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Protecting the Heart to Protect the Kidney: Enhance Cardiac Stability and Prevent Renal Decline

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Disclaimer

I have received supports and honorarium for delivering continuous medical education and research from:

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There is an urgent unmet medical need for people living with HF

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More than 60 million people worldwide are living with HF[1]

HF is one of the leading causes of hospitalization[2,3] and the **number 1 cause of hospitalization in patients over 65 years old**[4]

Hospital readmission rates after HHF are as high as ~**30%** within 90 days[5]

Approximately **30%** of patients who are hospitalized with HF **die within 1 year**[6]

HF, heart failure

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211; 2. Blecker S *et al. J Am Coll Cardiol.* 2013;61:1259; 3. Ambrosy AP *et al. J Am Coll Cardiol.* 2014;63:1123; 4. Azad N, Lemay G. *J Geriatr Cardiol.* 2014;11:329; 5. Fonarow GC *et al. J Am Coll Cardiol.* 2007;50:768; 6. Shah KS *et al. J Am Coll Cardiol.* 2017;70:2476.

MYHF
MALAYSIA NATIONAL HEART FAILURE REGISTRY

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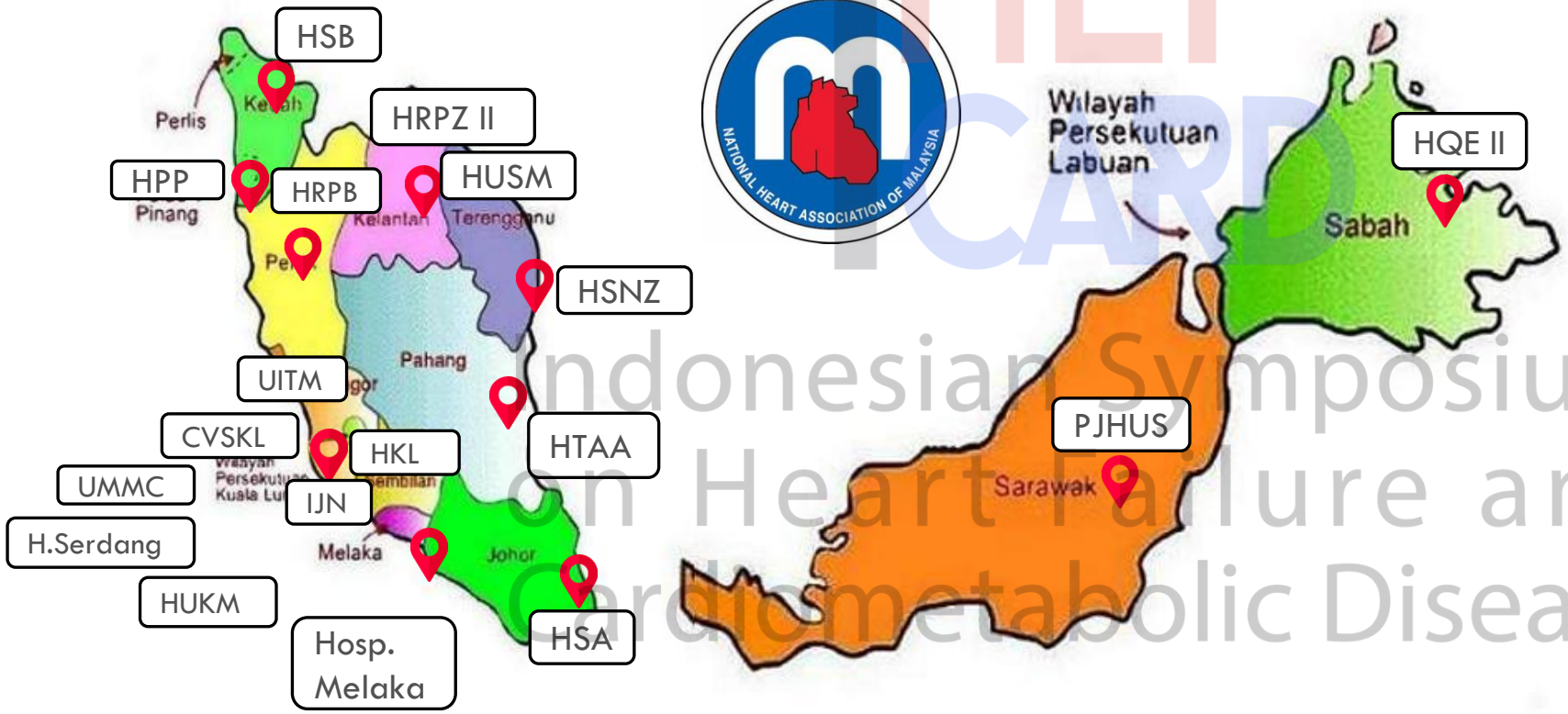
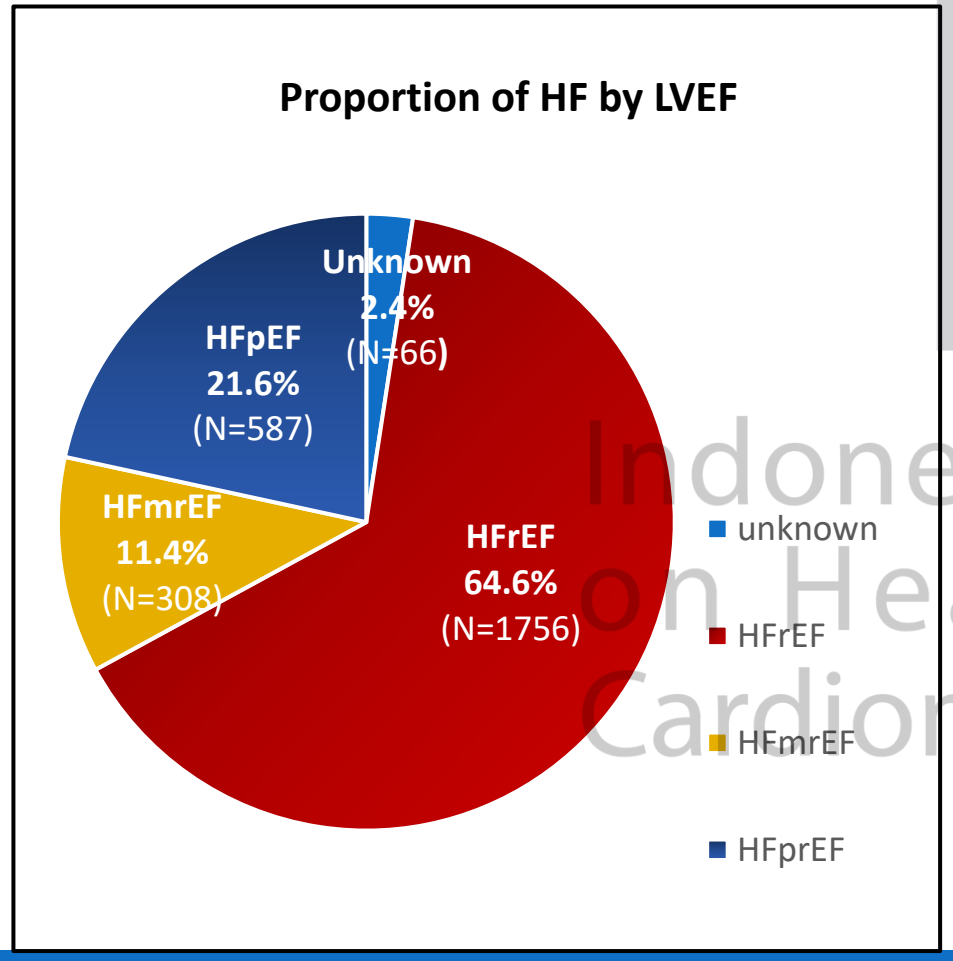
The First Prospective Multicenter Registry of HF Patients in Malaysia

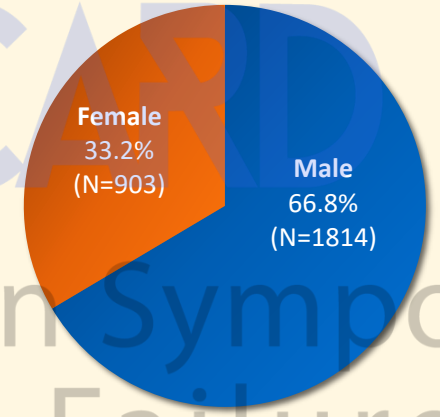


- Prospective heart failure (HF) registry set up in 2019
- Total 2,673 patients hospitalized for HF were analyzed
- 1-year follow up from 2019-2020

HSB, Hospital Sultanah Bahiyah; HRPZ II, Hospital Raja Perempuan Zainab II; HPP, Hospital Pulau Pinang; HRPB, Hospital Raja Permaisuri Bainun, HSNZ, Hospital Sultanah Nur Zahirah; HUKM, Hospital Universiti kebangsaan Malaysia; UMMC, University Malaya Medical Centre; IJN, Institut Jantung Negara; UitM, University Teknologi Mara; HKL, Hospital Kuala Lumpur; HSA, Hospital Sultanah Aminah; PJS, Pusat Jantung Negara; HQE II, Hospital Queen Elizabeth II
Available from: myhf.my

