11th ANNUAL HEART FAILURE UPDATE 2024

Friday May 24 - Saturday May 25

Marriott Chateau Champlain, Montreal, Quebec

CHFS SCIC

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

𝕏 @CanHFSociety #HFupdate

Plenary 3: The Rainbow Connection

Welcome and Congress Day 2
Opening Remarks

Shelley Zieroth
MD, FCCS, FHFSA (hon), FESC, FACC, FHFA, FRCPC

We extend our respect to all First Nations, Inuit and Métis peoples for their valuable past and present contributions to this land we call Canada. We acknowledge the Indigenous Peoples of all the lands that we are each on today, and reaffirm our commitment and responsibility as individuals, to improving relationships between nations and to collaborating in a spirit of reconciliation.

Faculty

Co-chairs:

- Shelley Zieroth, MD, FCCS, FHFSA (hon), FESC, FACC, FHFA, FRCPC
- Marco Metra, MD

Presenters:

- Lisa Mielniczuk, MD, FRCPC
- Sheldon Tobe, MD
- Margot Davis, MD, MSc, FRCPC, FCCS
- Lisa Anderson, MD
- Jackie Ratz

Disclosures

	Dr. Shelley Zieroth	Dr. Marco Metra
Any direct financial payments including receipt of honoraria	No disclosures	Consulting honoraria of minimal amount from Astra-Zeneca, Abbott Structural Heart, Bayer, Boheringer Ingelheim, NovoNordisk, Roche diagnostics
Membership on advisory boards or speakers' bureaus	AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Cytokinetics, Eli Lilly, GSK, Janssen, Medtronic, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Salubrisbio, Servier and Vifor Pharma.	No disclosures
Funded grants or clinical trials	AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis and Pfizer	No disclosures
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	Canadian Medical and Surgical KT Group, CCS, CHFS, Charite, EOCI, Liv, Medscape, Ology, PACE-CME, Radcliffe, Reach MD, Translational Medicine Academy	No disclosures

Learning Objectives

1. Employ novel treatment approaches and interdisciplinary collaboration to improve outcomes in patients living with heart failure.
2. Optimize therapies in individuals with heart failure and comorbidities.
3. Diagnose patients living with heart failure with an aim to deliver holistic care.

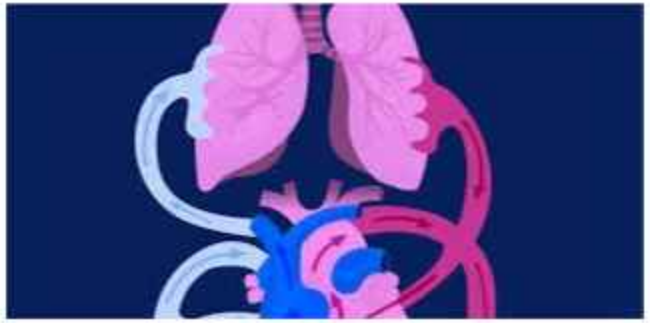
Housekeeping

- To collect your MOC Section 1 credits, please remember to complete both the session evaluation and the congress evaluation
- The evaluation QR code can be found on your tables and will be displayed on the screen after the presentation

The Heart-Lung Connection: Pulmonary Hypertension in Left Heart Disease

Lisa M Mielniczuk MD FRCPC

Professor of Medicine, University of Ottawa Heart Institute
Director, Advanced Heart Diseases Program
Tier 1 Research Chair in Heart Function, University of Ottawa
Chair, Pulmonary Hypertension Association of Canada
Vice President, Canadian Heart Failure Society



Disclosures

- I have received consulting fees/research fees/honoraria from:
  - Janssen
  - Servier
  - Novartis
  - Bayer
  - Astra Zeneca
  - Merck
  - BI
  - NovoNordisk
- Salary Support:
  - Heart and Stroke Foundation of Ontario
  - University of Ottawa
- I will discuss off-label use of medications

Learning Objectives

1. Recognize the interaction of heart failure with common respiratory comorbidities including COPD
2. Discuss the diagnosis and treatment of pulmonary hypertension
3. Identify opportunities to reduce cardiorespiratory risk

Classification of Pulmonary Hypertension

Text

History of Hemodynamics in PAH

2. Normal pulmonary arterial pressure at rest

The figures given in the report of the WHO Expert Committee on Chronic Cor Pulmonale (4) may be regarded as valid. The mean pressure in the pulmonary artery does not normally exceed 15 mm Hg when the subject is at rest in a lying position. This value is little affected by age and never exceeds 20 mm Hg. Hypertension is definitely present if the pressure exceeds 25 mm Hg.

PH is Defined by mPAP ≥ 25 mmHg

Retrospective Meta-Analysis
Clinical Studies (N = 47)
N = 1,187 Patients

Resting Supine RHC (N = 882)

Measurement	Mean (SD)
mPAP (mmHg)	14 (3.3)
CO (L/min)	7.3 (2.3)
CI (L/min/m^2)	4.1 (1.3)
PVR (WU)	0.93 (0.4)

mPAP, mean pulmonary artery pressure
CO, cardiac output
PVR, pulmonary vascular resistance

Kovacs G, et al. Eur Respir J 2009;34:888-94.

CI, cardiac index; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; SD, standard deviation.

The Evolution Of (Re)defining PH In Left Heart Disease

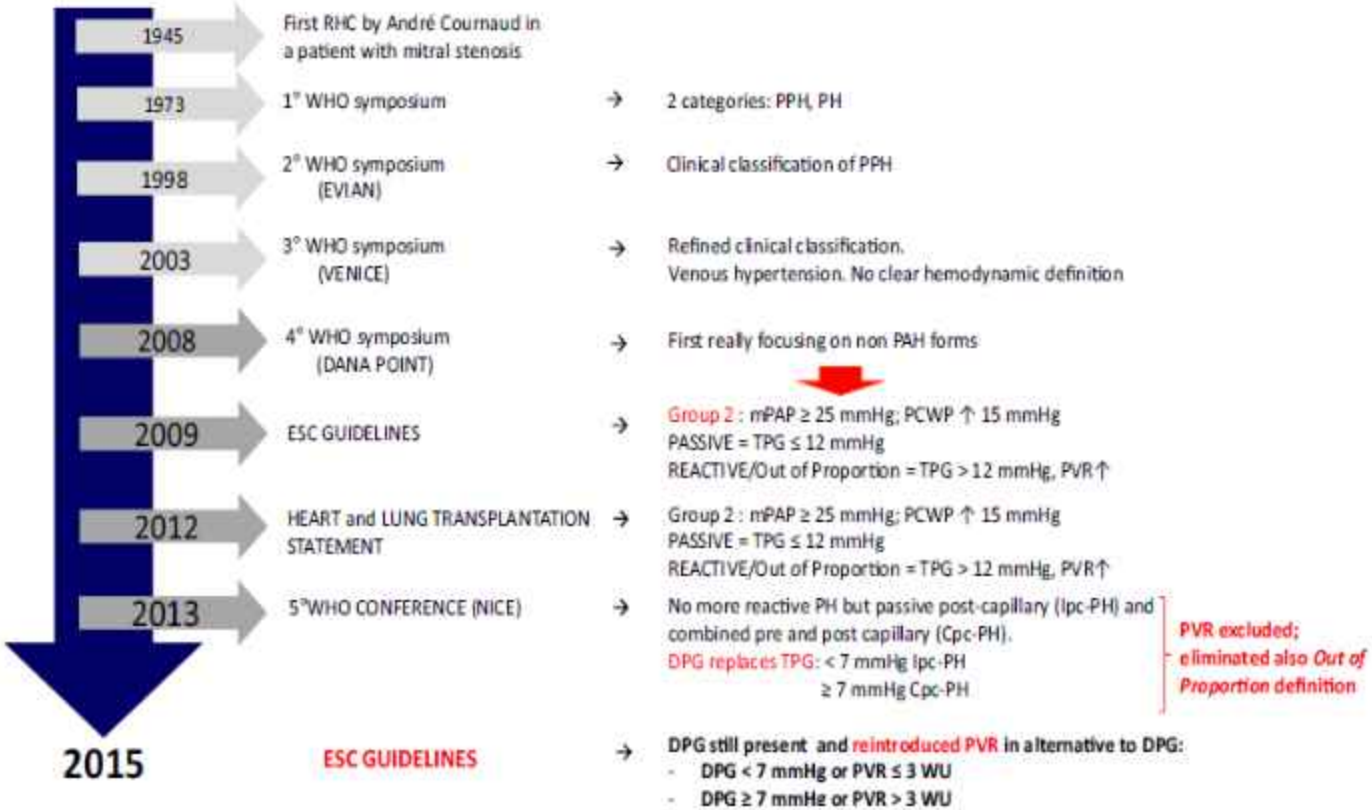


Table 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Labate; Curr Heart Fail Rep 2016; 13:281

How Common is PH in Heart Failure?

- Prevalence varies
  - Population
  - Diagnostic approach
  - Definition used
- TOPCAT TR velocity> 2.9m/sec was 36%
- Population based cohort: 83%

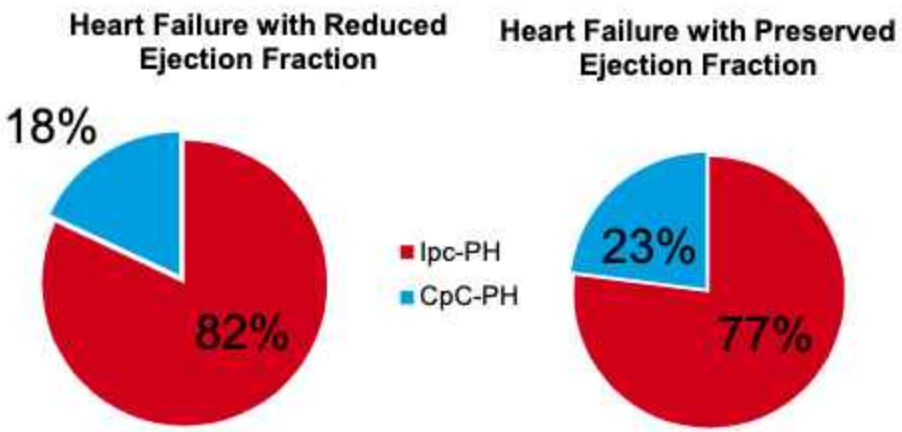


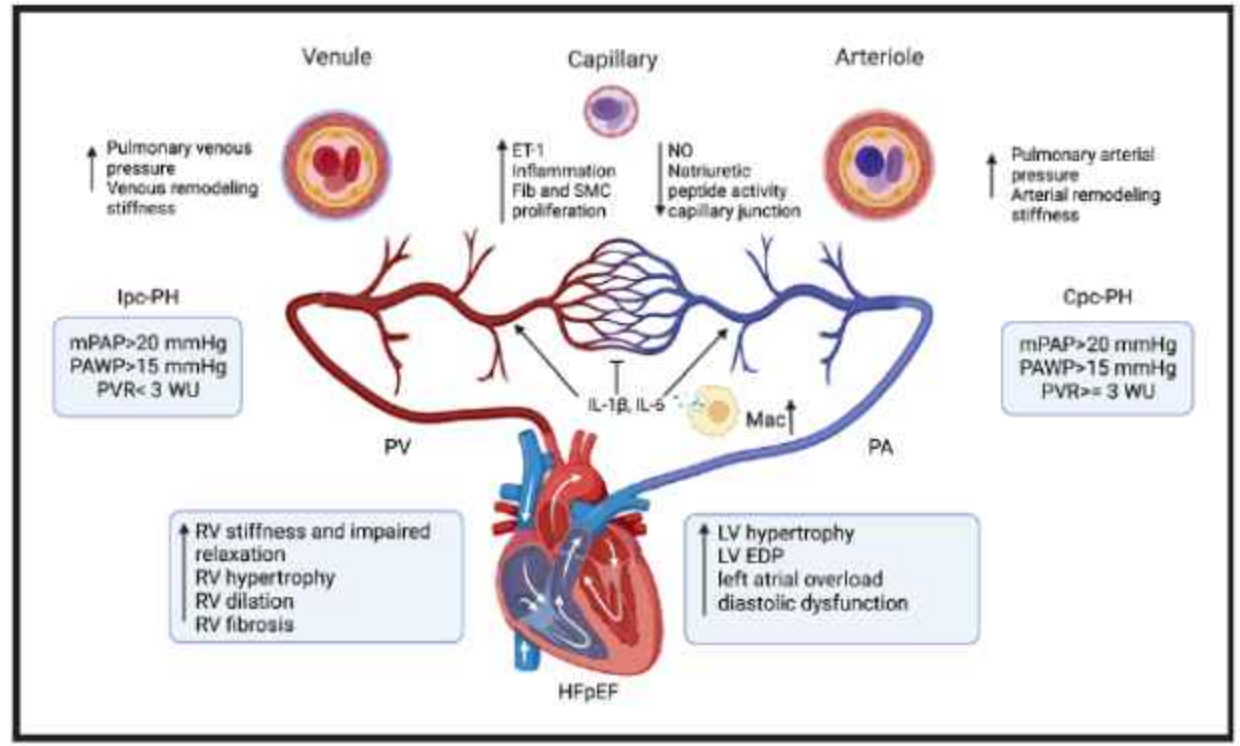
Table 3. Prevalence of PH in HFpEF

Study	Years	Population	Diagnostics	Definition	Prevalence of PH, %	Severity
Lam et al[9]	2003–2005	Olmsted County Heart Failure Surveillance Study	Echocardiography-estimated PASP	Framingham criteria LVEF ≥50% Echocardiography PASP >35 mm Hg	83	PASP 48 (37–56) mm Hg
Gerges et al[18]	Retrospective cohort 1996–2003	Medical University of Vienna	Echocardiography, RHC	HF signs and symptoms LVEF ≥45% mPAP ≥25 mm Hg	54.4	Cpc-PH: mPAP 45.6±12.8 mm Hg Ipc-PH: mPAP 36.4±8.1 mm Hg
	Prospective cohort 2012–2013				63	Cpc-PH: mPAP 44.2±13.2 mm Hg Ipc-PH: mPAP 34.3±7.0 mm Hg
Leung et al[19]	1996–2007	Dartmouth Dynamic Registry	LHC/RHC	LVEDP >15 mm Hg LVEF ≥50% mPAP >25 mm Hg	52.5	mPAP 34.2±7.8 mm Hg
Shah et al[20]	2006–2012	TOPCAT, echocardiography cohort	Echocardiography-measured TRV	LVEF ≥45% HF hospitalization or elevated BNP/NT-proBNP TRV >2.9 m/s	36	Mean TRV 3.28±0.33 m/s
Melenovsky et al[21]	2005–2012	Mayo Clinic	Echocardiography, RHC	Framingham criteria LVEF ≥50% PAWP ≥15 mm Hg mPAP > 25 mm Hg	81	mPAP 36±11 mm Hg
Mohammed et al[22]	2003–2009	Mayo Clinic, Olmstead County HFpEF cohort	Echocardiography	Framingham criteria LVEF ≥50% PASP >40 mm Hg	64.5	
Ho et al[12]	2006–2017	Massachusetts General Hospital	Invasive CPET	EF ≥50% mPAP/CO >3 mm Hg/L/min	41 (exercise PH)	

Gerges C; Am J Resp Crit Care Med 2015; 1234-1246

Brittain E. Circ 2022;146e73-e88

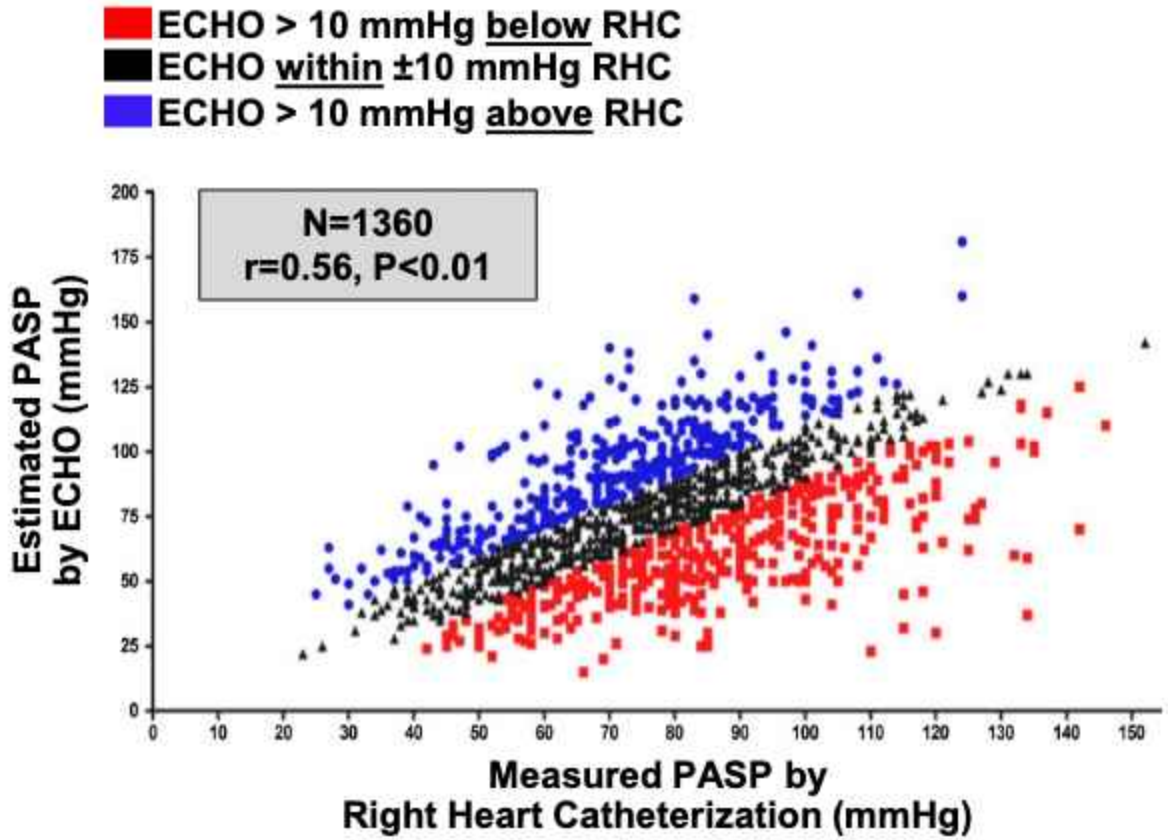
Development of PH in Left Heart Disease

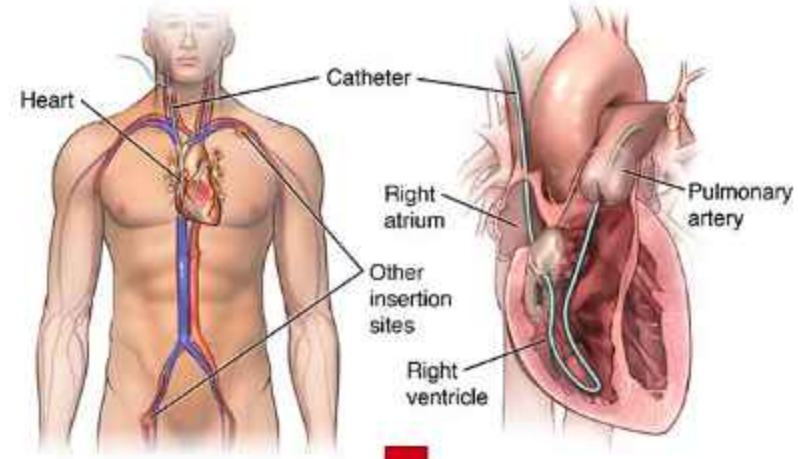


Z Dai, Circ Res. 2023; 133: 899-901

Hemodynamic Assessment of PAH

ECHO *vs. Right Heart Catheterization*



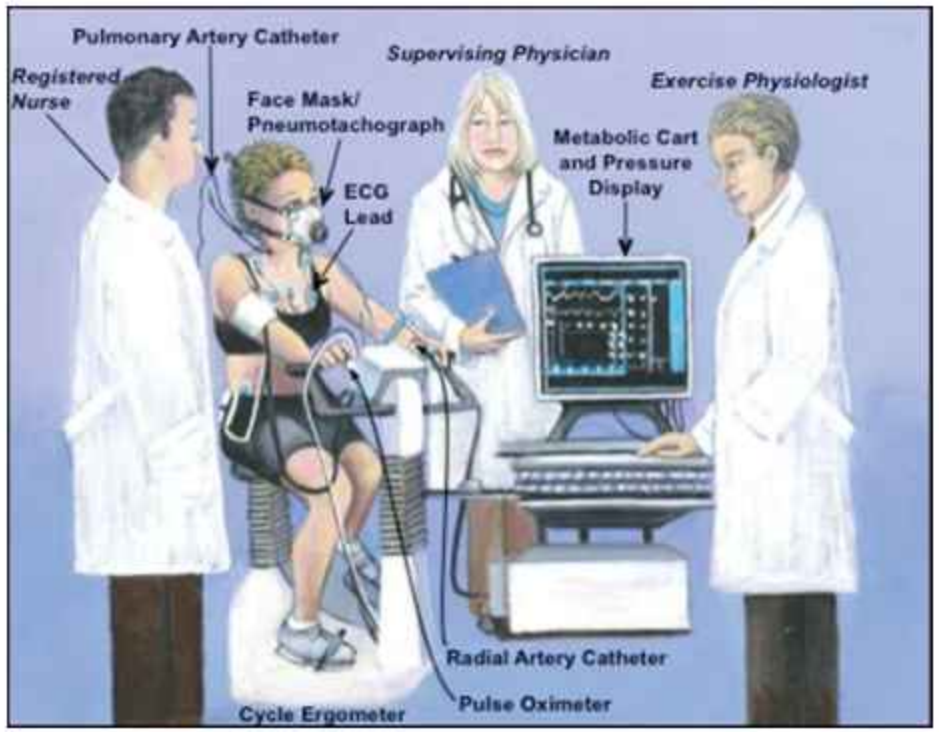


Right Atrial Pressure
Right Ventricular Pressure
Pulmonary Artery Pressure (PAP)
Pulmonary Artery Wedge Pressure (PAWP)
Cardiac Output (Thermodilution/Fick)
Oxyhemoglobin Saturation Levels

Pulmonary Vascular Resistance
Intracardiac Shunts

PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; RHC, right heart catheterization.
Farber HW et al. Congest Heart Fail 2011;17:56-63.

Is there a Role for Provocative Testing?



- Degree of mPAP increase in response to change in CO: mPAP/CO
  - Normal 0.5-3 mmHg/L/min
  - Max value of mPAP of 30 at a CO of 10 l/min
- **Exercise induced PH: mPAP/CO (mmHg/L/min)> 3**
- mPAWP > 25 mmHg with exercise
- **Occult PH-LHD**
  - mPAP/CO (mmHg/L/min)> 3
  - mPAWP/CO>2 mmHg/L/min

- Fluid Challenge:
  - 7 ml/kg bolus of NS over 5 min
  - PWP> 18 mmHg suggests PH-LHD

Eismen: Circ HF 2018; 11: e004750

D'alto. Chest 2017151:119-26
Ltaief, Z. In J Mol Sci 2023,24

Therapeutic Goals in The Management of PH-LHD

Mechanisms

- Decrease PAWP and improve compliance
- Prevent RV remodeling
- Reduce PVR
- Prevent or treat RV-PA uncoupling

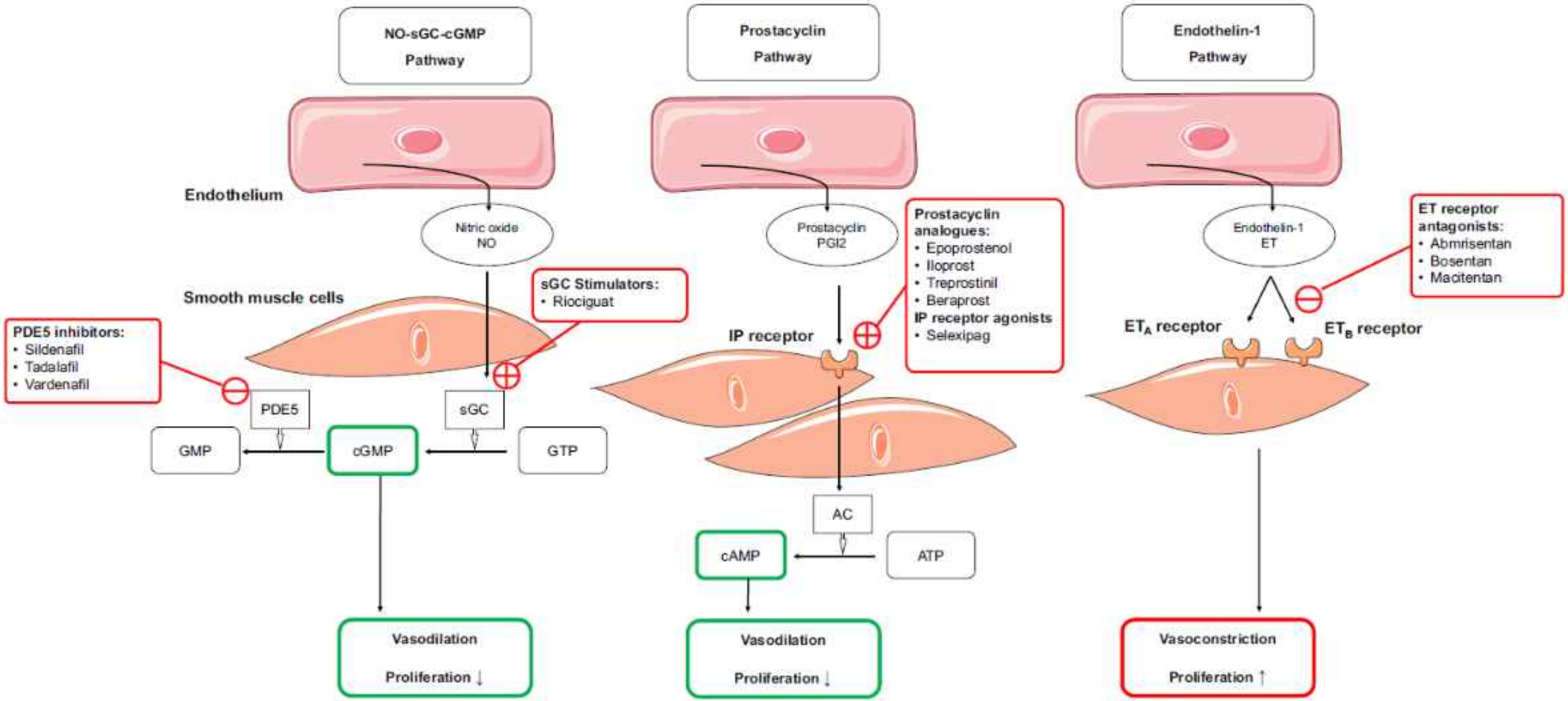
Actions

- Guideline-Directed medical therapies for heart failure
- Drugs approved for Pulmonary Arterial Hypertension?
- Novel non-pharmacologic interventions?

Outcomes

- Prevention of PH/right heart failure
- Improved patient outcomes

The Use of Pulmonary Vasodilator Therapy in PH-LHD



Papathanasiou et al. Pharm and Thera 2-2-: 107619

Repurposing Pulmonary Vasodilators

Parameter	Hoenderm is et al (n=52)	MELODY-1 (n=60)	DYNAMIC (n=114)
Cause of HF	HFPEF	HF EF>30%	HPEF
Mean age (y)	74	71	71
Median NTproBNP	1087	2472	859
Mean PVR (WU)	2.5	6.5	2.9
Mean PWP (mmHg)	20.4	19.8	21
Mean PAP (mmHg)	35	47	36
Intervention	Sildenafil	macitentan	Riociguat
Outcome/Result	No change in PAP, hemodynamics or clinical endpoints	Increased fluid retention	Improvement in cardiac output, no other benefits

SOUTHPAW:
HFPEF EF>40%
RHC confirmed Group 2 PH

Oral Treprostinil → SOUTHPAW → terminated

Macitentan → SERANADE → Completed 143/300 enrollment

SERENADE
HFPEF EF>40%
Pulmonary vascular disease or RV dysfunction

- No difference in Change in NTproBNP
- No difference in time to worsening HF
- More fluid retention in active arm

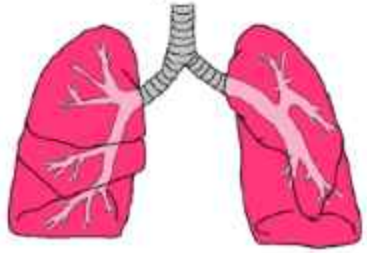
Sotatercept in CpC-PH due to HFPEF: CADENCE Study

- Recruiting
- Phase II RCT
- Sotatercept vs placebo
  - Cpc PH due to HFpEF
    - PVR>320, mPAP>20, PCWP 15-3
- Primary Outcome:
  - PVR over 24 weeks
- Secondary Outcomes:
  - 6 MWT
  - Time to first clinical worsening
  - Change in mPAP, PCWP, others
  - Echo parameters
  - NTproBNP, NYHA,

Clin Trials. Gov NCT04945460

The Potential of GDMT

Pulmonary Vasculature

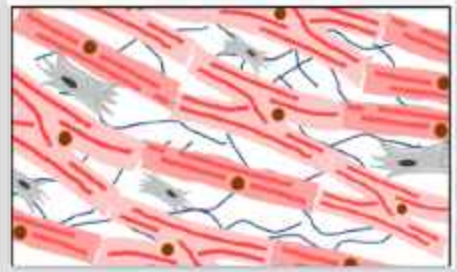


SGLT2 I
- Reduce PA pressures
- Reduce adverse remodeling

GLP1 RA
- Reduce inflammation, fibrosis, and adverse remodeling
- Increase nitric oxide

ARNI
- Reduce PA pressures
- Reduce adverse remodeling

RV myocardium

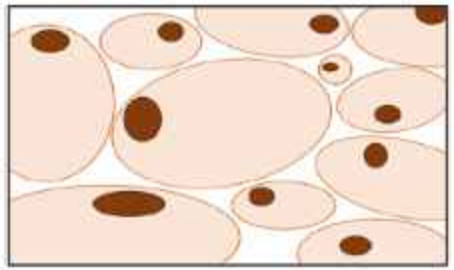


SGLT2 I
- Reduce RV pressures
- Improve metabolism
- Reduce inflammation
- Reduce adverse remodeling

GLP1 RA
- Improved RV function
- Reduce inflammation
- Cardioprotective in ischemia
- Reduce adverse remodeling

ARNI
- Reduce RV pressures
- Reduce adverse remodeling
- Reduce hypertrophy

Adipose

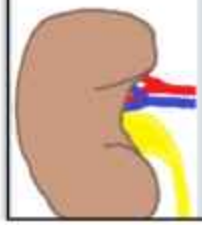


SGLT2 I
- Improve insulin sensitivity

GLP1 RA
- Improve insulin sensitivity
- Weight loss
- Brown fat thermogenesis

ARNI
- Potentially improve insulin sensitivity

Renal



SGLT2 I
- Enhance osmotic diuresis

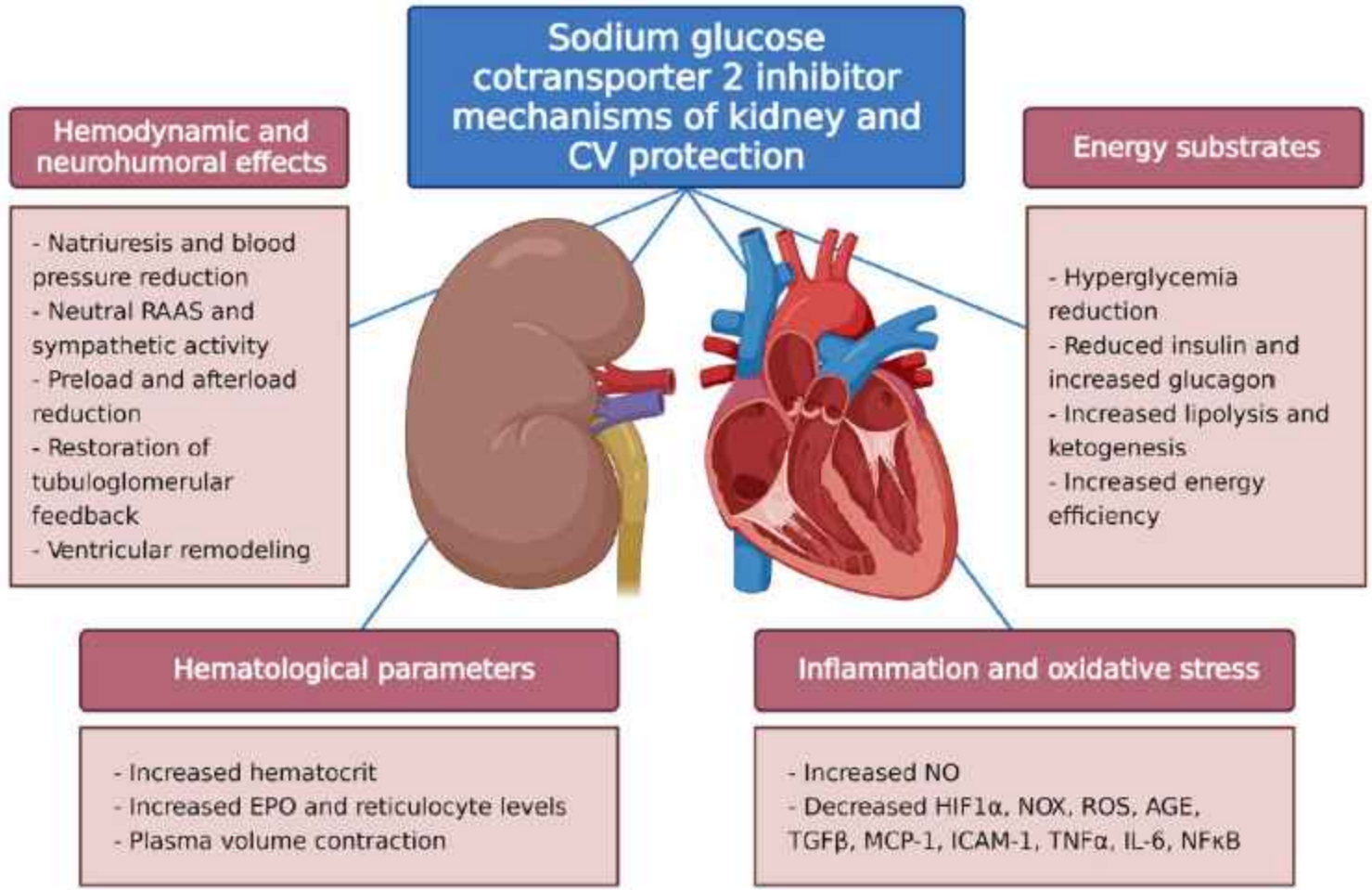
ARNI
- Enhance natriuresis

King E, Pulmonary Circulation 2022;12:e12028

Beyond Diuresis..Potential Mechanisms of Benefit

Potential Indirect/Systemic Effects of SGLT2I

- ❑ ↓ weight
- ❑ ↓ afterload /arterial stiffness
- ❑ ↓ adipocytokine production
- ❑ ↑natirureis /diuresis
- ❑ ↑ metabolic efficiency
- ❑ ↑ Erythopoietin
- ❑ ↑ Regenerative stem cell production



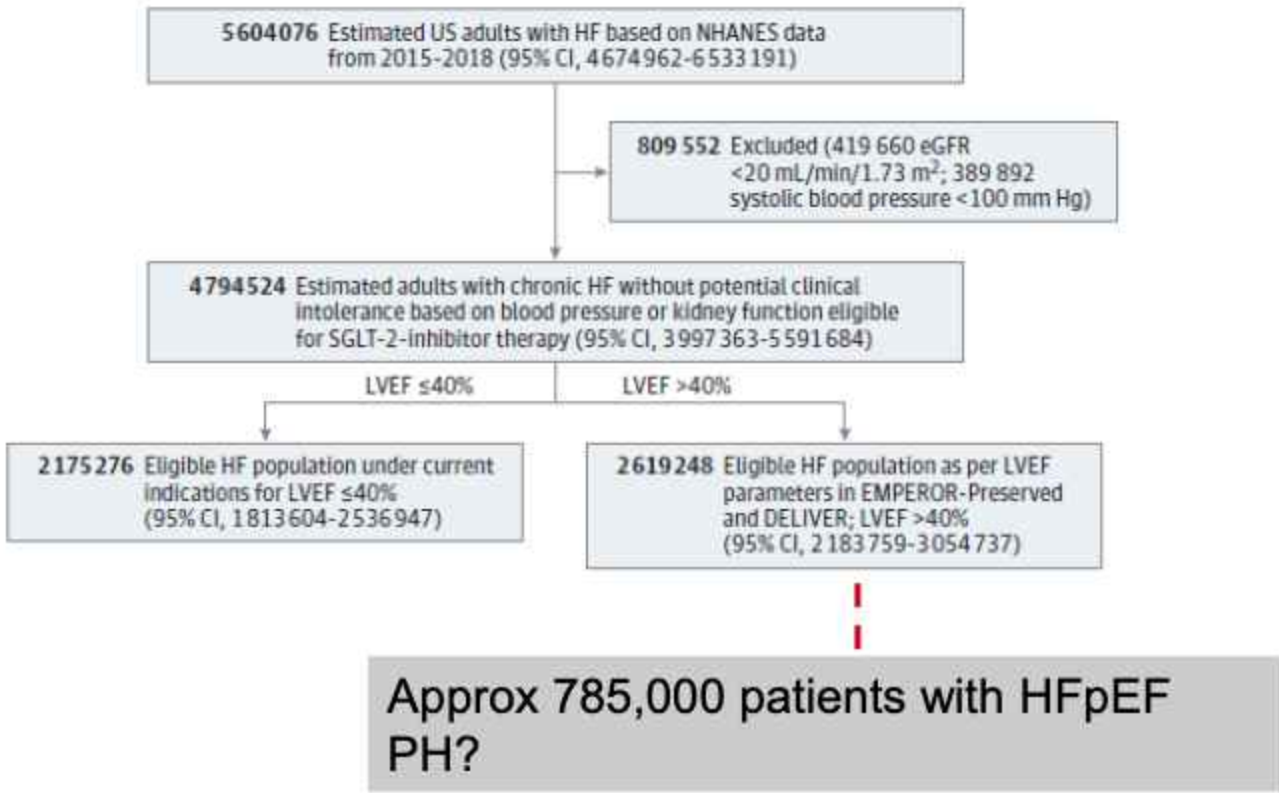
Potential Direct Myocardial Effects of SGLT2I

- ❑ ↓ LV mass
- ❑ ↓ Na/H exchanger
- ❑ ↓ myocardial endoplasmic reticulum stress
- ❑ ↓ epicardial fat
- ❑ ↓ NLRP2 inflammasome
- ❑ ↑ coronary microvascular function

Liu, H. Metabolism Clin and Exp. 2022;126:154918

Population-Level Implications of SGLT2I Use in PH-LHD

Figure 1. Total Heart Failure (HF) Population Estimated From the National Health and Nutritional Examination Survey (NHANES) That Would be Eligible for Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitor Therapy



Approx 785,000 patients with HFpEF PH?

