# SGLT2 INHIBITORS

June 15, 2022

Kelley R. Branch, MD, MSc
Nayan Arora, MD
UW Cardiometabolic ECHO

University of Washington
Cardiometabolic
ECHO

# Objectives

- Describe SGLT2I for 2 diabetes in terms of mechanism of action, efficacy, side effects, CV/renal disease benefit, and use in liver/NASH
- Discuss side-effect profile and risk with patient
- Translate to use in patients with renal disease, heart failure and CV disease

# Disclosures

- Dr. Kelley Branchhas research grants from the NIH, Population Health Research Institute, Bayer, Sanofi, Eli Lilly, Kestra, & Medic One Foundation. Consulting fees from Bayer, Janssen, Amgen, Sana, Kestra, & Hanmi.

- Dr. Nayan Arora has no disclosures.

# Cardiovascular complications are the main cause of mortality in diabetes

Patients with microvascular complications due to T2D are more likely to have a major CV event[1]

Hyperglycaemia has a causal effect on the risk of major CV events[2]

Chronic hyperglycaemia is associated with low-grade inflammation and accelerated atherosclerosis[3]

## Brain

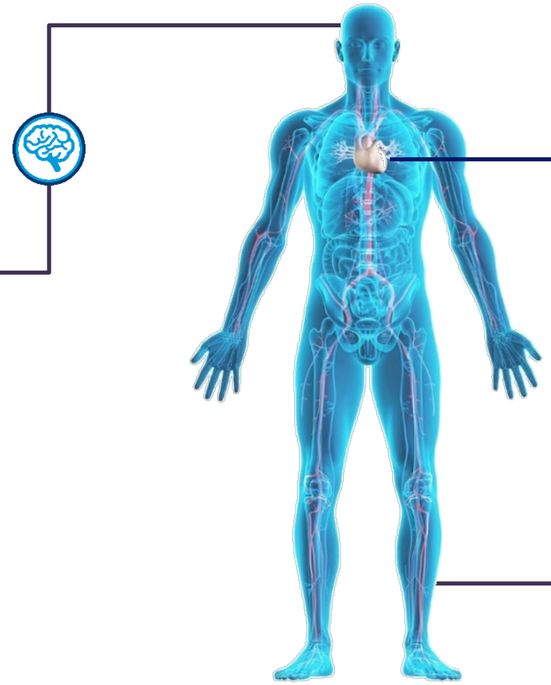
**4x**

Higher risk of coronary artery disease and stroke

For every 1% increase in

$HbA_{1c}$, the risk of stroke

is increased by up to **30%** [5]



## Heart

**2/3**

Of deaths in T2D are attributable to CV disease [7]

2-6x higher risk of mortality from CV events [8]

**2.5x**

Higher risk of developing congestive heart failure [9]

## PAD

**1/3**

of patients with T2D over 50 years of age have PAD.
This increases the risk of heart attack and stroke [6]

*Adapted from American Association of Clinical Endocrinology (AACE)*

# Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

**Currently available :**

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro )

**Not available :**

- Sotogliflozin (Zynquista ) – *SGLT2/SGLT1*
- Ipragliflozin
- Luseogliflozin
- Tofogliflozin

# SGLT2 inhibitors: Physiologic Actions

- Selectively blocks SGLT2 transporter responsible >90% of nephron glucose reabsorption
- ↓glucose and sodium absorption -> glycosuria, natriuresis.
- ↑ Hyperglycemia = ↑ glycosuria
- Minimal risk of hypoglycemia as SGLT2i action is independent of insulin

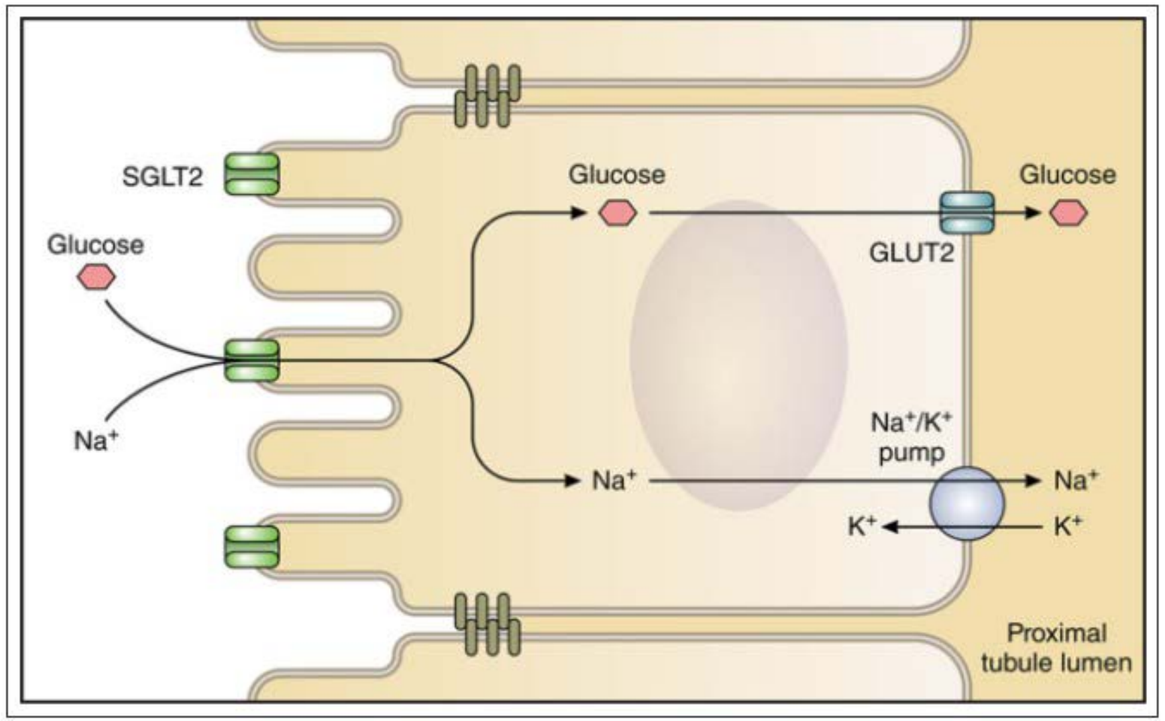



**Figure 1. The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule.** Modified from Bakris et al[4] with permission of the publisher. Copyright © 2009, Elsevier.

*Adapted from American Association of Clinical Endocrinology (AACE). Heerspink HJL. Circulation. 2016;134:752 –772*

# SGLT2 inhibitors

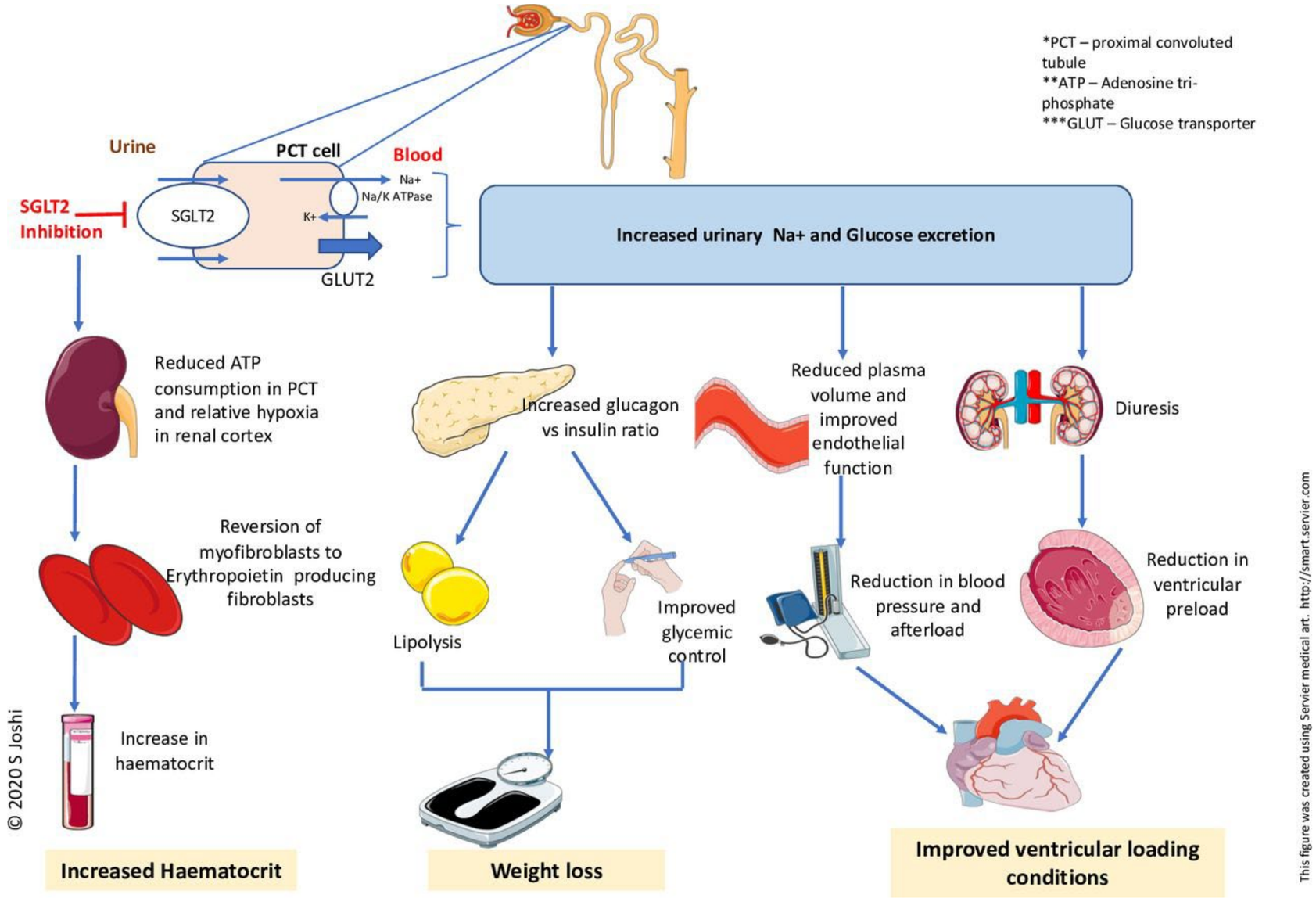
## Mechanisms for Cardioprotection

- Reduce preload (↓hypertension) and afterload (↓central venous pressure)
- Improved anti-inflammatory vs. pro-inflammatory cytokine
- Reduced cardiac fibrosis
- Increased hematocrit, erythropoietin production
- Improved cardiac metabolic efficiency

## Mechanisms for Renoprotection

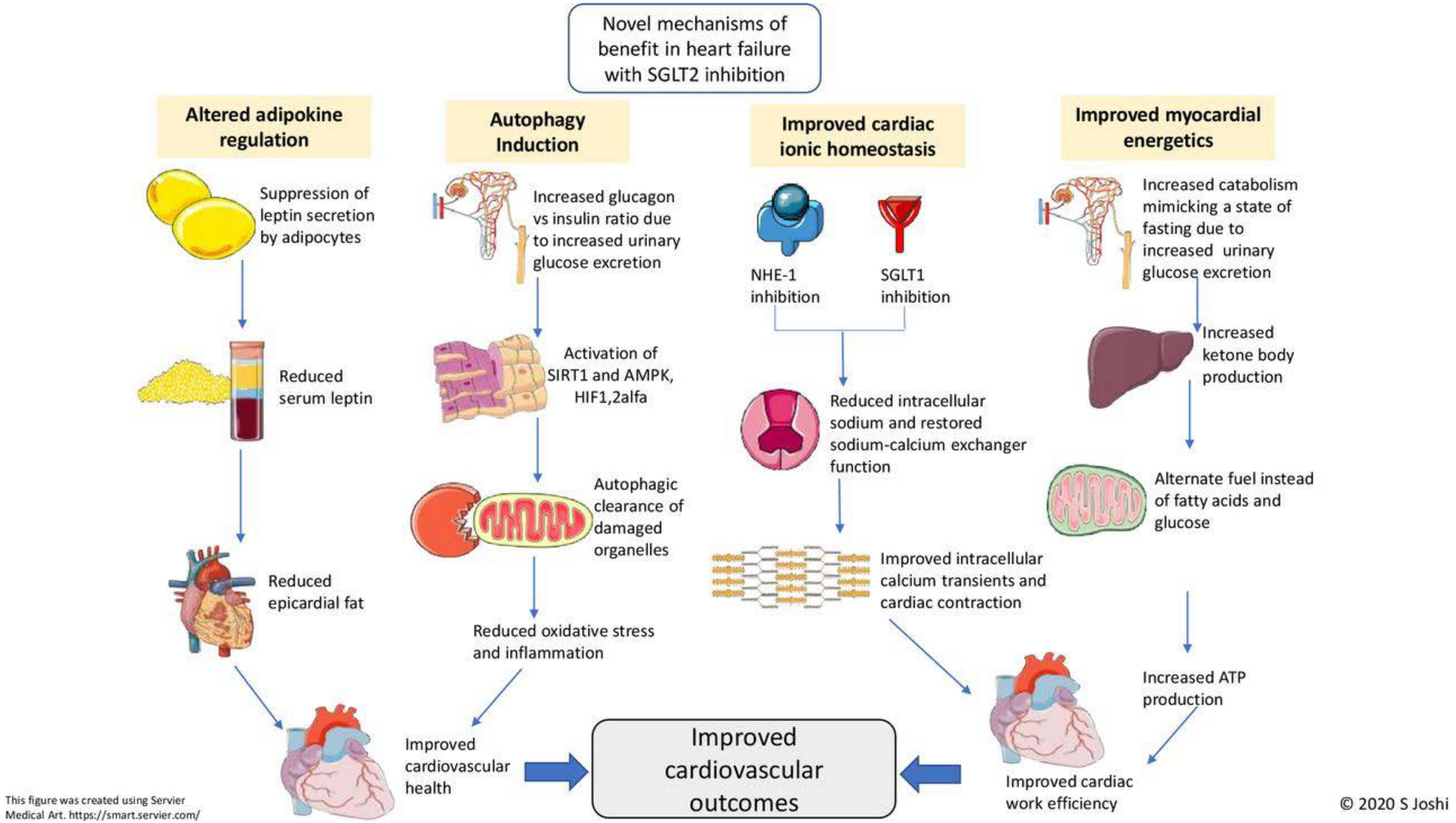
- Glycosuria
- Natriuresis
- Decreased glomerular pressure
- Reduced albuminuria

