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CURRENT OPINION
Obesity and metabolic syndrome

Addressing cardiovascular risk in type 2 diabetes mellitus: a report from the European Society of Cardiology Cardiovascular Roundtable

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Introduction

Type 2 diabetes mellitus (T2DM) is a recognized risk factor for cardiovascular (CV) disease (CVD).[1] In a large, prospective, cohort study of individuals ≥30 years of age, 18% of patients with diabetes developed incident CVD over 5.5 years of follow-up.[2] Diabetes in itself increases mortality risk, but the mortality rate nearly doubles in combination with manifestations of CVD [e.g. myocardial infarction (MI) or stroke], translating into an estimated reduction in life expectancy of 12 years.[3] Despite this alarming risk, 30–50% of patients with diabetes do not meet guideline-recommended treatment goals for managing CV risk.[4,5] Only 14% of NHANES (National Health and Nutrition Examination Survey) and BRFSS (Behavioral Risk Factor Surveillance System Survey) participants with diabetes achieved HbA1c, blood pressure, LDL-cholesterol, and non-smoking goals.[4] Accordingly, providing optimal cardioprotective treatment strategies remains a major unmet need in this population. Addressing this treatment gap is imperative because of the burdensome prevalence of T2DM, which impacts an estimated 58 million people in Europe, 46 million in the United States, and it is expected to reach 629 million globally by 2045.[6]

Among glucose-lowering therapies, the sodium-glucose cotransporter-2 (SGLT-2) inhibitors empagliflozin and canagliflozin and the glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide and semaglutide reduced the risk of a primary composite outcome of CV death, MI, and stroke when added to standard of care in patients with T2DM who already had or were at risk for CVD (Supplementary material online, *Table S1*).

More than 20 prospective completed or ongoing CV outcome trials (CVOTs) involving approximately 190 000 participants[7] were initiated to fulfil the regulatory requirements for clinical investigation of new drugs for diabetes mellitus issued in 2008 by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA).[8,9] The requirements were developed to address concerns surrounding the CV safety of some oral glucose-lowering drugs. These studies ruled out an excess risk of major adverse CV events for saxagliptin, alogliptin, sitagliptin, lixisenatide, and exenatide.[10] In addition to the demonstration of CV safety, empagliflozin,

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canagliflozin, liraglutide, and semaglutide also improved CV outcomes.[11–14] This evidence has been incorporated in the labels for empagliflozin, liraglutide, and semaglutide for patients with T2DM and established CVD,[15,16] and prompt integration into management pathways for such patients has been suggested.[17] Several large CVOTs are ongoing with other members of the SGLT-2 inhibitor and GLP-1 receptor agonist classes as well as other glucose lowering therapies. These studies will provide further evidence concerning CV safety and efficacy, and they will also contribute data in broader (i.e. lower risk) patient populations with T2DM. In addition, real world data from large international pharmacoepidemiology cohort studies have shown an association between the new initiation of SGLT-2 inhibitors and a lower risk for major CV outcomes when compared with other glucose lowering drugs.[18,19]

The data from the reported CVOTs have to different degrees been integrated into both diabetes and cardiology guidelines in several countries (Supplementary material online, *Table S2*). Despite these recommendations, adoption of these cardioprotective therapies in clinical practice remains relatively low.[20,21]

The Cardiovascular Round Table (CRT) of the European Society of Cardiology (ESC) is a strategic forum for high-level dialogue that brings together ESC leadership, academia, regulatory agencies, and industry to facilitate collaboration with a goal of improving CV health in Europe. The ESC CRT convened a workshop in February 2018 to discuss how:

(1) best to empower clinicians (i.e. general practitioners/primary care physicians, endocrinologists, and cardiologists) to integrate recent evidence-based glucose-lowering therapies into clinical practice;
(2) ESC can promote evolution in guidelines to assist clinicians with the practical implementation of evidence-based therapies;
(3) cardiology, endocrinology, and primary care disciplines can collaborate to improve the management and care of patients with T2DM and CVD; and
(4) to design future clinical trials of glucose-lowering drugs based on accumulating knowledge.

This manuscript summarizes the key outputs from the workshop and describes concepts around collaborative steps to improve implementation of therapy that combines glucose control with CV benefit in patients with T2DM and established CVD or at high CV risk.

Overview of recent evidence

The completed randomized trials that have demonstrated a beneficial effect of glucose-lowering drugs on CV outcomes are shown in Supplementary material online, *Table S1*. In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the primary composite outcome of CV death, non-fatal MI, or non-fatal stroke compared with placebo in patients with T2DM and established CVD when added to standard glucose lowering therapy.[14] The risk reduction in the composite endpoint was driven primarily by the effect on CV death (Supplementary material online, *Table S1*). Both CV and all-cause mortality were significantly reduced in patients randomized to empagliflozin. Notably, heart failure hospitalization was also significantly reduced.

