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Guideline Recommendations and the Positioning of Newer Drugs in Type 2 Diabetes

Nikolaus Marx¹, Melanie Davies², Peter J. Grant³, Chantal Mathieu⁴, John R. Petrie⁵,
Francesco Cosentino^{6*}, John B. Buse^{7*}

¹ Department of Internal Medicine, University Hospital Aachen, RWTH Aachen University, Germany

² Diabetes Research Centre, University of Leicester, Leicester, UK

³ Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK

⁴ Clinical and Experimental Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium

⁵ Institute of Cardiovascular and Medical Sciences; BHF Glasgow Cardiovascular Research Centre; University of Glasgow, UK

⁶ Unit of Cardiology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden

⁷ Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC

*Corresponding authors

Abstract

Cardiovascular outcome trials in patients with type 2 diabetes (T2DM) at high risk have led to remarkable advances in our understanding of the efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i) to reduce cardiorenal events. The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the European Society of Cardiology have recently published recommendations for management of such patients. Many health care workers have tended to focus on the differences between the endocrinologists' consensus and the cardiologists' guidelines while recent reports show that only a minority of people with T2DM with preexisting CV disease or heart failure receive the treatments advocated by both. A subset of members of both writing groups were convened to emphasise where commonalities exist and to propose an integrated paradigm that encompasses the views incorporated in the ESC and ADA/EASD management approaches.

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by the presence of hyperglycaemia and leading to the development of micro- and macrovascular complications. Overall there is a 2 to 3-fold risk of cardiovascular (CV) disease in diabetes which is further magnified in the presence of chronic renal impairment {Mulnier, 2008 #10060; Bell, 2015 #10061}. In addition to atherosclerotic cardiovascular disease (ASCVD), patients with diabetes exhibit an increased risk for heart failure, which is associated with further increases in morbidity and mortality {McAllister, 2018 #9968}. Glycemic control has been shown to effectively reduce the incidence and worsening of microvascular complications such as retinopathy, but has - at best - moderate effects on the development of macrovascular complications or heart failure {, 1998 #9449; Patel, 2008 #3887} which have remained stubbornly resistant to therapeutic innovations {Udell, 2015 #10065}.

However, over the last decade, several large cardiovascular outcome trials (CVOTs) have provided data on the efficacy of glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i) to reduce cardiorenal events in people living with T2DM at high CV risk. The American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the European Society of Cardiology (ESC) have recently published strong recommendations for prescribing these agents in such patients {Davies, 2018 #10016; Buse, 2020 #10054; Cosentino, 2020 #10062}. Much has been made of the differences in recommendations which largely center on how “high risk” is defined and the role of metformin as first line therapy and we have concerns that this focus has contributed to clinical inertia to the detriment of patient care. Over the last 5 years there has been a growth in clinical evidence for the beneficial CV effects of SGLT2i and GLP-1RA in people living with T2DM, and it is of major concern that the number of patients receiving these life-saving drugs remains so low {Dennis, 2019 #10063}. A subset of the writing group members was convened to find common ground and explore opportunities to integrate our efforts. In this expert consensus paper developed after round table discussions between members of the two writing groups we propose an integrated paradigm that encompasses the views incorporated in the ESC, ADA and EASD in their different approaches to management. We launch a message of ‘awakening,’

encouraging the medical community to apply the evidence originating from large studies and taken up in the guidelines/consensus to their clinical practice.

Evidence for SGLT2-inhibitors

The effect of SGLT2-inhibitors on CV endpoints has been examined in five placebo-controlled CVOTs in patients with T2DM, providing consistent, strong evidence for the amelioration of both, cardiovascular and renal complications. In the EMPA-REG OUTCOME trial Empagliflozin {Zinman, 2015 #9038} and in the CANVAS program Canagliflozin {Neal, 2017 #9572} significantly reduced 3-point MACE in a population of patients with elevated CV risk (Table 1). In addition, Canagliflozin significantly reduced 3-point-MACE in a diabetes population with chronic kidney disease (CKD; CREDENCE trial) {Perkovic, 2019 #9979}. DECLARE TIMI-58, a trial assessing CV effects of Dapagliflozin vs. placebo in patients with diabetes did not find a significant reduction of 3-point MACE, possibly due to the lower risk cohort recruited with about 60% of participants without prevalent CV disease, but multiple risk factors {Wiviott, 2018 #9939}. The VERTIS CV trial with Ertugliflozin also did not show a reduction in MACE, despite the fact that people with already existing CV events were studied (ADA Presentation). Convincingly, in all of these trials the SGLT2 inhibitors investigated showed a significant reduction of the combined endpoint of heart failure hospitalization or CV death. This beneficial effect of SGLT2-inhibitors on heart failure-related events has been confirmed by recent data from the DAPA-HF trial as well as the EMPEROR-reduced trial examining the effect of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF) with or without diabetes. In both studies, dapagliflozin in DAPA-HF, or empagliflozin in EMPEROR-reduced led to a reduction in the combined endpoint of HF worsening or CV death compared to placebo independent of the presence of diabetes {McMurray, 2019 #10001;Packer, 2020 #140}.