Demographics hospitalized HF patients





Mean age 60.1 years

Mean age HFpEF 65.3 years

HFpEF patients were 7.5 years older than HFrEF

MYHF
MALAYSIA NATIONAL HEART FAILURE REGISTRY

Comorbidities across EF spectrum

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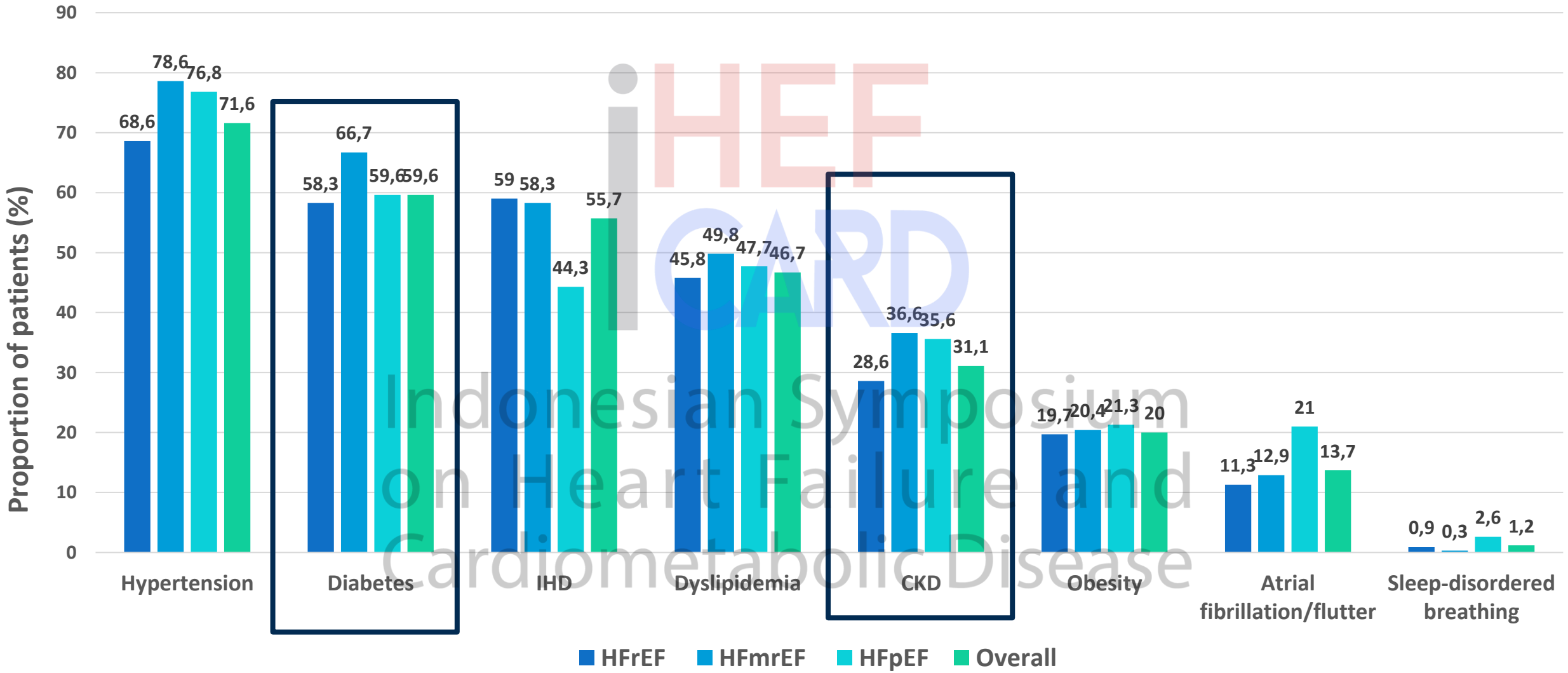
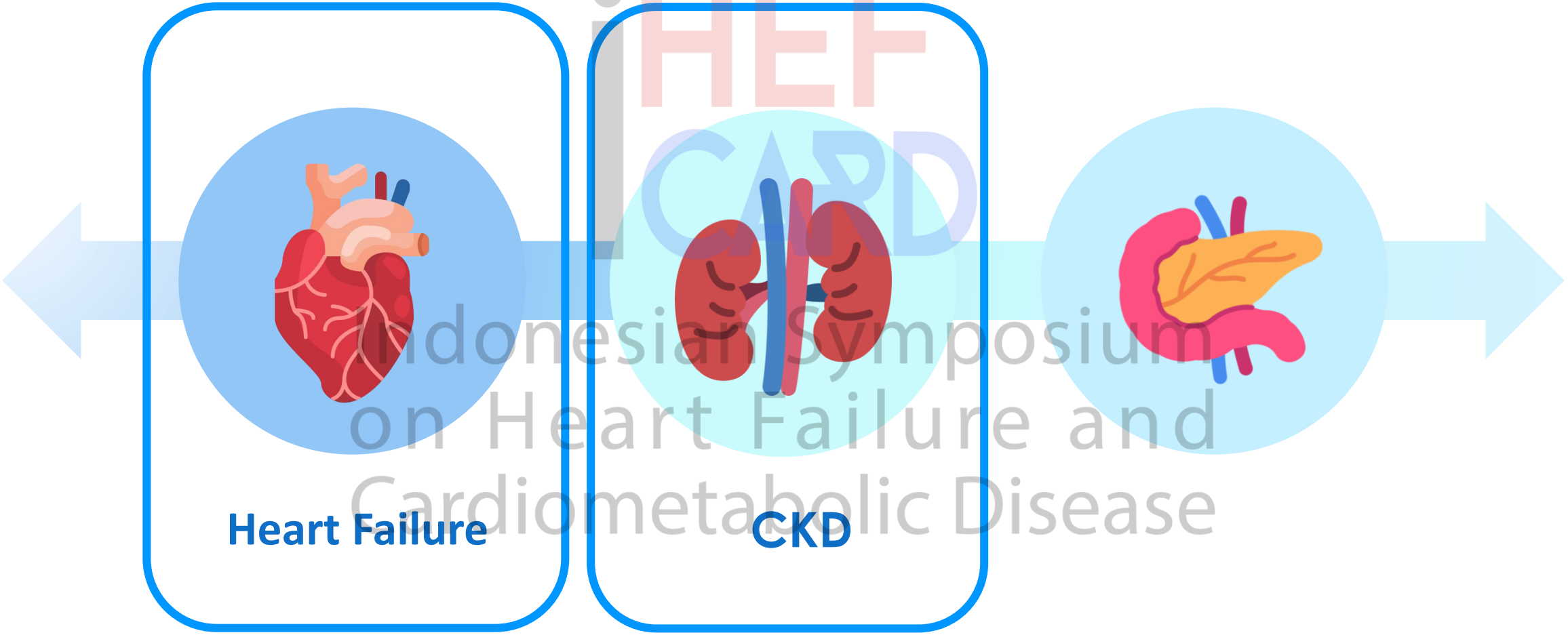


Azmee et al., Key Characteristics and Short Term Outcome of HFpEF Patients – Insights from MYHF Registry. Free paper presented at NHAM Congress 2023, 16-18th June 2023.

Cardio-Renal-Metabolic (CRM) conditions are interconnected – a major burden and often co-exist



Acute/chronic disorder of one can induce dysfunction in another

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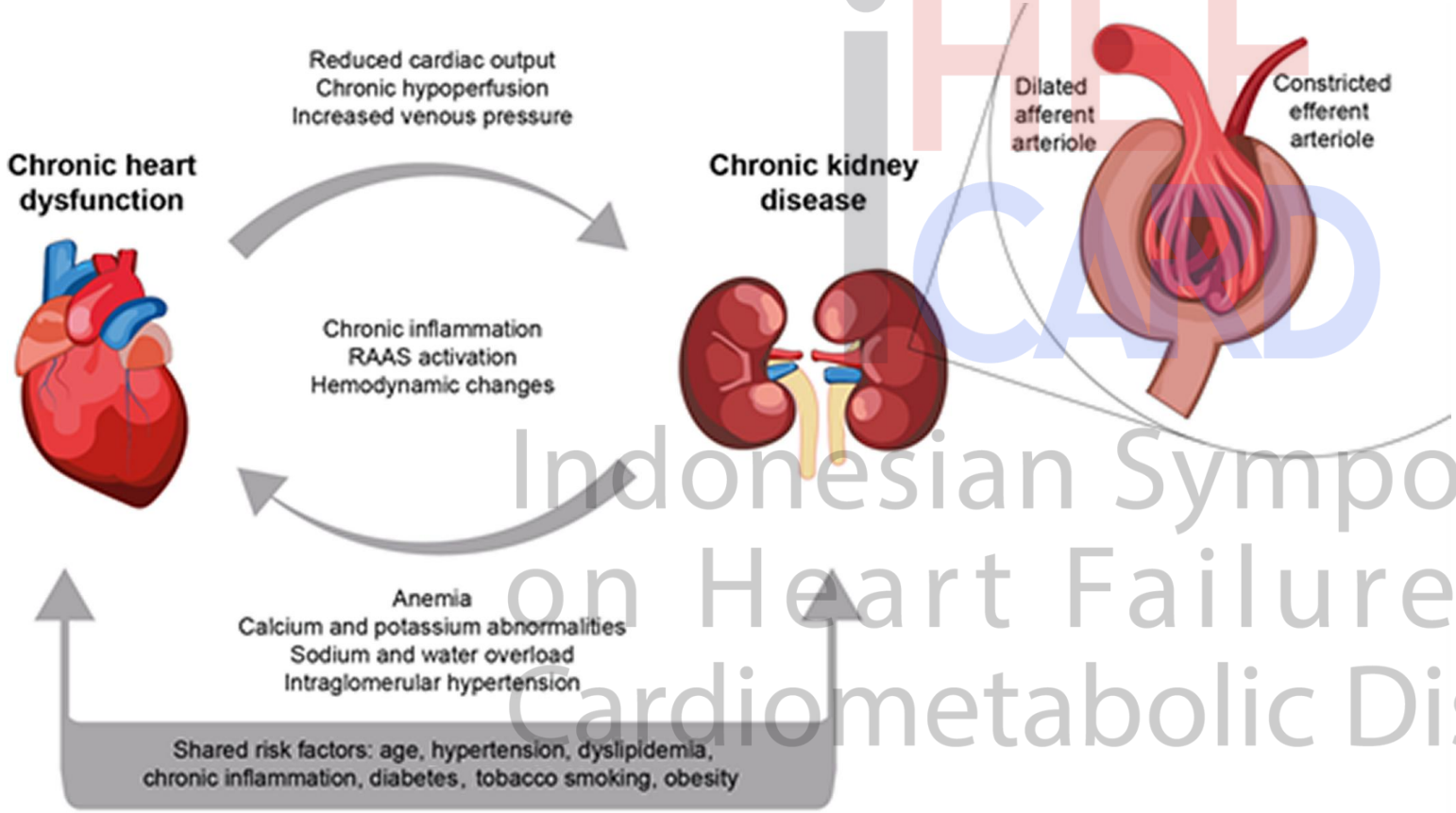
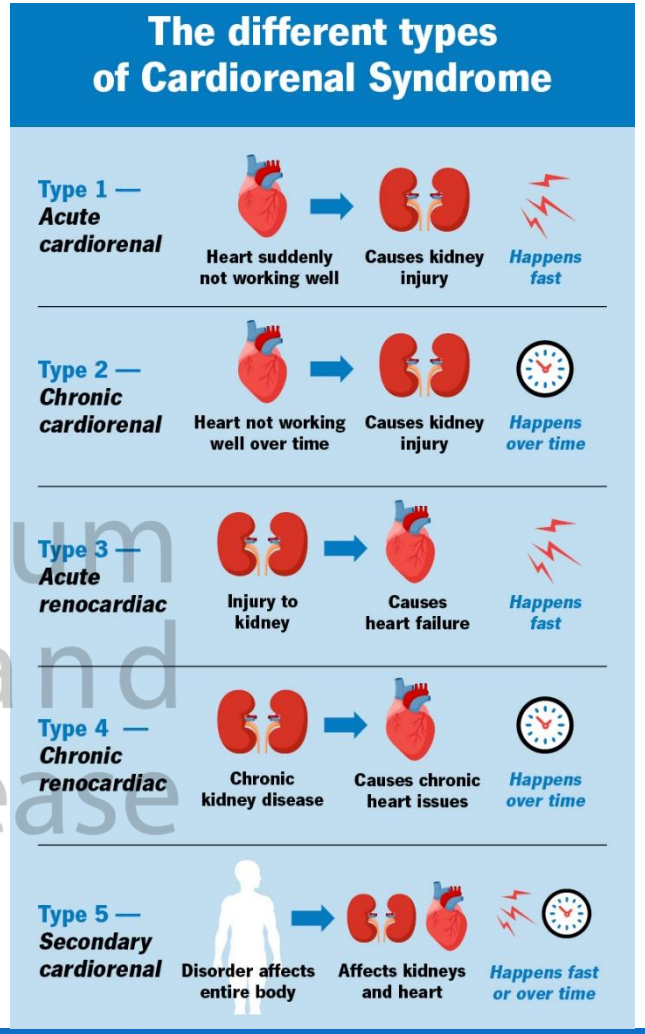
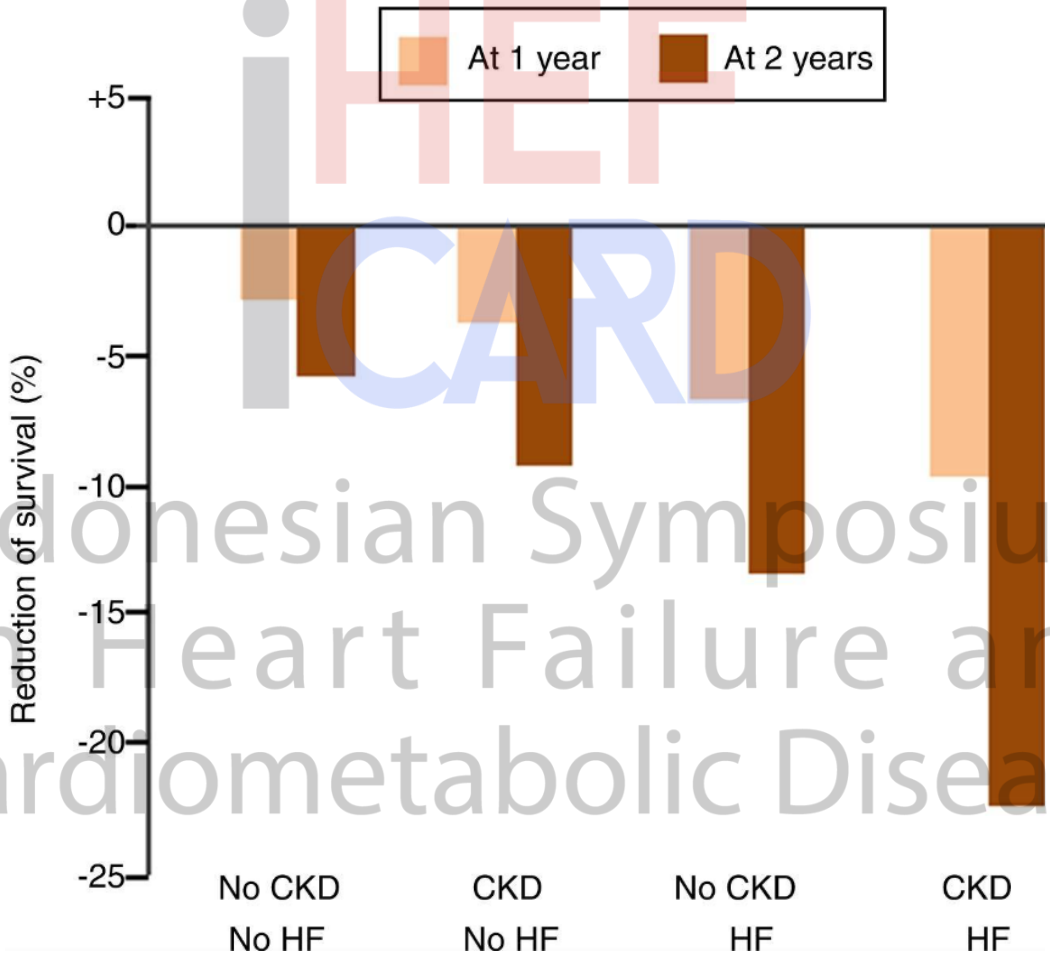