Canagliflozin is also a SGLT-2 inhibitor that was tested in the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program.[13] Compared with placebo, canagliflozin significantly reduced the risk of the primary composite endpoint (CV death, non-fatal MI, or non-fatal stroke, Supplementary material online, *Table S1*) when added to standard of care. The magnitude of the treatment effect was similar across all components of the composite endpoint. All-cause mortality was not significantly reduced in the canagliflozin arm compared with placebo. In reducing hospitalization for heart failure, canagliflozin showed a possible benefit by exploratory analysis. Interestingly, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) clinical trial, evaluating the efficacy and safety of canagliflozin vs. placebo when used in addition to standard of care for patients with chronic kidney disease and T2DM, has been stopped early based on the achievement of pre-specified efficacy criteria.[22]

The GLP-1 receptor agonist liraglutide was studied in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial.[12] Liraglutide reduced the risk of the composite of CV death, non-fatal MI, or non-fatal stroke compared with standard care (Supplementary material online, *Table S1*), with consistent reductions across all components of the composite endpoint. Both CV and all-cause mortality were significantly reduced by liraglutide.

Semaglutide, another GLP-1 receptor agonist, was evaluated in the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) trial.[11] Semaglutide was non-inferior to standard care for reducing the risk of the composite primary endpoint of CV death, non-fatal MI, or non-fatal stroke. While not formally pre-specified, semaglutide was superior to standard care ($P = 0.02$), with the effect mainly driven by the reduction of stroke and MI (Supplementary material online, *Table S1*).

The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial permitted enrolment of patients without prior CV events, but these patients accounted for only 27% of the study population.[23] Despite this allowance, the overall incidence of events in the EXSCEL population was similar to the trials that required pre-existing CVD for inclusion (*Figure 1*), as demonstrated by the placebo event rate in EXSCEL of 40 events per 1000 patient-year for the primary composite endpoint.[23] In this study, exenatide was noninferior to placebo, but it did not significantly reduce the primary composite outcome of CV death, non-fatal MI, or non-fatal stroke.[23] Previously, also lixisenatide confirmed its safety, but with no superior effect on CVD in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) Trial in patients with a recent acute coronary syndrome.[24]

Real world evidence data from a large population comparative effectiveness propensity matched study has provided complementary data, however, with a different methodology. The results are consistent with data from randomized CVOTs with SGLT-2 inhibitors. In CVD-REAL (The Comparative Effectiveness of Cardiovascular Outcomes) and CVD-REAL-2 an association with a lower risk for all cause and CVD, heart failure hospitalization as well as MI and stroke, was shown with new initiation of a SGLT-2 inhibitor when compared with other glucose lowering drugs.[18,19] These studies suggest that the CV benefit associated with a SGLT-2 inhibitor is consistent in T2DM patients with and without CVD at baseline. Noteworthy, in the CVD-REAL all available SGLT-2 inhibitors were evaluated. Similar results have been shown by the EASEL (Evidence for Cardiovascular Outcomes with Sodium glucose co-transporter 2 inhibitors in the

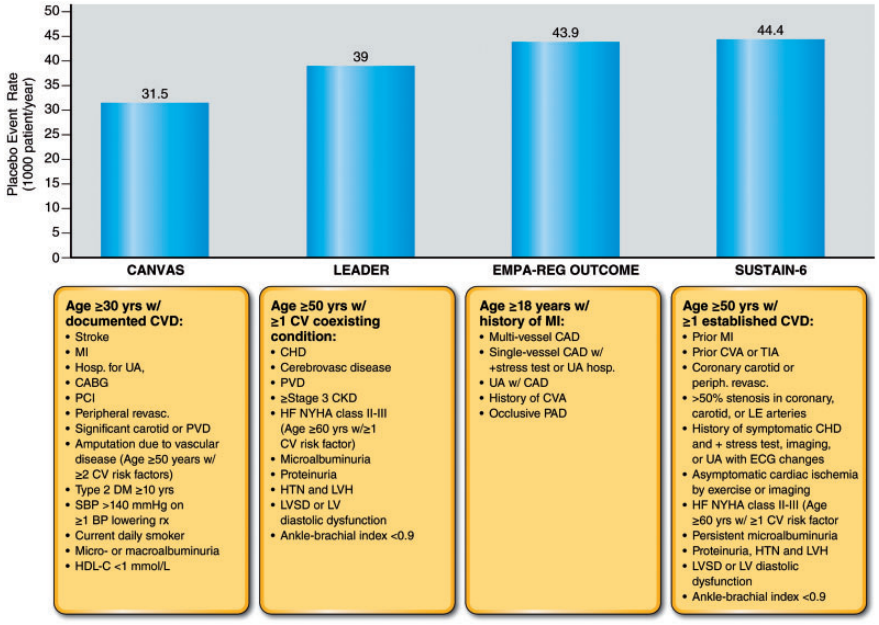

Figure 1 Cardiovascular events of study populations placebo event rates per 1000 patient-year for the primary composite outcome (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in the CANVAS Program, LEADER, EMPA-REG OUTCOME, and SUSTAIN-6. Cardiovascular risk definitions used in each study are shown. CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hosp, hospitalization; HTN, hypertension; LE, lower extremity; LVH, left ventricular hypertrophy; LV, left ventricular; LVSD, left ventricular systolic dysfunction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; revasc, revascularization; SBP, systolic blood pressure; TIA, transient ischaemic attack; UA, unstable angina.

real world) study in a US based population.[25] In similar, smaller retrospective cohort studies, significant associations between the use of GLP-1 receptor agonists and a reduced risk of mortality, acute MI, cerebrovascular accidents, and the combined outcome in the general population of patients with T2DM were observed.[26–29]

To whom do these results apply?

