# Hope or Hype?

## Diabetes Treatment and CV Disease

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# Learning Outcomes

**By the end of this session you will be able to:**

- Understand new CV evidence for diabetes medications
- Understand the impact of different CVOTs on management of diabetes
- Tailor clinical recommendations for patients with CV risk

# Background

# Diabetes and CV Disease

- A close link between DM and heart disease was described at least a century ago
- People with DM present rates of mortality due to heart disease from **two to four times higher** than those without DM[1]
- Macrovascular disease is the principal cause of death representing **80%** of mortality[2]
- T2DM confers a **two to five-fold higher** risk of developing HF and a **60–80% greater** probability of death from CV causes in those who have established HF[3]
- Optimised glycaemic control has modest effects in reducing CVD endpoints
- Optimal control of all risk factors can reduce CV mortality **by 50%**

1. Matheus et al. Int J Hypertens. 2013; 2013: 653789
2. Nwaneri C, Cooper H, Bowen-Jones D. British J Diabetes Vascular Dis. 2013;13:192–207
3. Schemthaner et al. BMC Endocr Disord. 2019; 19:64

# Categorisation of CV risk in patients with DM

**Very High-risk**

- Patients with DM and established CVD
- Or other target organ damage [a]
- Or ≥3 major risk factors [b]
- Or early onset T1DM of long duration (>20 years)

**High-risk**

- Patients with DM duration ≥10 years without target organ damage plus any other risk factors

**Moderate risk**

- Young patients[c] with DM duration <10 years, without any risk factors

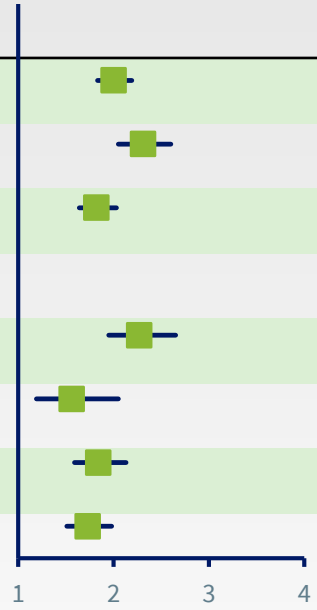
[a]Proteinuria, eGFR<30, left ventricular hypertrophy or retinopathy [b]Age, HTN, dyslipidaemia, smoking, obesity [c]T1DM <35 years or T2DM <50 years

**Adapted from 2019 ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal)**

# Diabetes and risk of vascular disease

Hazard Ratios for vascular outcomes in people with vs without diabetes

| | No of cases | Hazard ratio | 95% CI |
|---|---|---|---|
| **Coronary heart disease** | 26,505 | 2.00 | 1.83; 2.19 |
| Coronary death | 11,556 | 2.31 | 2.05; 2.60 |
| Non-fatal MI | 14,741 | 1.82 | 1.64; 2.03 |
| **Stroke subtypes** | | | |
| Ischaemic stroke | 3,799 | 2.27 | 1.95; 2.65 |
| Haemorrhagic stroke | 1,183 | 1.56 | 1.19; 2.05 |
| Unclassified stroke | 4,973 | 1.84 | 1.59; 2.13 |
| **Other vascular deaths** | 3,826 | 1.73 | 1.51; 1.98 |

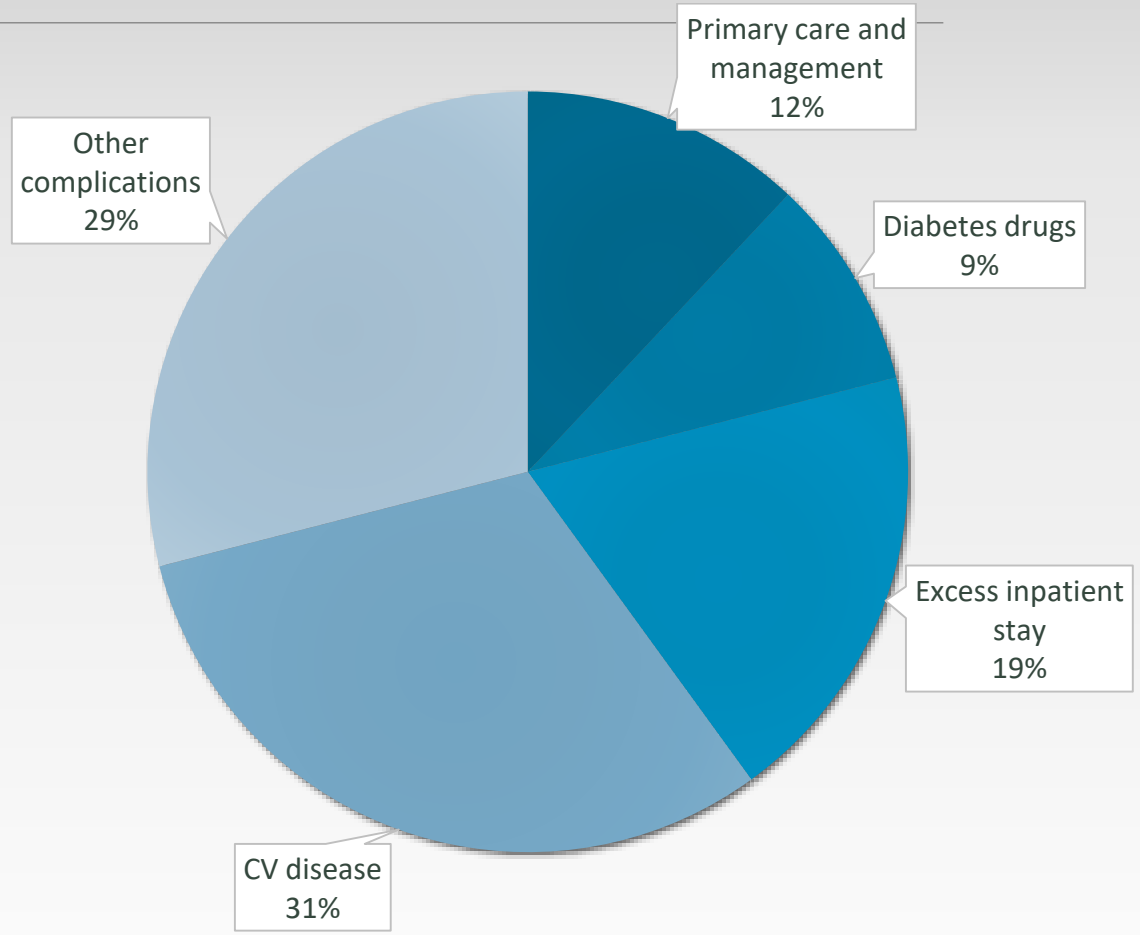



**Adapted from Emerging Risk Factors Collaboration; *Lancet* 2010; 375:2215–22**

# Financial Burden

- Cost to treat diabetes-related **complications** is **three to four-fold** the cost of prescribing diabetes medications[1]

  - 79% of the total UK diabetes spend is devoted to managing complications
  - A large proportion (31%) is directly related to diabetes-induced CVD
  - Only 9% is spent on diabetes medications

