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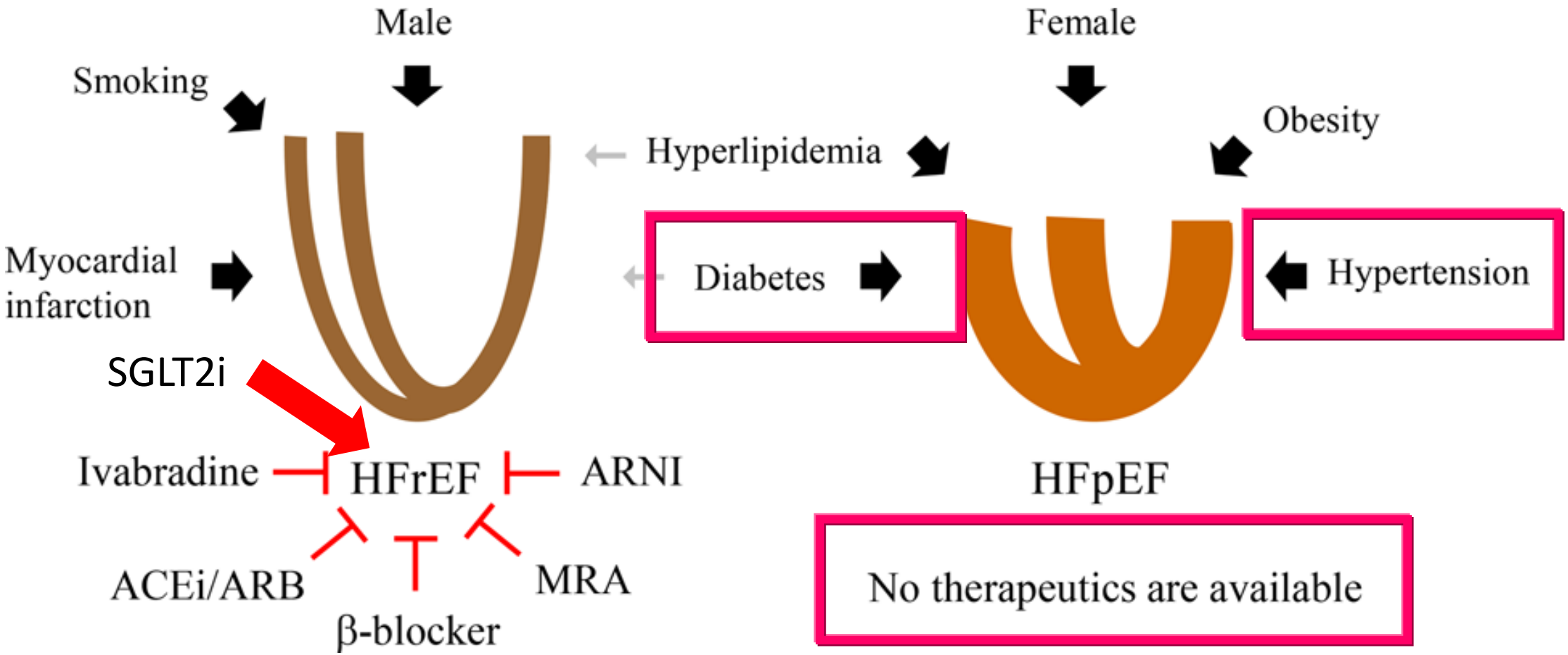
Heart Failure with Preserved Ejection Fraction

Keith C. Ferdinand, MD, FACC, FAHA, FASPC, FNLA
Gerald S. Berenson Endowed Chair in Preventative Cardiology
Professor of Medicine
Tulane University School of Medicine
New Orleans, LA

Heart Failure with Preserved Ejection Fraction: 2019



Yoon S, Eom GH. *Exp Mol Med*. 2019;51(12):1-9.

EMPEROR-Preserved in the Context of Other Studies

Trial	Treatment arms	Primary endpoint	Results	Risk reduction	P-value
EMPEROR-Preserved (2021)	Empaglifozin vs. placebo	CV death + HHF	0.79 (0.69 – 0.90)	-21%	0.0003
PARAGON-HF	Sacubitril/valsartan vs valsartan	CV death + total (first and recurrent) HHF	0.87 (0.75 – 1.01)	-13%	0.06
TOPCAT (2014)	Spironolactone vs placebo	CV death + HHF + aborted cardiac arrest	0.89 (0.77-1.04)	-11%	0.14
I-PRESERVE (2008)	Irbesartan vs placebo	All-cause mortality + CV Hospitalization	0.95 (0.86-1.05)	-5%	0.35
PEP-CHF (2006)	Perindopril vs placebo	All-cause mortality + HHF	0.92 (0.70-1.21)	-8%	0.5
CHARM-Preserved (2003)	Candesartan vs placebo	CV death + HF	0.86 (0.74-1.00)	-14%	0.05

Anker SD et al. *N Engl J Med*. 2021 Aug 27. doi: 10.1056/NEJMoa2107038. Epub ahead of print.

Which of the following has a statistically significant risk reduction in HFpEF?

a) Empagliflozin
b) Sacubitril/valsartan
c) Spironolactone
d) Irbesartan

Anker SD et al. *N Engl J Med*. 2021 Aug 27. doi: 10.1056/NEJMoa2107038. Epub ahead of print.

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

August 27, 2021

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

S.D. Anker, J. Butler, G. Filippatos, J.P. Ferreira, E. Bocchi, M. Böhm, H.-P. Brunner–La Rocca, D.-J. Choi, V. Chopra, E. Chuquiure-Valenzuela, N. Giannetti, J.E. Gomez-Mesa, S. Janssens, J.L. Januzzi, J.R. Gonzalez-Juanatey, B. Merkely, S.J. Nicholls, S.V. Perrone, I.L. Piña, P. Ponikowski, M. Senni, D. Sim, J. Spinar, I. Squire, S. Taddei, H. Tsutsui, S. Verma, D. Vinereanu, J. Zhang, P. Carson, C.S.P. Lam, N. Marx, C. Zeller, N. Sattar, W. Jamal, S. Schnaidt, J.M. Schnee, M. Brueckmann, S.J. Pocock, F. Zannad, and M. Packer, for the EMPEROR-Preserved Trial Investigators*

Anker SD, Butler J, Filippatos G, et al. *New England Journal of Medicine*. 2021. doi:10.1056/nejmoa2107038