SGLT-2 inhibitors and GLP-1 receptor agonists such as empagliflozin, canagliflozin, liraglutide, and semaglutide can all be prescribed to improve glycaemic control in adult patients with T2DM, irrespective of the CV risk profile. Moreover, these agents also improve CV outcomes, an effect which has not been shown for other glucose lowering therapies. These findings suggest that glucose lowering is not the primary mechanism to reduce cardiovascular risk. Rather, these agents likely exert their cardioprotective effects through other mechanisms[30] or by their ancillary effects on cardiovascular risk factors (*Table 1*[31–50]). Thus, the focus should shift away from only glucose control, at least for prevention of CVD, although glucose control remains important to reduce microvascular complications. Metformin, which is uniformly recommended as first line therapy showed a positive effect on CVD only in a small subgroup of obese subjects in UKPDS 34,[41] however, this effect has been questioned by other evidence.[34,35,51] Despite the observed benefits, prescription of the novel, evidence-based therapies is delayed until patients have demonstrated inadequate glycaemic control on metformin. In view of the reduction of major CV events and death, physicians need to consider such prioritization of these therapies much earlier in the disease trajectory. There is no evidence to indicate that a different type of response should occur in treatment-naïve patients or those with HbA1c <7% (53 mmol/mol).

The patients represented in the CVOTs discussed all had, or were at high risk for, CVD (*Table 2*, *Figure 1*).[11–14,23,52–54] Whether similar CV outcome effects would occur in lower risk patients without known CVD is not known. Ongoing trials will provide data addressing this issue. In the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial, approximately 70% of enrolled patients are without established CVD.[54] In the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial, 59.4% of enrolled patients have multiple risk factors for CVD and 40.6% have atherosclerotic CVD.[52] On 24 September 2018 AZ in a press release announced positive results from the DECLARE-TIMI 58 cardiovascular outcome trial. Dapagliflozin met the primary composite endpoint of a statistically-significant reduction in hospitalization for heart failure or CV death in a broad patient population. (https://www.astrazeneca.com/media-centre/press-releases/2018/farxiga-achieved-a-positive-result-in-the-phase-iii-declare-timi-58-trial-a-large-cardiovascular-outcomes-trial-in-17000-patients-with-type-2-diabetes-24092018.html).

Table 1 Comparison of glucose-lowering drug classes[31–50]

	SGLT-2 inhibitors	GLP-1 receptor agonist	DPP4-inhibitor	Thiazolidinediones	Metformin	Oral sulfonylurea[a]	Alpha Glucosidase inhibitors	Meglitinides
Examples of agents in class	Empagliflozin Canagliflozin Dapagliflozin	Liraglutide, Semaglutide, Exenatide, Lixisenatide, Dulaglutide, Albiglutide	Alogliptin, Saxagliptin, Linagliptin, Sitagliptin Vildagliptin	Rosiglitazone Pioglitazone	Metformin	Glipizide Glimepiride Glyburide	Acarbose, miglitol	Nateglinide Repaglinide
Primary mechanism of glucose lowering	Decrease renal glucosereabsorption-Increase urinary glucose excretion	Activates the GLP-1 receptor, enhances insulin secretion, increases glucose-dependent insulin synthesis and *in vivo* secretion of insulin from pancreatic beta cells in presence of elevated glucose	Inhibits DPP-4 enzyme resulting in prolonged active incretin levels (i.e. slows inactivation of GLP-1 and GIP), thereby increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells (and therefore, decreasing hepatic glucose production)	PPAR gamma agonist; enhances insulin sensitivity in skeletal muscle, liver, and adipose tissue[33,38]	Reduces hepatic glucose production; improves insulin sensitivity	Stimulate insulin secretion from pancreatic β-cells	Delayed carbohydrate digestion and absorption through small intestine; delays post-prandial rise in plasma glucose	Stimulates insulin production from pancreas; primarily lower post-prandial glucose
Cardiovascular events	↓	↓	↔Possible ↑HF hospitalization, uncertain whether drug specific or class effect	[c]MI or stroke: ↔ or ↓[c]HF: ↑	Possibly ↓ (limited evidence)↑ in combination with SU	↑CV death tolbutamide vs. placebo or insulin, ↑ in observational studies; RCT data lacking[33]	↔[39]	↔[40]
Ancillary effects on cardiovascular risk factors								
Body weight	↓	↓	↔	↑	↔ to ↓	↑	↔	↑
Blood pressure	↓	↓	↔ or ↓	↔	↔ to ↓	↔	↓[68]	↔
Heart rate	↔	↑	↔	↔	↔	↔	NR	↔
Lipid profile	↑LDL, ↑HDL	↔ or ↓LDL, ↔ or ↑HDL, ↔ or ↓TG[36]	↔LDL, ↑HDL, ↔TG[36]	↔ or ↑LDL, ↑HDL, ↔ or ↓TG, improves LDL/HDL ratio	↓LDL, ↔HDL, ↓TG	↔ to ↓LDL-C, ↓HDL-C, ↑TG	↔LDL ↔HDL, ↓TG	↔LDL ↔HDL, ↓TG