Projected Event Reductions Over 3 Years

232 589 – 282 879 HF events

172 870 – 231 018 HF hospitalizations

Fonarow G, JAMA Cardiol 2023; 8:66-73

Pre-Clinical SGLT2 Inhibitor Use in PH

Improved Vascular Remodeling (MCT model)

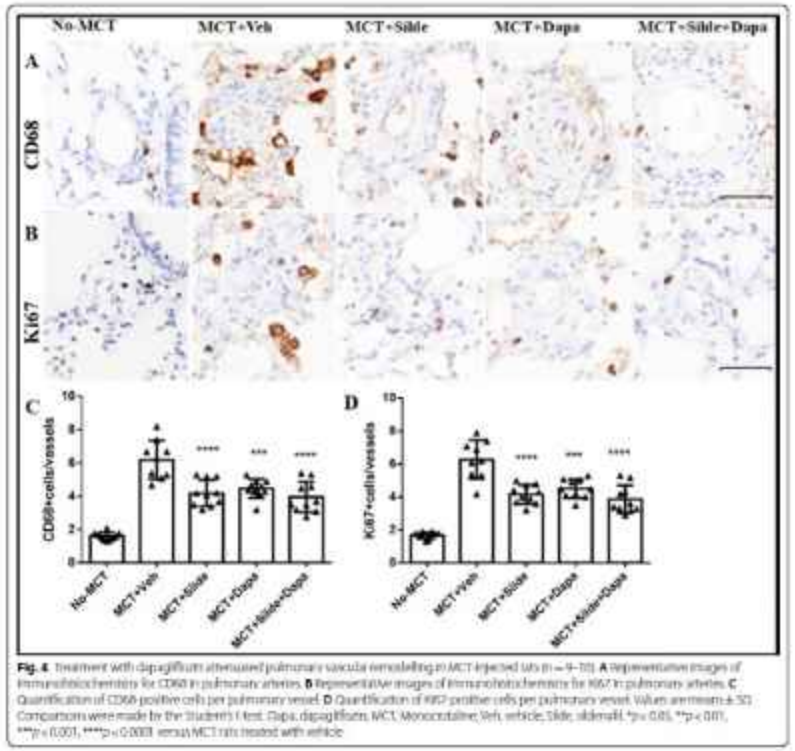
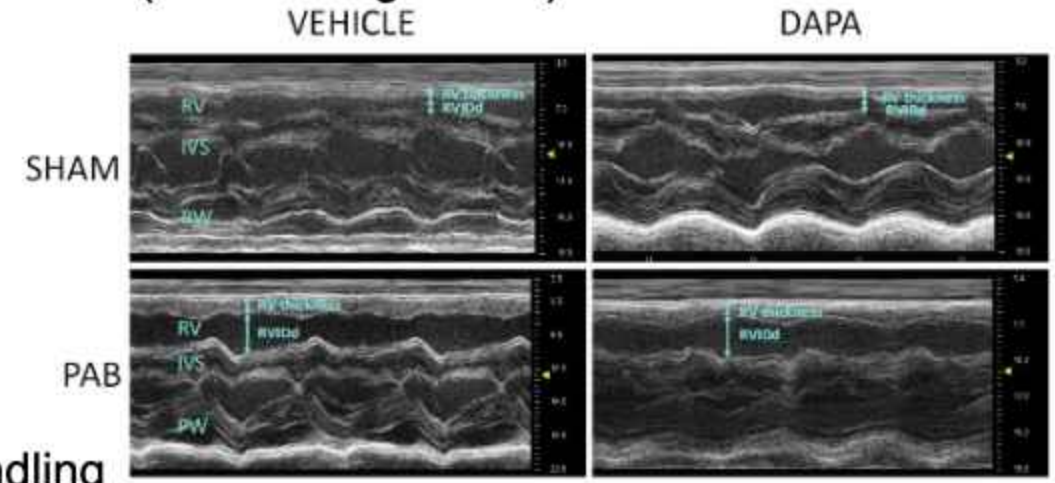


Fig. 4 Treatment with dapagliflozin attenuated pulmonary vascular remodelling in MCT-injected rats (n = 9–10). **A** Representative images of immunohistochemistry for CD68 in pulmonary arteries. **B** Representative images of immunohistochemistry for Ki67 in pulmonary arteries. **C** Quantification of CD68-positive cells per pulmonary vessel. **D** Quantification of Ki67-positive cells per pulmonary vessel. Values are means ± SD. Comparisons were made by the Student's *t* test. Dapa, dapagliflozin; MCT, Monocrotaline; Veh, vehicle; Silde, sildenafil. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 versus MCT rats treated with vehicle

Tang, Yi. BMc Pul Med 2022;22:142

Improved RV Mass and Remodeling (PA Banding model)



Connelly K. CV Drugs and Therapy. 2022

Restores Calcium Handling (MCT model)

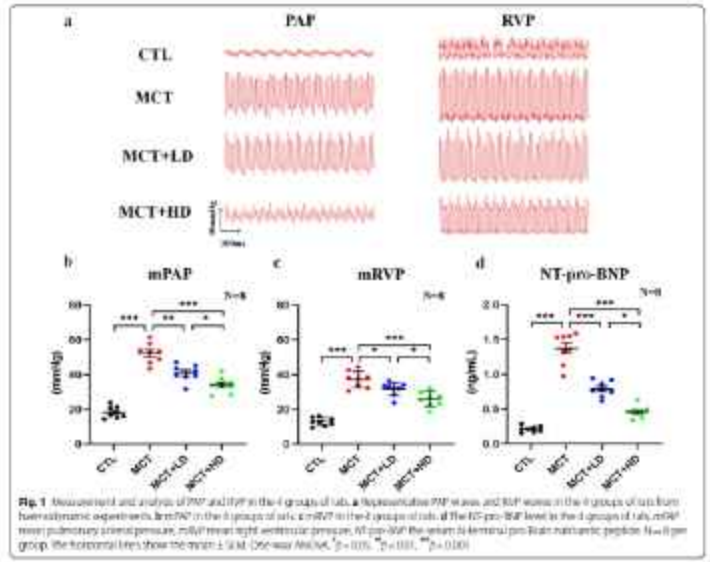
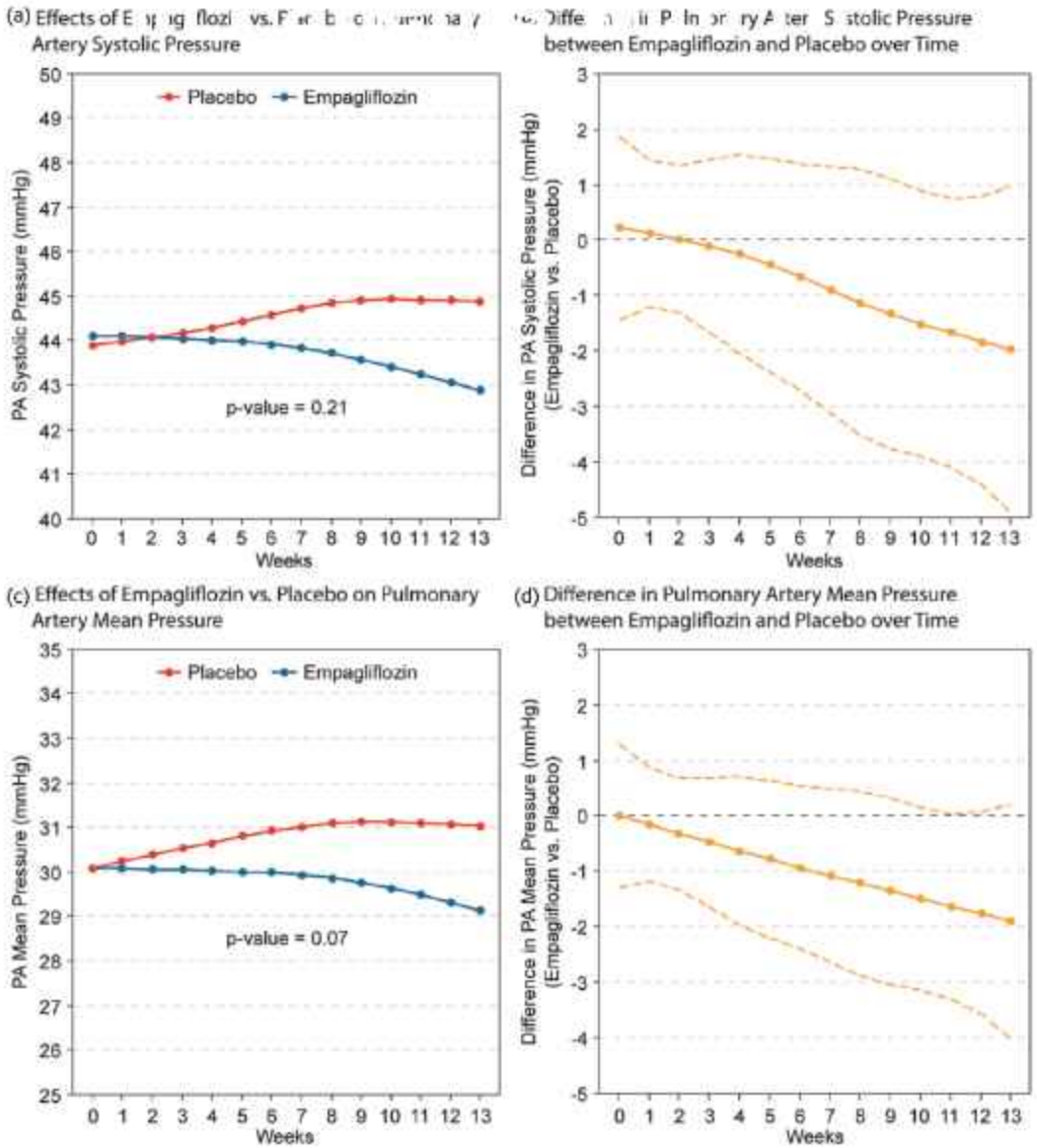
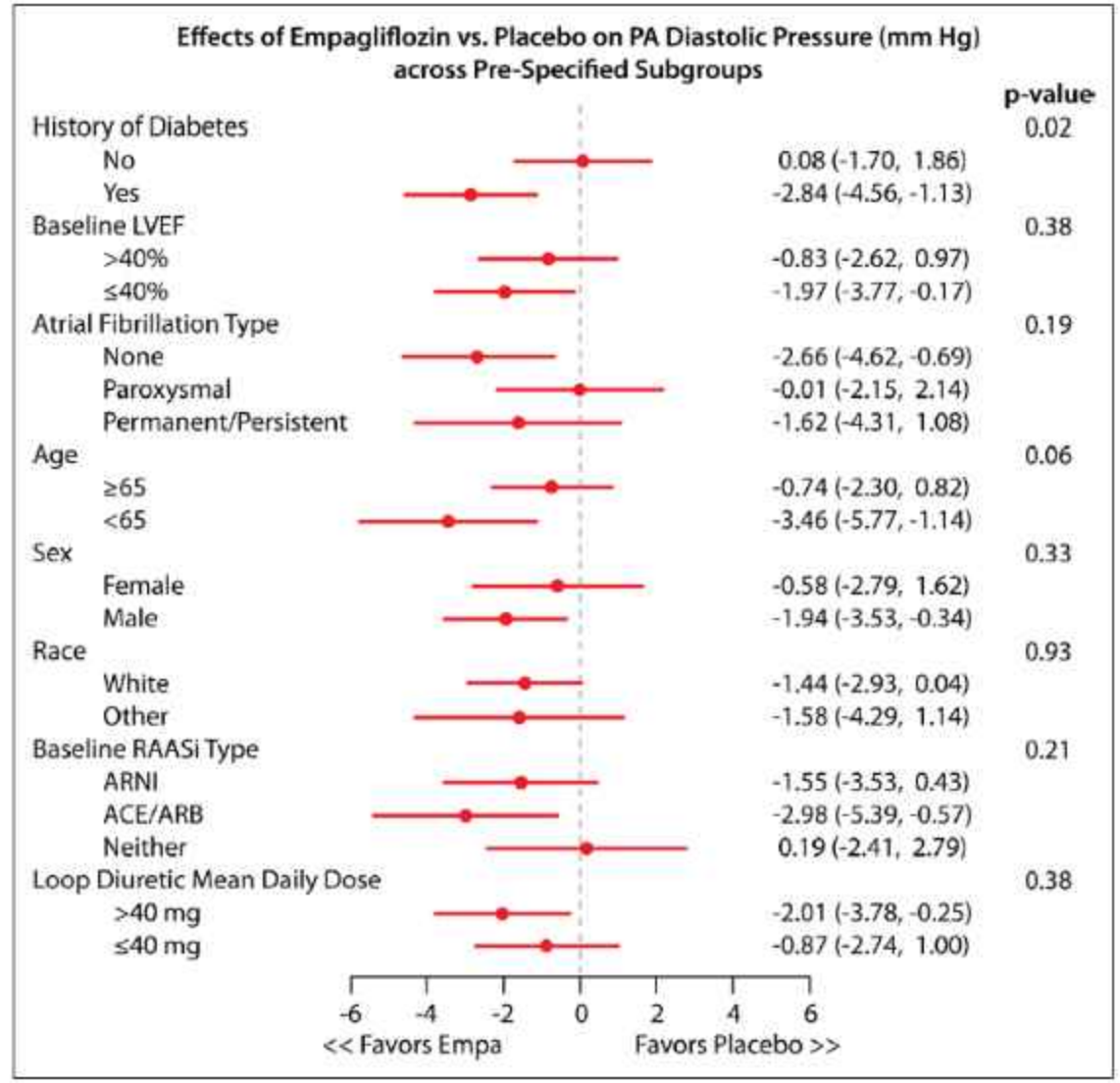


Fig. 1 Measurement and analysis of PAP and RVP in the 4 groups of rats. **a** Representative PAP waves and RVP waves in the 4 groups of rats from haemodynamic experiments. **b** mPAP in the 4 groups of rats. **c** mRVP in the 4 groups of rats. **d** The NT-pro-BNP level in the 4 groups of rats. mPAP mean pulmonary arterial pressure, mRVP mean right ventricular pressure, NT-pro-BNP the serum N-terminal pro-B-type natriuretic peptide. N = 8 per group. The horizontal lines show the mean ± S.E.M. One-way ANOVA, *p < 0.05, **p < 0.01, ***p < 0.001

Wu, Cardiov Diab 2022;21:197

Empagliflozin Effects on Pulmonary Artery Pressure

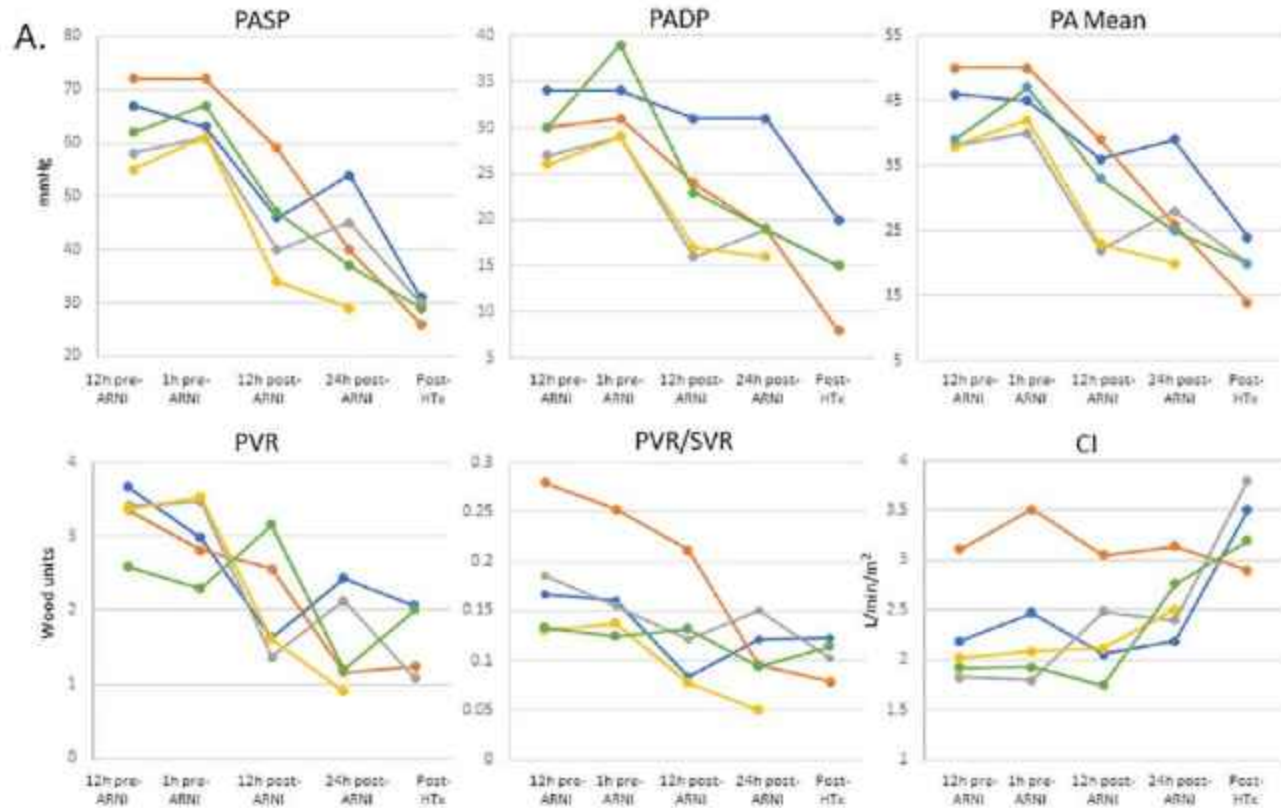




Nassif M, Circulation. 2021; 143:1673.

ARNI Reversing PH in End Stage HF Patients Awaiting Transplantation

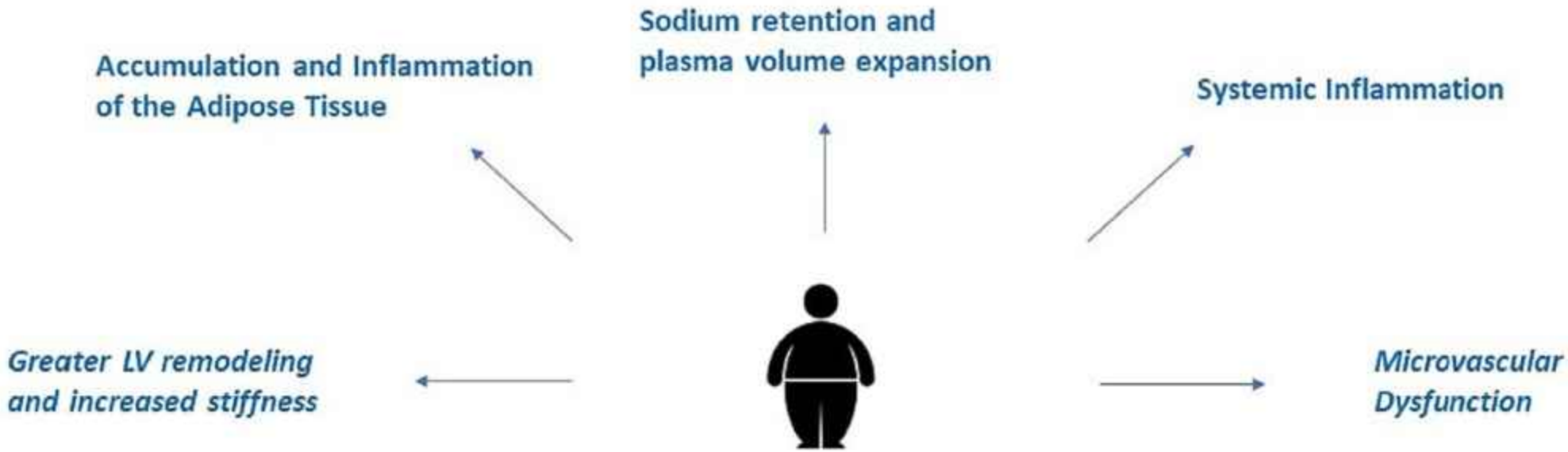
- Small case series of 5 patients
  - Inotrope dependent
- 24 hour results (PAC)
  - Reduction in PASP, PVR, TPG
  - PAPi increased



COMPLETED Treatment of PH With Angiotensin II Receptor Blocker and Neprilysin Inhibitor in HFpEF Patients With CardioMEMS Device (ARNIMEMS-HFpEF) **ClinicalTrials.gov ID** NCT04753112

Zern E. Circ Heart Fail 2020;13(2):e006696

The Impact of Obesity on PH-LHD



Potential benefit of Glucagon-like peptide-1 receptor agonists

↓ reactive oxygen species and systemic inflammation

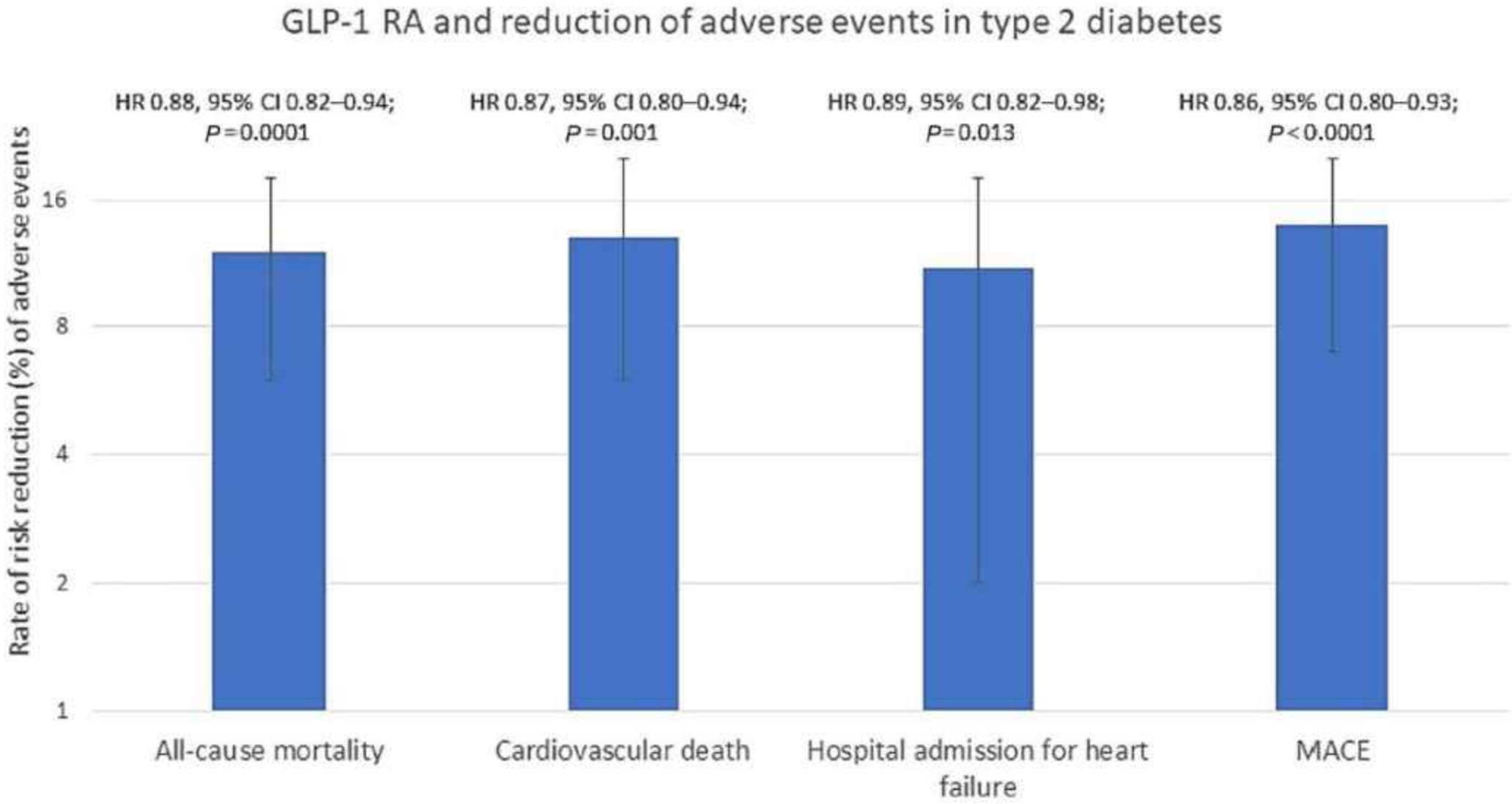
↓ diastolic filling pressures and unloading of the LV

↓ renin-angiotensin-aldosterone system activation

↓ plasma volume expansion

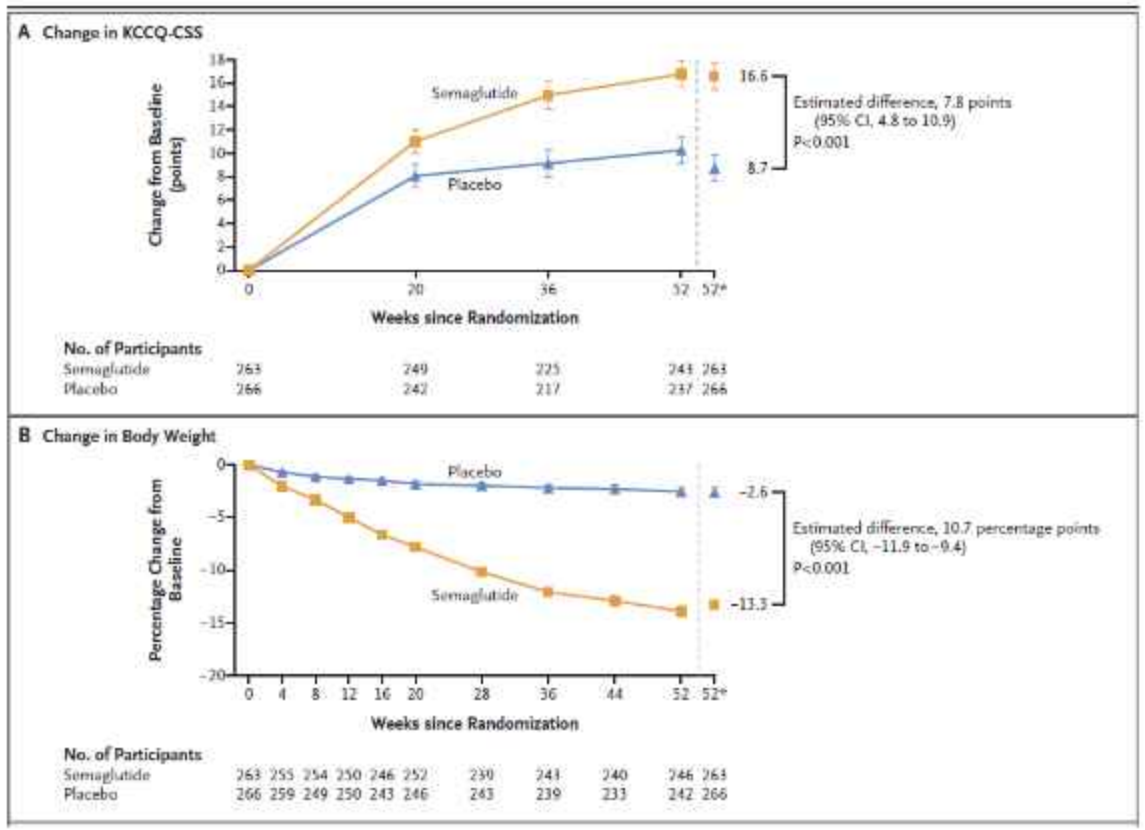
Cimino G, ESC Heart Failure 2023;

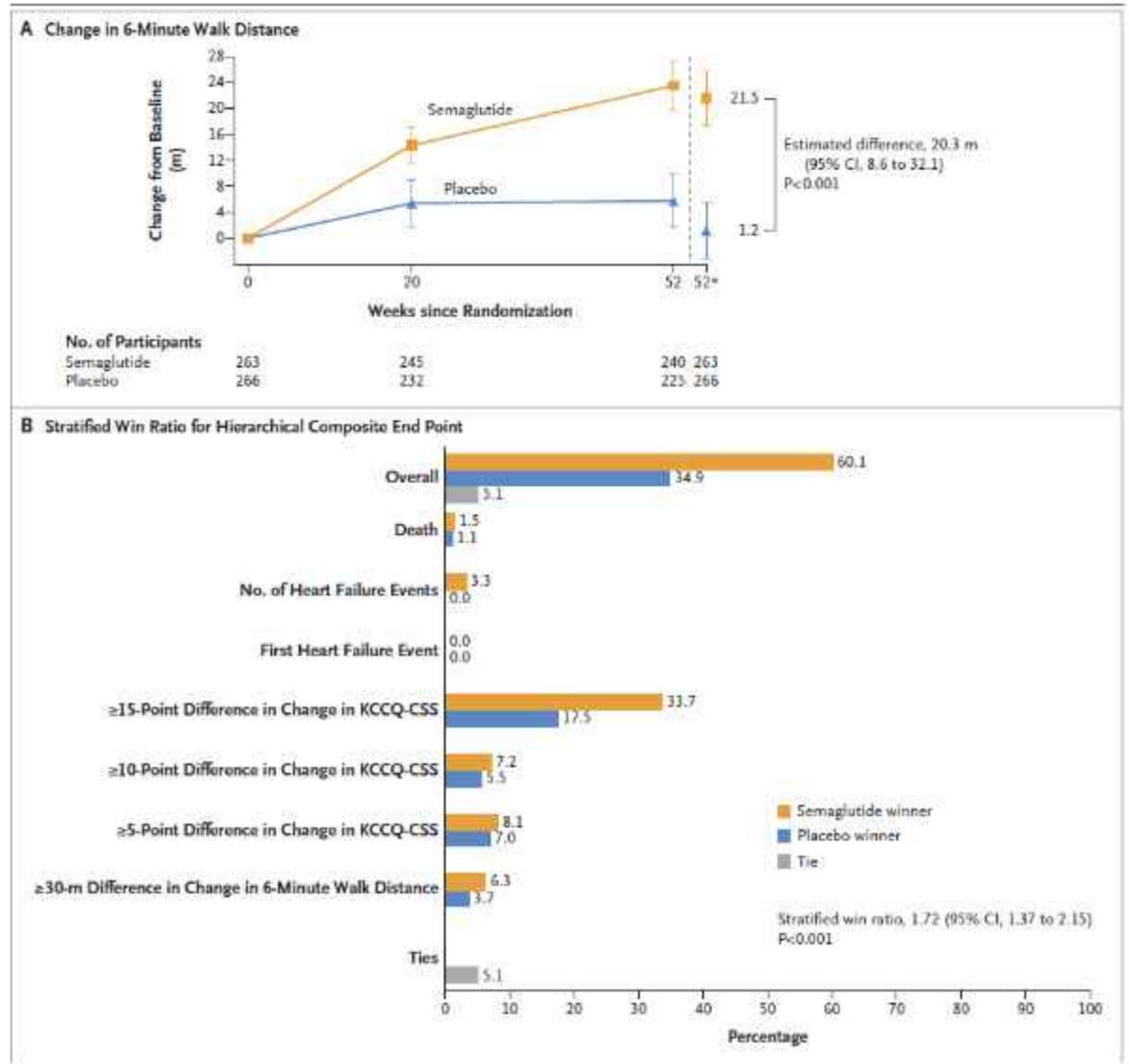
Benefits of GLP 1 Receptor Antagonists in Patients



Semaglutide in Patients with HFpEF and Obesity (STEP-HFpEF)

Favourable Changes in:
- ✓ Quality of life
- ✓ Body weight
- ✓ Exercise tolerance





Kosiborod MN. NEJM 2023, 389:1069-84

Pre-Clinical GLP1 Therapy Use in PH Models

Glucagon-like peptide-1 (GLP-1) mediates the protective effects of dipeptidyl peptidase IV inhibition on pulmonary hypertension

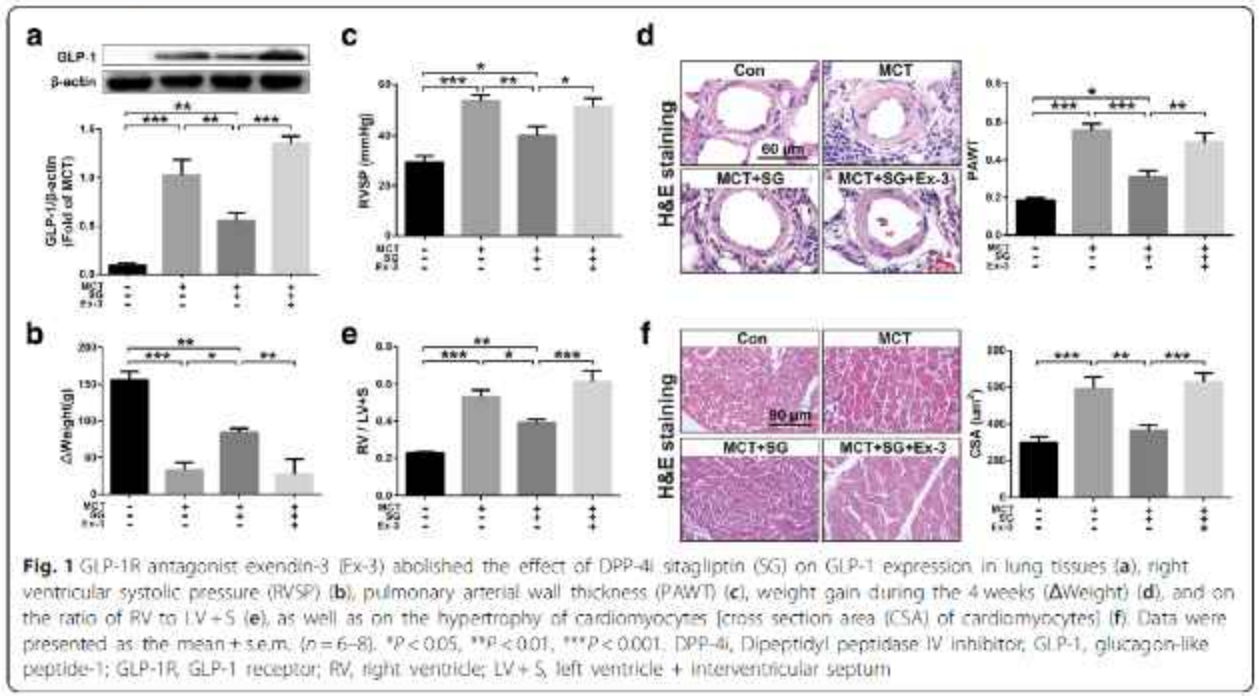


Fig. 1 GLP-1R antagonist exendin-3 (Ex-3) abolished the effect of DPP-4i sitagliptin (SG) on GLP-1 expression in lung tissues (**a**), right ventricular systolic pressure (RVSP) (**b**), pulmonary arterial wall thickness (PAWT) (**c**), weight gain during the 4 weeks (ΔWeight) (**d**), and on the ratio of RV to LV + S (**e**), as well as on the hypertrophy of cardiomyocytes [cross section area (CSA) of cardiomyocytes] (**f**). Data were presented as the mean + s.e.m. ($n = 6–8$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. DPP-4i, Dipeptidyl peptidase IV inhibitor; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; RV, right ventricle; LV + S, left ventricle + interventricular septum

GLP-1 receptor agonist ameliorates experimental lung fibrosis

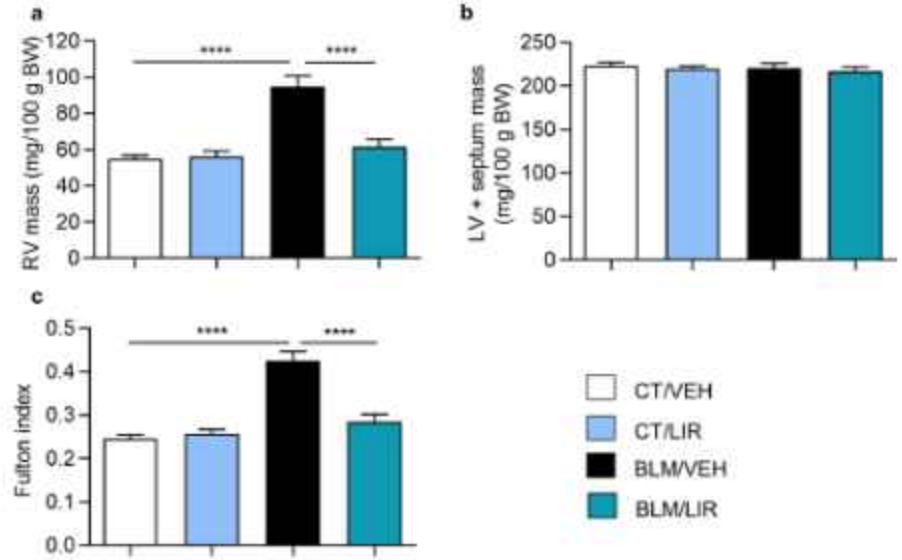
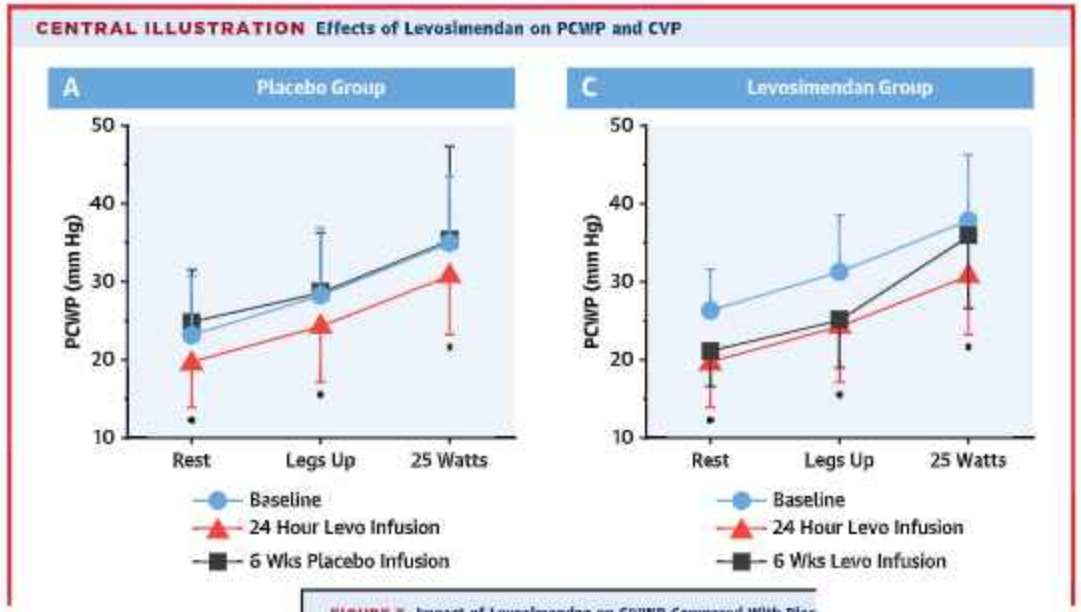


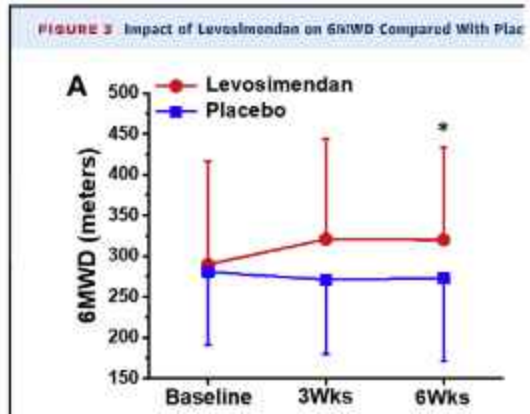
Figure 7. Day 21 heart ventricular masses. Bars represent mean, and error bars SEM. n = 8 in CT groups and n = 12 in BLM groups. Two-way ANOVA following Bonferroni's multiple comparison test. $^{****}p < 0.0001$. (**a**) Right Ventricle (RV) mass normalized to 100 g of body weight (BW). (**b**) Left ventricle plus septum (LV + S) mass, normalized to 100 g of body weight (**c**) Fulton index, a marker of ventricular hypertrophy. Values represent the product of RV weight divided by LV + S weight.

Wang J, J Biomed Sci 2019:6
Fandino J, Sci Rep 2020:18091

Additional Therapies of Interest

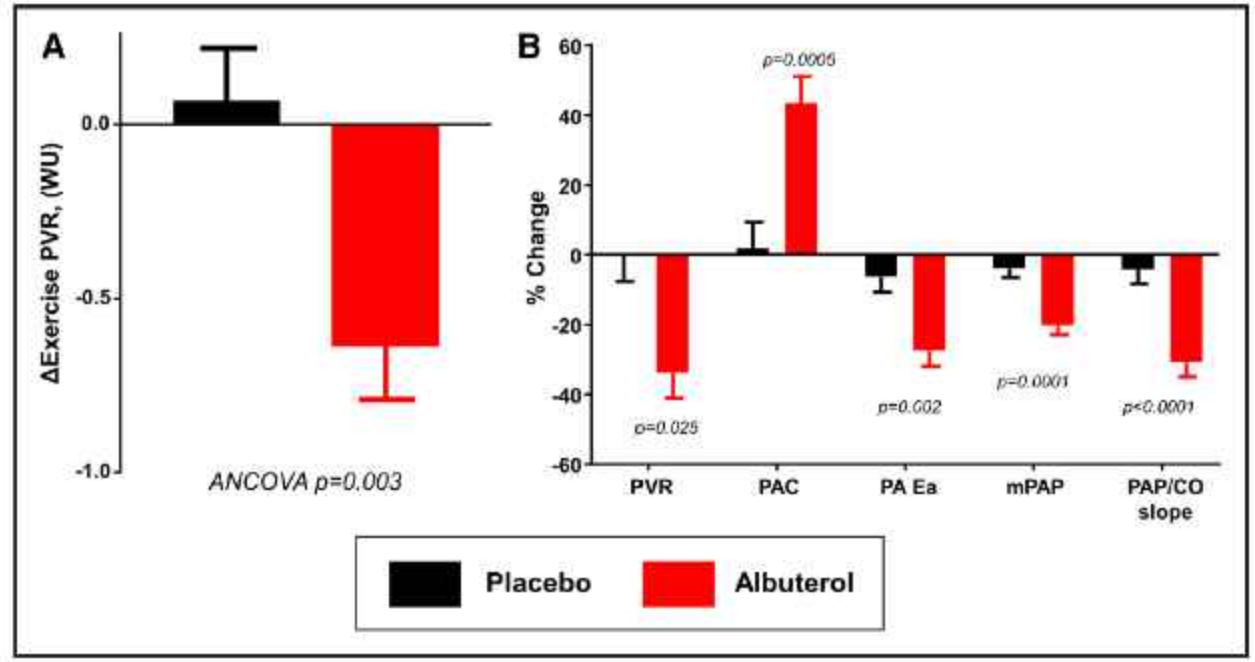
Levosimendan in HFpEF Pulmonary Hypertension





Brener, M. J Card Fail 2021; 1023

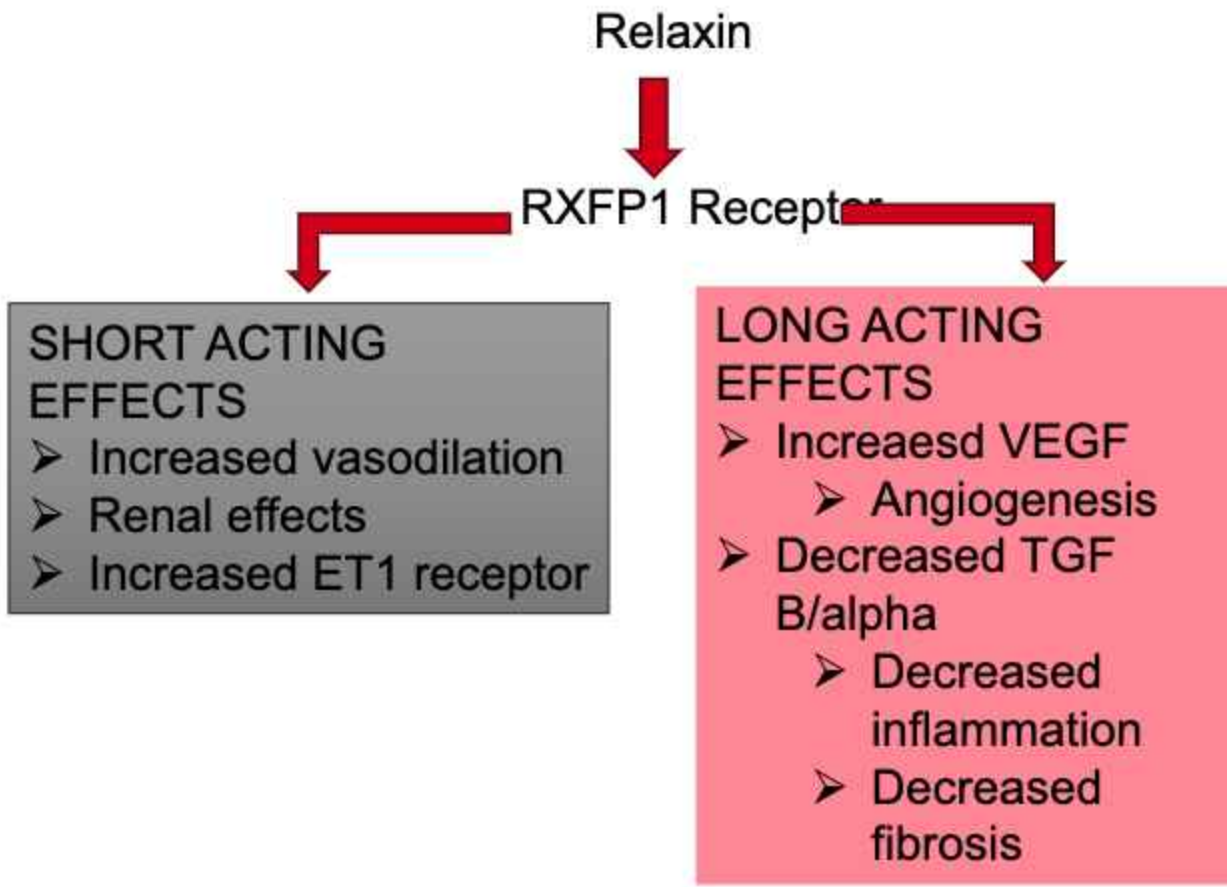
Albuterol and Pulmonary Vascular Reserve in HFpEF



Reddy, Circ Res 2019;124:306

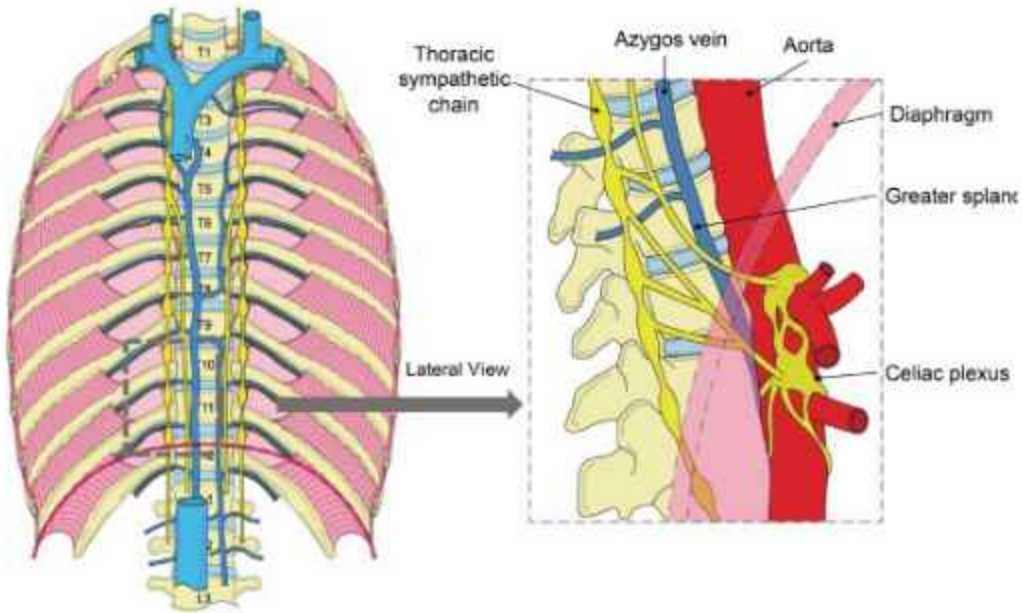
AZT3427 In Patients with HF and Group 2 PH (Re-PHIRE)

- 220 patients with confirmed PH-LHD
- RCT
- AZD3427 vs. placebo sc q 2 weeks for 24 weeks
- Dose finding
- Primary endpoint
  - Change in PVR at 24 weeks
- Secondary
  - Change in mean PAP, PCWP, CO, SV, EF
  - Change in echo parameters (PASP, TAPSE/PAP, TRV, LVGLS
  - 6 MWT, KCCQ, NYHA, NTproBNP