# Benefits of SGLT2inhibitors



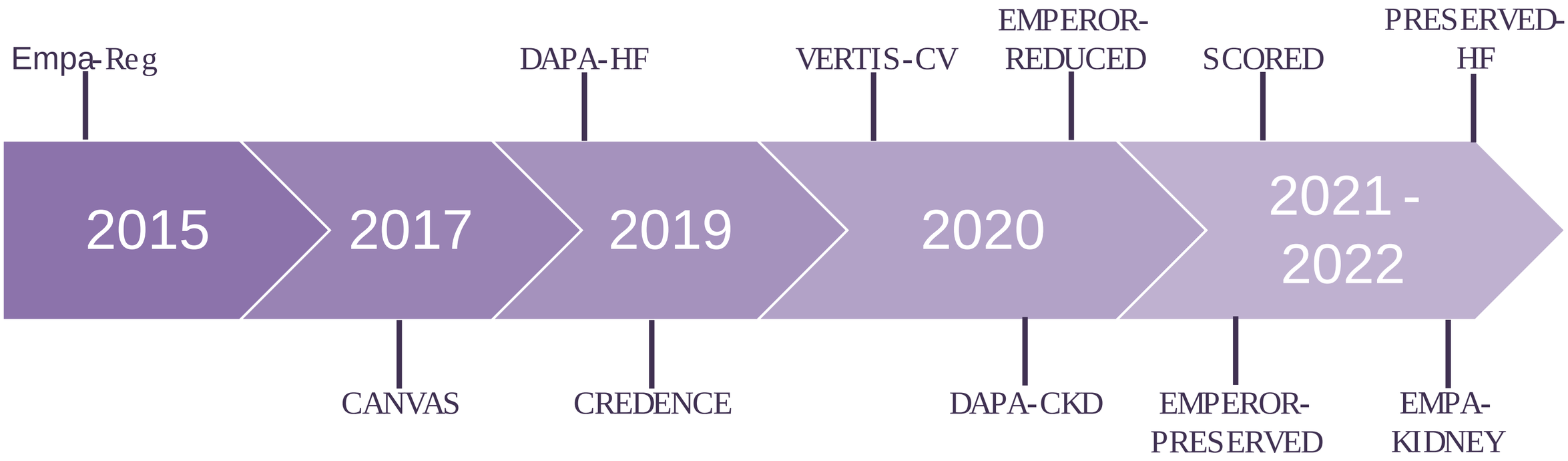

*Joshi SS, et al. Heart 2021;107:1032-1038.*

# Benefits of SGLT2inhibitors




*Adapted from Joshi SS, et al. Heart 2021;107:1032-1038.*

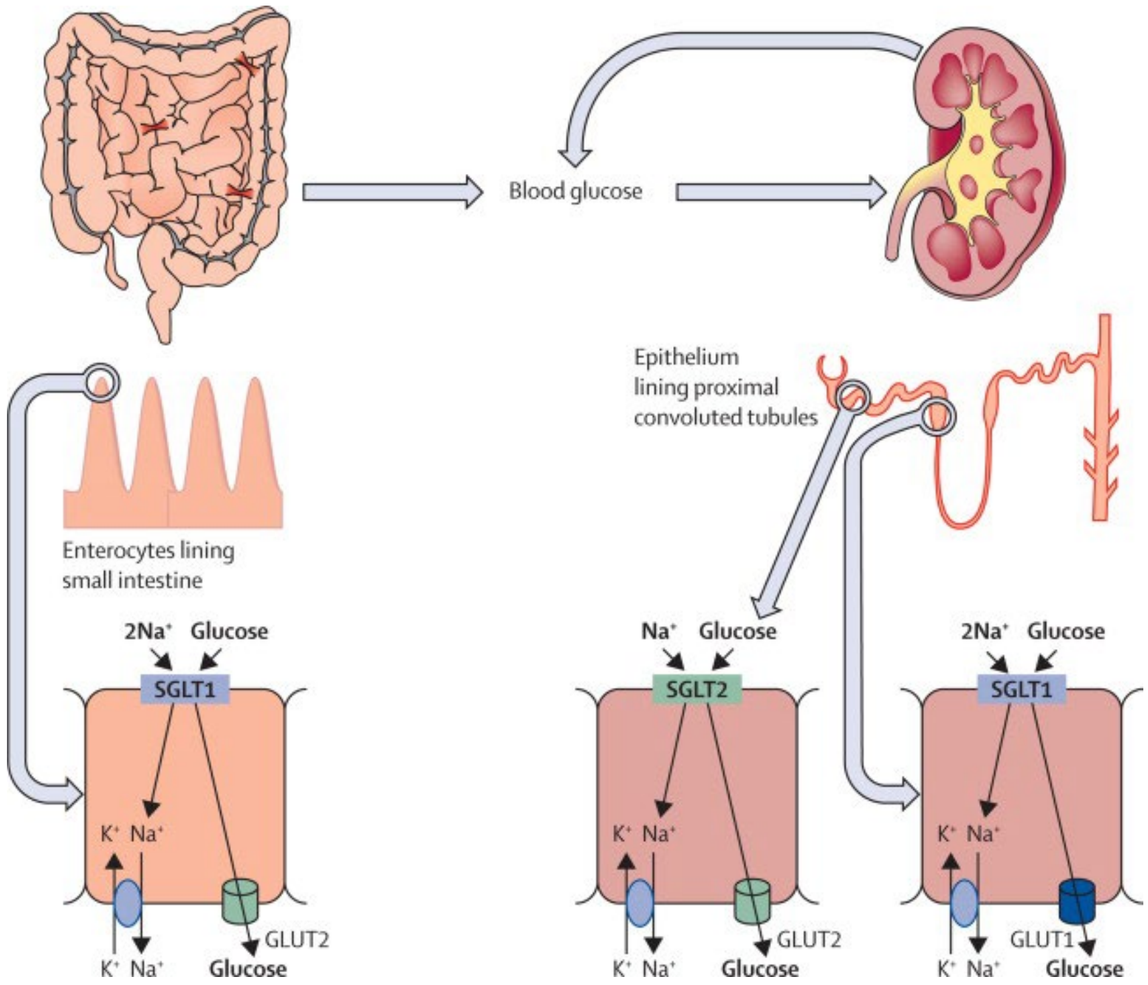
# SGLT2 Inhibitor Trials



# SGLT2 & SGLT1 – Additive Benefits?

- SGLT1 absorbs glucose in small intestine, contributes to reabsorption of nephrotic glucose
- All SGLT2i are selective blockers– *some SGLT1i antagonism*

| Molecule | SGLT2 (IC50 nM) | SGLT1 (IC50 nM) | SGLT2 selectivity over SGLT1 |
|---|---|---|---|
| Empagliflozin | 3.10 | 8,300 | ~2,500 – fold |
| Ertugliflozin | 0.87 | 1,960 | ~2,000 – fold |
| Dapagliflozin | 1.20 | 1,400 | ~1,200 – fold |
| Canagliflozin | 2.70 | 710 | ~250 – fold |
| Sotagliflozin | 1.80 | 36 | ~20 – fold |

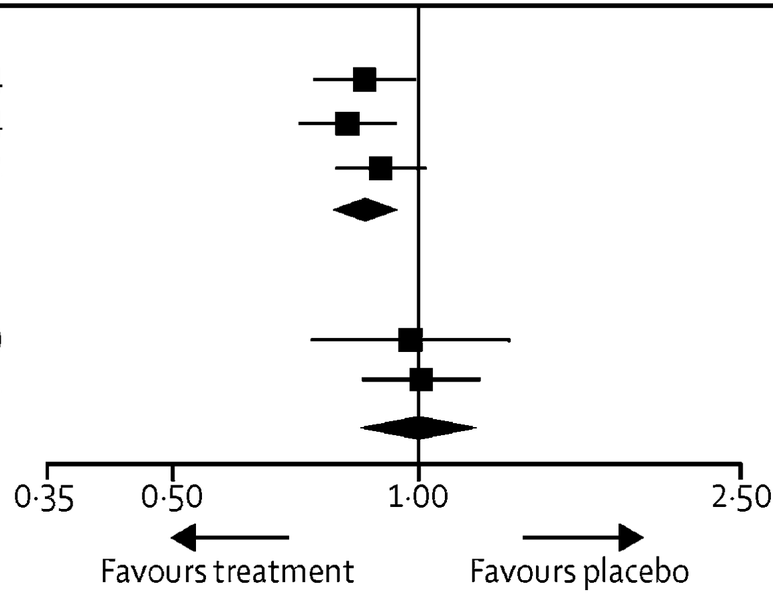



*Tahrani AA, et al. Lancet Diab Endocrin 201;1:140 -51. Cinti F, et al. Drug Design Devel Therapy 2019;11:2095 -19.*

# SGLT2 Inhibitors: Outcome Trials

## Major Adverse Cardiovascular Events

| | Patients | | | Events | Events per 1000 patient-years | | Weight (%) | HR | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | Treatment (n) | | Placebo (n) | | Treatment | Placebo | | | |
| **Patients with atherosclerotic cardiovascular disease** | | | | | | | | | |
| EMPA-REG OUTCOME | 4687 | Empa | 2333 | 772 | 37·4 | 43·9 | 29·4 | | 0·86 (0·74–0·99) |
| CANVAS Program | 3756 | Cana | 2900 | 796 | 34·1 | 41·3 | 32·4 | | 0·82 (0·72–0·95) |
| DECLARE-TIMI 58 | 3474 | Dapa | 3500 | 1020 | 36·8 | 41·0 | 38·2 | | 0·90 (0·79–1·02) |
| **Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)** | | | | | | | | | **0·86 (0·80–0·93)** |
| **Patients with multiple risk factors** | | | | | | | | | |
| CANVAS Program | 2039 | Cana | 1447 | 215 | 15·8 | 15·5 | 25·9 | | 0·98 (0·74–1·30) |
| DECLARE-TIMI 58 | 5108 | Dapa | 5078 | 539 | 13·4 | 13·3 | 74·1 | | 1·01 (0·86–1·20) |
| **Fixed effects model for multiple risk factors (p=0·98)** | | | | | | | | | **1·00 (0·87–1·16)** |



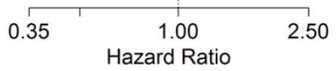

*Zelniker TA, et al. Lancet 2018;393:31-39.*

# SGLT2 Inhibitors: Outcome Trials

## MACE Components

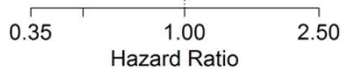
### MI

| | Patients | Events | Treatment Events per 1000 pt-yrs | Placebo Events per 1000 pt-yrs | Weights (%) | HR [95% CI] |
|---|---|---|---|---|---|---|
| EMPA-REG OUTCOME | 7020 | 349 | 16.8 | 19.3 | 20.5 | 0.87 [0.70, 1.09] |
| CANVAS Program | 10142 | 421 | 11.2 | 12.6 | 25.0 | 0.89 [0.73, 1.09] |
| DECLARE-TIMI 58 | 17160 | 834 | 11.7 | 13.2 | 54.5 | 0.89 [0.77, 1.01] |
| **FE Model (P-value = 0.0177)** | | | | | | **0.89 [0.80, 0.98]** |



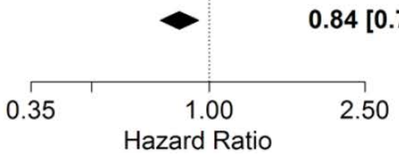

### Stroke

| | Patients | Events | Treatment Events per 1000 pt-yrs | Placebo Events per 1000 pt-yrs | Weights (%) | HR [95% CI] |
|---|---|---|---|---|---|---|
| EMPA-REG OUTCOME | 7020 | 233 | 12.3 | 10.5 | 19.2 | 1.18 [0.89, 1.56] |
| CANVAS Program | 10142 | 309 | 7.9 | 9.6 | 29.0 | 0.87 [0.69, 1.09] |
| DECLARE-TIMI 58 | 17160 | 518 | 7.5 | 7.8 | 51.8 | 0.96 [0.81, 1.14] |
| **FE Model (P-value = 0.64)** | | | | | | **0.97 [0.86, 1.10]** |




### CVD

| | Patients | Events | Treatment Events per 1000 pt-yrs | Placebo Events per 1000 pt-yrs | Weights (%) | HR [95% CI] |
|---|---|---|---|---|---|---|
| EMPA-REG OUTCOME | 7020 | 309 | 12.4 | 20.2 | 25.1 | 0.62 [0.49, 0.77] |
| CANVAS Program | 10142 | 453 | 11.6 | 12.8 | 34.3 | 0.87 [0.72, 1.06] |
| DECLARE-TIMI 58 | 17160 | 494 | 7.0 | 7.1 | 40.6 | 0.98 [0.82, 1.17] |
| **FE Model (P-value = 0.0023)** | | | | | | **0.84 [0.75, 0.94]** |

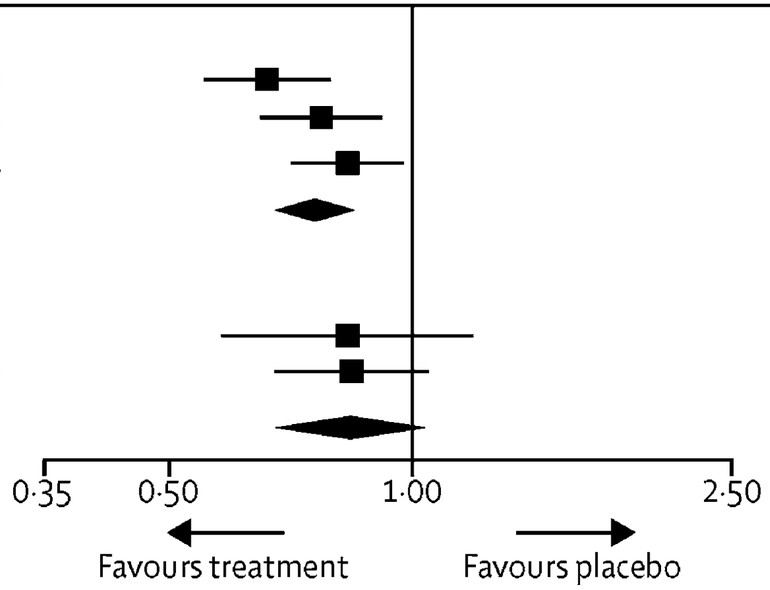



*Zelniker TA, et al. Lancet 2018;393:31-39.*

# SGLT2 Inhibitors: Outcome Trials

## Hospitalization for Heart Failure and CV Death

| | Patients | | | Events | Events per 1000 patient-years | | Weight (%) | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Treatment (n) | | Placebo (n) | | Treatment | Placebo | | |
| **Patients with atherosclerotic cardiovascular disease** | | | | | | | | |
| EMPA-REG OUTCOME | 4687 | Empa | 2333 | 463 | 19·7 | 30·1 | 30·9 | 0·66 (0·55–0·79) |
| CANVAS Program | 3756 | Cana | 2900 | 524 | 21·0 | 27·4 | 32·8 | 0·77 (0·65–0·92) |
| DECLARE-TIMI 58 | 3474 | Dapa | 3500 | 597 | 19·9 | 23·9 | 36·4 | 0·83 (0·71–0·98 |
| **Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)** | | | | | | | | **0·76 (0·69–0·84)** |
| **Patients with multiple risk factors** | | | | | | | | |
| CANVAS Program | 2039 | Cana | 1447 | 128 | 8·9 | 9·8 | 30·2 | 0·83 (0·58–1·19) |
| DECLARE-TIMI 58 | 5108 | Dapa | 5078 | 316 | 7·0 | 8·4 | 69·8 | 0·84 (0·67–1·04) |
| **Fixed effects model for multiple risk factors (p=0·0634)** | | | | | | | | **0·84 (0·69–1·01)** |




*Zelniker TA, et al. Lancet 2018;393:31-39.*

# SGLT2i: Improves major cardiac events, especially hospitalization from heart failure

## How about patients with heart failure?

***Preserved and reduced LV ejection fraction?***

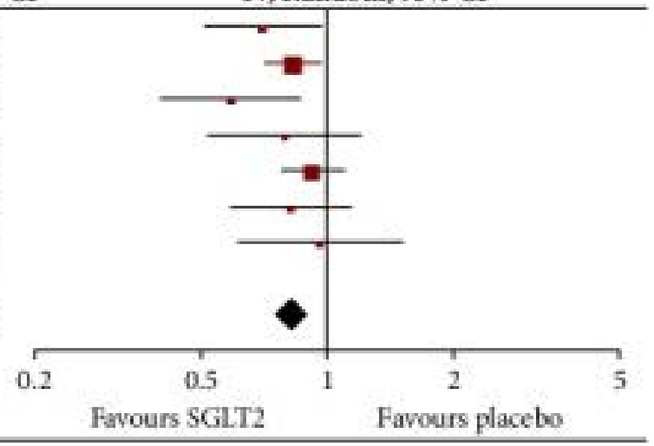
# SGLT2 Inhibitors: Outcome Trials with HF

## All Cause Mortality

| Study or Subgroup | | log[Hazard Ratio] | SE | SGL T2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| CANVAS | Cana | -0.3567 | 0.1616 | 803 | 658 | 9.1% | 0.70 [0.51, 0.96] |
| DAPA-HF | Dapa | -0.1863 | 0.0797 | 2373 | 2371 | 37.6% | 0.83 [0.71, 0.97] |
| DECLARE-TIMI 58 | Dapa | -0.5276 | 0.1983 | 318 | 353 | 6.1% | 0.59 [0.40, 0.87] |
| EMPAREG | Empa | -0.2357 | 0.2134 | 462 | 244 | 5.2% | 0.79 [0.52, 1.20] |
| EMPEROR-REDUCED | Empa | -0.0834 | 0.0908 | 1863 | 1867 | 29.0% | 0.92 [0.77, 1.10] |
| SOLOIST-WHF | Soto | -0.1985 | 0.168 | 608 | 614 | 8.5% | 0.82 [0.59, 1.14] |
| VERTIS CV | Ertu | -0.0408 | 0.2314 | 319 | 159 | 4.5% | 0.96 [0.61, 1.51] |
| **Total (95% CI)** | | | | **6746** | **6266** | **100.0%** | **0.83 [0.75, 0.91]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.81$, $df = 6$ ($P = 0.45$); $I^2 = 0\%$

