# Clinical application of SGLT2is for cardiologists

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# Prevalence of cardiovascular disease in younger people with type 1 diabetes

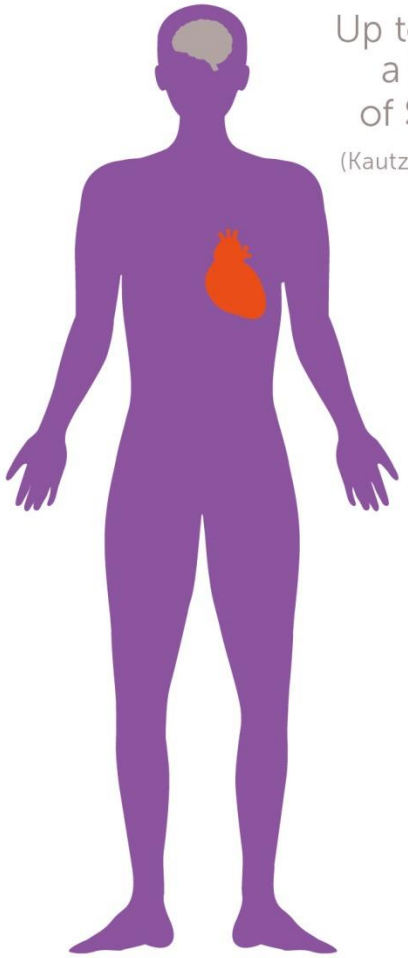
International Diabetes Federation

**In studies of younger people with type 1 diabetes living in high- and middle-income countries:**

Up to **16%** had a history of **CVD**

includes stroke, coronary artery disease, and peripheral artery disease

(David, 2010)



Up to **2%** had a history of **STROKE**

(Kautzy-Willer, 2013)

Up to **1%** had a history of **HEART ATTACK**

(Koivisto, 1996)

Mean age of study population: 25 to 44 years

www.idf.org/cvd

# Prevalence of cardiovascular disease in middle-aged people with diabetes

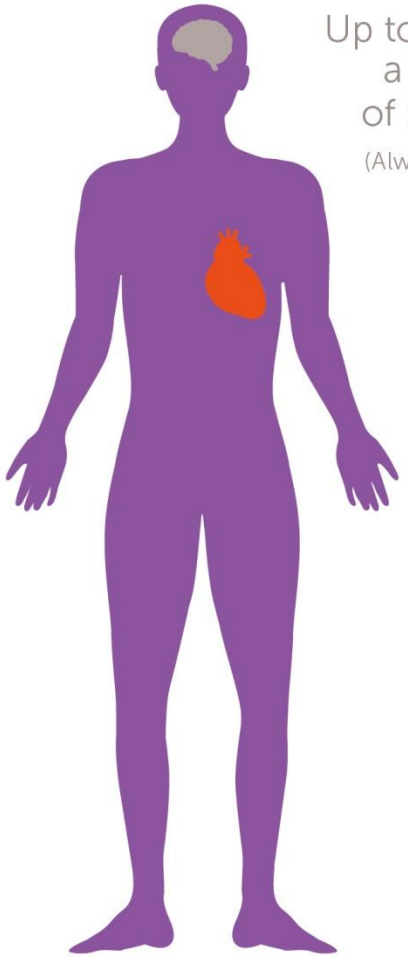
International Diabetes Federation

**In studies of middle-aged people with diabetes living in high- and middle-income countries:**

Up to **41%** had a history of **CVD**

includes stroke, coronary artery disease, and peripheral artery disease

(van Hateren, 2009)



Up to **10%** had a history of **STROKE**

(Alwakeel, 2008)

Up to **14%** had a history of **HEART ATTACK**

(Alwakeel, 2008)

Mean age of study population: 50 to 69 years

www.idf.org/cvd

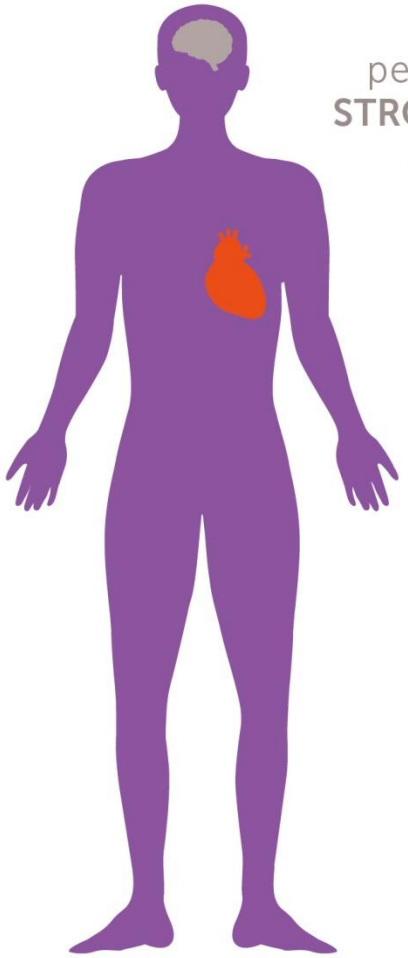
# Cardiovascular disease mortality in middle-aged people with diabetes

International Diabetes Federation

**In studies of middle-aged people with diabetes living in high- and middle-income countries:**

Up to **27** per 1,000 died from **CVD** each year

(Miot, 2012)



Up to **9** per 1,000 died **STROKE** each year

(Mlacak, 1999)

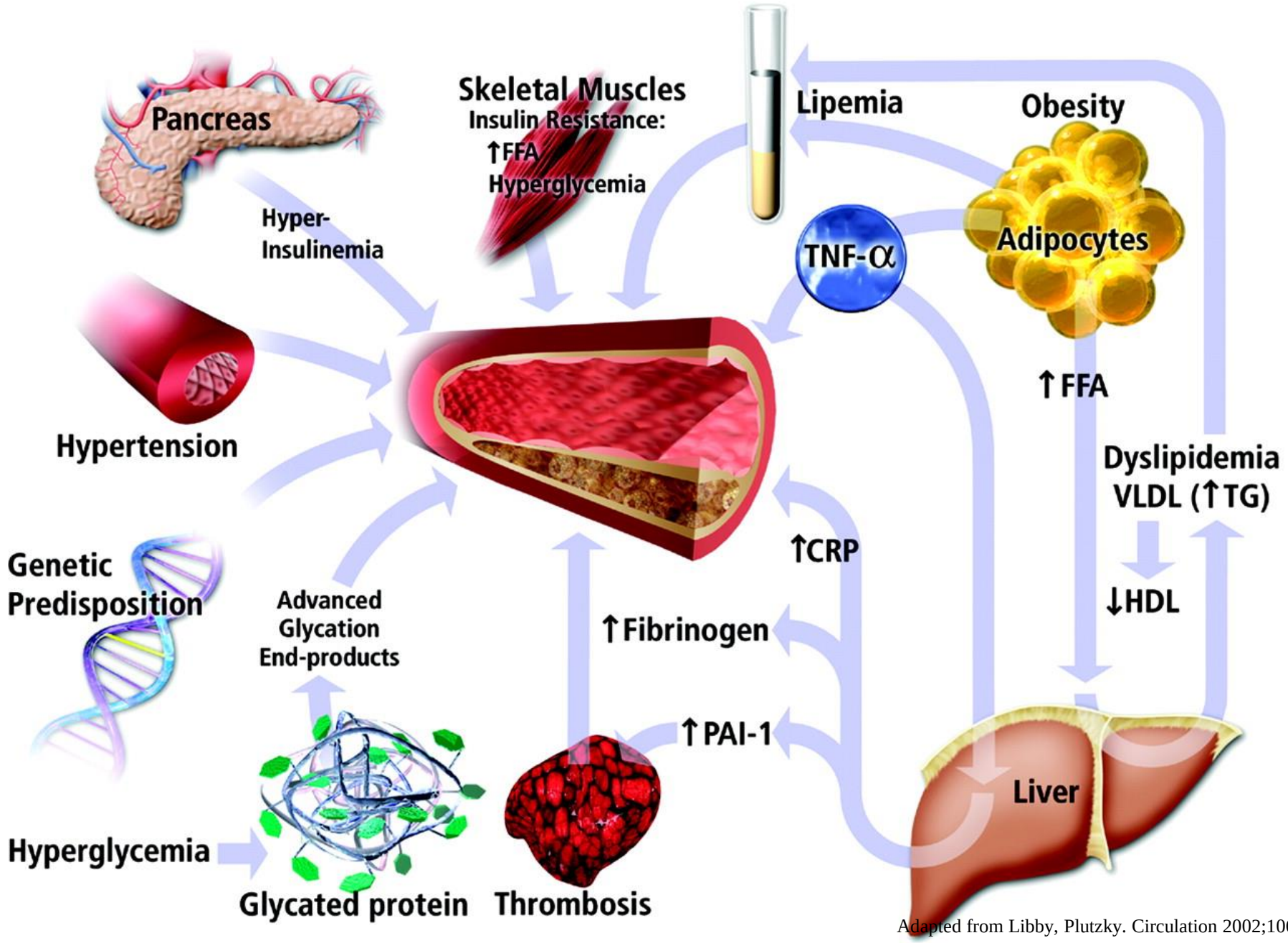
Up to **7** per 1,000 died from **CORONARY ARTERY DISEASE** each year

(Bidel, 2006)

