LAUNCHING THE MOONSHOT FOR HEART FAILURE: TRAVELLING TOWARDS THE TOTALITY OF EVIDENCE TOGETHER

SATURDAY MAY 8, 2021 / 12:35 – 1:25 PM ET

CHFS SCIC

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

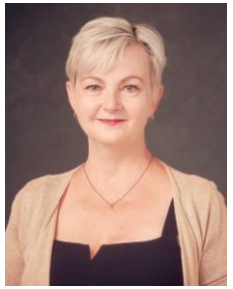
Welcome and Introductions

Shelley Zieroth, MD, FRCPC, FCCS, FHFSA(hon), FESC, FACC, FHFA
Professor, Cardiology, University of MB
Immediate Past President, Canadian Heart Failure Society
Winnipeg, MB

Planning Committee & Faculty

Chair: Shelley Zieroth, MD, FRCPC, FCCS, FHFSA(hon), FESC, FACC, FHFA
Professor, Cardiology, University of MB
Immediate Past President, Canadian Heart Failure Society
Winnipeg, MB

Javed Butler MD, MPH, MBA
Patrick H. Lehan Chair in Cardiovascular Research
Professor and Chairman, Department of Medicine
Professor of Physiology
University of Mississippi Medical Center
Jackson, MS



Jarmila (Jackie) Ratz - HeartLife Foundation of Canada - MB Champion
Canadian Women's Heart Health Alliance –
Patient Advisory Committee Co-Chair (2018-2020) Advocacy Working Group (2020 - 2022)
Winnipeg, MB

Disclosure of Commercial Support

Specific details of relationship:

- This program is made possible through a grant from Boehringer-Ingelheim and Eli-Lilly

Potential for conflict(s) of interest:

- Speakers have received honoraria from BI-Lilly Pharmaceuticals Canada

Mitigating Potential Bias

Potential biases are acknowledged and are mitigated by presenting data supported by national and international guidelines, and as follows:

- Information presented is evidence-based
- Material has been developed and reviewed by a Planning Committee

Off-label uses of drugs will be discussed and identified as such by the speaker

Agenda

TIME (EDT)	TOPIC	SPEAKER
12:35 pm	Welcome & Introductions: **THE URGENCY TO TREAT**	Shelley Zieroth, MD
12:40 pm	**WHAT'S IN A MOONSHOT FOR ME?**	Jarmila (Jackie) Ratz
12:52 pm	**OPTIMIZING HEART FAILURE TREATMENT: NEED FOR EARLY AND OPTIMAL REGIMEN**	Javed Butler, MD
1:07 pm	**PANEL DISCUSSION AND Q&A**	Shelley Zieroth, MD, Jarmila (Jackie) Ratz & Javed Butler, MD
1:22 pm	Closing Remarks	Shelley Zieroth, MD

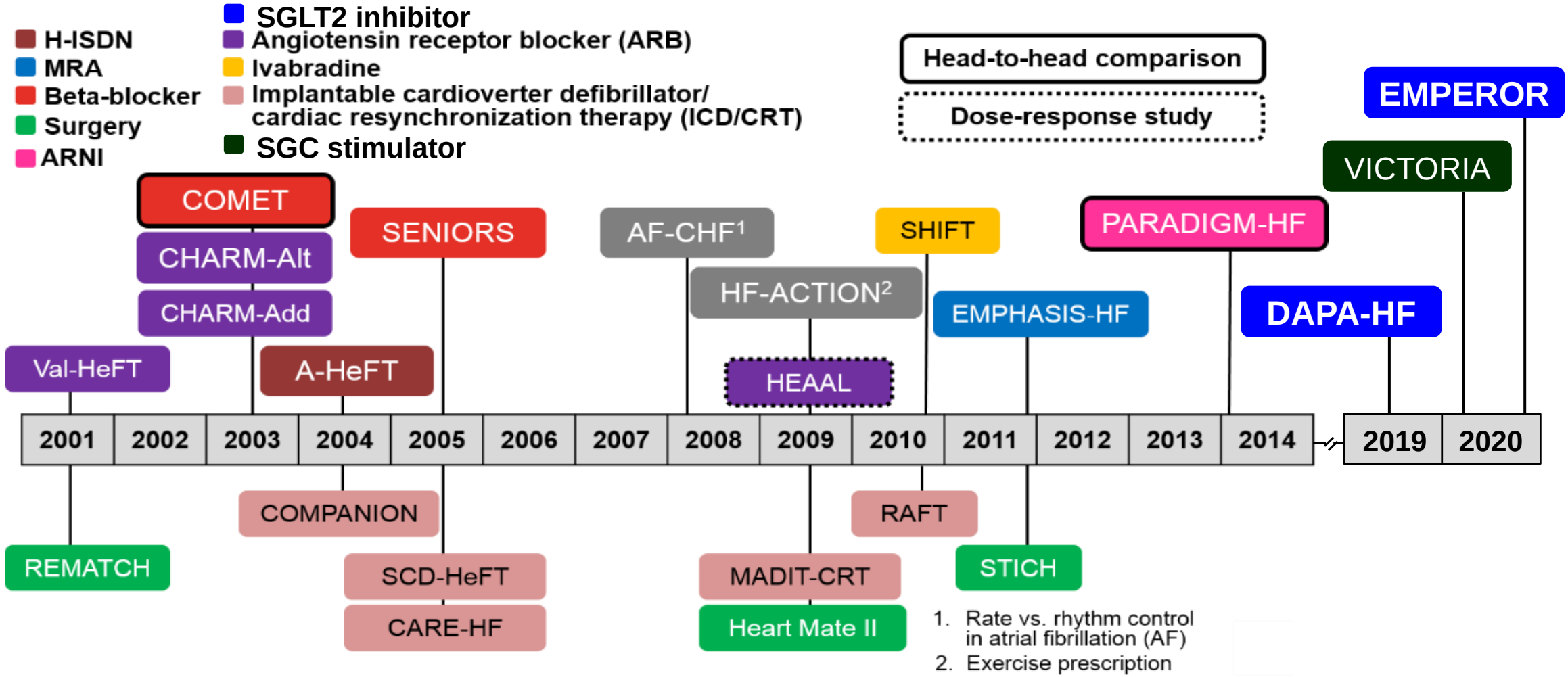
Learning Objectives

- Recognize the necessity to treat heart failure with the same urgency as other diseases with high-mortality rates
- Summarize the foundational evidence that support best practices for successful management of HFrEF
- Appreciate the cardiovascular and renal risk lowering benefits and functional improvements associated with SGLT2i’s

The Urgency To Treat

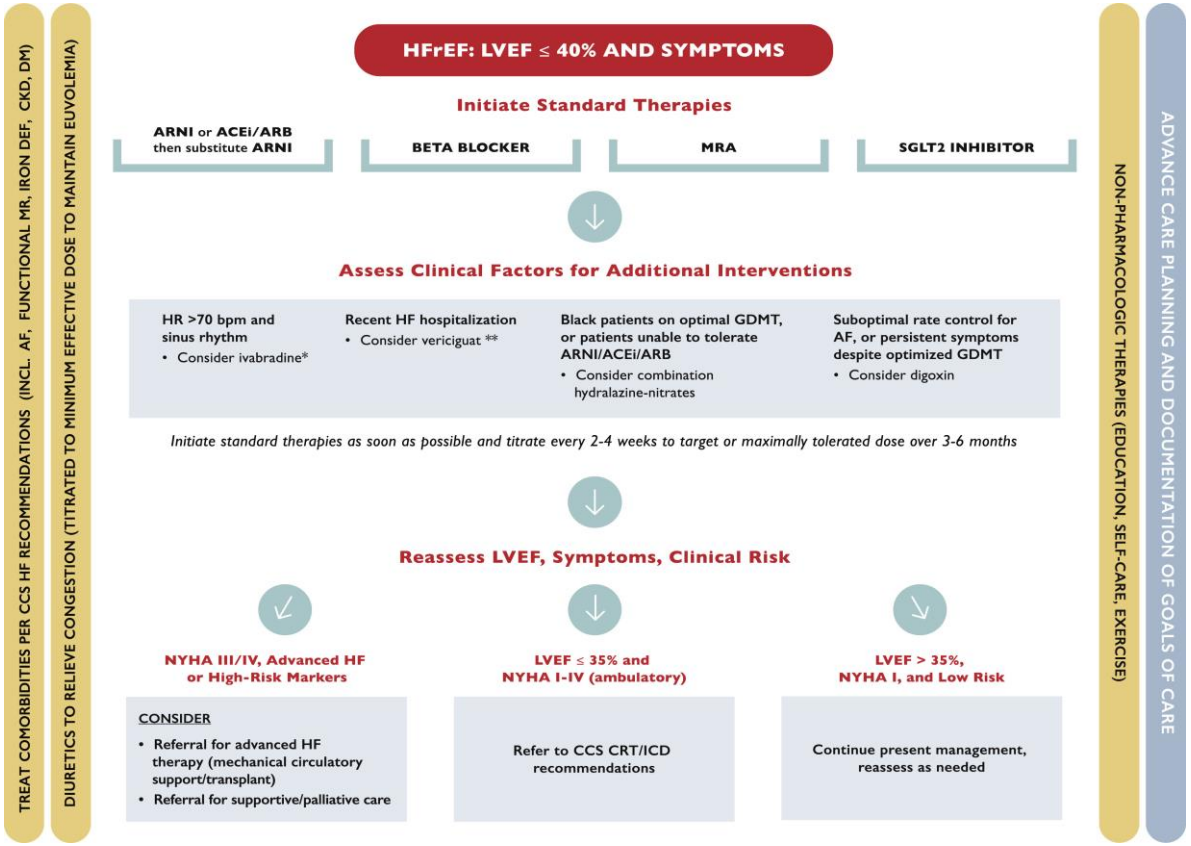
Shelley Zieroth, MD, FRCPC, FCCS, FHFSA(hon), FESC, FACC, FHFA
Professor, Cardiology, University of MB
Immediate Past President, Canadian Heart Failure Society
Winnipeg, MB

