ACTing on the EVIDENCE

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Cardiovascular Protection in Diabetes: Core Principles for Primary Care Practitioners

Cardiovascular and renal protection in diabetes

An educational programme for general practice developed by international experts.

What you will gain…

Participation in this fully accredited CPD programme gives you the opportunity to learn how:

- To interpret cardiovascular outcomes trials with regard to diabetic populations and endpoints
- To implement evidence-based therapies to achieve cardiovascular and renal protection

How you will learn…

'Acting on the Evidence' offers you the opportunity to freely obtain CPD points

- This module is worth three CPD points and fulfils the third objective of ACT 1.

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Module 2: Cardiovascular outcomes trials in diabetes

Introduction

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Globally, numerous guidelines emphasise a multifactorial approach as necessary to modify cardiovascular risk in type 2 diabetes mellitus (T2DM) (Figure 1). While guidelines may vary in terms of their specific recommendations for lipid-lowering agents, it is most often recommended that a high-intensity statin be used for people with diabetes and known atherosclerotic cardiovascular disease (ASCVD). Moderate-intensity statins are recommended for people younger than 40 years with diabetes and atherosclerotic risk factors, for those with diabetes aged 40-75 years, as well as those older than 75 years without ASCVD.[1]

Blood pressure targets vary from country to country, but all guidelines highlight the importance of blood pressure control to reduce the risk of cardiovascular events. Low-dose aspirin is generally indicated for secondary prevention, although it is no longer routinely recommended for primary prevention in diabetes patients with no known cardiovascular disease (CVD).

When it comes to glycaemic control, there is a recent trend towards individualising HbA_{1c} targets but some guidelines recommend an HbA_{1c} <7%.[1] It is commonly accepted that every 1% reduction in HbA_{1c} is associated with a reduced risk of the long-term micro- and macrovascular complications of T2DM.[1]

When developing evidence-based treatment approaches for managing cardiovascular risk in T2DM, a review of cardiovascular outcomes trials (CVOTs) of the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 (SGLT-2) inhibitors, together with real-world evidence, can be of great value.

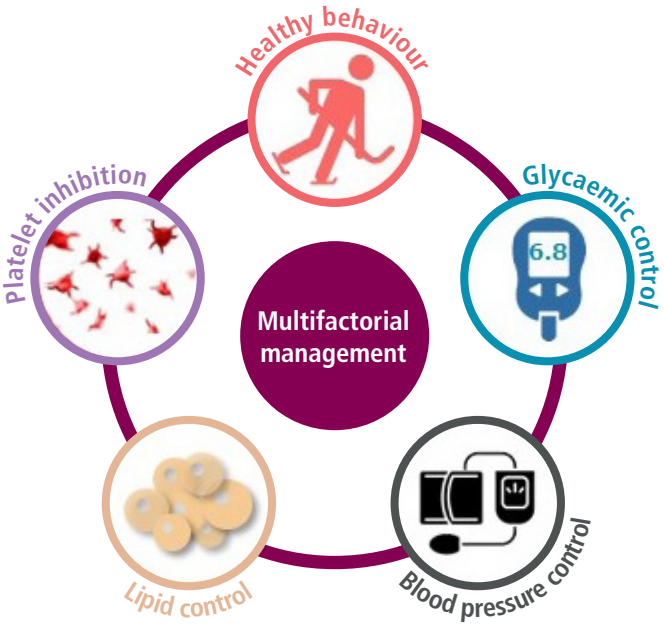


Figure 1. Multifactorial approach to modifying cardiovascular risk in T2DM

Other modules

Module 1
Cardiovascular prevention and heart failure in diabetes

Module 3
Renal protection in type 2 diabetes

Module 4
Review of renal therapies prior to SGLT-2 inhibitors

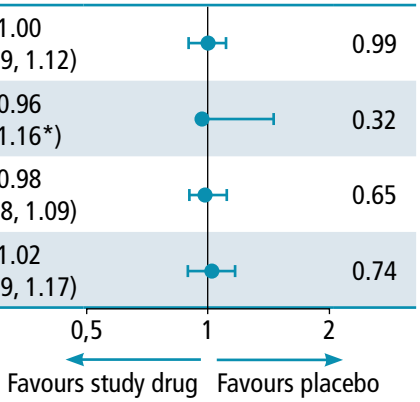
Module 5
Renal benefits of SGLT-2 inhibitors in diabetes

Module 6
Safety of SGLT-2 inhibitors and side-effects

Primary outcomes from DPP-4 inhibitor CVOTs

Four DPP-4 inhibitor CVOTs are now complete and have reported on primary outcomes: SAVOR-TIMI 53 (saxagliptin),[2] EXAMINE (alogliptin),[3] TECOS (sitagliptin)[4] and CARMELINA (linagliptin).[5] These studies demonstrated the cardiovascular safety of DPP-4 inhibitors, but not superiority in respect of the primary endpoints of three-point or four-point major adverse cardiovascular events (MACE) (Figure 2).

