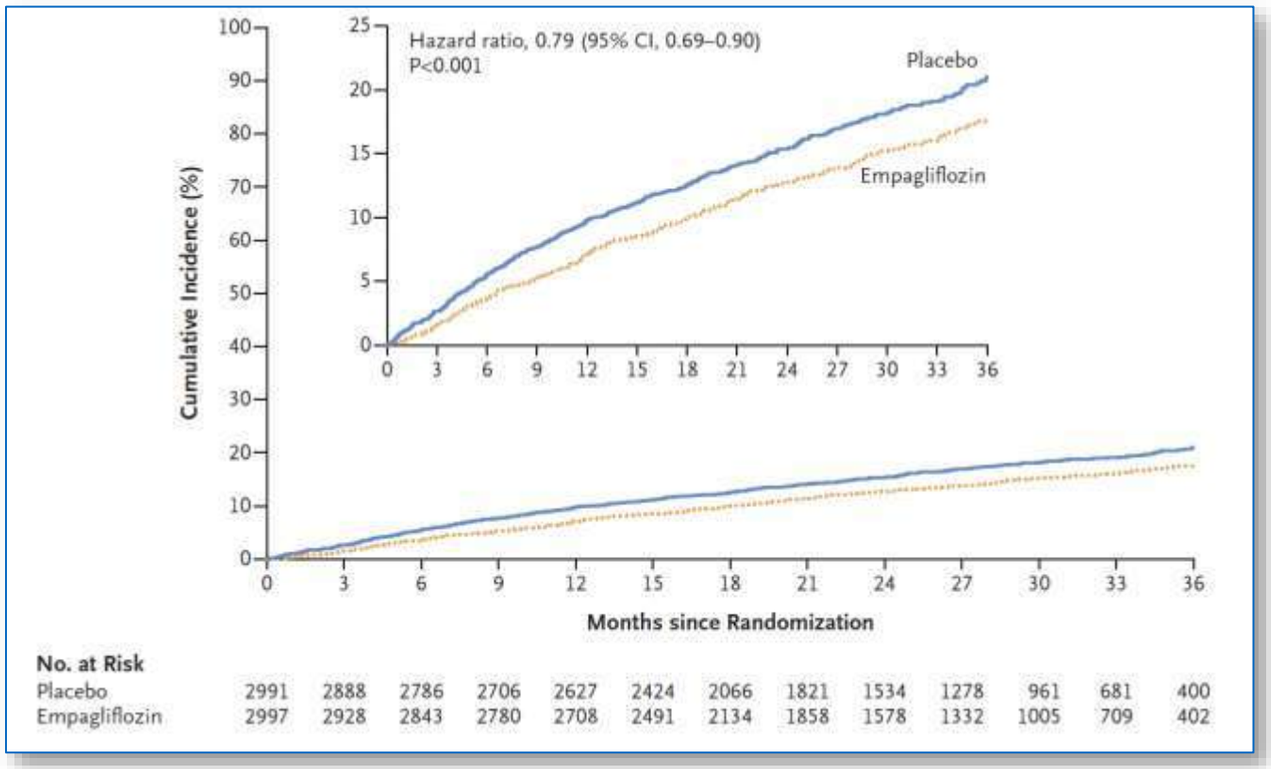
Empa-Reduced



N Engl J Med 2020;

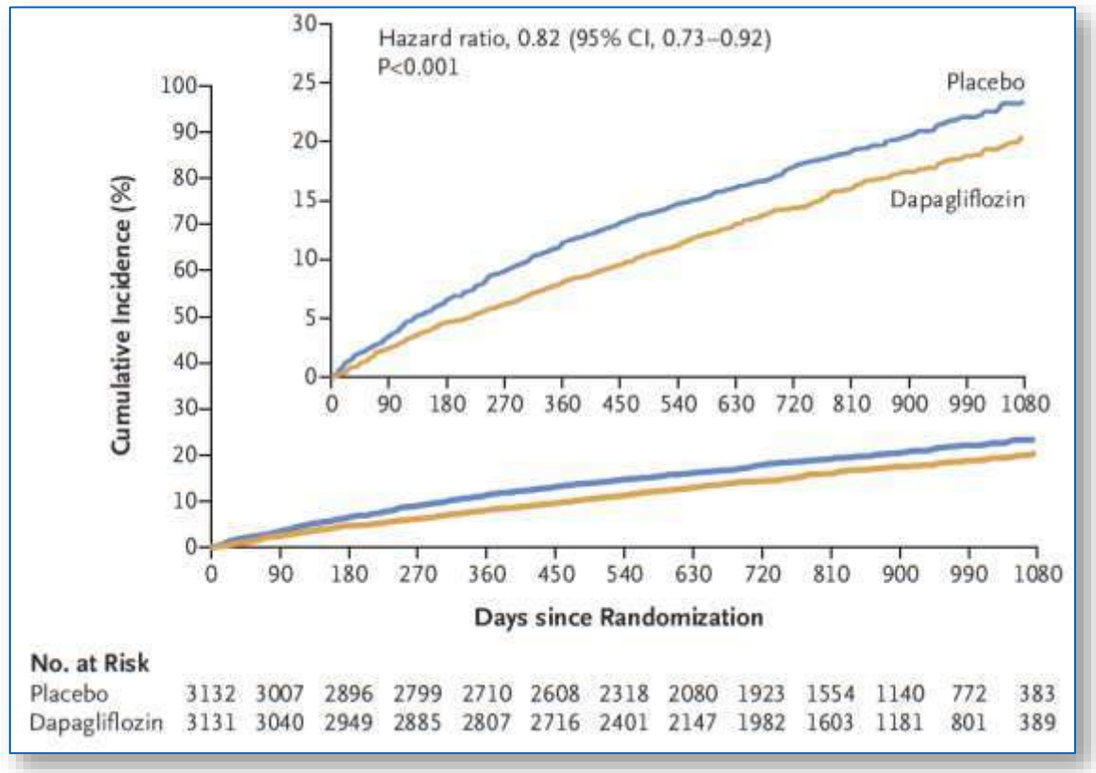
Sodium-Glucose Transport Inhibition in Heart Failure with preserved Ejection Fraction

EMPA-Preserved



N Engl J Med 2021;385:1451-61.

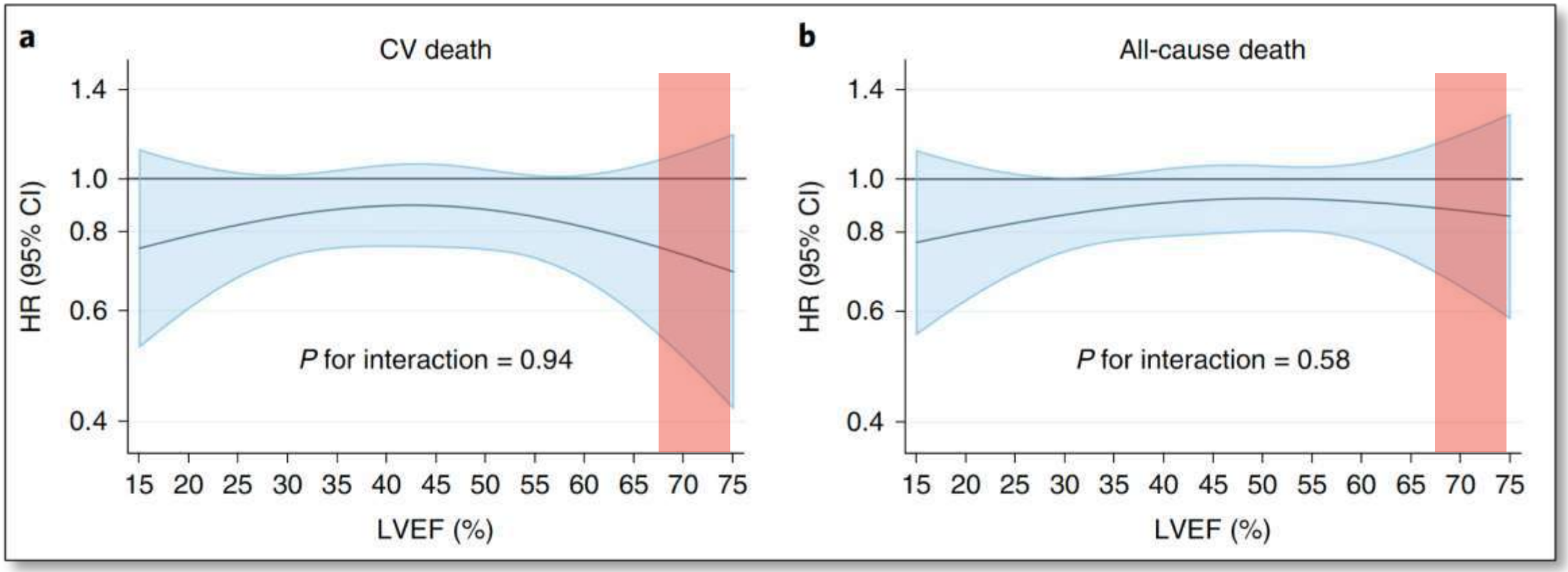
DELIVER



N Engl J Med 2022;387:1089-98.

OPEN

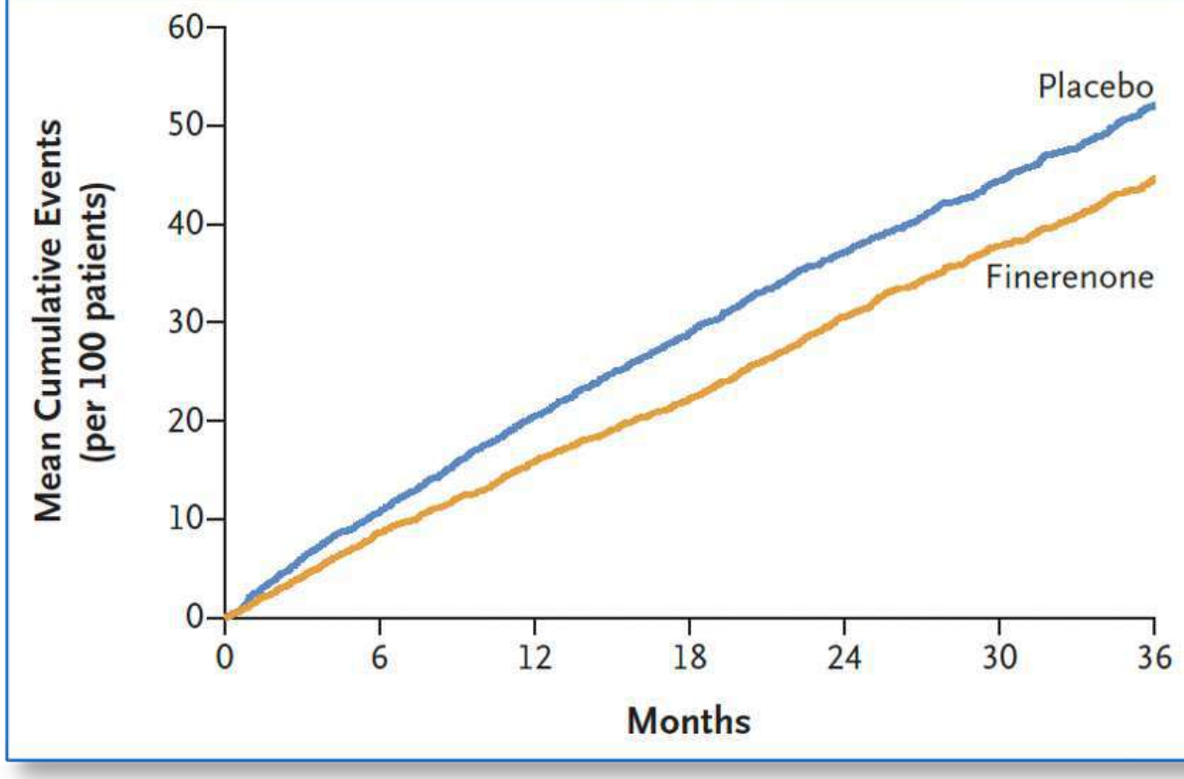
Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER



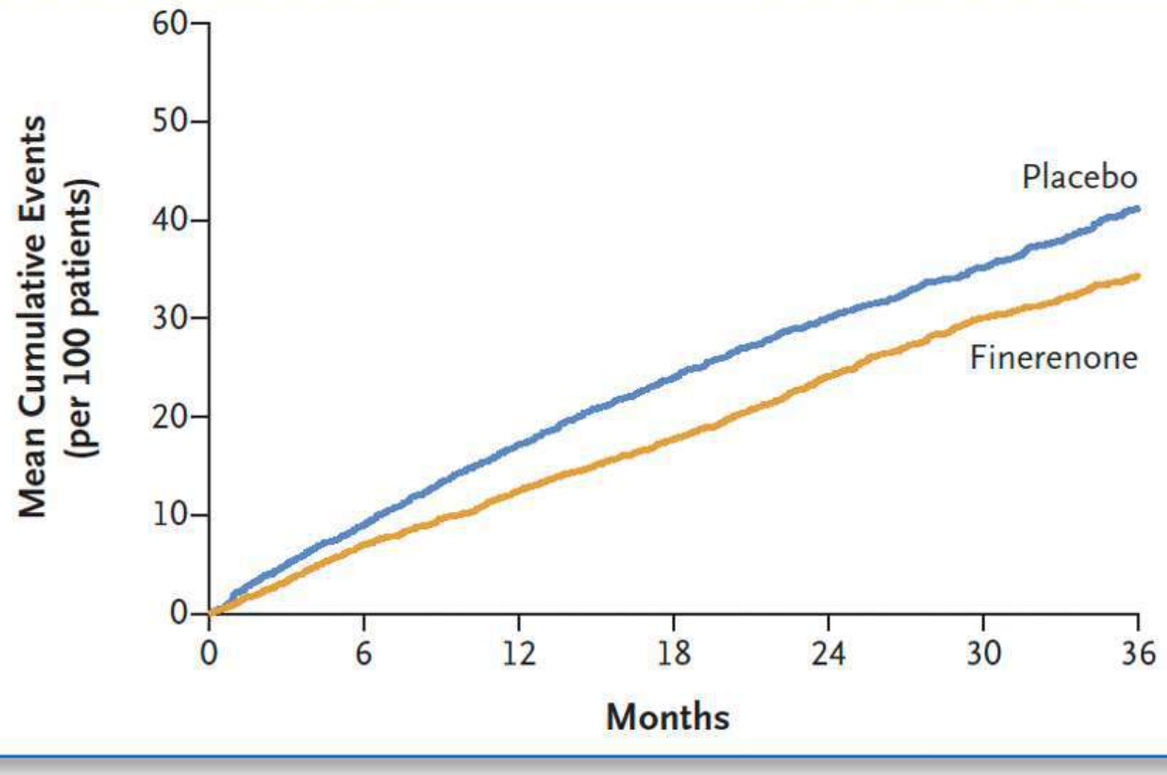
Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs,

