

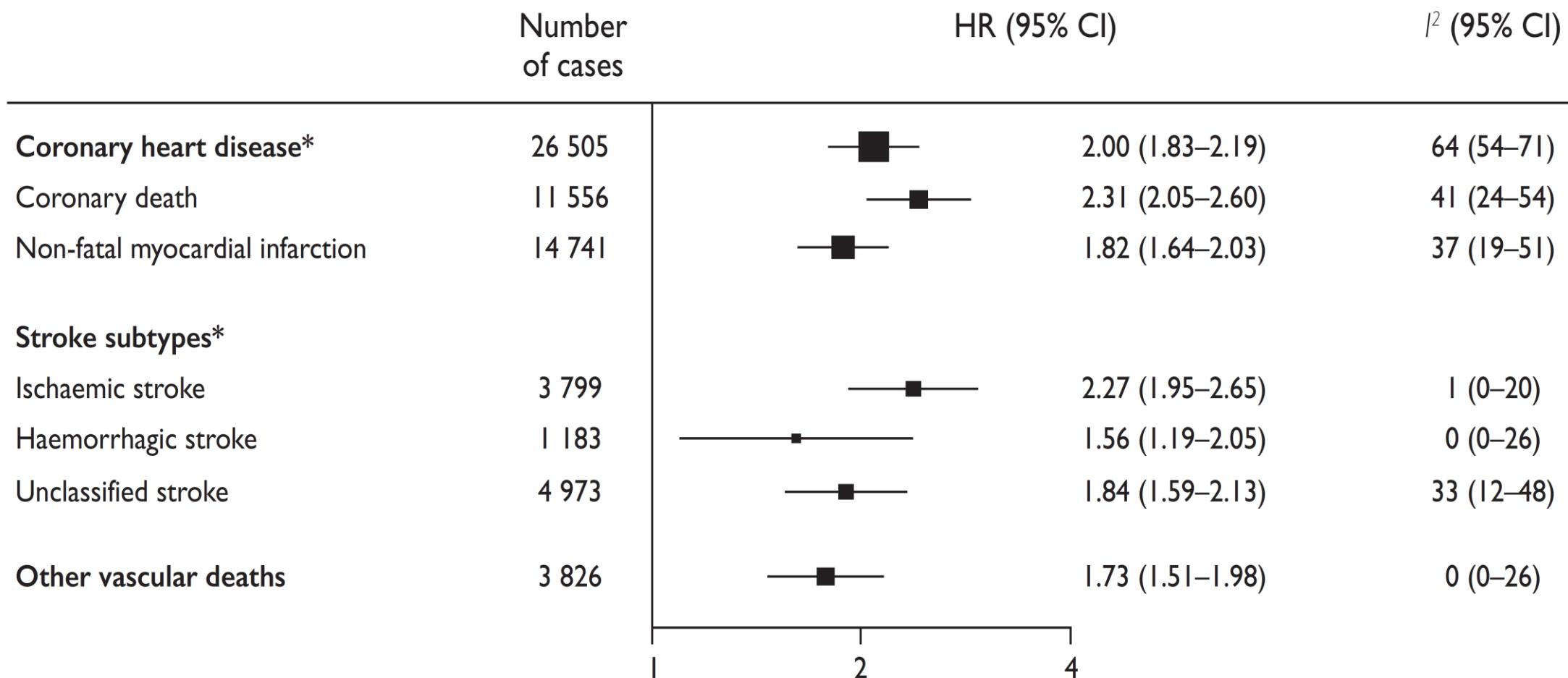
Có gì mới từ khuyến cáo ESC 2019 về điều trị đái tháo đường: kết nối tim mạch & nội tiết

GS TS ĐĂNG VẠN PHƯỚC
CHỦ TỊCH HỘI TIM MẠCH VIỆT NAM

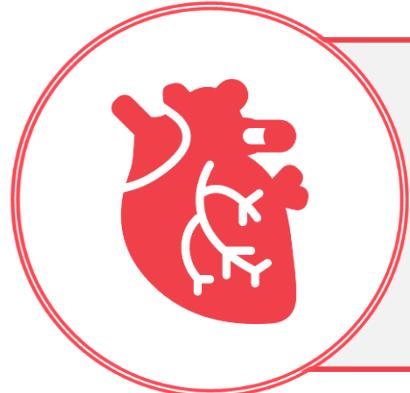
Contents

1. Why cardiologists care about diabetes?
2. ESC guideline 2019: what's new in type 2 diabetes management?
3. Considerations in clinical practice when on new glucose lowering agents.

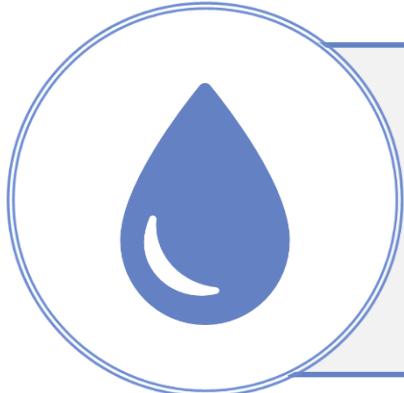
Diabetes* doubles the risk of vascular events



Type 2 diabetes is a common comorbidity in patients with heart failure



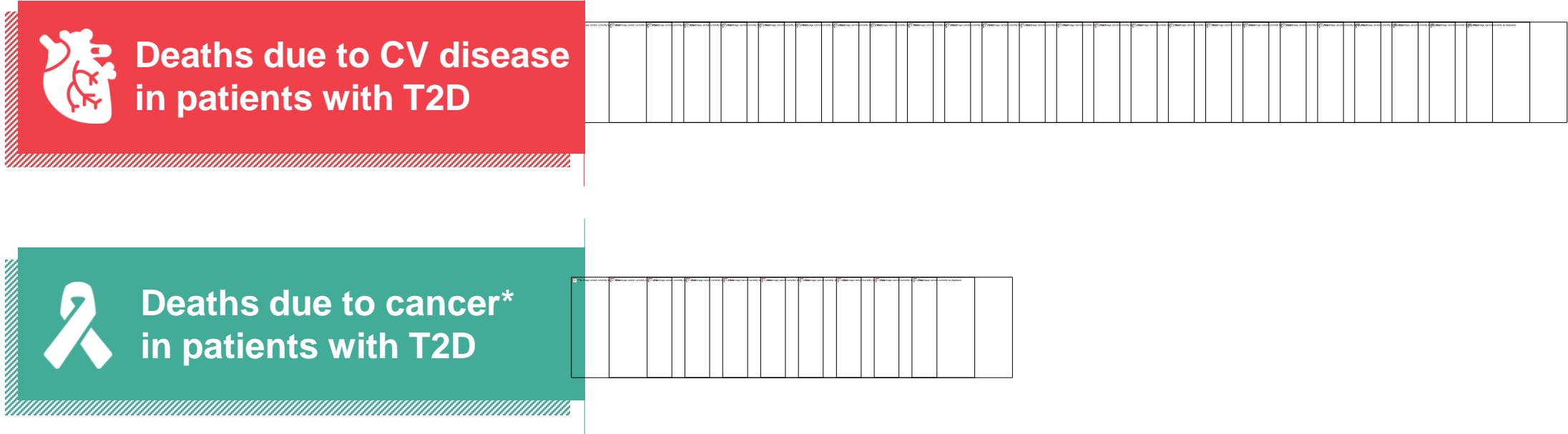
~30% of patients with heart failure also have diabetes¹



2.5× higher rate of chronic heart failure in patients with T2D compared with those without T2D²

CV disease in patients with T2D is responsible for more deaths than cancer* in the general population

