KOMPLEXNÍ KARDIO VASKULÁRNÍ CENTRUM VFN Praha

# Gliflozíny – stratifikovaná prevence rozvoje srdečního selhání

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**Prague Prevention 2023**

Autoklub Praha 25.1.2023

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# Gliflozíny u srdečního selhání (HF)

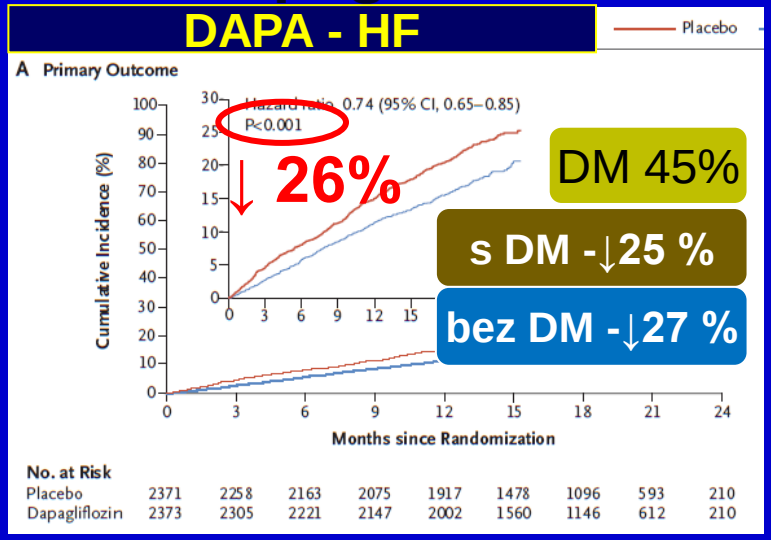
*Primární kompozitní cíl:* ***zhoršení/hospitalizace HF + KV úmrtí)***

## Dapagliflozin

### HFrEF

*EF < 40%*

**DAPA - HF**




DM 45%

s DM -↓25 %

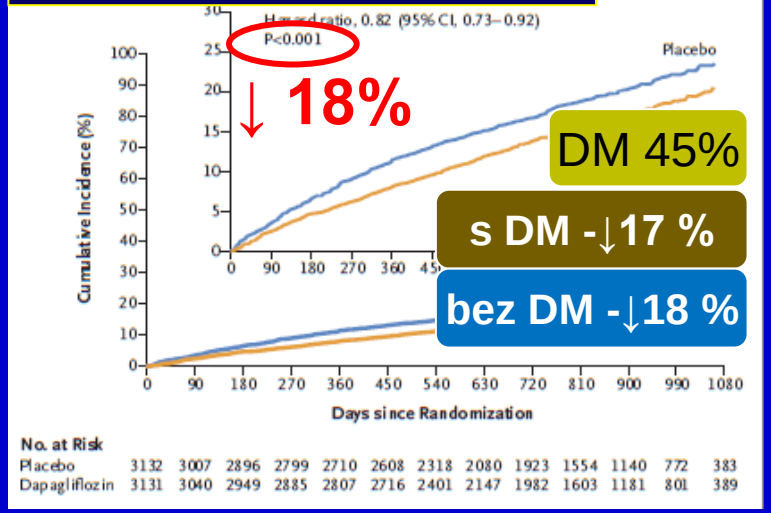
bez DM -↓27 %

McMurray JJV et al. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

### HFpEF + HFmrEF

*EF > 40%*

**DELIVER**




DM 45%

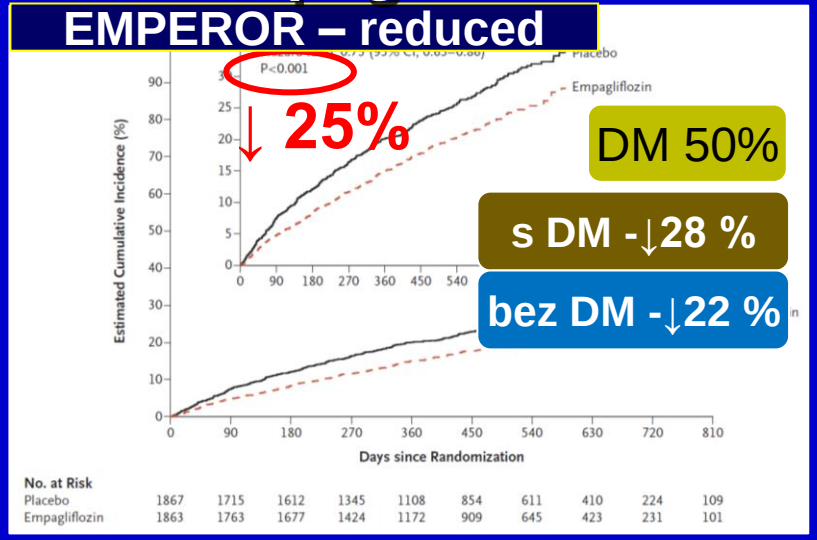
s DM -↓17 %

bez DM -↓18 %

Solomon SD et al. N Engl J Med 2022;387:1089-98.

## Empagliflozin

**EMPEROR – reduced**



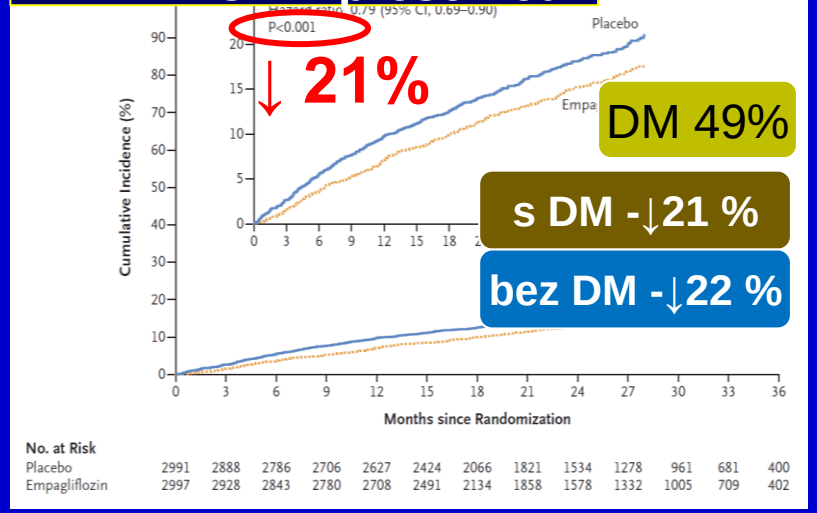

DM 50%

s DM -↓28 %

bez DM -↓22 %

Packer M. et al. N Engl J Med, 2020 Oct 8;383(15):1413-1424.

**EMPEROR – preserved**




DM 49%

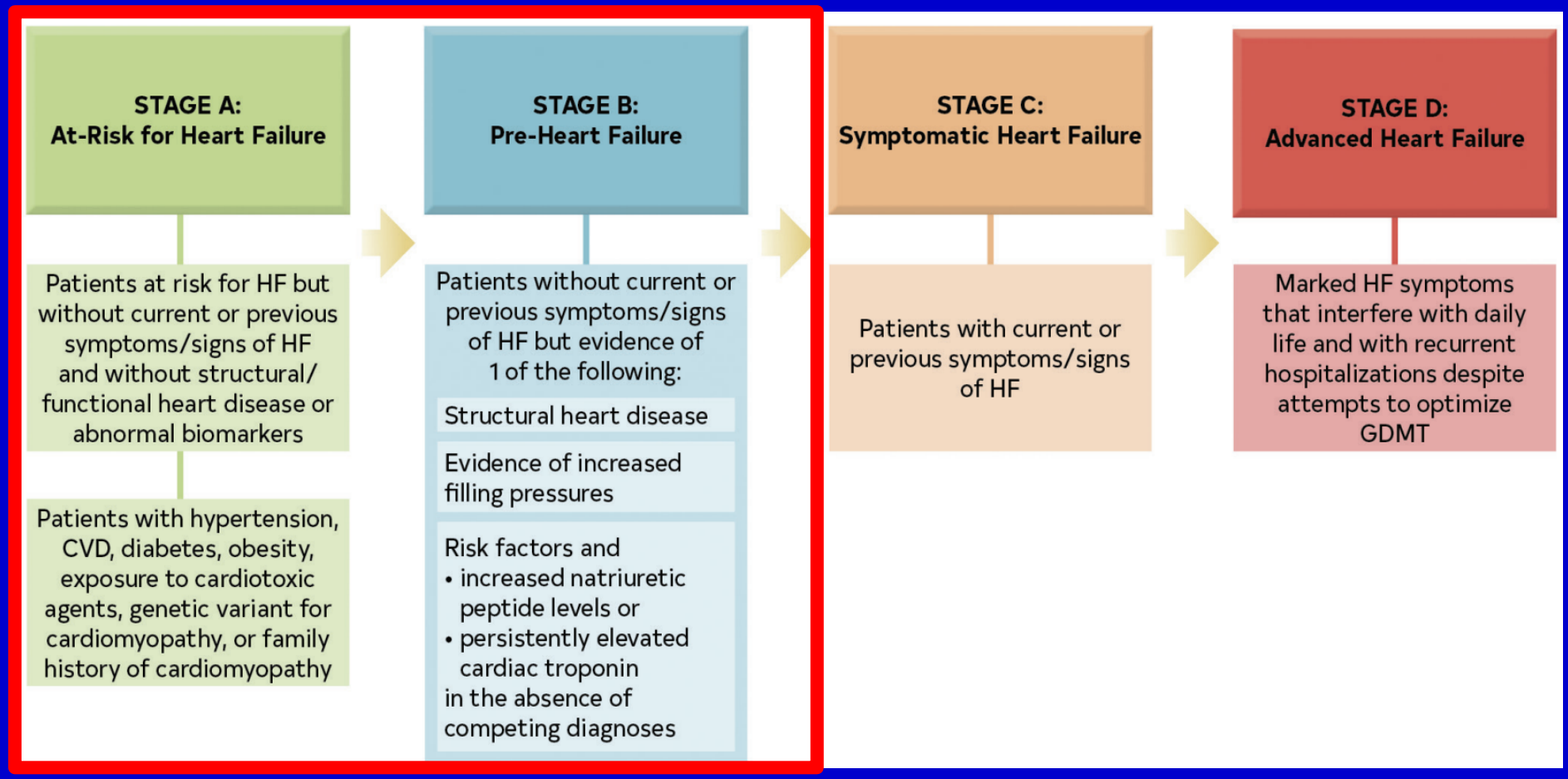
s DM -↓21 %

bez DM -↓22 %

Anker S.D. et al. N Engl J Med, 2021 Oct 14; 385:1451-61.

