

NHF 04.11.21

Reviderte europeiske retningslinjer for hjertesvikt 2021.



Rune Mo

Klinikk for hjertemedisin

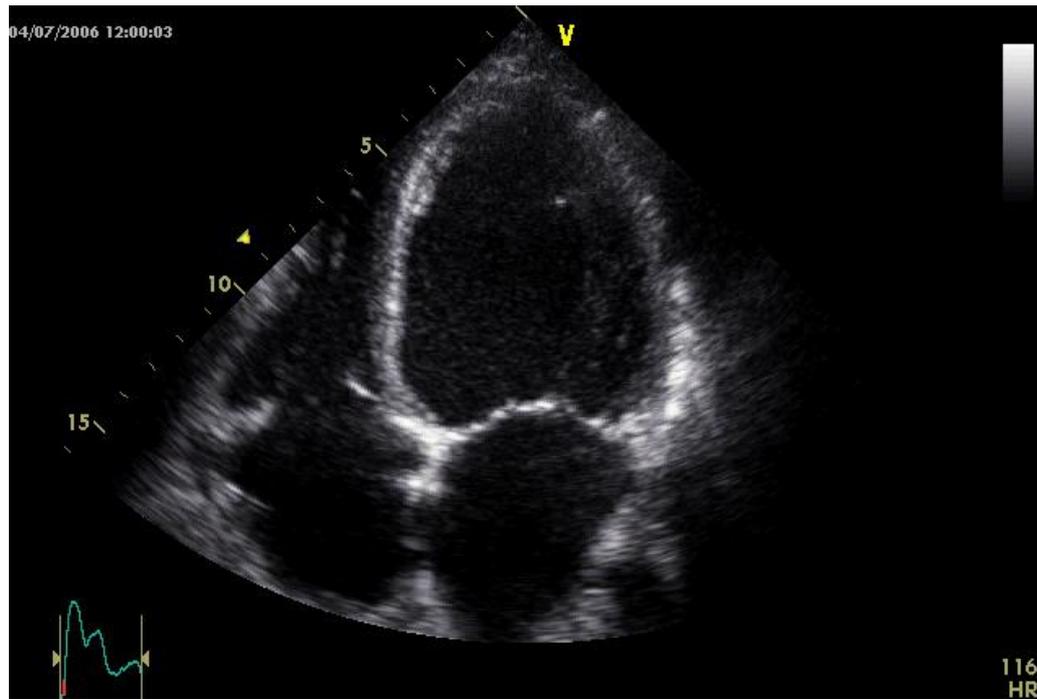


ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

SGLT2-hemmere

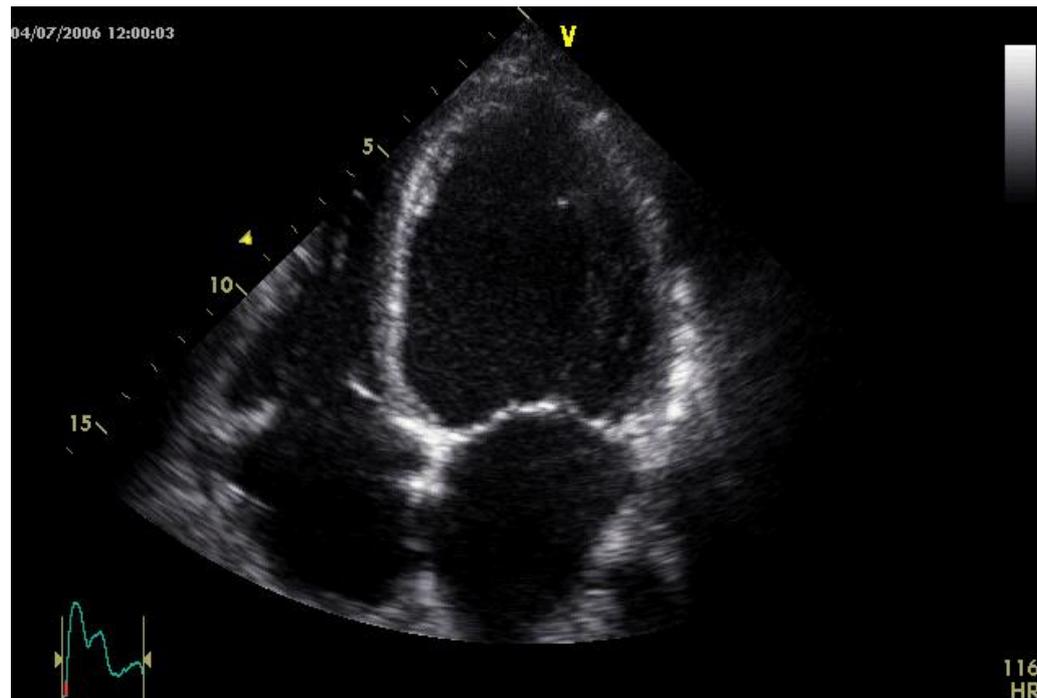
- **Hva** vet vi om SGLT2i ved hjertesvikt?
- **Hvorfor** virker SGLT2i ved hjertesvikt?
- **Hvem** skal vi behandle med SGLT2i?
- **Hvordan** skal vi gi behandling med SGLT2i?

Hva er hjertesvikt?



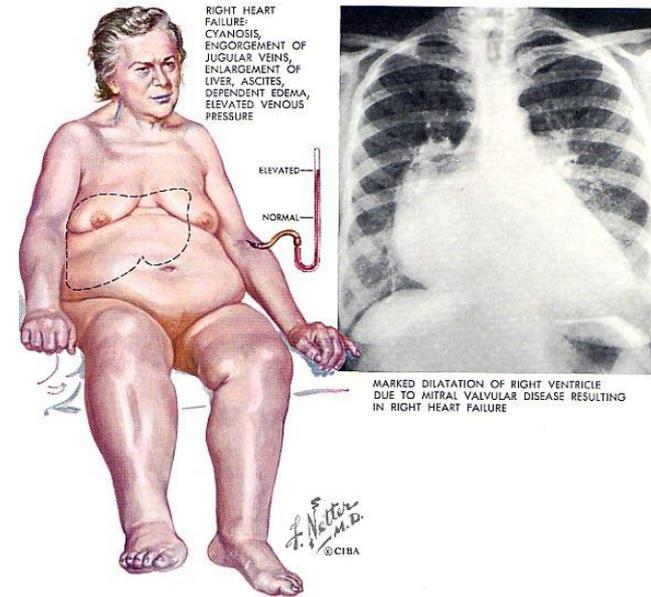
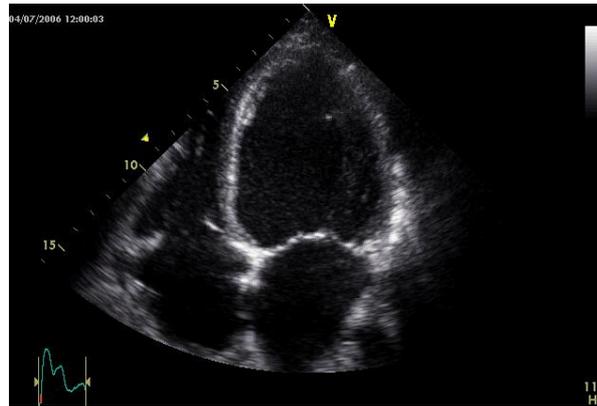
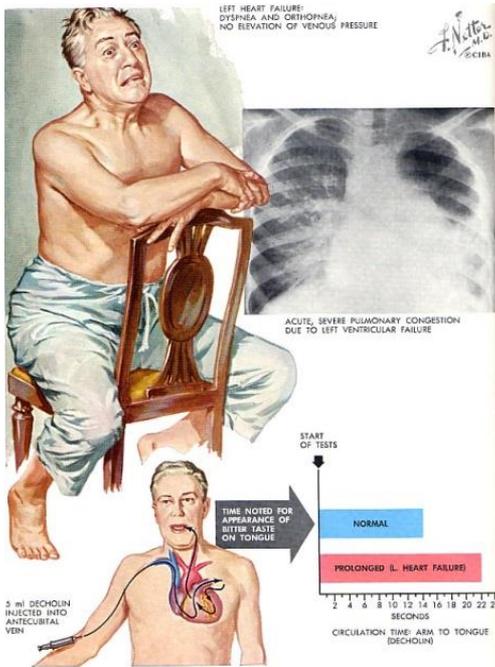
Sviktende hjerte(pumpe)funksjon.

Hva er hjertesvikt?



