

# SGLT2 hämmare och deras plats i terapin: Hjärta/Kärl

Frieder Braunschweig

Överläkare, professor

ME Kardiologi, Hjärt-Kärlcentrum

Karolinska Universitetssjukhuset, Stockholm

Medlem i expertgrupp hjärta och kärl, Stockholms läkemedelskommitté



**Karolinska  
Institutet**

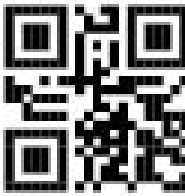
**KAROLINSKA**  
UNIVERSITY HOSPITAL



## Redovisning av jäv

Föreläsningar och deltagande i kliniska studier de senaste fem åren för flera olika läkemedels- och medtechföretag där all ersättning har gått till min arbetsgivare Region Stockholm.

# Förkortningar



HFrEF	Heart Failure with reduced Ejection Fraction ( $\leq 40\%$ )
HFmrEF	Heart Failure with mildly reduced Ejection Fraction (41-49%)
HFpEF	Heart Failure with preserved Ejection Fraction ( $\geq 50\%$ )
MRA	Mineralcorticoidreceptor-antagonister
ARNI	Angiotensinreceptor-neprilysininhibitor
CRT	Cardiac Resynchronization Therapy
ICD	Implantable Cardioverter Defibrillator



COMMENT | VOLUME 5, ISSUE 9, P673-675, SEPTEMBER 2017

Download Full Issue



Purchase



Subscribe



Save



Share



Reprints



Request



## SGLT2 inhibitors in the real world: too good to be true?

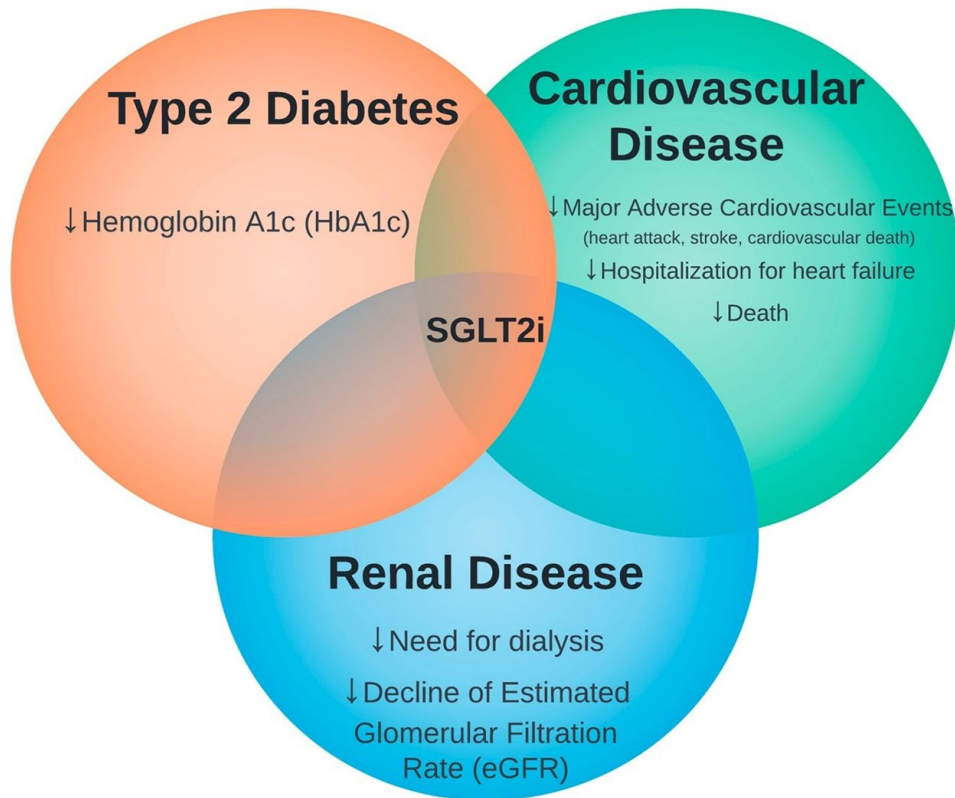
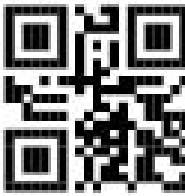
David Fitchett

Published: August 03, 2017 • DOI: [https://doi.org/10.1016/S2213-8587\(17\)30259-0](https://doi.org/10.1016/S2213-8587(17)30259-0)

PlumX Metrics



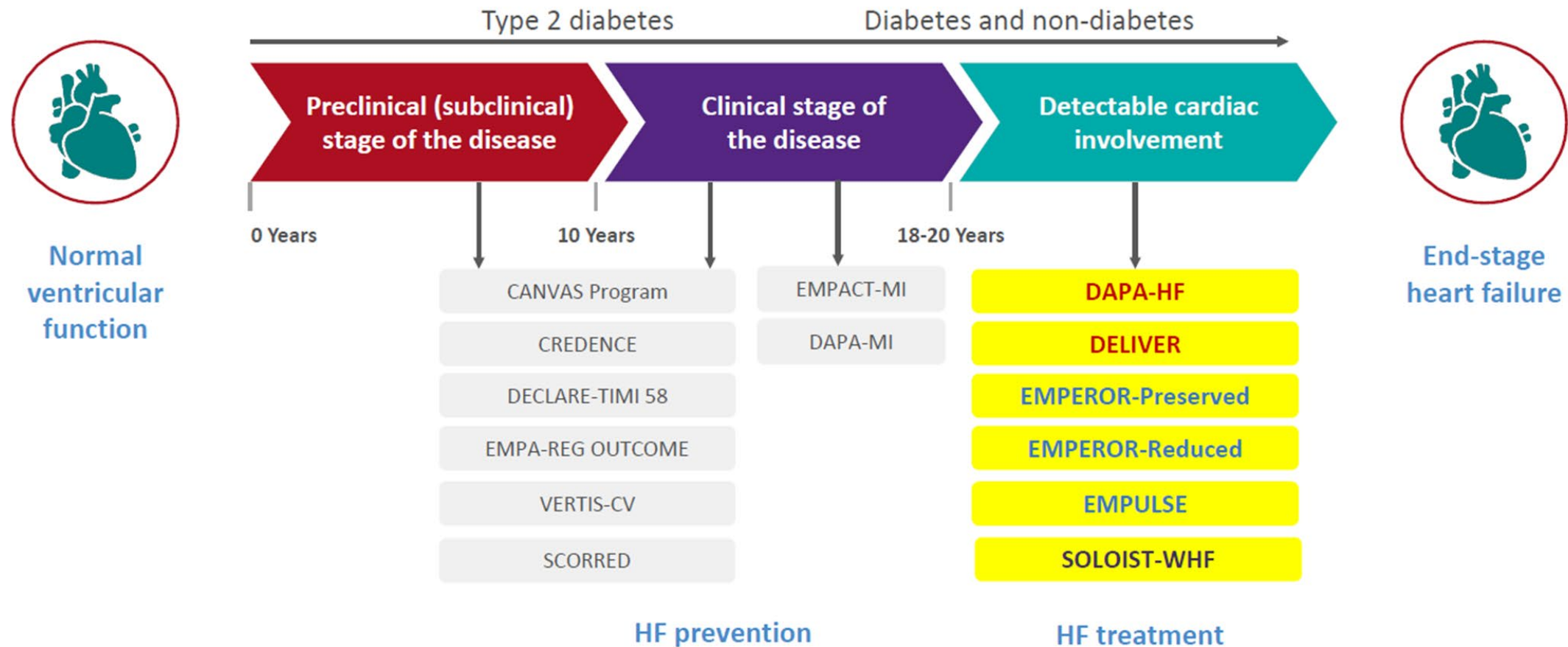
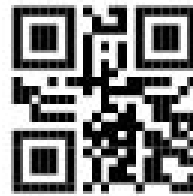
# SGLT2-h vid hjärt-kärlsjukdom



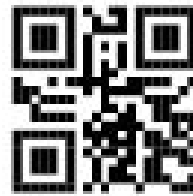
- SGLT2-h vid hjärtsvikt
- Plats i behandlingen vid hjärtsvikt
- Ny behandlingsparadigm vid hjärtsvikt
- Påverkan på riktlinjer
- Hur använda i praktiken
- Övriga användningsområden?



# SGLT2-h vid hjärtsvikt, en lång resa

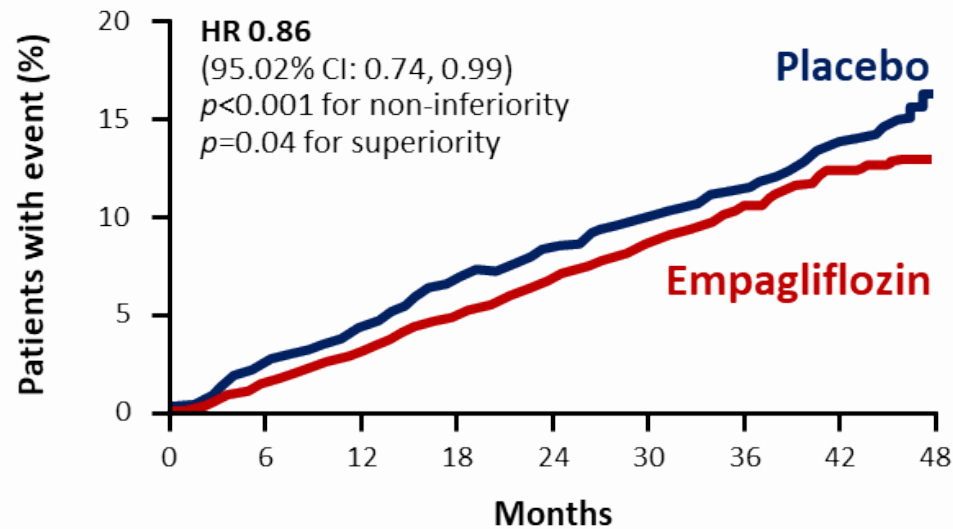


# SGLT2-h vid diabetes mellitus typ II



## EMPA-REG OUTCOME study

Adults with type 2 diabetes and established CV disease  
CV death, non-fatal MI, or non-fatal stroke

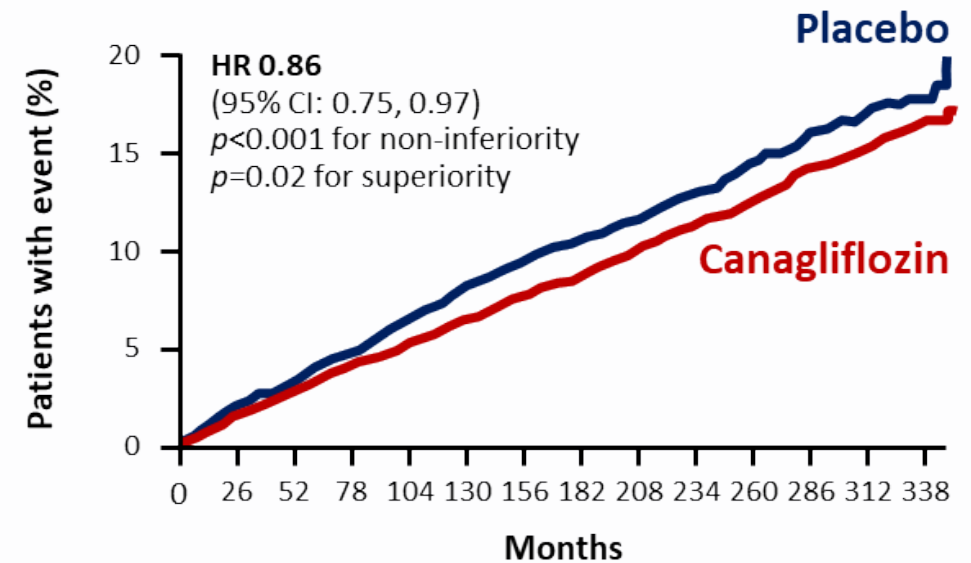


Patients at risk:

Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

## CANVAS Program

CV death, non-fatal MI, or non-fatal stroke



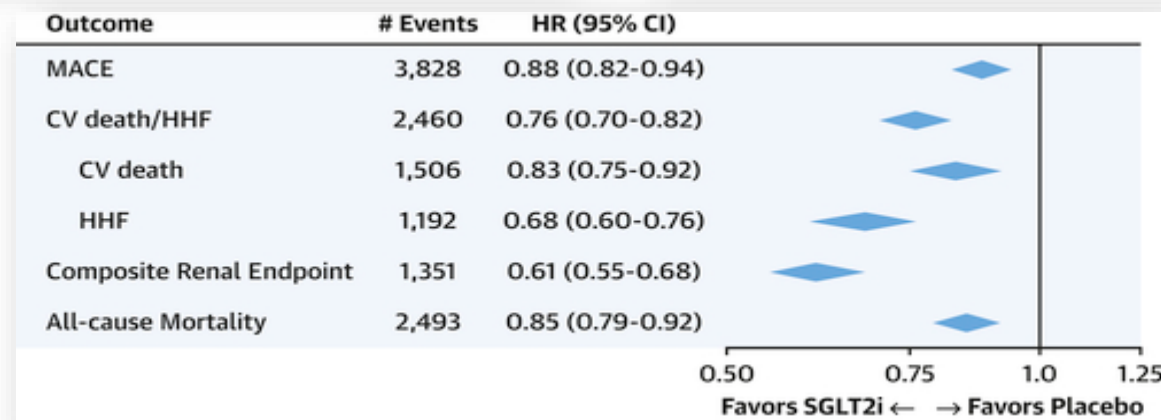
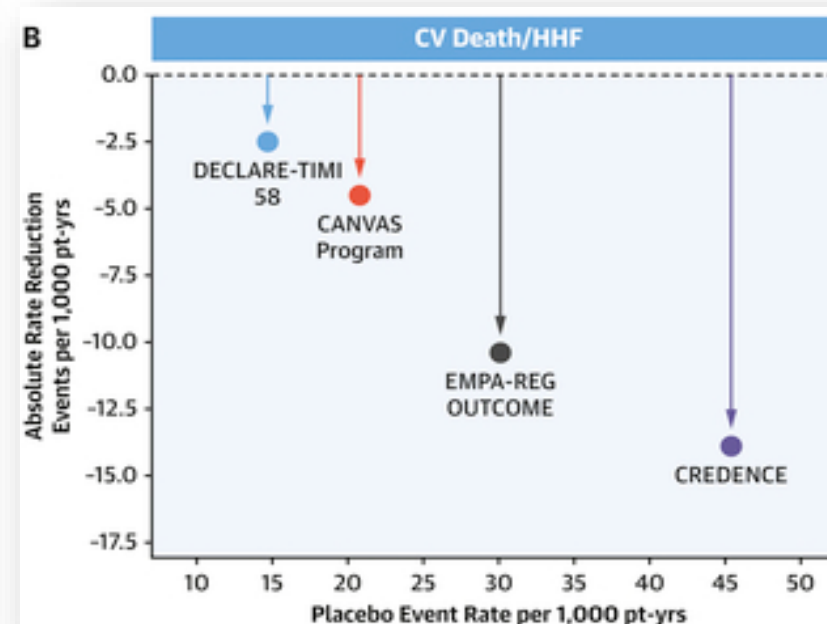
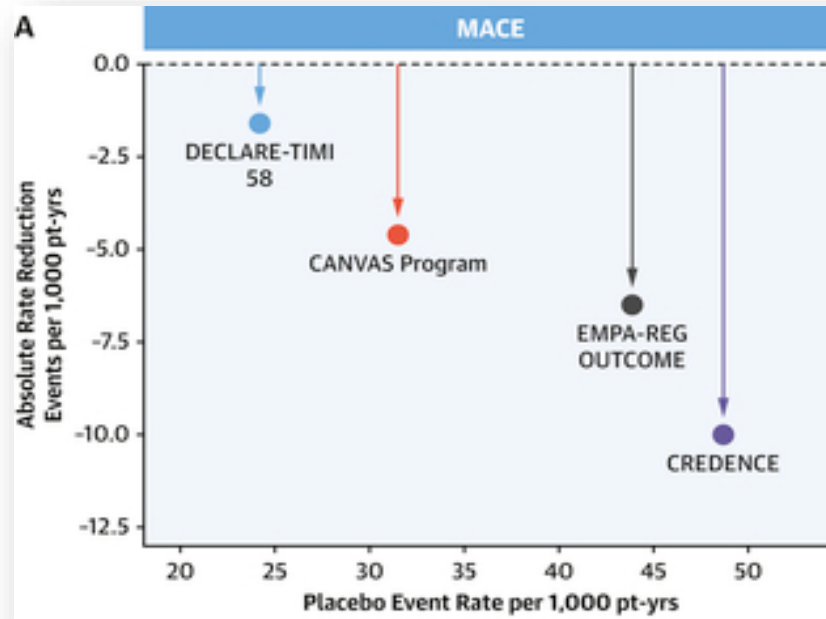
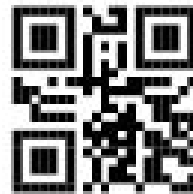
Patients at risk:

Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216

Zinman B et al. N Engl J Med. 2015;37:2117–2128

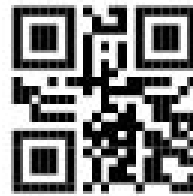
Neal B et al. N Engl J Med. 2017;377:644-657

# SGLT2-h vid diabetes typ II





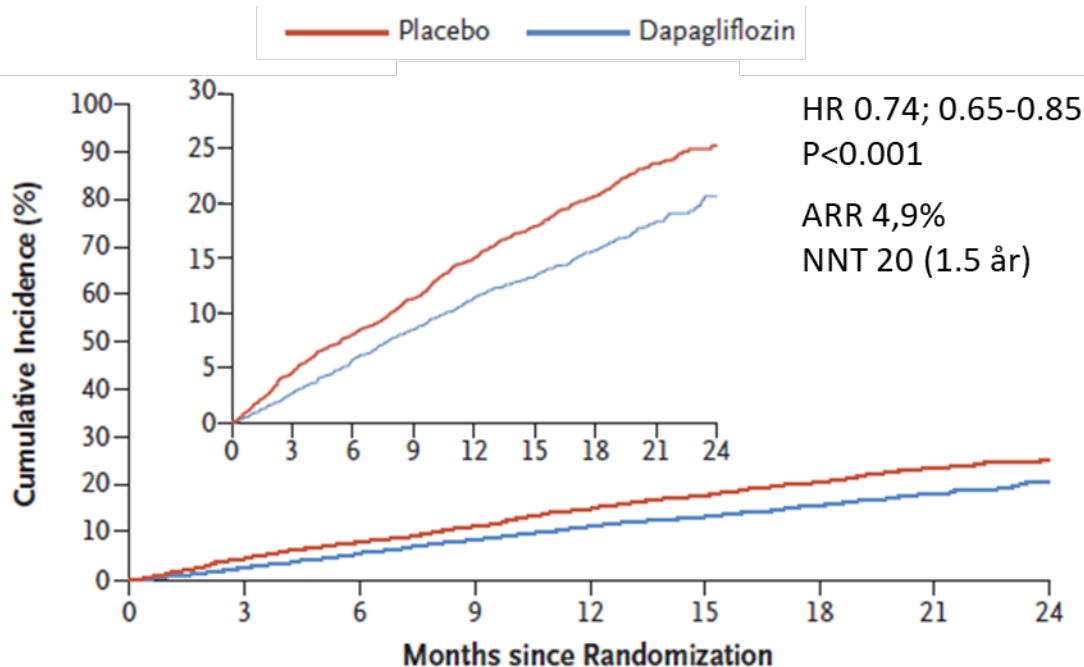
# SGLT2-h: studier vid HFrEF



## DAPA-HF

(n=4744; NYHA II-IV, EF ≤ 40%)

### HF hospitalization or cardiovascular death



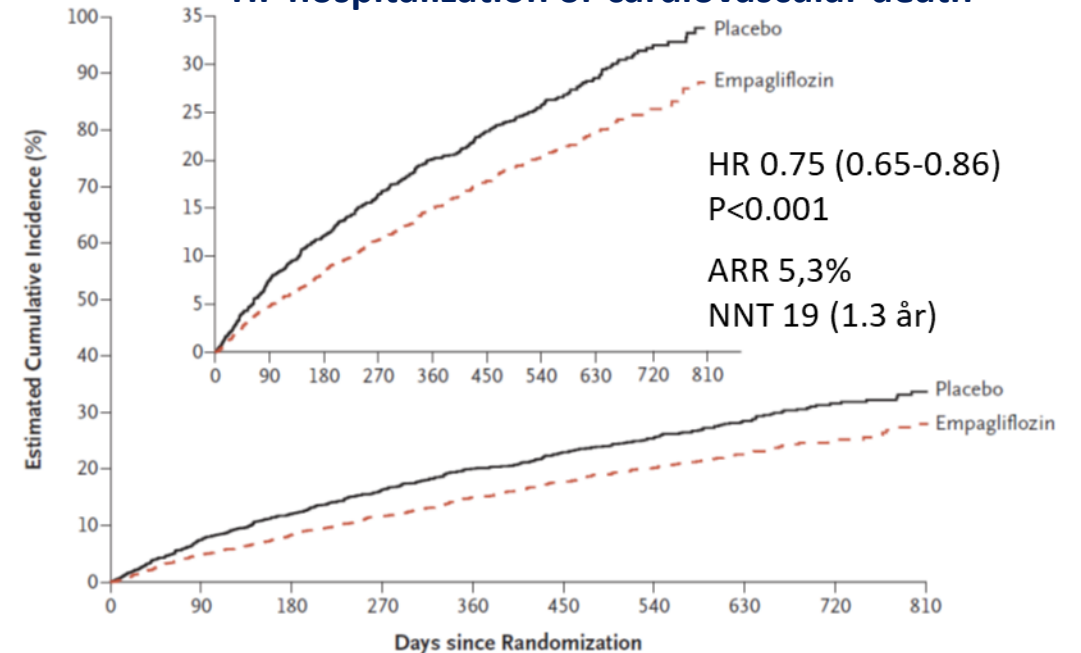
**HF Hospitalization** HR 0.70 (0.59-0.83)  
**CV death** HR 0.82 (0.69-0.98)  
**All cause death** HR 0.83 (0.71-0.97)

McMurray et al, N Engl J Med 2019

## EMPEROR reduced

(n=3730, NYHA II-IV, EF ≤ 40%)

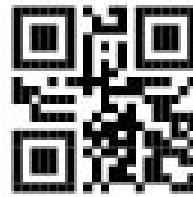
### HF hospitalization or cardiovascular death



**HF Hospitalization** HR 0.69 (0.59-0.81)  
**CV death** HR 0.92 (0.75-1.12)  
**All cause death** HR 0.92 (0.77-1.10)

Packer et al, N Engl J Med 2020

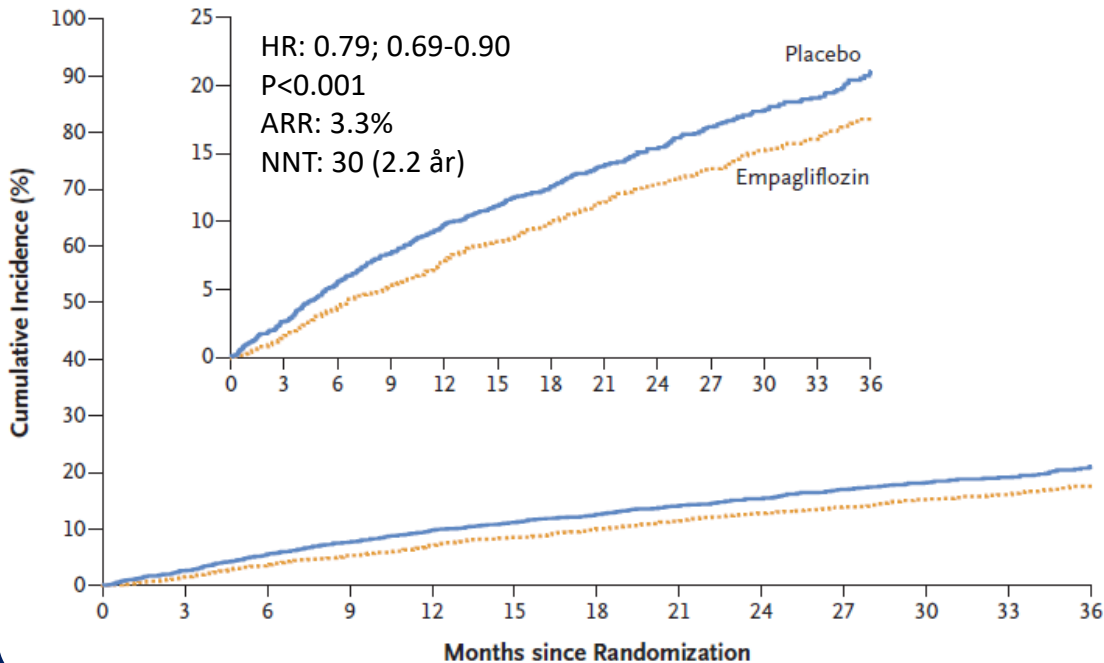
# SGLT2-h: studier vid HFmrEF och HFpEF



## EMPEROR preserved

(n=5988, NYHA II-IV, EF > 40%)