Test for overall effect: $Z = 3.89$ ($P = 0.0001$)




*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

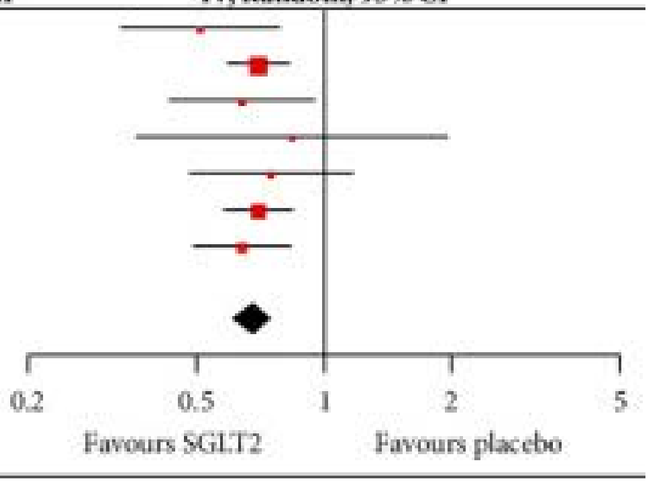
# SGLT2 Inhibitors: Outcome Trials with HF

## Heart Failure Hospitalization

| Study or Subgroup | | log[Hazard Ratio] | SE | SGL T2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| CANVAS | Cana | -0.6733 | 0.2221 | 803 | 658 | 5.6% | 0.51 [0.33, 0.79] |
| DAPA-HF | Dapa | -0.3567 | 0.0872 | 2373 | 2371 | 36.2% | 0.70 [0.59, 0.83] |
| DECLARE-TIMI 58 | Dapa | -0.4463 | 0.2029 | 318 | 353 | 6.7% | 0.64 [0.43, 0.95] |
| DEFINE-HF | Empa | -0.1744 | 0.4323 | 131 | 132 | 1.5% | 0.84 [0.36, 1.96] |
| EMPAREG | Empa | -0.2877 | 0.2277 | 462 | 244 | 5.3% | 0.75 [0.48, 1.17] |
| EMPEROR-REDUCED | Empa | -0.3567 | 0.0959 | 1863 | 1867 | 29.9% | 0.70 [0.58, 0.84] |
| SOLOIST-WHF | Soto | -0.4463 | 0.1363 | 608 | 614 | 14.8% | 0.64 [0.49, 0.84] |
| **Total (95% CI)** | | | | **6558** | **6239** | **100.0%** | **0.68 [0.61, 0.75]** |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.59$, df = 6 (P = 0.86); $I^2 = 0\%$

Test for overall effect: Z = 7.38 (P < 0.0001)

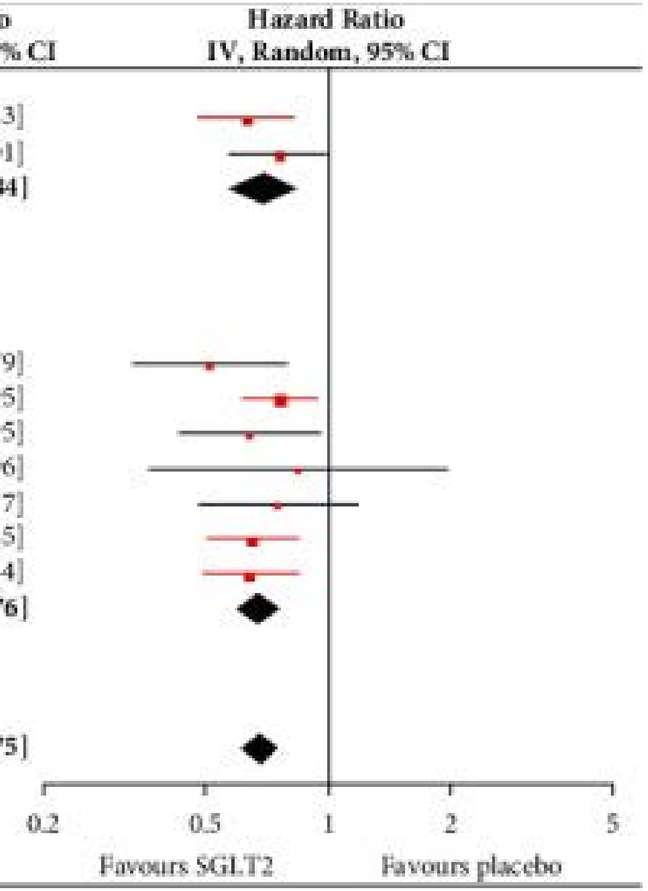



*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

# SGLT2 Inhibitors: Outcome Trials with HF

## Heart Failure Hospitalization by Diabetic Status

| Study or Subgroup | | log[Hazard Ratio] | SE | SGLT2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **Hospitalisation for Heart Failure - Non Diabetic Population** | | | | | | | |
| DAPA-HF | Dapa | -0.462 | 0.1387 | 1298 | 1307 | 14.6% | 0.63 [0.48, 0.83] |
| EMPEROR-REDUCED | Empa | -0.2744 | 0.1468 | 936 | 938 | 13.0% | 0.76 [0.57, 1.01] |
| **Subtotal (95% CI)** | | | | **2234** | **2245** | **27.6%** | **0.69 [0.56, 0.84]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.86$, df = 1 (P = 0.35); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 3.70 (P = 0.0002) | | | | | | | |
| **Hospitalisation for Heart Failure - Diabetic Population** | | | | | | | |
| CANVAS | Cana | -0.6733 | 0.2221 | 803 | 658 | 5.7% | 0.51 [0.33, 0.79] |
| DAPA-HF | Dapa | -0.2744 | 0.1122 | 1075 | 1064 | 22.3% | 0.76 [0.61, 0.95] |
| DECLARE-TIMI 58 | Dapa | -0.4463 | 0.2029 | 318 | 353 | 6.8% | 0.64 [0.43, 0.95] |
| DEFINE-HF | Empa | -0.1744 | 0.4323 | 131 | 132 | 1.5% | 0.84 [0.36, 1.96] |
| EMPAREG | Empa | -0.2877 | 0.2277 | 462 | 244 | 5.4% | 0.75 [0.48, 1.17] |
| EMPEROR-REDUCED | Empa | -0.4308 | 0.1339 | 927 | 929 | 15.6% | 0.65 [0.50, 0.85] |
| SOLOIST-WHF | Soto | -0.4463 | 0.1363 | 608 | 614 | 15.1% | 0.64 [0.49, 0.84] |
| **Subtotal (95% CI)** | | | | **4324** | **3994** | **72.4%** | **0.68 [0.60, 0.76]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.48$, df = 6 (P = 0.75); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 6.27 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | | | | **6558** | **6239** | **100.0%** | **0.68 [0.61, 0.75]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 8 (P = 0.82); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 7.28 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.89), $I^2 = 0\%$ | | | | | | | |

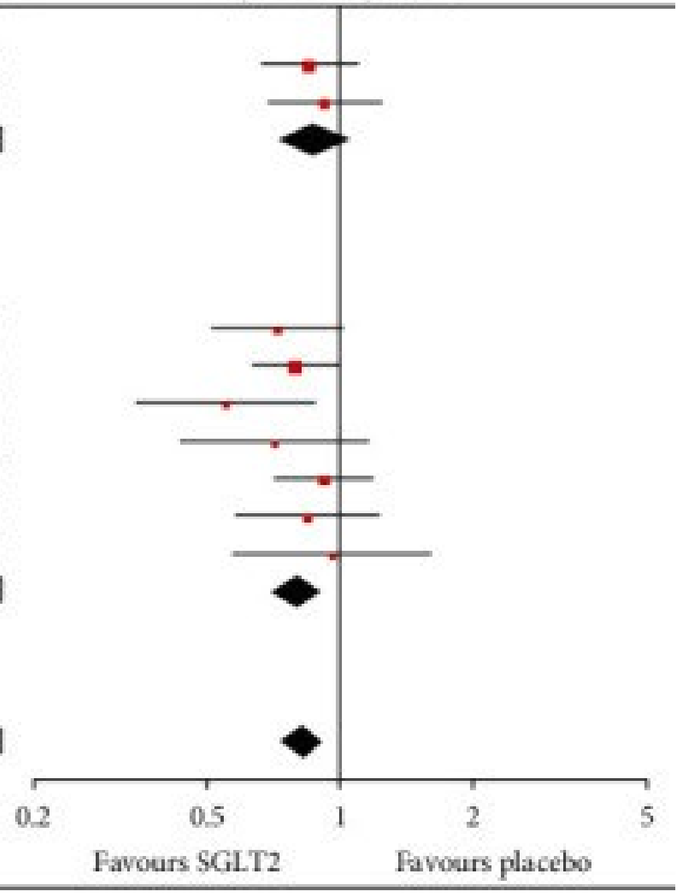



*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

# SGLT2 Inhibitors: Outcome Trials with HF

## CV Death by Diabetic Status

| Study or Subgroup | | log[Hazard Ratio] | SE | SGLT2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **Cardiovascular Death - Non Diabetic Population** | | | | | | | |
| DAPA-HF | Dapa | -0.1625 | 0.1291 | 1298 | 1307 | 17.6% | 0.85 [0.66, 1.09] |
| EMPEROR-REDUCED | Empa | -0.0834 | 0.1542 | 936 | 938 | 12.3% | 0.92 [0.68, 1.24] |
| **Subtotal (95% CI)** | | | | **2234** | **2245** | **30.0%** | **0.88 [0.72, 1.07]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.15$, df = 1 (P = 0.69); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 1.31 (P = 0.19) | | | | | | | |
| **Cardiovascular Death - Diabetic Population** | | | | | | | |
| CANVAS | Cana | -0.3285 | 0.1759 | 803 | 658 | 9.5% | 0.72 [0.51, 1.02] |
| DAPA-HF | Dapa | -0.2357 | 0.1155 | 1075 | 1064 | 22.0% | 0.79 [0.63, 0.99] |
| DECLARE-TIMI 58 | Dapa | -0.5978 | 0.2454 | 318 | 353 | 4.9% | 0.55 [0.34, 0.89] |
| EMPAREG | Empa | -0.3425 | 0.2559 | 462 | 244 | 4.5% | 0.71 [0.43, 1.17] |
| EMPEROR-REDUCED | Empa | -0.0834 | 0.1322 | 927 | 929 | 16.8% | 0.92 [0.71, 1.19] |
| SOLOIST-WHF | Soto | -0.1744 | 0.189 | 608 | 614 | 8.2% | 0.84 [0.58, 1.22] |
| VERTIS CV | Ertu | -0.0408 | 0.266 | 319 | 159 | 4.1% | 0.96 [0.57, 1.62] |
| **Subtotal (95% CI)** | | | | **4512** | **4021** | **70.0%** | **0.80 [0.70, 0.91]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.57$, df = 6 (P = 0.60); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 3.48 (P = 0.0005) | | | | | | | |
| **Total (95% CI)** | | | | **6746** | **6266** | **100.0%** | **0.82 [0.74, 0.91]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.37$, df = 8 (P = 0.72); $I^2 = 0\%$ | | | | | | | |
| Test for overall effect: Z = 3.63 (P = 0.0003) | | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.65$, df = 1 (P = 0.42). $I^2 = 0\%$ | | | | | | | |

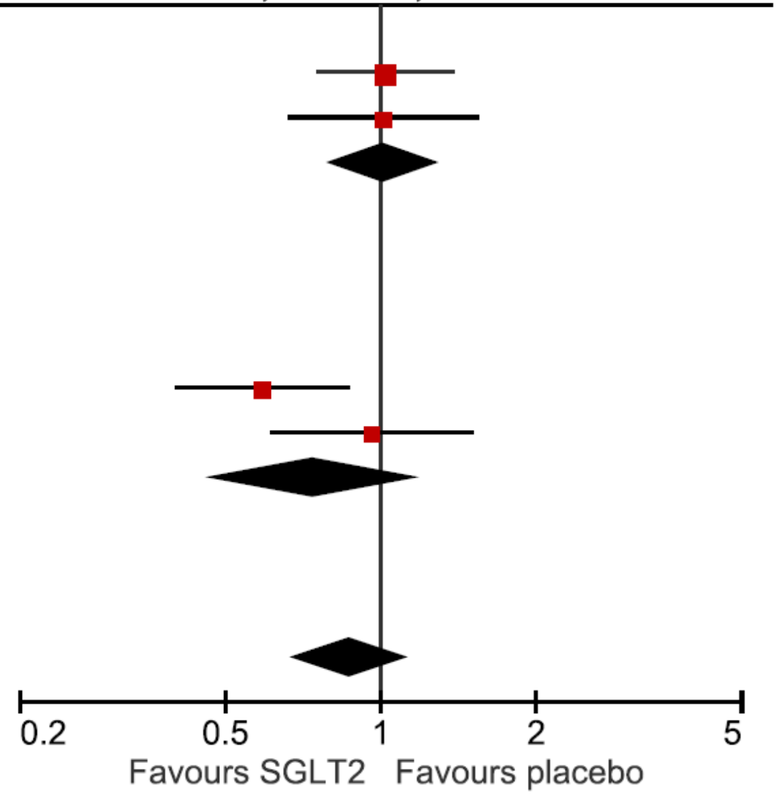



*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

# SGLT2 Inhibitors & HF: Outcome Trials

## All Cause Mortality by HF Type

| Study or Subgroup | log[Hazard Ratio] | SE | SGLT2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **All cause mortality - HFpEF** | | | | | | |
| DECLARE-TIMI 58 Dapa | 0.0198 | 0.1569 | 84 | 81 | 31.5% | 1.02 [0.75, 1.39] |
| VERTIS CV Ertu | 0.01 | 0.2171 | 63 | 30 | 22.6% | 1.01 [0.66, 1.55] |
| **Subtotal (95% CI)** | | | **147** | **111** | **54.1%** | **1.02 [0.79, 1.30]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0% | | | | | | |
| Test for overall effect: Z = 0.13 (P = 0.90) | | | | | | |
| **All cause mortality - HFrEF** | | | | | | |
| DECLARE-TIMI 58 Dapa | -0.5276 | 0.1983 | 38 | 68 | 25.0% | 0.59 [0.40, 0.87] |
| VERTIS CV Ertu | -0.0408 | 0.2314 | 54 | 27 | 20.9% | 0.96 [0.61, 1.51] |
| **Subtotal (95% CI)** | | | **92** | **95** | **45.9%** | **0.74 [0.46, 1.19]** |
| Heterogeneity: Tau² = 0.07; Chi² = 2.55, df = 1 (P = 0.11); I² = 61% | | | | | | |
| Test for overall effect: Z = 1.23 (P = 0.22) | | | | | | |
| **Total (95% CI)** | | | **239** | **206** | **100.0%** | **0.88 [0.67, 1.14]** |
| Heterogeneity: Tau² = 0.03; Chi² = 5.49, df = 3 (P = 0.14); I² = 45% | | | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | | | |
| Test for subgroup differences: Chi² = 1.32, df = 1 (P = 0.25), I² = 24.3% | | | | | | |