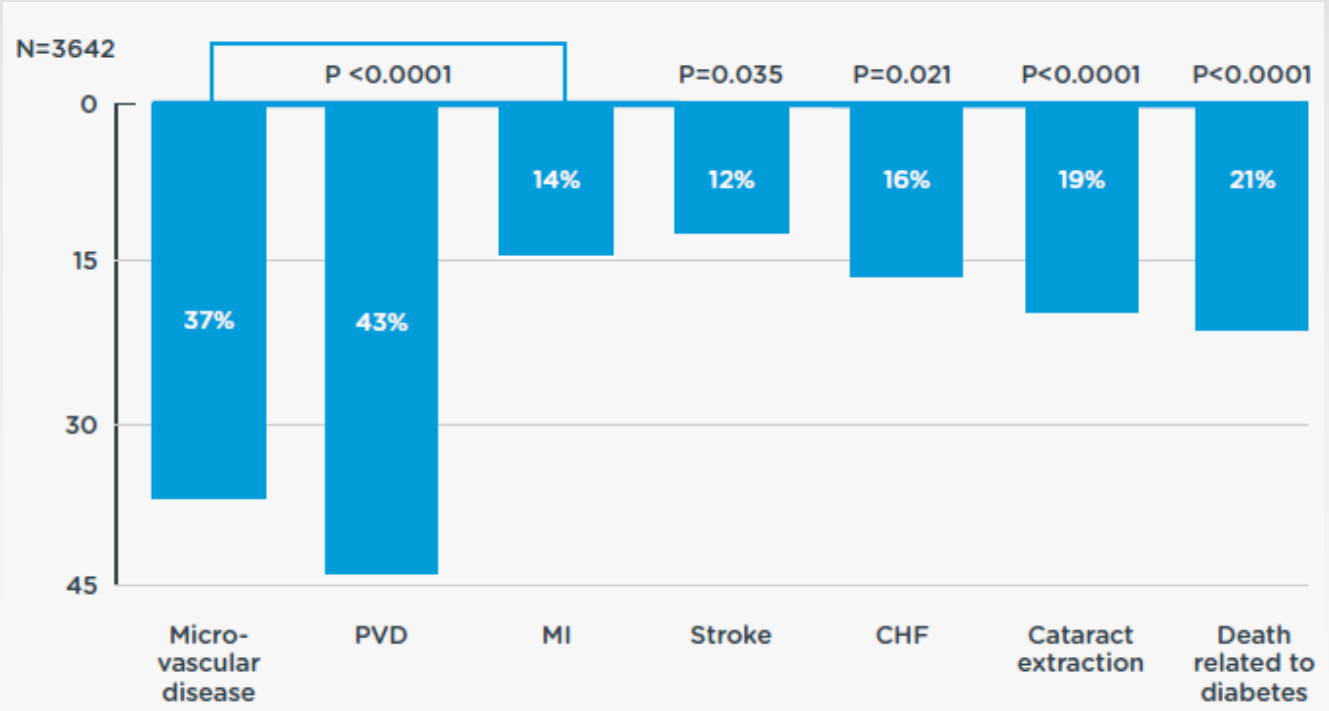




1. Diabetes.co.uk. Cost of diabetes. www.diabetes.co.uk/cost-of-diabetes.html
2. Adapted from slide provided by Hannah Beba

# Early Evidence

- Legacy effect of tighter glycaemic control for the prevention of future complications
- The incidence of clinical complications was significantly associated with hyperglycaemia
- Any reduction in HbA1c is likely to reduce the risk of complications
- Metformin reduces macrovascular risk in people who are overweight
- Younger cohorts with relatively recent onset of diabetes and low CV risk




Reduction of Diabetes-related complications per 1% reduction in HbA1c (UKPDS 35)

Adapted from Stratton M et al. BMJ. 2000. 12;321(7258):405-12

# Cardiovascular Outcome Trials (CVOTs)

# Where it all started…

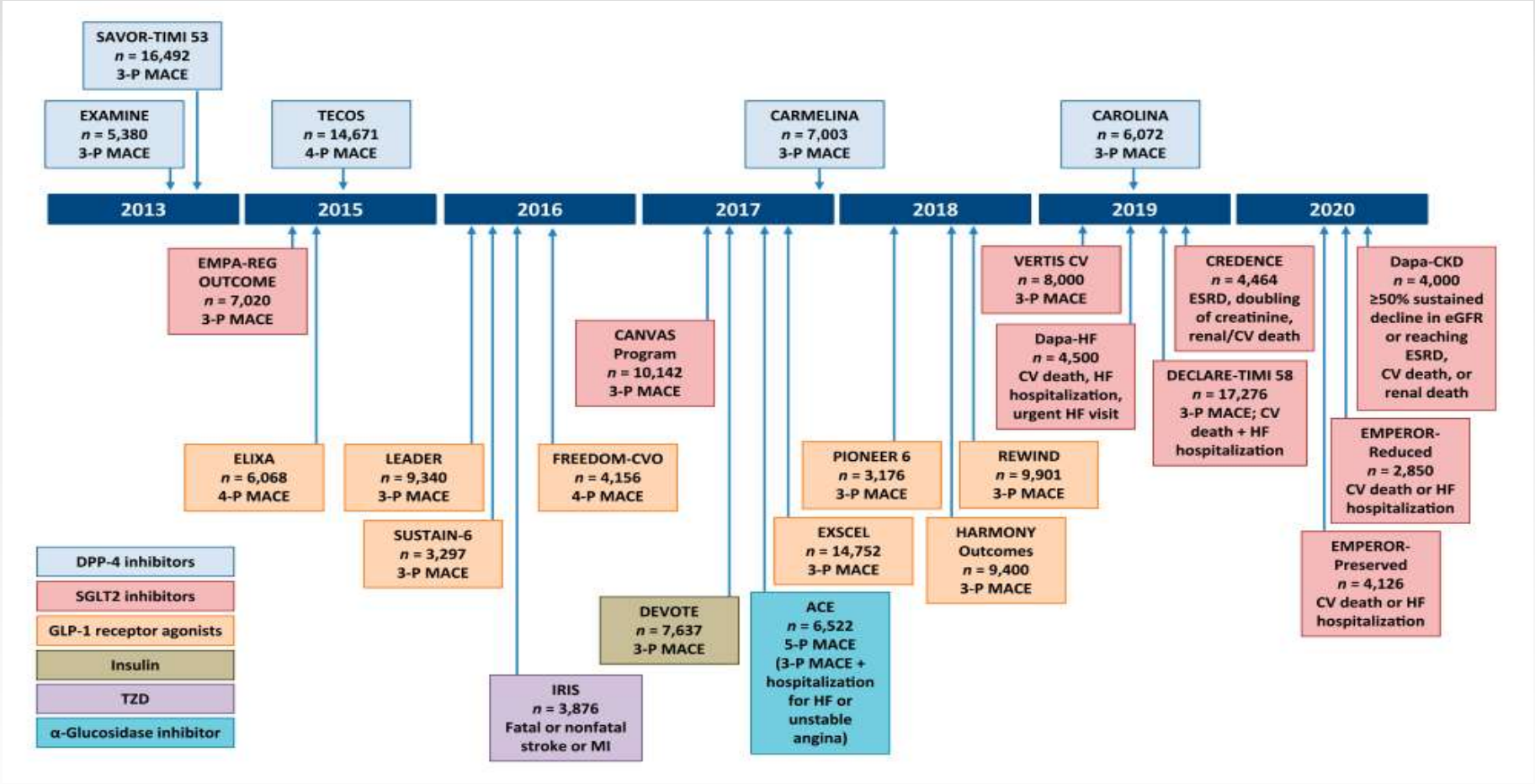
- In 2008 FDA provided recommendations on how to evaluate CV risk in new antidiabetic therapies to treat T2DM[1]

- Focus on:
  - ✓Recognising burden of CVD in T2DM
  - ✓Minimising unacceptable CV risk by mandating long-term safety trials
  - ✓Establishing new CV trial endpoints (CV mortality, MI, stroke, hospitalisation for ACS)
  - ✓Inclusion of patients at higher risk of CV events (advanced disease, elderly, renal impairment)

**Established primary outcome: MACE (major adverse cardiac event) - a composite of CV death, nonfatal MI, or nonfatal stroke**

**1. Food and Drug Administration. Guidance for industry: diabetes mellitus evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf**

# CVOTs Timeline




Adapted from Cefalu et al. Diabetes Care. 2018 Jan;41(1):14-31. http://care.diabetesjournals.org/content/diacare/41/1/14.full.pdf

# DDP-4 Inhibitors

## ❑ Alogliptin (EXAMINE)[1]

- CV safety in those with recent ACS: no worse than placebo for MACE
- Increasing trend of risk of HF hospitalisation

## ❑ Saxagliptin (SAVOR-TIMI 53)[2]

- CV safety: no worse than placebo for MACE
- Increased risk of HF hospitalisation

## ❑ Linagliptin (CARMELINA)[3]

- CV safety in those with high CV risk: non-inferiority for MACE over a median of 2.2 years

## ❑Sitagliptin (TECOS)[4]

- CV safety in those with established  CVD: no worse than placebo for MACE and HF hospitalisation

1.White et al. N Engl J Med 2013;369:1327–35
2. Scirica et al. N Engl J Med 2013;369:1317–26
3. Rosenstock et al. JAMA. 2019;1;321(1):69-79
4.Green et al. N Engl J Med 2015;16;373:232–42