# AHA/ACC/HFSA guidelines 2022

## *Stadia rozvoje HF*




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

# Pravěk SGLT2i

https://www.kudyznudy.cz/aktuality/nahlednete-do-pravekeho-sveta-ocima-zdenka-buriana

# SGLT2i a DM s aterosklerotickým kardiovaskulárním onemocněním (ASKVO) nebo jejími rizikovými faktory (RF)

## Srovnání populací

*– metanalýza 2019: 3 CVOT u SGLT2i*

**Etablovaná ASCVD x rizikové faktory CVD**

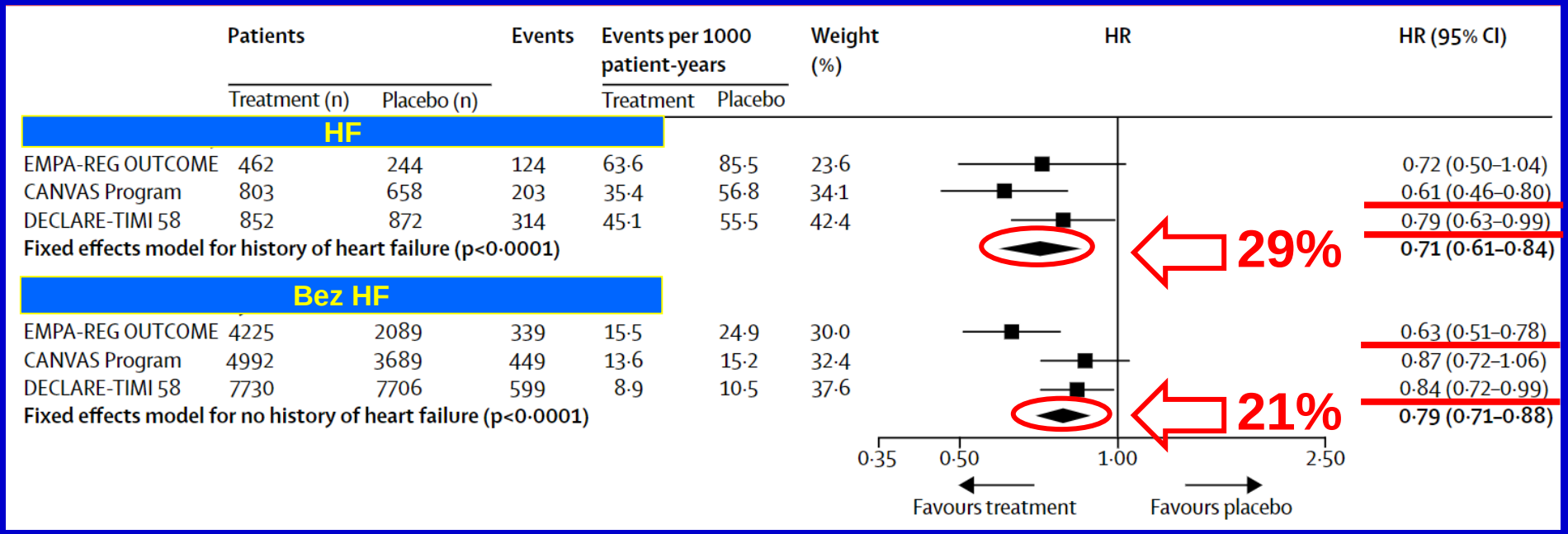
| | pouze ASKVO | mix ASKVO a RF | mix ASKVO a RF |
|---|---|---|---|
| | EMPA-REG OUTCOME[1] | CANVAS Program[2] | DECLARE-TIMI 58[3] |
| Drug | Empa | Cana | Dapa |
| Doses analysed | 10 mg, 25 mg (once daily) | 100 mg, 300 mg (once daily) | 10 mg (once daily) |
| Median follow-up time, years | 3·1 | 2·4 | 4·2 |
| **Celkový počet pacientů** | 7020 **7.020** | 10 142 **10.142** | 17 160 **17.160** |
| Age, mean | 63·1 | 63·3 | 63·9 |
| Women | 2004 (28·5%) | 3633 (35·8%) | 6422 (37·4%) |
| **ASKVO** | 7020 **100%** | 6656 **~ 66%** | 697[illegible] **~ 41%** |
| **Srdeční selhání** | 706 **~ 10%** | 1461 **~ 14%** | 1724 **~ 10%** |
| Patients with eGFR <60 mL/min per 1·73 m² | 1819 (25·9%) | 2039 (20·1%) | 1265 (7·4%) |

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Zelniker TE et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

# Gliflozíny u DM – primární prevence HF

## Hospitalizace pro HF a KV úmrtí




**HF** ↓32 %

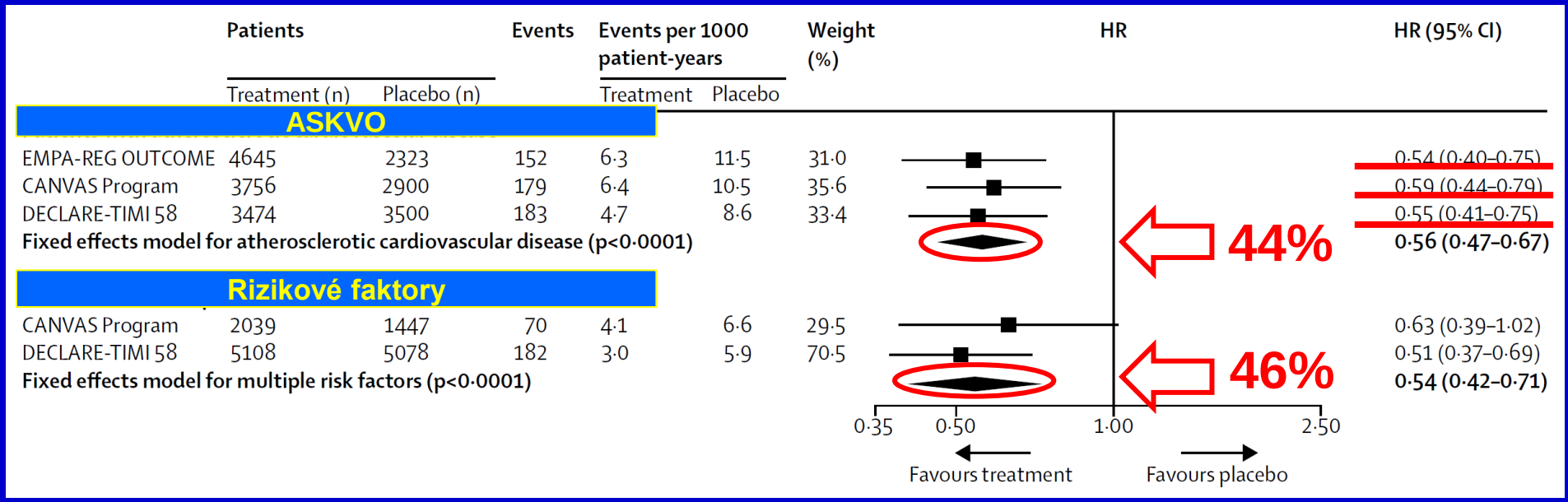
**Bez HF** ↓29 %

**Hospitalizace pro HF**

Zelniker TE et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

# SGLT2i a CVOT

## Zhoršení renálních funkcí, renální selhání a úmrtí renálních příčin




**ASCVD**

**↓17 %**

**Celková mortalita**

**RF**

**NS (↓10 %)**

Zelniker TE et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

# SGLT2i u CKD - primární prevence HF

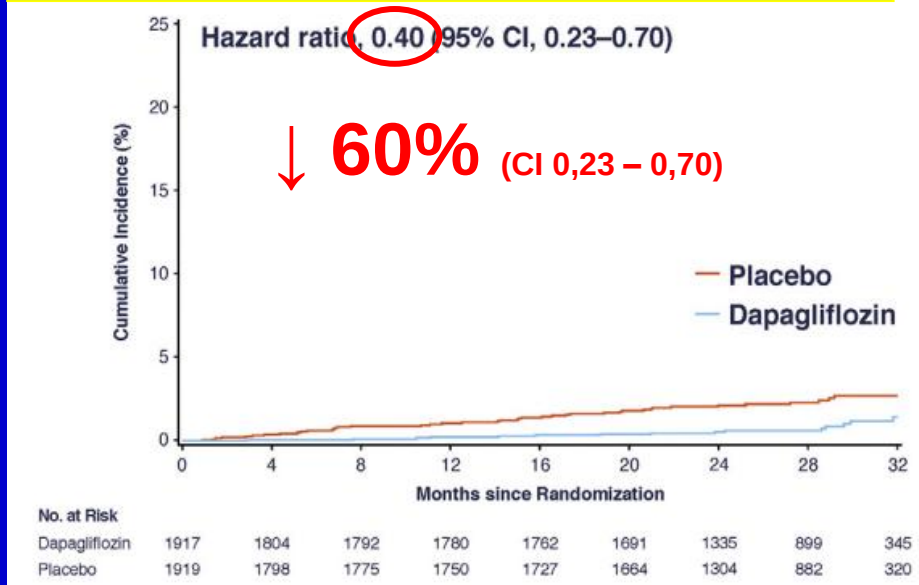
## Studie DAPA-CKD (dapagliflozin 10 mg x placebo)

(4304 pt, GFR 25-75 ml/min, sledování 2,4 roků)

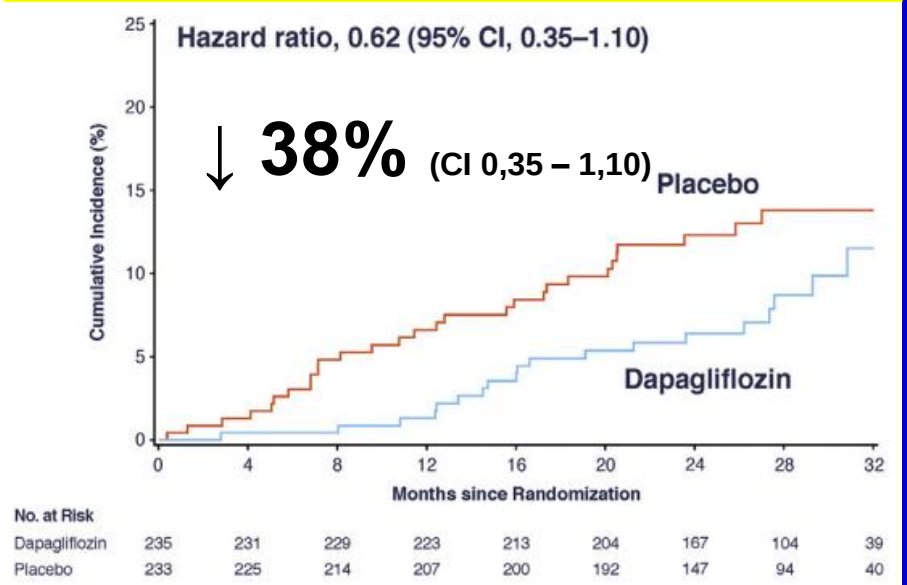
DM 67% | GFR ~ 43 ml/min | HF ~ 11% | HHF ↓49 %, CI (0,34-0,76)

## Hospitalizace pro HF

### Bez HF




### HF




McMurray JJV et al. Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure. JACC Heart Fail. 2021 Nov;9(11):807-820.