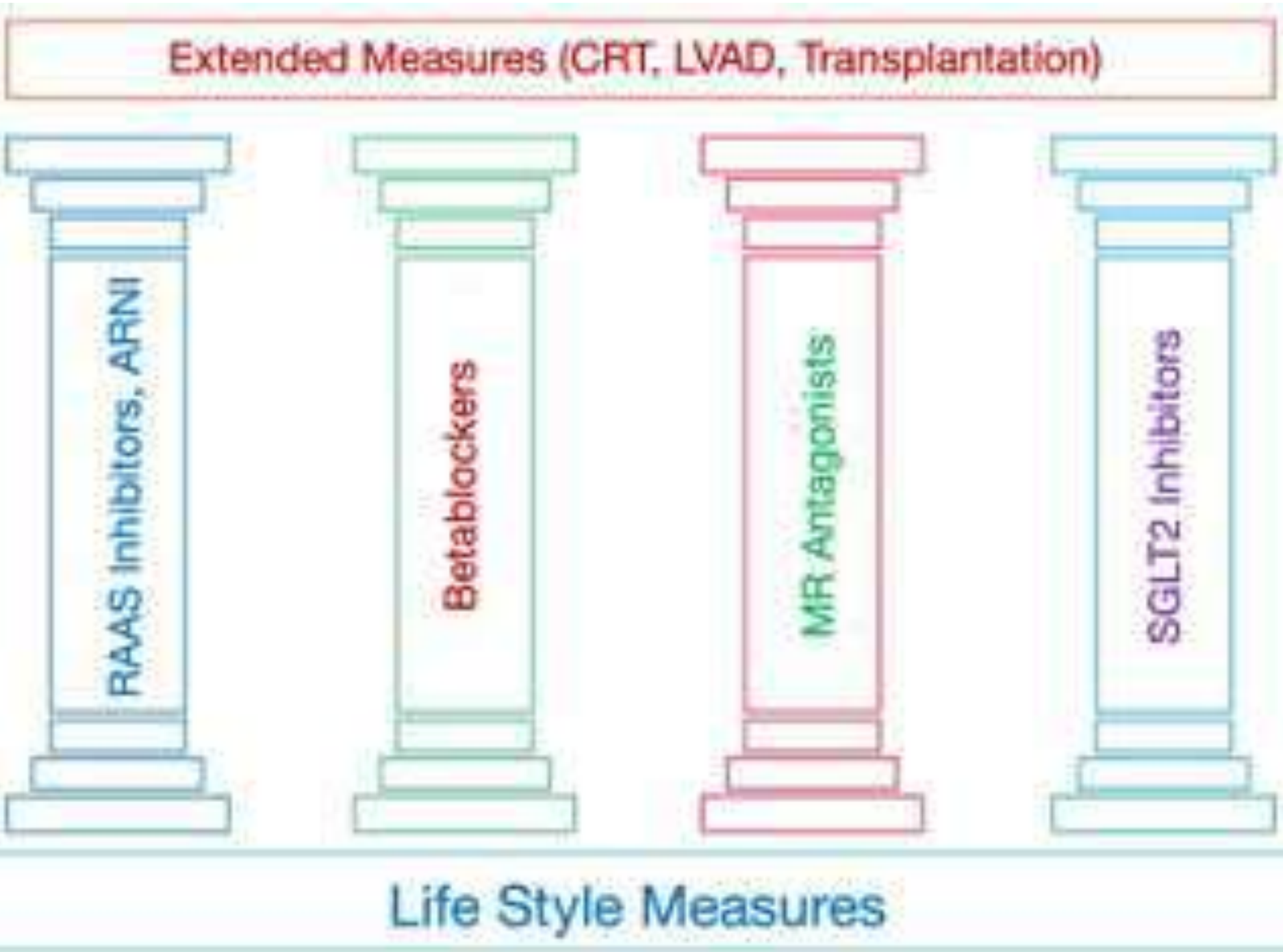
Worsening Heart Failure Events & Death from CV Causes



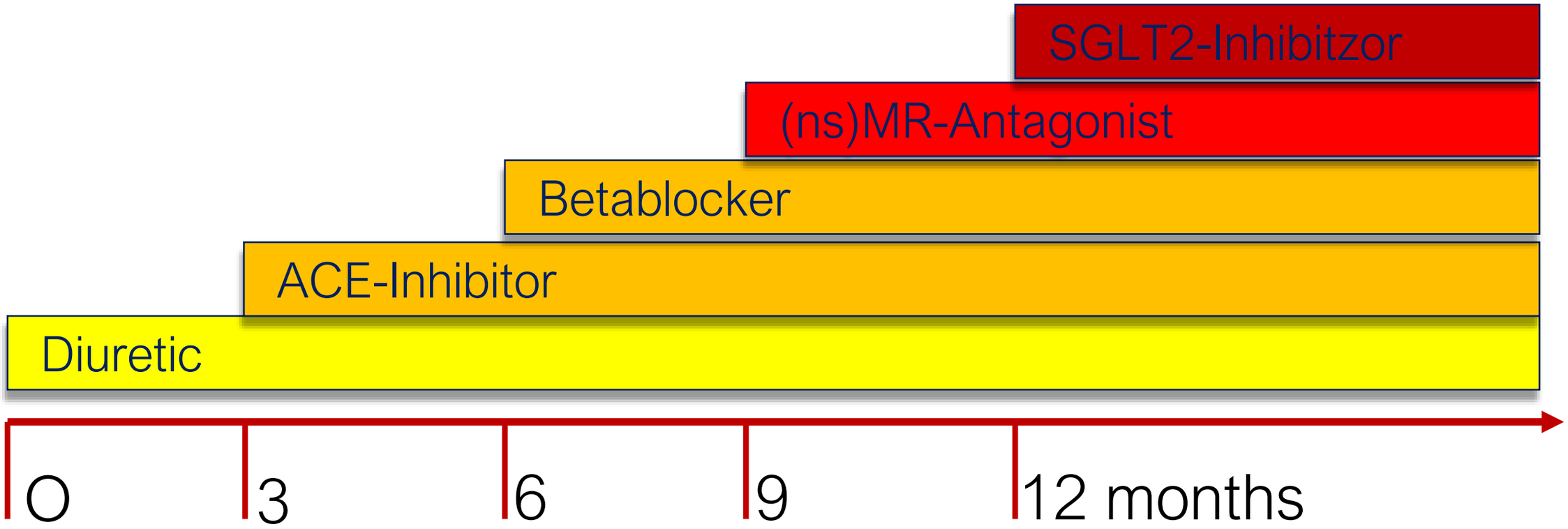
Total Worsening Heart Failure Events



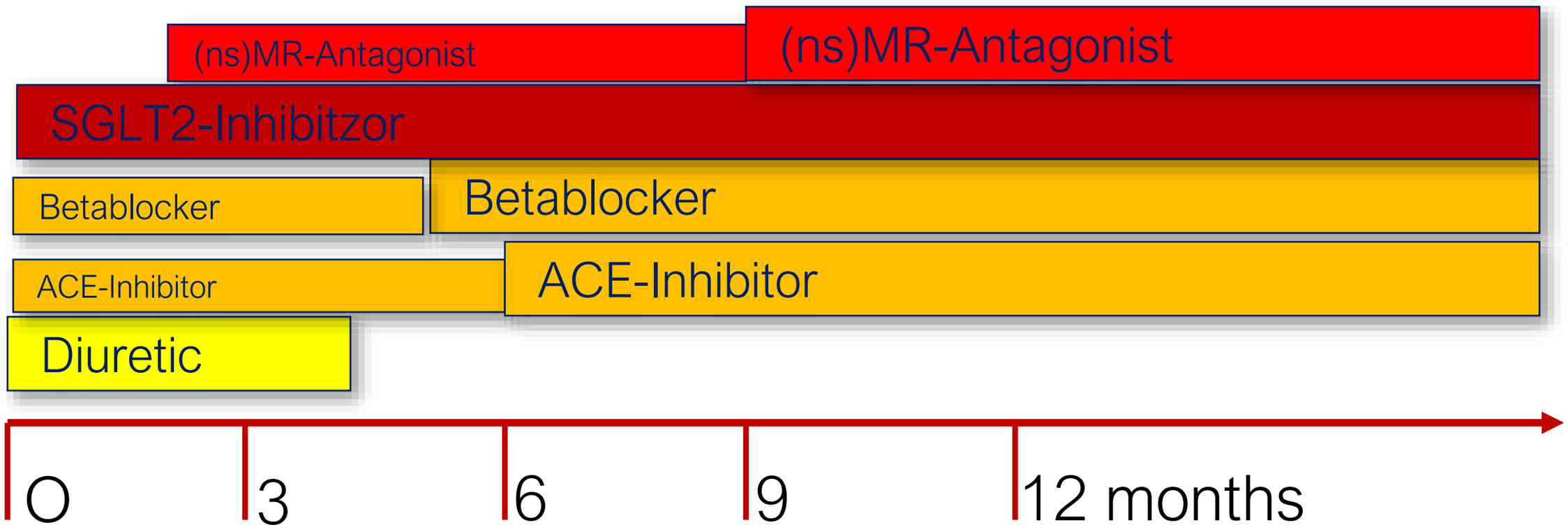
Lumping Management: Heart Failure is HFrEF



The Traditional Stepwise Model of HF Management



The New Concept of Rapid Iplementation of HF Management



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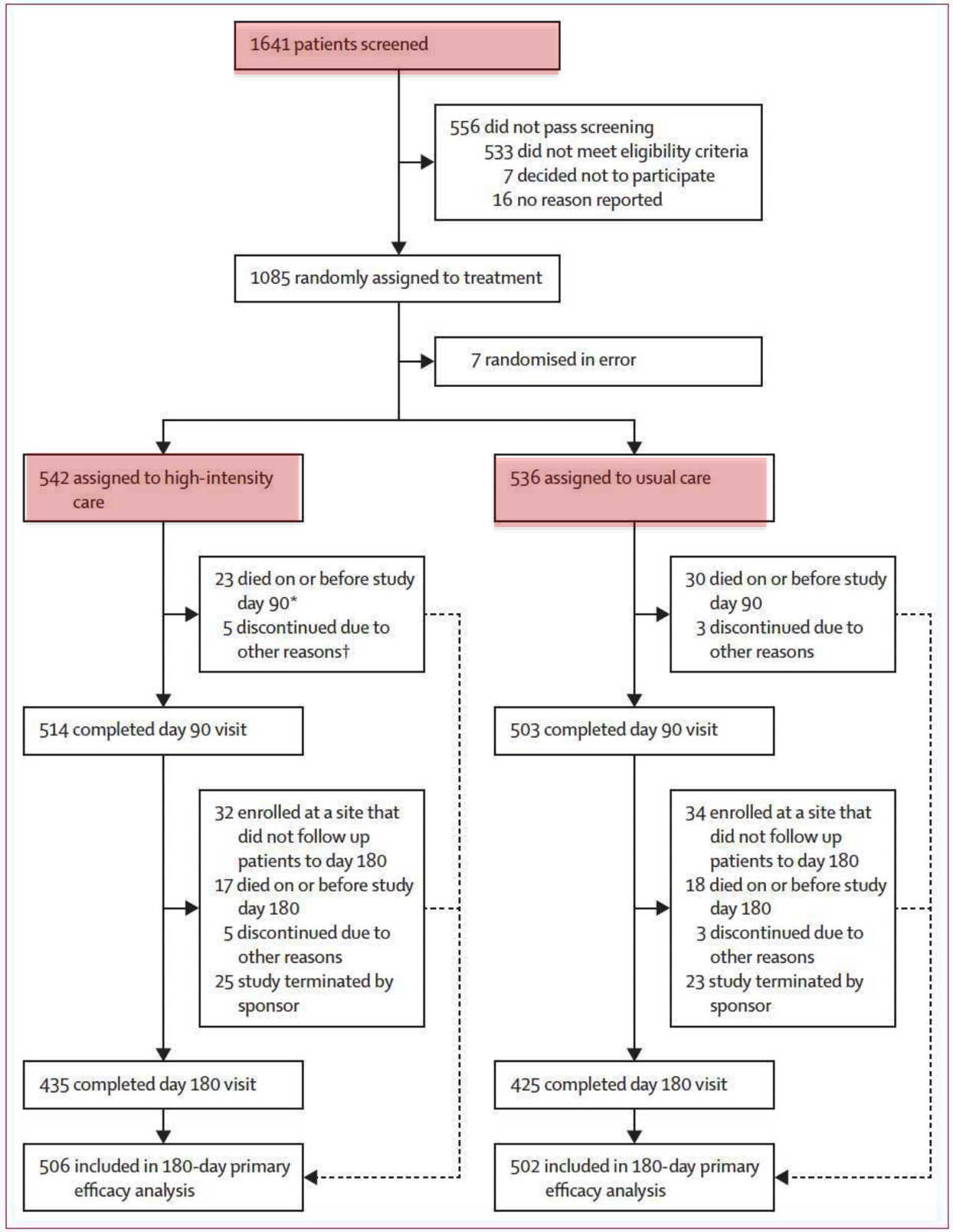

ficacy of up-titration of guideline-
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nen-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski,
vosadova, Koji Takagi, Albertino Damasceno, Hadiza Saidu, Etienne Gayat,

Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

University of Zurich[UZH] Imperial College London KING'S College LONDON

Safety, tolerability, and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

-Solal, Rafael Diaz, Gerasimos Filippatos, Marco Metra, Piotr Ponikowski,
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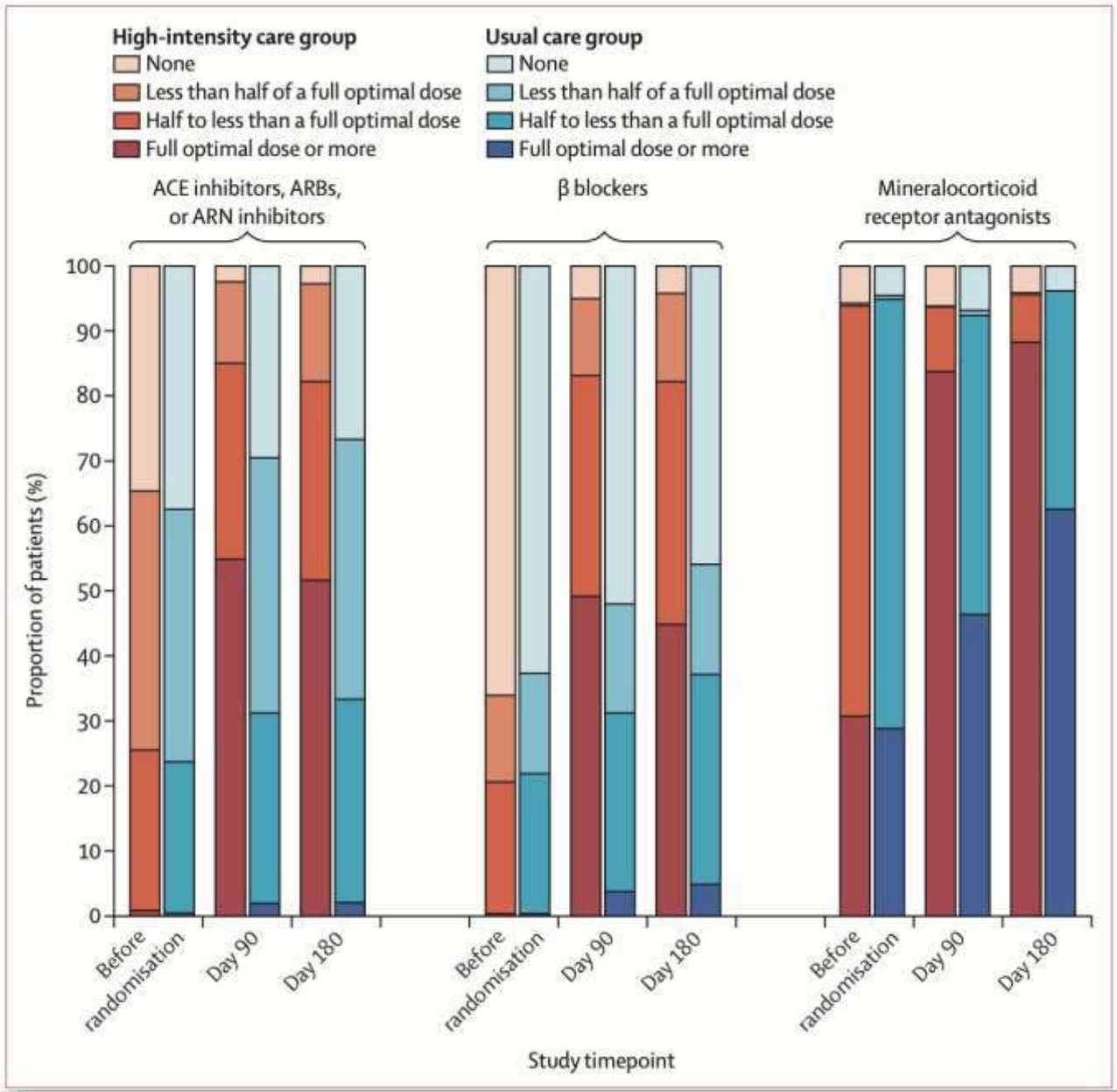
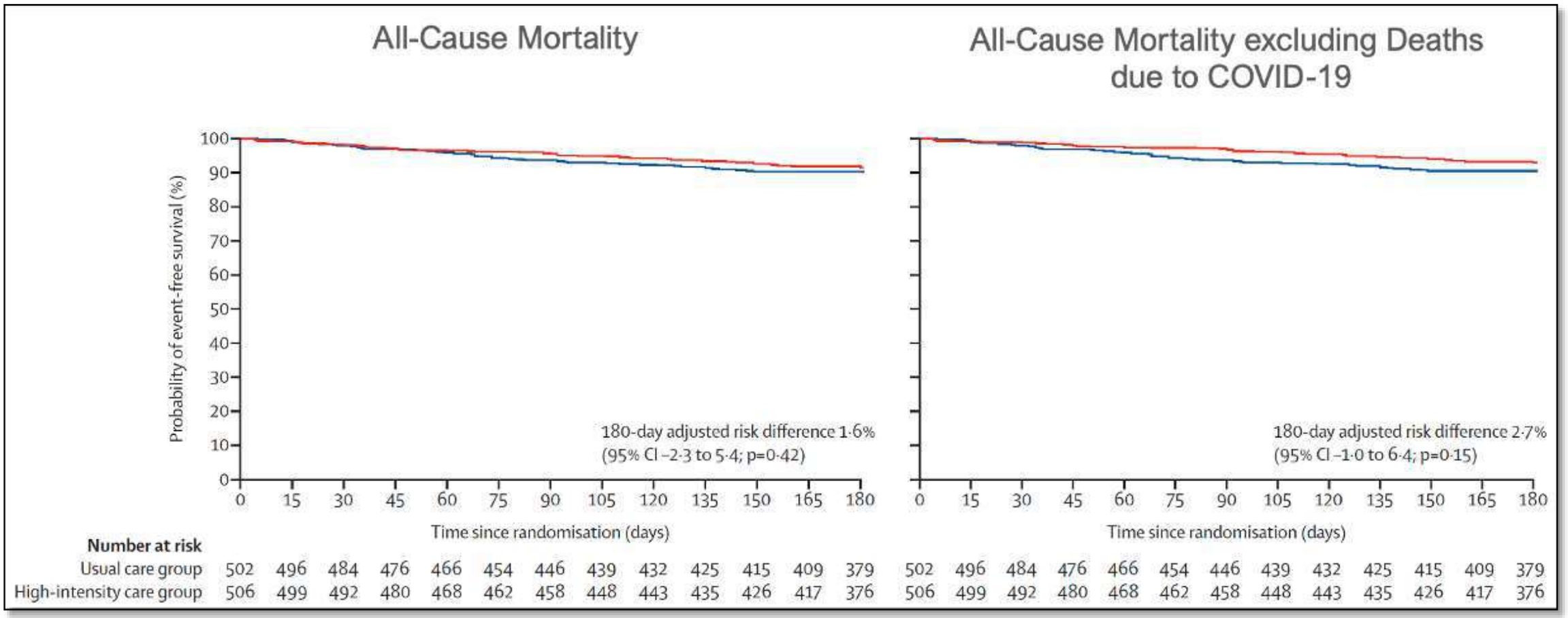
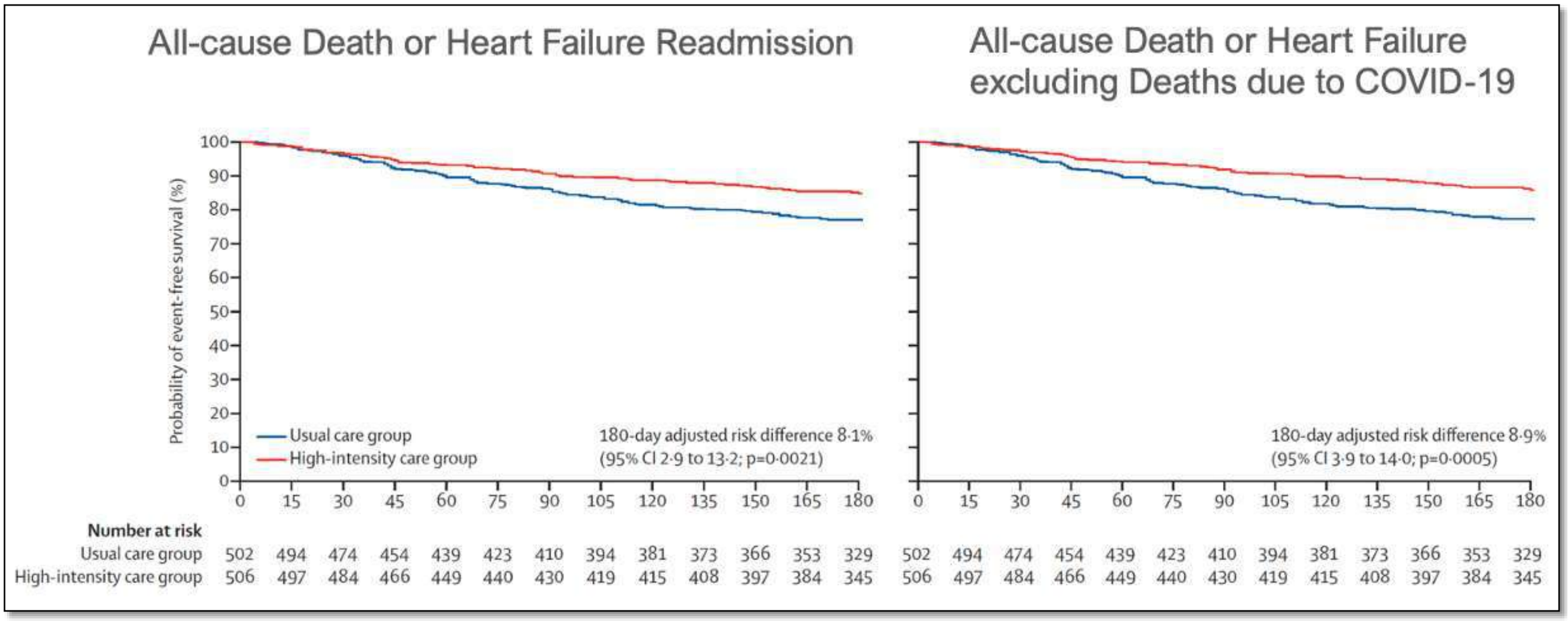


Safety, tolerability, efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF):



Lancet 2022; 400: 1938–52

Safety, tolerability, efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF):



Lancet 2022; 400: 1938–52

Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

University of Zurich[UZH] | Imperial College London | King's College London

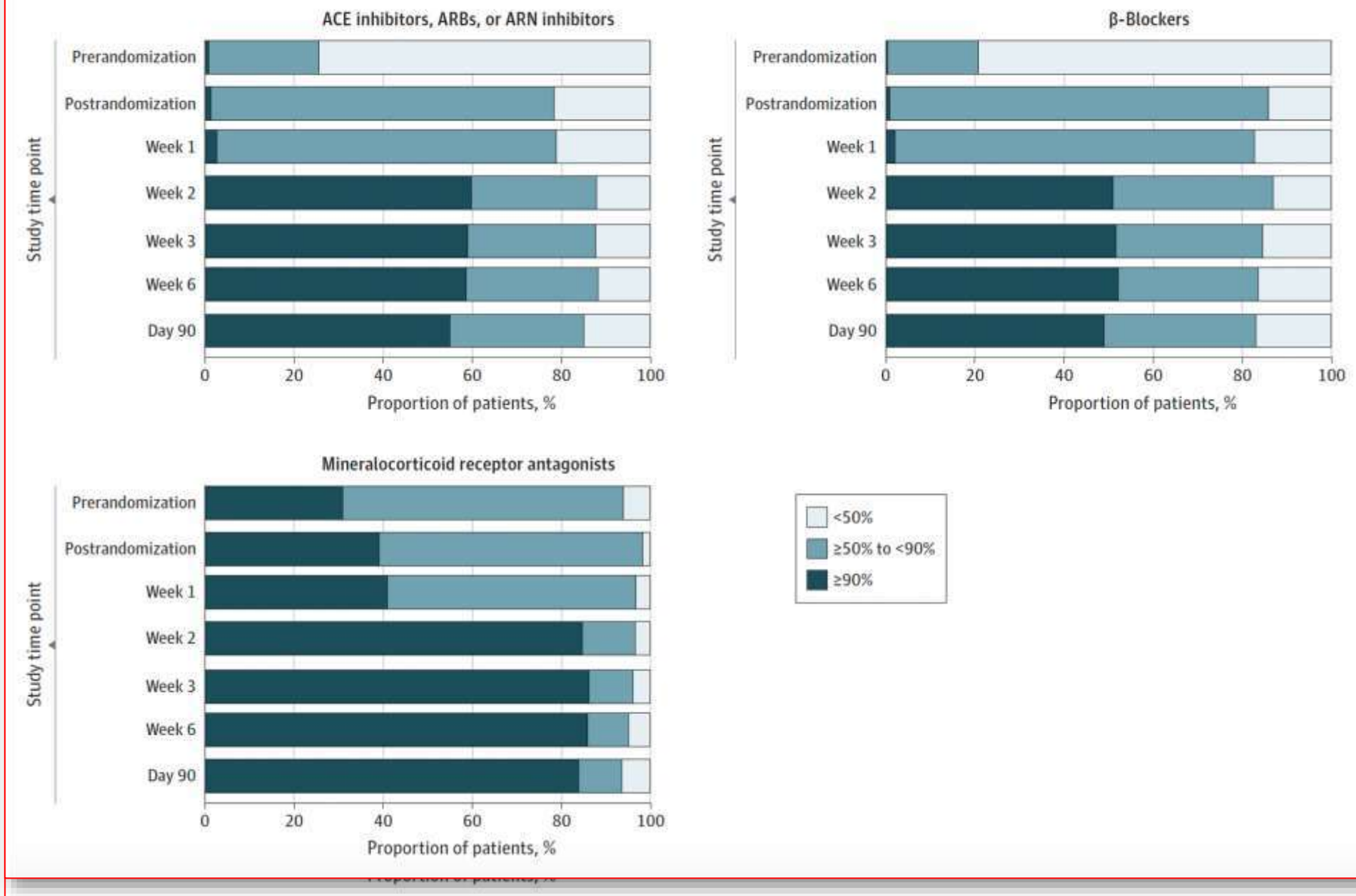
JAMA Cardiology | Original Investigation

Optimization of Evidence-Based Heart Failure Medications After an Acute Heart Failure Admission

A Secondary Analysis of the STRONG-HF Randomized Clinical Trial

na Adamo, MD; Mattia Arrigo, MD;
, MD; Ovidiu Chioncel, MD, PhD;
, MD; Etienne Gayat, MD, PhD;
; Peter S. Pang, MD;
akagi, MD;
aa, MD, PhD

Change in Doses of Guideline-Directed Medical Therapy in the High-Intensity Arm byWeek to Day 90



Starting Drugs in Heart Failure:
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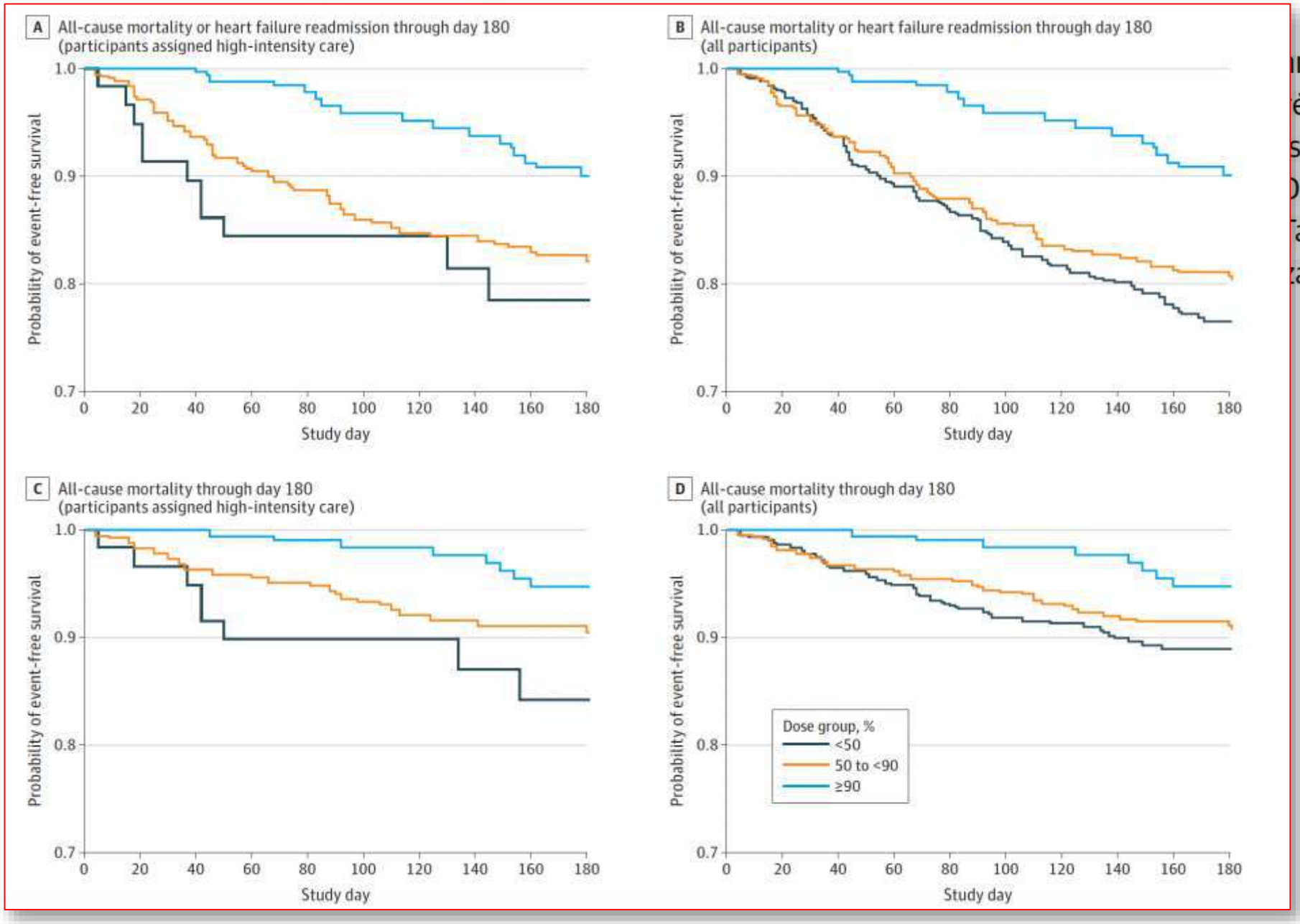


Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

University of Zurich[UZH] | Imperial College London | KING'S College LONDON

ESC
Europea
of Cardi

RESEARCH
rdiomyopathie

Accel
heart

Li Shen[1,2]
Muthiah V
Lars Køb
Xingwei Z

Desai[3],
on[3],

	RASi	BB	MRA	ARNI	ARNI	SGLT2i
Trial	SOLVD-treatment	MERIT-HF	EMPHASIS-HF	PARADIGM-HF	PARADIGM-HF vs. SOLVD-treatment and CHARM-alternative	DAPA-HF
Number of patients	2569	3991	2737	8399	–	4744
study patients	NYHA II–IV, LVEF ≤ 35%	NYHA II–IV, LVEF ≤ 40%	NYHA II, LVEF ≤ 35%	NYHA II–IV, LVEF ≤ 40%	–	NYHA II–IV, LVEF ≤ 40%
Key baseline therapy	BB 8%, potassium sparing diuretic 9%	RASi 96%, MRA 8%	RASi 94%, BB 87%	RASi 100%, BB 93%, MRA 56%	–	RASi 94%, BB 96%, MRA 71%, ARNI 11%
Test treatment	Enalapril	Metoprolol CR/XL	Eplerenone	Sacubitril/valsartan	Sacubitril/valsartan	Dapagliflozin
Control treatment	Placebo	Placebo	Placebo	Enalapril	Putative placebo	Placebo
Discontinuation percentage in the experimental arm	32.5%	13.9%	16.3%	17.8%	–	10.5%
Mean daily dose in those taking the study drug/ target dose	16.6 mg/20 mg	159 mg/ 200 mg	39.1 ± 13.8 mg/50 mg	375 ± 71 mg/ 400 mg	–	98.1% taking the target dose of 10 mg daily
Cardiovascular death or heart failure hospitalization						
HR (95% CI) Treatment vs. Control	0.72 (0.64–0.80)	0.69 (0.60–0.80)[a]	0.63 (0.54–0.74)	0.80 (0.73–0.87)	0.57 (0.50–0.66)	0.75 (0.65–0.85)
All-cause death						
HR (95% CI) Treatment vs. control	0.84 (0.74–0.95)	0.66 (0.53–0.81)	0.76 (0.62–0.93)	0.84 (0.76–0.93)	0.72 (0.61–0.85)	0.83 (0.71–0.97)
Cardiovascular death						
HR (95% CI) Treatment vs. control	0.83 (0.72–0.94)	0.62 (0.50–0.78)	0.76 (0.61–0.94)	0.80 (0.71–0.89)	0.66 (0.56–0.79)	0.82 (0.69–0.98)
Heart failure hospitalization						
HR (95% CI) Treatment vs. control	0.64 (0.56–0.74)	0.69[b]	0.58 (0.47–0.70)	0.79 (0.71–0.89)	0.51 (0.42–0.61)	0.70 (0.59–0.83)

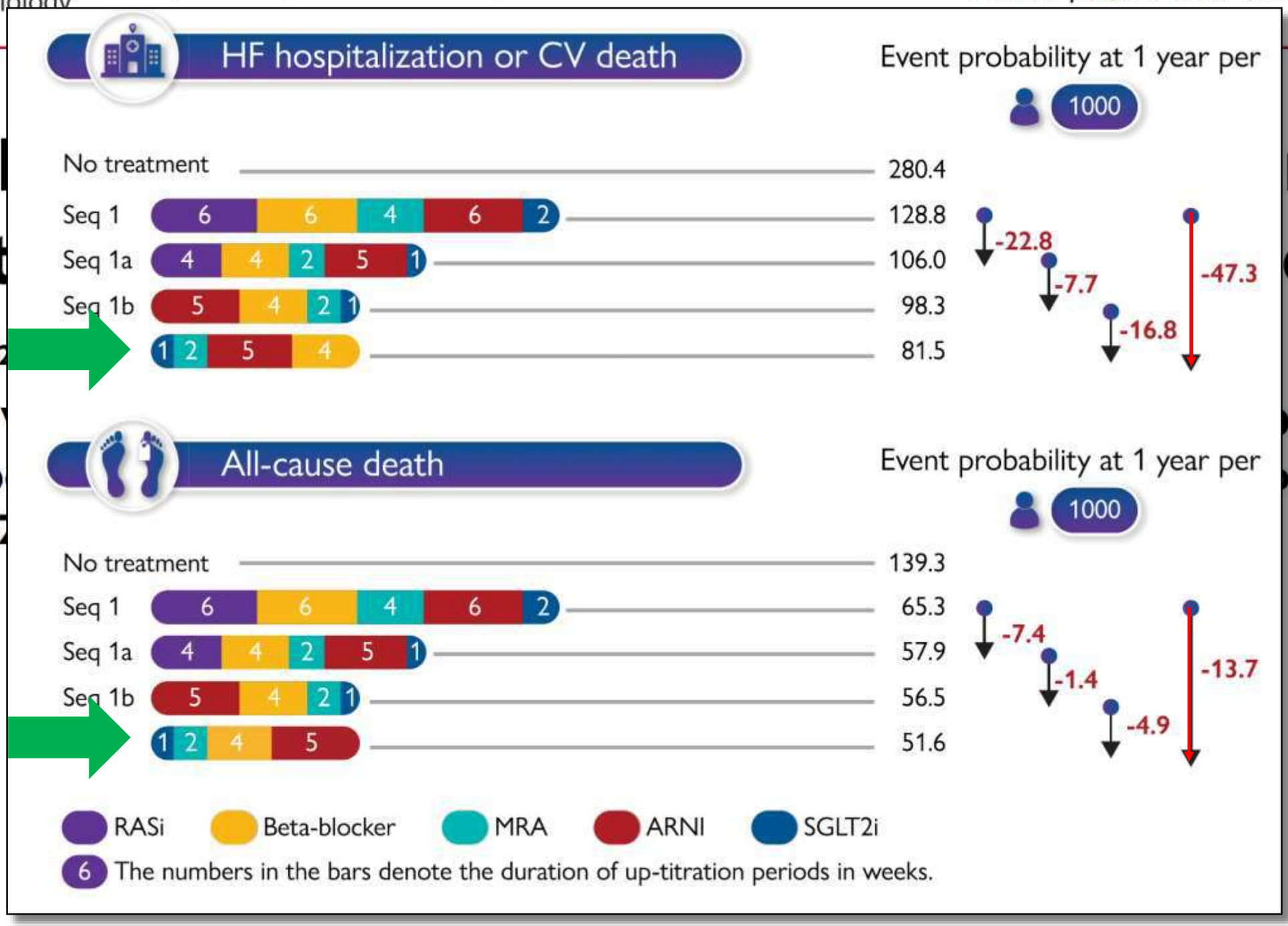
ESC European Society of Cardiology

European Heart Journal (2022) **43**, 2573–2587
https://doi.org/10.1093/eurheartj/ehac210

CLINICAL RESEARCH
Heart failure and cardiomyopathie

Accel r heart on

Li Shen[1,2]
Muthiah Y esai[3],
Lars Køb n[3],
Xingwei Z



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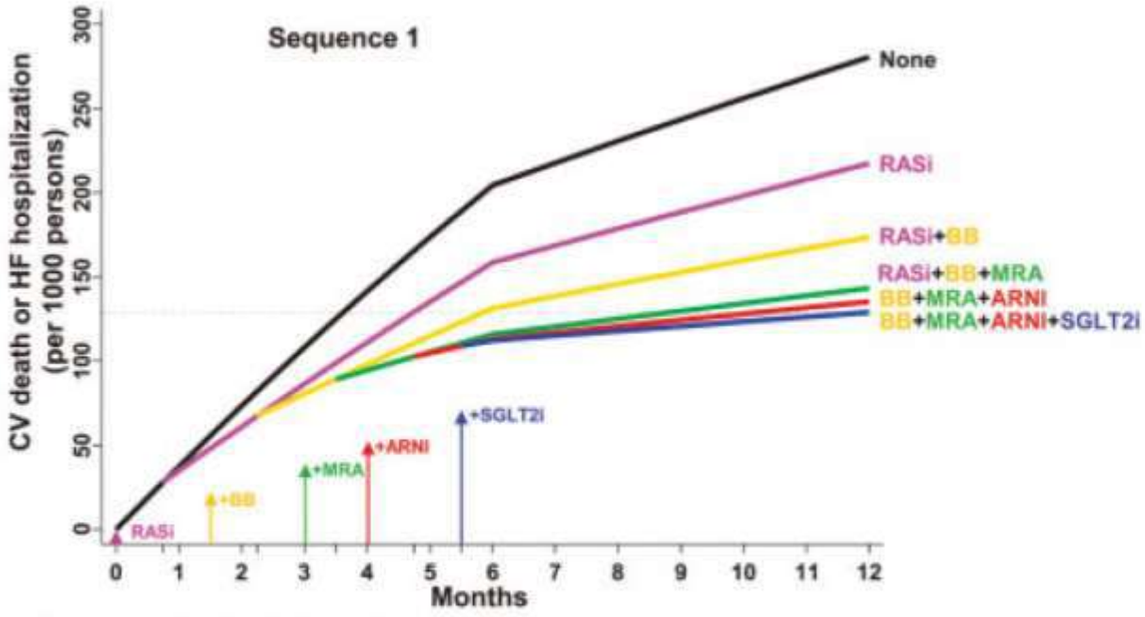
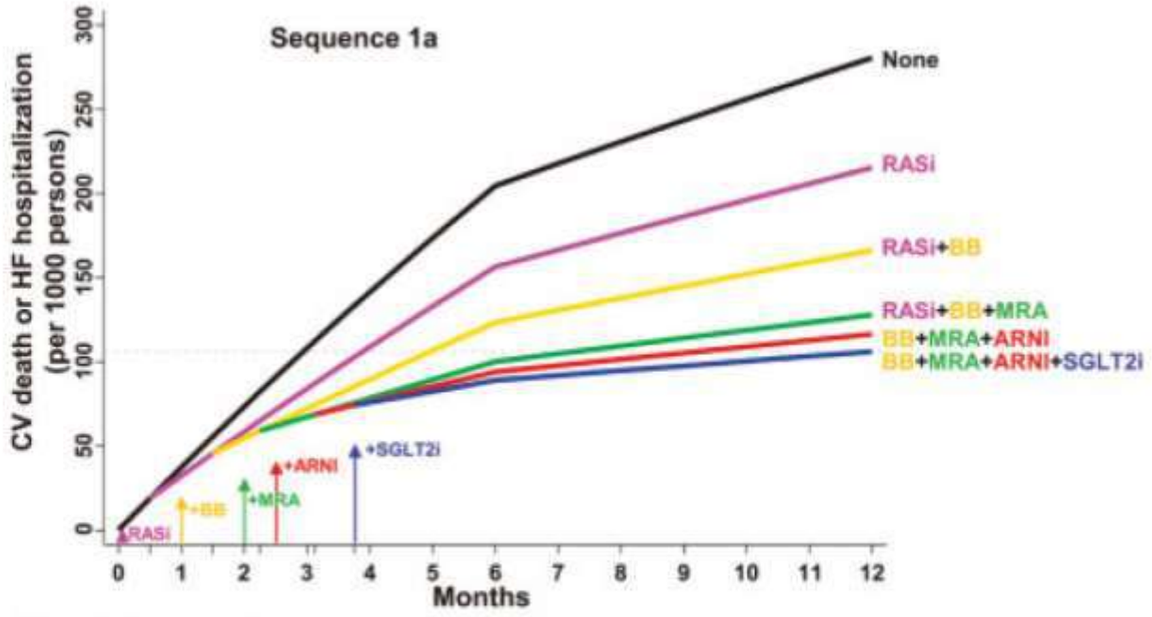
Accelerated and personalized therapy for heart failure with reduced ejection fraction

Li Shen[1,2], Pardeep Singh Jhund[2], Kieran Francis Docherty[2], Muthiah Vaduganathan [3], Mark Colquhoun Petrie [2], Akshay Suvas Desai[3], Lars Køber[4], Morten Schou [5], Milton Packer [6,7], Scott David Solomon[3], Xingwei Zhang[1], and John Joseph Valentine McMurray [2]*



Cumulative number of events per 1000 persons

None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq 1	0	35	61	80	95	105	112	115	118	121	123	126	129



Cumulative number of events per 1000 persons

None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq 1a	0	32	54	67	76	82	89	92	95	97	100	103	106

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

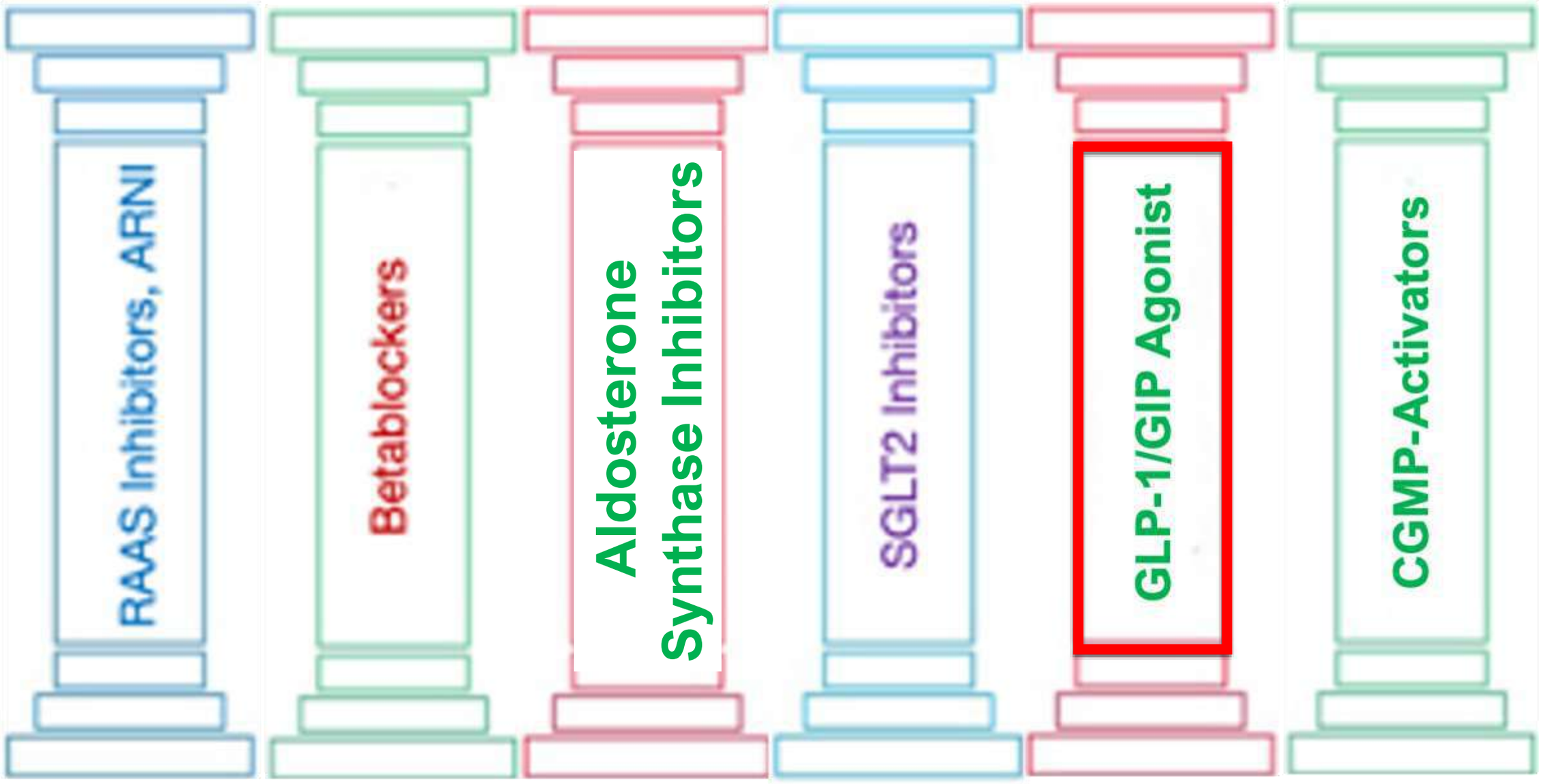
Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