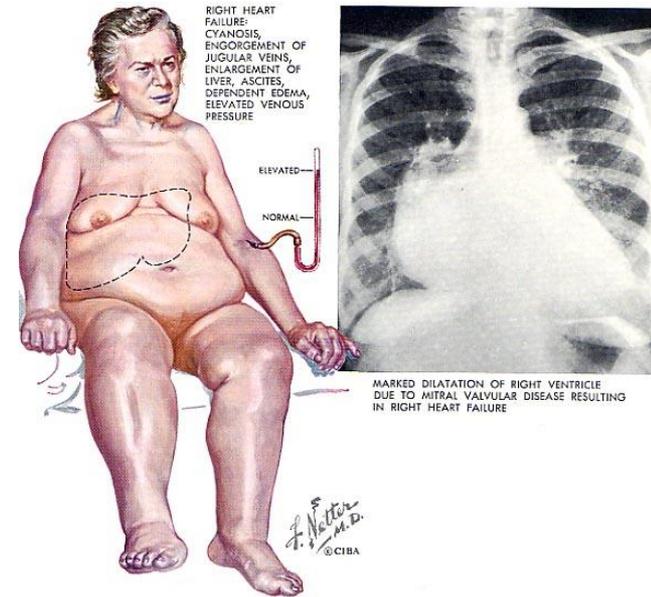
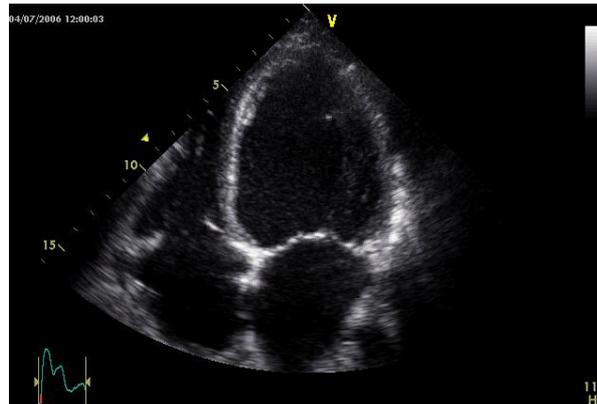
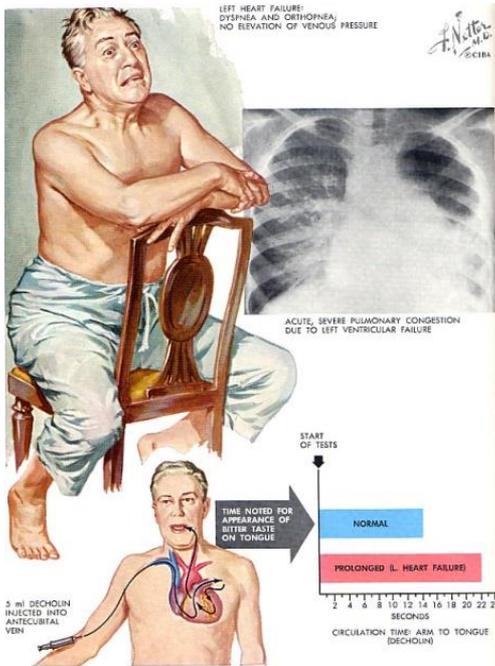
Strukturell eller funksjonell hjertesykdom.

Hjertesvikt



Symptomer og tegn.

Hjertesvikt



Fatigue, dyspnoe, ødemer.



ESC

European Society
of Cardiology

European Heart Journal (2021) **00**, 1–128

doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

McDonagh T, Metra M et al. Eur Heart J 2021; 00, 1-128.

Published online 27.08.21



2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Definition of heart failure

- Clinical **syndrome**.
- **Symptoms** (e.g. breathlessness, ankle swelling, fatigue).
- **Signs** (e.g. elevated JVP, pulmonary crackles, oedema).
- Structural and/or functional **cardiac abnormality**.
- **Reduced cardiac output** and/or **elevated intracardiac pressures** at rest or during stress.

Klassifisering av hjertesvikt

- en liten (språklig) endring fra 2016 til 2021

HFrEF	HFmrEF	HFpEF
Symptoms ± Signs ^a	Symptoms ± Signs ^a	Symptoms ± Signs ^a
LVEF ≤40%	LVEF 41 – 49% ^b	LVEF ≥50%
–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides ^c



HFmrEF: Fra *mid-range* til *mildly reduced*!

Årsaker til hjertesvikt

- Ischemisk kardiomyopati (koronar hjertesykdom)
- Hypertensiv kardiomyopati

- Valvulær kardiomyopati (primær klaffefeil)
- Infeksiøs kardiomyopati (myokarditt)
- Metabolsk kardiomyopati (hemokromatose)
- Endokrin kardiomyopati (diab. mell., thyreose)
- Systemsykdommer (sarkoidose, SLE, amyloidose)
- Toxisk kardiomyopati (alkohol, medikamenter)
- Primær kardiomyopati (dilatert, hypertrof, restriktiv)
- Sjeldne årsaker (HIV, Chagas' sykdom etc.)

Livstidsrisiko for hjertesvikt

20%

Djousse L, Driver JA, Gaziano JM. Relation between modifiable lifestyle factors and lifetime risk of heart failure.

JAMA. 2009;302:394–400.

5-års mortalitet ved hjertesvikt

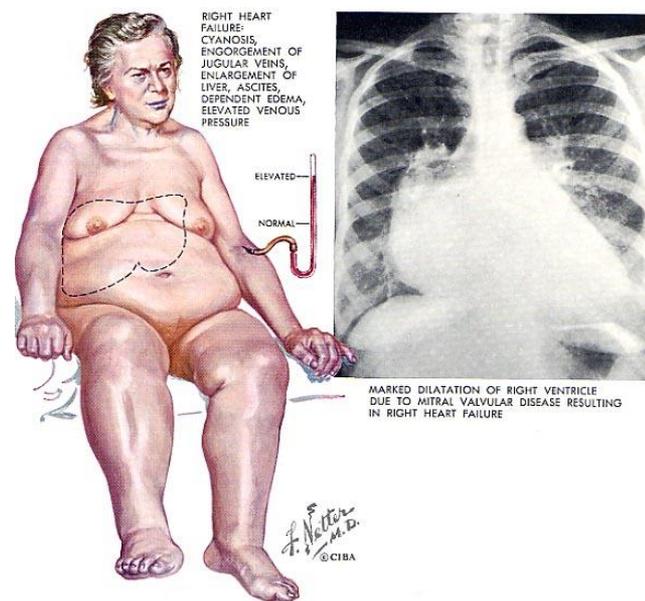
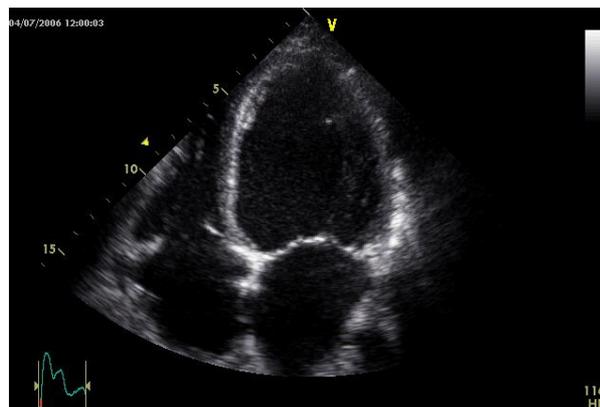
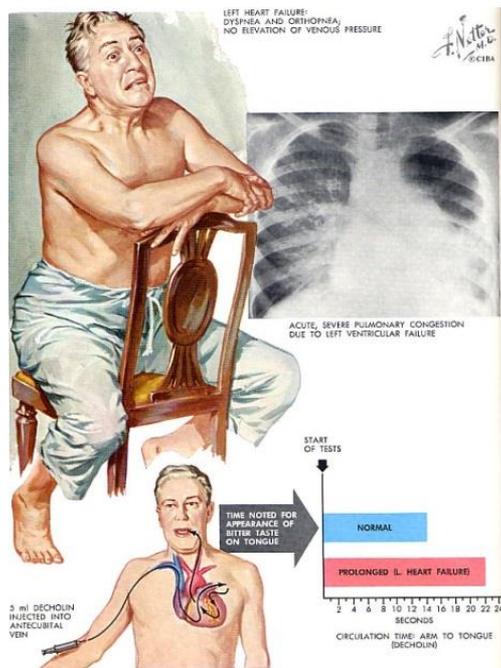
50%

Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population.