Continued

Table 1 *Continued*

	SGLT-2 inhibitors	GLP-1 receptor agonist	DPP4-inhibitor	Thiazolidinediones	Metformin	Oral sulfonylurea[a]	Alpha Glucosidase inhibitors	Meglitinides
Key adverse effects								
	Genital mycotic infections (caution in patients with recurrent genitourinary sepsis), mild fracture risk, DKA with stress[50] Amputation, caution in patients with PAD (canagliflozin)	GI, retinopathy complications	Possible ↑HF hospitalization, uncertain whether drug specific or class effect	Peripheral oedema, precipitate or exacerbate HF	GI, B12 deficiency	Hypoglycaemia	GI	Hypoglycaemia

ACC/AHA, American College of Cardiology/American Heart Association; ADA, American Diabetes Association; CANVAS, Canagliflozin Cardiovascular Assessment Study; DPP4, dipeptidyl peptidase-4; DM, diabetes mellitus; ESC, European Society of Cardiology; GI, gastrointestinal; GIP, glucose-dependent insulinotrophic polypeptide; GLP-1, glucagon-like peptide 1; HDL, high-density lipoprotein; HF, heart failure; IRIS, insulin resistance intervention after stroke; LDL, low-density lipoprotein; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; NR, not reported; PAD, peripheral arterial disease; PPAR, peroxisome proliferator activated receptor; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RCT, randomized control trial; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; SGLT-2, sodium-glucose cotransporter-2; SU, sulfonylurea; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TC, total cholesterol; TG, triglycerides; ↑, increase; ↓, decrease; ↔, neutral.

[a]UKPDS ($n = 753$)[41]: metformin vs. conventional (i) any DM-related endpoint[b] [HR 0.68, 95% confidence interval CI 0.53–0.87]; (ii) DM-related death[b] (HR 0.58, 95% CI 0.37–0.91); (iii) all-cause mortality (HR 0.64, 95% CI 0.45–0.91); (iv) MI (HR 0.61, 95% CI 0.41–0.89). Concerning signal of increased mortality with metformin + SU[33–35,41]; UKPDS efficacy results not confirmed in meta-analyses of RCTs.[33–35]

[b]Three pre-defined primary outcome analyses: (i) diabetes-related clinical endpoint: sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy requiring photocoagulation, blindness in one eye, or cataract extraction; (ii) diabetes-related death: death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hypoglycaemia, or hyperglycaemia, and sudden death; (iii) all-cause mortality.

[c]Conflicting evidence with rosiglitazone; meta-analysis suggested increased risk of MI and CV death,[42,43]; the risk of MI in RECORD was inconclusive [hazard ratio (HR) 1.14, 95% CI 0.80–1.63], but it confirmed an increased HF risk (HR 2.10, 95% CI 1.35–3.27).[44] However, methodological criticisms of both the meta-analysis and RECORD have been published.[45,46] In PROactive, pioglitazone reduced the secondary endpoint of all-cause mortality, non-fatal MI, and stroke (HR 0.84, 95% CI 0.72–0.98; $P = 0.027$), but it increased HF hospitalizations.[47] Pioglitazone also demonstrated a lower rate of stroke or MI vs. placebo in IRIS.[48]