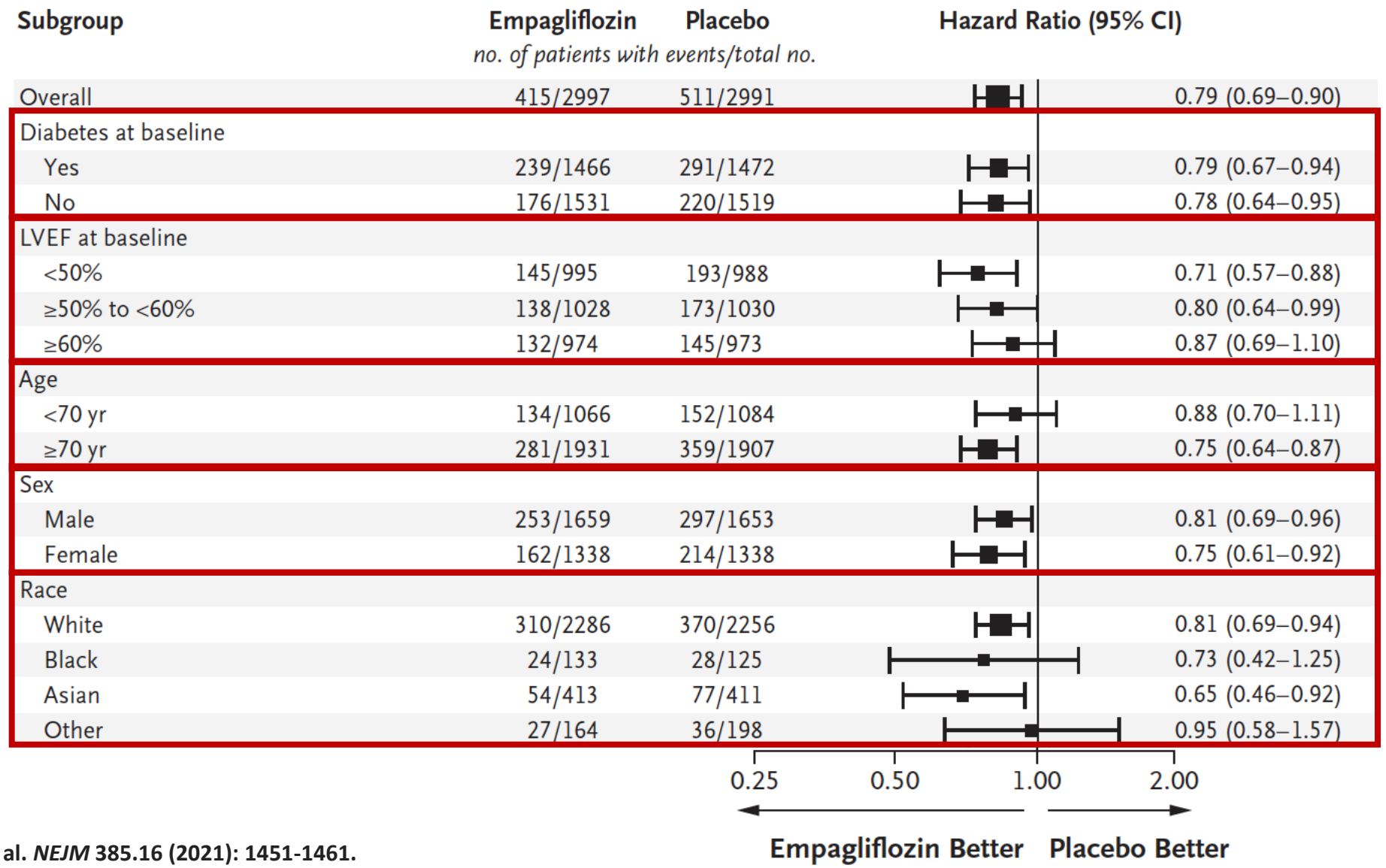
N=5988
class II–IV heart failure and ejection fraction >40%

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

Subgroup Analysis



Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

Baseline Medications

Type of medication – number (%)	Empaglifozin (n=2997)
Inhibitor of RAS with or without neprilysin inhibitor	2428 (81.0)
Sacubitril/valsartan	65 (2.2)
Mineralocorticoid receptor antagonist	1119 (37.3)
Beta blocker	2598 (86.7)
Digitalis glycosides	293 (9.8)

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

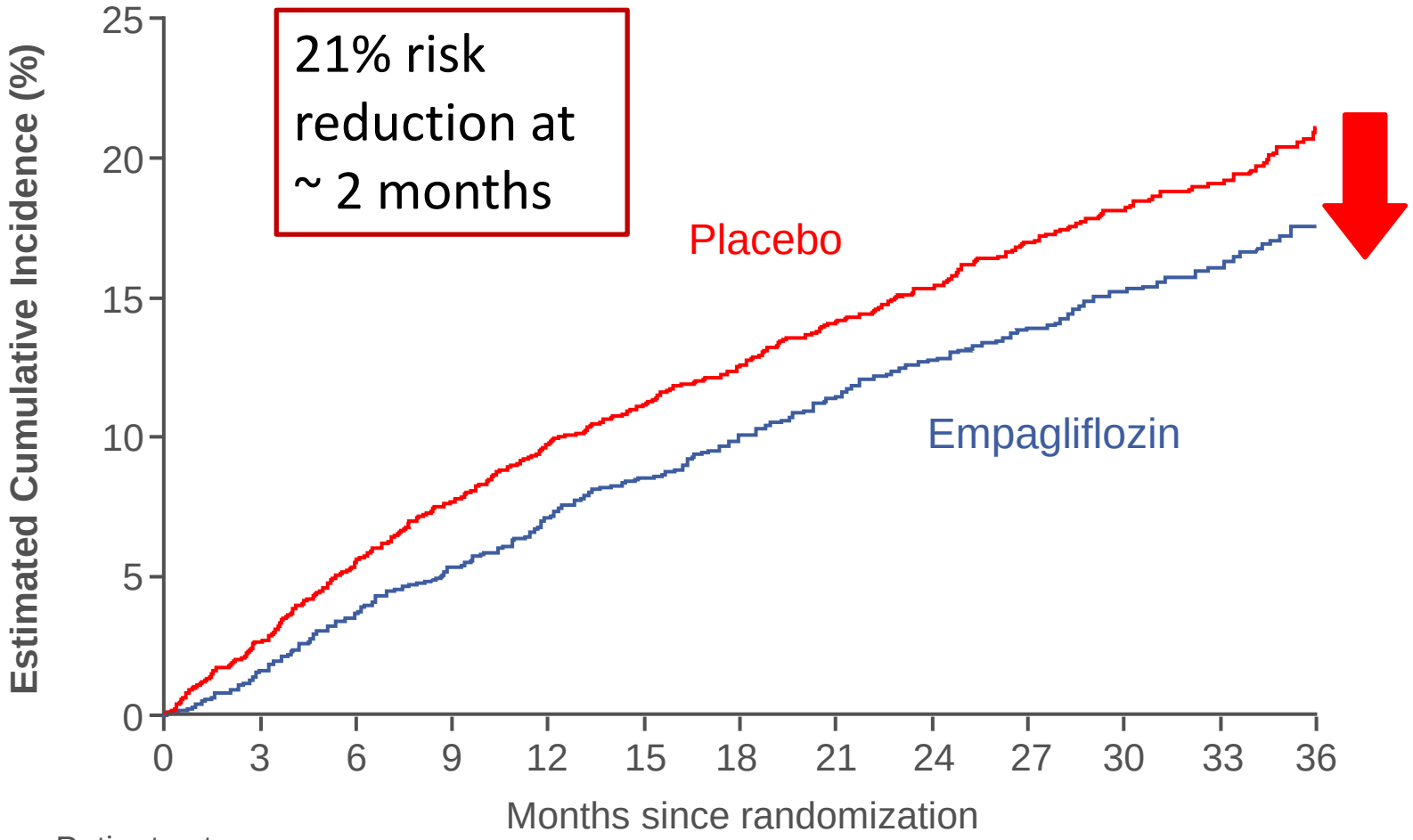
Secondary Outcomes: Laboratory and Other Measurements