HFrEF: Positive trials 2001–2020



Adapted from McMurray JJV. Eur J Heart. 2015;36:3467-70

2021 CCS/CHFS Heart Failure Guidelines Update: Therapeutic Approach to Patients With HFrEF

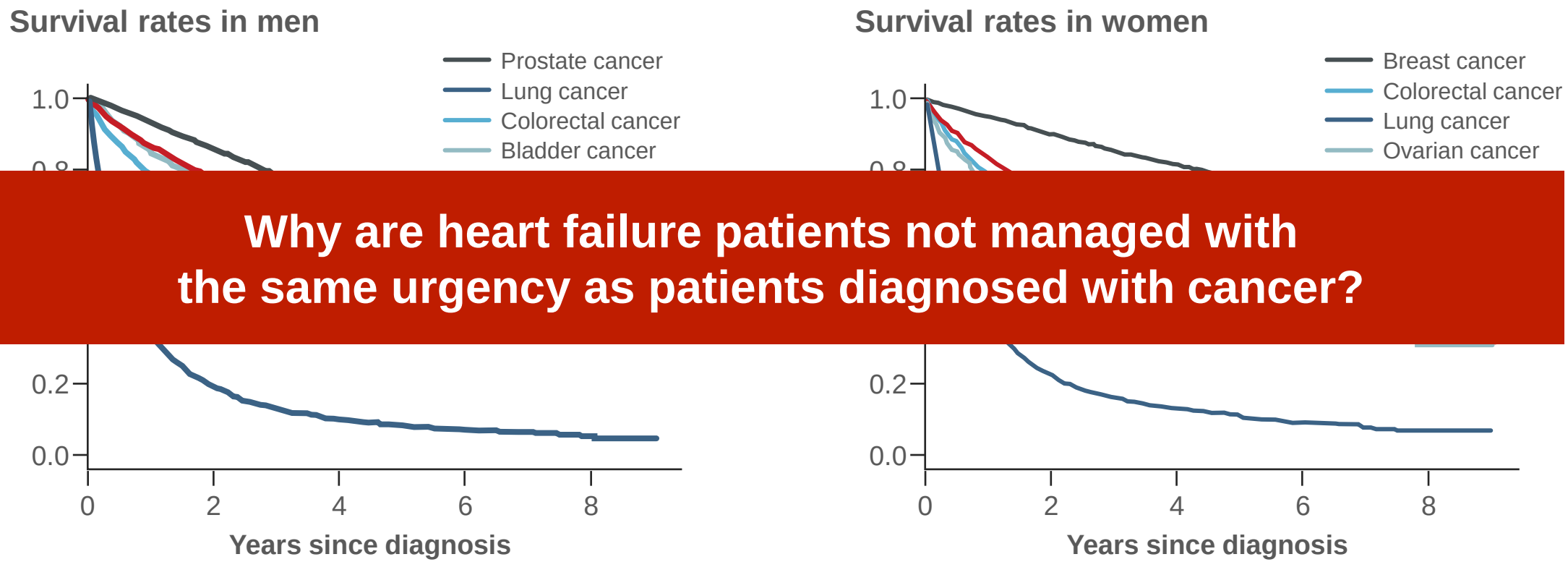


ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT, sodium glucose transport. * Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) 77 bpm in sinus rhythm. ** Vericiguat is not yet approved for use in Canada.

Canadian Journal of Cardiology 2021 37531-546DOI: (10.1016/j.cjca.2021.01.017)

Mortality Rate is Higher for Heart Failure Than Many Cancers

The mortality rate for patients with chronic HF is as high as 50% at 5 years post-diagnosis[1,2,3]



Why are heart failure patients not managed with the same urgency as patients diagnosed with cancer?

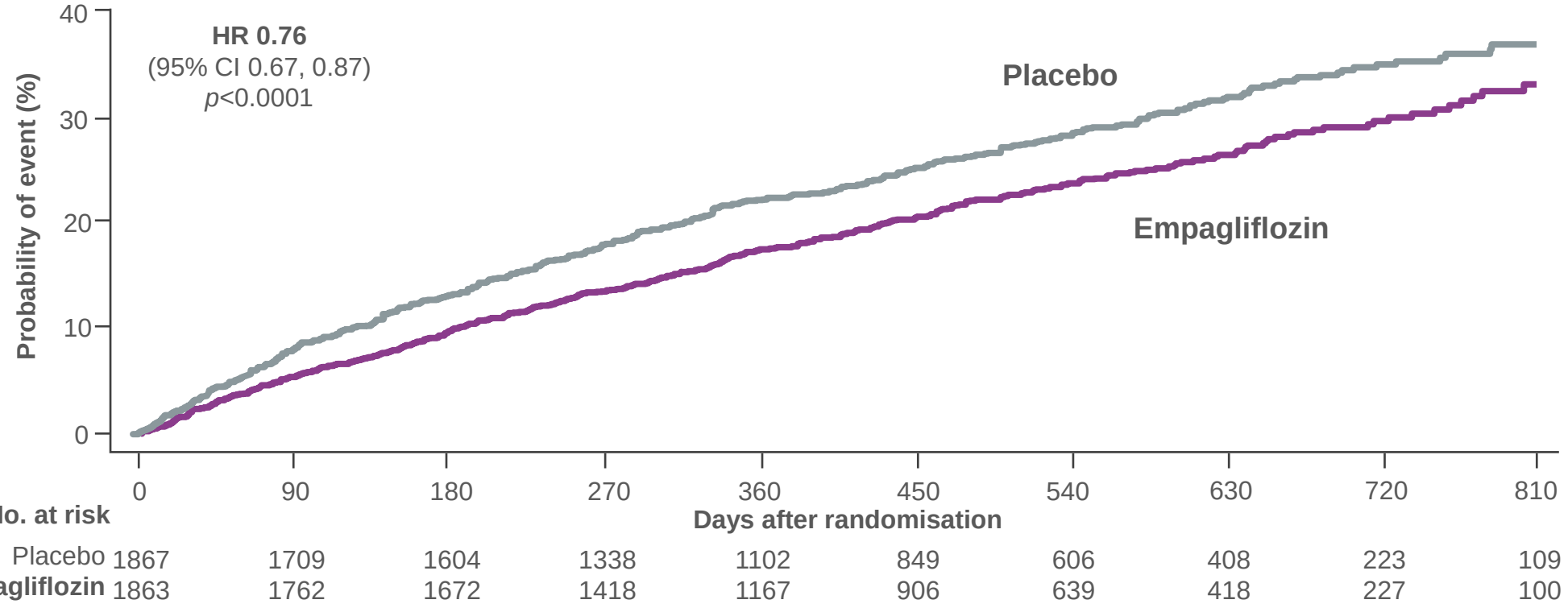
MED/ENT/0409
HF, heart failure
1. Mamas et al. Eur J Heart Fail. 2017;19(9):1095-1104; 2. Benjamin et al. Circulation 2017;135(10):e146-e603; 3. Roger et al. JAMA 2004;292:344–50


Heart Failure
MOONSHOT

What’s in a Moonshot for Me?

Jarmila (Jackie) Ratz - HeartLife Foundation of Canada - MB Champion
Canadian Women's Heart Health Alliance - Patient Advisory Committee Co-Chair (2018-2020) / Advocacy Working Group (2020 - 2022)
Winnipeg, MB

EMPEROR REDUCED: Time to all-cause mortality, hospitalization for heart failure, or emergency department or urgent care visits for heart failure requiring IV therapy

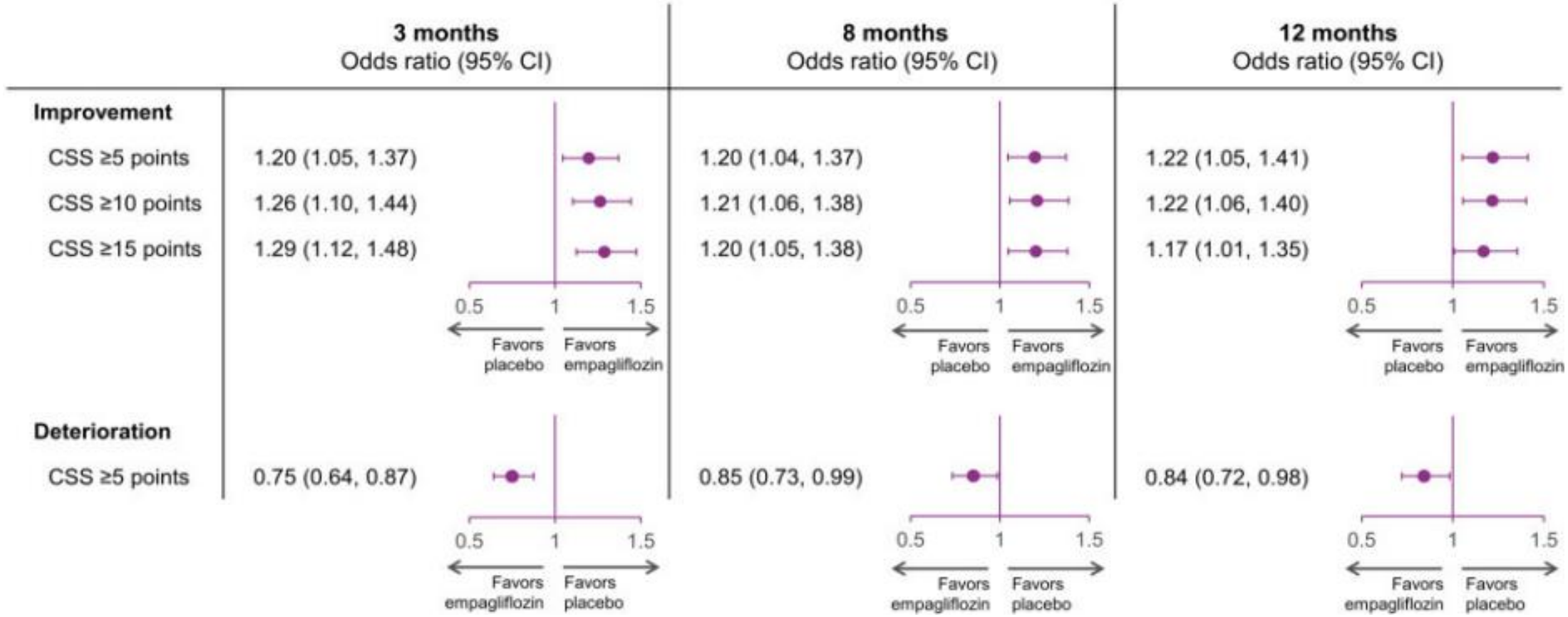


Statistically significant difference 12 days after randomization
Statistical significance was sustained from day 34.