# DDP-4 Inhibitors

| | EXAMINE[1] | SAVOR-TIMI 53[2] | TECOS[3] |
|---|---|---|---|
| **Intervention** | Alogliptin | Saxagliptin | Sitagliptin |
| **Inclusion Criteria** | T2DM + ACS within 15-90 days | T2DM + Hx or risk factors for ASCVD | T2DM + pre-existing CVD |
| **Median follow-up** | 1.5 yrs | 2.1 yrs | 3.0 yrs |
| **Prior ASCVD (%)** | 100 | 78 | 74 |
| **Prior HF (%)** | 28 | 13 | 18 |
| **Primary Outcome** | 3-P MACE<br>HR=0.96 (UL<1.16) | 3-P MACE<br>HR=1.00 (0.89-1.12) | 4-P MACE (3-P MACE + hosp. for unstable angina)<br>HR=0.98 (0.89-1.08) |
| **CV Death** | 0.85 (0.66-1.10) | 1.03 (0.87-1.22) | 1.03 (0.89-1.19) |
| **MI** | 1.08 (0.88-1.33) | 0.95 (0.80-1.12) | 0.95 (0.81-1.11) |
| **Stroke** | 0.91 (0.79-1.19) | 1.11 (0.88-1.39) | 0.97 (0.79-1.19) |
| **HF Hospitalisation** | **1.19 (0.90-1.58)** | **1.27 (1.07-1.51)** | 1.01 (0.90-1.14) |

1. White et al. N Engl J Med 2013;369:1327–35 2. Scirica et al. N Engl J Med 2013;369:1317–26 3.Green et al. N Engl J Med 2015;16;373:232–42

# Summary: DDP-4 Inhibitors CVOTs

- MACE safety demonstrated by non-inferiority
- No significant MACE benefit
- Saxagliptin – Increased risk of HF
- FDA warning – especially in those with underlying HF or renal disease
- CAROLINA[1] – Linagliptin compared with Glimepiride shows non-inferior risk for MACE– first active comparator CVOT. Awaiting full results

1. https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-and-lilly-announce-carolina-cardiovascular-outcome-trial

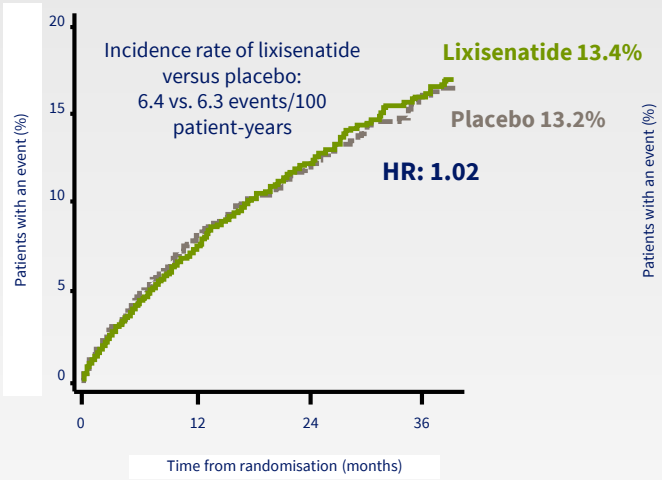
# GLP-1 Analogues

- **Lixisenatide (ELIXA)[1]**
  - 4-P MACE safety but no benefit
- **Exenatide OW (EXSCEL)[2]**
  - 3-P MACE safety but not superiority
  - High level of discontinuation (43%) – reasonable design of 6 monthly visits and limited external support may explain the low treatment adherence and persistence
- **Liraglutide (LEADER)[3]**
- **Semaglutide (SUSTAIN-6)[4]**
- **Dulaglutide (REWIND)[5]**

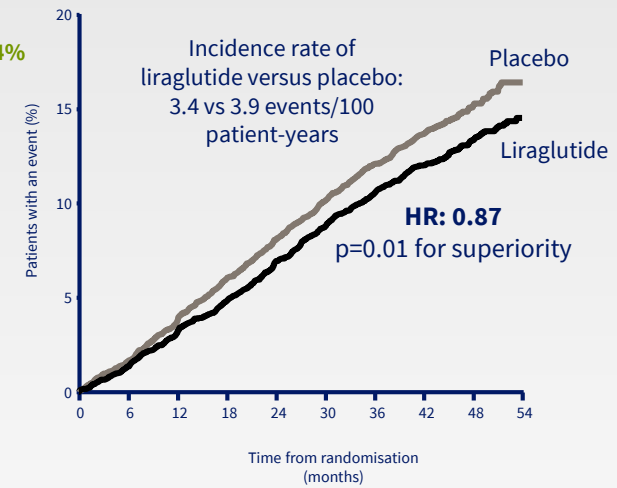
1. Pfeffer et al. N Engl J Med 2015; 373:2247-2257 2. Holman et al. N Engl J Med 2017; 377:1228-1239 3 .Marso P, Daniels GH et al. N Engl J Med 2016; 354:311-22
4. Marso SP, Bain SC, Consoli A et al. N Engl J Med 2016; 375:1834-184 5. https://clinicaltrials.gov/ct2/show/study/NCT01394952

# Primary Outcome 3-P MACE: CV death, non-fatal MI, or non-fatal stroke

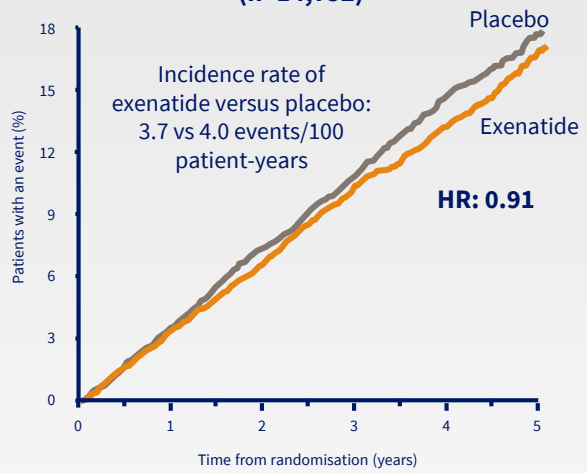
**ELIXA[1]**
**(n=6,068)**



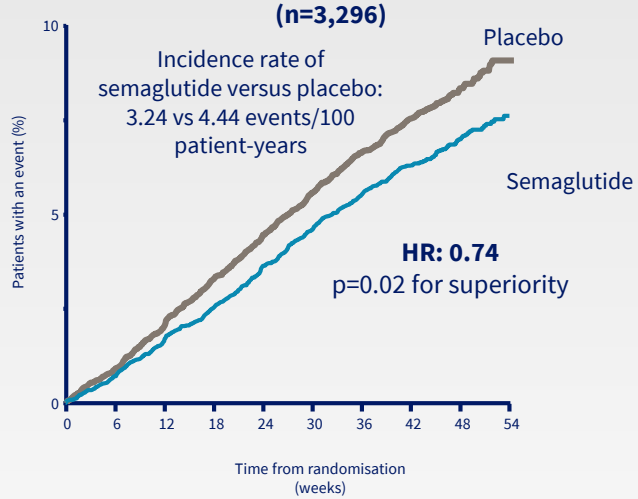

**LEADER[2]**
**(n=9,340)**




**EXSCEL[3]**
**(n=14,752)**




**SUSTAIN-6[4]**
**(n=3,296)**





Adapted from 1. Pfeffer et al. N Engl J Med 2015; 373:2247-2257 2. Marso P, Daniels GH et al. N Engl J Med 2016; 354:311-22
3. Holman et al. N Engl J Med 2017; 377:1228-1239 4. Marso SP, Bain SC, Consoli A et al. N Engl J Med 2016; 375:1834-184

| | LEADER - Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (n=9340) Majority of population received Liraglutide 1.8mg daily |
|---|---|
| **Inclusion Criteria** | • T2DM , HbA1c ≥ 7.0%<br>• Age≥ 50 + established CVD (MI, Stroke, CHD, HF) or CKD stage 3<br>• Age≥ 60 + ≥1 CV risk factor (microalbuminuria or proteinuria, hypertension with LVH, left ventricular systolic or diastolic dysfunction) |
| **Median follow-up** | 3.8 yrs |
| **Prior ASCVD (%)** | 81 |
| **Prior HF (%)** | 18 |
| **Primary Outcome** | **3-P MACE 0.87 (0.78-0.97)** |
| **Key Secondary Outcome** | Expanded MACE (3-P MACE + revascularisation, unstable angina, hosp. for HF) 0.88 (0.81-0.96) |
| **CV Death** | **0.78 (0.66-0.93)** |
| **MI** | 0.86 (0.73-1.00) |
| **Stroke** | 0.86 (0.71-1.06) |
| **HF Hospitalisation** | **0.87 (0.73-1.05)** |
| **All-cause Mortality** | 0.85 (0.74-0.97) |

Marso P, Daniels GH et al. N Engl J Med 2016; 354:311-22

# Things to take away – LEADER (2016)

- Significant reduction of MACE/all-cause mortality compared to placebo
- Reduced risk of HF and unstable angina hospitalisations
- Majority of population received Liraglutide 1.8mg daily
- Powered for non-inferiority and superiority