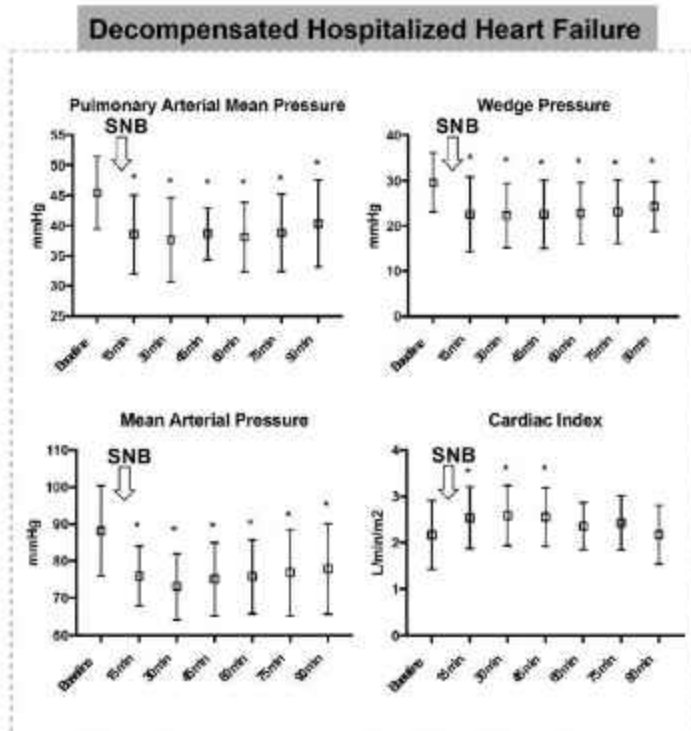


Clin Trials. Gov NCT05737940

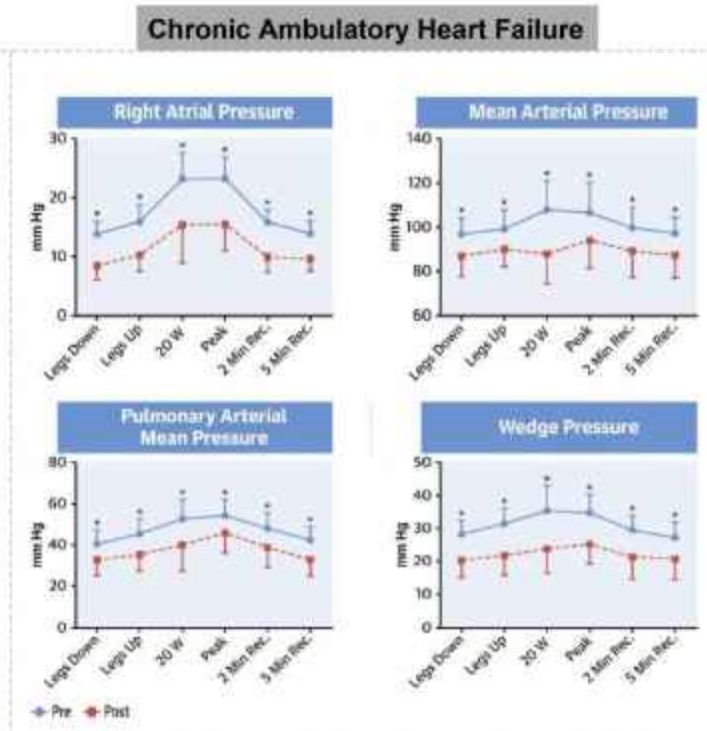
Splanchic Nerve Modulation in Heart Failure



Splanchnic—HF-1

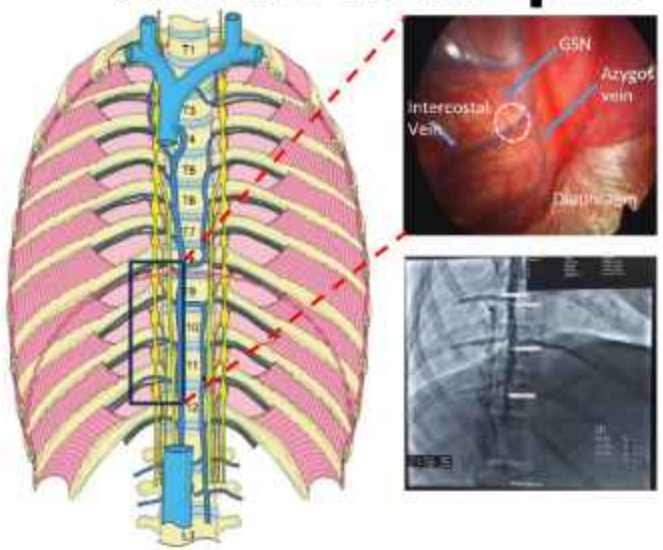


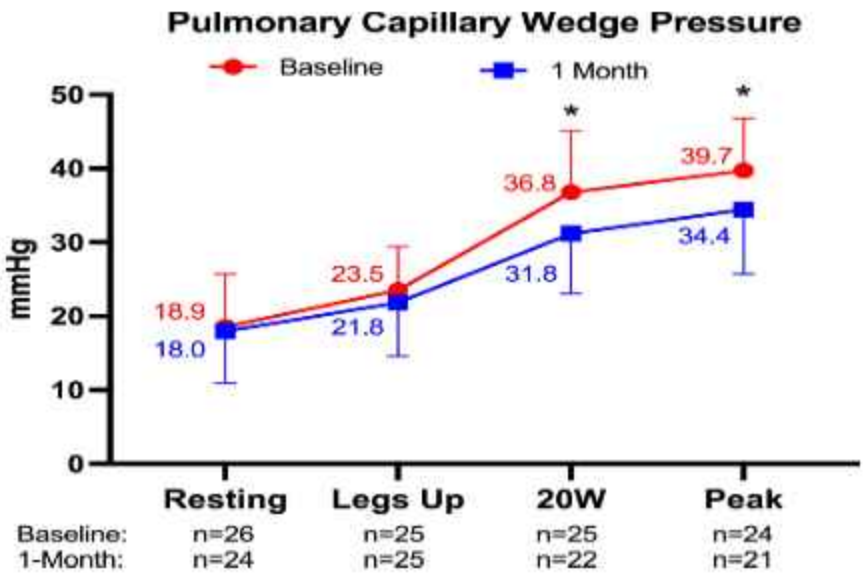
Splanchnic—HF-2 Study

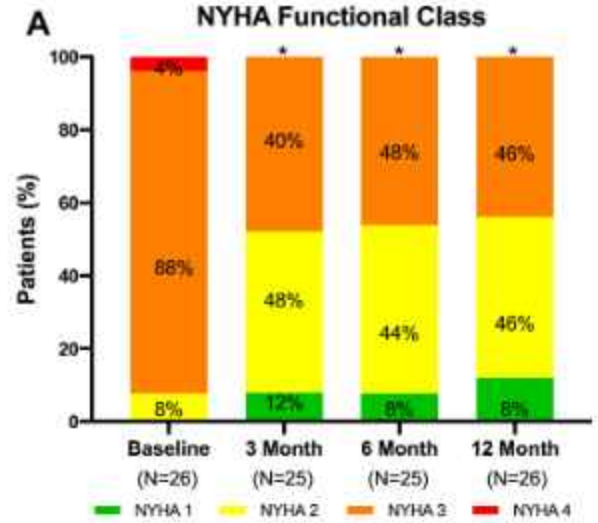


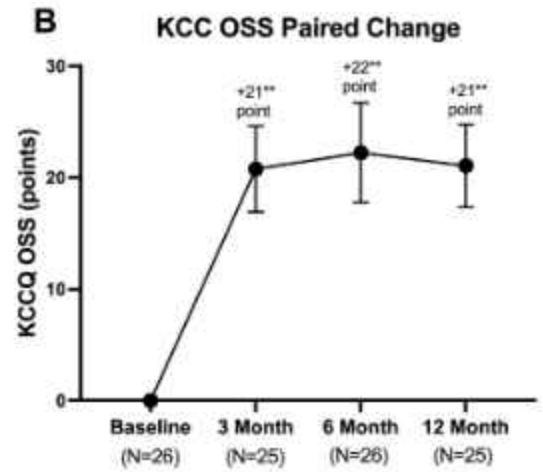
Fudim M. Eur J Heart Fail 2021; 23:1076-85

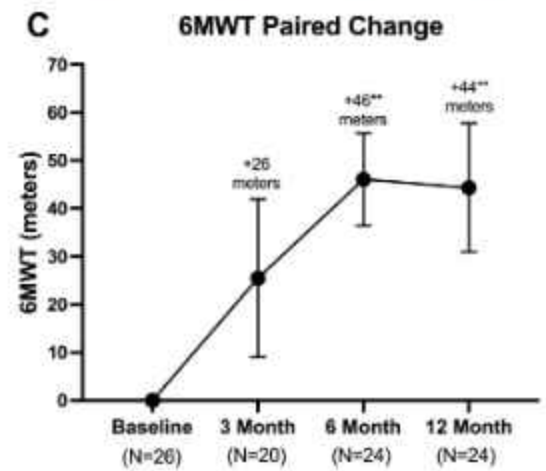
Endovascular Ablation of the Right Side Greater Splanchnic Nerve in HFpEF (REBALANCE-HF)

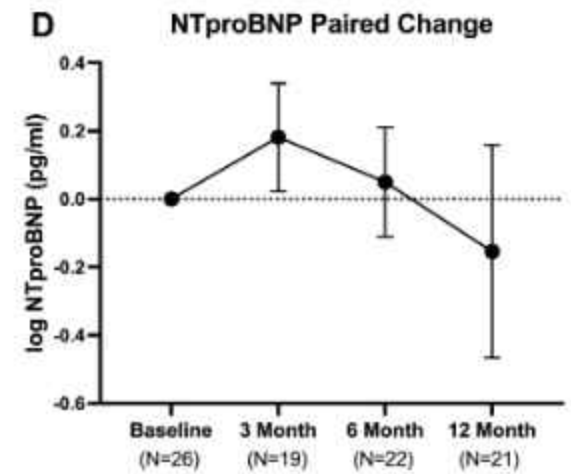








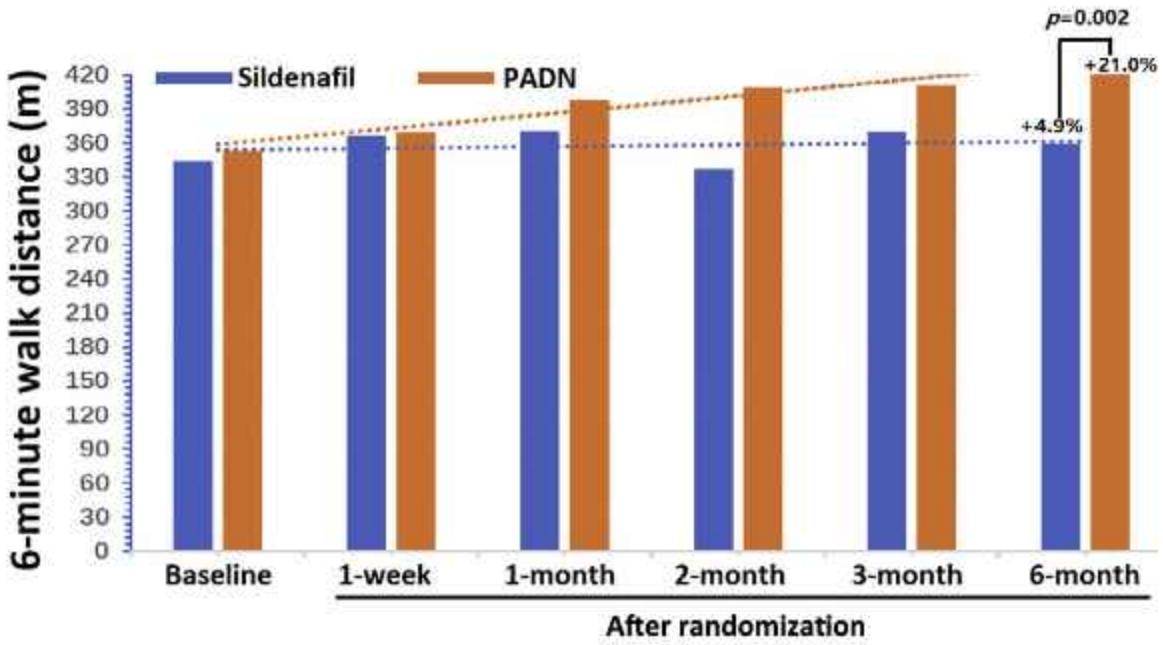




Fudim M, J Card Fail 2024 Jan

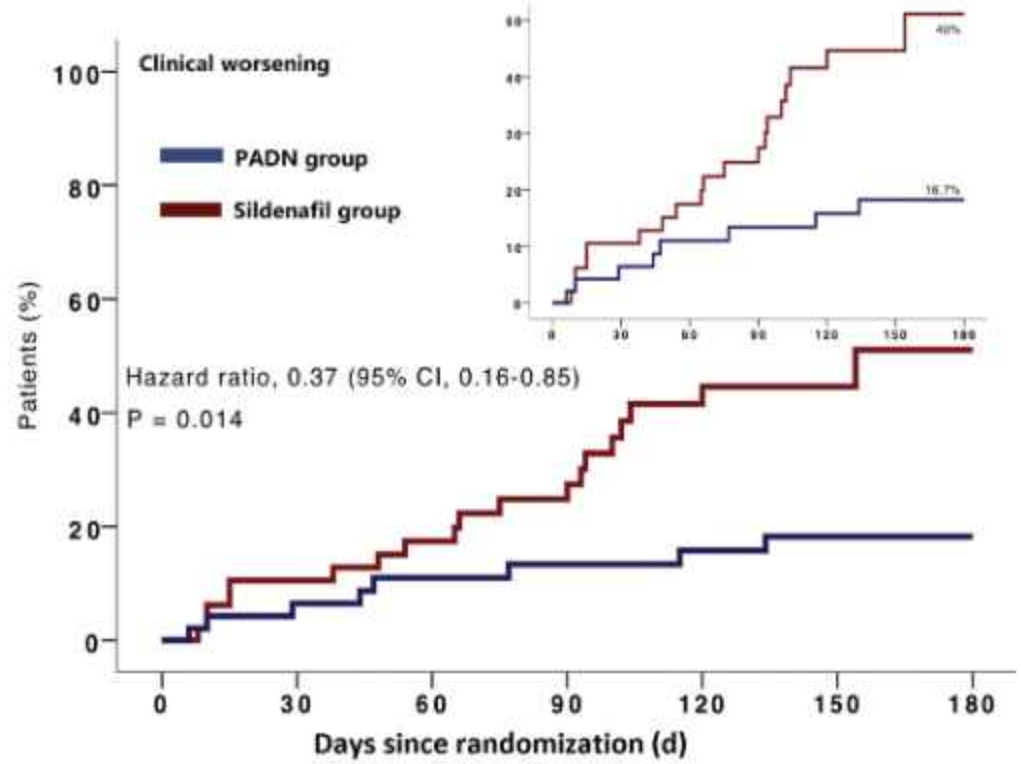
Safety and Efficacy of Pulmonary Artery Denervation for Patients with Cpc-PH

FIGURE 3 Changes of 6-Min Walk Distance Over the Time in Both Sildenafil and PADN Groups



Pulmonary artery denervation (PADN) resulted in significant improvements in 6-min walk distance.

FIGURE 2 Kaplan-Meier Survival Analysis



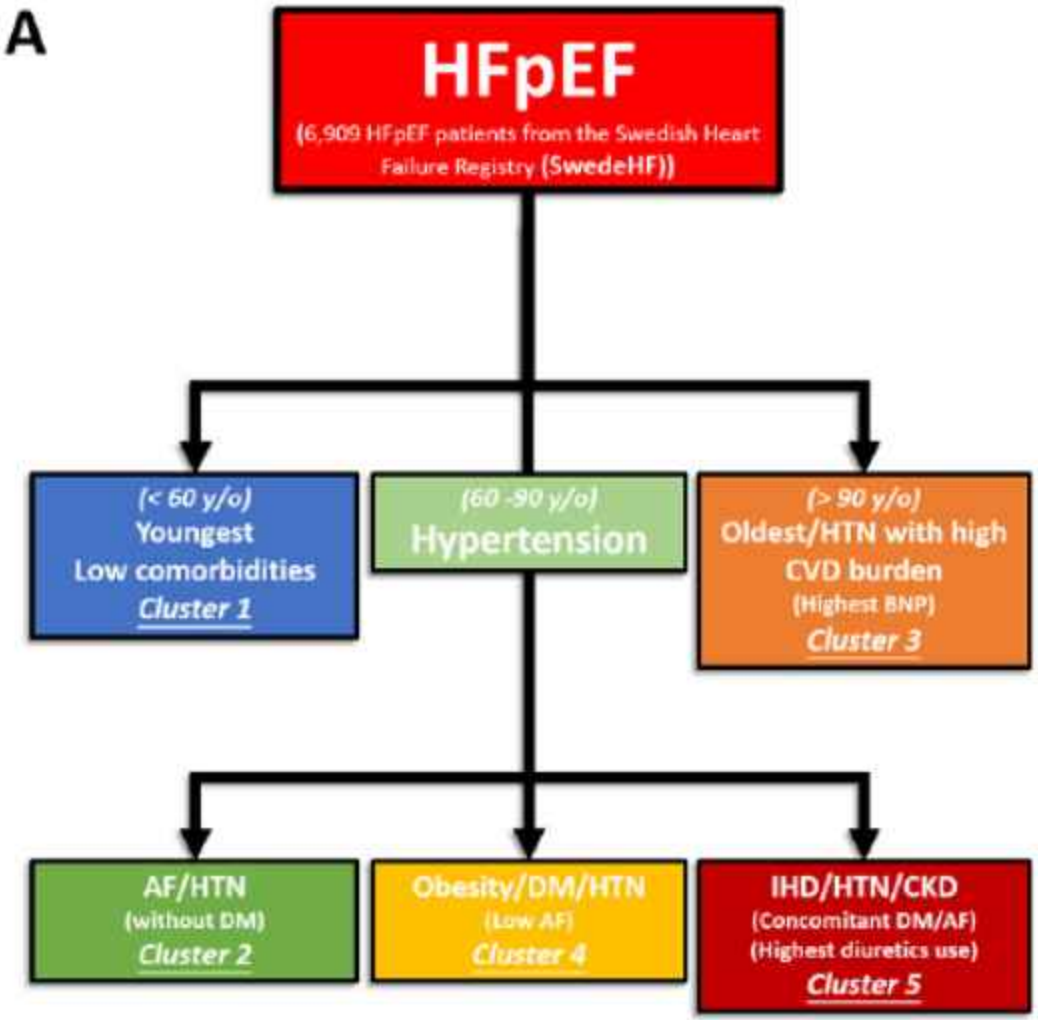
No. at risk

PADN	48	45	43	42	41	40	40
Sildenafil	50	45	42	38	32	32	30

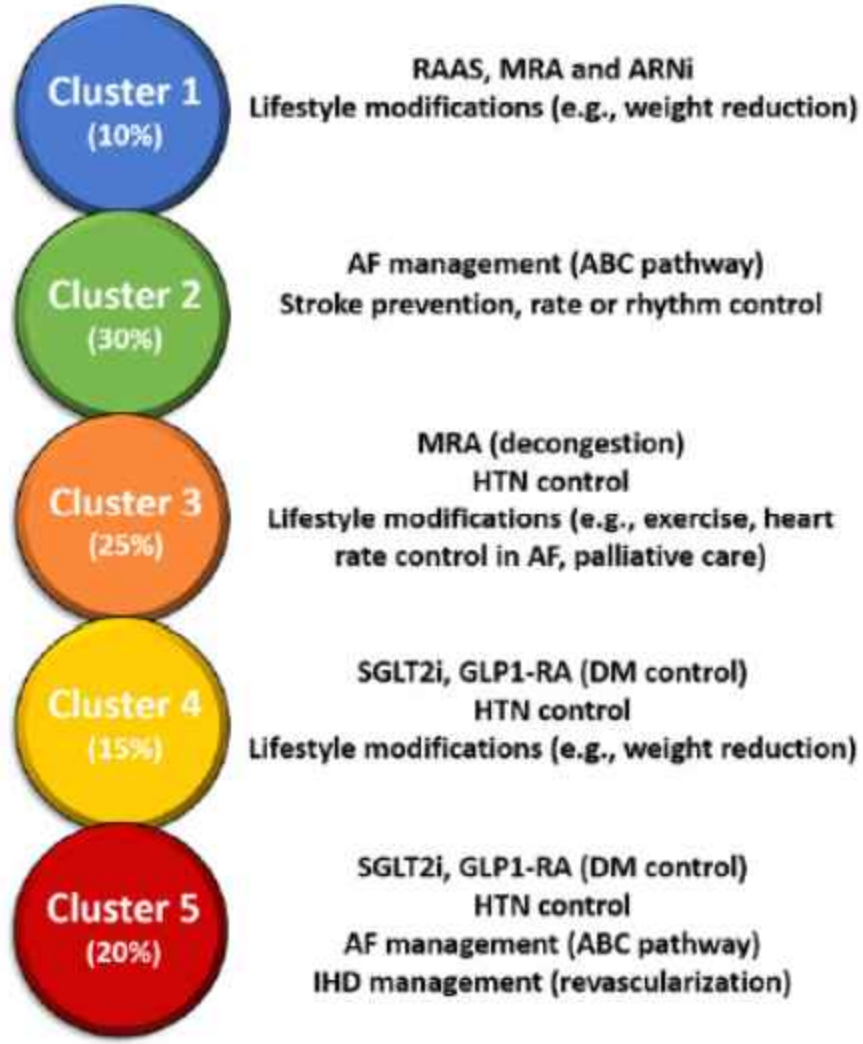
Zhang H, JACC CV Imaging. 2019;12:274-84

What Is the Right Patient? Precision Therapeutics

A

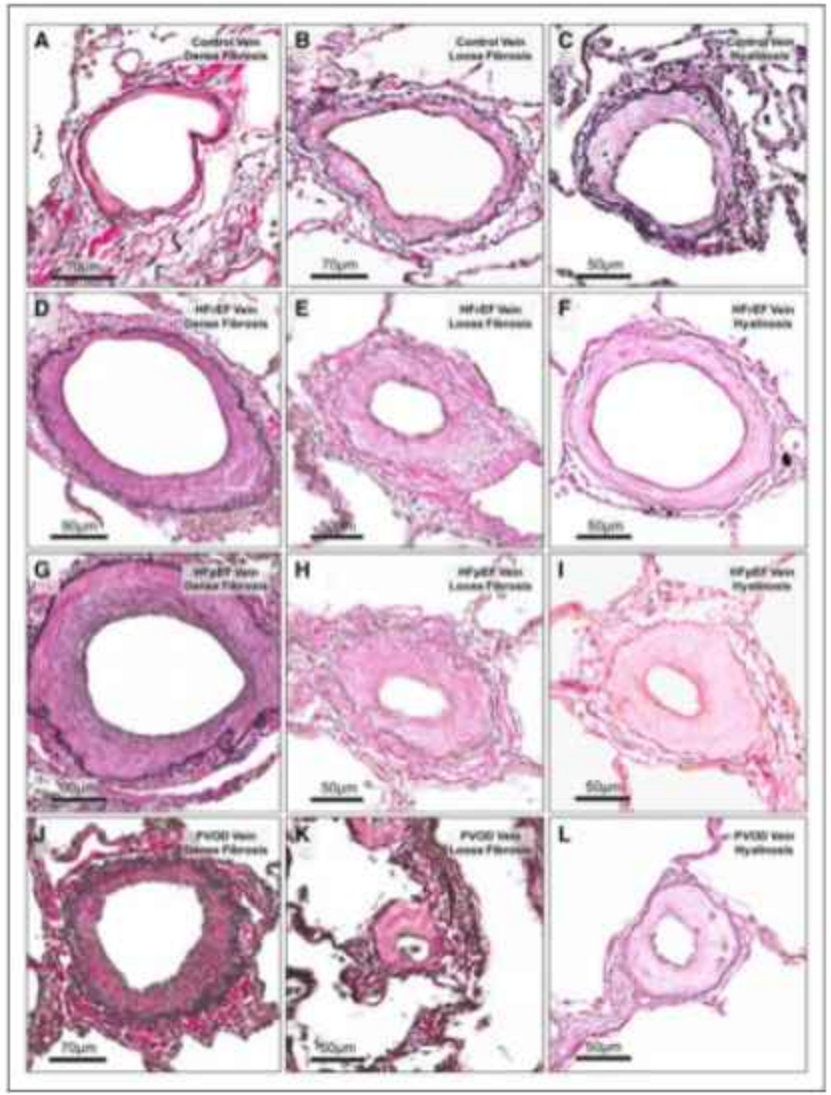


B



Lin C. J of Personalized Med. 2023; 13,746

What is the Right Therapeutic Target?

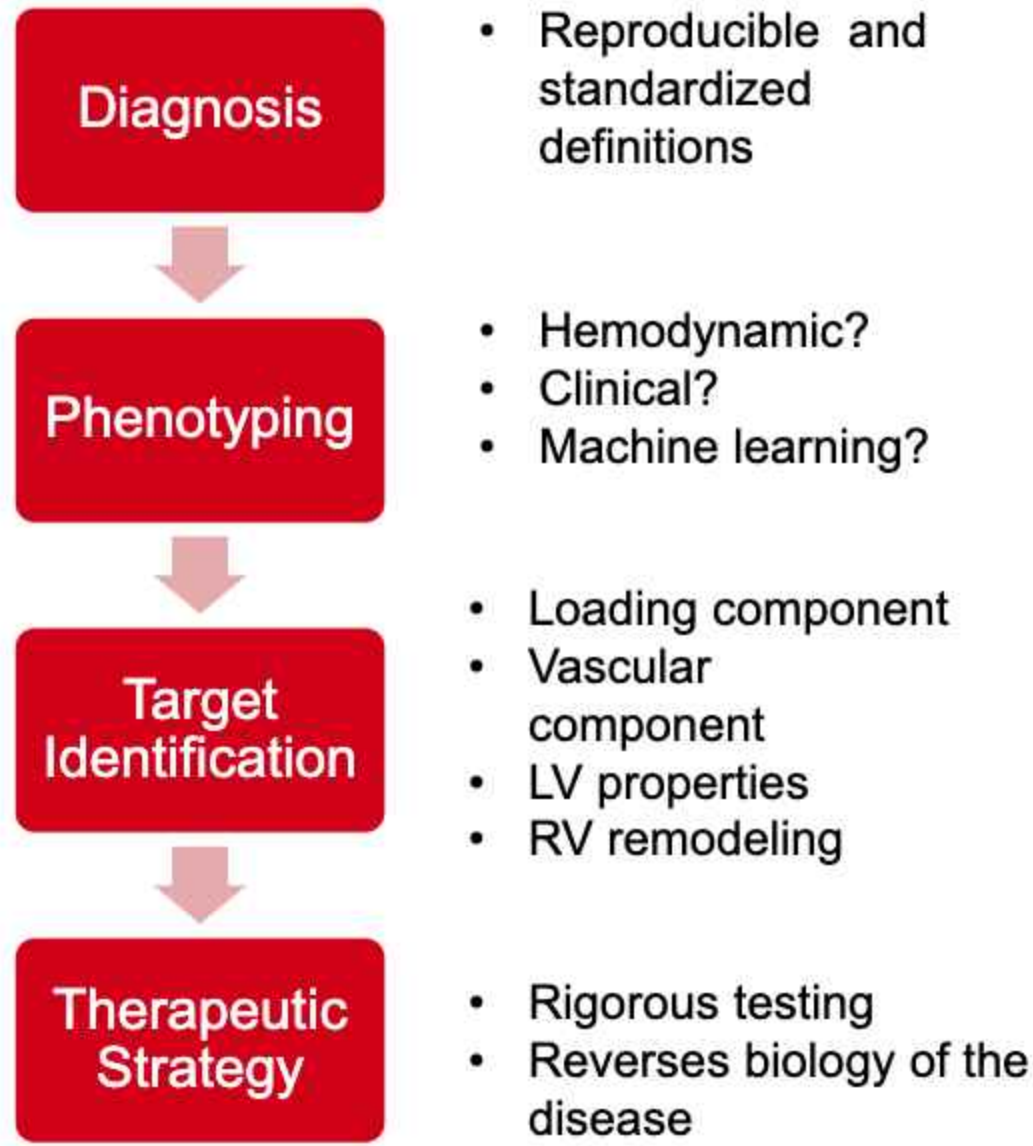


Fayyaz A. Circulation 2018;137:1796

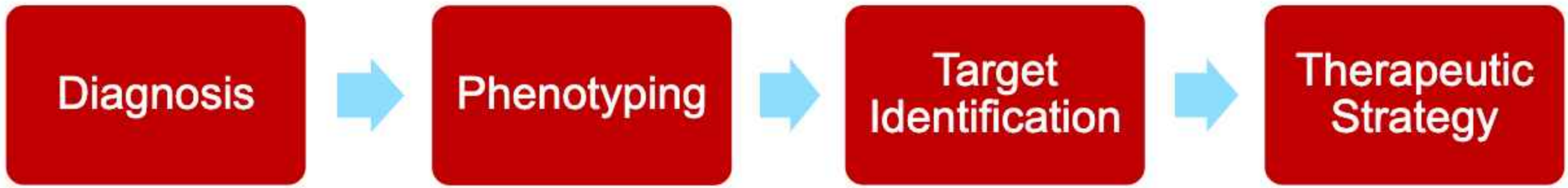
- PH in Left heart disease is multifactorial
- Hemodynamic definitions and targeting hemodynamic outcomes may be incomplete
  - RV dysfunction?
  - RV metabolism?
  - PA compliance?
  - RV-PA coupling?
  - Splanchnic vasodilation?
  - Counteracting genetic predisposition?
  - Targeted pulmonary venous remodeling?

Summary Thoughts

- PH in left heart disease is common, complex and currently lacks a definitive targeted treatment regimen
- PAH therapies should not routinely be used for management
- Optimization of GDMT, left heart therapies critical
- Schemata for future research in PH-LHD needed



Schemata for Future Research in PH-LHD



- Reproducible and standardized definitions

- Hemodynamic?
- Clinical?
- Machine learning?

- Loading component
- Vascular component
- LV properties
- RV remodeling

- Rigorous testing
- Reverses biology of the disease
- Improved outcomes

2022 Management Recommendations for PH-LHD

Recommendation Table 22 — Recommendations for pulmonary hypertension associated with left heart disease

Recommendation Table 22A

Recommendations	Class[a]	Level[b]
In patients with LHD, optimizing treatment of the underlying condition is recommended before considering assessment of suspected PH[27,28]	I	A
RHC is recommended for suspected PH in patients with LHD, if it aids management decisions	I	C
RHC is recommended in patients with severe tricuspid regurgitation with or without LHD prior to surgical or interventional valve repair	I	C
For patients with LHD and suspected PH with features of a severe pre-capillary component and/or markers of RV dysfunction, referral to a PH centre for a complete diagnostic work-up is recommended[29,47,142]	I	C
In patients with LHD and CpcPH with a severe pre-capillary component (e.g. PVR >5 WU), an individualized approach to treatment is recommended	I	C
When patients with PH and multiple risk factors for LHD, who have a normal PAWP at rest but an abnormal response to exercise or fluid challenge, are treated with PAH drugs, close monitoring is recommended	I	C
In patients with PH at RHC, a borderline PAWP (13–15 mmHg) and features of HFpEF, additional testing with exercise or fluid challenge may be considered to uncover post-capillary PH[133,143]	IIb	C
Drugs approved for PAH are not recommended in PH-LHD[c] [631,678,683,684,701,706]	III	A

2022 Management Recommendations for PH-LHD

Recommendation Table 22B

	GRADE			
Recommendations	**Quality of evidence**	**Strength of recommendation**	**Class[a]**	**Level[b]**
No recommendation can be given for or against the use of PDE5is in patients with HFpEF and combined post- and pre-capillary PH	Low	None	–	–
The use of PDE5is in patients with HFpEF and isolated post-capillary PH is not recommended	Low	Conditional	**III**	**C**

CpcPH, combined post- and pre-capillary PH; ERA, endothelin receptor antagonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with

Know and identify	Know and identify the associated findings of PH on echo
Develop and approach	Develop an approach to diagnosis for patients presenting with possible PH
Understand	Understand the role of supportive and targeted PAH therapies
Do not use	Do not use PAH specific therapy to treat non-group I PH

Heart-Kidney-Metabolic Connection

Sheldon Tobe

MD, MScCH (HPTE), FRCPC, FACP, FAHA

Disclosures - Dr. Sheldon Tobe

Professor of Medicine, University of Toronto and Northern Ontario School of Medicine

Ad Boards/Speakers Bureau/Consulting: None

Scientific Committee/Speaker: Astra-Zeneca, Bayer, Boehringer Ingelheim, Janssen, Lilly, Otsuka, PfizerLiv, CHEP+

Grants/Research: CIHR, KMH

Learning Objectives

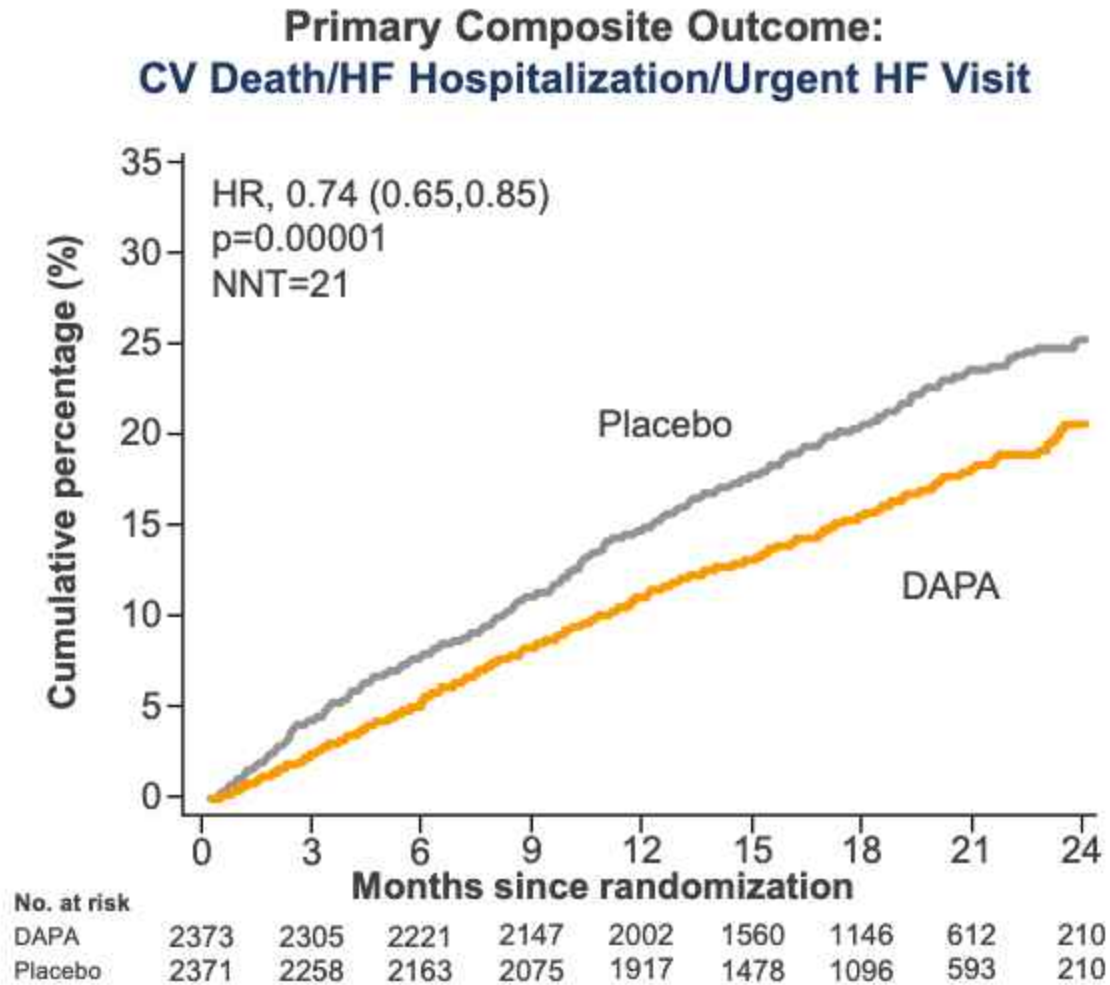
1. Discuss the overlapping role of SGLT2i and GLP1 RA in HF, CKD and obesity
2. Review the highlights of recent cardio-kidney-metabolic guidelines

The Heart and The Kidney in Heart Failure

- Worsening renal function over time is associated with worse cardiovascular outcomes
- Falling GFR in heart failure is due to cardiac induced disrupted hemodynamics, ischemia, and inflammation causing kidney fibrosis and glomerular senescence
- Therefore, if the kidney function is falling slowly, look to the heart as a possible explanation
- Short-term rapid falls in eGFR due to diuretics, RASi, and SGLT2i are not associated with worse long-term outcomes

Tobe SW, *Canadian J Cardiology* vol 34: 2018, 1261-1263

DAPA-HF: Dapagliflozin in Patients with HFrEF



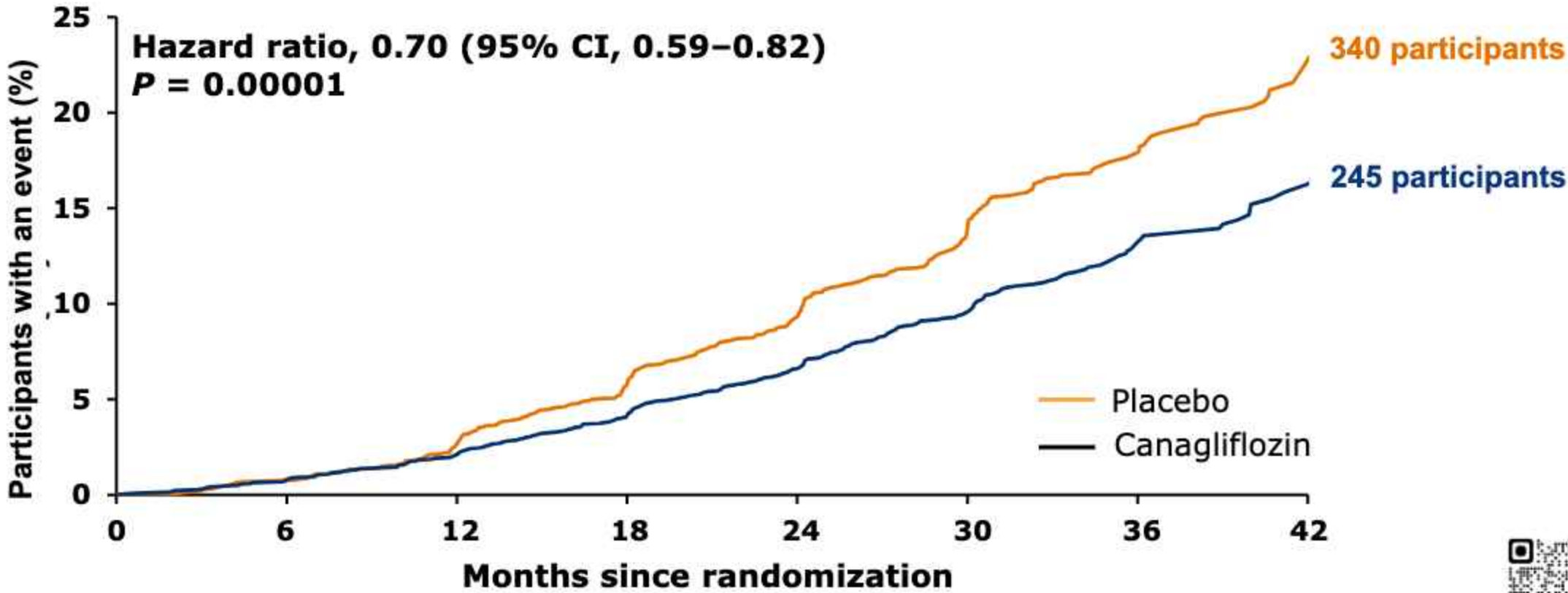
CV, cardiovascular; DAPA, dapagliflozin; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NNT, number needed to be treated to prevent prespecified outcomes within 1 year
Adapted from: McMurray JJV et al. *N Engl J Med* 2019;381(21):1995-2008.

KDIGO Heat Map

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR				Albuminuria		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	≥ 90	EMPA-REG, CANVAS, DECLARE		
	G2	Mildly decreased	60-89			CREDENCE DAPA-CKD EMPA-Kidney
	G3a	Mildly to moderately decreased	45-59			CREDENCE DAPA-CKD EMPA-Kidney
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

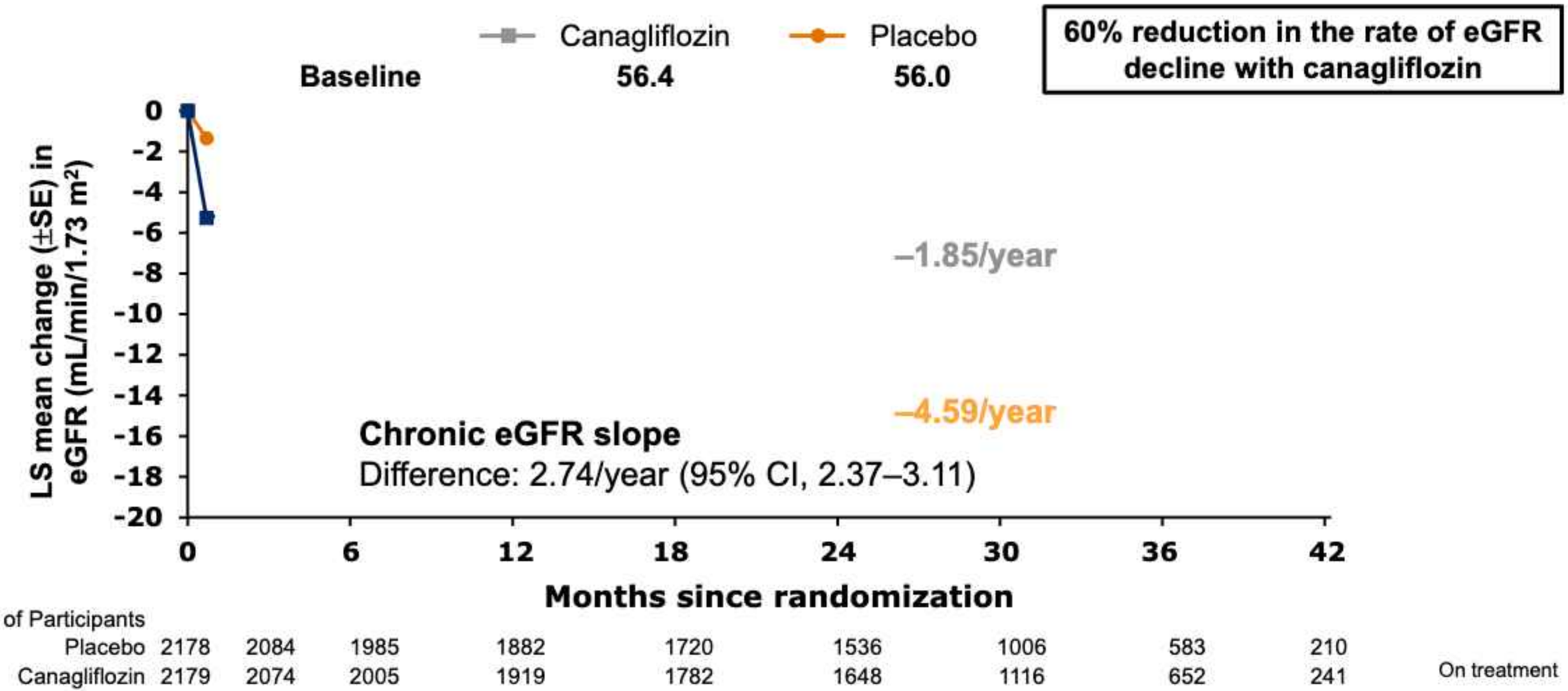
CREDENCE Primary Outcome: ESKD, Doubling of Serum Creatinine, or Renal or CV Death



No. at risk								
Placebo	2199	2178	2132	2047	1725	1129	621	170
Canagliflozin	2202	2181	2145	2081	1786	1211	646	196

Perkovic V, *NEJM* 2019 380: 2295-2306 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).

Acute and Long-term Effects on eGFR



Perkovic V, *NEJM* 2019 380: 2295-2306 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).

Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	**0.00001**	
Secondary			✓
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✓
4. Hospitalization for heart failure	**0.61 (0.47–0.80)**	**<0.001**	✓
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✓
6. CV death	0.78 (0.61–1.00)	0.0502	✓
7. All-cause mortality	0.83 (0.68–1.02)	–	Not significant
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

Perkovic V, *NEJM* 2019 380: 2295-2306 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation).

DAPA CKD

RCT Protocol

Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)

Rationale and trial protocol

Multicentre ~ 400
Target n = 4300
Patients with and without type 2 diabetes

≥ 18 years
25–75 ml/min/1.73 m²
uACR ≥ 200 mg/g

Polycystic kidney disease
Lupus nephritis
ANCA vasculitis
Type I diabetes

Interventions

Dapagliflozin 10 mg

1:1

Placebo

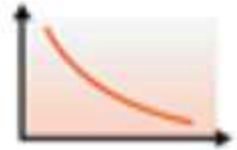
Follow-up

~ 45 months

Event-driven (681 events)

Primary outcome

Composite renal endpoint



≥ 50% decline in eGFR

End-stage kidney disease

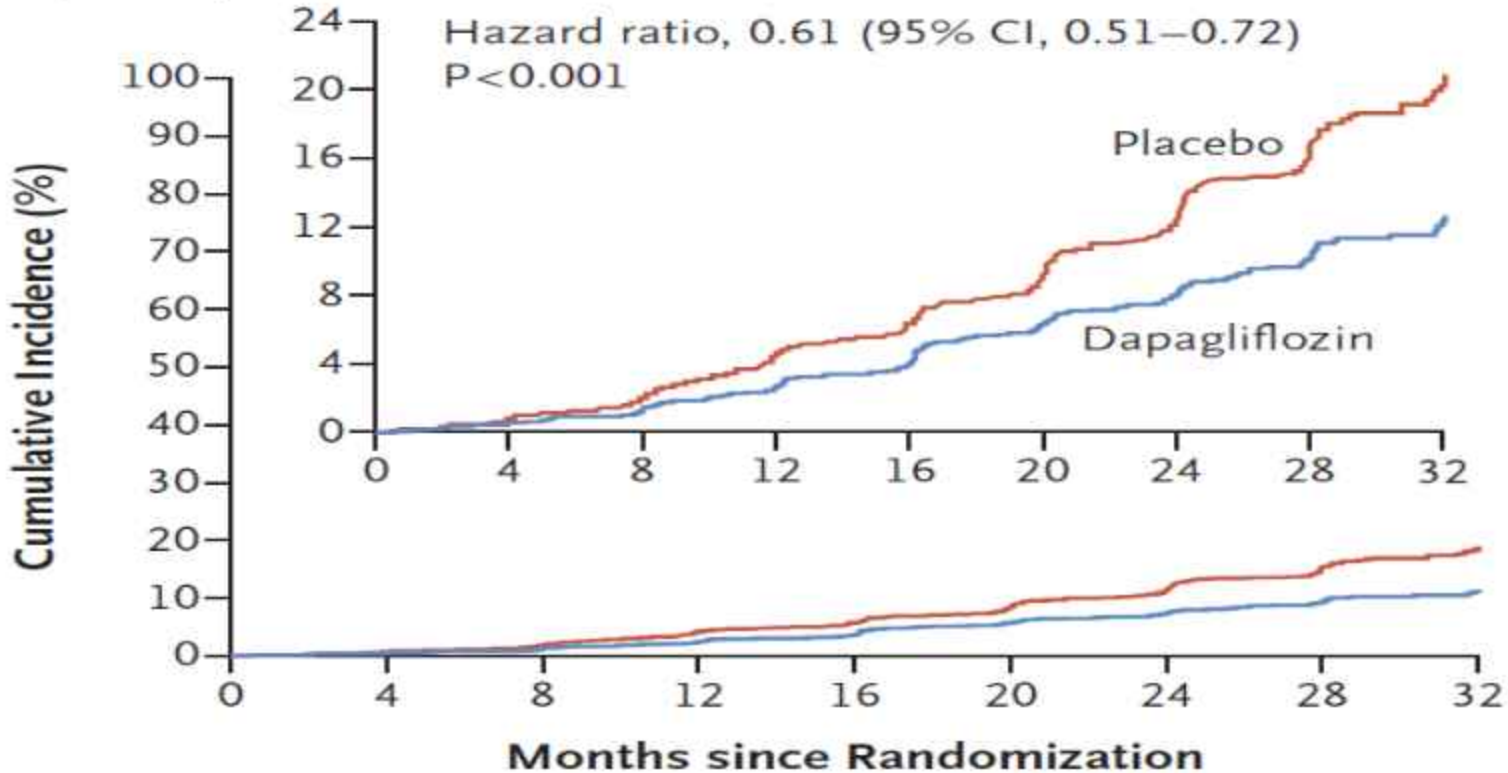
Renal or cardiovascular death

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Heerspink HJL et al. NDT (2019)
@NDTSocial

DAPA-CKD: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death

A Primary Composite Outcome



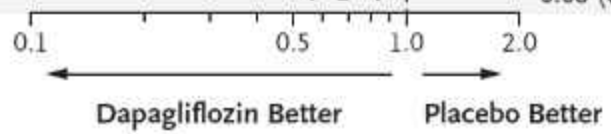
No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

Heerspink HJL, *NEJM* 2020, 383, p1436-1446 DOI: 10.1056/NEJMoa2024816

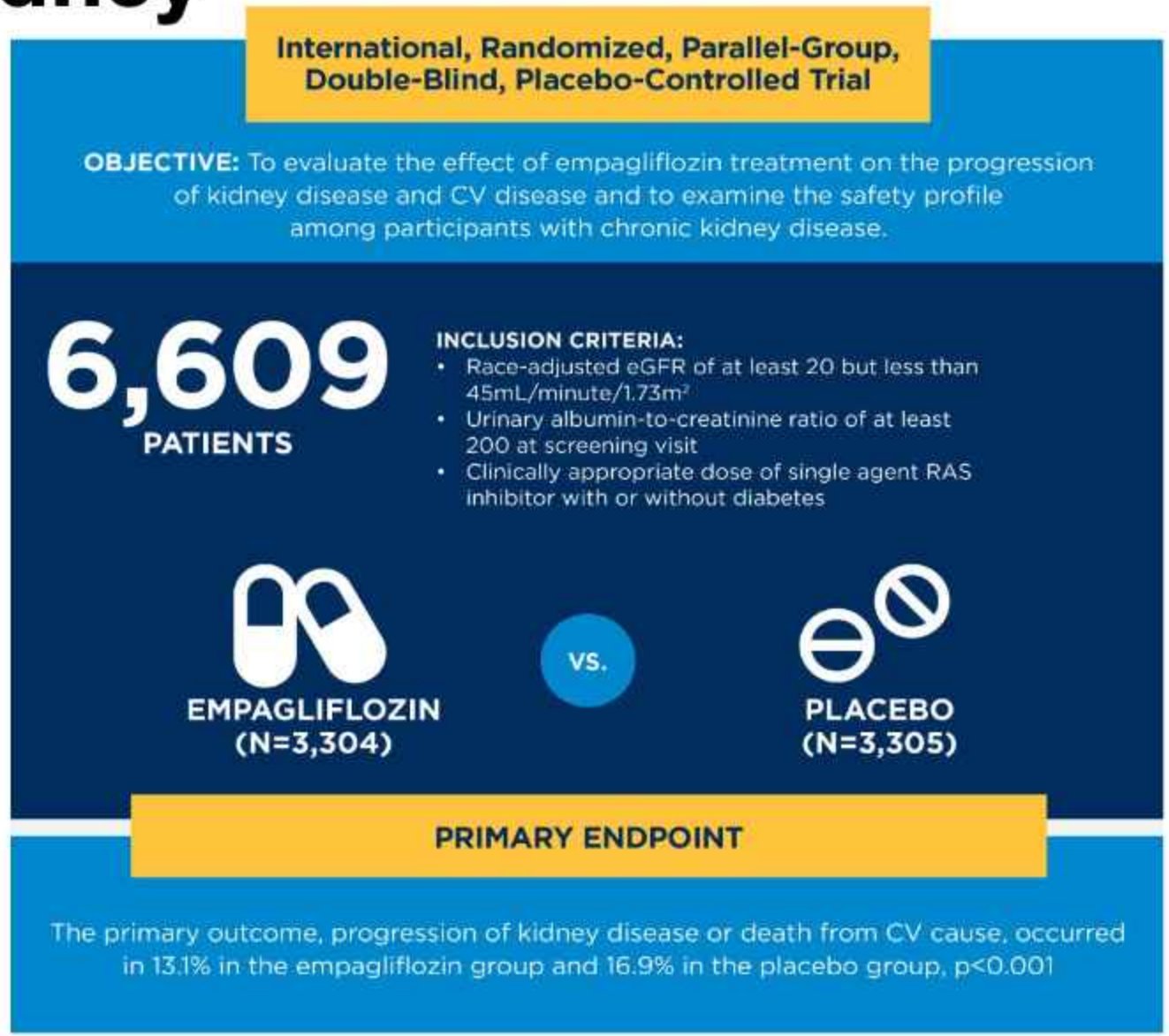
DAPA-CKD Primary Composite Outcome: Prespecified Subgroup Analyses

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



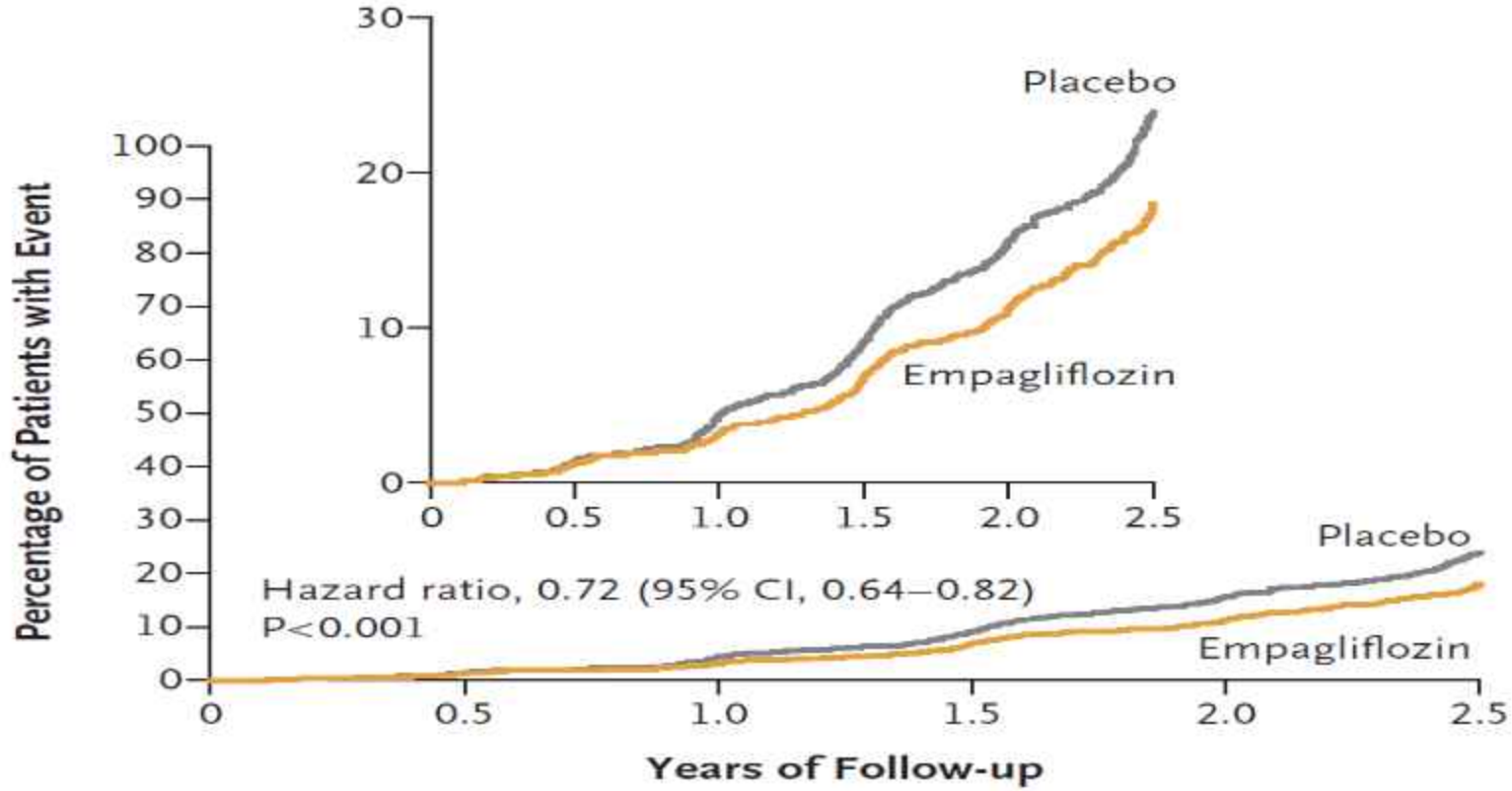
Heerspink HJL, *NEJM* 2020 DOI: 10.1056/NEJMoa2024816

EMPA-Kidney



Herrington WG, *NEJM* 2022 Nov 4 doi: 10.1056/NEJMoa2204233

EMPA-Kidney
Progression of Kidney Disease or CV Death

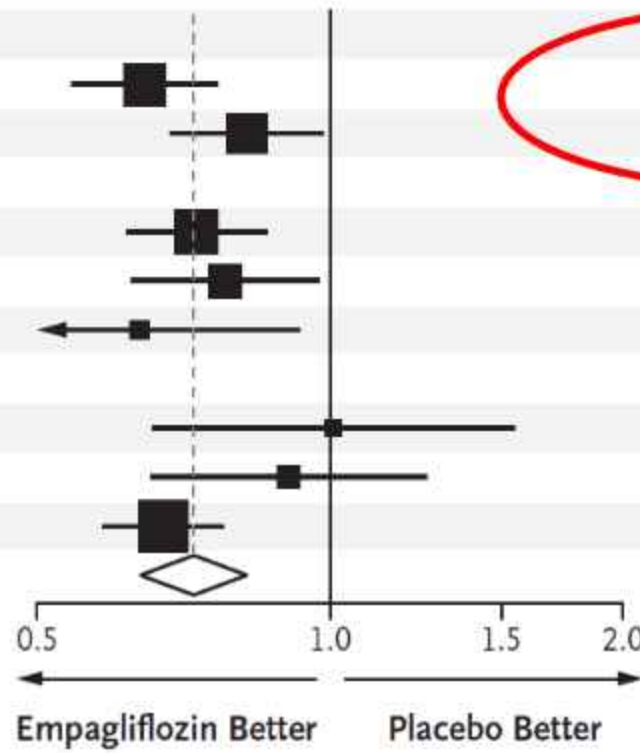


No. at Risk						
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624

Herrington WG, *NEJM* 2022 Nov 4 doi: 10.1056/NEJMoa2204233

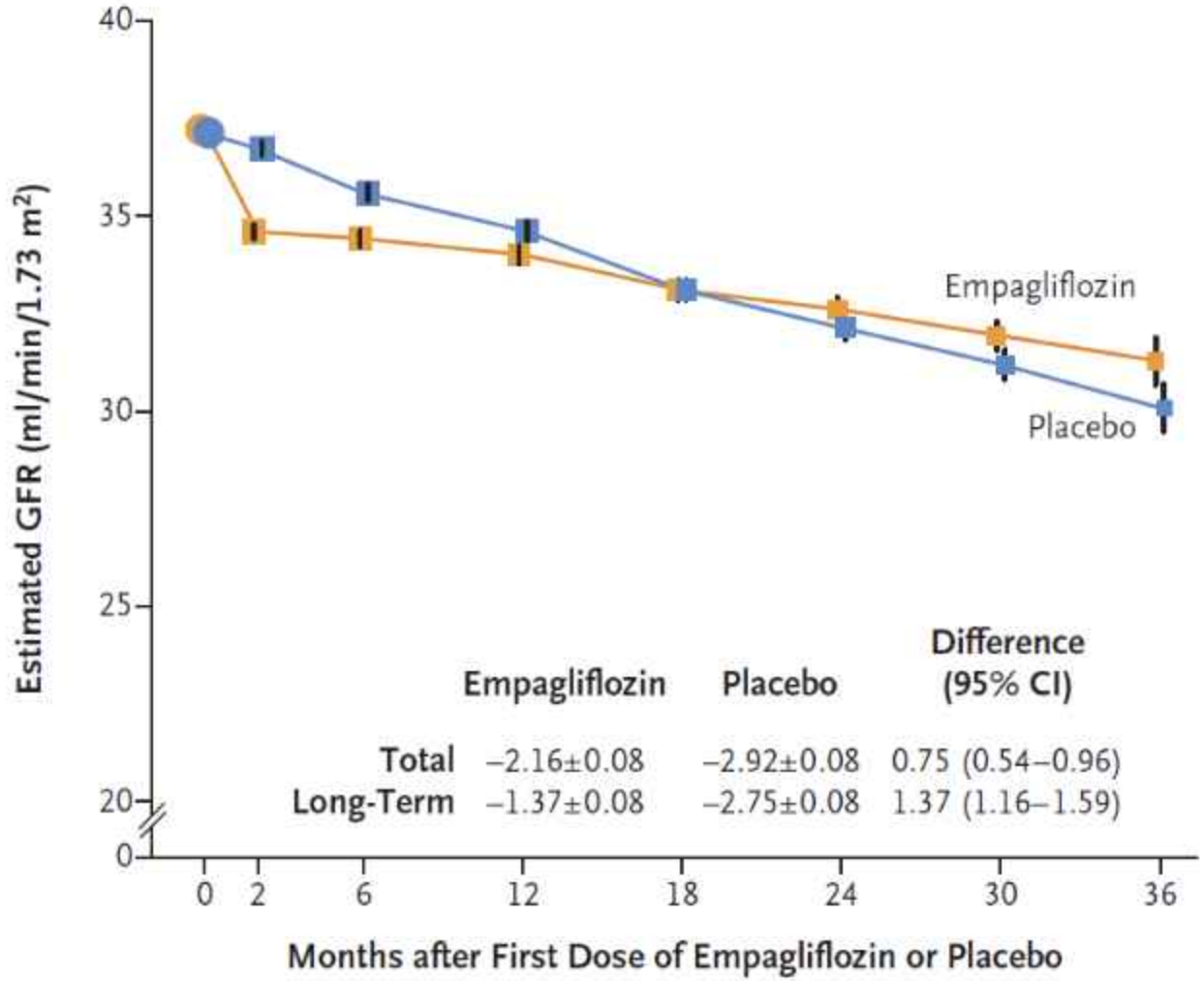
EMPA-Kidney Subgroup Analysis of Primary Outcome

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



Herrington WG, *NEJM* 2022 Nov 4 doi: 10.1056/NEJMoa2204233

Acute and Long Term eGFR Trajectories – EMPA-Kidney



	Empagliflozin	Placebo	Difference (95% CI)
Total	−2.16±0.08	−2.92±0.08	0.75 (0.54–0.96)
Long-Term	−1.37±0.08	−2.75±0.08	1.37 (1.16–1.59)

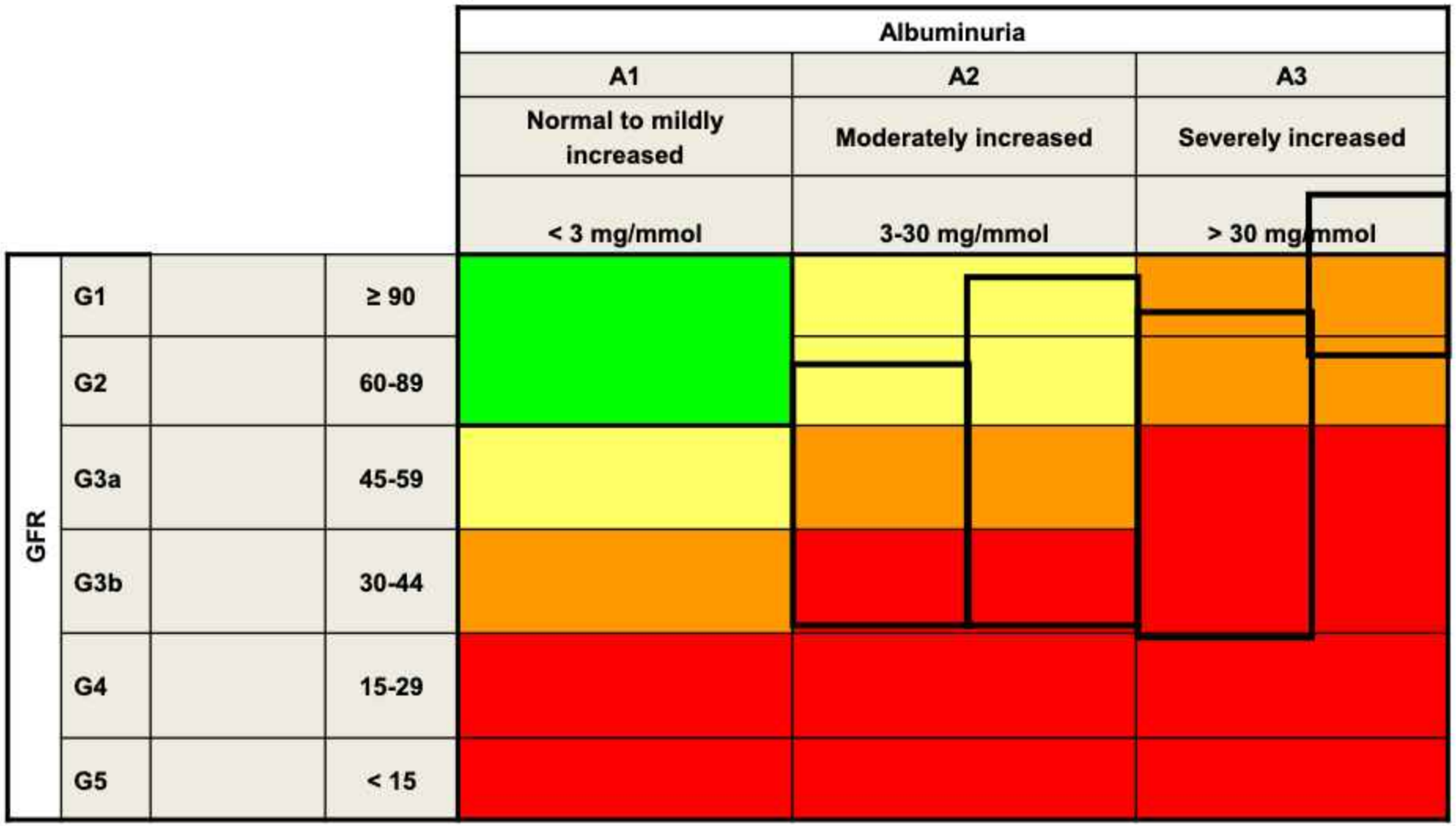
Herrington WG, *NEJM* 2022 Nov 4 doi: 10.1056/NEJMoa2204233

Finerenone (Kerendia)

- A non-steroidal mineralocorticoid receptor antagonist (MRA)
- Unlike spironolactone and eplerenone:
  - Little BP lowering effect
  - Less hyperkalemia

Agarwal R, *et al. Eur Heart J* 2021;42:152–161

Fidelio: A3: eGFR 25-75, A2 25-60 and retinopathy
Figaro: A3: eGFR 60+, A2 25-90



Agarwal R, *European Heart Journal*, 2021, https://doi.org/10.1093/eurheartj/ehab777

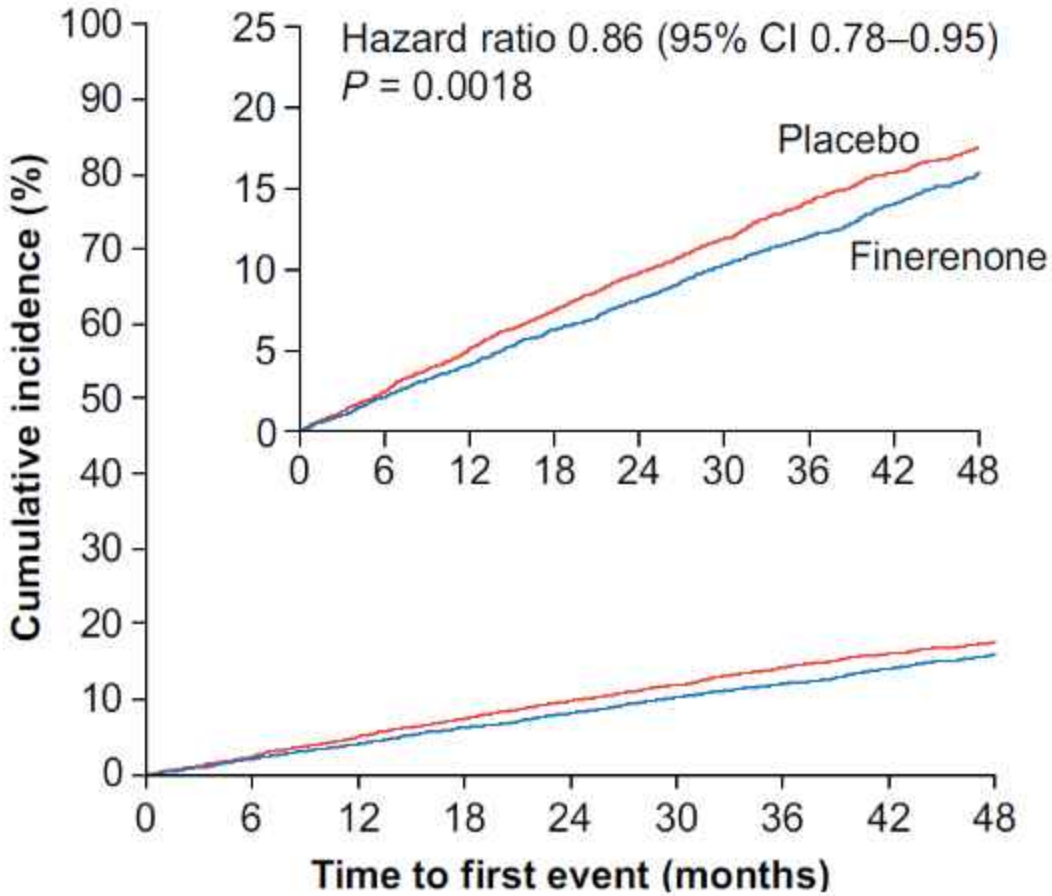
FIDELIO and FIGARO Studies – Pooled Analysis = FIDELITY

	FIDELIO-DKD	FIGARO-DKD
N	5734	7437
Max RASi	√	√
K ≤ 4.8	√	√
HFrEF	No	No
Follo-up	2.6 years	3.4 years
Primary outcome	Time to ESRD, >40% fall in eGFR or renal death	Time to CV death, non-fatal MI, non-fatal stroke, HHF
FIDELITY composite renal	**Death, dialysis, doubling of creatinine (57% fall in eGFR)**	

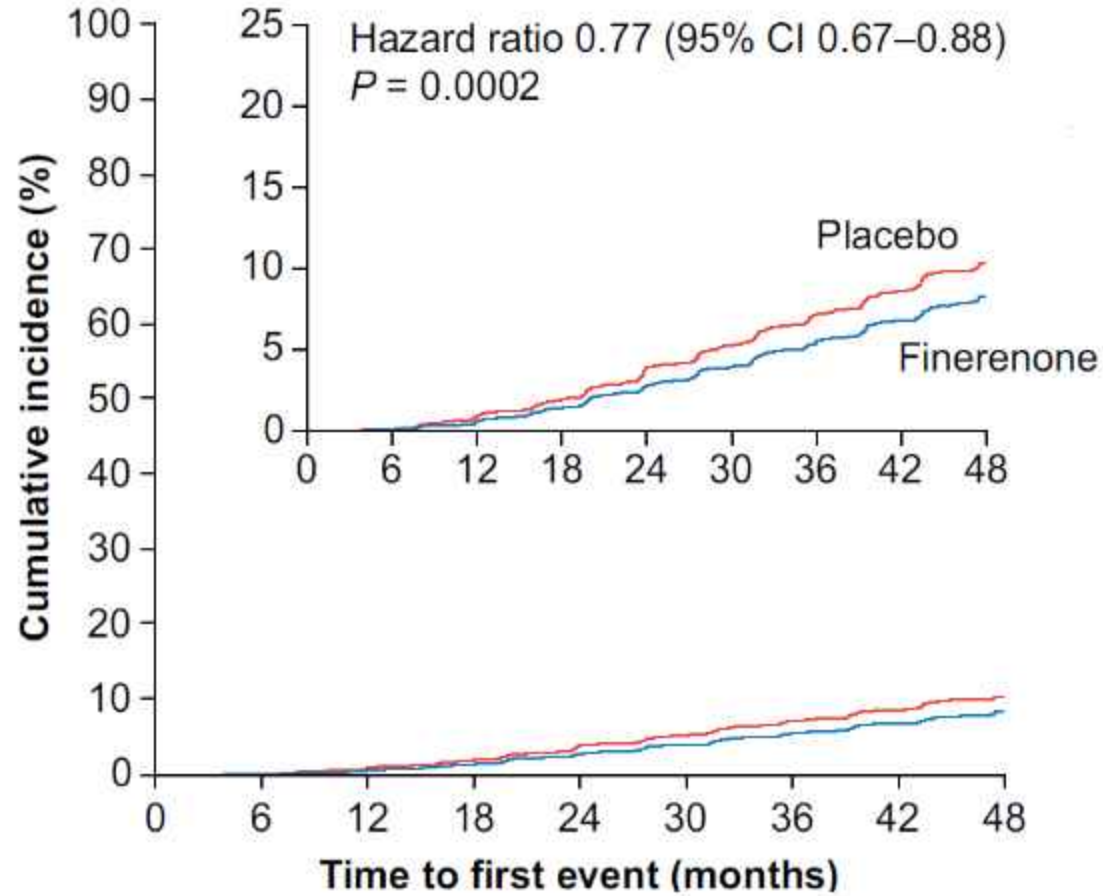
Agarwal R, *European Heart Journal*, 2021, https://doi.org/10.1093/eurheartj/ehab777

FIDELITY – CV and Kidney Outcomes

A Composite cardiovascular outcome



B eGFR ≥57% composite kidney outcome



Agarwal R, *European Heart Journal*, 2021, https://doi.org/10.1093/eurheartj/ehab777

Semaglutide Impact on Obesity-Related HFpEF with and without DM

- STEP-HFpEF (n=529), STEP-HFpEF DM(n=616)
- Treated with semaglutide 2.4 mg weekly vs placebo
- Dual endpoints; change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, and Bodyweight
- Secondary endpoints at 52 weeks: change from BL to 52 weeks in 6-min walk, CRP, Hierarchical composite: all-cause death, HF events, changes in KCCQ-CSS)

Butler J, *Lancet* 2024.

Semaglutide Impact on Obesity-Related HFpEF with and without DM

	Semaglutide (n=573)	Placebo (n=572)	HR (95%CI)	p
KCCQ-CSS	15.0	7.5		< 0.0001
% bodyweight	-11.4	-3.0		< 0.0001
SBP mmHg	-4.6	-1.7		0.0052
NTproBNP ratio week 52 to BL	0.78 (0.65)	0.95 (0.80)		
HF events per 100 pt years	1.3	4.9	0.27 (0.12 – 0.56)	0.0004

Butler J, *Lancet* 2024.

Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW)

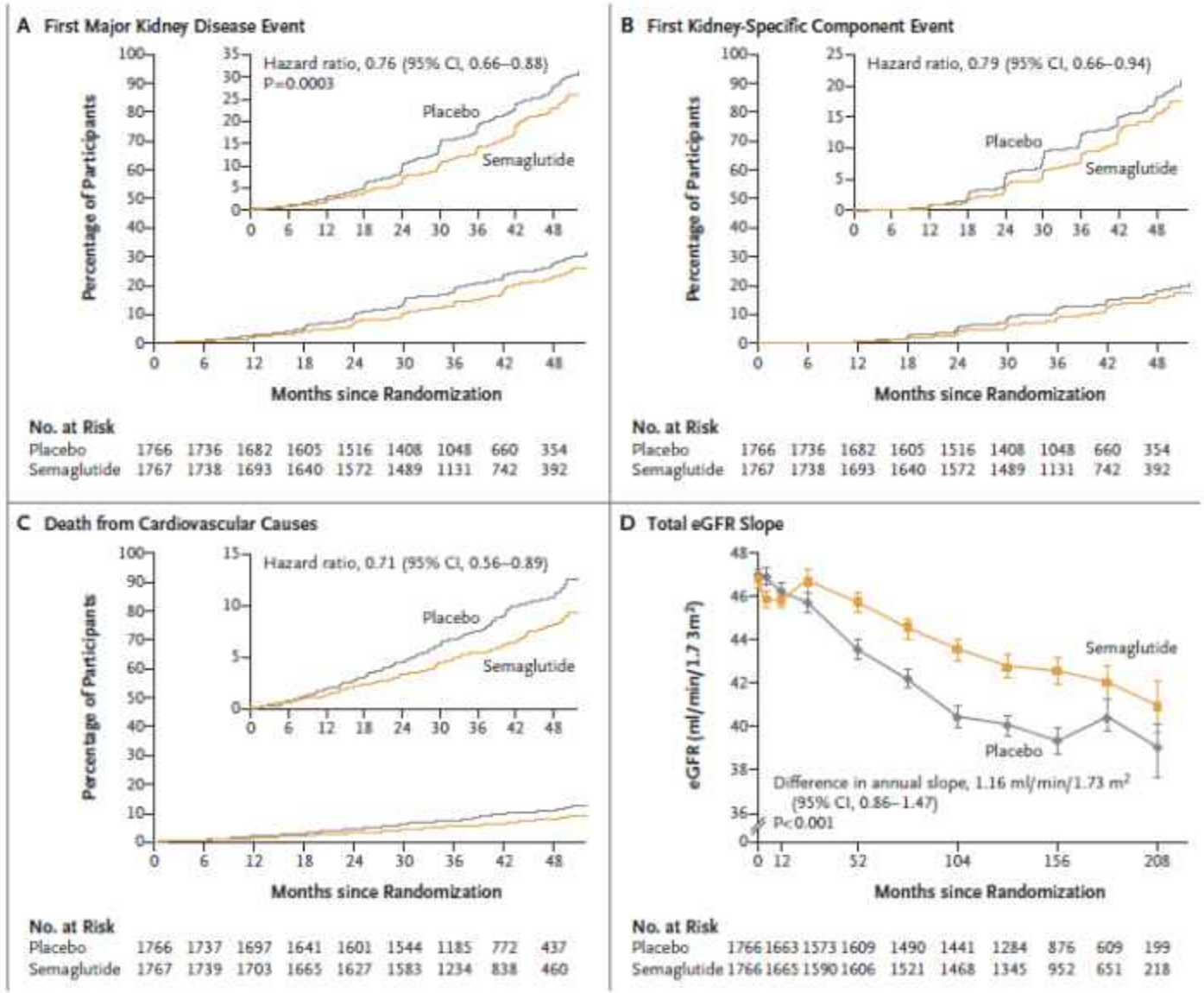
- Study population:
  - T2DM,
  - CKD eGFR 50-75 and UACR 30-500 mg/mmol
  - or eGFR 25-50 an dUACR > 10 and < 500,
  - on max tolerated RASi
- Primary outcome measure:
  - eGFR < 15 ml/min or dialysis, or Tx
- Secondary
  - Rate of change of eGFR
  - MACE
  - All cause death

Rossing P, NDT 2023 doi.org/10.1093/ndt/gfad009

FLOW Study Population

- N = 3534
- Mean age 66.9
- Male 69.7%
- BP at BL – 138.6/76.4 mmHg
- A1c 7.8%
- Mean T2DM – 17.4 years
- SGLT2i – 15.5%
- RASi - 95.3%
- Statins – 75%

Rossing P, NDT 2023 doi.org/10.1093/ndt/gfad009



Vlado Perkovic, NEJM - Yesterday

Diabetes Care
American Diabetes Association

Impact of Canagliflozin on Kidney and Cardiovascular Outcomes by Type 2 Diabetes Duration: A Pooled Analysis of the CANVAS Program and CREDENCE Trials

Sheldon W. Tobe, Thomas A. Mavrakanas, Harpreet S. Bajaj, Adeera Levin, Navdeep Tangri, April Slee, Brendon L. Neuen, Vlado Perkovic, Kenneth W. Mahaffey, Wally Rapattoni, and Fernando G. Ang

Diabetes Care 2024;47(3):501–507 | https://doi.org/10.2337/dc23-1450

Impact of Canagliflozin on Kidney, Albuminuria and Cardiovascular outcomes by Type 2 Diabetes duration: Pooled analysis of the CANVAS Program and CREDENCE trials.

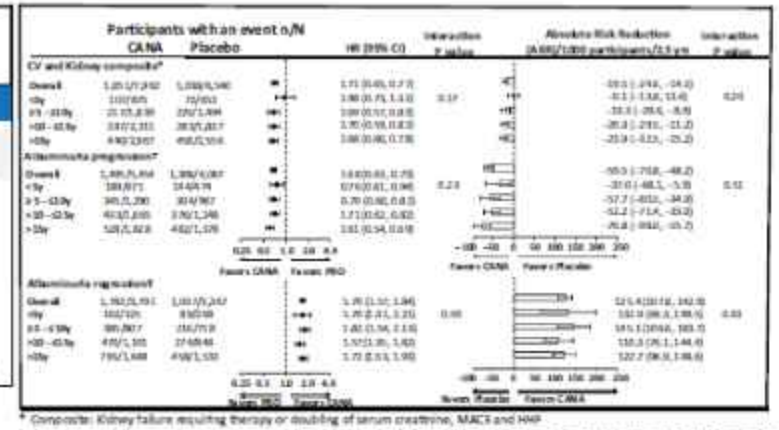
Sheldon W. Tobe, Thomas A. Mavrakanas, Harpreet S. Bajaj, Adeera Levin, Navdeep Tangri, April Slee, Brendon L. Neuen, Vlado Perkovic, Kenneth W. Mahaffey, Wally Rapattoni, Fernando G. Ang

Canagliflozin consistently confers cardiorenal benefits in patients regardless of type 2 diabetes duration.

Post hoc analysis of integrated pooled, patient level data (n=14,542) — CANVAS Program (n=10,142) and CREDENCE (n=4,401)

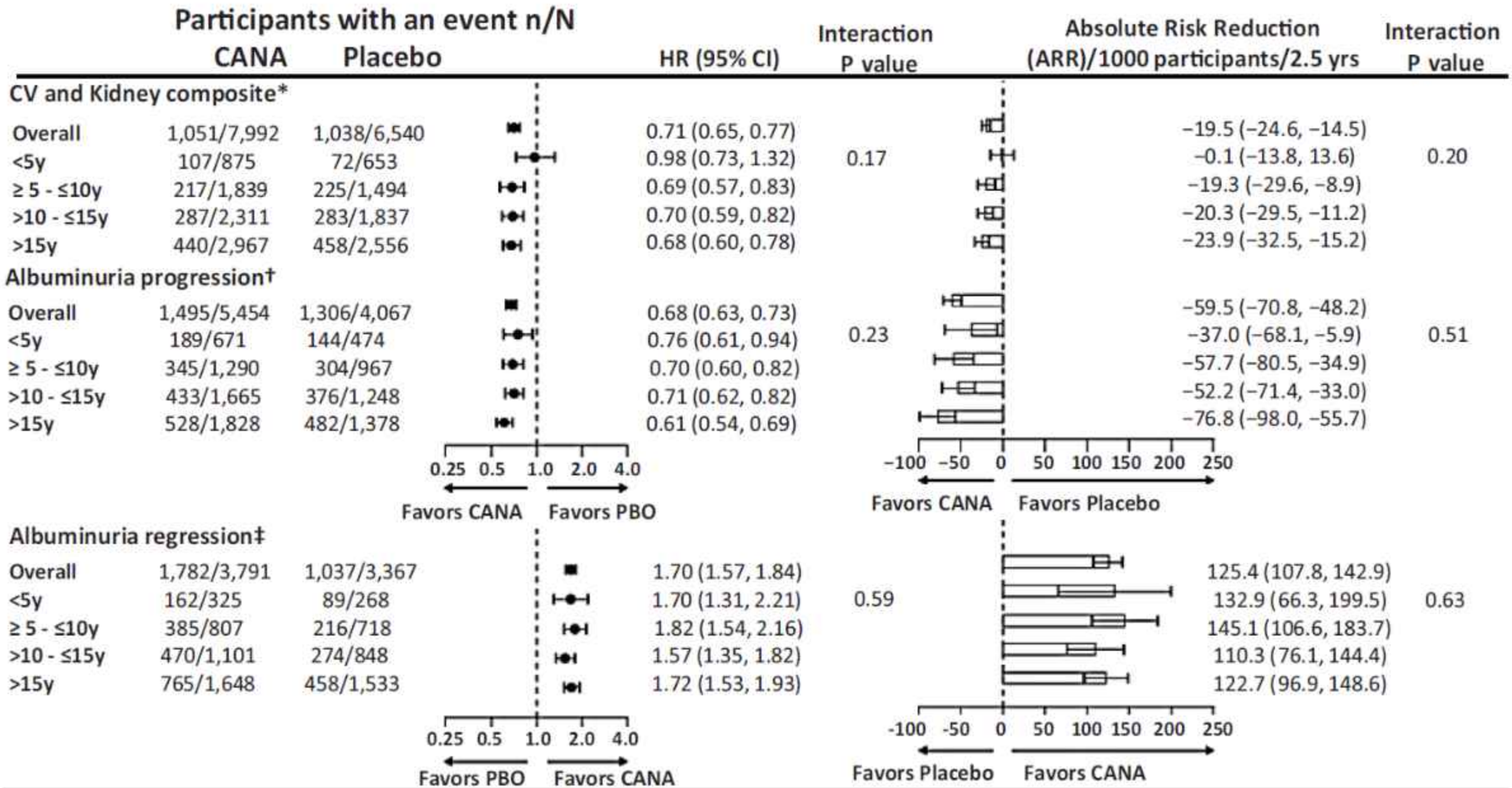
Characteristic*	Duration of type 2 diabetes (T2D), years			
	≤5 n=1,528	>5 - ≤10 n=3,333	>10 - ≤15 n=4,148	>15 n=5,523
Age, y	59.5 (5.9)	62.0 (6.5)	62.7 (6.1)	65.3 (6.1)
Female, %	33.4	33.5	36.0	36.3
Type 2 diabetes duration, y	2.7 (1.3)	7.7 (1.7)	12.8 (1.3)	22.4 (4.1)
History Hypertension %	88.2	91.7	91.7	93.8
eGFR mL/min/1.73m²	77.0 (21.8)	73.0 (22.0)	72.7 (21.8)	65.1 (20.9)
UACR, mg/mmol	1.7 (0.8, 23.3)	2.8 (0.9, 52.0)	3.6 (0.9, 47.8)	10.6 (1.2, 84.1)

*Data are mean (SD) or median (IQR) unless otherwise noted.
ClinicalTrials.gov identifier: NCT01032629, NCT01989754, and NCT01065779.