Table 2 Patient characteristics from cardiovascular outcome trials

	[a]EMPA-REG[14]	[b]CANVAS Program[13] (*N* = 10 142)	[c]LEADER[12] (*N* = 9340)	[b]SUSTAIN-6[11] (*N* = 3297)	[d]EXSCEL[23] (*N* = 14 752)	[b]DECLARE-TIMI 58[52] (*N* = 17 160)	[b]VERTIS-CV[53] (*N* = 8237)	[b]REWIND[54] (*N* = 9901)
Mean age	63.1 ± 8.6	63.3 ± 8.3	64.2 ± 7.2	64.6 ± 7.4	62 (56, 68)[e]	63.8 ± 6.8	64.4 ± 8.1	66.2 ± 6.5
Male (%)	71.2	64.2	64.5	60.7	62	62.6	70	53.7
White (%)	72.6	78.3	NR	83.0	75.5	79.6	87.8	NR
Mean body weight (kg)	86.2 ± 18.9	NR	91.9 ± 21.2	92.1± 20.6	NR	NR	NR	88.7 ± 18.5
Mean BMI (kg/m^2)	30.6 ± 5.3	32.0 ± 5.9	32.5 ± 6.3	32.8 ± 6.2	31.8 (28.2, 36.2)[e]	32.1 ± 6.0	32.0 ± 5.4	32.3 ± 5.7
Mean glycated haemoglobin (%)	8.07 ± 0.85	8.2 ± 0.9	8.7 ± 1.6	8.7 ± 1.5	8 (7.3, 8.9)[e]	67 ± 9.7	8.3 ± 0.9	7.3 ± 1.1
Mean SBP (mmHg)	135.3 ± 16.9	136.6 ± 15.8	135.9 ± 17.8	135.6 ± 17.2	NR	135 ± 15.5	NR	137.2 ± 16.8
Mean eGFR (mL/min/1.73 m^2)	74.2 ± 21.6	76.5 ± 20.5	eGFR: ≥90: 34.7% 60–89: 41.4% 30–59: 21.4% <30: 2.5%	eGFR: ≥90: 30% 60–89: 41.5% 30–59: 25.2% <30: 3.3%	76.6 (61.3, 92)[e]	86.1 ± 21.8	76 ± 20.9	77.6 ± 24.1
Duration of diabetes mellitus (years)	57.0% >10 years	13.5 ± 7.8	12.8 ± 8.0	13.9 ± 8.1	12 (7, 17)[e]	≤5 years, 22.4% >5 ≤ 10 27.6% >10 ≤ 15 23% >15 ≤ 20 14.2% >20 12.9%	12.9 ± 8.3	10.0 ± 7.2
Risk factors of manifestation of CV disease								
Hypertension (%)	NR	90	Reported as HTN and LVH in age ≥60 years CVD risk factors subset: 5.3	92.8	NR	89.4	NR	93.2
CAD (%)	75.6	56.4	Established CV disease: 82.1	60.5	53		established CVD 99 (established CV disease)	NR
Multivessel CAD (%)	46.5	NR	NR	NR	NR	12.3	NR	NR
History of MI (%)	46.7	NR	Reported in age ≥50 years established CVD subset: 31.4	32.5	73.3 (prior CV event)	20.9	47.8	16.2
CABG (%)	25.1	NR	Prior revascularization in age ≥50 years established CVD subset: 39.3	NR	NR	9.8 (PCI: 21.3)	21.9 (PCI: 41.3)	Revascularization: 18.1
History of stroke (%)	23.1	Cerebrovascular disease: 19.3	Prior stroke or TIA (age ≥50 years)	11.6 (ischaemic) 3.3 (haemorrhagic)	Cerebrovascular disease 16.8	6.5 (ischaemic)	20.9	5.3 (ischaemic)

Continued

Table 2 *Continued*

	[a]EMPA-REG[14]	[b]CANVAS Program[13] (*N* = 10 142)	[c]LEADER[12] (*N* = 9340)	[b]SUSTAIN-6[11] (*N* = 3297)	[d]EXSCEL[23] (*N* = 14 752)	[b]DECLARE-TIMI 58[52] (*N* = 17 160)	[b]VERTIS-CV[53] (*N* = 8237)	[b]REWIND[54] (*N* = 9901)
			established CVD subset): 15.6					
PAD (%)	21.0	20.8	Ankle-brachial index >0.9: 2.4%	NR	19	6.0	18.8	NR
Single-vessel CAD (%)	10.6	NR	NR	NR	NR	NR	NR	NR
Heart failure (%)	9.9	14.4	17.9	23.6	15.8	9.9	21.6	8.6
Anti-hyperglycaemic therapy (alone or in combination)								
Metformin (%)	73.8	77.2	75.8	73.2	76.4	78.5		81.0
Insulin (%)	48	50.2	43.7	58.0	46.2	39.6		24.2
Sulfonylurea (%)	43	43.0	50.8	42.8	36.7	41.1		57.0
DPP-4 inhibitor (%)	11.3	12.4	<0.1	0.2	15.2	16.0		0.9
Thiazolidinedione (%)	4.2	NR	6.3	2.3	4	NR		1.7
GLP-1 receptor agonist (%)	2.7	4.0	0	NR	0	4.2		NR
SGLT-2 inhibitor (%)	NR	NR	NR	0.2	1.2	n/a		0.1
Meglitinides (%)	NR	NR	3.8	2.6	<0.1	NR		0.7
Monotherapy (%)	29.4	NR	NR		41.7	NR		49.8
Dual therapy (%)	48.2	NR	NR	NR	33.6	NR		39.3
Antihypertensive therapy (%)	94.9	RAAS-inhibitor: 80 Beta-blocker: 53.5 Diuretic: 44.3	92.7	93.5	ACEI: 48.1 ARB: 31.7 Diuretic: 43.7 BB: 55.5 MRA: 6.2 CCB: 32.4	89.4		ACEi or ARB: 81.4 MRA: 4.7 Diuretic: 46.4 Beta-blocker: 45.5 CCB: 34.2
Lipid lowering therapy (%)	81.5	74.9	76.3	76.5	77.9	71.3		76.1

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CV, cardiovascular; CVD, cardiovascular disease; DPP-4 inhibitor, dipeptidyl peptidase-4; HTN, hypertension, LVH, left ventricular hypertrophy; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NR, not reported; PAD, peripheral artery disease; RAAS, renin angiotensin aldosterone system; TIA, transient ischaemic attack.

