



Future Perspectives in Heart Failure and Cardiomyopathies

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LUMPERS

SPLITTERS



ESC

European Society
of Cardiology

European Heart Journal (2019) **0**, 1–5

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VIEWPOINT

Lumpers and splitters: the bumpy road to precision medicine

Thomas F. Lüscher^{1,2*}

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From Unity to Diversity

Lumpers

*Heart failure
is all alike*

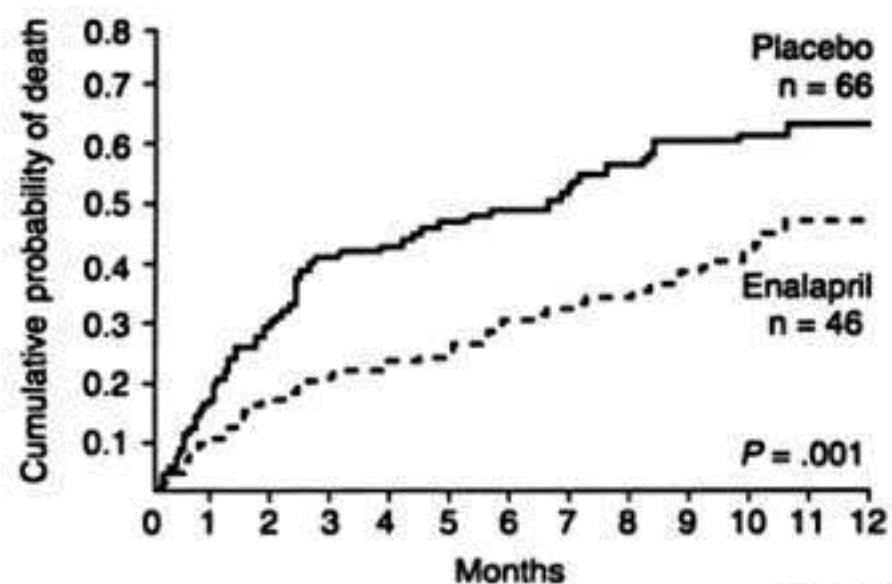
Splitters

*There are multiple
forms of heart failure*



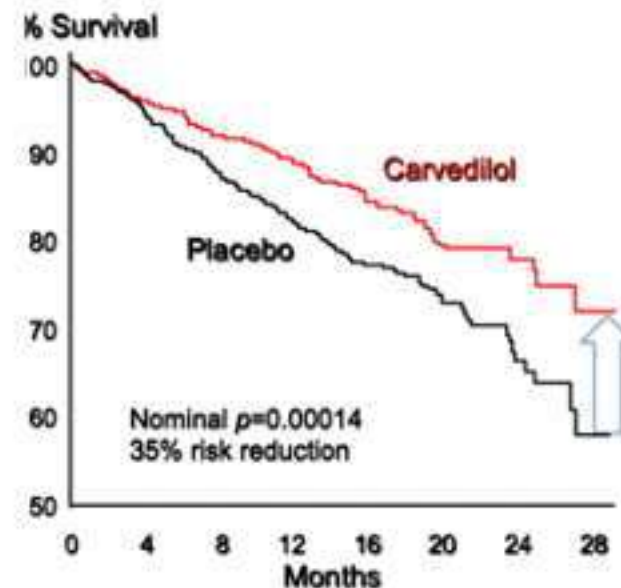
Lumping or the Seminal Trials: Heart Failure is HFrEF

CONSENSUS TRIAL
(ENALAPRIL vs. Placebo)
NYHA IV

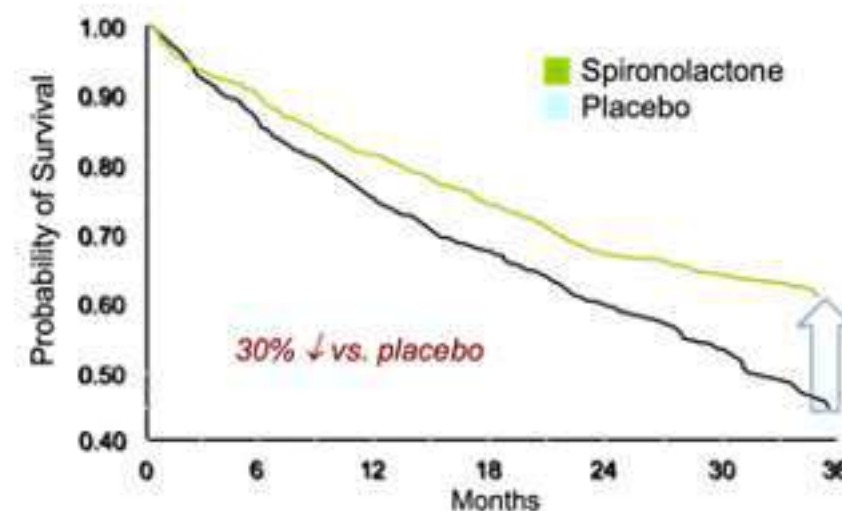


N Engl J Med. 1987

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

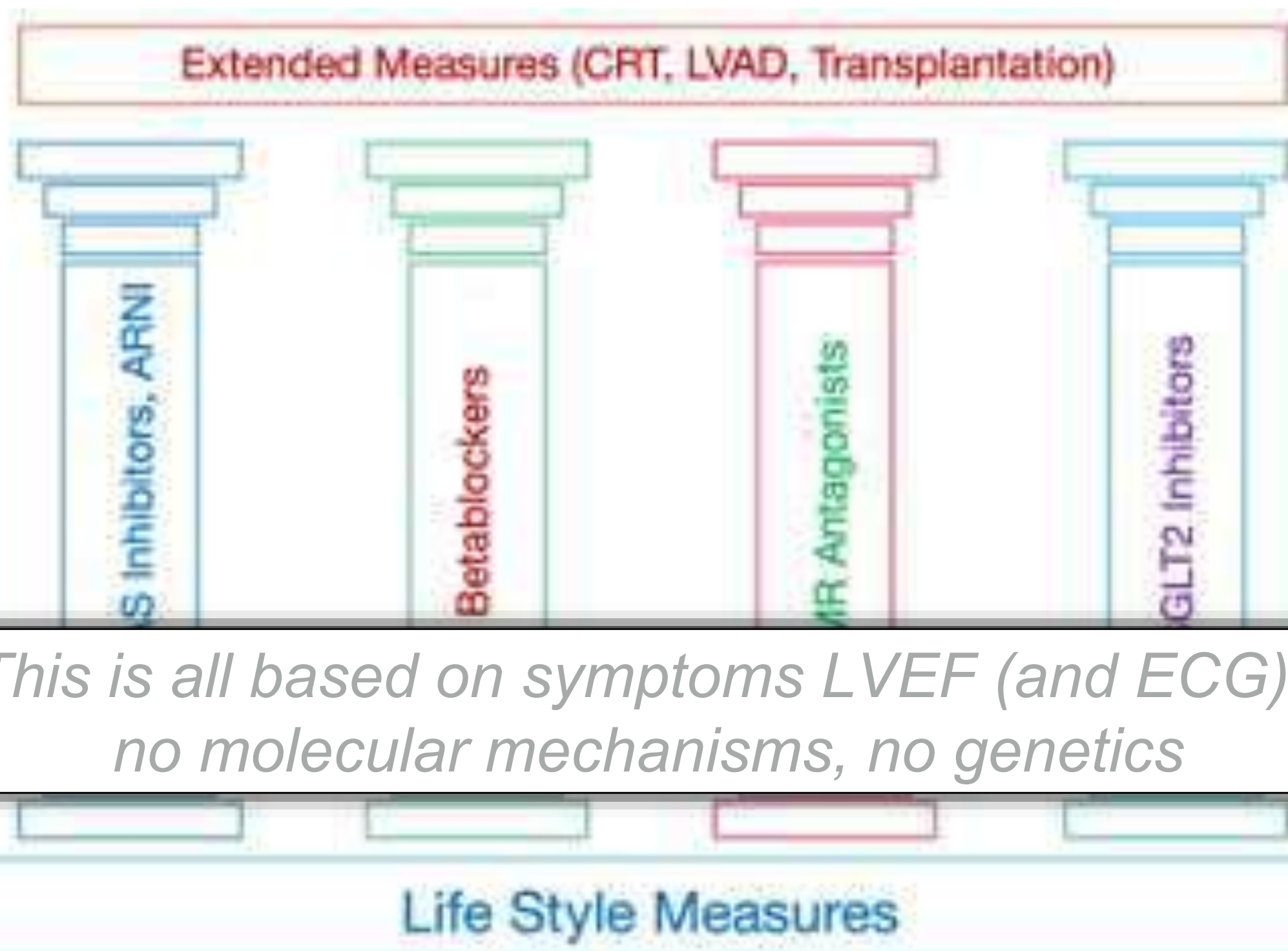


RALES TRIAL
(Spironolactone vs. Placebo)
LVEF <35%





Lumping Management: Heart Failure is HFrEF

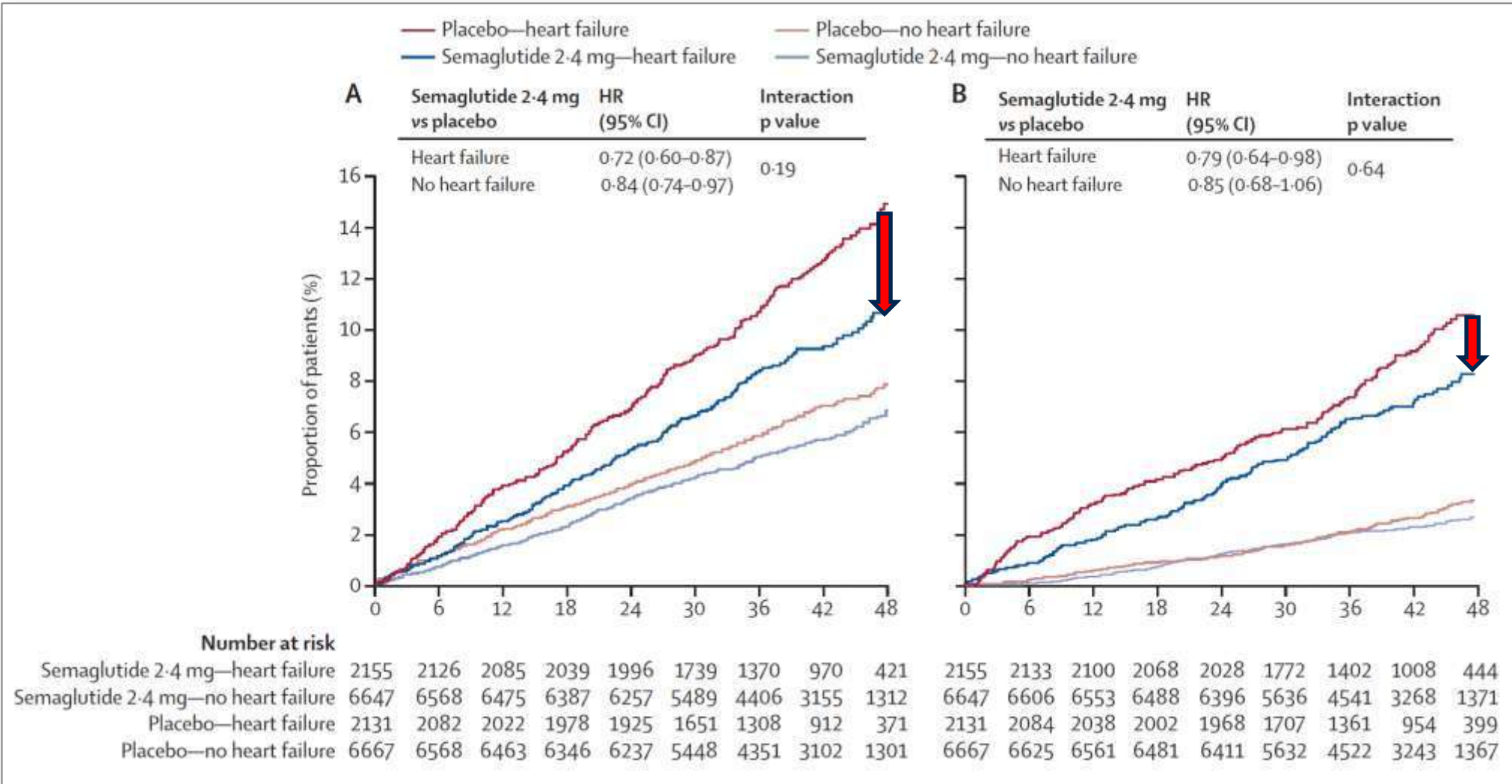


*This is all based on symptoms LVEF (and ECG),
no molecular mechanisms, no genetics*



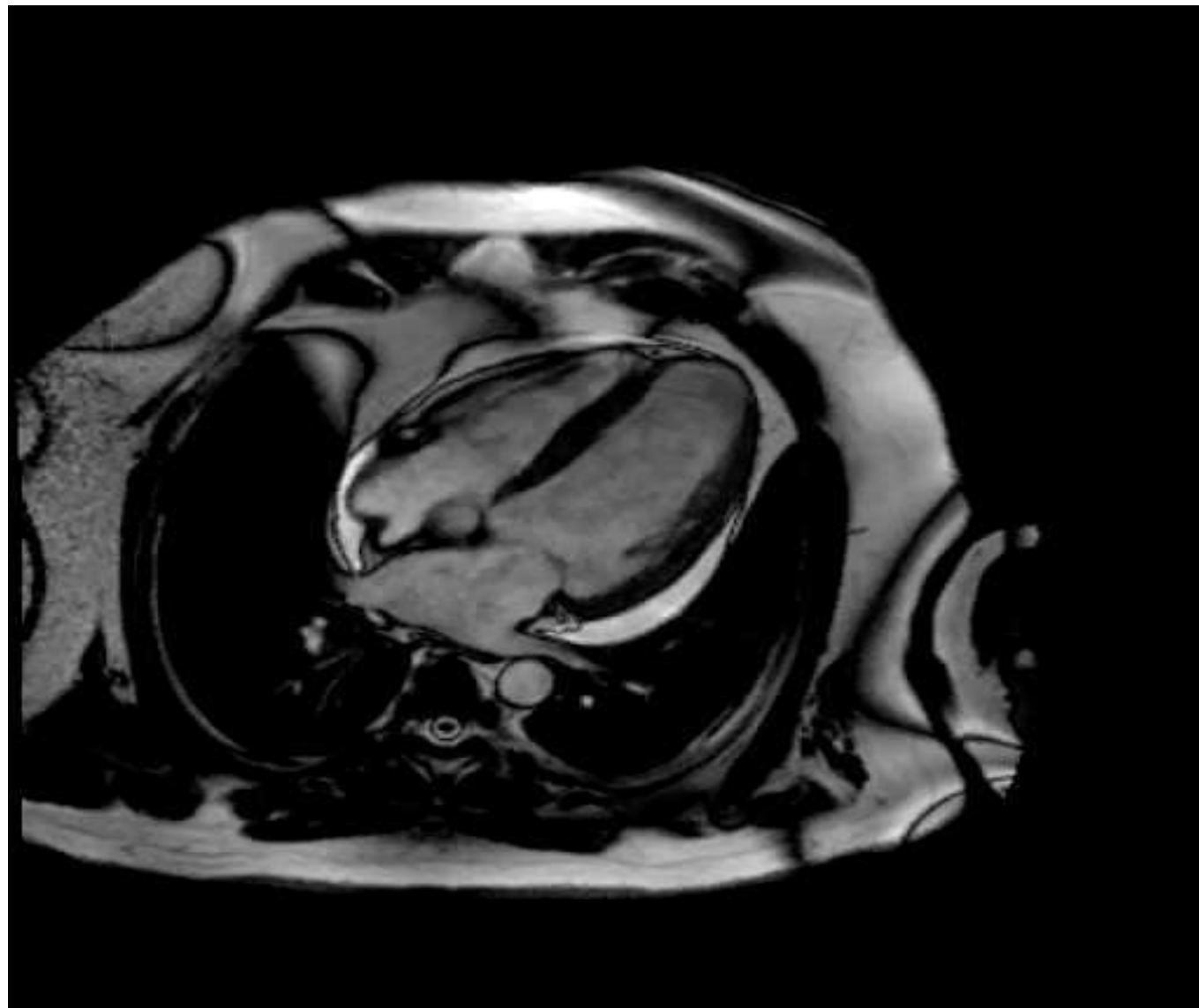
Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial

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





Ischaemic Cardiomyopathy (HFrEF after STEMI in the LAD)



Can we Prevent Ischaemic CMP?

Primary Prevention

- Lipid lowering
- Blood pressure control
- Antidiabetics

Primary PCI

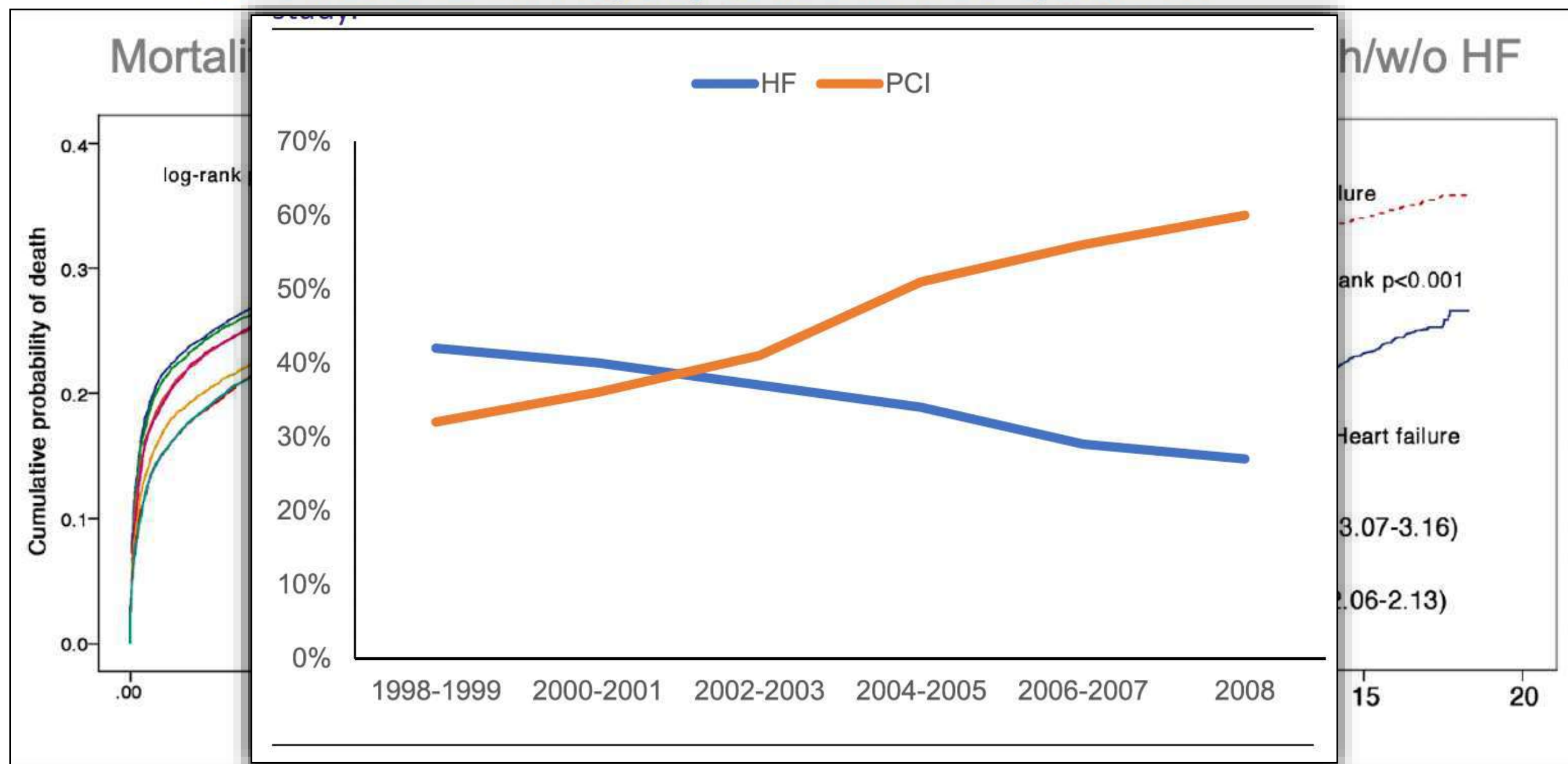
Secondary Prevention

- HF medication
- Lipid lowering
- Blood pressure control
- Antidiabetics



Incidence, Temporal Trends, and Prognostic Impact of Heart Failure Complicating Acute Myocardial Infarction

The SWEDEHEART Registry (Swedish Web-System for





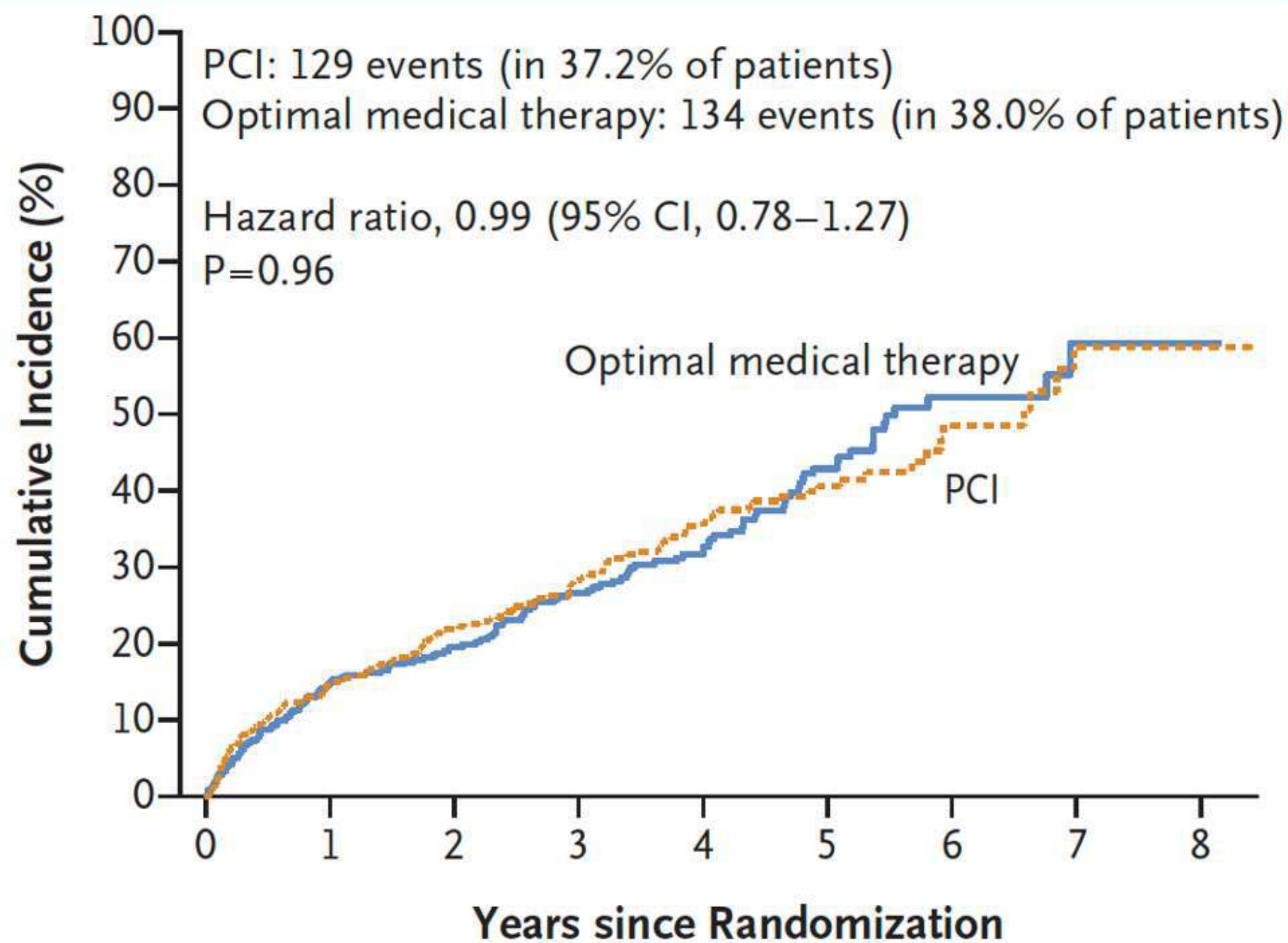
The Spectrum of Heart Failure and what it means for clinical practice