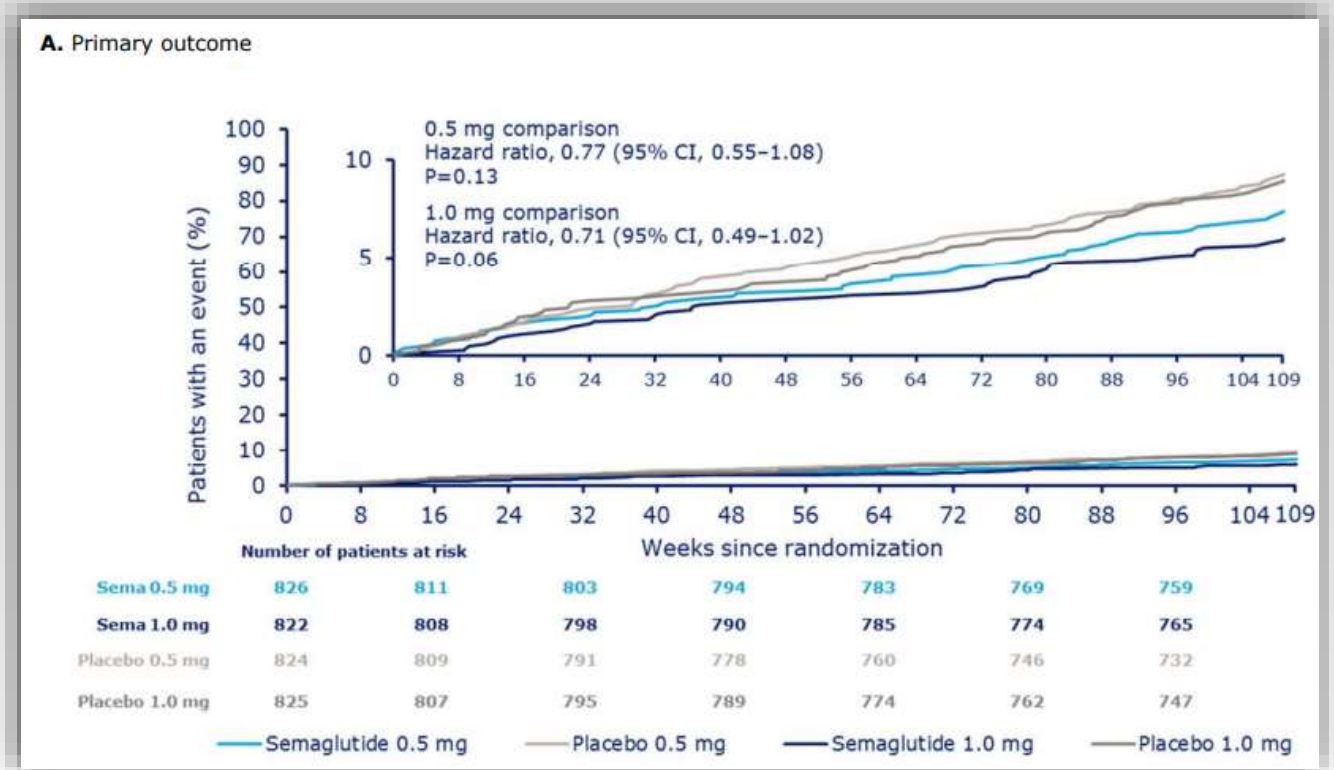
**Adapted from Marso P, Daniels GH et al. N Engl J Med 2016; 354:311-22**

| | SUSTAIN-6 - Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (n=3297) Semaglutide 0.5mg or 1mg weekly |
|---|---|
| **Inclusion Criteria** | • T2DM , HbA1c ≥ 7.0%<br>• Age≥ 50 + established CVD (MI, Stroke, CHD, HF) or CKD with eGFR<60<br>• Age≥ 60 + ≥1 CV risk factor (microalbuminuria or proteinuria, hypertension with LVH, left ventricular systolic or diastolic dysfunction) |
| **Median follow-up** | 2.1 yrs |
| **Prior ASCVD (%)** | 60 |
| **Prior HF (%)** | 25 |
| **Primary Outcome** | **3-P MACE 0.74 (0.58-0.95)** |
| **Key Secondary Outcome** | Expanded MACE (3-P MACE + revascularisation, unstable angina, hosp. for HF) 0.74 (0.62-0.89) |
| **CV Death** | 0.98 (0.65-1.48) |
| **MI** | **0.74 (0.51-1.08)** |
| **Stroke** | **0.61 (0.38-0.99)** |
| **HF Hospitalisation** | **1.11 (0.77-1.61)** |
| **All-cause Mortality** | 1.05 (0.74-1.50) |

**Marso SP, Bain SC, Consoli A et al. N Engl J Med 2016; 375:1834-184**

# Things to take away
# SUSTAIN-6 (2016)

- Lower CV risk driven mainly by significant reduction of non-fatal stroke and non-fatal MI composites
- No significant difference in rate of CV death
- Demonstrated CV safety in the trial population but not superiority for HF hospitalisations and all-cause mortality
- Analysis of dose-effect




Adapted from Marso SP, Bain SC, Consoli A et al. N Engl J Med 2016; 375:1834-184

# Things to take away – SUSTAIN-6 (2016)

- **RETINOPATHY:**

  - ✓Diabetic retinopathy complications occurred in 50 patients (3.0%) in the semaglutide group and 29 (1.8%) in the placebo group (HR=1.76)
  - ✓Caution should be exercised when using semaglutide in patients with diabetic retinopathy treated with insulin
  - ✓Regular monitoring advised

| | REWIND - Dulaglutide and cardiovascular outcomes in type 2 diabetes: a double-blind, randomised placebo-controlled trial (n=9901) Dulaglutide 1.5mg weekly |
|---|---|
| **Inclusion Criteria** | • T2DM , HbA1c ≤ 9.5%<br>• Age≥ 50 + established CVD (MI, Stroke, revascularisation, admission for unstable angina)<br>• Age≥ 55 + Myocardial ischaemia, coronary, carotid or lower extremity artery stenosis >50%, LVH, eGFR<60ml/min or albuminuria<br>• Age 60 + ≥2 CV risk factors (tobacco use, dyslipidaemia, hypertension or abdominal obesity) |
| **Median follow-up** | 5.4 yrs |
| **Prior ASCVD (%)** | 31 |
| **Primary Outcome** | **3-P MACE 0.88 (0.79-0.99)** |
| **CV Death** | 0.91 (0.78-1.06) |
| **MI** | 0.96 (0.79-1.16) |
| **Stroke** | **0.76** (0.61-0.95) |
| **HF Hospitalisation** | 0.93 (0.77-1.12) |
| **All-cause Mortality** | 0.90 (0.80-1.01) |

https://clinicaltrials.gov/ct2/show/study/NCT01394952

# Things to take away – **REWIND (2019)**

- Longest CVOT to date – longest follow-up (5.4 yrs), largest proportion of women (46%), lowest baseline median HbA1c (7.2%)
- Inclusion of a population with lower CVD risk (only 31% had established CVD) - ?relevance in primary prevention
- Secondary outcome comprised a composite clinical microvascular outcome (incl. retinal and renal disease)
- Lower CV risk driven mainly by significant reduction of non-fatal stroke
- All-cause mortality and hospitalisations for HF did not differ between groups

# Summary: GLP-1 Analogues CVOTs

- Heterogeneity and differing outcomes seen due to patients characteristics, study designs and treatment persistence/discontinuation
- PK/PD differences – short acting Lixisenatide (acting mostly on prandial glucose) vs. longer acting Liraglutide/Semaglutide (acting mostly on fasting – carry over into prandial)
- All CVOTs for GLP-1 have shown increased heart rate with no harmful effect observed to date

- Renal outcomes in Liraglutide, Semaglutide and Dulaglutide
- Retinopathy – Semaglutide
- REWIND and generalisation of CV benefit to wider T2DM populations with low/no risk of CVD

# SGLT-2 Inhibitors

- Dapagliflozin (DECLARE TIMI 58[1], DAPA-HF[2])
- Canagliflozin (CANVAS Program)[3]
- Empagliflozin (EMPA-REG OUTCOME)[4]
- Ertugliflozin (VERTIS –CV) awaiting publication

1. Wiviott et al. N Engl J Med 2019; 380:347-57 2. McMurray et al. N Engl J Med 2019. Available from https://www.nejm.org/doi/full/10.1056/NEJMoa1911303
3 . Neal et al. N Engl J Med 2017;377:644–57 4. Zinman et al. N Engl J Med 2015;373:2117–28