[a]Data shown are from pooled empagliflozin arm.

[b]Data shown are from the total pooled cohort.

[c]Data shown are from liraglutide arm.

[d]Data shown are from exenatide arm.

[e]Median (Q1, Q3).

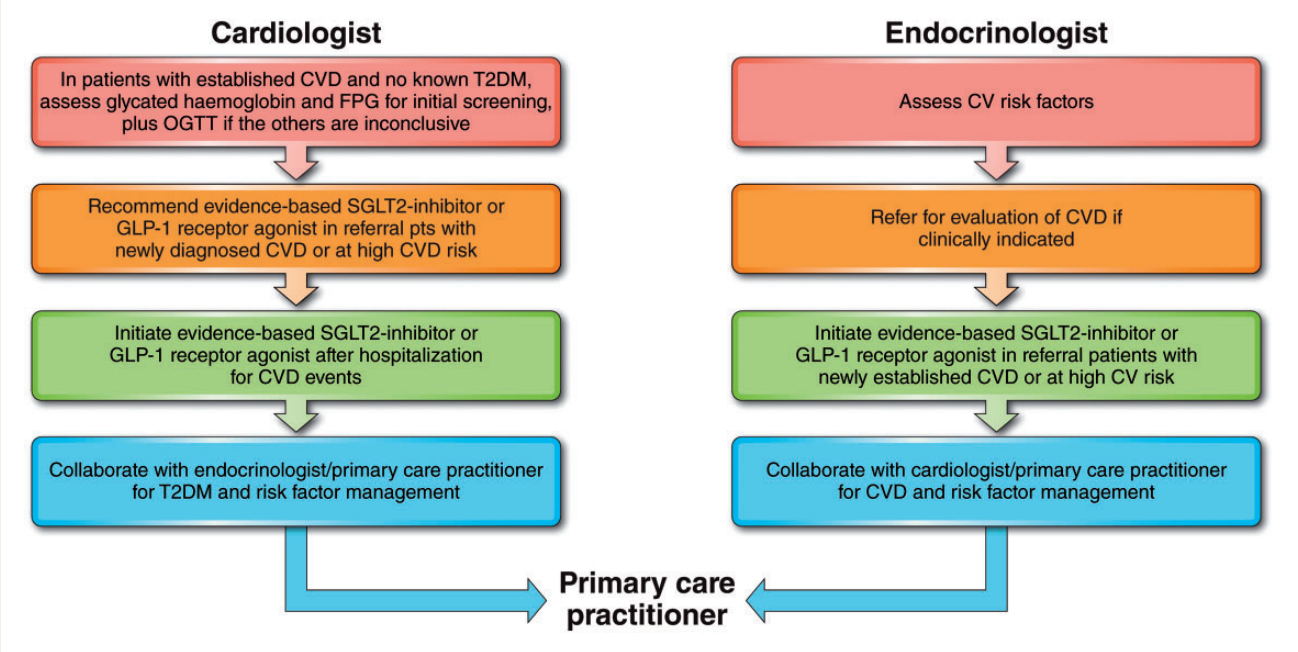

Figure 2 Individual responsibilities and opportunities for collaboration between cardiologists, endocrinologists, and primary care practitioners cardiologists and endocrinologists both have individual roles in assessing and treating cardiovascular risk in patients with Type 2 diabetes. Treatments to reduce cardiovascular risk can be initiated by either specialist, but two-way communication is essential to optimal monitoring and continuation of therapy. Primary care practitioners are involved across all stages, playing a central role and interfacing with both cardiologists and endocrinologists. ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; d/c, discharge; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose cotransporter-2; T2DM, type-2 diabetes mellitus.

Interestingly, the proportion of adults with T2DM in the United States who met the eligibility criteria for each of the 4 SGLT-2 inhibitor CVOTs was defined in a recent analysis using data from NHANES.[55] Of the identified population of 23 941 512 adults, 4.1% met the criteria for EMPA-REG OUTCOME, 4.8% for VERTIS-CV (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease), 8.8% for the CANVAS program, and 39.8% for the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) trial.

Implementation of evidence

So far, the clinical uptake of evidence-based cardioprotective SGLT-2 inhibitors and GLP-1 receptor agonists has been low, despite the body of evidence demonstrating improved CV outcomes with these agents in patients with T2DM and pre-existing CVD or risk factors. An analysis from the Diabetes Collaborative Registry showed that 5.2% of the patients who met the eligibility criteria for EMPA-REG OUTCOME were prescribed an SGLT-2 inhibitor.[21] Accordingly, 6% of those similar to the LEADER population were prescribed a GLP-1 receptor agonist.[21] Endocrinologists were more likely than either cardiologists or primary care physicians to prescribe an SGLT-2 inhibitor or a GLP-1 receptor agonist in this observational analysis.[21] An interim report of survey data suggests that a substantial proportion of patients are unaware of the relationship between diabetes mellitus and CV risk, and many underestimate their own risk of CVD.[56] Improvement in the utilization of the new treatment modalities, reducing CV risk, will require collaboration between endocrinologists, cardiologists, and primary care physicians (*Figure 2*).[57,58] It is acknowledged that delays in health technology assessments or payer approval may also impede uptake of new evidence into clinical practice. Reimbursement agencies should expedite their assessments of these agents to minimize delays in patient access to therapies shown to improve clinical outcomes.