University of
Zurich^{UZH}



Imperial College
London



No. at Risk

PCI	347	295	262	179	130	80	32	14	3
Optimal medical therapy	353	299	276	191	142	82	33	10	1



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



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Zurich



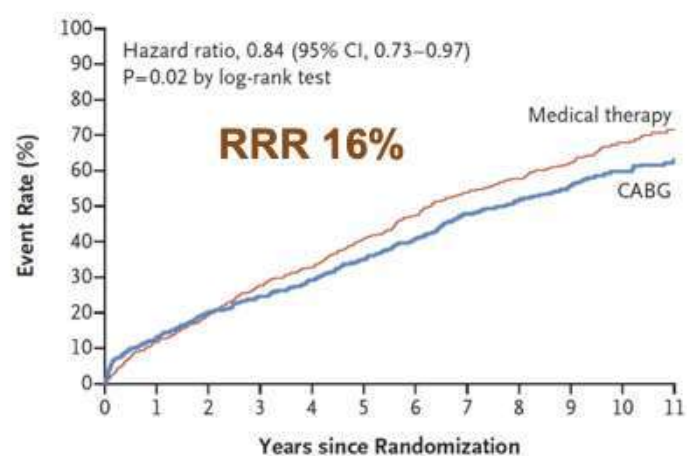
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London

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Percutaneous Coronary

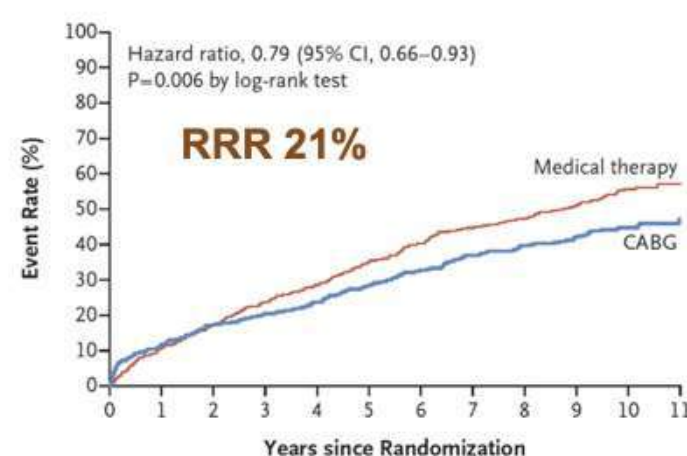
Aorto-Coronary Bypass (ACBP)

Death from any cause



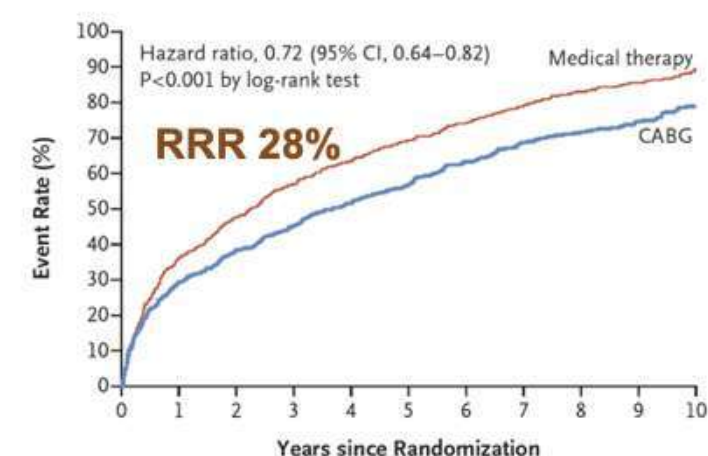
No. at Risk	602	532	487	435	404	357	315	274	248	164	82	37
Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

Death from CV cause

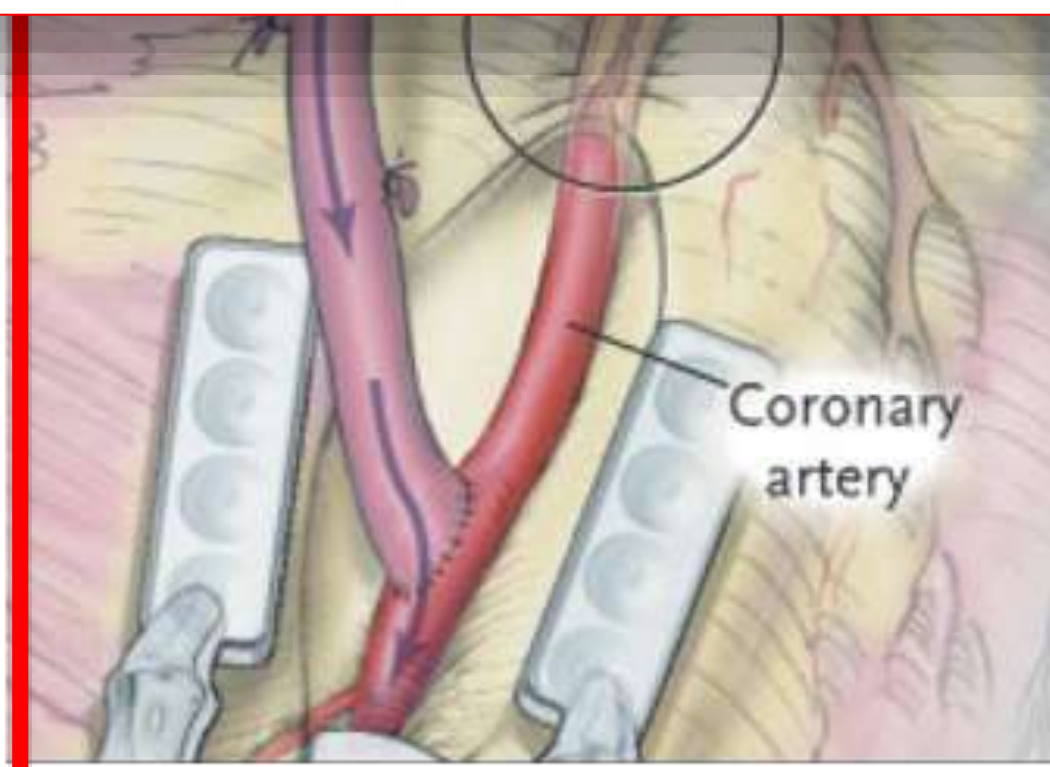
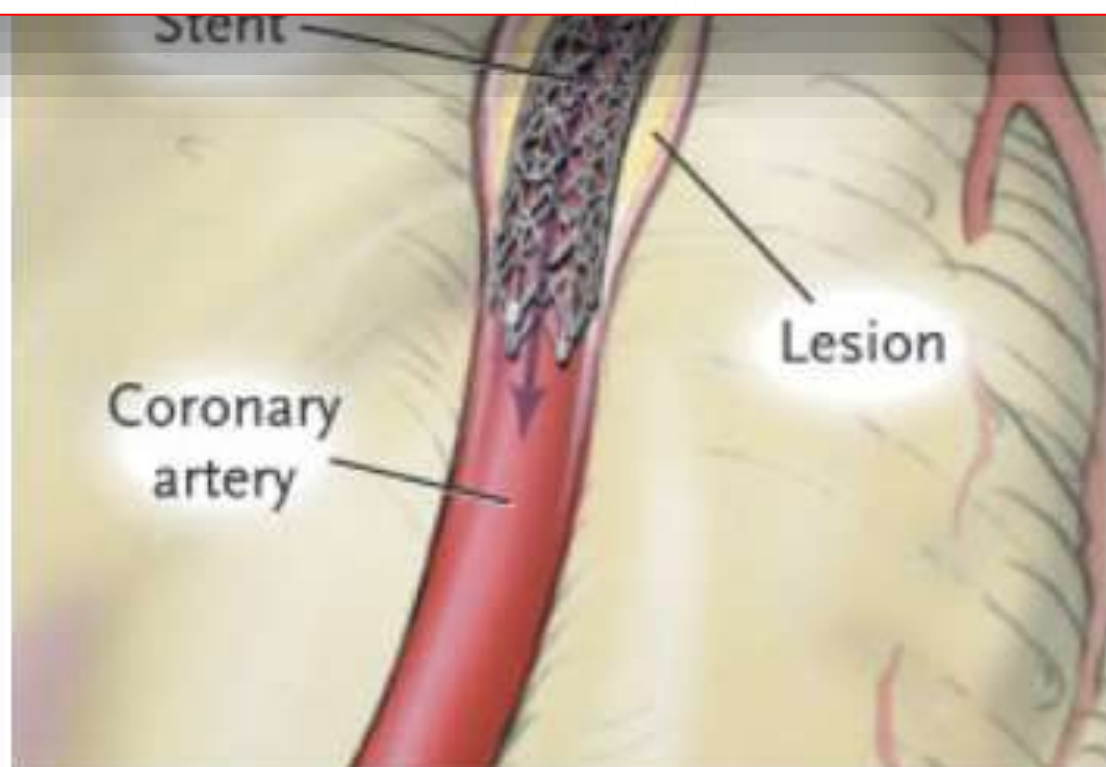


No. at Risk	602	532	487	435	404	357	315	274	248	164	82	37
Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

Death/Hospitalisation



No. at Risk	602	385	314	259	219	185	152	123	98	57	19
Medical therapy	602	385	314	259	219	185	152	123	98	57	19
CABG	610	431	376	334	293	259	218	184	166	106	43

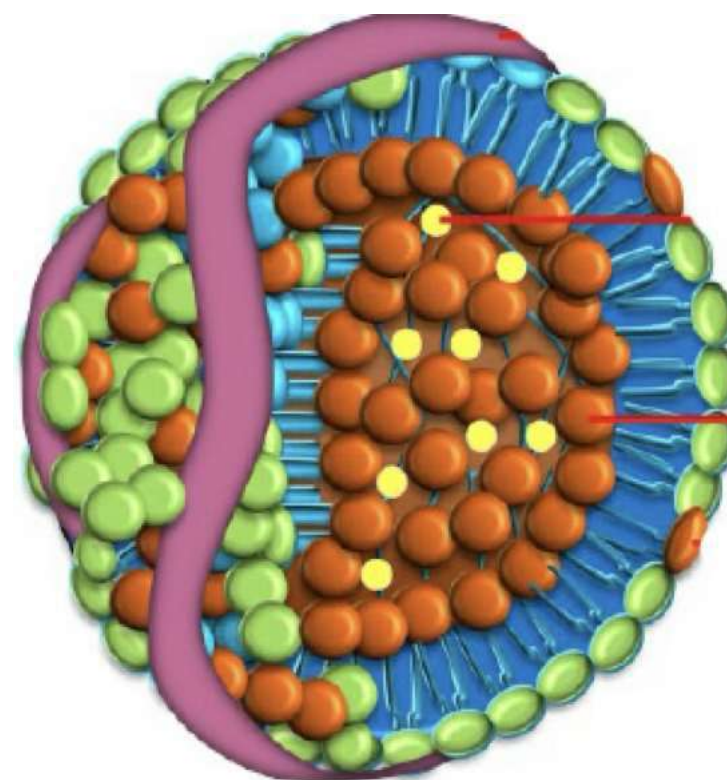
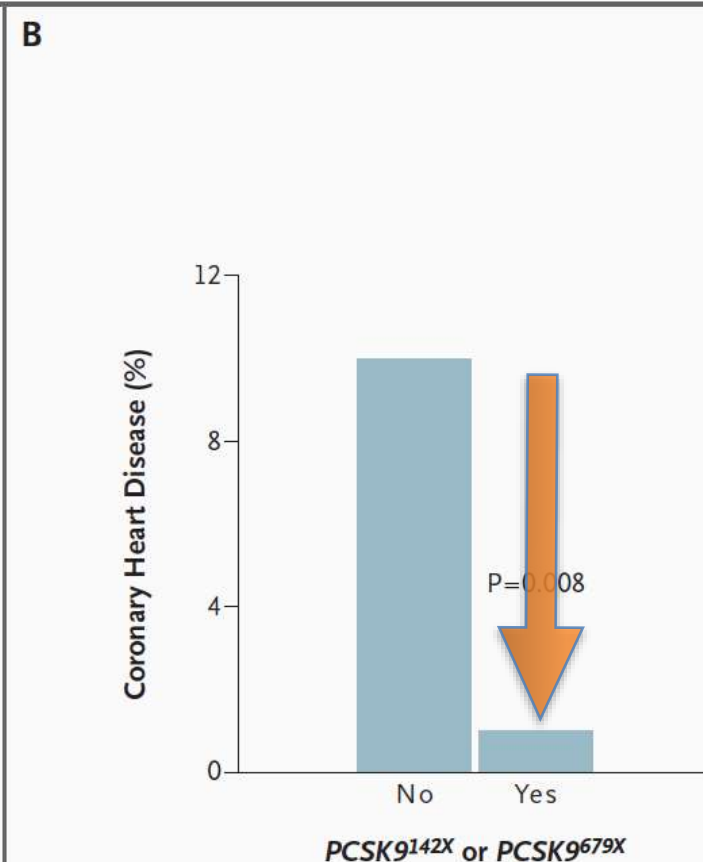
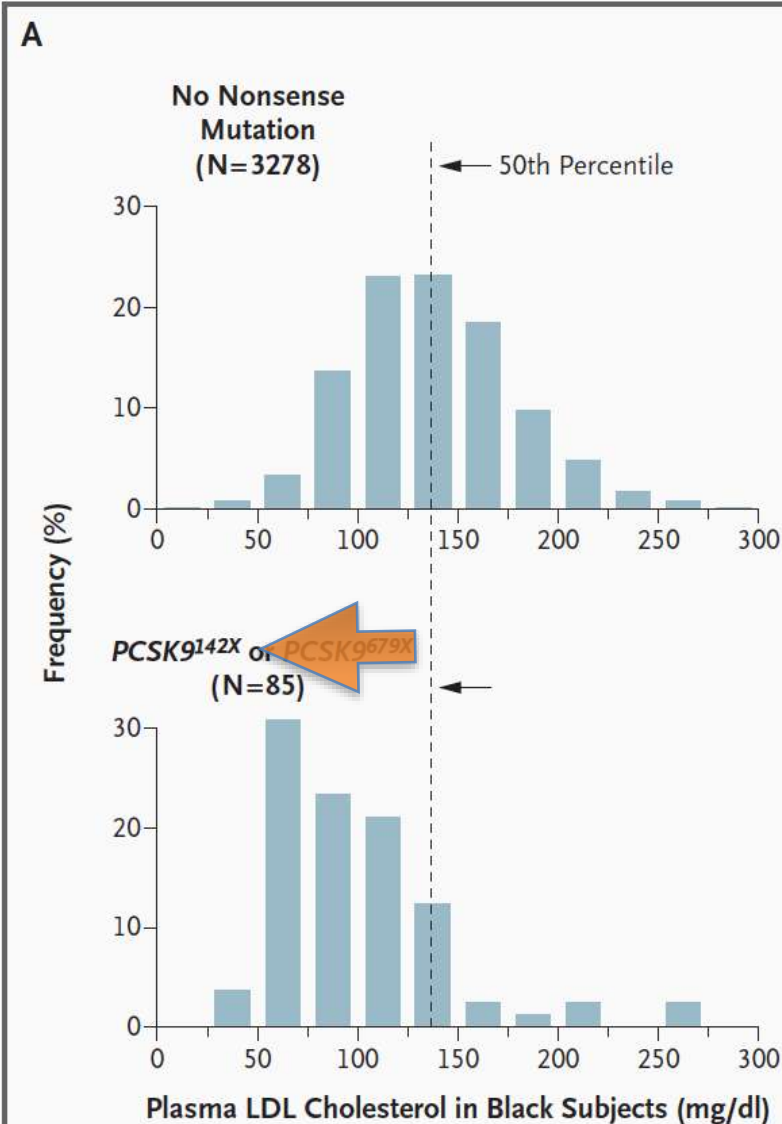


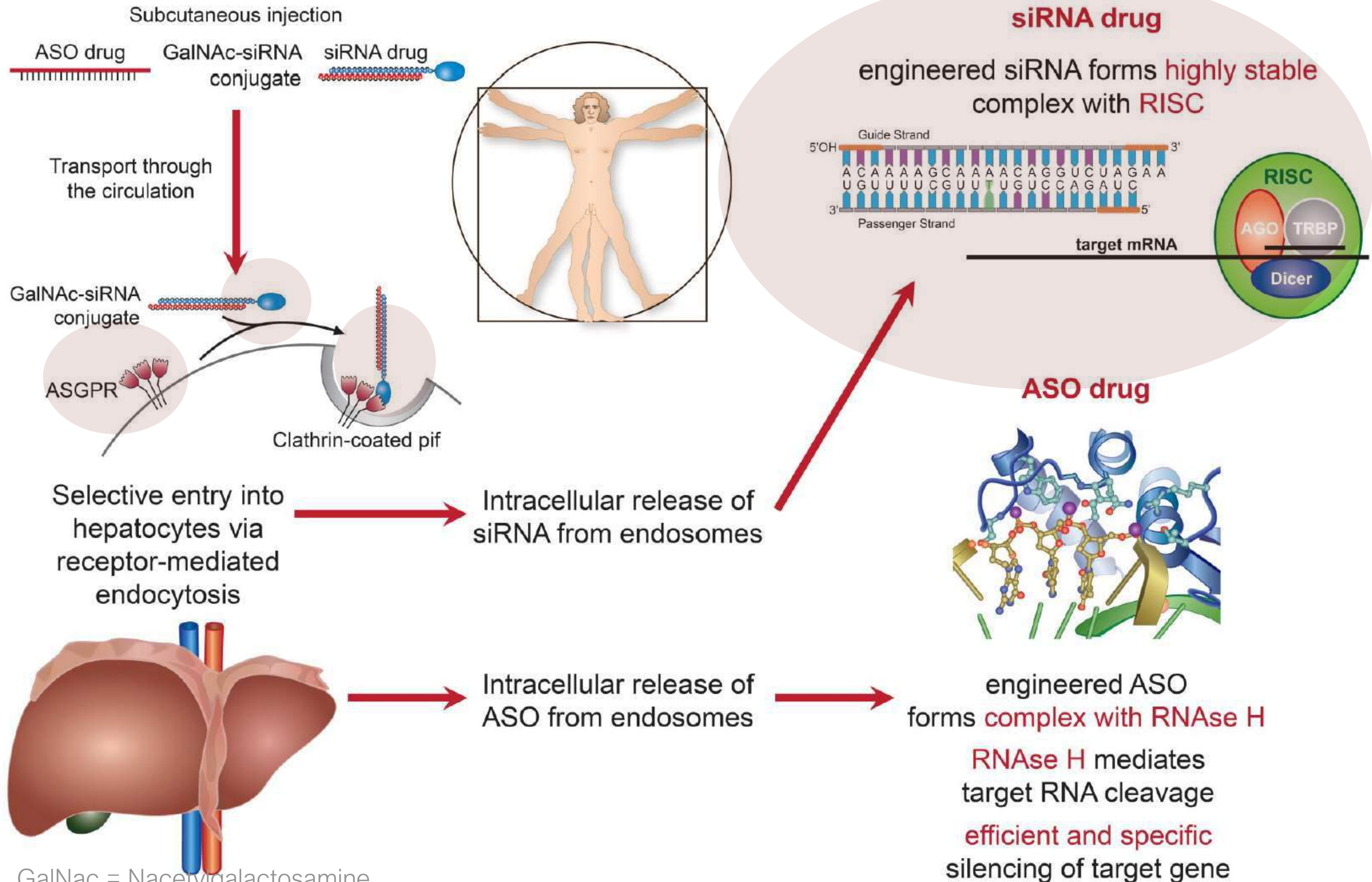


Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D.,

Ph.D.

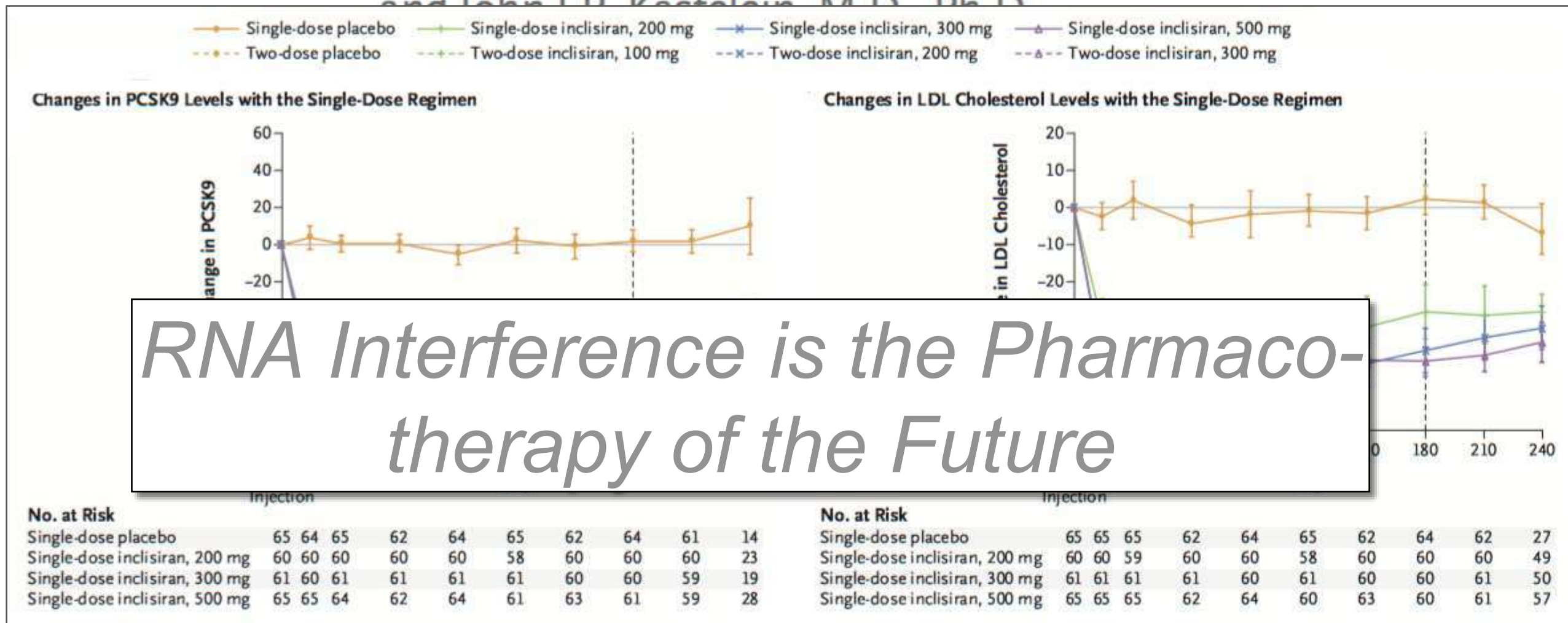




GalNac = Nacetylgalactosamine
ASGR = Asialoglycoprotein receptor

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D.,
David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D.,
Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D.,
Peter Wijngaard, Ph.D., R. Scott Wright, M.D.,
and John D. Kasteleijn, M.D., Ph.D.