Laboratory and other measurements (adjusted change from baseline to 52 weeks)

Variable	Empagliflozin	Placebo	Adjusted mean difference / geometric mean ratio (95% CI)
Glycated hemoglobin (%) in patients with diabetes – mean (SE)	- 0.16 ± 0.02	0.03 ± 0.02	- 0.19 (- 0.25 to - 0.14)
Hematocrit (%) – mean (SE)	1.94 ± 0.07	- 0.41 ± 0.07	2.36 (2.17 to 2.54)
NT-proBNP (pg/mL) – median (IQR)	- 29 (- 335 to 263)	- 9 (- 286 to 322)	0.95 (0.91 to 0.99)
Body weight (kg) – mean (SE)	- 1.39 ± 0.09	- 0.11 ± 0.09	- 1.28 (- 1.54 to - 1.03)
Systolic blood pressure (mm Hg) – mean (SE)	- 1.8 ± 0.3	- 0.6 ± 0.3	- 1.2 (- 2.1 to - 0.3)
Uric acid (mg/dL)	- 0.90 ± 0.03	- 0.10 ± 0.03	- 0.80 (- 0.88 to - 0.72)

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

Primary endpoint – Composite of cardiovascular death or heart failure hospitalization



Patients at risk							
Placebo	2991	2786	2627	2066	1534	961	400
Empagliflozin	2997	2843	2708	2134	1578	1005	402

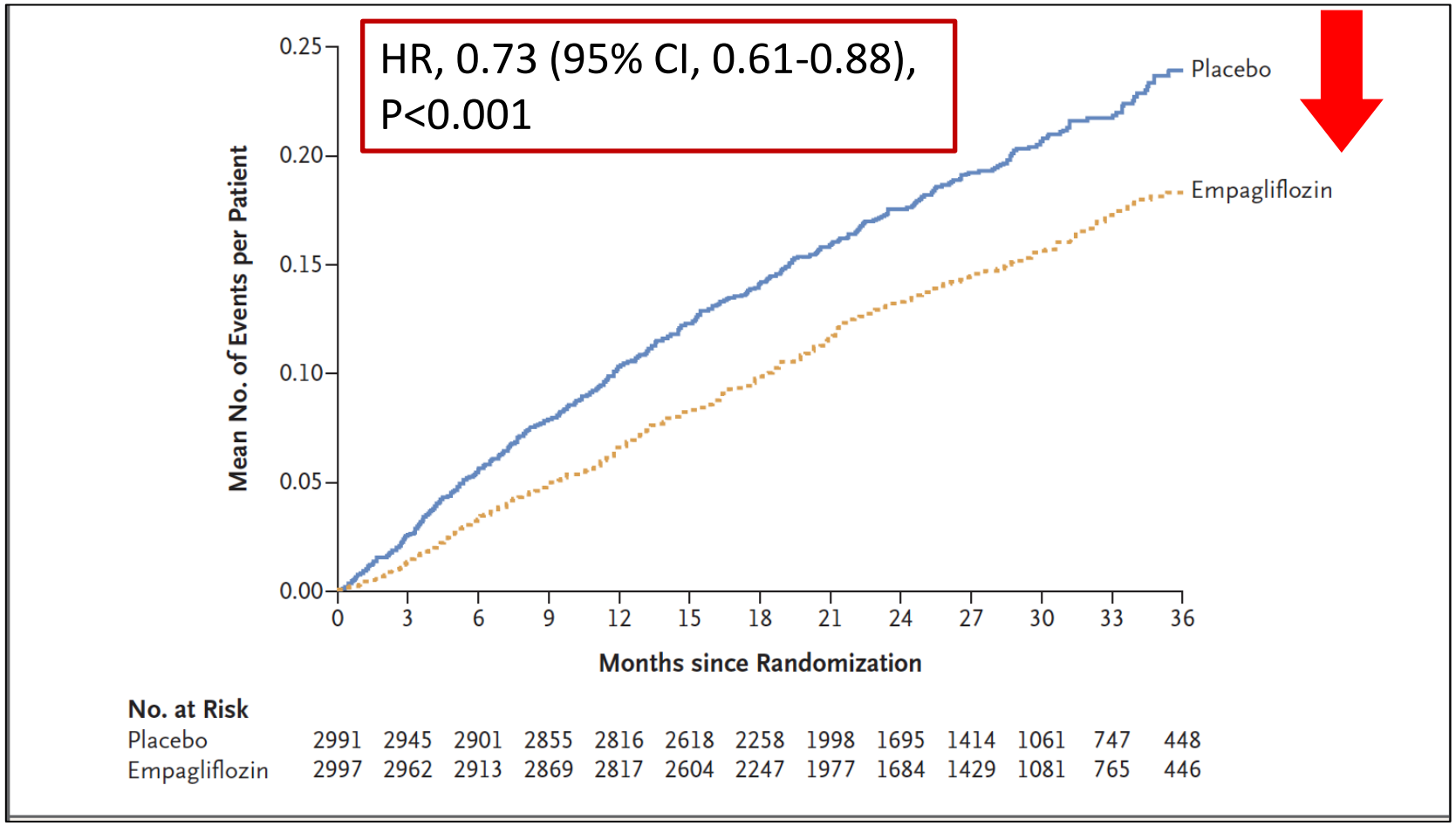
HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

