

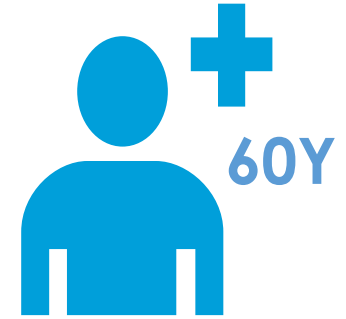
המהפכה התרופתית באי ספיקת לב

ד"ר אבישי גרופר

המכון לאי ספיקת לב, שיבא, תל השומר

יו"ר החוג לאי ספיקת לב באיגוד הקרדיולוגי

Case presentation – A.B.



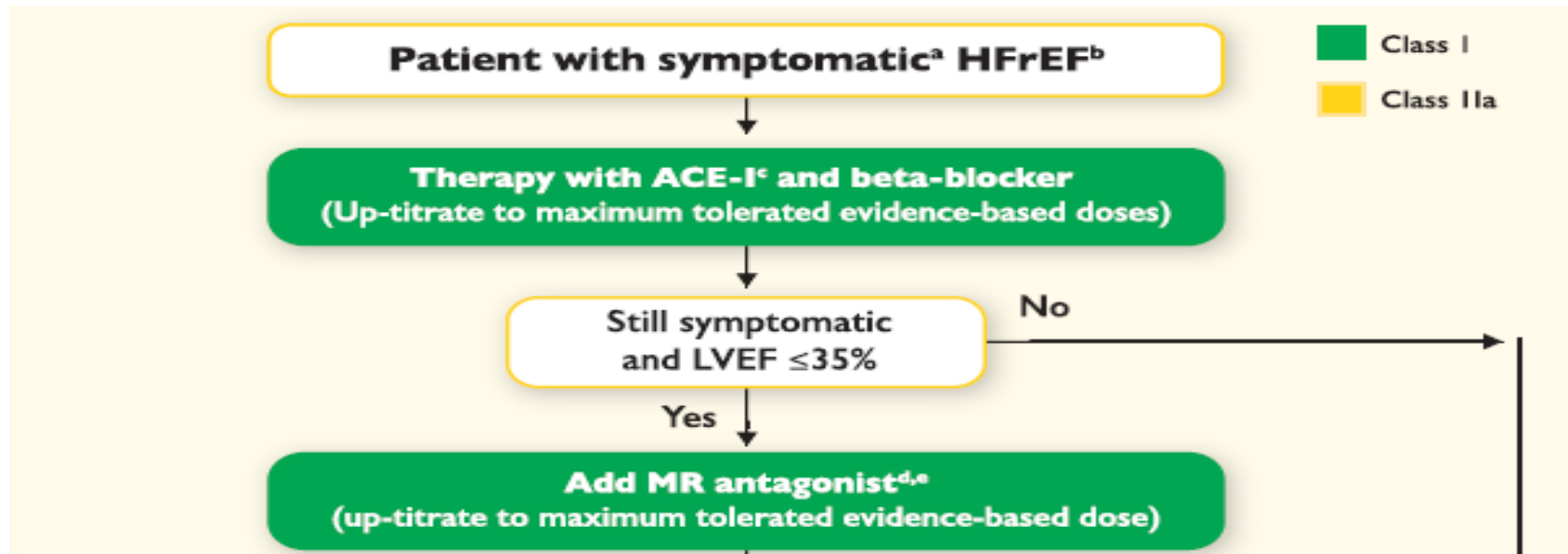
4.3.2020

New onset of HF symptoms
NYHA 3

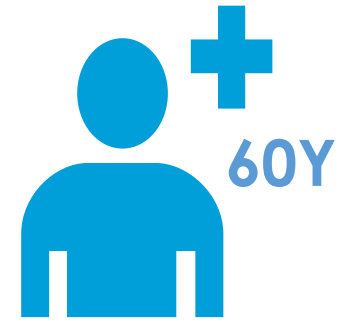
Moderate LV dilatation, EF=10%
Moderate MR
Moderate RV dysfunction
Moderate TR

Normal coronary arteries

Treatment:
Fusid 40mg
Bisoprolol 1.25mg
Ramipril 1.25mg



Case presentation – A.B.



20.2.2020

New onset of HF symptoms

Moderate LV dilatation, EF=10%
Moderate MR
Moderate RV dysfunction
Moderate TR

Normal coronary arteries

Treatment:
Fusid 40mg
Bisoprolol 1.25mg
Ramipril 1.25mg

4.3.2020

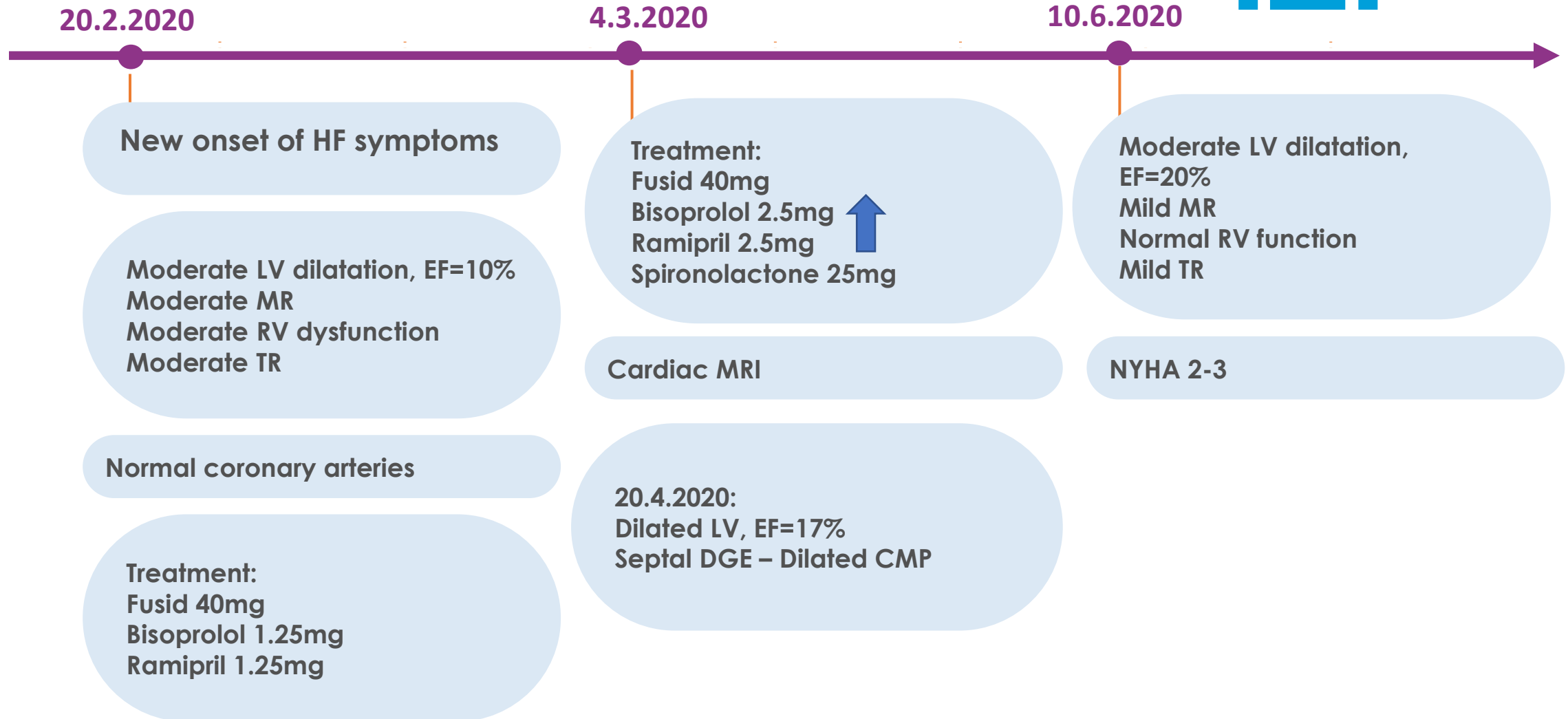
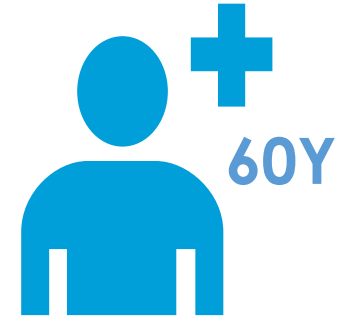
Treatment:
Fusid 40mg
Bisoprolol 2.5mg
Ramipril 2.5mg
Spironolactone 25mg