2.5 times more deaths than cancer*



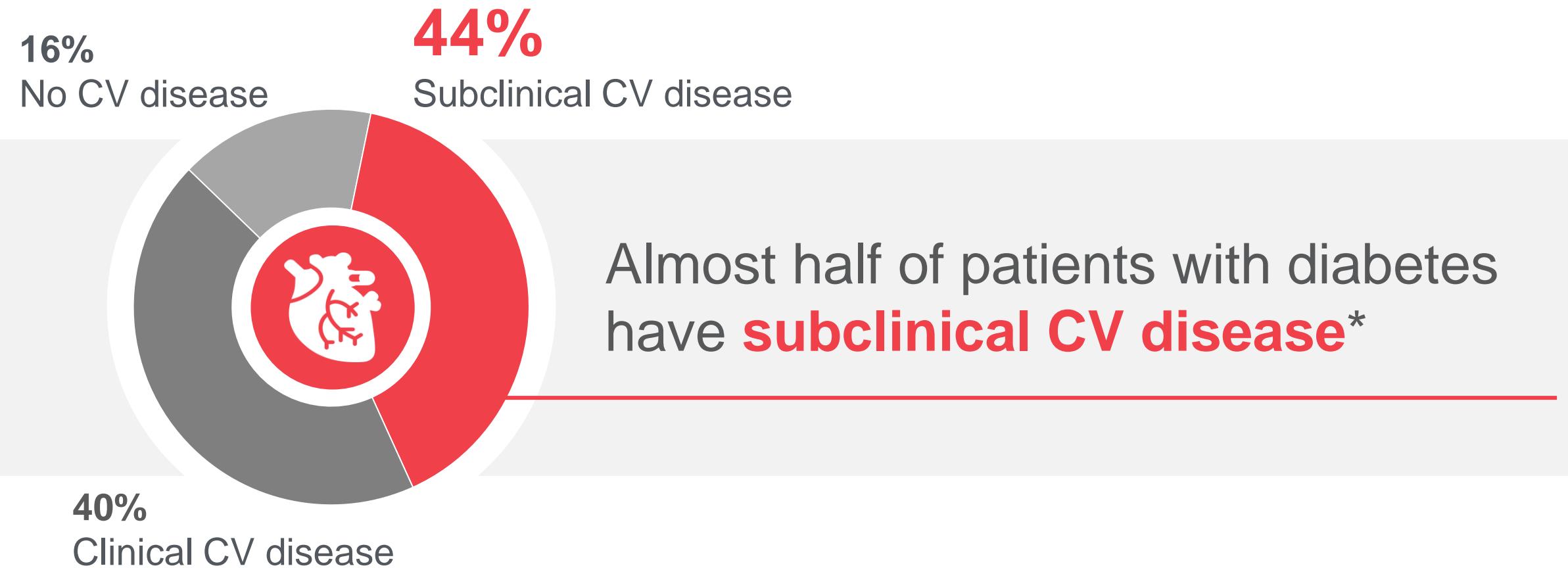
24-year follow-up of 7461 patients with T2D and 37,271 controls from the Skaraborg Diabetes Register

*Solid tumour cancers only

CV, cardiovascular disease; T2D, type 2 diabetes

Andersson T et al. Diabetes Res Clin Prac 2018;138:81

CV disease is frequently asymptomatic and unrecognised



Prevalence of subclinical CV disease across 1343 patients with diabetes aged ≥ 65 years in the US

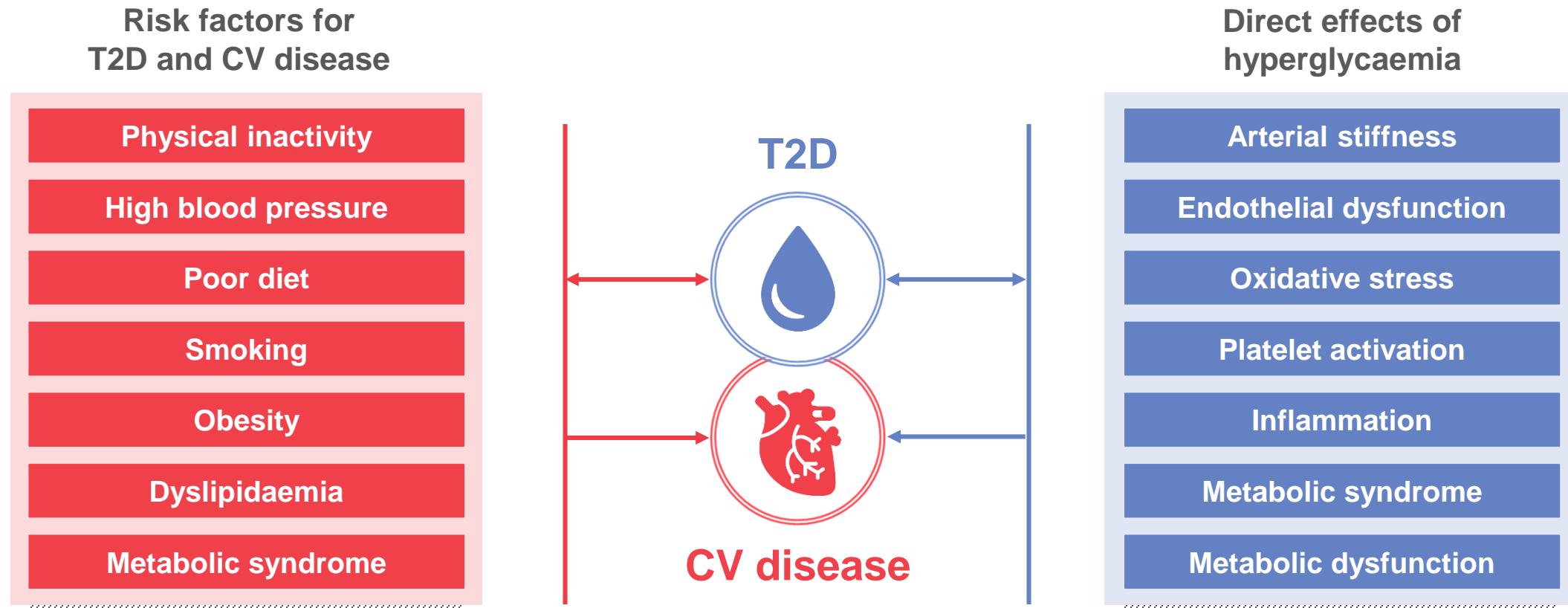
*Absence of prevalent clinical disease at baseline: ankle–brachial index ≤ 0.9 , internal carotid artery wall thickness >80 th percentile, common carotid artery wall thickness >80 th percentile, carotid stenosis $>25\%$, major electrocardiogram abnormalities (based on the Minnesota code), and a Rose Questionnaire positive for claudication or angina pectoris in the absence of clinical diagnosis of angina pectoris or claudication

CV, cardiovascular

Kuller LH et al. Arterioscler Thromb Vasc Biol 2000;20:823

The pathophysiology of CV disease in patients with T2D is complex

T2D shares common risk factors with CV disease and contributes to vascular damage



2019 ESC Guidelines on Diabetes, Pre-diabetes and Cardiovascular Diseases

Developed in collaboration with EASD

Francesco Cosentino, MD, PhD, FESC

Unit of Cardiology
Karolinska Institute & University Hospital
Stockholm



What is new in the 2019 guidelines?