Endocrinologist's role

The goals of diabetes management are to reduce complications related to diabetes, especially macrovascular and microvascular disease. Macrovascular events can be decreased by optimizing CV risk factor control (e.g. smoking cessation, blood pressure control, treating dyslipidaemia) to meet guideline recommended targets and prescribing glucose-lowering therapies that lower CV risk; achieving glycaemic control also reduces microvascular complications.[59] Endocrinologists and primary care and other referring physicians need to work collaboratively to ensure prevention of CV events is a distinct treatment goal for patients with T2DM, complementary to glycaemic control.[17] Thus, mitigation of CV risk by implementing an evidence-based SGLT-2 inhibitor or GLP-1 receptor agonist should be a high priority.[60]

Only SGLT-2 inhibitors (i.e. empagliflozin, canagliflozin) and some GLP-1 receptor agonists (i.e. liraglutide, semaglutide) reduce the risk of CV events, whereas other agents do not. Although in PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events),

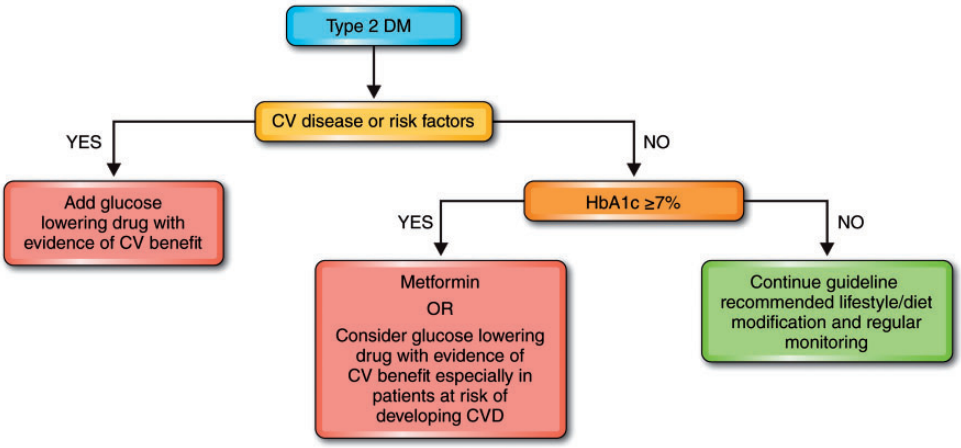

Figure 3 Proposed algorithm for therapy selection. CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus.

pioglitazone reduced the secondary endpoint of all-cause mortality, non-fatal MI, and stroke (hazard ratio 0.84, 95% confidence interval 0.72–0.98; $P = 0.027$), it also increased HF hospitalizations.[47] Pioglitazone also demonstrated a lower rate of stroke or MI vs. placebo in patients with a recent (6 months) ischaemic stroke or transient ischaemic attack and insulin resistance but no diabetes mellitus in the IRIS (Insulin Resistance Intervention after Stroke) trial.[48] Sulfonylureas are a less favourable choice for glycaemic control in general because of the high risk for hypoglycaemia related to their use and the uncertainty about their CV safety.[61] Dipeptidyl peptidase-4 (DPP-4) inhibitors are often considered by endocrinologists as the first add on after metformin for glycaemic control, but they are not superior to placebo for reducing CV events in major outcome trials.[32,62,63] The evidence for metformin for CVD risk reduction is limited, as already addressed. Endocrinologists should select therapies based on the available data as well as ancillary drug features [e.g. effects on body weight, blood pressure, hypoglycaemic risk, side effect profile (*Table 1*)], and patient-specific characteristics (e.g. comorbidities, risk for adverse effects, frailty, patient preferences, cost) (*Table 1*, *Figure 3*).

Cardiologist's role

Patients with established cardiovascular disease and no known diabetes mellitus

Diabetes mellitus is a major risk factor for CV events. Cardiologists should ensure patients with CVD are screened appropriately for diabetes.[64] Current guidelines recommend measuring HbA1c and fasting plasma glucose (FPG) for initial screening, supplemented by an oral glucose tolerance test if the HbA1c and FPG are inconclusive.[58,60,65]

Patients with established cardiovascular disease and known diabetes mellitus

Cardiologists should assess glycaemic control as noted above, achieve optimal management of CV risk factors, and prescribe or recommend glucose-lowering therapies that also reduce CV events in patients with established CVD and T2DM. Cardiologists should emphasize these approaches to primary care physicians who refer patients for CV evaluations and to whom patients with CVD are referred.