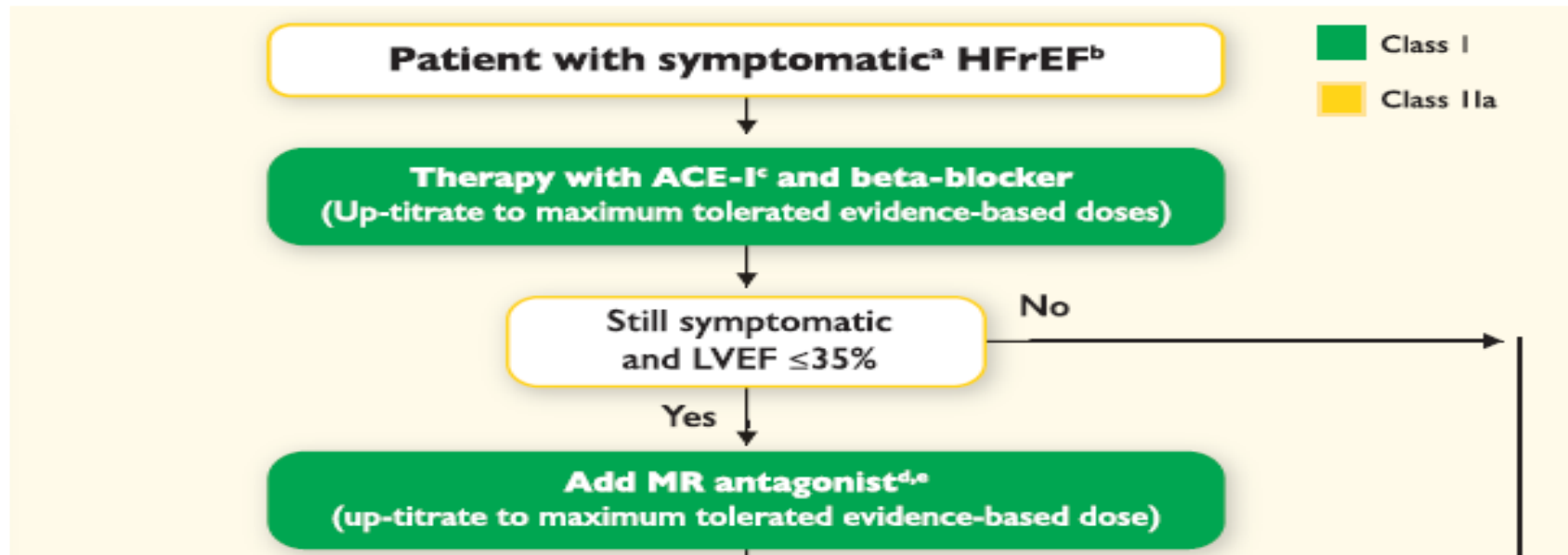


Cardiac MRI

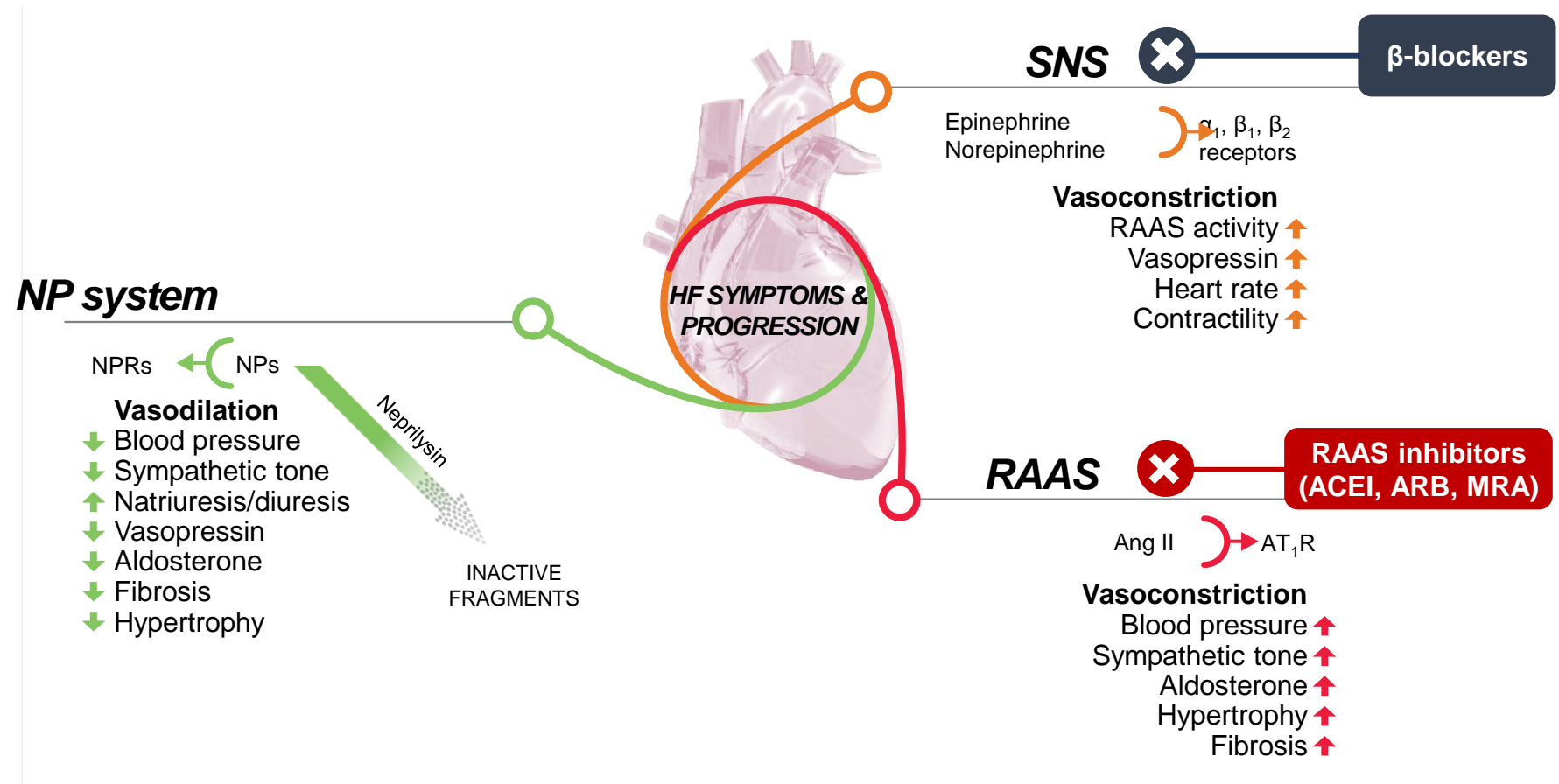
20.4.2020:
Dilated LV, EF=17%
Septal DGE – Dilated CMP

Case presentation – A.B.



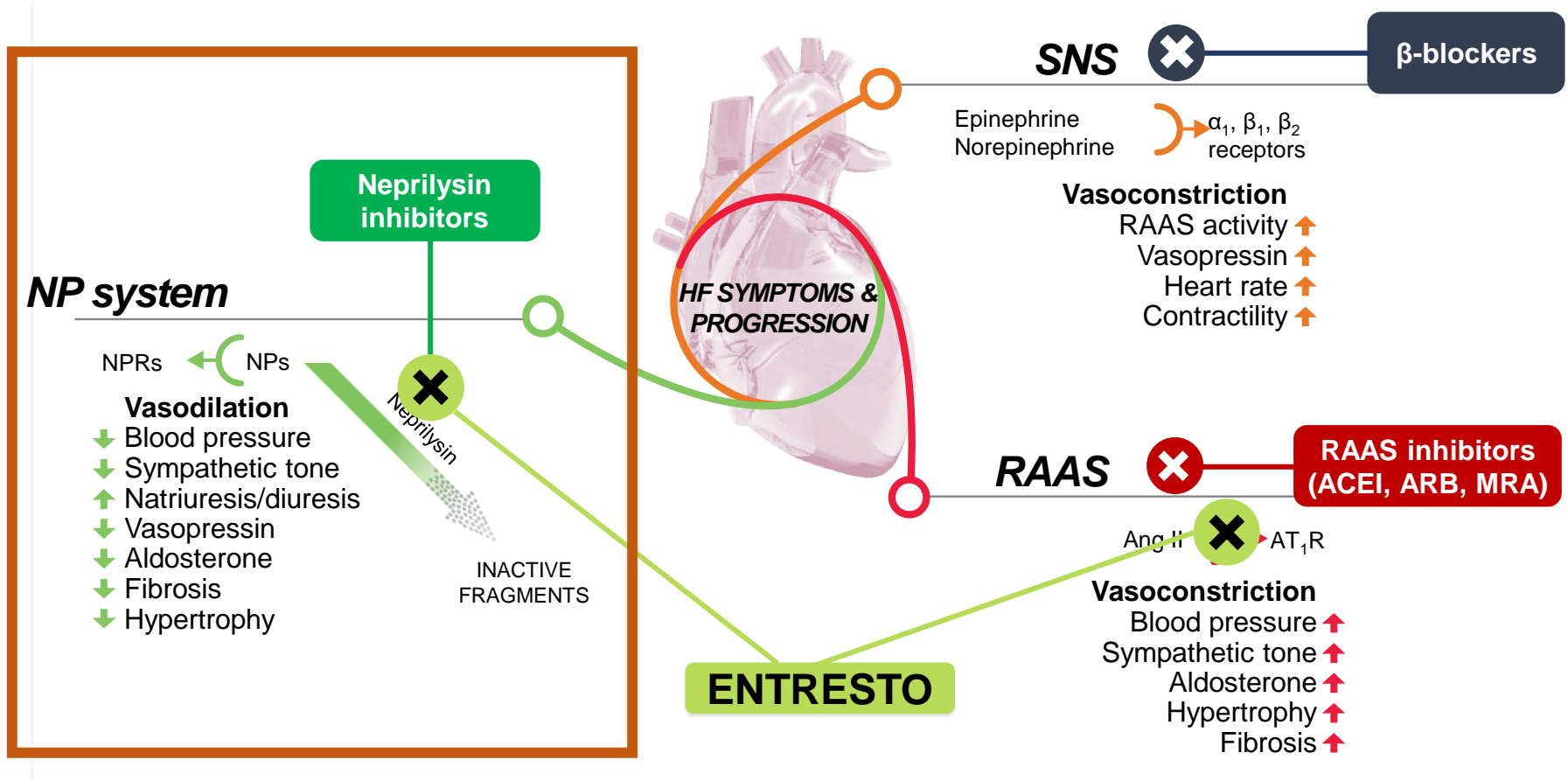


Evolution of pharmacologic approaches in HF:



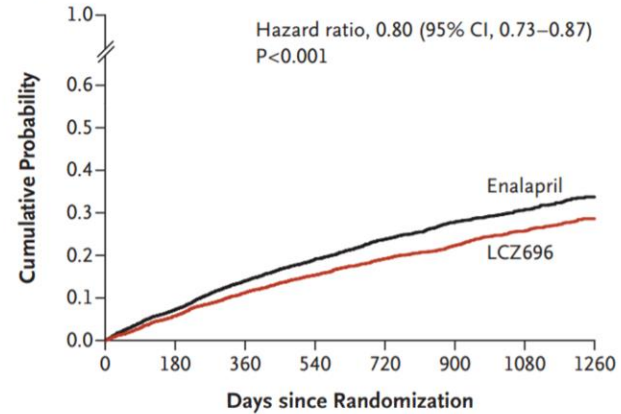
Evolution of pharmacologic approaches in HF:

ENTRESTO as a new alternative to an ACEI or ARBs in patients with HFrEF

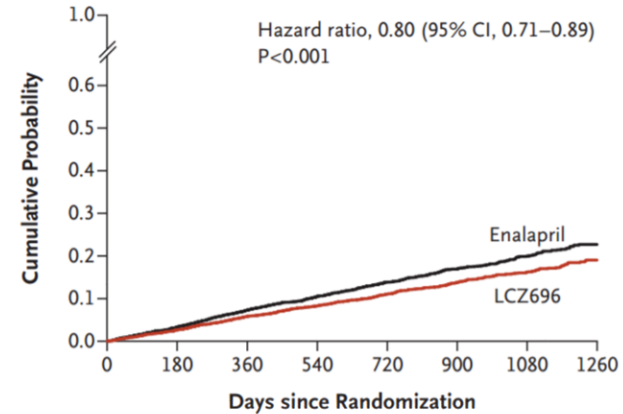


PARADIGM-HF: study outcomes

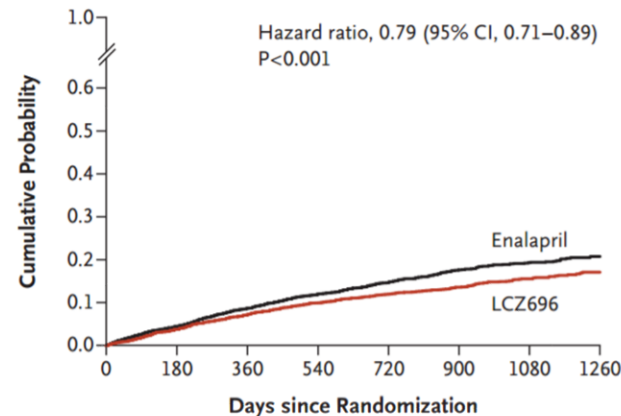
Primary End Point



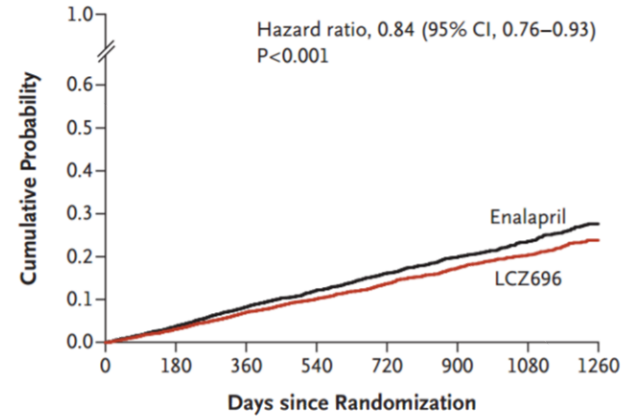
Death from Cardiovascular Causes



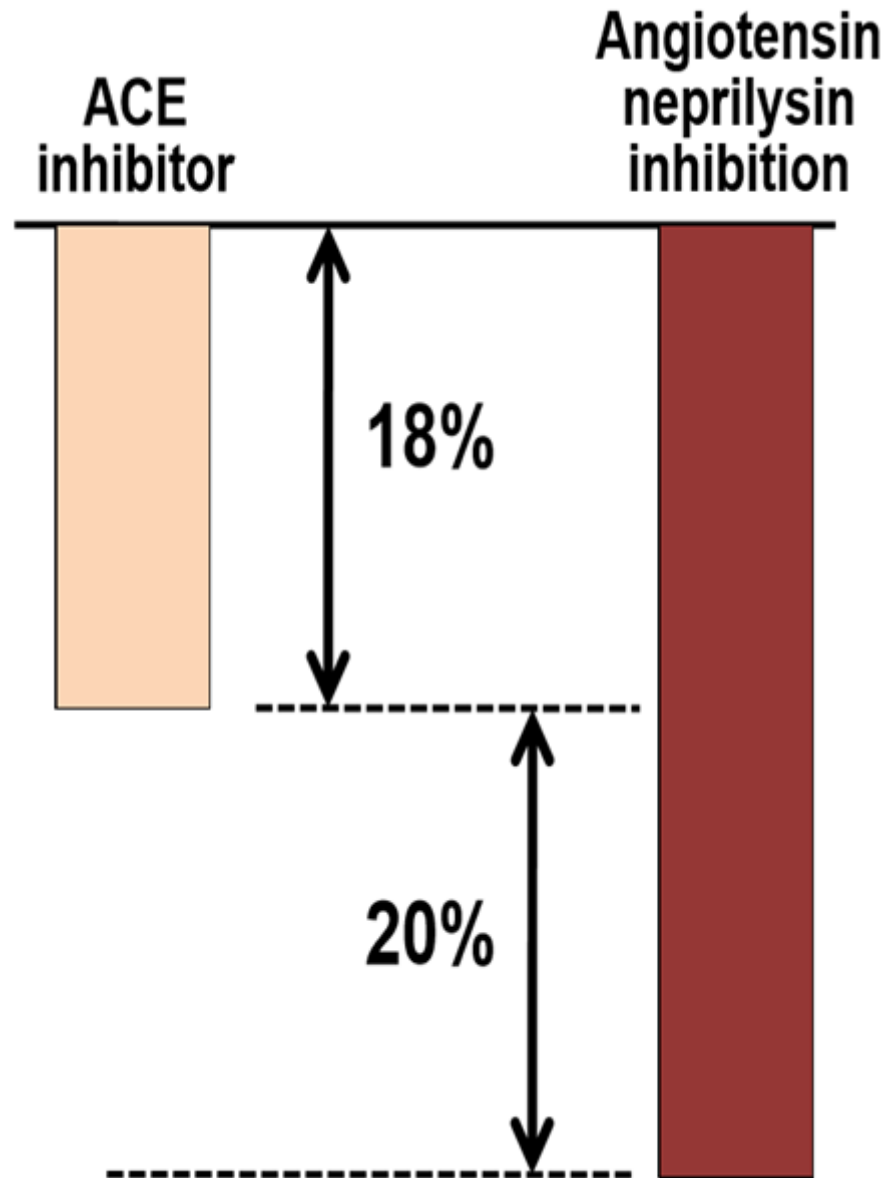
Hospitalization for Heart Failure



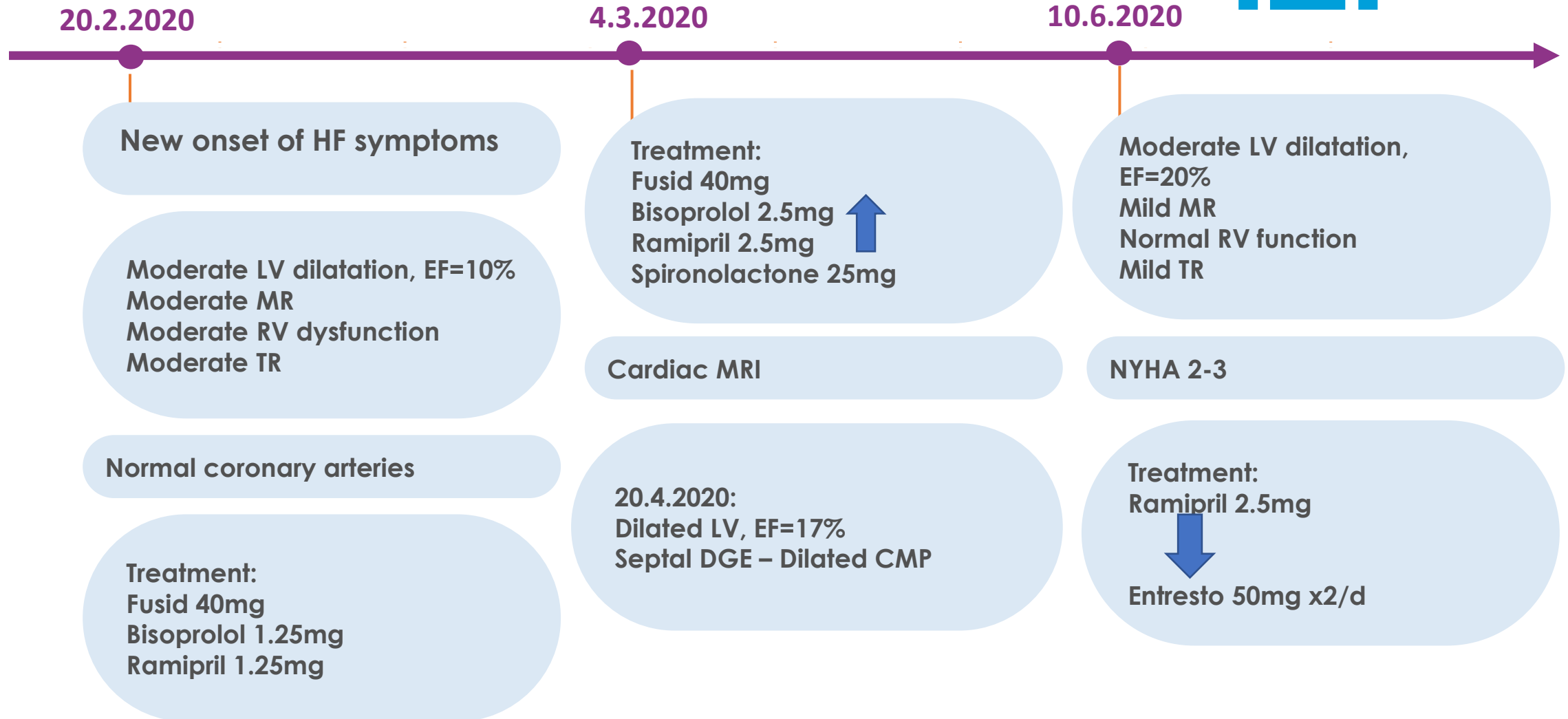
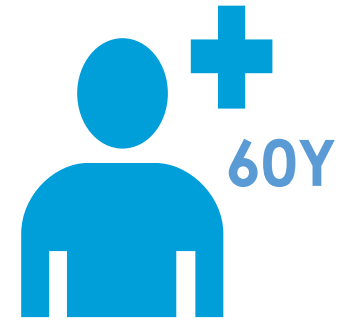
Death from Any Cause