Trial	Primary endpoint	Number of events, n (%)		HR (95% CI)	P-value
		Study drug	Placebo		
SAVOR-TIMI 53 (saxagliptin)	3P-MACE	613 (7.3)	609 (7.2)	1.00 (0.89, 1.12)	0.99
EXAMINE (alogliptin)	3P-MACE	305 (11.3)	316 (11.8)	0.96 (≤1.16*)	0.32
TECOS (sitagliptin)	4P-MACE	695 (9.6)	695 (9.6)	0.98 (0.88, 1.09)	0.65
CARMELINA (linagliptin)	3P-MACE	420 (12.1)	34 (12.4)	1.02 (0.89, 1.17)	0.74



Data are not from head-to-head trials and should not be directly compared

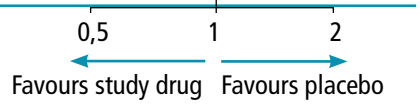
*Upper boundary of the one-sided repeated CI

Figure 2. Primary outcomes (MACE) from completed DPP-4 inhibitor CVOTs

Primary outcomes from GLP-1 RA CVOTs

There are five complete GLP-1 RA trials, showing heterogeneity in their results (the REWIND trial with dulaglutide is now available).[1] ELIXA,[6] using lixisenatide in a post-acute coronary syndrome (ACS) population, demonstrated cardiovascular safety but not superiority with regard to the primary endpoint of four-point MACE. The LEADER[7] (liraglutide), SUSTAIN-6[8] (semaglutide) and HARMONY Outcomes[9] trials (albiglutide) all demonstrated superiority for three-point MACE. The EXSCEL[10] trial, using once-weekly exenatide, just missed achieving superiority at a P-value of 0.06 (Figure 3).

Trial	Primary endpoint	Patients with event/analysed		HR (95% CI)	P-value
		Study drug	Placebo		
ELIXA (Lixisenatide)	4P-MACE	406/3034	399/3034	1.02 (0.89, 1.17)	0.81*
LEADER (liraglutide)	3P-MACE	608/4668	694/4672	0.87 (0.78, 0.97)	0.01*
SUSTAIN-6 (semaglutide)	3P-MACE	108/1648	146/1649	0.0.74 (0.58, 0.95)	0.02
EXSCEL (exenatide)	3P-MACE	839/7356	905/7396	0.91 (0.83, 1.00)	0.06*
HARMONY Outcomes (albiglutide)	3P-MACE	338/4717	428/4715	0.78 (0.68, 0.90)	<0.01*



Data are not from head-to-head trials and should not be directly compared

*Upper boundary of the one-sided repeated CI

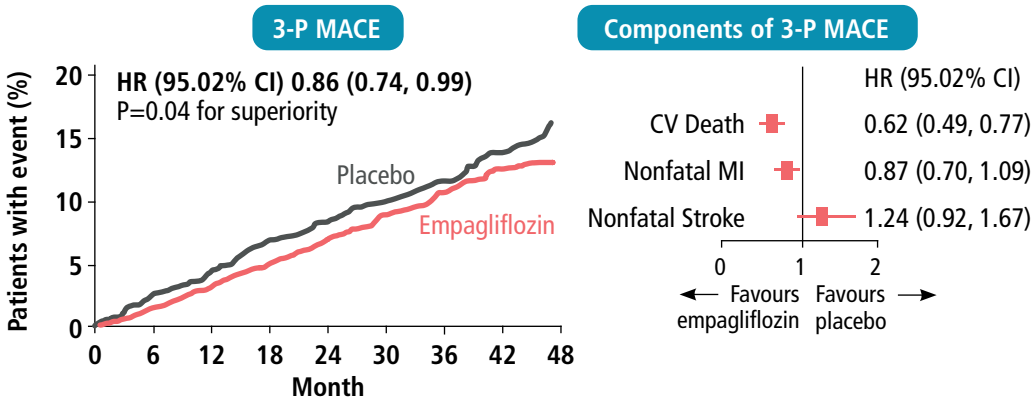
Figure 3. Primary outcomes from completed GLP-1 RA CVOTs

SGLT-2 inhibitor CVOTs

Three SGLT-2 inhibitor CVOTs have been completed: EMPA-REG OUTCOME, the CANVAS Program and DECLARE-TIMI 58.