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



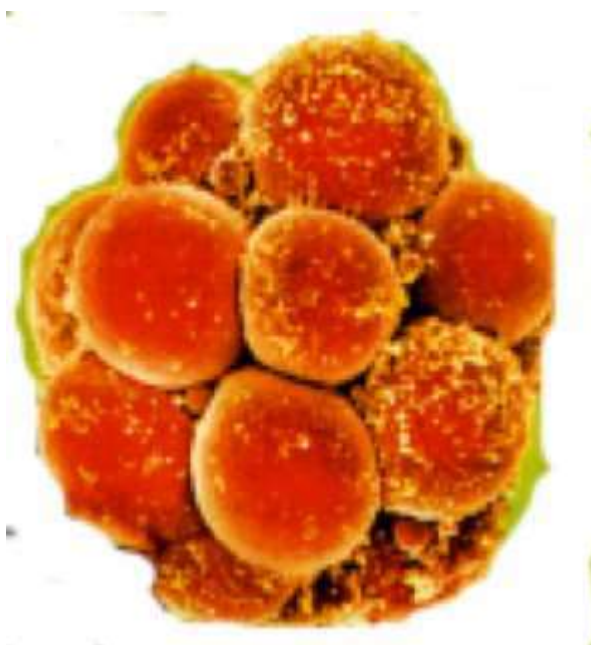
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London

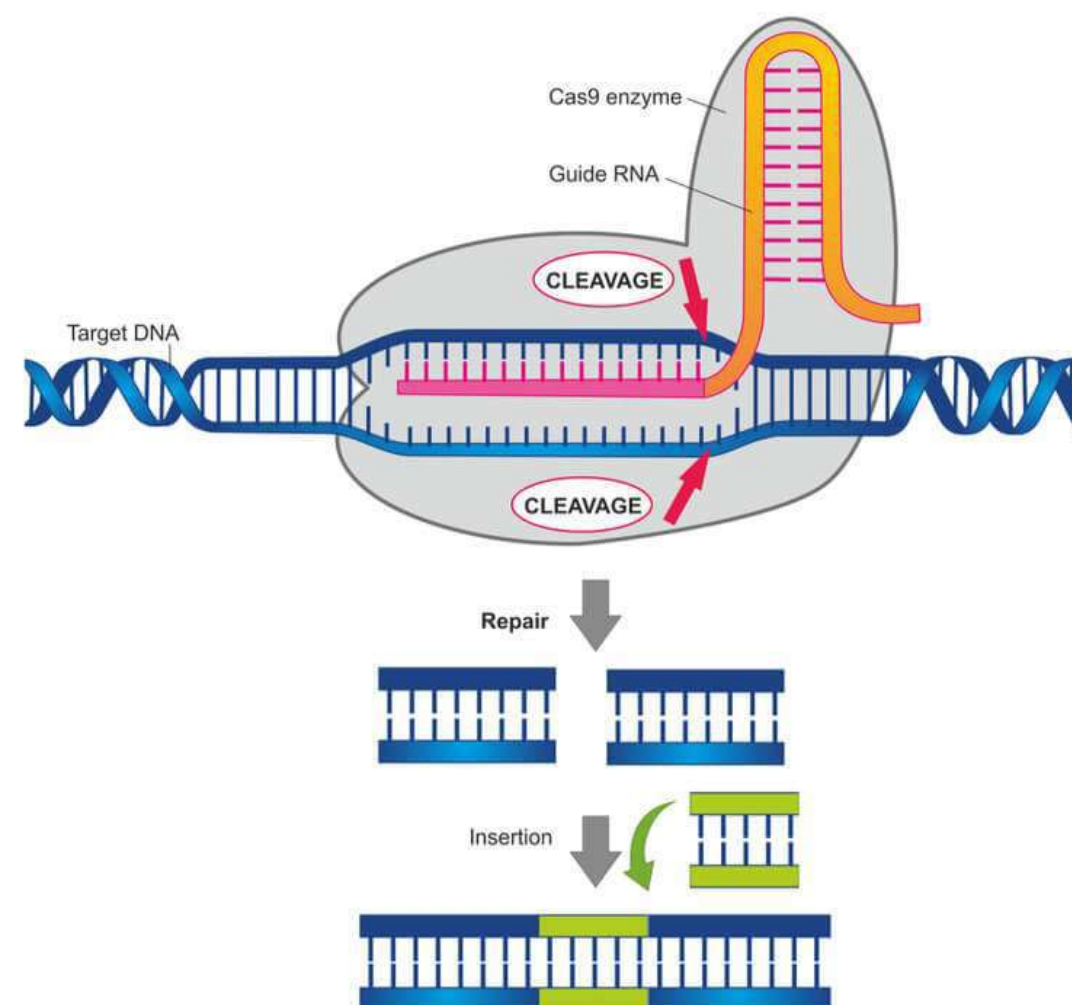


Emmanuelle Charpentier and Jennifer Doudna



Crisper Cas 9: *The Gene Scissor*

Clustered Regularly Interspaced Short Palindromic Repeats



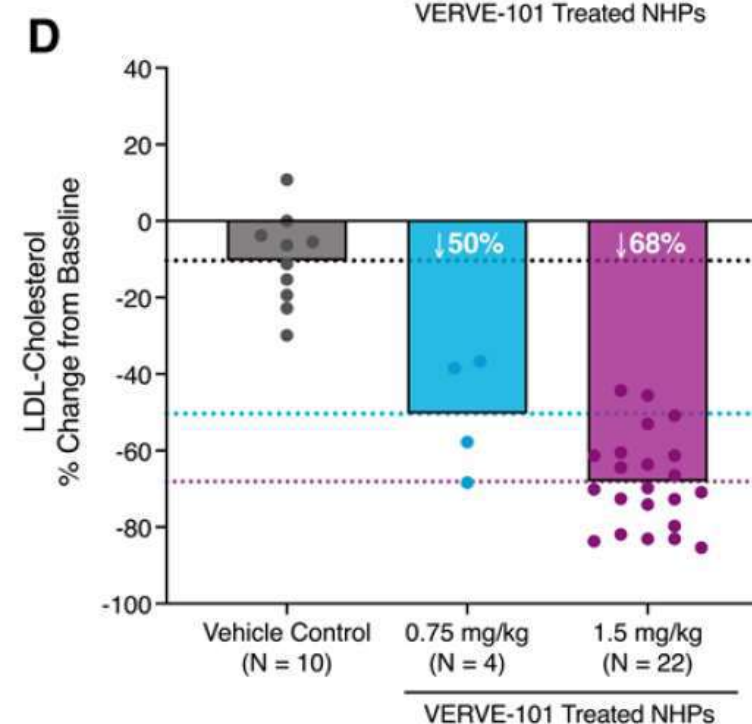
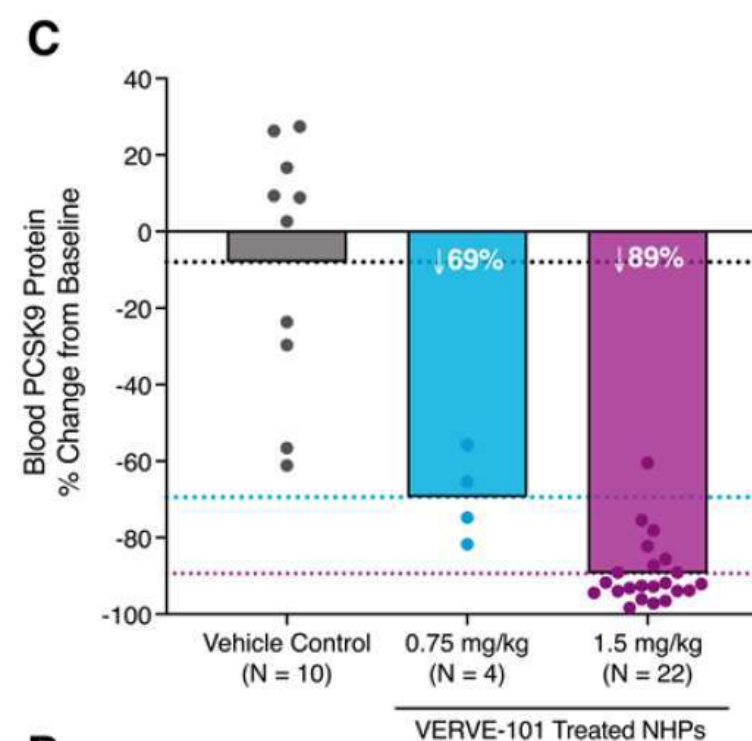
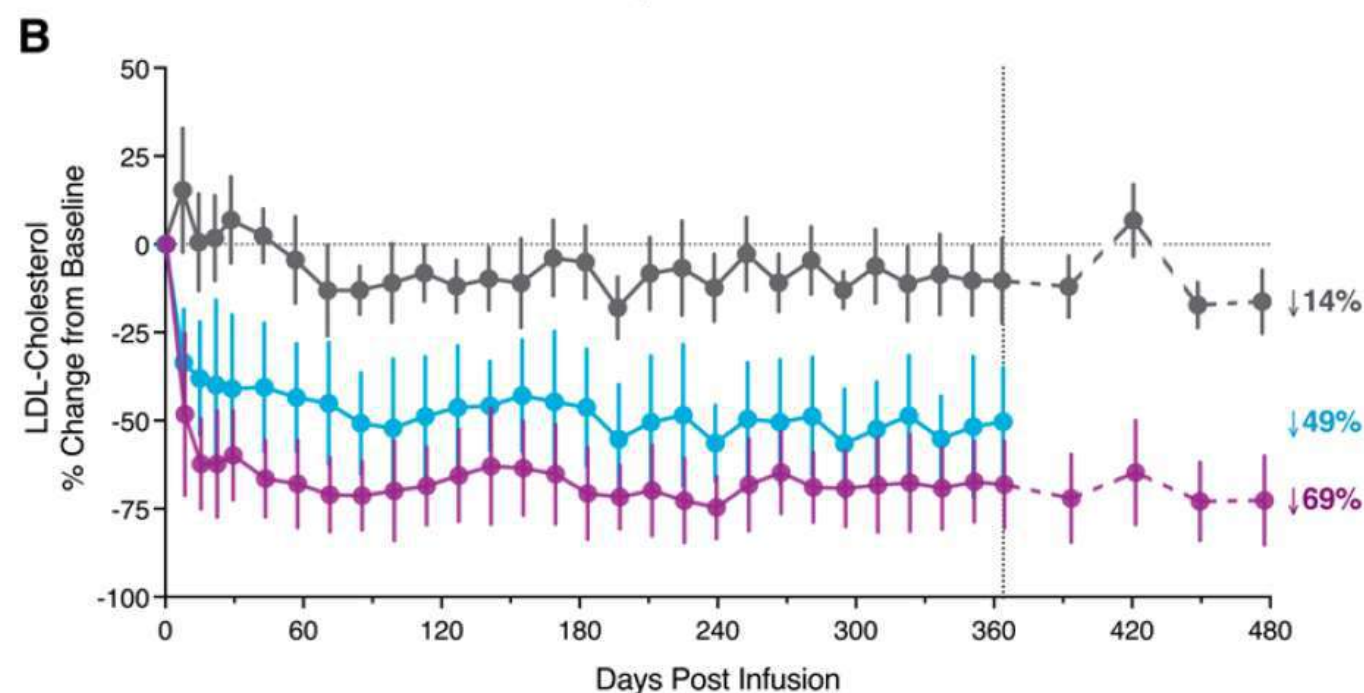
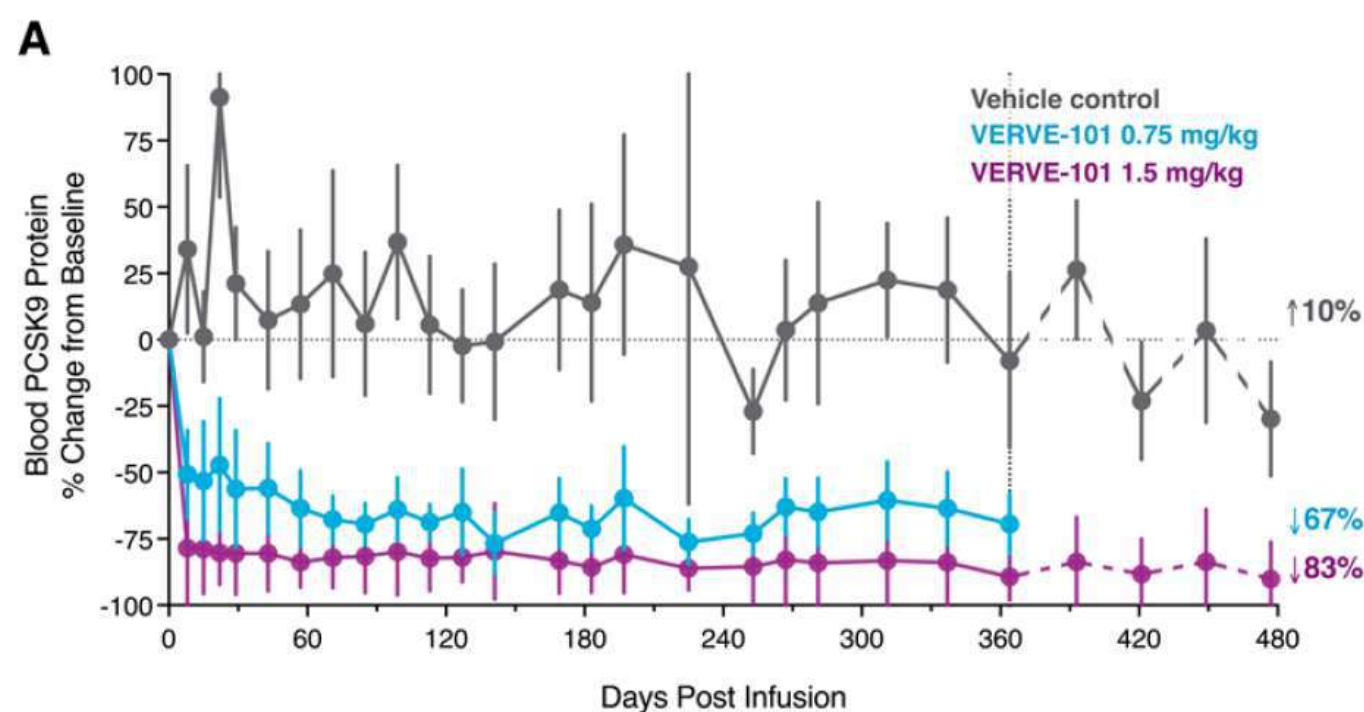


Efficacy and Safety of an Investigational Single-

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



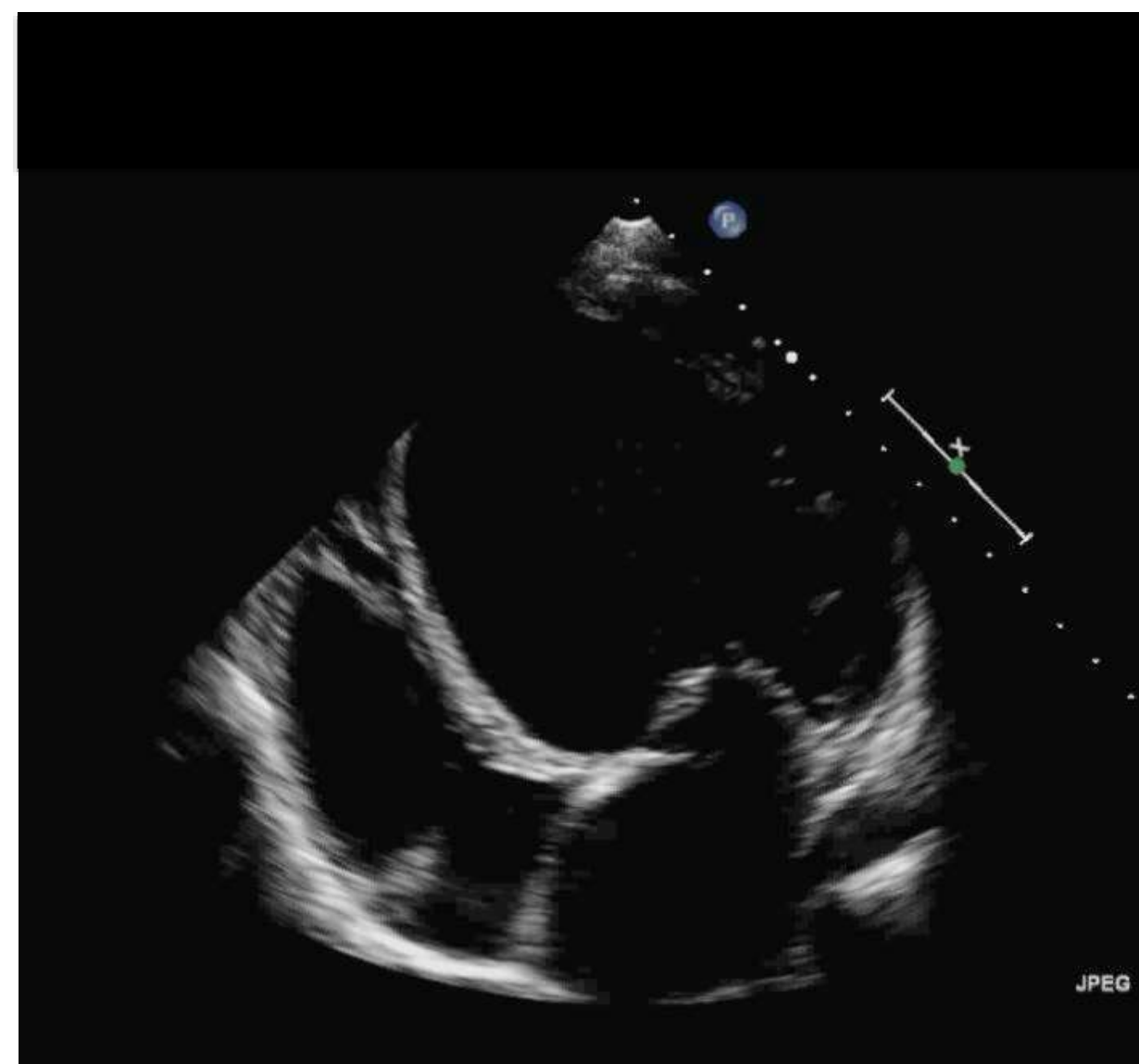
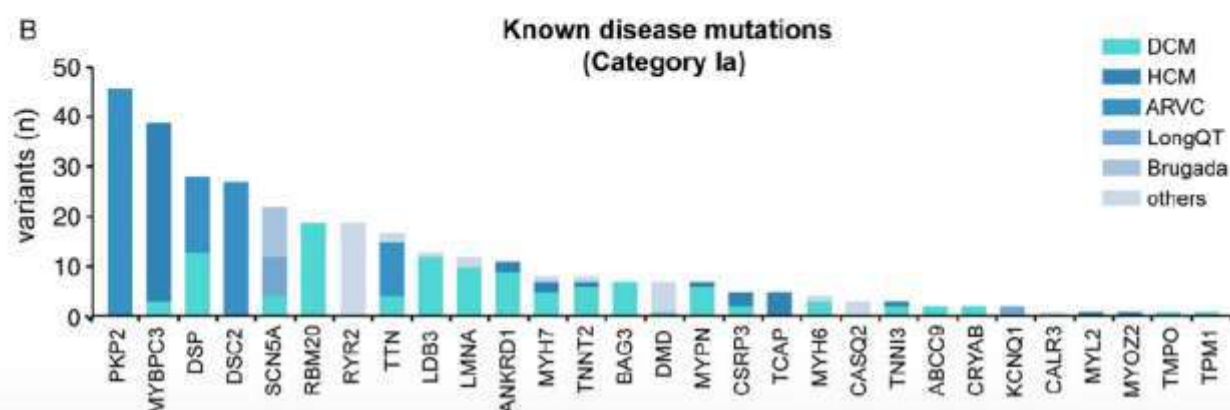
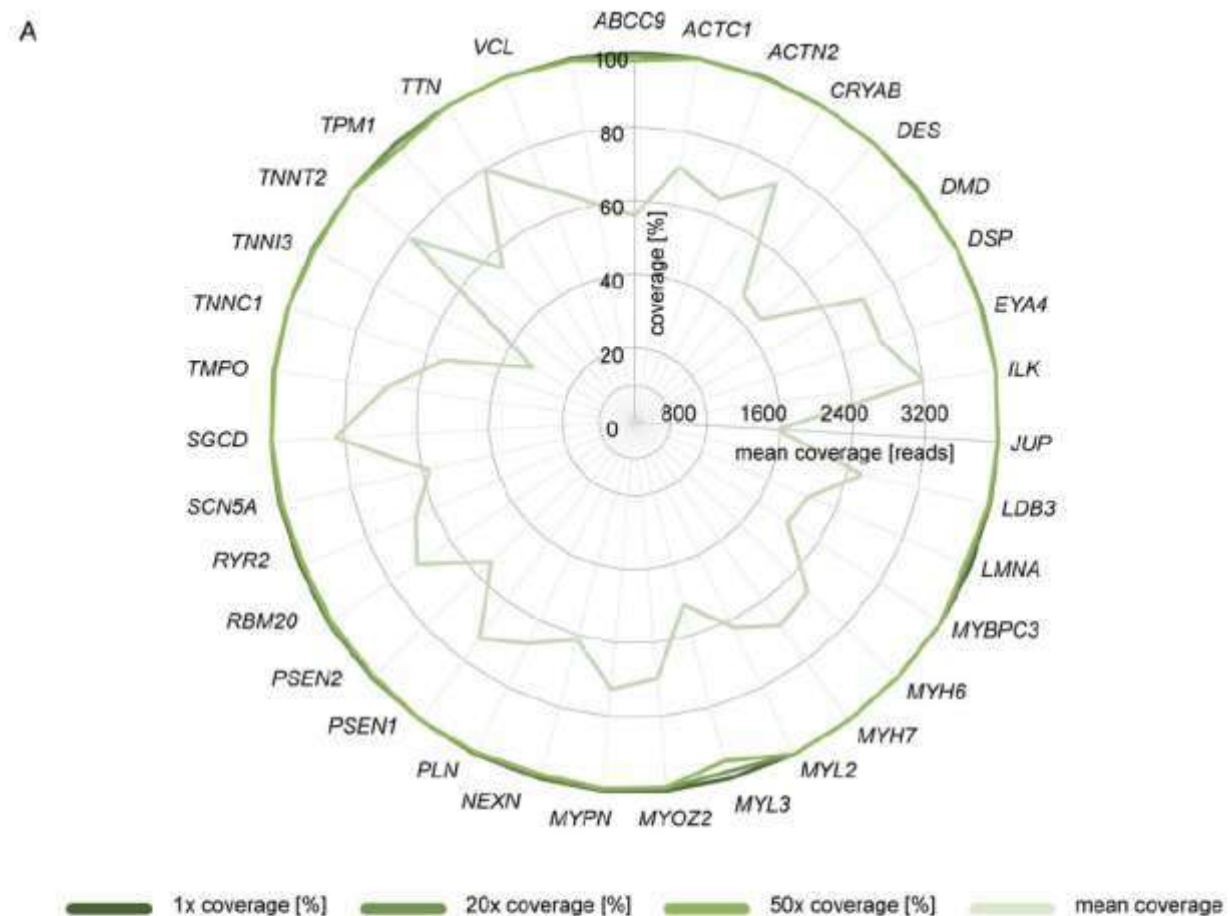
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London