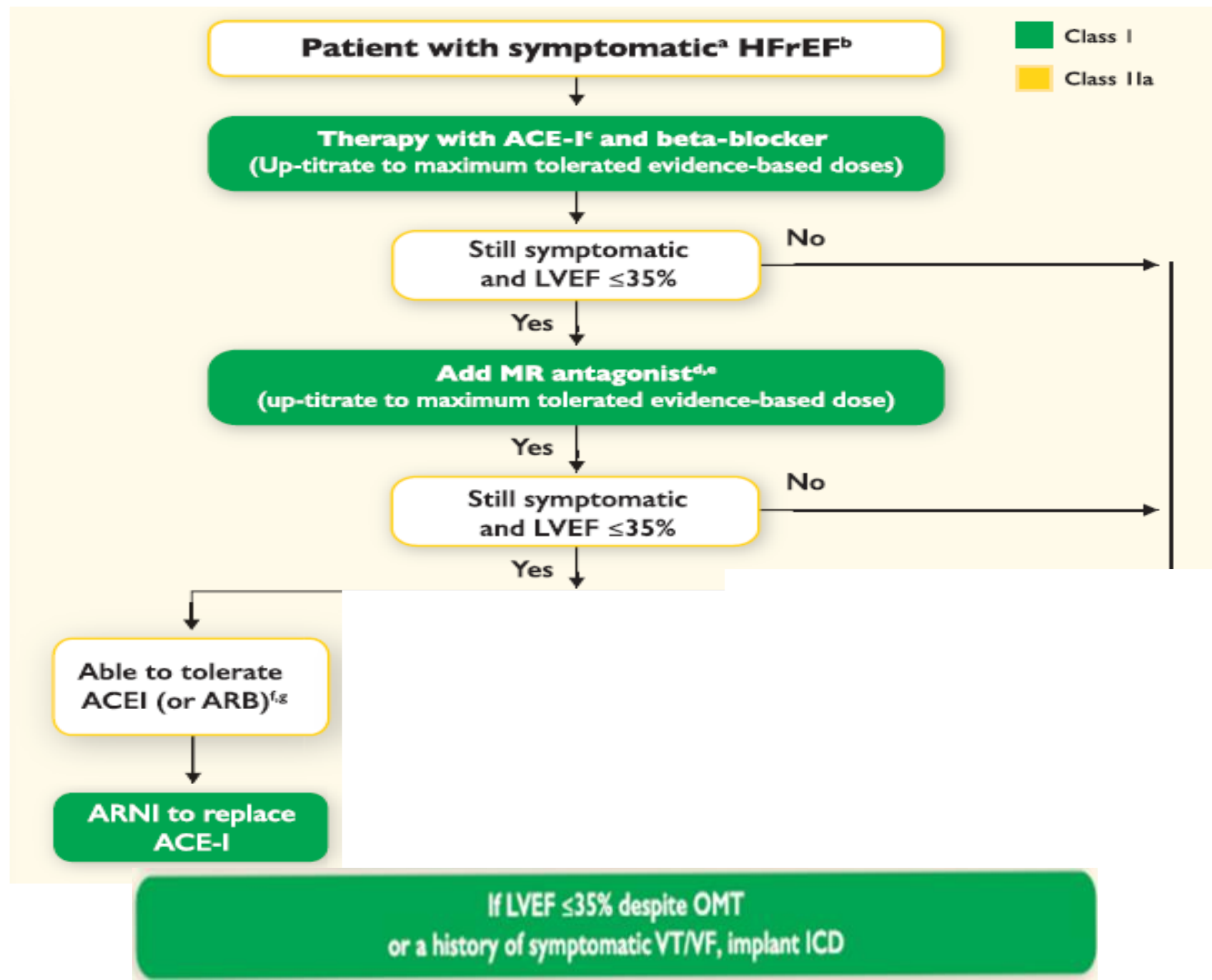


**Decrease in
CV mortality**

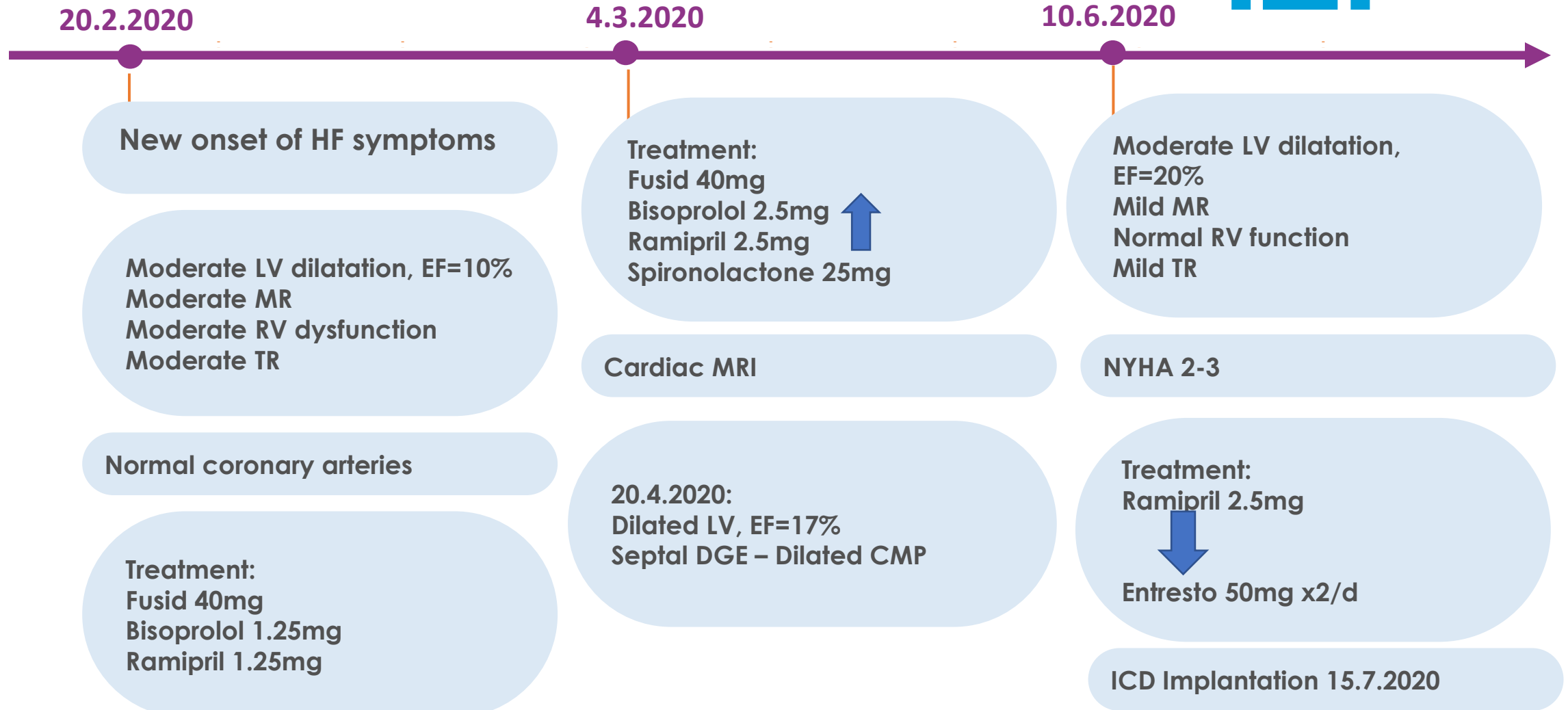
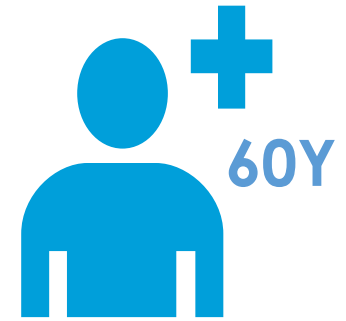


Case presentation – A.B.



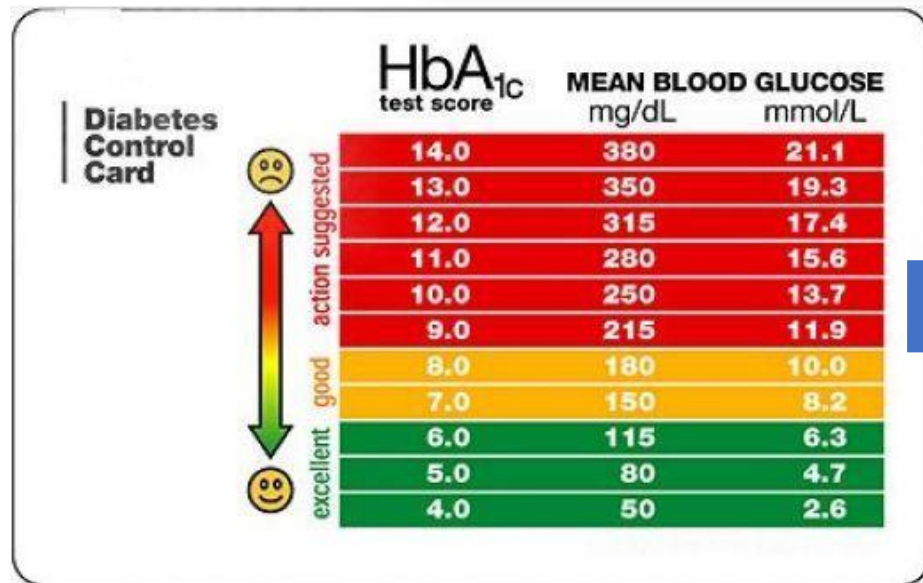


Case presentation – A.B.



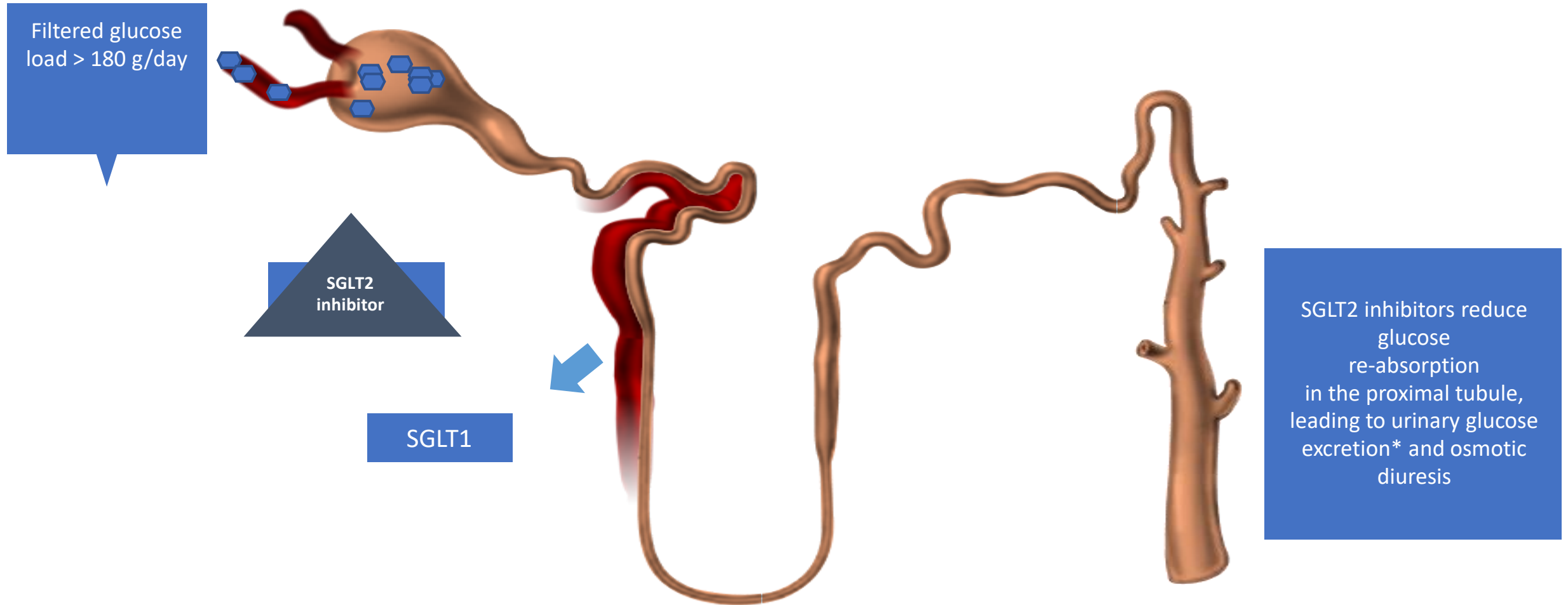
The change in the paradigm of antidiabetic treatment goals

From glucocentricity to reduction of CV risk and mortality



SGLT2 inhibition – mode of action

Urinary glucose excretion via SGLT2 inhibition^{1,2}



SGLT, sodium glucose co-transporter. *Loss of ~ 78 g of glucose per day = 312 calories/day.

1. Gerich JE. *Diabet Med.* 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int.* 2009;75:1272–1277;

3. Ferrannini E et al *Nat Rev Endocrinol* 2012; 8: 495. Figure reprinted by permission

from McMillan Publishers Ltd *Nat Rev Endocrin* 2012

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; $P=0.04$ for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome ($P=0.08$ for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

CONCLUSIONS

Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE-TIMI 58 Investigators*

ABSTRACT

BACKGROUND

The cardiovascular safety profile of dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2 that promotes glucosuria in patients with type 2 diabetes, is undefined.