Peter A. McCullough. Journal of the American Heart Association. Cardiorenal Nexus: A Review With Focus on Combined Chronic Heart and Kidney Failure, and Insights From Recent Clinical Trials, Volume: 11, Issue: 11, DOI: (10.1161/JAHA.121.024139)

Coexisting CKD+HF is associated with high morbidity and mortality



Adjusted survival of patients by CKD and HF status, 2015–2016.

Kidney function declines faster in heart failure patients

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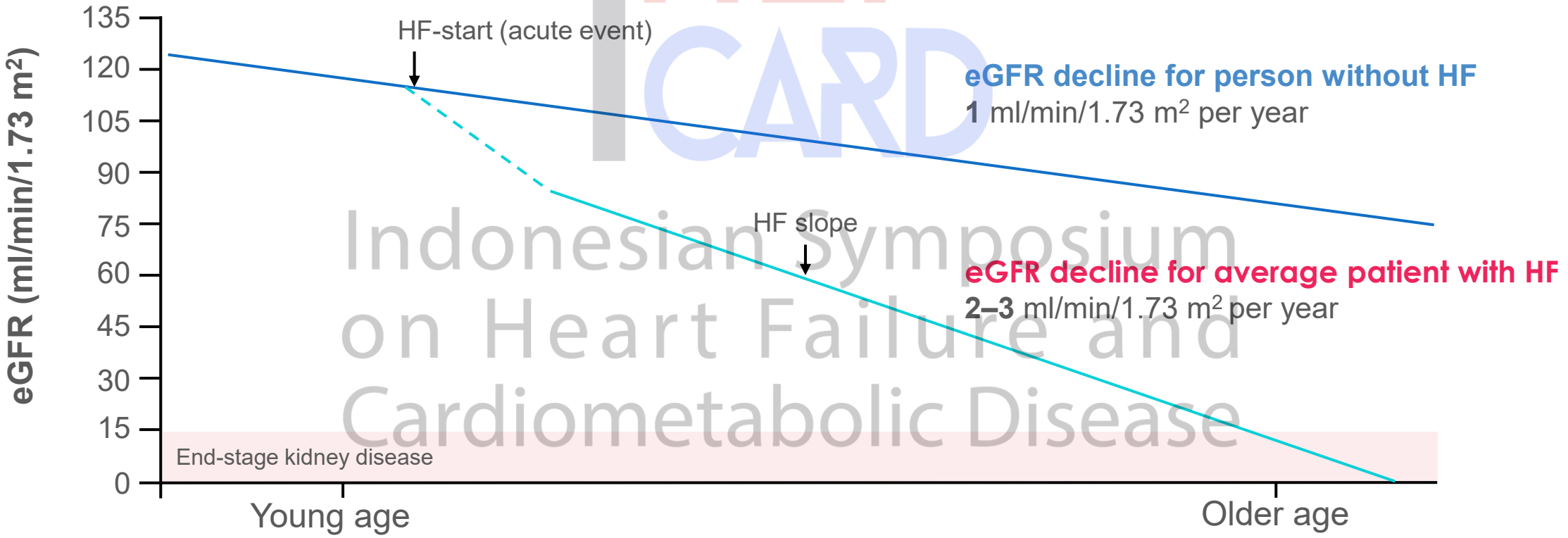
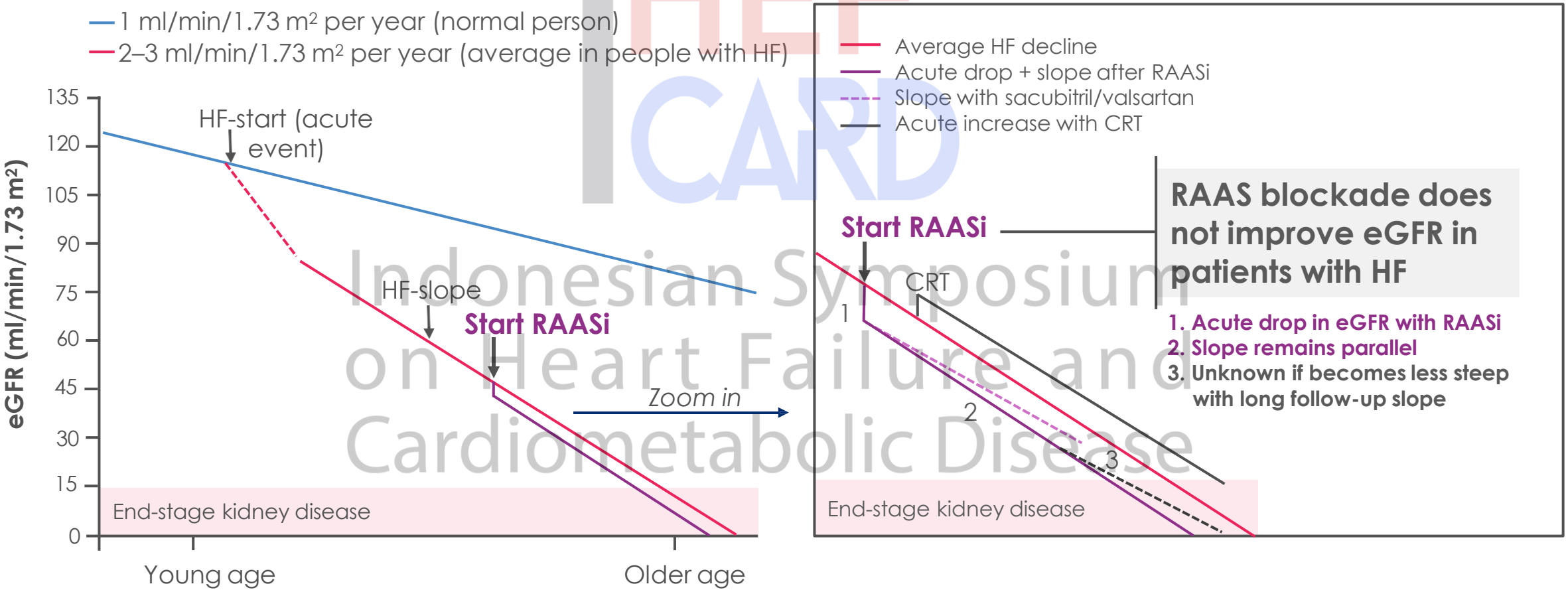
Kidney function over time: patients with and without HF



Adapted from: Mullens W *et al. Eur J Heart Fail* 2020;22:584

No treatment options have been identified that provide sufficient kidney protection in patients with heart failure

Kidney function in patients with HF following treatment initiation



CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; RAASi, renin–angiotensin–aldosterone system inhibitor
Adapted from Mullens W *et al. Eur J Heart Fail*. 2020;22:584

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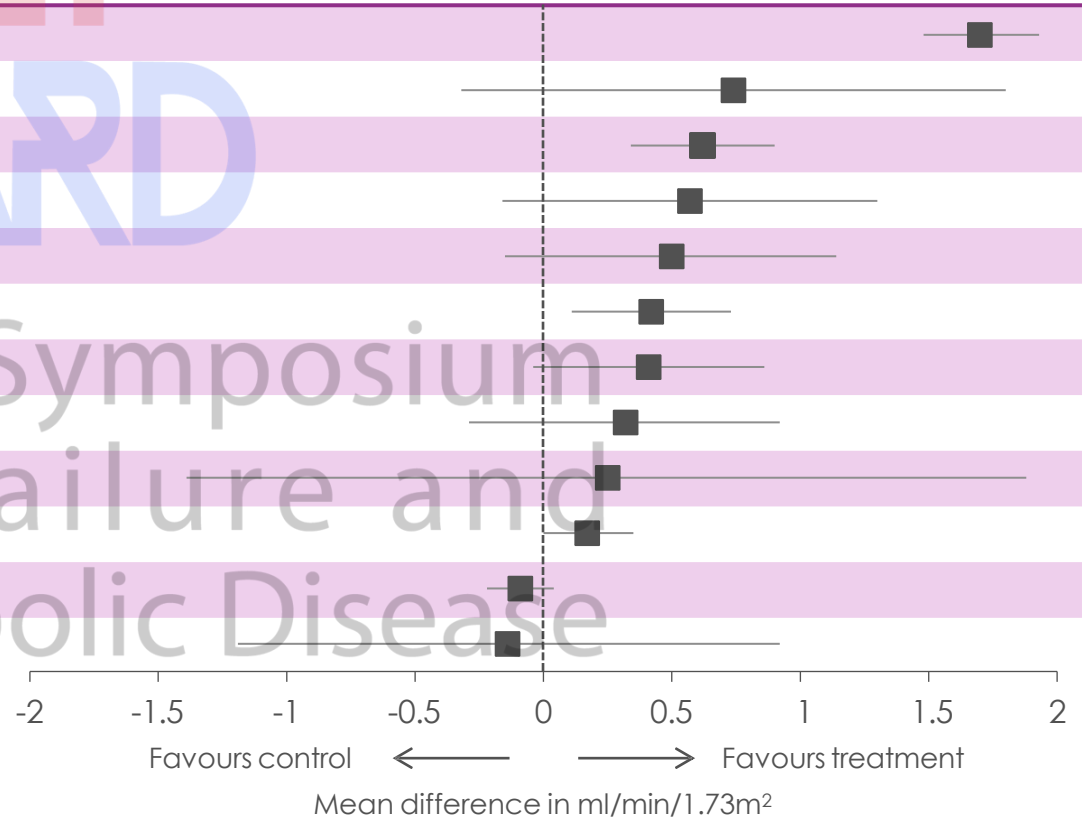
Effects of different interventions on chronic eGFR slope