Mean age of study population: 49 to 69 years

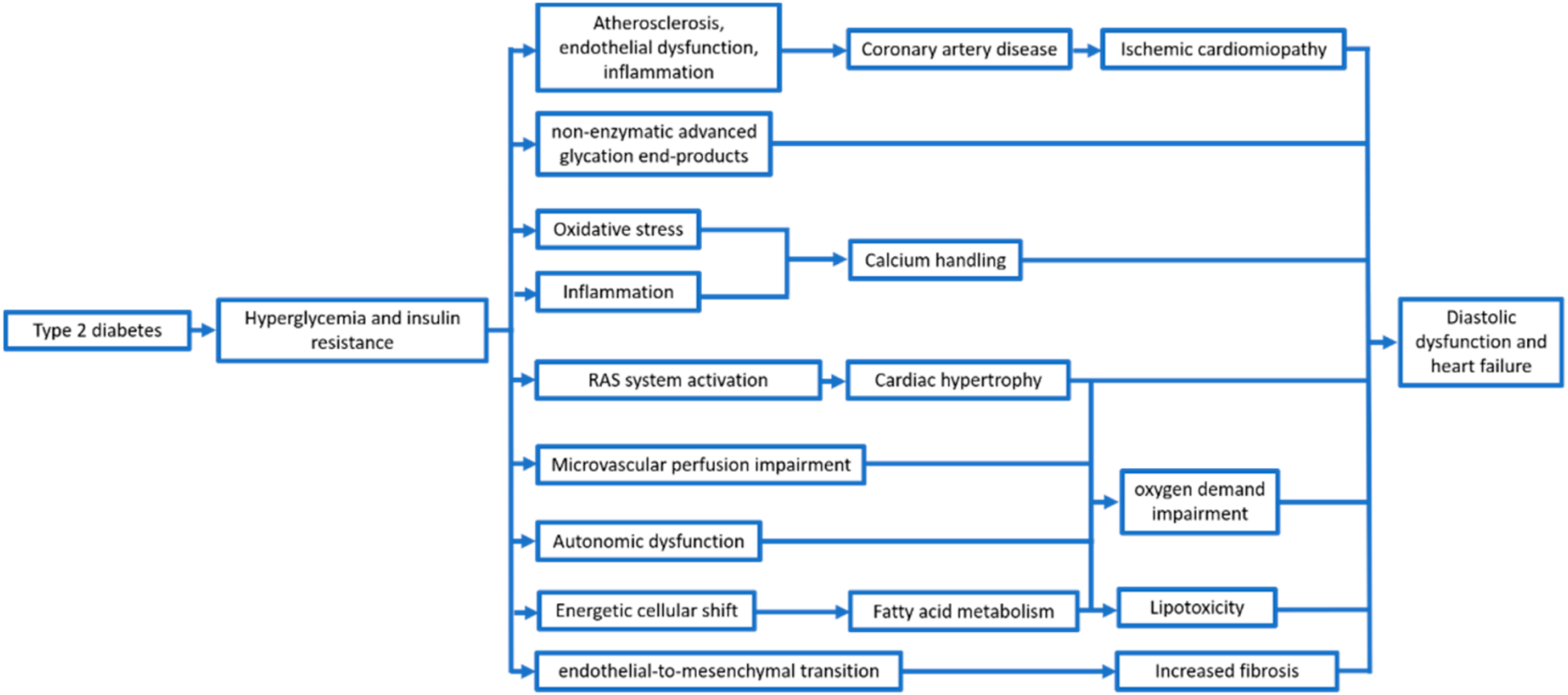
www.idf.org/cvd

# Many factors contribute to increased CV risk in T2D

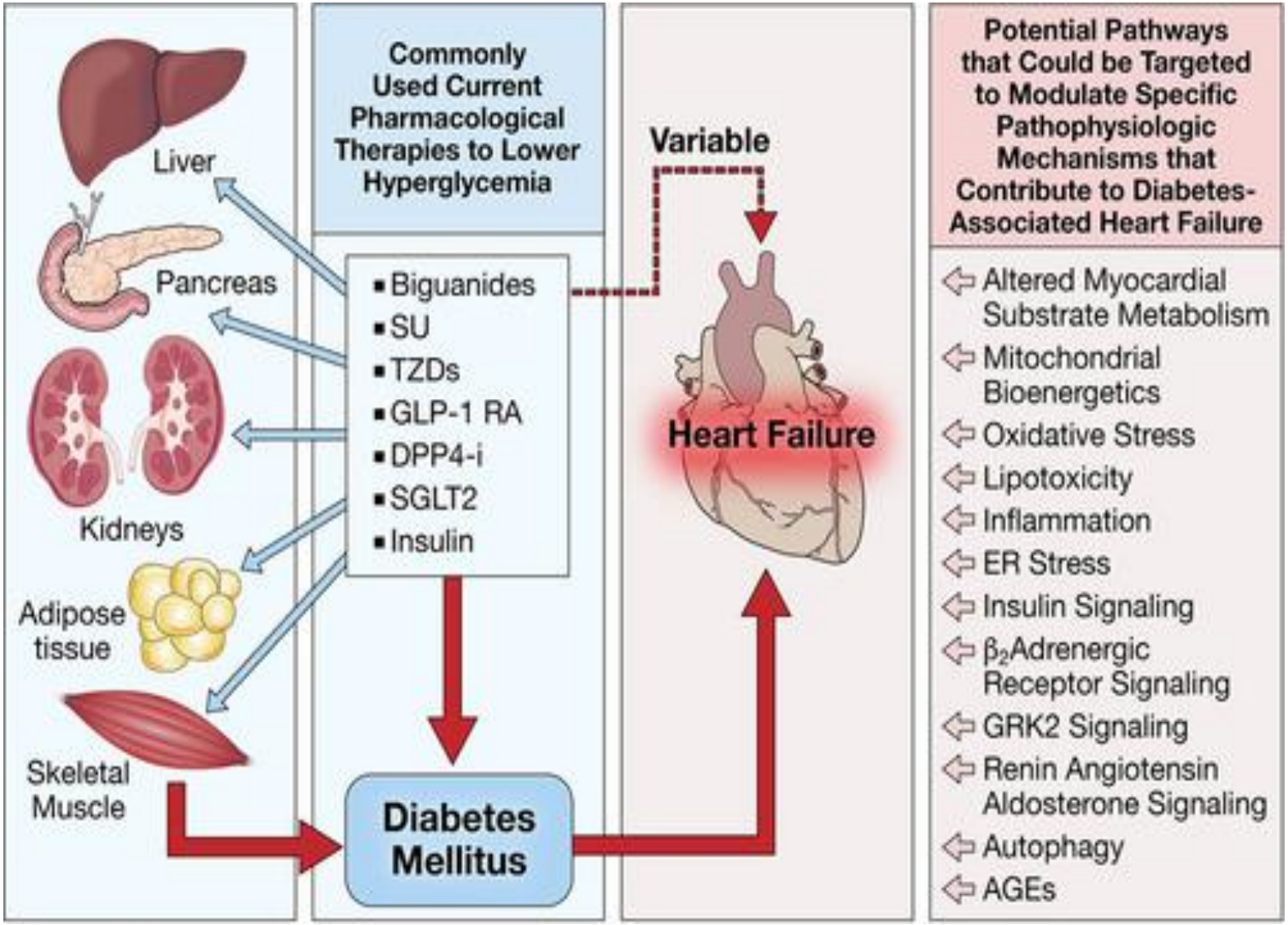



Adapted from Libby, Plutzky. Circulation 2002;106:2760–63

# Main mechanisms leading to ventricular dysfunction in type 2 diabetes patients




https://www.mdpi.com/ijms/ijms-22-05863/article_deploy/html/images/ijms-22-05863-g001.png



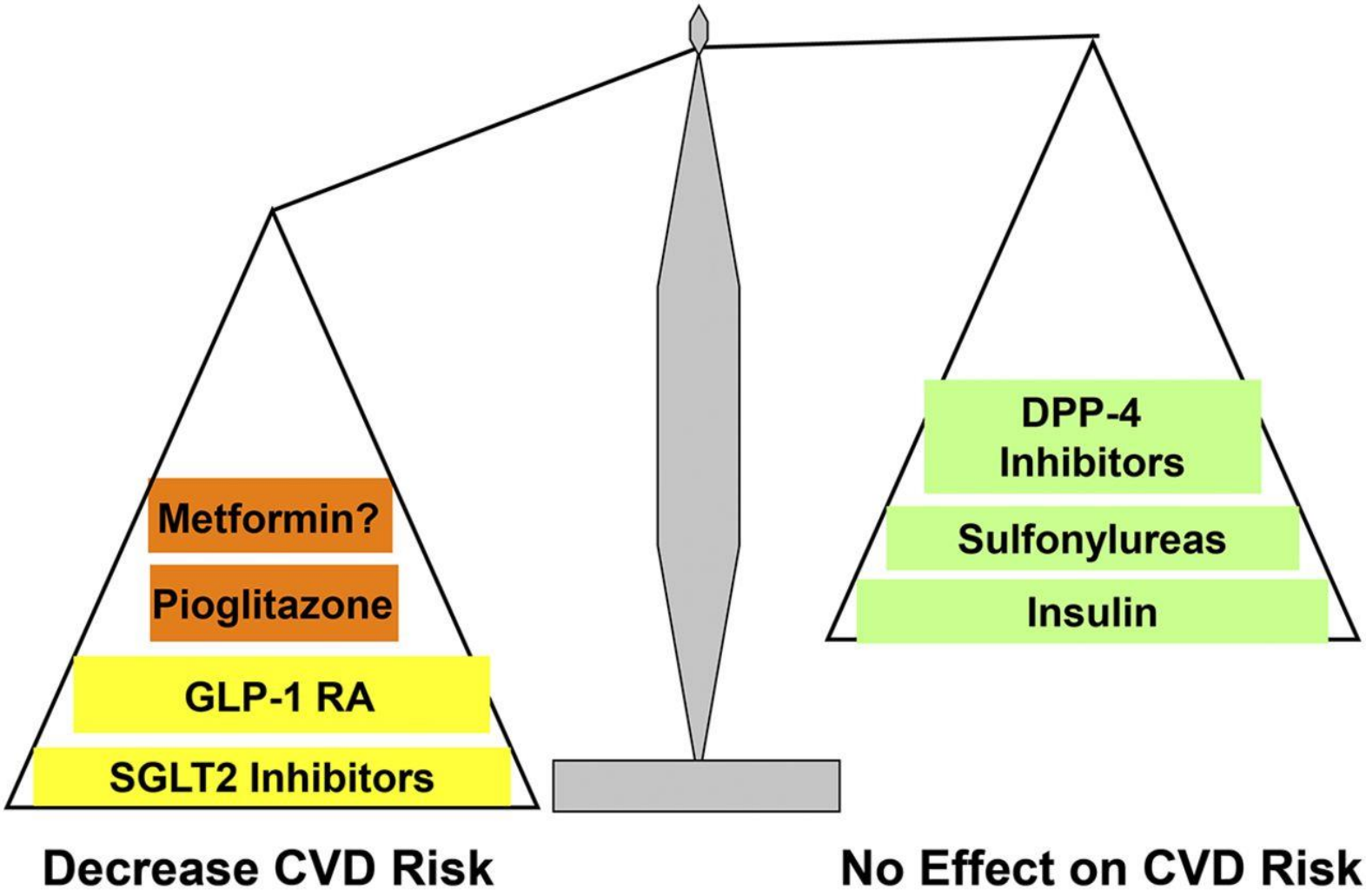

Helena C. Kenny. Circulation Research. Heart Failure in Type 2 Diabetes Mellitus, Volume: 124, Issue: 1, Pages: 121-141, DOI: (10.1161/CIRCRESAHA.118.311371)

# Effects on CVD risk among glucose-lowering agents

| Specific effects on CVD Risk | Non-Specific effects on CVD Risk |
| --- | --- |
| Metformin? | DPP-4 inhibitors |
| Pioglitazone | Sulfonylureas |
| GLP-1 receptor agonists * | Glinide |
| SGLT2 inhibitors * | Alpha-glucosidase inhibitors? |
| | Insulin |

* evidenced by CVOTs

# Cardiovascular risk profile of antidiabetes medications.




Muhammad Abdul-Ghani et al. Dia Care 2017;40:813-820

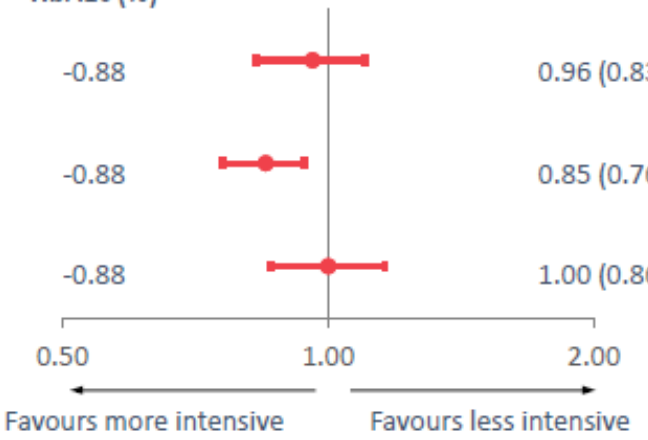


American Diabetes Association.

- **Pioglitazone**
  - Leading to a 42% increased risk of incident heart failure
- **Dipeptidyl peptidase 4 inhibitors**
  - Appear to have a neutral effect on major adverse cardiovascular events
- **Insulin for type 2 diabetes**
  - 27% increase in all-cause mortality
  - 23% increase in hospitalisation for heart failure.

# Meta-analysis of intensive glucose control in T2DM: major CV events including heart failure

| | Number of events | | | HR (95% CI) |
|---|---|---|---|---|
| | More intensive | Less intensive | Difference in HbA1c (%) | |
| Stroke | 378 | 370 | -0.88 | 0.96 (0.83, 1.10) |
| Myocardial infarction | 730 | 745 | -0.88 | 0.85 (0.76, 0.94) |
| Hospitalization for or death from heart failure | 459 | 446 | -0.88 | 1.00 (0.86, 1.16) |



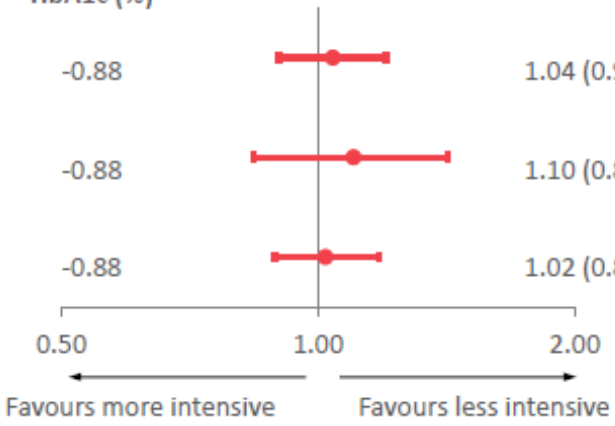

- Meta-analysis of 27,049 participants and 2370 major vascular events from:
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

Turnbull FM et al. Diabetologia 2009;52:2288–2298

Zinman, et al. NEJM. 2015

# Meta-analysis of intensive glucose control in T2DM: mortality

| | Number of events | | | |
|---|---|---|---|---|
| | More intensive | Less intensive | Difference in HbA1c (%) | HR (95% CI) |
| All-cause mortality | 980 | 884 | -0.88 | 1.04 (0.90,1.20) |
| CV death | 497 | 441 | -0.88 | 1.10 (0.84,1.42) |
| Non-CV death | 476 | 432 | -0.88 | 1.02 (0.89,1.18) |