# Gliflozíny jako antihypertenziva?

Circulation

EDITORIAL

## Are SGLT2 Inhibitors New Hypertension Drugs?

Article, see p 1735

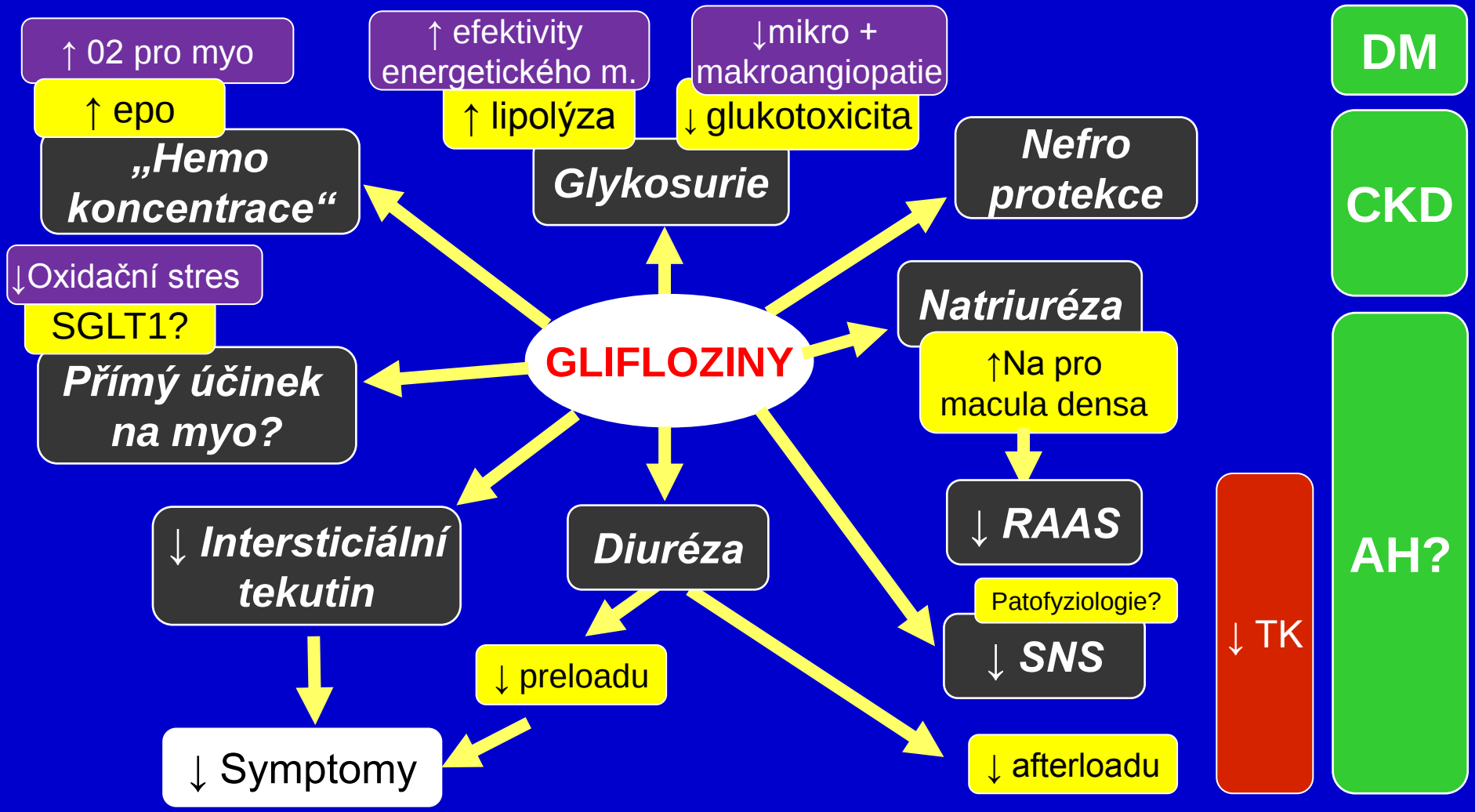
Recent large, randomized, placebo-controlled clinical trials have demonstrated that treatment with SGLT2 (sodium-glucose cotransport 2) inhibitors (SGLT2i) significantly reduces the rate of cardiovascular events (including heart failure

Kario K et al. Are SGLT2 Inhibitors New Hypertension Drugs? CIRC. Volume 143, Issue 18, 4 May 2021; Pages 1750-1753

# Patofyziologie benefitu gliflozinů u HF

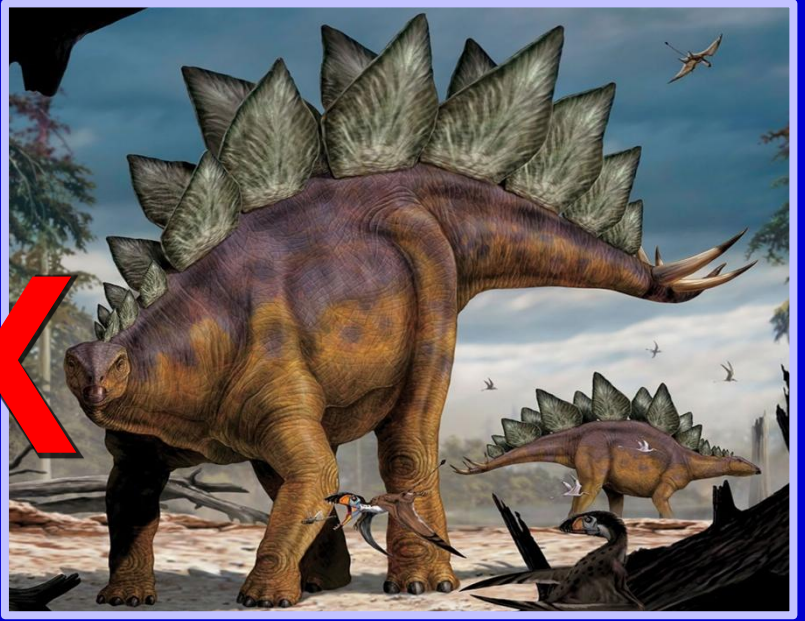
**HF** … r, mr, p EF … s nebo bez DM

**„preHF“**



# Nové poznatky u gliflozinů …

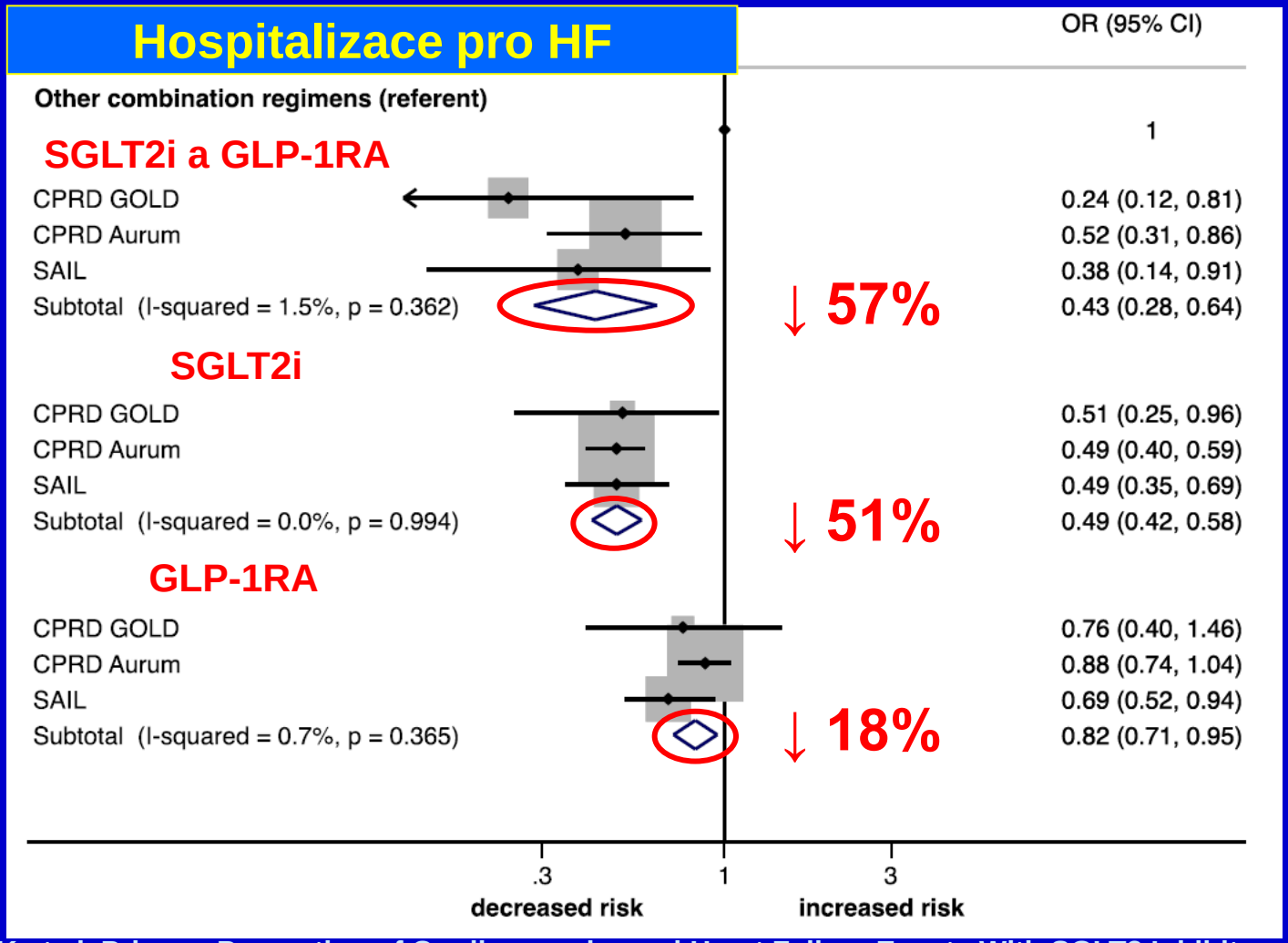
X



# SGLT2i u DM a primární prevence HF

## RWE Databáze Anglie + Wales (terapie DM s SGLT2 x bez nich)

(case –control 1:20 z 336.00 pt, 3 databáze, DM bez KVO)