Intervention	Disease
Empagliflozin	Diabetes
Allopurinol	CKD
RASB v control	CKD, diabetes, glomerular disease
RASB v CCB	CKD, diabetes
Alb targeted protocol	CKD
Intensive blood pressure control	CKD, diabetes
Nurse care	CKD
Low protein diet	CKD, glomerular disease
Immunosuppression	Glomerular disease
Simvastatin+ezetimibe	CKD
Intensive glucose	Diabetes
Sulodexide	Diabetes

Treatment effect on chronic eGFR slope (95% CI)



Values are based on single studies under Alb Protocol, Allopurinol, EMPA, GLUC, Simva/Eze, Sulodexide; values for the rest are based on group of studies under each level. Alb, albuminuria; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RASB, renin-angiotensin system blockade

Inker LA *et al. J Am Soc Nephrol.* 2019;30:1735

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SGLT2 inhibitors are one of the foundational therapies for HFrEF

HFrEF treatment

Foundational therapy[1,2]

- ARNI/ACEi*
- Beta blocker
- MRA
- SGLT2 inhibitor

\+ **Diuretics** (as needed for fluid retention)[1,2]

- ✓ **Initiation** and **titration** of medications should be adapted and **optimized to meet the patient's individual need**[1,2]
- ✓ If **initiated simultaneously, low starting doses** are recommended[2]
- ✓ If **initiated sequentially, no need to achieve target doses** before initiating next medication[2]

This slide focuses on the specific treatment pillars of HFrEF therapy. *For patients who are intolerant to ACE inhibitors or ARNIs because of side effects, ARBs are recommended.[1,2]
ACE(i), angiotensin-converting enzyme (inhibitor); ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2.

1. McDonagh TA *et al. Eur Heart J*. 2021;42:3599; 2. Heidenreich PA *et al. J Am Coll Cardiol*. 2022;79:e263.

Many mechanisms may contribute to the beneficial effects on heart failure seen with SGLT2 inhibitor

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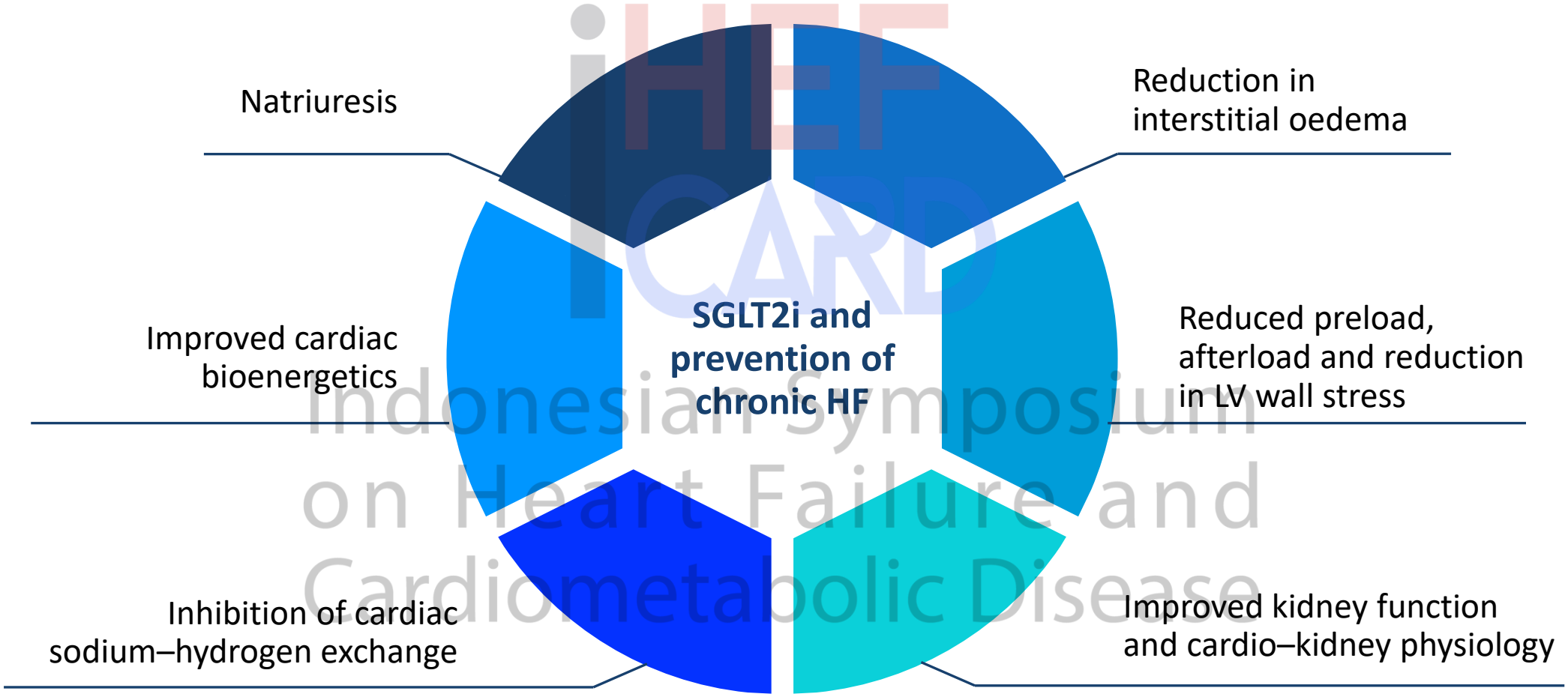
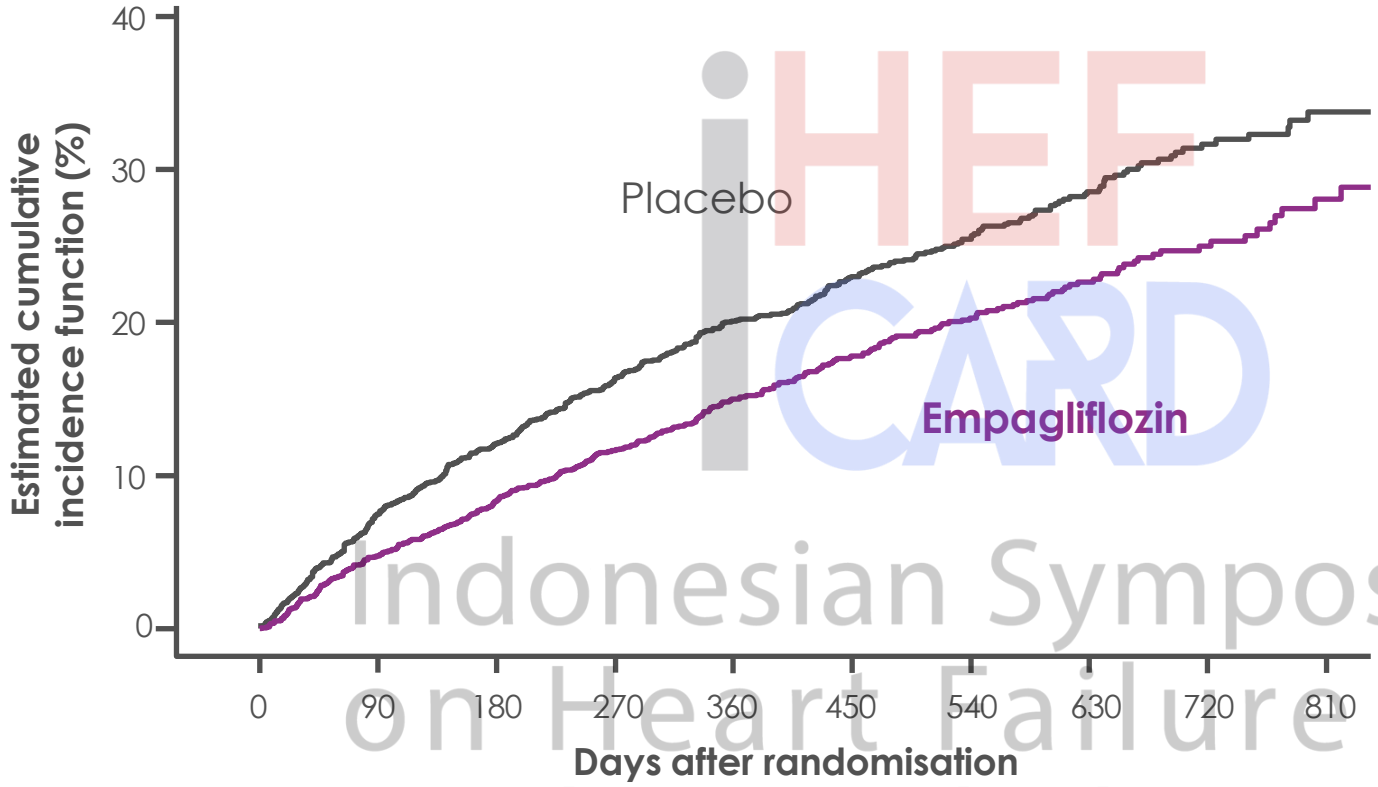


HF, heart failure; LV, left ventricular; SGLT2i, sodium-glucose co-transporter-2 inhibitor
Farkouh ME & Verma S. *J Am Coll Cardiol* 2018;71:2505

EMPEROR REDUCED Primary endpoint:
First adjudicated CV death or hospitalisation 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