METHODS

We randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite ($\geq 40\%$ decrease in estimated glomerular filtration rate to < 60 ml per minute per 1.73 m² of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

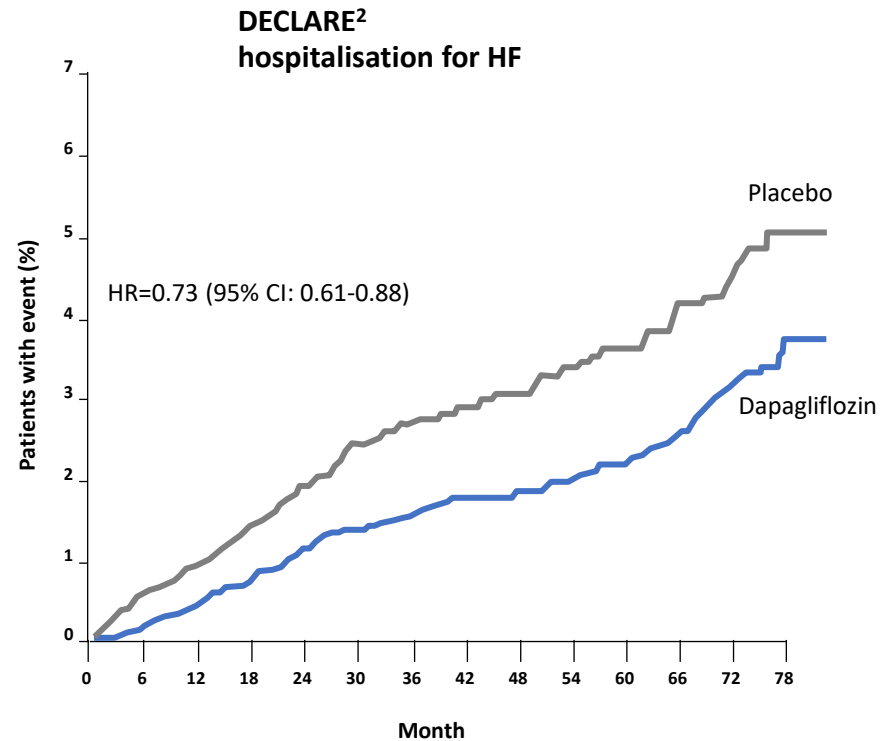
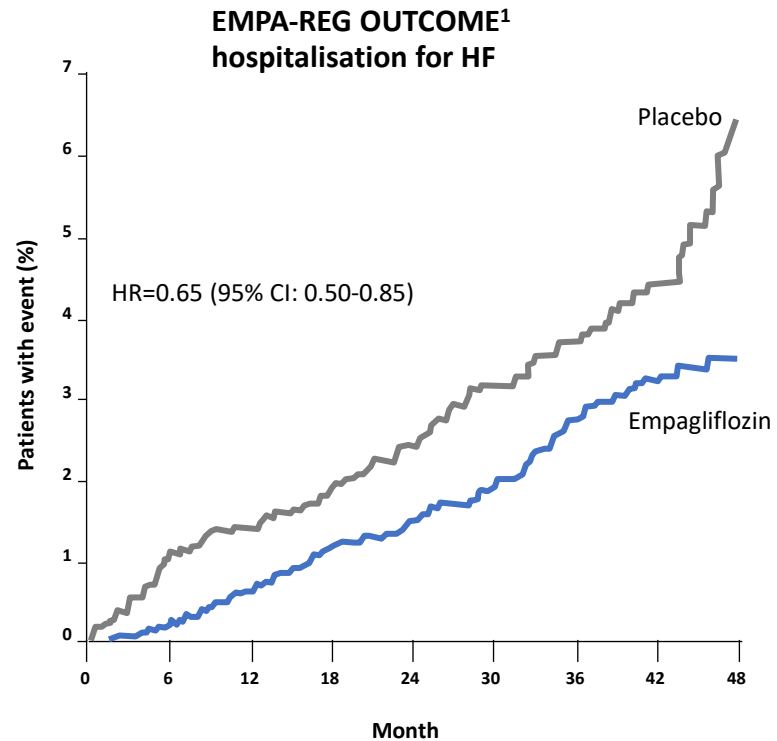
RESULTS

We evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years. In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], < 1.3 ; $P<0.001$ for noninferiority). In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; $P=0.17$) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; $P=0.005$), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, $P=0.02$), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, $P<0.001$).

CONCLUSIONS

In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure. (Funded by AstraZeneca; DECLARE-TIMI 58 ClinicalTrials.gov number, NCT01730534.)

New insights into HF prevention have emerged from trials examining SGLT2 inhibitor use in T2D



CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

1. Zinman B, et al. *N Engl J Med*. 2015;373:2117–2128. 2. Wiviott S, et al. *N Engl J Med*. 2019;380:347-357.

SGLT2 inhibitors in HFrEF patients

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Böhme, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diaz, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

ABSTRACT

BACKGROUND

In patients with type 2 diabetes, inhibitors of sodium–glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

METHODS

In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

RESULTS

Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; $P<0.001$). A first worsening heart failure event occurred in 257 patients (10.9%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT06086124.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl, Glasgow G12 8TA, United Kingdom, or at john.mcmurray@glasgow.ac.uk.

A complete list of DAPA-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 19, 2019, at NEJM.org.

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DOI: 10.1056/NEJMoa1911343

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuqulure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

ABSTRACT

BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

METHODS

In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

RESULTS

During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; $P<0.001$). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; $P<0.001$). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (−0.55 vs. −2.28 ml per minute per 1.73 m² of body-surface area per year, $P<0.001$), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Packer at Baylor Heart and Vascular Institute, 621 N. Hall St., Dallas, TX 75226, or at milton.packer@baylorhealth.edu.

*A complete list of the EMPEROR-Reduced investigators is provided in the Supplementary Appendix, available at NEJM.org.

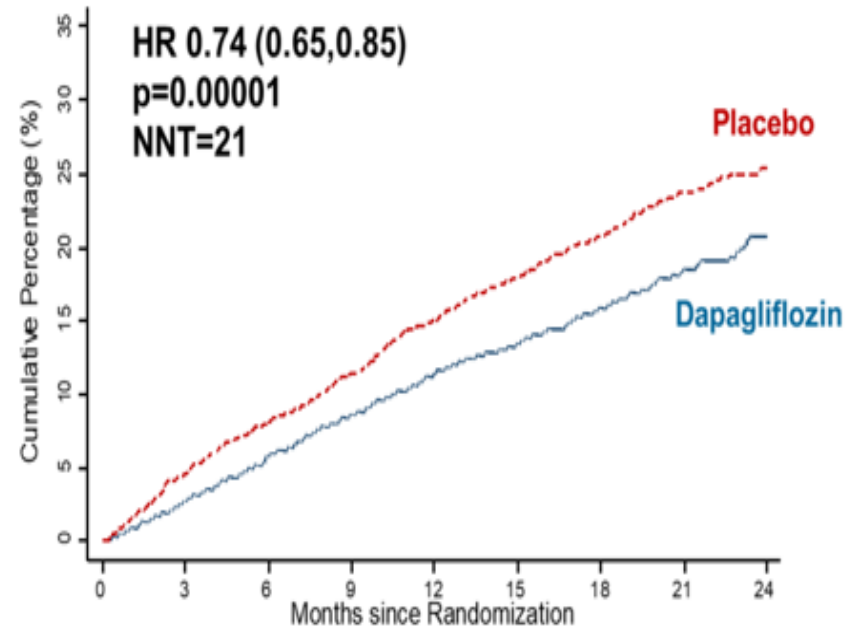
This article was published on August 28, 2020, at NEJM.org.

N Engl J Med 2020;383:1413–24.
DOI: 10.1056/NEJMoa2022190

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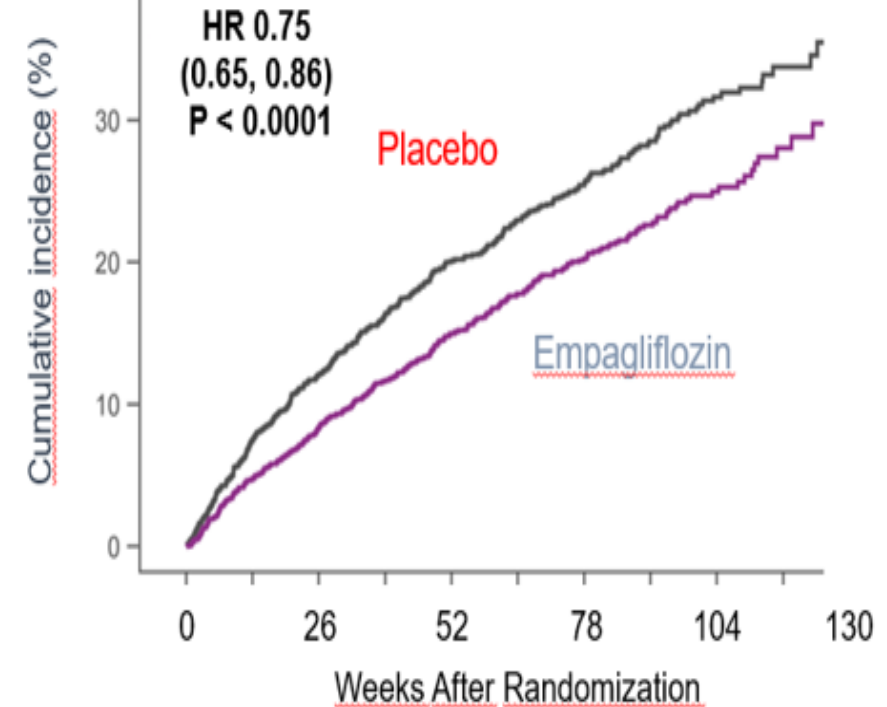
SGLT2 inhibitors in HFrEF patients