### HF hospitalization or cardiovascular death



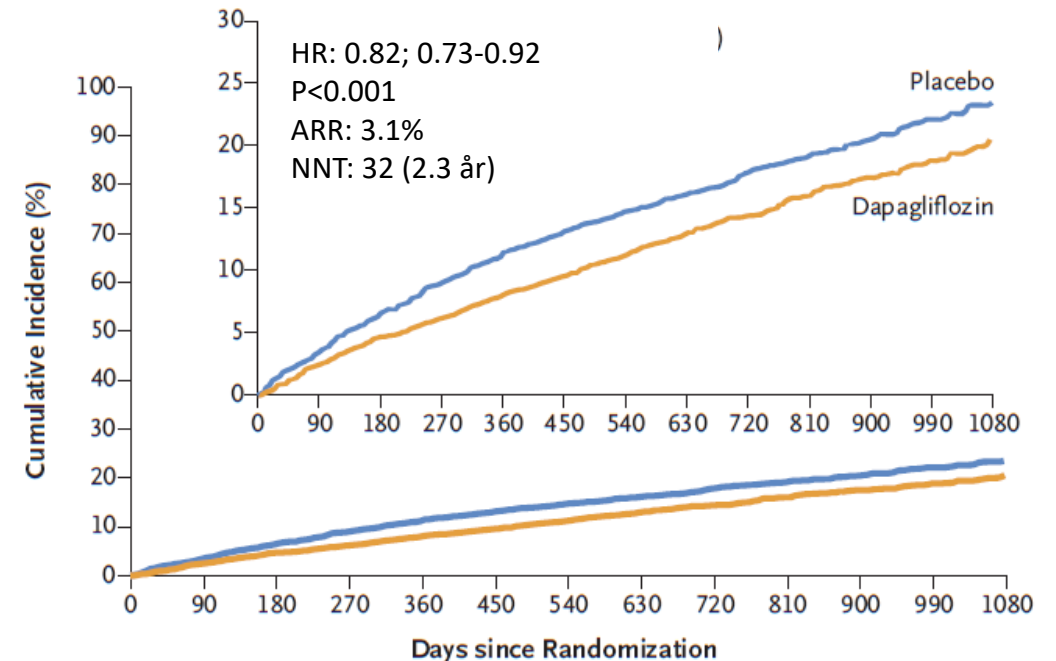
<b>HF Hospitalization</b>	HR 0.69 (0.59-0.81)
<b>CV death</b>	HR 0.91 (0.76-1.09)
<b>All cause death</b>	HR 1.00 (0.87-1.15)

Anker et al, N Engl J Med 2021

## DELIVER

(n=3131, EF > 40%; elevated NT-proBNP)

### HF hospitalization/urgent visit or cv death



<b>HF hosp/urgent visit</b>	HR 0.79 (0.69-0.91)
<b>CV death</b>	HR 0.88 (0.74-1.05)
<b>All cause death</b>	HR 0.94 (0.83-1.07)

Solomon et al, N Engl J Med 2022



# SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials



*Muthiah Vaduganathan\**, *Kieran F Docherty\**, *Brian L Claggett*, *Pardeep S Jhund*, *Rudolf A de Boer*, *Adrian F Hernandez*, *Silvio E Inzucchi*, *Mikhail N Kosiborod*, *Carolyn S P Lam*, *Felipe Martinez*, *Sanjiv J Shah*, *Akshay S Desai*, *John J V McMurray†*, *Scott D Solomon†*

## Summary

**Background** SGLT2 inhibitors are strongly recommended in guidelines to treat patients with heart failure with reduced ejection fraction, but their clinical benefits at higher ejection fractions are less well established. Two large-scale trials, DELIVER and EMPEROR-Preserved, in heart failure with mildly reduced or preserved ejection fraction have been done, providing power to examine therapeutic effects on cardiovascular mortality and in patient subgroups when combined with the earlier trials in reduced ejection fraction.

*Lancet* 2022; 400: 757–67

Published Online

August 27, 2022

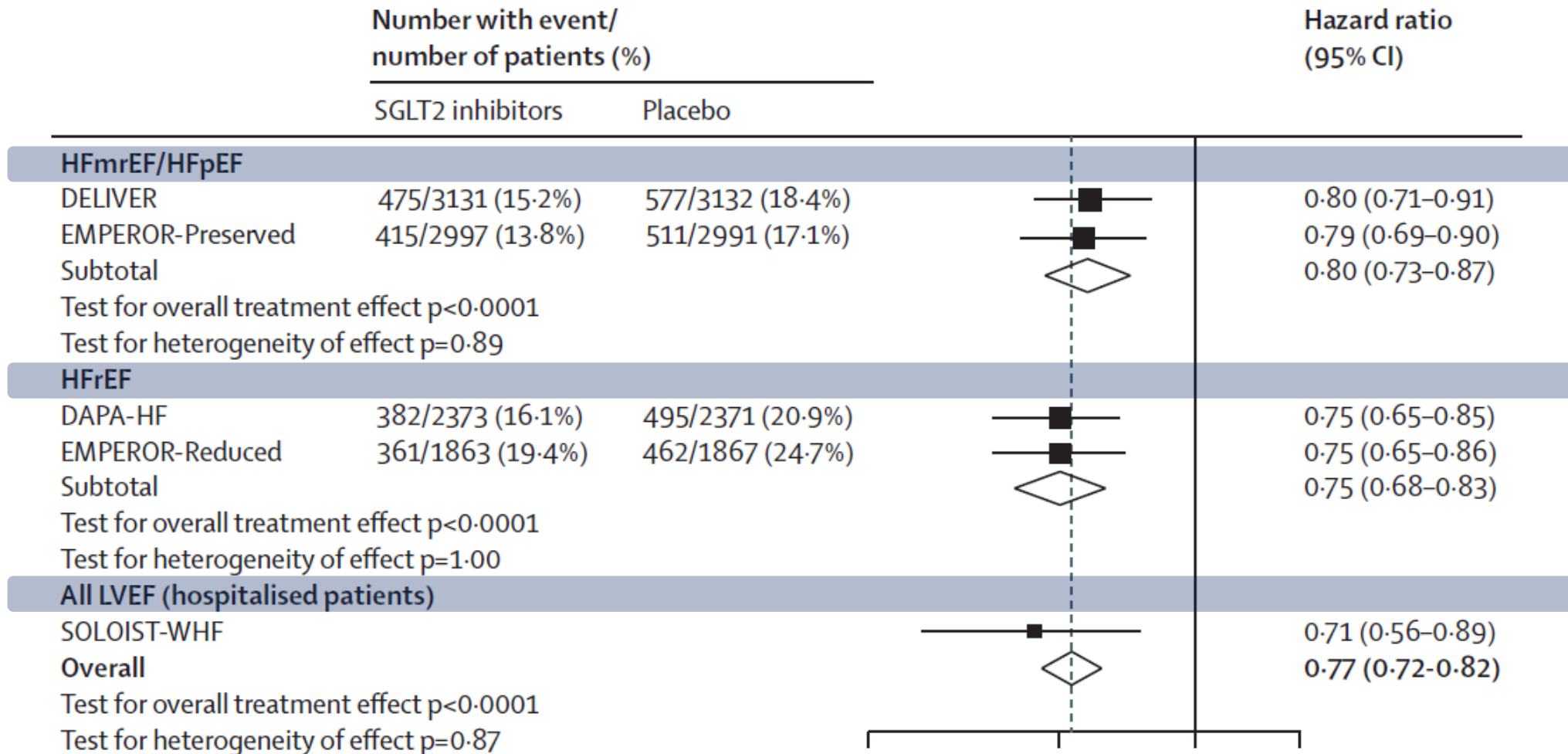
[https://doi.org/10.1016/S0140-6736\(22\)01429-5](https://doi.org/10.1016/S0140-6736(22)01429-5)