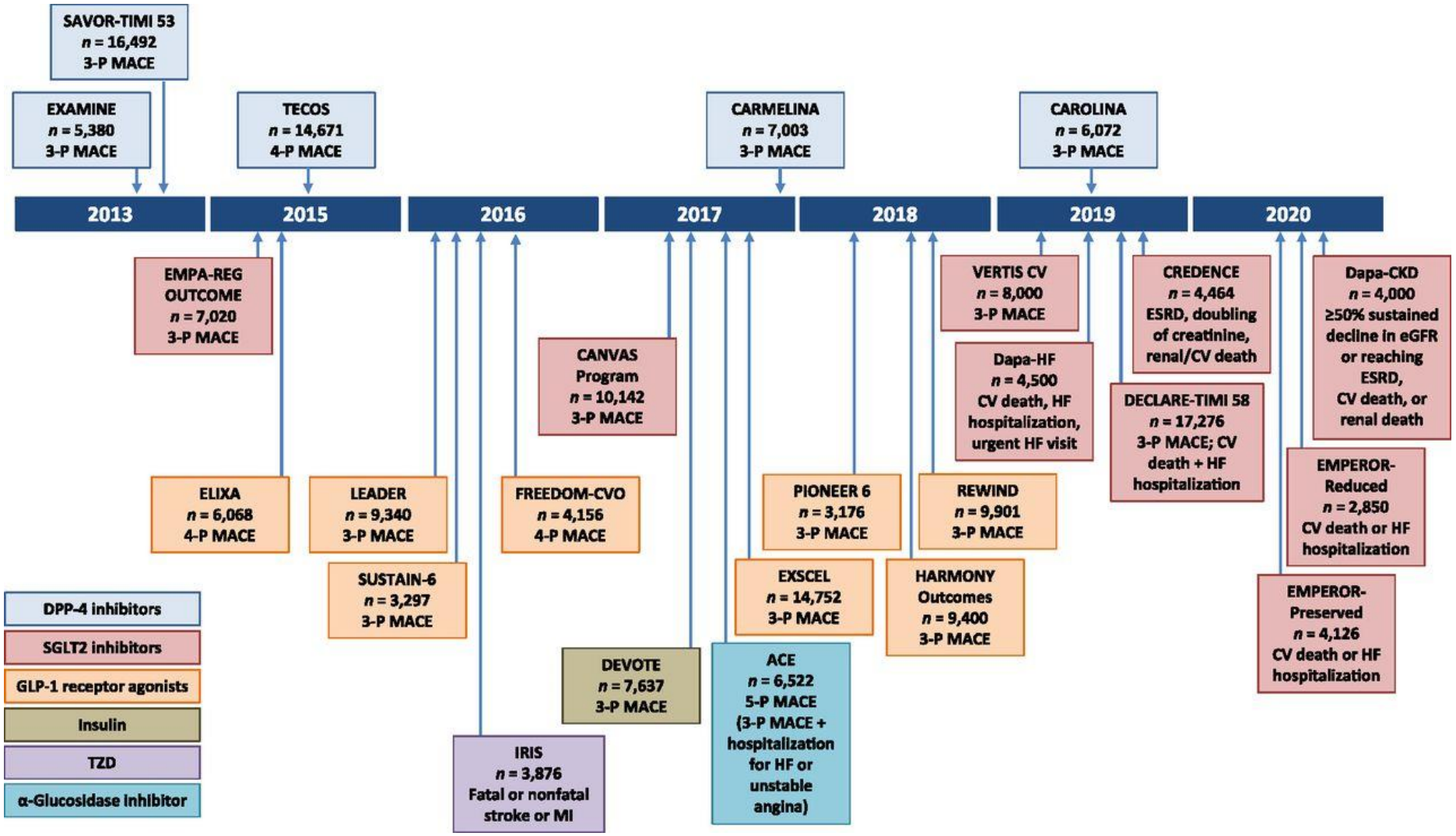

- Meta-analysis of 27,049 participants and 2370 major vascular events from
  - ADVANCE
  - UKPDS
  - ACCORD
  - VADT

HR, hazard ratio; CV, cardiovascular

Turnbull FM et al. Diabetologia 2009;52:2288–2298

Zinman, et al. NEJM. 2015

**Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.**




William T. Cefalu et al. Dia Care 2018;41:14-31



American Diabetes Association.

Heart Failure Reviews
https://doi.org/10.1007/s10741-021-10106-9

# New antidiabetic therapy and HFpEF: light at the end of tunnel?

Marijana Tadic[1] · Carla Sala[2] · Sahrai Saeed[3] · Guido Grassi[4] · Giuseppe Mancia[5] · Wolfang Rottbauer[1] · Cesare Cuspidi[4,6]

Accepted: 6 April 2021

# Cardiovascular Outcomes Studies

| Study | n | Design | MACE Outcome | CV Death | HF Hospitalization |
|---|---|---|---|---|---|
| EMPA-REG OUTCOME 2015 | 7020 | RDBPCT | Empagliflozin: 490 (10.5%)<br>Placebo: 282 (12.1%)<br>HR: **0.86** (95% CI 0.74-0.99); p<0.001 NI and 0.04 SP | Empagliflozin: 172 (3.7%)<br>Placebo: 137 (5.9%)<br>HR: **0.62** (95% CI 0.49-0.77); p<0.001 | Empagliflozin: 126 (2.7%)<br>Placebo: 95 (4.1%)<br>HR: **0.65** (95% CI 0.50-0.85); p=0.002 |
| CANVAS Program 2017 | 10142 | RDBPCT | Canagliflozin: 29.6/1000 PY<br>Placebo: 31.5/1000 PY<br>HR: **0.86** (95% CI 0.75-0.97); p<0.001 NI and 0.02 SP | Canagliflozin: 11.6/1000 PY<br>Placebo: 12.8/1000 PY<br>HR: 0.87 (95% CI 0.72-1.06)^ | Canagliflozin: 5.5/1000 PY<br>Placebo: 8.7/1000 PY<br>HR: **0.67** (95% CI 0.52-0.87)^ |
| DECLARE-TIMI 58 2018 | 17160 | RDBPCT | Dapagliflozin: 756 (8.8%)<br>Placebo: 803 (9.4%)<br>HR: 0.93 (95% CI 0.84-1.03); p<0.001 NI and p=0.17 SP | Dapagliflozin: 245 (2.9%)<br>Placebo: 249 (2.9%)<br>HR: 0.98 (95% CI 0.82-1.17) | Dapagliflozin: 212 (2.5%)<br>Placebo: 286 (3.3%)<br>HR: **0.73** (95% CI 0.61-0.88) |
| VERTIS CV 2020 | 8246 | RDBPCT | Ertugliflozin: 653 (11.9%)<br>Placebo: 327 (11.9%)<br>HR: 0.97 (95% CI 0.85-1.11); p<0.001 NI | Ertugliflozin: 341 (6.2%)<br>Placebo: 184 (6.7%)<br>HR: 0.92 (95% CI 0.77-1.11)^ | Ertugliflozin: 139 (2.5%)<br>Placebo: 99 (3.6%)<br>HR: **0.70** (95% CI 0.54-0.90)^ |

CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = Major adverse cardiovascular event; NI = non-inferiority; PY = patient years; RDBPCT = Randomized, double-blind, placebo-controlled trial; SP = superiority

^Exploratory

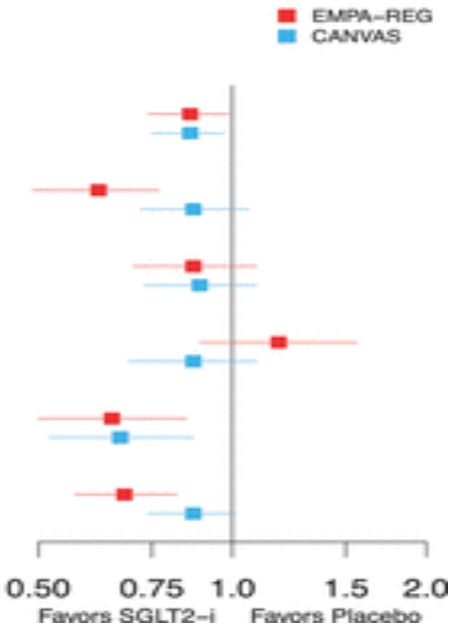


l J Med 373;22. N Engl J Med 377;7. N Engl J Med 380;4. N Engl J Med 383;15.

**A Trial Design Summary**


**B Summary of key cardiovascular outcomes**

| | Active Rate per 1000 patient-years | Placebo Rate per 1000 patient-years | Hazard Ratio (95% CI) |
|---|---|---|---|
| MACE-3 | 37.4 | 43.9 | 0.86 (0.74 – 0.99) |
| | 26.9 | 31.5 | 0.86 (0.75 – 0.97) |
| CV Death | 12.4 | 20.2 | 0.62 (0.49 – 0.77) |
| | 11.6 | 12.8 | 0.87 (0.72 – 1.06) |
| Fatal and nonfatal MI | 16.8 | 19.3 | 0.87 (0.70 – 1.09) |
| | 11.2 | 12.6 | 0.89 (0.73 – 1.09) |
| Fatal and nonfatal stroke | 12.3 | 10.5 | 1.18 (0.89 – 1.56) |
| | 7.9 | 9.6 | 0.87 (0.69 – 1.09) |
| Heart failure hospitalization | 19.4 | 14.5 | 0.65 (0.50 – 0.85) |
| | 5.5 | 8.7 | 0.67 (0.52 – 0.87) |
| All cause mortality | 19.4 | 28.6 | 0.68 (0.57 – 0.82) |
| | 17.3 | 19.5 | 0.87 (0.74 – 1.01) |

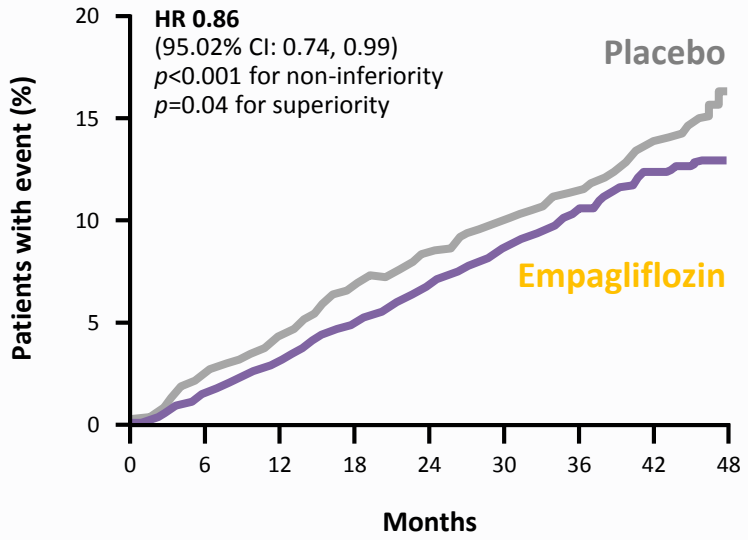



M. Angelyn Bethel. Circulation. Class Effect for Sodium Glucose-Cotransporter-2 Inhibitors in Cardiovascular Outcomes, Volume: 137, Issue: 12, Pages: 1218-1220, DOI: (10.1161/CIRCULATIONAHA.117.030117)

# Overview of CVOT findings for SGLT2 inhibitors

## EMPA-REG OUTCOME study[1]

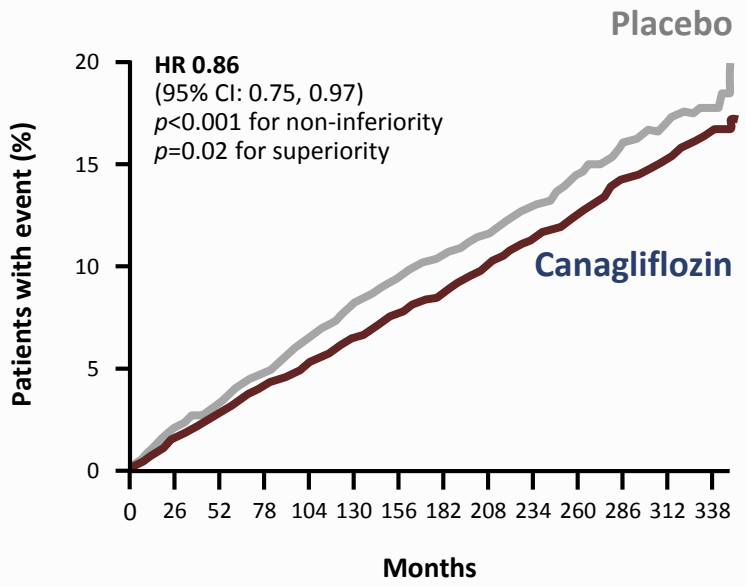
Adults with type 2 diabetes and established CV disease
CV death, non-fatal MI, or non-fatal stroke




| 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[2]