- ✓ Reclassification of CV risk
- ✓ New treatment algorithm with glucose lowering agents for management/prevention of CVD
- ✓ New recommendations regarding the role of aspirin and NOACs in diabetes
- ✓ Duration of DAPT post ACS in diabetes
- ✓ New lipid targets relating to severity of CV risk/new recommendations for the use of PCSK9 inhibitors
- ✓ Individualized blood pressure targets

ESC 2019 - Reclassification of CV risk

2016 European Guidelines on CVD Prevention in Clinical Practice

Risk categories

Very high-risk	Subjects with any of the following: <ul style="list-style-type: none">Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima-media thickness of the carotid artery.DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.Severe CKD (GFR <30 mL/min/1.73 m²).A calculated SCORE ≥10%.
High-risk	Subjects with: <ul style="list-style-type: none">Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg.Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).Moderate CKD (GFR 30–59 mL/min/1.73 m²).A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

www.escardio.org/guidelines

European Heart Journal 2016;37:2315–2381-doi:10.1093/eurheartj/ehw106



2019 ESC Guidelines on Diabetes, Pre-diabetes and Cardiovascular Diseases

Table 7 Cardiovascular risk categories in patients with diabetes^a

Very high risk	Patients with DM and established CVD or other target organ damage ^b or three or more major risk factors ^c or early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

^bProteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

European Heart Journal (2019) 00, 1–69

Glucose lowering agents - new evidence from CVOT

2013



European Heart Journal (2013) **34**, 3035–3087
doi:10.1093/eurheartj/eht108

ESC GUIDELINES

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD



2019



ESC
European Society of Cardiology
European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

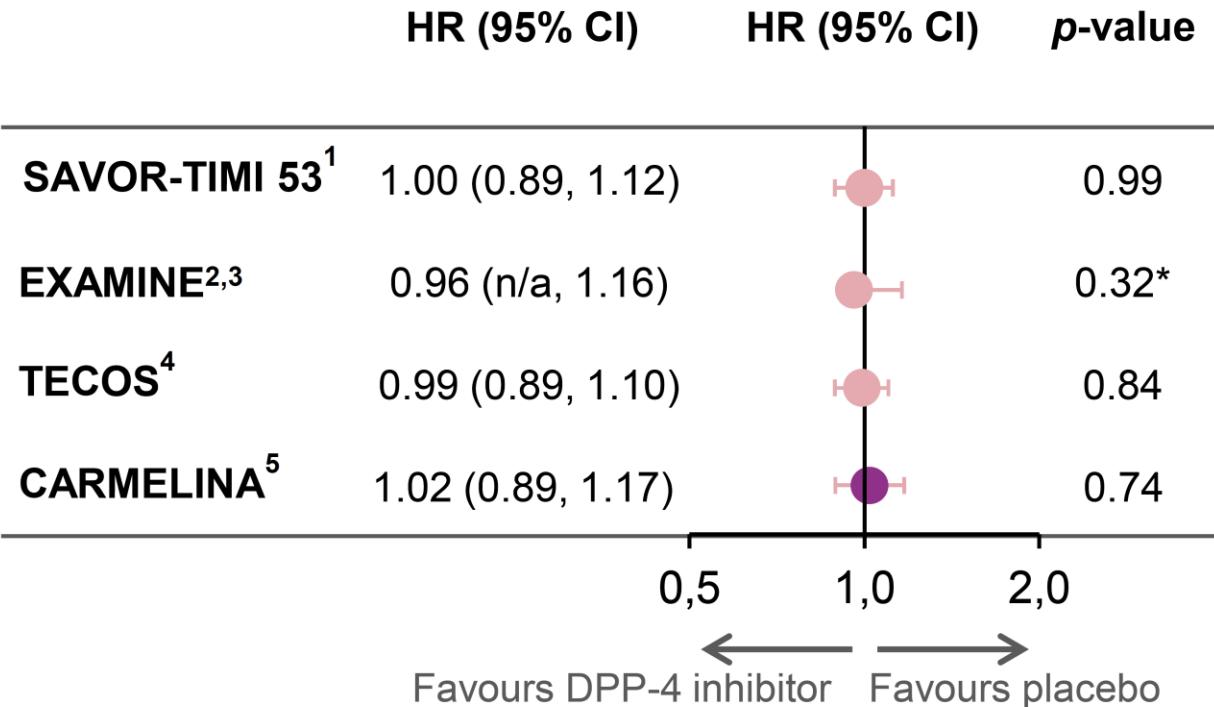
ESC GUIDELINES



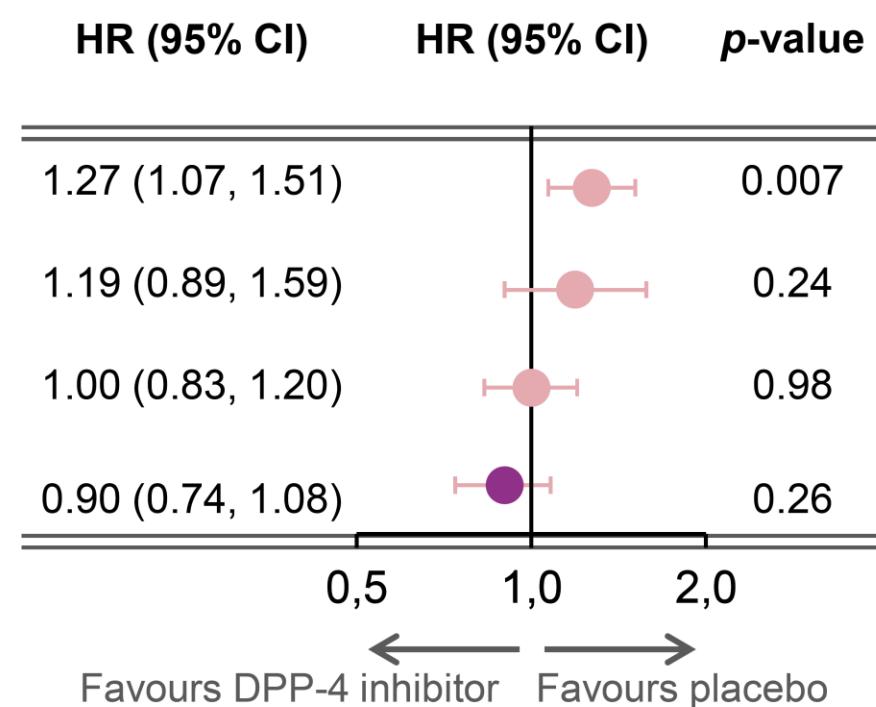
2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

CVOTs with DPP4i (MACE endpoint and HHF)

3P-MACE



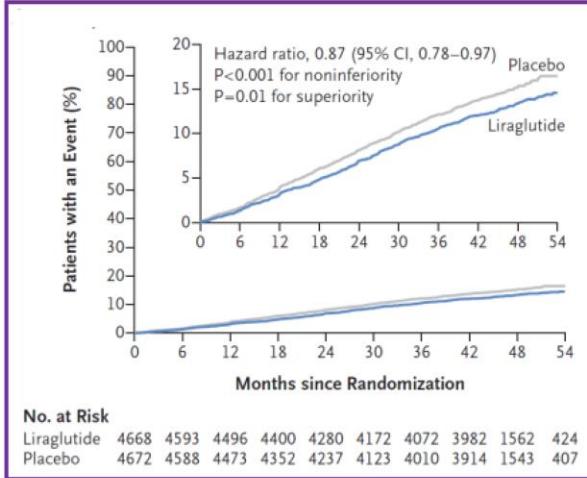
Hospitalisation for heart failure^{5,6}



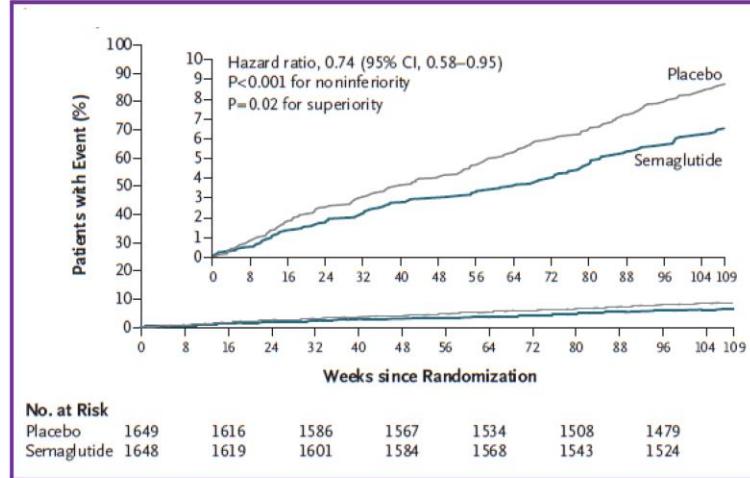
1. Scirica BM et al. *N Engl J Med* 2013;369:1317; 2. White WB et al. *N Engl J Med* 2013;369:1327; 3. Zannad F et al. *Lancet* 2015;385:2067-76;
4. Green JB et al. *N Engl J Med* 2015;373:232; 5. Rosenstock J et al. *JAMA* 2018; doi: 10.1001/jama.2018.18269; 6. McGuire D. et al. *JAMA Cardiol* 2016;1:126