See [Comment](#) page 711

# Metaanalys av de pivotala studierna

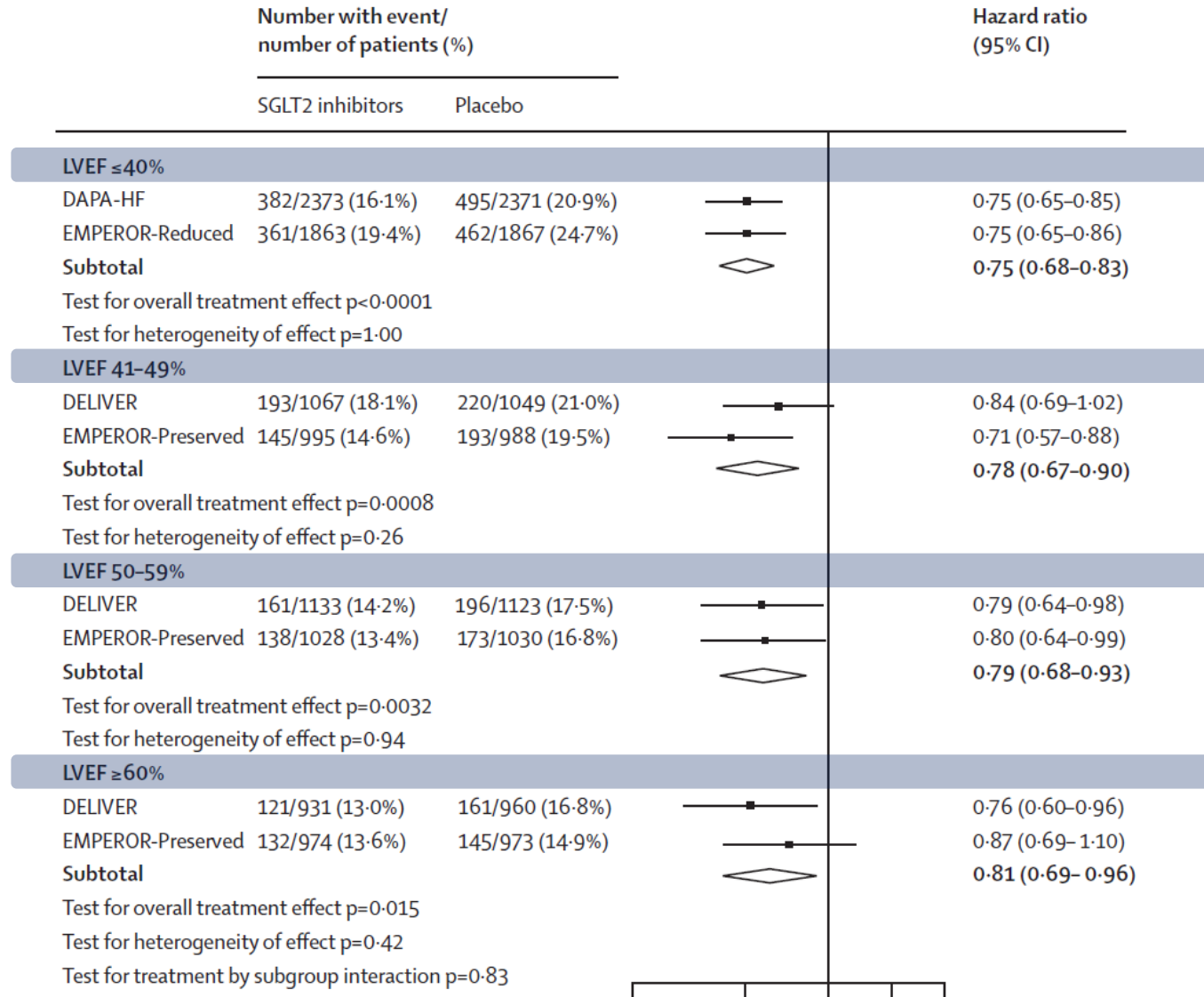


## Cardiovascular death or heart failure hospitalisation

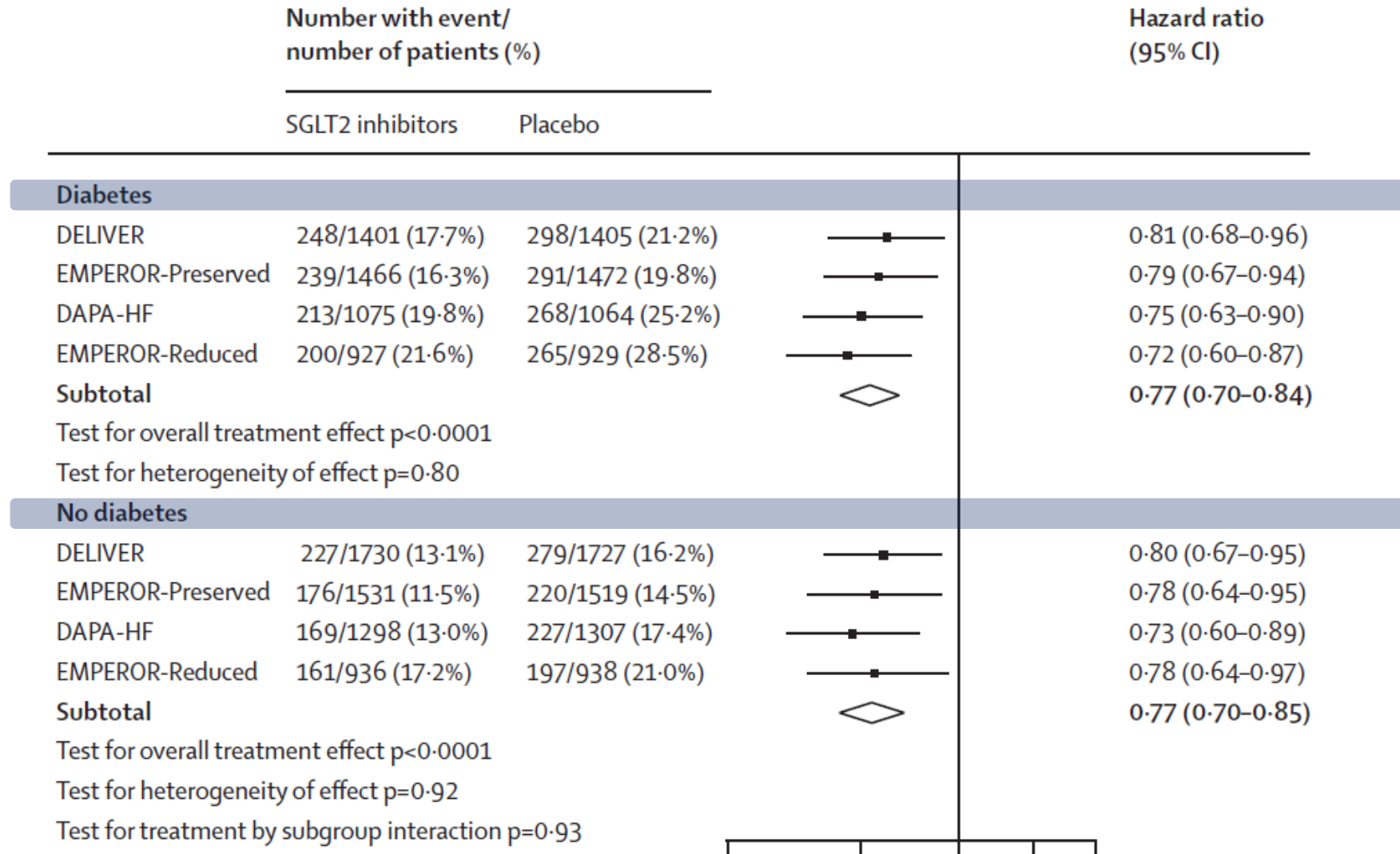




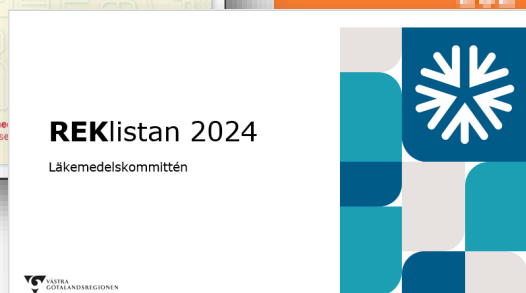
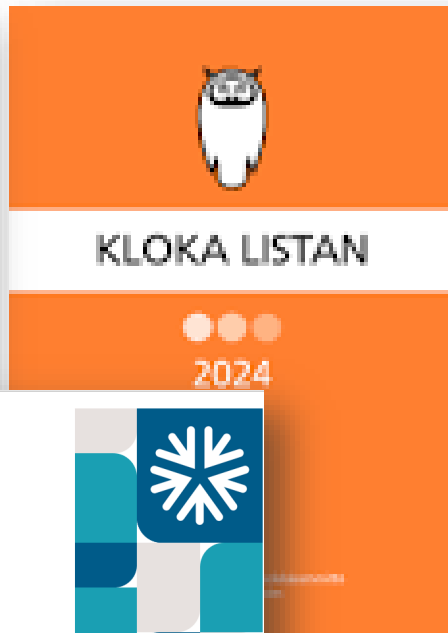
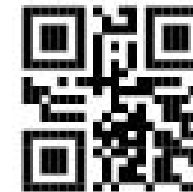
# Metaanalysis: LVEF



# Metaanalys: diabetes y/n



# Aktuella riktlinjer



**LOK**  
Nätverk för Sveriges Läkemedelskommittéer

## Läkemedelsbehandling vid kronisk hjärtsvikt

Publicerad 2023-09-13

**LOK:s arbetsgrupp för framtagande av dessa riktlinjer**  
Björn Kornhall, LAG hjärta-kärl i Skåne  
Bert Andersson, Sahlgrenska universitetssjukhuset  
Frieder Braunschweig, Karolinska universitetssjukhuset

ESC European Society of Cardiology  
European Heart Journal (2021) 42, 3599–3726  
doi:10.1093/eurheart/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

Authors/Task Force Members: Theresa A. McDonagh\* (Chairperson) (United Kingdom), Marco Metra\* (Chairperson) (Italy), Marianna Adamo (Task Force Coordinator) (Italy), Roy S. Gardner (Task Force Coordinator) (United Kingdom), Andreas Baumbach (United Kingdom), Michael Böhm (Germany), Haran Burri (Switzerland), Javed Butler (United States of America), Jelena Celutkienė (Lithuania), Ovidiu Chioncel (Romania), John G.F. Cleland (United Kingdom), Andrew J.S. Coats (United Kingdom), Maria G. Crespo-Leiro (Spain), Dimitrios Farmakis (Greece), Martine Gilard (France), Stephane Heymans

ESC European Society of Cardiology  
European Heart Journal (2023) 00, 1–13  
https://doi.org/10.1093/eurheart/ehad195

**ESC GUIDELINES**

## 2023 Focused Update of the 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

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY  
© 2022 BY THE AMERICAN HEART ASSOCIATION, INC., THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION, AND THE HEART FAILURE SOCIETY OF AMERICA  
PUBLISHED BY WILEY

**CLINICAL PRACTICE GUIDELINE: FULL TEXT**

## 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Viss.nu | Region Stockholm

## Hjärtsvikt

Medicinskt område: Hjärta och kärl

ICD-10-SE: I50.1: Vänsterhjärtsvikt, I50.1A: För nedsatt ejektionsfraktion (HFrEF), I50.1B: För lätt nedsatt EF (HFmrEF), I50.1C: För bevarad EF (HFpEF), I500: För högerhjärtsvikt

Publicerat: December 1996  
Uppdaterat: Juni 2022

2023-06-16

## Vårdförlopp hjärtsvikt nydebuterad

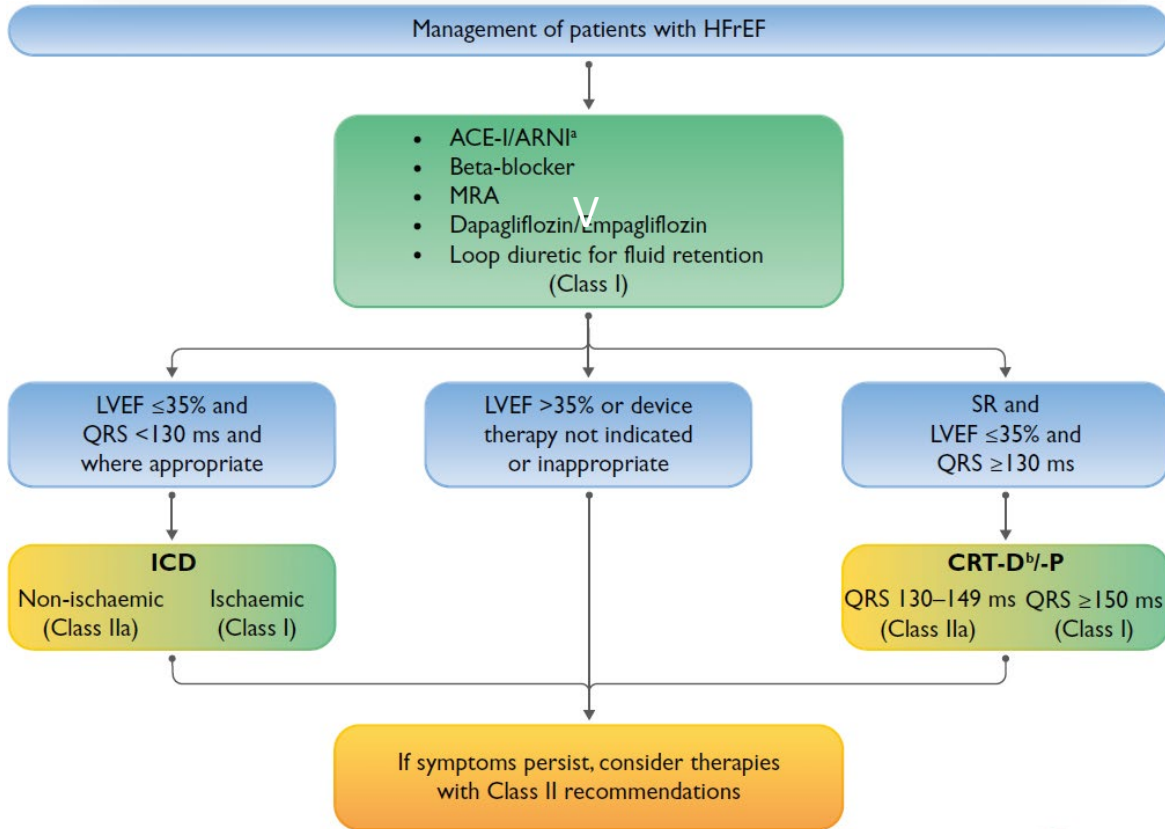
Här finns stödmaterial till det personcentrerade och sammanhållna vårdförloppet för nydebuterad hjärtsvikt.

Vårdförlopp för nydebuterad hjärtsvikt hittar du under kunskapsstöd för hjärta och kärl på Nationellt kliniskt kunskapsstöd.

[Hjärta och kärl, Nationellt kliniskt kunskapsstöd](#)

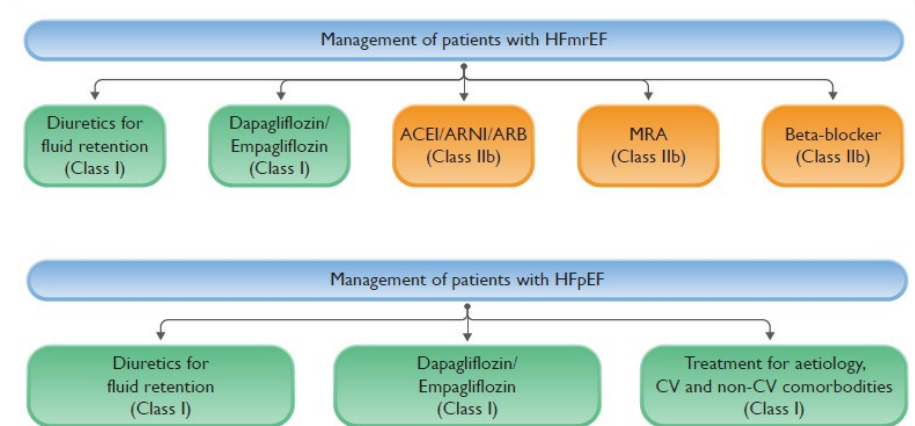
## 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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