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

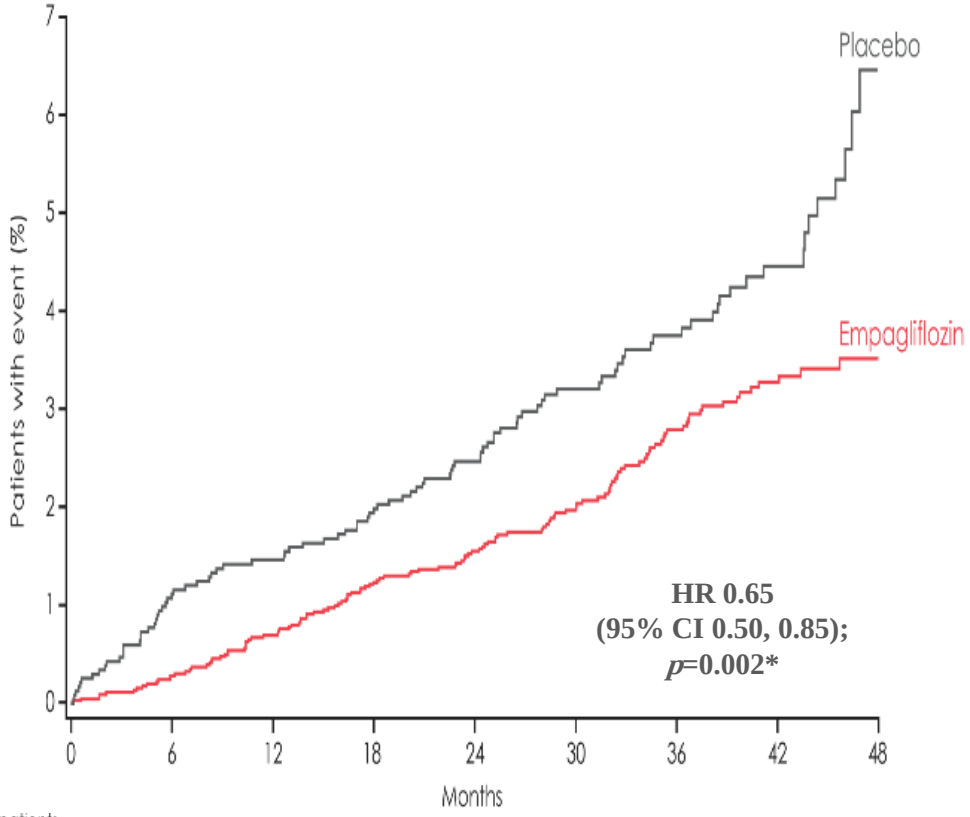



| Patients at risk: | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Canagliflozin | 5795 | 5672 | 5566 | 5447 | 4343 | 2984 | 2555 | 2513 | 2460 | 2419 | 2363 | 2311 | 1661 | 448 |
| Placebo | 4347 | 4239 | 4153 | 4061 | 2942 | 1626 | 1240 | 1217 | 1187 |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

1. Zinman B *et al. N Engl J Med.* 2015;37:2117–2128. 2. Neal B *et al. N Engl J Med.* 2017;377:644-657.

# Heart failure outcome with SGLT2 inhibitors

## Hospitalisation for heart failure

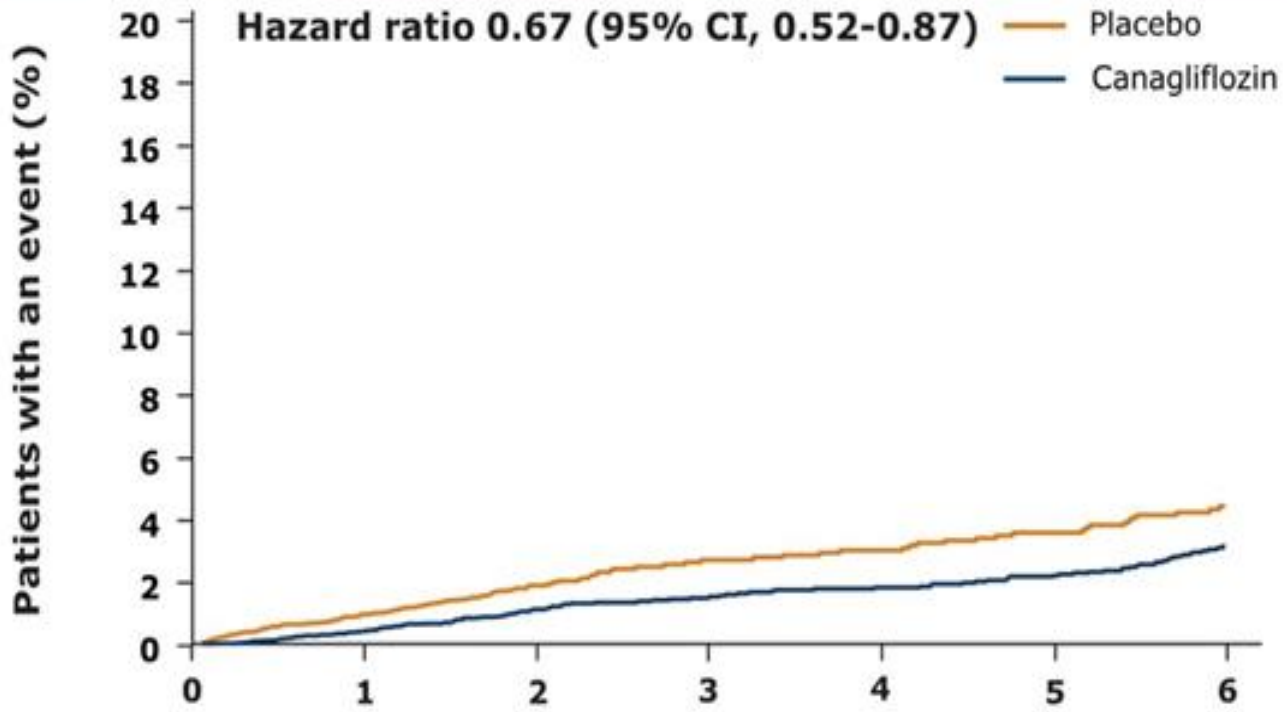



| No. of patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Empagliflozin | 4687 | 4614 | 4523 | 4427 | 3988 | 2950 | 2487 | 1634 | 395 |
| Placebo | 2333 | 2271 | 2226 | 2173 | 1932 | 1424 | 1202 | 775 | 168 |

RRR for HHF is 35%; rates of HHF: 2.7% (empagliflozin) vs 4.1% (placebo); ARR for HHF is 1.4%
*Nominal *p*-value. Cumulative incidence function
ARR, absolute risk reduction; CV, cardiovascular; HHF, hospitalisation for heart failure; RRR, relative risk reduction
Zinman B *et al. N Engl J Med* 2015;373:2117

# Heart failure outcome with SGLT2 inhibitors

## Hospitalization for Heart Failure




| No. of patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo | 4347 | 4198 | 3011 | 1274 | 1236 | 1180 | 829 |
| Canagliflozin | 5795 | 5653 | 4437 | 2643 | 2572 | 2498 | 1782 |

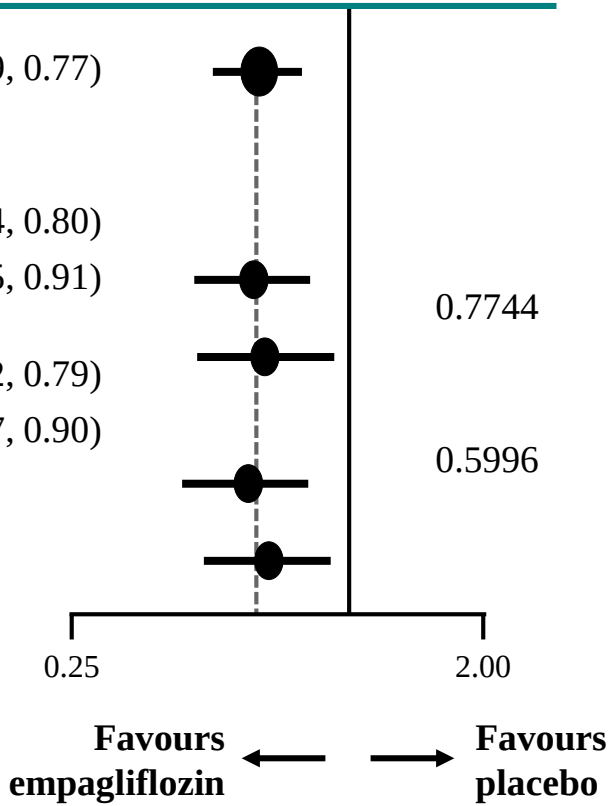
Intent-to-treat analysis

Presented at the 77th Scientific Sessions of the American Diabetes Association; June 12, 2017; San Diego, CA.

CANVAS Program

# Reduced risk of CV death was not associated with change in $HbA_{1c}$ during the EMPA-REG OUTCOME study

| | Patients with event/analysed | | | |
|---|---|---|---|---|
| | Empagliflozin | Placebo | HR (95% CI) | *p* value |
| **All patients** | 172/4687 (3.7) | 137/2333 (5.9) | 0.62 (0.49, 0.77) | |
| **Change from baseline in $HbA_{1c}$ at the last value in the trial** | | | | |
| Any reduction | 109/2957 (3.7) | 74/1158 (6.4) | 0.60 (0.44, 0.80) | |
| Increase or no change | 63/1728 (3.6) | 63/1175 (5.4) | 0.64 (0.45, 0.91) | 0.7744 |
| Reduction of ≥0.3% | 97/2614 (3.7) | 65/974 (6.7) | 0.58 (0.42, 0.79) | |
| Reduction of <0.3% or increase | 75/2071 (3.6) | 72/1359 (5.3) | 0.65 (0.47, 0.90) | 0.5996 |

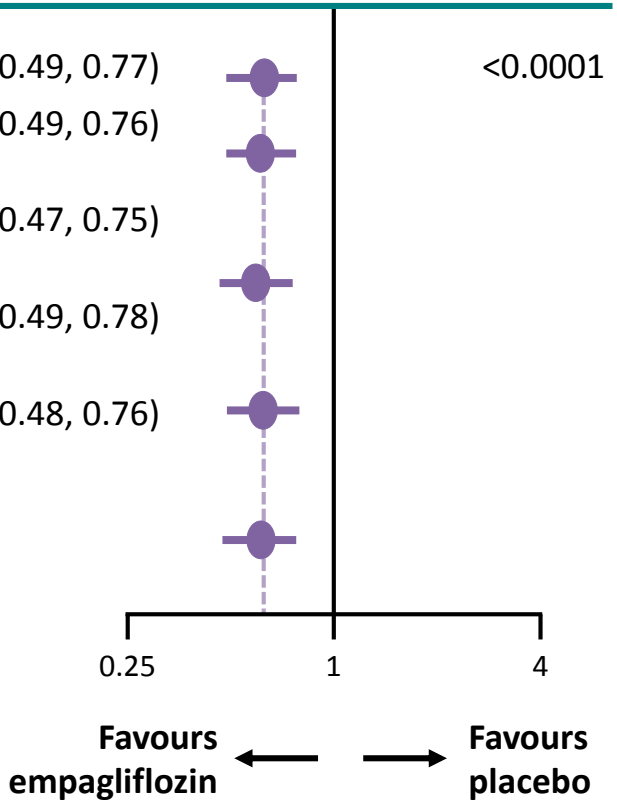



**Post-hoc analysis. Cox regression analysis in patients treated with ≥1 dose of study drug. P-values relate to tests of the homogeneity of treatment group differences among subgroups (test for treatment by subgroup interaction) with no adjustment for multiple testing CI, confidence intervals; $HbA_{1c}$, glycated haemoglobin.**

Inzucchi S, *et al.* Poster presented at Diabetes UK Professional Conference, 14-16 March 2018, London, UK.