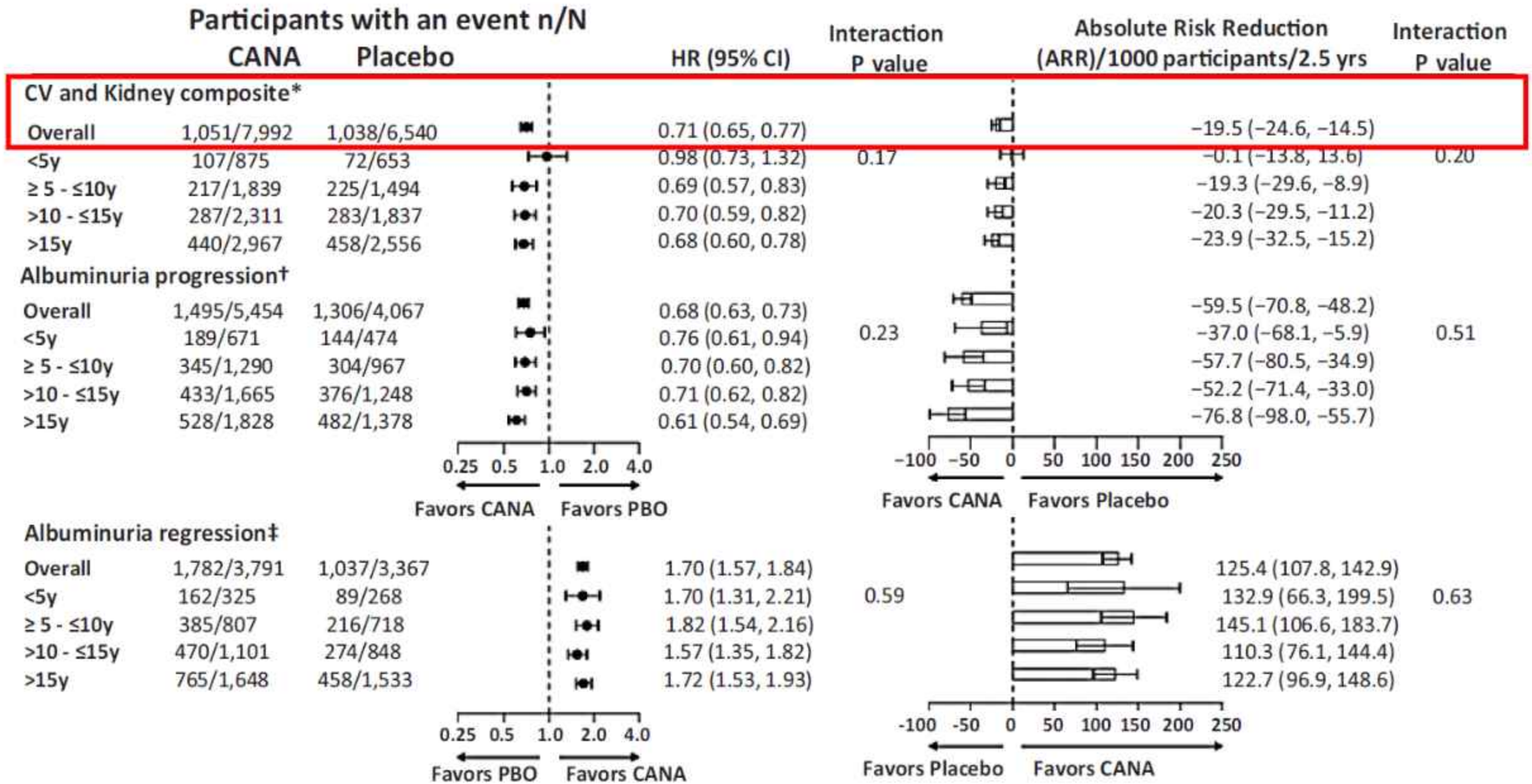


* Composite: Kidney failure requiring therapy or doubling of serum creatinine, MACE and HHF

- Regardless of the duration of type 2 diabetes, canagliflozin demonstrated sustained reduction of CV and kidney outcomes. The total risk reduction was greater in individuals with higher cardiovascular and kidney risk.
- Within 5 years of type 2 diabetes diagnosis, canagliflozin positively impacted on albuminuria progression and regression, an important consideration in primary care



Tobe, S. *Diabetes Care* 2024.



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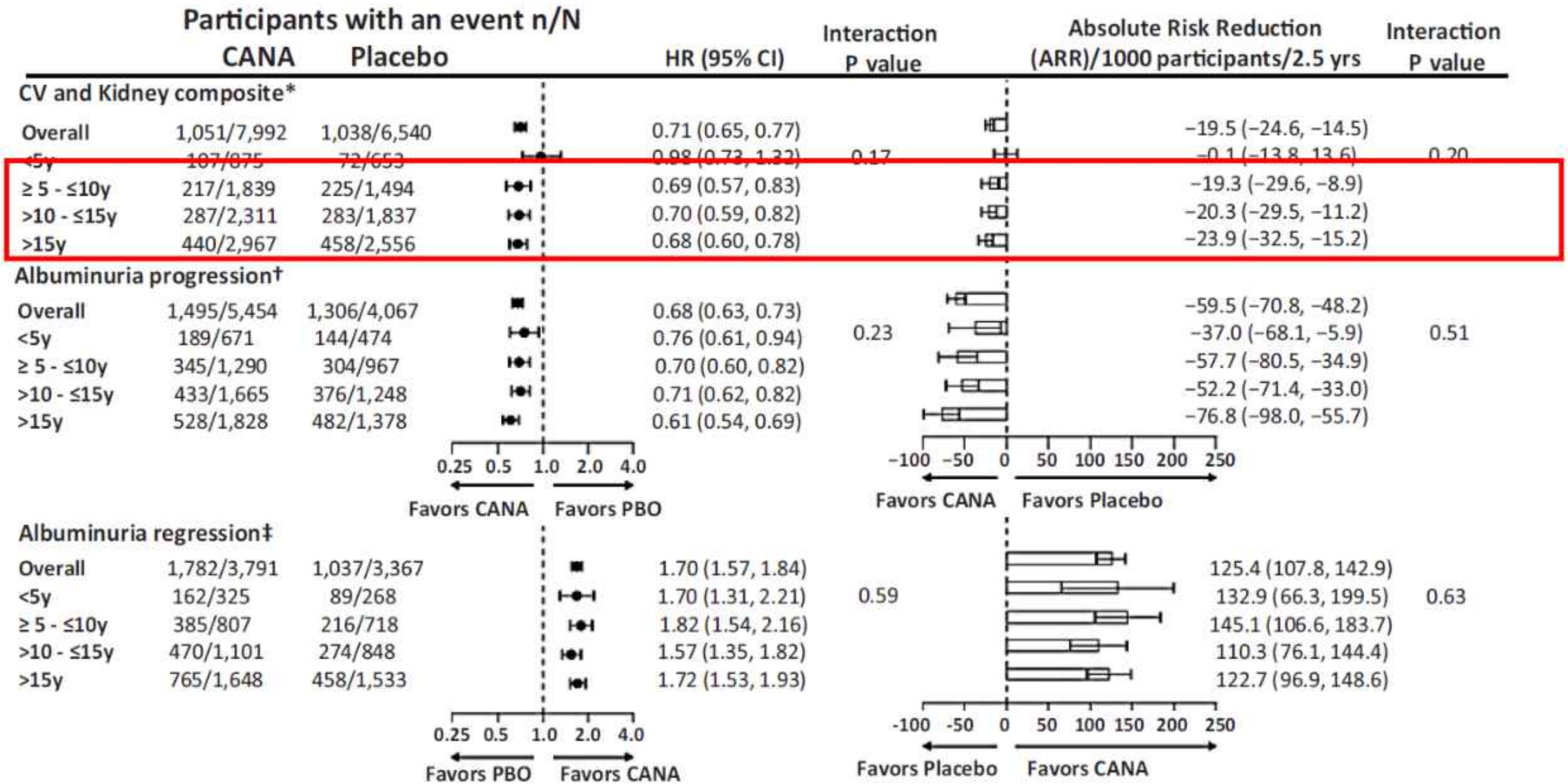

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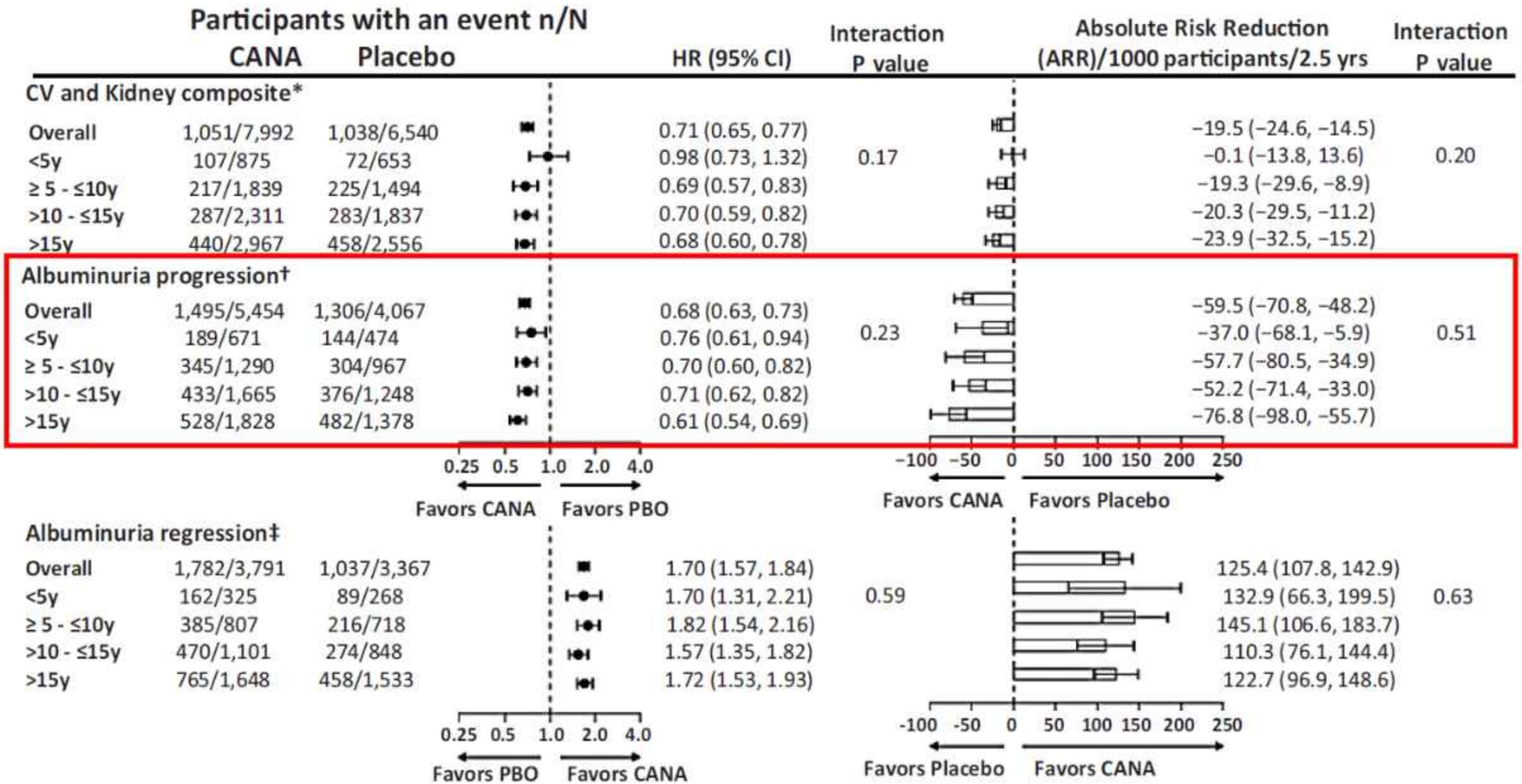

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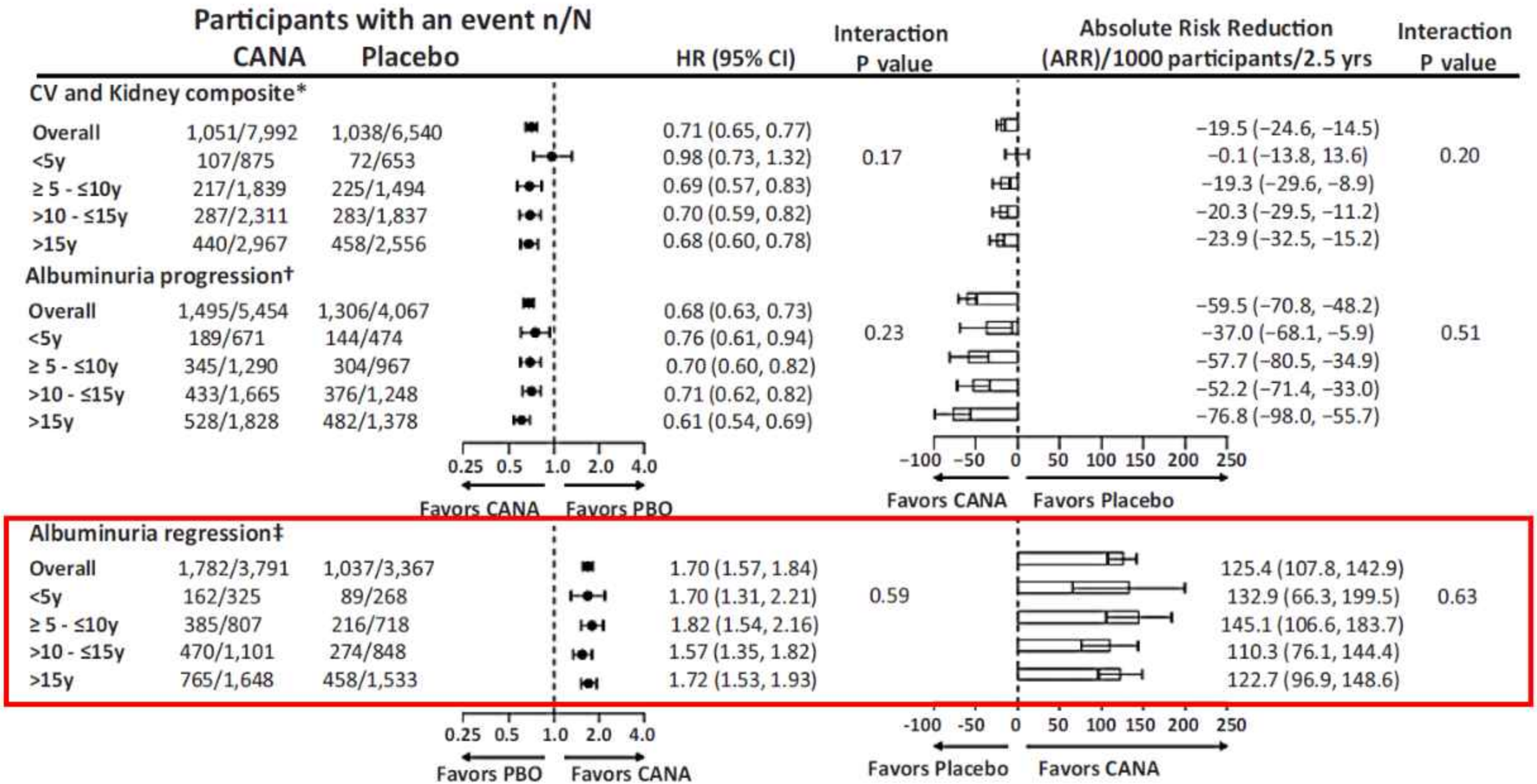
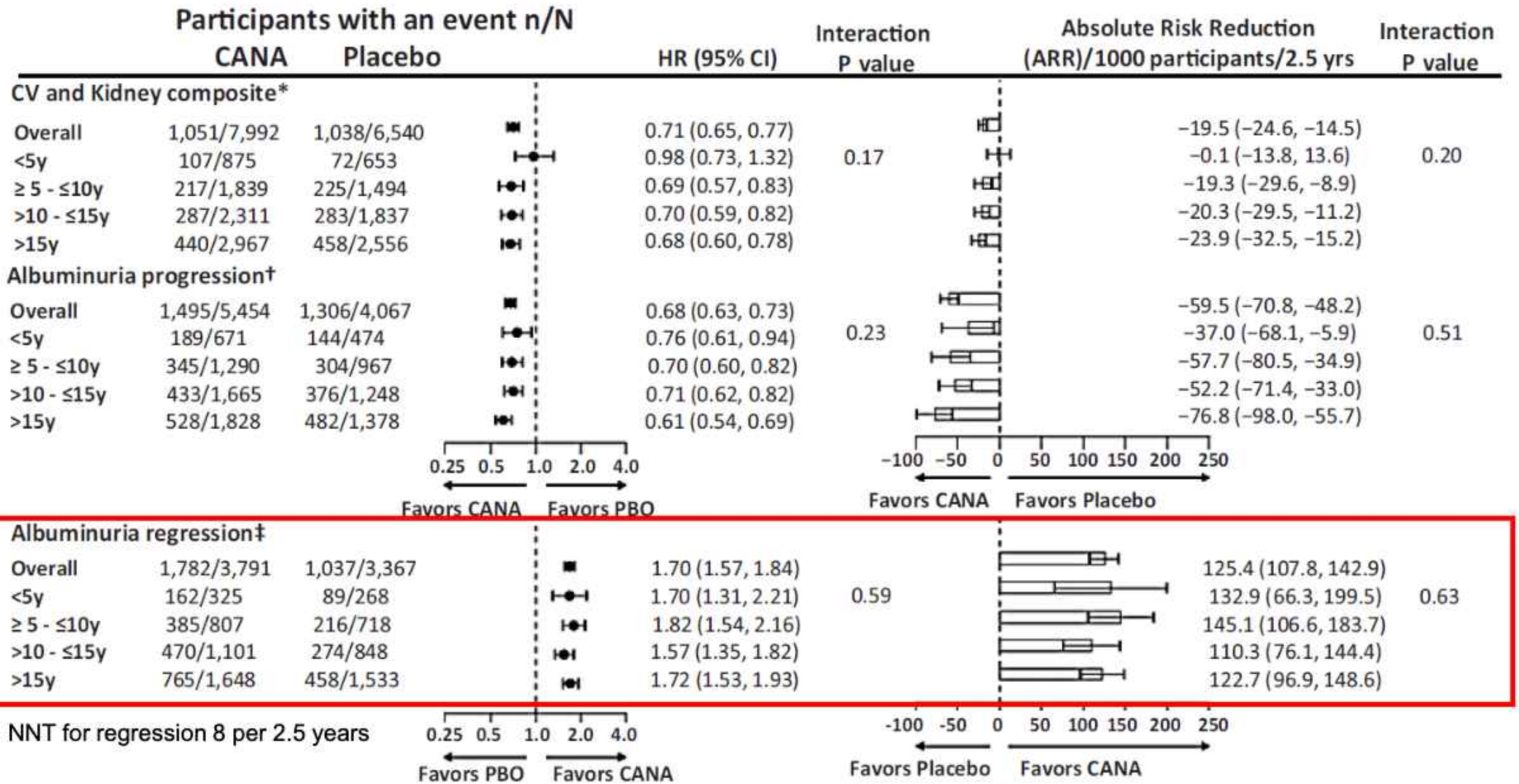
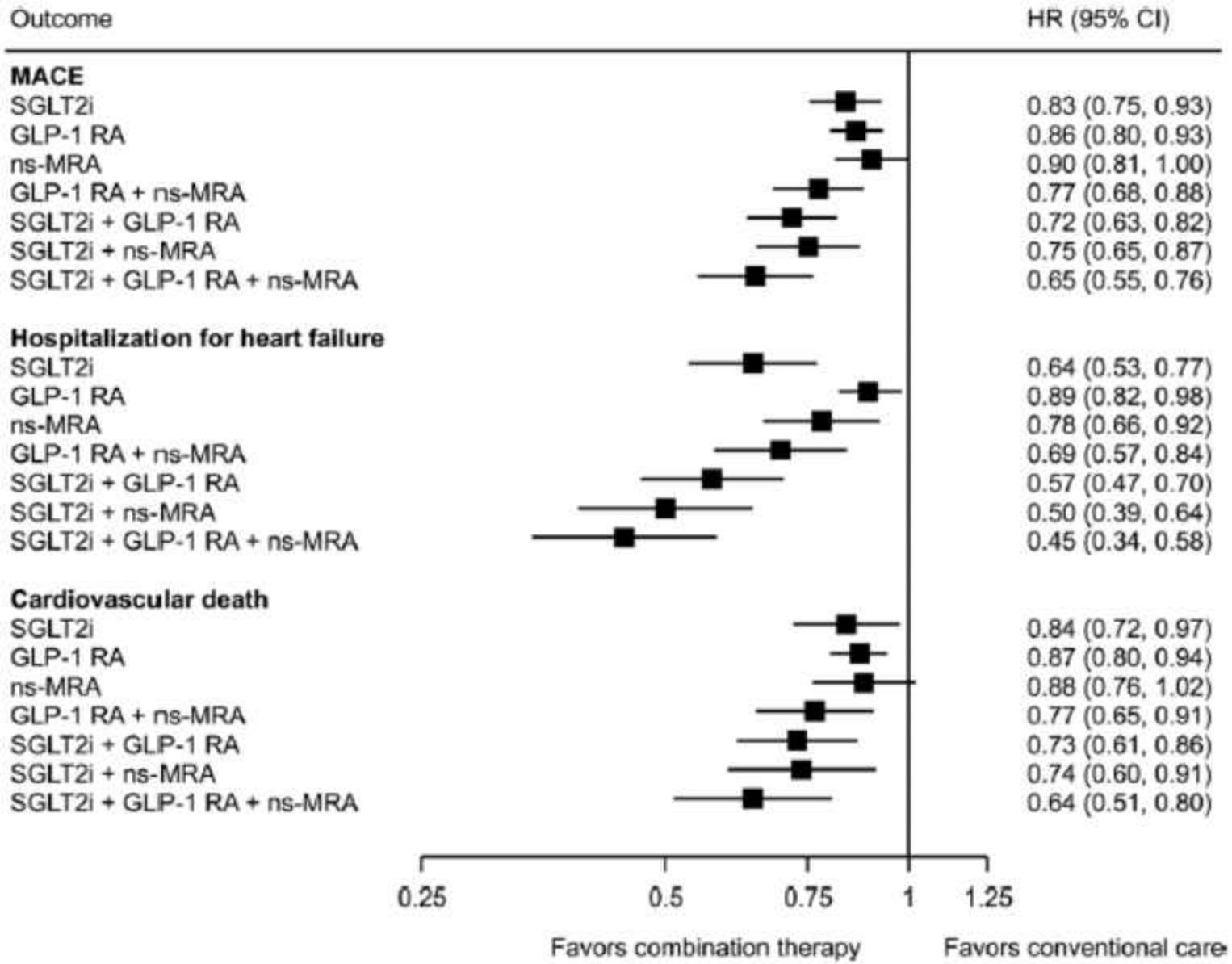


Tobe, S. *Diabetes Care* 2024.



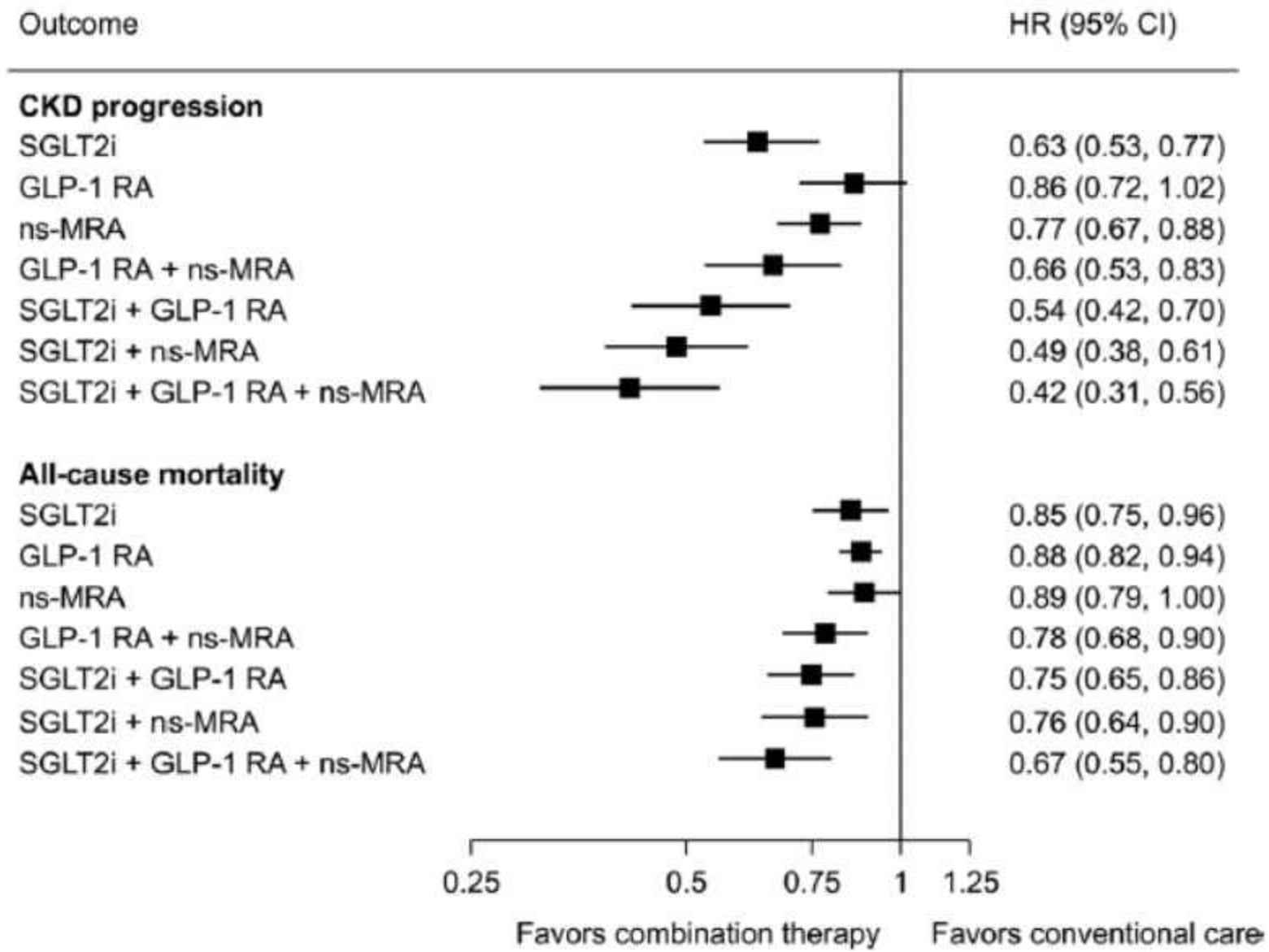
Tobe, S. *Diabetes Care* 2024.

Estimated Effects on CV/Kidney Outcomes by Combinations of SGLT2i, GLP-1RA, ns-MRA



Neuen BL_*Circulation* 2024.

Estimated Effects on CV/Kidney Outcomes by Combinations of SGLT2i, GLP-1RA, ns-MRA



Neuen BL_*Circulation* 2024.

Heart-Cancer Connection

Margot K. Davis
MD, MS, FRCPC, FCCS
University of British Columbia

Disclosure / Conflict of Interest

Margot Davis, MD SM FRCPC FCCS

Relationships with for profit and/or non-profit organization:

- Grant/Research Support: Pfizer
- Speakers Bureau/Honoraria: Pfizer, BI/Lilly, Alnylam, Bayer, Janssen, Ferring, CHFS, CCS, BC Cancer Agency, Canadian Women's Heart Health Alliance, UBC CPD
- Consulting Fees: AstraZeneca, Ionis, Novo Nordisk, Bayer, Janssen, Ferring, Pfizer, Alnylam, Anthos, Jazz Pharmaceuticals

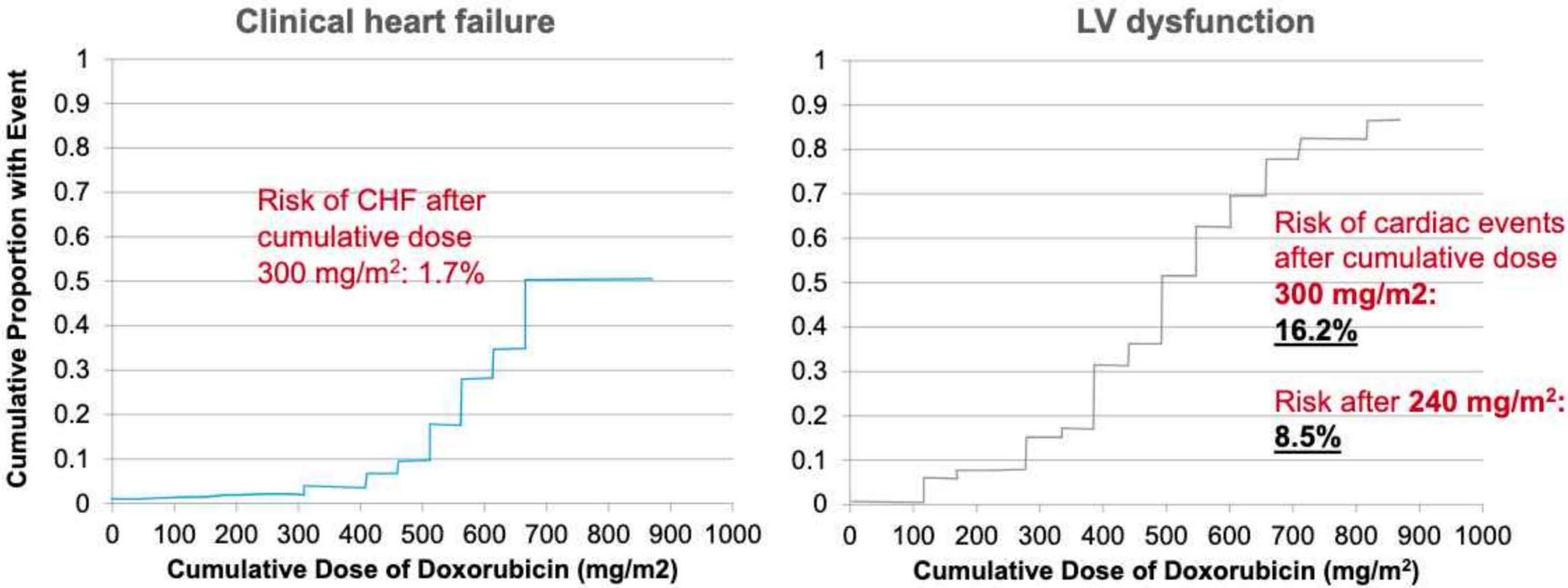
Learning Objectives

1. Review recent recommendations for cancer treatment-related cardiac toxicity screening for the most common clinical scenarios
2. Adapt long-term follow-up for cancer survivors with or at risk of developing cardiotoxicities
3. Recognize the cardiac “emergencies” secondary to cancer treatment (such as immune checkpoint inhibitors, myocarditis and HF in patients receiving anthracycline and/or HER2 inhibitors)

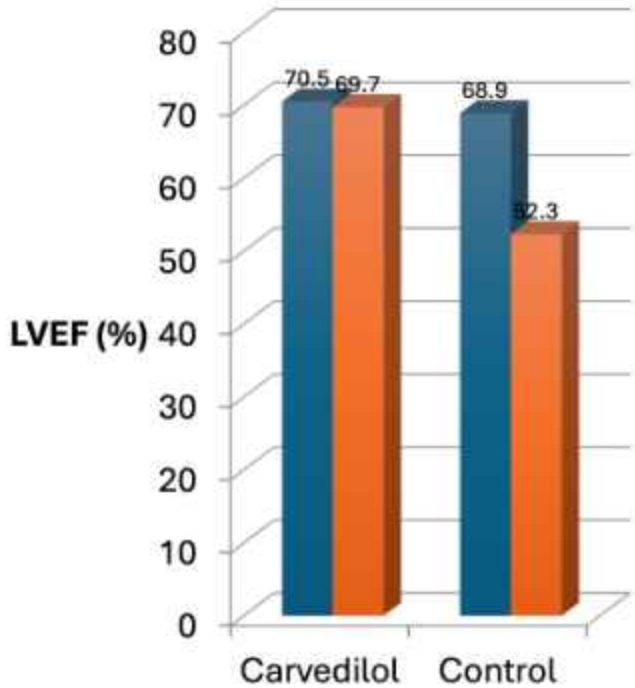
Anthracyclines

Congestive Heart Failure in Patients Treated with Doxorubicin

A Retrospective Analysis of Three Trials



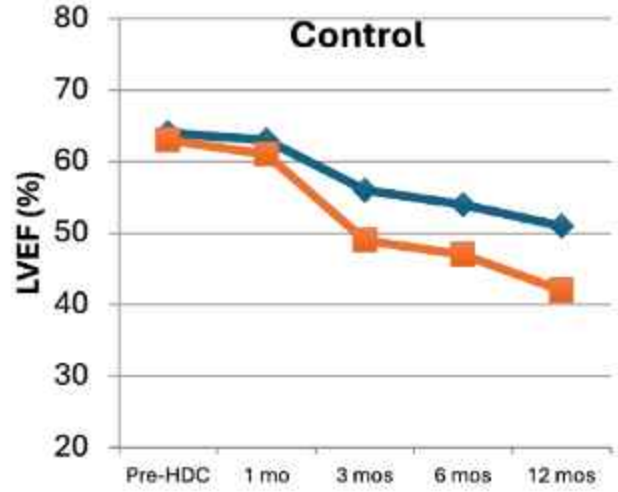
Cancer 2003;97:2869–79

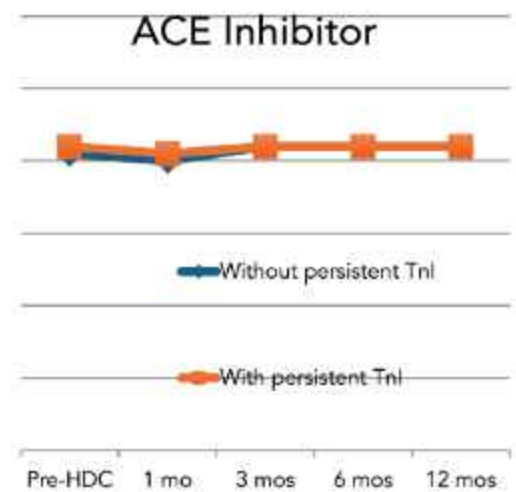


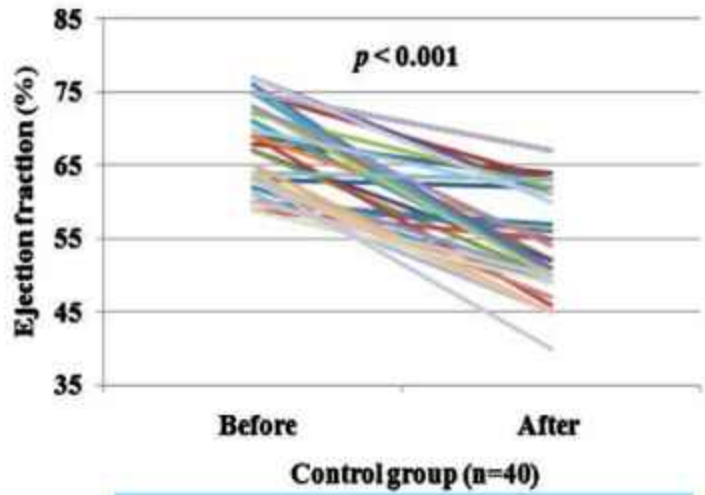
50 patients with lymphoma or breast cancer, treated with anthracyclines

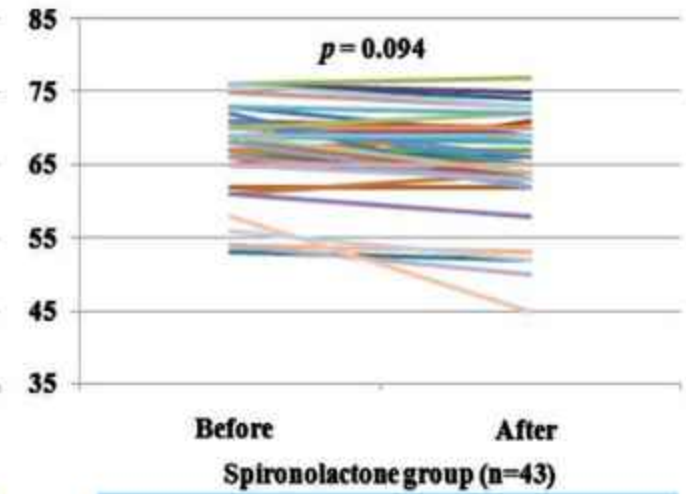
Median Adriamycin dose 520 mg/m2 (or Epirubicin 780 mg/m2)

Followed for 6 months









Median anthra doses:	
Doxorubicin	394 mg/m2
Epirubicin	727 mg/m2

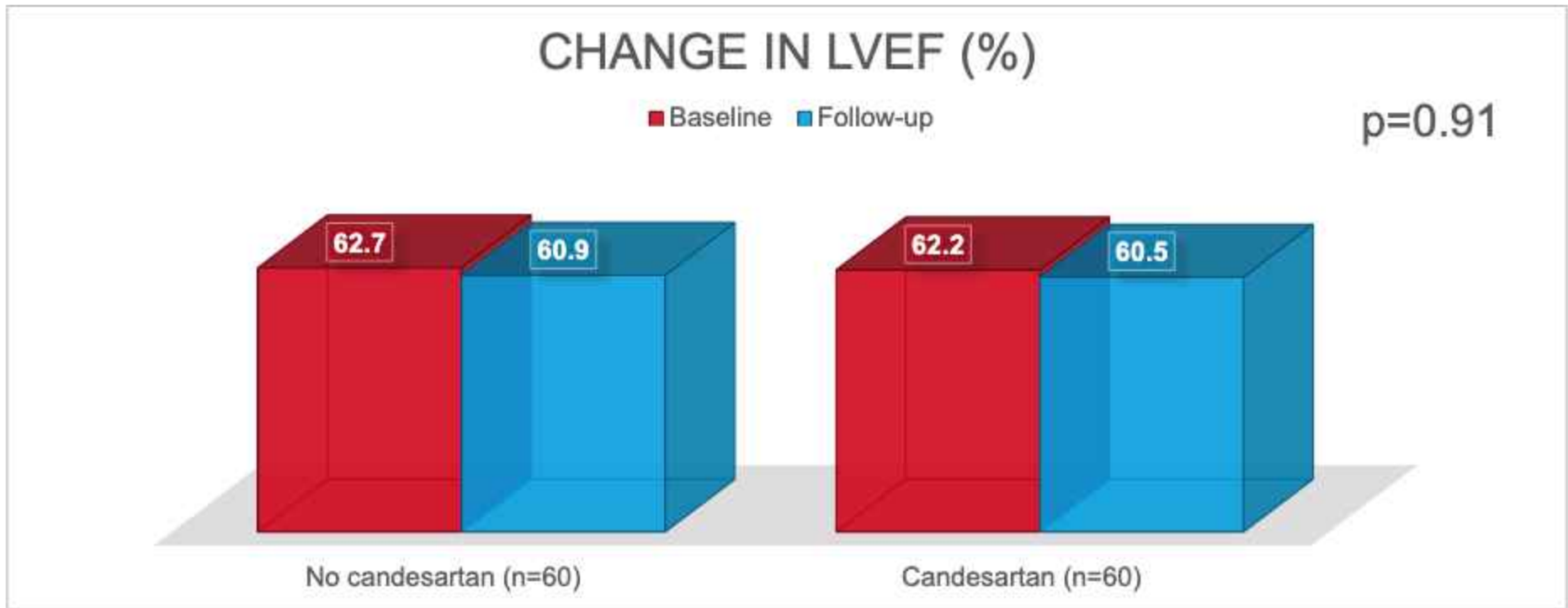
Median anthra doses:	
Doxorubicin	430 mg/m2
Epirubicin	689 mg/m2

Circulation. 2006;114:2474-2481

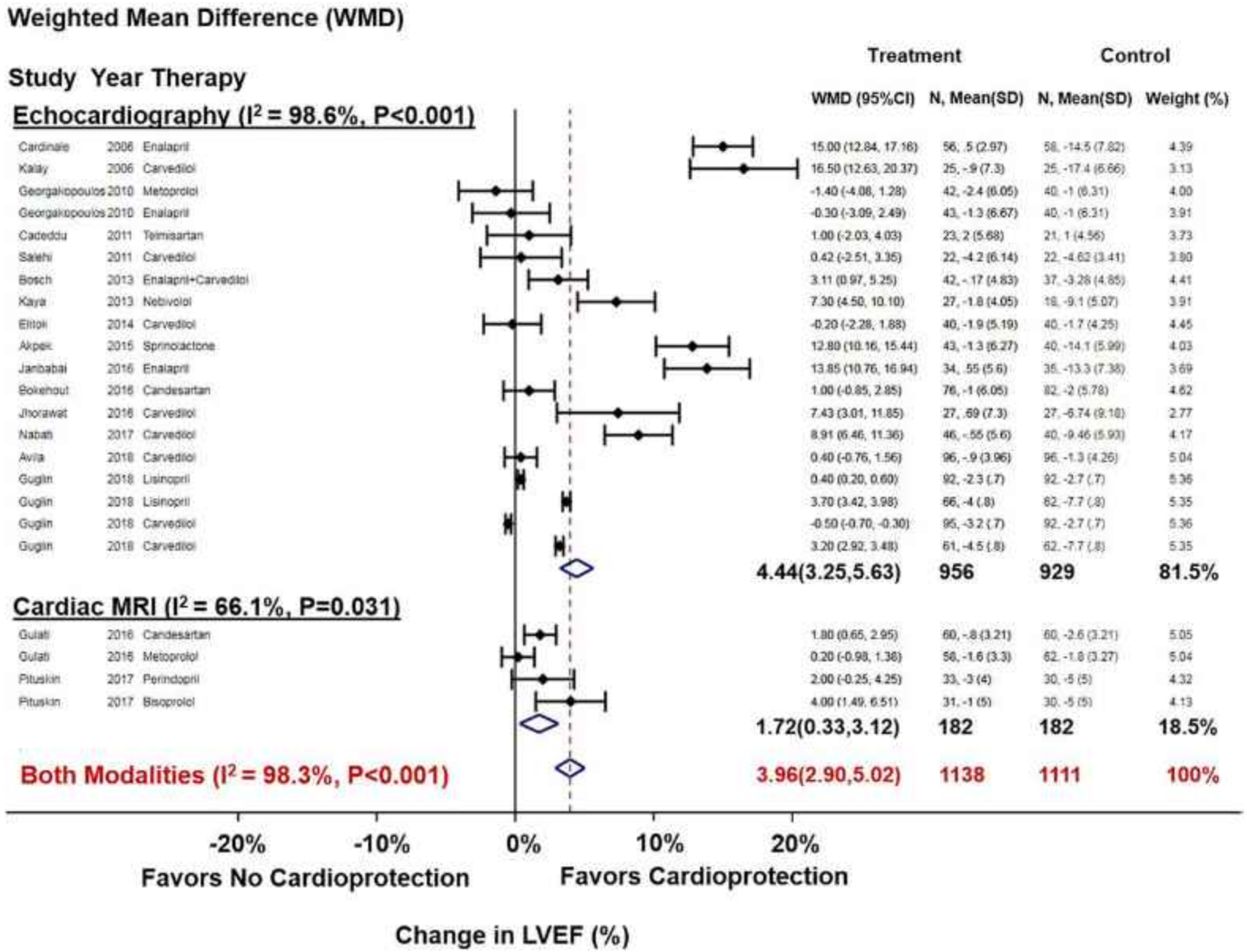
J Am Coll Cardiol 2006;48:2258–62

European J of Heart Fail 2014;17(1):81-9

PRADA: Candesartan vs. placebo in breast cancer patients receiving anthracyclines +/- trastuzumab – 2-year follow-up



Eur Hear J 2016;37:1671-80.