## 2023 Focused Update of the 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)

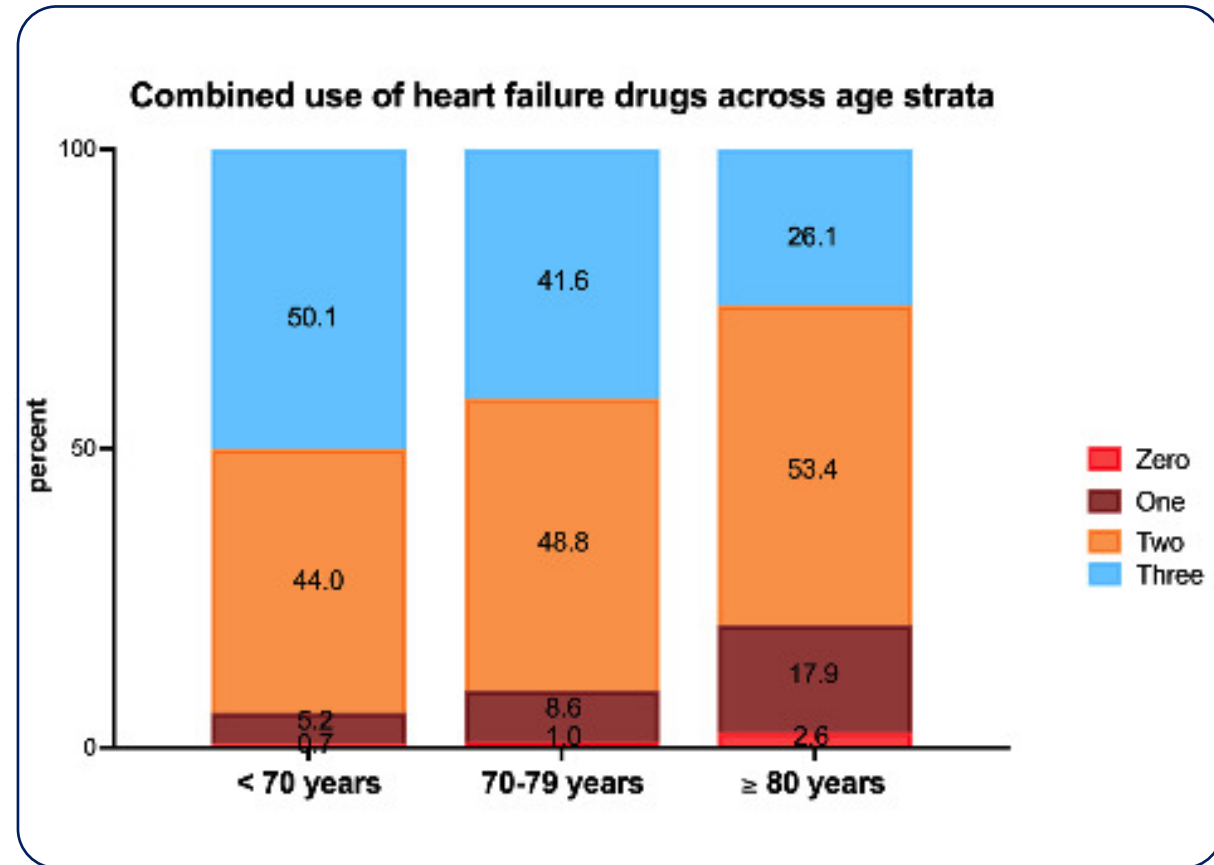
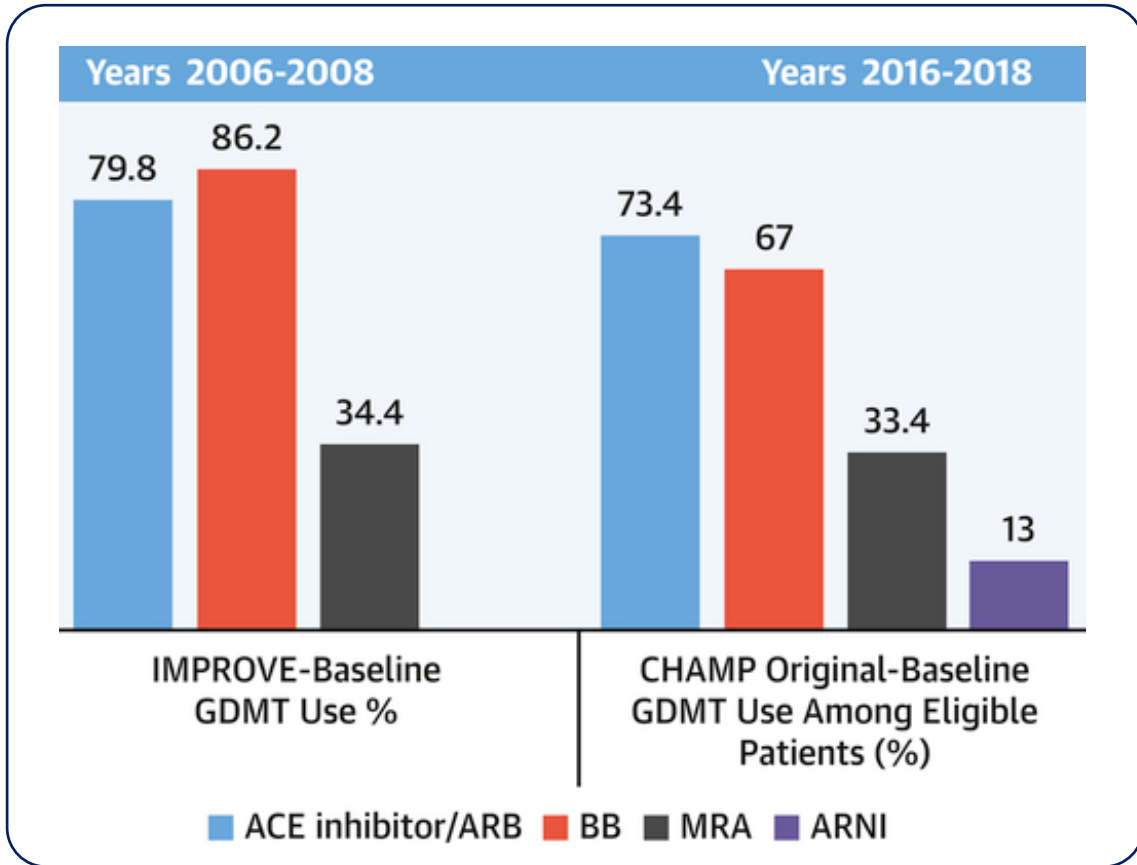
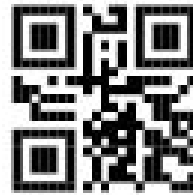


**Recommendation Table 3** — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

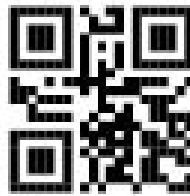
Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
An <u>intensive strategy of initiation and rapid up-titration</u> of evidence-based treatment <u>before discharge and during frequent and careful follow-up visits in the first 6 weeks</u> following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death. <sup>c,d,e 16</sup>	I	B



# Låg följsamhet till riktlinjer

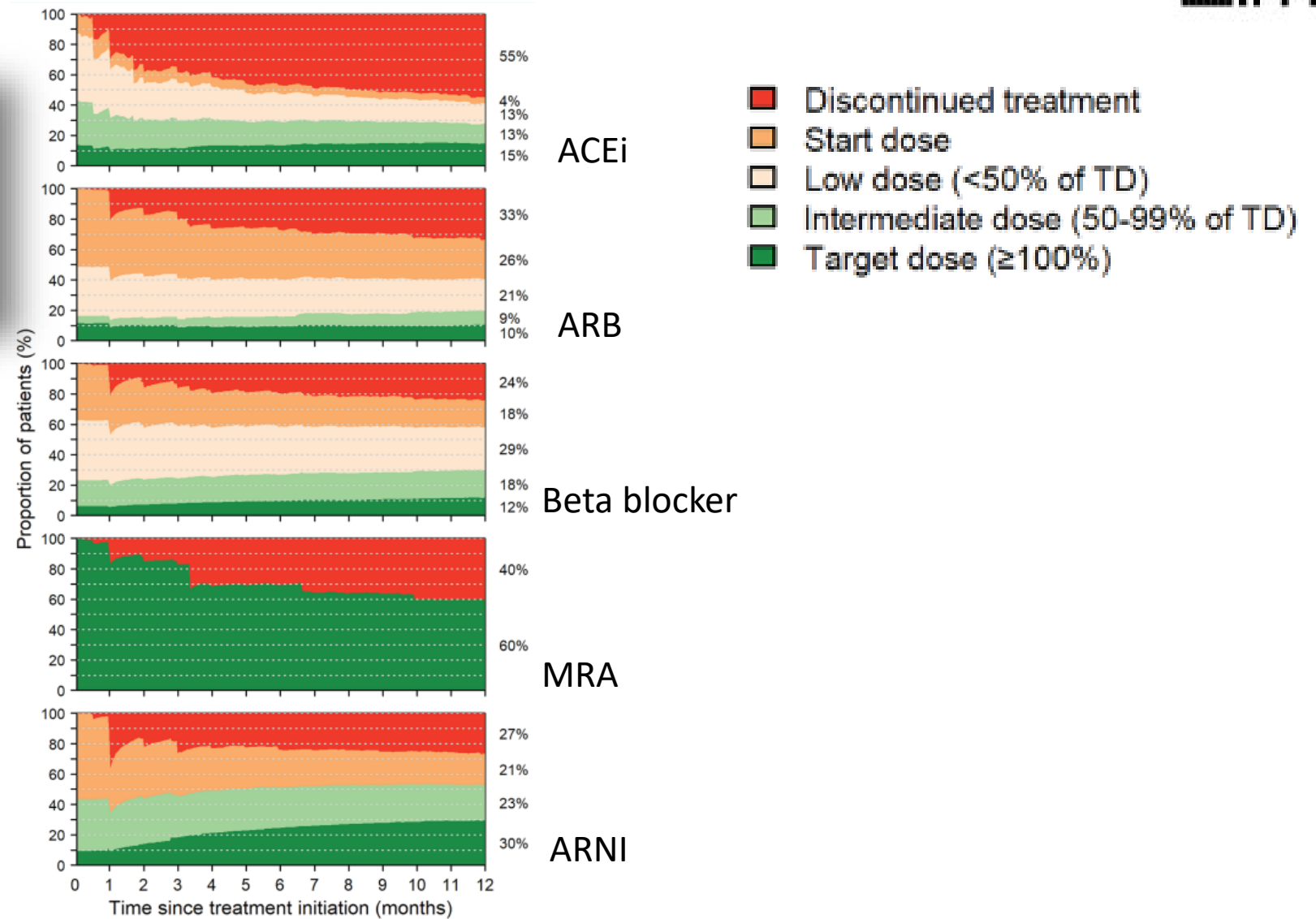


# Sekventiell behandling (HFrEF)

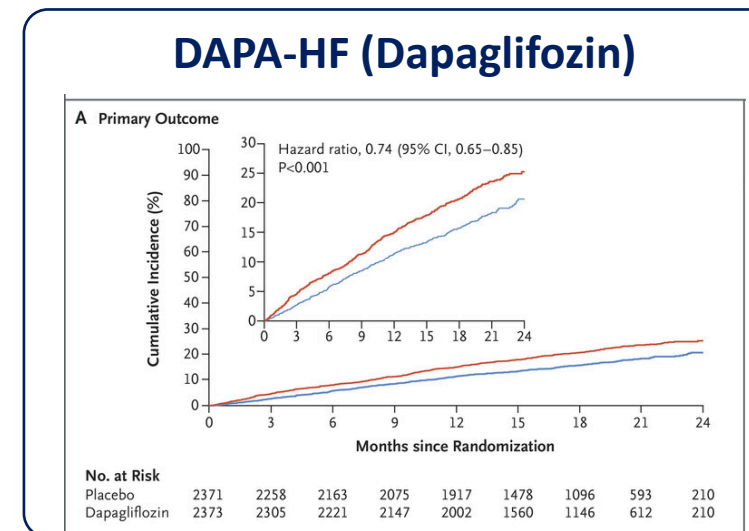
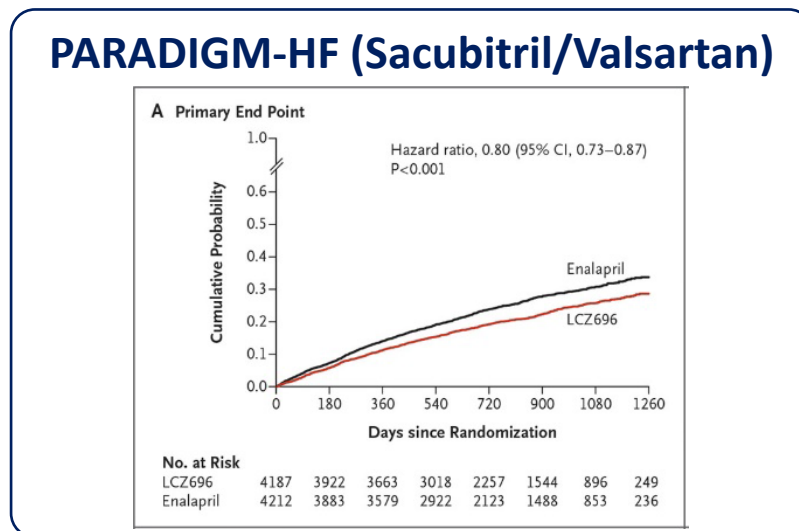
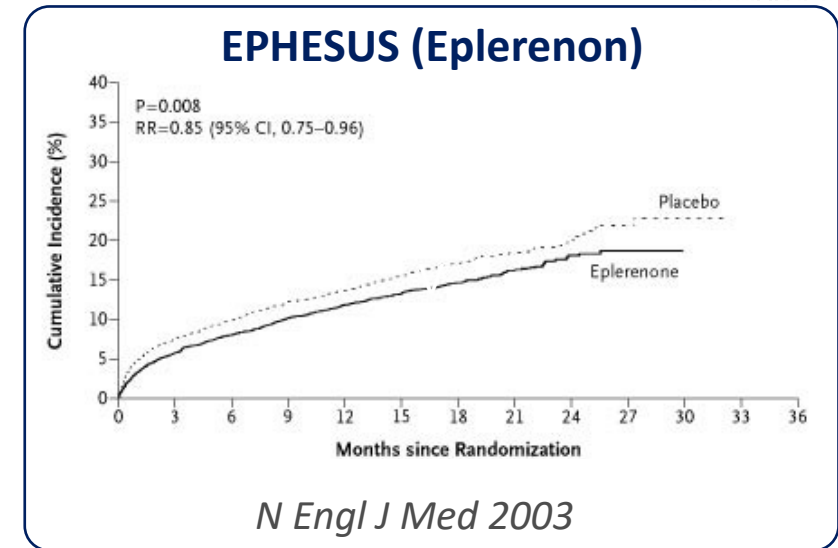
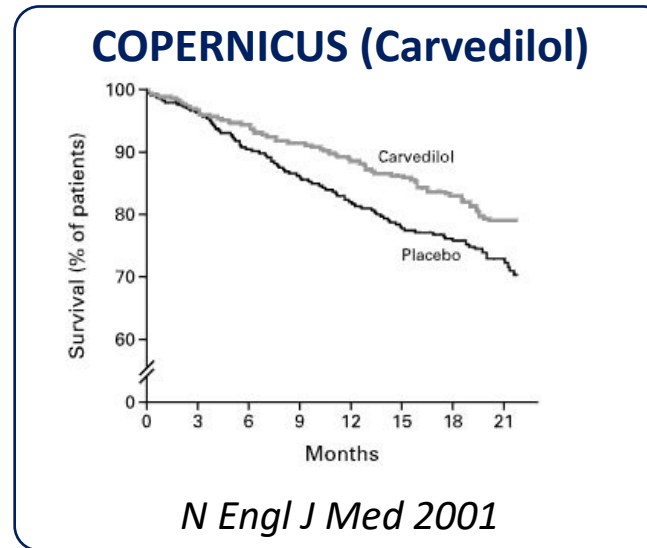
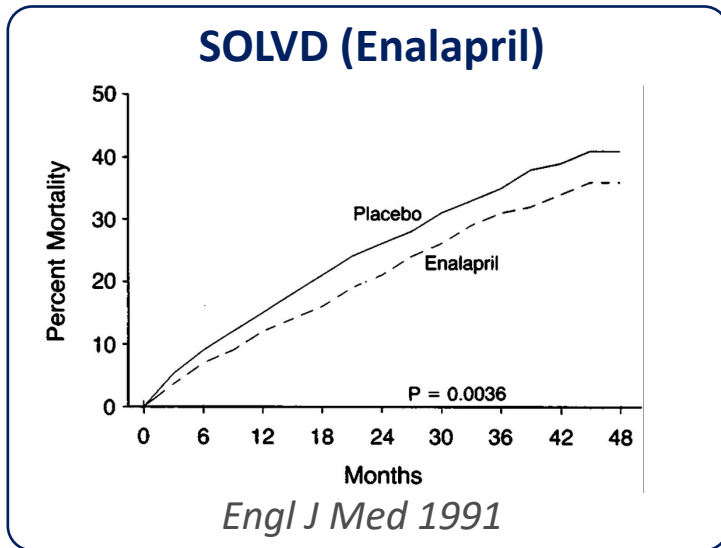
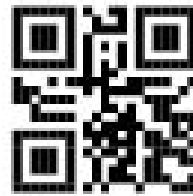


## Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden)

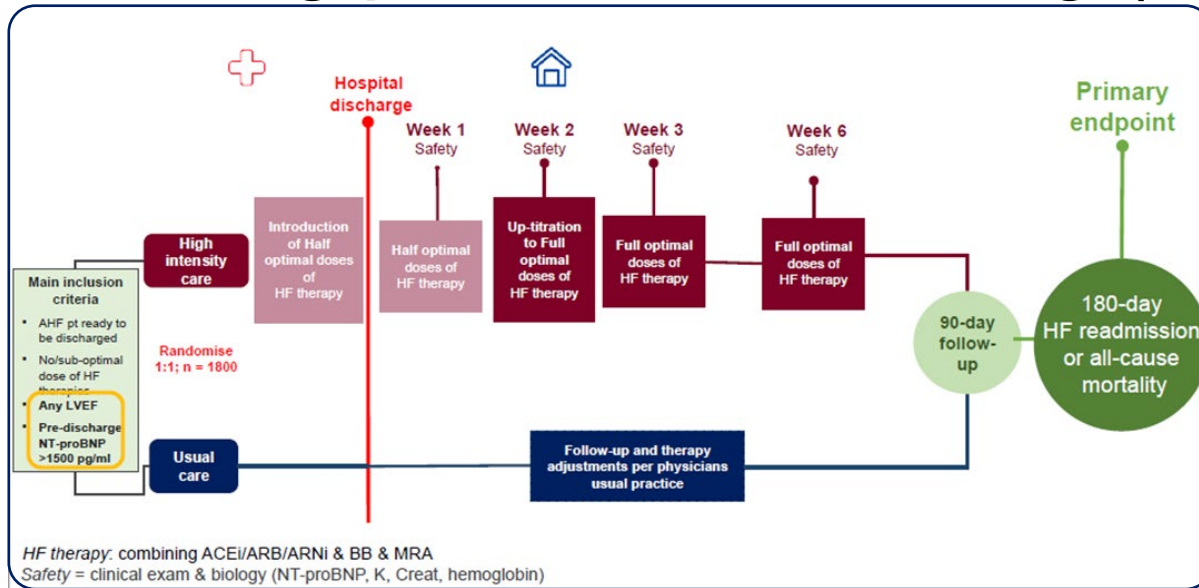
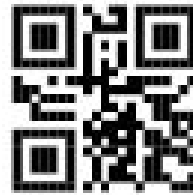
Gianluigi Savarese<sup>1\*</sup>, Johan Bodegard<sup>2</sup>, Anna Norhammar<sup>3</sup>, Peter Sartipy<sup>2,4</sup>, Marcus Thuresson<sup>5</sup>, Martin R. Cowie<sup>6,7</sup>, Gregg C. Fonarow<sup>8</sup>, Muthiah Vaduganathan<sup>9</sup>, and Andrew J.S. Coats<sup>10,11,12,13</sup>



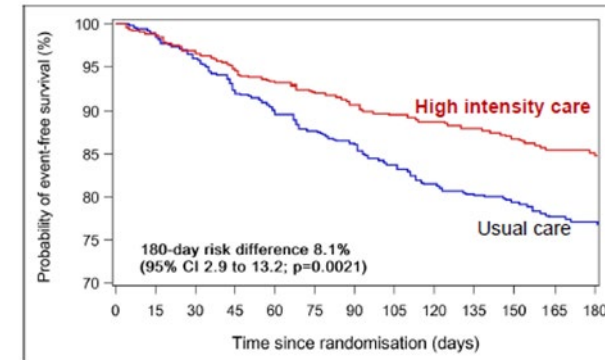
# Tidiga effekter av basbehandling (HFrEF)



# Tidig parallell behandling (STRONG-HF)



## Primary endpoint: 180-Day Readmission for HF or All-Cause Death

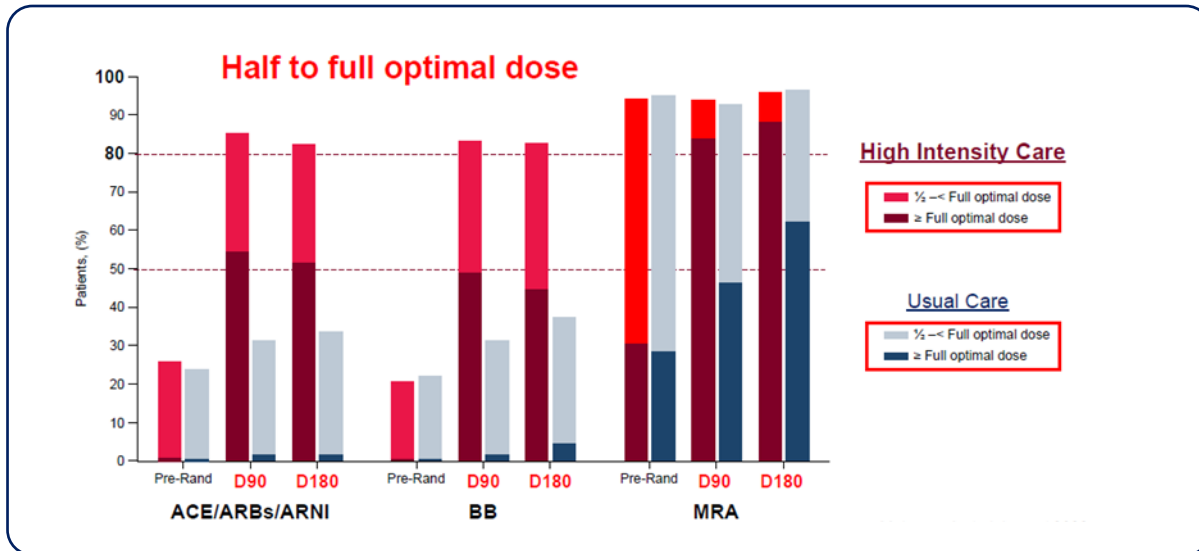
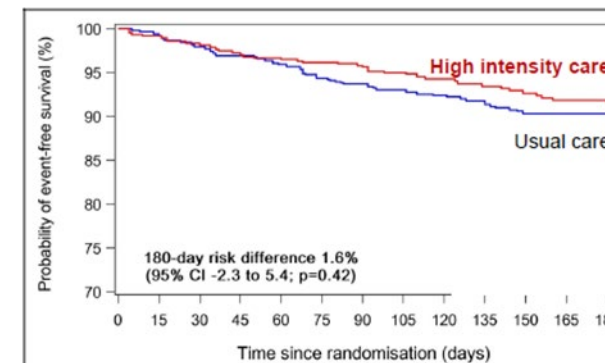


## Secondary endpoints:

Change from Baseline to Day 90 in EQ-5D VAS

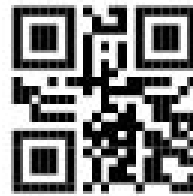
High Intensity	Usual Care	Treatment effect	P value
10.7 (0.9)	7.2 (0.9)	3.5 (1.7 to 5.2)	< 0.0001

## 180-Day All-Cause Death





# LOK: vägledning vid behandling av HFrEF



Diuretika vid ödem/stas Elkonvertering av förmaksflimmer	Ischemisk hjärtsjukdom	Uttalad stas	Nedsatt njurfunktion	Hypotension	Hyper-tension	Flimmer (normofrekvent)	Hög frekvens (oavsett rytm)	Intravenöst järn (vid järnbrist) Hälsosamma levnadsvanor	
	<i>Börja med:</i>								
	BB + SGLT2h	SGLT2h + ACEh*	SGLT2h + BB	SGLT2h	ACEh* + BB	SGLT2h + ACEh*	BB + SGLT2h		
	<i>Snart därefter tillägg av:</i>								
	ACEh* + MRA	BB + MRA	ACEh*	BB + ACEh* + MRA	SGLT2h + MRA	BB + MRA	ACEh* + MRA		
	<i>Vid fortsatt symtomatisk hjärtsvikt:</i>								
	ACEh/ARB bytes till ARNI								
	<i>Övriga åtgärder att överväga vid fortsatt symtomatisk hjärtsvikt</i>								
	CRT-P/CRT-D (vid breda QRS); ICD								
	Ivabradin; Digoxin; Vericiguat; Nitrat mm								
Klaffintervention; flimmerablation; revaskularisering									
Hjärtrtransplantation; hjärtpump									

**LOK**  
Nätverk för Sveriges Läkemedelskommittéer

## Läkemedelsbehandling vid kronisk hjärtsvikt

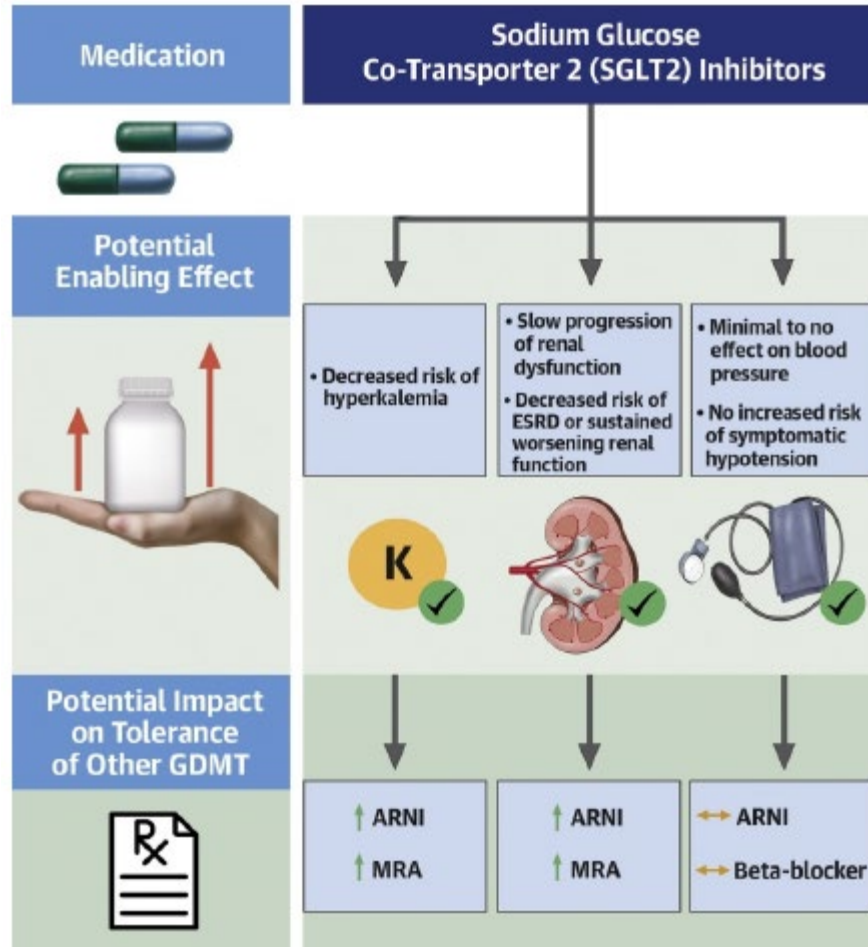
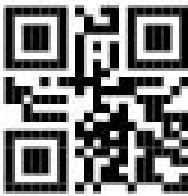
Publicerad 2023-09-13

LOK:s arbetsgrupp för framtagande av dessa riktlinjer  
Björn Kornhall, LAG hjärta-kärl i Skåne  
Bert Andersson, Sahlgrenska universitetssjukhuset  
Frieder Braunschweig, Karolinska universitetssjukhuset

Gröna fält: rekommenderas i första hand. Alla bör användas vid HFrEF. SGLT2 bör övervägas vid HFmrEF, övriga kan övervägas vid HFmrEF.