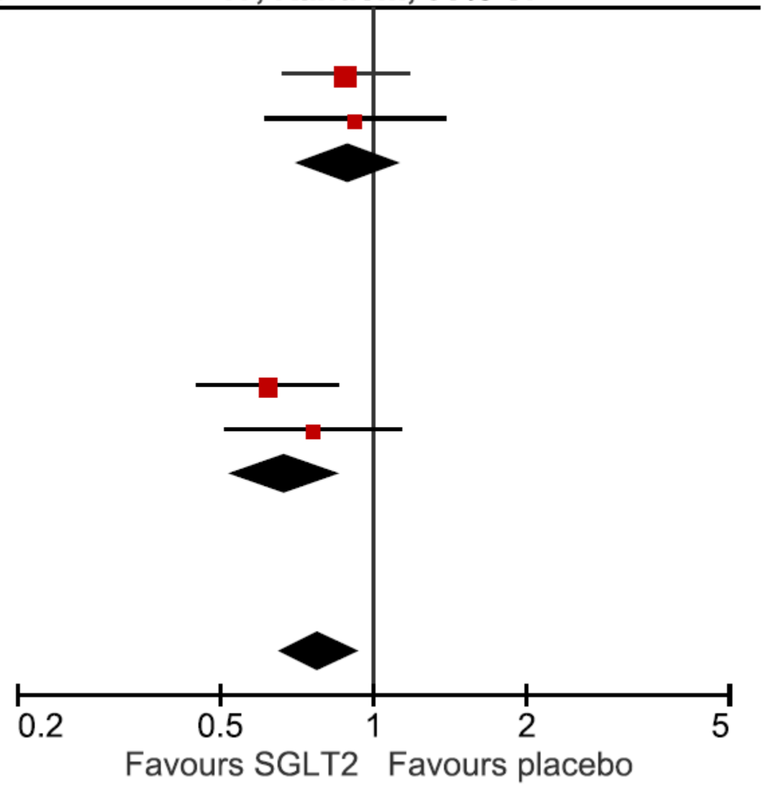



*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

# SGLT2 Inhibitors & HF: Outcome Trials

## CV Death or HF Hospitalization by HF Type

| Study or Subgroup | | log[Hazard Ratio] | SE | SGLT2 Total | Placebo Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **HHF or Cardiovascular death - HFpEF** | | | | | | | |
| DECLARE-TIMI 58 | Dapa | -0.1278 | 0.1468 | 92 | 99 | 34.5% | 0.88 [0.66, 1.17] |
| VERTIS CV | Ertu | -0.0834 | 0.2097 | 68 | 35 | 18.0% | 0.92 [0.61, 1.39] |
| **Subtotal (95% CI)** | | | | **160** | **134** | **52.5%** | **0.89 [0.71, 1.13]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0% | | | | | | | |
| Test for overall effect: Z = 0.94 (P = 0.35) | | | | | | | |
| **HHF or Cardiovascular death - HFrEF** | | | | | | | |
| DECLARE-TIMI 58 | Dapa | -0.478 | 0.1635 | 59 | 95 | 28.5% | 0.62 [0.45, 0.85] |
| VERTIS CV | Ertu | -0.2744 | 0.2035 | 62 | 38 | 19.0% | 0.76 [0.51, 1.13] |
| **Subtotal (95% CI)** | | | | **121** | **133** | **47.5%** | **0.67 [0.52, 0.86]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.44); I² = 0% | | | | | | | |
| Test for overall effect: Z = 3.12 (P = 0.002) | | | | | | | |
| **Total (95% CI)** | | | | **281** | **267** | **100.0%** | **0.78 [0.65, 0.94]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.28, df = 3 (P = 0.35); I² = 9% | | | | | | | |
| Test for overall effect: Z = 2.69 (P = 0.007) | | | | | | | |
| Test for subgroup differences: Chi² = 2.64, df = 1 (P = 0.10), I² = 62.2% | | | | | | | |




*Tsampasian V, et al. Cardiol Res Pract 2021; doi: 10.1155/2021/9927533*

# SGLT2i(ë SGLT1}: Summary

- Most benefit in those with **cardiovascular disease & heart failure**
- **Reduce hospitalization for heart failure** – ***all drugs***
- No significant change in stroke
- Improvement in CV death – *Empagliflozin, Dapagliflozin*
- Additional benefit with pre -existing heart failure (reduced EF)
  - Improve mortality and CV mortality – *Dapagliflozin, canagliflozin*
  - Better outcomes with reduced ejection fraction

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

NO

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

CONSIDER INDEPENDENTLY C
INDIVIDUALIZED A1C TARGET, O

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

ROCEED AS BELOW

**+ASCVD/Indicators of High Risk**

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

EITHER/ OR

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1]

If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa[1]
- TZD[2]
- DPP-4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

**+HF**

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]


NEED TO
T GAIN OR
HT LOSS

SGLT2i

target

GLP-1 RA with good efficacy for weight loss[10]

target

y required,
LP-1 RA not
dicated, use
est risk of
in

BLY

GLP-1 RA)
neutrality

erated or
atient already
s addition of:

asal insulin

**COST IS A MAJOR ISSUE[11,12]**

SU[4] | TZD[12]

If A1C above target

TZD[12] | SU[4]

If A1C above target

**Insulin therapy** basal insulin with lowest acquisition cost

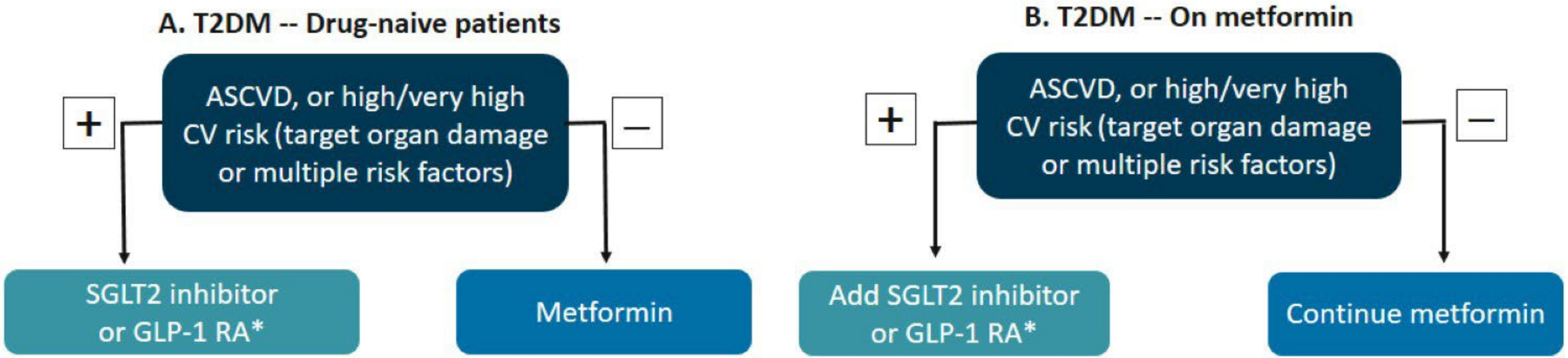
**OR**

Consider other therapies based on cost

1. Proven CVD benefit means it has label indication of reducing CV
2. Low dose may be better tolerated though less well studied for CV
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual ag with regard to indicated level of eGFR for initiation and continued
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduct in HF and to reduce CKD progression in CVOTs. Canagliflozin an dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.

e become new clinical considerations regardless of background ations.
n the relevant trials were on metformin at baseline as y.

# ESC/EASD Guidelines: Novel Glucose–Lowering Drugs




| Very high CV risk | High CV risk |
|---|---|
| Patients with DM and established CVD<br>• or other target organ damage†<br>• or three or more major risk factors‡<br>• or early onset T1DM of long duration (> 20 years) | Patients with DM duration ≥ 10 years without target organ damage plus any other additional risk factor |

*Use drugs with proven CVD benefit.
†Proteinuria, renal impairment defined as eGFR < 30 mL/min/1.73 $m^2$, LVH, or retinopathy.
‡Age, hypertension, dyslipidemia, smoking, obesity.
Cosentino F, et al. *Eur Heart J.* 2020;41:255-323.

# Drug Selection: SGLT2i vs GLP1 RA

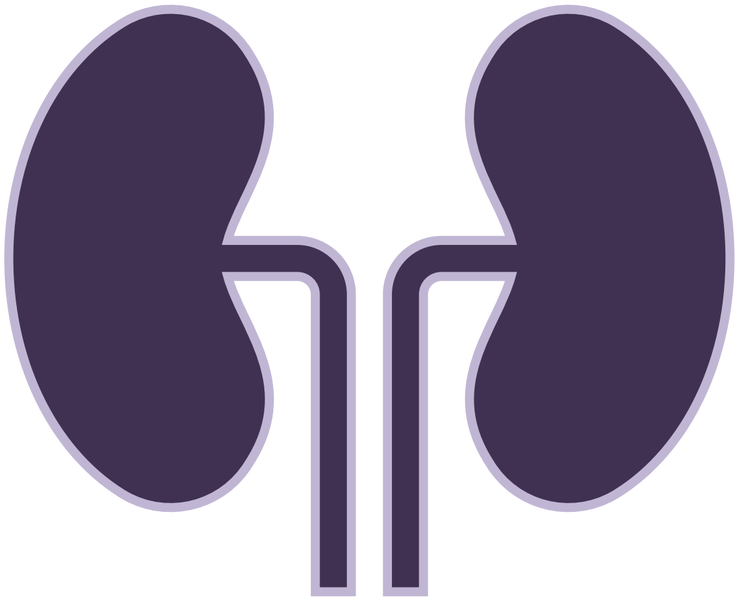
AACE/ ADA/ EASD/ ACC Guideline Summary

- Metformin monotherapy for DM2.
- Consider adding GLP-1 RA or SGLT2i inhibitor independent of HbA1c target.
- Consider GLP-1 RA or SGLT2i prior to metformin for higher CVD risk

- If *atherosclerotic CVD* **or** *stroke* predominates:
  **Choose** GLP-1 RA with proven benefit

- If *heart failure* **or** *CKD* predominates:
  **Choose** SGLT2i with proven benefit

*CKD = chronic kidney disease; CVD = cardiovascular disease*



# SGLT2 Inhibitors: A Nephrologists Perspective

Nayan Arora, MD
Clinical Assistant Professor
University of Washington

# A Nephrologists Approach to Diabetes

- Prevent progression of kidney disease
- Reduce CV events

- Glycemic Control
- Blood Pressure Management
- Albuminuria Reduction
- RAAS Inhibitors, SGLT2 Inhibitors, MRAs (Finerenone), GLP-1 Agonists?

1993

CSG Captopril Trial

Type 1 Diabetes

N=409

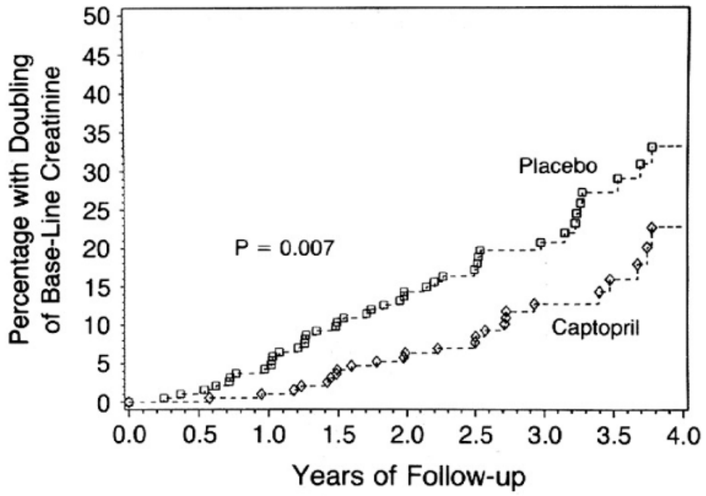
Intervention: Captopril v Placebo

3 year median follow up

Primary Outcome: Creatinine Doubling

# CSG Captopril Trial

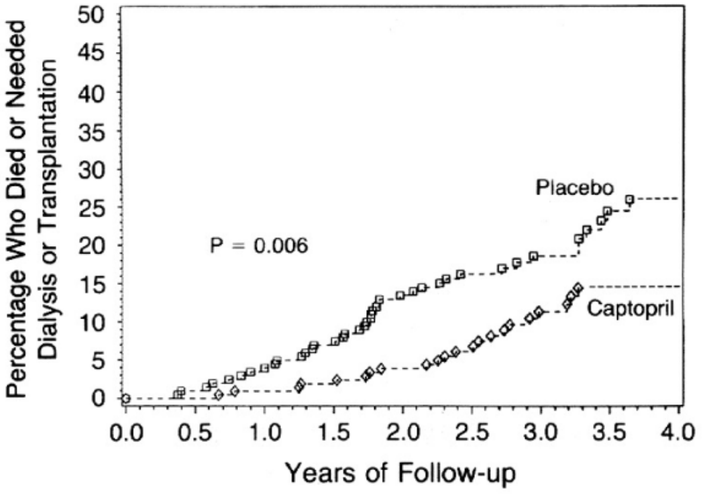
A




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 202 | 184 | 173 | 161 | 142 | 99 | 75 | 45 | 22 |
| Captopril | 207 | 199 | 190 | 180 | 167 | 120 | 82 | 50 | 24 |

48% Reduction in Primary Outcome
NNT= 11

B




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 202 | 198 | 192 | 186 | 171 | 121 | 100 | 59 | 26 |
| Captopril | 207 | 207 | 204 | 201 | 195 | 140 | 103 | 64 | 37 |

Death= 3.9 vs 6.9%

Dialysis or Transplant= 9.7 vs 15.3%

50% Reduction in death, dialysis or Txp
NNT=10

# The Dark Ages…

## Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

Linda F. Fried, M.D., M.P.H., Nicholas Emanuele, M.D., Jane H. Zhang, Ph.D., Mary Brophy, M.D., Todd A. Conner, Pharm.D., William Duckworth, M.D., David J. Leehey, M.D., Peter A. McCullough, M.D., M.P.H., Theresa O'Connor, Ph.D., Paul M. Palevsky, M.D., Robert F. Reilly, M.D., Stephen L. Seliger, M.D., et al

## Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes

Hans-Henrik Parving, M.D., D.M.Sc., Barry M. Brenner, M.D., Ph.D., John J.V. McMurray, M.D., Dick de Zeeuw, M.D., Ph.D., Steven M. Haffner, M.D., Scott D. Solomon, M.D., Nish Chaturvedi, M.D., Frederik Persson, M.D., Akshay S. Desai, M.D., M.P.H., Maria Nicolaides, M.D., Alexia Richard, M.Sc., Zhihua Xiang, Ph.D., et al., for the ALTITUDE Investigators*