# SGLT-2 Inhibitors CV trial design

| | DECLARE-TIMI 58[1] | CANVAS[2] | EMPA-REG OUTCOME[3] |
|---|---|---|---|
| **Intervention** | Dapagliflozin 10mg OD | Canagliflozin 100mg OD and 300mg OD | Empagliflozin 10mg OD and 25mg OD |
| **Participants** | 17 160 | 10 142 | 7 020 |
| **Median follow-up** | 4.2 yrs | 3.6 yrs | 3.1 yrs |
| **Age (mean)** | 37.4 | 35.8 | 28.5 |
| **Prior ASCVD (%)** | **40.6** | **65.6** | **99** |
| **Prior HF (%)** | **10.0** | **14.4** | **10.1** |
| **eGFR<60 (%)** | 7.4 | 20.1 | 25.9 |

1.Wiviott et al. N Engl J Med 2019; 380:347-57 2. Neal et al. N Engl J Med 2017;377:644–57
3. Zinman et al. N Engl J Med 2015;373:2117–28

# SGLT-2 Inhibitors CV trial design

| | DECLARE-TIMI 58[1] | CANVAS[2] | EMPA-REG OUTCOME[3] |
|---|---|---|---|
| **Inclusion Criteria** | • T2DM, Aged ≥40, HbA1c 6.5-12%<br>• CrCl ≥ 60ml/min<br>• Established ASCVD (IHD, stroke or PAD) and/or multiple CV risk factors<br>• Men aged ≥ 55 **OR** women aged ≥ 60 with ≥ 1 CV risk factors:<br>Hypertension<br>Dyslipidaemia (LDL-C >3.36mmol/L or use of lipid lowering medications)<br>Use of tobacco | • T2DM, HbA1c 7.0-10.5%<br>• CrCl ≥ 30ml/min<br>• Age ≥30 with Hx of symptomatic ASCVD (stroke, MI, unstable angina) **OR**<br>• Age ≥50 with ≥2 CVD risk factors:<br>Diabetes duration of ≥ 10 years<br>SBP>140mmHg while receiving ≥1 antihypertensive therapies<br>Current smoker<br>Micro or macroalbuminuria<br>HDL-C <1mmol/L | • T2DM, HbA1c 7.0-10.0%<br>• BMI≤ 45 or less, eGFR≥ 30<br>• Established CVD:<br>History of MI > 2months prior Evidence of multi-vessel CAD<br>Evidence of single vessel CAD<br>Unstable angina >2months prior and with CAD<br>History of stroke >2 months prior<br>Occlusive PAD |

1.Wiviott et al. N Engl J Med 2019; 380:347-57 2. Neal et al. N Engl J Med 2017;377:644–57
3. Zinman et al. N Engl J Med 2015;373:2117–28

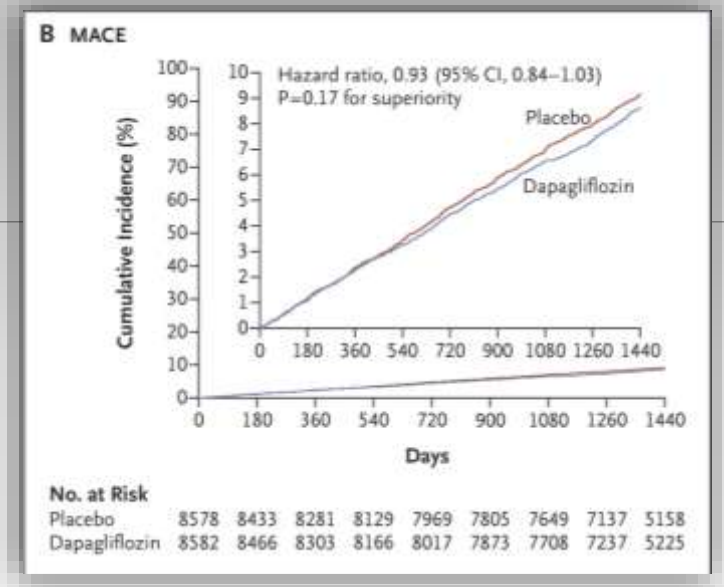
# SGLT-2 Inhibitors MACE results

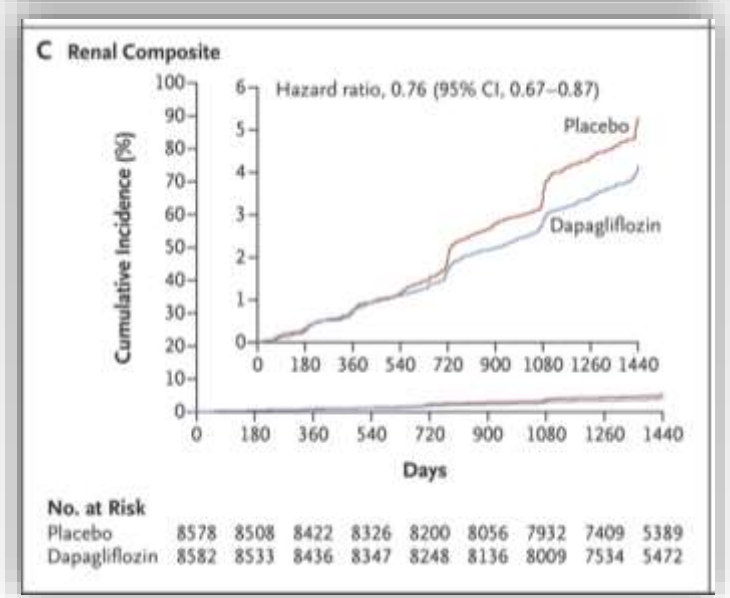
| | DECLARE-TIMI 58[1] | CANVAS[2] | EMPA-REG OUTCOME[3] |
|---|---|---|---|
| **Primary Outcome** | **3-P MACE**<br>**HR=0.93 (0.84-1.03)** | **3-P MACE**<br>**HR=0.86 (0.75-0.97)** | **3-P MACE**<br>**HR=0.86 (0.74-0.99)** |
| **Key Secondary Outcome** | Renal composite<br>HR=0.76 (0.67-0.87) | All-cause mortality, progression of albuminuria | 4-P MACE (3-P MACE + hosp for unstable angina)<br>HR=0.89 (0.78-1.01) |
| **CV Death** | 0.98 (0.82-1.17) | 0.96 (0.77-1.18)<br>0.87 (0.72-1.06) | **0.62 (0.49-0.77)** |
| **MI** | 0.89 (0.77-1.01) | 0.89 (0.73-1.09) | 0.87 (0.70-1.09) |
| **Stroke** | 1.01 (0.84-1.21) | **0.87 (0.69-1.09)** | 1.18 (0.89-1.56) |
| **HF Hospitalisation** | **0.73 (0.61-0.88)** | **0.67 (0.52-0.87)** | **0.65 (0.50-0.85)** |
| **All-cause Mortality** | 0.93 (0.82-1.04) | 0.87 (0.74-1.01)<br>0.90 (0.76-1.01) | 0.68 (0.57-0.82) |

**1.Wiviott et al. N Engl J Med 2019; 380:347-57 2. Neal et al. N Engl J Med 2017;377:644–57**
**3. Zinman et al. N Engl J Med 2015;373:2117–28**

# Things to take away
# DECLARE-TIMI 58 (2019)

- No significant reduction of 3P-MACE
- No significant reduction in stroke and overall CV death
- Reduction of hospitalisation for heart failure
- The majority of patients did not have a history of HF (only 10%), so primary prevention is notable
- Improvement in the renal composite and reduction of progression of renal disease (≥ 40% eGFR reduction to <60ml/min, ESRD, or renal or CV death)
- Noted higher rates of DKA and genital infections