EMPA-REG OUTCOME

The EMPA-REG OUTCOME study of empagliflozin was the first trial to demonstrate cardiovascular superiority of a new glucose-lowering agent, significantly reducing three-point MACE (14%) and cardiovascular death (38%). Empagliflozin demonstrated a non-significant decrease in nonfatal myocardial infarction (MI) and a non-significant increase in nonfatal stroke (Figure 4).[11]



No. at risk

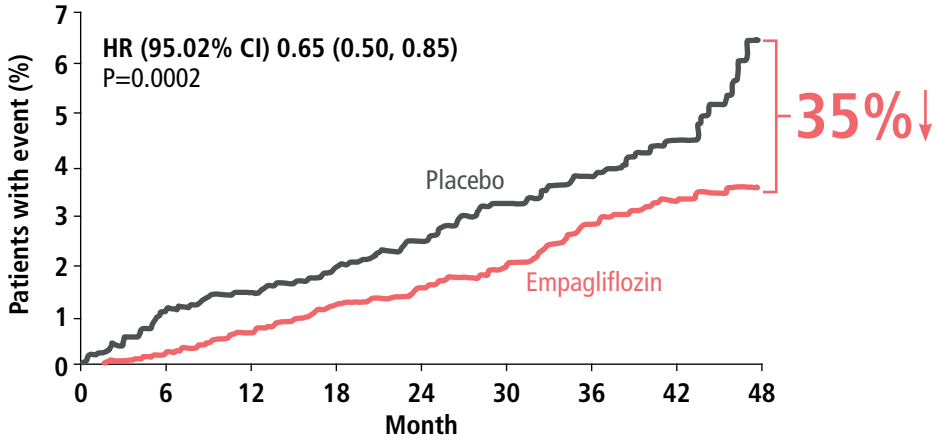
EMPA	4 687	4 580	4 455	4 328	3 851	2 821	2 359	1 534	370
Placebo	2 333	2 256	2 194	2 112	1 875	1 380	1 161	741	166

3P-MACE: 3-point major adverse cardiovascular events; CV: cardiovascular; EMPA: empagliflozin; MI: myocardial infarction

Figure 4. EMPA-REG OUTCOME: Empagliflozin significantly lowered three-point MACE

Empagliflozin was also associated with a significant 35% reduction in hospitalisation for heart failure

Empagliflozin was also associated with a significant 35% reduction in hospitalisation for heart failure (HF), a pre-specified secondary outcome of the EMPA-REG trial, which had an exclusive cohort of patients with established CVD (Figure 5).[11]



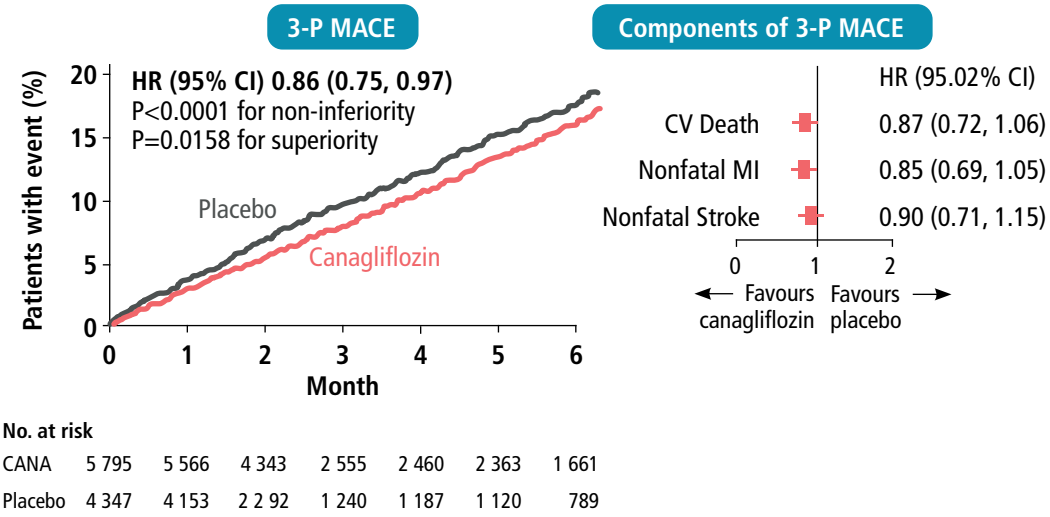
No. at risk

Empagliflozin	4 687	4 614	4 523	4 427	3 988	2 950	2 487	1 634	395
Placebo	2 333	2 271	2 226	2 173	1 932	1 424	1 202	775	168

Figure 5. EMPA-REG OUTCOME: Empagliflozin significantly prevented hospitalisation for HF

CANVAS Program

The CANVAS Program[12] studied canagliflozin in patients with established CVD, who represented two-thirds of the cohort, and patients with multiple risk factors, who made up the remainder. Significant 14% reduction was observed in the primary three-point MACE endpoint, but none of the individual components of the three-point MACE was statistically significantly reduced (Figure 6).