CVOT with GLP1-RA (3P-MACE endpoint)

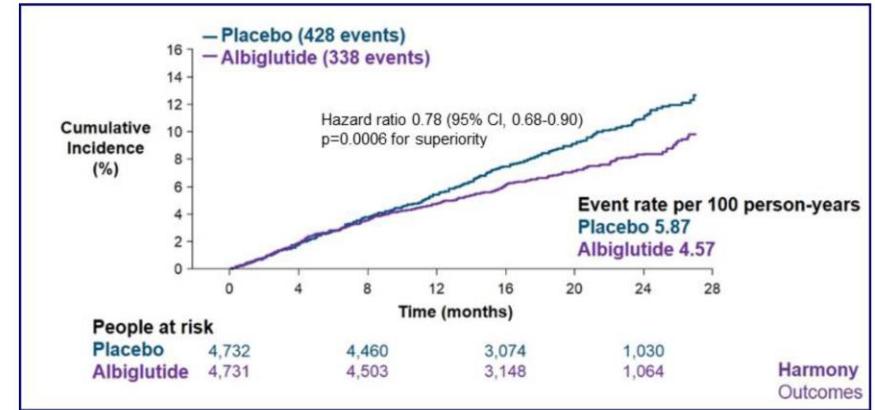
LEADER¹



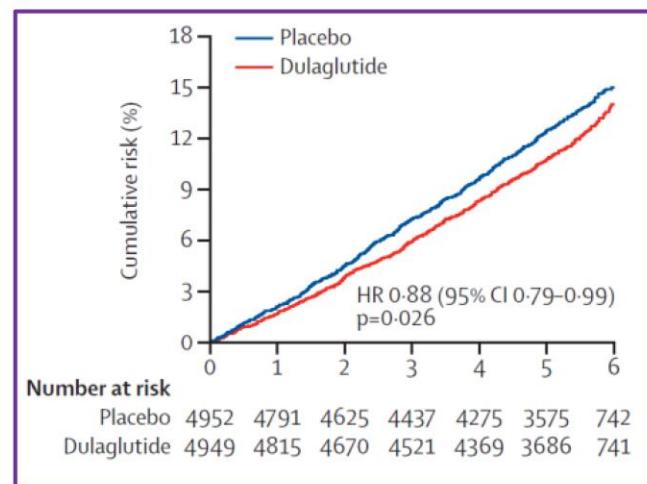
SUSTAIN-6²



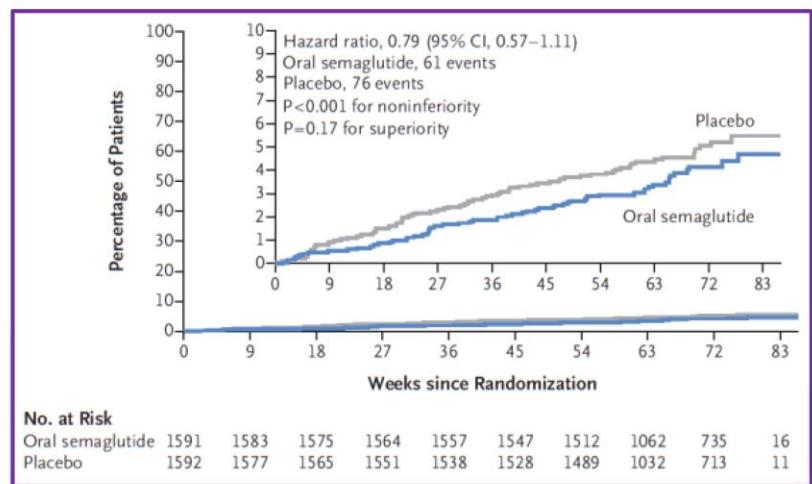
HARMONY³



REWIND⁴



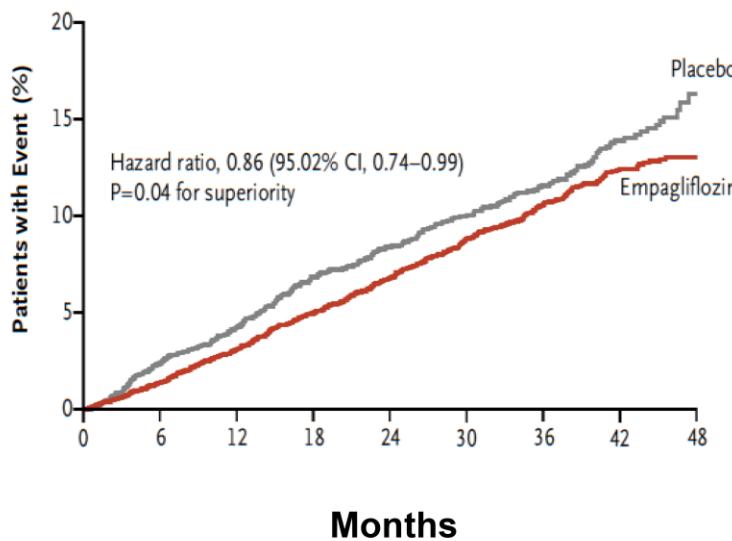
PIONEER-6⁵



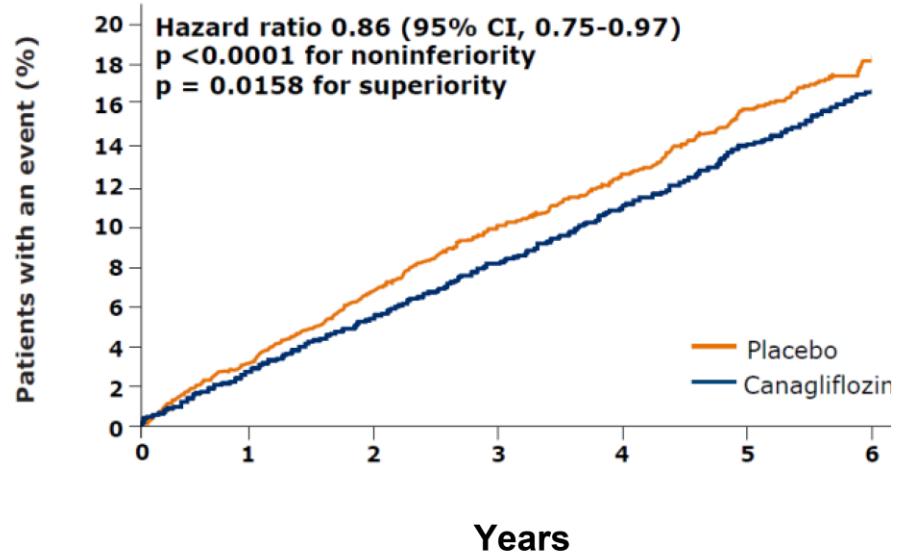
1. Marso et al. *N Engl J Med.* 2016
2. Marso SP et al. *N Engl J Med.* 2016
3. Hernandez AF et al. *Lancet* 2018
4. Gerstein H et al. *Lancet* 2019
5. Husain M et al. *N Engl J Med* 2019