IV, intravenous; HR, hazard ratio
Pre-specified exploratory endpoints
Packer et al. Circulation 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.051783

EMPEROR REDUCED: Patients with symptomatic HFrEF randomized to empagliflozin were more likely to improve their KCCQ-CSS and less likely to deteriorate

Responder analysis for KCCQ-CSS at 3, 8, and 12 months



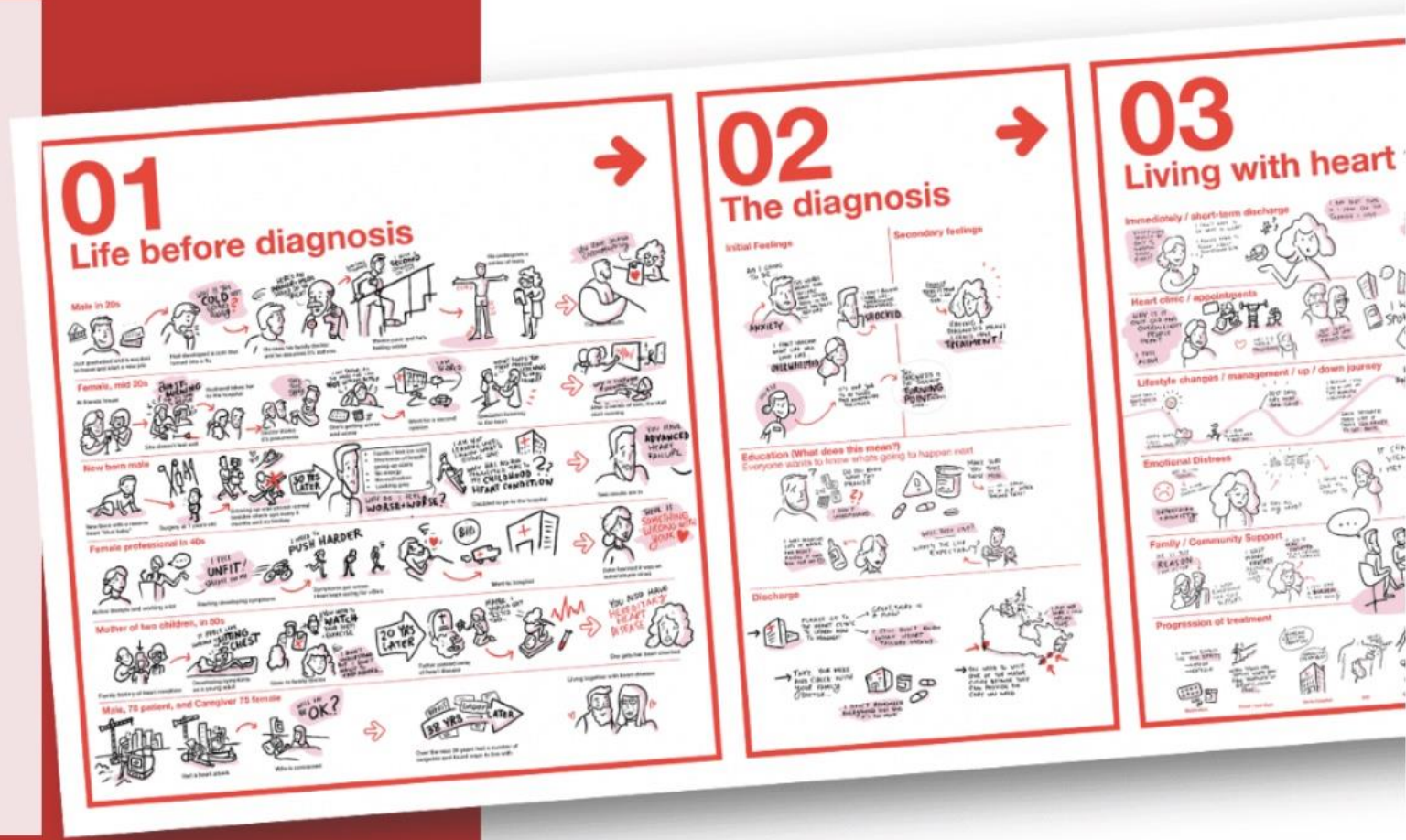
J Butler, M Packer et al. European Heart Journal (2021) 00, 1–10 doi:10.1093/eurheartj/ehaa1007

Patient Journey

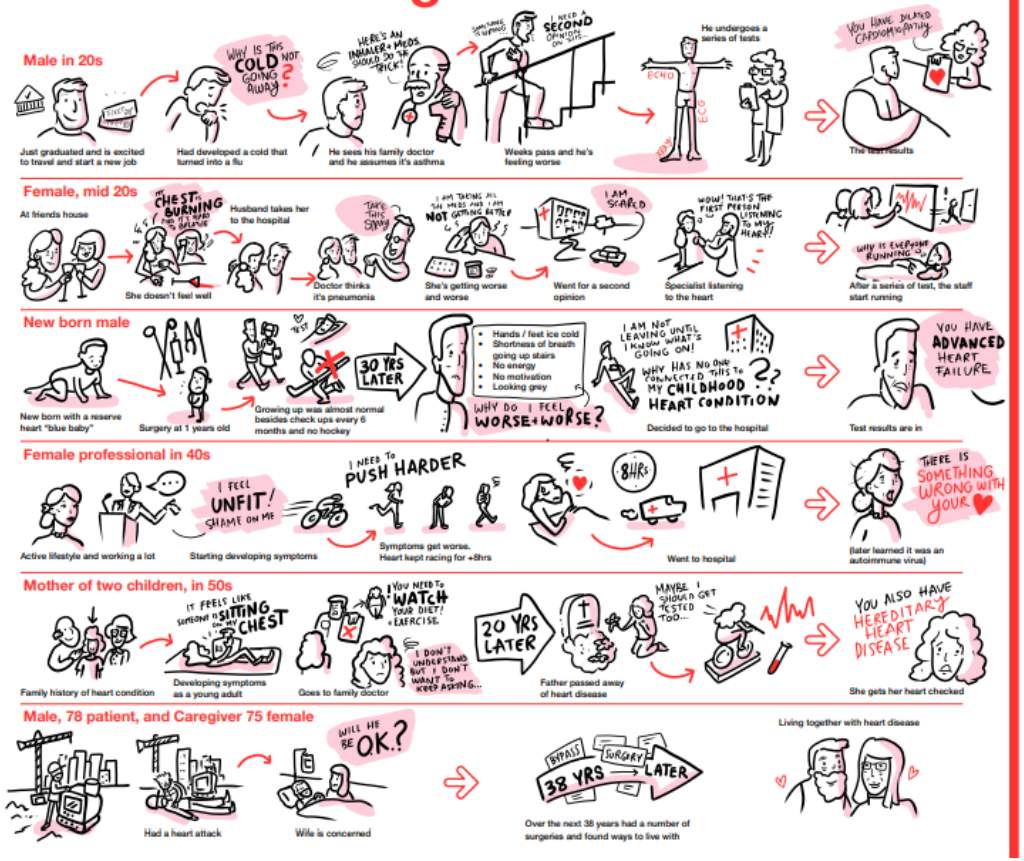
The patient journey map captures and summarizes real stories, emotions, questions, and lifestyle challenges heart failure patients experience in their care continuum. By truly empathizing with and learning what heart failure patients experience today, we can highlight the current needs, pain points, and wishes on how to improve care.

We're taking the first step to ensure the patient's voice is heard.

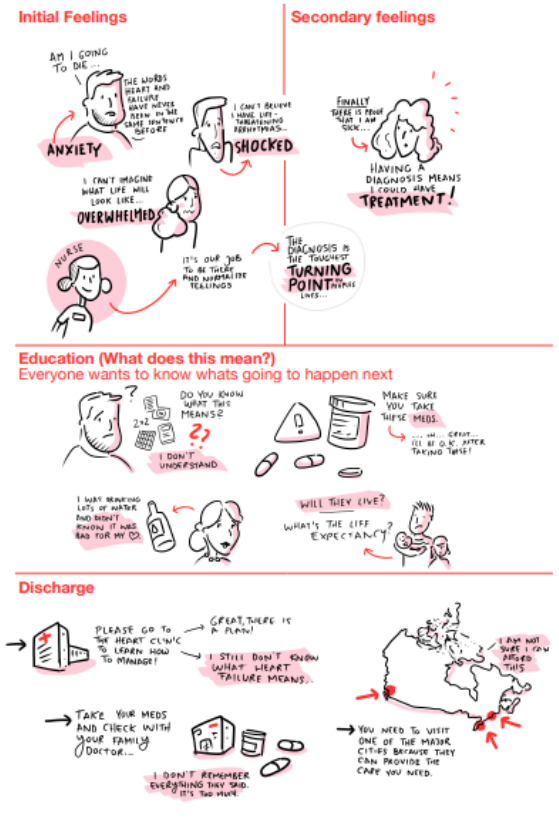
Download



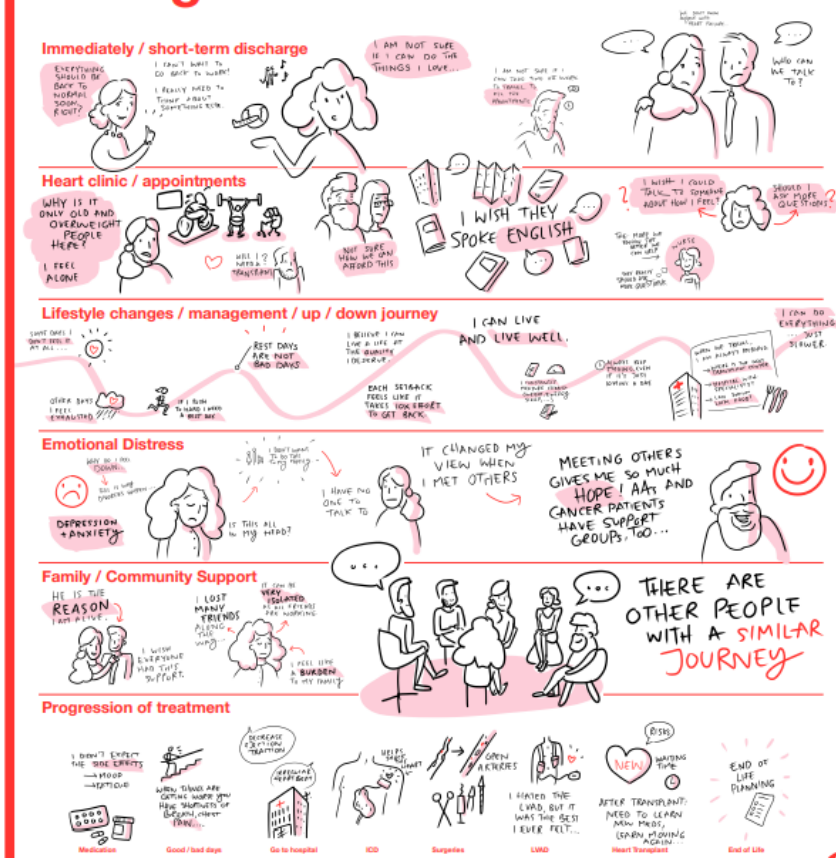
01
Life before diagnosis



02
The diagnosis



03
Living with heart failure



Patient Charter of Rights

Our heart failure patient and caregiver charter was created to support our advocacy towards the implementation of a national standard of care for Canadians living with heart failure and their caregivers.