Clinical Research

## Sulodexide Fails to Demonstrate Ren Diabetic Nephropathy

David K. Packham, Rory Wolfe, Anne T. Reutens, Tomas Berl, Hiddo Lambers H

ORIGINAL ARTICLE

## Type 2 Diabetes and Stage 4 Chronic Kidney Disease

## A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

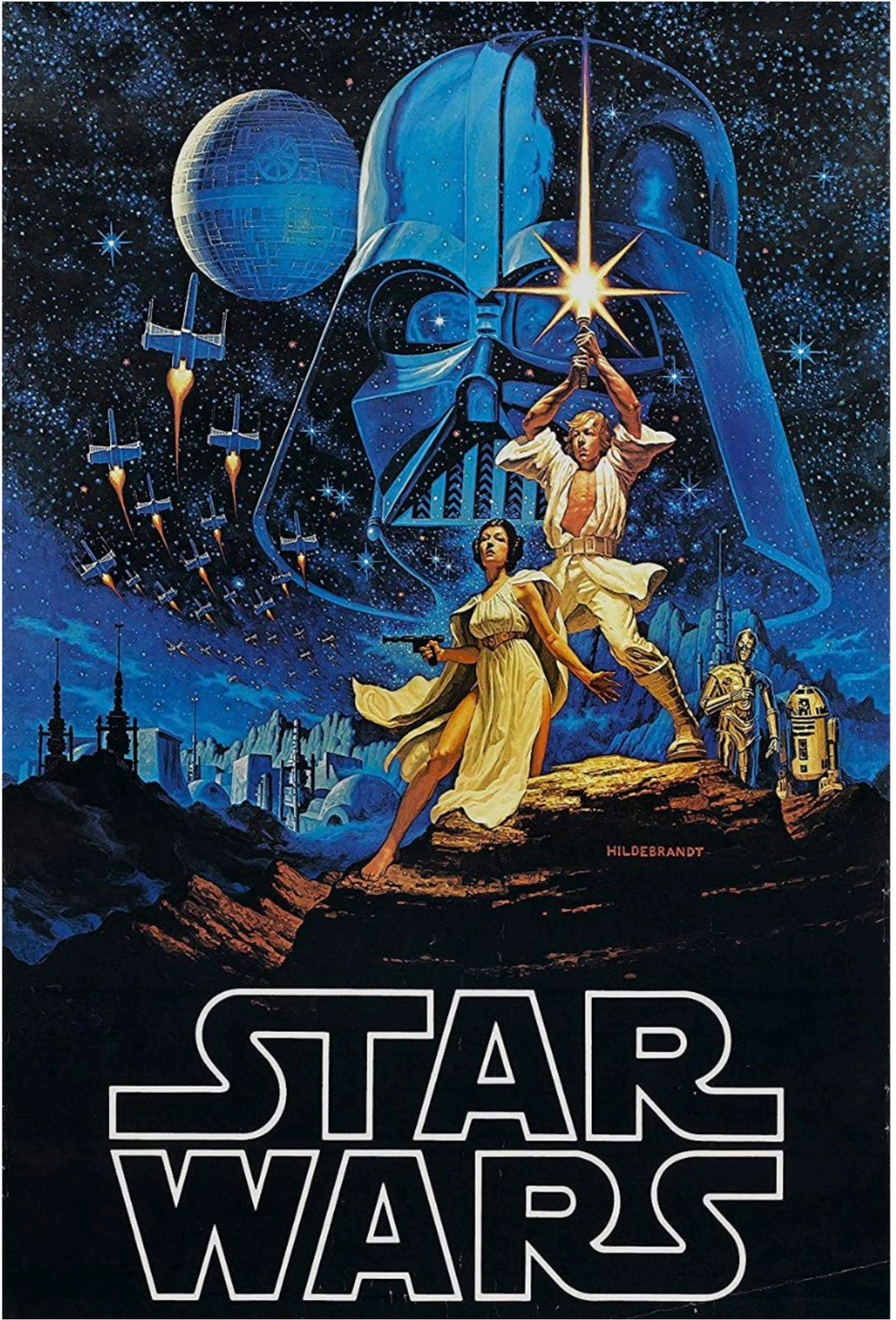
Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin C Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Ke M.P.H., Janet B. McGill, M.D., et al., for

Clinical Research

## Sulodexide Fails to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy

David K. Packham, Rory Wolfe, Anne T. Reutens, Tomas Berl, Hiddo Lambers Heerspink, Richard Rohde, Sara Ivory, Julia Lewis, Itamar Raz, Thomas B. Wiegmann, Juliana C.N. Chan, Dick de Zeeuw, Edmund J. Lewis, Robert C. Atkins and for the Collaborative Study Group

JASN January 2012, 23 (1) 123-130; DOI: https://doi.org/10.1681/ASN.2011040378




# A New Hope…

The NEW ENGLAND JOURNAL of MEDICINE

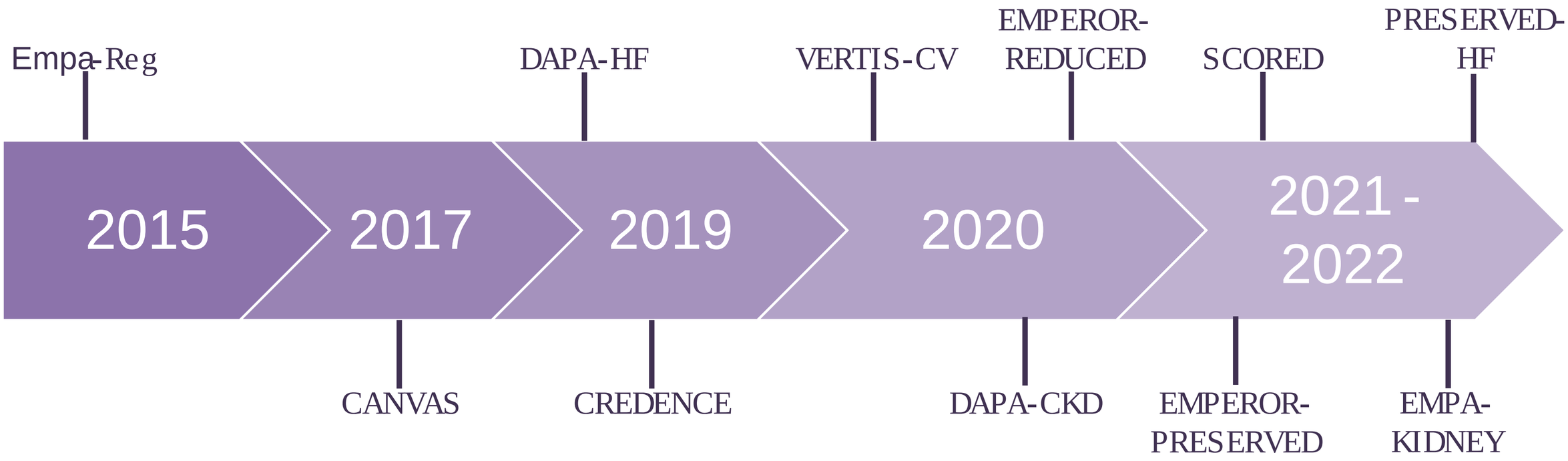
ORIGINAL ARTICLE

## Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

ABSTRACT

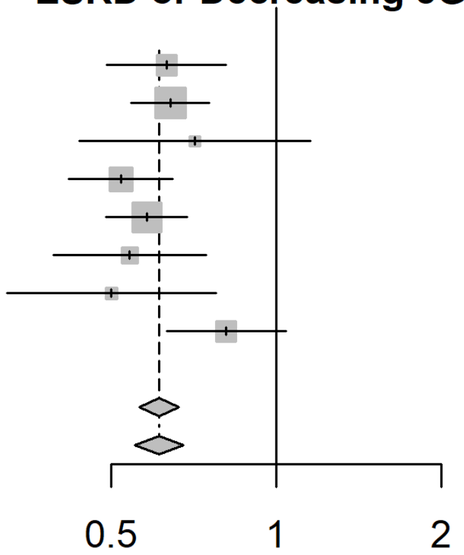
# SGLT2 Inhibitor Trials



# Worsening Kidney Function or ESKD

| Study | Drug | Trial | NSGLT2 | NPBO | HR | 95%-CI | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| CANVAS Program | Cana | CVOT | 5790 | 4344 | 0.63 | [0.49; 0.81] | 11.1% | 12.4% |
| CREDENCE | Cana | CKD | 2200 | 2197 | 0.64 | [0.54; 0.75] | 25.9% | 21.7% |
| DAPA-HF | Dapa | CHF | 2373 | 2371 | 0.71 | [0.44; 1.15] | 3.0% | 4.1% |
| DECLARE-TIMI-58 | Dapa | CVOT | 8574 | 8569 | 0.52 | [0.42; 0.65] | 14.7% | 15.2% |
| DAPA-CKD | Dapa | CKD | 2152 | 2152 | 0.58 | [0.49; 0.69] | 23.9% | 20.7% |
| EMPAREG | Empa | CVOT | 4687 | 2333 | 0.54 | [0.39; 0.74] | 6.8% | 8.5% |
| EMPEROR-REDUCED | Empa | CHF | 1863 | 1867 | 0.50 | [0.32; 0.78] | 3.6% | 4.9% |
| VERTIS-CV | Ertu | CVOT | 5493 | 2745 | 0.81 | [0.63; 1.04] | 11.1% | 12.5% |
| **Fixed effect model** | | | | | **0.61** | **[0.56; 0.66]** | **100.0%** | **--** |
| **Random effects model** | | | | | **0.61** | **[0.55; 0.68]** | **--** | **100.0%** |

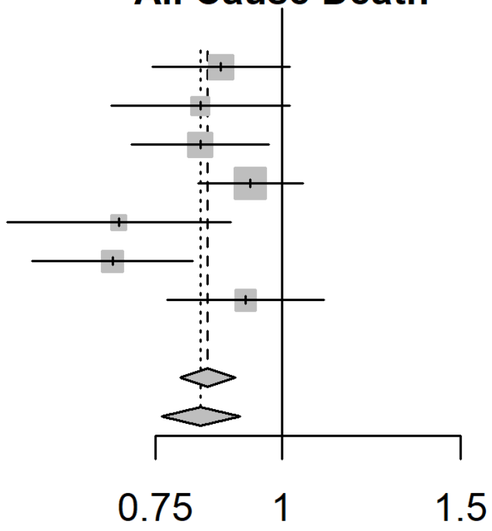
Heterogeneity: $I^2$ = 26%, $\tau^2$ = 0.0056, $p$ = 0.22



# Cause Mortality

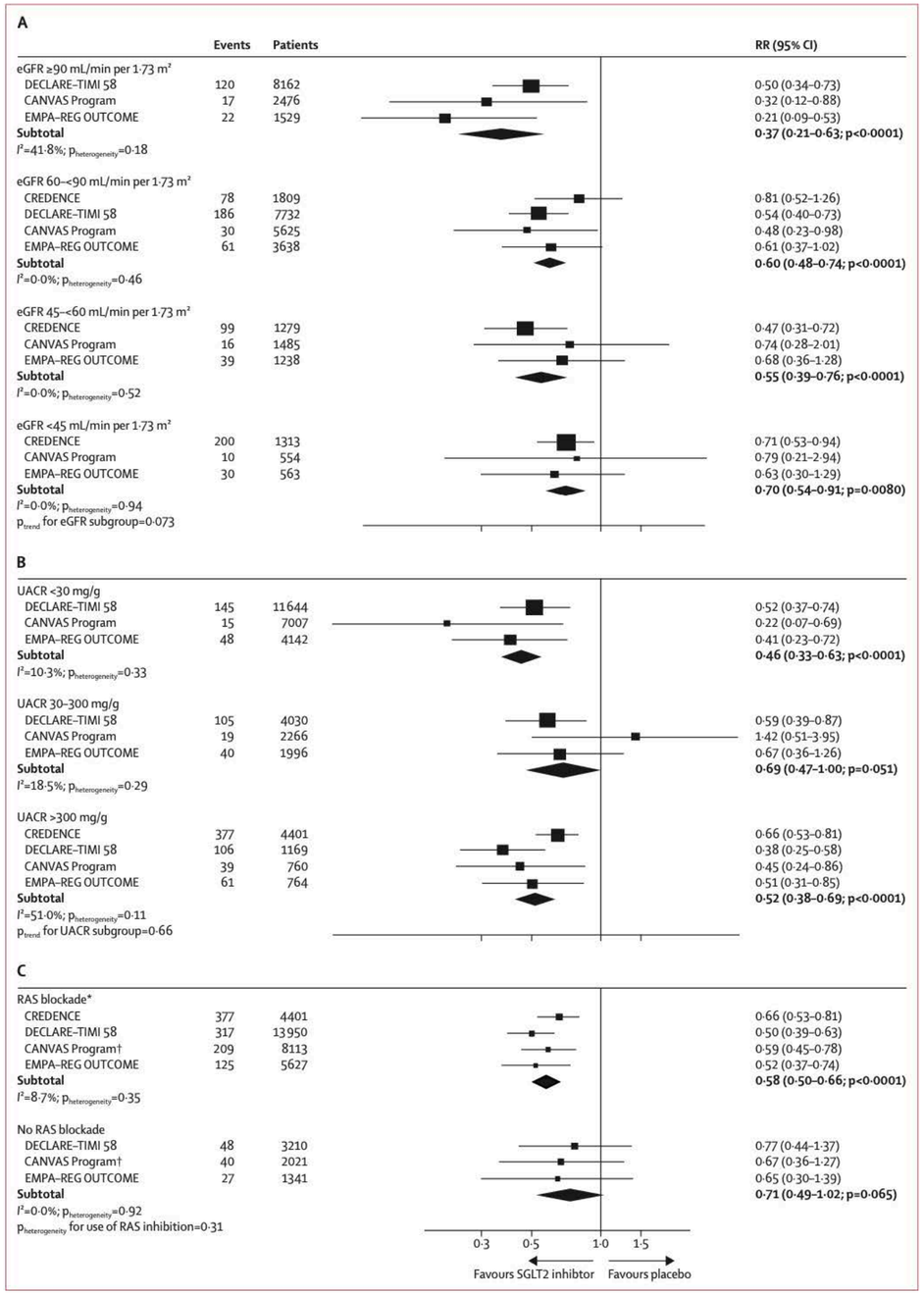
| Study | Drug | Trial | NSGLT2 | NPBO | HR | 95%-CI | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| CANVAS Program | Cana | CVOT | 5790 | 4344 | 0.87 | [0.74; 1.02] | 16.2% | 16.0% |
| CREDENCE | Cana | CKD | 2200 | 2197 | 0.83 | [0.68; 1.02] | 9.5% | 11.9% |
| DAPA-HF | Dapa | CHF | 2373 | 2371 | 0.83 | [0.71; 0.97] | 16.1% | 15.9% |
| DECLARE-TIMI-58 | Dapa | CVOT | 8574 | 8569 | 0.93 | [0.83; 1.05] | 27.8% | 20.0% |
| DAPA-CKD | Dapa | CKD | 2152 | 2152 | 0.69 | [0.54; 0.89] | 6.1% | 8.9% |
| EMPAREG | Empa | CVOT | 4687 | 2333 | 0.68 | [0.57; 0.82] | 11.9% | 13.6% |
| EMPEROR-REDUCED | Empa | CHF | 1863 | 1867 | 0.92 | [0.77; 1.10] | 12.3% | 13.8% |
| **Fixed effect model** | | | | | **0.84** | **[0.79; 0.90]** | **100.0%** | **--** |
| **Random effects model** | | | | | **0.83** | **[0.76; 0.91]** | **--** | **100.0%** |

Heterogeneity: $I^2$ = 48%, $\tau^2$ = 0.0067, $p$ = 0.07



# SGLT2i vs ARBs

| | SGLT2i | ARB |
|---|---|---|
| All Cause Mortality | **0.76** | 0.97 |
| Composite Kidney Outcome | **0.61** | 0.75 |
| Effect on ESKD | 0.80 | 0.77 |
| HF Hospitalization | 0.69 | 0.73 |