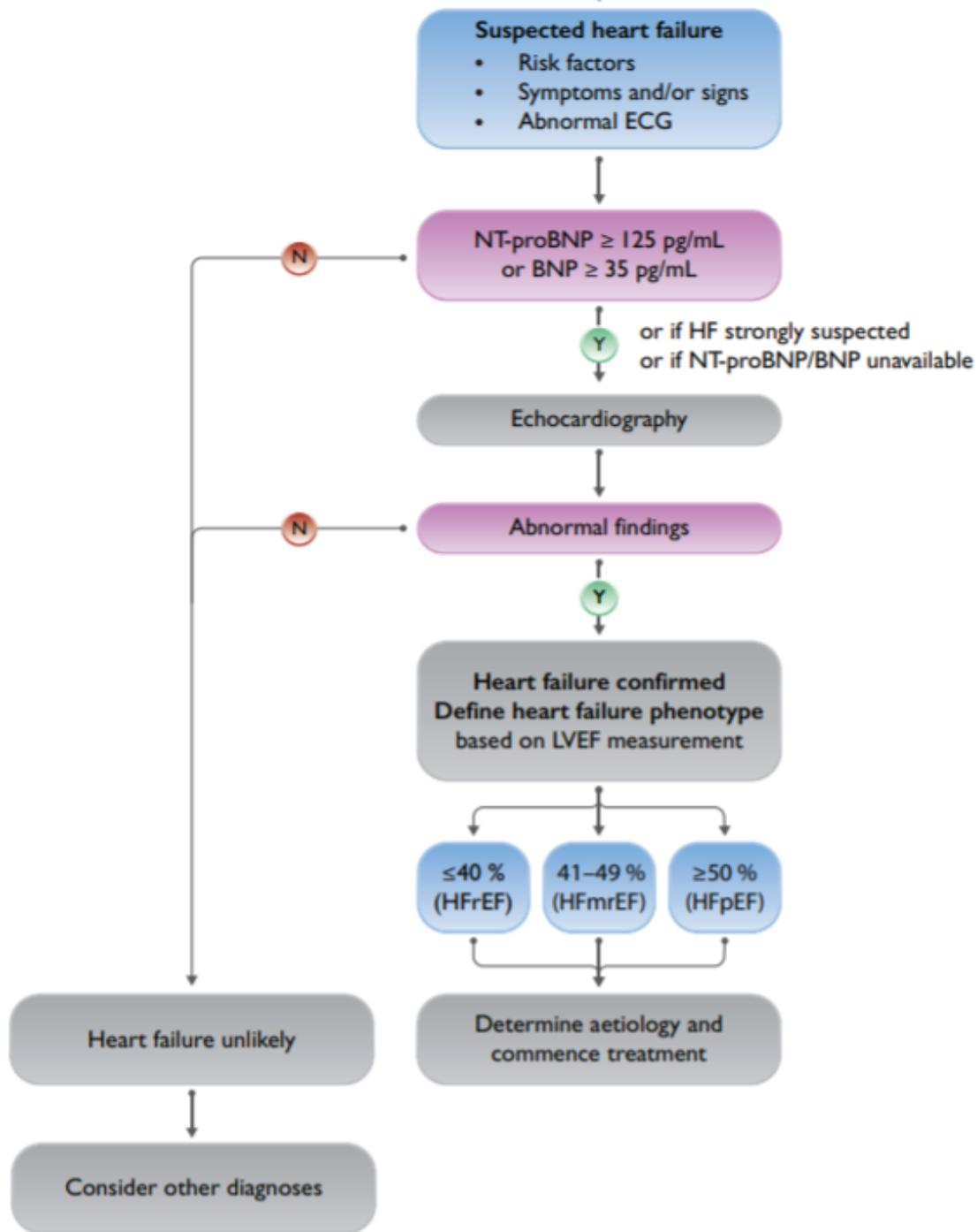
JAMA. 2004;292:344–50.

Levy D, Kenchaiah S, Larson MG et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002;347:1397–402.

Utredning av hjertesvikt



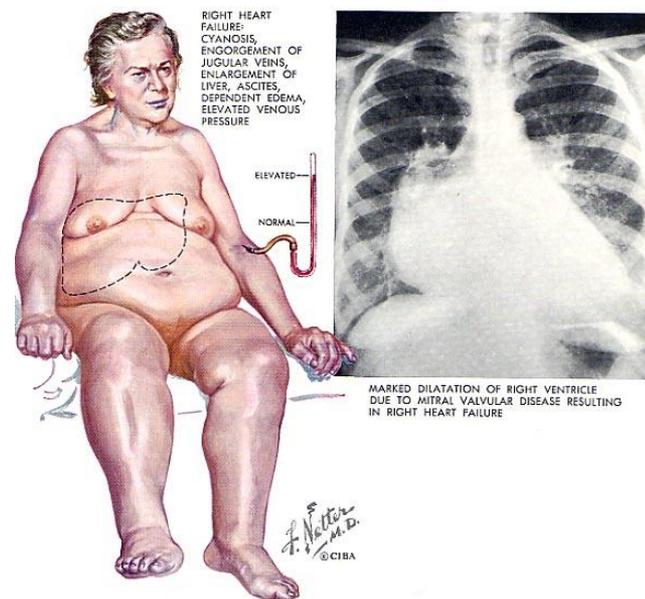
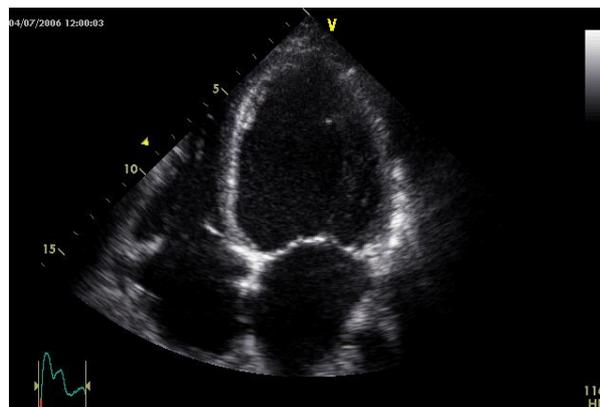
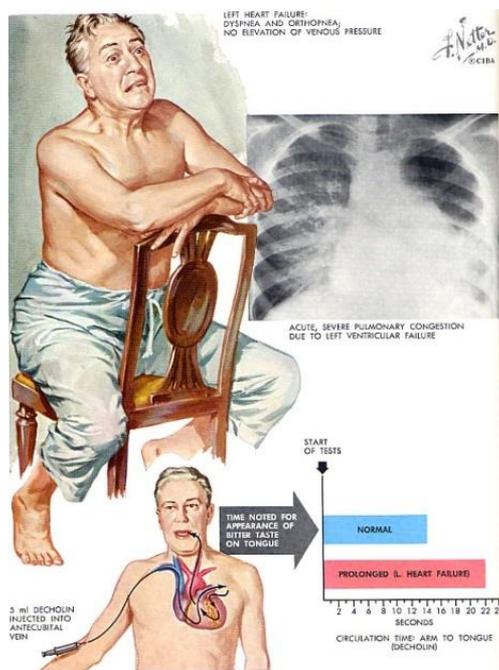
Diagnose, klassifisering og årsaksavklaring!



Anbefalte undersøkelser ved mistanke om hjertesvikt (alle pasienter)

Recommendations	Class ^a	Level ^b
BNP/NT-proBNP ^c	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

Behandling av hjertesvikt



Symptomer, livskvalitet, sykkelighet (sykehusinnleggelses) og mortalitet!

Behandling av HFrEF - nye anbefalinger

- Dapagliflozin og empagliflozin anbefales!
- ACE-hemmer/ARNI, betablokker, MRA og SGLT2-hemmer bør startes så raskt og sikkert som mulig!
- Vericiguat kan vurderes!

Management of patients with HFrEF

- ACE-I/ARNI^a
- Beta-blocker
- MRA
- Dapagliflozin/Empagliflozin
- Loop diuretic for fluid retention (Class I)

LVEF \leq 35% and
QRS <130 ms and
where appropriate

ICD

Non-ischaemic (Class IIa) Ischaemic (Class I)

LVEF >35% or device
therapy not indicated
or inappropriate

SR and
LVEF \leq 35% and
QRS \geq 130 ms

CRT-D^b/-P

QRS 130-149 ms (Class IIa) QRS \geq 150 ms (Class I)

If symptoms persist, consider therapies
with Class II recommendations

Medikamentell behandling av HFrEF

An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.^{110–113}

A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.^{114–120}

An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.^{121,122}

Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.^{108,109}

Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.¹⁰⁵

Andre aktuelle medikamenter

- **Loop diuretika**

- Kombinasjon med thiazid?
- Laveste dose for å opprette normovolemi!

- **Ivabradine**

- Supplement ved SR > 70(75?)/min
- Når betablokker er kontraindisert

- **Vericiguat** (sGC-aktivator)

- **Hydralazin + ISDN**

- Supplement hos afroamerikanere
- Når ACEi/BB/MRA er kontraindisert.

- **Digoxin**

- **Omecamtiv mecarbil**
(kardial myosin-aktivator)

Oppsummering - basisbehandling HFrEF

- ACEI/ARNI + BB + MRA + SGLT2i (dapagliflozin, empagliflozin).
- ARNI som førstevalg (før ACEi) kan vurderes.
- ARB ved intoleranse/kontraindikasjoner for ACEi/ARNI.

Congress News



Day 3

ESC Congress **Paris 2019**

Together with **World Congress of Cardiology**

Monday 2 September

Top picks

PAGE 2 Ticagrelor in diabetes

Long-awaited results of THEMIS

PAGE 4 Does remote ischaemia conditioning improve outcomes after STEMI?

Results of the CONDI-2/ERIC-PPCI trial revealed

PAGE 6 A HISTORIC moment for cardiac troponin

Can a single test be used to rule out MI?

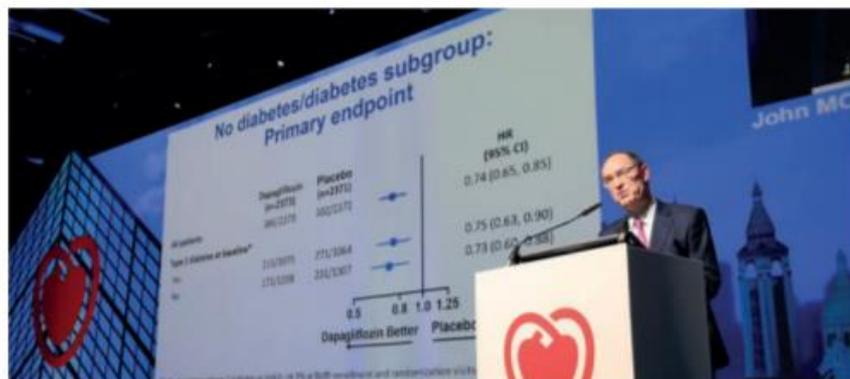
PAGE 15 Home-based education to reduce AF hospitalisation

Promising data from the HELP-AF trial

Dapagliflozin reduces cardiovascular events in HFrEF, not just diabetes

"Yesterday, we presented once-in-a-lifetime findings that sodium-glucose co-transporter-2 (SGLT2) inhibitors are truly a treatment for heart failure (HF) and not just diabetes," says Professor John McMurray (University of Glasgow, Glasgow, UK), speaking about his Hot Line presentation on the DAPA-HF trial.