# Reduced risk of CV death was not associated with BP, LDL-cholesterol or $HbA_{1c}$ control over time

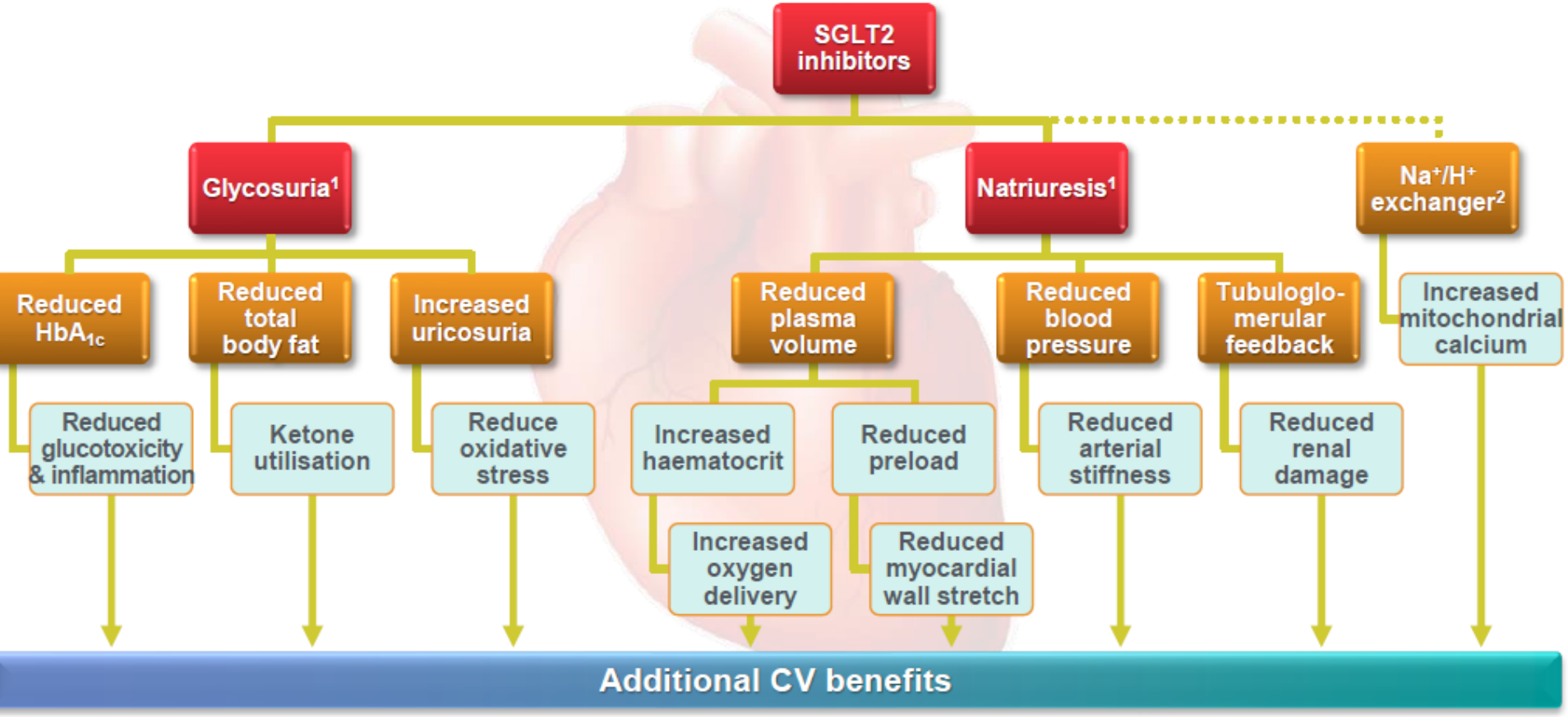
| CV death | Patients with event/analysed (%) Empagliflozin | Placebo | HR (95% CI) | *p* value |
|---|---|---|---|---|
| Main analysis | 172/4687 (3.7) | 137/2333 (5.9) | 0.62 (0.49, 0.77) | <0.0001 |
| Adjusted for time-dependent control of BP* | 172/4687 (3.7) | 137/2333 (5.9) | 0.61 (0.49, 0.76) | |
| Adjusted for time-dependent control of LDL-C † | 167/4615 (3.6) | 136/2308 (5.9) | 0.59 (0.47, 0.75) | |
| Adjusted for time-dependent control of $HbA_{1c}$ ‡ | 172/4685 (3.7) | 137/2333 (5.9) | 0.62 (0.49, 0.78) | |
| Adjusted for time-dependent control of BP, LDL-C and $HbA_{1c}$ | 167/4614 (3.6) | 136/2308 (5.9) | 0.61 (0.48, 0.76) | |




*(SBP <140 mmHg and DBP <90mmHg). †(LDL-cholesterol <100mg/dl). ‡($HbA_{1c}$<7.5%).
Post-hoc analysis. Cox regression analysis in patients treated with ≥1 dose of study drug.
Main analysis did not adjust for baseline or time-dependent control of BP, LDL-cholesterol or HbA1c.

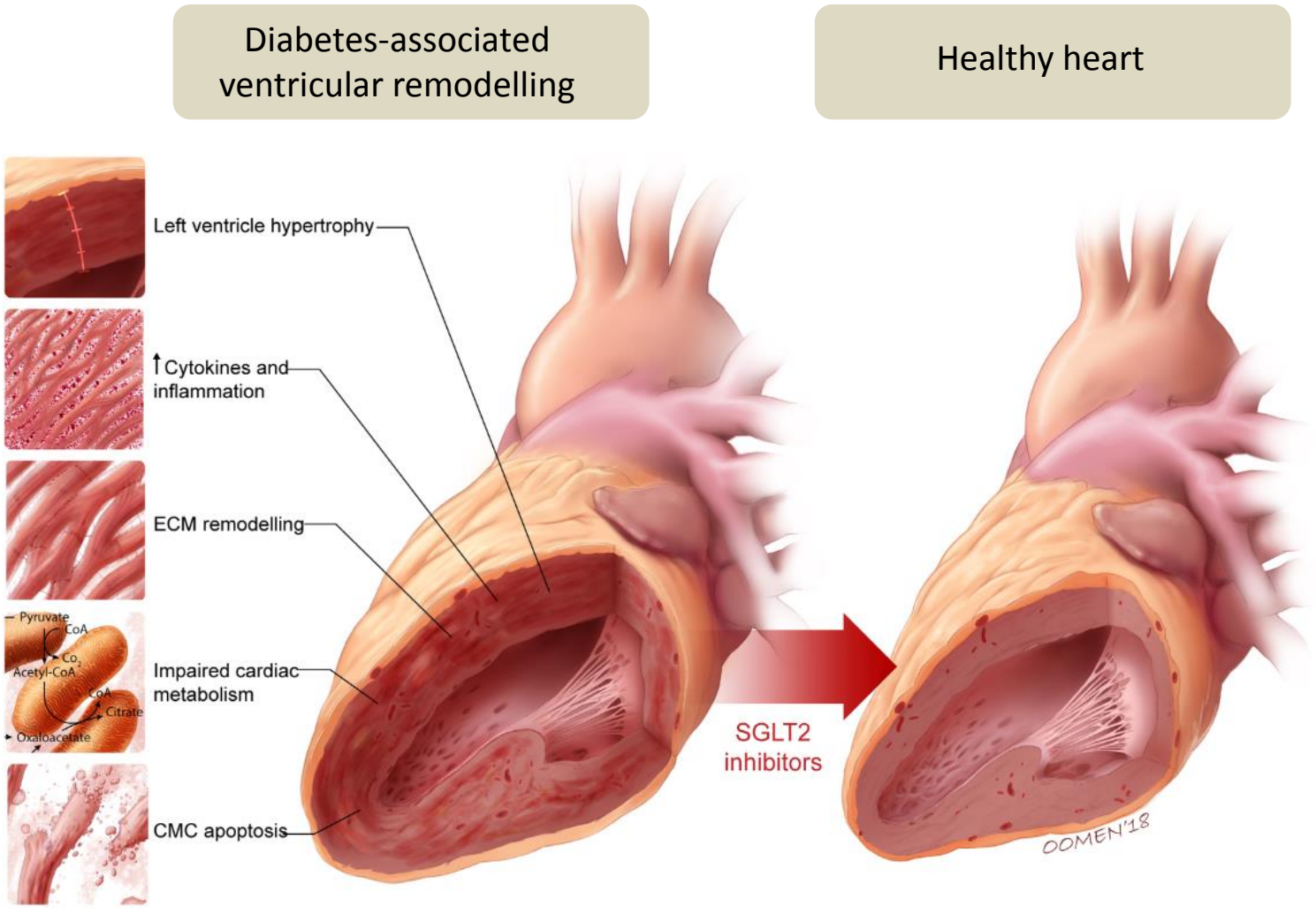
Fitchett D, et al. Poster presented at Diabetes UK Professional Conference, 14-16 March 2018, London, UK.