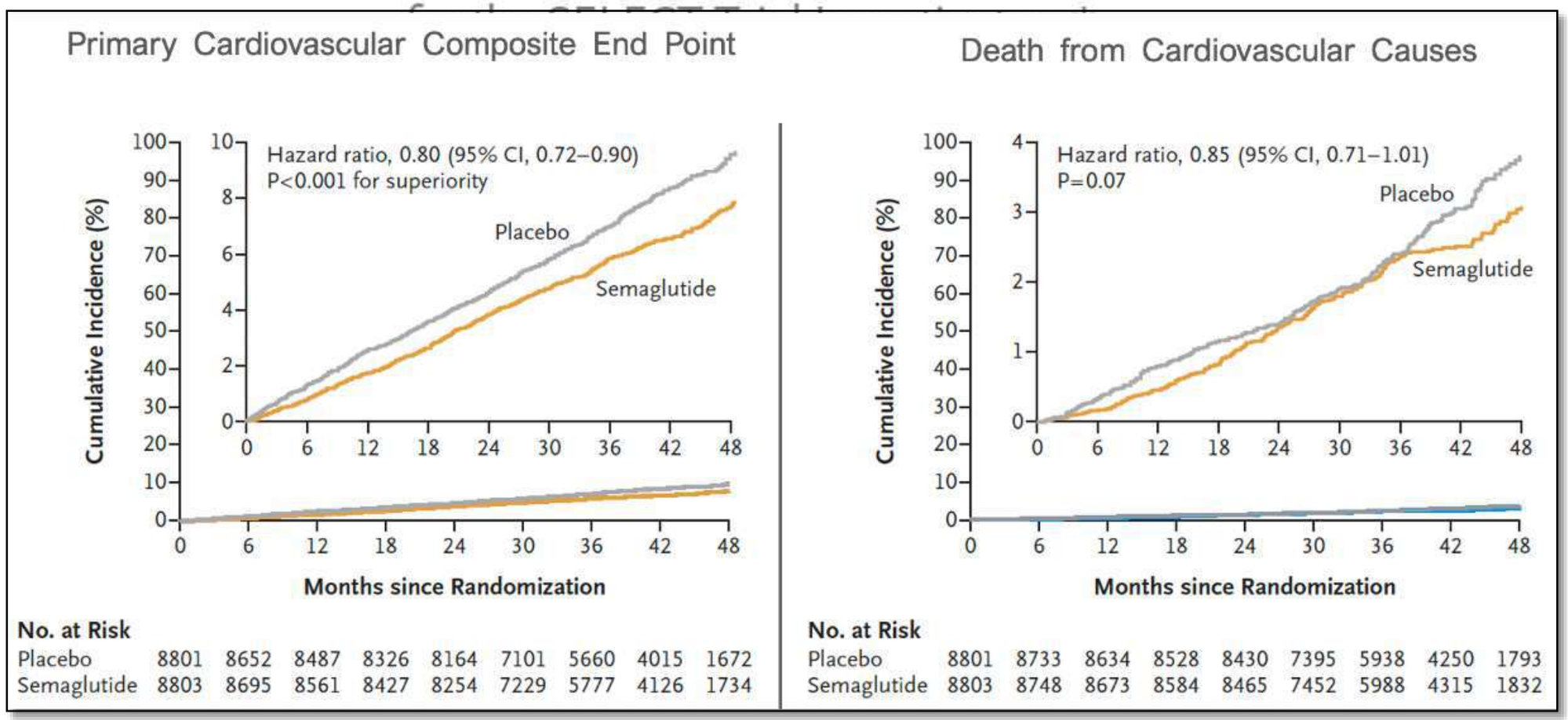
Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors are recommended to reduce the risk of HF hospitalization or CV death.[35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

What could be the future of HF Management?



Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D.,



The Spectrum of Heart Failure
and what it means for clinical practice

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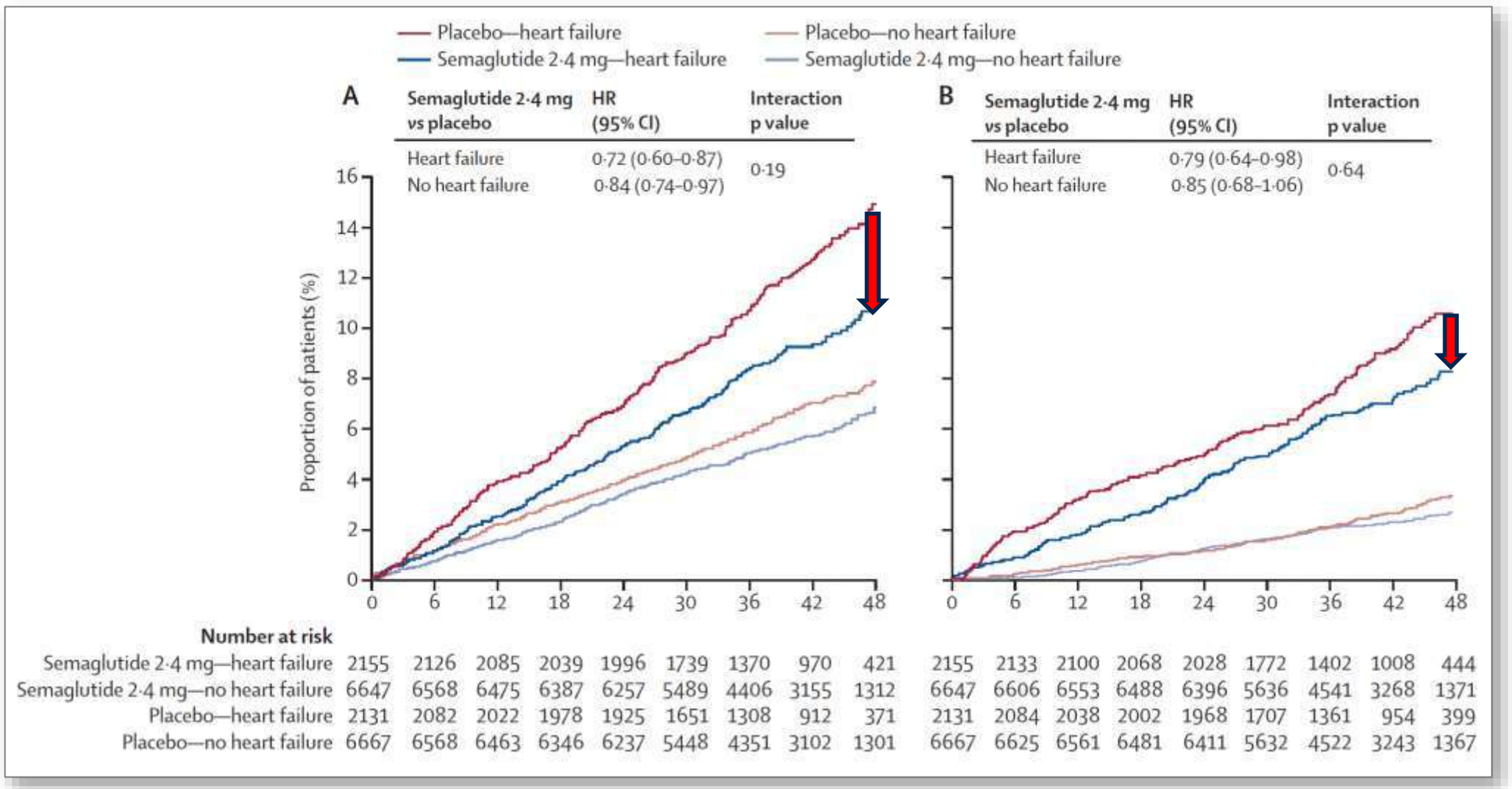
Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

John Deanfield, Subodh Verma, Benjamin M Scirica, Steven E Kahn, Scott S Emerson, Donna Ryan, Ildiko Lingvay, Helen M Colhoun, Jorge Plutzky, Mikhail N Kosiborod, G Kees Hovingh, Søren Hardt-Lindberg, Ofir Frenkel, Peter E Weeke, Søren Rasmussen, Assen Goudev, Chim C Lang, Miguel Urina-Triana, Mikko Pietilä, A Michael Lincoff, for the SELECT Trial Investigators

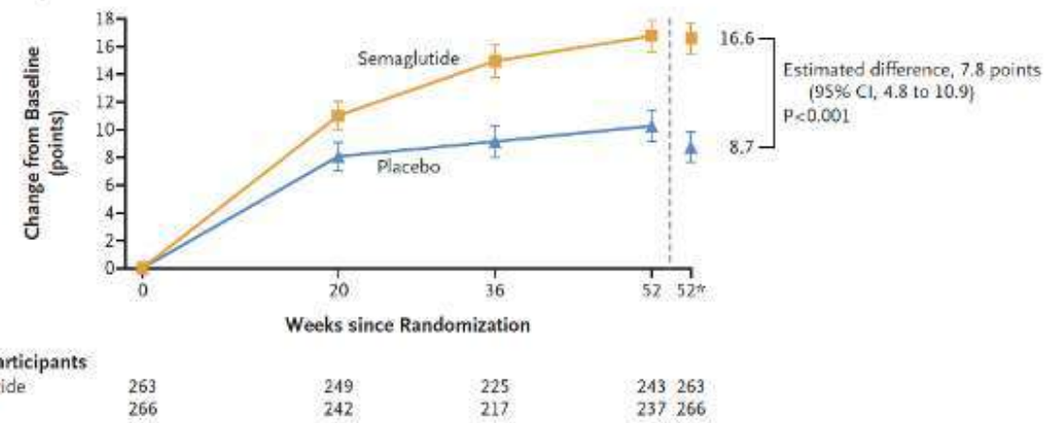
oa OPEN ACCESS

Lancet 2024; 404: 773–86



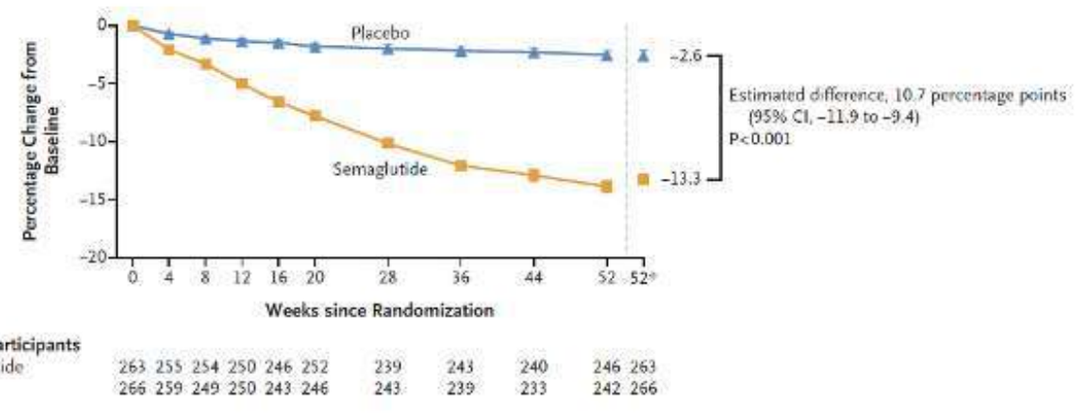
Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Change in KCCQ-CSS



No. of Participants					
Semaglutide	263	249	225	243	263
Placebo	266	242	217	237	266

Change in Body weight

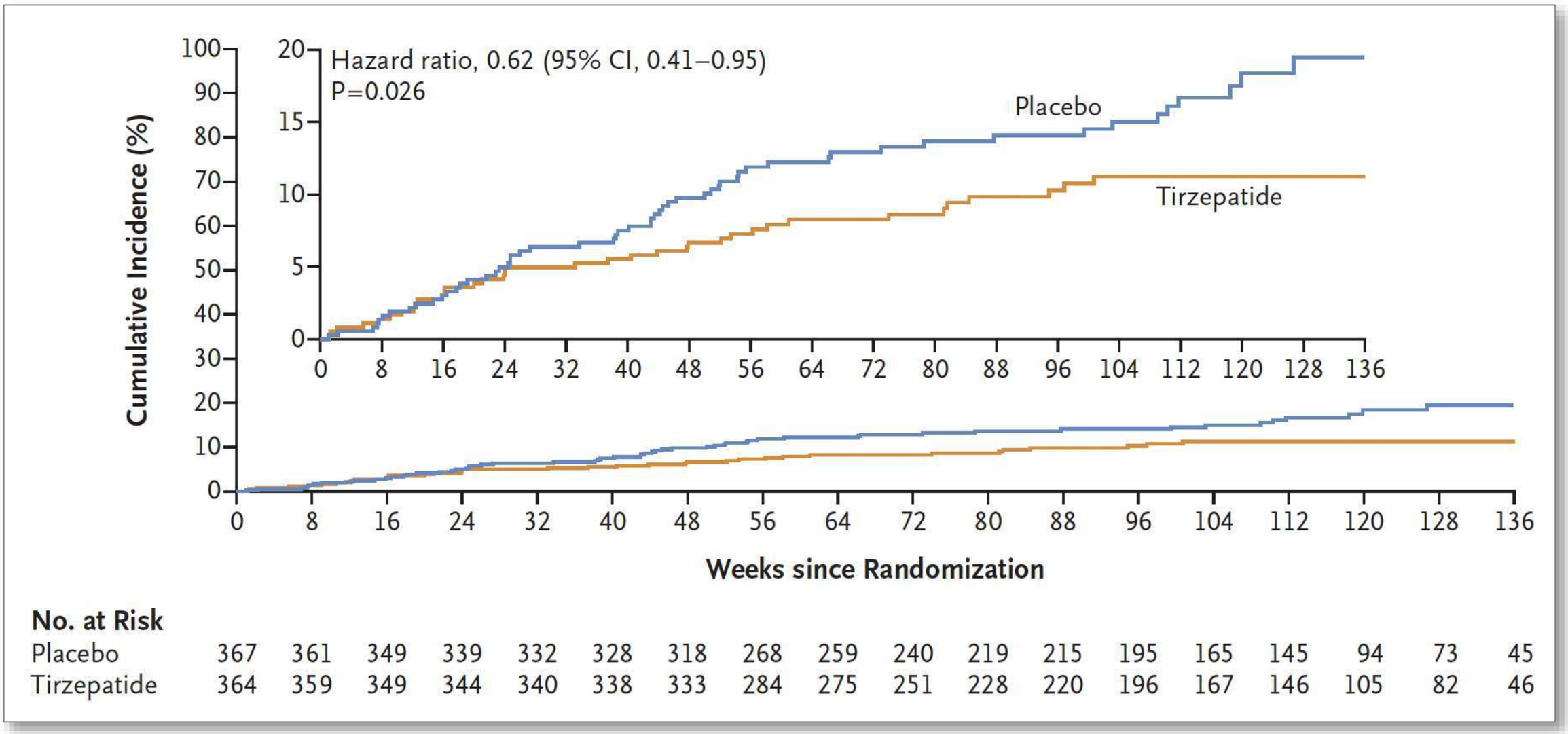


No. of Participants										
Semaglutide	263	255	254	250	246	252	239	243	240	246	263
Placebo	266	259	249	250	243	246	243	239	233	242	266