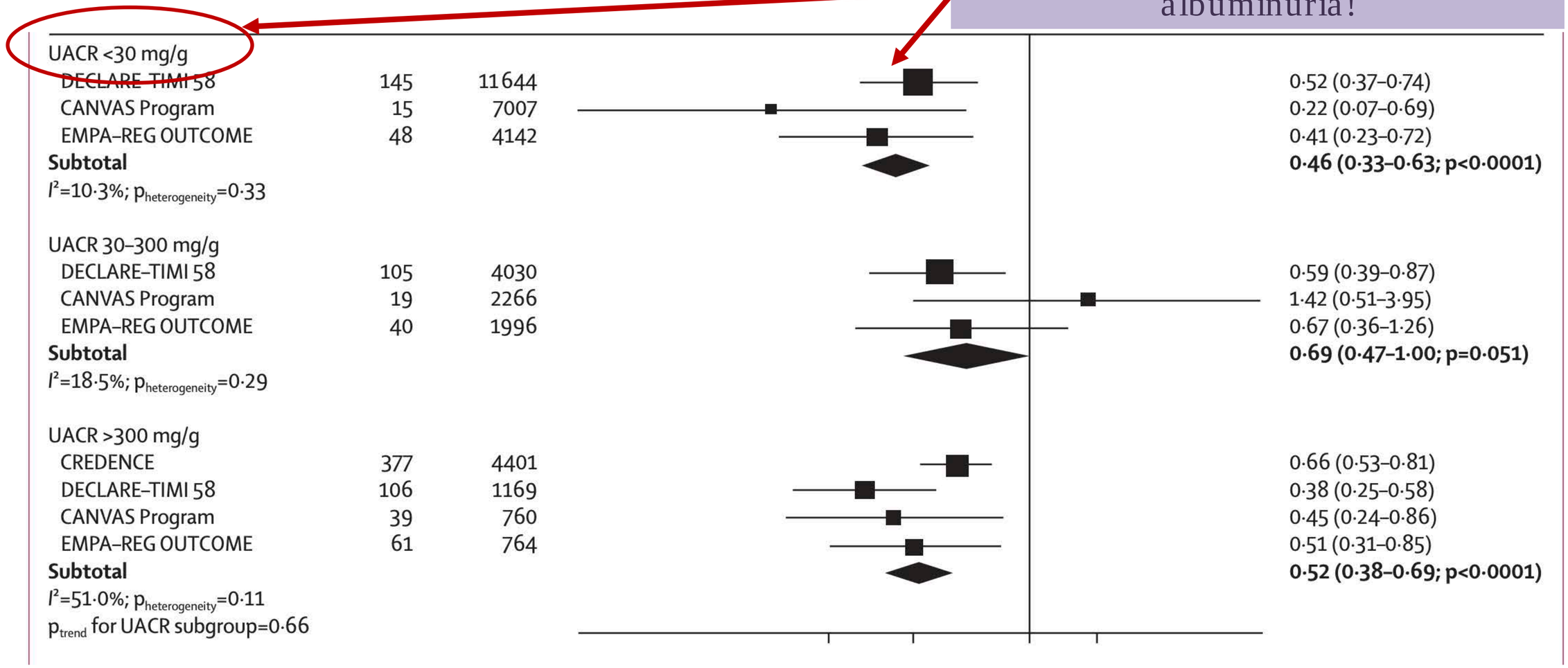


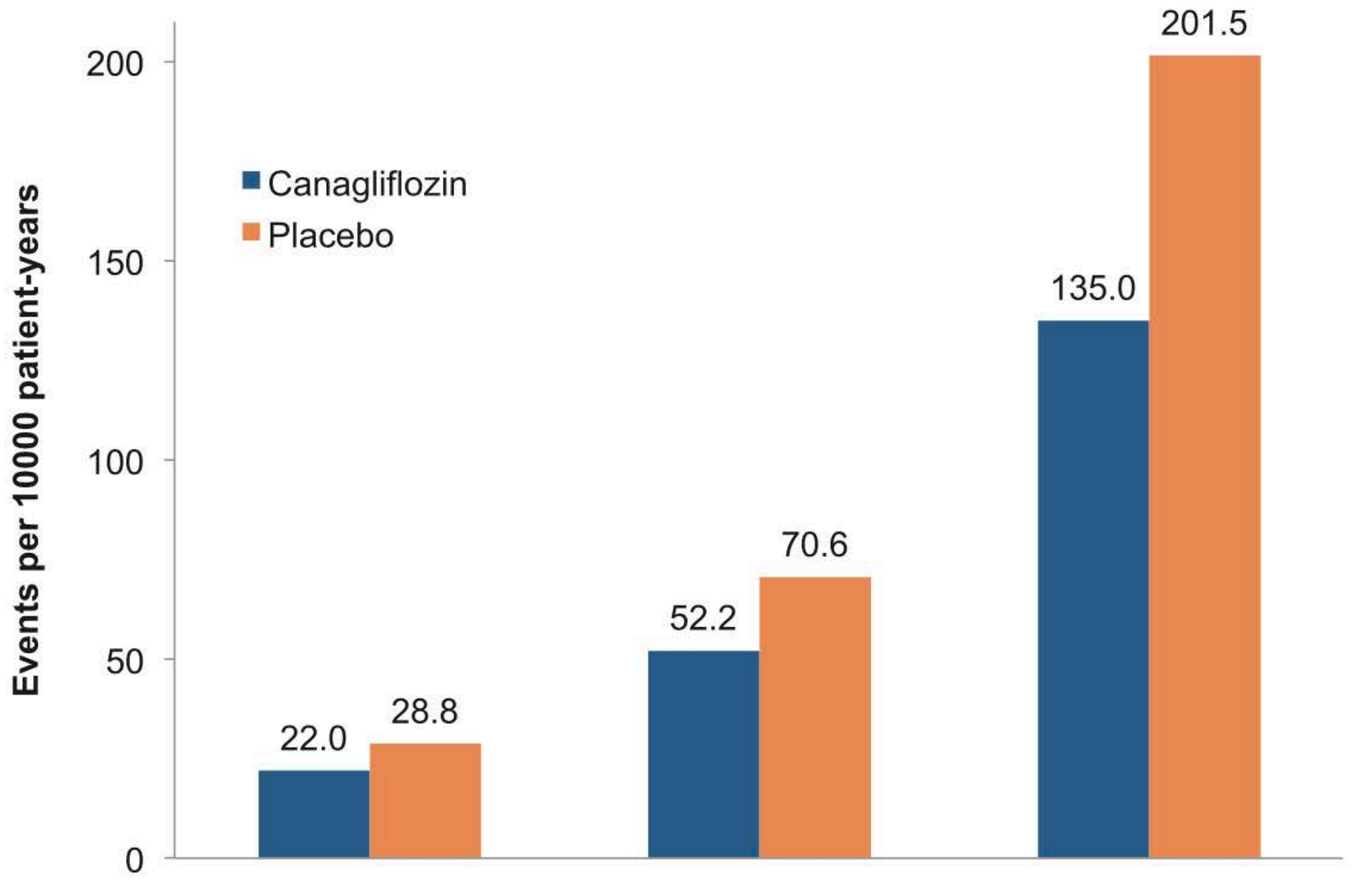



Neuen et al. Lancet Diabetes Endocrinol. 2019

# Patient Selection

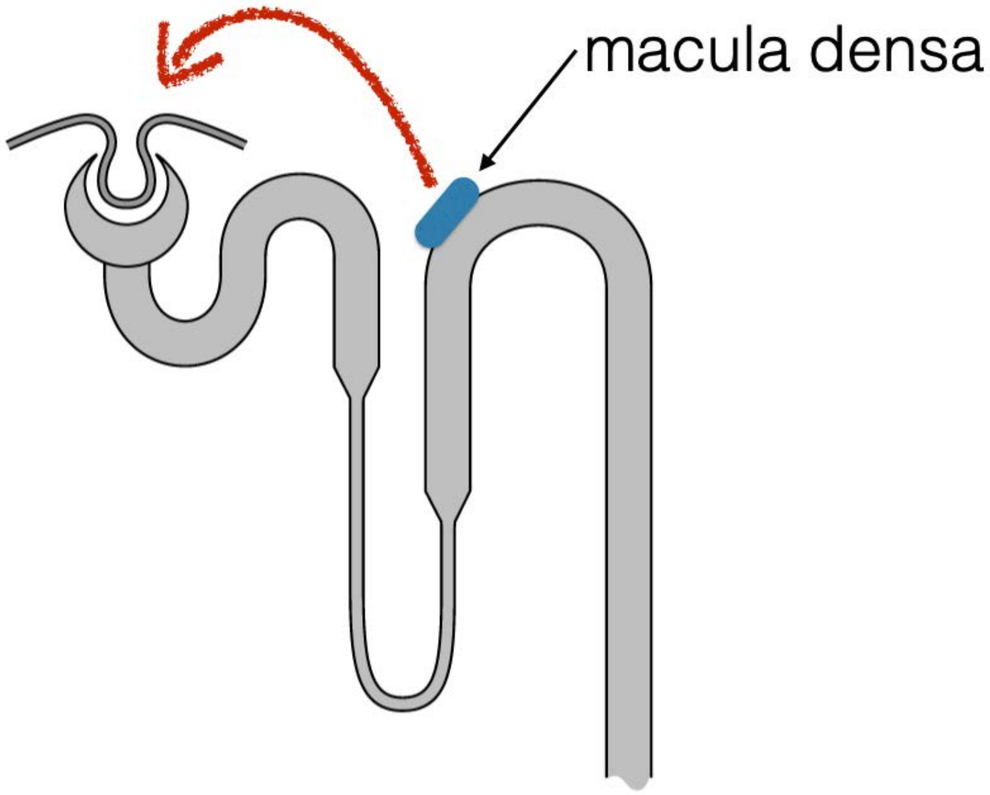
SGLTi works in the absence of albuminuria!

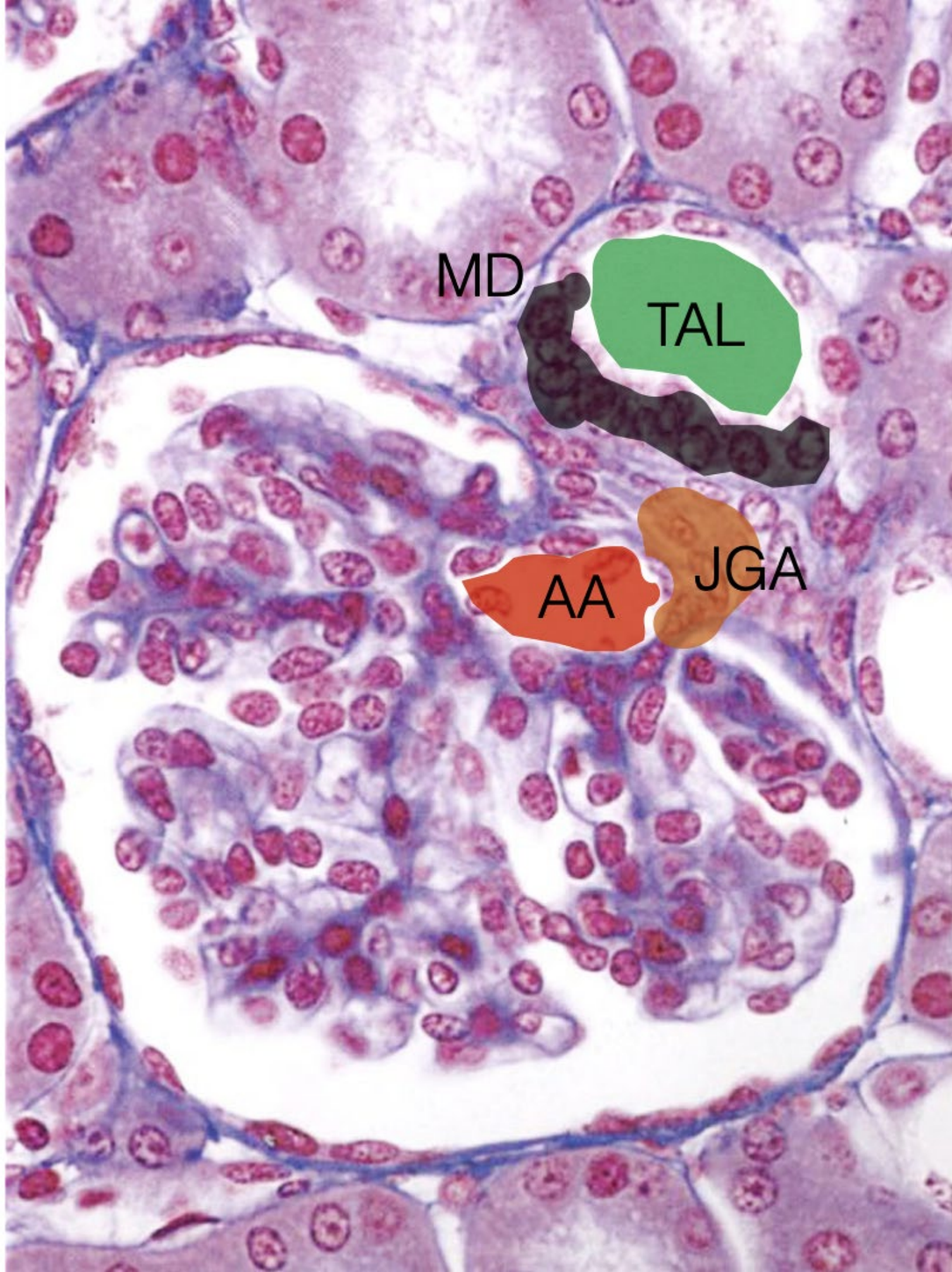




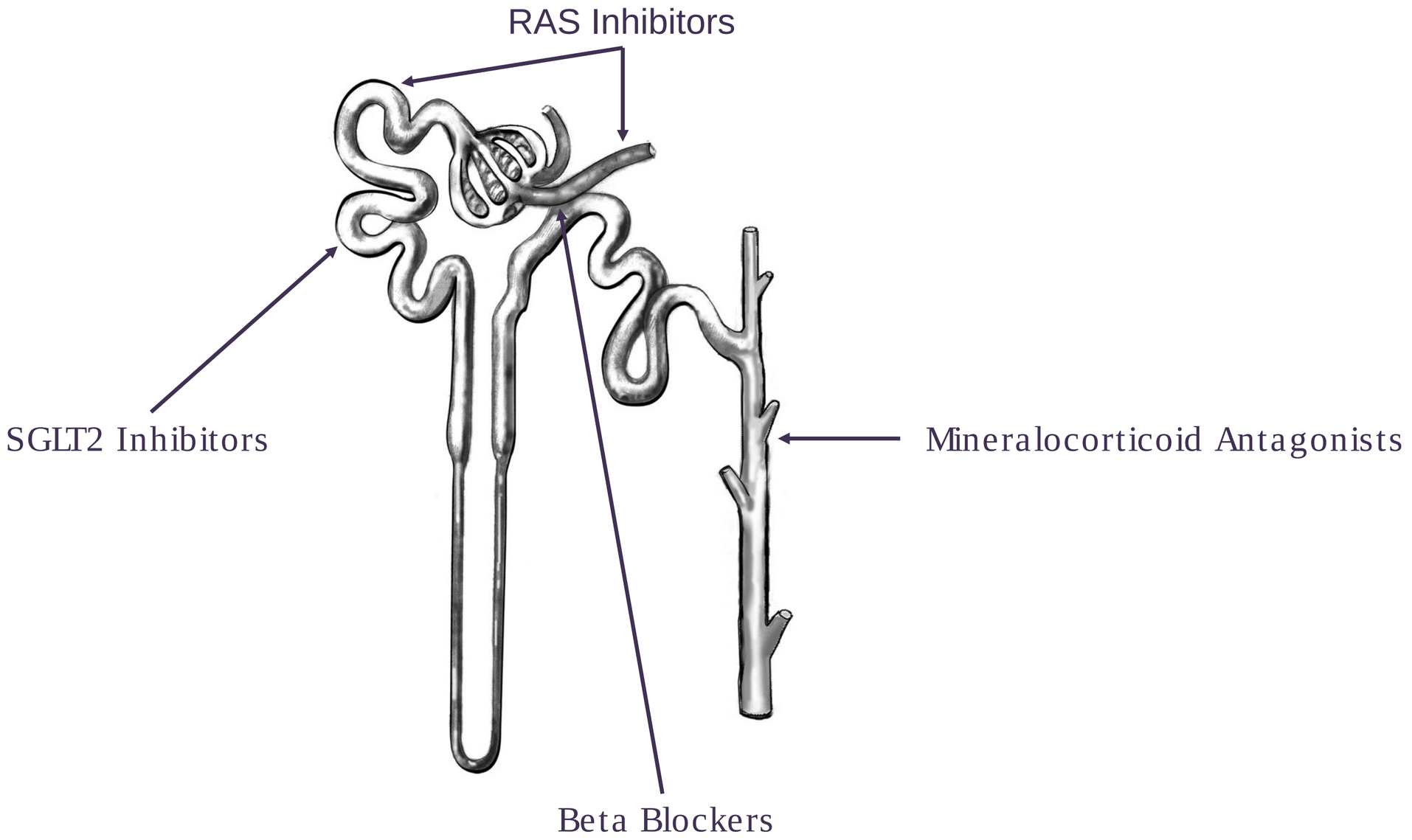

| UACR (mg/g) | ≤1000 | >1000-<3000 | ≥3000 |
|---|---|---|---|
| Absolute risk reduction[a] (2.6 years) | -17 | -45 | -119 |