No. at risk							
CANA	5 795	5 566	4 343	2 555	2 460	2 363	1 661
Placebo	4 347	4 153	2 2 92	1 240	1 187	1 120	789

3P-MACE: 3-point major adverse cardiovascular events; CV: cardiovascular; EMPA: empagliflozin; MI: myocardial infarction

Figure 6. CANVAS Program: Canagliflozin significantly lowered three-point MACE

Canagliflozin demonstrated a significant 33% reduced risk of hospitalisation for HF

Canagliflozin demonstrated a significant 33% reduced risk of hospitalisation for HF, a pre-specified secondary endpoint of the trial (Figure 7). In terms of prevention of HF, comparison of the primary prevention cohort versus the secondary prevention cohort showed relatively similar reductions in HF in both groups (Figure 8).

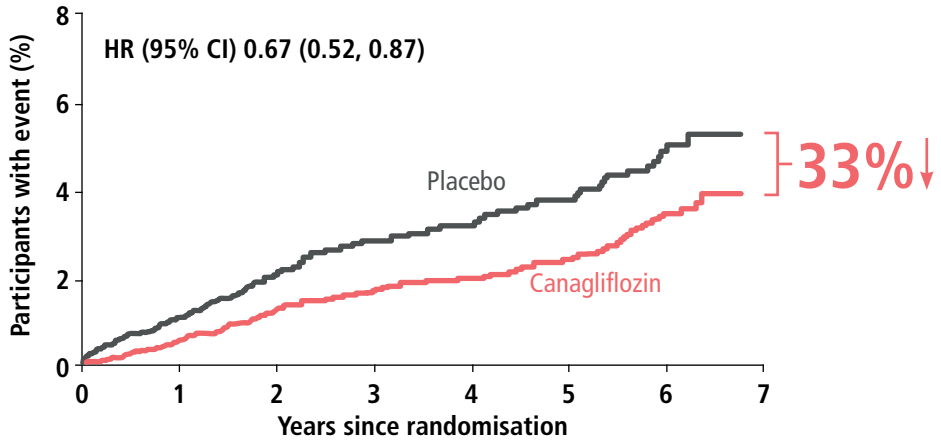


Figure 7. CANVAS Program: Canagliflozin significantly prevented hospitalisation for HF

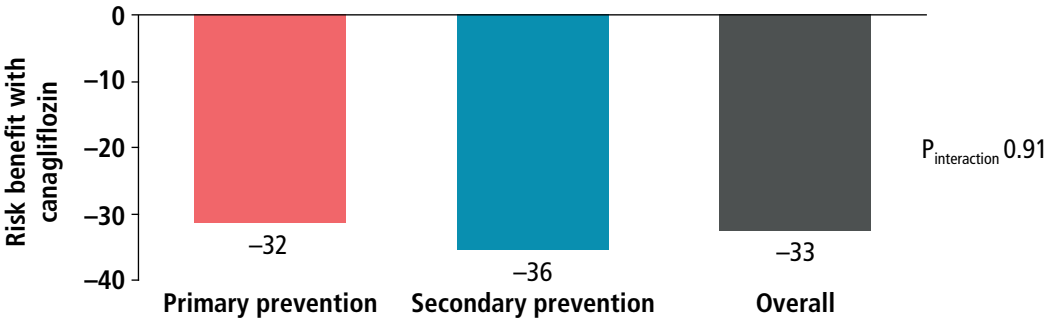
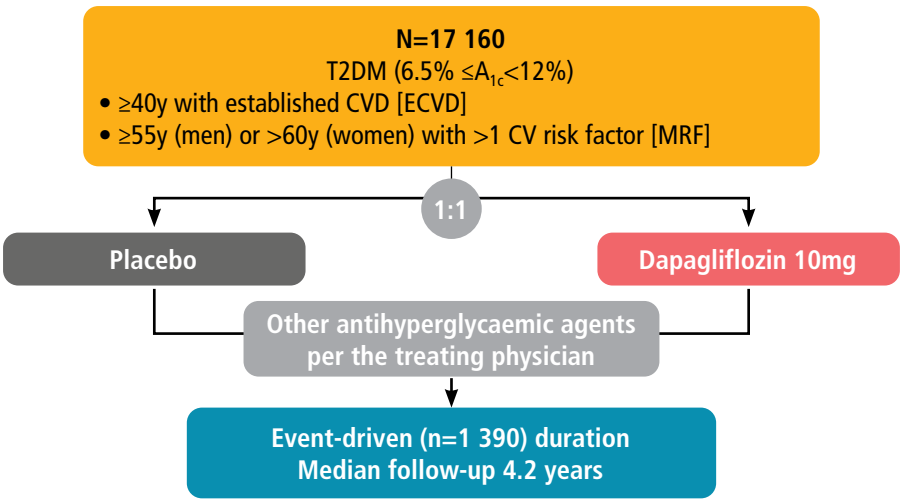