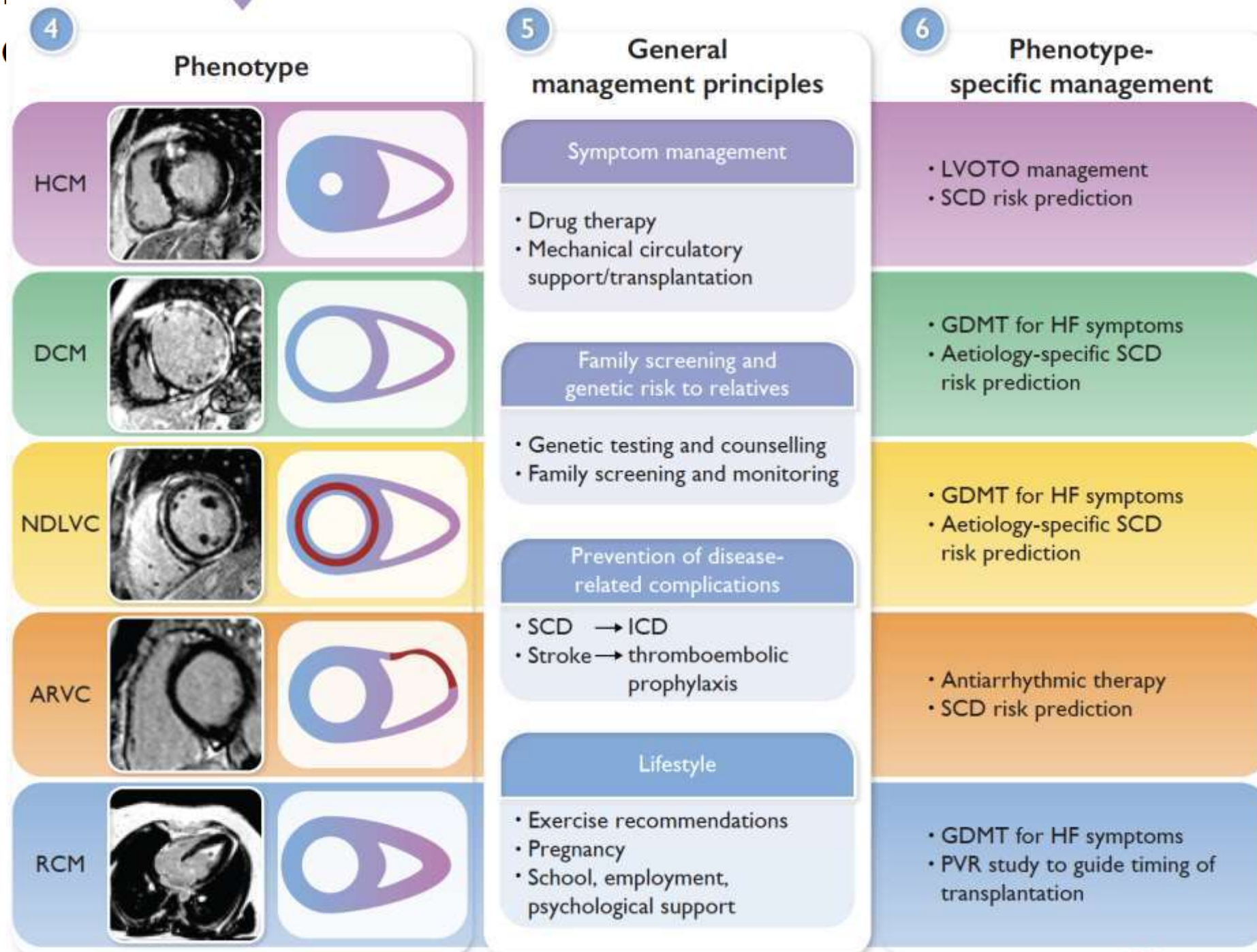
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LONDON

Dilated Cardiomyopathy





2023 ESC Guidelines for the management of cardiomyopathies



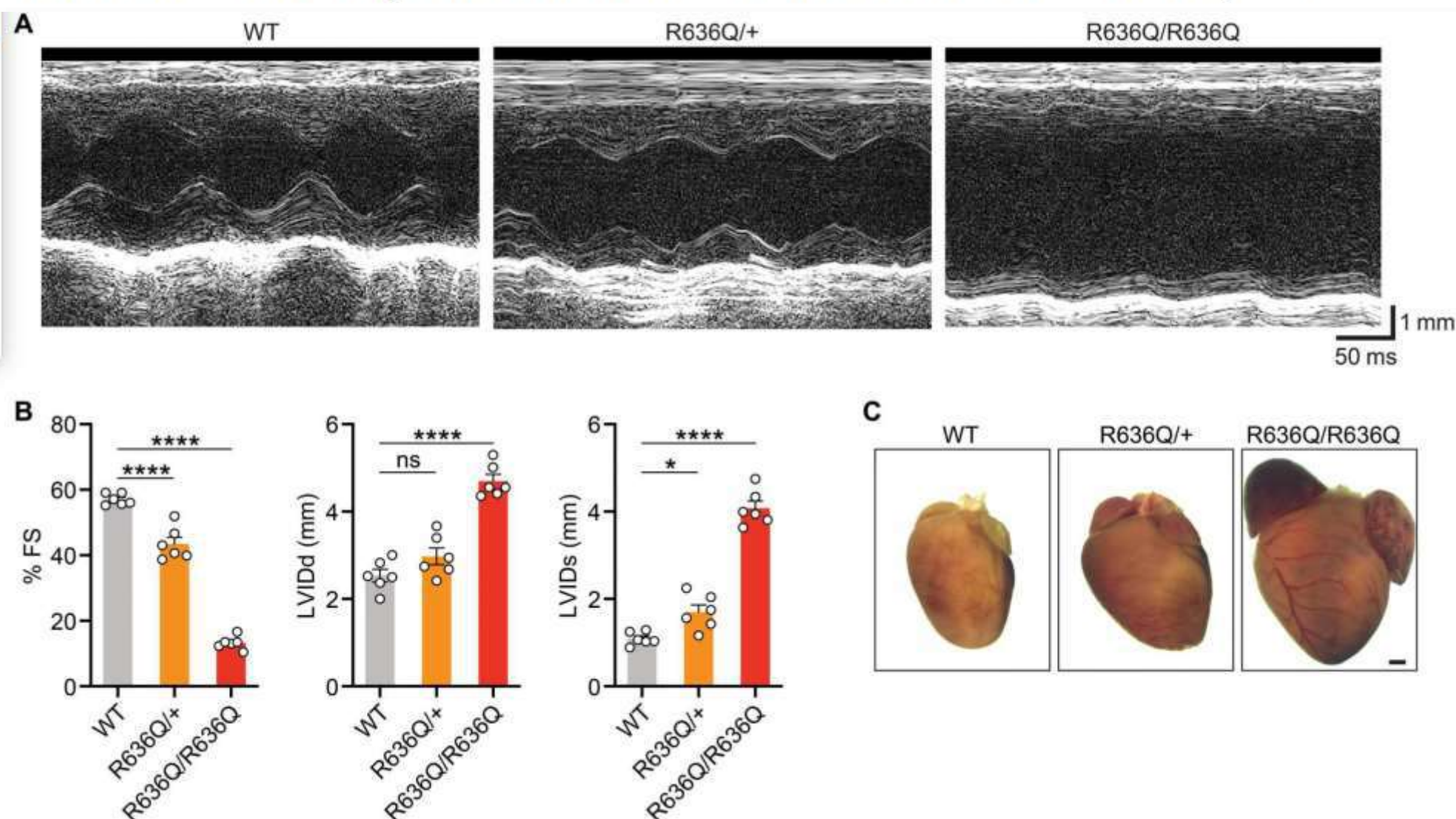
f
ology (ESC)



GENE EDITING

Precise genomic editing of pathogenic mutations in *RBM20* rescues dilated cardiomyopathy

Takahiko Nishiyama^{1,2,3}, Yu Zhang^{1,2,3}, Miao Cui^{1,2,3}, Hui Li^{1,2,3}, Efrain Sanchez-Ortiz^{1,2,3}, John R. McAnally^{1,2,3}, Wei Tan^{1,2,3}, Jiwoong Kim⁴, Kenian Chen⁴, Lin Xu⁴, Rhonda Bassel-Duby^{1,2,3}, Eric N. Olson^{1,2,3*}





Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy

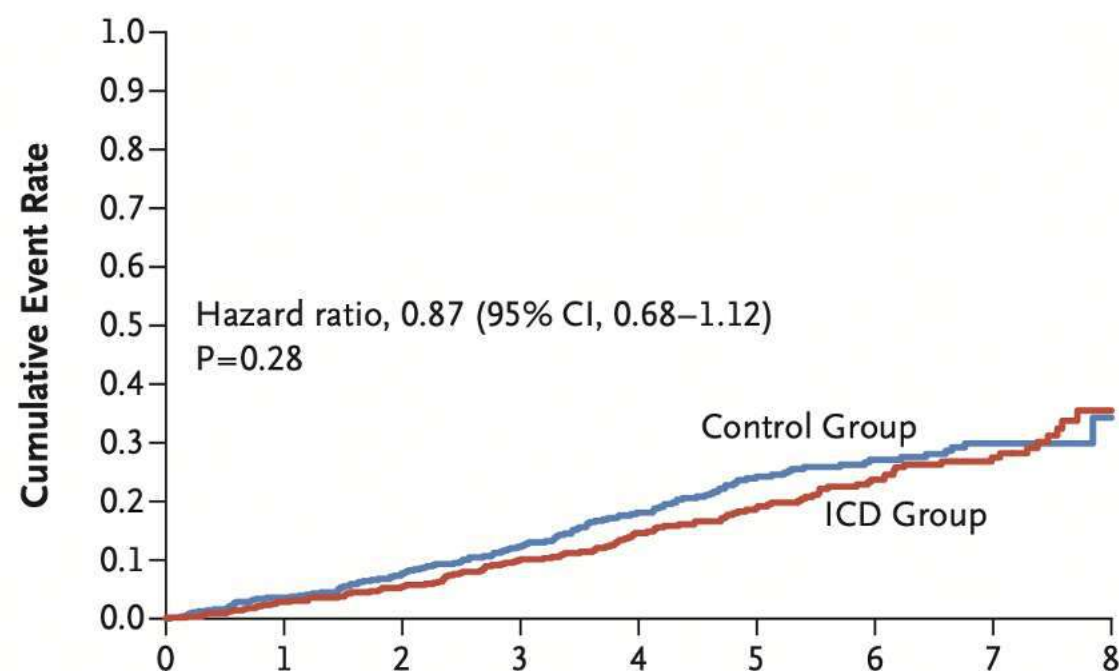
*Here again splitting is the next step:
What is the risk of sudden death based on
genetics and the degree of fibrosis?*

Lars Køber, M.D., D.M.Sc.,
Lars Videbæk, M.D., D.M.Sc.,
Flemming H. Steffensen, M.D.,
Anna M. Thomsen, M.D.,

D.M.Sc.,
D.M.Sc.,
es, M.D.,
C.,

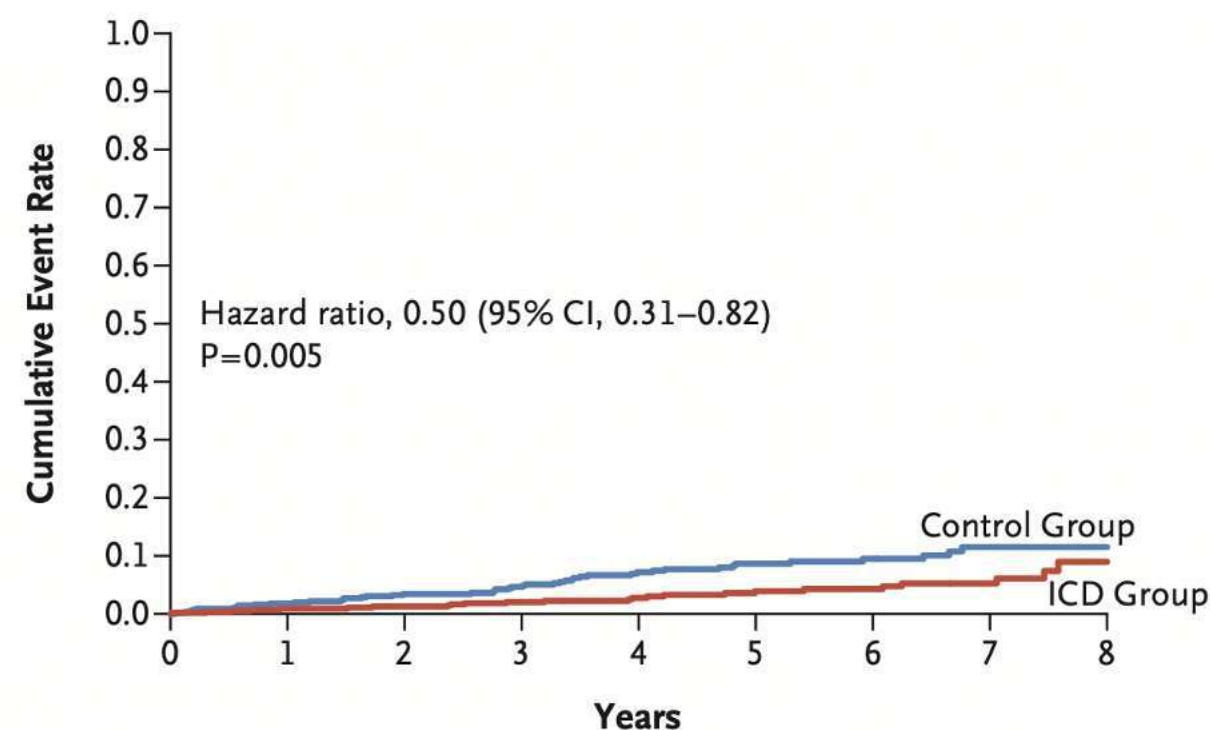
Regitze Videbæk, M.D., Christian Hassager, M.D., D.M.Sc., Jesper H. Svendsen, M.D., D.M.Sc.,
Dan E. Høfsten, M.D., Ph.D., Christian Torp-Pedersen, M.D., D.M.Sc.,
and Steen Pehrson, M.D., D.M.Sc. for the DANISH Investigators*

Death from Any Cause



No. at Risk	0	1	2	3	4	5	6	7	8
Control Group	560	540	517	438	344	248	169	88	12
ICD Group	556	540	526	451	358	272	186	107	17

Sudden Cardiac Death



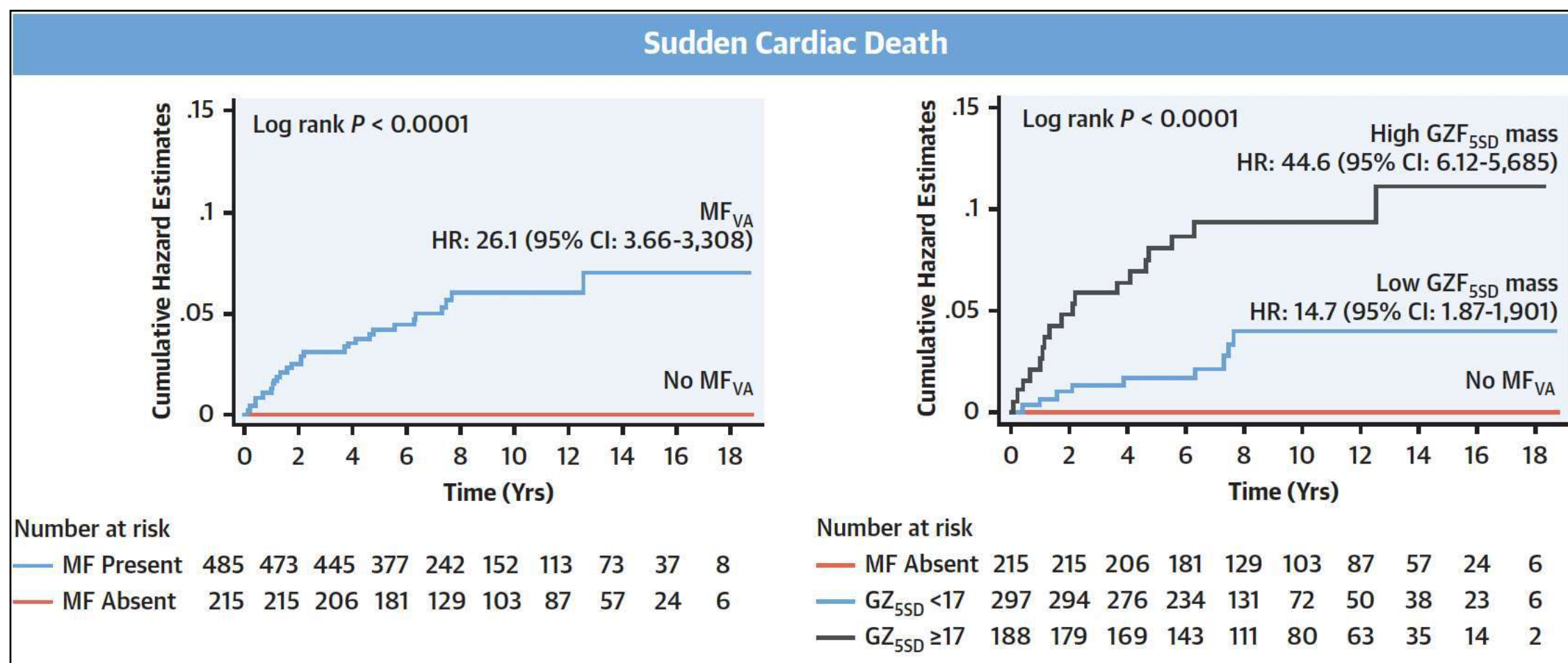
No. at Risk	0	1	2	3	4	5	6	7	8
Control Group	560	540	517	438	344	248	169	88	12
ICD Group	556	540	526	451	358	272	186	107	17



Myocardial Fibrosis Predicts Ventricular Arrhythmias and Sudden Death After Cardiac Electronic Device Implantation



Francisco Leyva, MD,^a Abbasin Zegard, MBChB,^{a,b} Osita Okafor, MBChB,^{a,b} Paul Foley, MD,^c Fraz Umar, MBChB,^d Robin J. Taylor, MD,^e Howard Marshall, MD,^b Berthold Stegemann, PhD,^a William Moody, MD,^b Richard P. Steeds, PhD,^b Brian P. Halliday, MD,^f Daniel J. Hammersley, MBChB,^f Richard E. Jones, MBChB,^f Sanjay K. Prasad, MD,^f Tian Qiu, PhD^b





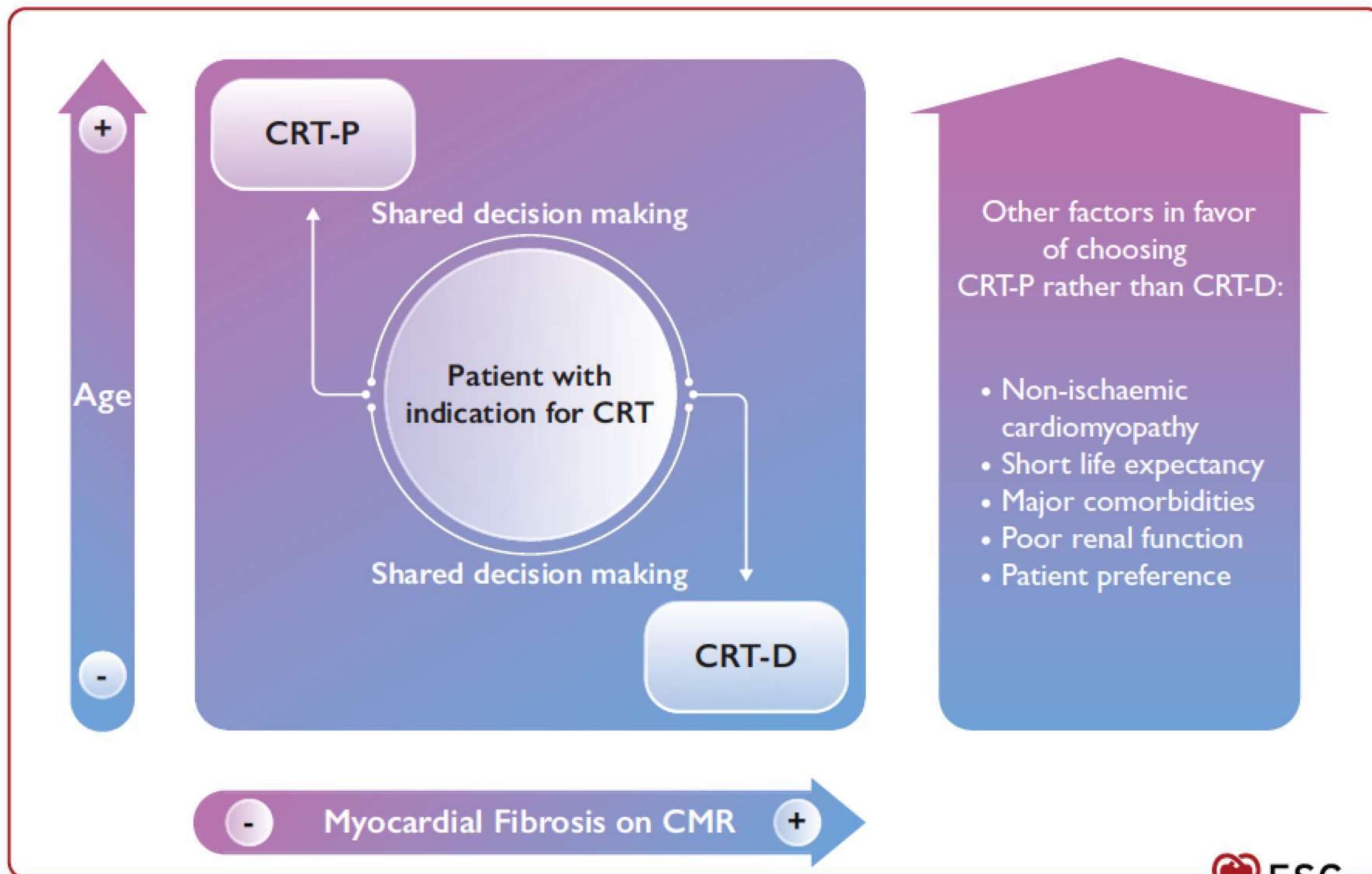
The Spectrum of Heart Failure and what it means for clinical practice