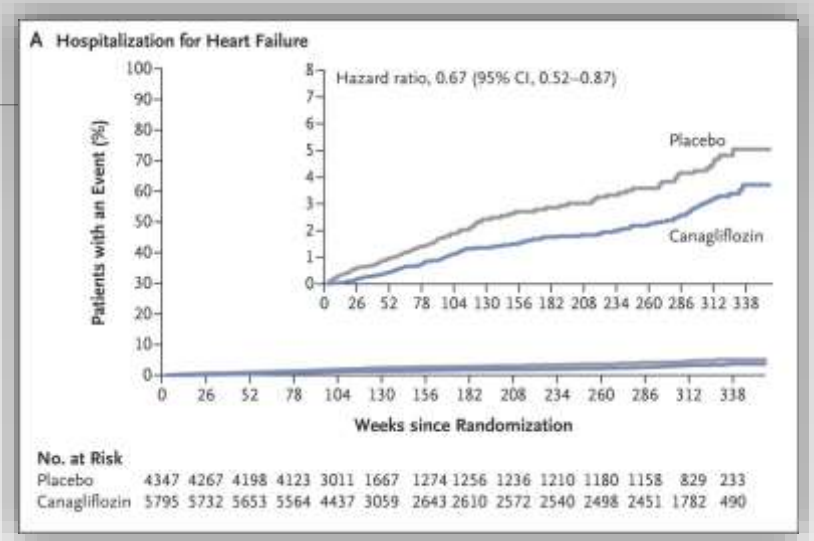


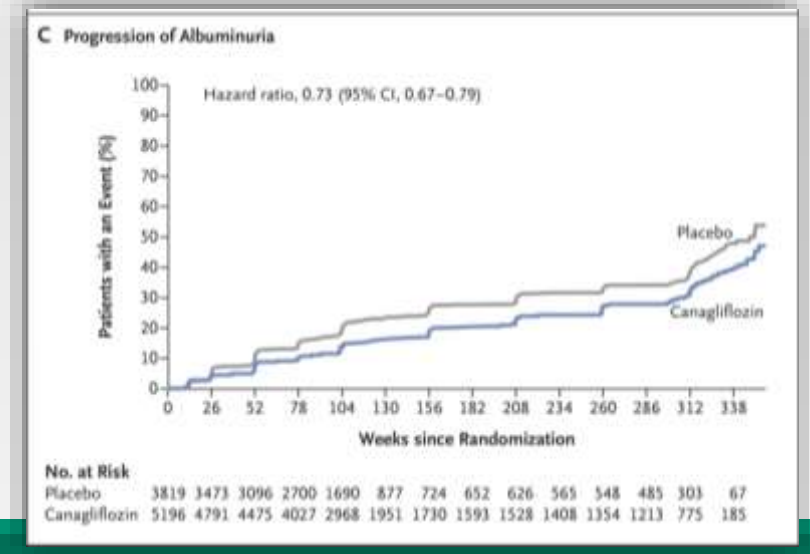




Adapted from Wiviott et al. N Engl J Med 2019; 380:347-57

# Things to take away
# CANVAS (2017)

- Significant lower risk of composite CV death and HF hospitalisations
- Reduction of risk of stroke in comparison with other SGLT2is
- Reduction in progression of albuminuria and need for RRT and renal death
- Increased rate of amputation
  - 6.3 vs 3.4 participants/1000 patient years
  - Mainly toes and lower-legs
  - Higher risk if history of amputation and PAD
- Increased risk of bone fractures by 26%

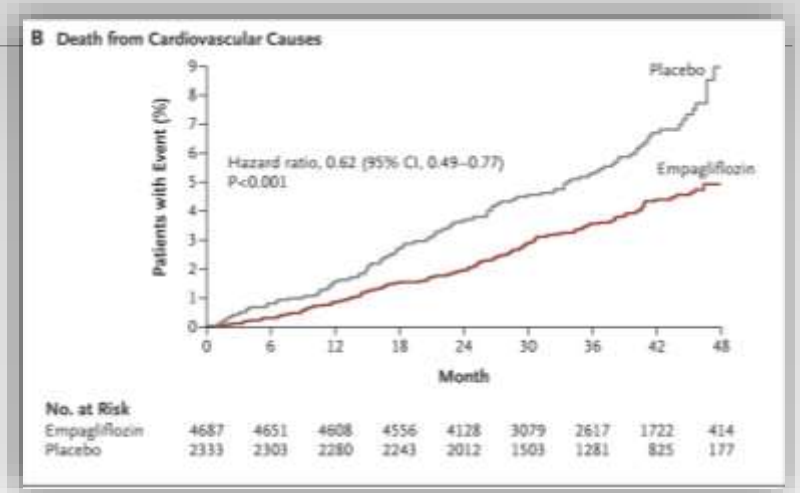


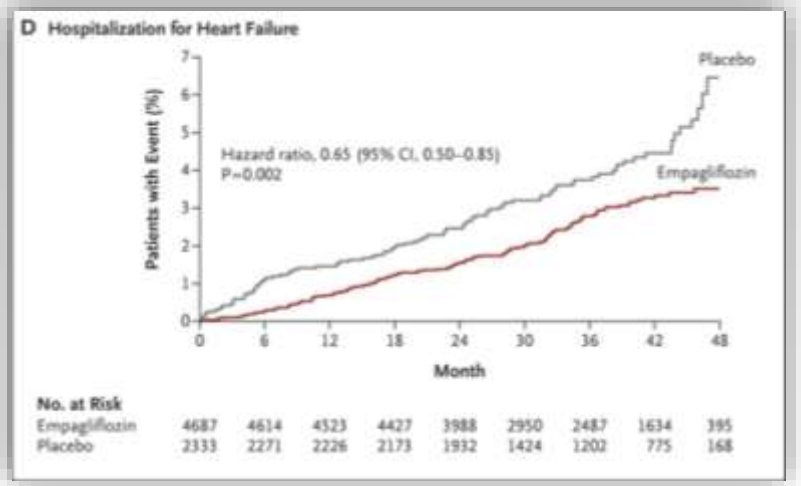




Adapted from Neal et al. N Engl J Med 2017;377:644–57

# Things to take away – EMPA-REG OUTCOME (2015)

- No significant difference concerning MI or stroke rates
- Significantly lower:
  - Death from CV causes in comparison with other SGLT2is
  - Hospitalisation from HF
  - Death from any cause in comparison with other SGLT2is
- 99% trial population had established CVD
- Increased rate of genital infections but no increase in other SE




Adapted from Zinman et al. N Engl J Med 2015;373:2117–28

| | DAPA-HF - Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (n=4744) Dapagliflozin 10mg OD |
|---|---|
| **Inclusion Criteria** | • With or without DM<br>• Age ≥18 years<br>• NYHA II-IV with LVEF ≤40%<br>• Elevated NT-proBNP levels<br>• Patients receiving background standard drug and device therapy for HFrEF, in accordance with recognised guidelines |
| **Median follow-up** | 18.2 months |
| **Primary Outcome** | **Composite of worsening HF (hospitalisation or urgent visit resulting in IV therapy for HF) or CV death**<br>**0.74 (0.65-0.85)** |
| **Worsening HF event** | **0.70 (0.59-0.83)** |
| **CV Death** | 0.82 (0.69-0.98) |

- Similar findings in those with or without diabetes
- ESC 2019: SGLT2 inhibitors are recommended to lower risk of HF hospitalisation if eGFR>30

McMurray et al. N Engl J Med 2019. Available from https://www.nejm.org/doi/full/10.1056/NEJMoa1911303

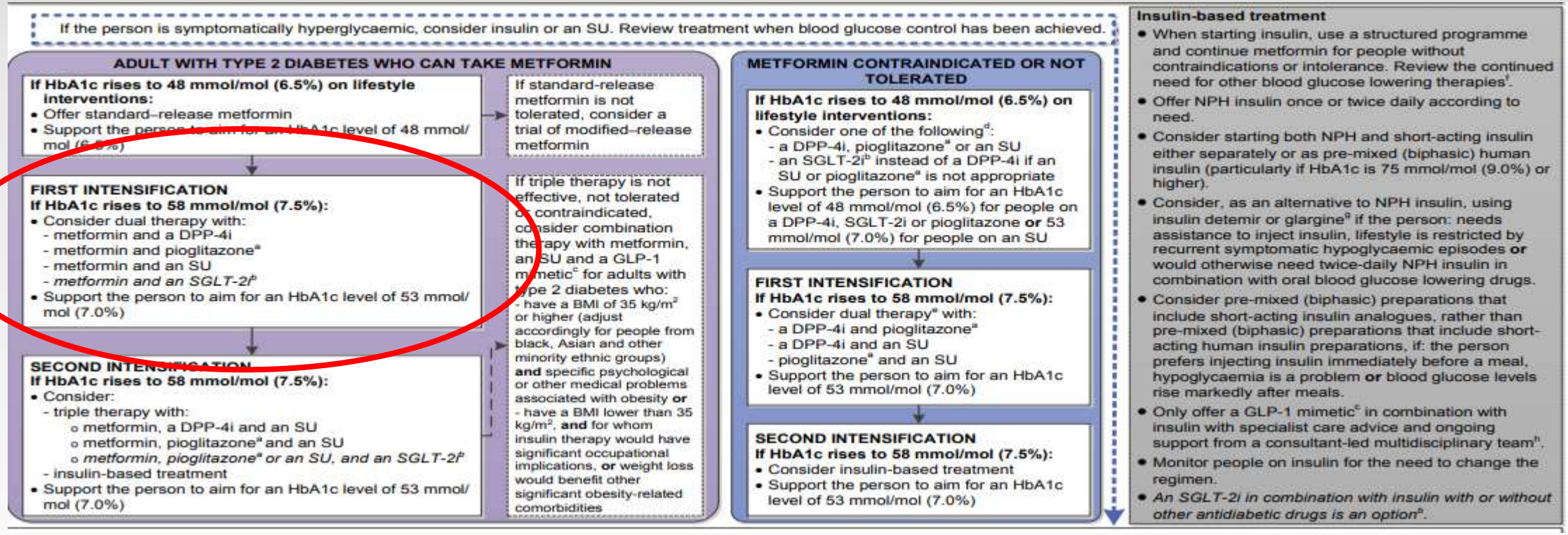
# Summary: SGLT-2 Inhibitors CVOTs

- No significant reduction of risk of stroke
- Clinically meaningful reduction in risk for HF hospitalisation by 31%
- Proven renoprotective effects: reduction in macroalbuminuria and risk of worsening kidney function