Hospitalizations for HF



22% risk reduction at ~ 2 months

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

Primary and Secondary CV Outcomes

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P- value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome – no (%)	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	<0.001
First hospitalization for heart failure	259 (8.6%)	4.3	352 (11.8%)	6.0	0.71 (0.60 – 0.83)	
Cardiovascular death	219 (7.3%)	3.4	244 (8.2%)	3.8	0.91 (0.76 – 1.09)	
Composite renal outcome – no (%)	108 (3.6%)	2.1	112 (3.7%)	2.2	0.95 (0.73 – 1.24)	
Death from any cause – no (%)	422 (14.1%)	6.6	427 (14.3%)	6.7	1.00 (0.87 – 1.15)	

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

Conclusions

- HF and EF >40%, empagliflozin reduced composite of CV death and HF hospitalization by 21% (P = 0.0003) → clinically meaningful effect
- Benefit of empagliflozin on primary endpoint consistent across all pre-specified subgroups, including LVEF, sex and diabetes
- Empagliflozin reduced total (first & recurrent) hospitalizations for HF by 27% (P=0.0009)
- EMPEROR-Preserved is first trial to show unequivocal clinical benefits with a drug in patients with HF and a preserved EF

Anker, Stefan D., et al. *NEJM* 385.16 (2021): 1451-1461.

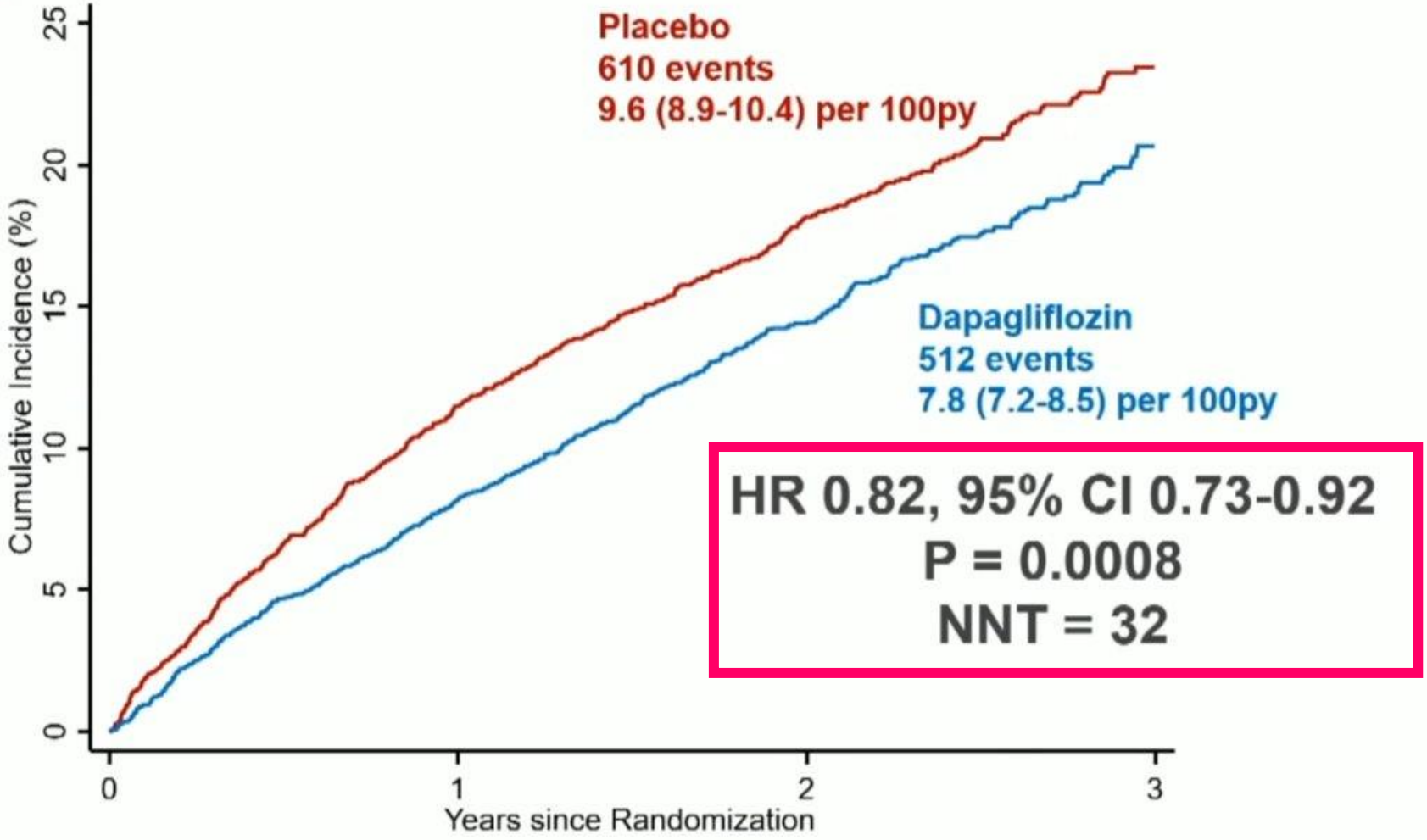
Dapagliflozin in HF with mildly reduced or HFpEF