Despite using different definitions of renal endpoints, all SGLT2-inhibitor studies also showed protection against progression of diabetic kidney disease. In the CVOT studies, these findings were secondary endpoints, but the CREDENCE study demonstrated a highly significant 30% reduction in the combined cardio-renal endpoint of composite of

ESKD, doubling of serum creatinine, death from kidney causes or CV death in people with T2DM and CKD {Perkovic, 2019 #9979}. In addition, most recently, DAPA-CKD, a dedicated trial in CKD patients with or without diabetes , demonstrated a significant reduction of the composite endpoint of sustained $\geq 50\%$ eGFR decline, ESKD, renal or CV death, a reduced risk of CV death or hospitalisation for heart failure, as well as a reduction of all-cause mortality independent of diabetes status.

Evidence for GLP-1 receptor agonists

GLP-1 receptor agonists are arguably the most effective glucose lowering medications and weight loss agents indicated for the treatment of T2DM. In a series of seven published CVOT's, four agents to date have demonstrated statistically significant reductions in the hazard ratio for the first occurrence of the 3-point MACE composite of non-fatal myocardial infarction, non-fatal stroke or CV death (liraglutide {Marso, 2016 #9446}, subcutaneous semaglutide {Marso, 2016 #9447}, albiglutide {Hernandez, 2018 #9925}, and dulaglutide {Gerstein, 2019 #9997})(Table 2). Two agents have shown numerical reductions in 3-point MACE (exenatide once weekly {Holman, 2017 #9600} and oral semaglutide {Husain, 2019 #9996}) and one was effectively neutral (lixisenatide {Pfeffer, 2015 #9030}) without evidence of cardiovascular harms or benefits. Meta-analyses of the trial results (overall population 56,004 participants), demonstrate a 12% reduction in 3-point MACE, 12% reduction in CV death, 11% reduction in all-cause mortality, 9% reduction in fatal/non-fatal MI, 16% reduction in fatal/non-fatal stroke, 9% reduction in heart failure hospitalization, and 17% reduction for a broad kidney composite outcome mainly driven by effects on albuminuria. {Kristensen, 2019 #10055; Marsico, 2020 #10056}

ADA / EASD recommendation and ESC guidelines

First, it is important to understand the context in which both documents were written. The ADA/EASD 'consensus' is based on a structured review of published evidence of pharmacological and non-pharmacological interventions in T2DM over a defined time period (Jan 2014 –Feb 2018) but without formal grading of the evidence, aimed at

HCPs in Europe and the US. The ESC document is a 'guideline' which weighed and graded evidence according to ESC criteria leading to 138 recommendations in 14 areas of practice and is targeted at practitioners in Europe.

The ADA/EASD recommended in 2018 {Davies, 2018 #10016} that, in the setting of T2DM, established CVD was a compelling indication for treatment with a GLP-1 receptor agonist or an SGLT2 inhibitor. In the 2019 update {Buse, 2020 #10054}, the ADA/EASD further suggested the following (direct quotation):

- In appropriate high-risk individuals with established T2DM, the decision to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death, or CKD progression should be considered independently of baseline HbA1c or individualized HbA1c target.
- Providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes.
- For patients with T2DM and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischemic stroke, unstable angina with ECG changes, myocardial ischemia on imaging or stress test, or revascularization of coronary, carotid, or peripheral arteries) where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with T2DM without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 mL min⁻¹ [1.73 m]⁻², or albuminuria.
- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR 30 to ≤60 mL min⁻¹ [1.73 m]⁻² or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with T2DM and HF, particularly those with HFrEF, to reduce hHF, MACE, and CV death.

- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE, and CV death in patients with T2DM with CKD.
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risks and benefits with comprehensive education on foot care and amputation prevention.