"HF is a very common complication of type 2 diabetes, occurring more frequently than stroke and as frequently as myocardial infarction," explains Prof. McMurray. "Trials have shown that, in addition to effectively



The Global Exchange Area

Broaden your professional development

Skills and knowledge required in cardiology today, including:

- > CVD research opportunities
- > Equity in cardiology

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019

Sponsor AstraZeneca

N= 4744

NYHA II-IV

EF \leq 40%

DM 40%

Dapagliflozin 10 mg x 1 vs. Placebo

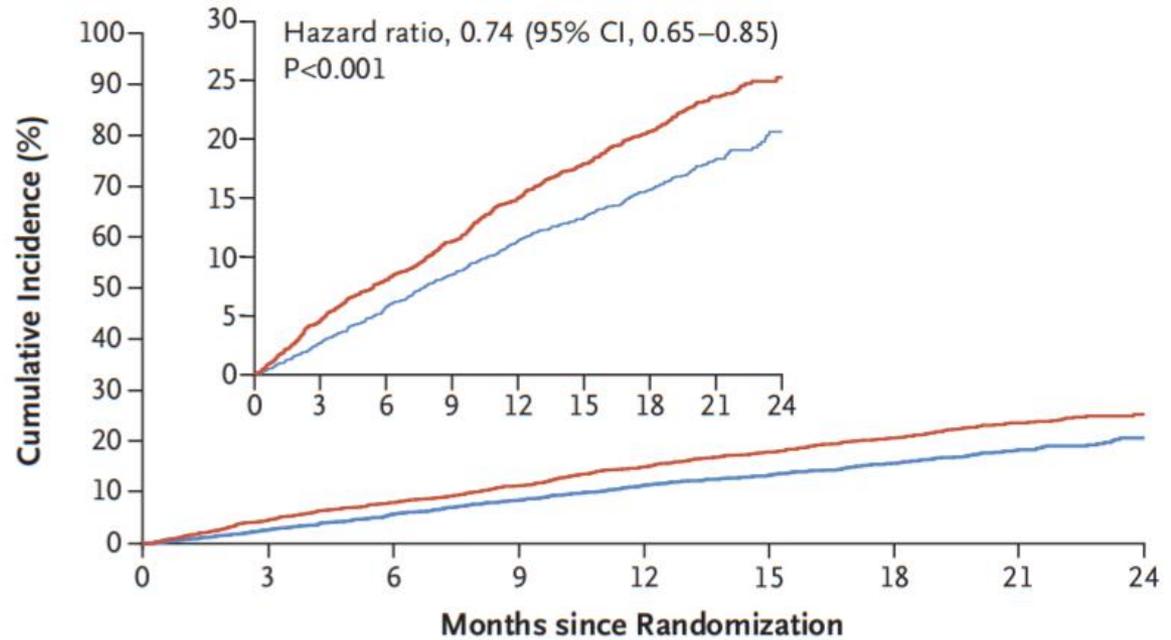
1°EP: worsening heart failure or
cardiovascular death.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019

A Primary Outcome



No. at Risk

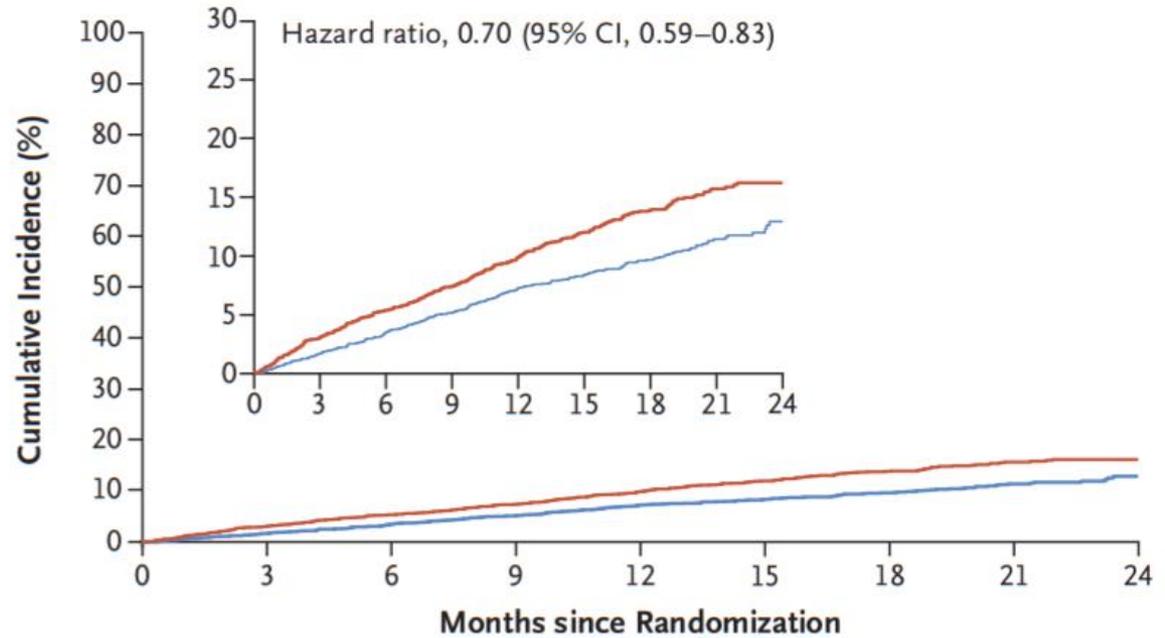
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019

B Hospitalization for Heart Failure



No. at Risk

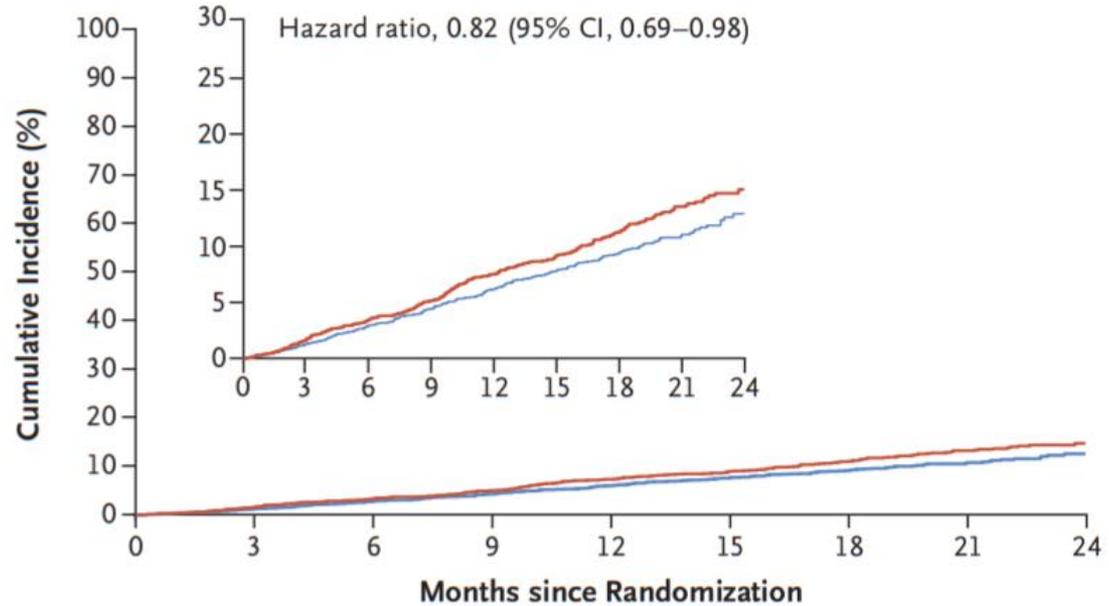
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212
Dapagliflozin	2373	2306	2223	2153	2007	1563	1147	613	210

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019

C Death from Cardiovascular Causes



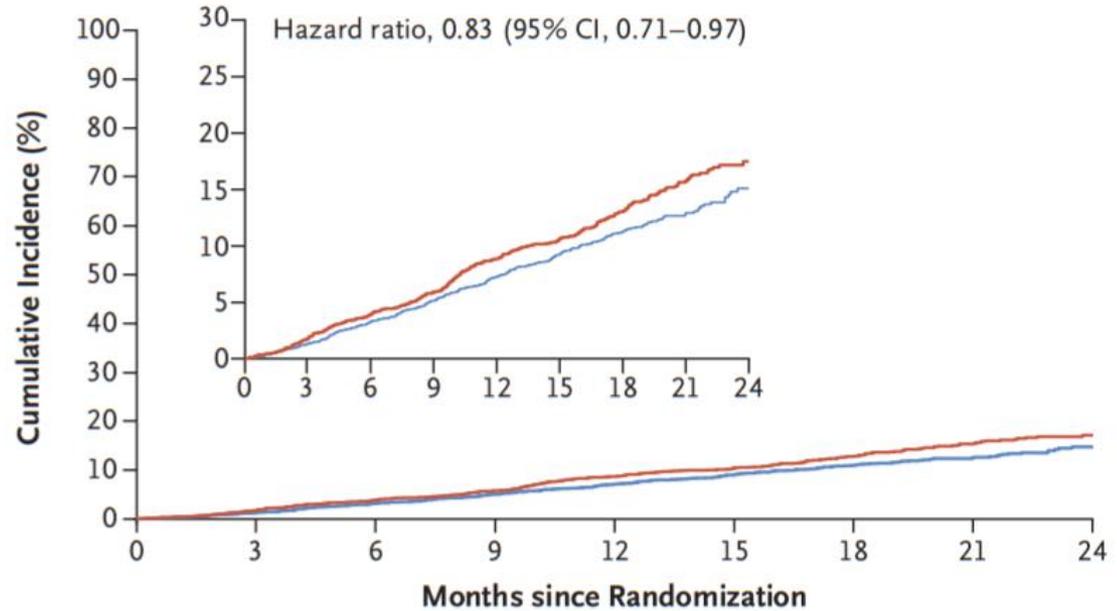
No. at Risk									
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234
Dapagliflozin	2373	2339	2293	2248	2127	1664	1242	671	232