Download

What Is A Patient/ Caregiver Charter?

A Patient/Caregiver Charter outlines a **set of rights and responsibilities** to support the creation and implementation of a national standard of care for Canadians living with HF and their caregivers.

Access to care, medical therapies, and support services varies widely from one region to the next. The overall goal of this Charter is to support establishment of **high quality care** that is provided consistently across the country. It provides a guide:

FOR PATIENTS AND CAREGIVERS:

- To know what to expect throughout their care continuum.
- To be empowered to ask the questions that matter to them.
- To understand their individual responsibilities for their own health.

FOR HEALTHCARE PROVIDERS:

- To understand the lived experience, recognize opportunities within their system of care, and identify solutions that will fit their local setting.

FOR POLICYMAKERS AND PRIVATE PAYERS:

- To guide the identification of opportunities within their jurisdictions and support development of solutions.


HeartLife
It's
About
Life
Not Failure

Optimizing Heart Failure Treatment
Need for Early and Optimal Regimen

Javed Butler, MD, MPH, MBA
Patrick H. Lehan Chair in Cardiovascular Research
Chairman and Professor of Medicine
Professor of Physiology and Biophysics
University of Mississippi
Jackson, MS

Many mechanisms have been suggested as contributing to the CV and kidney effects of SGLT2 inhibitors

↑ **Glucosuria**	↓ Glucose toxicity ↓ Inflammation ↓ Oxidative stress ↓ Atherosclerosis
↓ **Calories**	↓ Epicardial fat ↓ Body fat ↓ Inflammation ↓ Fibrosis ↑ Cardiac contractility
↓ **Insulin: glucagon ratio**	↑ Ketone metabolism ↑ Mitochondrial ATP ↑ Myocardial energy
↑ **Uricosuria**	↓ Plasma uric acid ↓ Oxidative stress ↓ Atherosclerosis

↑ **TGF**	↑ Afferent arteriole constriction ↓ Glomerular hypertension ↓ Albuminuria ↓ Hyperfiltration
↓ **Intracellular Na^+ in cardiomyocytes**	↓ Cardiac Na^+/H^+ exchange ↓ Oxidative stress
↓ **Ventricular arrhythmia**	
↓ **Blood pressure**	↓ Arterial stiffness

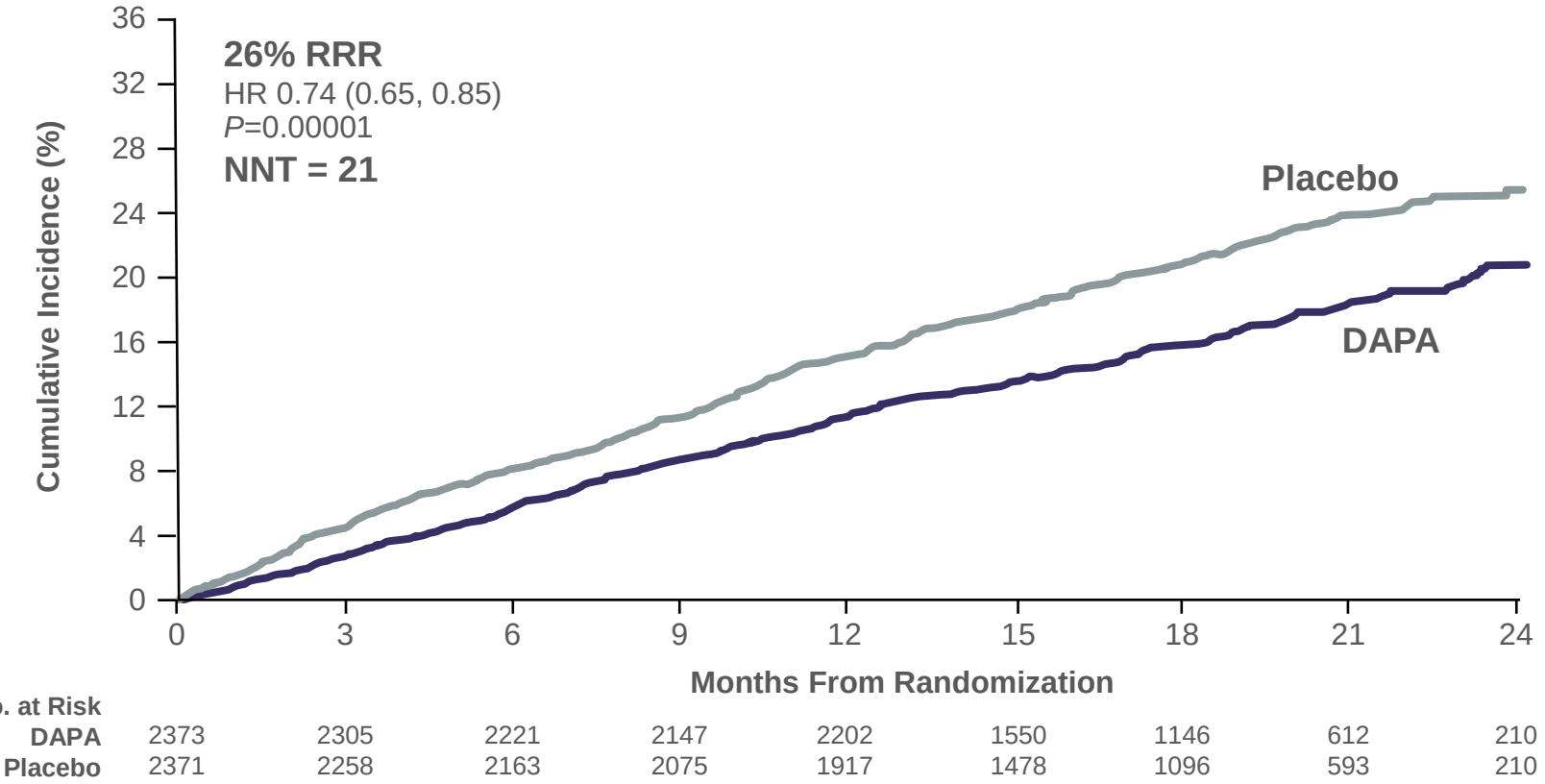
↑ **Haemodynamic changes**	↓ Plasma volume ↓ LV wall stress ↓ Arterial wall structure/function
↓ **Cardiac preload**	↓ Atrial pressure ↓ Myocardial stretch ↓ Risk of arrhythmia
↓ **Cardiac afterload**	↓ Myocardial O_2 demand
↑ **Haematocrit**	↑ Myocardial and renal O_2 supply

This material is for educational purposes only with the intent to communicate the results of the published EMPEROR-Reduced Trial. Empagliflozin is not indicated for patients with Heart Failure. Please review local approved product indication for more information.

ATP, adenosine triphosphate; CV, cardiovascular; LV, left ventricular; SGLT2, sodium-glucose co-transporter-2; TGF, tubuloglomerular feedback

1. Verma S *et al. JAMA Cardiol* 2017;2:939; 2. Rajasekeran H *et al. Kidney Int* 2016;89:524; 3. Verma S & McMurray J. *Diabetologia* 2018;61:2108; 4. Pham SV & Chilton RJ. *Am J Cardiol* 2017;120:S53; 5. Abdelgadir E *et al. J Clin Med Res* 2018;10:615; 6. Heerspink HJ *et al. Kidney Int* 2018;94:26

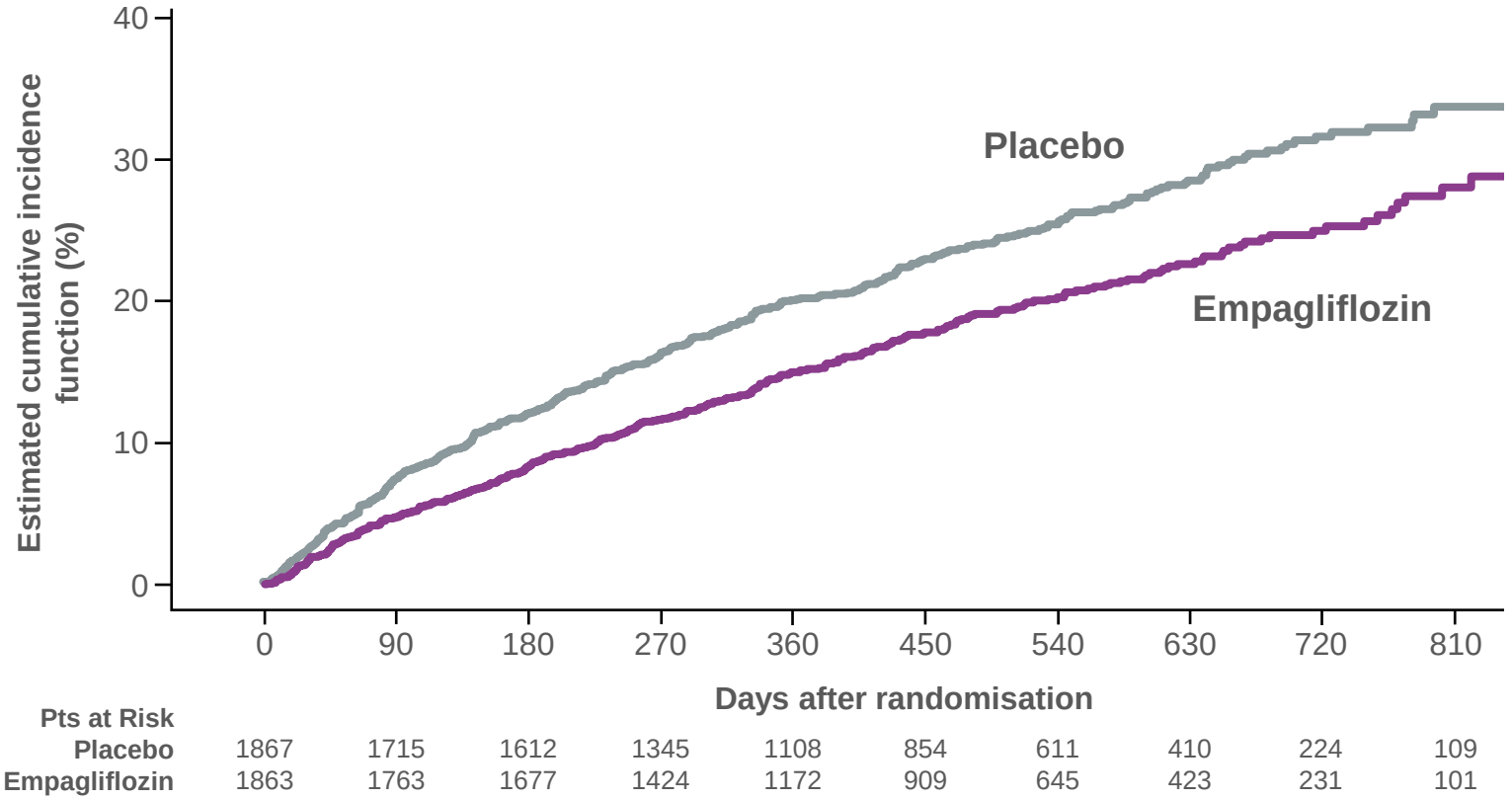
Primary Endpoint: CV Death or hHF or an URGENT HF Visit[1,2]



NNT=number needed to treat; RRR=relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381(21)1995-2008; 2. McMurray J. Presented at: European Society of Cardiology Congress; September 1, 2019; Paris, France.