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Zurich^{UZH}

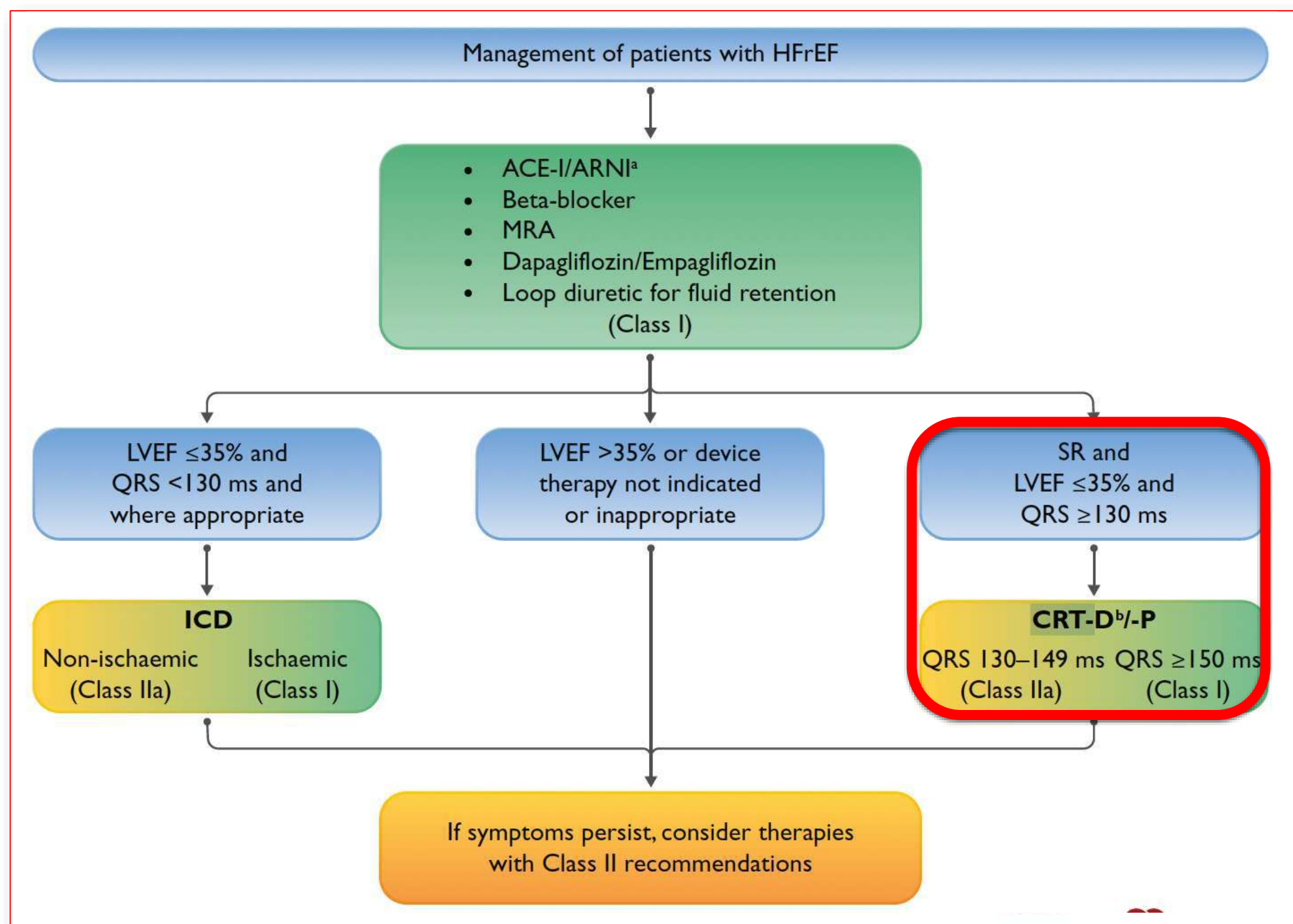


Imperial College
London





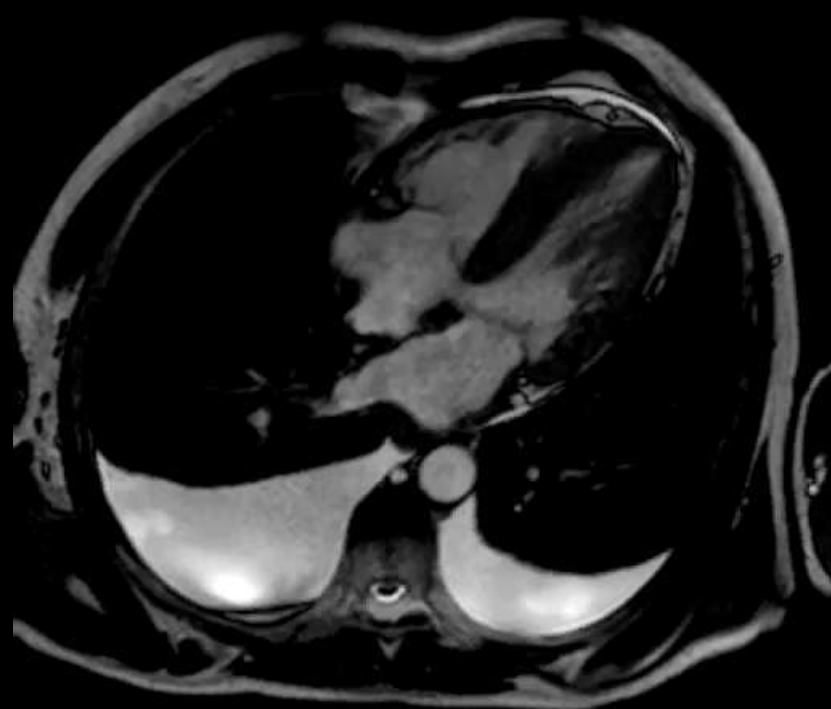
Further Splitting: Dyssynchronous Left Ventricle: A Case for Cardiac Resynchronization Therapy





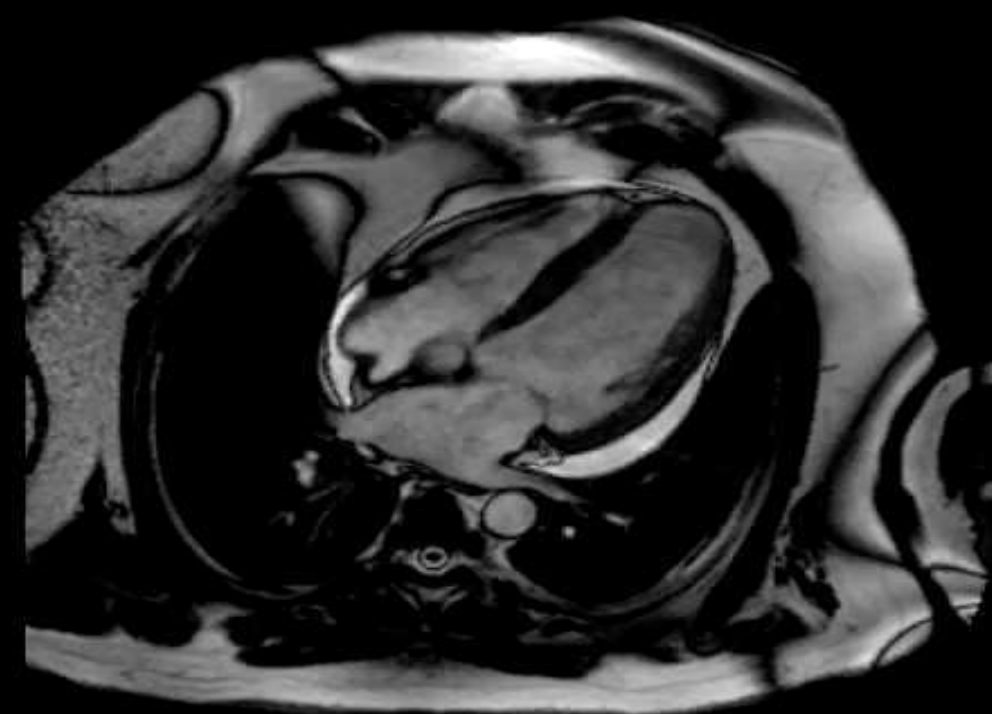
Ejection Fraction

HFpEF



- Ejection Fraction 70%
- LVEDP 24 mmHg
- LVH
- Fibrosis
- BNP 980 ng/ml

HFmrEF

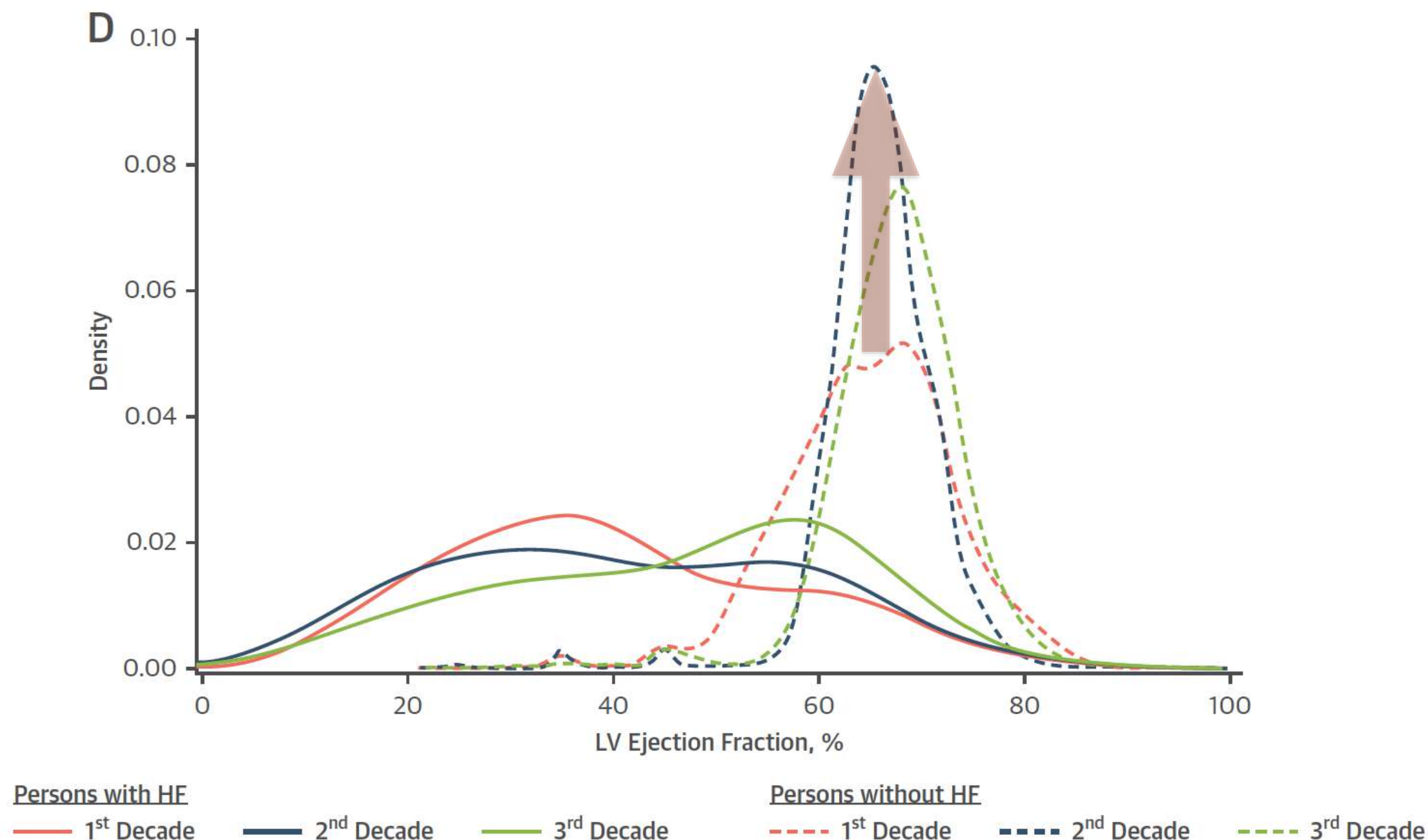


- Ejection Fraction 30%
- LVEDP 27 mmHg
- Remodelling
- Scar
- BP 2100 ng/ml



Epidemiology of Left Ventricular Systolic Dysfunction and Heart Failure

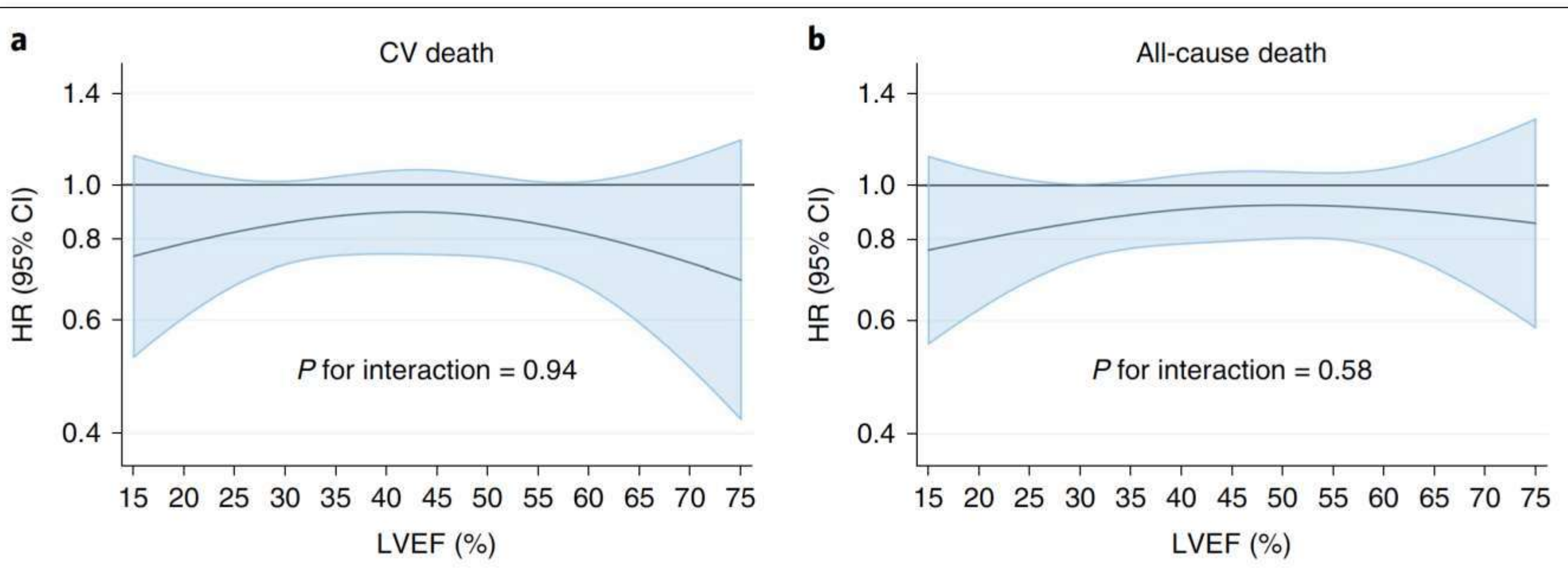
Probability Density Function of LV Ejection Fraction Across Decades in People with and without HF





OPEN

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

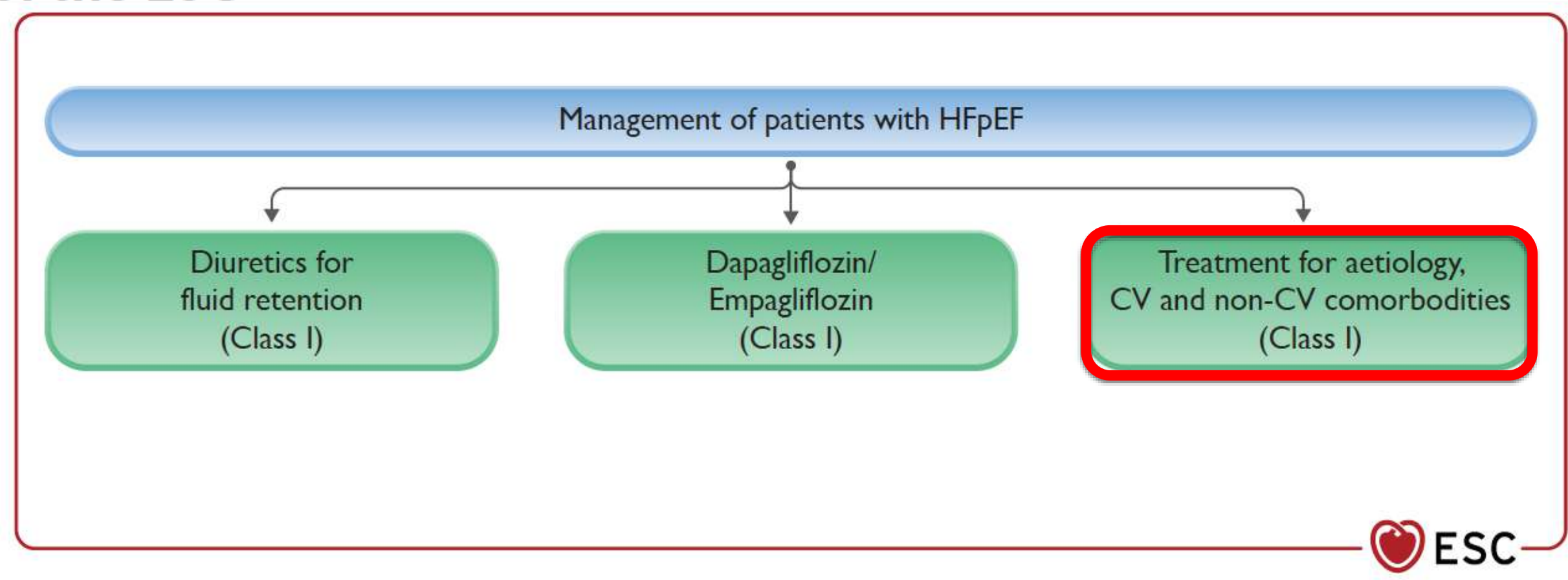




2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

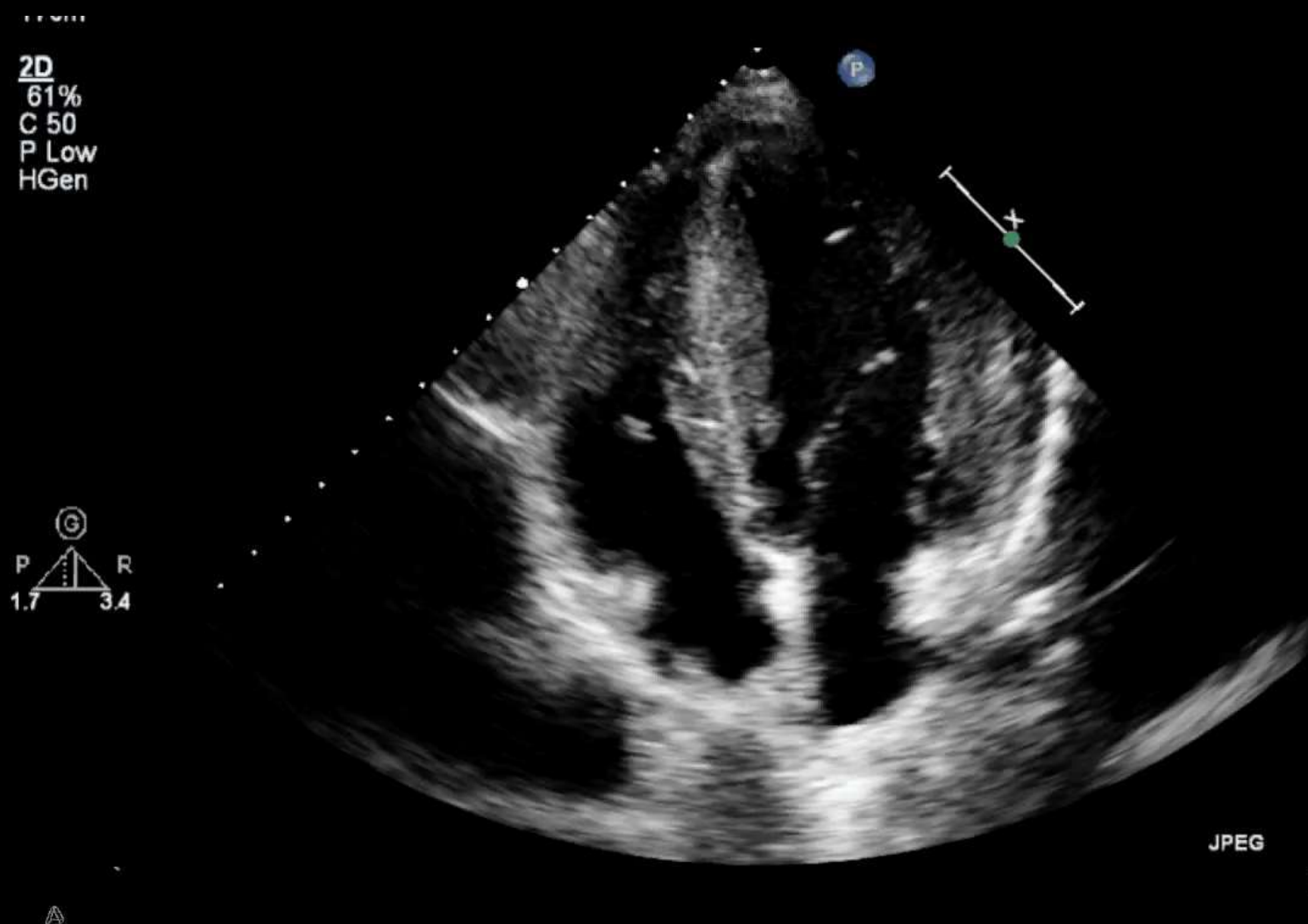
Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC





Hypertensive Heart Disease with severe LVH and HFpEF

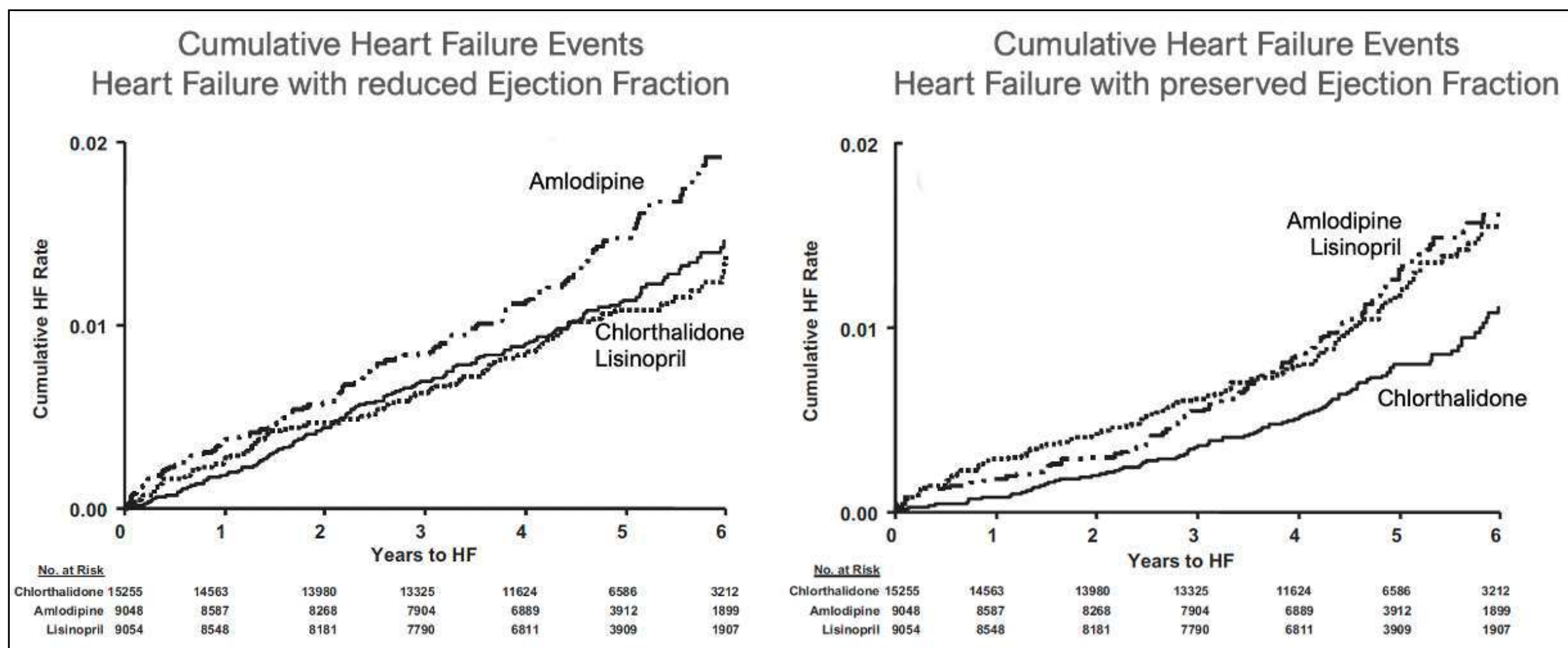


- LVH stiffens the heart
- High BP increases LVEDP and PAP
- This causes Dyspnoea and exercise intolerance
- Antihypertensive therapy might help
- Outcomes?