Figure 8. CANVAS Program: Prevention of HF in both primary and secondary prevention populations

DECLARE-TIMI 58

DECLARE-TIMI 58 is the largest of the SGLT-2 inhibitor trials, with more than 17 000 patients recruited under broad entry criteria: HbA_{1c} between 6.5 and 12%; ≥40 years with established CVD; or ≥55 years for men and ≥60 years for women with at least one additional cardiovascular risk factor (dyslipidaemia, hypertension, smoking). Participants were randomised to either placebo or dapagliflozin 10mg daily (Figure 9), with a median follow-up of 4.2 years.[13] The primary safety endpoint was three-point MACE and there were dual primary efficacy endpoints consisting of both MACE and hospitalisation for HF or cardiovascular mortality. In this event-driven trial, 41% of the patients had established CVD and 59% had multiple risk factors; the latter constituted the primary prevention cohort.

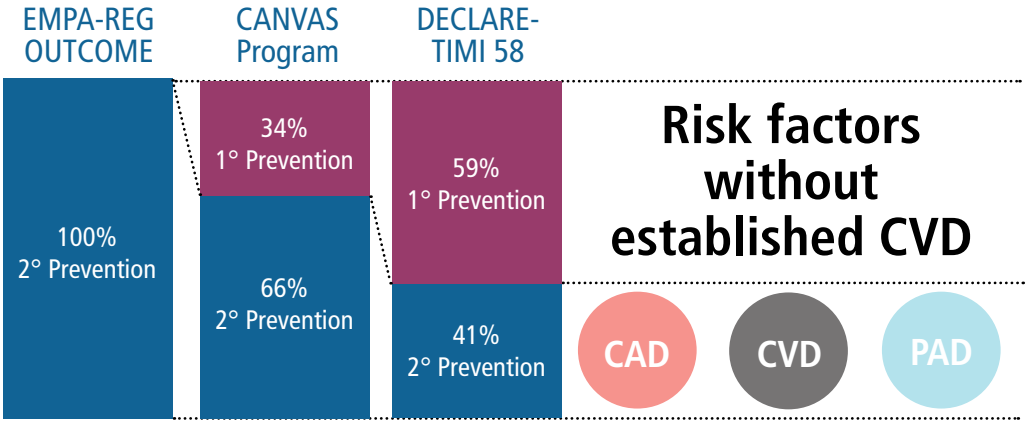


CV: cardiovascular; ECVD: established cardiovascular disease; MRF: multiple risk factors; T2DM: type 2 diabetes

Figure 9. DECLARE-TIMI 58 study design

In respect of the different study populations across the three SGLT-2 inhibitor CVOTs, DECLARE-TIMI 58 clearly had the broadest population and, therefore, the results most generalisable to patients encountered in everyday clinical practice

In respect of the different study populations across the three SGLT-2 inhibitor CVOTs, DECLARE-TIMI 58 clearly had the broadest population and, therefore, the results most generalisable to patients encountered in everyday clinical practice (Figure 10). With regard to baseline characteristics (Figure 11), DECLARE-TIMI 58 differed from the other studies in that there was only a small number of patients with eGFR <60ml/min/1.73m^2 and median follow-up was much longer (4.2 years) with a greater number of accrued events (1 559 events).



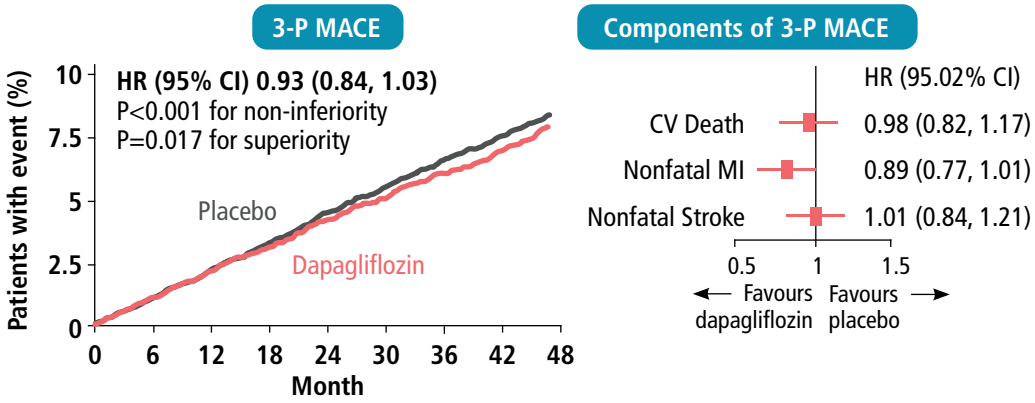
CAD: coronary artery disease; CVD: cardiovascular disease; PAD: peripheral arterial disease