RRR 25%

ARR 5.2%

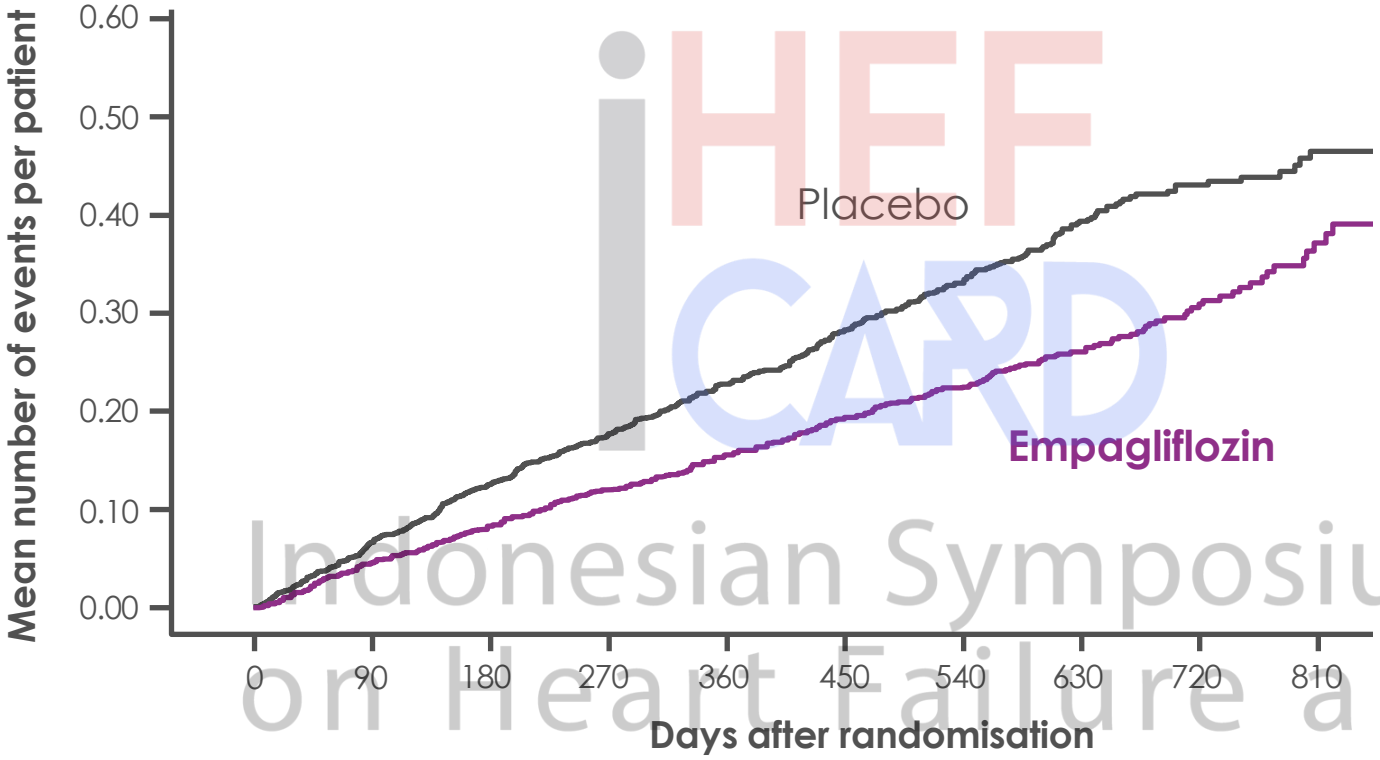
NNT = 19

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

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.

EMPEROR REDUCED Key secondary:
Adjudicated total hospitalisations for heart failure (first and recurrent)



Patients at risk

Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

RRR 30%

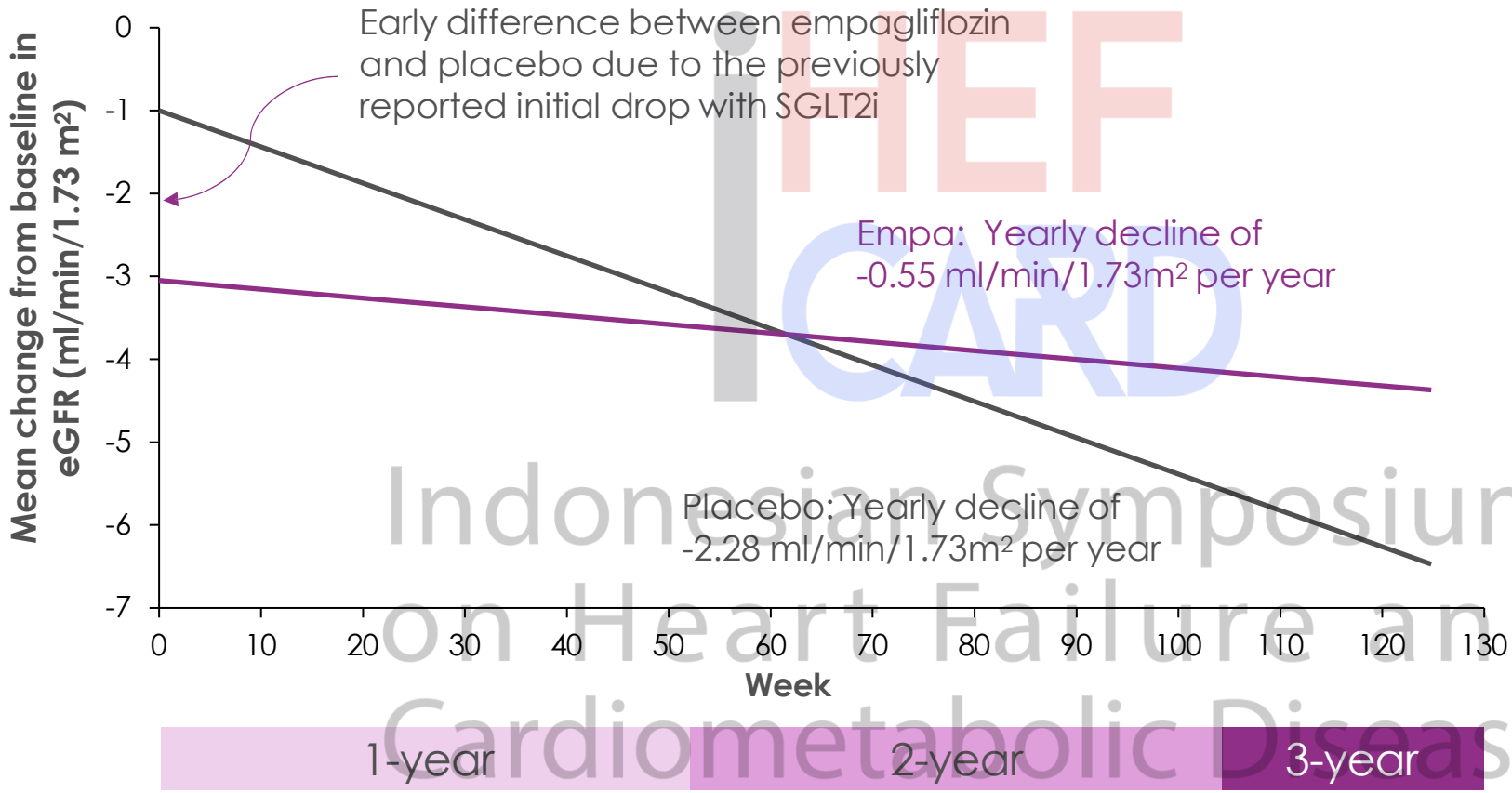
HR 0.70
(95% CI 0.58, 0.85)
p<0.001

Emagliflozin: 388 events
Placebo: 553 events

Analysis of first and recurrent HHF accounting for CV death as terminal event using a joint frailty model. Model includes covariates age, baseline eGFR, treatment, region, baseline diabetes status, sex, and baseline LVEF, estimated dependence between adjudicated HHF and adjudicated CV death, and variance of frailty. CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction
Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

EMPEROR REDUCED Key secondary endpoint: eGFR slope

Empagliflozin protected the kidney by slowing the progression of kidney disease



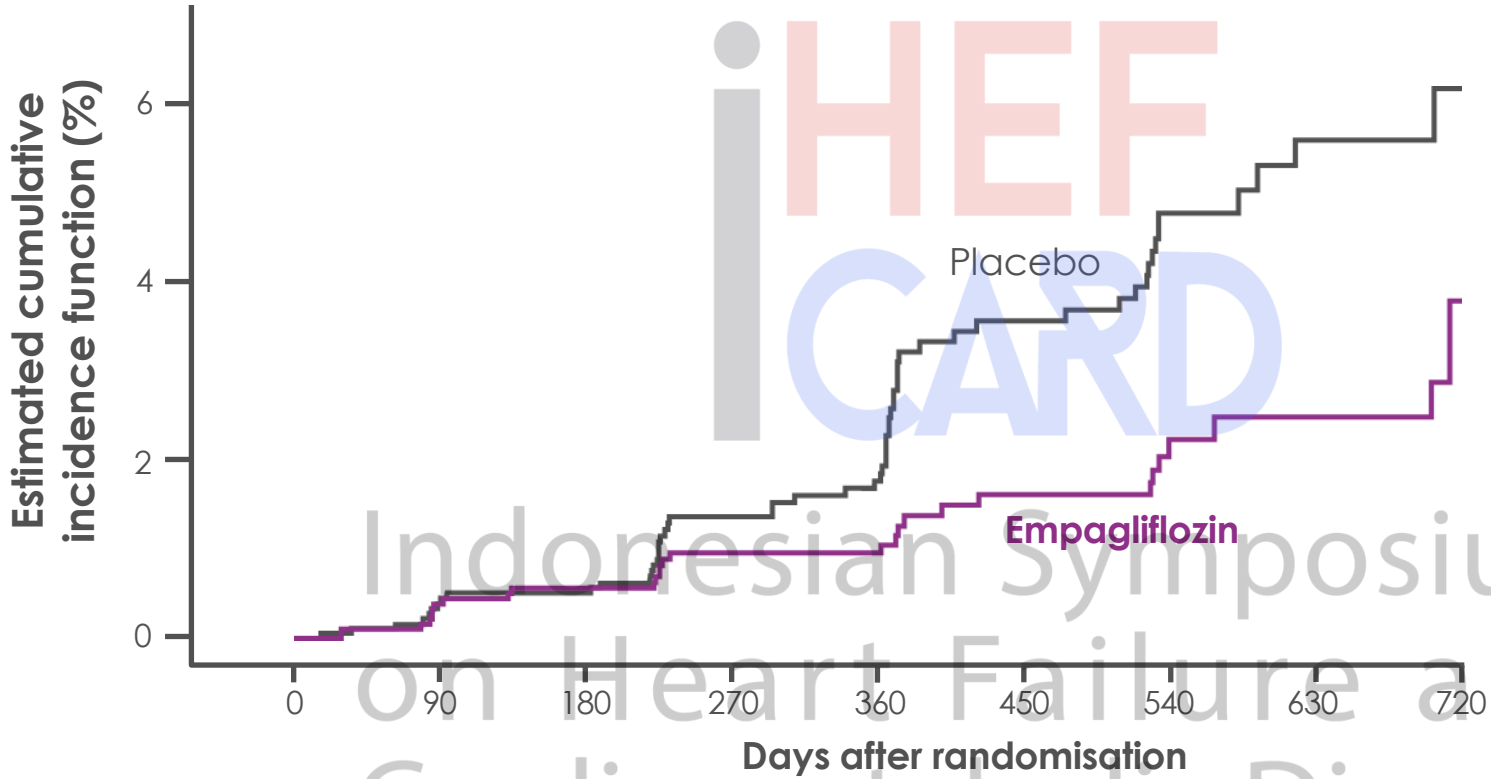
eGFR Slope = **rate of decline**

eGFR slope is a measure for **long-term renal function**

+1.73
eGFR slope difference
ml/min/1.73 m2 per year
p<0.001

eGFR slope is analyzed based on on-treatment data using a random coefficient model including age and baseline eGFR as linear covariates and sex, region, baseline LVEF, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients
eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter-2 inhibitor. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.