# Tubular – Glomerular Feedback

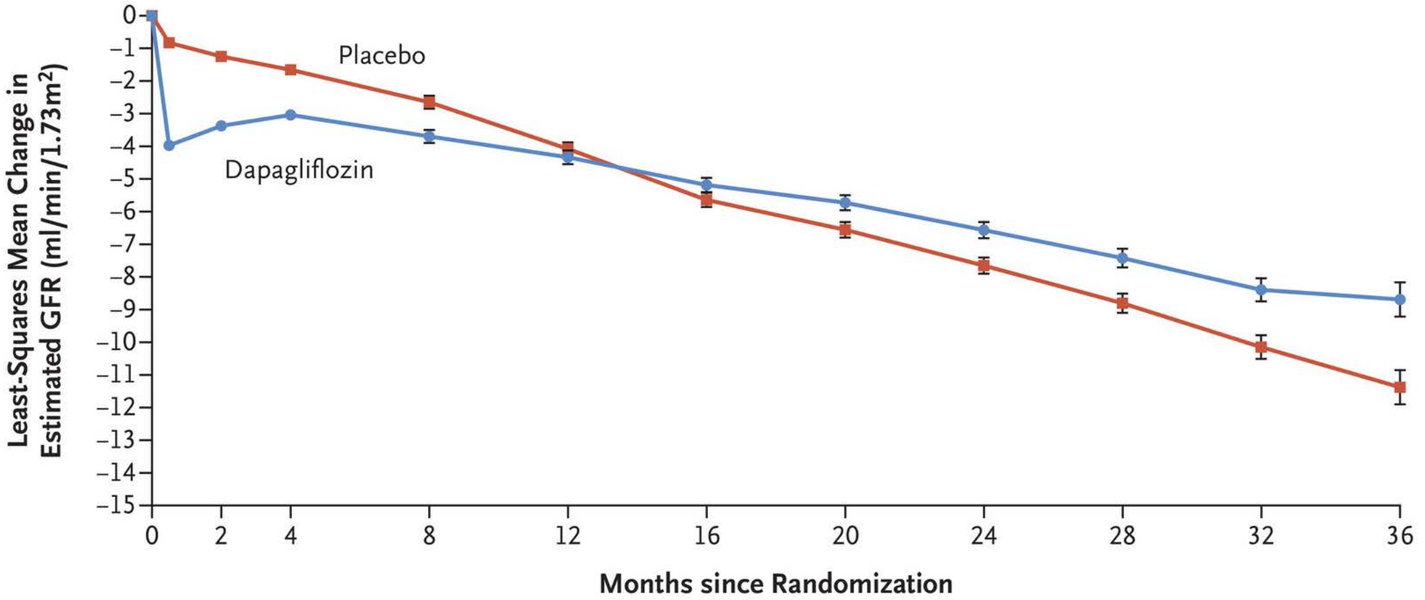


# Heart Failure Treatment Through the Nephron

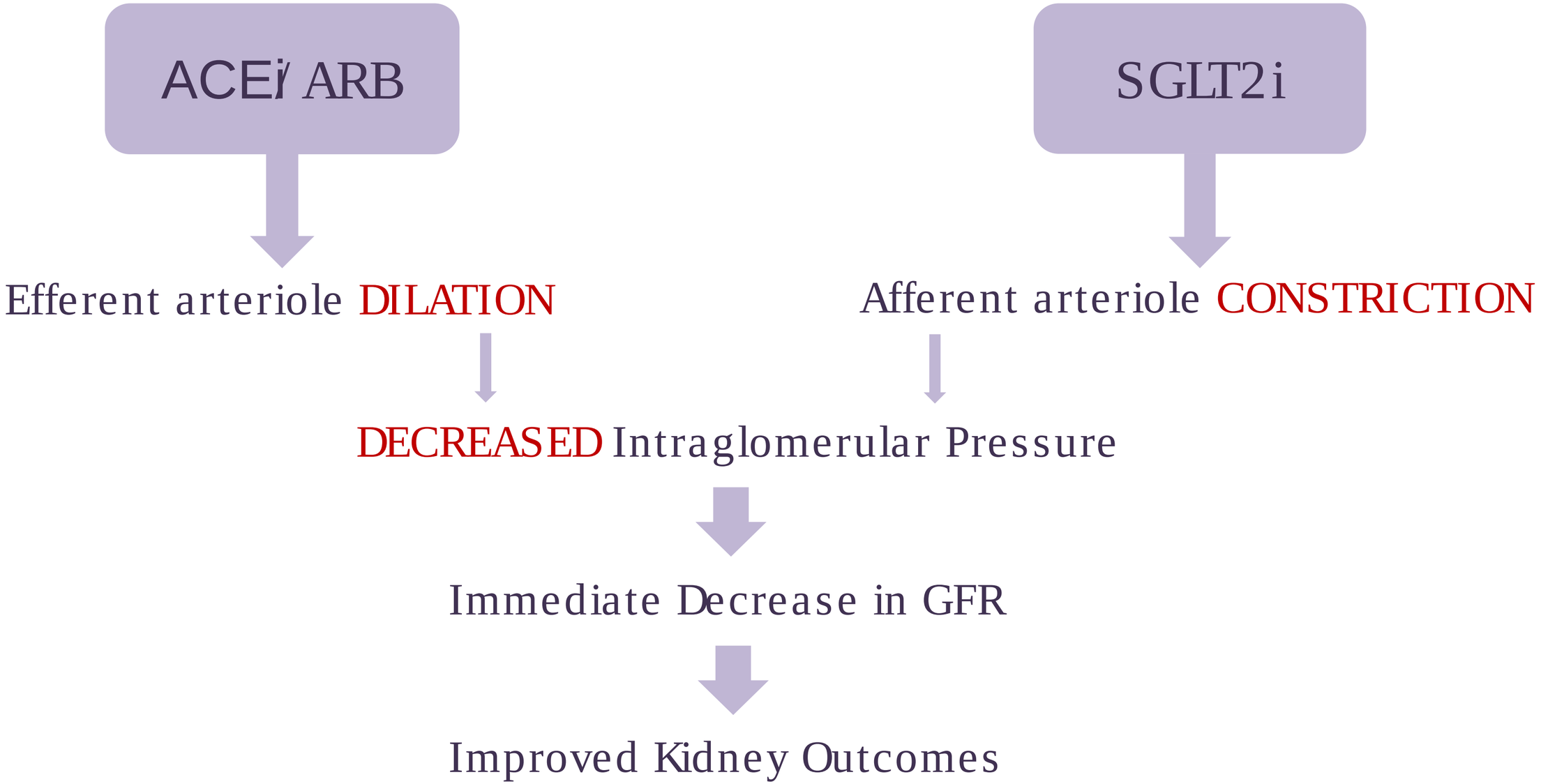


# The AKI Myth



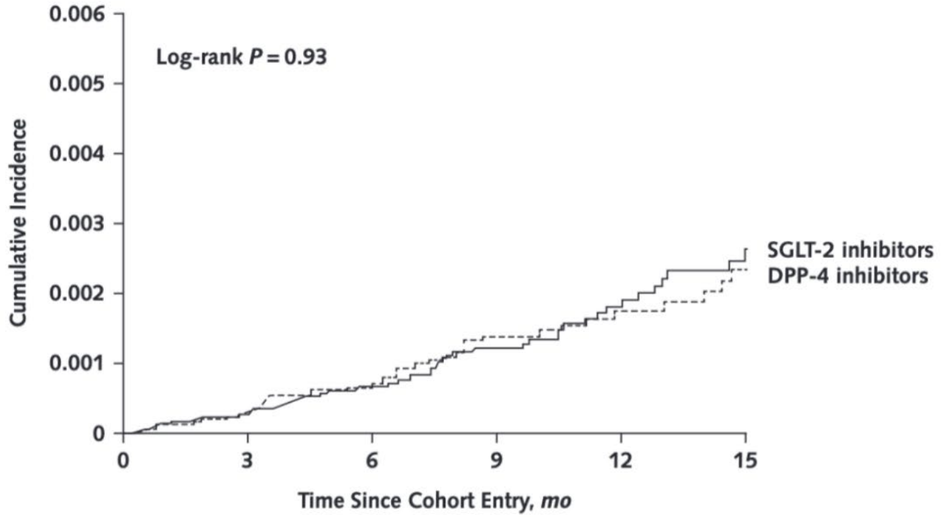

**No. of Participants**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2152 | 2029 | 1981 | 1866 | 1795 | 1753 | 1672 | 1443 | 935 | 447 | 157 |
| Dapagliflozin | 2152 | 2031 | 2001 | 1896 | 1832 | 1785 | 1705 | 1482 | 978 | 496 | 157 |

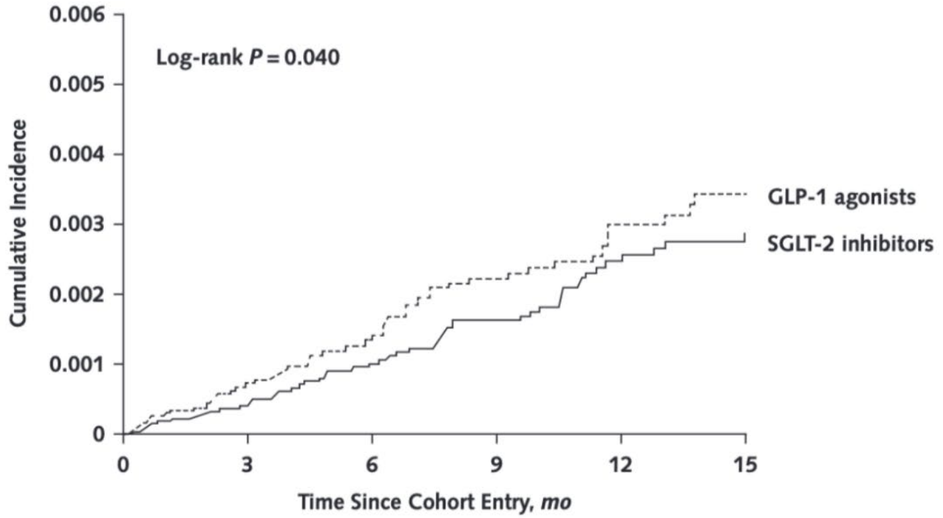

ACEi/ ARB
SGLT2i
Efferent arteriole DILATION
Afferent arteriole CONSTRICTION
DECREASED Intraglomerular Pressure
Immediate Decrease in GFR
Improved Kidney Outcomes

# Risk of UTIs

- US Based Databased of Commercial Claims
- 2013 - 2015
- Cohort 1: SGLT2i v DPP4i (n=123,752)
- Cohort 2: SGLT2i v GLP1a (n=111,978)
- Propensity Matched




| At risk, *n* | | | | | | |
|---|---|---|---|---|---|---|
| Receiving DPP-4 inhibitor | 61 876 | 44 268 | 30 983 | 20 951 | 13 675 | 8679 |
| Receiving SGLT-2 inhibitor | 61 876 | 45 804 | 32 513 | 22 800 | 15 280 | 9405 |




| At risk, *n* | | | | | | |
|---|---|---|---|---|---|---|
| Receiving GLP-1 agonist | 55 989 | 40 032 | 28 219 | 20 305 | 14 648 | 10 088 |
| Receiving SGLT-2 inhibitor | 55 989 | 42 276 | 30 099 | 22 642 | 16 745 | 11 387 |

Dave et al. Annals Intern Med. 2019

# Genital Mycotic Infections

~2-4 fold increased risk

Generally easily treated with topical antifungals or occasionally fluconazole

Rarely leads to permanent drug cessation

# Diabetic Ketoacidosis

| | SGLT2i (%) | Placebo (%) | Hazard Ratio/Risk difference (vs placebo) | P Value |
|---|---|---|---|---|
| Credence n=4401 | 11 (0.22) | 1 (0.02) | RR 10.80 (1.39, 83.65) | |
| EMPAREG n=7.020 | 4 (0.1) | 1 (<0.1) | RR 1.99 (0.22, 17.80) | |
| CANVAS n=10,142 | 0.06 | 0.03 | HR 2.33 (0.76, 7.17) | 0.14 |
| DECLARE n=17143 | 27 (0.3) | 12 (0.1) | RR 2.18 (1.10, 4.30) | 0.02 |
| VERTIS CV n=8238 | 19 (0.3) | 2 (0.1) | | |
| EMPEROR Reduced n=3726 | 0 (0.0) | 0 (0.0) | | |
| DAPAHF n=4744 | 3 (0.1) | 0 (0.0) | | NA |
| DAPA CKD n=4298 | 0 | 2 (<0.1) | | 0.50 |

83% Sick when they developed DKA!

**Table S6. Baseline Characteristics of Participants With Diabetic Ketoacidosis Adverse Events**

| | Participants with Diabetic Ketoacidosis* (n = 12) | All Participants (n = 4401) |
|---|---|---|
| Background insulin treatment—no. (%) | 11 (91.7) | 2884 (65.5) |
| Background metformin treatment—no. (%) | 4 (33.3) | 2545 (57.8) |
| Duration of diabetes—yr | 23.8 | 15.8 |
| Glycated hemoglobin—% | 8.9 | 8.3 |
| Glycated hemoglobin >10%—no. (%) | 3 (25.0) | 450 (10.2) |
| eGFR—mL/min/1.73 $m^2$ | 54.0 | 56.2 |
| Screening eGFR ≥30 to <45 mL/min/1.73 $m^2$—no. (%) | 7 (58.3) | 1313 (29.8) |
| History of diabetic ketoacidosis | 2 (16.7) | 4 (0.1) |

*Precipitating factors (primarily recent or concurrent illness, recent reduction in insulin dose, or drugs affecting carbohydrate metabolism) were identified by the adjudication committee for 83% of cases (10 of 12 events) in the canagliflozin group and 100% (1 event) in the placebo group. With the exception of 1 case, concomitant blood glucose levels were >250 mg/dL (>13.9 mmol/L).

Stop this medication if you have any signs of symptoms of an allergic reaction such as hives, itching, rash, throat swelling or difficulty breathing

You may notice an increase in urine output after starting this medication

Your blood pressure may decrease

- Monitor your blood pressure at home as your blood pressure may decrease after starting this medication
- Dizziness with standing is a common symptom, which generally resolves within 2 weeks, however, please contact me if you experience debilitating dizziness/lightheadedness of symptoms persist beyond 2 weeks

Observe "sick day" rules

- If you are feeling ill (fever, infection, poor appetite, nausea, vomiting, diarrhea) and are unable to maintain adequate hydration HOLD this medicine until you feel better for 24 hours.
- If you have a severe illness please go to the Emergency Room

Hold this medication for 48 hours prior to any scheduled surgery that requires you to be NPO (not eat or drink) the night before the procedure

This medication should generally be held if you are admitted to the hospital. Please confer with your inpatient doctors.