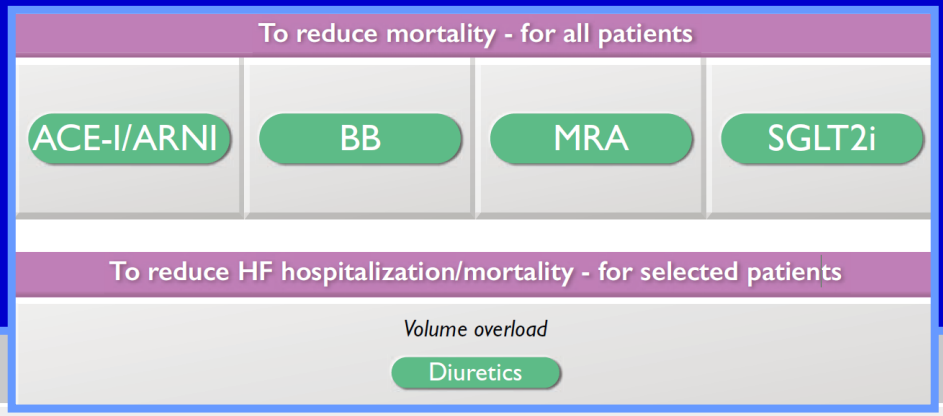

Wright AK et al. Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes. Diabetes Care. 2022 Apr 1;45(4):909-918.

# Evropská doporučení HF 2021

## HFrEF → SGLT2i

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368
ESC GUIDELINES

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

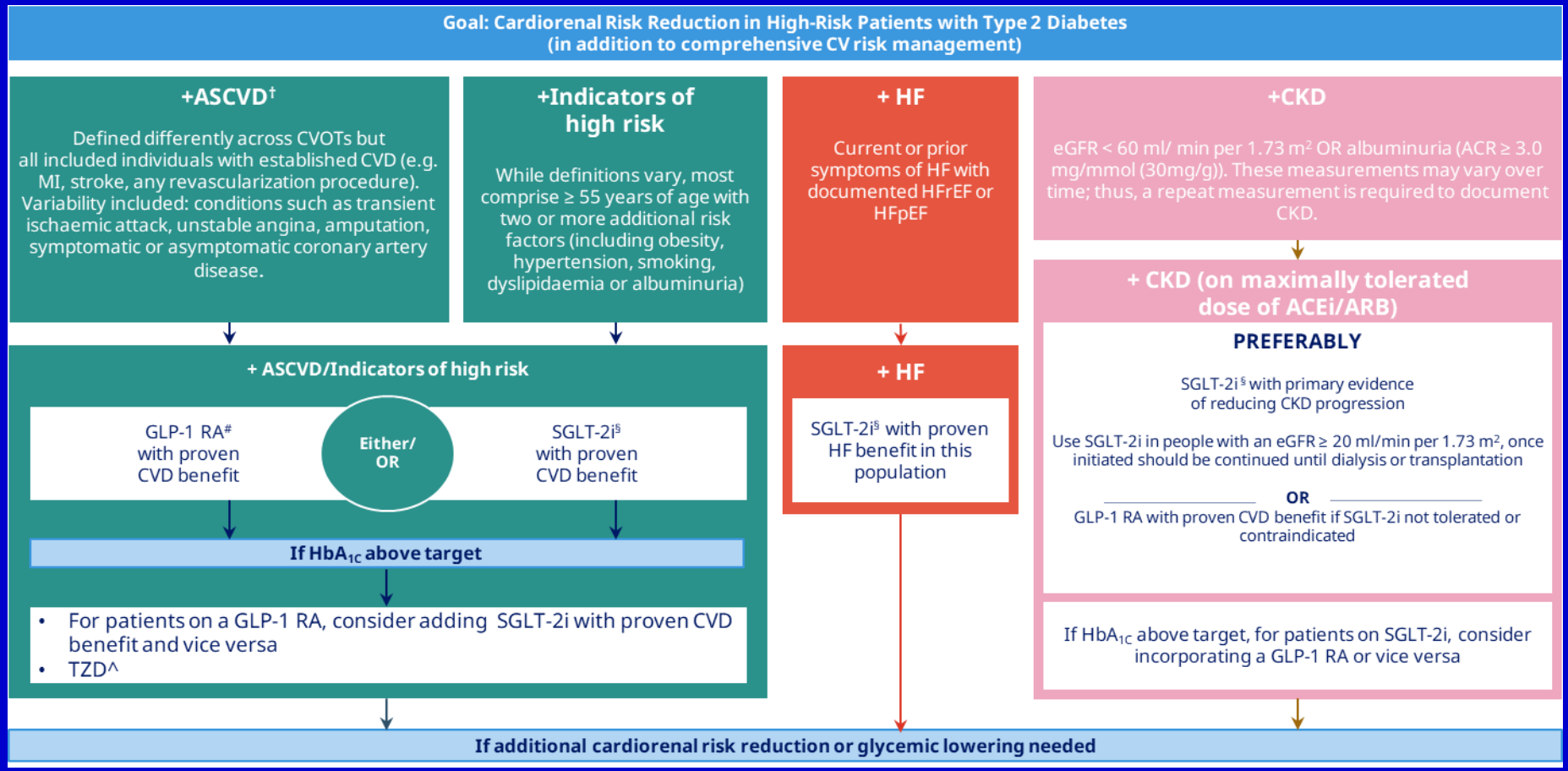



| Recommendations | Class[a] | Level[b] |
|---|---|---|
| ACEi — ded for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113] | I | A |
| BB — nmended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120] | I | A |
| MRA — ded for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122] | I | A |
| SGLT2i — liflozin are recommended for patients with HFrEF to reduce the risk d death.[108,109] | I | A |
| ARNI — ecommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF h.[105] | I | B |

McDonagh TA et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal (2021) 42, 35993726

# ADA/EASD consensus treatment algorithm

## 2022

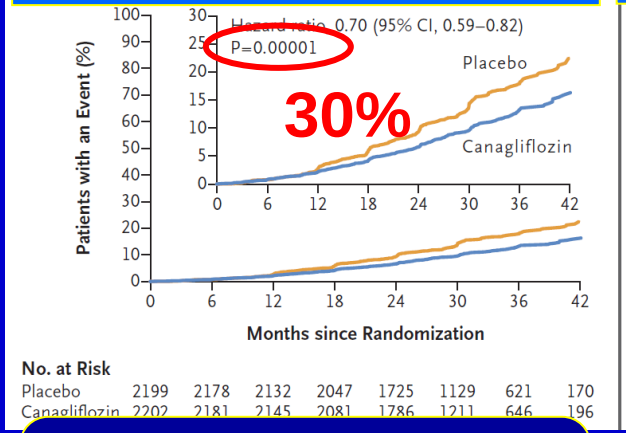


# DM + renální poškození a SGLT2i

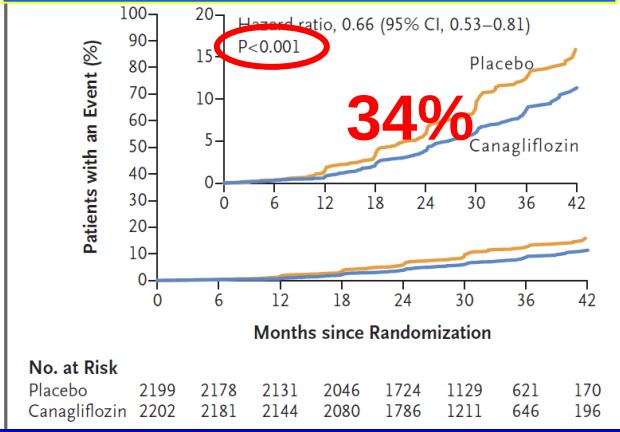
## Studie CREDENCE (Cana 100mg x placebo)

(4401 pt, GFR 30-90 ml/min, všichni RAAS blokátory…)

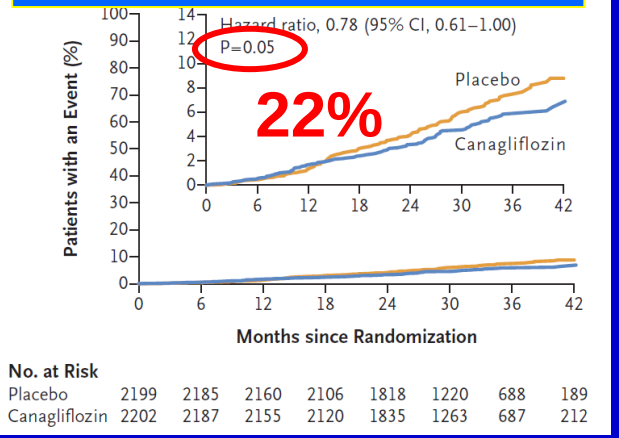
**Primární kompozitní cíl**




**Renálně specifický kompozitní cíl**




**Úmrtní z CV příčin**




**ESKD + 2x kreat + CV a renální úmrtí**

**GFR ~ 56 ml/min**

**HF ~ 15%**

**↓31 %** CV úmrtí nebo hospitalizace pro HF **P < 0,001**

**↓39 %** Hospitalizace pro HF **P < 0,001**


Perkovic V et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306.