Primary Endpoint: CV Death or Worsening HF

Full Population

DELIVER

Further evidence to support SGLT2i as foundational HF therapy

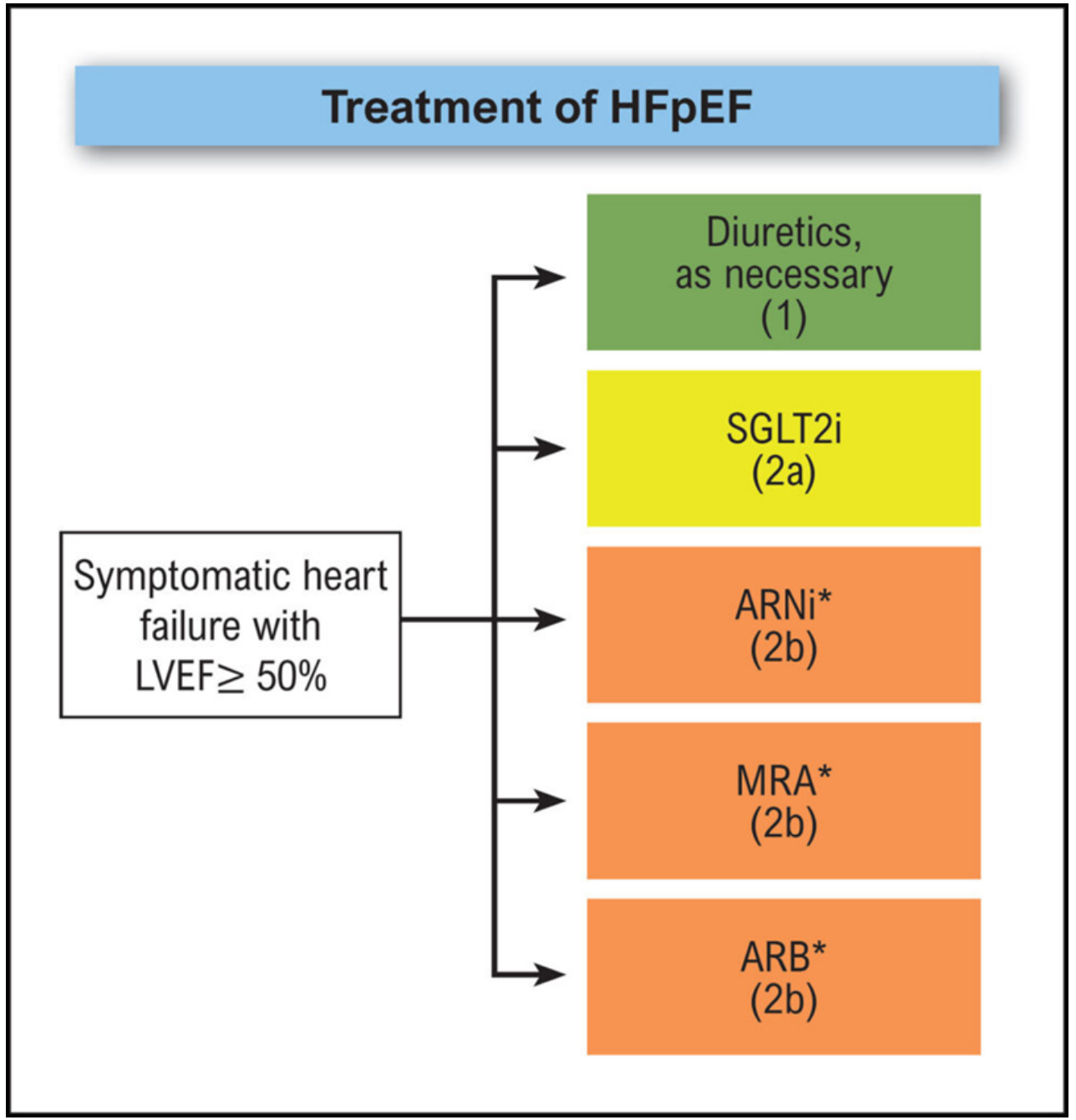


Solomon SD, et al. N Engl J Med. 2022 Aug 27

2022 AHA/ACC/HFSA Guideline

- New recommendations for HFpEF:
- SGLT2 inhibitors (2a) ,
- MRAs (2b) and ARNi (2b).
- Several prior recommendations renewed including: treatment of HTN (1), treatment of AF (2a), use of ARBs (2b) avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (3-no Benefit).

Heidenreich PA et al. JACC. 2022; 79.17: e263-e421



Heidenreich PA et al. JACC. 2022; 79.17: e263-e421

7.7. Preserved EF (HFpEF)

7.7.1. HF With Preserved Ejection Fraction

Recommendations for HF With Preserved Ejection Fraction* Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.

Heidenreich PA et al. JACC. 2022; 79.17: e263-e421

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2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]
3: No-Benefit	B-R	7. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective.[12,13]

Heidenreich PA et al. JACC. 2022; 79.17: e263-e421

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Amyloid Cardiomyopathy

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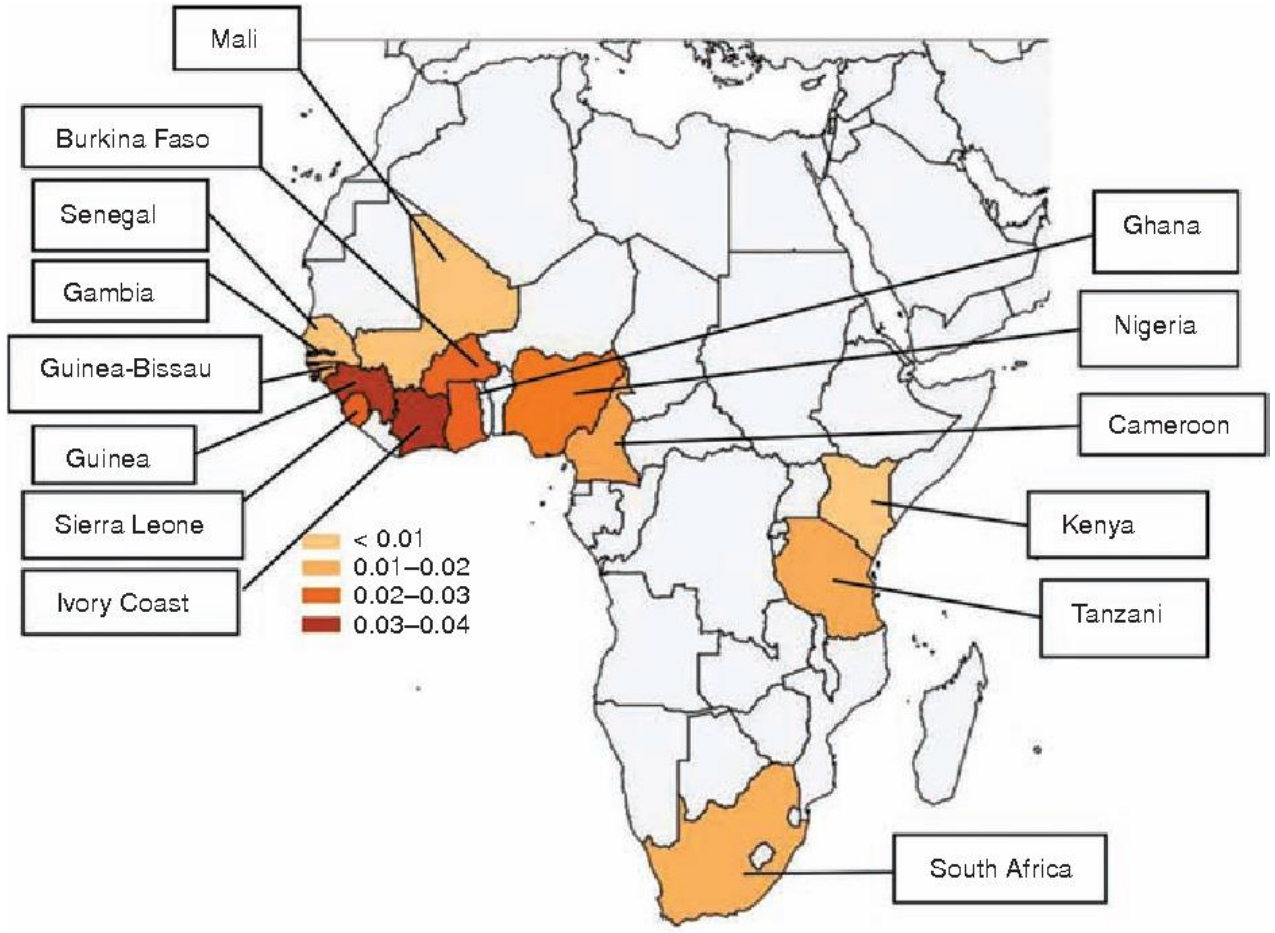
New Orleans, LA