# Multiple mechanisms may contribute to CV benefits with SGLT2 inhibitors




1. Heerspink HJL, *et al. Circulation* 2016;134:752–72; 2. Baartscheer A, *et al. Diabetologia* 2017;60:568

# Cardiovascular protection by SGLT2 inhibitors

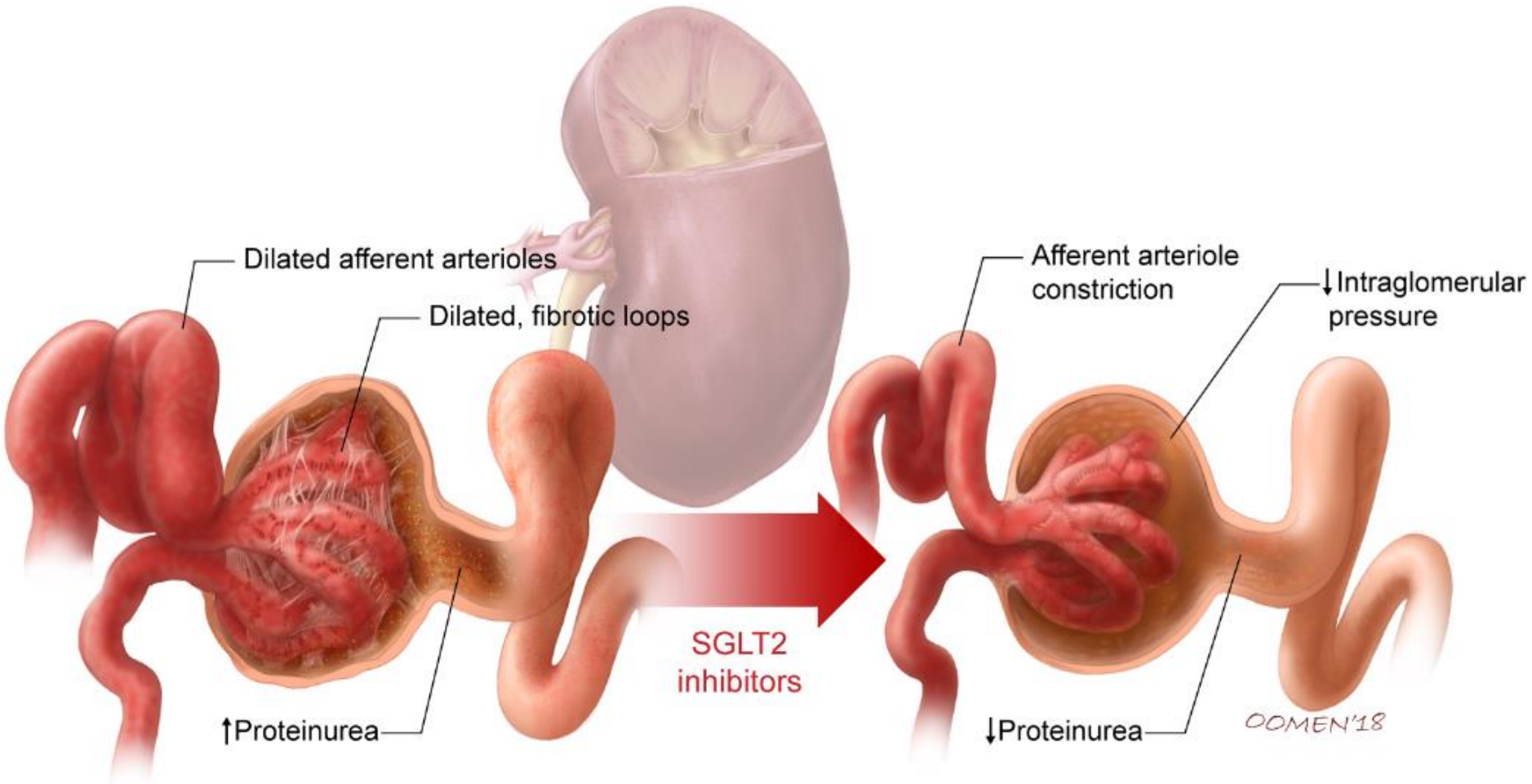



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7



Diabetologia

# SGLT2 inhibitors improve ventricular loading conditions

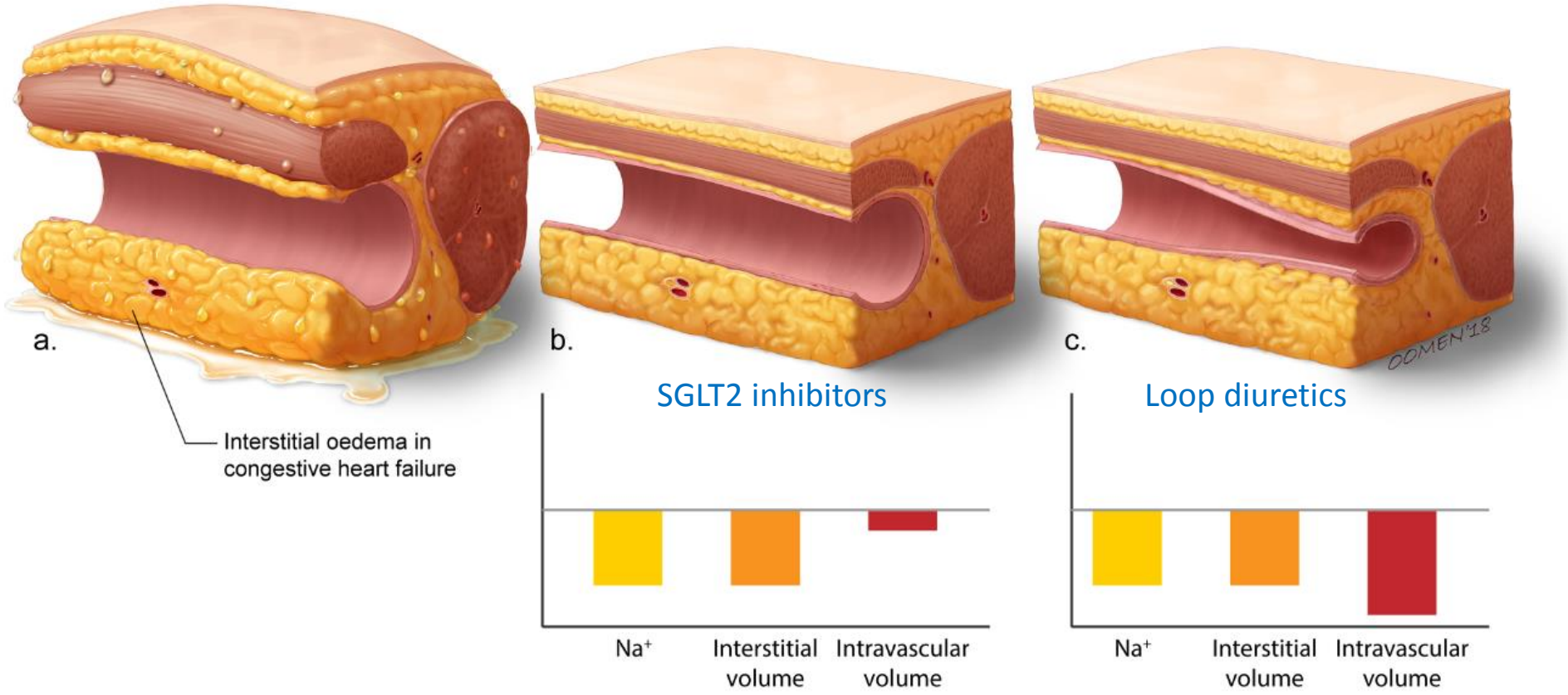



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7



Diabetologia

# SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics

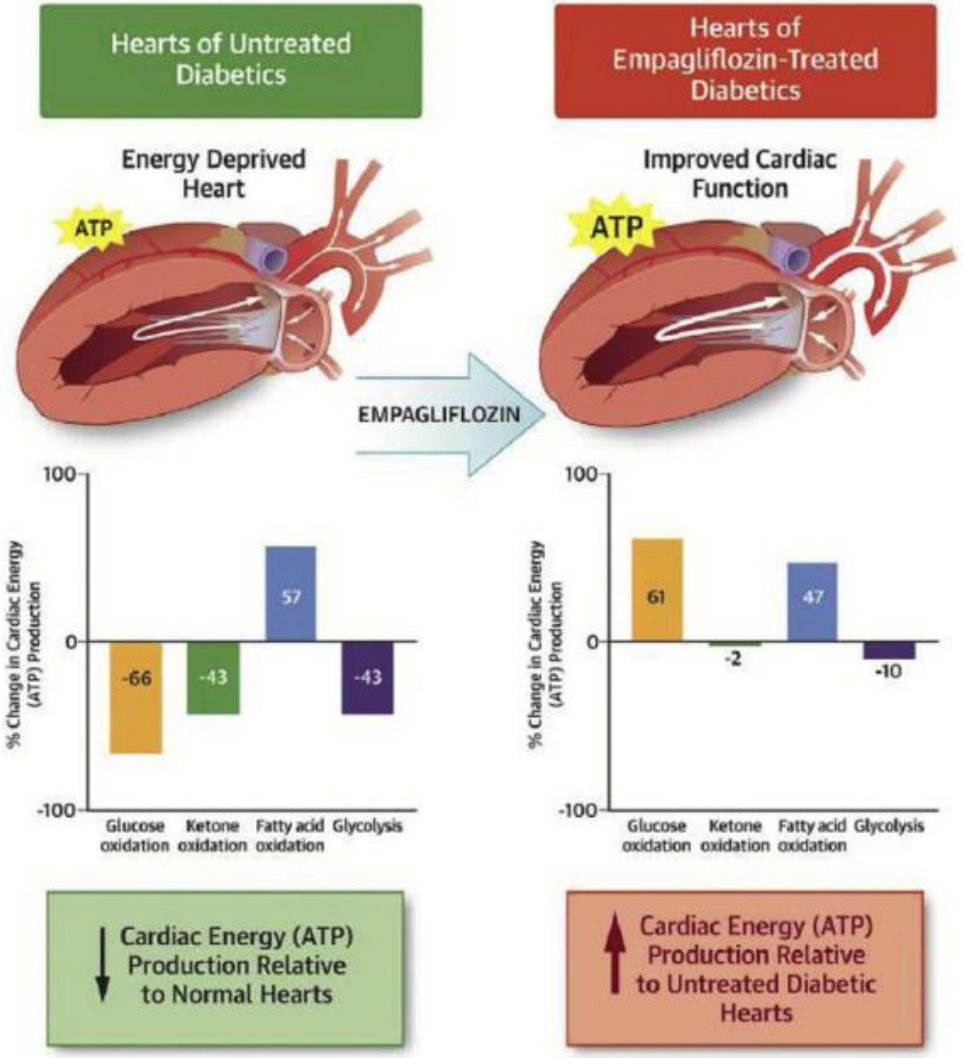



Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7



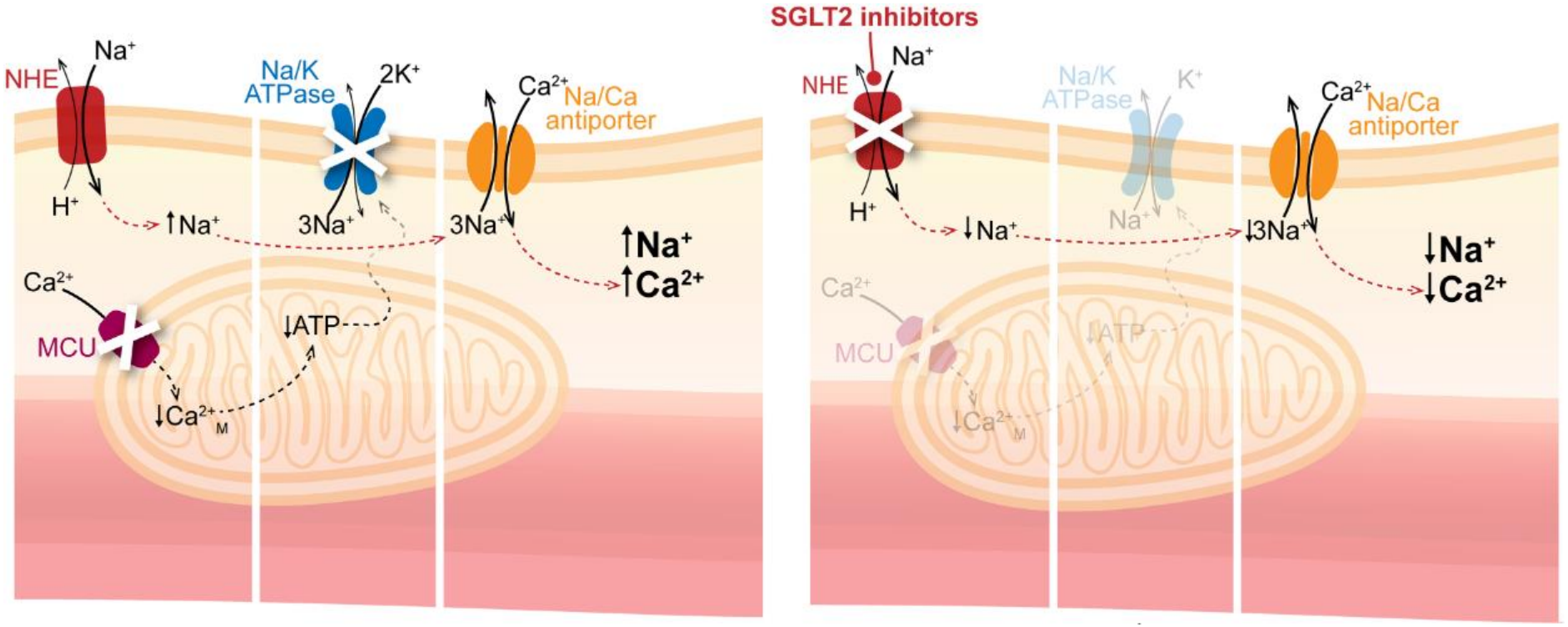
Diabetologia

# Myocardial energetics




Verma S et al. Empagliflozin increases cardiac energy production in diabetes. *JACC Basic Trans Sci.* 2018;3:575 − 587.)

# SGLT2 inhibition and direct effects on Na+/H+ exchange in the myocardium




Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7



Diabetologia

Xiang et al. Cardiovasc Diabetol (2021) 20:78
https://doi.org/10.1186/s12933-021-01266-x

Cardiovascular Diabetology

REVIEW Open Access

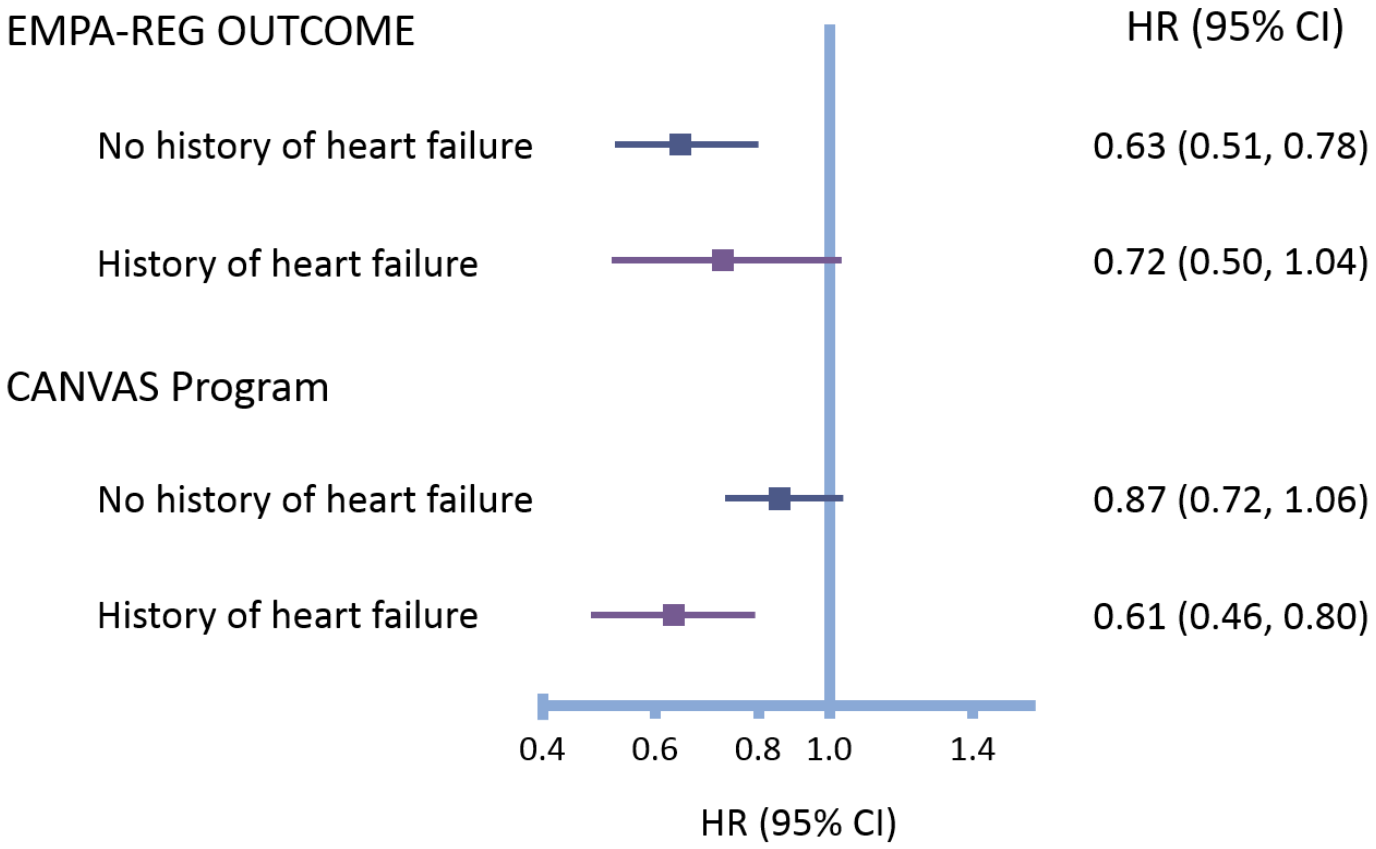
# Cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors in diabetic and nondiabetic patients

Boyang Xiang, Xiaoya Zhao and Xiang Zhou*

**Abstract**

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were developed as antidiabetic agents, but accumulating evidence has shown their beneficial effects on the cardiovascular system. Analyses of the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) suggested that these benefits