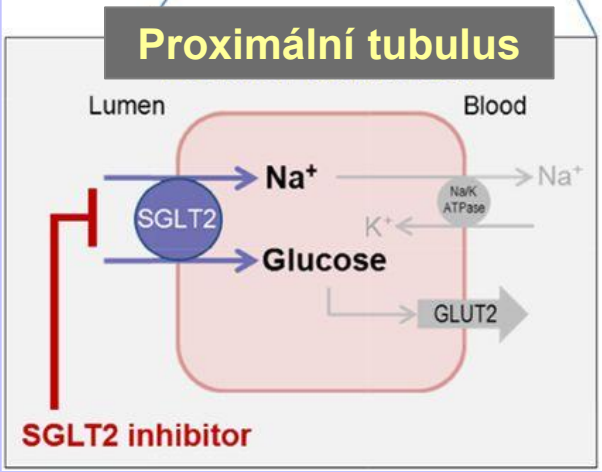
# 1. Gliflozíny ➡ antidiabetika

**Vasokonstrikce afferentní arterioly →**
**↓ glomerulární hyperfiltrace**

**↑ $Na^+/Cl^-$ dodávka**
**makula densa**

**↑ Na+**
**↑ glukóza**

**↑ k. močová**




**↑ glykosurie**
**↑ natriuréza**

***Výsledný efekt***
**↓ glykémie**
**↓ hmotnosti**
**↓ TK**
… Mírná hemokoncentrace

**SGLT2i – KV bezpečnost?**

**Canagliflozin**
**Dapagliflozin**
**Empagliflozin**
**CVOT**

*Ertugliflozin*
*Ipragliflozin*
*Luseogliflozin …*

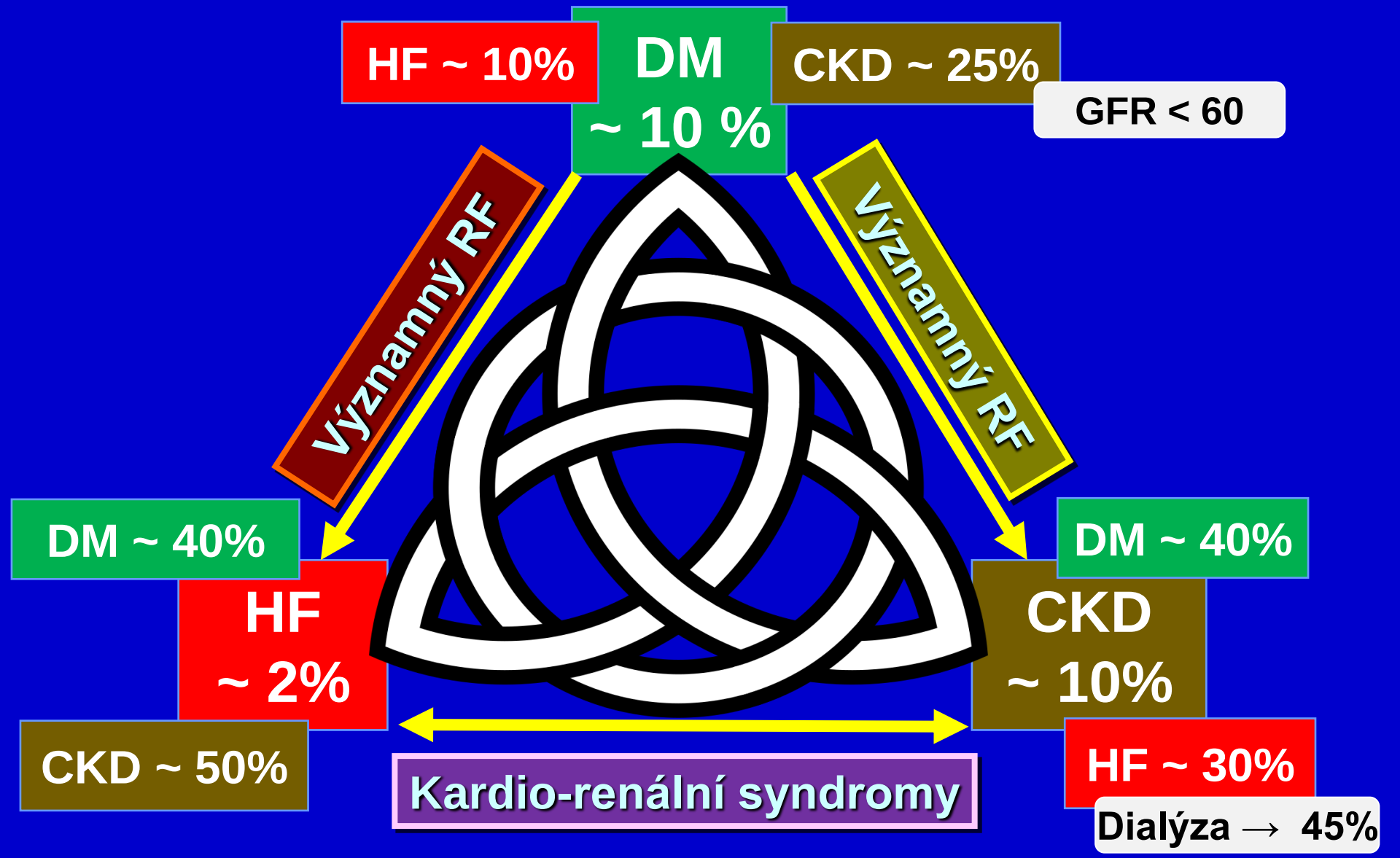
Upraveno dle Erik J.M. van Bommel et al. SGLT2 Inhibition in the Diabetic Kidney—From Mechanisms to Clinical Outcome
CJASN April 2017, 12 (4) 700-710

# Gliflozíny u DM: ASCVD x RF

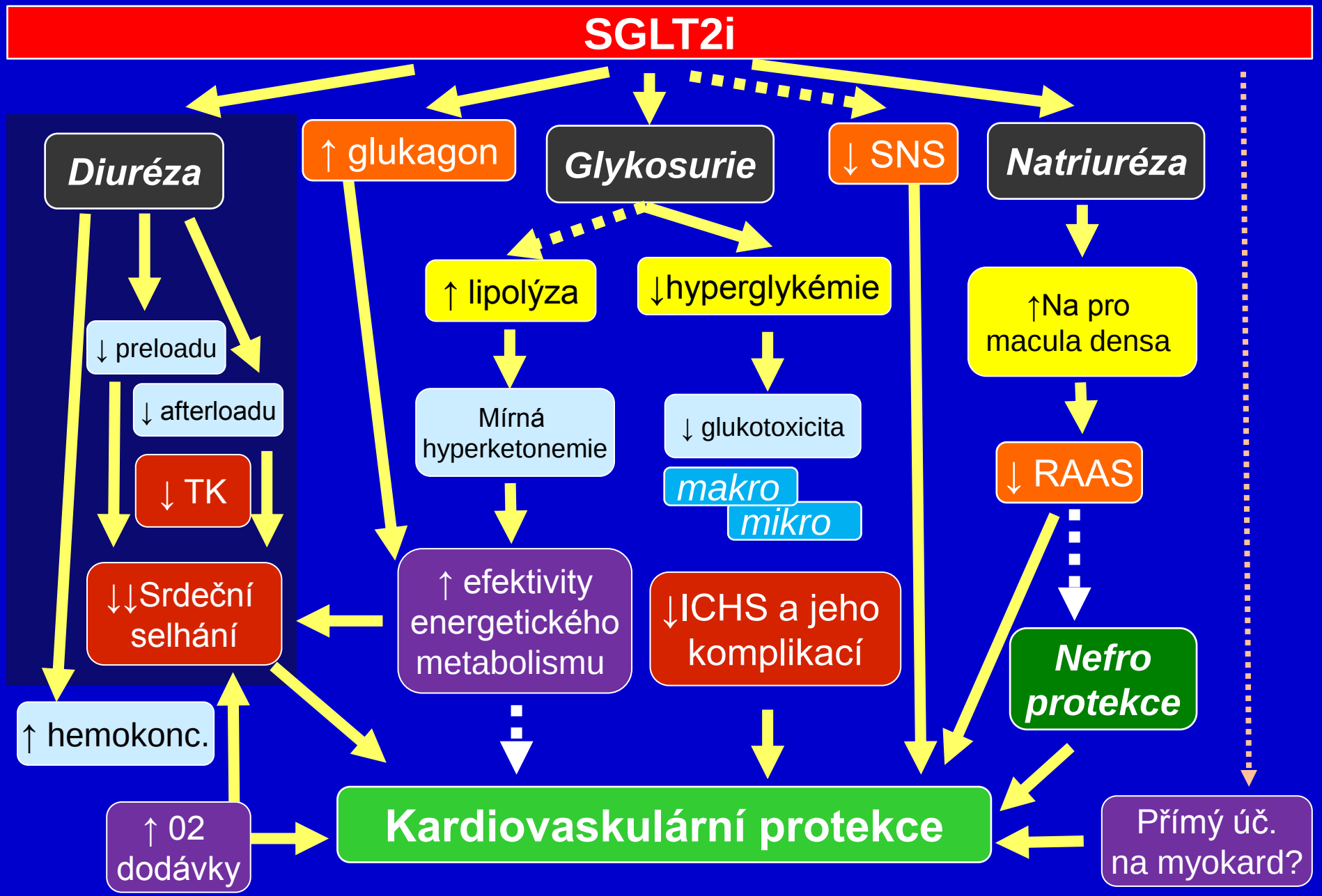
| ASCVD | | RF |
|---|---|---|
| ↓15 % | MACE (IM+CMP+KV úmrtí) | NS ( ↓1 %) |
| ↓15 % | IM | NS ( ↓1 %) |
| ↓ 20 % | KV úmrtí | NS ( ↑2 %) |
| NS ( ↓2 %) | CMP | NS ( ↑1 %) |

Zelniker TE et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

# Triquetra DM – CKD – HF



# Patofyziologie KV benefitu gliflozinů

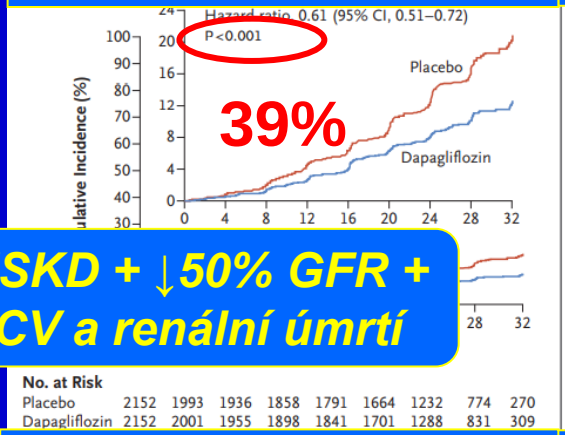


# CKD u DM i neDM a SGLT2i

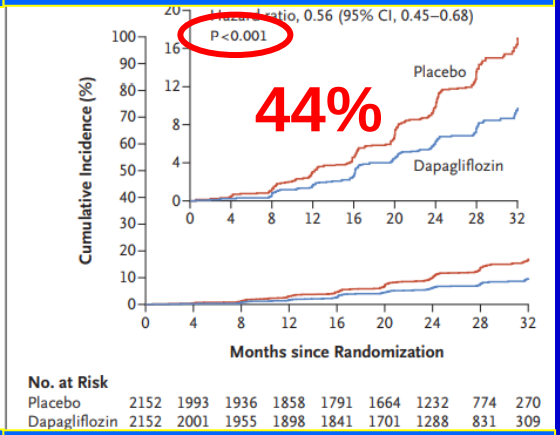
## Studie DAPA-CKD (Dapa 10 mg x placebo)

(4304 pt, GFR 25-75 ml/min)