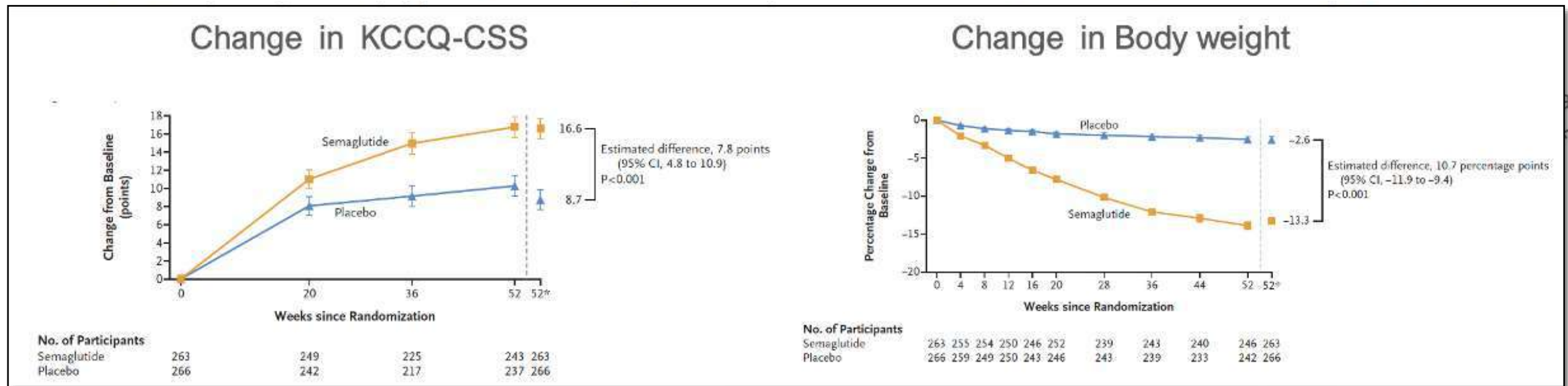


Heart Failure With Preserved and Reduced Left Ventricular Ejection Fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Barry R. Davis, MD, PhD; John B. Kostis, MD; Lara M. Simpson, PhD; Henry R. Black, MD; William C. Cushman, MD; Paula T. Einhorn, MD; Michael A. Farber, MD; Charles E. Ford, PhD; Daniel Levy, MD; Barry M. Massie, MD; Shah Nawaz, MD;
for the ALLHAT Collaborative Research Group



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



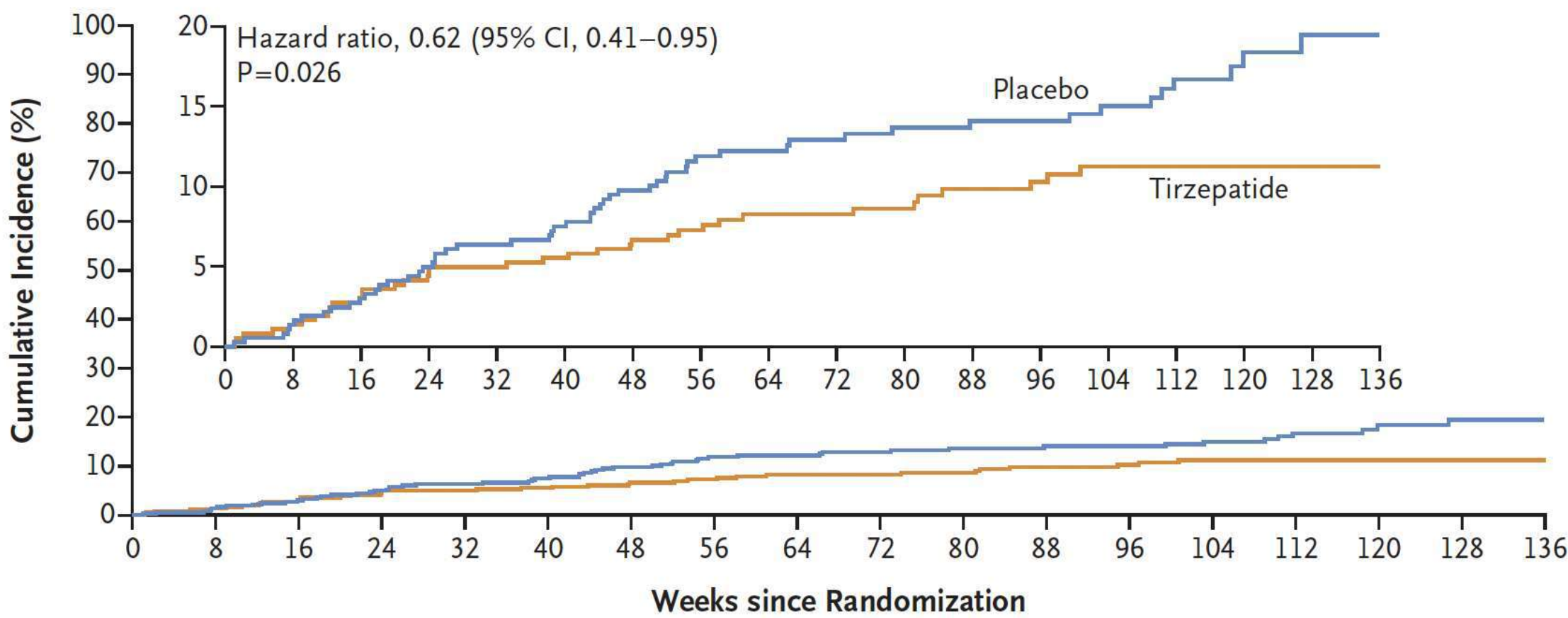
Obesity HFpEF





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*



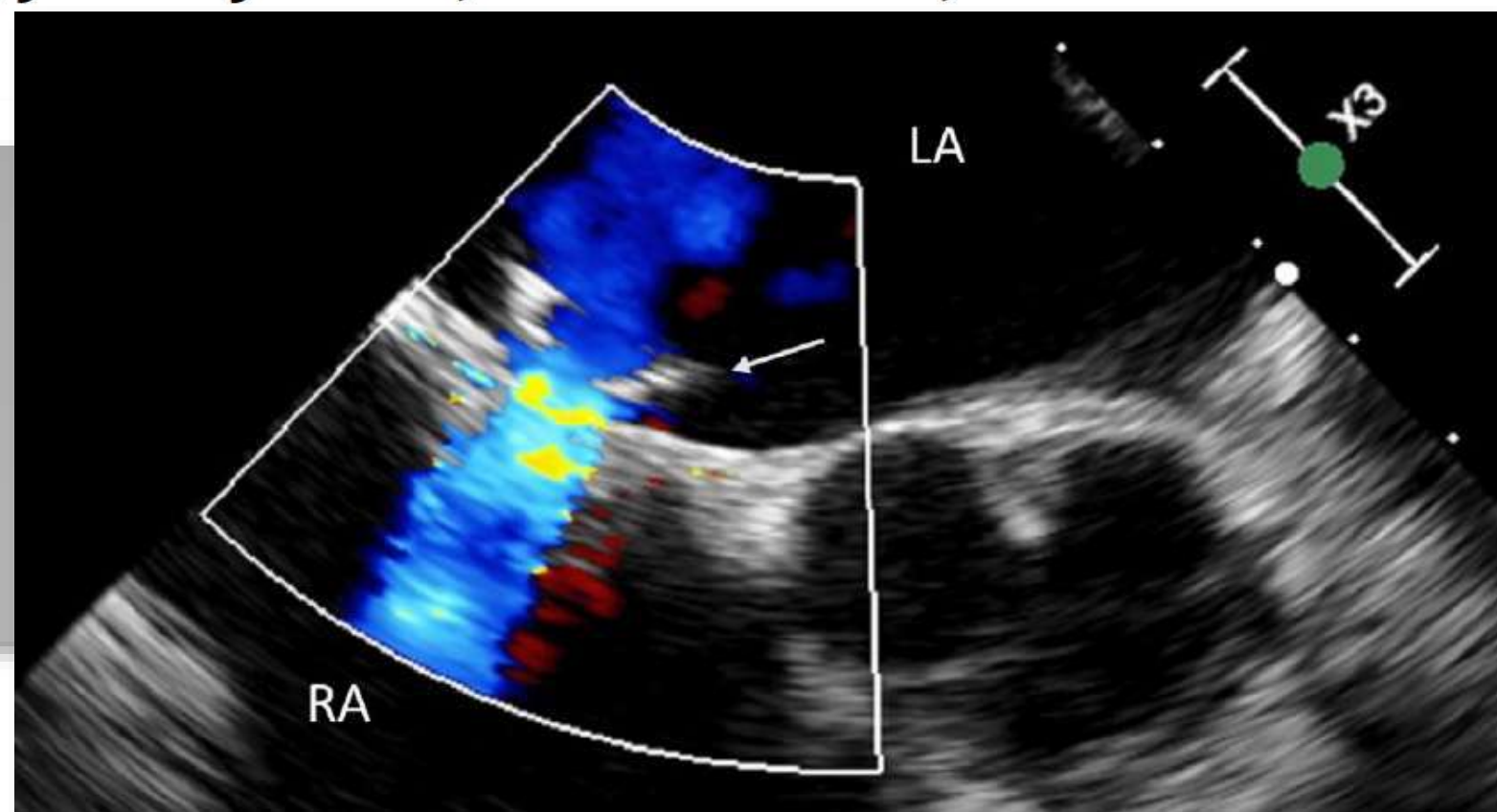
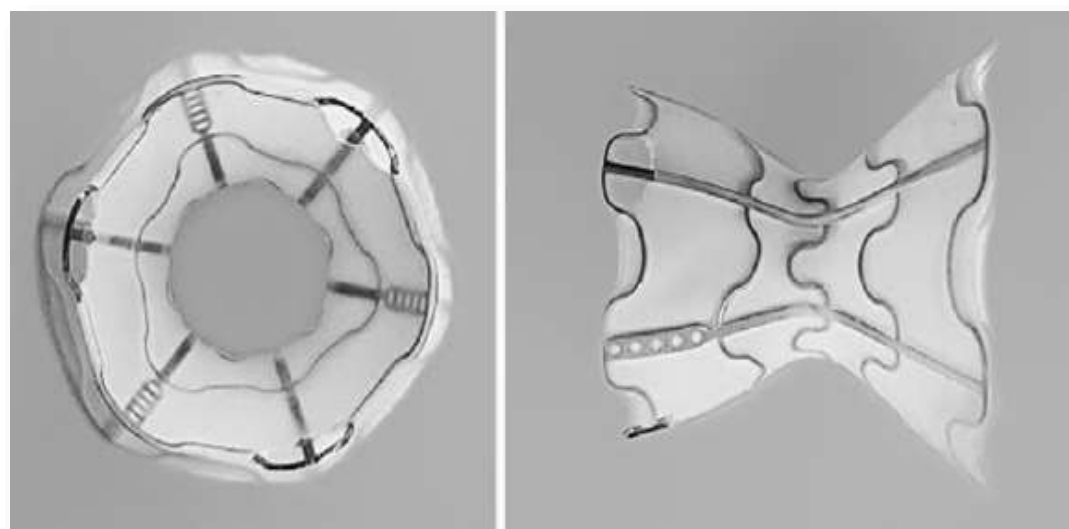
No. at Risk

Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45
Tirzepatide	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46



Interatrial shunt therapy in advanced heart failure: Outcomes from the open-label cohort of the RELIEVE-HF trial

Josep Rodés-Cabau^{1*}, JoAnn Lindenfeld², William T. Abraham³, Michael R. Zile⁴, Saibal Kar⁵, Antoni Bayés-Genís^{6,7}, Neal Eigler⁸, Richard Holcomb⁹, Julio Núñez¹⁰, Elizabeth Lee¹¹, Michal Laufer Perl¹², Gil Moravsky¹³, Michael Pfeiffer¹⁴, John Boehmer¹⁴, John Gorcsan¹⁴, Jeroen J. Bax¹⁵, Stefan Anker¹⁶, and Gregg W. Stone¹⁷





ESC

European Society
of Cardiology

European Journal of Heart Failure (2024) **26**, 1078–1089

doi:10.1002/ejhf.3215

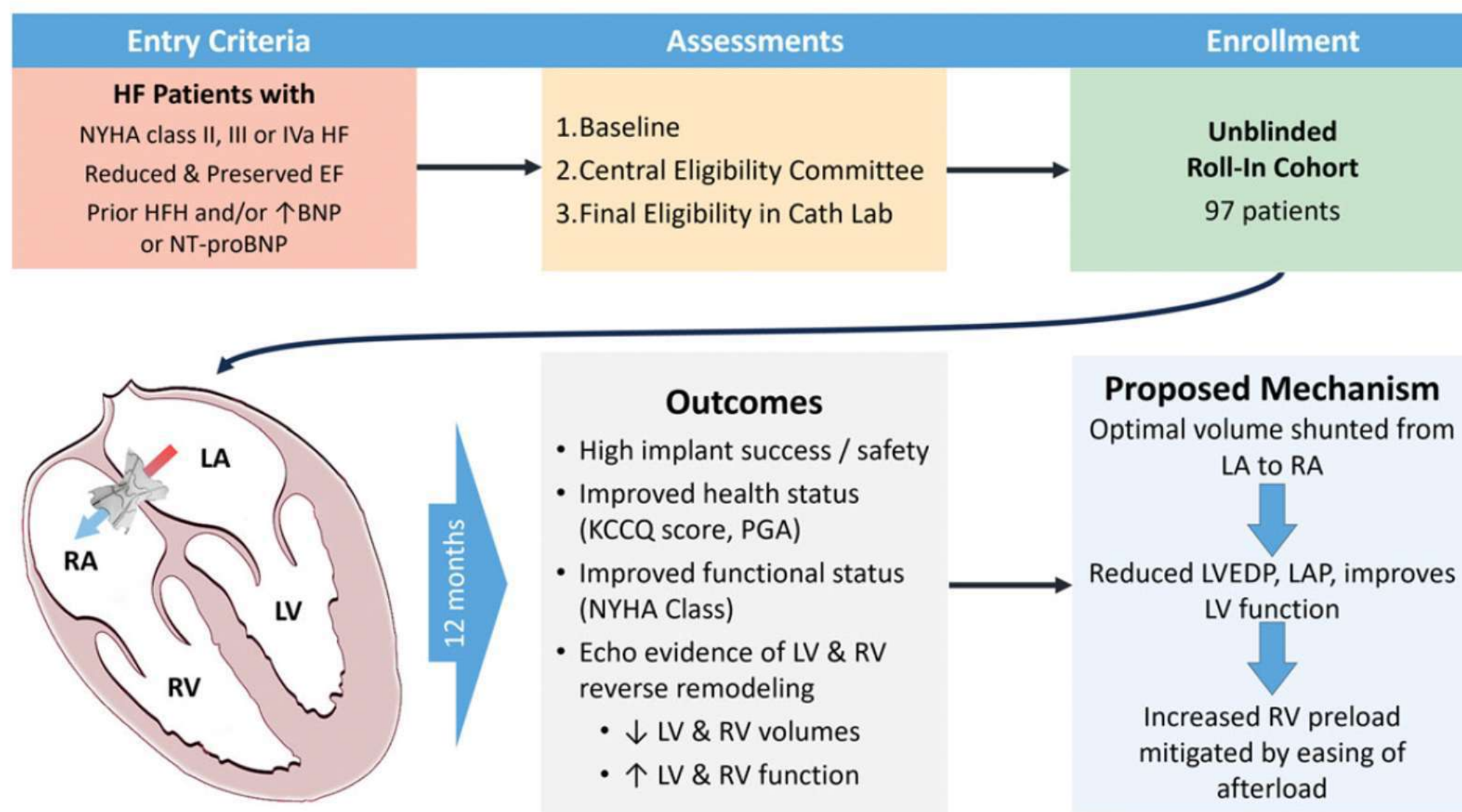
RESEARCH ARTICLE

Interatrial shunt therapy in advanced heart

fail
of t

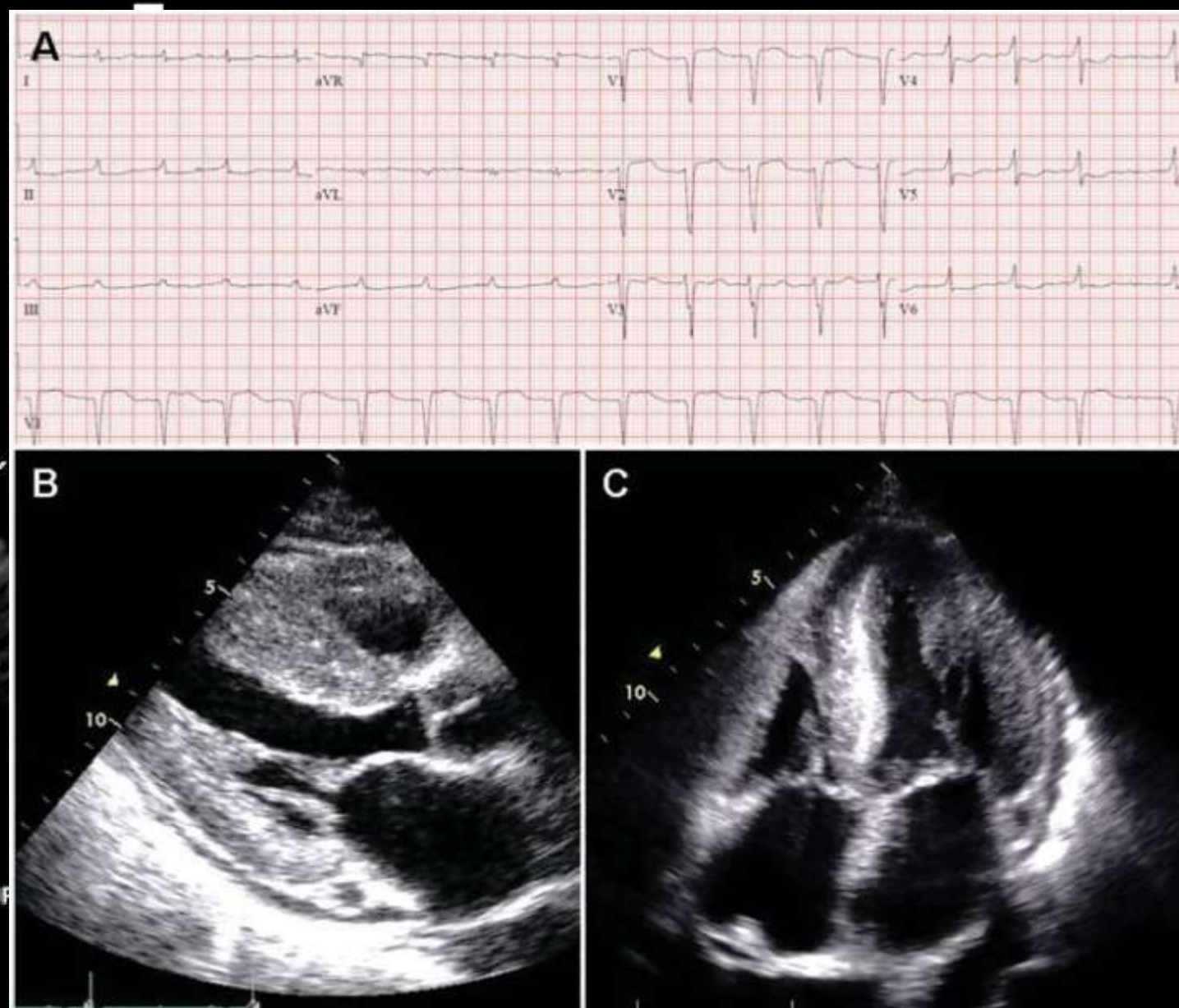
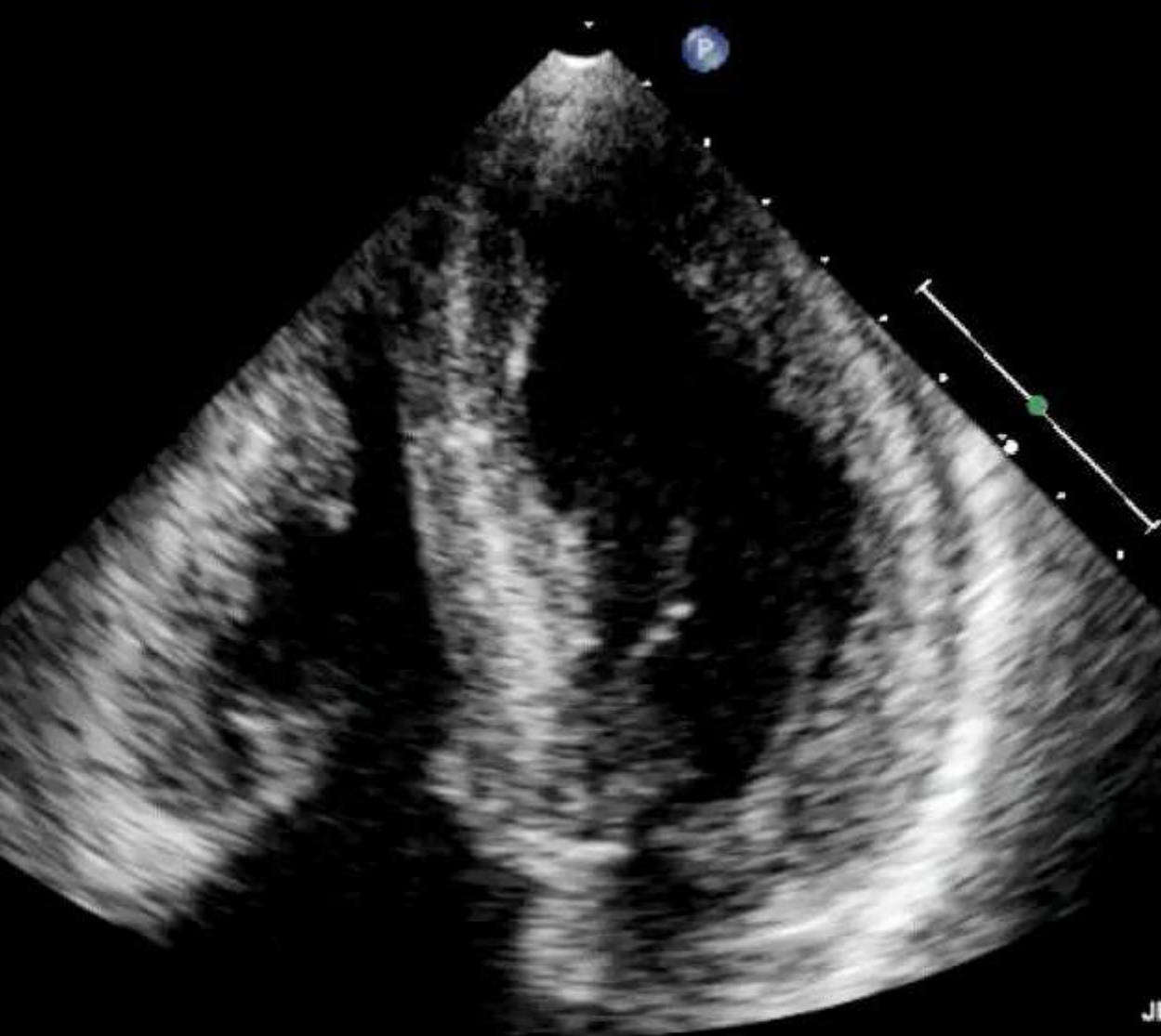
Josep
Saibá
Elizak
John I
and C