CVOT with SGLT2i (3P-MACE endpoint)

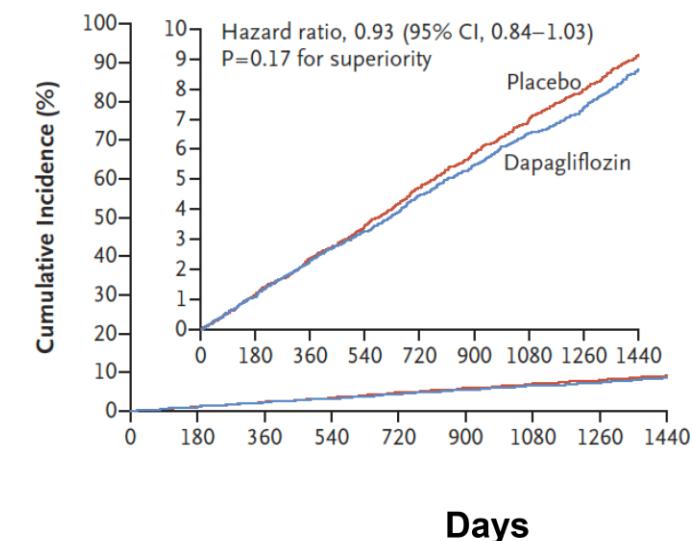
EMPA-REG Outcome¹



CANVAS Program²



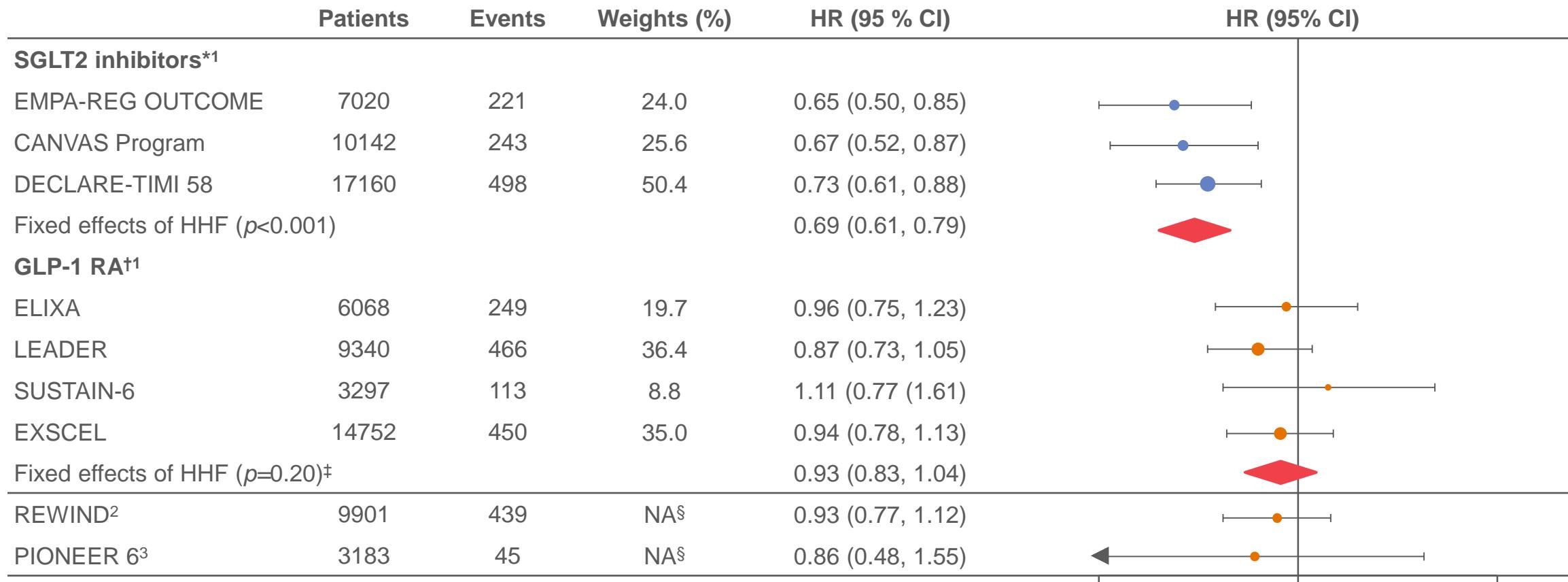
DECLARE³



1. Zinman B et al. N Engl J Med. 2015
2. Neal B et al. N Engl J Med 2017
3. Wiviott SD et al. N Engl J Med 2018

Similar patterns in the reduction in risk of HHF have been demonstrated across SGLT2 inhibitor CVOTs

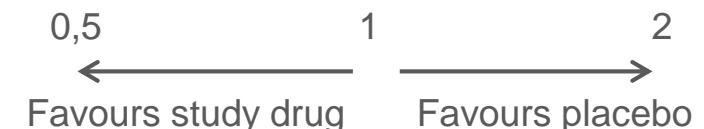
GLP-1 RAs have demonstrated no benefits in HHF



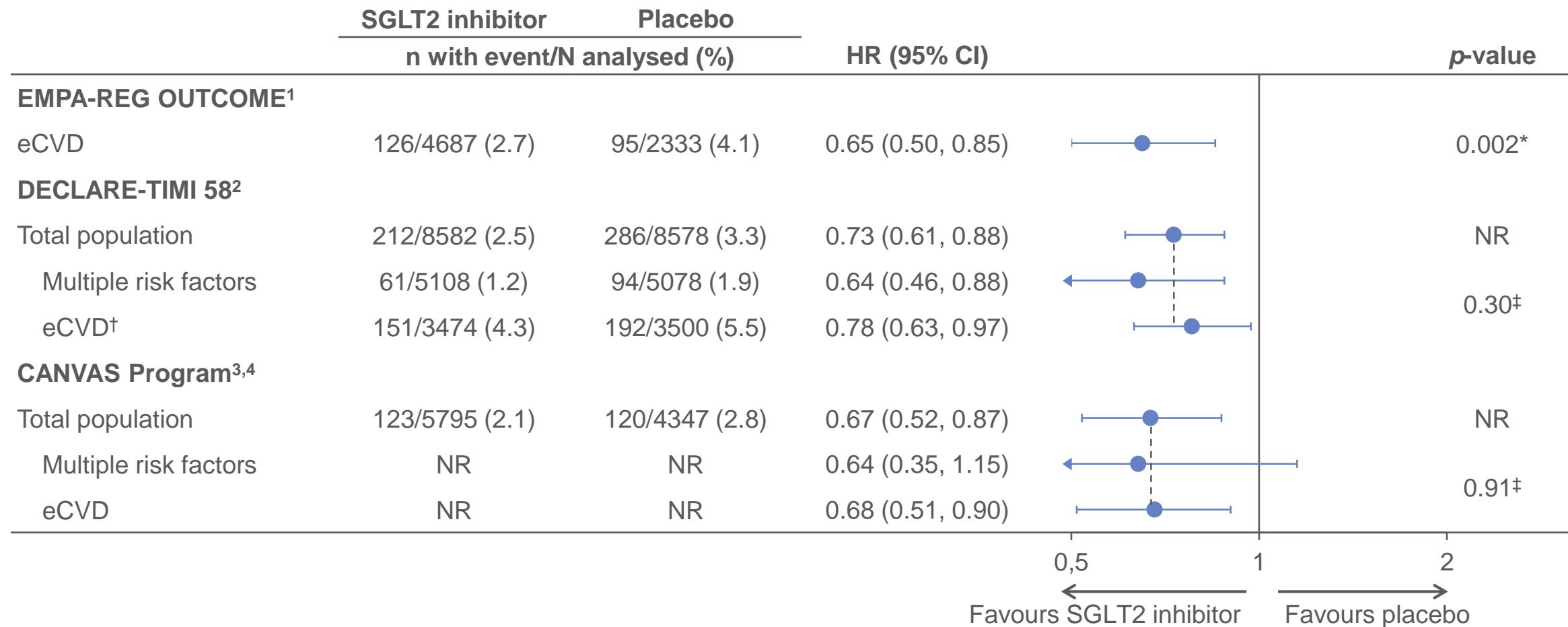
*Q statistic=0.60; $p=0.74$, $P=0\%$; †Q statistic=1.48; $p=0.69$, $P=0\%$; [‡]Harmony Outcomes did not directly report on HHF outcomes and was not included in the meta-analysis for this endpoint; [§]Not included in meta-analysis