**Primární kompozitní cíl**




**Renálně specifický komp. cíl**

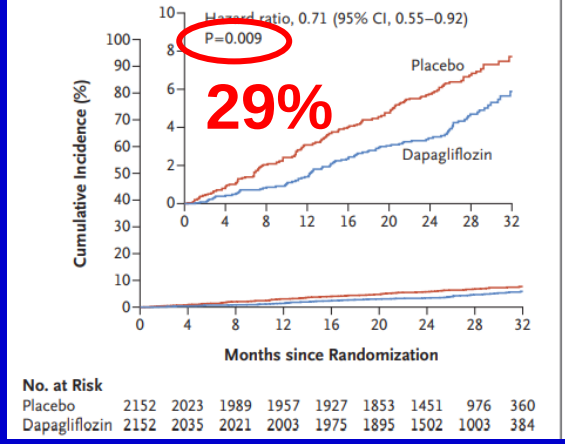



***ESKD + ↓50% GFR + CV a renální úmrtí***

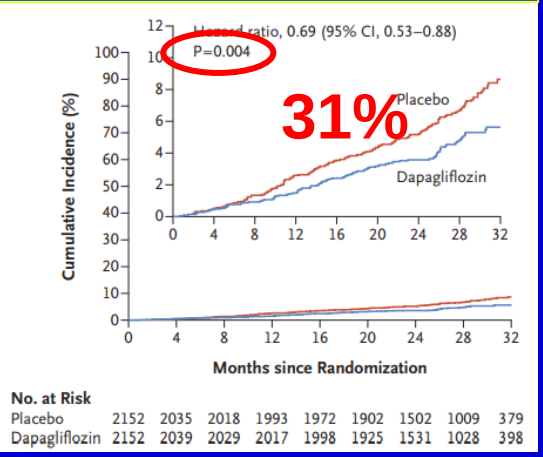
No. at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2152 | 1993 | 1936 | 1858 | 1791 | 1664 | 1232 | 774 | 270 |
| Dapagliflozin | 2152 | 2001 | 1955 | 1898 | 1841 | 1701 | 1288 | 831 | 309 |

**CV úmrtí + HHF**




**Úmrtní ze všech příčin**




No. at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2152 | 2023 | 1989 | 1957 | 1927 | 1853 | 1451 | 976 | 360 |
| Dapagliflozin | 2152 | 2035 | 2021 | 2003 | 1975 | 1895 | 1502 | 1003 | 384 |

No. at Risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2152 | 2035 | 2018 | 1993 | 1972 | 1902 | 1502 | 1009 | 379 |
| Dapagliflozin | 2152 | 2039 | 2029 | 2017 | 1998 | 1925 | 1531 | 1028 | 398 |

**DM 67%**

**GFR ~ 43 ml/min**

**HF ~ 11%**

**HHF**

**↓49 %**

**CI (0,34-0,76)**

Heerspink HJL et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020;383:1436-46.

# SGLT2i u HFpEF *(+mrEF)*

## Studie EMPEROR-preserved (Empa 10 mg x placebo)

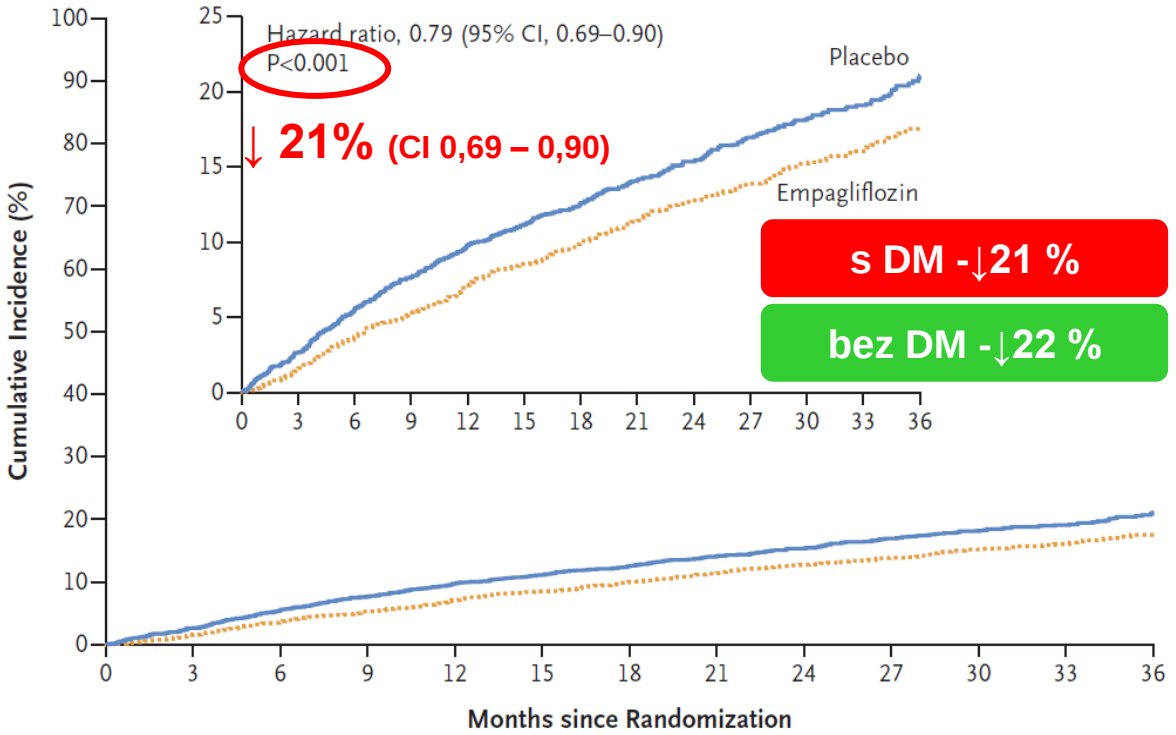
(5988 pt s HF s EF > 40% + s/bez DM, 26 měsíců)

**Hospitalizace HF + CV úmrtí**

**EF ~ 54%**
EF 41-49 … 33%
EF 50-59 … 34%
EF ≥ 60 ….. 33%

**ICHS … 35%**
**DM …... 49%**
**AH …… 90%**
**AF …… 50%**

### Primární kompozitní cíl



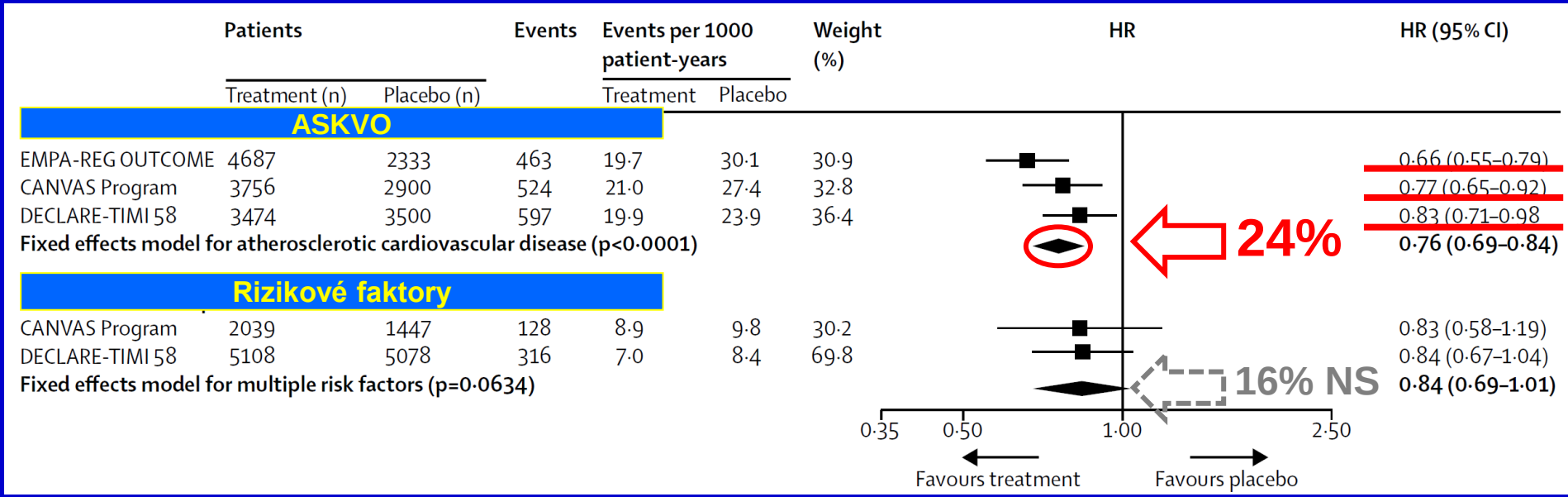

No. at Risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 |

Anker S.D. et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med, 2021 Oct 14; 385:1451-61.

# Gliflozíny u DM s ASKVO nebo RF

## Hospitalizace pro HF a KV úmrtí




**ASCVD**

**↓29 %**

**Hospitalizace pro HF**

**RF**

**↓36 %**

Zelniker TE et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019 Jan 5;393(10166):31-39.

# SGLT2i u HFrEF

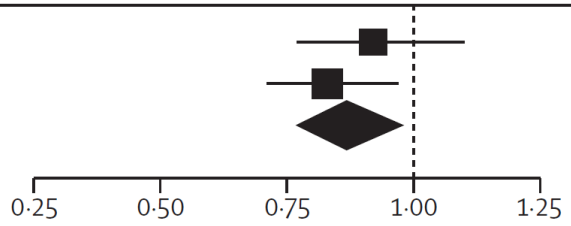
## Meta-analýza DAPA-HF a EMPEROR-reduced

### Úmrtí ze všech příčin

↓13% (CI 0,77 – 0,98)

| | Number with event/number of patients (%) | | HR (95% CI) |
|---|---|---|---|
| | SGLT2 inhibitor | Placebo | |
| EMPEROR-Reduced | 249/1863 (13·4%) | 266/1867 (14·2%) | 0·92 (0·77–1·10) |
| DAPA-HF | 276/2373 (11·6%) | 329/2371 (13·9%) | 0·83 (0·71–0·97) |
| **Total** | | | **0·87 (0·77–0·98)** |

Test for overall treatment effect p=0·018
Test for heterogeneity of effect p=0·39

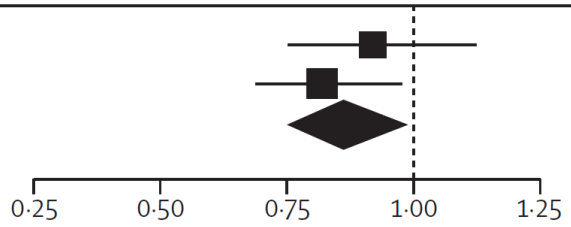



### Úmrtí z CV příčin

↓14% (CI 0,76 – 0,98)

| | Number with event/number of patients (%) | | HR (95% CI) |
|---|---|---|---|
| | SGLT2 inhibitor | Placebo | |
| EMPEROR-Reduced | 187/1863 (10·0%) | 202/1867 (10·8%) | 0·92 (0·75–1·12) |
| DAPA-HF | 227/2373 (9·6%) | 273/2371 (11·5%) | 0·82 (0·69–0·98) |
| **Total** | | | **0·86 (0·76–0·98)** |

Test for overall treatment effect p=0·027
Test for heterogeneity of effect p=0·40




**Efekt empagliflozinu a dapagliflozinu na hospitalizace pro HF byl konzistentní ve dvou nezávislých studiích a napovídá, že tyto léky také zlepšují renální cíle a redukují celkovou a KV mortalitu u pacientů s HF**

Zannad F et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet, 2020 Sep 19;396(10254):819-829.