The 2019 ESC guidelines on diabetes prediabetes and CVD published {Cosentino, 2020 #10062} recommend that patients with diabetes should be classified according to three accepted levels of cardiovascular risk and treated accordingly independent of baseline HbA1c levels. The guidelines suggest the following:

- Patients at **very high risk** include those with DM and established CVD, or other target organ damage (proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy), or three or more major risk factors, or early onset T1DM of long duration (>20 years). **High risk** patients are defined as those with DM duration ≥10 years without target organ damage plus any other additional risk factor, and patients at **moderate risk** are young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. (Risk factors include: age ≥50, hypertension, dyslipidemia, smoking, obesity).
- In patients at moderate risk metformin should be considered as first line therapy (Class IIa C recommendation).
- Patients with atherosclerotic cardiovascular disease (ASCVD) as well as those at high or very high risk should be treated with an SGLT2 inhibitor or a GLP-1 RA (Class IA recommendation). If HbA1c values are not at target in these patients, metformin should be added. Further intensification of glucose control should be achieved with additional glucose-lowering drugs to reduce microvascular events.

In the future, studies need to show whether these drugs will be standard for the prophylaxis of CVD and / or CKD in uncomplicated T2DM rather than for therapeutic purposes only.

Differences between the Consensus and Guidelines

The original ADA/EASD consensus was published in Dec 2018 prior to the full publication of a number of the larger CVOTs, including REWIND, DECLARE and CREDENCE (6-8). These trials contributed evidence particularly in those with multiple CV risk factors, primary renal outcome data and included data on those with HbA1c's below or at target range. The ESC guideline published in Sept 2019 was able to consider this evidence. The ADA/EASD consensus was subject to a brief update in Dec 2019 to reflect these additional data.

The definition and consideration of 'at risk' groups differs. The ADA/EASD consensus identifies specific 'high risk' groups based on the inclusion criteria articulated in the CVOTs whereas the ESC guideline uses its own definition of cardiovascular risk categories modified from the 2016 guidelines and includes people with type 1 diabetes. The ESC definition of 'high' CV risk is based on duration of diabetes plus additional risk factor (age, hypertension, dyslipidaemia, smoking, obesity) and would mean the vast majority of people with T2DM would be defined as 'high' CV risk {Caparrotta, 2020 #10064} however it is difficult to judge how closely this group reflects those recruited to CVOTs such as DECLARE and REWIND.

The positioning of the use of glucose lowering therapies in CV protection differs. The ADA/EASD consensus gives preference to the use of GLP-1 RA with regards to reduction in major adverse cardiovascular event (MACE) in those with established atherosclerotic cardiovascular disease (ASCVD) as well as those with 'high risk indicators', however the SGLT2-i are preferred in those with CKD and heart failure (HF). The ESC guideline suggests the use of either GLP1-RA or SGLT2i in patients with ASCVD or high or very high CV risk but does not differentiate between use of the classes in specific sub-groups (1).

The area of difference which has attracted most attention is the positioning of metformin. In many of these CVOTs patients were on metformin baseline therapy, but there is no evidence to suggest that the presence of metformin might have influenced the results {Inzucchi, 2020 #141}. The ADA/EASD consensus retains metformin as 'foundational' treatment but explicitly questions whether this is a 'quirk of history' rather than truly evidence-based and highlights that GLP-RA and/or SGLT2i should be added

early regardless of HbA1c. In contrast, the ESC guidelines remove the requirement to start with metformin as first line in those drug naïve with ASCVD or at high or very high CV risk, preferring initial therapy with either a GLP-1RA or SGLT2i.

Similarities between the Consensus and Guidelines

The main common point between the two documents is that both expert groups put the patient at the center of the care pathway and derive their guidance on therapies for diabetes from evidence provided by major clinical trials in people with T2DM, with the ADA/EASD consensus also bringing in real world evidence. Both documents attempt to integrate care to manage the high levels of morbidity and mortality associated with T2DM and emphasize the importance of a multifactorial approach to T2DM, including glucose lowering therapy, but also blood pressure control, statins and in very high risk patients antiplatelet therapy. The importance of diet and lifestyle is emphasized in both documents. Of importance in both documents is that choices of agents in the treatment of people with diabetes needs to build on evidence that moves beyond HbA1c. Both documents recognise the strong evidence for agents from the GLP1-RA and SGLT2i class and put these agents high up in the decision tree. Both documents clearly state that the concept of individualised care is central to the management of diabetes and therapeutic decisions depend on many factors including patient characteristics, co-morbidities, patient preferences and priorities.