CVOT, cardiovascular outcomes trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalisation for heart failure; SGLT2, sodium-glucose co-transporter-2

1. Zelniker TA et al. Circulation 2019;139:2022; 2. Gerstein HC et al. Lancet 2019;394:121; 3. Husain M et al. N Engl J Med 2019;381:841



SGLT2 inhibitor effects on HF are consistent in patients with or without established CV disease



Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

Empagliflozin is not indicated in all countries for CV risk reduction, and is not indicated for the treatment of heart failure

*Nominal p-value; [†]Defined as presence of atherosclerotic CV disease,² see individual publications for full definitions; [‡]p-value for interaction

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; eCVD, established cardiovascular disease; HF, hospitalisation for heart failure;

MRF, multiple risk factors; NR, not reported; SGLT2, sodium-glucose co-transporter-2

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

4. Mahaffey KW et al. *Circulation* 2017;137:323

SGLT2i: renal outcome

	CANVAS/ CANVAS-R ¹ Canagliflozin	CREDENCE ² Canagliflozin	DECLARE-TIMI 58 ³ Dapagliflozin	EMPA-REG OUTCOME ⁴ Empagliflozin	VERTIS-CV ⁵ Ertugliflozin
Baseline renal function ^a	eGFR: 76.5 30.2%; UACR: >30	eGFR: 56.2 ACR: 927	eGFR: 85.2	25.9%; eGFR: <60 36%; UACR: >30	22.0%; eGFR: <60 42.2%; UACR: >30
Renal outcomes	Albuminuria progression: 0.73 (0.67-0.79) Renal function ^b : 0.60 (0.47-0.77)	Primary composite outcome ^c : 0.70 (0.59-0.82)	Renal composite outcome ^d : 0.53 (0.43-0.66)	Incident or worsening nephropathy: 0.61 (0.53-0.70) Renal composite outcome ^e : 0.54 (0.40-0.75)	Renal composite outcome ^{e,f} : TBA

■ Statistically superior to placebo

■ Statistically noninferior to placebo

■ No data available

^a eGFR in mL/min/1.73 m². ^b 40% reduction in eGFR, renal-replacement therapy, or renal death. ^c ESRD, doubling of serum creatinine, or death from renal or cardiovascular disease.

^d ≥40% decrease in eGFR to <60, ESRD, or death from renal cause. ^e Doubling of serum creatinine, initiation of renal-replacement therapy, or death from renal disease.

^f Renal transplantation.

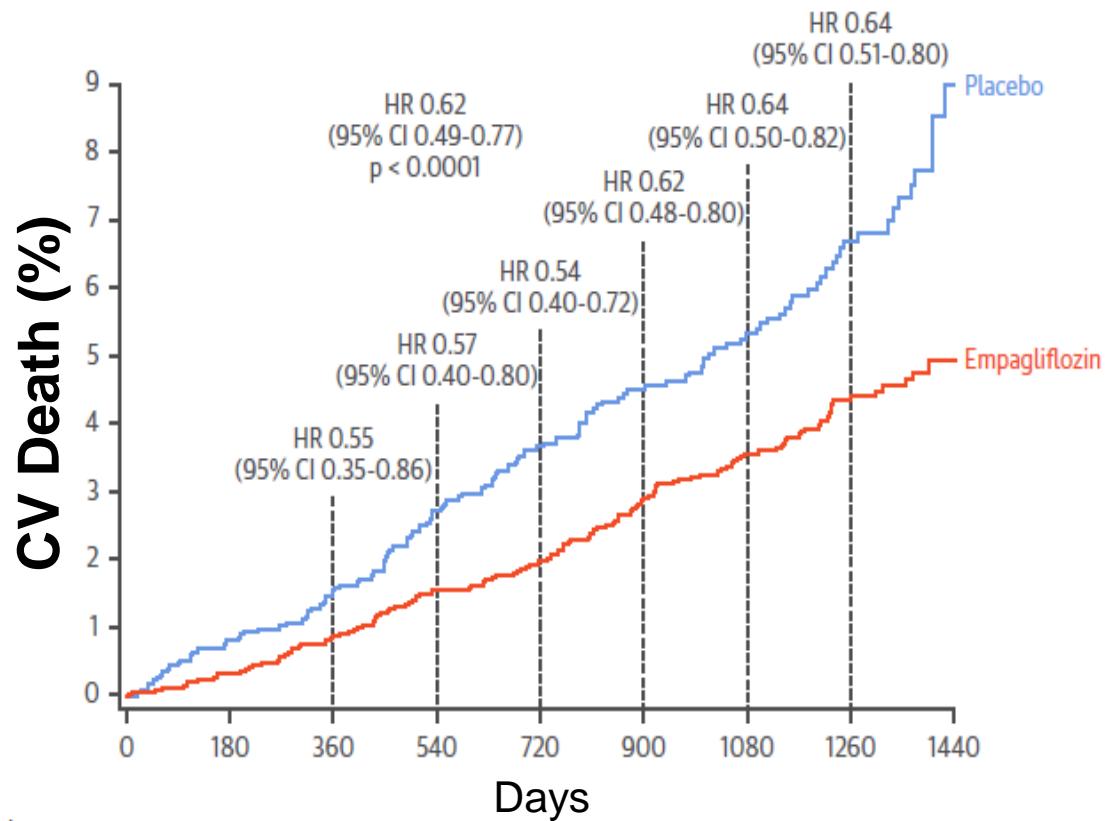
1. Neal B et al. *N Engl J Med*. 2017;377:644-657. 2. Perkovic V et al. *N Engl J Med*. 2019;380:2295-2306. 3. Wiviott SD. *N Engl J Med*. 2019;380:347-357.