Figure 10. Comparison of SGLT-2 inhibitor CVOT study cohorts

	EMPA-REG OUTCOME	CANVAS Program	DECLARE-TIMI 58
	100% 2°	34% 1°:66% 2°	59% 1°:41% 2°
Age (years)	63	63	64
Male (%)	71	64	63
BMI (kg/m^2)	31	32	32
A_{1c} (%)	8.1	8.2	8.3
eGFR<60ml/min/1.73m^2 (%)	26	20	7
Median follow-up (years)	2.4	3.1	4.2
Number of events	772	1 011	1 559

Figure 11. Details of SGLT-2 inhibitor CVOT study cohorts

With regard to three-point MACE, dapagliflozin was non-inferior for cardiovascular safety with a 7% reduced risk that was not statistically significant (Figure 12). In respect of the individual MACE components, the hazard ratio was 0.98 for cardiovascular death, 0.89 for nonfatal MI and 1.01 for nonfatal stroke.



No. at risk

DAPA	8 582	8 466	8 303	8 166	8 017	7 873	7 708	7 237	5 225
Placebo	8 578	8 433	8 281	8 129	7 969	7 805	7 649	7 137	5 158

3P-MACE: 3-point major adverse cardiovascular events; CV: cardiovascular; DAPA: dapagliflozin; MI: myocardial infarction

Figure 12. DECLARE-TIMI 58: Dapagliflozin was safe with regard to three-point MACE

Dapagliflozin significantly lowered cardiovascular death and hospitalisation for HF with a 17% relative risk reduction

Dapagliflozin significantly lowered cardiovascular death and hospitalisation for HF with a 17% relative risk reduction, similar to that seen in other completed trials. It is relevant to note there is relatively early separation of the curves (Figure 13).

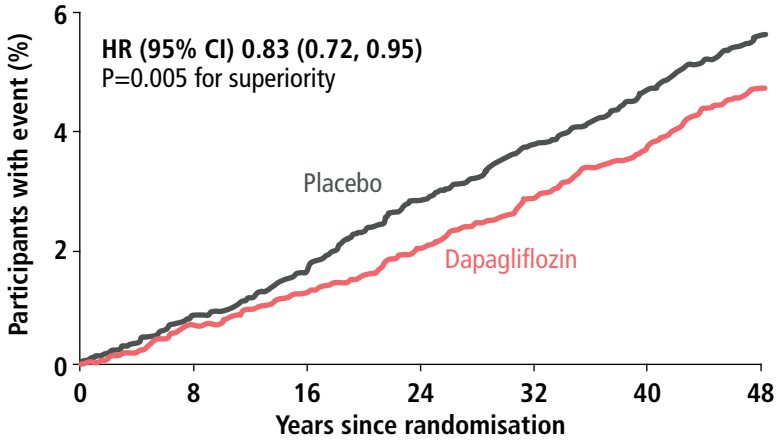
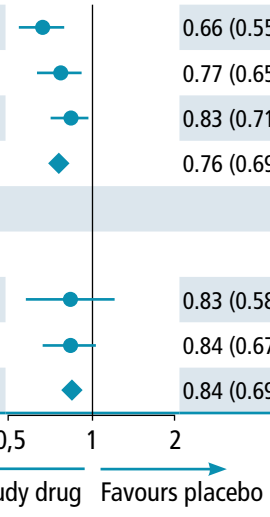


Figure 13. DECLARE-TIMI 58: Dapagliflozin significantly lowered cardiovascular death/hospitalisation for HF

Meta-analysis of SGLT-2 inhibitor CVOTs

Meta-analysis of the three SGLT-2 inhibitor CVOTs examined the risk of hospitalisation for HF and cardiovascular death, stratified by the presence or absence of CVD.[14] In those patients with established CVD, all three trials reduced this endpoint to a significant degree, and pooled results indicate a significant 24% risk reduction (Figure 14). In patients with multiple risk factors an overall 16% relative risk reduction, not statistically significant, was seen.