CV Death/HF hospitalization/Urgent HF visit



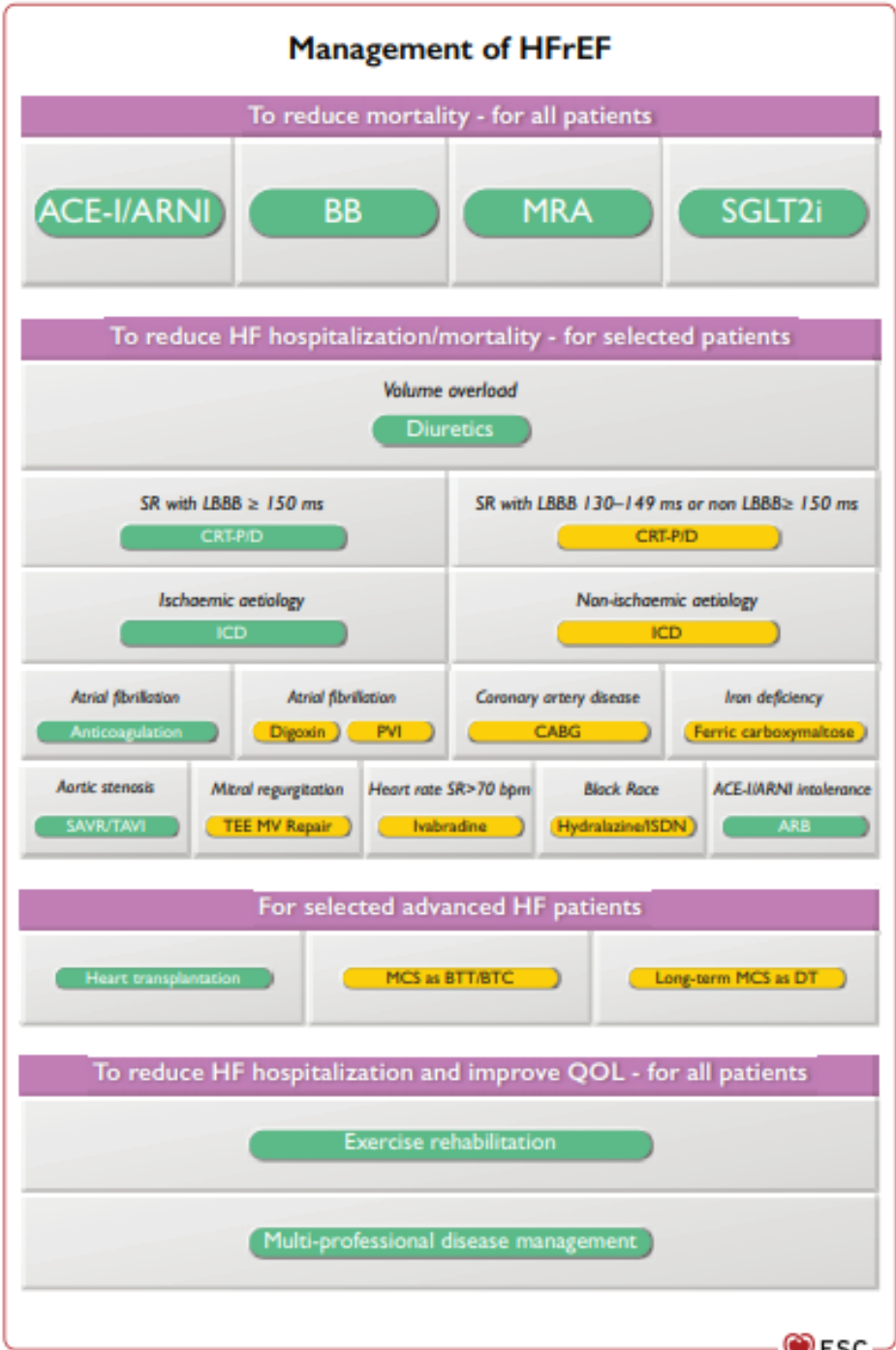
Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Cardiovascular Death or
Hospitalization for Heart Failure



Patients at risk											
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109	
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101	

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



Management of HFrEF

To reduce mortality - for all patients

ACE-I/ARNI

BB

MRA

SGLT2i

ICD

Atrial fibrillation
Anticoagulation

Atrial fibrillation
Digoxin PVI

Coronary artery disease
CABG

Iron deficiency
Ferric carboxymaltose

Aortic stenosis
SAVR/TAVI

Mitral regurgitation
TEE MV Repair

Heart rate SR>70 bpm
Ivabradine

Black Race
Hydralazine/ISDN

ACE-I/ARNI intolerance
ARB

For selected advanced HF patients

Heart transplantation

MCS as BTT/BTC

Long-term MCS as DT

To reduce HF hospitalization and improve QOL - for all patients

Exercise rehabilitation

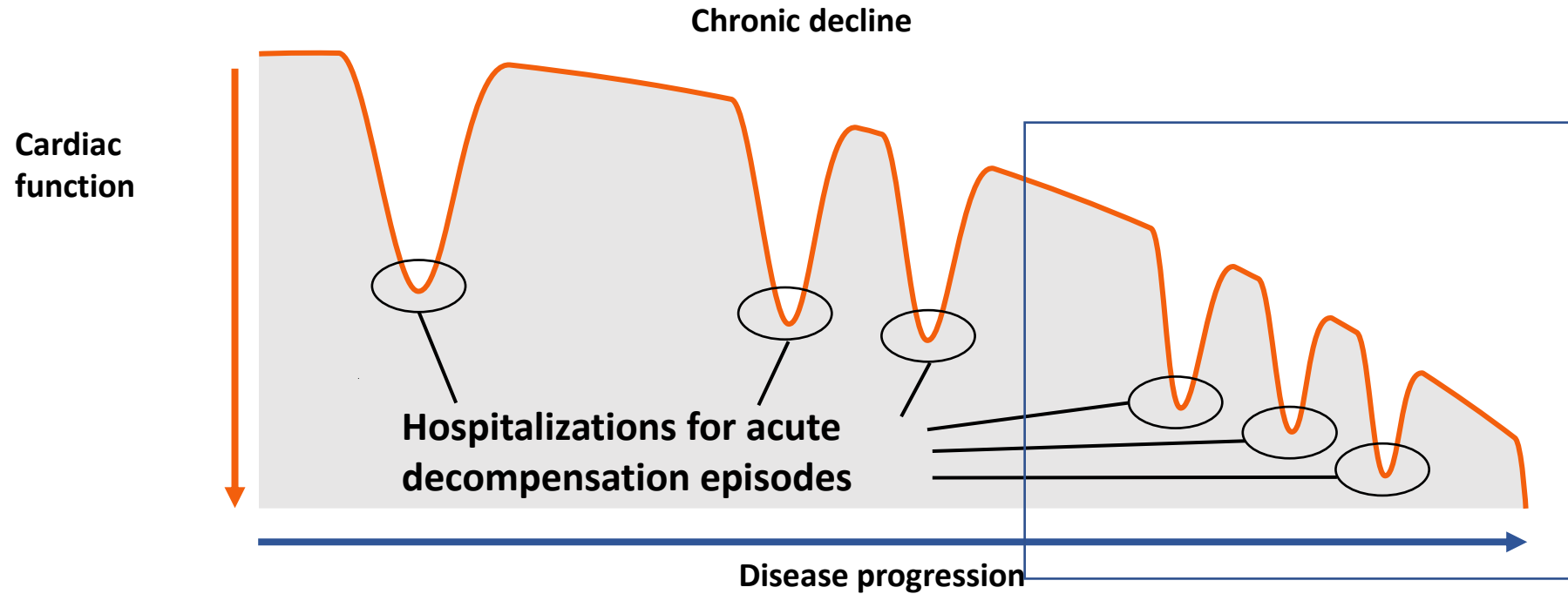
Multi-professional disease management

enotypic overview of management of heart failure with reduced ejection fraction

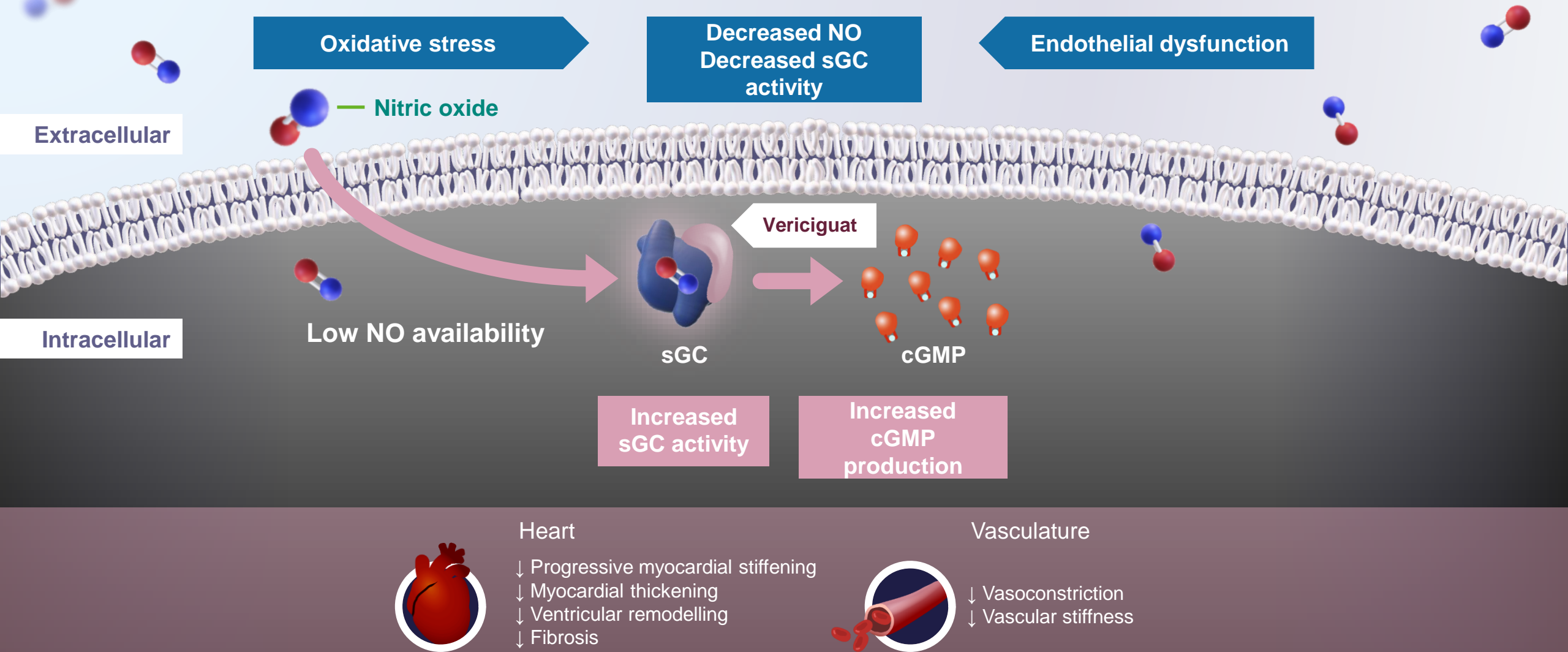
Angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; BB = beta-blocker; beats per minute; BTC = bridge to candidacy; CABG = coronary artery bypass graft; CRT-P = cardiac resynchronization therapy with pacemaker; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge. Colour code for classes of recommendation: Green for Class of recommendation I; Yellow for Class of recommendation IIa (see Table 1 for further details on classes of recommendation).

The Figure shows management options with Class I and IIa recommendations. See the specific Tables for those with Class IIb recommendations.