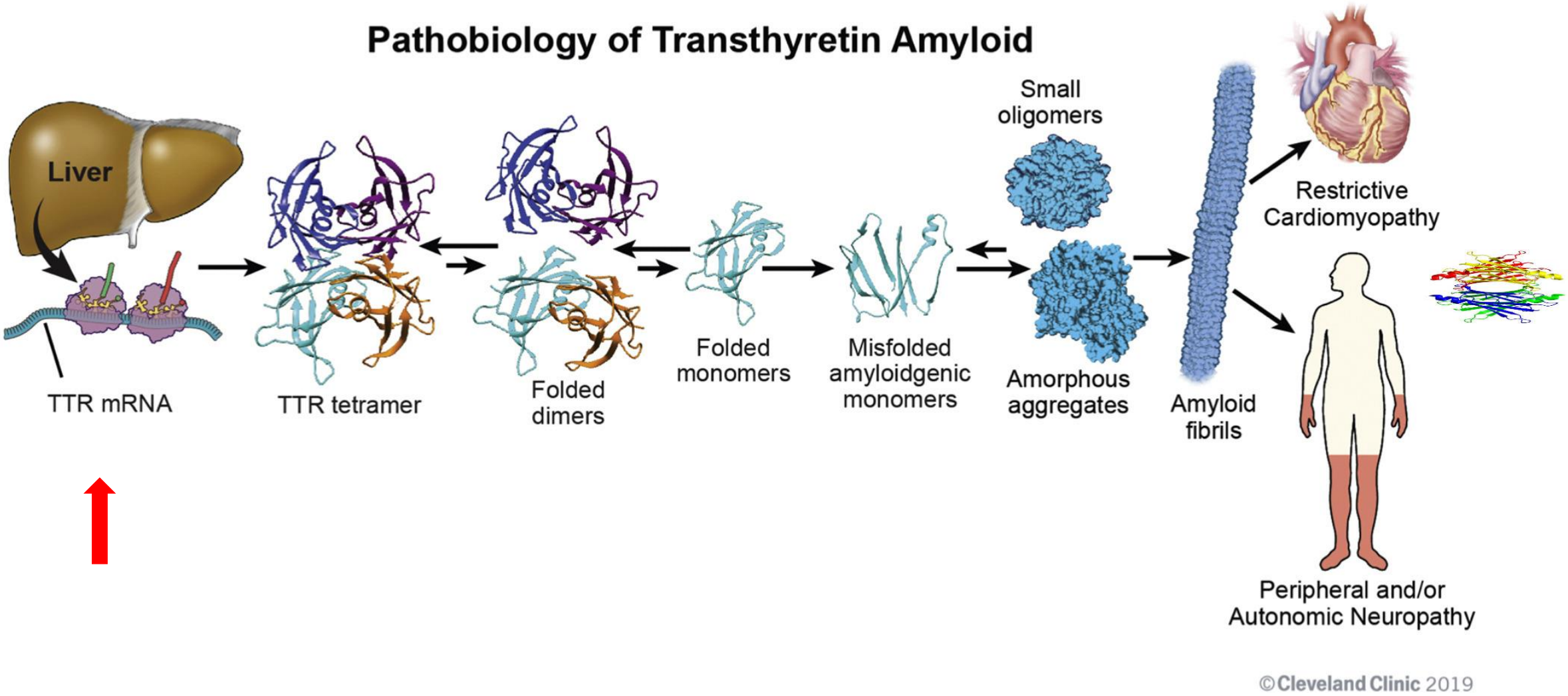
Distribution TTR V122I Allele in Africa: Various Locales Genotyped for the V122I Allele

DNA N≈ 2,700



Joel N Buxbaum, Frederick L Ruberg ***Genetics in Medicine*** **2017**
DOI:10.1038/gim.2016.200

TTR V122I Cardiac Amyloidosis: An Age-dependent AD Cardiomyopathy Commonly Overlooked as Cause of Significant Heart Disease in Elderly AAs



Rutberg,F. et al *Journal of the American College of Cardiology*
Volume 73, Issue 22, June 2019

Which of the following is true regarding pathobiology of transthyretin amyloid?

a) Increase in TTR tetramers
b) Misfolded monomers
c) Dilated cardiomyopathy
d) More common in Asian American individuals