4. Zinman B et al. *N Engl J Med*. 2015;373:2117-2128. 5. Cannon CP et al. *Am Heart J*. 2018;206:11-23.

PeerView.com

Empagliflozin and CV Death

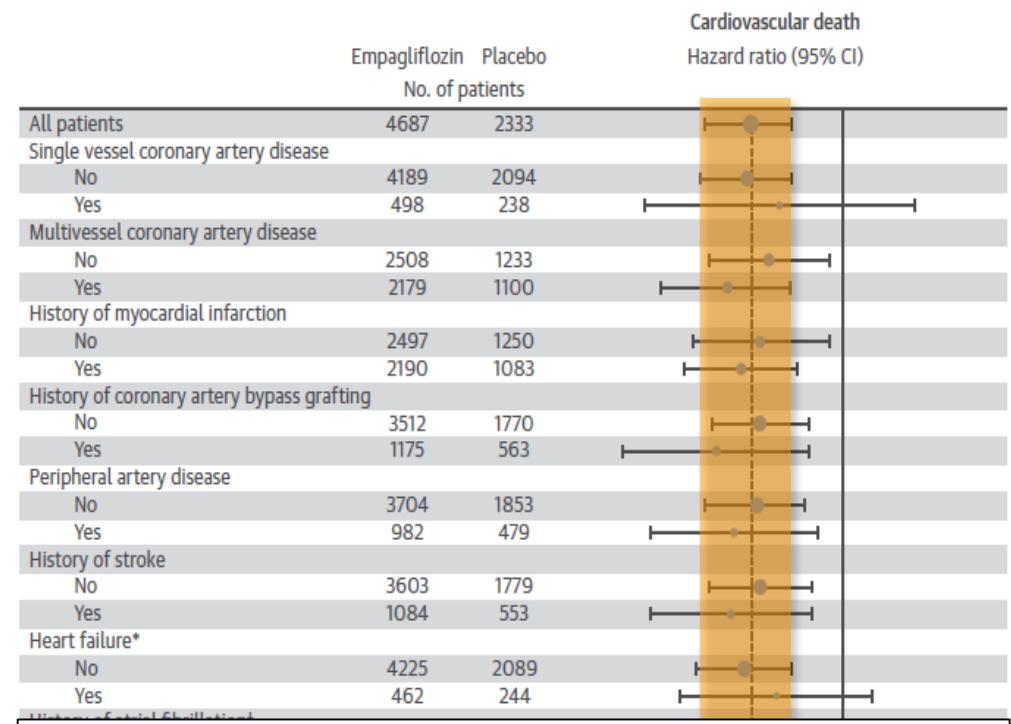
CV Death Over Time



No. of patients								
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722
Placebo	2333	2303	2280	2243	2012	1503	1281	825

Cox regression analyses in patients treated with ≥ 1 dose of study drug

CV Death by CV Disease



2 or 3 high CV risk categories:
 5.2% vs. 11.1%
NNT=17
 (to prevent 1 CV Death over 3 yrs)

ESC 2013: role of diabetes drug - Glycemic control

Recommendations	Class	Level
It is recommended that glucose lowering is instituted in an individualized manner taking duration of DM, co-morbidities and age into account.	I	C
It is recommended to apply tight glucose control, targeting a near-normal HbA _{1c} (<7.0% or <53 mmol/mol) to decrease microvascular complications in T1DM and T2DM.	I	A
A HbA _{1c} target of ≤7.0% (≤53 mmol/mol) should be considered for the prevention of CVD in T1 and T2 DM.	IIa	C
Basal bolus insulin regimen, combined with frequent glucose monitoring, is recommended for optimizing glucose control in T1DM.	I	A
Metformin should be considered as first-line therapy in subjects with T2DM following evaluation of renal function.	IIa	B

ESC 2019 - New treatment algorithms

Type 2 DM - Drug naïve patients

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)*

SGLT2 inhibitor or GLP-1 RA Monotherapy§

If HbA_{1c} above target

Add Metformin

If HbA_{1c} above target

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD (not in HF pat)
- SU

Metformin Monotherapy

If HbA_{1c} above target

DPP-4i GLP-1 RA SGLT2i if eGFR adequate TZD

If HbA_{1c} above target

SGLT2i or TZD SGLT2i or TZD GLP-1 RA or DPP-4i or TZD SGLT2i or DPP-4i or GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

- Consider the addition of sulfonylurea OR basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
 - Consider basal insulin with lower risk of hypoglycaemia

Type 2 DM – On metformin

ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)*

Add SGLT2 inhibitor or GLP-1 RA§

If HbA_{1c} above target

If HbA_{1c} above target

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD (not in HF pat)
- SU

Continue Metformin Monotherapy

If HbA_{1c} above target

DPP-4i GLP-1 RA SGLT2i if eGFR adequate TZD

If HbA_{1c} above target

SGLT2i or TZD SGLT2i or TZD GLP-1 RA or DPP-4i or TZD SGLT2i or DPP-4i or GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

- Consider the addition of sulfonylurea OR basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
 - Consider basal insulin with lower risk of hypoglycaemia



Recommendations for glucose lowering treatment for patients with diabetes

Recommendations for glucose-lowering treatment for patients with diabetes

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
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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
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ACS = acute coronary syndromes; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; GLP1-RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.

^aClass of recommendation.

^bLevel of evidence.

^cSee Table 7.

Heart Failure & Diabetes

Key messages

- Patients with pre-DM and DM are at increased risk of developing HF.
- Patients with DM are at greater risk of HF with reduced ejection fraction (HF_{REF}) or HF with preserved ejection fraction (HF_{P EF}); conversely, HF increases the risk of DM.
- The coexistence of DM and HF imparts a higher risk of HF hospitalization, all-cause death, and CV death.
- Guideline-based medical and device therapies are equally effective in patients with and without DM; as renal dysfunction and hyperkalaemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g. RAAS blockers) are advised.
- First-line treatment of DM in HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone, and rosiglitazone are not recommended for patients with DM and HF.

Recommendations	Class ^a	Level ^b
SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) are associated with a lower risk of HF hospitalization in patients with DM, and are recommended. ^{306,311,496}	I	A
Metformin should be considered for DM treatment in patients with HF, if the eGFR is stable and >30 mL/min/1.73 m ² . ^{484,485}	IIa	C
GLP1-RAs (lixisenatide, liraglutide, semaglude, exenatide, and dulaglutide) have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF. ^{158,176,297,299,300,303,498,499}	IIIb	A
The DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on the risk of HF hospitalization, and may be considered for DM treatment in patients with HF. ^{293,294}	IIIb	B
Insulin may be considered in patients with advanced systolic HF _{REF} . ⁵⁰⁰	IIIb	C
Thiazolidinediones (pioglitazone and rosiglitazone) are associated with an increased risk of incident HF in patients with DM, and are not recommended for DM treatment in patients at risk of HF (or with previous HF). ^{279,491–493}	III	A
The DPP4 inhibitor saxagliptin is associated with an increased risk of HF hospitalization, and is not recommended for DM treatment in patients at risk of HF (or with previous HF). ²⁹¹	III	B

Empagliflozin outcomes trials in chronic HFpEF and HFrEF

	EMPEROR-Preserved ^{1,2}	EMPEROR-Reduced ^{3,4}	
 Study drug	Empagliflozin 10 mg qd	Empagliflozin 10 mg qd	
 Population	HFpEF (LVEF >40%) with or without T2D Elevated NT-proBNP (pg/ml) Patients without AF >300	HFrEF (LVEF ≤40%) with or without T2D Ejection fraction (%) ≥36 to ≤40 ≥31 to ≤35 ≤30 ≤40% + HHF within 12 months	NT-proBNP (pg/ml) Patients without AF* ≥2500 ≥1000 ≥600 ≥600
N	Sample size	Approx. 5250 patients	Approx. 3600 patients
 Primary endpoint	Time to first event of adjudicated CV death or adjudicated HHF		

Empagliflozin is not indicated for the treatment of heart failure

*NT-proBNP-based enrichment of the population: patients with a higher ejection fraction require a higher NT-proBNP level for inclusion

AF, atrial fibrillation; CV, cardiovascular; LVEF, left ventricular ejection fraction; HHF, hospitalisation for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

1. ClinicalTrials.gov. NCT03057951 (accessed Jun 2019); 2. Butler J et al. ESC-HF 2018; poster P972; 3. ClinicalTrials.gov. NCT03057977 (accessed Jun 2019);

4. Packer M et al. Eur J Heart Fail 2019; doi: 10.1002/ejhf.1536

DELIVER and SOLOIST-WHF trials

	DELIVER ¹	SOLOIST-WHF ^{2,3}
 Study drug	Dapagliflozin 10 mg qd	Sotagliflozin
 Population	HFpEF (LVEF >40%)	Worsening HFpEF or HFrEF in patients with T2D
N Sample size	4700	6667*
 Primary endpoint	Time to first occurrence of CV death, HHF or urgent HF visit	Time to first occurrence of CV death or HHF in: <ul style="list-style-type: none">• Patients with LVEF <50%• Total patient population