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019

D Death from Any Cause



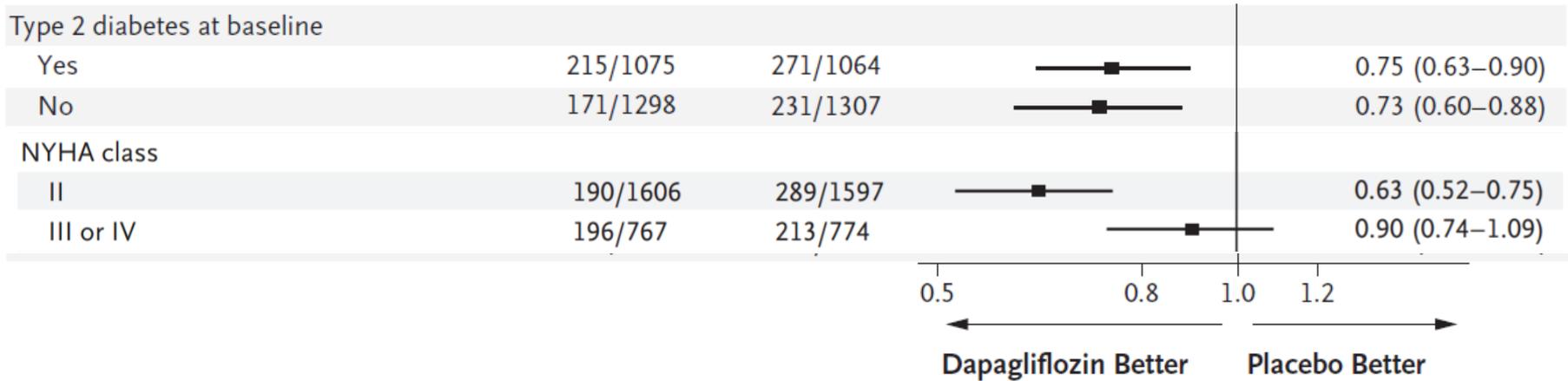
No. at Risk

Placebo	2371	2330	2279	2231	2092	1638	1221	665	235
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

McMurray et al. NEJM September 19, 2019



DAPA-HF: Ingen signifikant forskjell i bivirkninger mellom dapagliflozin og placebo

	Dapagliflozin (N = 2373)		Placebo (N = 2371)	
	values	events/100 patient-yr	values	events/100 patient-yr
Safety outcomes				
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	
Adverse events of interest — no./total no. (%)				
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	
Fracture	49/2368 (2.1)		50/2368 (2.1)	
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	
Fournier's gangrene	0	—	1/2368 (<0.1)	

McMurray et al. NEJM September 19, 2019

The NEW ENGLAND JOURNAL of MEDICINE

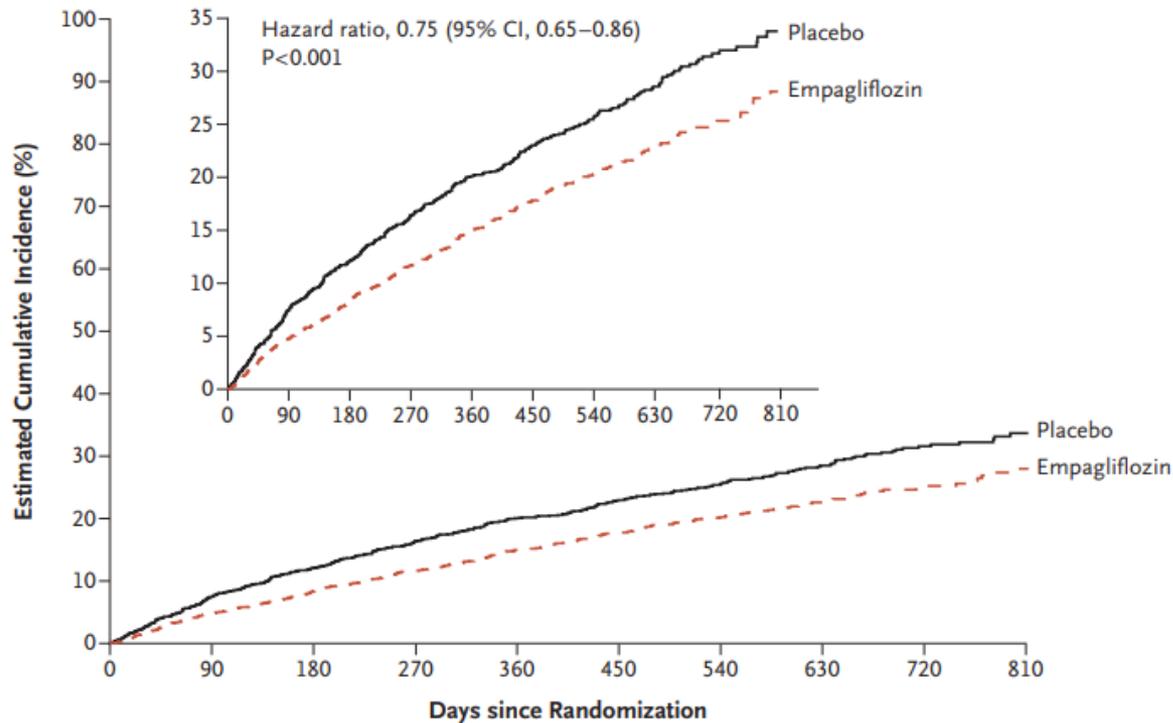
ESTABLISHED IN 1812

OCTOBER 8, 2020

VOL. 383 NO. 15

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Packer et al. N Engl J Med 2020;383:1413-24



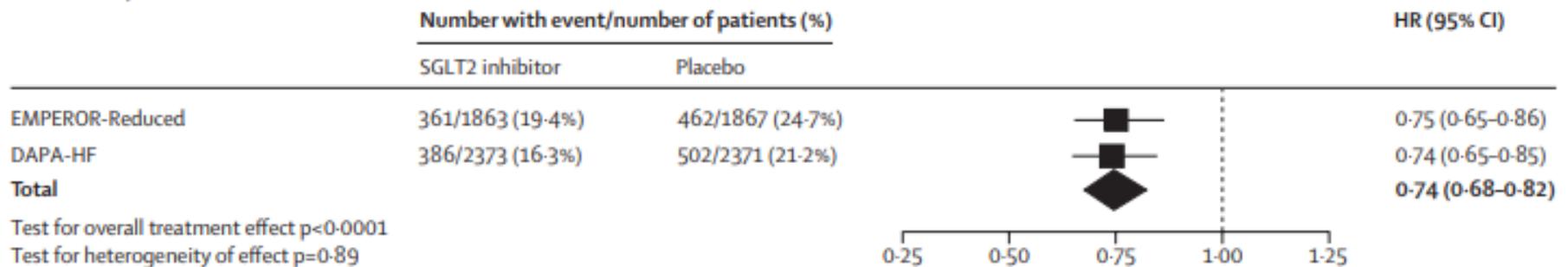
EMPEROR-Reduced: Små forskjeller i bivirkninger mellom empagliflozin og placebo

Selected adverse events of interest	Empagliflozin (n=1863)	Placebo (n=1863)
	N (%)	N (%)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Volume depletion	197 (10.6)	184 (9.9)
Ketoacidosis	0 (0.0)	0 (0.0)
Hypoglycemic events*	27 (1.4)	28 (1.5)
In patients with type 2 diabetes	20 (2.2)	22 (2.4)
In patients without type 2 diabetes	7 (0.7)	6 (0.6)
Urinary tract infections	91 (4.9)	83 (4.5)
Complicated urinary tract infections	19 (1.0)	15 (0.8)
Genital infections	31 (1.7)	12 (0.6)
Complicated genital infections	6 (0.3)	5 (0.3)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputation	13 (0.7)	10 (0.5)

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer

C First hospitalisation for heart failure or cardiovascular death





ESC

European Society
of Cardiology



HFA

Heart Failure
Association

**Heart Failure Association of the European Society of Cardiology Update
on Sodium Glucose Co-transporter-2 Inhibitors in Heart Failure**

**(an update on the Sodium–glucose co-transporter 2 inhibitors in heart
failure: beyond glycaemic control. The position paper of the Heart Failure
Association of the European Society of Cardiology)**