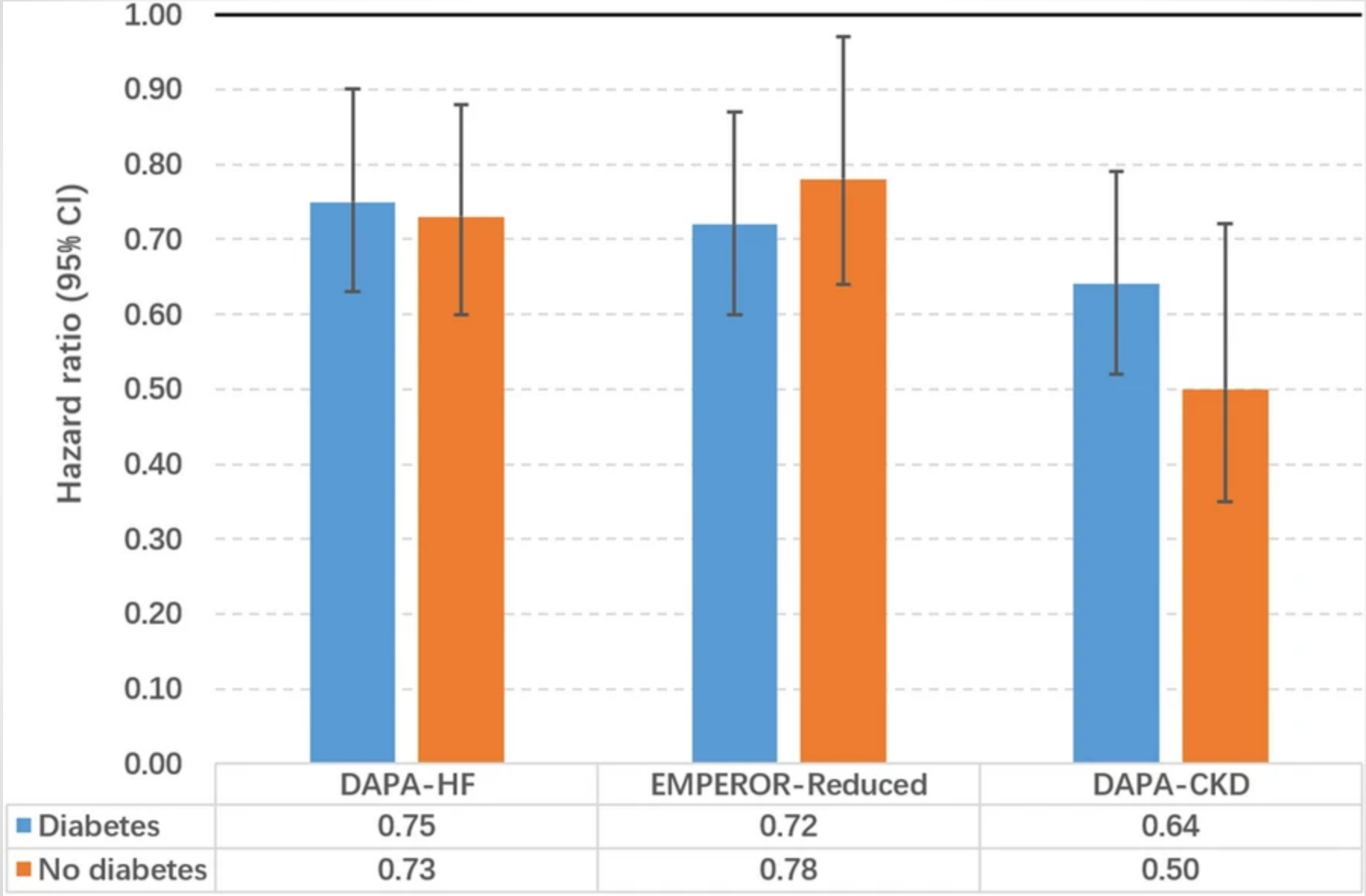
# The cardiovascular benefits with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) in participants with and without a history of heart failure




Verma and McMurray (2018) Diabetologia DOI 10.1007/s00125-018-4670-7

Diabetologia

# Cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors in diabetic and nondiabetic patients




| | DAPA-HF | EMPEROR-Reduced | DAPA-CKD |
|---|---|---|---|
| Diabetes | 0.75 | 0.72 | 0.64 |
| No diabetes | 0.73 | 0.78 | 0.50 |

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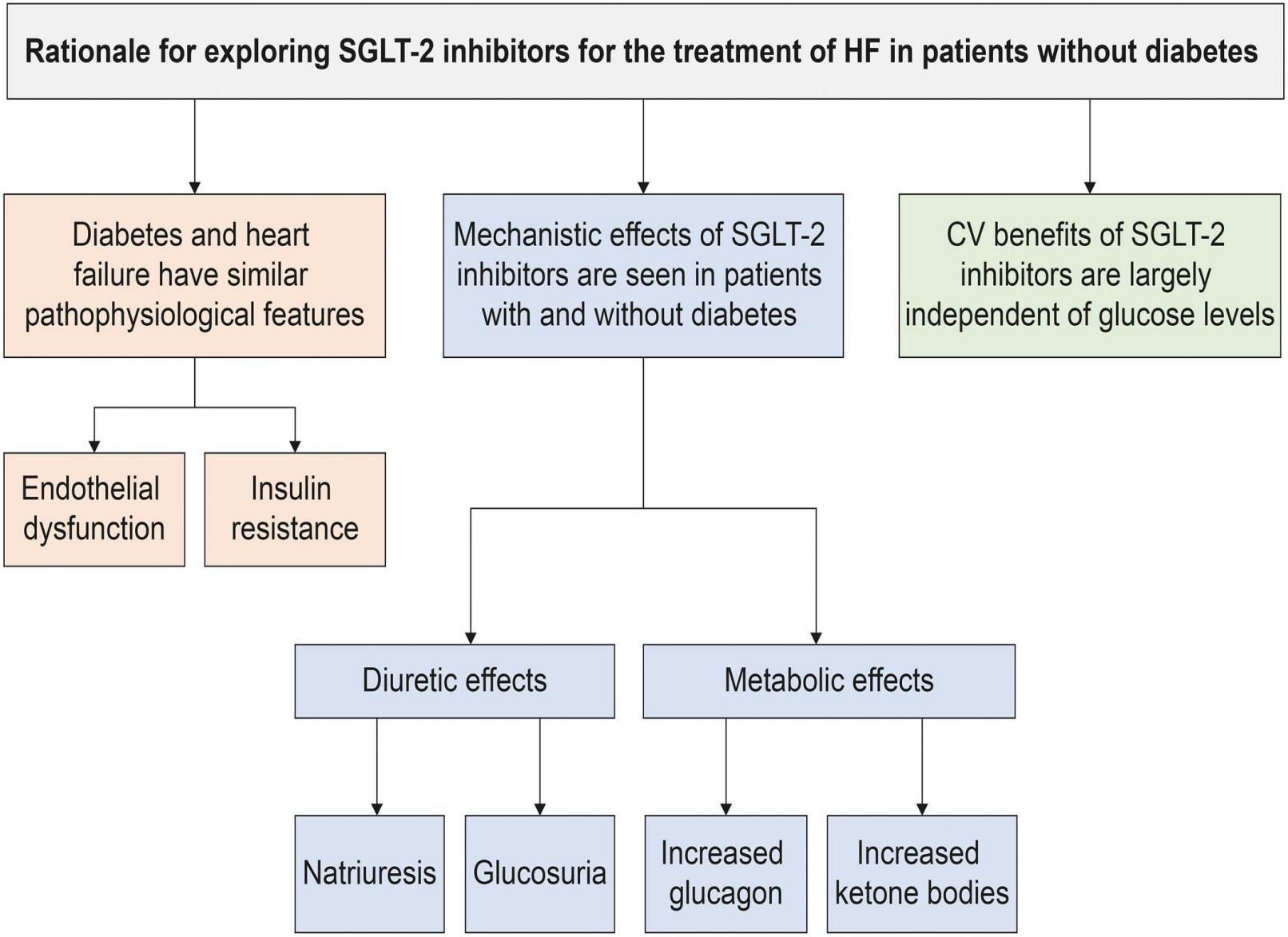
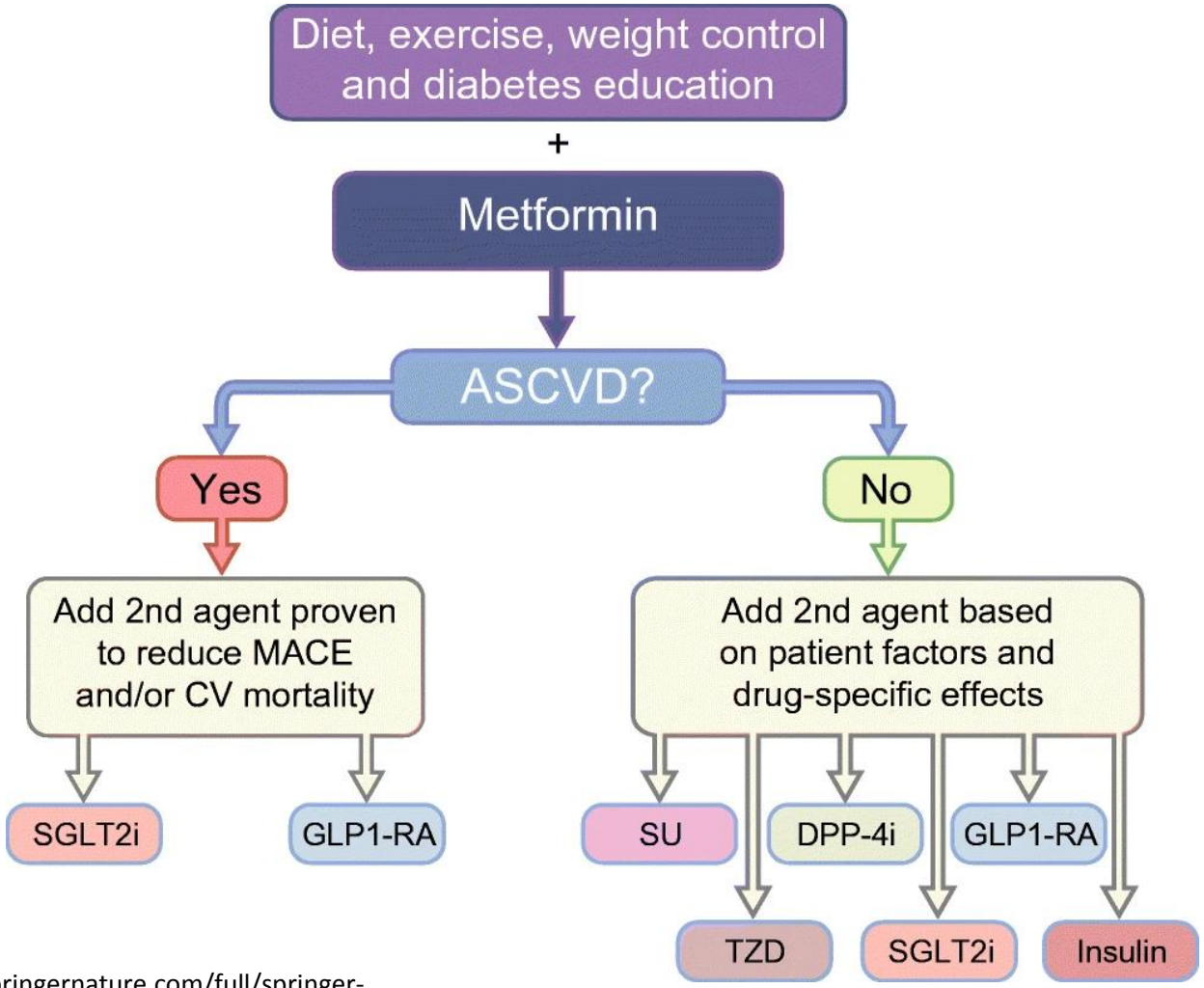



Carolyn S. P. Lam. Journal of the American Heart Association. SGLT-2 Inhibitors in Heart Failure: Current Management, Unmet Needs, and Therapeutic Prospects, Volume: 8, Issue: 20, DOI: (10.1161/JAHA.119.013389)

Summary of latest ADA guidelines for the use of glucose-lowering drugs in individuals with type 2 diabetes in monotherapy and dual combination therapy.