Composite renal endpoint (end-stage kidney disease or sustained profound decrease in eGFR)



Patients at risk

Placebo	1867	1592	1501	1136	1058	681	357	259	76
Empagliflozin	1863	1599	1532	1155	1062	687	391	276	78

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

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. Data on file

EMPEROR-Reduced: Adverse event profile was favourable even in patients with compromised kidney function

	eGFR 30 to <45 ml/min/1.73 m²		eGFR <30 ml/min/1.73 m²	
	Empagliflozin (N=345)	Placebo (N=348)	Empagliflozin (N=114)	Placebo (N=89)
AEs leading to discontinuation	73 (21.2)	85 (24.4)	33 (28.7)	26 (29.2)
Serious AEs	159 (46.1)	183 (52.6)	75 (65.2)	50 (56.2)
AEs of special interest				
Acute kidney failure	50 (14.5)	52 (14.9)	25 (21.7)	16 (18.0)
Urinary tract infection	16 (4.6)	30 (8.6)	12 (10.4)	4 (4.5)
Genital infection	8 (2.3)	1 (0.3)	1 (0.9)	0
Volume depletion	36 (10.4)	42 (12.1)	19 (16.5)	15 (16.9)
Hypotension	33 (9.6)	39 (11.2)	12 (10.4)	13 (14.6)
Confirmed hypoglycaemia	4 (1.2)	7 (2.0)	5 (4.3)	3 (3.4)
Bone fracture	9 (2.6)	12 (3.4)	3 (2.6)	3 (3.4)

All values in table are shown as n (%)
eGFR, estimated glomerular filtration rate
Data on file

EMPEROR-Reduced: Adverse event profile was favourable even in very old patients

	Age 75 to <85 years		Age ≥85 years	
	Empagliflozin (N=445)	Placebo (N=455)	Empagliflozin (N=58)	Placebo (N=41)
AEs leading to discontinuation	95 (21.3)	101 (22.2)	20 (34.5)	13 (31.7)
Serious AEs	200 (44.9)	230 (50.5)	34 (58.6)	24 (58.5)
AEs of special interest				
Acute kidney failure	42 (9.4)	46 (10.1)	8 (13.8)	8 (19.5)
Urinary tract infection	32 (7.2)	28 (6.2)	5 (8.6)	2 (4.9)
Genital infection	11 (2.5)	3 (0.7)	0	0
Volume depletion	56 (12.6)	57 (12.5)	7 (12.1)	5 (12.2)
Hypotension	45 (10.1)	51 (11.2)	7 (12.1)	4 (9.8)
Confirmed hypoglycaemia	5 (1.1)	5 (1.1)	0	0
Bone fracture	15 (3.4)	17 (3.7)	4 (6.9)	3 (7.3)

All values in table are shown as n (%)
Data on file

EMPEROR-Reduced: Volume depletion was not increased by empagliflozin, even in high-risk patients

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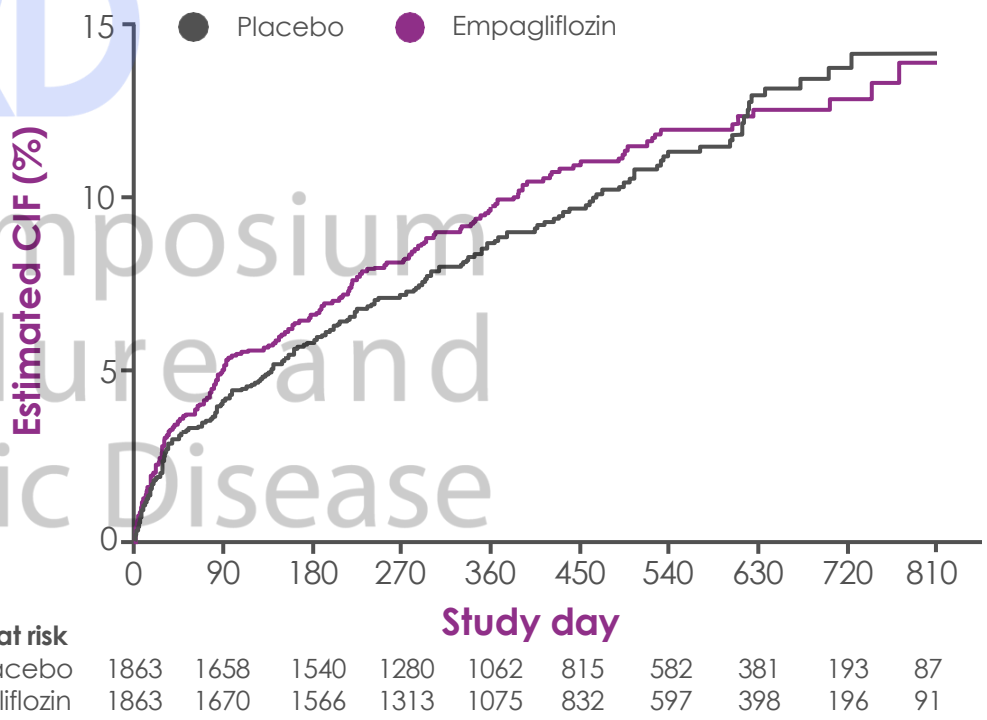
Volume depletion events, n (%)	Empagliflozin (n=1863)	Placebo (n=1863)
All reported events	197 (10.6)	184 (9.9)
Serious AEs	43 (2.3)	33 (1.8)
AEs leading to discontinuation	14 (0.8)	6 (0.3)

Not influenced by:

- Diabetes
- Kidney function
- Age
- Ejection fraction
- Systolic blood pressure
- Neprilysin inhibition



CIF, cumulative incidence function
Data on file

EMPEROR-Reduced: Symptomatic hypotension was not increased by empagliflozin, even in high-risk patients

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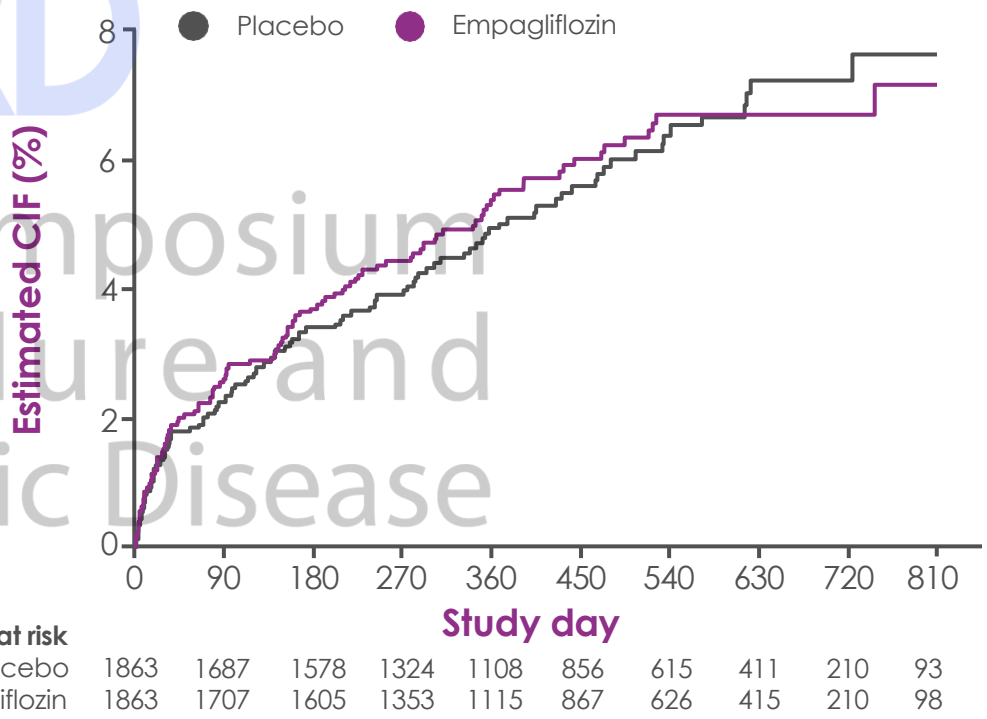
Hypotension events, n (%)	Empagliflozin (n=1863)	Placebo (n=1863)
All events	106 (5.7)	103 (5.5)
Events within first 30 days of treatment	30 (1.6)	28 (1.5)

Not influenced by:

- Diabetes
- Kidney function
- Age
- Ejection fraction
- Systolic blood pressure
- Neprilysin inhibition



CIF, cumulative incidence function
Data on file

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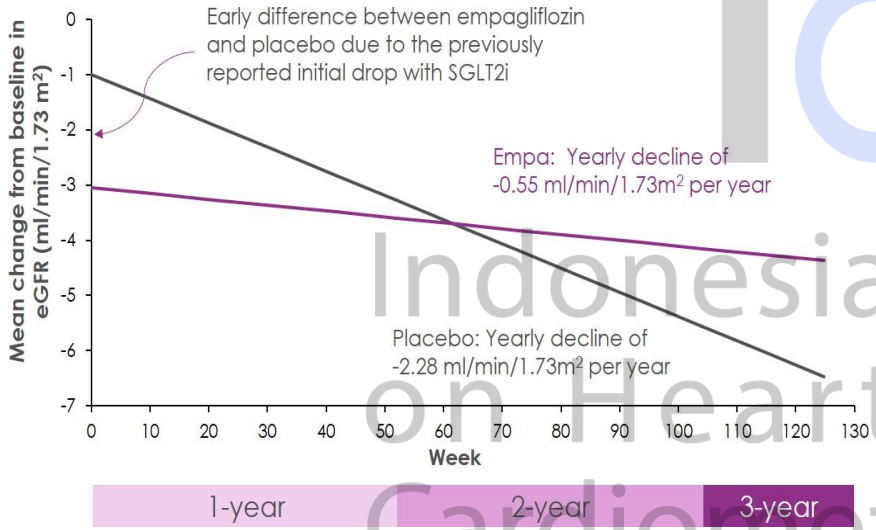
Subgroup analysis by diabetes status: Key secondary endpoint – eGFR slope

Empagliflozin slowed progression of kidney function decline in patients with and without diabetes

eGFR slope in the overall population[1]



+ 1.73 ml/min/1.73 m²/year
95% CI:1.10, 2.37
p<0.0001

eGFR slope difference between empagliflozin and placebo:[2]

With diabetes:
+ 2.21 ml/min/1.73 m²/year
95% CI: 1.31, 3.10

Without diabetes:
+ 1.27 ml/min/1.73 m²/year
95% CI: 0.38, 2.16

Interaction *p*-value: 0.15

1. Packer M *et al. N Engl J Med*. 2020;383(15):1413; 2. Anker SD *et al. Circulation* 2020. doi: 10.1161/CIRCULATIONAHA.120.051824

Composite renal outcome (end-stage kidney disease or sustained profound decrease in eGFR)

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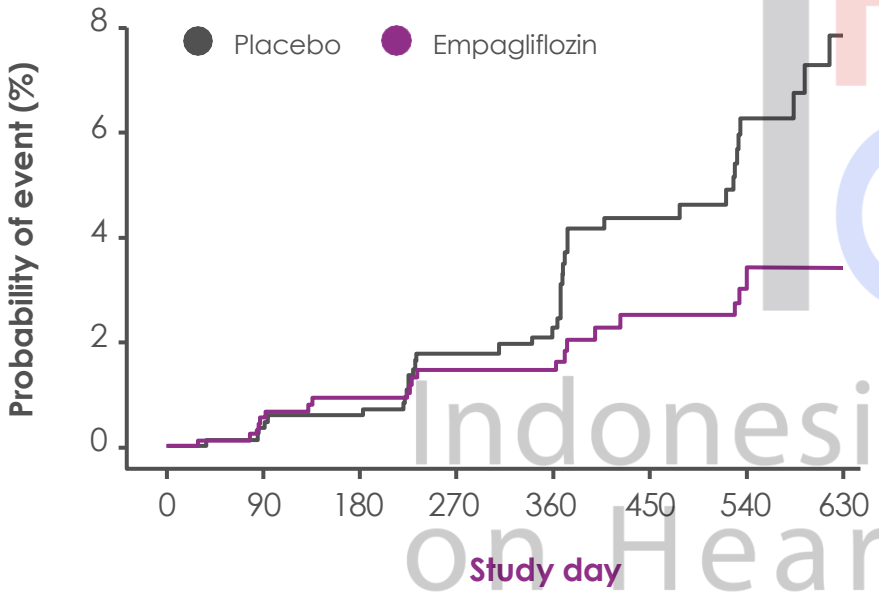
With diabetes