Pooled effects of neurohormonal therapies versus placebo on changes in LVEF from baseline to follow-up

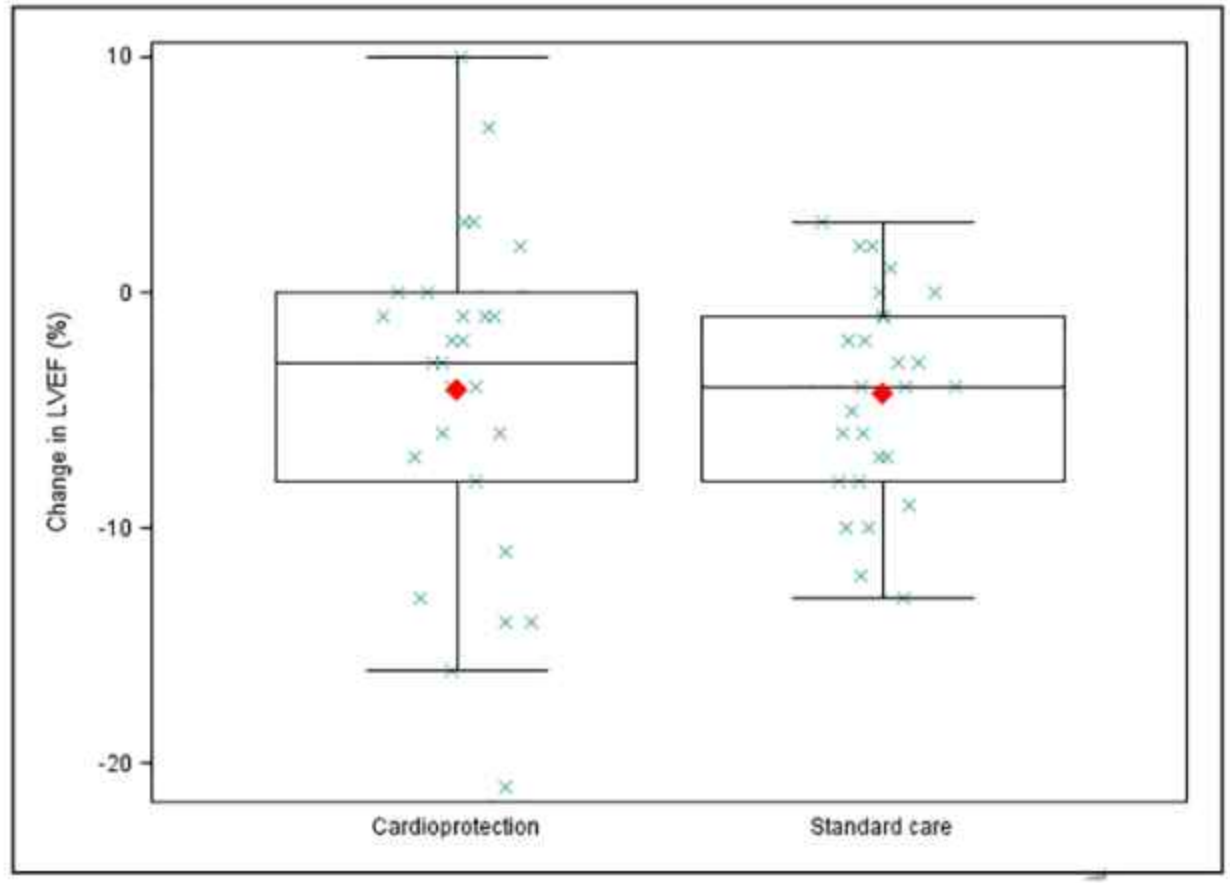
Muthiah Vaduganathan et al. J Am Coll Cardiol CardioOnc 2019;1:54-65

PROACT

- Presented at ACC 2024 (Austin *et al.*)
- 111 patients undergoing treatment for breast CA (62%) or NHL (38%)
- All received anthracyclines, median doxorubicin equivalent 328 mg/m2
- Randomized to enalapril (mean dose 17.7 mg) vs. placebo
- Primary endpoint: proportion with troponin T rise – no difference
- Secondary endpoints:
  - Trop I rise – no difference
  - Change in LVEF – no difference
  - Change in GLS – no difference

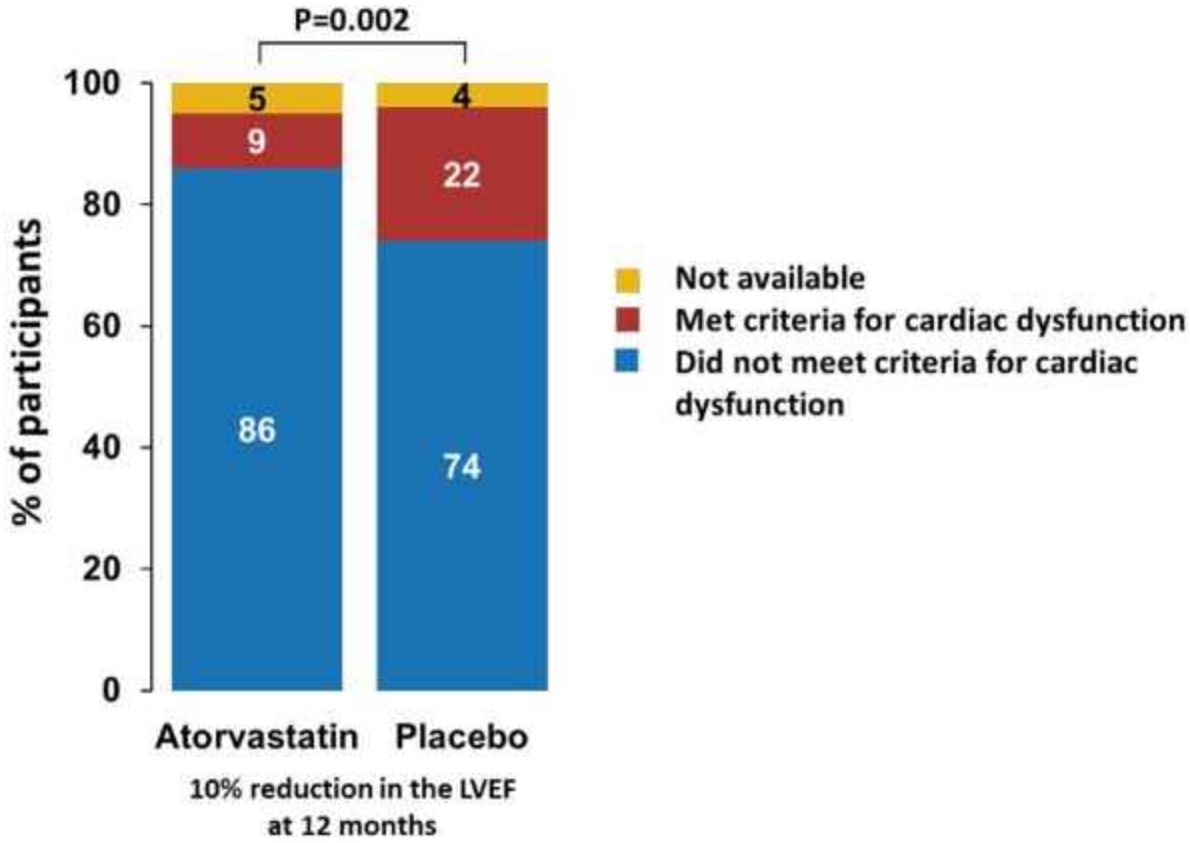
Utility of a hsTn-guided cardioprotection strategy

- 175 high-risk patients (top hsTn I tertile) receiving anthra for breast cancer or NHL
- Randomized to hsTn-guided cardioprotection with ARB/BB vs standard care
- Age adjusted difference in LVEF between arms: -0.37%



Henriksen et al. Circulation. 2023;148:00–00. DOI: 10.1161/CIRCULATIONAHA.123.064274

STOP-CA: Atorvastatin in lymphoma patients receiving anthracyclines

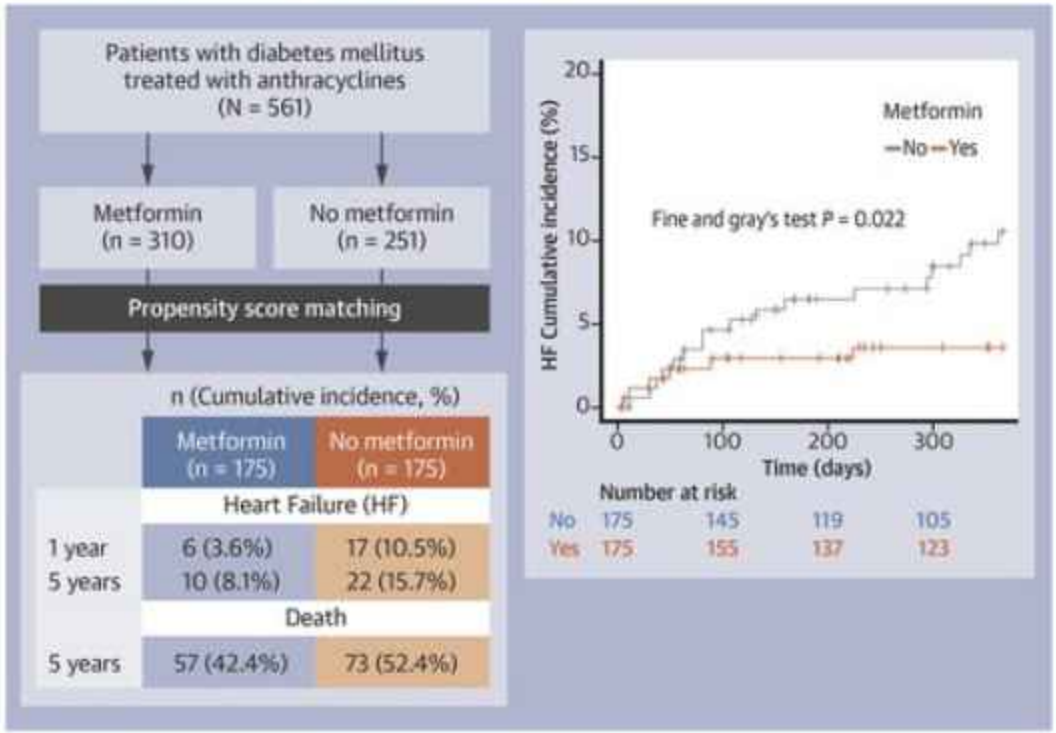


- 300 lymphoma patients, median doxorubicin dose 300mg/m2
- Randomized to atorva 40 vs. placebo
- Cardiotoxicity in 9% vs. 22%
- Well tolerated
- No difference in △LVEF (4% vs 5%) or clinical HF

- Contrast similar but negative trial in breast cancer/lymphoma patients – no difference in LVEF or proportion with 10% decline
- Median anthra 240 mg/m2

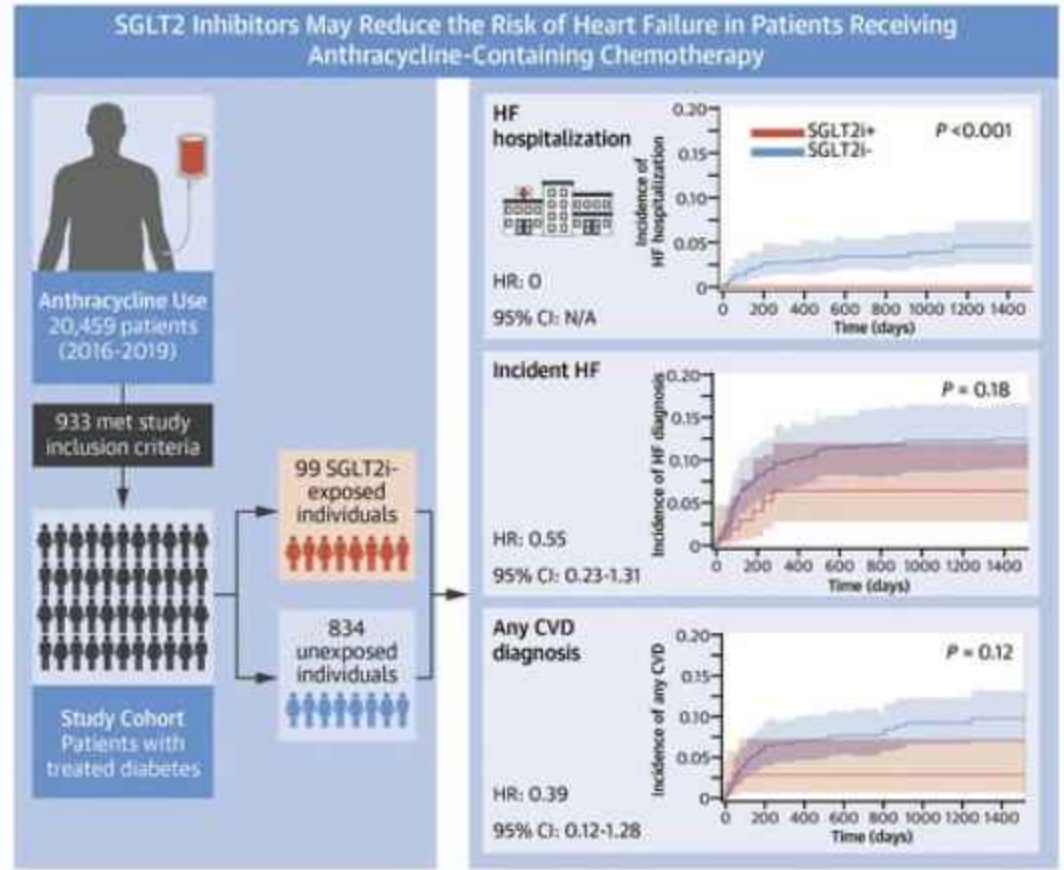
Neilan et al., ACC 2023
August 18, 2022 NEJM Evid 2022; 1 (9)

CENTRAL ILLUSTRATION: Study Design and Outcomes

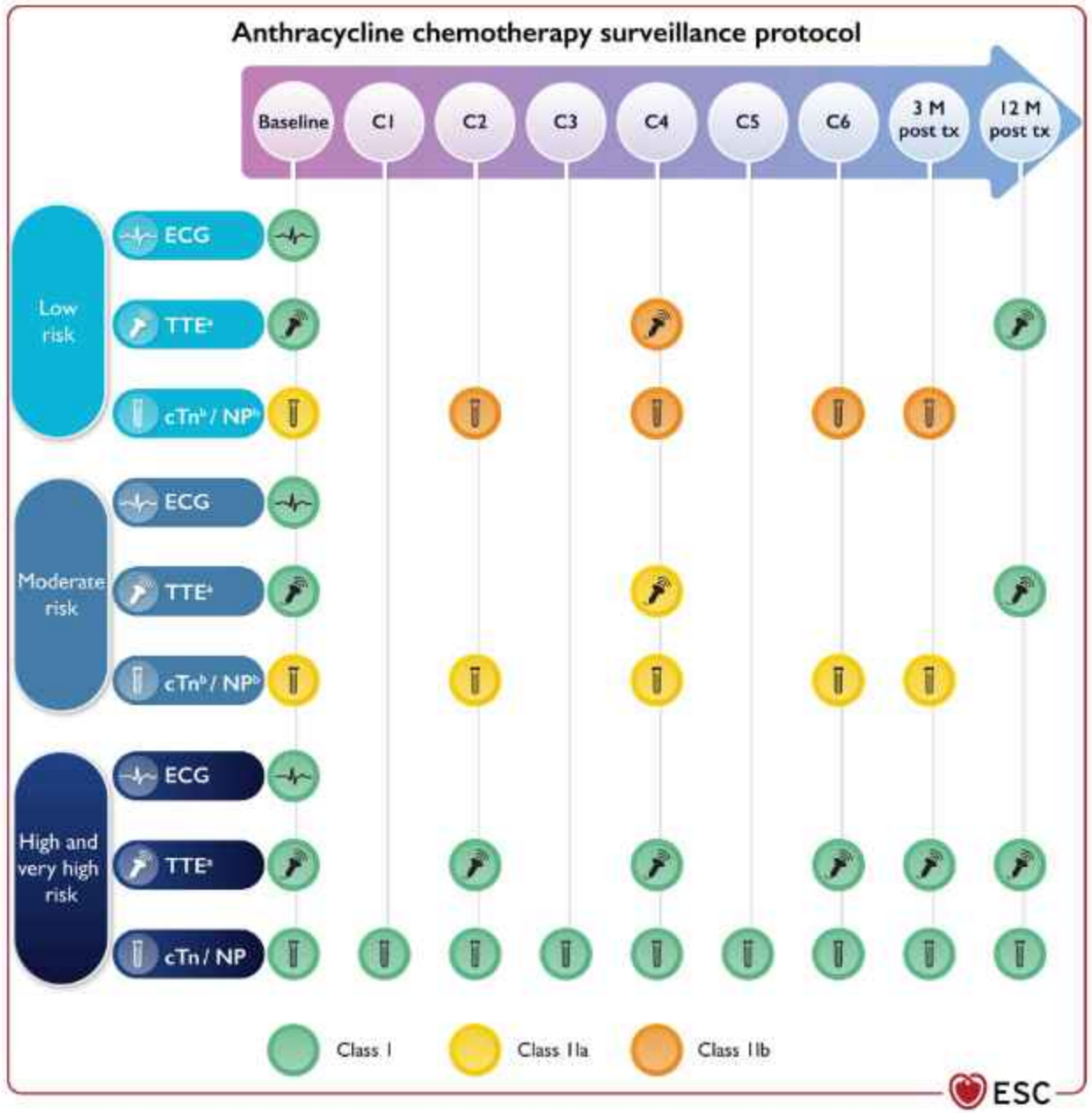


Onoue T, et al. J Am Coll Cardiol CardioOnc. 2023;5(5):674-682.

CENTRAL ILLUSTRATION: The Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Anthracycline Cardiotoxicity



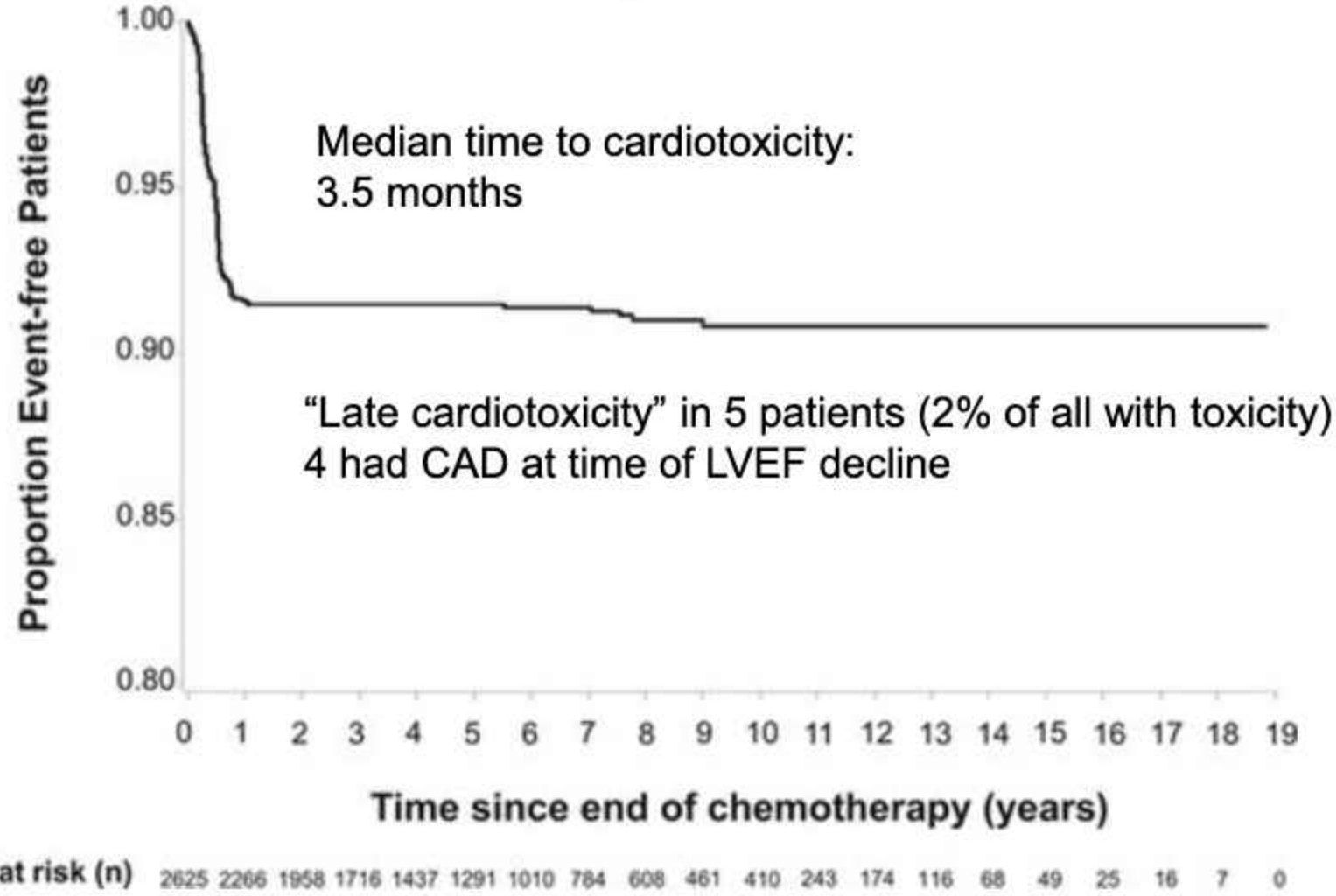
Abdel-Qadir H, et al. J Am Coll Cardiol CardioOnc. 2023;5(3):318-328.



CV toxicity monitoring in patients receiving anthracyclines

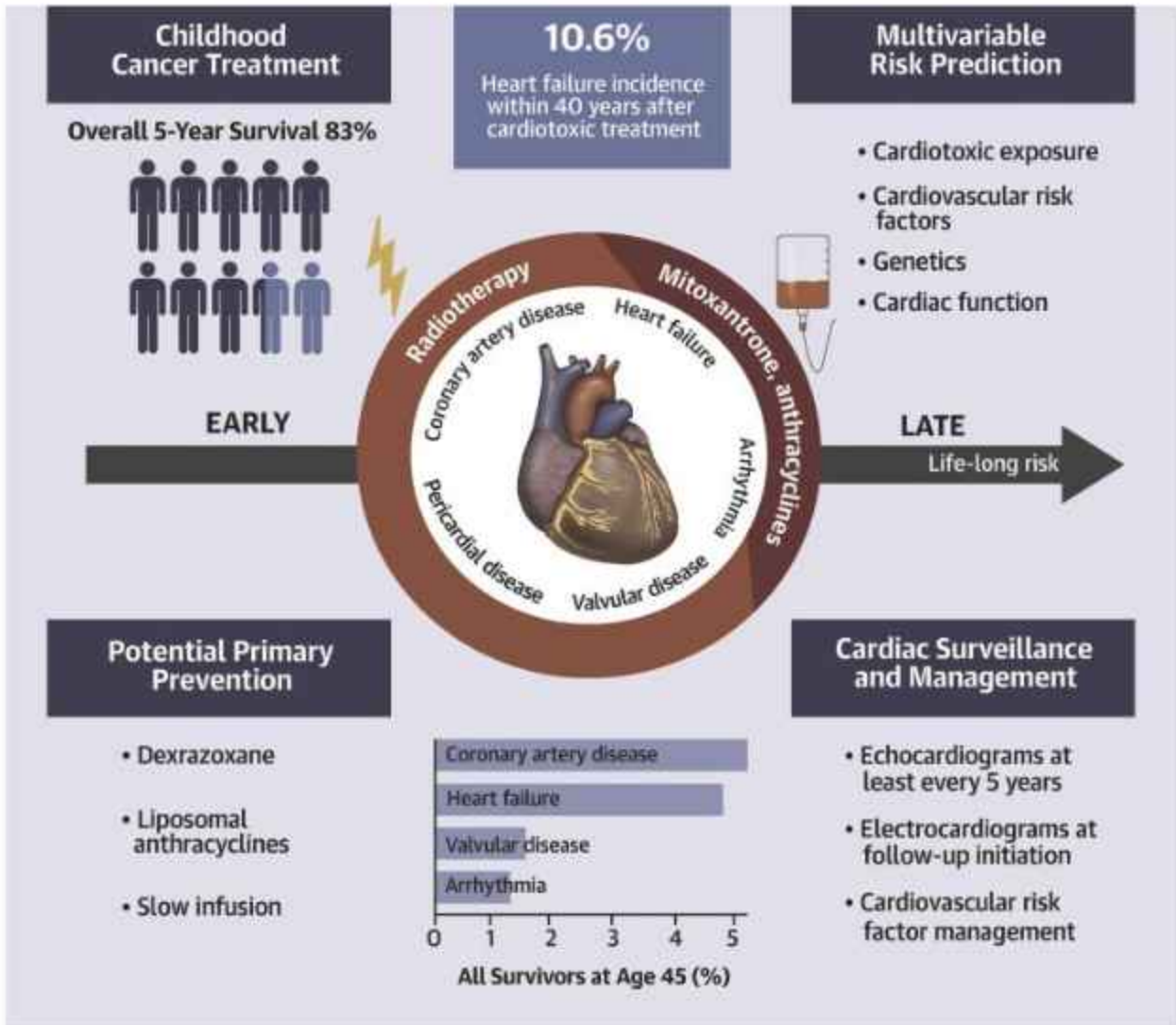
European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361

Timing of anthracycline cardiotoxicity in adults

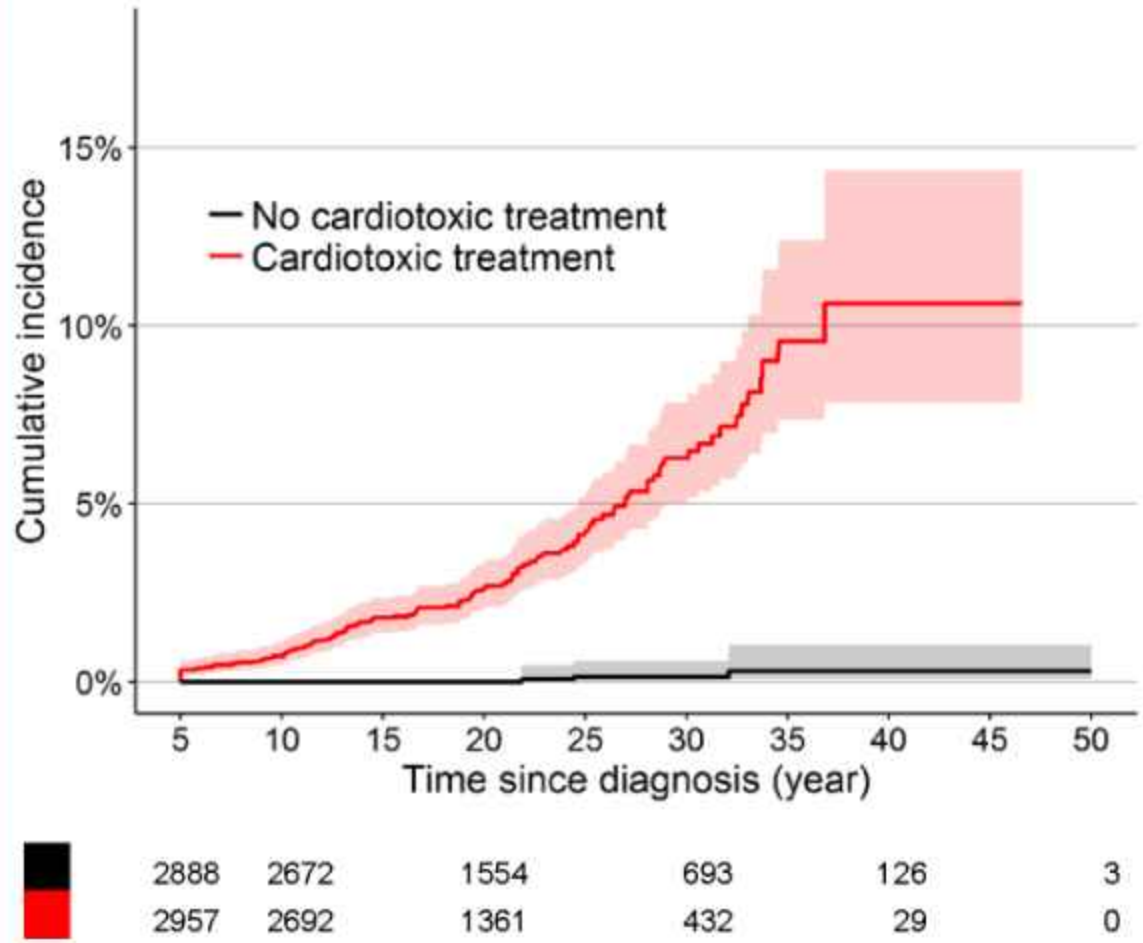


Cardinale. Circulation. Volume: 131, Issue: 22, Pages: 1981-1988

CENTRAL ILLUSTRATION: Overview of Clinical Practice in Childhood Cancer Survivors at Risk for Cardiotoxicity



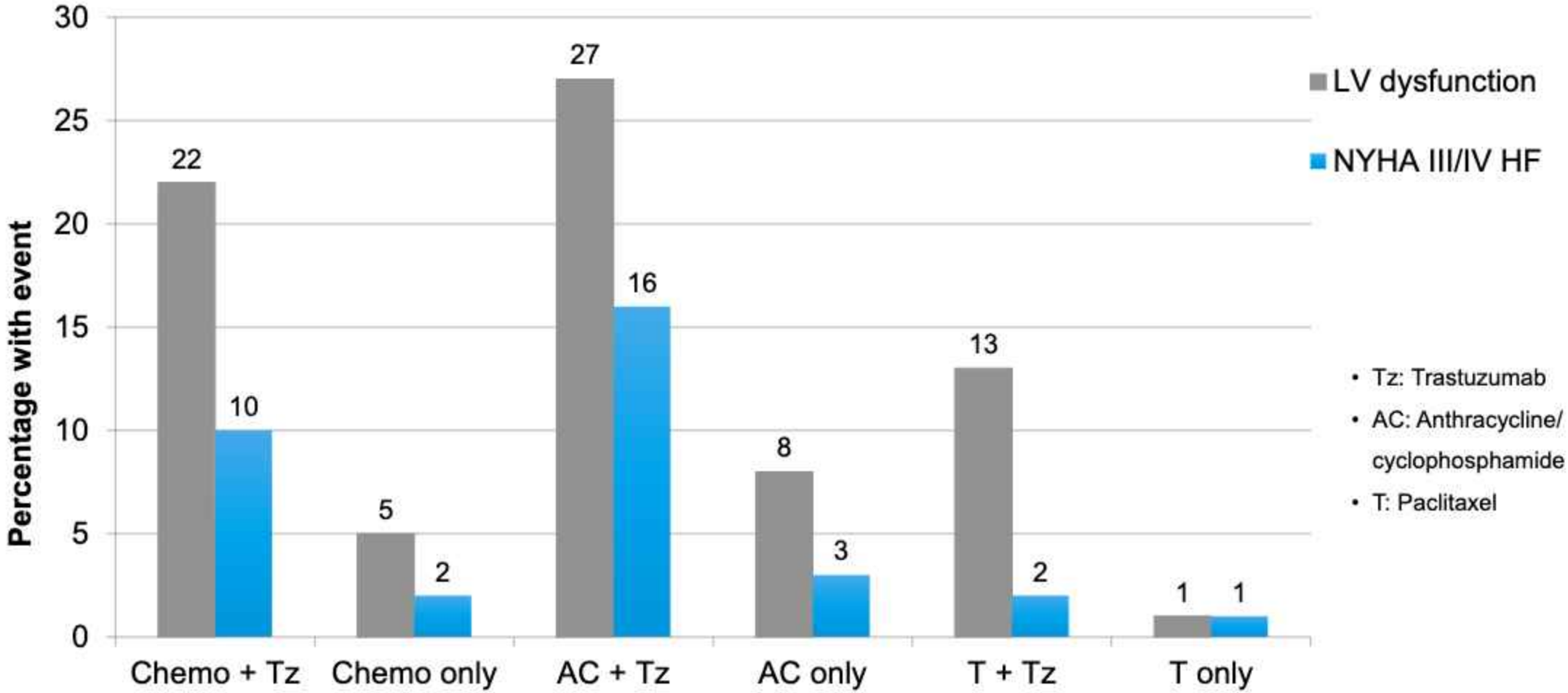
Leerink, J.M. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):363-78.



Feijen et al. Journal of the American Heart Association. 2019;8:e009122

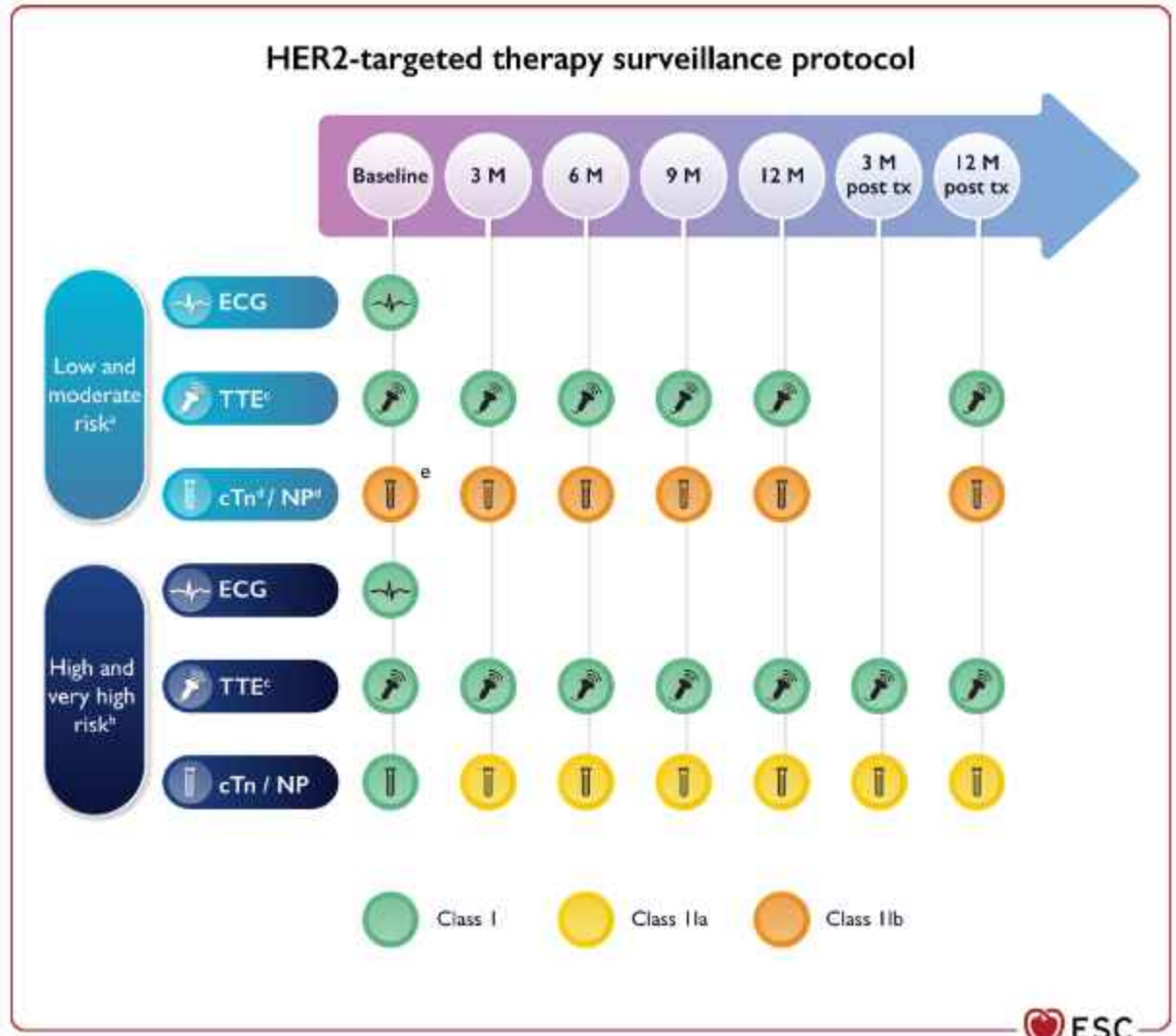
Trastuzumab

Incidence of cardiotoxicity in metastatic trastuzumab trial



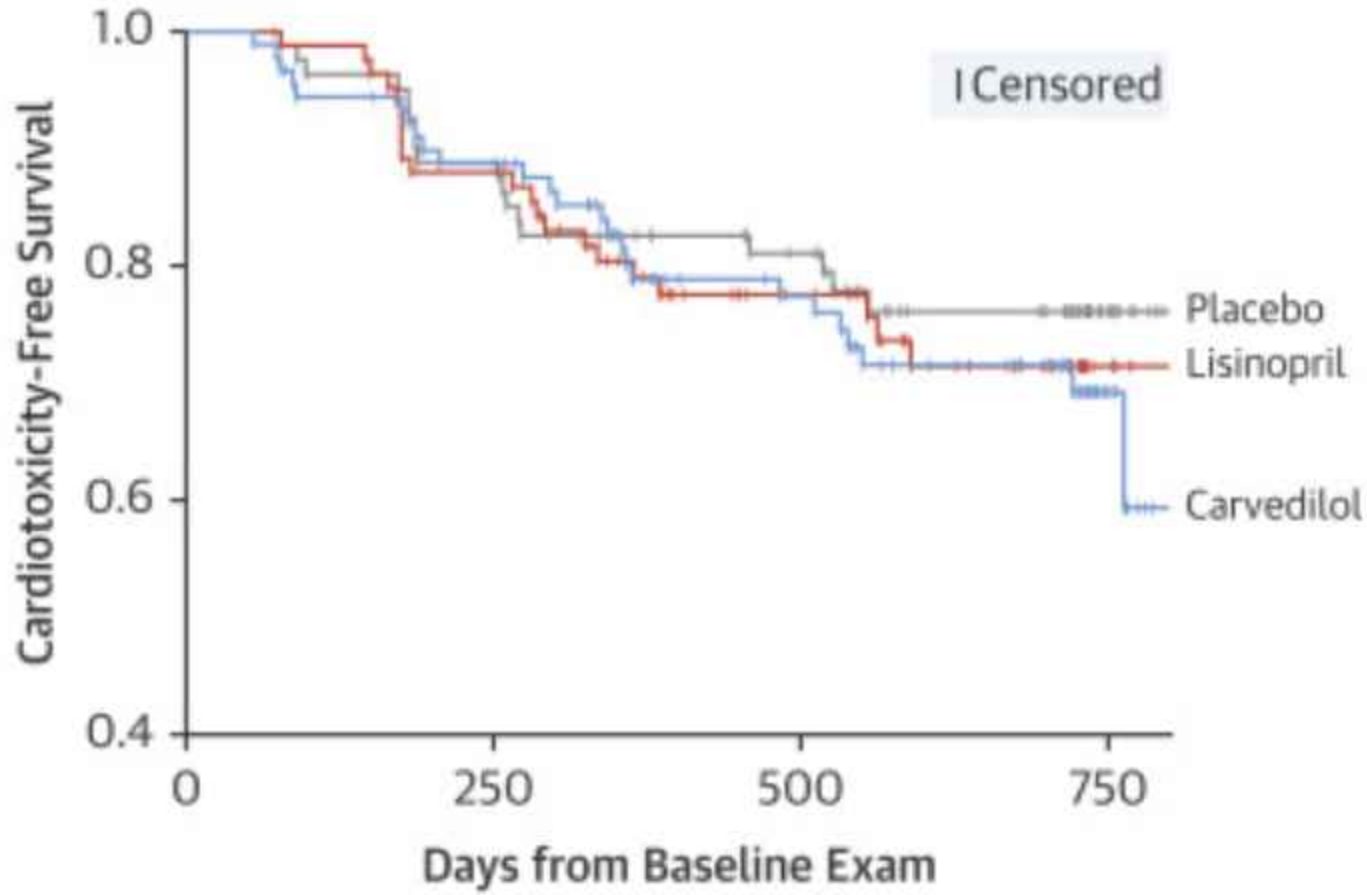
N Engl J Med 2001; 344:783-92.

CV toxicity monitoring in patients receiving trastuzumab



European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361

Prevention of CRTCD in trastuzumab-treated patients

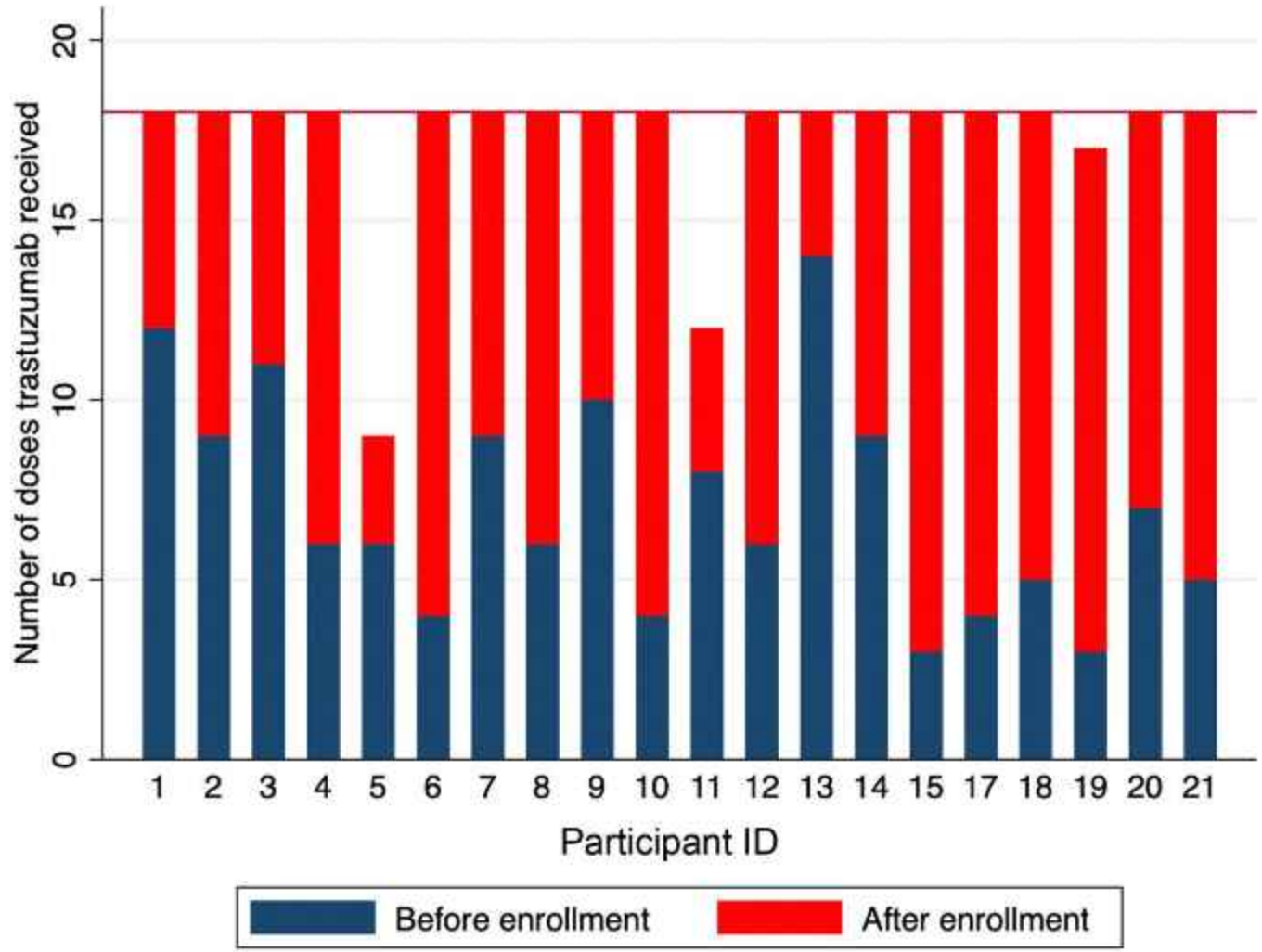


No. at Risk:				
Carvedilol	90	78	54	11
Lisinopril	84	72	46	7
Placebo	83	71	53	13

Guglin et al. J Am Coll Cardiol. 2019;73(22):2859-68

SCHOLAR

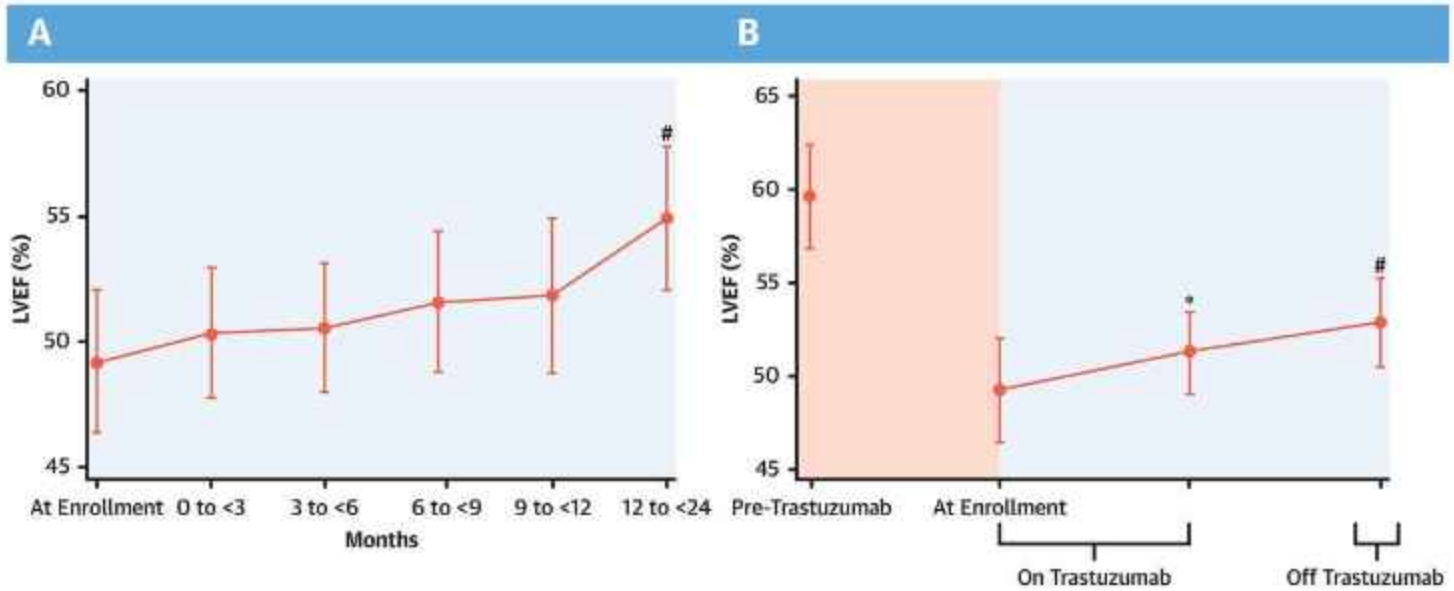
- 20 patients with mild LV dysfunction during trastuzumab
- Aggressively treated with ACE and beta blockers, trastuzumab continued unless LVEF <40% with symptomatic HF or LVEF <35%



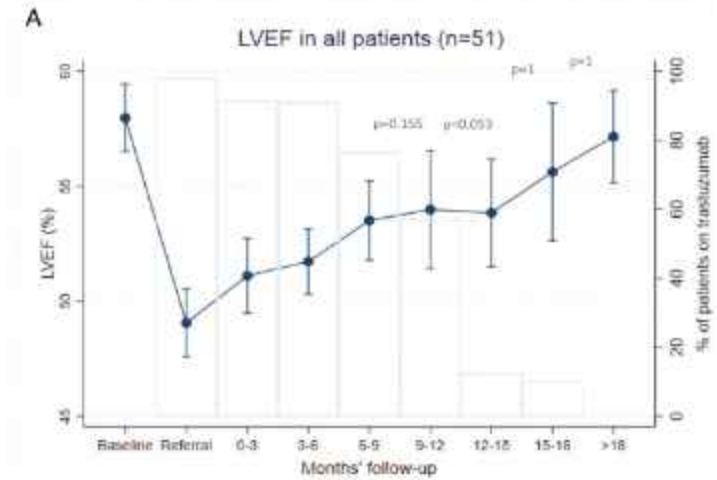
Darryl P. Leong et al. J Am Coll Cardiol CardioOnc 2019;1:1-10

Improvement in LVEF despite continued trastuzumab

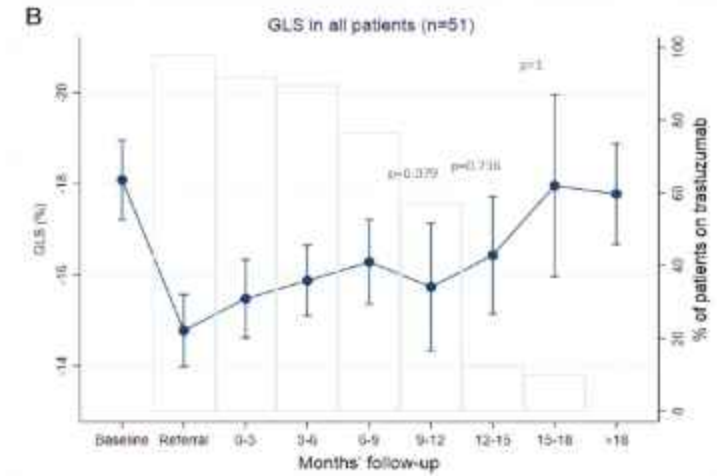
CENTRAL ILLUSTRATION: Continuing Trastuzumab Despite Mild Cardiotoxicity: LVEF Over Time



Leong, D.P. et al. J Am Coll Cardiol. 2019;1(1):1-10.