	Patients		Events	Events per 1 000 patient years		Hazard Ratio (95% CI)
	Treatment n/N	Placebo n/N		Treatment	Placebo	
With ECVD						
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19.7	30.1	0.66 (0.55–0.79)
CANVAS Program	3756/6656	2900/6656	524	21.0	27.4	0.77 (0.65–0.92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19.9	23.9	0.83 (0.71–0.98)
Fixed effects model for ECVD (P<0.0001)						0.76 (0.69–0.84)
With multiple risk factors						
CANVAS Program	2039/3486	1447/3486	128	8.9	9.8	0.83 (0.58–1.19)
DECLARE-TIMI 58	5108/10186	5078/10186	316	7.0	8.4	0.84 (0.67–1.04)
Fixed effects model for multiple risk factors (P=0.0634)						0.84 (0.69–1.01)



Data are not from head-to-head trials and should not be directly compared

CV: cardiovascular; ECVD: established cardiovascular disease; HHF: hospitalisation for heart failure

Figure 14. Meta-analysis of SGLT-2 inhibitor CVOTs: Hospitalisation for HF and cardiovascular death stratified by the presence of established CVD

What have we learned from real-world studies?

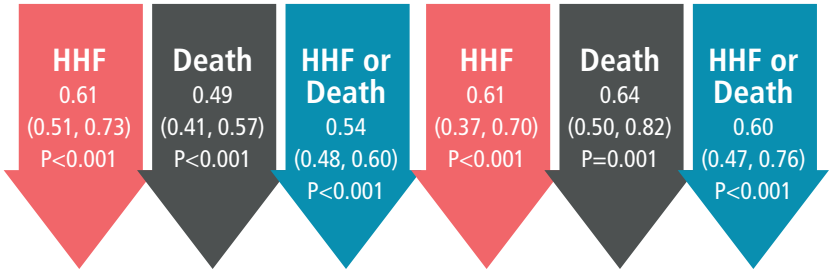
Recent real-world evidence is important for evaluating the cardiovascular benefits of SGLT-2 inhibition. The CVD-REAL 1 dataset includes several Scandinavian countries, Germany, the United Kingdom and the United States; the CVD-REAL 2 dataset originates from Australia, Canada, Israel, Japan, Singapore, and South Korea. In CVD-REAL 1, the most commonly used SGLT-2 inhibitors were canagliflozin and dapagliflozin, whereas 75% of therapeutic use was with dapagliflozin in CVD-REAL 2 (Figure 15).[15,16]

These real-world results complement what has been observed in SGLT-2 inhibitor randomised controlled trials

Hospitalisation for HF and cardiovascular death

In the CVD-REAL 2 population only a minority had a history of CVD and HF; nonetheless, there was significant reduction in hospitalisation for HF, for death, and for the composite of hospitalisation for HF or death in both datasets. These real-world results complement what has been observed in SGLT-2 inhibitor randomised controlled trials.

	CVD-REAL 1	CVD-REAL 2
Countries	Germany, Denmark, Norway, Sweden, UK and USA	Australia, Canada, Israel, Japan, Singapore and South Korea
New SGLT-2i users	154 528 Cana 52.7% | Dapa 41.8% | Empa 5.5%	235 064 Cana 4% | Dapa 75% | Empa 9% Ipra 8% | Tofo 3% | Luseo 1%
Other oral AHAs	154 528	235 064
CVD history	13%	27%
HF history	3.1%	6.8%



AHAs: antihyperglycaemic agents; CVD: cardiovascular disease; HHF: hospitalisation for heart failure; HF: heart failure; SGLT-2i: sodium-glucose co-transporter-2 inhibitor

Figure 15. CVD-REAL

Cardiorenal outcomes and mortality

Multiple mechanisms have been proposed to explain the cardiorenal protective benefit of SGLT-2 inhibitors

Analysis of the CVD-REAL 1 Scandinavian dataset, comparing dapagliflozin to DPP-4 inhibitors, showed that patients who were treated with dapagliflozin had a reduced risk of hospitalisation for kidney disease, hospitalisation for HF, MACE and all-cause mortality (Figure 16).[17]

Multiple mechanisms have been proposed to explain the cardiorenal protective benefit of SGLT-2 inhibitors. Majority opinion supports a primary volume effect that is related to natriuresis, but there is also evidence in support of reduction in interstitial oedema, reduced preload and afterload with reduction in left ventricular wall stress, improved renal function and cardiorenal physiology, inhibition of cardiac sodium-hydrogen exchange and improved cardiac bioenergetics.

	Dapagliflozin N=8 582		DPP-4 inhibitor N=25 746		Weighted average estimates N=34 328		
	No. of events	Rate/ 100 PY	No. of events	Rate/ 100 PY	HR	95% CI	P-value
Hospitalisation for kidney disease	52	0.64	417	1.64	**0.38**	**0.29, 0.51**	**<0.001**
Hospitalisation for heart failure	77	0.95	375	1.47	**0.63**	**0.50, 0.81**	**<0.001**
MACE	83	1.83	372	2.57	**0.71**	**0.56, 0.90**	**0.004**
All-cause death	106	1.04	468	1.44	**0.73**	**0.59, 0.91**	**0.004**