Petar M. Seferović^{*1,2}; Gabriele Fragasso³; Mark Petrie⁴; Wilfried Mullens^{5,6}; Roberto Ferrari⁷; Thomas Thum⁸; Johann Bauersachs⁹; Stefan D. Anker^{10,11}; Robin Ray¹²; Yuksel Çavuşoğlu¹³; Marija Polovina^{1,14}; Marco Metra¹⁵; Giuseppe Ambrosio¹⁶; Krishna Prasad¹⁷; Jelena Seferović^{1,18}; Pardeep S. Jhund¹⁹; Giuseppe Dattilo²⁰; Jelena Čelutkienė²¹; Massimo Piepoli²²; Brenda Moura²³; Ovidiu Chioncel^{24,25}; Tuvia Ben Gal²⁶; Stephane Heymans²⁷; Tiny Jaarsma²⁸; Loreena Hill²⁹; Yuri Lopatin³⁰; Alexander R. Lyon³¹; Piotr Ponikowski³²; Mitja Lainščak^{32,34}; Ewa Jankowska³²; Christian Mueller³⁵; Francesco Cosentino³⁶; Lars H. Lund³⁷; Gerasimos S. Filippatos³⁸; Frank Ruschitzka³⁹; Andrew J.S. Coats⁴⁰; Giuseppe M.C. Rosano^{*41}

Seferovic et al. Eur J Heart Fail 2020 22(11) 1984-1986.



In HF and reduced ejection fraction already receiving guideline directed medical therapy, regardless of the presence of T2DM,

Dapagliflozin
Empagliflozin

are recommended to reduce the combined risk of HF hospitalisation and CV death

Seferovic et al. Eur J Heart Fail 2020 22(11) 1984-1986.

SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis

15 randomiserte studier med 20,241 pasienter, 10,594 (52.3%) fikk SGLT2i.

SGLT2i reduserte

- **total mortalitet** (HR 0.86; 95% CI 0.79–0.94; $p = 0.0007$; $I^2=0\%$)
- **kardiovaskulær mortalitet** (HR 0.86; 95% CI 0.78–0.96; $p = 0.006$; $I^2=0\%$)
- **sammensatt KV mortalitet, sykehusinnleggelser/andre akutte hjertesvikthendelser** hos menn, kvinner, alder < 65, alder ≥ 65 , mørkhudete og hvite, eGFR < 60, eGFR ≥ 60 , NYHA II, NYHA \geq III, og HFpEF.

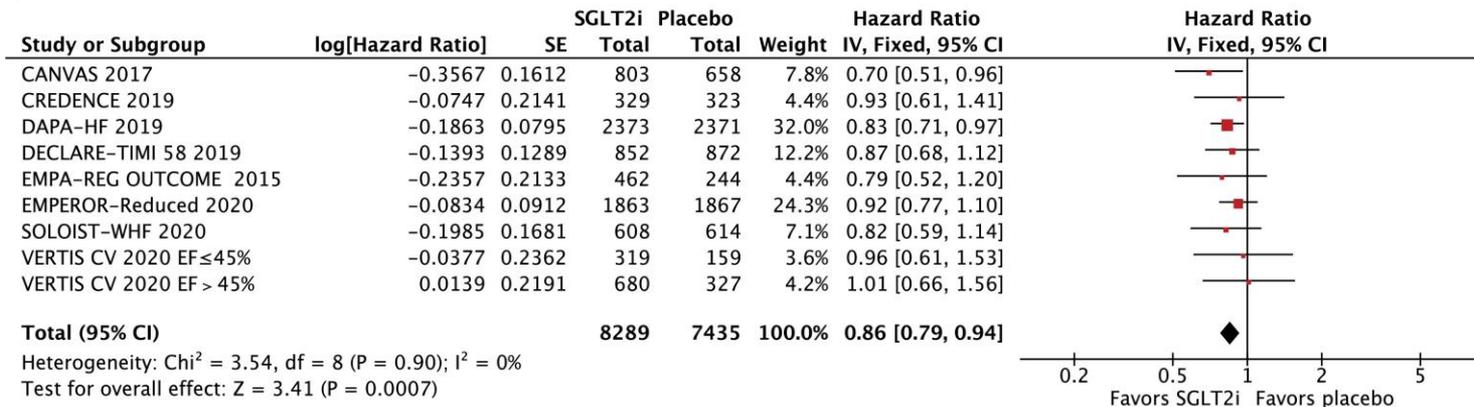


Cardoso R et al., EClinicalMedicine Volume 36 (June 2021)

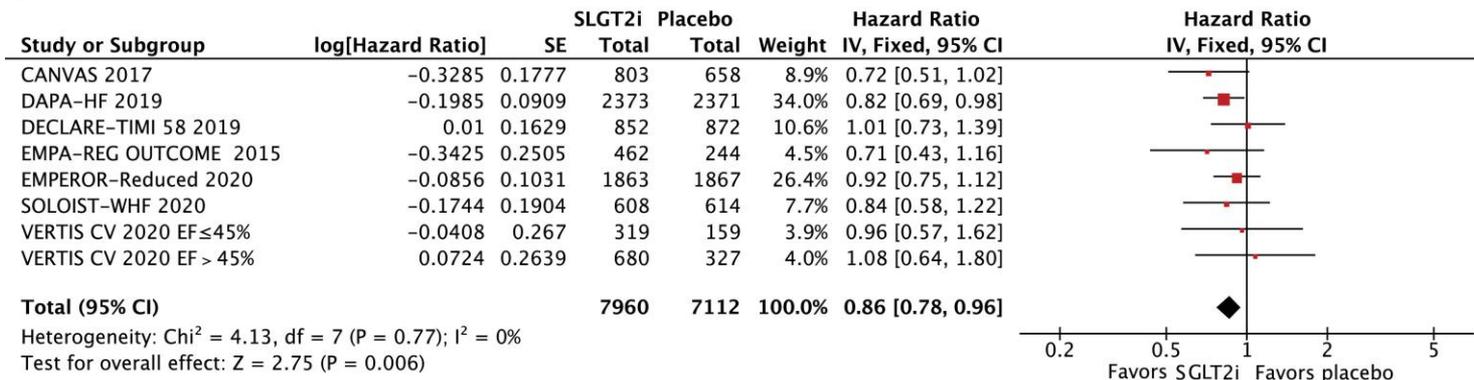
DOI 10.1016/j.eclinm.2021.100933

SGLT2i reduserer total og kardiovaskulær mortalitet med 14%

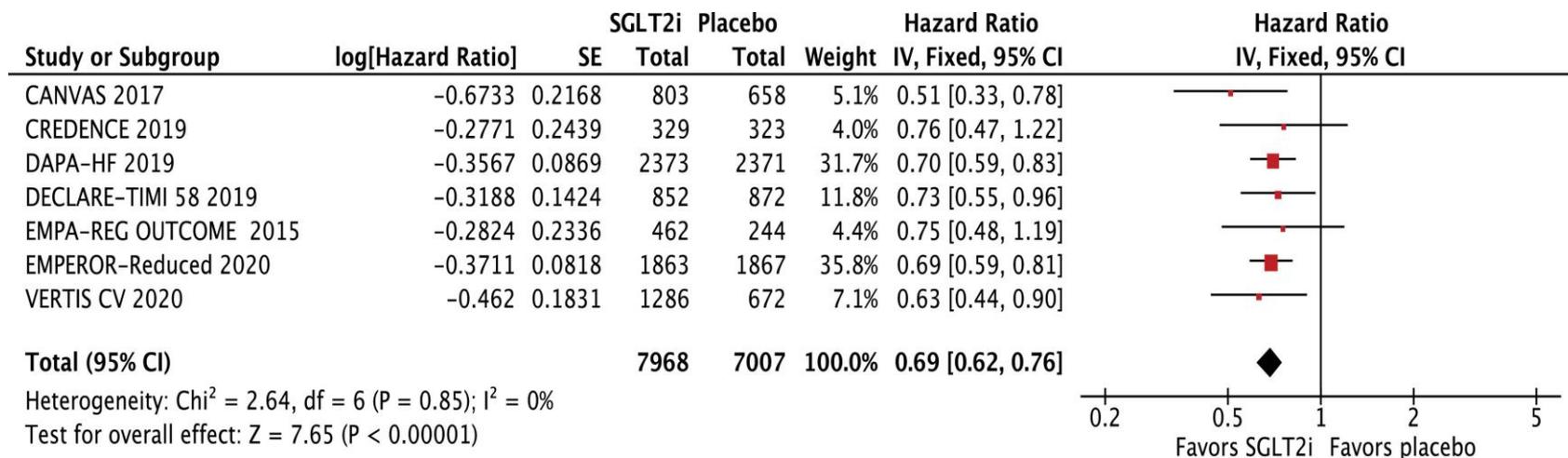
A



B



SGLT2i reduserer sykehusinnleggelser for hjertesvikt med 31%



Cardoso R et al., *EClinicalMedicine* Volume 36 (June 2021)
 DOI 10.1016/j.eclinm.2021.100933

Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure



Joshi SS, Singh T, Newby DE, et al. Heart 2021;107:1032–1038.

Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure

Conventional mechanisms

Diuresis and reduction in blood pressure

Improved glycaemic control

Weight loss

Increase in red blood cell mass and haematocrit

Novel mechanisms

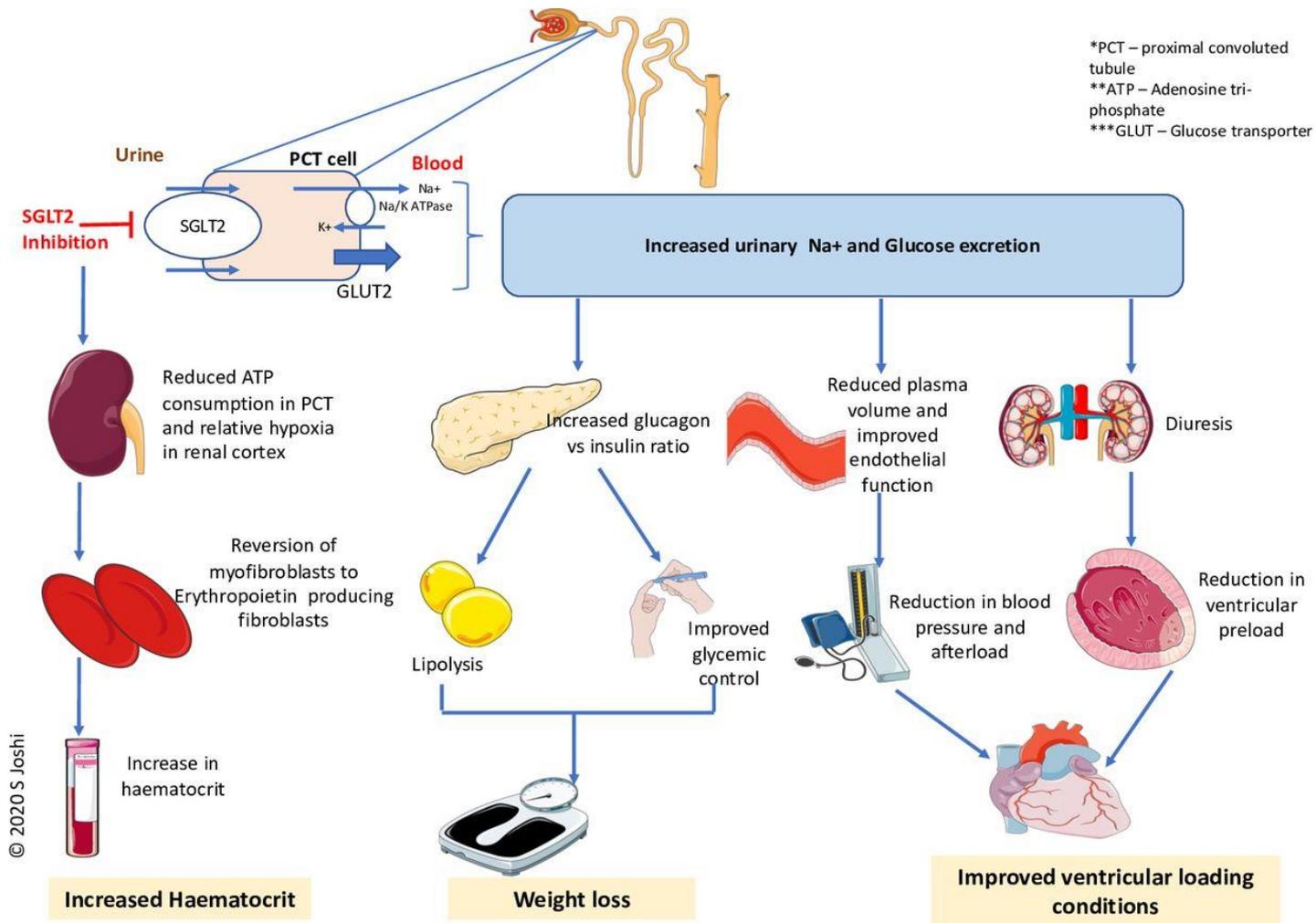
Improved myocardial energetics

Improved myocardial ionic homeostasis

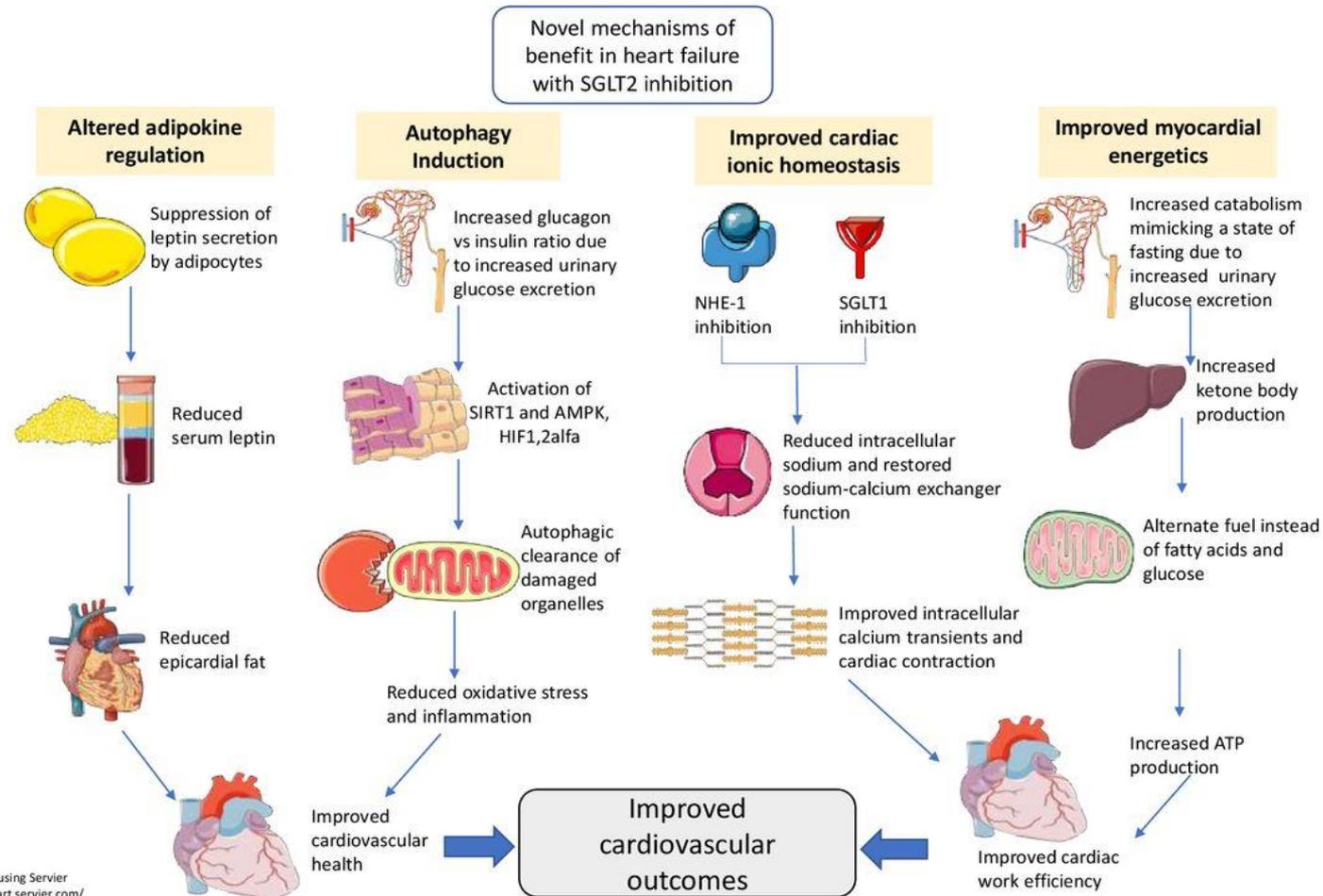
Autophagy

Altered adipokine regulation

Conventional mechanisms of action of SGLT2i.



Proposed novel mechanisms of action of SGLT2i in heart failure.



Joshi SS, Singh T, Newby DE, et al. *Heart* 2021;107:1032–1038.



«Studies examining the mechanistic role of SGLT2 inhibitor therapy in cardiovascular health will be instrumental in shaping our understanding of heart failure and diabetic cardiomyopathy and may open avenues for the development of future drug therapies that target these pathways.»

Joshi SS, Singh T, Newby DE, et al. Heart 2021;107:1032–1038.

Management of HFrEF

To reduce mortality - for all patients

Management of HFrEF

To reduce mortality - for all patients

ACE-I/ARNI

BB

MRA

SGLT2i

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

Prinsipper og spørsmålstegn!

- Opptitrering mot måldoser/maksimalt tolererte doser.
- Betablokkere kan startes samtidig med ACEi (men oppstart anbefales hos normovolemiske, stabile pas.).
- MRA anbefales hos alle pasienter med HFrEF.
- ARNI til alle (som ville blitt inkludert i PARADIGM)?
- SGLT2i til alle?