HR 0.53 (CI 95% 0.31, 0.90)

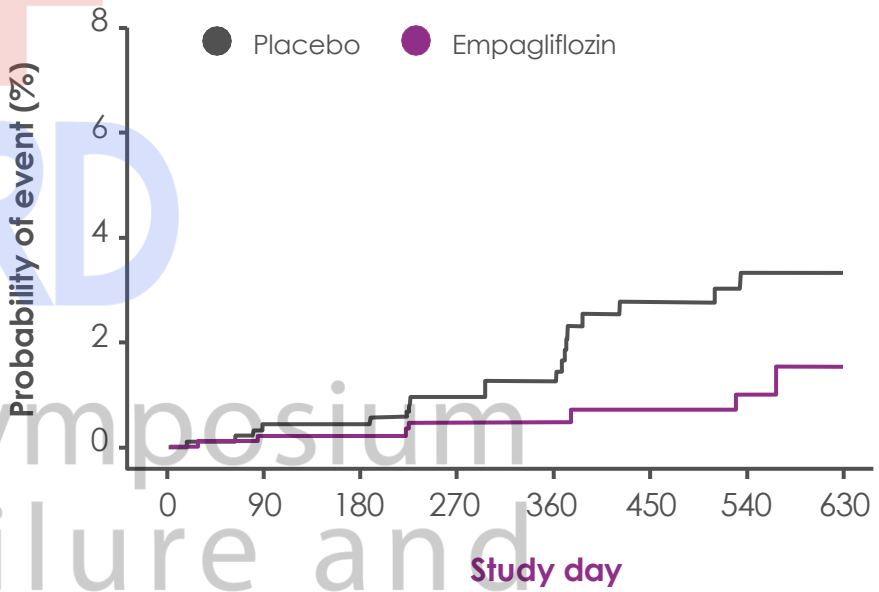
Interaction *p*=0.65



Patients at risk								
Placebo	929	786	740	565	526	331	179	127
Empagliflozin	927	793	75	573	535	347	201	143

Without diabetes

HR 0.42 (CI 95% 0.19, 0.97)



Patients at risk								
Placebo	938	805	760	571	532	350	178	132
Empagliflozin	936	805	777	581	526	340	190	133

CI, confidence interval; HR, hazard ratio

*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

Anker SD *et al. Circulation* 2020. doi: 10.1161/CIRCULATIONAHA.120.051824

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SGLT2 inhibitors are a foundational therapy in patients with HFpEF

HFpEF treatment

Foundational therapy[1,2]

SGLT2 inhibitor

+

Diuretics (as needed for fluid retention)[1,2]

- ✓ **SGLT2 inhibitors** are the **only treatment with a Class I recommendation** for **patients with HFpEF** in ESC Guideline[1]
- ✓ **Highest class of recommendation (2a)** for SGLT2 inhibitors in AHA/ACC/HFSA Guideline[2]

This slide focuses on the specific treatment pillars of HFpEF therapy.

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HFpEF, heart failure with preserved ejection fraction; HFSA, Heart Failure Society of America; SGLT2, sodium-glucose co-transporter-2.

1. McDonagh TA *et al. Eur Heart J.* 2023;doi.org/10.1093/eurheartj/ehad195; 2. Heidenreich PA *et al. J Am Coll Cardiol.* 2022;79:e263.

EMPEROR-Preserved: Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF

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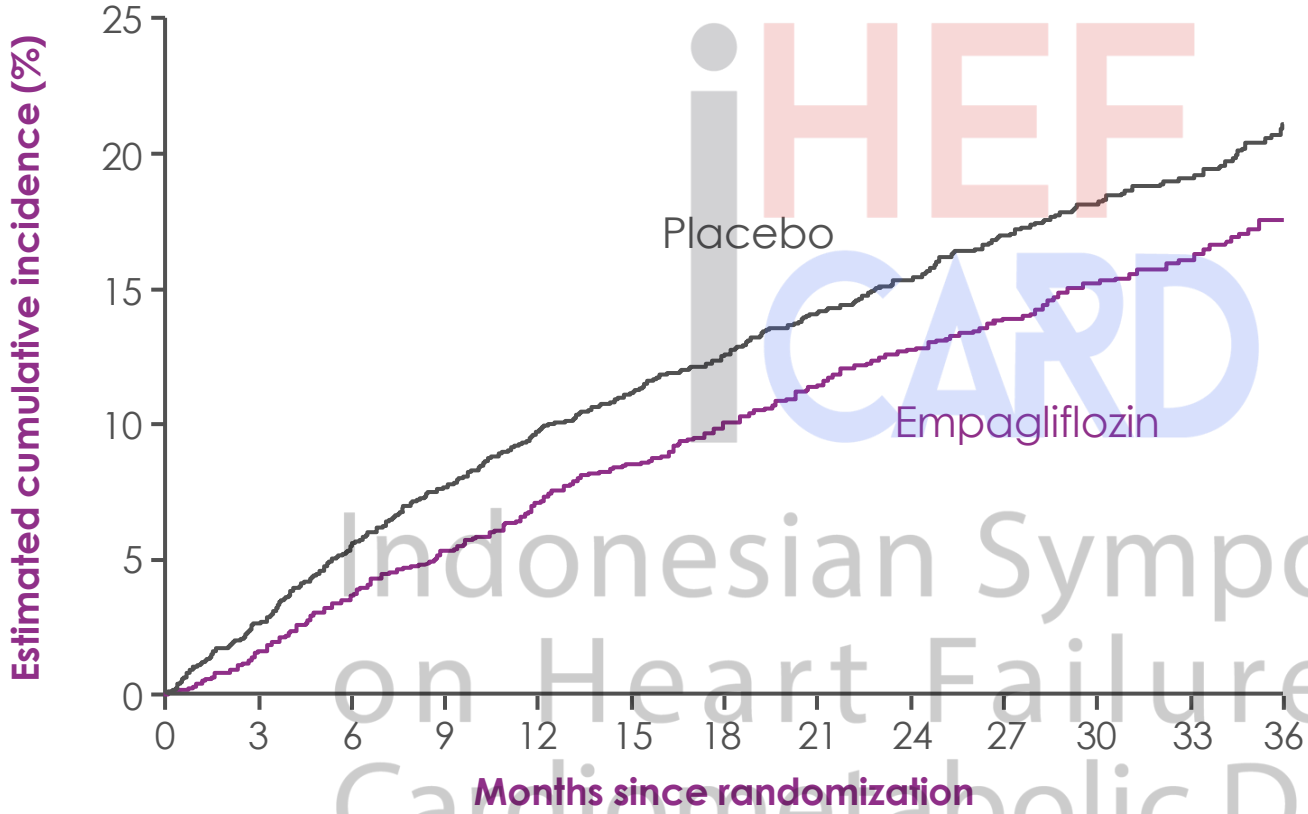


RRR 21% | **ARR 3.3%** | **NNT*=31**

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Patients at risk

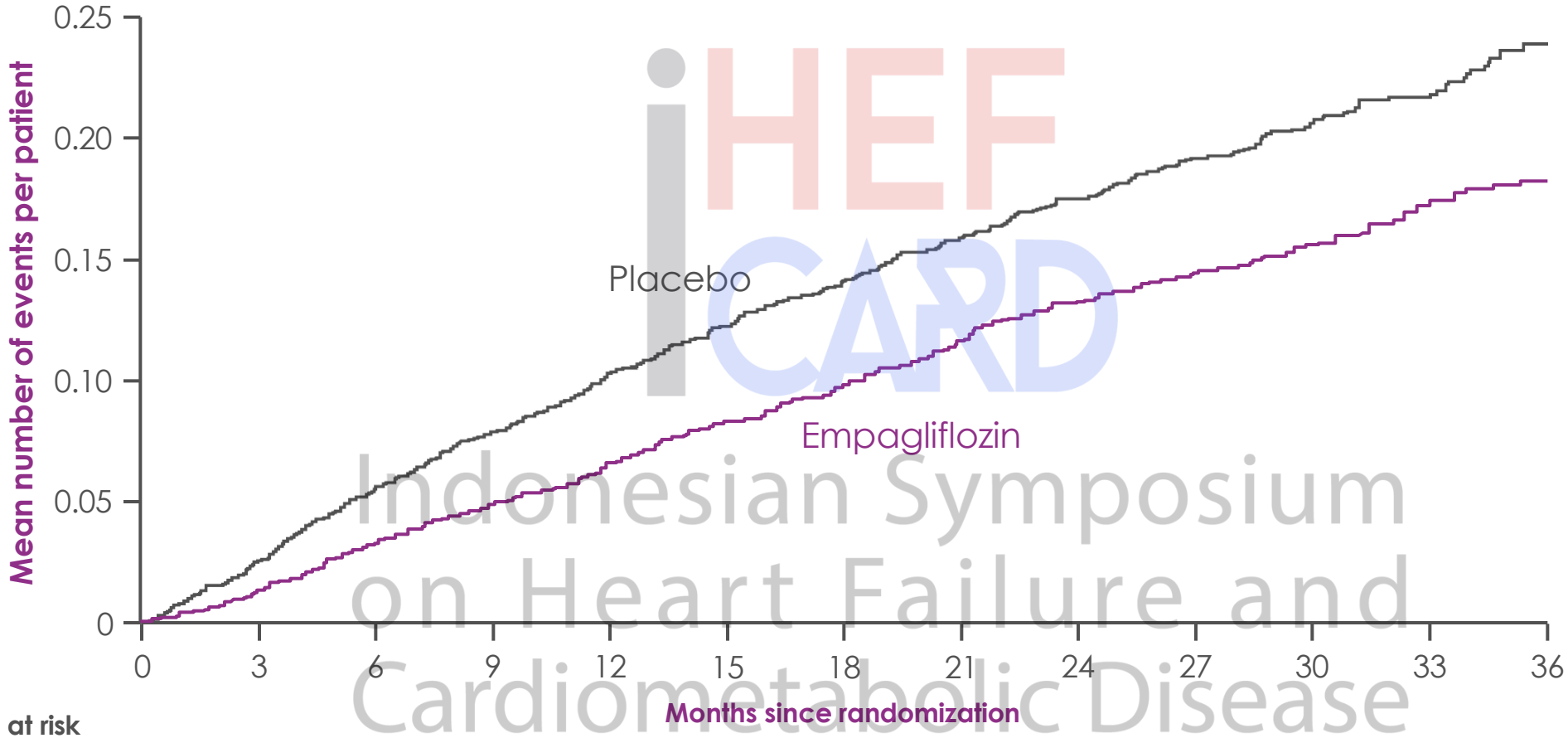
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years

Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction. Anker *S et al. N Engl J Med.* 2021;385:1451.