Obesity HFpEF

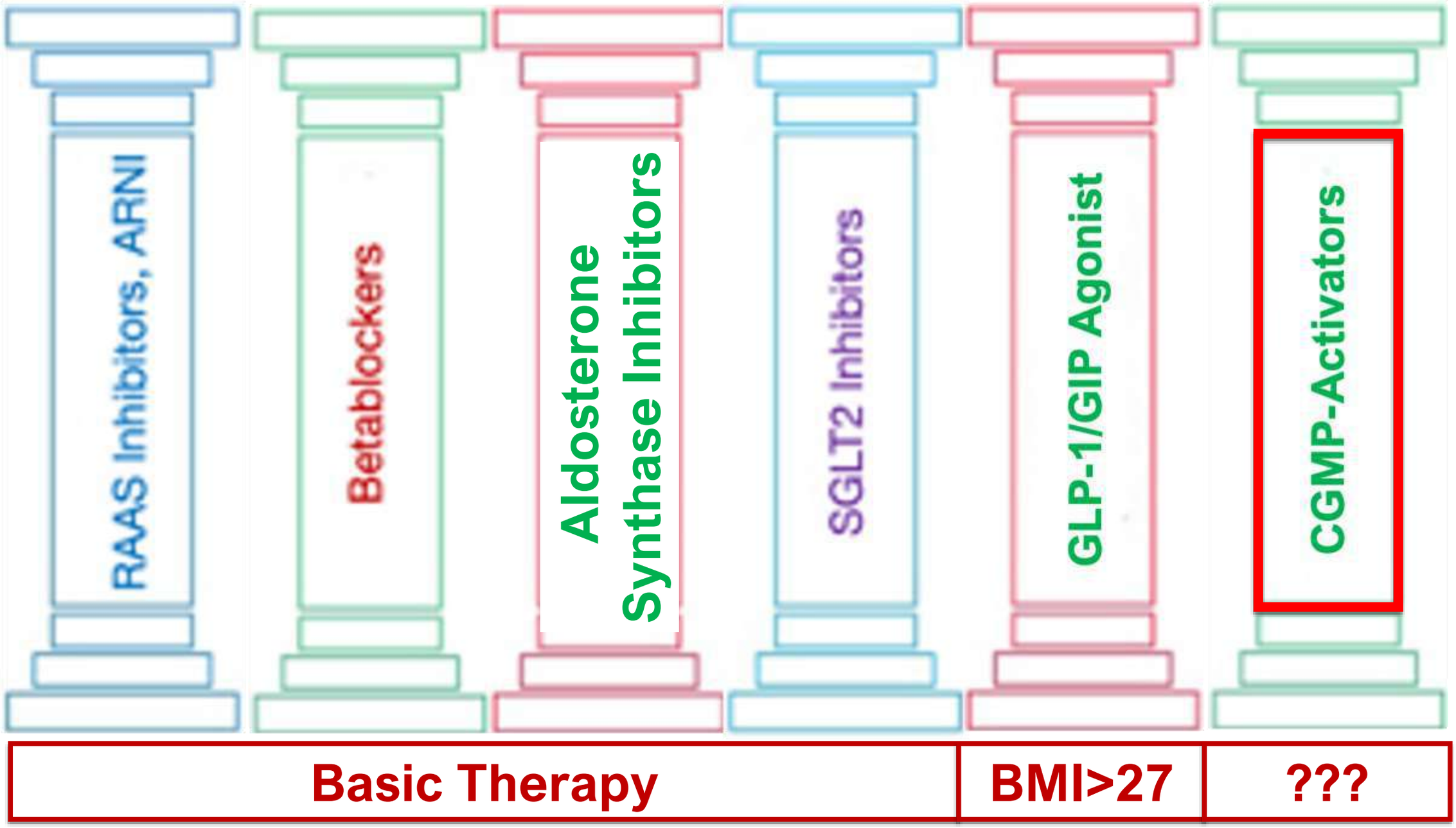
Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Milton Packer, M.D., Michael R. Zile, M.D., Christopher M. Kramer, M.D., Seth J. Baum, M.D., Sheldon E. Litwin, M.D., Venu Menon, M.D., Junbo Ge, M.D., Govinda J. Weerakkody, Ph.D., Yang Ou, Ph.D., Mathijs C. Bunck, M.D., Karla C. Hurt, B.S.N., Masahiro Murakami, M.D., and Barry A. Borlaug, M.D., for the SUMMIT Trial Study Group*



New Engl. J. Med. 2024; .DOI: 10.1056/NEJMoa2410027

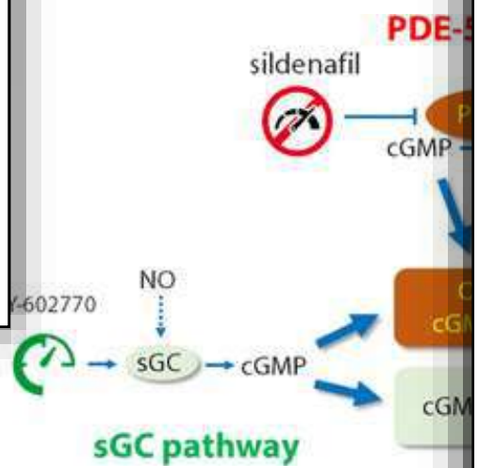
What could be the future of HF Management?

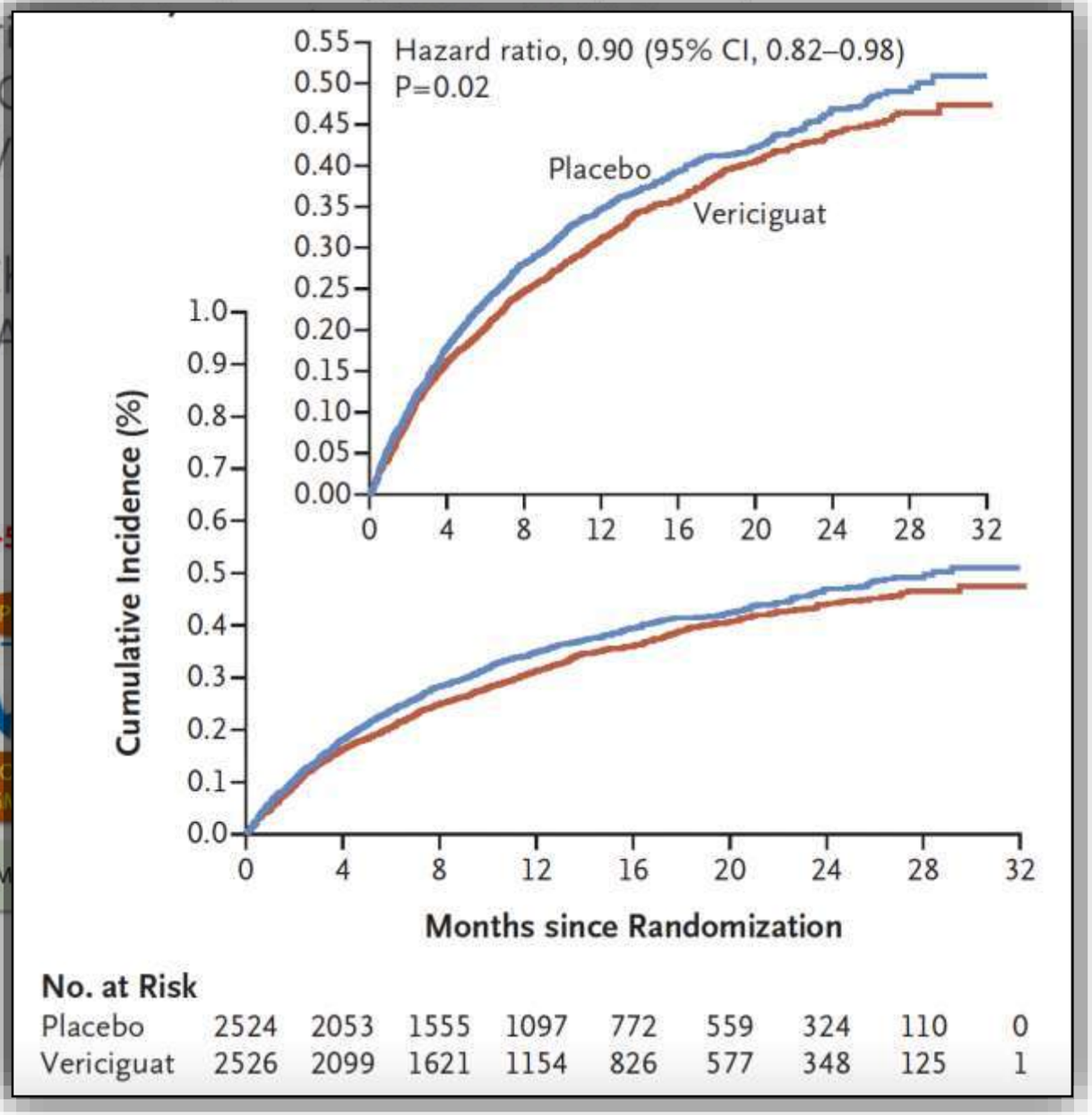


Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D.,
Justin Ezekowitz, M.B., B.Ch., Adr
Javed Butler, M.D., M.P.H., M.B.A., C
Piotr Ponikowski, M.D., Adriaan A. V
Steven E. McNulty, M.S., Mahesh J.
Joerg Koglin, M.D., Ph.D., and C
for the VICTORIA

Event Rates
Placebo 38.5%/32 months
Vericiguat 35.5%/32 months
Difference 3%
P value 0.02
NNT 33

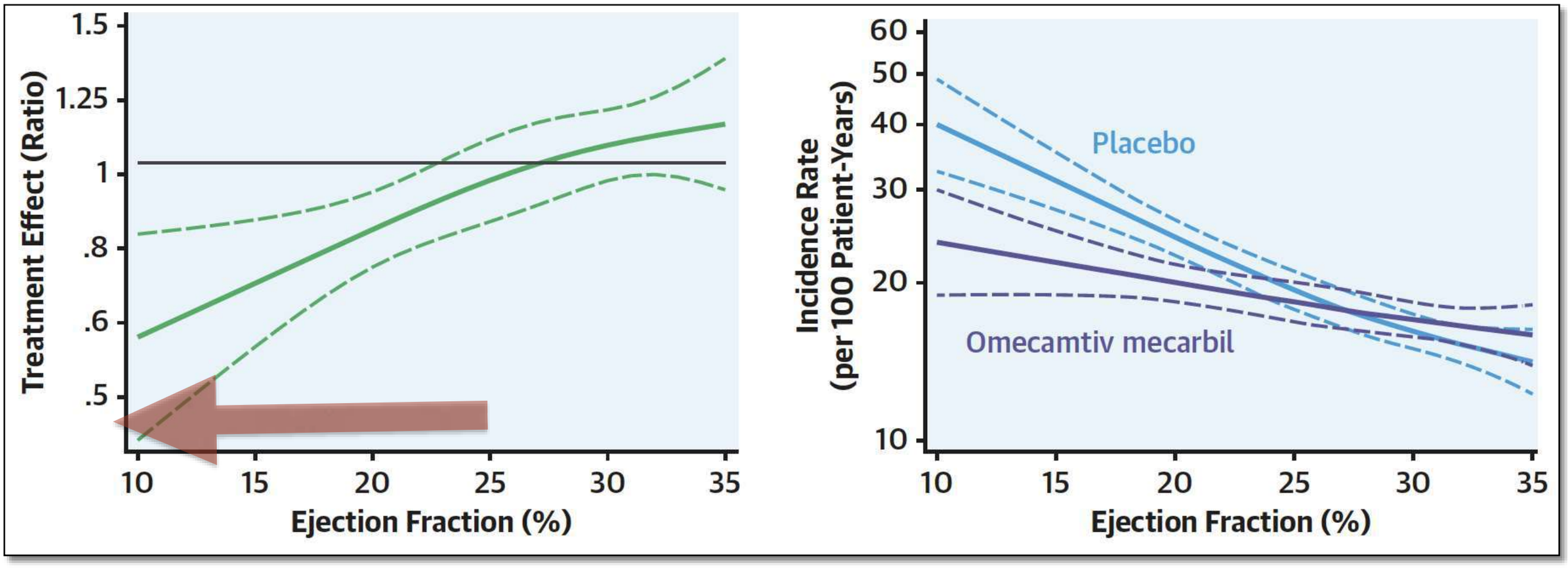




What's New in Pharmacotherapy?

- Cardiac Myosin Activators?
- Steroids?
- Aldosterone Synthase Inhibitors
- Endothelin Receptor Antagonists
- Angiotensinogen Silencing

Effect of Ejection Fraction on Clinical Outcomes in Patients Treated With Omecamtiv Mecarbil in GALACTIC-HF



(J Am Coll Cardiol 2021;78:97–108

Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

University of Zurich[UZH] | Imperial College London | King's College London

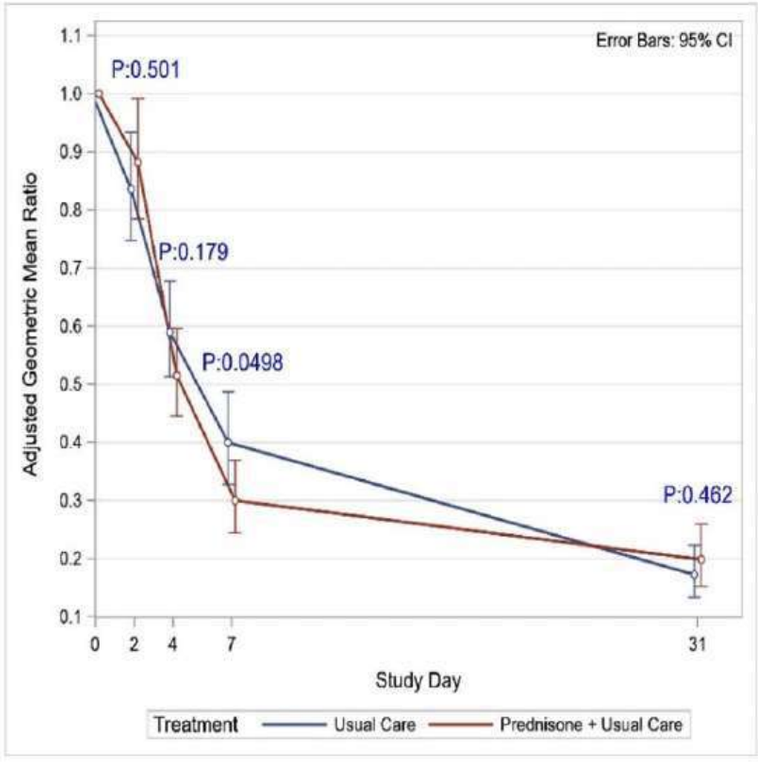
ESC European Society of Cardiology

European Jo
doi:10.1002

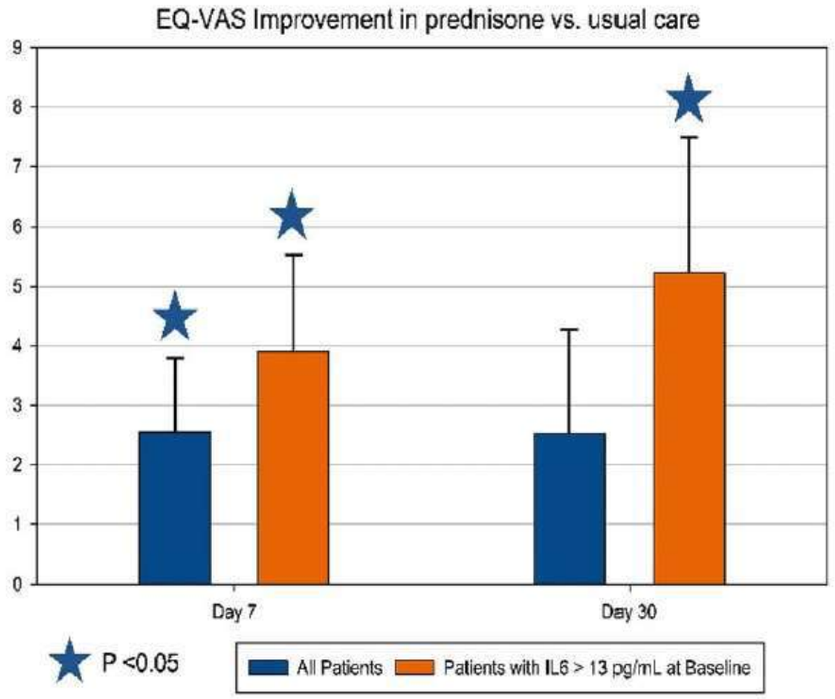
Burst steroid
The CORTAH
pilot trial

Gad Cotter[1,2,3]*, Beth A
Christopher Edwards[3], I
Andranik Mshetsyan[8], D
Jozine M. ter Maaten[6], J
Ovidiu Chioncel[13], Malh
Marco Metra[15], Douglas