HFmrEF - nye anbefalinger for behandling

Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. ¹³⁷	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ¹¹	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁵	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{12,119}	IIb	C
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ²⁴⁶	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. ^{13,247}	IIb	C

HFpEF – anbefalinger for behandling

Recommendations	Class ^a	Level ^b
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. ¹³⁷	I	C

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

N = 5988

Hjertesvikt NYHA II-IV

EF > 40%

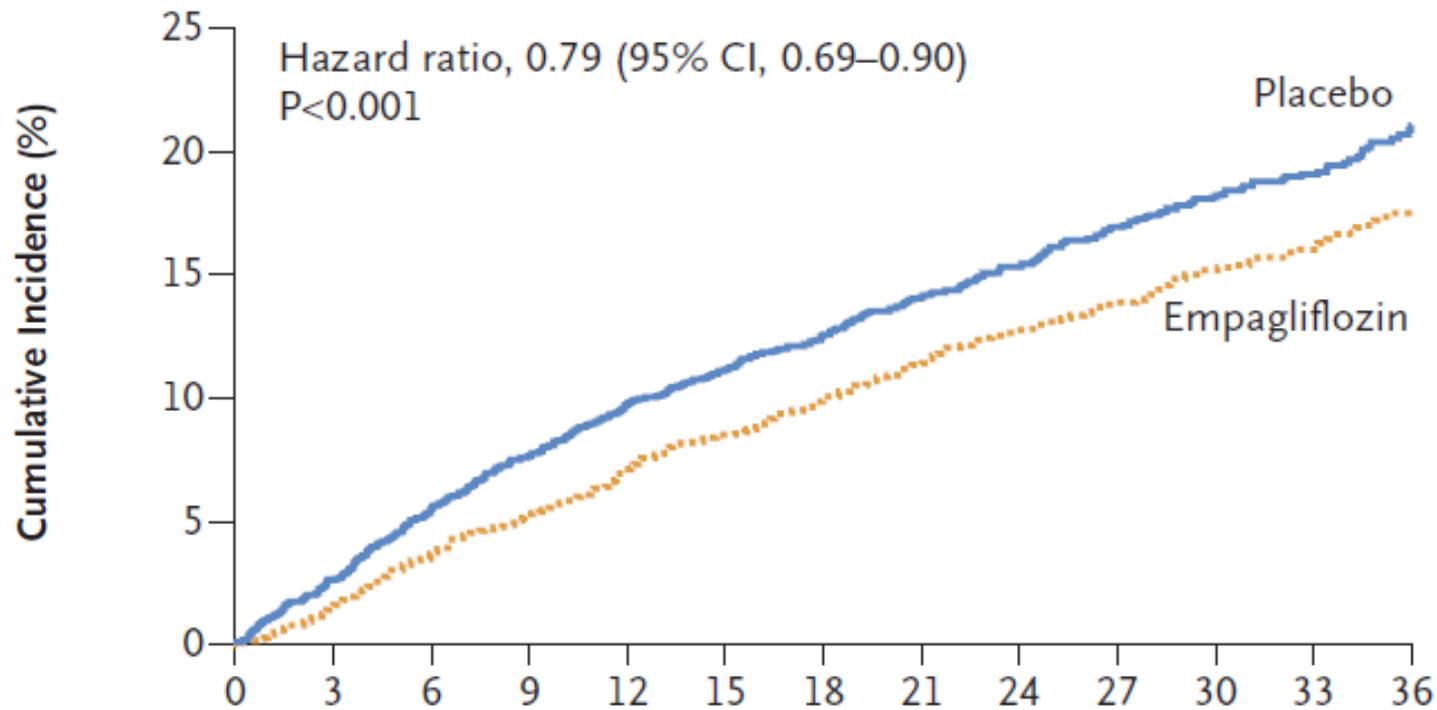
Gjennomsnittsalder 72 år

45% kvinner

Empagliflozin (10 mg) mot placebo

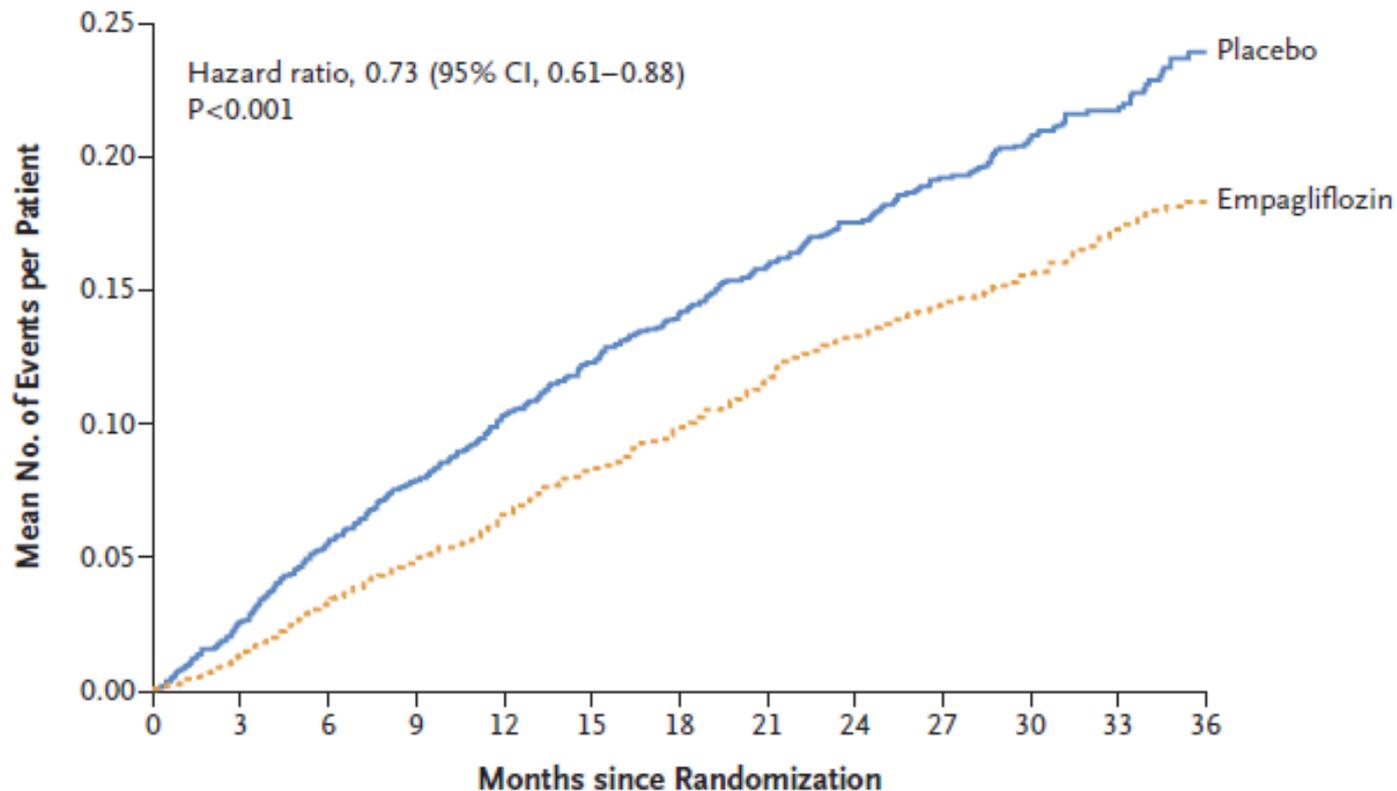
Primary Outcome

Composite of Cardiovascular Death or Hospitalization for Heart Failure.



Anker SD et al. *N Eng J Med* 2021. DOI: 10.1056/NEJMoa2107038

Hospitalizations for Heart Failure.



Anker SD et al. *N Eng J Med* 2021. DOI: 10.1056/NEJMoa2107038

PRESERVED-HF: Dapagliflozin Improves Symptoms, Physical Limitations in HFpEF

“This is the largest KCCQ benefit ever reported in any trial with a drug for HFrEF or HFpEF,” Milton Packer notes.

by [Todd Neale](#) | SEPTEMBER 13, 2021

PRESERVED-HF:

N = 324

Hjertesvikt NYHA II-IV

EF \geq 45% (median 60%)

Gjennomsnittsalder 70 år

57% kvinner

Dapagliflozin vs. placebo

Oppfølging 12 uker

Forbedret 6 min gangtest (20.1 meter; $P = 0.007$).

Forbedret livskvalitet (KCCQ 4.5 poeng; $P = 0.009$).

Forebygging av hjertesvikt

Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations. ^{287–290}	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations. ^{291,292}	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations. ^{293–297}	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF. ^{298–302}	I	C

Hvem skal behandles med hva?

- Behandling av HFrEF:
 - Dapagliflozin og empagliflozin anbefales.
 - Rask initiering av behandling med alle effektive medikamentklasser (ACEi/ARNI, BB, MRA, SGLT2i)
- HFmrEF
 - ACE/ARB, ARNI, BB, MRA kan vurderes.
- HFpEF
 - Screening og behandling for CV og ikke-CV årsaker og komorbiditeter anbefales

SGLT2-hemmere

- **Hva** vet vi om SGLT2i ved hjertesvikt?
 - *Sterk dokumentasjon på redusert sykkelighet og dødelighet.*
- **Hvorfor** virker SGLT2i ved hjertesvikt?
 - *Kjente og ukjente virkningsmekanismer*
- **Hvem** skal vi behandle med SGLT2i?
 - *Pasienter med HFrEF (og HFpEF?)*
- **Hvordan** skal vi gi behandling med SGLT2i?
 - *Fast dose, sammen med BB, ACEi/ARNI og MRA*

Gaps in evidence

.... pragmatic studies on the order of adding disease-modifying drugs for HFrEF....

McDonagh T, Metra M et al. Eur Heart J 2021; 00, 1-128.