EMPEROR-Preserved: Key secondary endpoint –adjudicated total HHF (first and recurrent)



Patients at risk

Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

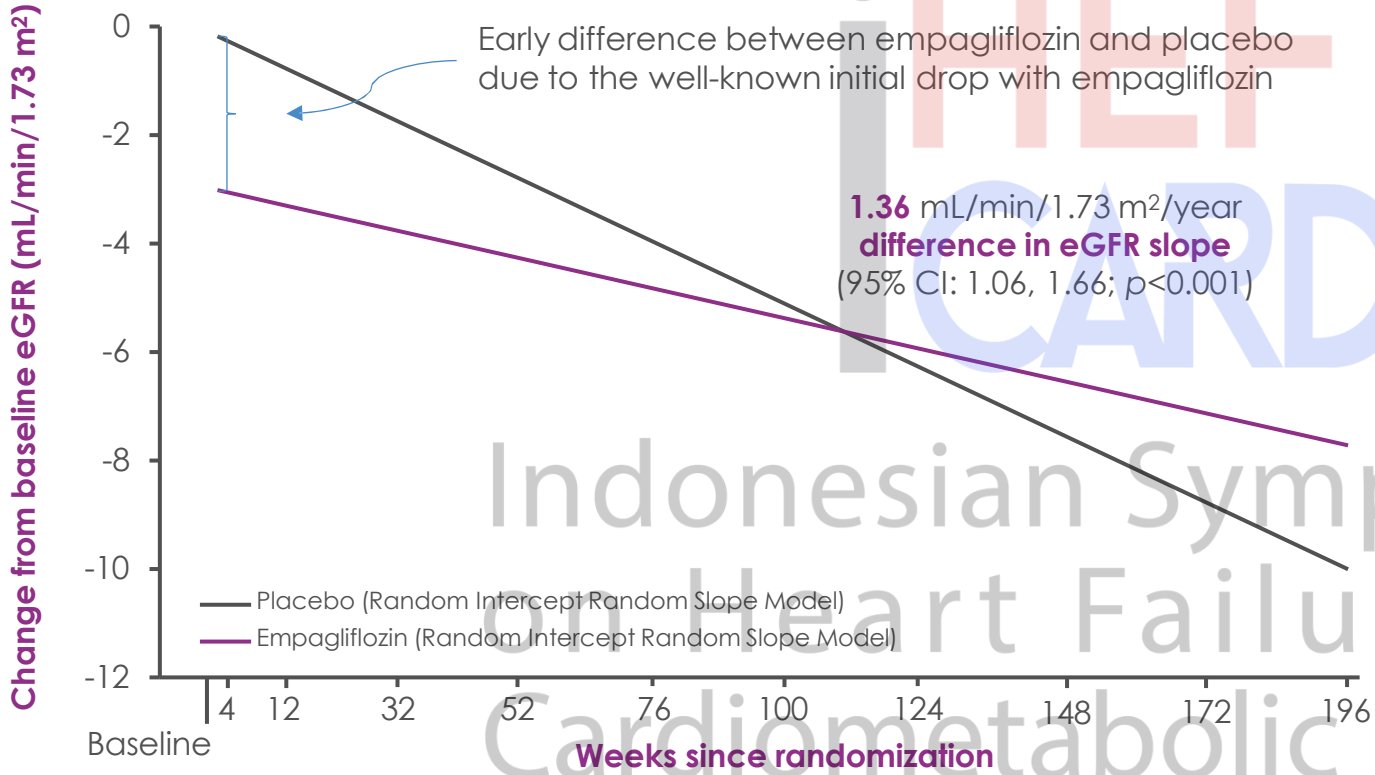
RRR 27%

HR: 0.73
(95% CI: 0.61, 0.88)
p<0.001

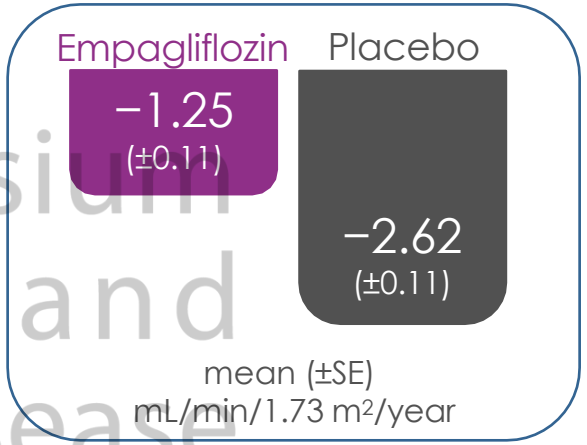
Empagliflozin: 407 patients with event
Placebo: 541 patients with event

CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; RRR, relative risk reduction.
Anker *S et al. N Engl J Med*. 2021;385:1451.

Empagliflozin protected the kidney by significantly slowing the decline in kidney function



The rate of eGFR decline in patients treated with empagliflozin was half that of patients treated with placebo



eGFR slope = rate of decline (and is a measure for long-term renal function). eGFR slope is analysed based on on-treatment data using a random intercept-random model including age, baseline eGFR and baseline LVEF as linear covariates and sex, region, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SE, standard error.

Developed from data reported in Anker S *et al. N Engl J Med*. 2021;385:1451.

Empagliflozin showed unequivocal benefits across EF in HF patients, regardless of T2D status

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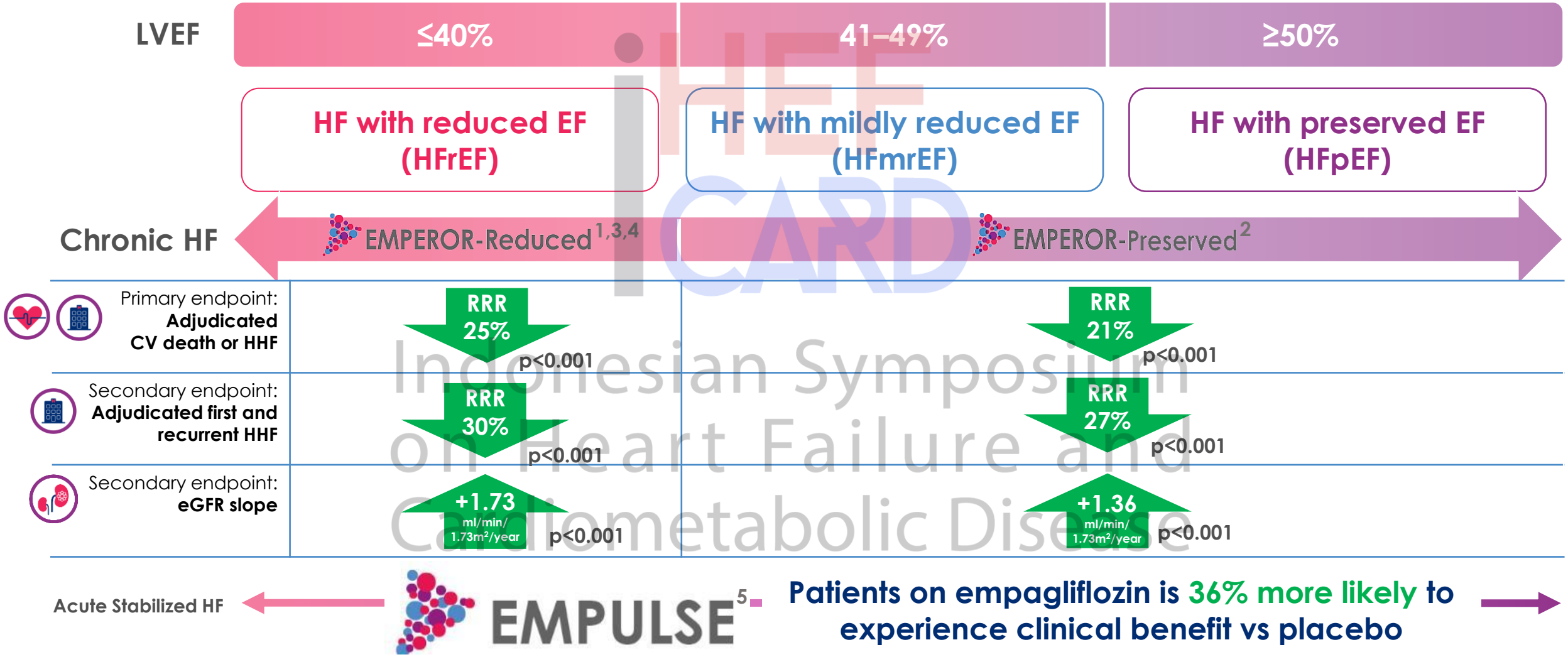

For heart failure indication this current SGLT2i is only indicated for Chronic Heart Failure

‡Evaluated with a win ratio based on a composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment. EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.

1. Packer M, et al. N Engl J Med. DOI: 10.1056/NEJMoa2022190; 2. Anker S *et al. N Engl J Med*. 2021; DOI: 10.1056/NEJMoa210703; 3. Packer et al., Presented during e-space 1st Cardio-renal-metabolic Global Web Conference, January 22 – 24, 2021; 4. Packer M et al. *Circulation*. 2021 DOI: 10.1161/CIRCULATIONAHA.121.056824. 5. Voors AA *et al. Nat Med*. 2022:28:568.

Dosing and titration of heart failure therapies

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	Once-daily dosing	Single dose	Titration
ACE inhibitors[1,2]	N/Y	N	Y
ARB[3,4]	N/Y	N	Y
ARNIs[5]	N	N	Y
Mineralocorticoid receptor antagonist[6,7]	Y	N	Y
Beta-blockers[8,9]	N/Y	N	Y
Loop diuretics[10]	N/Y	N	Y
SGLT2 inhibitors[11,12]	Y	Y	N

SGLT2 inhibitors require single dosing, once a day, with no need for titration

ACE, Angiotensin-converting enzyme; ARB, Angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; SGLT2, sodium-glucose co-transporter-2

1. Vasotec Prescribing Information. May 2020; 2. ALTACE Prescribing Information. 2020; 3. DIOVAN Prescribing Information. 2020; 4. ATACAND Prescribing Information. 2020; 5. Entresto Prescribing Information. 2020; 6. Aldactone Prescribing Information. 2020; 7. INSPRA Prescribing Information; 2020 8. ZEBETA Prescribing Information. 2020; 9 COREG Prescribing Information. 2020; 10. LASIX Prescribing Information. 2020; 11. FARXIGA Prescribing Information. 2020; 12. Boehringer Ingelheim Pharmaceuticals. Jardiance® (empagliflozin) summary of product characteristics. Jan 2020

Summary

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1. HF and CKD frequently coexist, leading to increased hospitalization, renal decline, and mortality
2. Cardio-renal protection should be a core treatment goal in heart failure management
3. SGLT2 inhibitors are now foundational therapy across the HF spectrum.
4. Empagliflozin significantly reduces HF hospitalizations and CV events in both HFrEF and HFpEF
5. Empagliflozin slows kidney function decline and reduces progression to severe renal outcomes.
6. Benefits are consistent regardless of diabetes status, kidney function, age, or ejection fraction, with a favorable safety profile.

Protecting the heart protects the kidney—early initiation of empagliflozin provides proven cardiorenal benefits across the spectrum of heart failure

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Thank you

Indonesian Symposium on Heart Failure and Cardiometabolic Disease