Zile⁴,
Gómez¹⁰,



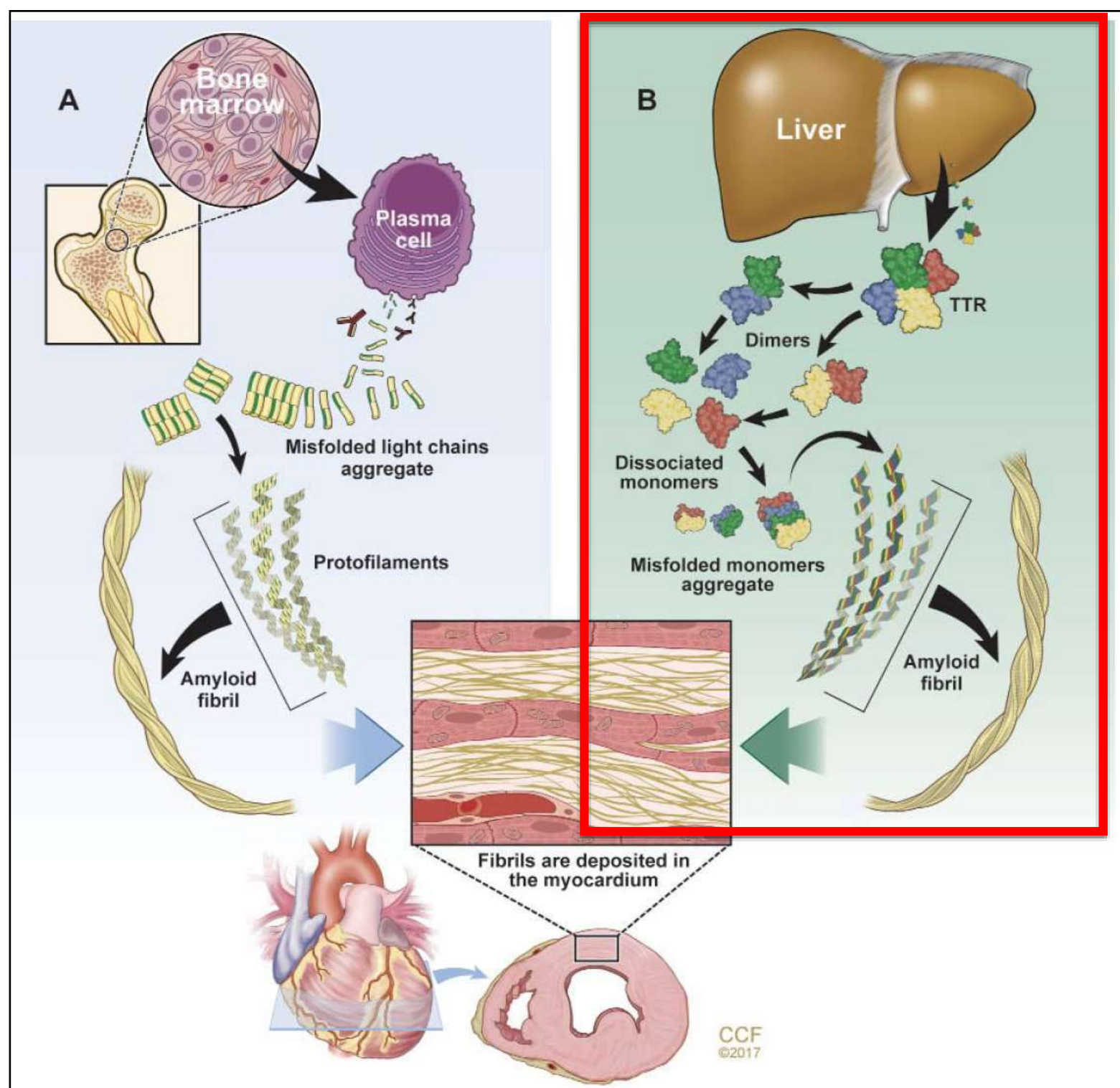


Amyloid Heart Disease





Plasmacytoma TTR Amyloidosis



Plasmacytoma

- Chemotherapy
- Bone marrow transplantation

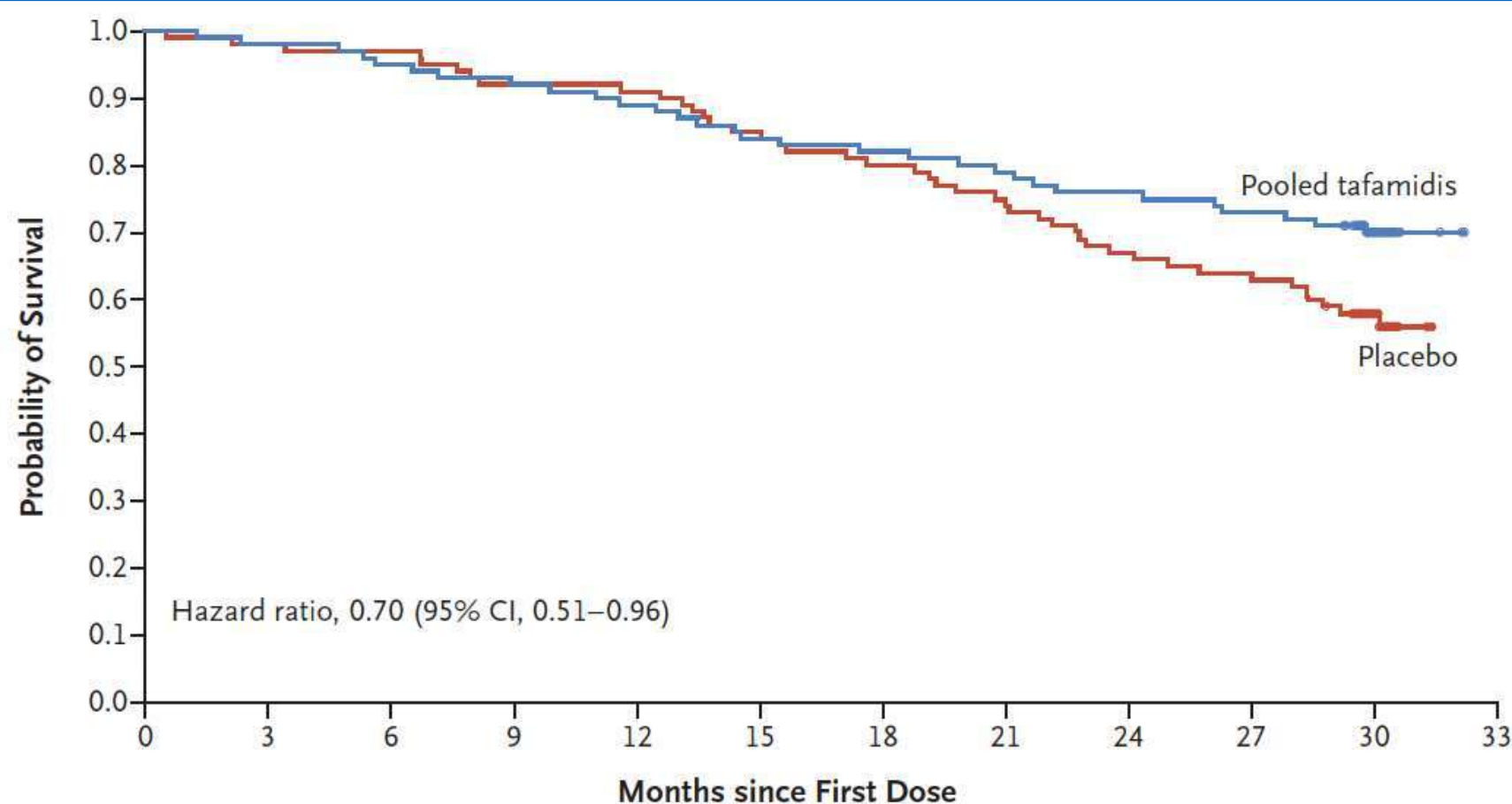
TTR Amyloidosis

- Tafamidis (preventing tetramer dissociation)
- Antibody (to remove amyloid from the heart)
- ASO (to prevent formation of protein)
- siRNA (to prevent formation of protein)



Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D.,
Balarama Gundapaneni, M.S., Perry M. Elliott, M.D.,
Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D.,
Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D.,
Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D.,
Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D.,
Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D.,
Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A.,
and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*



No. at Risk (cumulative no. of events)

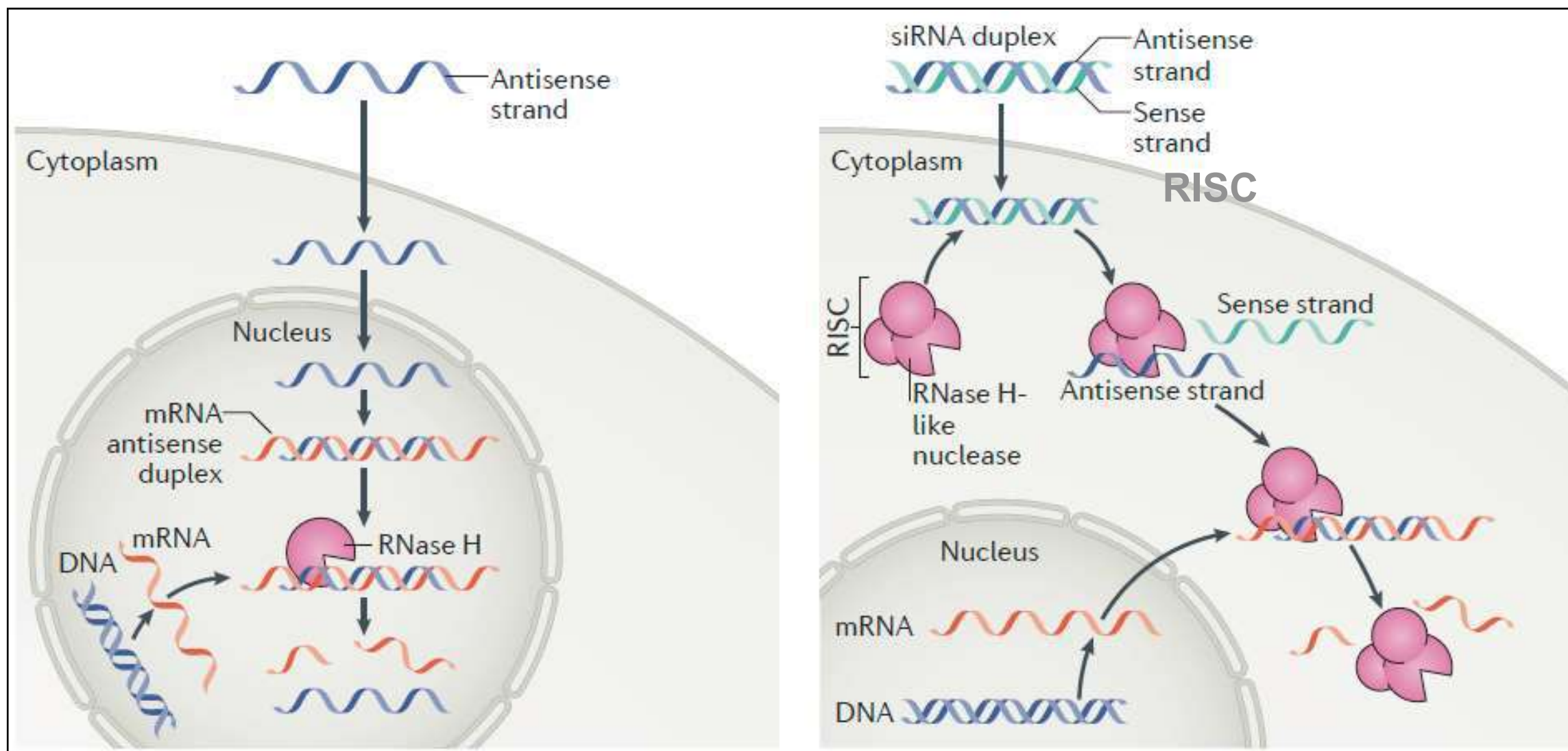
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)



Revolution in Pharmacotherapy: ASO and siRNA

Antisense Technology

RNA Interference



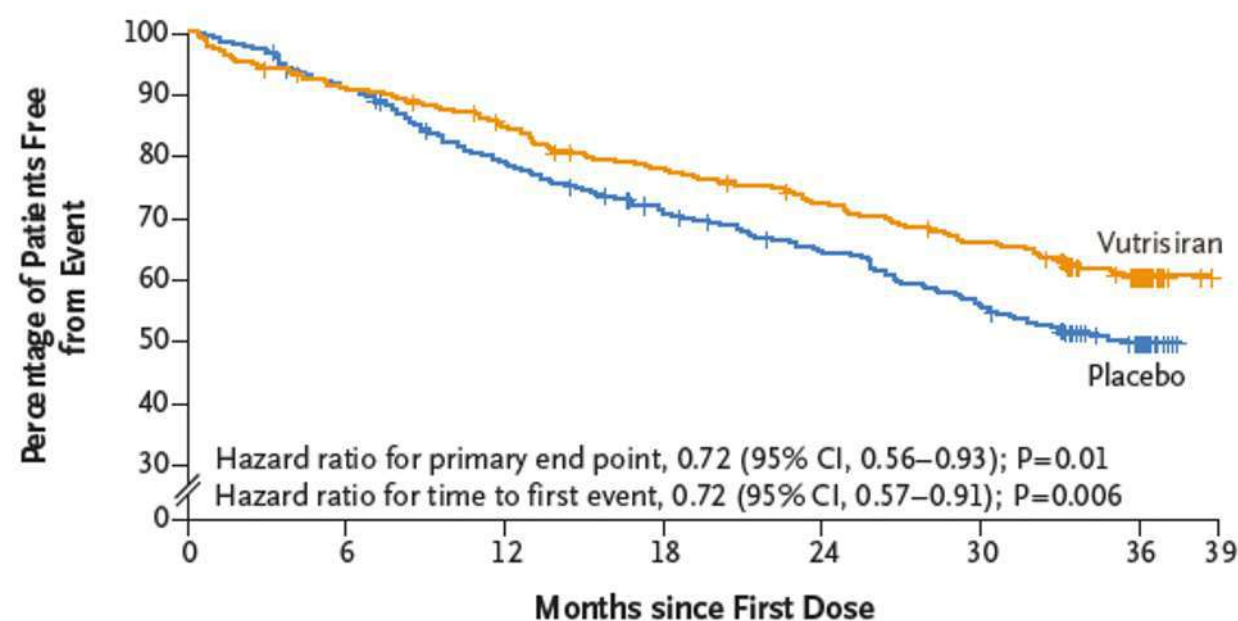
RISC = **R**NA-**I**nduced **S**ilencing **C**omplex



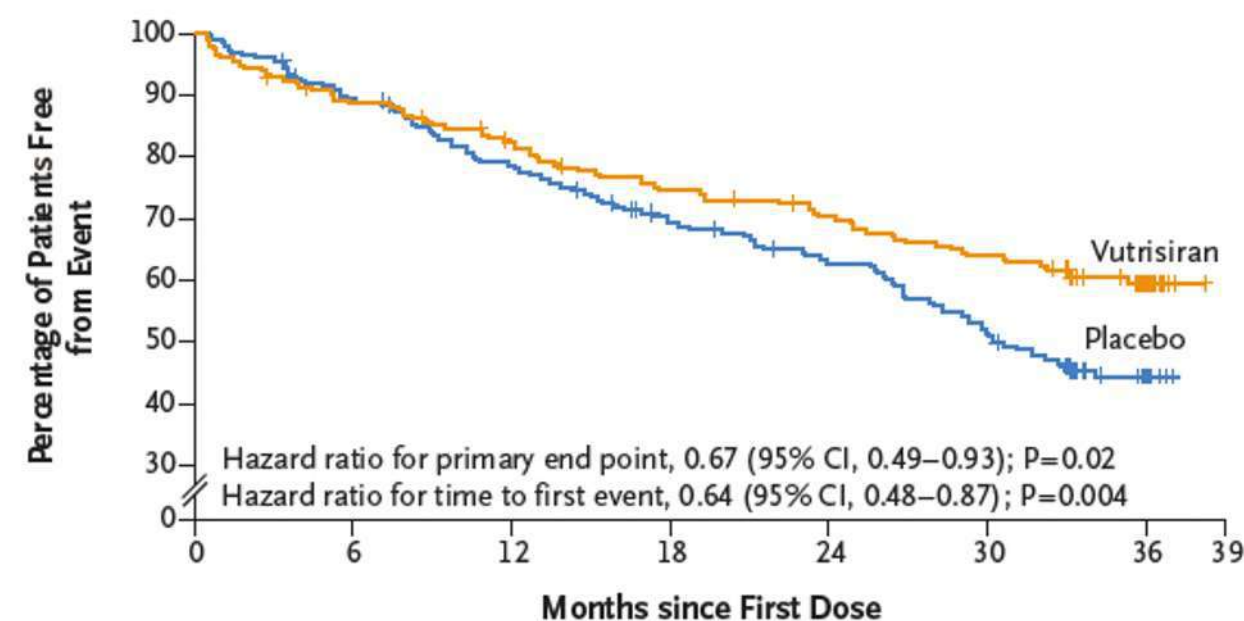
Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

M. Fontana, J.L. Berk, J.D. Gillmore, R.M. Witteles, M. Grogan, B. Drachman, T. Damy, P. Garcia-Pavia, J. Taubel, S.D. Solomon, F.H. Sheikh, N. Tahara, J. González-Costello, K. Tsujita, C. Morbach, Z. Pozsonyi, M.C. Petrie, D. Delgado, P. Van der Meer, A. Jabbour, A. Bondue, D. Kim, O. Azevedo, S. Hvitfeldt Poulsen, A. Yilmaz, E.A. Jankowska, V. Algalarrondo, A. Slugg, P.P. Garg, K.L. Boyle, E. Yureneva, N. Silliman, L. Yang, J. Chen, S.A. Eraly, J. Vest, and M.S. Maurer, for the HELIOS-B Trial Investigators*

Time to 1st Event: Overall Population



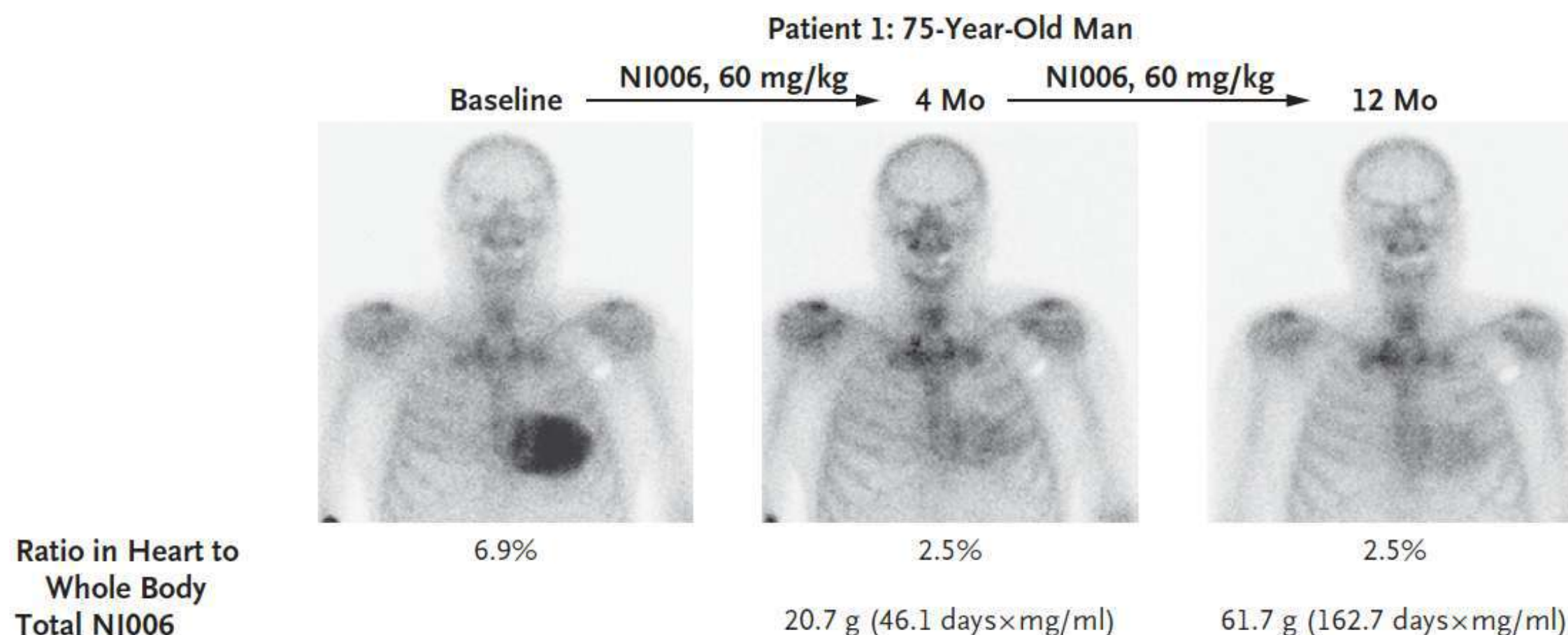
Time to 1st Event: Monotherapy Population





Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

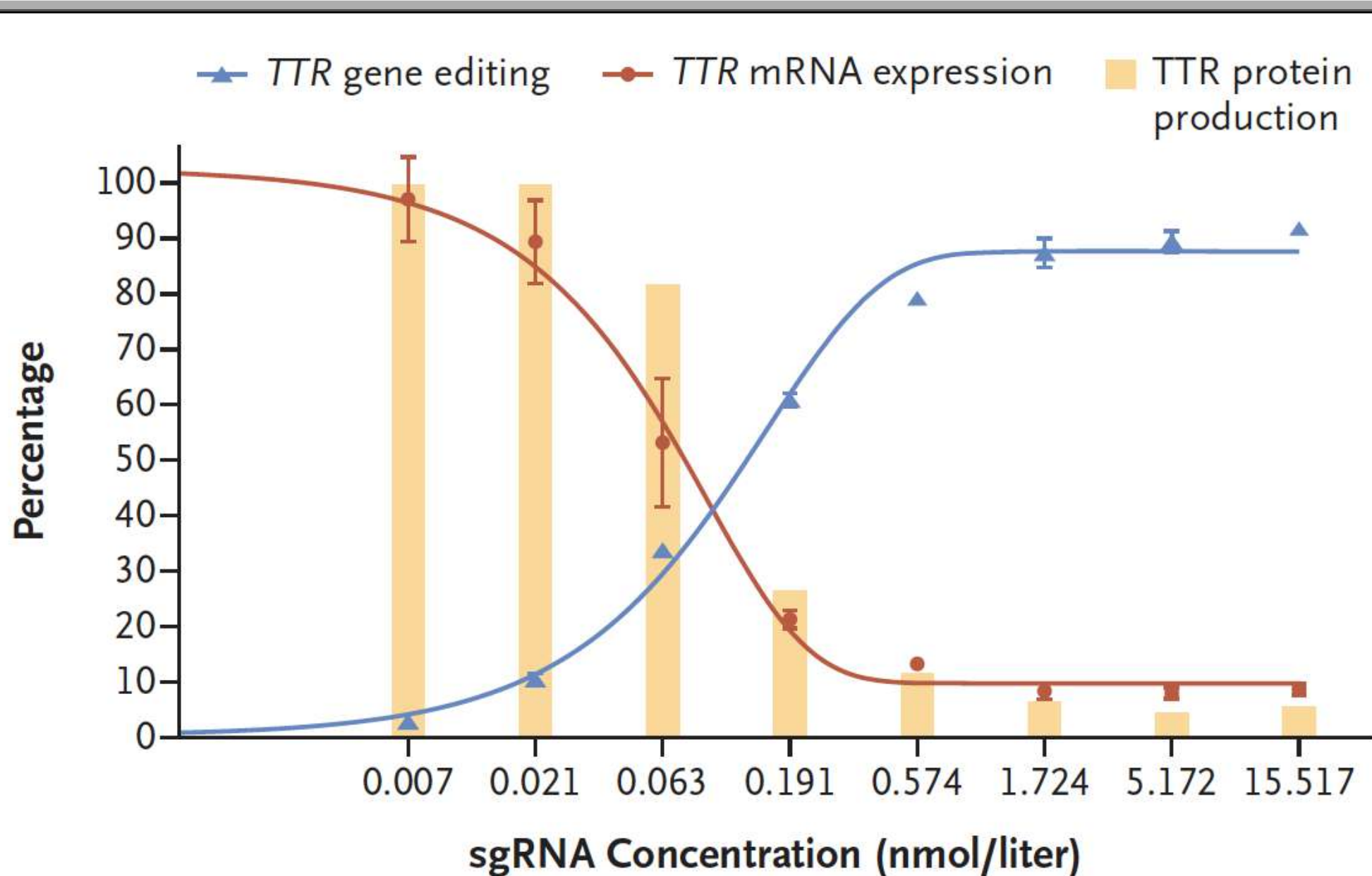
Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.