Primary endpoint: 25% RRR in first adjudicated CV Death or hospitalization for heart failure



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

RRR 25%

ARR 5.2%

NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years

Placebo:
462 patients with event
Rate: 21.0/100 patient-years

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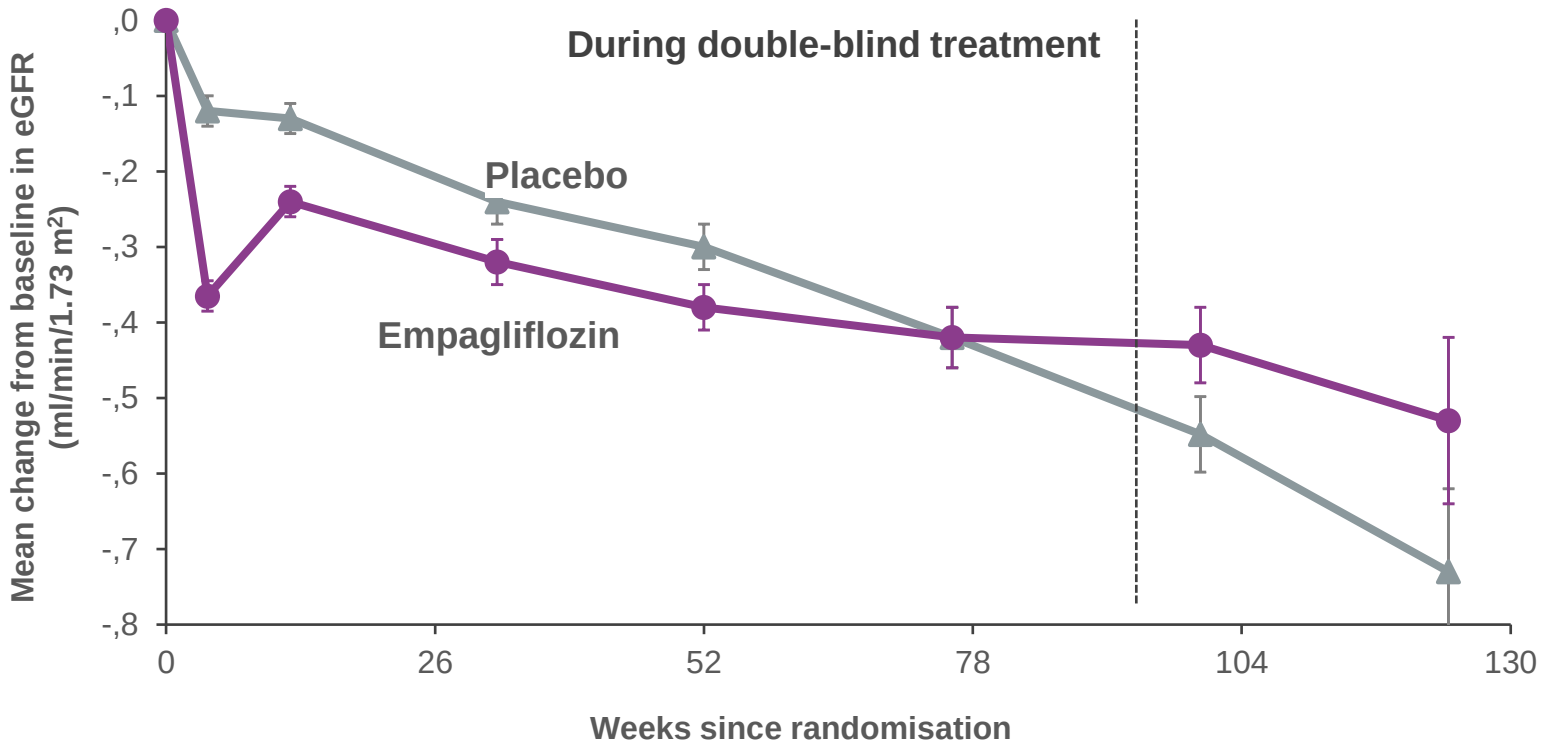
Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190

Significant eGFR slope difference of Empagliflozin vs Placebo



In 966 patients, eGFR was reassessed at the end of the trial, 23-42 days after the withdrawal of double blind therapy, thus allowing unconfounded assessment of the effects of the treatment.

Over 16 months, eGFR deteriorated by

- 4.2 ml/min/1.73m²
on placebo

- 0.9 ml/min/1.73m²
on Empagliflozin

P <0.0001

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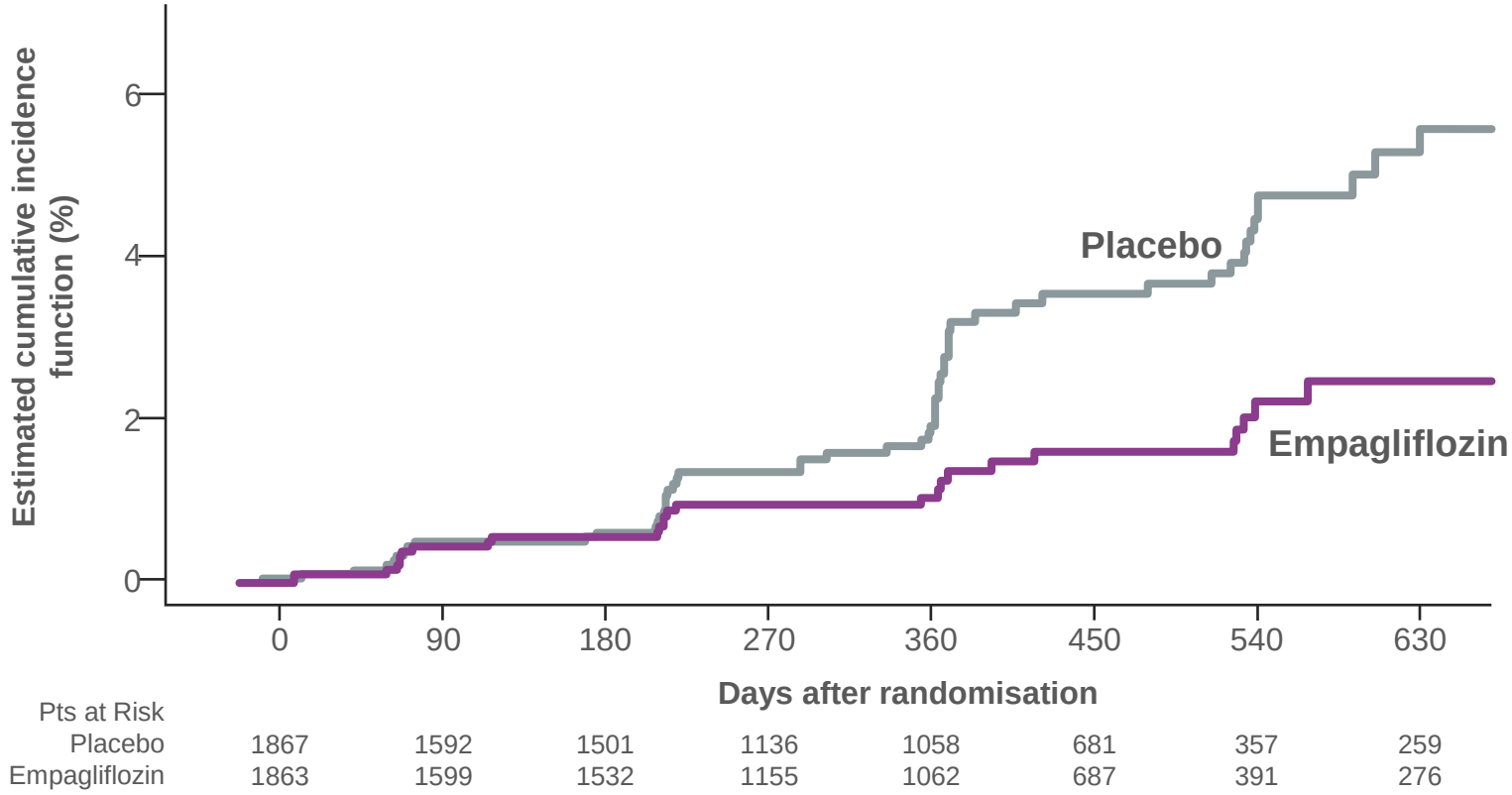
Empagliflozin reduced composite renal endpoint (end-stage kidney disease or sustained profound decrease in eGFR) by 50% RRR*



Pts at Risk								
Placebo	1867	1592	1501	1136	1058	681	357	259
Empagliflozin	1863	1599	1532	1155	1062	687	391	276

RRR 50%

ARR 1.5%

HR 0.50
(95% CI 0.32, 0.77)

Empagliflozin:
30 patients with event
Rate: 1.6/100 patient-years

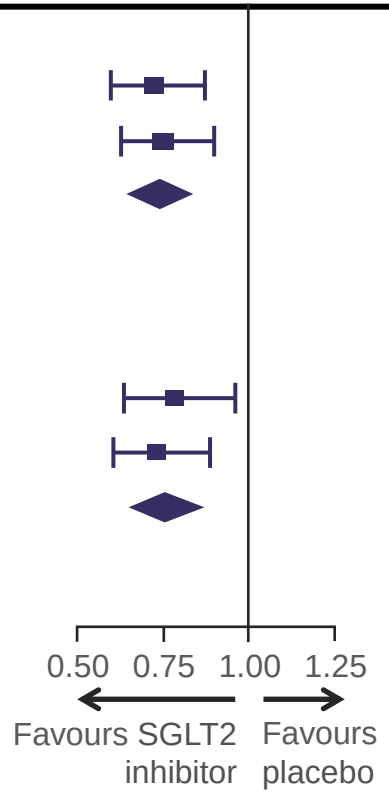
Placebo:
58 patients with event
Rate: 3.1/100 patient-years

This material is for educational purposes only with the intent to communicate the results of the published EMPEROR-Reduced Trial. Empagliflozin is not indicated for patients with Heart Failure. Please review local approved product indication for more information.