Another strategy that may improve implementation is to ensure all patients with T2DM hospitalized for an acute coronary syndrome or other manifestation of CVD are discharged on an evidence-based glucose-lowering agent or, at a minimum, recommend implementation of these compounds by the patient's primary care physician. This approach could be integrated into existing processes designed to ensure CV patients are discharged on other evidence-based therapies including antithrombotics, angiotensin converting enzyme inhibitors, statins, and beta-blockers. Cardiologists should actively communicate the treatment plan to the patient's primary care physician and/or endocrinologists to ensure therapy is continued and appropriately monitored post-discharge.

Educational initiatives supported by professional organizations such as the ESC may help raise physician awareness of the evidence supporting anti-hyperglycaemic drugs that reduce CV risk. Specific initiatives are already underway. The ESC in partnership with the European Association of Preventive Cardiology has initiated an educational program on Diabetes and Cardiovascular Disease. The program will increase awareness of diabetes as a cardiovascular risk factor and provide educational resources on cardiovascular risk management and treatment to a broad group of health care professionals through webinars, hands-on seminars, access to scientific peer-review publications, dedicated sessions at congresses, and social medial platforms. In addition, the ESC in collaboration with the European Association for the Study of Diabetes (EASD) has already established a joint task force to develop guidelines on diabetes, prediabetes, and cardiovascular disease, and the new guideline will be published in 2019. Another important step is to the raise awareness of healthcare budget agencies on the potential for long-term savings which might be achieved by the timely introduction of newer treatment options.

Primary care practitioner's role

In view of the rising epidemic of diabetes, a model of care where more patients are being managed in primary care is being implemented globally.[66] Primary care practitioners therefore have a major role in management of people with diabetes. However, evidence-based interventions are not being implemented in primary care and there is a need for further education, empowerment and upskilling of health care professionals working in primary care. Educational initiatives as mentioned above would also apply to primary care.

Implications for future research

Cardiovascular outcome trials in T2DM have yielded a large body of evidence over a relatively short time interval that is unprecedented in the field. More discussion is needed to resolve current controversies such as, should:

(1) excluding CV harm still be sufficient for approval of a glucose-lowering drug?
(2) demonstration of a CV benefit for all glucose lowering drugs using expensive randomized controlled trials be required by regulators?
(3) CV safety trials be repeated for every new agent in an existing class?
(4) new trials be conducted against drugs with proven benefit for CVD rather than compared with placebo?

In addition to these putative research priorities, investigation of lower risk populations (e.g. patients without pre-existing CVD) is of particular interest since there is a lag between diabetes diagnosis and the occurrence of manifest CVD. Early management of T2DM may potentially improve clinical outcomes, but this hypothesis needs to be tested in CVOTs. Substantial resources and investments will be required to study therapies in lower risk patients, since long follow-up (>10 years) will be needed to accrue sufficient events to robustly evaluate the effectiveness of CV prevention strategies. The extent to which robustly conducted randomized, pragmatic trials or randomized registry trials could provide reliable data on the effects of SGLT-2 inhibitors or GLP-1 receptor agonists in lower risk patient populations warrants consideration. The usefulness of these types of trials will depend on the strength of the treatment effect and adherence to treatment, which could be harder to discern in a pragmatic trial where less stringent operational control of some trial components, among them data collection, monitoring and concomitant therapies, has the potential to introduce interpretative challenges. Cost-effectiveness analyses and studies assessing the impact of new agents on health-related quality of life or patient reported outcomes is a needed area of research.

Regulatory implications

Providing clear guidance to health care professionals and patients is an important purpose of product labels such as the Summary of Product Characteristics. Currently, there is a clear difference between the indication wording used by the European Medicines Agency and FDA for empagliflozin, liraglutide, and semaglutide (Supplementary material online, *Table S3*). In the United States, the labels include distinct indications 'to reduce the risk of CV death (empagliflozin)' and 'to reduce major adverse CV events (liraglutide)' in patients with T2DM and established CVD. In Europe, a CV indication is not specified, but reference is made to the clinical efficacy and safety section. However, this approach may not be easily understood by physicians or patients, limiting access to these therapies. The EMA has recently issued a new draft guideline on clinical investigation of medicinal products for the treatment or prevention of diabetes mellitus.[67]

Conclusion

Patients with T2DM are at high risk of CV death and adverse CV outcomes. By using evidence-based therapies, physicians can improve both glucose control and, importantly, the CV outcome for patients with T2DM at high risk for or with established CVD. Uptake of these therapies in the majority of indicated patients has not yet been realized, despite rigorous evidence from CVOTs and guideline recommendations. Collaboration between endocrinologists, cardiologists, internists, primary care physicians, HTA assessors, and reimbursement agencies is essential to achieving optimal implementation of the evidence. Clinical and scientific opinion leaders in cardiology and endocrinology have a responsibility to identify effective methods of disseminating knowledge to ensure indicated patients have access to and are offered these life-prolonging and morbidity reducing therapies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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