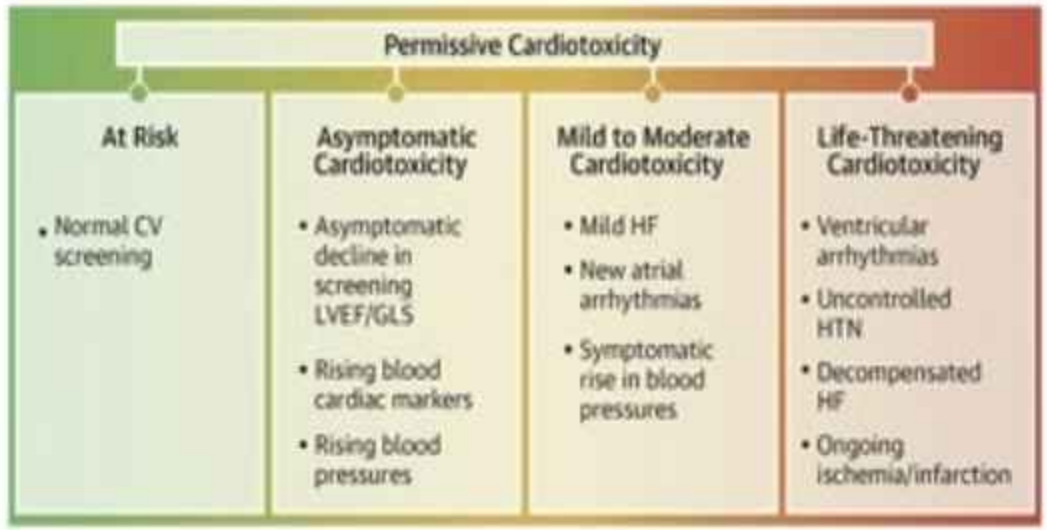
Months until recovered LV	0-3	3-6	6-9	9-12	12-15	15-18	>18	No. with LVEF<54 at final follow-up
Total No.: 51	10	11	8	2	1	3	5	11



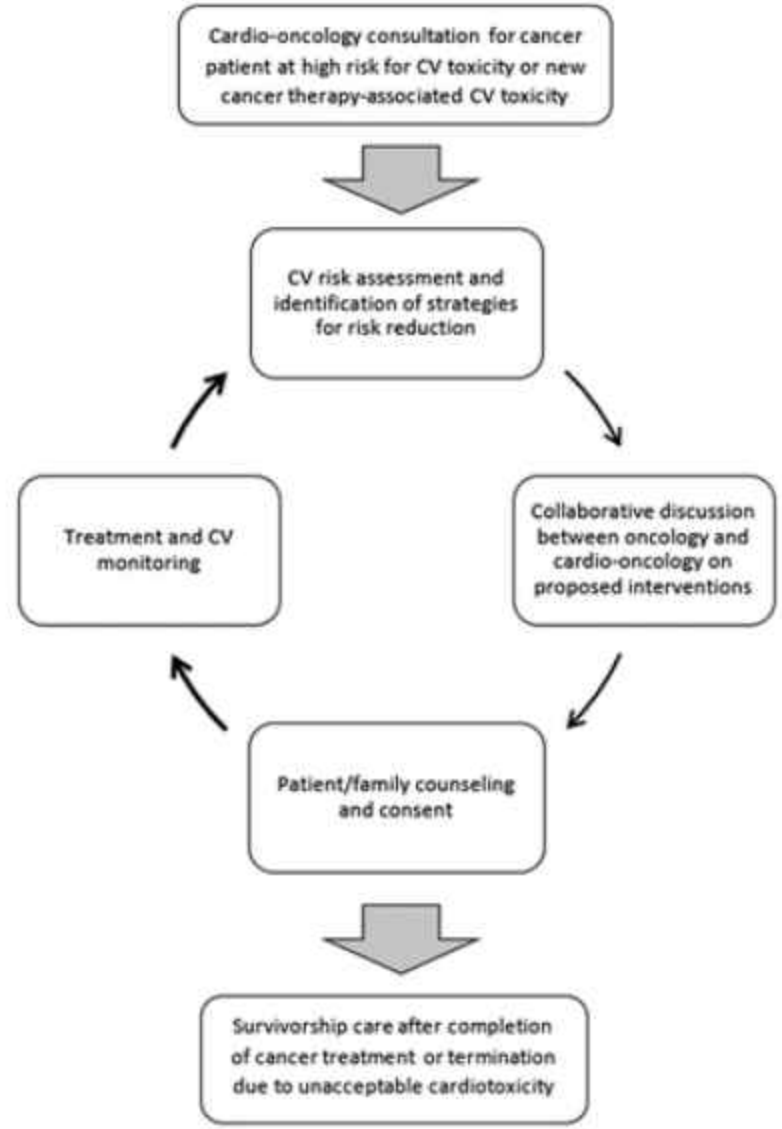
Months until recovered GLS	0-3	3-6	6-9	9-12	12-15	15-18	>18	No. with GLS>-17 at baseline at final follow-up
Total No.: 51	18	13	4	1	1	0	3	11

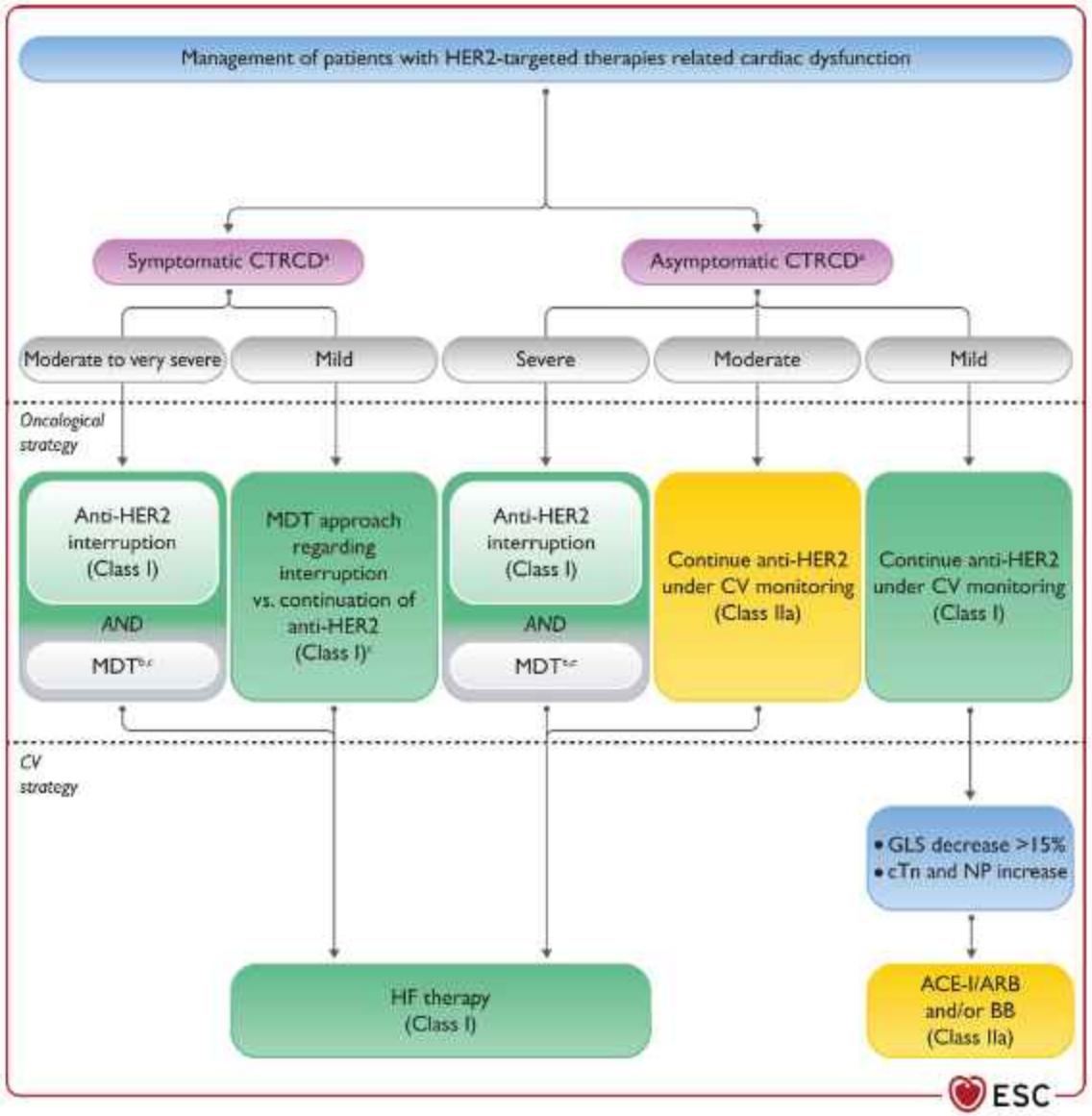
The Oncologist, Volume 28, Issue 9, September 2023, e712–e722

Permissive Cardiotoxicity



Porter C, et al. J Am Coll Cardiol CardioOnc. 2022;4(3):302-312.





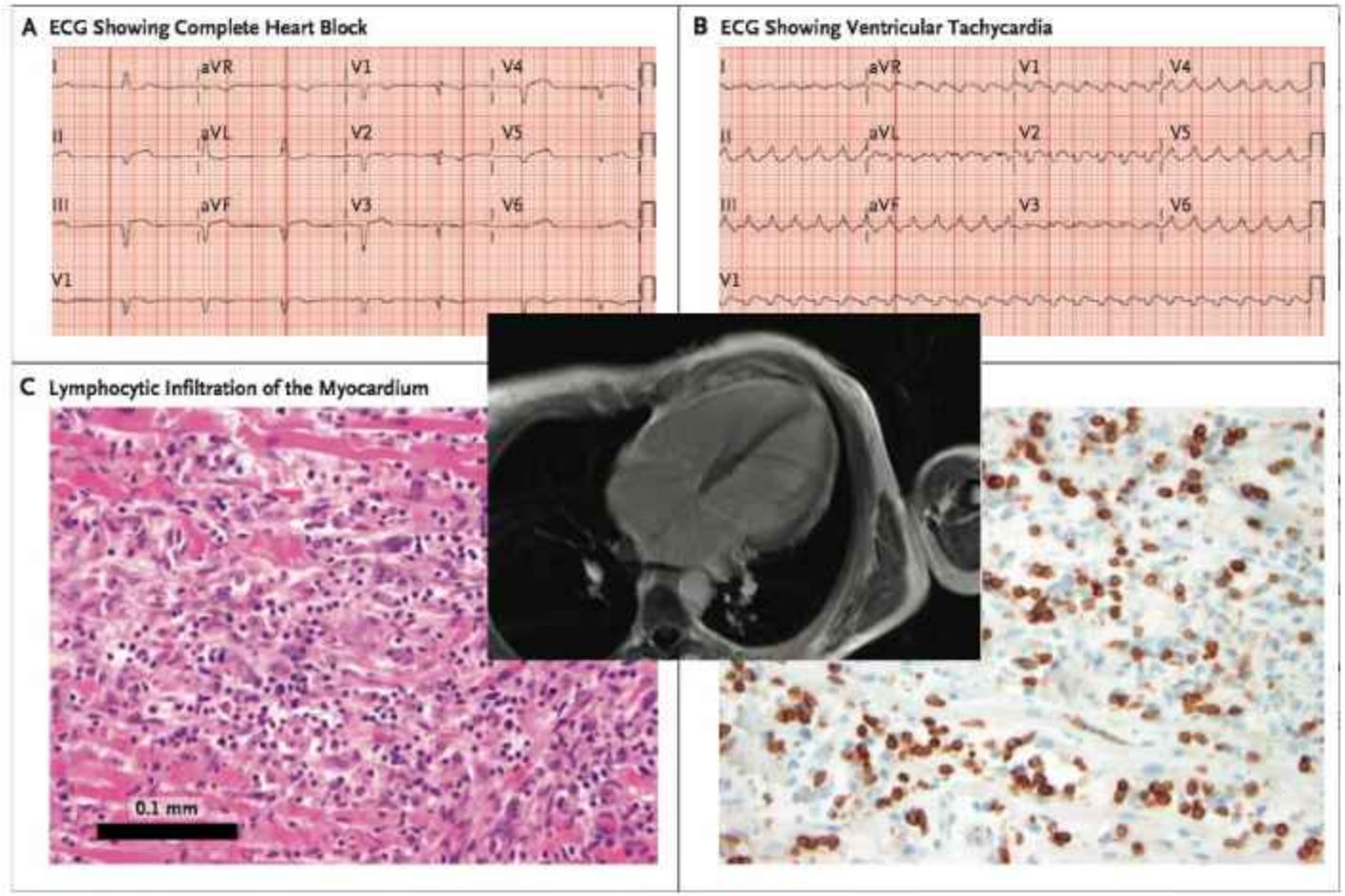
Management of HER2-targeted therapy-related cardiac dysfunction

European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361

Immune checkpoint inhibitors

Myocarditis with checkpoint inhibition

- Incidence 1.14% in small multicentre registry
  - 54% had no other immune AE
- May be fulminant and fatal
- Frequent conduction system abnormalities
- More common in patients receiving combination therapy



J Am Coll Cardiol 2018;71:1755–64
N Engl J Med 2016;375:1749-55
Ann Intern Med. September 2017. doi:10.7326/L17-0396.

Management of myocarditis

1. No randomized data to guide management; ATRIUM in progress!
2. Stopping ICI and hi-dose steroids are standard therapy

	No MACE (n = 19)	MACE (n = 16)	p Value
Initial steroid dose, mg	160.0 (0.0–1,000.0)	72.5 (0.0–1,000.0)	0.055
Initial steroid dose/body weight, (mg/kg)	2.06 (0.00–20.20)	0.84 (0.00–14.40)	0.041
Time from admission to steroid administration, h	18.3 ± 12.8	27.2 ± 17.5	0.12

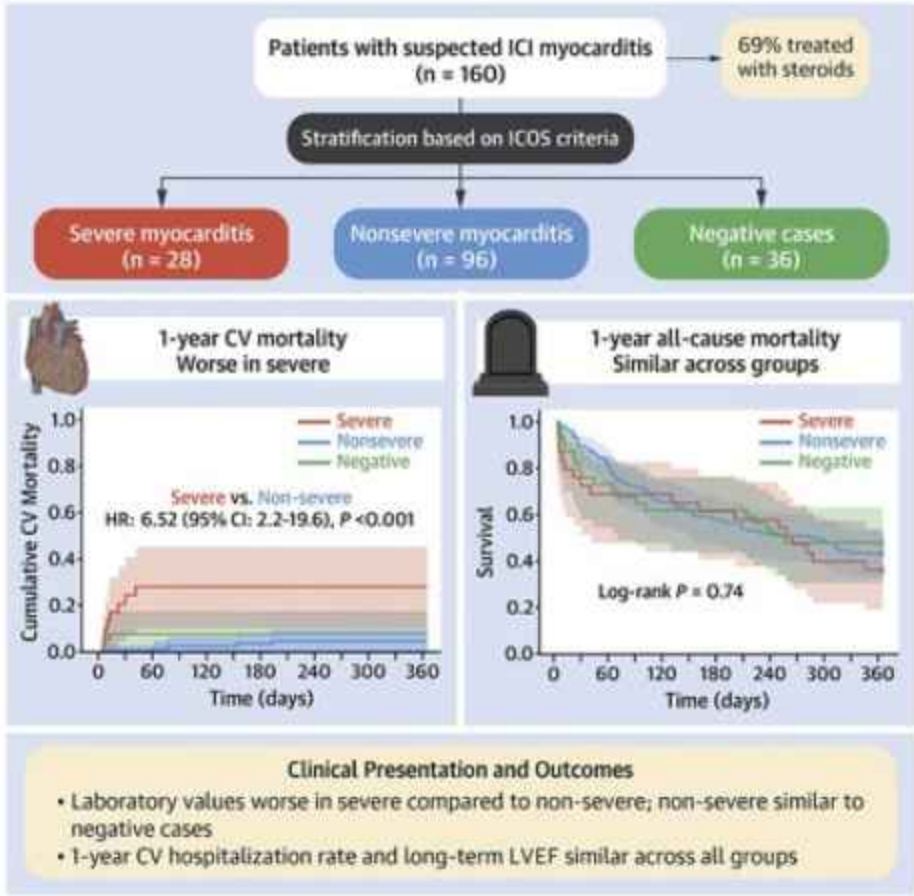
3. If steroid-responsive, wean slowly, monitor troponin
4. If fulminant or steroid resistant, add second-line immunosuppression
5. Decision to rechallenge complex and requires multi-stakeholder input!

Continue steroids and taper over at least 4 to 6 weeks (longer if needed for clinical and biomarker response)
Consider initiation of other immune-modulators if patient is not responding clinically to steroids

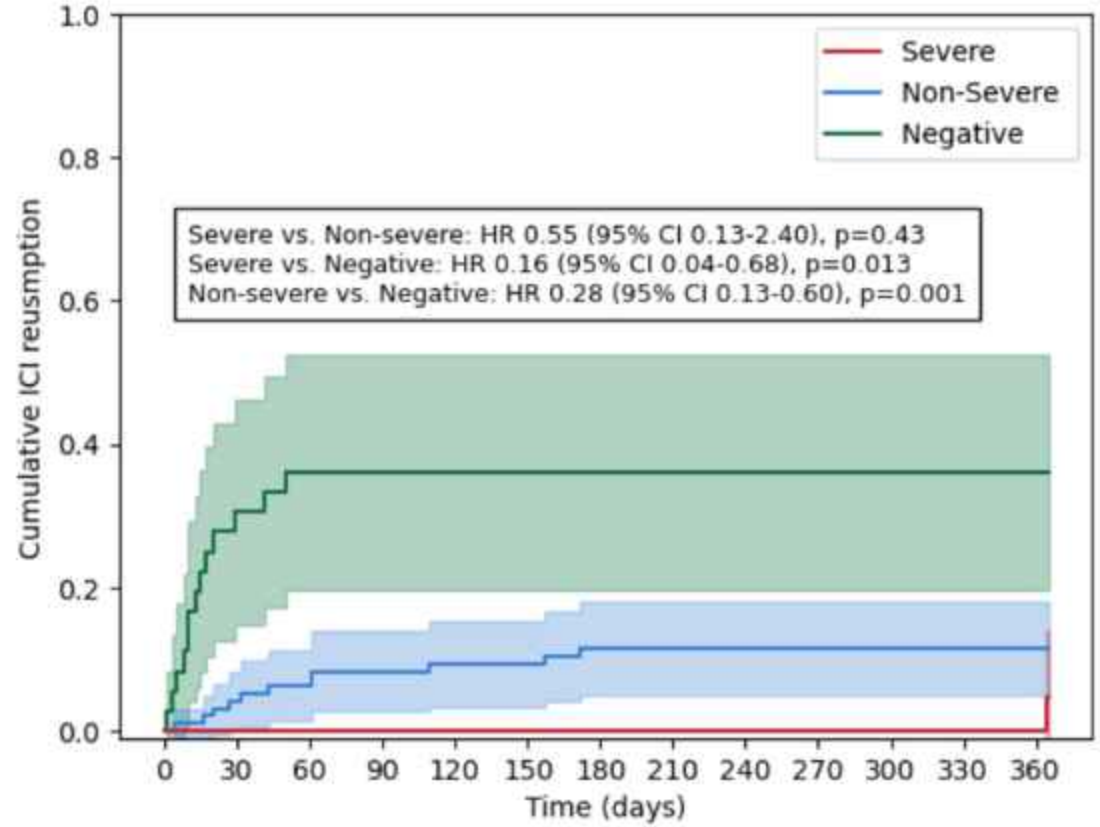
- Infliximab
- Intravenous Immunoglobulin
- Plasmapheresis
- Abatacept
- Alemtuzumab
- Anti- thymocyte globulin
- Mycophenolate

Wang, D. Y. et al. JAMA Oncol 4, 1721–1728 (2018).
J Am Heart Assoc. 2020;9:e013757.
Eur Heart J, ehac244, https://doi.org/10.1093/eurheartj/ehac244

CENTRAL ILLUSTRATION: 1-Year Outcomes in Patients With Severe vs Nonsevere Immune Checkpoint Inhibitor Myocarditis

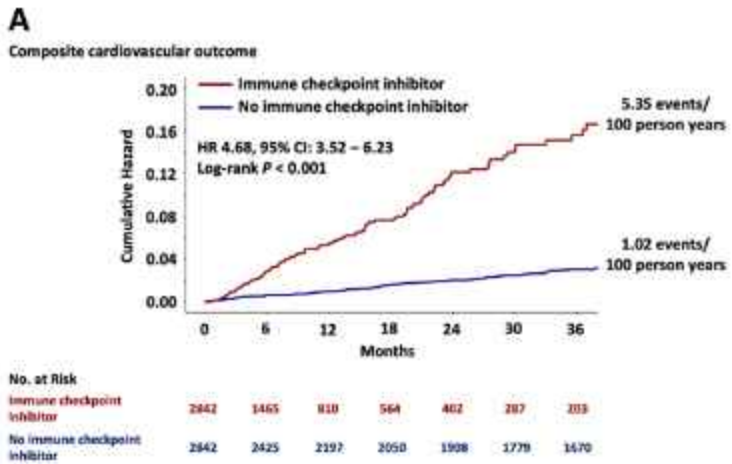


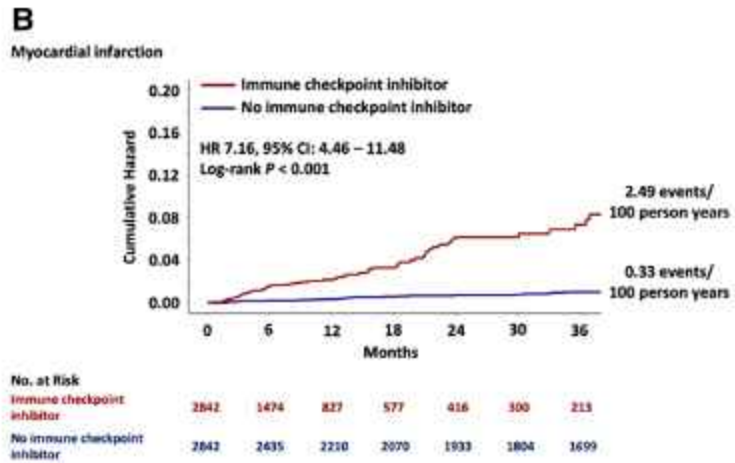
Itzhaki Ben Zadok O, et al. J Am Coll Cardiol CardioOnc. 2023;5(6):732-744.

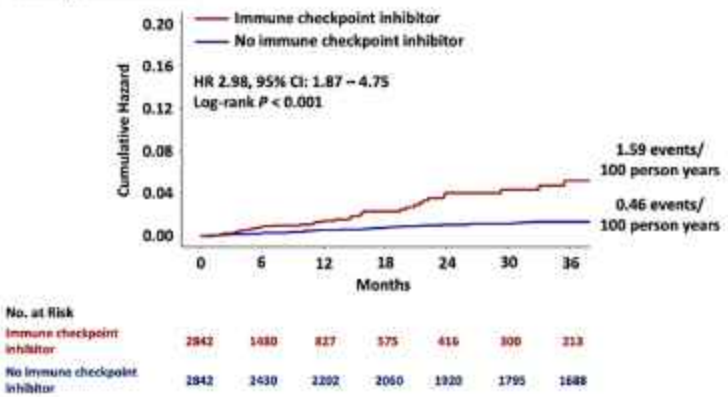


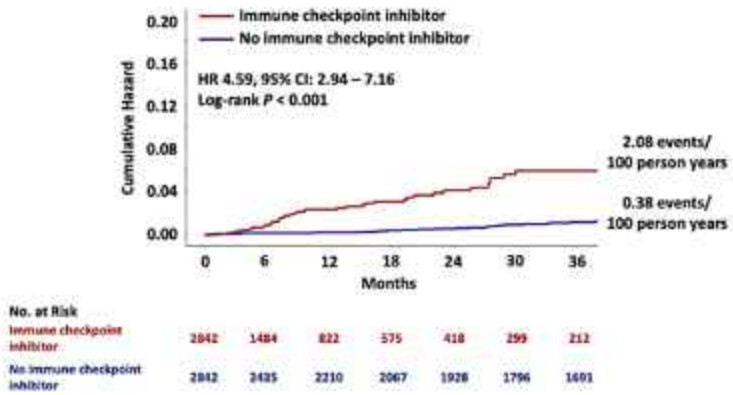
Number of events							
Severe	0	0	0	0	0	0	1
Non-severe	0	6	9	11	11	11	11
Negative	0	13	13	13	13	13	13

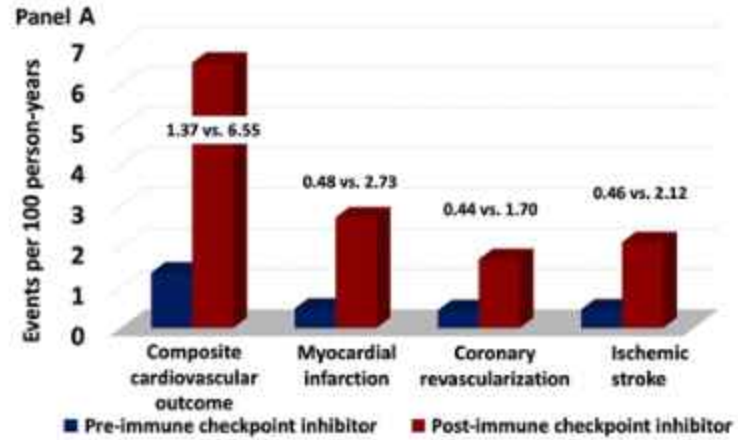
Atherosclerotic CVD Events Associated with ICI

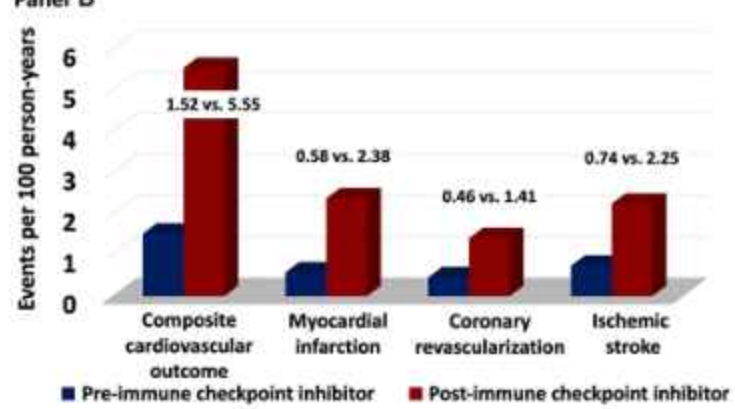












Circulation Volume 142, Issue 24,15 December 2020

Conclusions

- Contemporary studies have not shown compelling benefit of cardioprotection with neurohormonal blockade in adults receiving anthracyclines
- Ongoing studies will hope to identify high-risk patients most likely to benefit from cardioprotection and identify novel agents for cardioprotection
- Adult survivors of childhood cancer require long-term surveillance for development of HF (and other CVD)
- A strategy of permissive cardiotoxicity can allow completion of trastuzumab (and other cardiotoxic therapies) in a majority of patients, with good cardiac outcomes
- Contemporary ICI myocarditis outcomes may be less bleak than previously reported, but long-term vigilance for ASCVD is important in survivors

Thank you

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2023 ESC Guidelines for the Management of Cardiomyopathies

Lisa Anderson,
Chair, British Society for Heart Failure
MD, FRCP

Declarations of Interest:
Speaker fees: Vifor, Alnylam. Advisory boards: Alnylam, Pharmacosmos. Research support: Pfizer

ESC

HFA
Heart Failure
Association

Disclosures

	Dr. Lisa Anderson
Any direct financial payments including receipt of honoraria	Alnylam, Abbott
Membership on advisory boards or speakers' bureaus	Pharmacosmos
Funded grants or clinical trials	Pfizer
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	No disclosures

Learning Objectives

1. Review the key aspects in the evaluation and management of cardiomyopathies
2. Describe the evidence to support new therapies for hypertrophic cardiomyopathy

ESC Recommendation Classes and Evidence Levels

Classes of recommendations

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

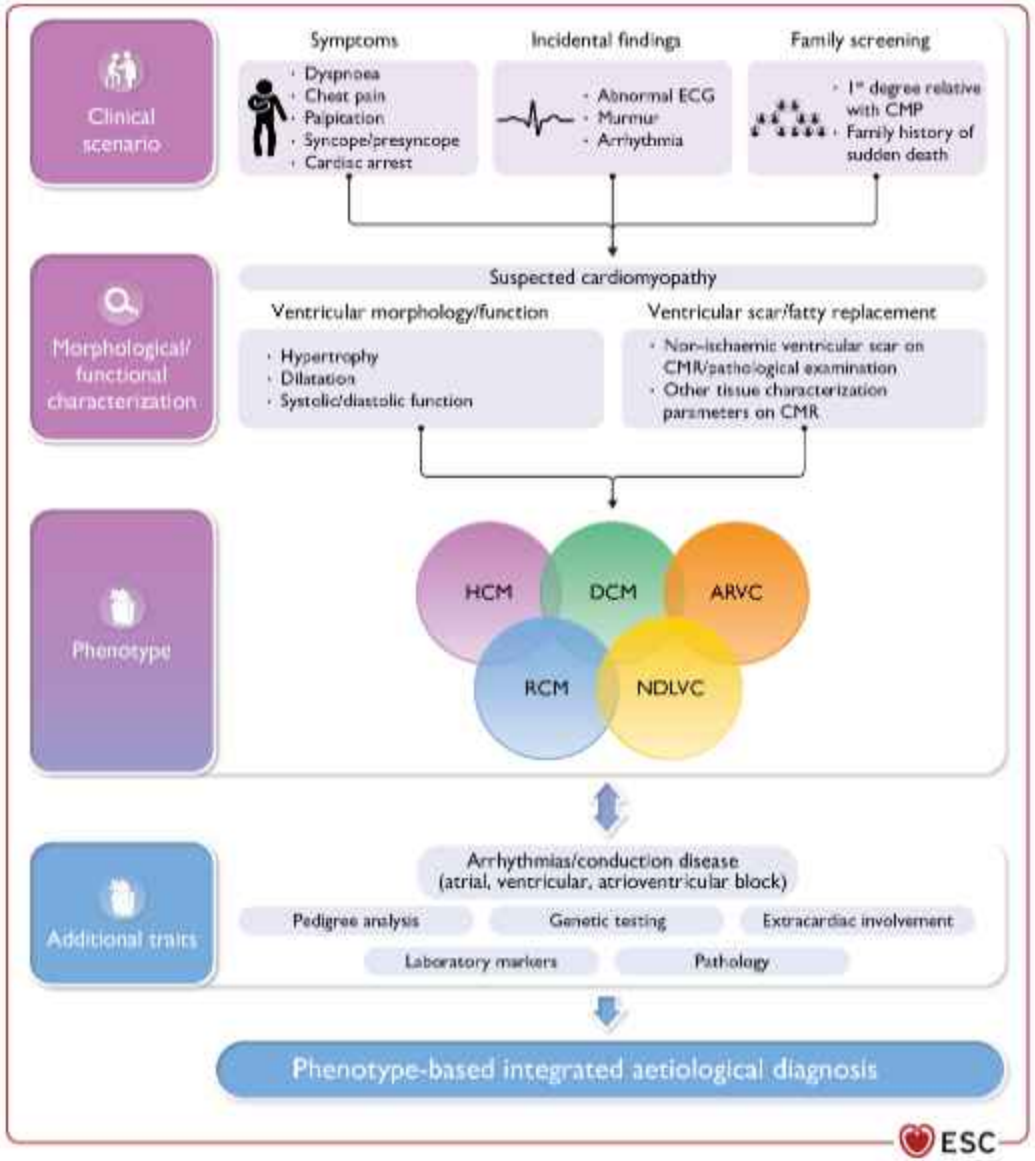
Recommendations for the provision of service of multidisciplinary cardiomyopathy teams

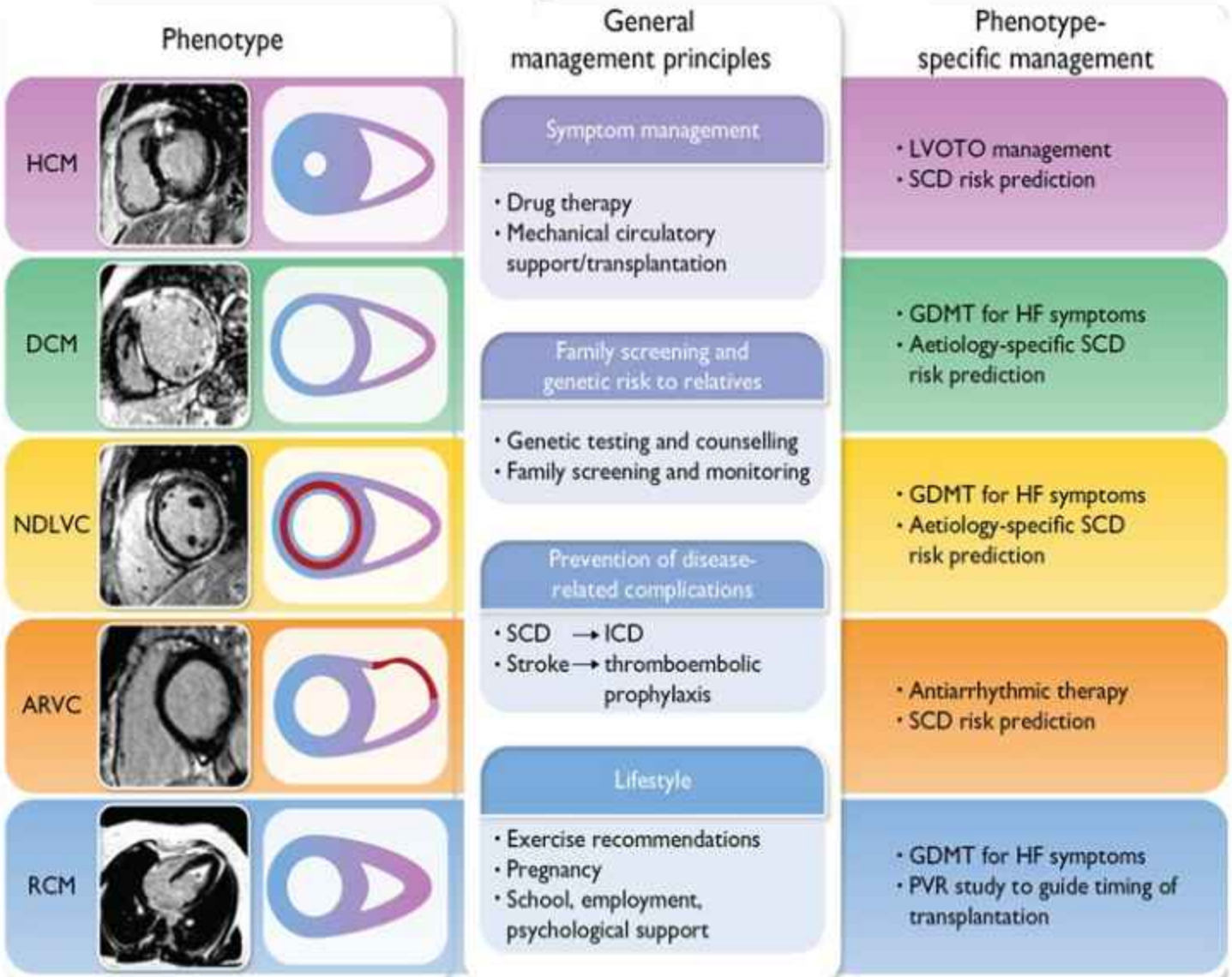
Recommendations	Class	Level
It is recommended that all patients with cardiomyopathy and their relatives have access to multidisciplinary teams with expertise in the diagnosis and management of cardiomyopathies.	I	C
Timely and adequate preparation for transition of care from paediatric to adult services, including joint consultations, is recommended in all adolescents with cardiomyopathy.	I	C

Recommendations for diagnostic work-up in cardiomyopathies

Recommendations	Class	Level
It is recommended that all patients with suspected or established cardiomyopathy undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging.	I	C
It is recommended that all patients with suspected cardiomyopathy undergo evaluation of family history and that a three- to four-generation family tree is created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance pattern, and identify at-risk relatives.	I	C