*Exploratory Endpoint; Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m^2 for patients with eGFR ≥30 ml/min/1.73 m^2 at baseline (<10 ml/min/1.73 m^2 for patients with eGFR <30 ml/min/1.73 m^2 at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Cox regression model including covariates age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, and baseline LVEF. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PY, patient years. ARR, absolute risk reduction; RRR, relative risk reduction; Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190

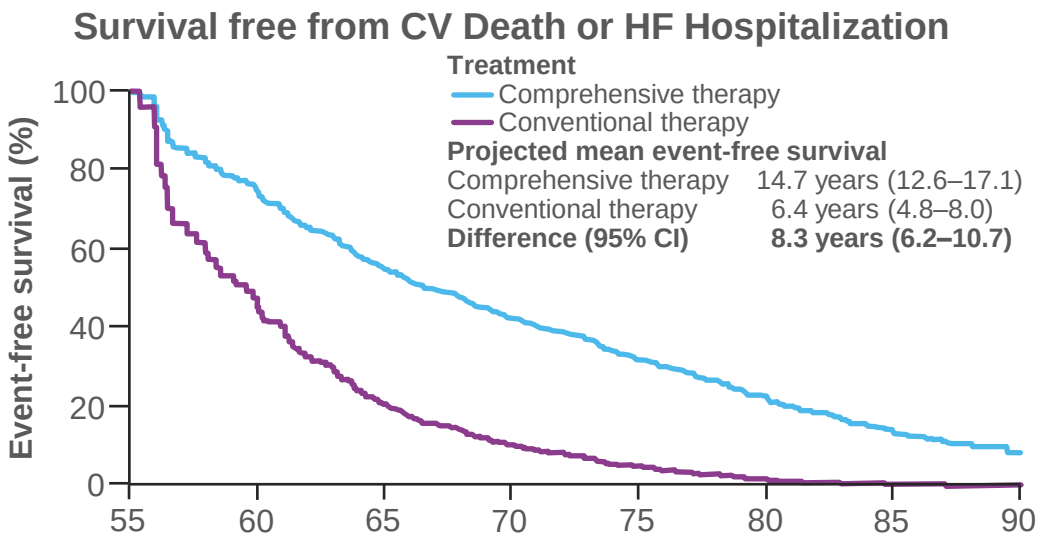
Diabetes status

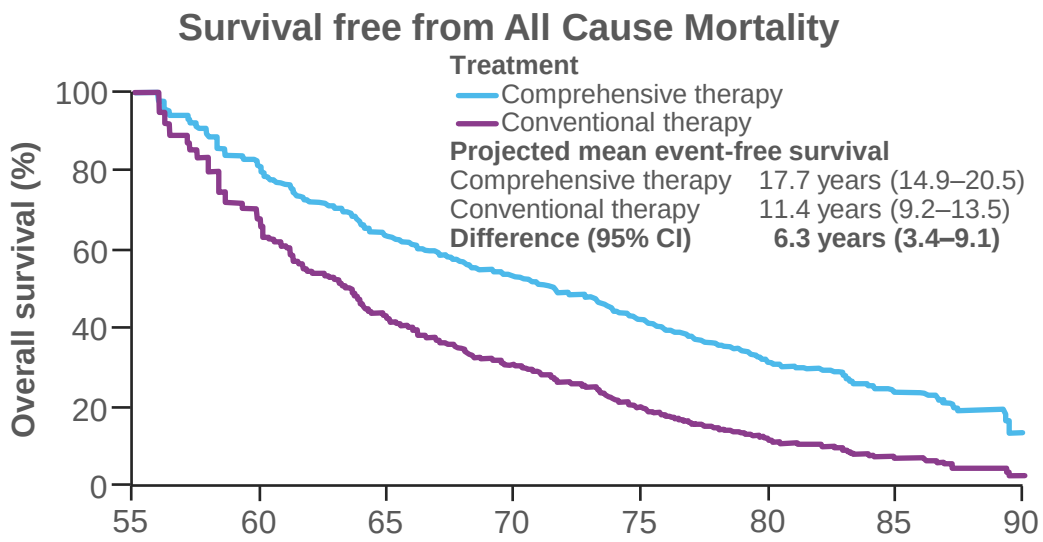
	SGLT2 inhibitor	Placebo	HR (95% CI)
	n with event/N analysed (%)		
With diabetes			
EMPEROR-Reduced	200/927 (21.6)	265/929 (28.5)	0.72 (0.60, 0.87)
DAPA-HF	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63, 0.90)
Subtotal			0.74 (0.65, 0.84)
Test for overall treatment effect, *p*<0.0001			
Test for heterogeneity of effect, *p*=0.76			
Without diabetes			
EMPEROR-Reduced	161/936 (17.2)	197/938 (21.0)	0.78 (0.64, 0.97)
DAPA-HF	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60, 0.88)
Subtotal			0.75 (0.65, 0.87)
Test for overall treatment effect, *p*<0.0001			
Test for heterogeneity of effect, *p*=0.65			



Test for treatment by subgroup interaction, *p*=0.81

Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials.





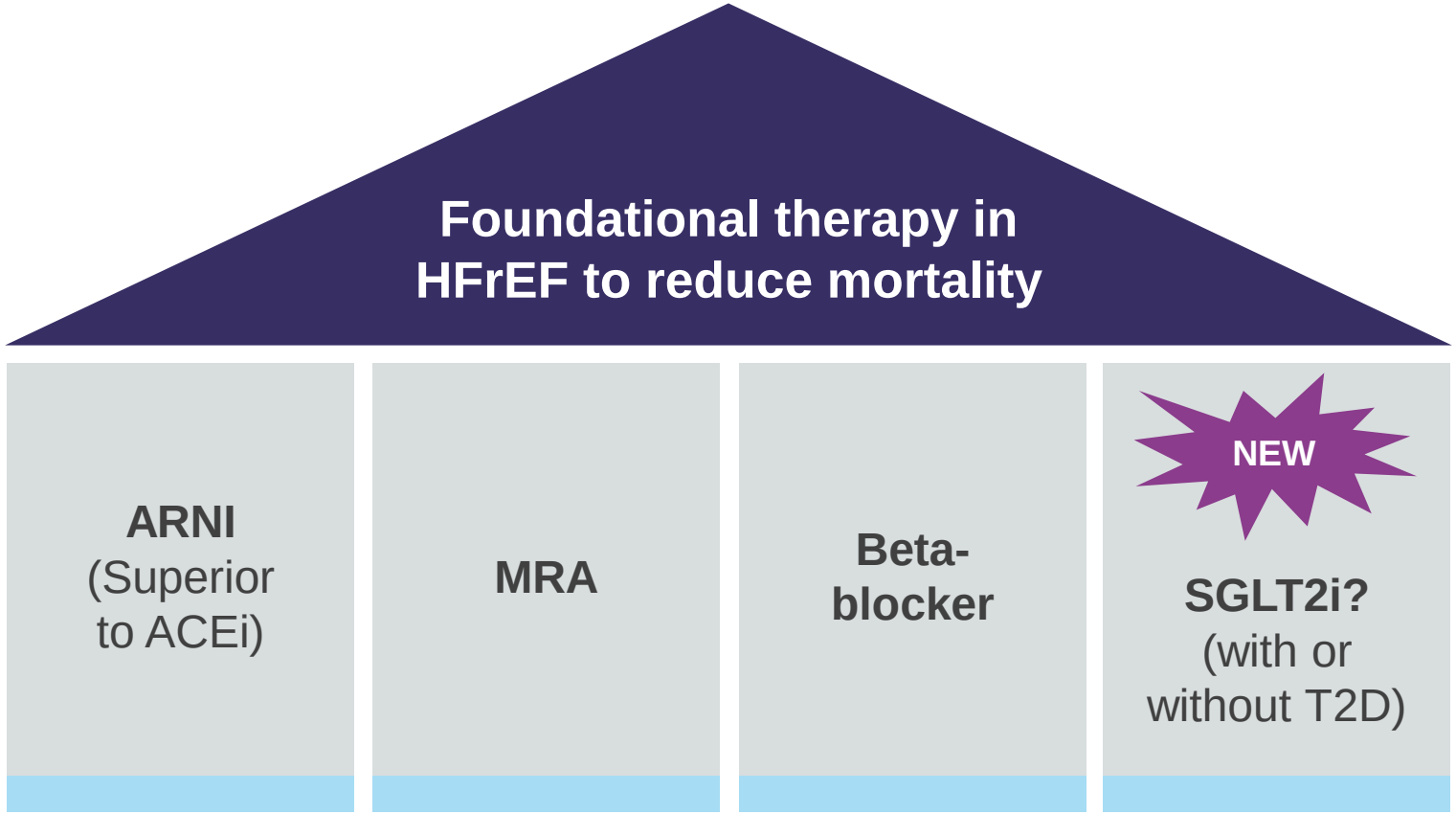
Compared to ACEI/ARB + BB:

1. Switch to ARNI
2. Start MRA
3. Start SGLT2i

Extend Your HFrEF Patient's Life by 6.3 Years

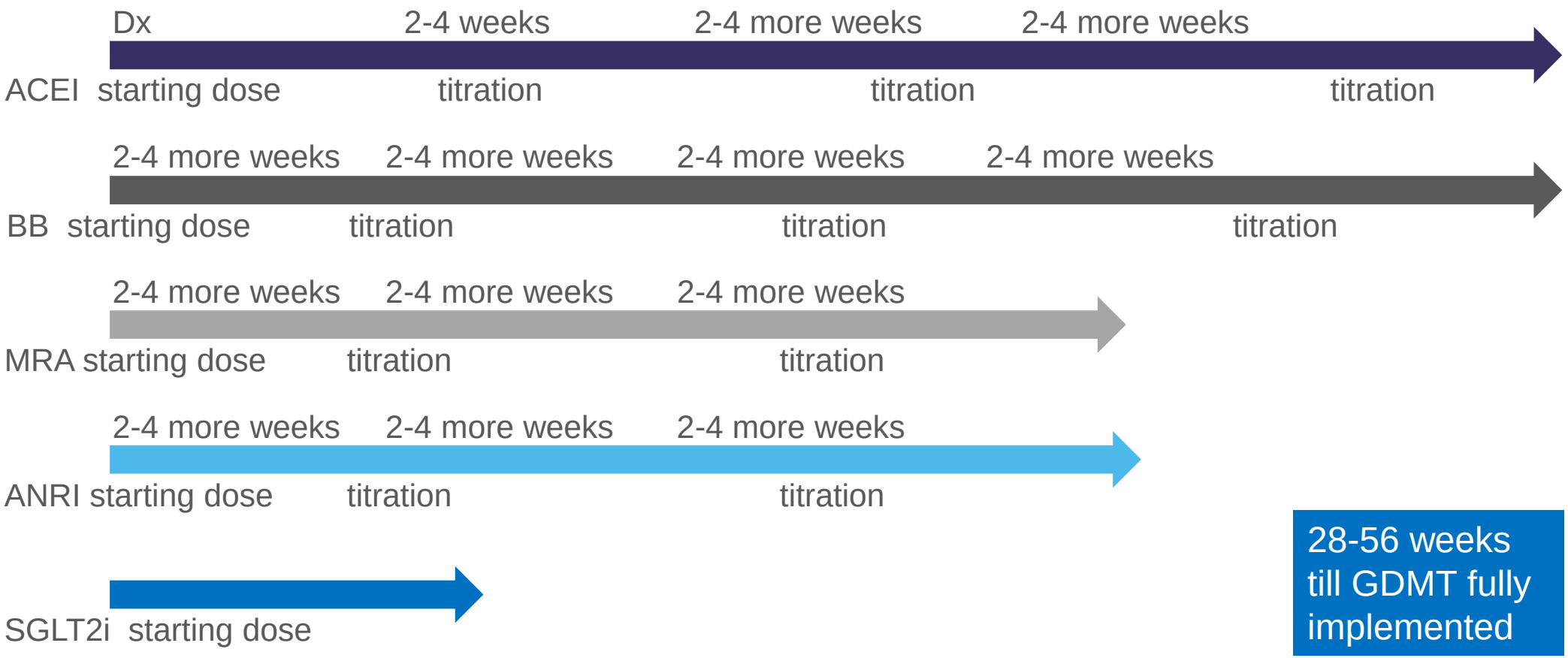
What is the Value to the Patient of Extending Median Survival by >6 Years?

Foundational therapies in heart failure use



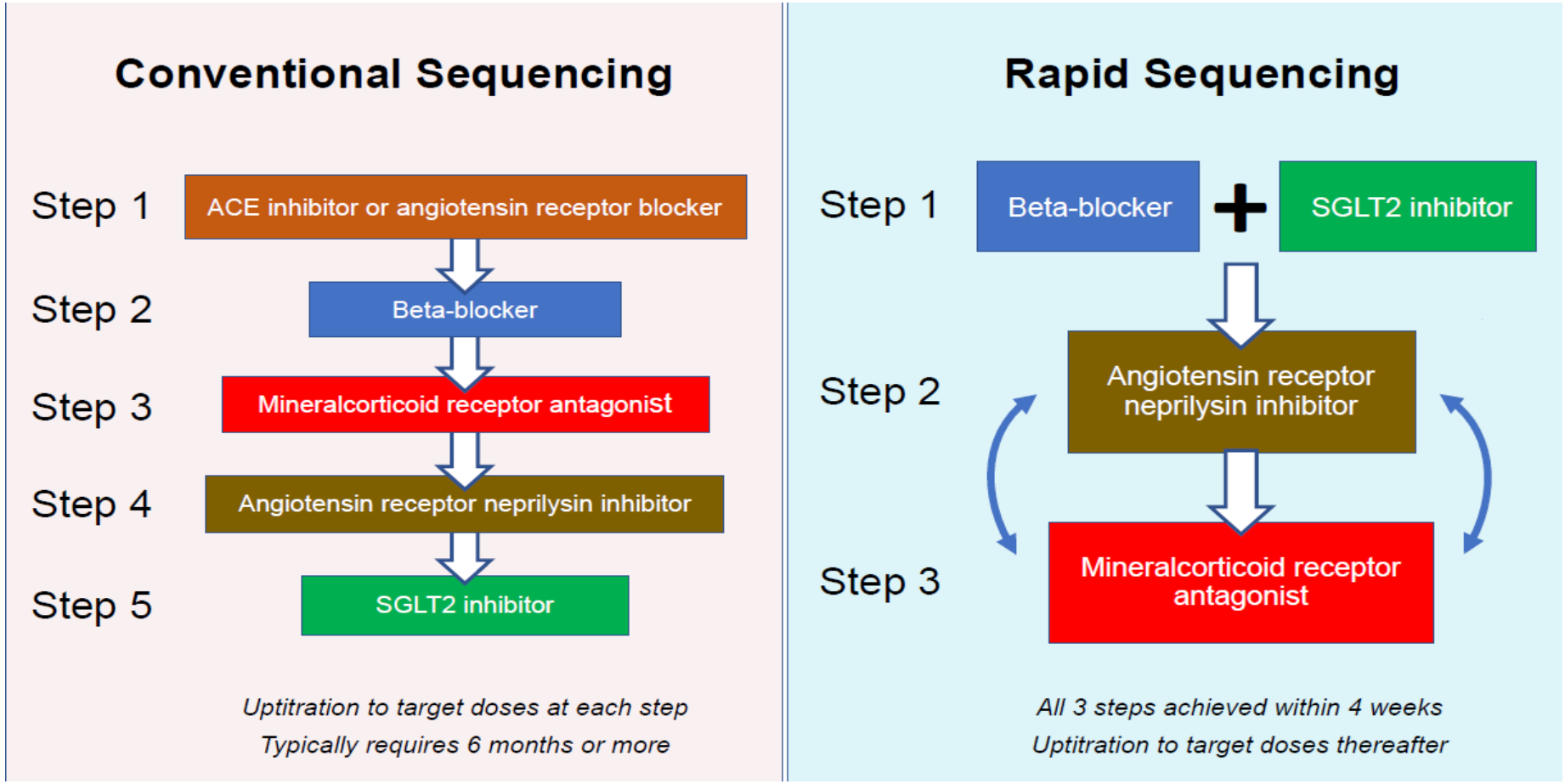
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MR, mineralocorticoid receptor; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes
Modified from Bhatt DL *et al. Cell Metab*. 2019;30:847