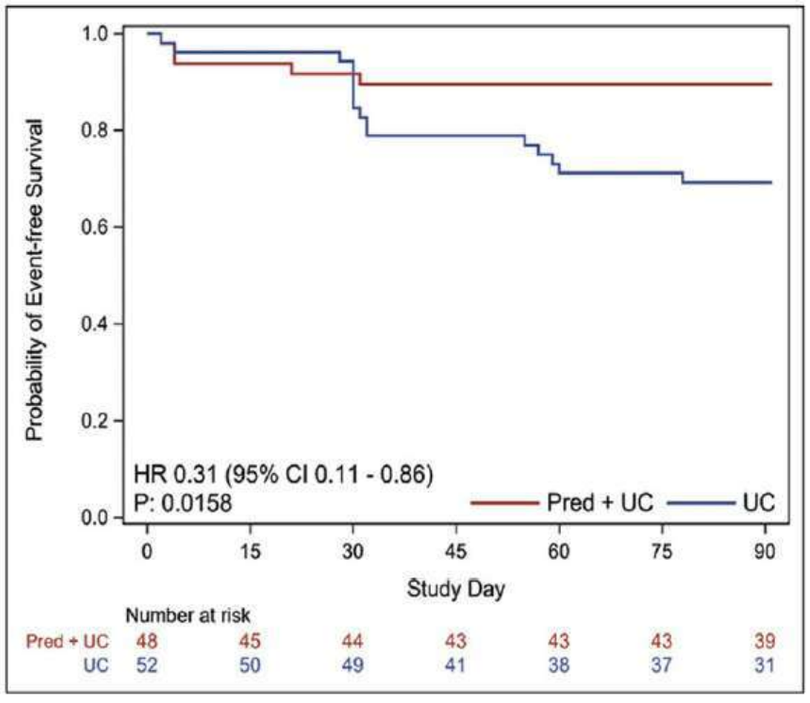
A Effects of Changes in CRP



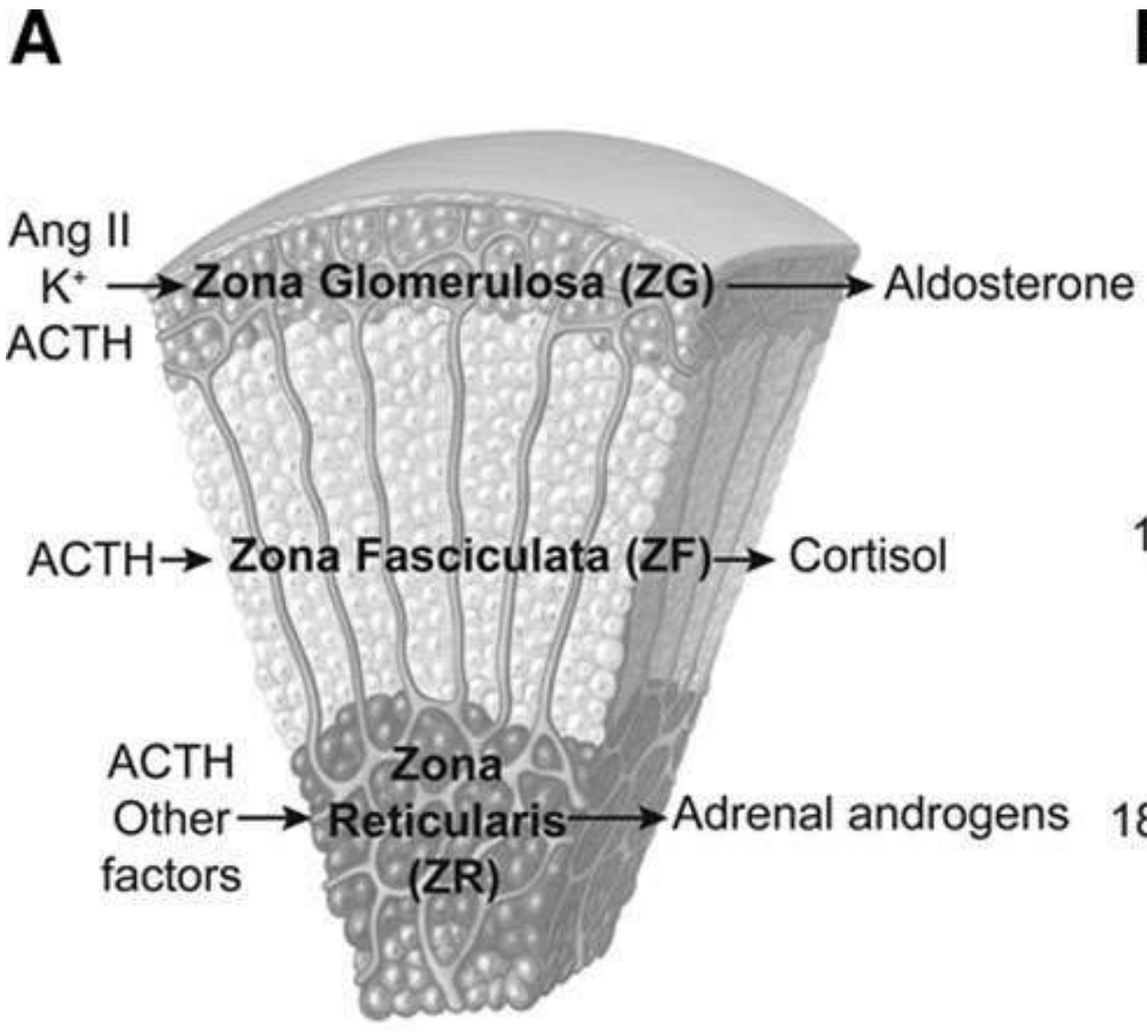
B Effects on changes in QoL by EQ VAS

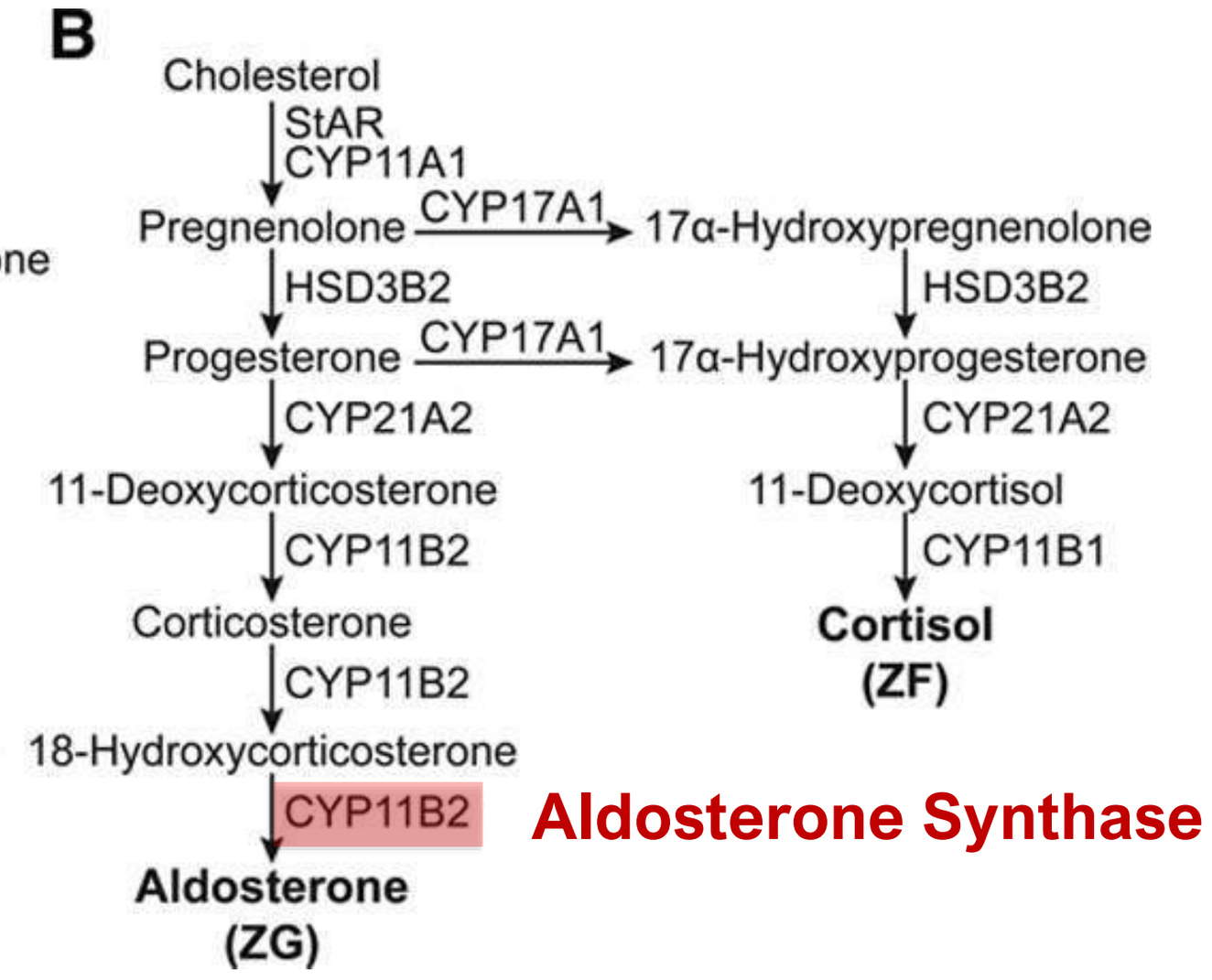


B Effects on time to WHF or Death



From Mineralocorticoid-Receptor Antagonism to Aldosterone Synthase Inhibition





Circulation. 2024;149:414–416. DOI: 10.1161/CIRCULATIONAHA.123.066314

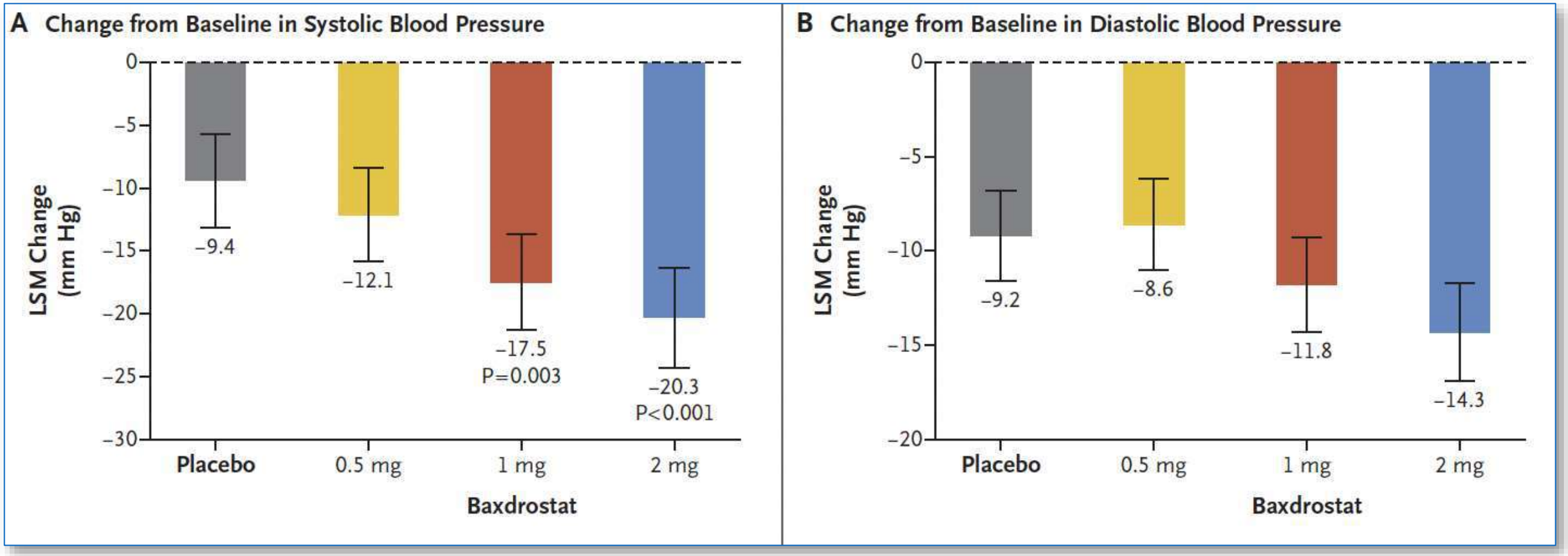
Starting Drugs in Heart Failure:
Which ones, how fast and in what order?