Gula fält: kan ges eller övervägas som behandling i andra hand.

# SGLT2h: Insättning



## Patientselektion, information

Välj rätt patient (ej DM typ I, LADA)  
 Info om nytta, biverkningar  
 Info om symtom vid ketoacidosis



## Undersökning

Blodtryck  
 Njurfunktion  
 Blodsocker



## Bakgrundsbehandling

Minska diuretika?  
 Minska andra diabetesläkemedel?



## Undvik dehydration

Information

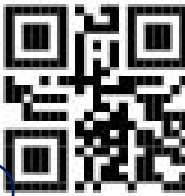


## Behandlingsuppehåll

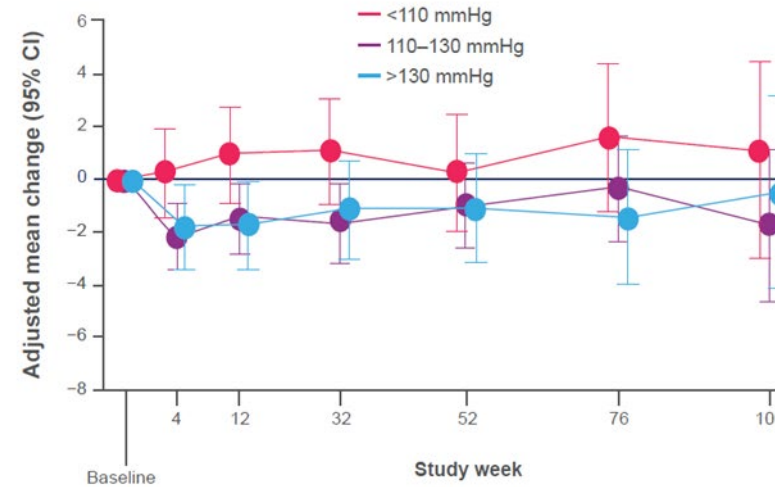
Akut sjukdom, diarré  
 Infektion med hög feber  
 Inför operationer  
 Diet med lågt kolhydratinnehåll eller fasta



# Insättning: vad händer med blodtrycket?

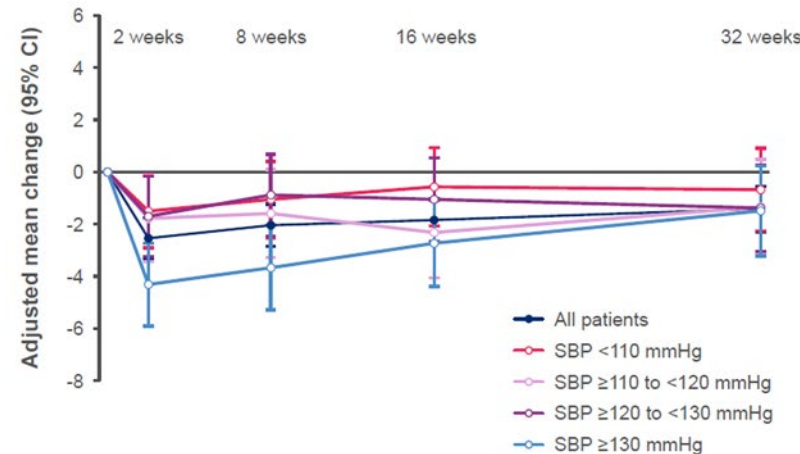


**EMPEROR-Reduced:**  
Placebo-corrected change in SBP from baseline (mmHg) in patients treated with empagliflozin



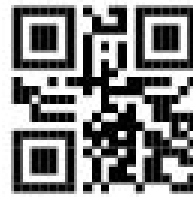
*Böhm et al, JACC 2021; 78: 1337*

**DAPA-HF:**  
Placebo-corrected change in SBP from baseline (mmHg) in patients treated with dapagliflozin

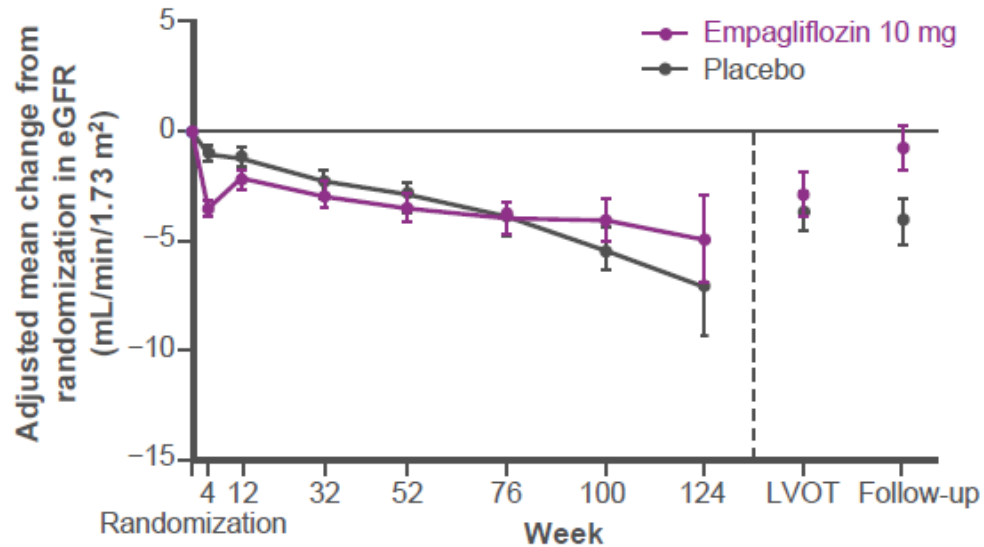


*Serenelli et al, EHJ 2020; 41: 3402*

# Insättning: vad händer med GFR?

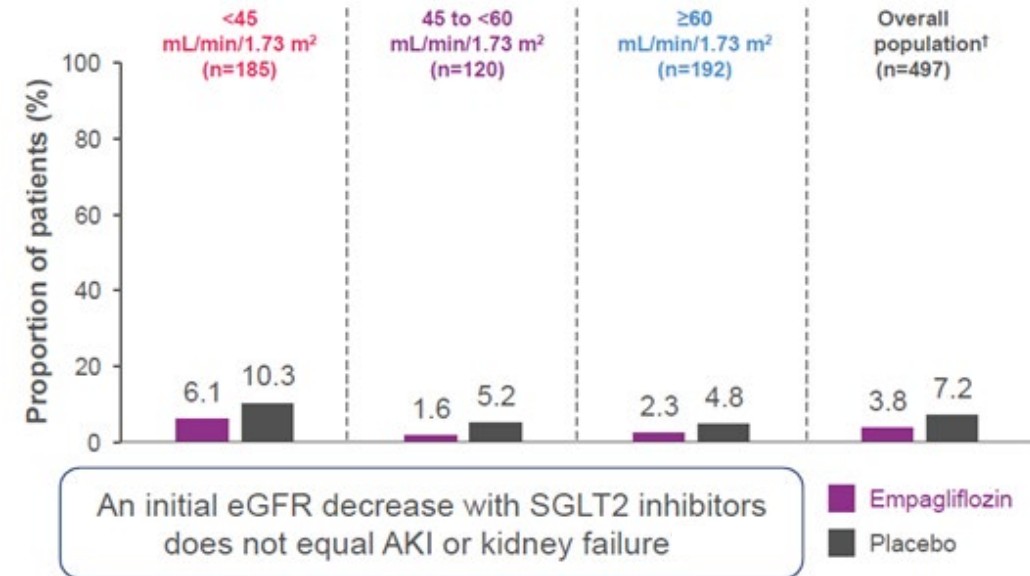


## eGFR change in EMPEROR reduced



Zannad et al, Eur J Heart Fail 2022;24:1829

## AKI events by treatment group and baseline eGFR following initiation in a hospital setting



Voors et al, Eur J Heart Fail 2022; 24: 1844

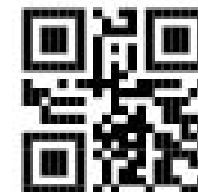


# Biverkning, komplikationer (Emperor reduced)



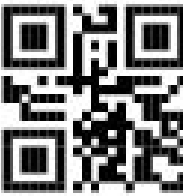
Karolinska  
Institutet

KAROLINSKA  
UNIVERSITY HOSPITAL



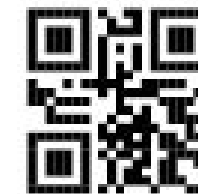
	Empagliflozin (n=1863) – N (%)	Placebo (n=1863) – N (%)
<b>Patients with any AEs</b>	1420 (76.2)	1463 (78.5)
<b>Serious AEs</b>	772 (41.4)	896 (48.1)
<b>Serious AEs of special interest</b>		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Confirmed severe hypoglycaemic events <sup>‡</sup>	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 tract infections	31 (1.7)	12 (0.6)
Complicated genital tract 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)

# Urogenitala infektioner



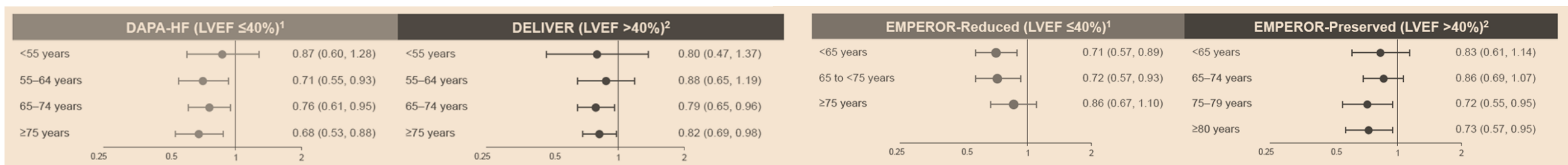
- Känd biverkning
- Risk redan ökad hos DM typ II patienter
- Ofta mildt förlopp
- Svarar på sedvanlig behandling
- Kräver inte nödvändigtvis avbrott i behandling
- Patientinformation!
- Genitalhygien extra betydelsefull
- Cave KAD

# SGLT2h hos de äldre



KLOK LÄKEMEDELSBEHANDLING AV DE MEST SJUKA ÄLDRE (MSÄ)

- Rekommenderade läkemedel vid HFrEF **minskar symtom**.
- Vanligt med **HFpEF** (samt hypertoni, FF, annan komorbiditet).
- **Dehydrering**: utsättning diuretika; överväg temporär utsättning av ACE-h, ARB, MRA och **SGLT2-h**.
- **Ortostatism**: reducera annan trycksänkande medicinering.
- **Utsättning**: ACE-h, ARB, SGLT2, digoxin och diuretika kan sättas ut direkt utan nedtrappning. Betablockerare trappas ner.
- **Behandlingsbegränsning/brytpunktsamtal** (ICD bör deaktiveras)