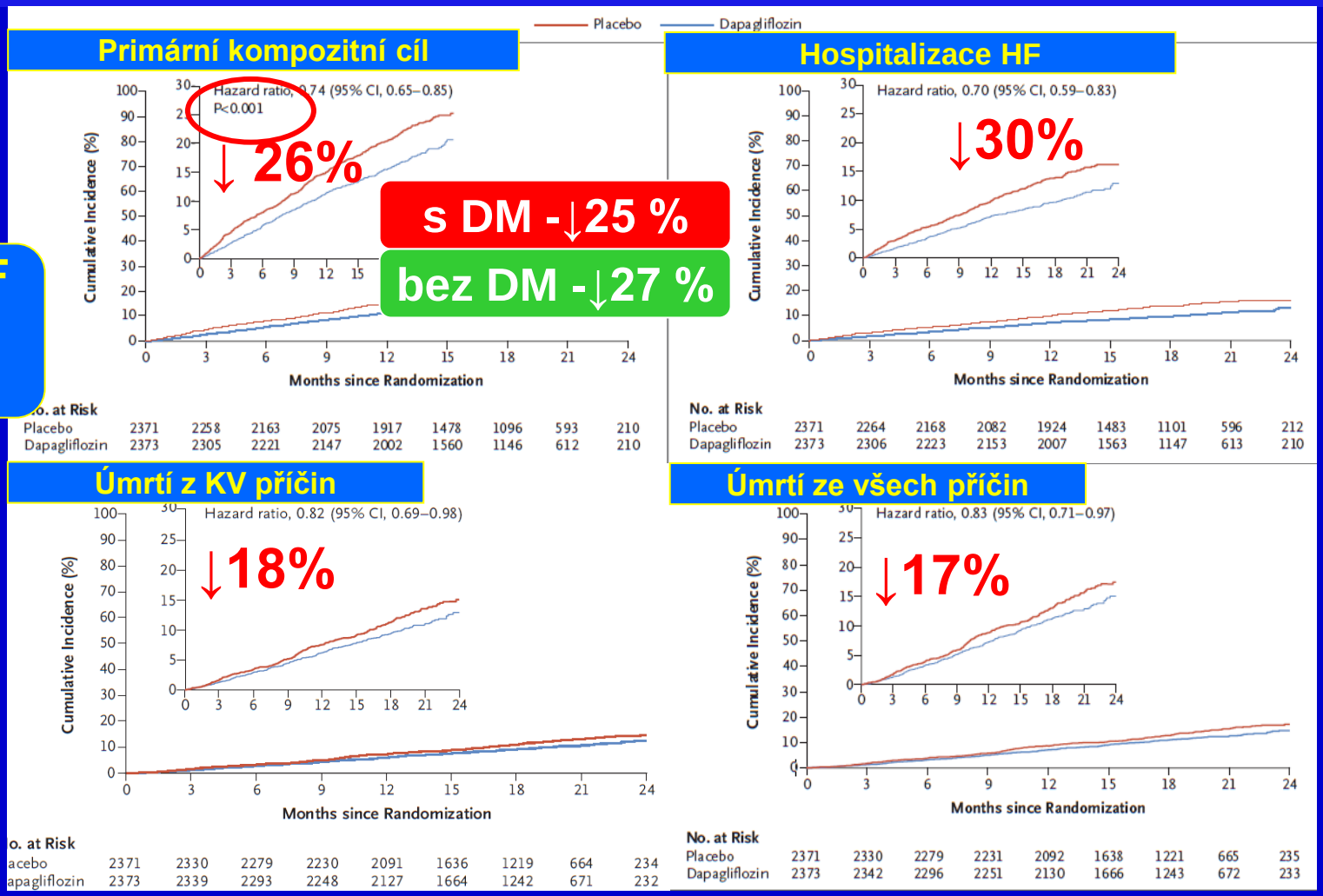
# SGLT2i u HFrEF

## Studie DAPA-HF (Dapa 10 mg x placebo)

(4744 pt s HF s EF < 40% + s/bez DM; medián 18 měsíců sledování)

**Zhoršení HF + CV úmrtí**

**DM 42% + 3% nových**




McMurray JJV et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

# SGLT2i u HFrEF

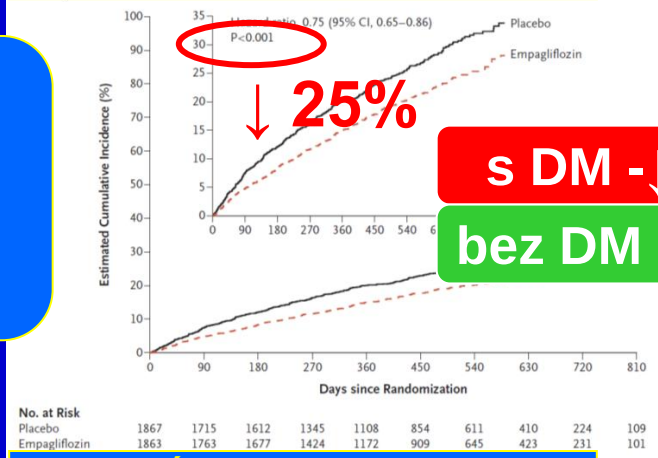
## Studie EMPEROR-reduced (Empa 10 mg x placebo)

(3730 pt s HF s EF < 40% + s/bez DM, 16 měsíců)

**Zhoršení HF + CV úmrtí**

**DM 50%**

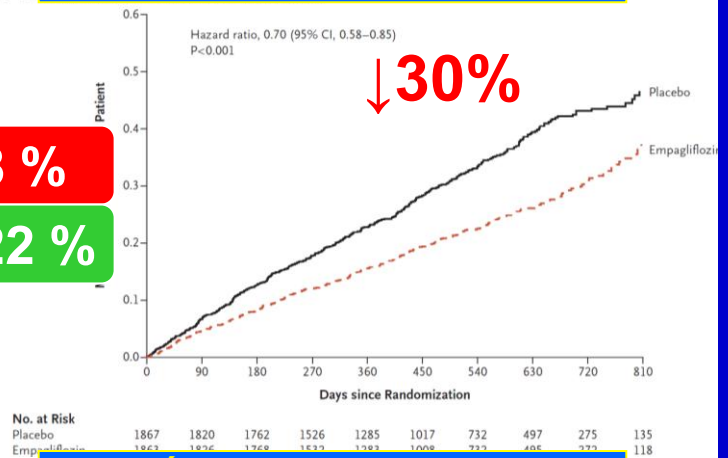
### Primární kompozitní cíl




**s DM -↓28 %**

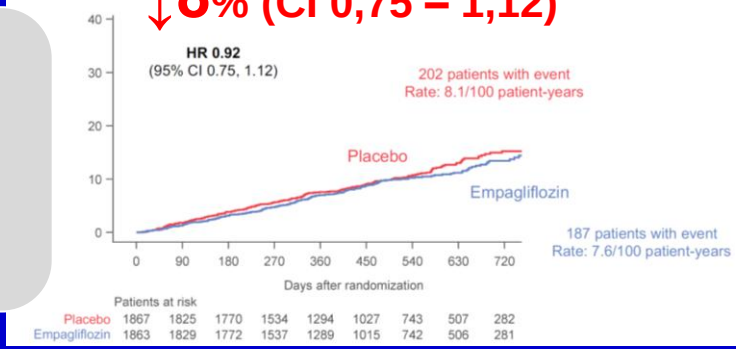
**bez DM -↓22 %**

### Hospitalizace HF




### Úmrtí z CV příčin

**↓8% (CI 0,75 – 1,12)**




### Úmrtí ze všech příčin

**↓8% (CI 0,77 – 1,10)**

**X**

Packer M. et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med, 2020 Oct 8;383(15):1413-1424.

# SGLT2i u HFpEF *(+ mrEF)*

## Studie EMPEROR-preserved (Empa 10 mg x placebo)

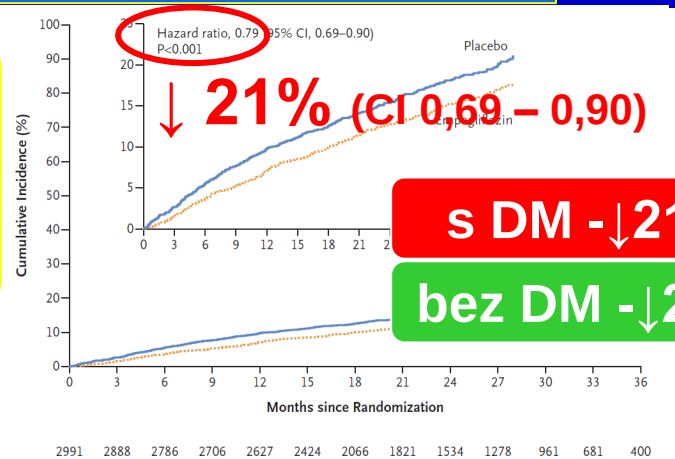
(5988 pt s HF s EF > 40% + s/bez DM, 26 měsíců)