University of Zurich[UZH] Imperial College London KING'S College LONDON

ESTABLISHED IN 1812 FEBRUARY 2, 2023 VOL. 388 NO. 5

Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

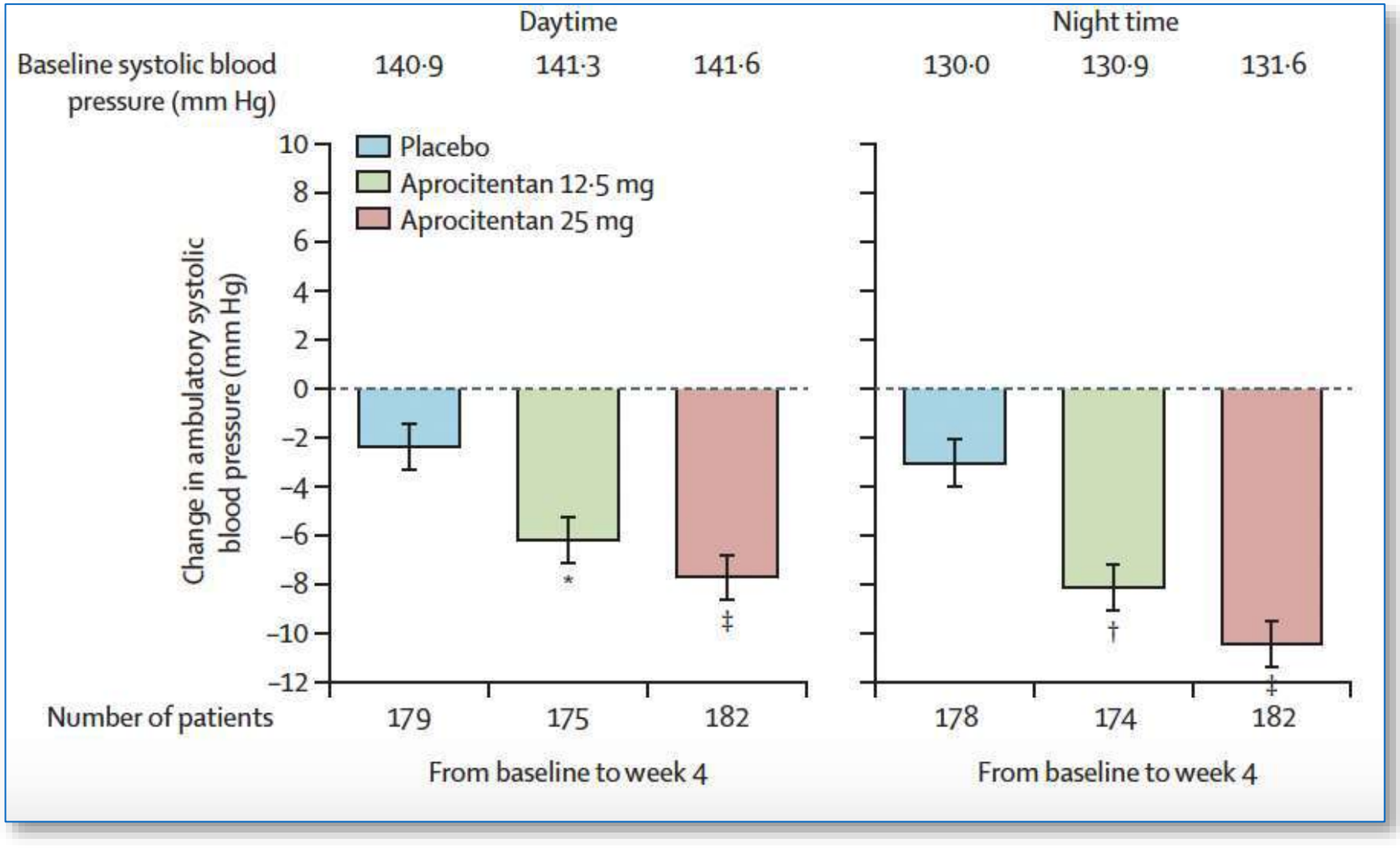
Mason W. Freeman, M.D., Yuan-Di Halvorsen, Ph.D., William Marshall, M.D., Mackenzie Pater, Ph.D., Jon Isaacsohn, M.D., Catherine Pearce, D.H.Sc., Brian Murphy, M.D., M.P.H., Nicholas Alp, M.D., Ajay Srivastava, M.D., Deepak L. Bhatt, M.D., M.P.H., and Morris J. Brown, M.D., for the BrigHTN Investigators*



N Engl J Med 2023;388:395-405.

Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial

*Markus P Schlaich, Marc Bellet, Michael A Weber, Parisa Danaietash, George L Bakris, John M Flack, Roland F Dreier, Mouna Sassi-Sayadi, Lloyd P Haskell, Krzysztof Narkiewicz, Ji-Guang Wang, on behalf of the PRECISION investigators**



Lancet 2022;400:1927-37

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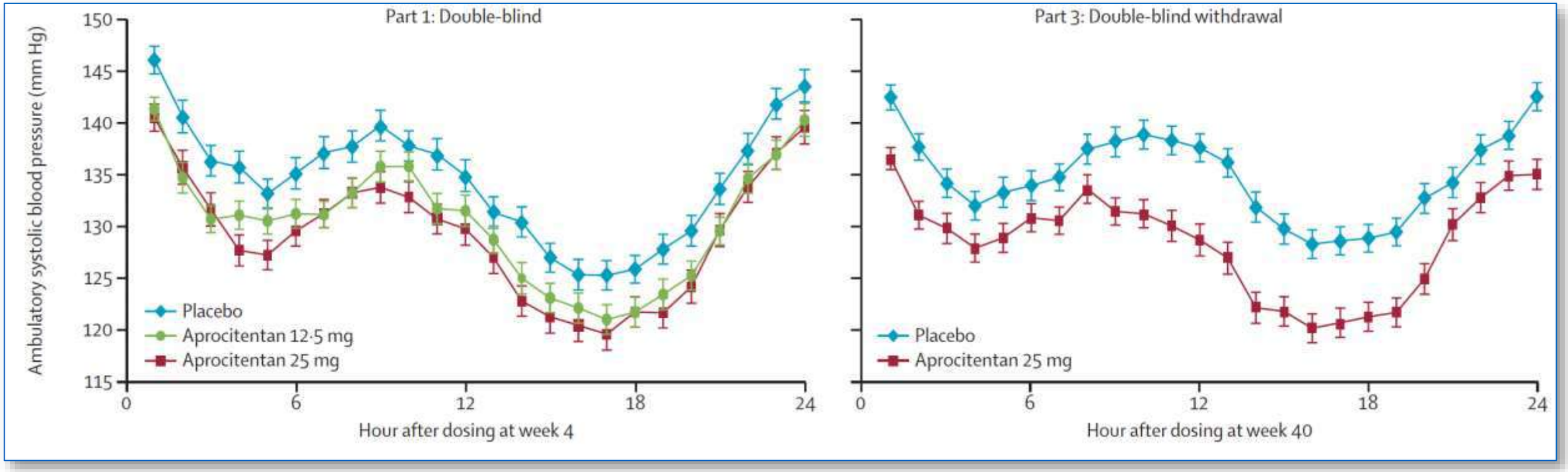
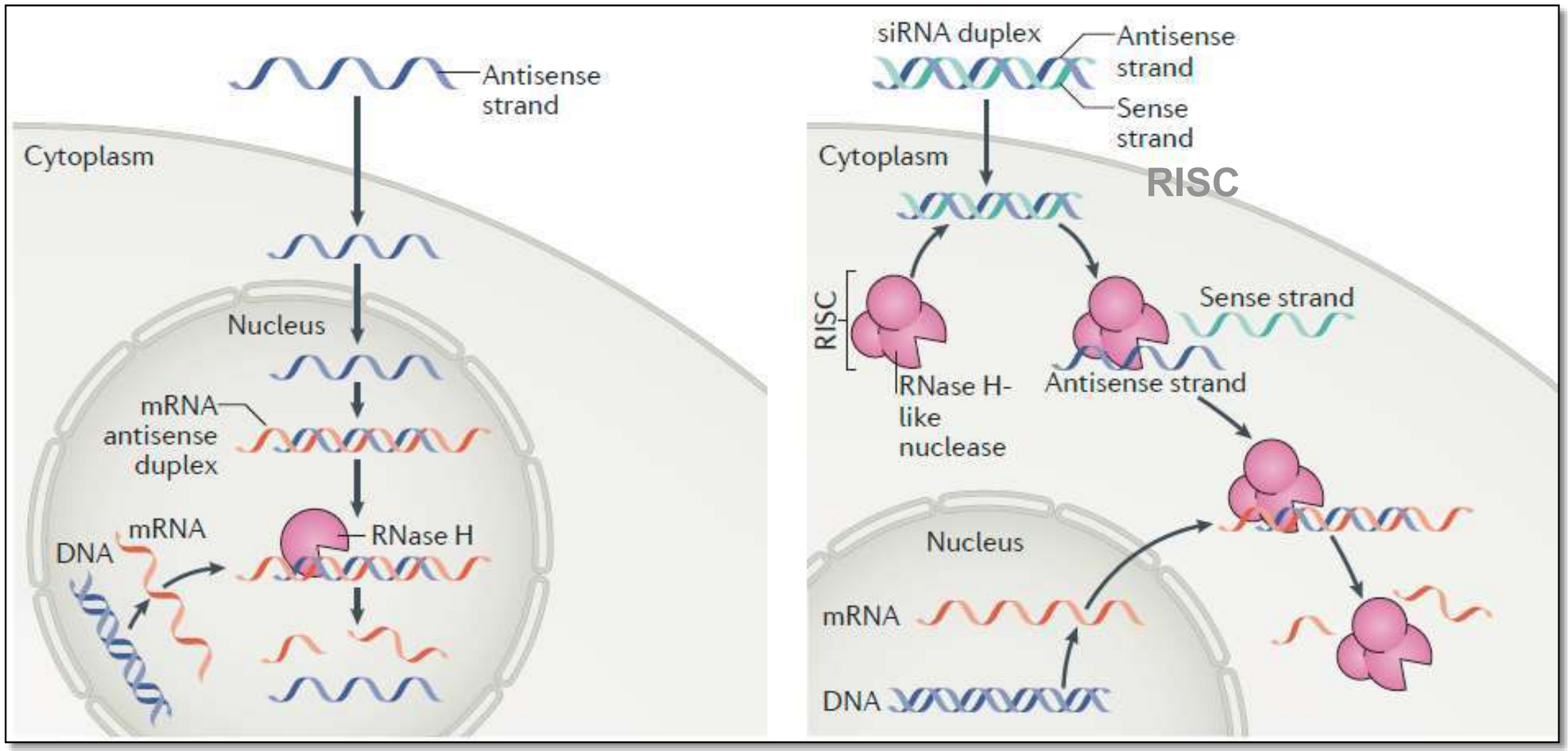


Lancet 2022;400:1927-37

Revolution in Pharmacotherapy: ASO and siRNA

Antisense Technology

RNA Interference



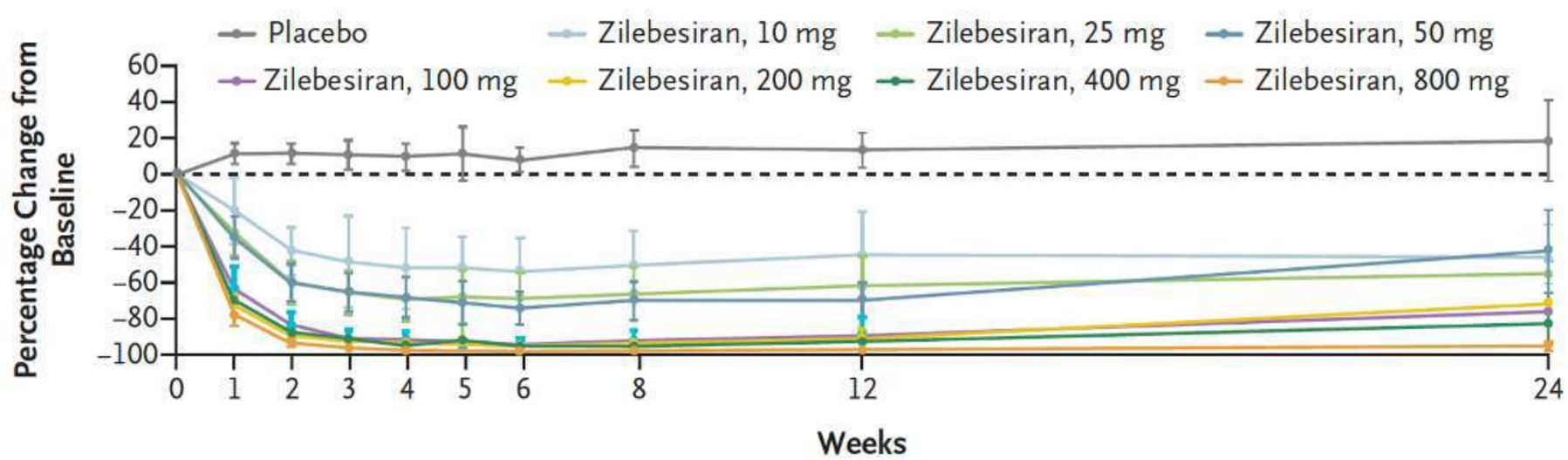
RISC = **R**NA-**I**nduced **S**ilencing **C**omplex

Nordestgaard et al. Nature Rev. Cardiol. 2018;15: 261-272

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H.,

Dose-Dependent Change in Angiotensinogen Plasma Levels

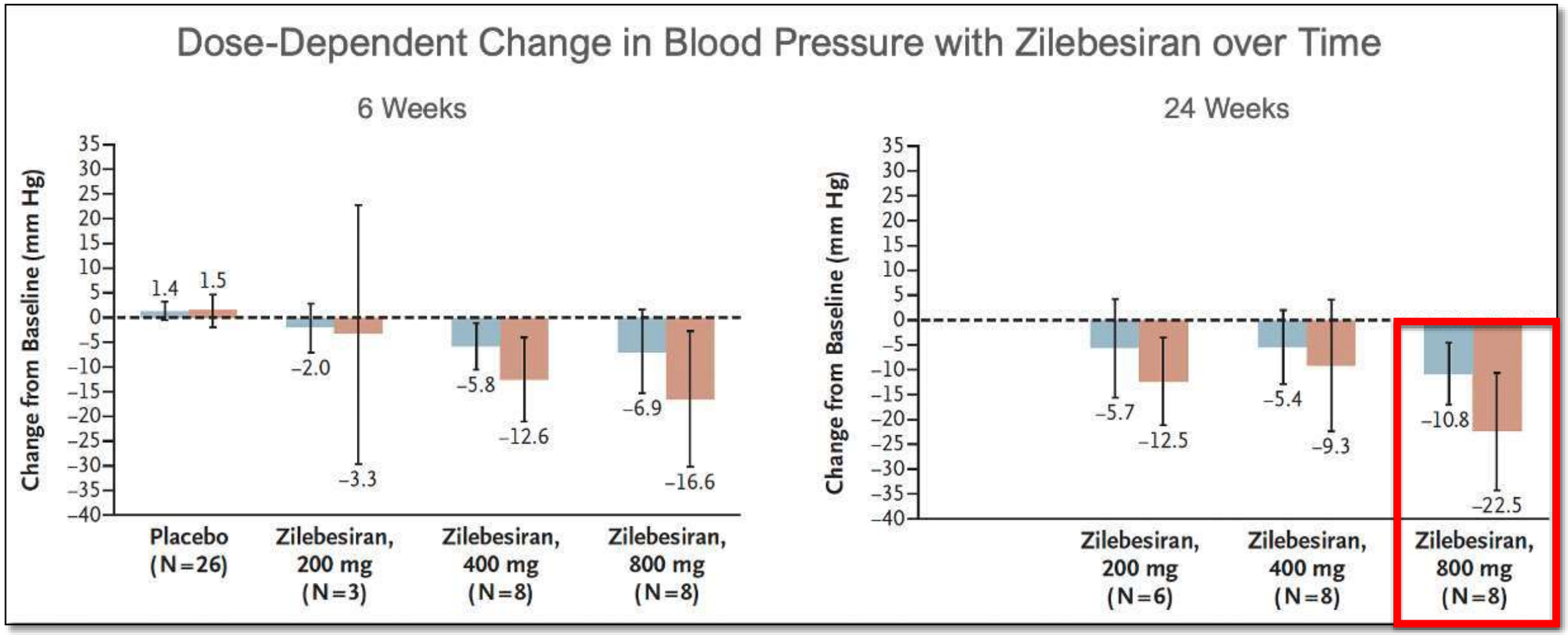


No. of Patients										
Placebo	28	28	28	28	27	17	26	27	28	12
Zilebesiran, 10 mg	8	8	8	8	8	8	8	8	8	5
Zilebesiran, 25 mg	8	8	8	8	8	8	8	8	8	8
Zilebesiran, 50 mg	8	8	8	8	8	8	8	7	7	7
Zilebesiran, 100 mg	8	7	8	8	8	8	8	8	7	7
Zilebesiran, 200 mg	8	8	8	7	6	2	3	7	8	8
Zilebesiran, 400 mg	8	8	8	8	8	0	8	8	8	8
Zilebesiran, 800 mg	8	8	8	8	8	0	8	8	8	8

N Engl J Med 2023;389:228-38.

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Akshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.



N Engl J Med 2023;389:228-38.

The Rapid Uptitration Pharmacotherapy in Heart Failure

- Add the fantastic four fast
- Increase dosage rapidly
- Monitor blood pressure, heart rate and rneal function