- **Safety and Tolerability:**
  - ✓Current license: can only be initiated if eGFR >60
  - ✓Side-effects are common – thrush, osmotic symptoms, possible dehydration
  - ✓Euglycaemic DKA – increased risk of almost two times higher in patients given SGLT2i than those given placebo
  - ✓Lower limb amputation and fractures (CANVAS)

# Guidelines

# NICE guideline NG28: Type 2 diabetes in adults: management (2015)

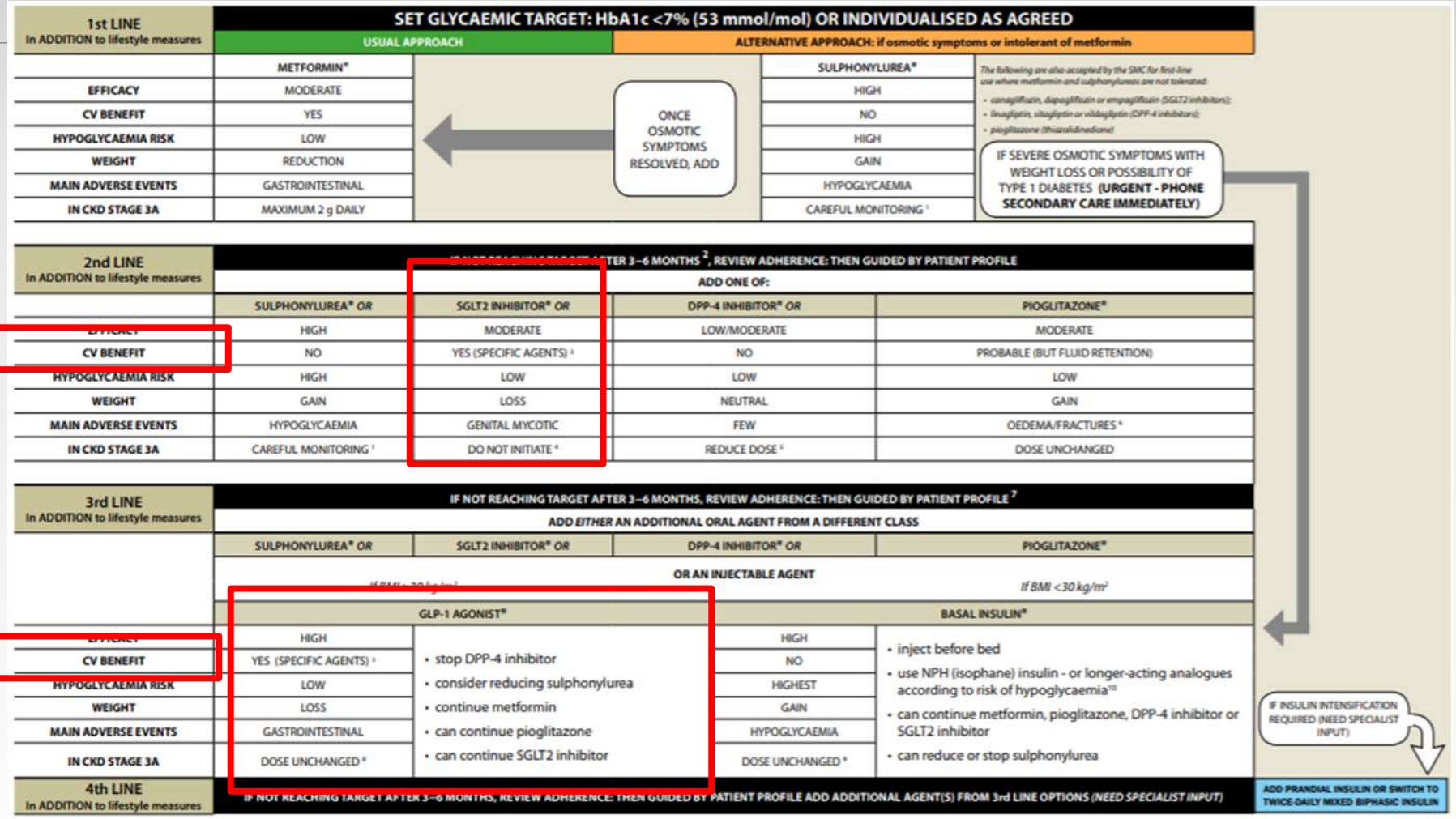



Adapted from NICE guideline NG28. Type 2 diabetes in adults: management. December2015. https://www.nice.org.uk/guidance/ng28/resources/algorithm-for-blood-glucose-lowering-therapy-in-adults-with-type-2-diabetes-pdf-2185604173

# SIGN type 2 diabetes guideline (2017)

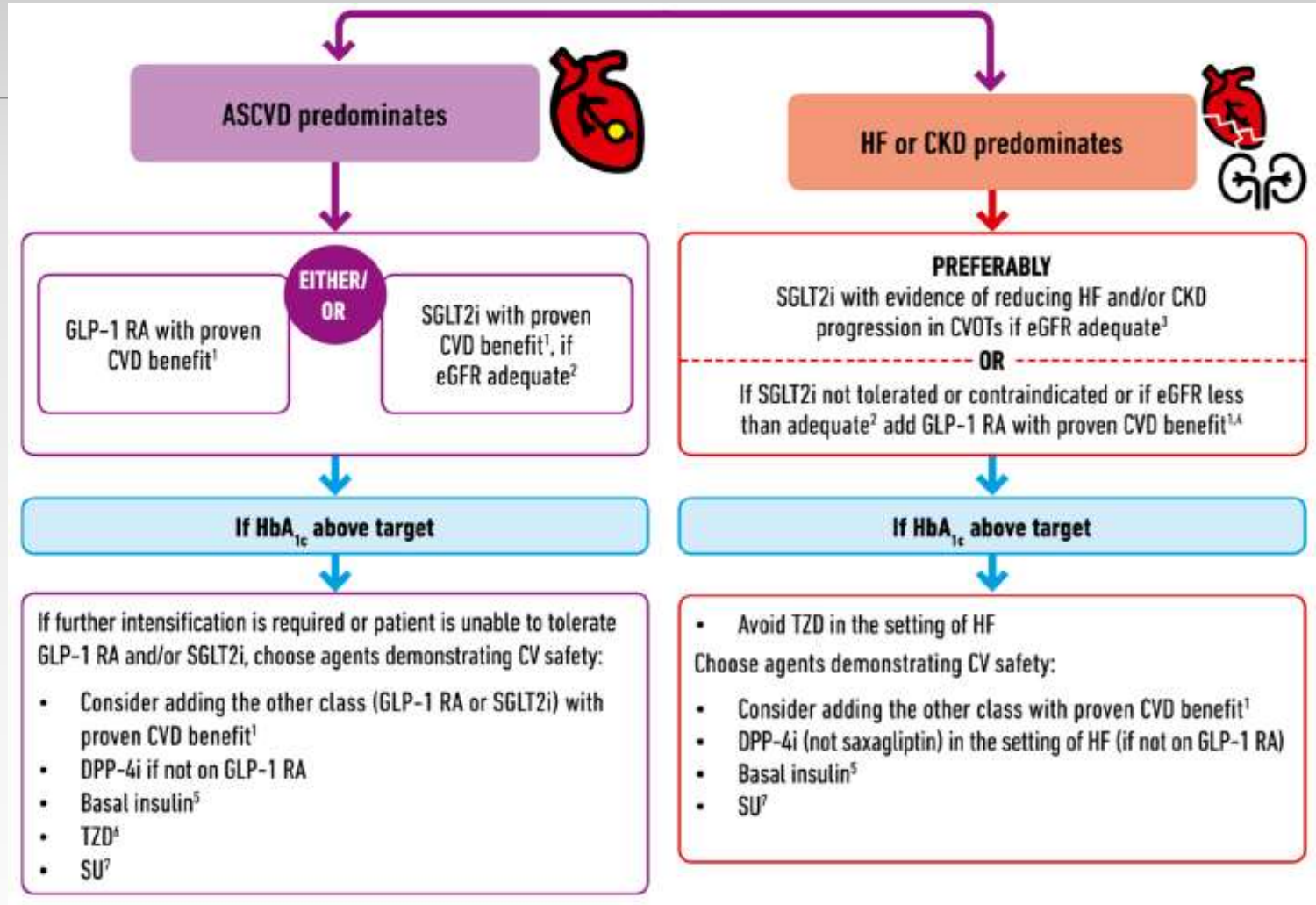
3. In individuals with T2DM and established CVD, SGLT2i with proven CV benefit (currently empagliflozin and canagliflozin) should be considered