Phenotype-based diagnosis and management

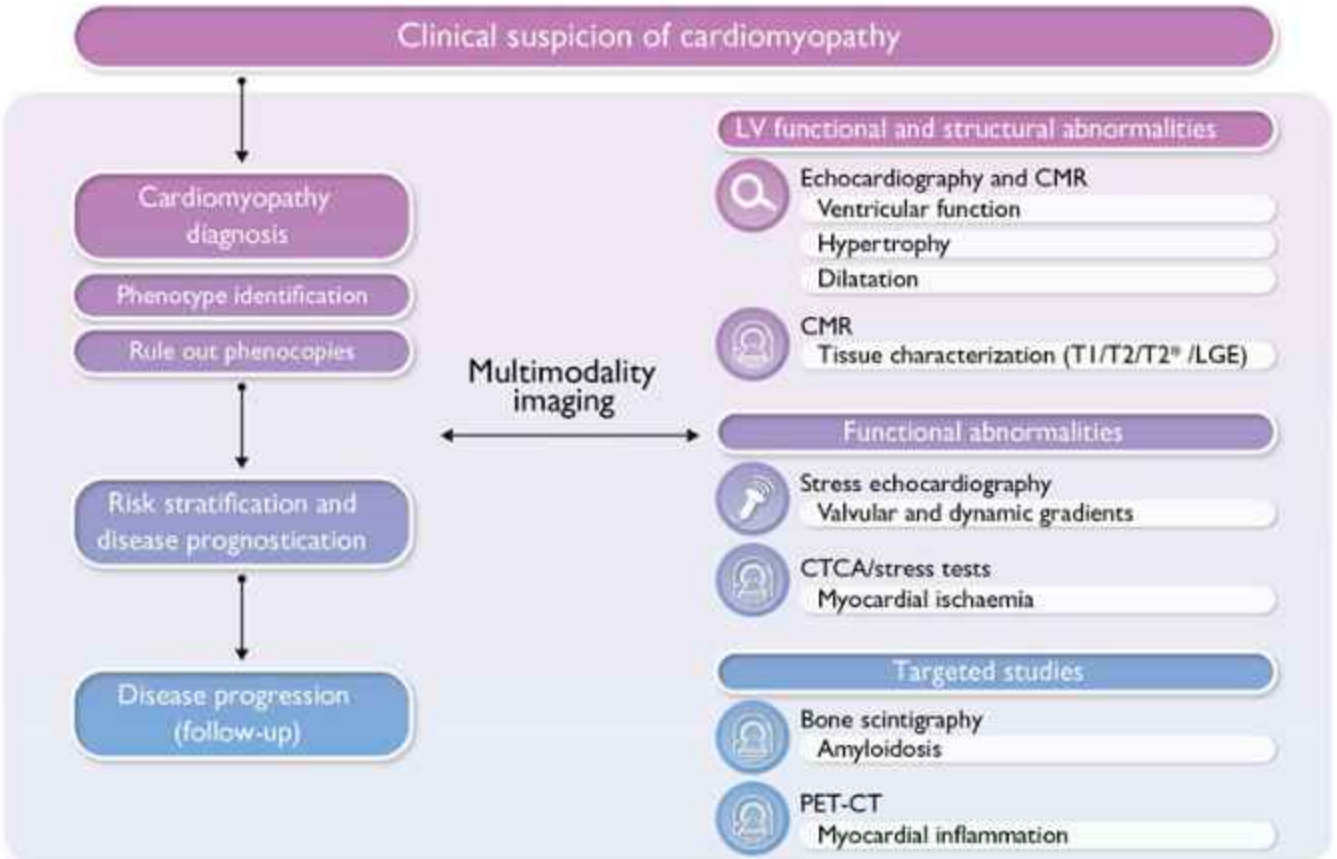


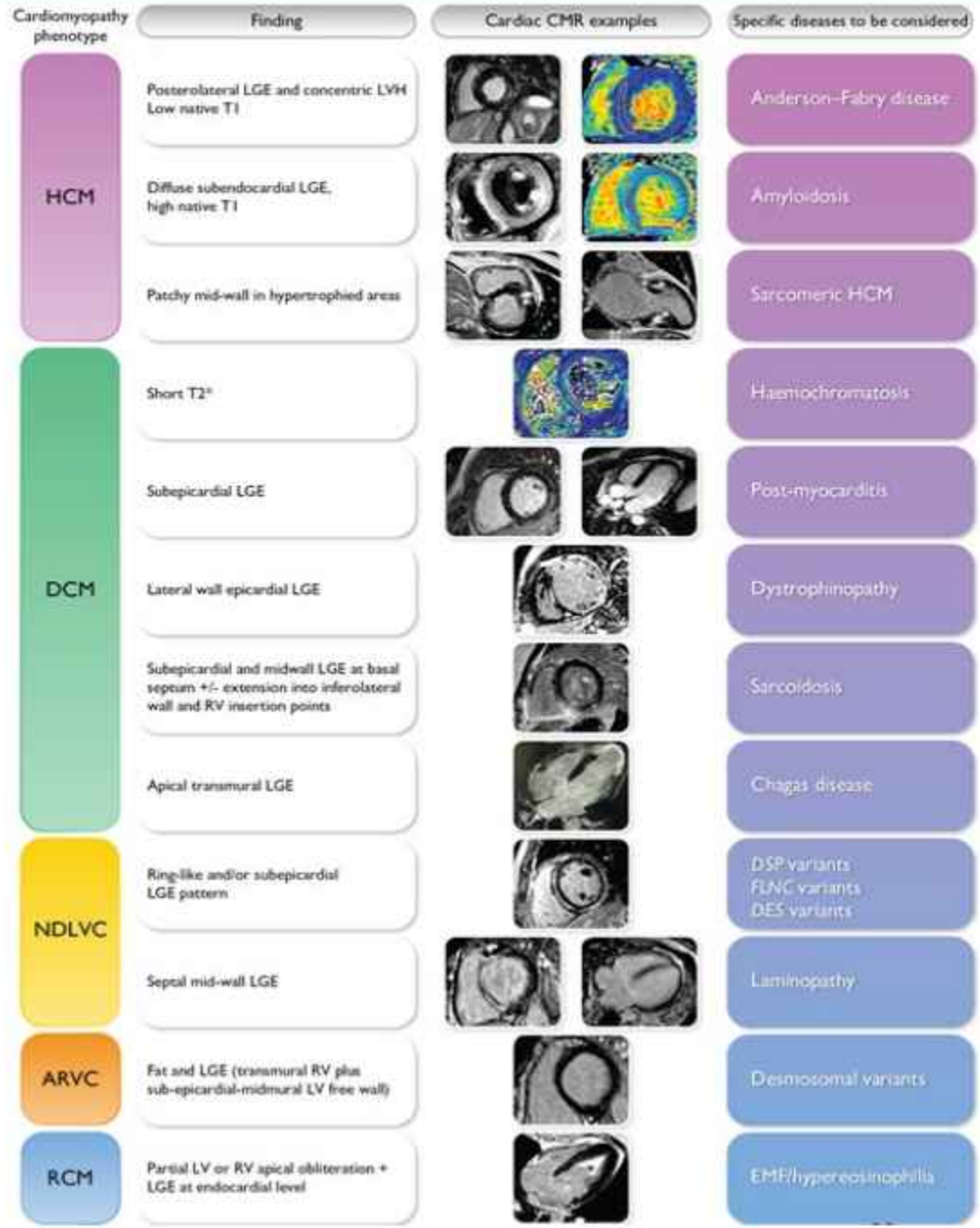


IN: Non-dilated LV Cardiomyopathy

OUT: Takotsubo, LV Non-Compaction

Multimodality Imaging in the Cardiomyopathies





Recommendations for cardiac magnetic resonance indication in patients with cardiomyopathy

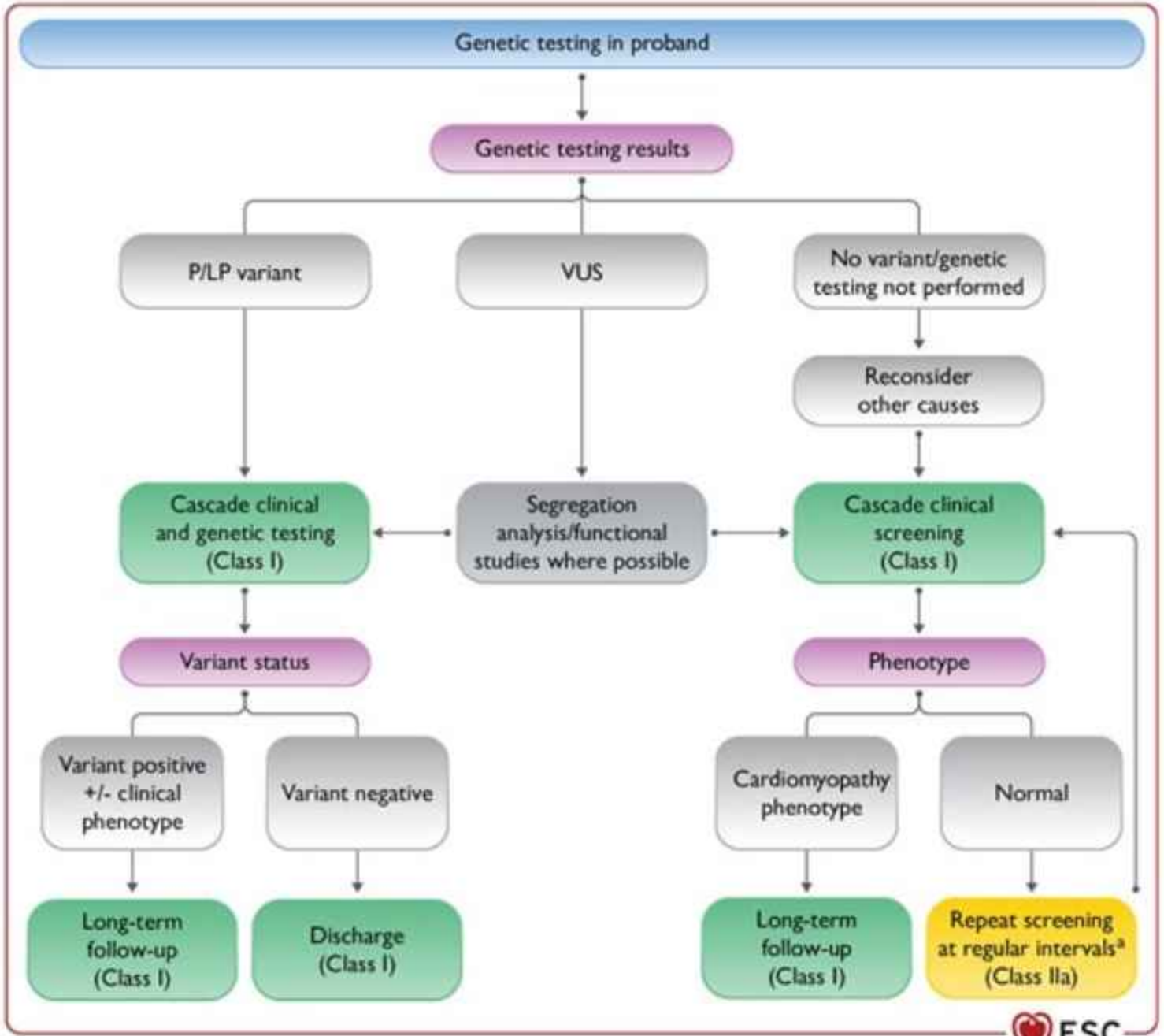
Recommendations	Class	Level
Contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation.	I	B
Contrast-enhanced CMR should be considered in patients with cardiomyopathy during follow-up to monitor disease progression and aid risk stratification and management.	IIa	C
Contrast-enhanced CMR should be considered for the serial follow-up and assessment of therapeutic response in patients with cardiac amyloidosis, Anderson–Fabry disease, sarcoidosis, inflammatory cardiomyopathies, and haemochromatosis with cardiac involvement.	IIa	C
In families with cardiomyopathy in which a disease-causing variant has been identified, contrast-enhanced CMR should be considered in genotype-positive/phenotype-negative family members to aid diagnosis and detect early disease.	IIa	B
In cases of familial cardiomyopathy without a genetic diagnosis, contrast-enhanced CMR may be considered in phenotype-negative family members to aid diagnosis and detect early disease.	IIb	C

2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Genetic Testing: Benefits

- Patient:
  - For diagnosis
  - For prognosis
  - Therapy decisions (ICD)
  - …. Therapies in the future?
- Relatives:
  - Absence of variant allows discharge from further follow-up
- Reproductive advice and management
  - Patients - risk to future generations
  - Parents – risk of recurrence
  - For pre-conception Counselling

Algorithm or family screening and follow-up of family members



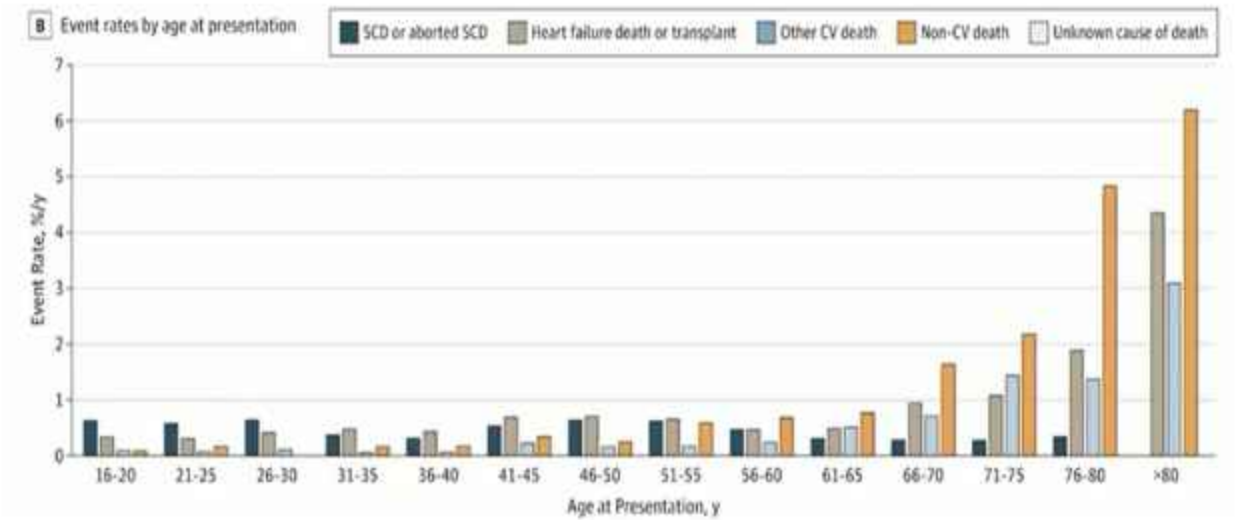
Recommendations for genetic counselling and testing in cardiomyopathies

Recommendations	Class	Level
Genetic counselling		
Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.	I	B
It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.	I	B
Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.	I	B
Family members		
It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).	I	B

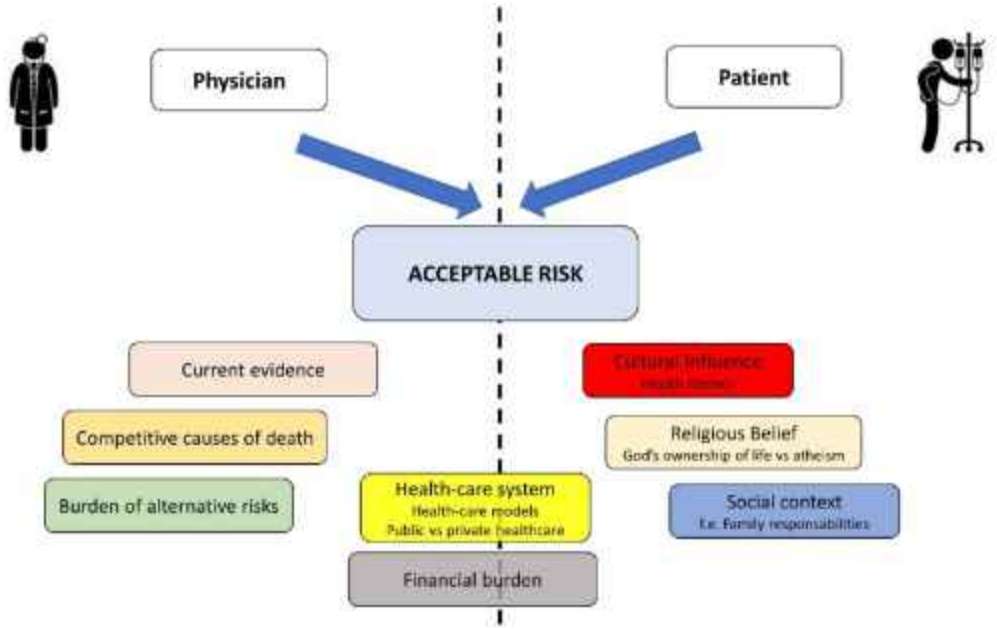
Recommendations for genetic counselling and testing in cardiomyopathies

Recommendations	Class	Level
Genetic counselling (continued)		
If prenatal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.	I	C
A discussion about reproductive genetic testing options with an appropriately trained healthcare professional should be considered for all families with a genetic diagnosis.	IIa	C
Index patients		
Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.	I	B
Index patients (continued)		
Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at *post mortem* if a genetic diagnosis would facilitate management of surviving relatives.	I	C

ICDs: Shared Decision Making



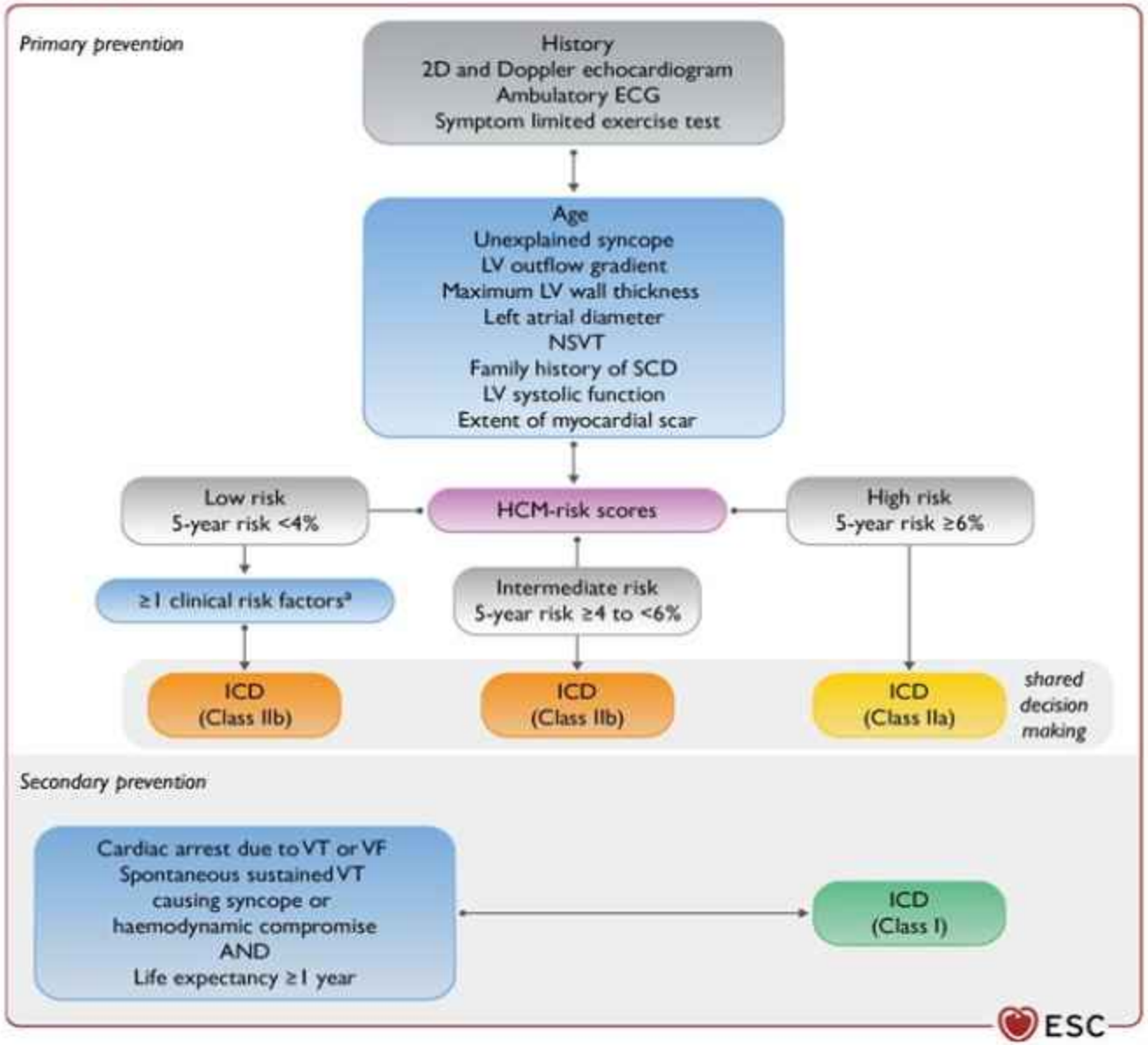
Lorenzini JAMA Card 2020

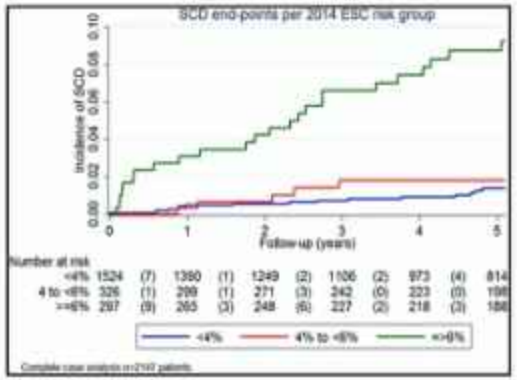


Finocchiaro Heart Failure Reviews 2022

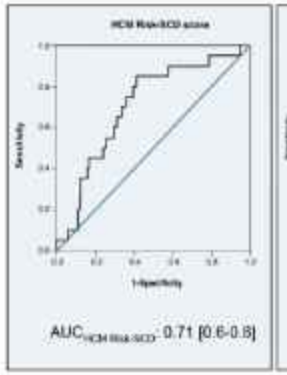
Primary prevention ICD in Cardiomyopathies

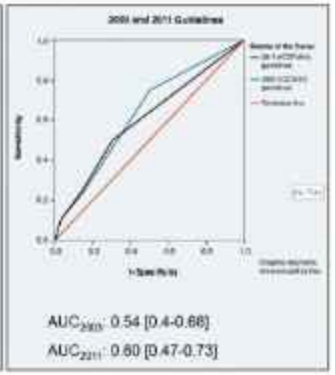
HCM





O'Mahoney Circ 2018



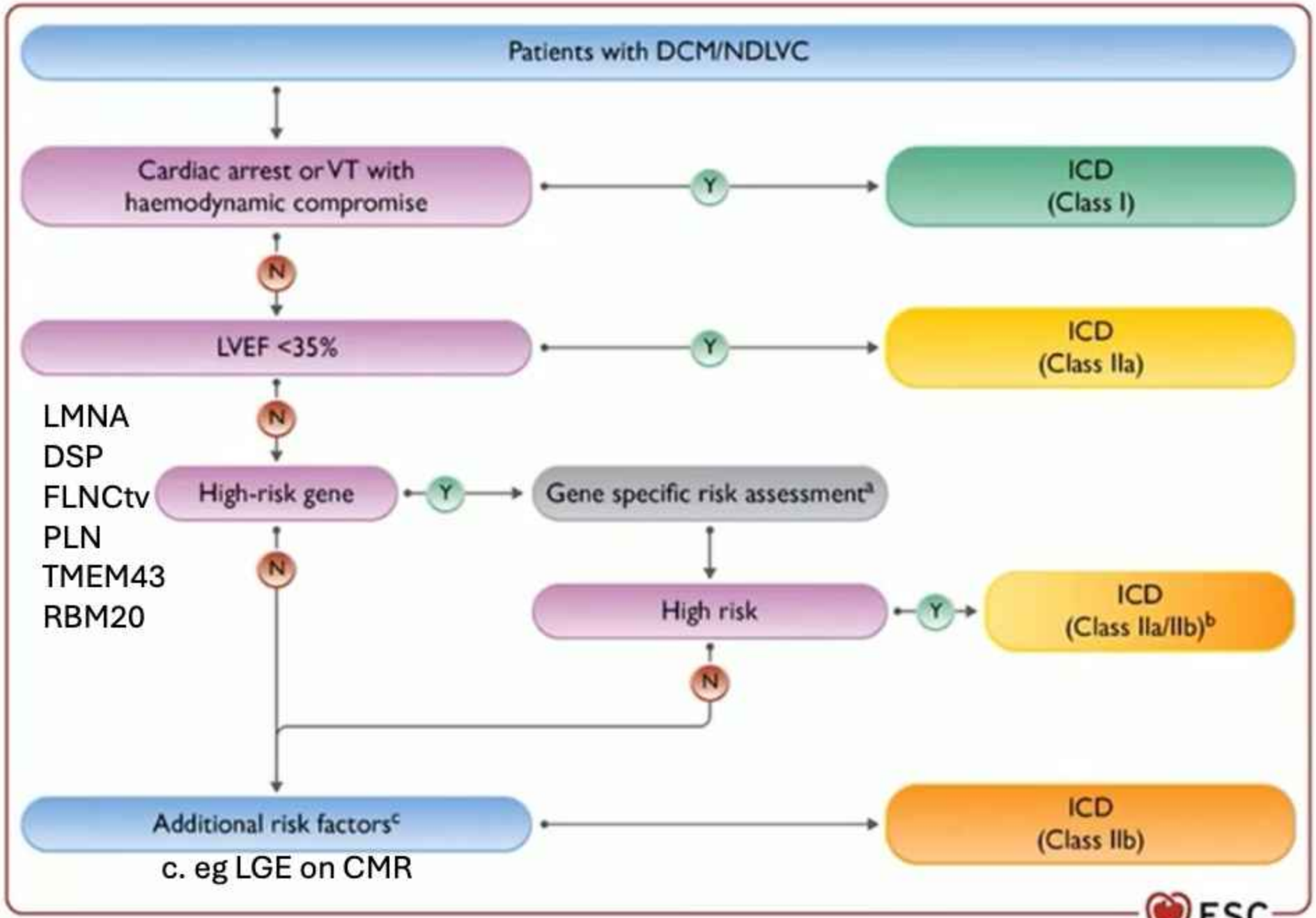


Vriesendorp Circ Ar EP 2015

ARVC

Primary prevention		
High-risk features should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.	IIa	B
The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.	IIa	B

ICD in DCM and NDLVC



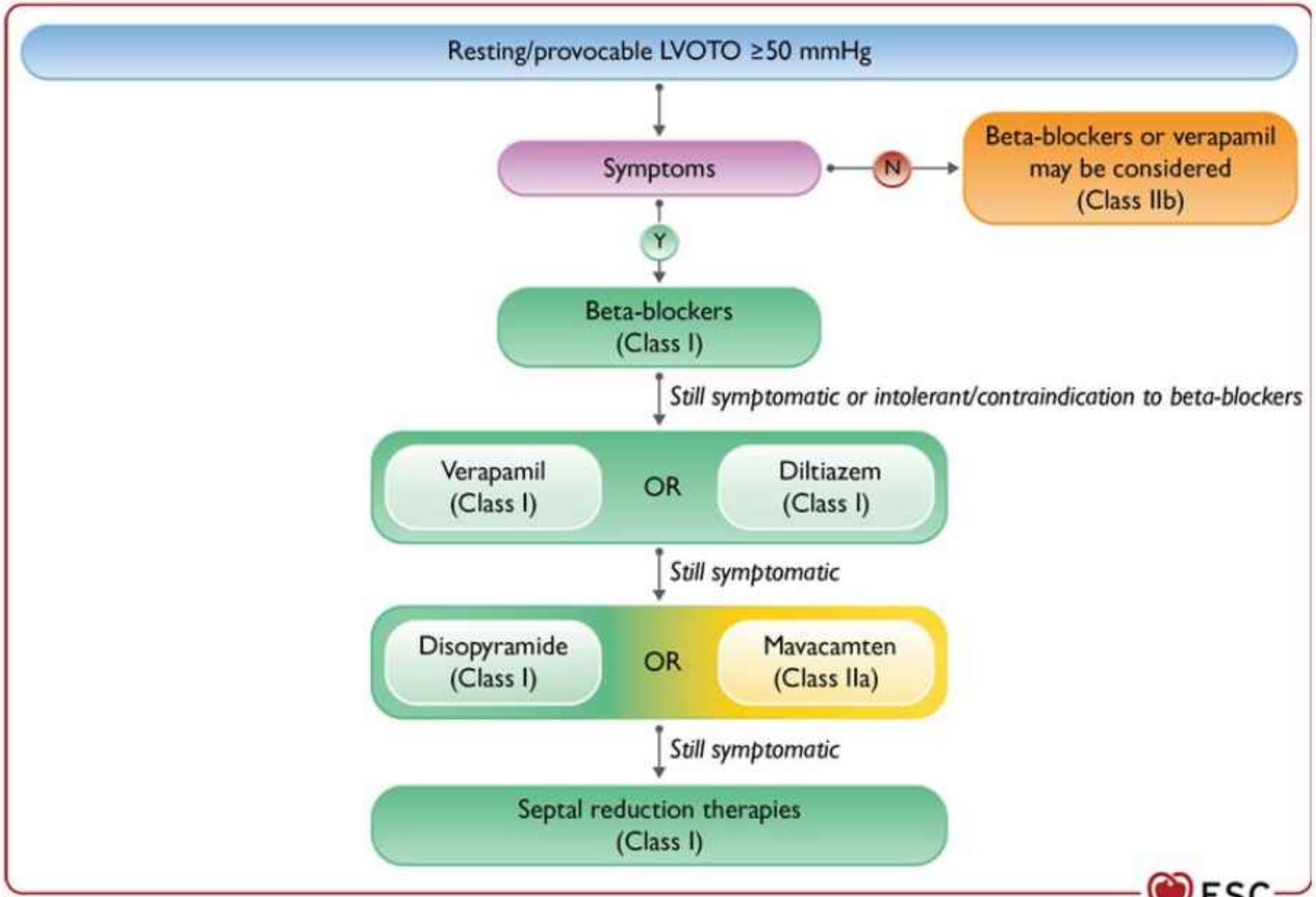
Recommendations for management of atrial fibrillation and atrial flutter in patients with cardiomyopathy

Recommendations	Class	Level
Control of symptoms and heart failure		
Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III AAD to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy.	I	B
Atrial fibrillation catheter ablation is recommended to reverse LV dysfunction in AF patients with cardiomyopathy when tachycardia-induced component is highly probable, independent of their symptom status.	I	B
Maintenance of sinus rhythm rather than rate control should be considered at an early stage for patients with a cardiomyopathy and AF without major risk factors for recurrence, regardless of symptoms.	IIa	C
Atrial fibrillation catheter ablation should be considered as first-line rhythm control therapy to improve symptoms in selected patients with cardiomyopathy and paroxysmal or persistent AF without major risk factors for recurrences as an alternative to class I or III AADs, considering patient choice, benefit, and risk.	IIa	C

Recommendations for exercise in the cardiomyopathies

Recommendations	Class	Level
All cardiomyopathies		
Regular low- to moderate-intensity exercise is recommended in all able individuals with cardiomyopathy.	I	C
An individualized risk assessment for exercise prescription is recommended in all patients with cardiomyopathy.	I	C
HCM		
High-intensity exercise and competitive sport should be considered in genotype-positive/phenotype-negative individuals who seek to do so.	IIa	C
High-intensity exercise and competitive sport may be considered in asymptomatic low-risk individuals with morphologically mild hypertrophic cardiomyopathy in the absence of resting or inducible left ventricular outflow obstruction and exercise-induced complex ventricular arrhythmias.	IIb	B
HCM (continued)		
High-intensity exercise, including competitive sport, is not recommended in high-risk individuals and in individuals with left ventricular outflow tract obstruction and exercise-induced complex ventricular arrhythmias.	III	C
ARVC		
Avoidance of high-intensity exercise, including competitive sport, may be considered in genotype-positive/phenotype-negative individuals in families with ARVC.	IIb	C
Moderate- and/or high-intensity exercise, including competitive sport, is not recommended in individuals with ARVC.	III	B
DCM and NDLVC		
Moderate- and high-intensity exercise should be considered in individuals who are gene positive and phenotype-negative (with the exception of pathogenic variants in *LMNA* and *TMEM43*) who seek to do so.	IIa	C
High-intensity exercise and competitive sport may be considered in a select group of asymptomatic and optimally treated individuals with a left ventricular ejection fraction ≥50% in the absence of exercise-induced complex arrhythmias.	IIb	C
Moderate-intensity exercise may be considered in asymptomatic and optimally treated individuals with a left ventricular ejection fraction of 40–49% in the absence of exercise-induced complex arrhythmias.	IIb	C
High-intensity exercise, including competitive sport, is not recommended in symptomatic individuals, those with a left ventricular ejection fraction ≤40%, exercise-induced arrhythmias or pathogenic variants in *LMNA* or *TMEM43*.	III	C

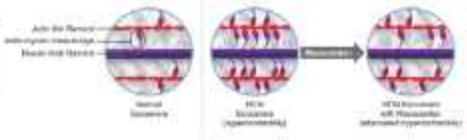
Management of LVOT Obstruction



Medical Management of LVOT Obstruction

Recommendations	Class	Level
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked LVOTO.	I	B
Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provoked LVOTO who are intolerant or have contraindications to beta-blockers.	I	B
Disopyramide, titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provoked LVOTO.	I	B
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provoked LVOTO.	IIa	A
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in symptomatic adult patients with resting or provoked LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/diltiazem, or disopyramide.	IIa	B

EXPLORER-HCM



Olivotto Lancet 2020

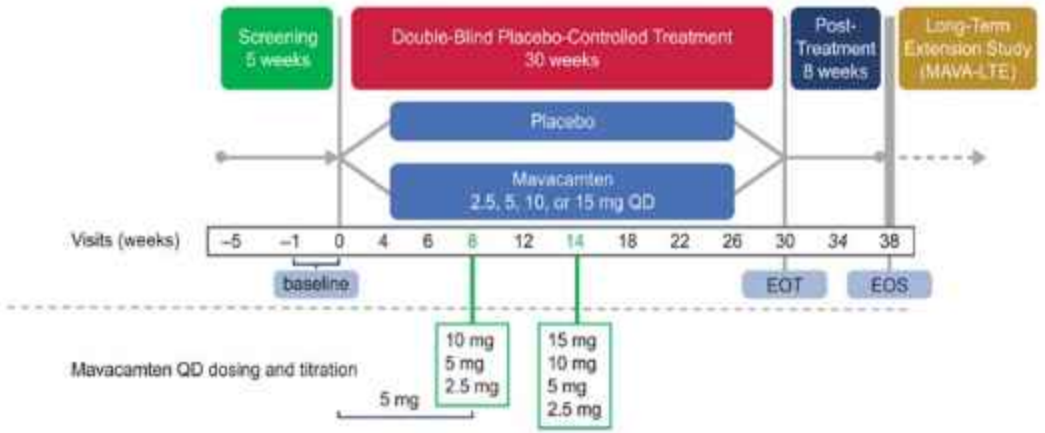
Phase 3 RCT: Mavacamten vs Placebo

Methods: N= 251, HCM, LVOT >50mmHg

mavacamten/placebo + BB/CCB – 30 weeks

PEP: ≥1·5 mL/kg/min ↑ (pVO2) + ≥1NYHA ↓

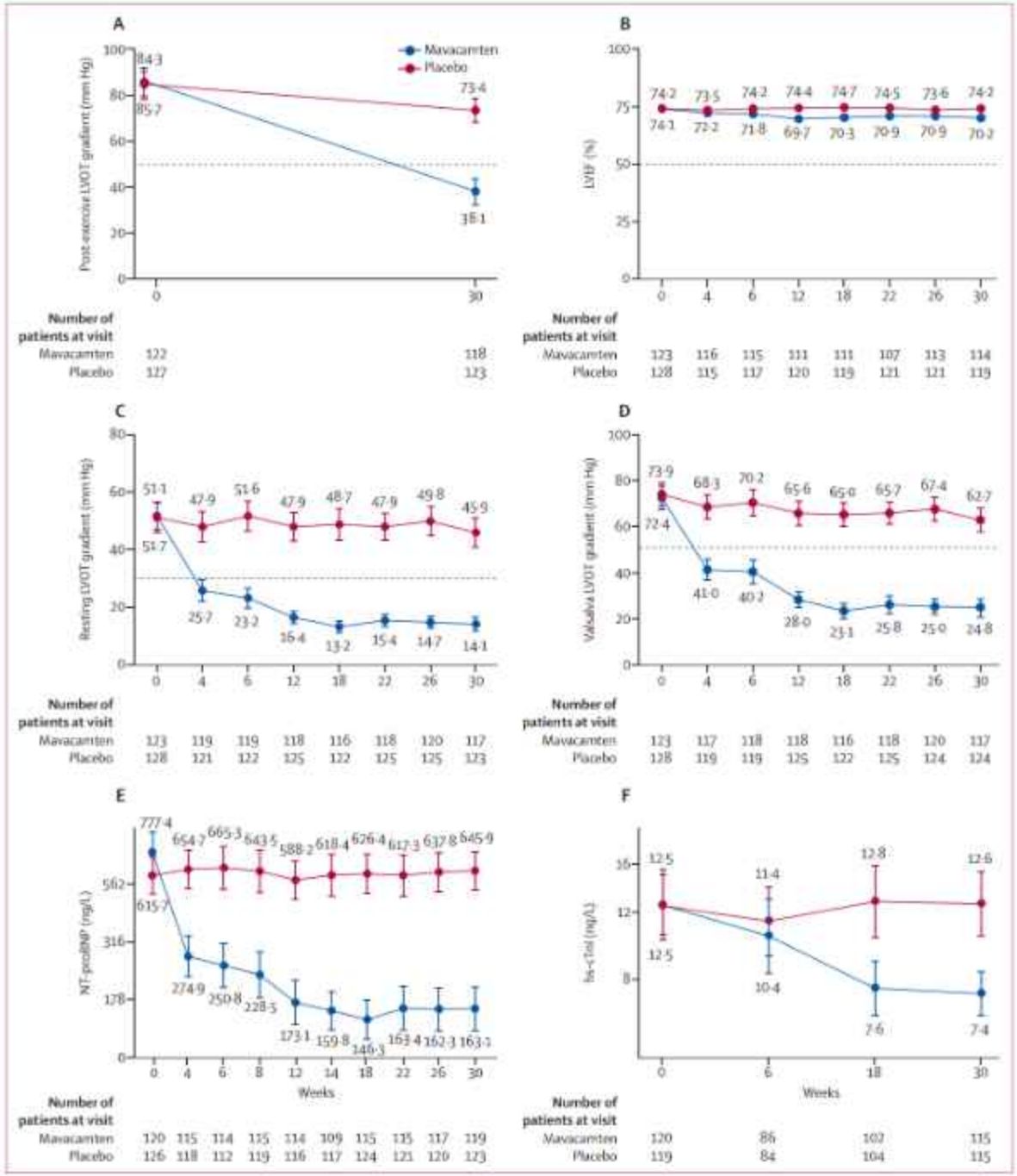
OR: ≥3·0 mL/kg/min pVO2 ↑ no NYHA ↓



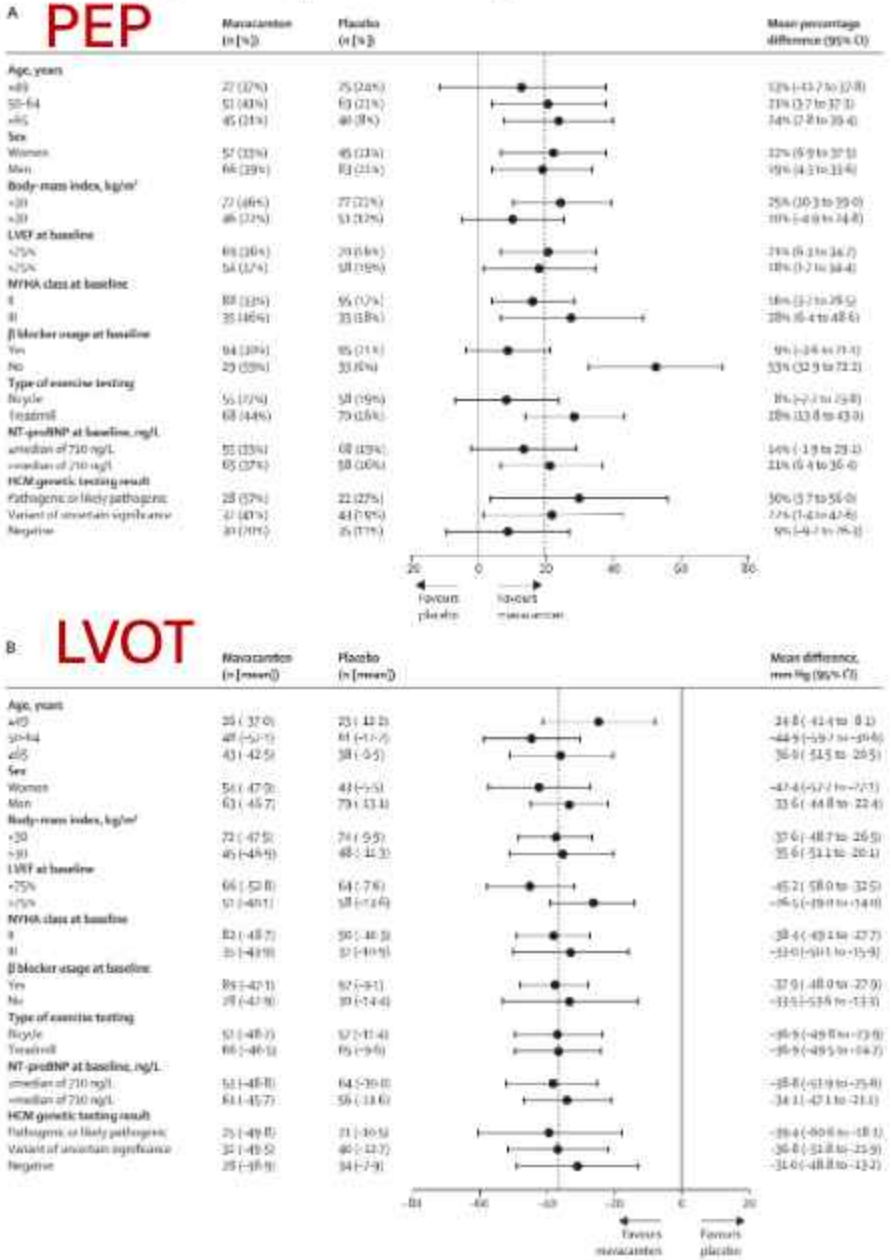
37% on mavacamten vs 17% on placebo met PEP p=0.0005

Post exercise gradient reduction = 36mmHg, p<0.0001

Greater increase VO2m p=0.0006 and KCCQ, p<0.0001



Subgroup Analysis: Outcomes



	Mavacamten group (n=123)	Placebo group (n=128)
Patients with ≥1 treatment-emergent adverse event	108 (88%)	101 (79%)
Total number of serious adverse events	11	20
Patients with ≥1 serious adverse event	10 (8%)	11 (9%)
Atrial fibrillation	2 (2%)	4 (3%)
Syncope	2 (2%)	1 (1%)
Stress cardiomyopathy	2 (2%)	0
Sudden death	0	1 (1%)
Transient ischaemic attack	0	1 (1%)
Cardiac failure congestive	0	1 (1%)
Diverticulitis	1 (1%)	0
Viral gastroenteritis	0	1 (1%)
Urinary tract infection	0	2 (2%)
Infection	1 (1%)	0
Rheumatoid arthritis	0	1 (1%)
Contusion	1 (1%)	0
Forearm fracture	1 (1%)	0
Dehydration	0	1 (1%)
Vocal cord polyp	0	1 (1%)
Cholesteatoma	0	1 (1%)
Prostate cancer	0	1 (1%)

Data are n (%).

Table 4: Summary of treatment-emergent adverse events and serious adverse events

Adverse Events

Left Ventricular Impairment
9 patients (7 mavacamten, 2 placebo)→ a transient ↓EF < 50%.

5 patients (3 mavacamten, 2 placebo) had protocol-driven temporary discontinuation for EF <50% during the 30-week trial
LVEF normalised in all, treatment resumed, completed study.

4 further patients on mavacamten →EF <50% at week 30 (end of study). LVEF recovered to baseline after the 8-week washout in 3/4

MAVA-LTE:
Open label, LTE, n=231, Both arms from Explorer started on mavacamten 5mg/d
Adjusted at 4, 8, 12, 24 weeks vs LVOT/EF
Interim analysis at 62 weeks – sustained LVOT, NYHA, NT-proBNP

Well tolerated but 3 HF and 2 ↓LVEF
Temp Rx discontinuation in 5.2% due to LVEF<50%, all recovered to >50%. 7 continued, 5 withdrew

Safety: regular monitoring for HF/LVSD – echo 4, 8, 12 weeks and 3m thereafter. Available in US through a Risk Evaluation and Mitigation Strategy (REMS program) – monitoring echos prior to Px.

ESC HFA 2024
Lisbon May 13.5.24

SEQUOIA-HCM study #HeartFailure2024

Aficamten for the treatment of symptomatic obstructive hypertrophic cardiomyopathy

Conclusion

Aficamten improves peak oxygen uptake (pVO2), improves limiting symptoms, and decreases left ventricular outflow tract (LVOT) pressure gradients in patients with obstructive hypertrophic cardiomyopathy (HCM).

Impact on clinical practice

Aficamten can reliably and safely eliminate LVOT obstruction in patients with obstructive HCM and was associated with substantial improvements in exercise capacity and symptoms.

Study objectives

The phase 3 SEQUOIA-HCM trial evaluated the efficacy and safety of aficamten versus placebo in adults with symptomatic obstructive HCM.

Study population

Symptomatic obstructive HCM

Reduced exercise capacity due to obstructive HCM

Where

14 countries in Asia, Europe and North America

101 sites

Who and what

282 patients

Randomised 1:1

aficamten

placebo

Follow-up: 24 weeks

Primary endpoint

Change in pVO2, assessed using cardio-pulmonary exercise testing, from baseline to week 24

↑ 1.8 ml/kg/min vs = 0.0 ml/kg/min

Least-squares mean difference between groups 1.7 ml/kg/min
95% CI 1.0, 2.4
p < 0.001

Secondary endpoints

≥1 NYHA class improvement at 24 weeks

Rate
58.5%
24.3%

p < 0.0001

Valsalva LVOT gradient <30 mmHg at 24 weeks

Rate
49.3%
3.6%

p < 0.0001

ESC

Summary

- Patient-centred guidelines, advocating holistic care
- Multiparametric assessment – 5 phenotypes –guiding management
- New phenotype = NDLVC
- CMR = class 1 indication for all at diagnosis
- Expanded genetic testing +++
- Risk assessment tools for ICD selection in HCM and ARVC
- Class 1 indications for AF ablation after failed/intolerant AAD (PAF/AF) or to reverse LV dysfunction if tachycardia element
- Exercise recommendations
- Class IIa indication for first in class myosin inhibitor, mavacamten for Rx of resting/ex LVOT gradient

2023 ESC Guidelines for the management of cardiomyopathies
(European Heart Journal; 2023 – doi:10.1093/eurheartj/ehad 194)

Lived Experience Commentary

Jackie Ratz

Disclosures

No disclosures

Q&A Period

All panelists

THANK YOU!

Please remember to complete the session evaluation

Next Up! Please proceed to the *Exhibit Hall (Samuel ABC) for a health break* and then to the *CAF' CONC' Theatre for a sponsored Theatre Symposium – Back to the Future: Inflammation in CVD*