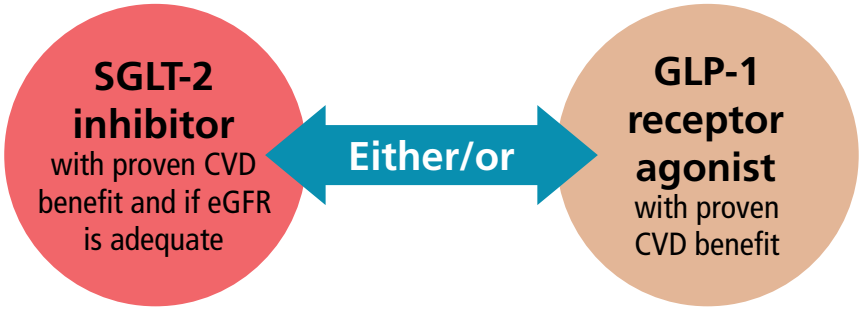
Figure 16. CVD-REAL: Dapagliflozin is superior to DPP-4 inhibitors in respect of cardiorenal outcomes and mortality

Translating the evidence into clinical practice

A recently updated American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) position statement provides guidance on incorporating trial and study evidence into clinical practice.[18]

Inadequate glycaemic control in the context of ASCVD

In patients with inadequate glycaemic control (independent of baseline HbA_{1c} or individualised HbA_{1c} target)[1] and where ASCVD predominates, a SGLT-2 inhibitor with proven cardiovascular benefit should be used if the eGFR is adequate, or a GLP-1 RA with proven cardiovascular benefit (Figure 17).[17]

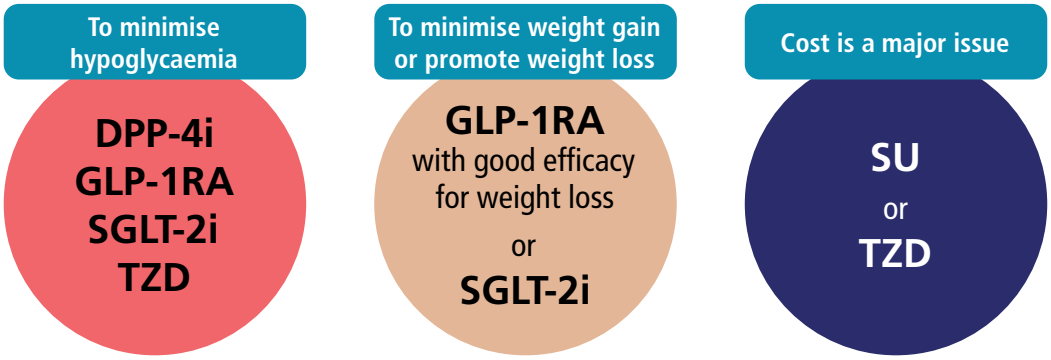


eGFR: estimated glomerular filtration rate; GLP-1: glucagon-like peptide-1; SGLT-2i: sodium-glucose co-transporter-2

Figure 17. Treatment options for individuals with inadequate glycaemic control (independent of baseline HbA_{1c} or individualised HbA_{1c} target) and where ASCVD predominates[1]

Inadequate glycaemic control in patients without established ASCVD

In patients without established ASCVD, use either a DPP-4 inhibitor, GLP-1 RA, SGLT-2 inhibitor, or thiazolidinedione to minimise hypoglycaemia. To minimise weight gain or to promote weight loss, use a GLP-1 RA with good efficacy for weight loss or an SGLT-2 inhibitor. If cost is a major issue, either a sulphonylurea or thiazolidinedione may be used (Figure 18). Accumulating evidence on SGLT-2 inhibitors underscores that they are not associated with a risk of hypoglycaemia, and typically promote weight loss.



DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2i: sodium-glucose co-transporter-2 inhibitor; SU: sulphonylurea; TZD: thiazolidinedione

Figure 18. Treatment guidance for individuals with inadequate glycaemic control without established ASCVD

There are currently large ongoing randomised controlled trials of SGLT-2 inhibitors in the treatment of established HF with reduced or preserved ejection fraction in people with and without T2DM: Dapa-Heart Failure, EMPEROR-Reduced, EMPEROR-Preserved, SOLOIST-Worsening Heart Failure and DELIVER. Results from Dapa-Heart Failure are now available at: https://www.denovomedica.com/modules/diabetes-and-heart-failure/

Key take-home messages

Cardiovascular protection in T2DM requires a focus on both MACE and HF, with multifactorial approaches yielding the highest risk reduction. CVOTs and clinical practice guidelines have identified antihyperglycaemic agents that are safe and superior in patients with established CVD. Finally, the results of DECLARE-TIMI 58 extend the benefit of SGLT-2 inhibition to a broader group of people with T2DM who have either multiple risk factors or established CVD.

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