Avoid the Atkins or Keto diet

Monitor your blood glucose levels as your insulin requirements may decrease when you start this medication

Wound on your legs, feet or groin

- If you notice a wound, ulcer or skin breakdown on your legs, feet or groin, HOLD this medication and contact me or your primary care provider or go to the emergency room

Burning with urination

- If you have burning with urination HOLD this medication and contact me or your primary care doctor

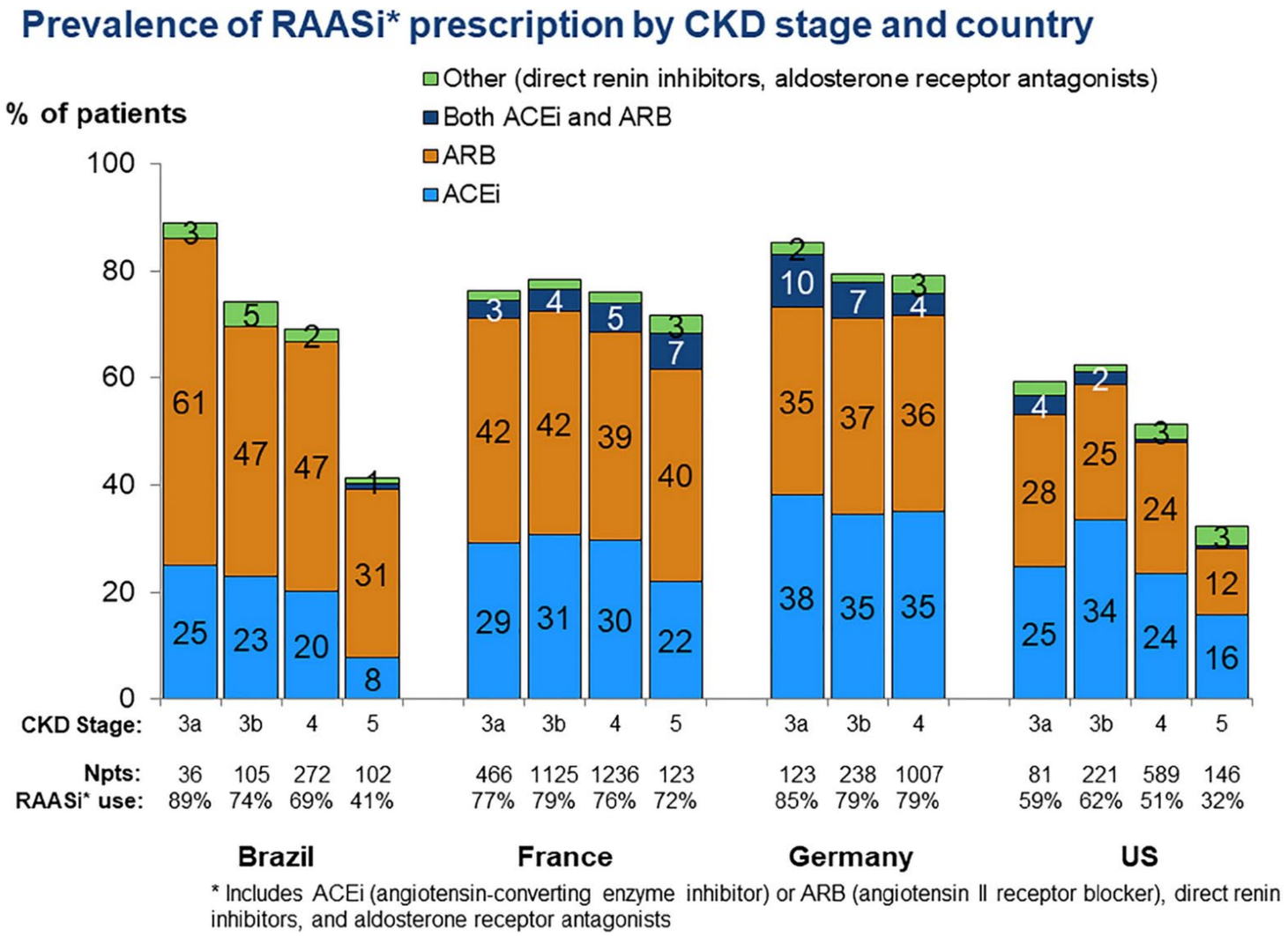
Redness or itching in the groin area or foul -smelling vaginal or penile discharge

- Keep your genital area clean
- If you notice any redness or itching in the genital area or are having any vaginal or penile discharge, HOLD this medication and inform me. You may need a cream or oral medication to treat an underlying fungal infection.

@NWiegley

| | EMPA-REG | CANVAS | CREDENCE | DECLARE-TIMI | DAPA-HF | DAPA-CKD |
|---|---|---|---|---|---|---|
| | N= 7020<br>Cohort: DM2, eGFR 74.1,<br>UACR: ~60% < 30 mg/g<br>Duration: 3.1 years<br>Empaglaflozin vs placebo<br>Event rate % | N= 10142<br>Cohort: DM2, eGFR 76.5,<br>UACR: 70% < 30 mg/g<br>Duration: 2.4 years<br>Canagliflozin vs placebo<br>Event rate per 1000 pt-yr | N= 4401<br>Cohort: DM2, eGFR 56.2 +/- 18.2<br>Mean UACR: 927 mg/g<br>Duration: 2.6 years<br>Canagliflozin vs placebo<br>Event rate per 1000 pt-yr | N= 17160<br>Cohort: DM2, eGFR 85.4 +/- 16<br>UACR: NA<br>Duration: 4.2 years<br>Dapagliflozin vs placebo<br>Event rate % | N= 4744<br>Cohort: DM2 and non-DM, eGFR 66 +/- 19.6; UACR NA<br>Duration: 18.2 months<br>Dapagliflozin vs placebo<br>Event rate % | N= 4304<br>Cohort: DM2 & non-DM; eGFR 43.1+/-12.4; UACR 949 mg/g<br>Duration: 2.4 years<br>Dapagliflozin vs placebo<br>Event rate % |
| **Hypoglycemia** | **No difference**<br>(1.3 vs 1.5) | **No difference** | **No difference** | **No difference** | **No difference**<br>(0.2 vs 0.2) | More in placebo<br>(0.7 vs 1.3) |
| **DKA** | Rare<br>**No Difference**<br>(0.1 vs < 0.1) | Rare<br>**higher in CANA**<br>(0.6 vs 0.3) | Rare<br>**higher in CANA**<br>(2.2 vs 0.2) | Rare<br>**higher in DAPA**<br>(0.3 vs. 0.1) | Rare<br>**3 cases in DAPA**<br>(0.1 vs 0) | Rare<br>0 in DAPA; 2 in placebo |
| **UTI** | **No difference**<br>Complicated (1.7 vs 1.8)<br>Uncomplicated (18.1 vs 18) | **No difference**<br>(40 vs 37) | **No difference**<br>(48 vs 45) | **No difference**<br>(1.5 vs 1.6) | **No difference** | **No difference** |
| **Genital mycotic infections** | **Higher in EMPA**<br>(6.4 vs 1.8) | **Higher in CANA**<br>(69 vs 18) | **Higher in CANA**<br>Men (8.4 vs 0.9)<br>Women (12.6 vs 6.1) | **Higher in DAPA**<br>Uncomplicated (0.9 vs 0.1)<br>6 cases- Fournier gangrene<br>(1 in DAPA; 5 in placebo) | **No difference**<br>(0 vs <0.1%)<br>1 case- Fournier gangrene<br>(0 in DAPA; 1 in placebo) | **No difference**<br>(0 vs <0.1%)<br>1 case-m Fournier gangrene<br>(0 in DAPA; 1 in placebo) |
| **Bone fracture** | **No difference**<br>(3.8 vs 3.9) | **Higher in CANA**<br>(15.4 vs 11.9) | **No difference**<br>(11.8 vs 12.1) | **No difference**<br>(5.3 vs 5.1) | **No difference**<br>(2.1 vs 2.1) | **Higher in DAPA**<br>(4% vs 3.2%) |
| **Limb amputation** | **No difference** | higher in CANA<br>(6.3 vs 3.4) | **No difference**<br>(12.3 vs 11.2) | **No difference**<br>(1.4 vs 1.3) | **No difference**<br>(0.5 vs 0.5) | **No difference**<br>(1.6 vs 1.8) |

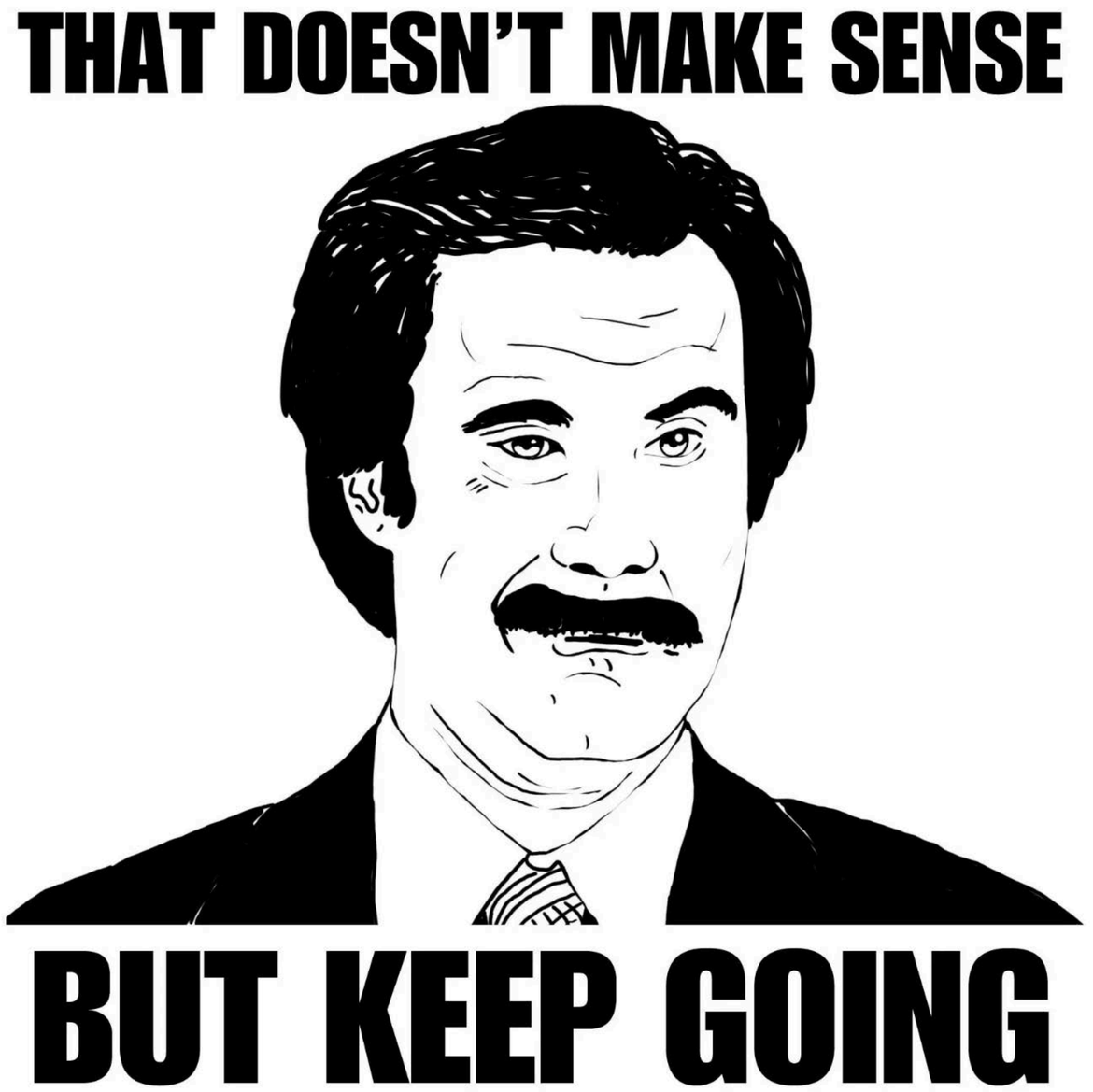
# Time to Get the Word Out!



It’s estimated that only 5% of patients with type 2 diabetes and chronic kidney disease are currently treated with SGLT2 inhibitors

Main barrier was clinical inertia

McCoy et al. Clin Diabetes. 2020



# Summary

- Well tolerated overall but counseling need to explain risk and sick days
- Limited glycemic benefit (0.6 -0.8% A1c lower) especially in GFR <45 ml/min/1.73m $^2$
- Improvement in HF across patients living with diabetes and in those with reduced EF HF without DM.
- All cause mortality reduced in meta -analysis.

# Summary

- Significant improvement in decreasing patient progression to ESRD and worsening EGFR across all GFRswith/without proteinuria

- Call to increase use for CV and renal benefits outside of glycemic control

# Questions?

# Cardiometabolic teleECHO™ Clinic

Patient Recommendation Form

**Presentation Date:** June 15th, 2022 **Presenter name:** Jaya DeElena, DNP, FNP-BC, ARNP

**Presenter Facility:** UW Neighborhood Clinics

**Case Report Recap:** Pt is a female, with history of diabetes and many micro and macrovascular complications including diabetic neuropathy, diabetic retinopathy with macular edema, osteomyelitis and partial right foot amputation with delayed wound healing, h/o of MI and CVA. Many comorbidities including BMI 38, dyslipidemia (LdL 137, Rheumatoid arthritis, urolithiasis, colitis, age related cataracts, vulvovaginitis.

- H/o intolerance/allergies to multiple medications: metformin, empagliflozin, SC semaglutide
- She has failed CGM trials: falls off, don't work.
- Strong FH of CAD, paternal side (dad, both paternal grandparents), Family Hx of breast cancer (mother & grandmother), sister colon cancer

**Current Medication(s) (including dose frequency):**

| Medication | Dose | Frequency |
|---|---|---|
| Rosuvastatin | 5 mg | Before bed once daily |
| Liraglutide SQ | 1.2 mg | Once daily |
| Glargine | 20 units | BID |
| Augmentin | 872-125 mg | BID |
| Doxycycline | 100 mg | BID |
| Nystatin 10000 powder | 1 application | daily |
| Oxycodone | 5 mg | PRN |
| Loperamide | 2 mg | PRN |
| Naproxen | 880 mg | PRN |
| Prednisolone-Moxiflox-Nepafaenac | 1-0.5-1 | 1 drop eye daily |

**Case Recommendations:**

0. Discuss in a non-judgmental way how much insulin the patient was taking prior to the surgery
1. Gather more data from CGM re-attempt and/or try checking fasting glucose levels for 2-3 days, 2-4 times prior to meals and bedtime since A1c does not currently match fasting glucose
2. Reduce glargine to 30 units once a day in the morning.
3. Consider prandial insulin 5-9 units depending on meal size or if it is too complicated, start at 5 units with one meal a day
4. Attempt to further maximize liraglutide by 1 click every 2-3 days. Increase from 1.2mg, then slowly get to goal of 1.8mg. Hold at dose if any GI issues.
5. Maximize Rosuvastatin. Start slow perhaps 10 then 20 then 40 and consider adding ezetimibe for optimal <70 LDL goal
6. Consider Ace or Arb (but may also have allergy so discuss) and check for albuminuria.

7. Monitor triglycerides. Therapy may be indicated but first do fasting lipid panel and address at later date. Must balance number of meds and side-effects vs benefit and cost.
8. Consider ASA therapy, if no allergy, due to MI and CVA
9. Explore with patient her adjustment to chronic medical conditions and the more recent partial right foot amputation she underwent. Adjustment can be considered in the form of emotional well-being, physical functioning, changes in lifestyle, quality of life, etc.
10. Screen for depression and refer/treat, accordingly.
11. Screen for diabetes distress using Diabetes Distress Scale. Responses can be used to guide conversation with patient about her attitude towards and challenges of having diabetes to assist with adjustment and treatment planning. (**www.diabetesdistress.org**)
12. Learn more about extent of patient's participation in physical rehabilitation (e.g., physical therapy, occupational), what progress has been made, and are more services necessary. Also, is patient able to return to the job she had/is it possible for her to do the work she did prior to the partial right foot amputation? If not, I recommend she seek vocational rehabilitation services through DSHS Division of Vocational Rehabilitation. (**www.dshs.wa.gov/dvr**)
13. Explore further with patient her plan for making changes to her eating habits and food choices. Is she setting realistic goals for herself? How confident is she that she can meet these goals? When she thinks about making goals for herself, is she considering short-term and long-term? For example, how likely is it that she can sustain being on a keto diet or a diet of Swiss cheese and watermelon? Such approaches are rigid and ultimately ineffective. I would ask patient to reconsider working with a nutritionist to assist with snack/meal planning, at least, that fits in with patient's typical ways of eating and lifestyle.
14. Obesity, diabetes, and colitis are medical conditions in which there is much focus on food and body. The nutritionist could also explore the patient's attitude towards food and concerns about body size/shape/weight to screen for disordered eating behaviors that could be negatively impacting her medical treatment. This exploration could also be done by other primary care providers as well if patient chooses to not participate in medical nutrition therapy.
15. Given patient's multiple medical conditions, some of which are influenced by lifestyle choices, you could explore with the patient what is her sense of self-agency regarding prevention/intervention and how does that impact her approach to making healthful changes. (**www.cancercontrol.cancer.gov/sites/default/files/2020-06/theory.pdf**)
16. Are there aspects of this patient's culture that her providers would benefit from considering when it comes to her treatment recommendations?

Nicole Ehrhardt, MD

_____*Nicole Ehrhardt* ____

**physician Signature Nicole Ehrhardt**

**Represent case Aug 2022**