*Patient numbers differ between ClinicalTrials.gov and EU Clinical Trials Register reports

CV, cardiovascular; LVEF, left ventricular ejection fraction; HF, heart failure; HHF, hospitalisation for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

1. ClinicalTrials.gov. NCT03619213; 2.ClinicalTrials.gov. NCT03521934; 3. EU Clinical Trials Register 2017-003510-16. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003510-16/SE> (all websites accessed Jun 2019)

Functional capacity studies with SGLT2 inhibitors

	EMPERIAL-Preserved ¹	EMPERIAL-Reduced ¹	DETERMINE-Preserved ²	DETERMINE-Reduced ³	
 Study drug	Empagliflozin 10 mg qd		Dapagliflozin 10 mg qd		
 Population	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	HFpEF (LVEF >40%)	HFrEF (LVEF ≤40%)	
 N	Sample size	300	300	400	300
 Primary endpoint	Change from baseline to Week 12 in exercise capacity (6MWT)		Change from baseline to Week 16 in exercise capacity (6MWT)		

6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction
1. Abraham WT et al. Eur J Heart Fail 2019;21:932; 2. ClinicalTrials.gov. NCT03877224; 3. ClinicalTrials.gov. NCT03877237 (all websites accessed Jun 2019)

Patient preferences for medication delivery¹⁻⁴

Oral agents are favored over injections

- Small pills are favored over large pills
- Once-daily regimens are favored over twice-daily regimens
- Twice-daily regimens are favored over more frequent dosing



Pens and autoinjectors are favored over vials and syringes

- Ergonomics, convenience, and portability are key attributes affecting device preferences
- Less frequent injections are preferred to more frequent injections
- Smaller needles are preferred to larger needles



1. Fields J et al. *Curr Ther Res Clin Exp.* 2015;77:79-82. 2. Fifer S et al. *BMC Health Serv Res.* 2018;18:675. 3. Ridyard CH et al. *Patient.* 2016;9:281-292.
4. Thieu VT et al. *Patient Prefer Adherence.* 2019;13:561-576.

GLP1-Ras: adverse events in ≥5% of patients

Adverse Event	Lixisenatide ¹	Exenatide BID ²	Exenatide ER ³	Liraglutide ⁴	Dulaglutide ⁵	Semaglutide ^{6,a}
Nausea	X	X	X	X	X	X
Vomiting	X	X		X	X	X
Diarrhea	X	X		X	X	X
Dyspepsia		X		X	X	
Constipation		X		X		X
Abdominal pain					X	X
Reduced appetite				X		
Hypoglycemia	X	X				
Injection-site reaction						
Injection-site nodule			X			
Headache	X					
Back pain						
Arthralgia						
Dizziness	X	X				
Jitteriness		X				
Asthenia		X				

^a Data refer to injectable formulation only.

1. Adlyxin (lixisenatide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471orig1s000lbl.pdf. Accessed July 31, 2019.

2. Byetta (exenatide BID) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf. Accessed July 31, 2019.

3. Bydureon (exenatide ER) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf. Accessed July 31, 2019.

4. Victoza (liraglutide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf. Accessed July 31, 2019.

5. Trulicity (dulaglutide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125469s007s008lbl.pdf. Accessed July 31, 2019.

6. Ozempic (semaglutide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf. Accessed July 31, 2019.

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GLP-1 RAs: Warnings and Precautions

Warnings/Precautions	Lixisenatide ¹	Exenatide BID ²	Exenatide ER ³	Liraglutide ⁴	Dulaglutide ⁵	Semaglutide ^{6,a}
Thyroid C-cell tumors				X	X	
Acute pancreatitis	X	X	X	X	X	X
Acute gallbladder disease			X	X		
Acute kidney injury	X		X	X	X	X
Do not use in patients with severe renal impairment or ESRD		X				
Hypoglycemia risk increases if used with SU or insulin	X	X	X	X	X	X
Anaphylaxis or hypersensitivity reactions	X	X	X	X	X	X
Immunogenicity	X		X			
Severe gastrointestinal disease, not recommended in gastroparesis	X	X	X		X	
Diabetic retinopathy						X
Injection-site nodules			X			
Do not share pen	X	X		X		X

^a Data refer to injectable formulation only.

1. Adlyxin (lixisenatide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471orig1s000lbl.pdf. Accessed July 31, 2019.

2. Byetta (exenatide BID) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf. Accessed July 31, 2019.

3. Bydureon (exenatide ER) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022200s026lbl.pdf. Accessed July 31, 2019.

4. Victoza (liraglutide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf. Accessed July 31, 2019.

5. Trulicity (dulaglutide) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125469s007s008lbl.pdf. Accessed July 31, 2019.

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SGLT2is: Adverse Events in ≥5% of patients

Adverse Event	Canagliflozin ¹	Dapagliflozin ²	Empagliflozin ³	Ertugliflozin ⁴
Female genital mycotic infections	X	X	X	X
URTI	X	X	X	
Increased urination	X			
Nasopharyngitis		X		

1. Invokana (canagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf. Accessed July 31, 2019.

2. Farxiga (dapagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf. Accessed July 31, 2019.

3. Jardiance (empagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf. Accessed July 31, 2019.

4. Steglatro (ertugliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf. Accessed July 31, 2019.

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SGLT2is: Contraindications, Warnings, and Precautions

Contraindications	Canagliflozin ¹	Dapagliflozin ²	Empagliflozin ³	Ertugliflozin ⁴
Do not use in patients with a history of hypersensitivity to this agent	X	X	X	X
Severe renal impairment, ESRD, or dialysis	X	X	X	X
Warnings/Precautions				
Lower limb amputation in patients with CVD, limb infections, or leg ulcers	X			X
Hypotension	X	X	X	X
Ketoacidosis	X	X	X	X
Acute kidney injury or renal impairment	X	X	X	X
Urosepsis and pyelonephritis	X	X	X	X
Hypoglycemia risk increases when used with insulin or SU	X	X	X	X
Fournier gangrene	X	X	X	X
Genital mycotic infections	X	X	X	X
Increased LDL-C	X	X	X	X
Hypersensitivity reactions	X		X	
Bladder cancer		X		
Bone fracture	X			

1. Invokana (canagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf. Accessed July 31, 2019.

2. Farxiga (dapagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf. Accessed July 31, 2019.

3. Jardiance (empagliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf. Accessed July 31, 2019.

4. Steglatro (ertugliflozin) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf. Accessed July 31, 2019.

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Discussion Questions



Would you consider switching all of your patients with T2D and ASCVD/high CV risk, heart failure, or CKD to a SGLT2i or GLP1 RA?

Summary



SGLT2i (empagliflozin, canagliflozin, or dapagliflozin) and GLP1-RA (Liraglutide, semaglutide, or dulaglutide) are recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce CV events¹



- Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death¹
- Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk to reduce the risk of death¹



SGLT2 inhibitors are the only class of glucose-lowering agents that have demonstrated a benefit on HHF, an effect that is consistent across the class¹



Ongoing and future trials for SGLT2 inhibitors will generate further evidence on their effects for patients with heart failure, with and without diabetes²⁻⁵

See notes page for abbreviations

1. European Heart Journal (2019) 00, 1-69; 2. ClinicalTrials.gov. NCT03057951 (accessed Jun 2019); 3. Butler J et al. ESC-HF 2018; poster P972; 4. ClinicalTrials.gov. NCT03057977 (accessed Jun 2019); 5. Packer M et al. Eur J Heart Fail 2019; doi: 10.1002/ejhf.1536