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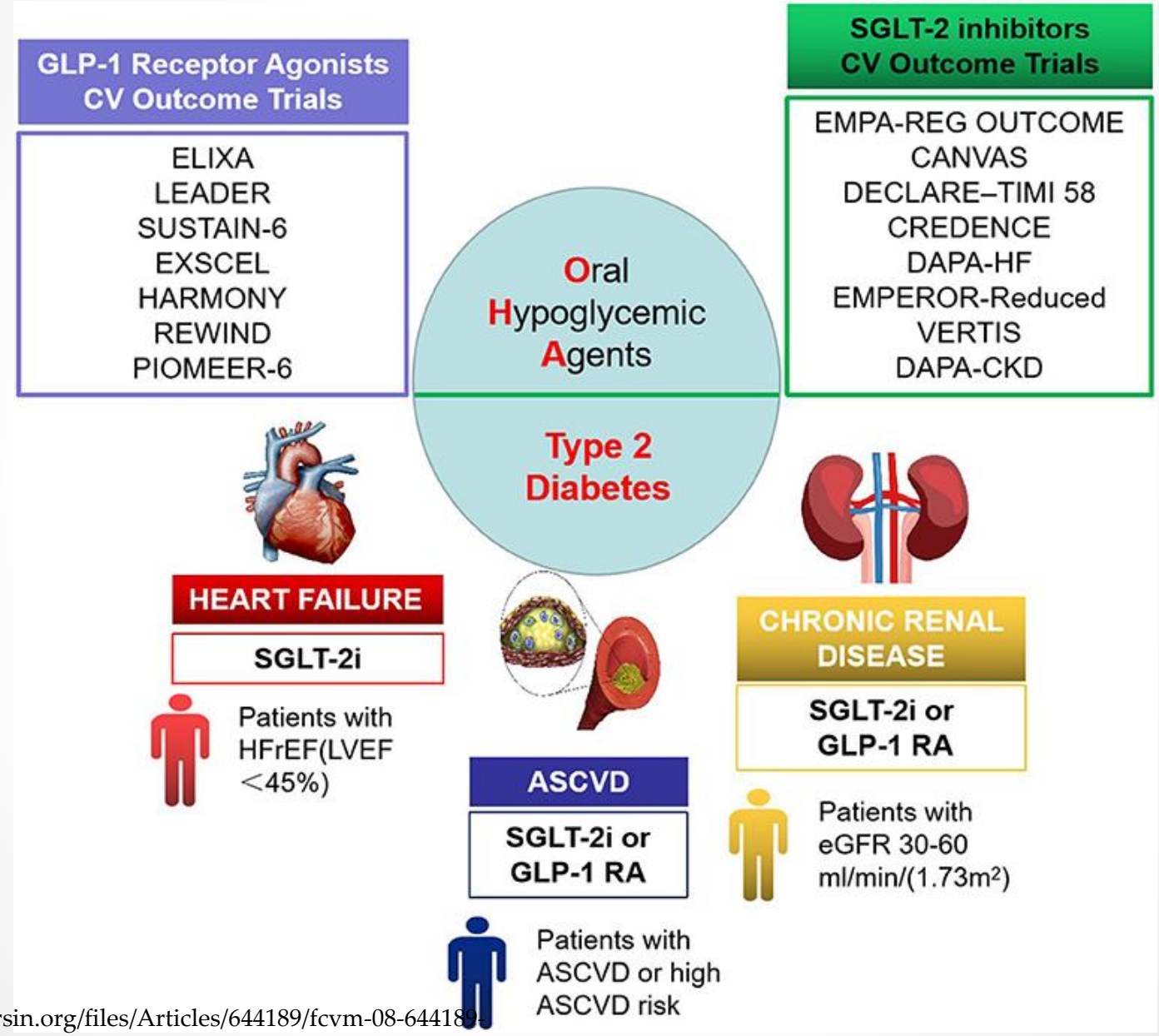
## Current Recommendations on Antidiabetic Drugs

| Organisation and Year of Publication | First-line Option(s) | Second-line Option(s) – On Metformin Monotherapy |
|---|---|---|
| European Society of Cardiology 2019[2] | ASCVD/high CV risk<br>SGLT2 inhibitors*† or GLP-1 RAs*<br>Without ASCVD/low CV risk<br>Metformin | ASCVD/high CV Risk<br>SGLT2 inhibitors*† or GLP-1 RAs*<br>Without ASCVD/low CV Risk<br>DPP-4 inhibitors/GLP-1 RAs/SGLT2 inhibitors/TZDs |
| American Diabetes Association 2020[3] | Metformin | High risk/established ASCVD<br>GLP-1 RAs* (preferred)/SGLT2 inhibitors*†<br>High risk/established CKD/HF<br>SGLT2 inhibitors*† (preferred)/GLP-1 RAs*<br>Without established or risk factors for ASCVD/CKD/HF<br>DPP-4 inhibitors/GLP-1 RAs/SGLT2 inhibitors/TZDs/SUs |
| International Diabetes Association 2017[4] | Metformin | SUs (except glibenclamide/glyburide)/DPP-4 inhibitors/SGLT2 inhibitors<br>Weight loss prioritised<br>GLP-1 RAs |
| National Institute for Health and Care Excellence 2015 (updated 2019)[64] | Metformin | DPP-4 Inhibitors/pioglitazone/sulphonylureas/SGLT2 inhibitors |

**With proven cardiovascular benefits, indication of reducing cardiovascular events. †Only if estimated glomerular filtration rate is adequate. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 RAs = glucagon-like peptide 1 receptor agonists; HF = heart failure; SGLT2 = sodium–glucose co-transporter 2; SU = sulphonylurea; TZDs = thiazolidinediones.*

# Cardiorenal benefit of oral hypoglycemic agents in therapeutic focus of type 2 diabetes mellitus (T2DM).

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# CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

**Use principles in Figure 1**

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

**Use metformin unless contraindicated or not tolerated**

**If not at $HbA_{1c}$ target:**

- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit[1] (See below)

**If at $HbA_{1c}$ target:**

- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit[1] (See below)

**OR** reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA

**OR** reassess $HbA_{1c}$ at 3 month intervals and add SGLT2i or GLP-1 RA if $HbA_{1c}$ goes above target

## ASCVD predominates

GLP-1 RA with proven CVD benefit[1]

**EITHER/ OR**

SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

**If $HbA_{1c}$ above target**

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

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit[1]
- DPP-4i if not on GLP-1 RA
- Basal insulin[5]
- TZD[6]
- SU[7]

## HF or CKD predominates

**PREFERABLY**

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

**OR**

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1,4]

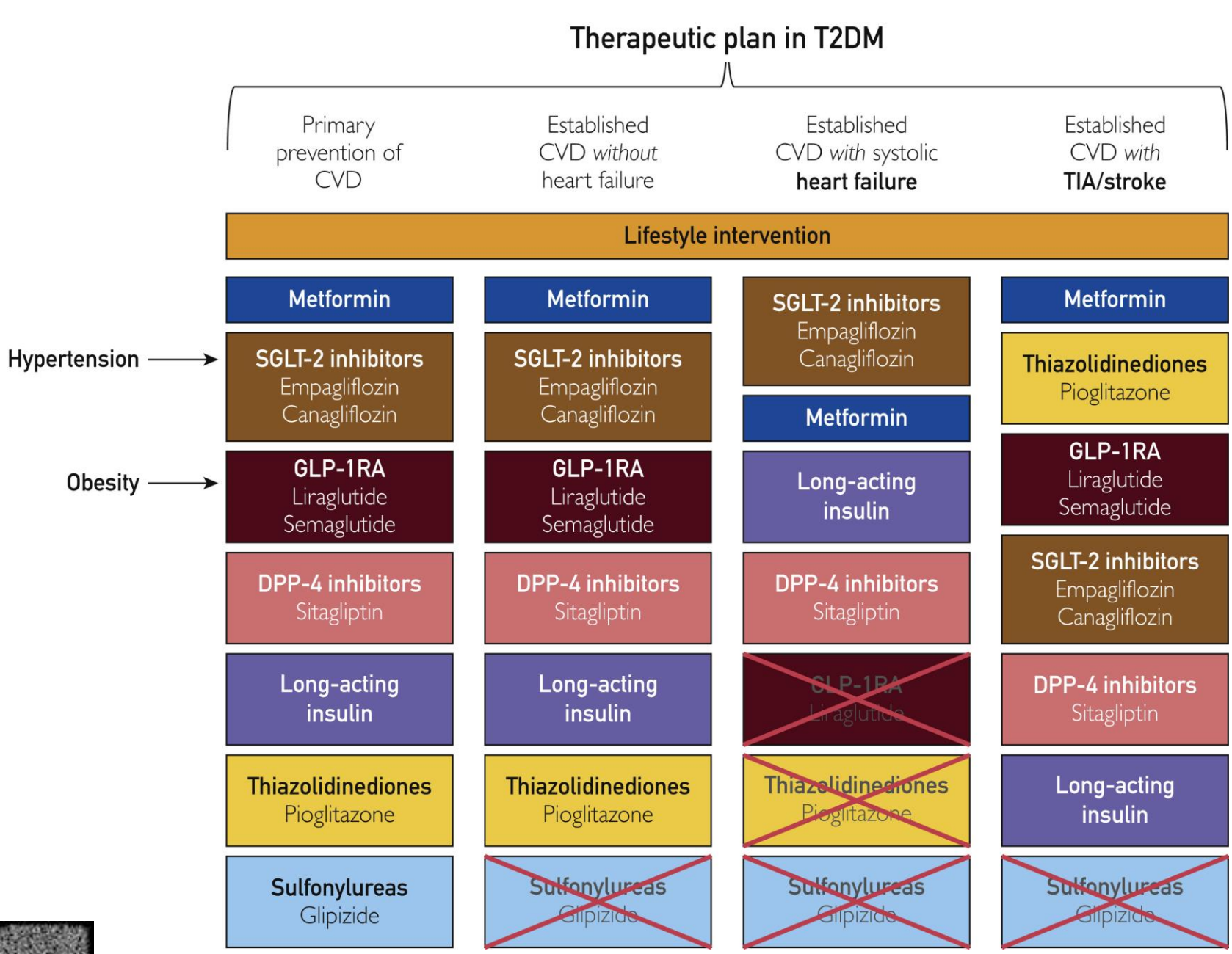
**If $HbA_{1c}$ above target**

- Avoid TZD in the setting of HF

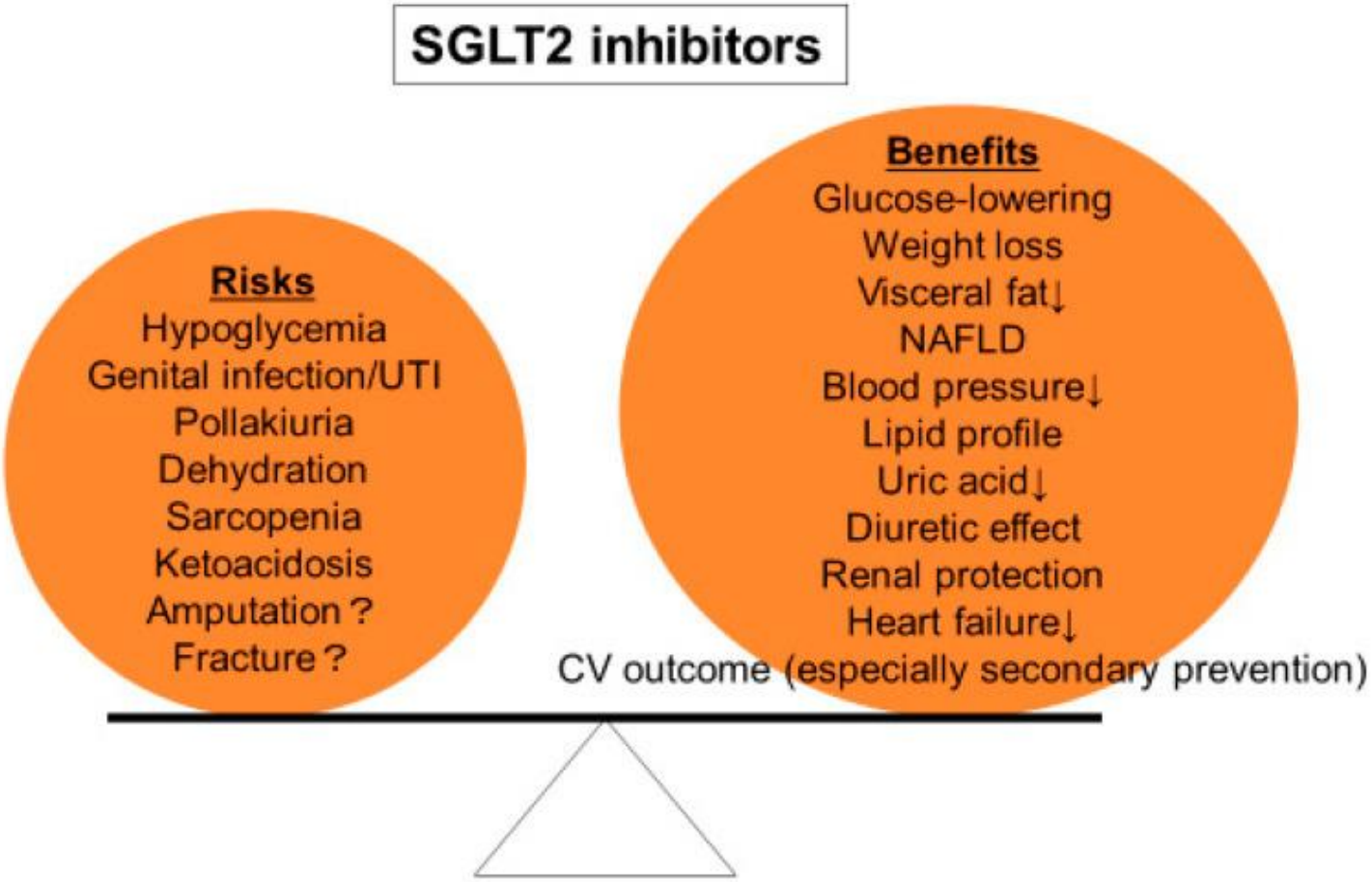
Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[5]
- SU[7]

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Caution with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycaemia



# Risks and benefits of SGLT2 inhibitors

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