Both agree that metformin should be first line therapy in newly diagnosed T2DM, however in the consensus it is recommended this is applied to all newly diagnosed T2DM, whilst the ESC guideline indicates that in the presence of CVD and in those with high / very high risk, SGLT-2i or GLP-1 should be first line. This difference is not as great as it sounds, as the ADA/EASD insists that patients at high risk for cardiorenal disease should be treated with SGLT2i or GLP-1RA independent of HbA1c. In addition, most patients rapidly progress to requiring combination therapy and the addition of metformin will probably be required soon after diagnosis.

A call to action – clinical messages

- 1) It is obvious from both the clinical trial data and market data, that there is an urgent need to provide clear messages to patients with diabetes and their providers. Only a small proportion of patients with diabetes and CVD are currently treated with GLP-1 RA or SGLT2i {McCoy, 2019 #10057} and most astonishingly, prescription of these potentially life-saving medications by cardiologists remains very low (between 1 and 5%) {Vaduganathan, 2019 #10059; Dave, 2020 #10058}. Both organisations agree on several compelling indications for with the use of GLP-1RA and SGLT2i which should be urgently implemented in clinical practice by cardiologists, endocrinologists, nephrologists, primary care providers, pharmacists and other licensed health care professionals. Subjects with T2DM and prevalent CVD or at high risk (prior MI, prior stroke, prior revascularization of any arterial bed, evidence of cardiac ischemia on any stress imaging procedure, a >50% arterial stenosis of presumed atherosclerotic origin, LVH) should be treated with a GLP-1RA or an SGLT2i.
- 2) those with T2DM and heart failure, particularly those with reduced ejection fraction should be treated with an SGLT2i.
- 3) Patients with T2DM with chronic kidney disease, particularly those with an estimated glomerular filtration rate (eGFR) 25-60 ml/min/1.73m² or urine albumin/creatinine ratio (UACR) >200 mg/g, should be treated with an SGLT2i. If that is not tolerated or not preferred, a GLP-1RA should be considered.
- 4) These treatment decisions should be made independent of background therapy, current levels of glycemic control or individualized treatment goals. The SGLT2i or GLP-1RA prescribed should have demonstrated outcome benefit in the relevant clinical setting.

Of note, treatment with GLP-1RA and SGLT2i does not mean that the patient's and provider's work is done. Focusing on lifestyle management, achieving appropriate glycemic targets to minimize microvascular disease and decrements in quality of life, as well as the full panoply of cardiovascular risk reduction strategies remain foundational therapies implemented in all the trials in which the benefits of GLP-1RA and SGLT2i were demonstrated. In addition, there needs to be a more integrated approach to

patient care involving those from a diabetes, CV and CKD background in order to individualize overall care and harmonise the use of these agents.

A call to action – clinical summary

It is over 50 years since the publication of the UGDP trial, the first attempt to improve CV outcomes in diabetes {Goldner, 1971 #10012}. At the conclusion of this trial it was suggested that macrovascular outcomes were unlikely to be improved solely by glycaemic control. Later studies such as UKPDS largely supported this view with the caveat that good glycaemic control appeared to create metabolic memory and improved CV outcomes over 10 -15 years. These findings are in marked contrast to those reported in relation to the development of retinopathy, where glycaemic control is consistently shown to ameliorate risk of this condition. In summary, the glucocentric view of vascular complications works in relation to retinopathy but is insufficient on its own in preventing and managing macrovascular disease in diabetes.

For many years diabetologists and other health care workers have lamented the seemingly unmanageable levels of macrovascular morbidity and mortality which became almost overwhelming with the concurrent development of renal disease. Moving forward again to 2020, we finally have in our armamentarium two groups of drugs that do what we have said we always wanted: they help to manage glycaemia and improve CV outcomes. The effects of SGLT2i on heart failure and renal impairment are particularly encouraging, no less the GLP-1RA on CV outcomes, weight loss and glycaemia. However at this historic moment in diabetes care, professionals from different medical specialties have been riven by uncertainty and disagreement about the precise positioning of these agents. We need to individually and collectively stop quibbling about where to draw distinctions, and ensure dissemination and implementation of points 1-4 above -- in your personal practice, among your colleagues and collaborators, in your health care system. It is a major worry that the very patients who will benefit from these agents, those at high risk with long standing diabetes, impaired renal function and underlying CV disease are being denied these evidence based agents through what is essentially, therapeutic inertia. All the myriad health care

professionals involved in diabetes care are asked to take note and to heed our call to action to prescribe newer glucose-lowering agents effectively and with confidence to improve the unacceptably high levels of cardiorenal morbidity and mortality in T2DM.