Traditional Sequencing of GDMT: Serial Strategy



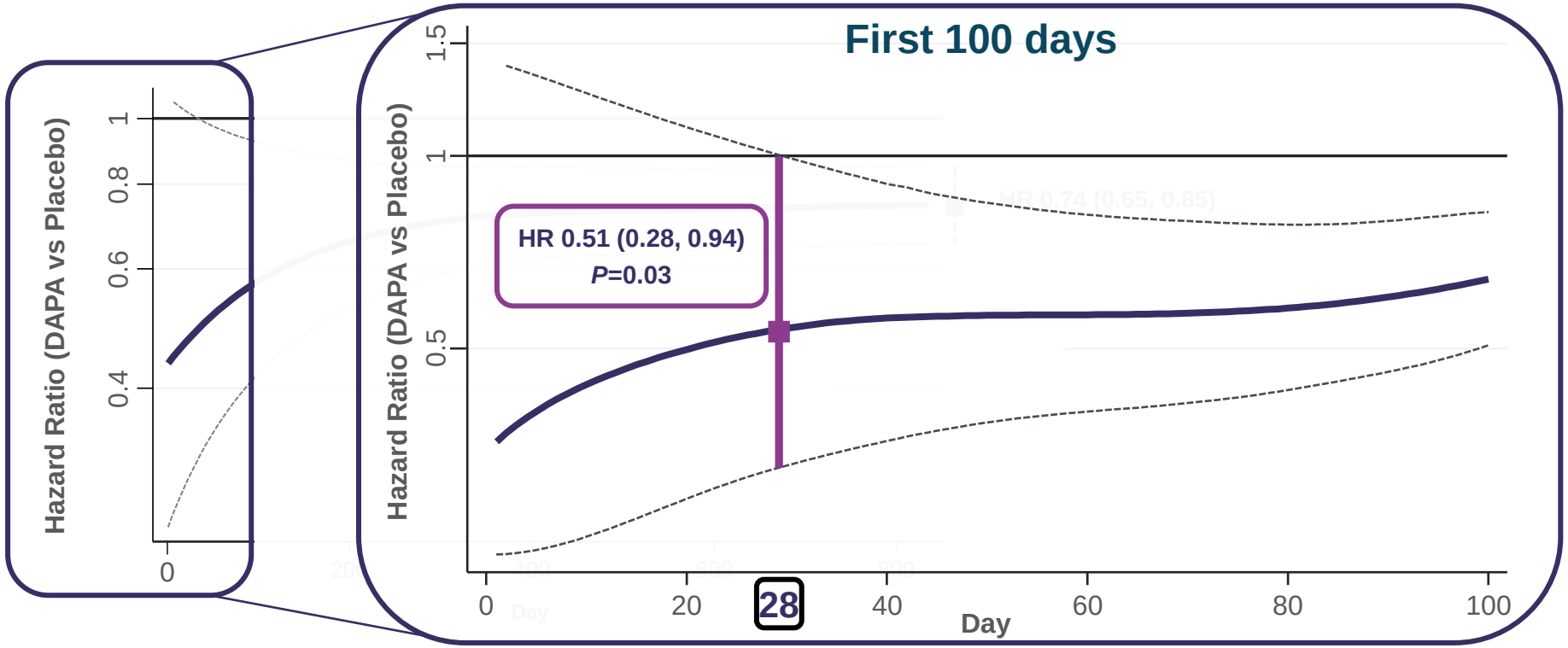
28-56 weeks till GDMT fully implemented

Novel Sequencing Strategies – Dual Start



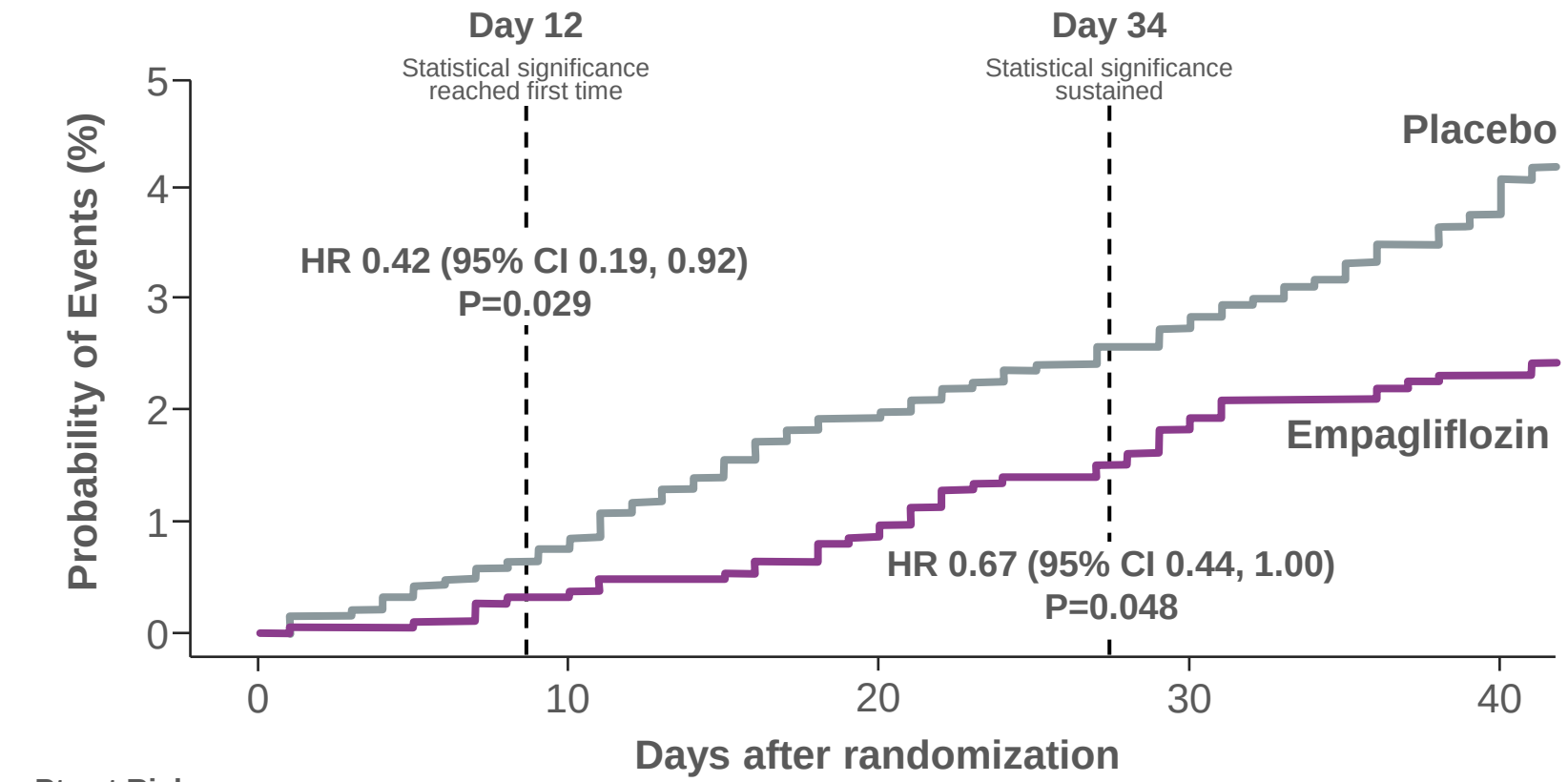
Eur J Heart Fail. 2021 Mar 11. doi: 10.1002/ejhf.2149

Early Benefit of Dapagliflozin on CV Death or WHF



Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

EMPEROR Reduced



Potential Scheme for GDMT Optimization

Early Relative Risk Reduction	Hospitalised or Outpatient	Day 1	Day 7–14	Day 14–28	Day 21–42	Beyond
↓42% of CV death or HF hospitalisation	ARNI			Titrate, as Tolerated	Titrate, as Tolerated	Maintenance/Further Optimization of Fundamental Therapies Consideration of EP Device Therapies/Mitra-Cip Consideration of Add On Therapies or Advances Therapies, if Refractory Manage Comorbidities
↓25% of death	β-blocker		Titrate, as Tolerated	Titrate, as Tolerated	Titrate, as Tolerated	
↓37% of CV death or HF hospitalisation	MRA			Titrate, as Tolerated		
↓58% of CV death or HF hospitalisation	SGLT2i					

Low Starting Doses
Prioritize Beta Blocker Titration

Benefits of each Rx demonstrated within 30 days of initiation
Cumulative benefits within 30 days (>75% relative risk reduction)

JAMA Cardiol. 2021 Mar 31. doi: 10.1001/jamacardio.2021.0496.

Novel Sequencing Strategies - Cluster

Cluster Scheme

Initiation and Titration of Foundational Therapy for Heart Failure with LVEF <40%

Recommended Total Time for Titration ≤ 12 weeks (3 months)

	Cluster A: Diuretic & SGLTi	+ Cluster B: ARNi & MRA	+ Cluster C: Beta Blocker & SNI*
Face to face with prescriber preferred	Encounter 1 (usually face-to-face, up to 3 medication initiations)		
	Start Preferred Cluster A Medication	Start Preferred Cluster B Medication	Start Preferred Cluster Medication*
	↓ 1–2 Weeks		
Either face to face or virtual visit with prescriber	Encounter 2 (whenever feasible, up to 3 medication initiations)		
	Titrate Cluster A Medication	Start Second Cluster B Medication	Adjust Cluster C Medication*
	↓ 1–2 weeks		
Virtual visit with prescriber preferred	Encounter 3 & ongoing (whenever feasible, up to 3 medication titrations)		
	Diuretic Titration as needed	Cluster B Medication Titration	Cluster C Medication Titration*
	↓ 1–2 weeks		
	Goal Foundational Therapy – Continue to actively manage as necessary Addition of Personalized Therapies as dictated by clinical presentation and setting (see Table2)		

Miller. Et al. Canadian Journal of Cardiology, 2021

Practical approach to SGLT2 inhibitors for treatment of cardiovascular disease

Indications

Patients with Type 2 DM[1]

or

Patients with chronic kidney disease (eGFR 25-90, UACR>20 mg/mmol)[2]

or

Patients with chronic HFrEF[3]

Contraindications

- CLI[3]
- eGFR<25[4]
- Allergy or intolerance to SGLT2i[5]

Do not initiate SGLT2i

Caution

- Volume depletion[5]
- Active GMI[6]
- Hypotension (Blood pressure<95 mmHg)*,[7]
- Prior CLI
- DKA[5] [specific to DM]
- History of severe hypoglycemia† [specific to DM]

Delay initiation of SGLT2i until condition resolved/ therapies modified to reduce risk

Outpatient Initiation

Start 10 mg od qam:
- Dapagliflozin[5]
- Empagliflozin[8]

Start 100 mg od qam:
- Canagliflozin[9]

Special Considerations

- Monitor for GMIs, counsel on proper hygiene[6]
- Concomitant dehydrating illness (SADMANS)‡,[10]
- Borderline renal function§,[5,6]
- Volume depletion‖,[5]

Potential drug-drug effects with:

Loop diuretics

- Optional dose reduction¶ if euvolemic; 30–50% dose reduction if volume depletion occurs[3]

Insulin or SU

- If DM w/A1C<7.5, consider dose reduction (i.e., 10–20% insulin, and/or 50% SU)[11]
- If episodes of hypoglycemia#, stop SU and dose reduce insulin[11]

Follow-up

Follow up routine as per underlying condition:
- Weight[6]
- Symptoms of hypotension[6]
- Adherence[6]
- Renal function (eGFR)**,††,[6]
- Blood glucose[6] [specific to DM]

This tool is available for download in the Initiatives & Programs section on www.heartfailure.ca

Abbreviations:

CLI: critical limb ischemia; **DKA:** diabetic ketoacidosis; **DM:** diabetes mellitus; **eGFR:** estimated glomerular filtration rate; **GMI:** genital mycotic infections; **HFrEF:** heart failure with reduced ejection fraction; **SGLT2i:** SGLT2 inhibitors; **SU:** sulfonylurea; **UACR:** urine albumin to creatinine ratio

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CHFS SCIC
Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

EMPOWER is the largest cardio-renal-metabolic programs for an SGLT2 inhibitor to date, involving more than 27,000 patients*

Aim: To explore the impact of empagliflozin on major clinical CV and renal outcomes in a spectrum of cardio-renal-metabolic conditions

EMPEROR-Reduced
Effects on HHF and CV mortality in HFrEF[1-2]
3730 patients

EMPEROR-Preserved
Effects on HHF and CV mortality in HFpEF[3-4]
5988 patients

EMPERIAL-Reduced
Effects on exercise capacity and patient-reported outcomes in HFrEF[5-6]
312 patients

EMPERIAL-Preserved
Effects on exercise capacity and patient-reported outcomes in HFpEF[6-7]
315 patients

EMPULSE
Effects of in-hospital initiation in acute HF on HF-related events and patient-reported outcomes[8]
500 patients

EMPACT-MI
Effects on HHF and mortality in post-MI patients with high risk of heart failure[9]
3300 patients

EMPA-VISION
Effects on cardiac physiology and metabolism in patients with heart failure[10]
72 patients

EMPA-KIDNEY
Effects on kidney disease progression and CV death in patients with chronic kidney disease[11]
6000 patients

EMPA-REG OUTCOME®
Effects on CV morbidity and mortality in patients with high CV risk and T2D[12]
7020 patients

EMPRISE
Real world effectiveness in patients with T2D in the United States, Europe and Asia[13-15]
230,000 patients

This material is for educational purposes only with the intent to communicate the results of the published EMPEROR-Reduced Trial. Empagliflozin is not indicated for patients with Heart Failure. Please review local approved product indication for more information.

*EMPRISE is an observational study and is, therefore, excluded from the total patient number. CV, cardiovascular; HHF, hospitalisation for heart failure; T2D, type 2 diabetes; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction 1. ClinicalTrials.gov. NCT03057977; 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Clinicaltrials.gov. NCT03057951; 4. Anker SD *et al. Eur J Heart Fail* 2019;21:1279; 5. ClinicalTrials.gov. NCT03448419; 6. Abraham WT *et al. Eur J Heart Fail* 2019;21:932; 7. ClinicalTrials.gov. NCT03448406; 8. ClinicalTrials.gov. NCT04157751; 9. Boehringer Ingelheim Pharmaceuticals, Inc. Press release. 2020. https://www.boehringer-ingelheim.com/press-release/dcri-collaboration-empact-mi ; 10. Clinicaltrials.gov. NCT03332212; 11. ClinicalTrials.gov. NCT03594110; 12. Zinman B *et al. N Engl J Med* 2015;373:2117; 13. ClinicalTrials.gov. NCT03363464; 14. ClinicalTrials.gov. NCT03817463; 15. Patorno E *et al. Circulation* 2019;139:2822 (all websites accessed Jul 2020)

What would be an ideal HFrEF Therapy to implement?

The Time is Now for SGLT2 Inhibitors for Heart Failure: A Call to Overcome Clinical Inertia


One-pill, once per day, with no dose titration


Substantially improves survival and prevents hospitalization


Meaningfully improves quality of life and functional status


Benefits appear rapidly within days to few weeks of initiation


Exceptionally well tolerated and safe


Does not lower blood pressure or does so very minimally


No adverse renal effects, and instead preserves kidney function and prevents dialysis


Affordable and accessible

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