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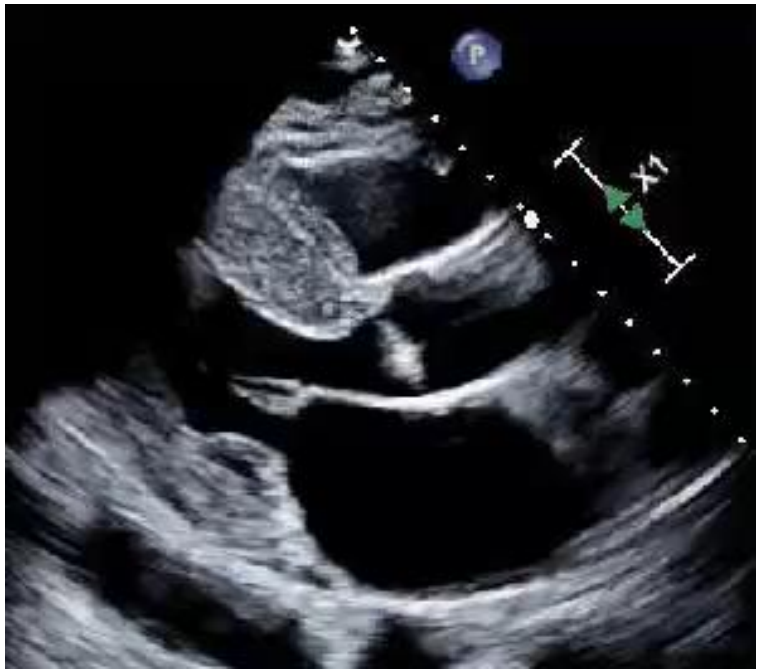
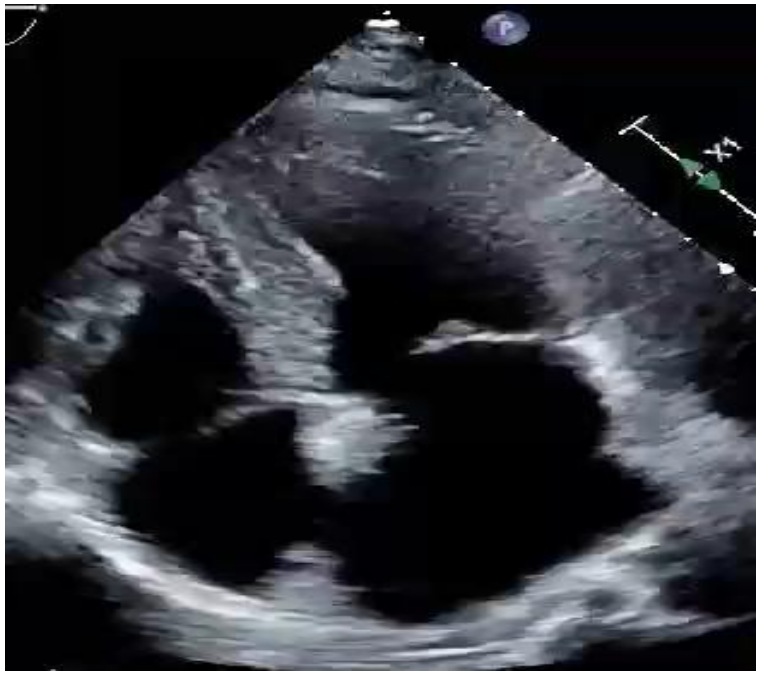
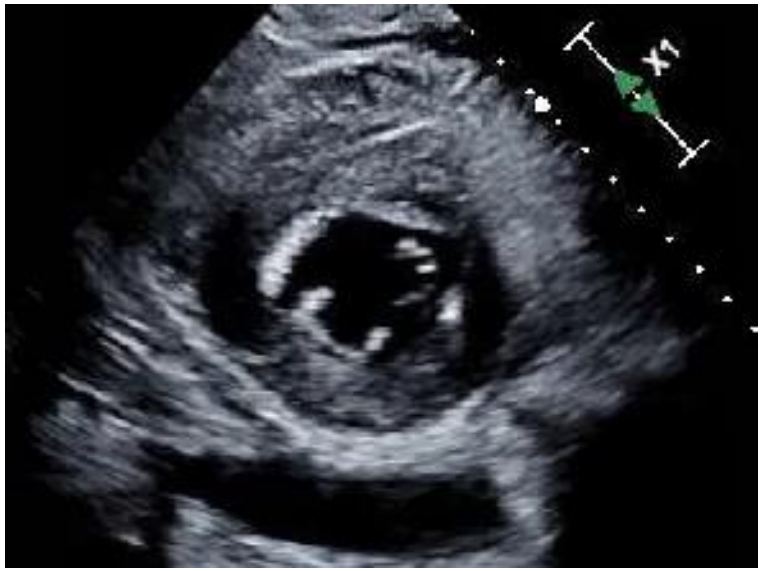
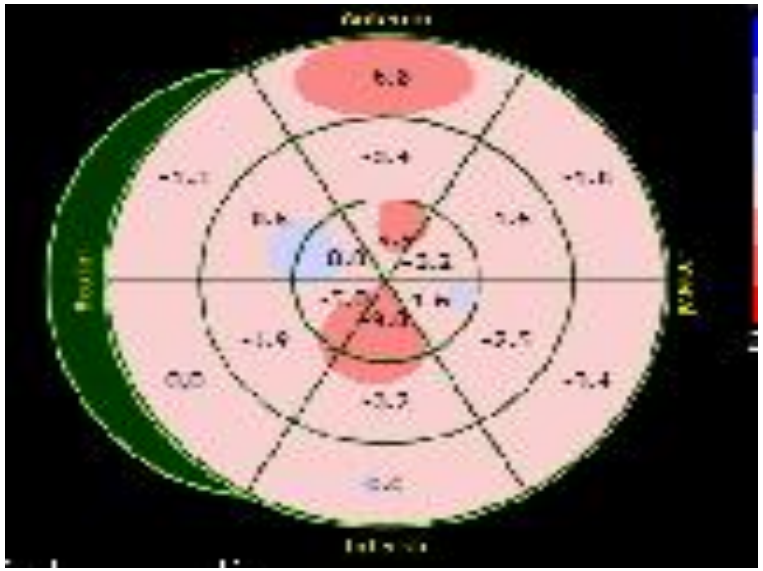