Heart Failure Deterioration



Vericiguat Increases sGC Activity to Improve Myocardial and Vascular Function¹⁻³

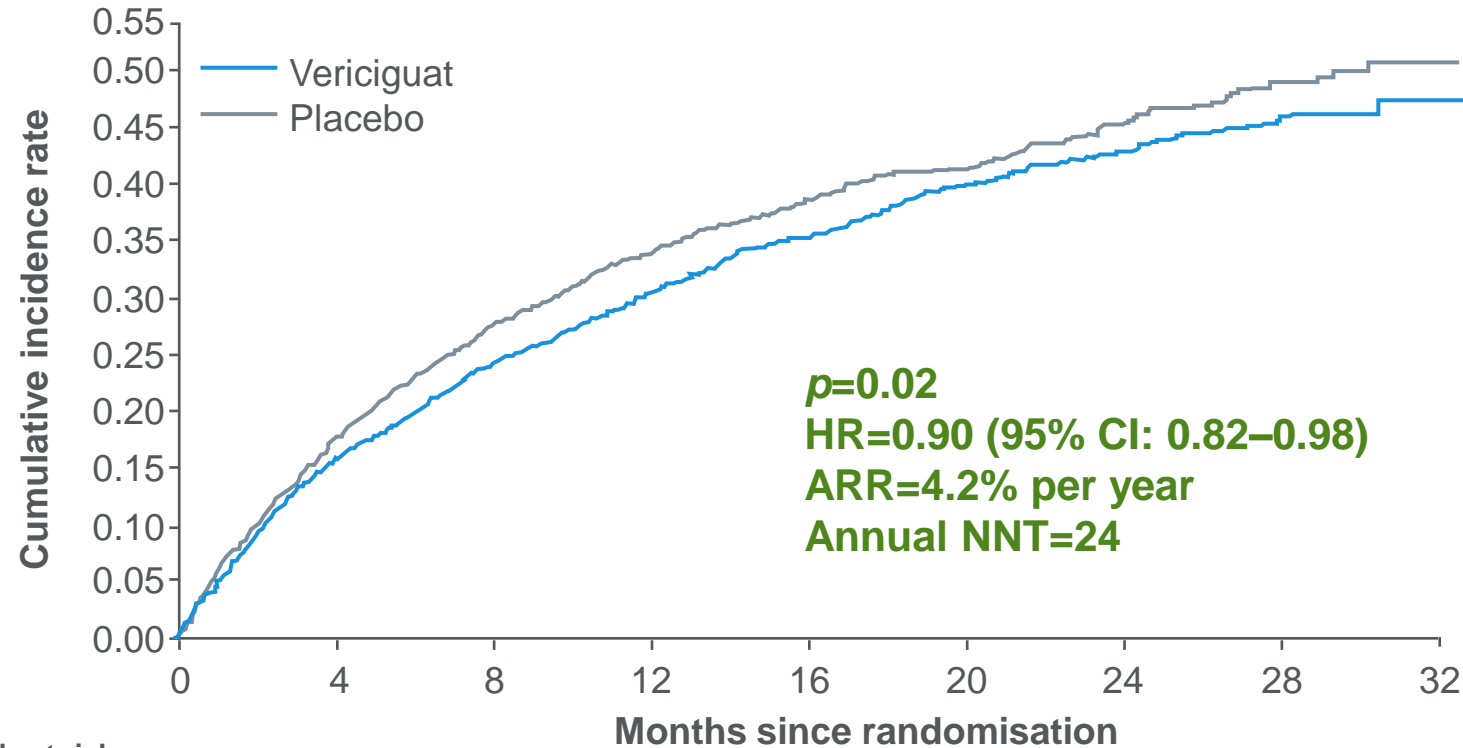


cGMP, cyclic guanosine monophosphate; NO, nitric oxide; sGC, soluble guanylate cyclase

1. Gheorghiade M et al. *Heart Fail Rev.* 2013;18:123–134; 2. Fulton DJR et al. *Antioxidants* (Basel). 2017;6:E54; 3. Breitenstein S et al. *Handb Exp Pharmacol.* 2017;243:225–247

Vericiguat Significantly Reduced the Annualised Absolute Risk of the Primary Composite Outcome by 4.2%

Time to CV death or first HF hospitalisation

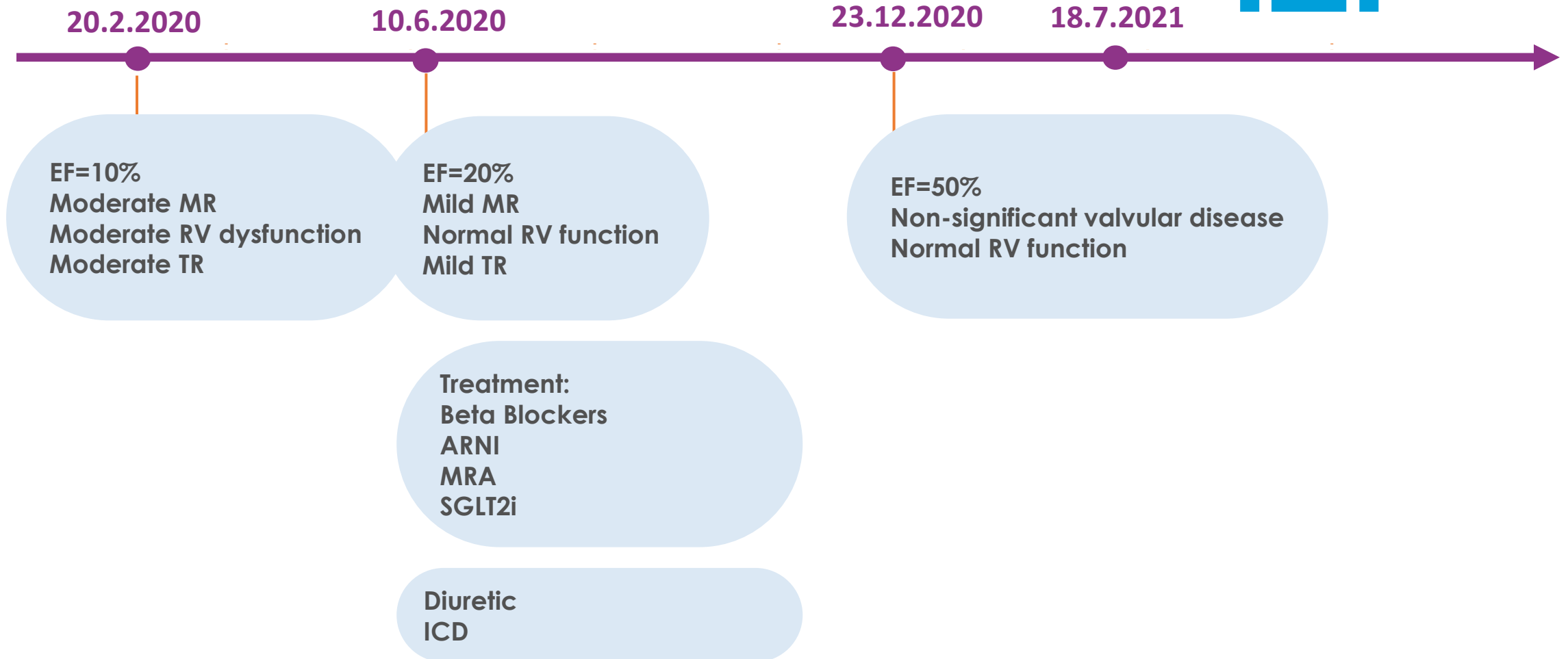
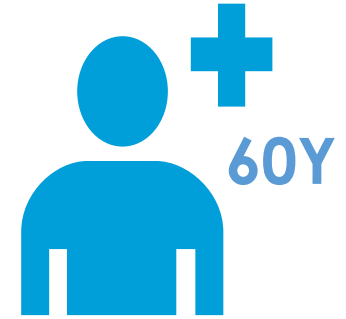


- Median follow-up period: **10.8 months**
- Event rate per 100 patient-years was **33.6% for vericiguat vs 37.8% for placebo**

No at risk:

Vericiguat	2526	2099	1621	1154	826	577	348	125	1
Placebo	2524	2053	1555	1097	772	559	324	110	0

Case presentation – A.B.

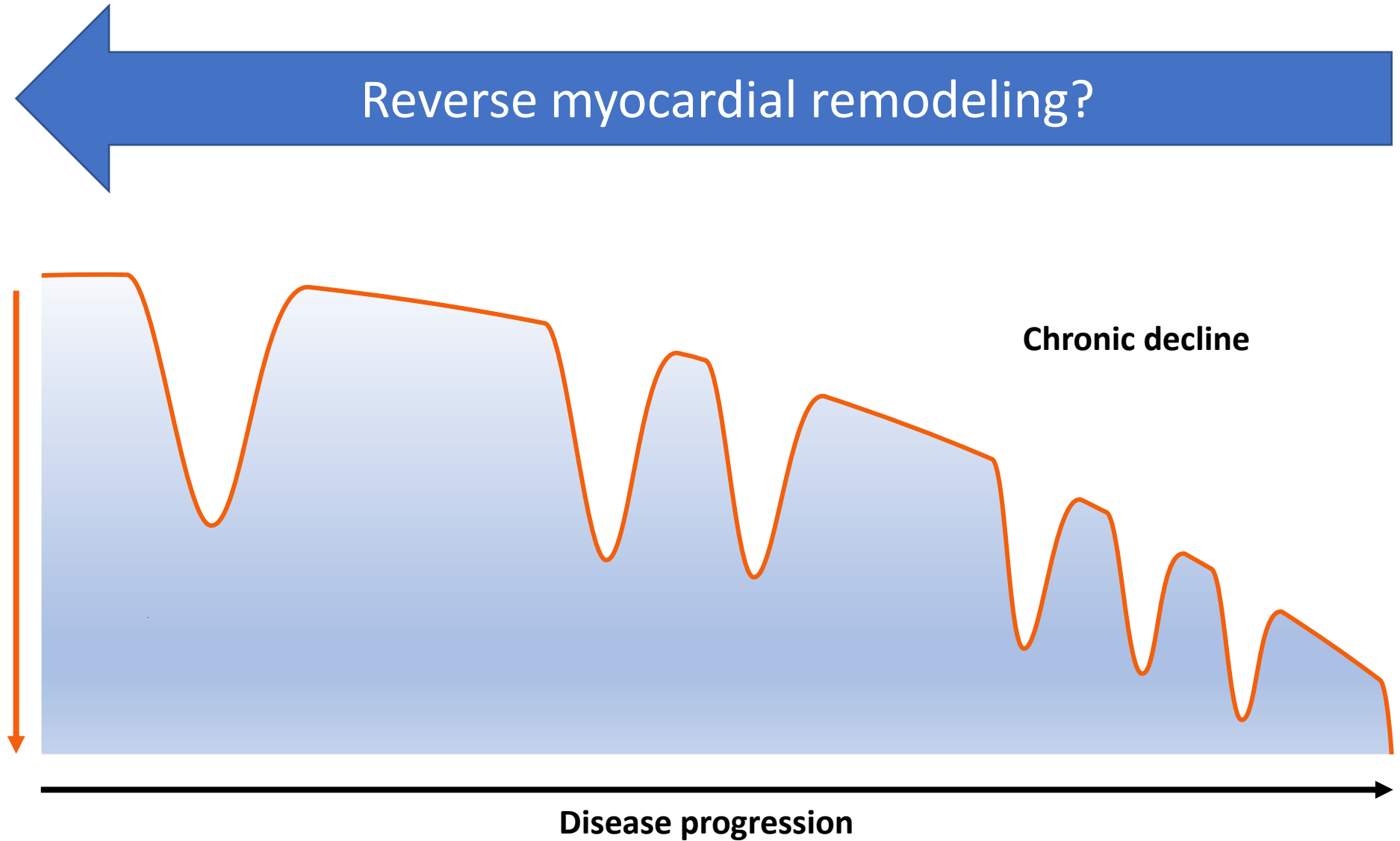


Reverse myocardial remodeling?