**Hospitalizace HF + CV úmrtí**

**HFpEF + HFmrEF**
*EF ~ 54%*

**DM 49%**

### Primární kompozitní cíl

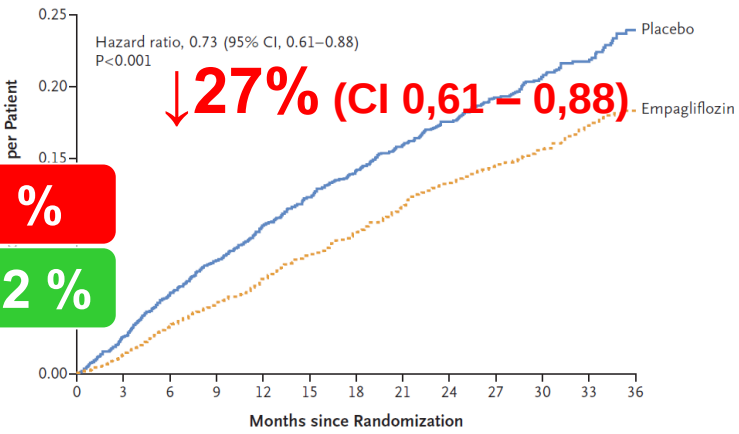



↓ 21% (CI 0,69 – 0,90)

s DM -↓21 %

bez DM -↓22 %

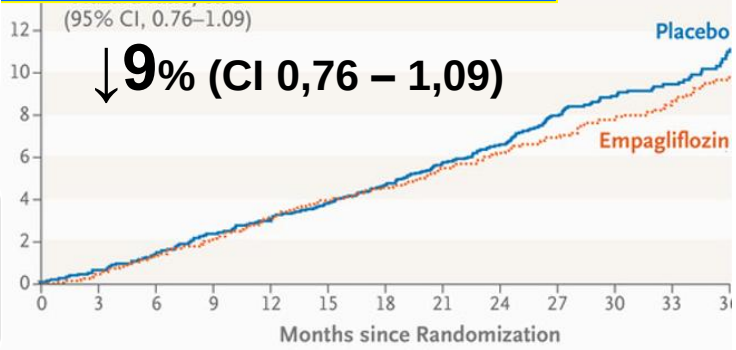
### Hospitalizace HF




↓27% (CI 0,61 – 0,88)

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

### Úmrtí z CV příčin




↓9% (CI 0,76 – 1,09)

### Úmrtí ze všech příčin

~ 0% (CI 0,87 – 1,15)

**X**

Anker S.D. et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med, 2021 Oct 14; 385:1451-61.

# SGLT2i u HFpEF *(+mrEF)*

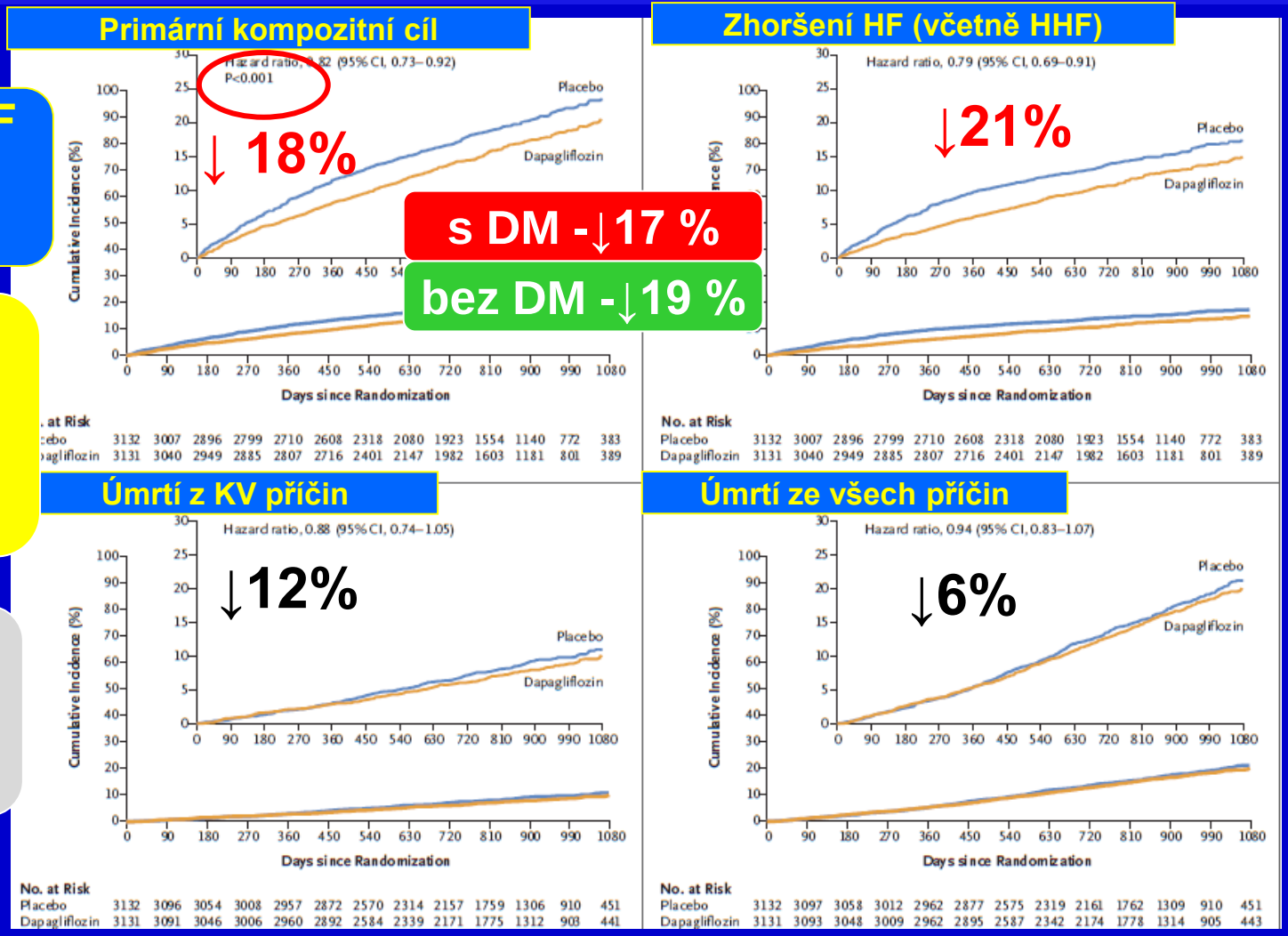
## Studie DELIVER (Dapa 10 mg x placebo)

(6263 pt s HF s EF > 40% + s/bez DM; medián 2,3 roků)

**Zhoršení HF + CV úmrtí**

**HFpEF + HFmrEF**
*EF ~ 54%*

**DM 45%**




Solomon SD et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med 2022;387:1089-98.

# CKD x HF efekt SGLT2i u HF či no HF

## Studie DAPA-CKD (Dapa 10 mg x placebo)

(4304 pt, GFR 25-75 ml/min)

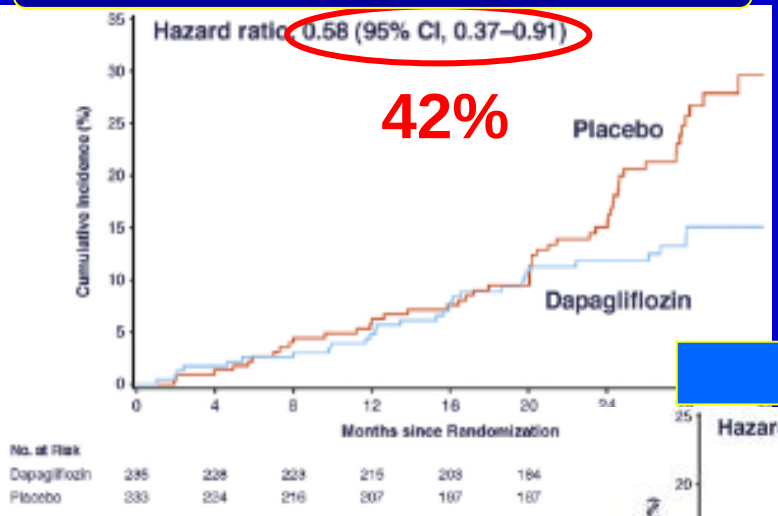
**Primární kompozitní cíl**

**ESKD + ↓50% GFR + KV a renální úmrtí**

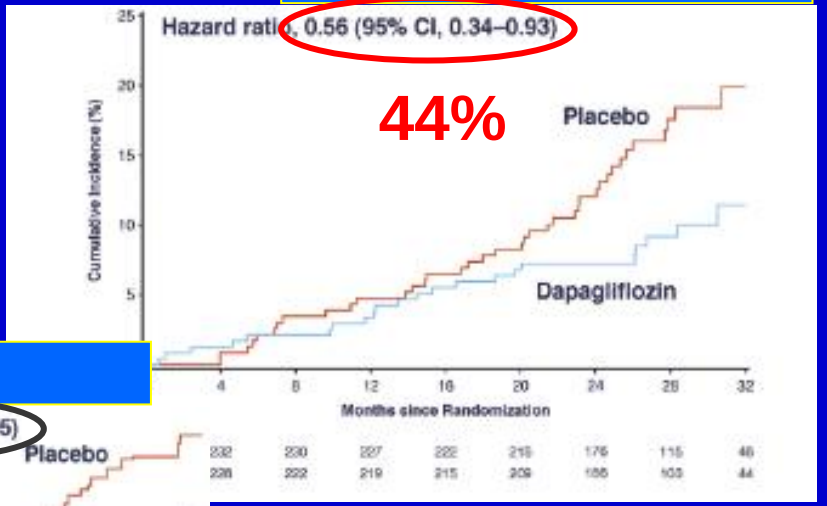
**HF ~ 11%**

**DM 77%**

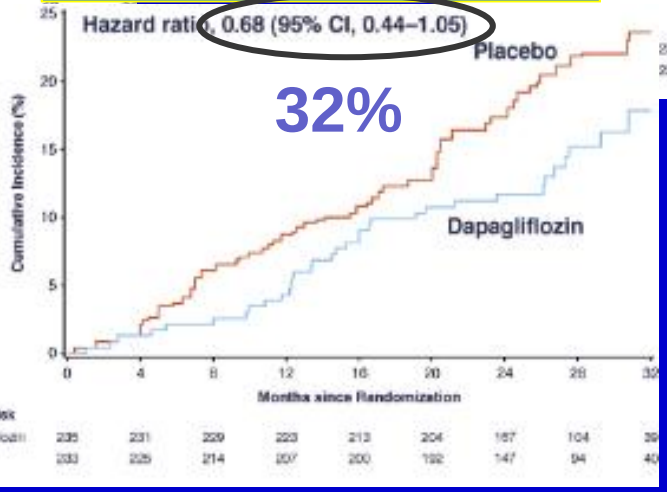
**GFR ~ 43 ml/min**




**Úmrtní ze všech příčin**




**CV úmrtí + HHF**




**Renálně specifický komp. cíl**

**ESKD + ↓50% GFR + renální úmrtí**

**↓ 55%**

**0.45 (0.23 to 0.87)**

**HHF**

**Hospitalizace pro srdeční selhání**

**↓ 38%**

**0.62 (0.35–1.10)**

McMUrray JJV et al. Effects of Dapagliflozin in Patients With Kidney Disease, With and Without Heart Failure. JACC Heart Fail. 2021 Nov;9(11):807-820.