The Distant Future of Management of TTR Amyloidosis

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

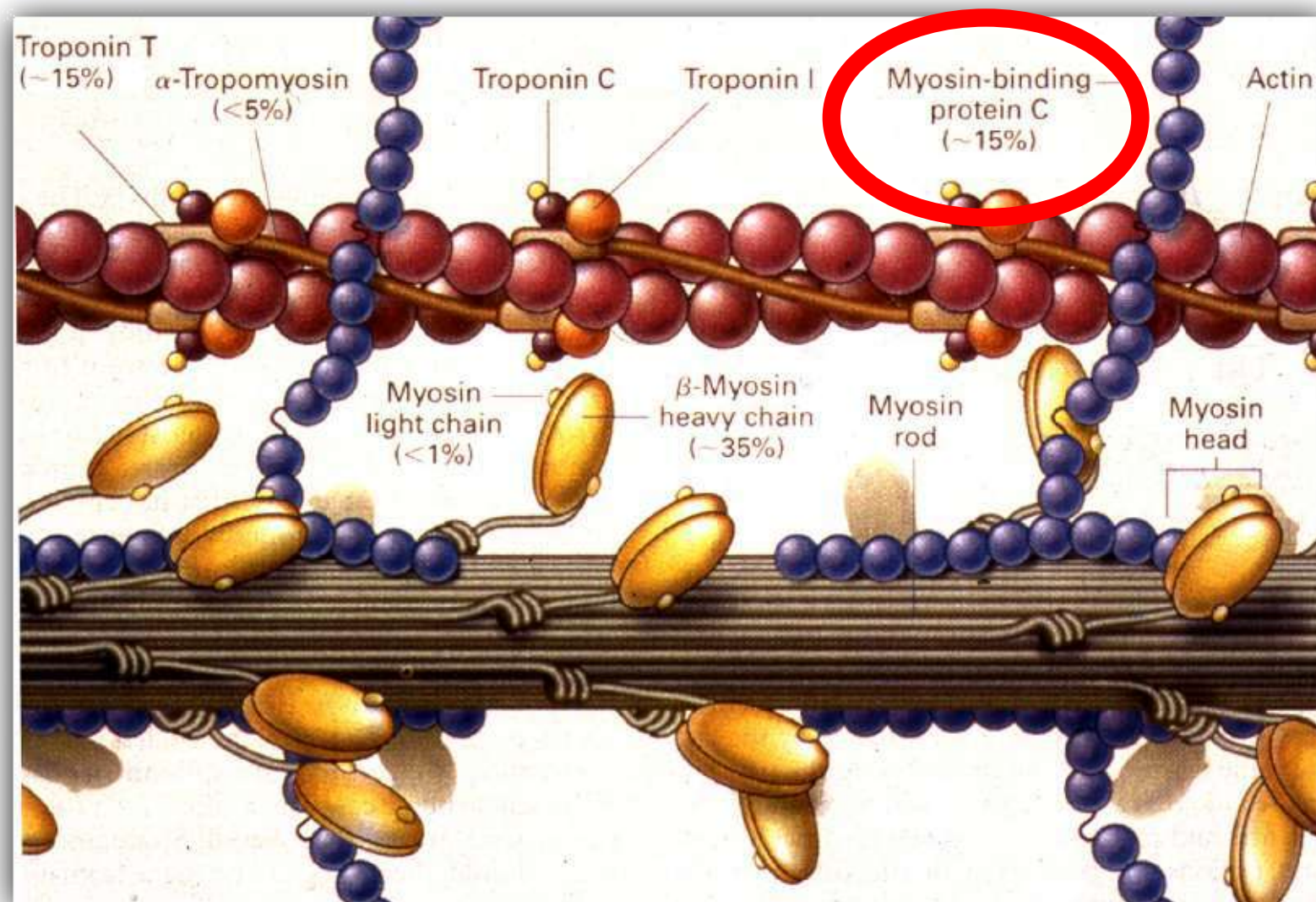
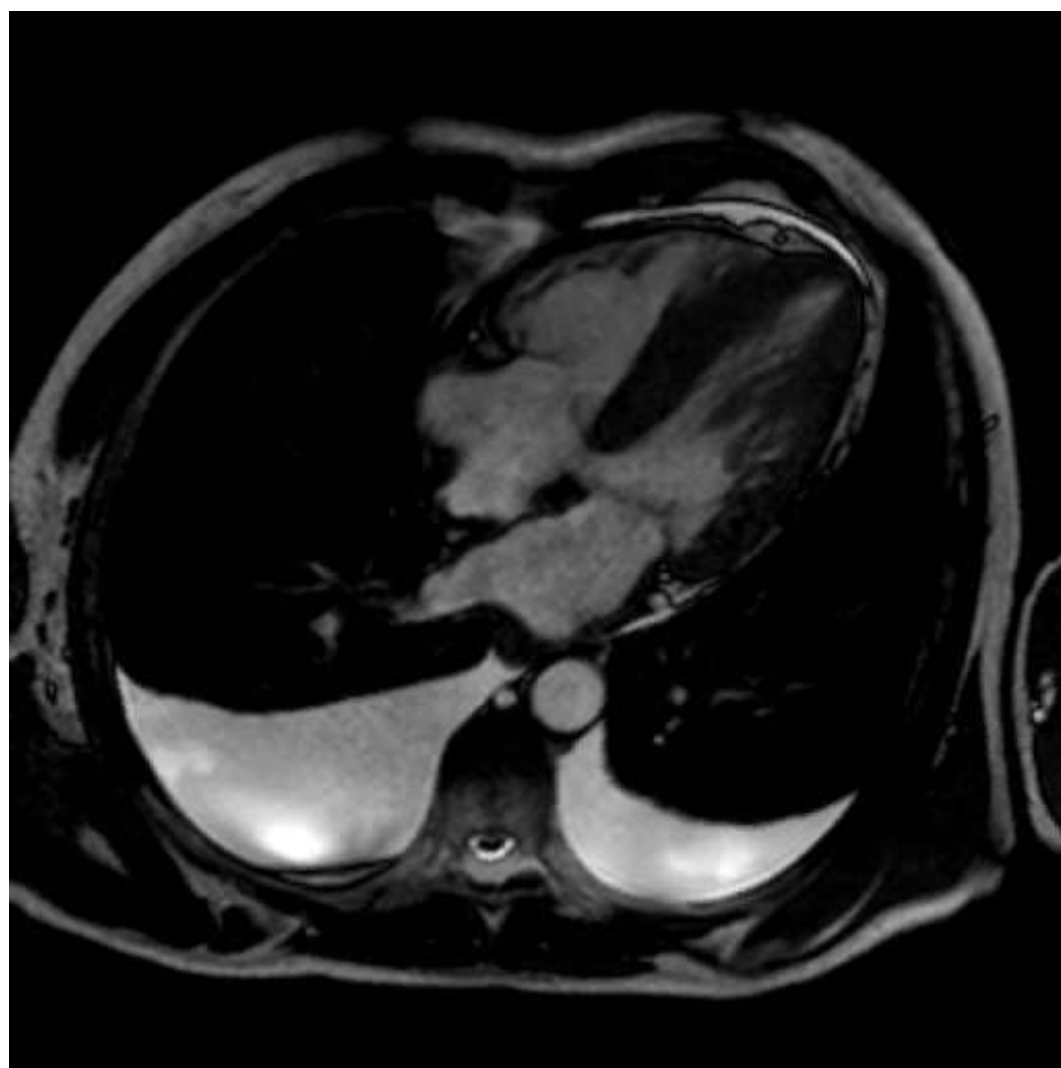


Marianne
Kathryn R
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Olivier H

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n Amaral, B.A.,
, Ph.D.,
browicz, Ph.D.,
Ph.D.,



Genetics of Hypertrophic Cardiomyopathy



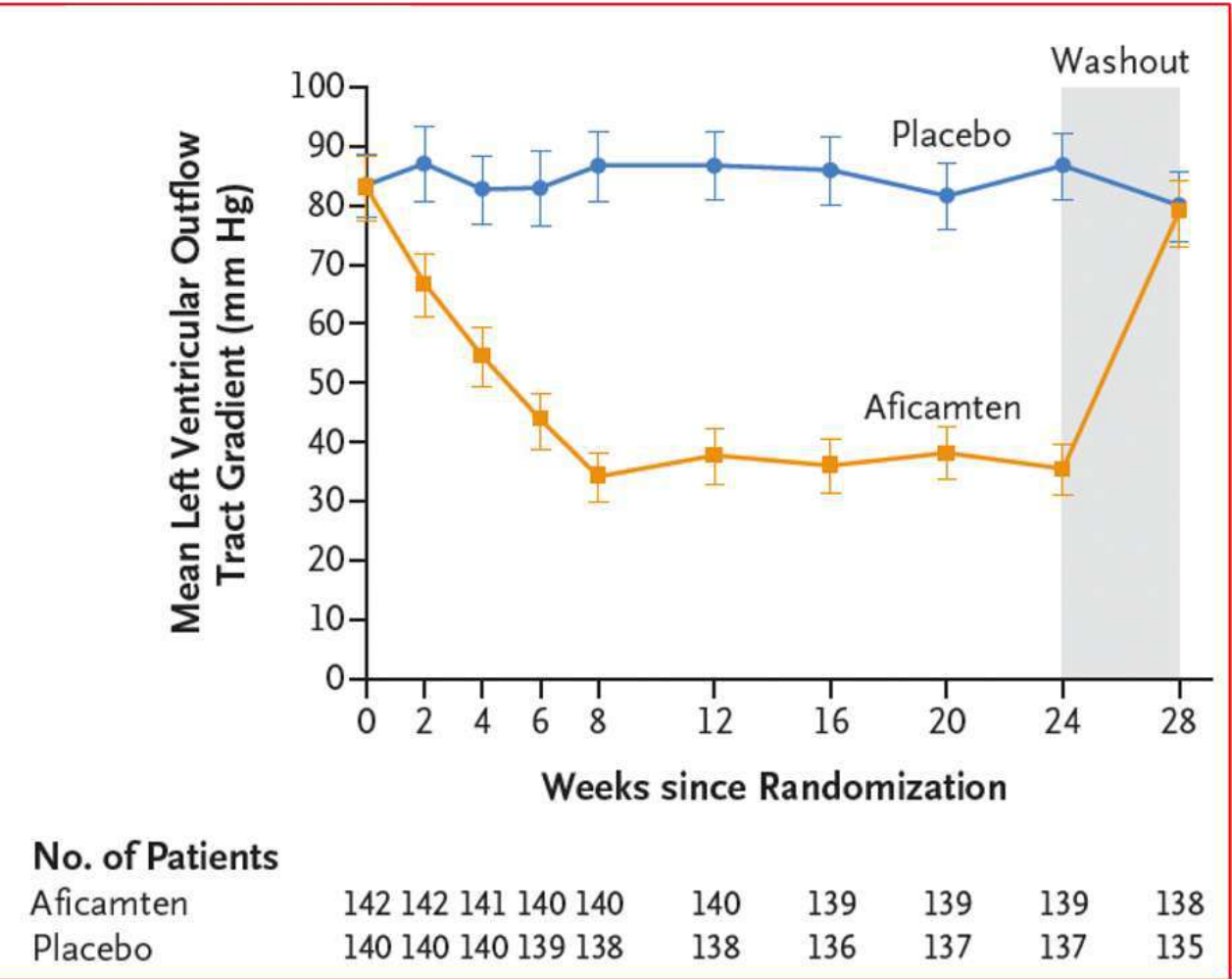
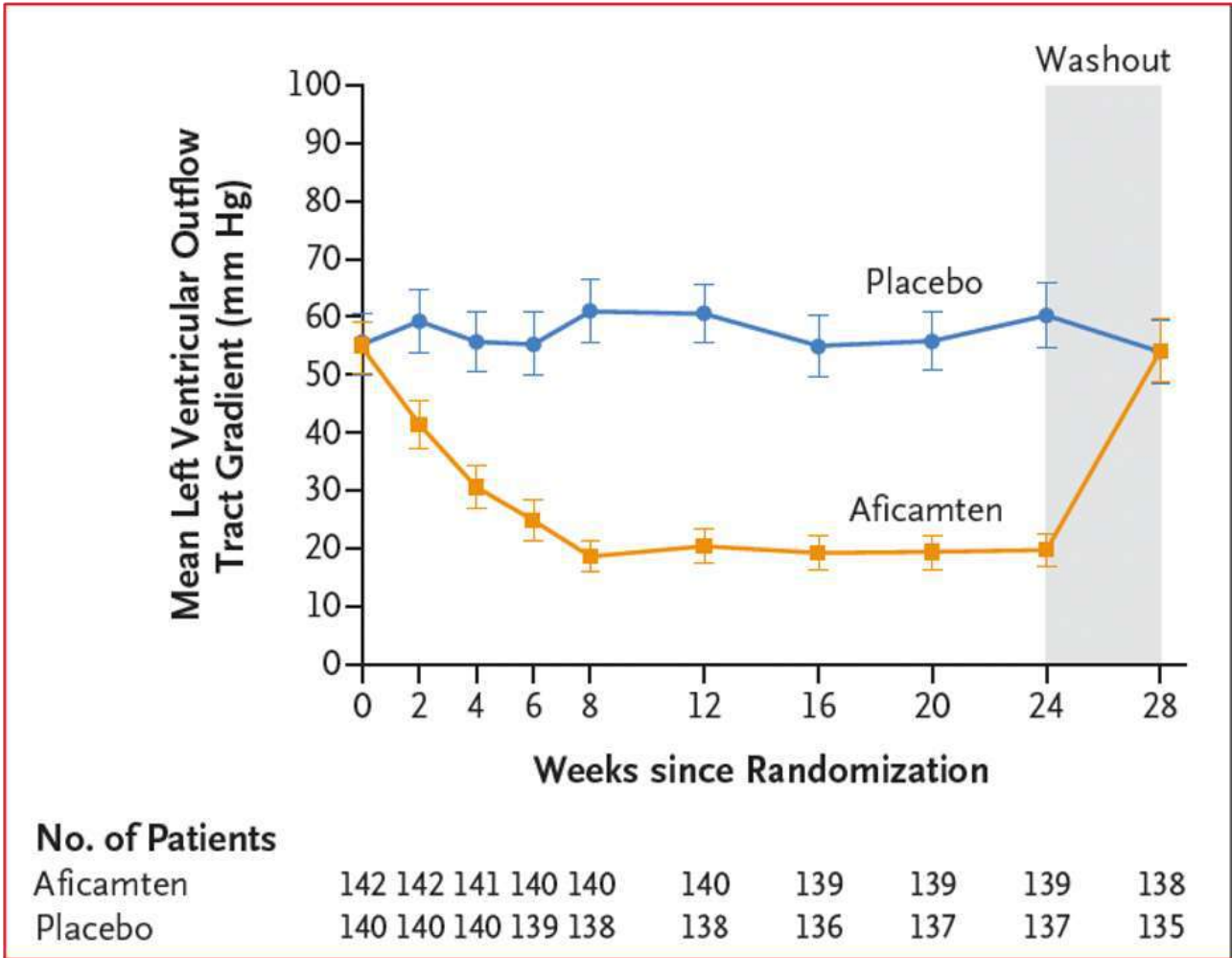


Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*

Change in Peak Resting LVOT Gradient at Baseline

Change in Peak Resting LVOT Gradient after Valsalva Maneuver

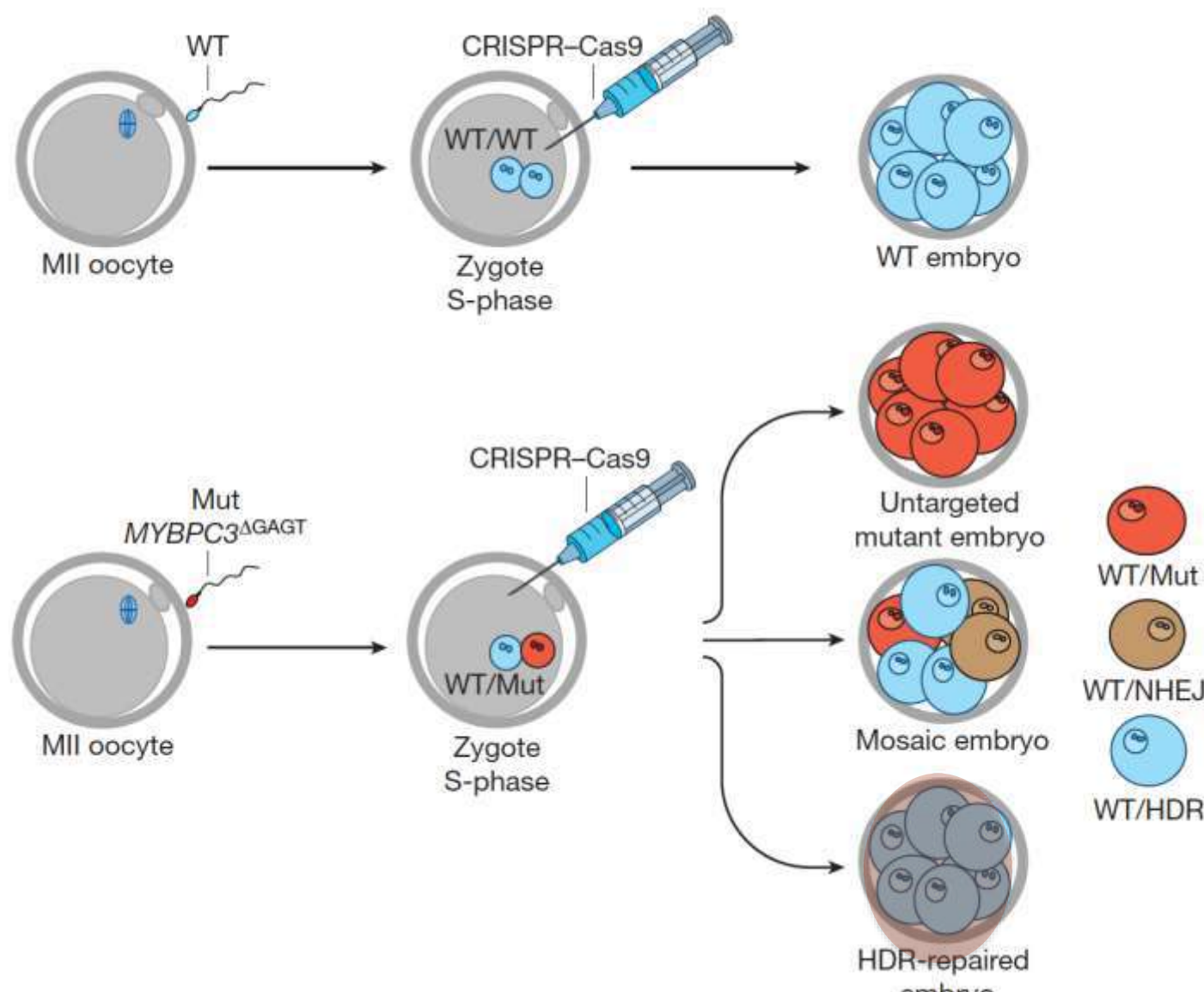




Correction of a pathogenic gene mutation in human embryos

Hong Ma^{1*}, Nuria Marti-Gutierrez^{1*}, Sang-Wook Park^{2*}, Jun Wu^{3*}, Yeonmi Lee¹, Keiichiro Suzuki³, Amy Koski¹, Dongmei Ji¹, Tomonari Hayama¹, Riffat Ahmed¹, Hayley Darby¹, Crystal Van Dyken¹, Ying Li¹, Eunju Kang¹, A.-Reum Park², Daesik Kim⁴, Sang-Tae Kim², Jianhui Gong^{5,6,7,8}, Ying Gu^{5,6,7}, Xun Xu^{5,6,7}, David Battaglia^{1,9}, George A. Kline⁹, David M. Lee⁹, Diego H. W. Costa¹⁰, Don P. Wolf¹, Stephen B. Heitner¹⁰, Juan Carlos Izpisua Belmonte^{1,10} & Shoukhrat Mitalipov^{1,10}§

Genome editing has potential for the targeted correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos. In this study, we used CRISPR-Cas9 to induce double-strand breaks (DSBs) at the *MYBPC3* locus in human embryos. In the presence of a wild-type maternal gene, the DSB was repaired accurately, resulting in wild-type embryos. In the presence of a mutant maternal gene, the DSB was repaired with the mutant allele, resulting in mutant embryos. However, in the presence of a wild-type maternal gene, the DSB was repaired with the wild-type allele, resulting in wild-type embryos. This suggests that the approach presented here is safe and effective for the correction of pathogenic gene mutations in human embryos.





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



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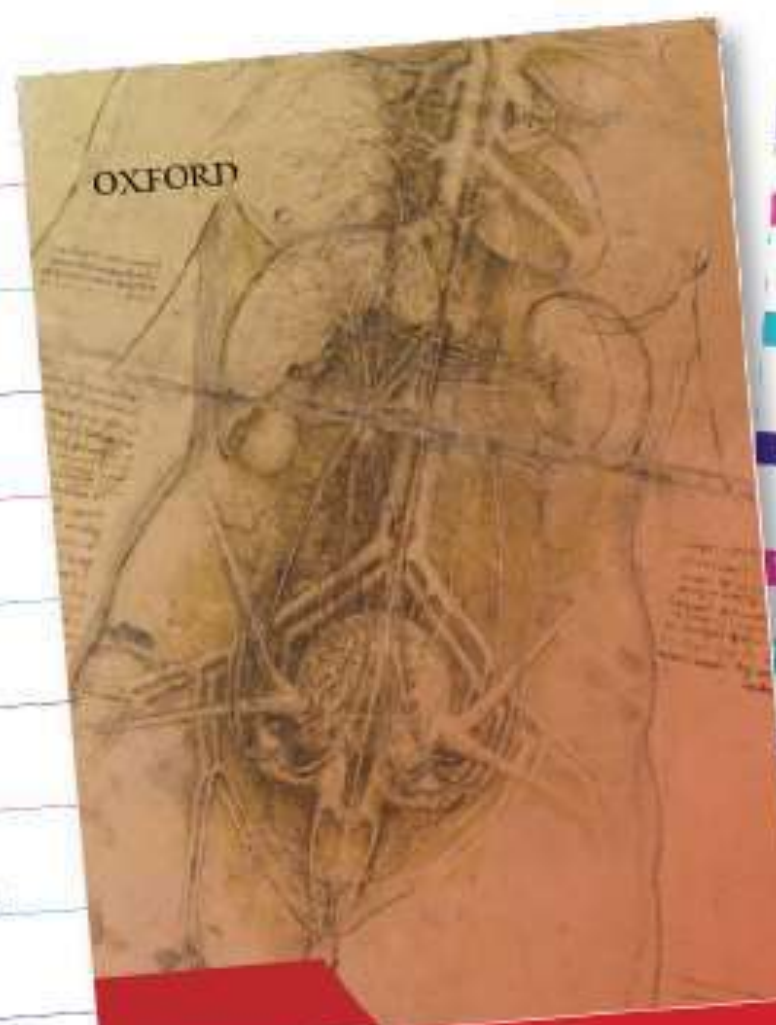


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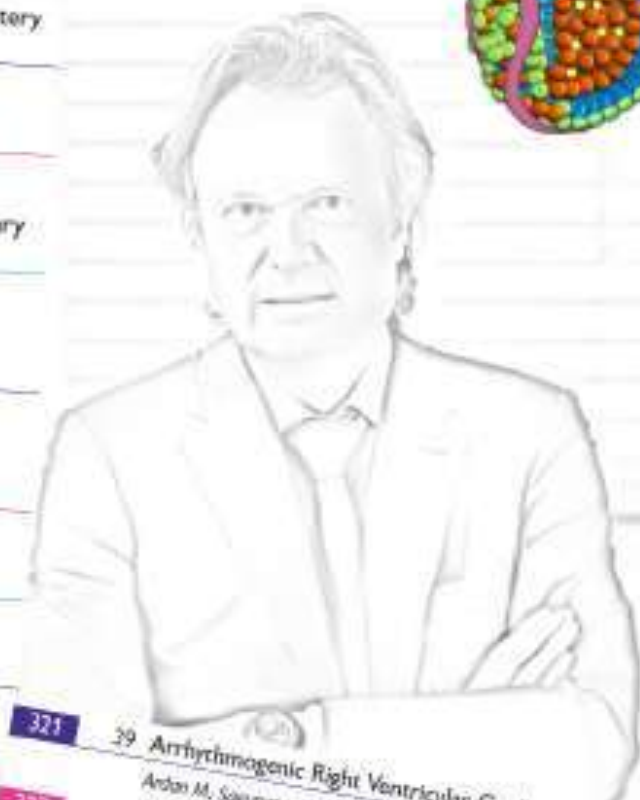
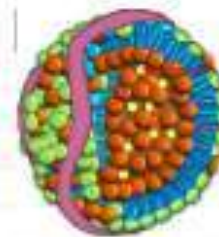
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The Spectrum of Heart Failure and what it means for clinical practice



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