Cardiac
function

Chronic decline

Disease progression



Original Article

Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure

Aws Almufleh^{1,2}, Jeffrey Mielniczuk¹

¹Division of Cardiology, U Sciences, King Saud Uni

Received September 15, 30, 2017

Received: 12 April 2018 | Revised: 4 May 2018 | Accepted: 9 May 2018

DOI: 10.1111/1755-5922.12435

ORIGINAL RESEARCH ARTICLE

WILEY Cardiovascular
Therapeutics

The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction

Pieter Martens^{1,2} 
Vandervoort^{1,3} | V

JAMA | Original Investigation

Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction

The Pleiotropic Effects of SGLT2 Inhibitors

Remodeling the Treatment of Heart Failure*

Lee R. Goldberg, MD, MPH

Circulation

ORIGINAL RESEARCH ARTICLE



Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF)

Clinical Drug Investigation
<https://doi.org/10.1007/s40261-022-01166-2>

REVIEW ARTICLE



Pharmacological Anti-Remodelling Effects of Disease-Modifying Drugs in Heart Failure with Reduced Ejection Fraction

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Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF

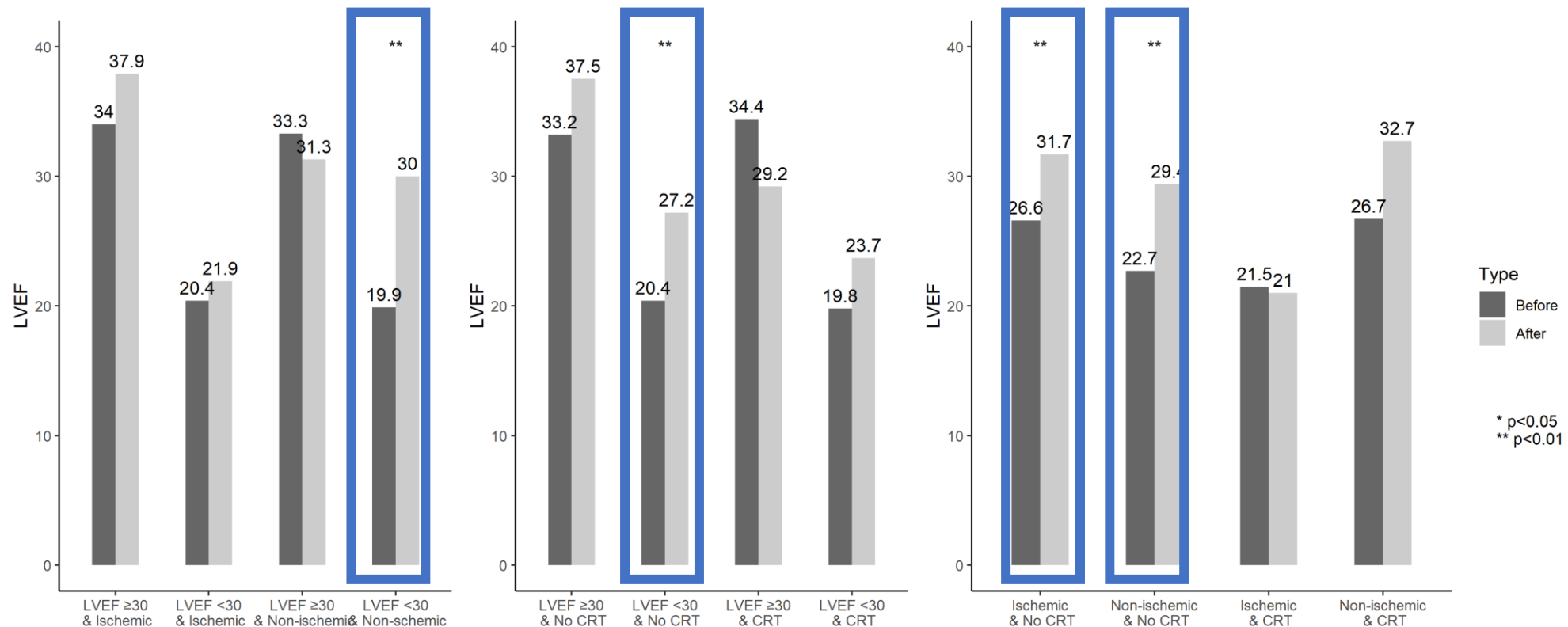


From the EMPA-TROPISM Study

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Characterization of heart failure patients with reverse left ventricular remodelling post-angiotensin receptor blockers/neprilysin inhibitors therapy

Leonid Maizels, Yishay Wasserstrum, Boris Fishman, Amitai Segev, David Ben-Nun, Anan Younis, Dov Freimark, Israel Mazin, Avishay Grupper



HFimpEF: HF with improved EF

Previous LVEF $\leq 40\%$ and a follow-up measurement of LVEF $>40\%$

Recommendation for HF With Improved Ejection Fraction Referenced studies that support the recommendation are summarized in the Online Data Supplements .		
COR	LOE	Recommendation
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and LV dysfunction, even in patients who may become asymptomatic. ¹

Recommendations for an implantable cardioverter-defibrillator in patients with heart failure

An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of an **ischaemic aetiology** (unless they have had a MI in the prior 40 days—see below), and an LVEF $\leq 35\%$ **despite ≥ 3 months of OMT**, provided they are expected to survive substantially longer than 1 year with good functional status.

I

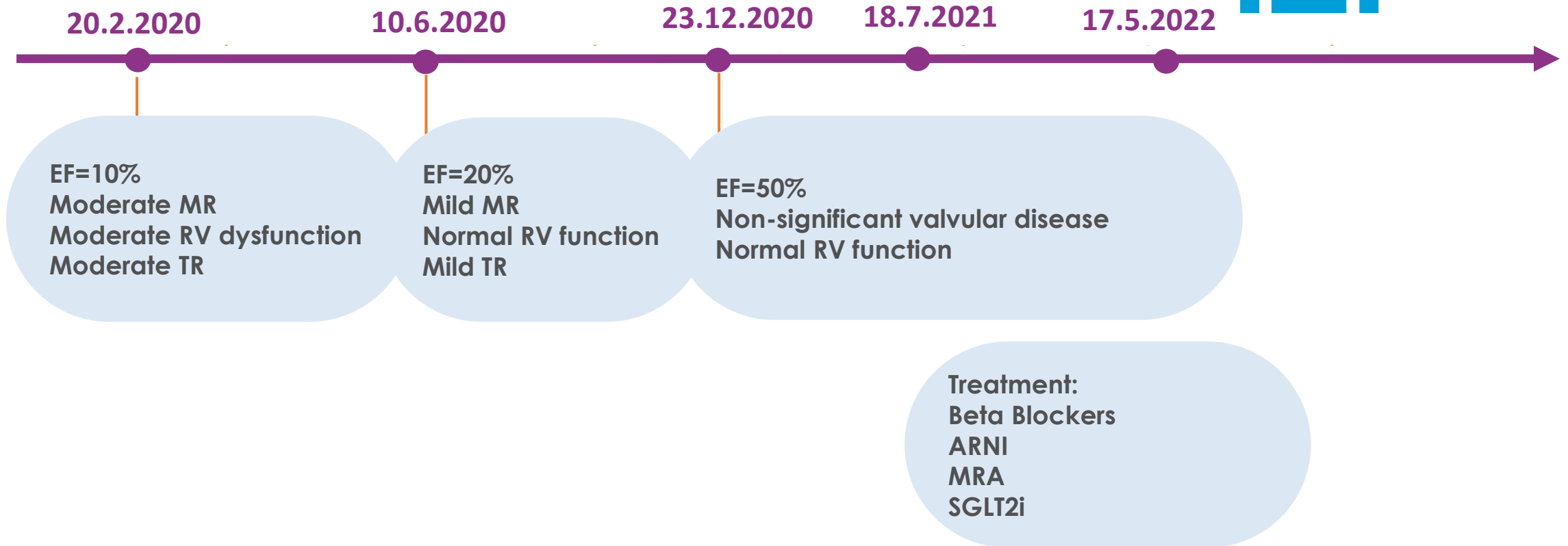
A

An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II-III) of a **non-ischaemic aetiology**, and an LVEF $\leq 35\%$ **despite ≥ 3 months of OMT**, provided they are expected to survive substantially longer than 1 year with good functional status.

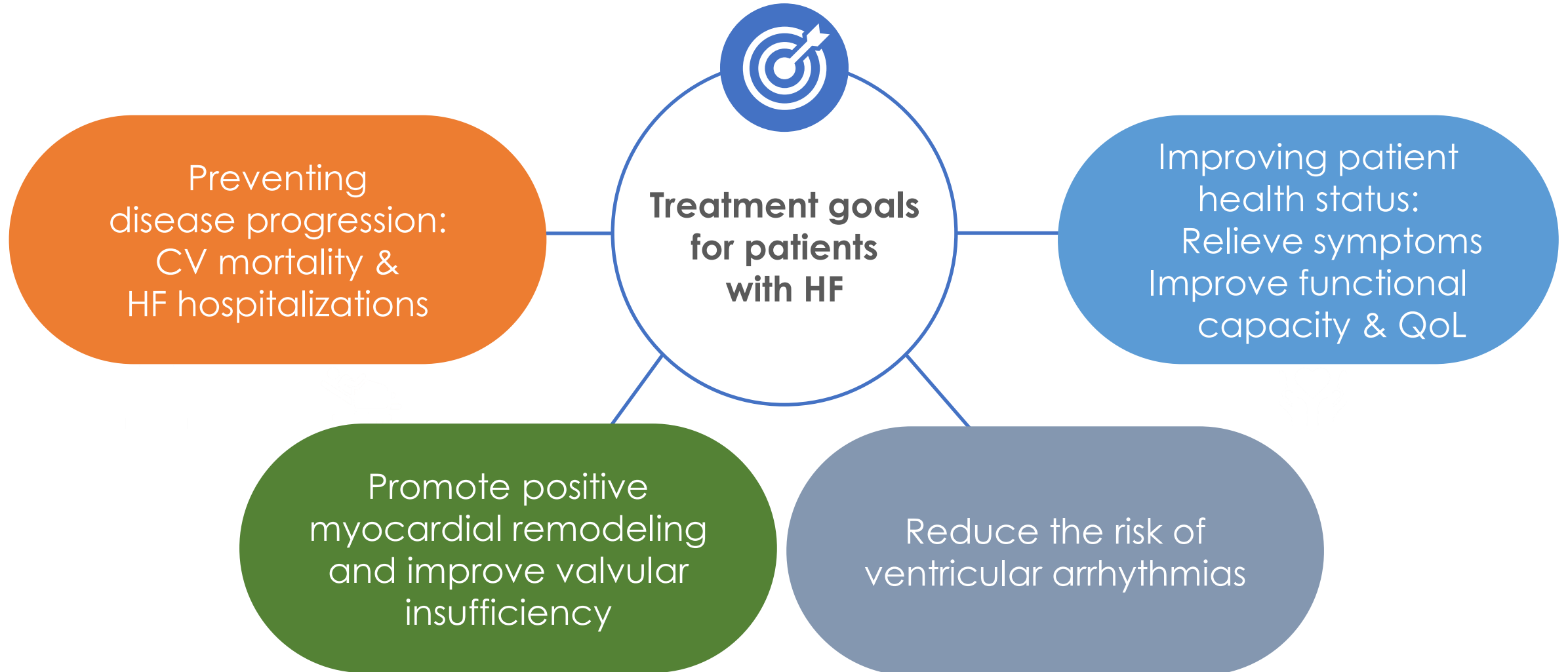
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Case presentation – A.B.



Optimal Medical Therapy for HFrEF



תודה על ההקשבה



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