<sup>1</sup>: Fillipatos et al, EJHF 2022; 24:2297

<sup>2</sup>: Böhm et al, JACC 2022;80:1

<sup>1</sup>: Martinez et al, Circulation 2020; 141:100

<sup>2</sup>: Peikert et al; Circ HF, 2022:15

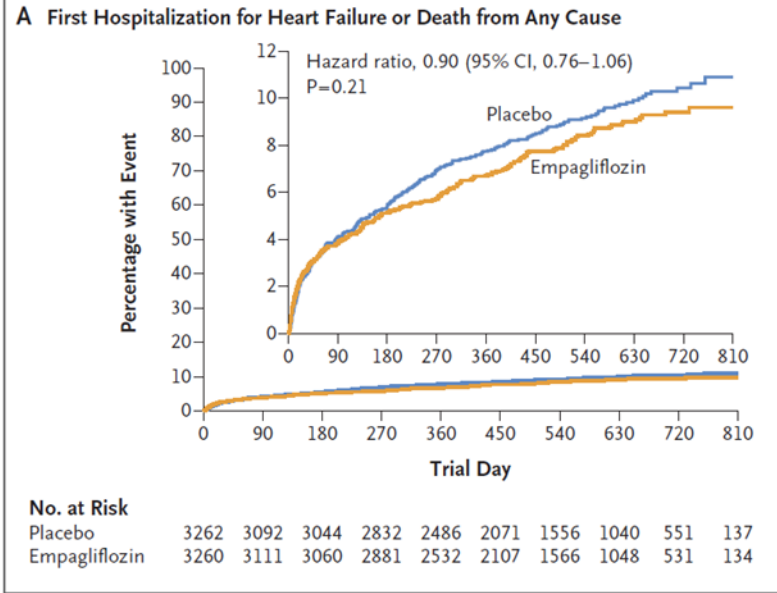
# SGLT2-h: post MI

The NEW ENGLAND JOURNAL of MEDICINE

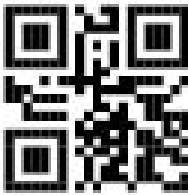
ORIGINAL ARTICLE

## Empagliflozin after Acute Myocardial Infarction

J. Butler, W.S. Jones, J.A. Udell, S.D. Anker, M.C. Petrie, J. Harrington, M. Mattheus, I. Zwiener, O. Amir, M.C. Bahit, J. Bauersachs, A. Bayes-Genis, Y. Chen, V.K. Chopra, G. Figtree, J. Ge, S.G. Goodman, N. Gotcheva, S. Goto, T. Gasior, W. Jamal, J.L. Januzzi, M.H. Jeong, Y. Lopatin, R.D. Lopes, B. Merkely, P.B. Parikh, A. Parkhomenko, P. Ponikowski, X. Rossello, M. Schou, D. Simic, P.G. Steg, J. Szachniewicz, P. van der Meer, D. Vinereanu, S. Zieroth, M. Brueckmann, M. Sumin, D.L. Bhatt, and A.F. Hernandez



NEJM Evidence

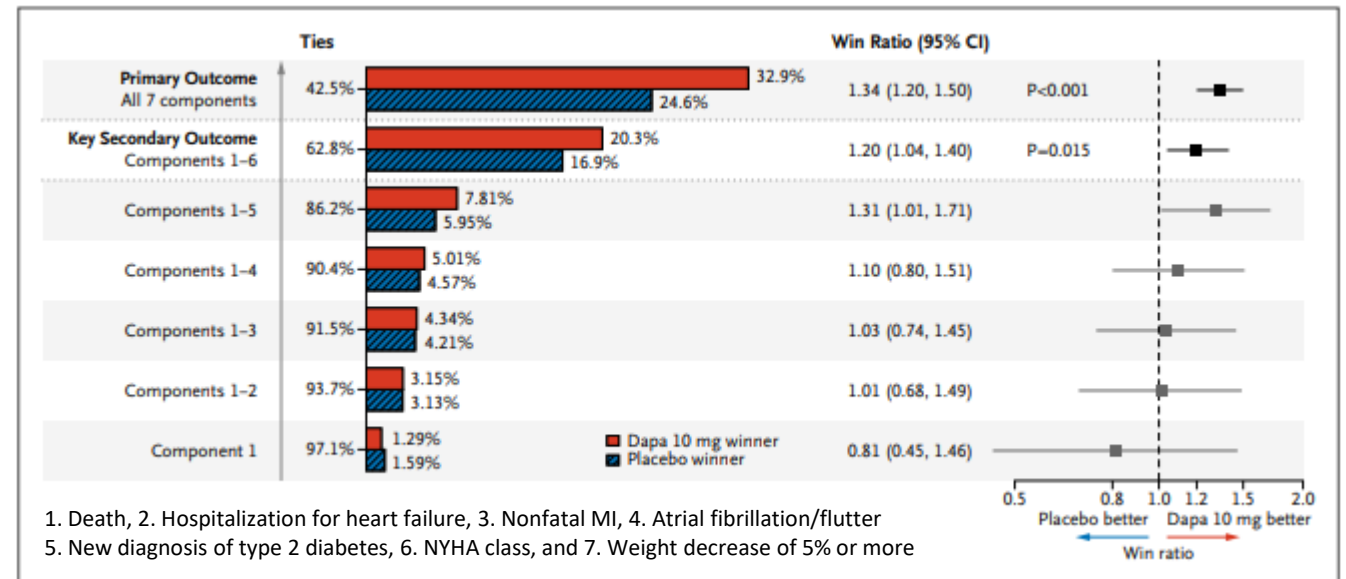


Published November 11, 2023  
NEJM Evid 2024; 3 (2)  
DOI: 10.1056/EVIDo2300286

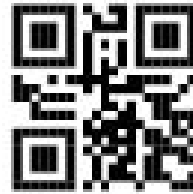
ORIGINAL ARTICLE

## Dapagliflozin in Myocardial Infarction without Diabetes or Heart Failure

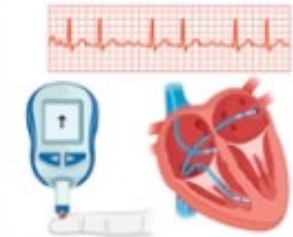
Stefan James, M.D., Ph.D.,<sup>1,2</sup> David Erlinge, M.D., Ph.D.,<sup>3</sup> Robert F. Storey, M.D., D.M.,<sup>4,5</sup> Darren K. McGuire, M.D.,<sup>6,7</sup> Mark de Belder, B.A. Cantab, M.B.B.S., M.A., M.D., F.R.C.P.,<sup>8</sup> Niclas Eriksson, Ph.D.,<sup>1</sup> Kasper Andersen, M.D., Ph.D.,<sup>2,9</sup> David Austin, M.D., F.R.C.P.,<sup>10,11</sup> Gabriel Arefalk, M.D., Ph.D.,<sup>9,12</sup> David Carrick, M.B.Ch.B., Ph.D., F.R.C.P.,<sup>13,14</sup> Robin Hofmann, M.D., Ph.D.,<sup>15</sup> Stephen P. Hoole, M.D., D.M.,<sup>16</sup> Daniel A. Jones, M.D., Ph.D.,<sup>17,18</sup> Kelvin Lee, M.R.C.P., Ph.D.,<sup>19,20</sup> Hans Tygesen, M.D., Ph.D.,<sup>21,22</sup> Peter A. Johansson, M.Sc.,<sup>23</sup> Anna Maria Langkilde, M.D., Ph.D.,<sup>23</sup> Wilhelm Ridderstråle, M.D., Ph.D.,<sup>23</sup> Ehsan Parvareh Rizi, M.D., Ph.D.,<sup>23</sup> John Deanfield, C.B.E. F.Med.Sci. B.A. Hons. (Cantab), M.B., B.Chir., F.R.C.P., F.E.S.C., F.A.C.C.,<sup>24</sup> and Jonas Oldgren, M.D., Ph.D.,<sup>1,2</sup> for the DAPA-MI investigators\*



# SGLT2-h: prevention av flimmer?



## CENTRAL ILLUSTRATION: Impact of SGLT2 Inhibitors on Recurrence of Atrial Fibrillation After Catheter Ablation



Patients with a history of type 2 DM who had undergone AF ablation

Baseline use of SGLT2i      No SGLT2i use

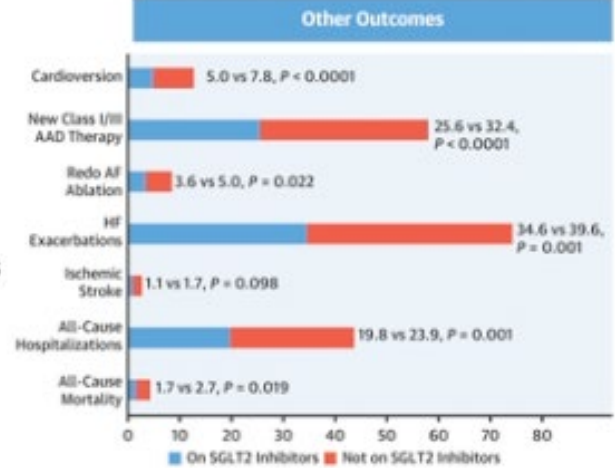
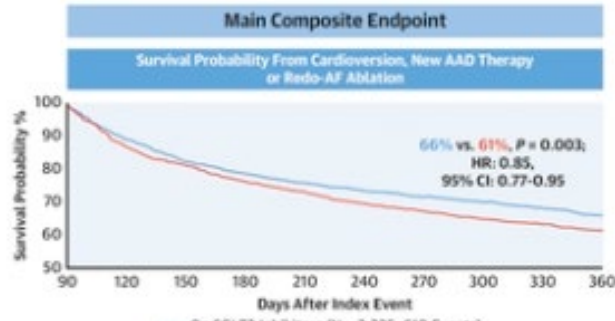
Propensity score matching

3-month blanking period after AF ablation

n = 2,225

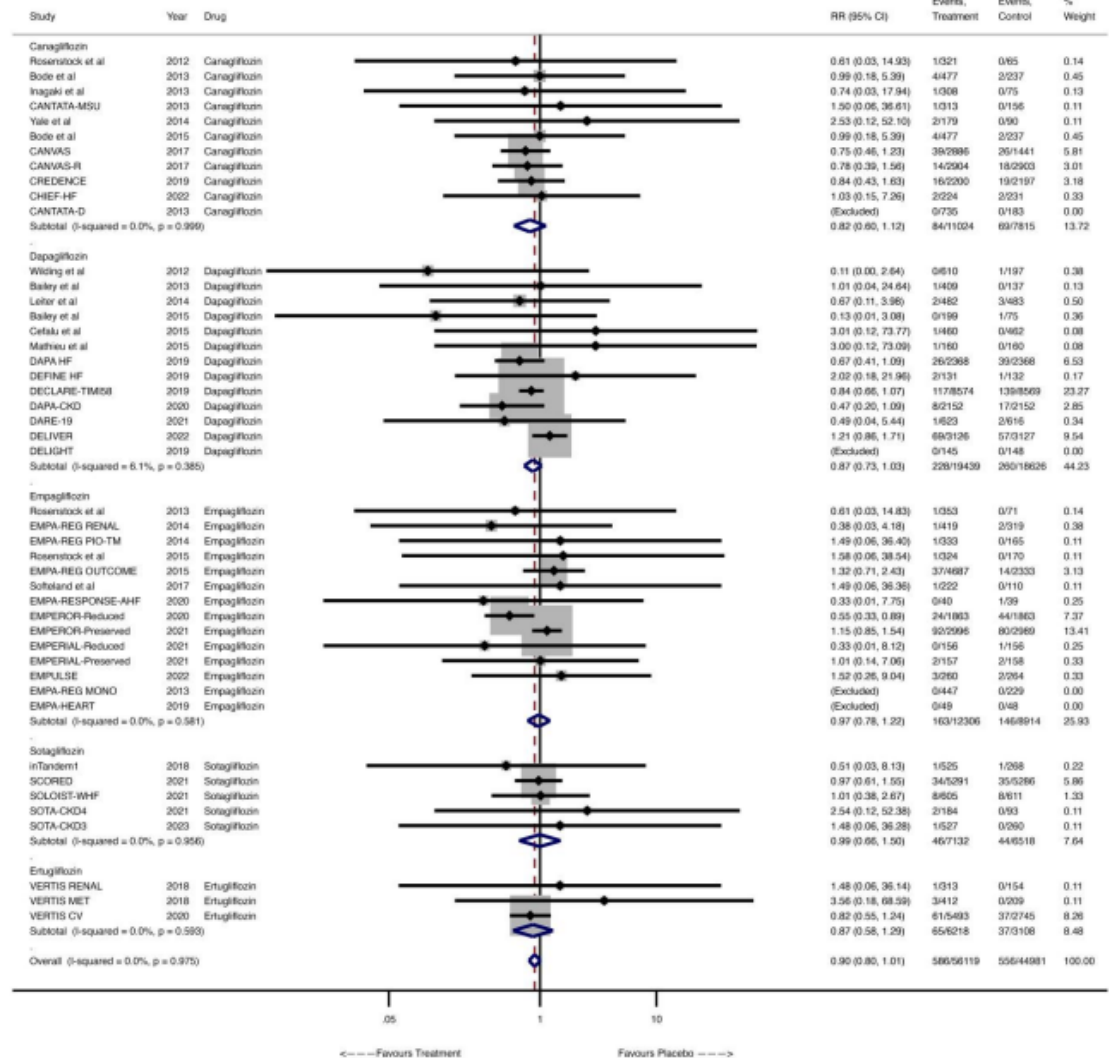
n = 2,225

Main composite endpoint:  
 • The need for cardioversion or,  
 • New class I or III AAD therapy or,  
 • Redo AF ablation



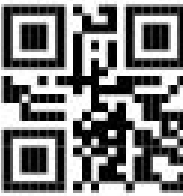
Abu-Qaoud MR, et al. J Am Coll Cardiol EP. 2023;9(10):2109-2118.

## Metaanalays: 46 trials, 101 100 patients





# Sammanfattning



## SGLT2 hämmare

- rekommenderas vid hjärtsvikt - oavsett LVEF, oavsett diabetes
- ger tidiga behandlingseffekter
- är relativt enkelt att administrera
- har relativt få biverkningar (cave ketoazidos)