For individuals with T2DM and established CVD, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered




Adapted from Scottish Intercollegiate Guidelines Network (SIGN 154). Pharmacological management of glycaemic control in people with type 2 diabetes. 2017. https://www.sign.ac.uk/assets/sign154.pdf

# EASD/ADA T2DM Consensus guidance (2018)




1.Proven CVD benefit means it has label indication of reducing CVD events For GLP1 RA strongest evidence for liraglutide>semaglutide>exenatide MR. For SGLT2i evidence modestly stronger for empagliflozin>canagliflozin

3. Both empagliflozin and canagliflozin have shown reduction HF

**Adapted from Davies MJ, et al. Diabetologia 2018;61:2461-98**

# ESC guideline on diabetes, pre-diabetes and CVD (2019)

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| **SGLT2 inhibitors** | | |
| Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311] | I | A |
| Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306] | I | B |
| **GLP1-RAs** | | |
| Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303] | I | A |
| Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176] | I | B |
| **Biguanides** | | |
| Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149] | IIa | C |
| **Insulin** | | |
| Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262] | IIa | C |
| **Thiazolidinediones** | | |
| Thiazolidinediones are not recommended in patients with HF. | III | A |
| **DPP4 inhibitors** | | |
| Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291] | III | B |

Class I: recommended or indicate

Class II: should be considered

Class II: not recommended

Level A: Multiple RCTs

Level B: Single RCT/ large non-RCT

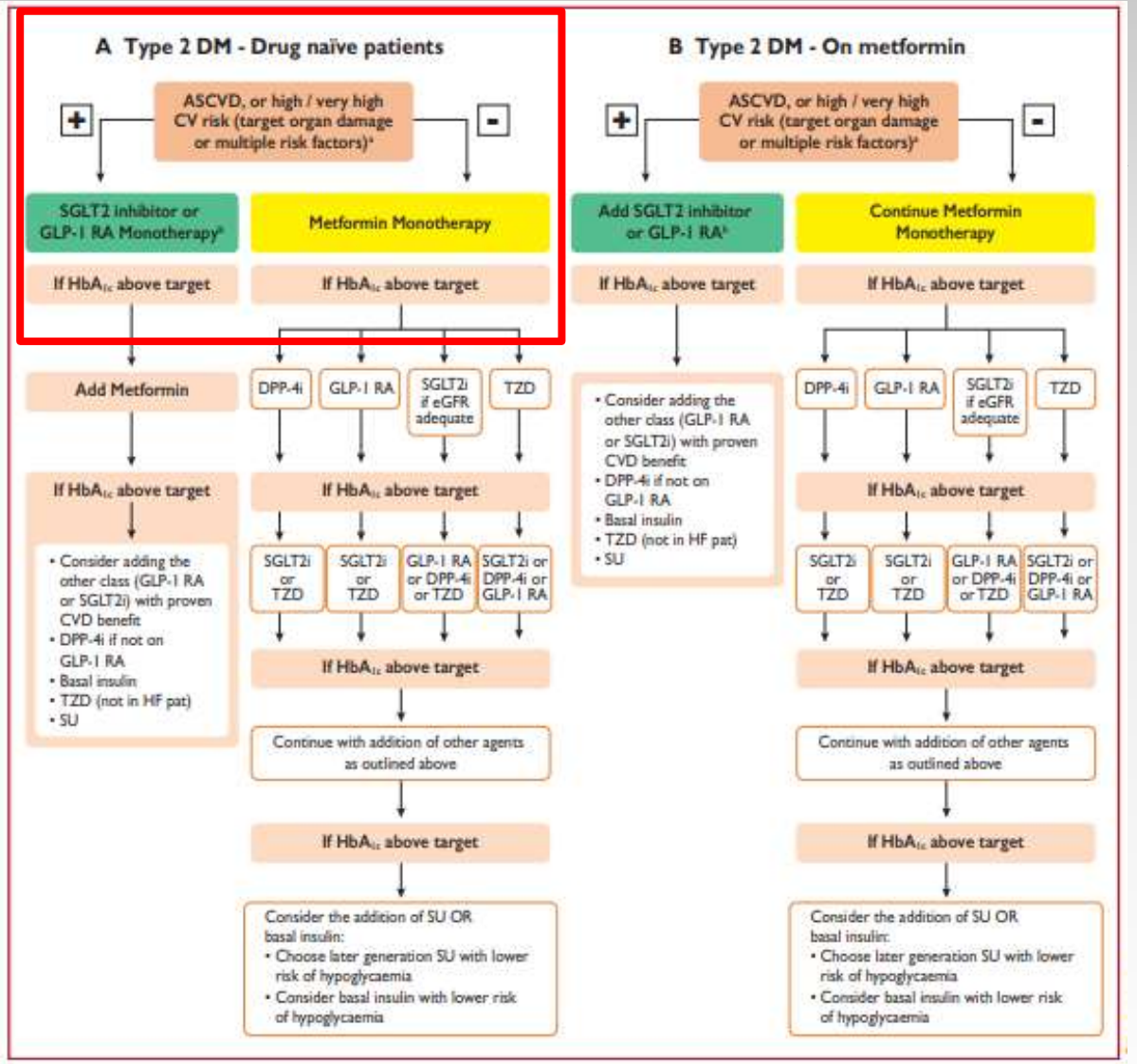
Level C: opinion of experts/ small studies

**Adapted from European Society of Cardiology. 2019 Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Diabetes-Pre-Diabetes-and-Cardiovascular-Diseases-developed-with-the-EASD**

# ESC guideline on diabetes, pre-diabetes and CVD (2019)

UKPDS suggest a beneficial effect of metformin in primary prevention. Although the evidence for metformin monotherapy from UKPDS is not as strong as with the novel drugs

Recommendation that the choice of drug to reduce CV events in patients with T2DM should be prioritised based on the presence of CVD and CV risk




Adapted from European Society of Cardiology. 2019 Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases developed in collaboration with the EASD. https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Diabetes-Pre-Diabetes-and-Cardiovascular-Diseases-developed-with-the-EASD

# Hope or Hype?

# Benefits of CVOTs

- Demonstrated CV safety
- Demonstrated CV benefit
- Focus attention on HF – older people with diabetes are more frequently affected by HF than MI
- Renal Outcomes – beyond the BP lowering and management of glycaemia

**Treating T2DM beyond glycaemia!**

# Limitations of CVOTs

- Majority of trial population has established CV disease - not representative of the larger population. Extrapolation only with considerable caution
- Lack of generalisability to a wider population due to heterogeneity of results,  patient characteristics and differences in outcomes
- Not able to assess long-term CV efficacy – only outcomes occurring <5 years of trial
- Not able to assess long-term safety – retinopathy, risk of amputations, fractures and DKA
- Lack of active comparator studies – placebo-controlled design only

# What the future holds

# The future of CVOTs

- More diverse populations including those with lower CV risk
- Longer term follow-up – identification of longer term safety issues and late beneficial effects
- Active comparators
- Standardised definitions – improve consistency and studies comparison
- Different endpoints (e.g. severity of disease, multiple events in the same patient)
- Involvement of patients – minimise treatment discontinuation, improve adherence

# Next Steps

- Update of national guidance

- Treatment individualisation
  - ✓Who will benefit?
  - ✓Contra-indications/Licensing restrictions
  - ✓Side-effects/Safety profile
  - ✓Co-morbidities
  - ✓ Medicines optimisation (review, switch and refine)

- Economic sustainability – cost-effectiveness

# My Answer is Hope

# Thank you!