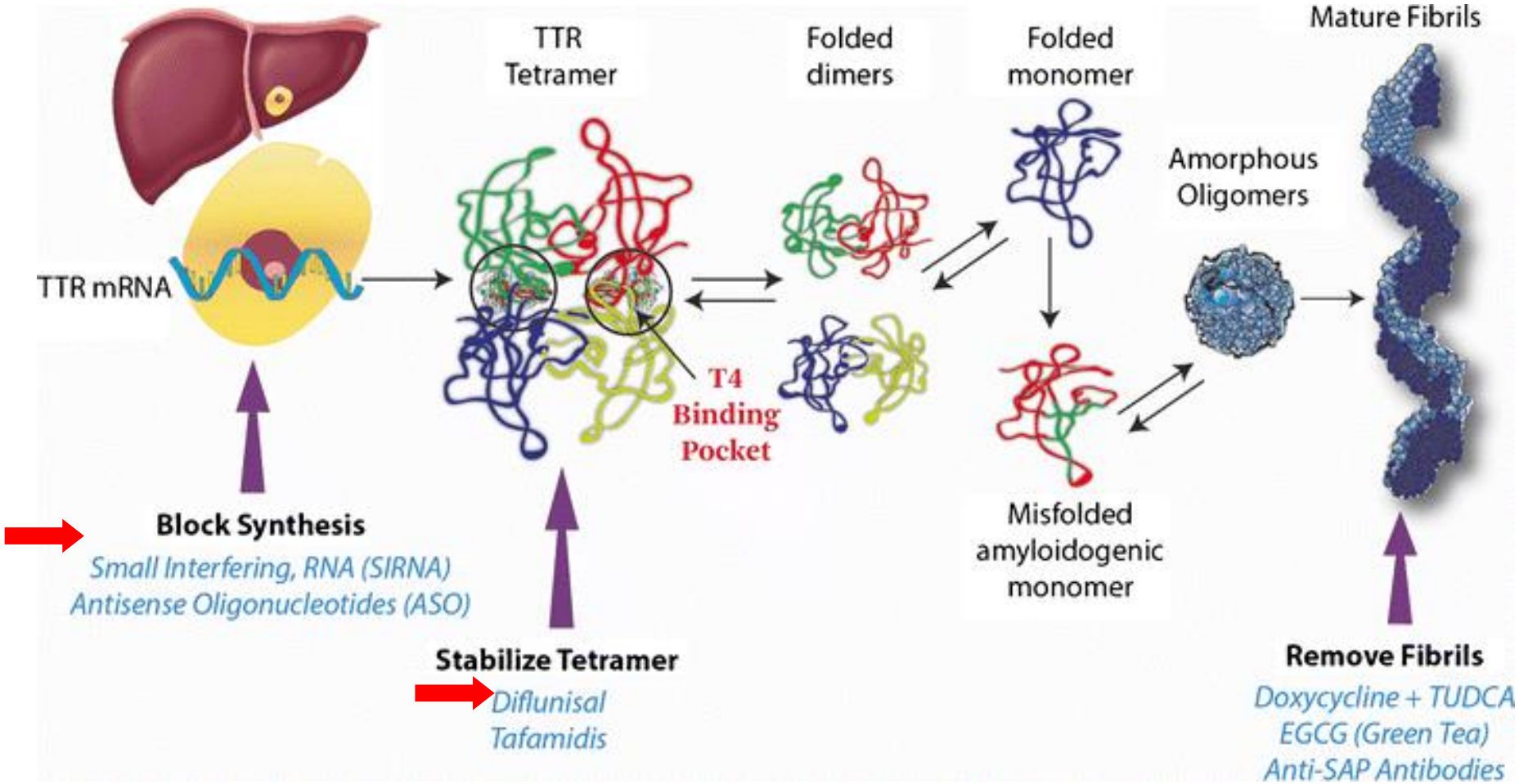




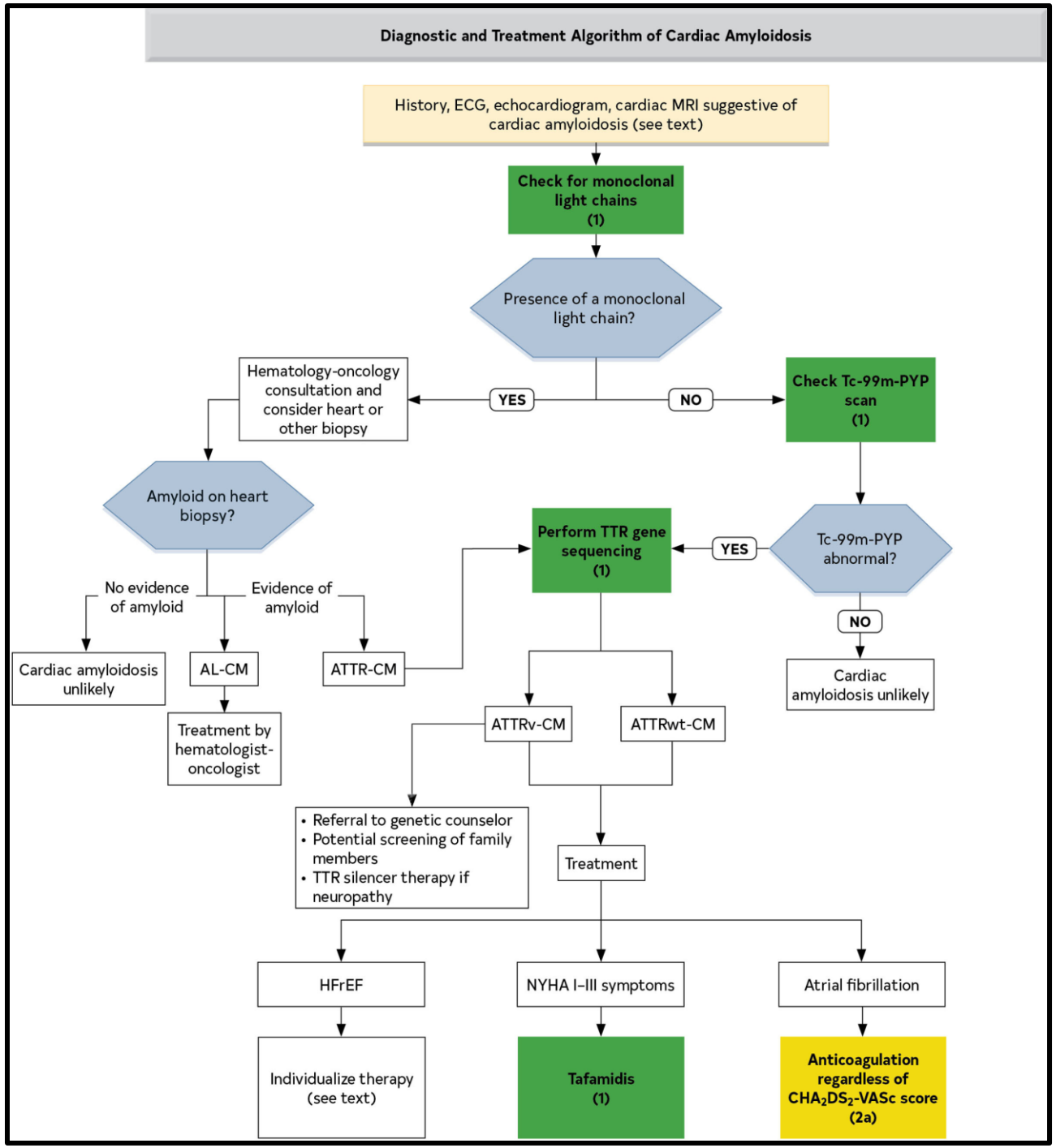


- A fib
- EF 15-20%
- LVH
- Concentric remodeling

Novel Drugs Targeting Transthyretin Amyloidosis



Current Heart Failure Reports
March 2014, Volume 11, Issue 1, pp 50–57



Heidenreich PA et al. JACC. 2022; 79.17: e263-e421