Table 1. CVOTs with SGLT2 inhibitors in T2DM

	EMPA-REG OUTCOME (empagliflozin)	CANVAS Program (canagliflozin)	DECLARE-TIMI 58 (dapagliflozin)	CREDESCENCE (canagliflozin)	VERTIS CV (ertugliflozin)
3P-MACE	HR 0.86 (95% CI 0.74, 0.99) p=0.04	HR 0.86 (95% CI 0.75, 0.97) p=0.02	HR 0.93 (95% CI 0.84, 1.03) p=0.17	HR 0.80 (95% CI 0.67, 0.95) p=0.01	HR 0.97 (95% CI 0.85, 1.11) p=0.17
Heart failure hospitalisation	HR 0.65 (95% CI 0.50, 0.85) p=0.002*	HR 0.67 (95% CI 0.52, 0.87)	HR 0.73 (95% CI 0.61, 0.88)	HR 0.61 (95% CI 0.47, 0.80) p<0.001	HR 0.70 (95% CI 0.54, 0.90)
CV death	HR 0.62 (95% CI 0.49, 0.77) p<0.001*	HR 0.87 (95% CI 0.72, 1.06)	HR 0.98 (95% CI 0.82, 1.17)	HR 0.78 (95% CI 0.61, 1.00) p=0.05	HR 0.92 (95% CI 0.77, 1.11)

*Nominal *p*-value

Table 2. CVOTs with GLP1-RA in T2DM

	ELIXA (lixisenatide)	LEADER (liraglutide)	SUSTAIN-6 (semaglutide sc)	EXSCCEL (exenatide)	HARMONY (albiglutide)	REWIND (dulaglutide)	PIONEER 6 (semaglutide po)
3P-MACE	HR 1.02 (95% CI 0.89, 1.17) p=0.81	HR 0.87 (95% CI 0.78, 0.97) p=0.01	HR 0.74 (95% CI 0.58, 0.95) p=0.02	HR 0.91 (95% CI 0.83, 1.00) p=0.06	HR 0.78 (95% CI 0.68, 0.90) p=0.0006	HR 0.88 (95% CI 0.79, 0.99) p=0.026	HR 0.79 (95% CI 0.57, 1.11) P=0.17
Stroke	HR 1.12 (95% CI 0.72, 1.58) p=0.54*	HR 0.89[†] (95% CI 0.72, 1.11) p=0.3*	HR 0.61[†] (95% CI 0.38, 0.99) p=0.04*	HR 0.85 (95% CI 0.70, 1.03)	HR 0.86 (95% CI 0.66, 1.14) p=0.3*	HR 0.76[†] (95% CI 0.61, 0.95) p=0.017*	HR 0.74[†] (95% CI 0.35, 1.57)
Myocardial infarction	HR 1.03 (95% CI 0.87, 1.22) p=0.71*	HR 0.88^{††} (95% CI 0.75, 1.03) p=0.11*	HR 0.74^{††} (95% CI 0.51, 1.08) p=0.12*	HR 0.97 (95% CI 0.85, 1.10)	HR 0.75 (95% CI 0.61, 0.90) p=0.003*	HR 0.96^{††} (95% CI 0.79, 1.16) p=0.65*	HR 1.18^{††} (95% CI 0.73, 1.90)
CV death	HR 0.98 (95% CI 0.78, 1.22) P=0.085*	HR 0.78 (95% CI 0.66, 0.93) P=0.007*	HR 0.98 (95% CI 0.65, 1.48) p=0.92*	HR 0.88 (95% CI 0.76, 1.02)	HR 0.93 (95% CI 0.73, 1.19) p=0.21*	HR 0.91 (95% CI 0.78, 01.06) p=0.21*	HR 0.49 (95% CI 0.27, 0.92)

[†] Non-fatal stroke only; ^{††} Non-fatal myocardial infarction only; *Nominal *p*-value

Table 3. Differences between **ADA / EASD recommendation and ESC guidelines**

	ADA / EASD	ESC
T2DM with established CVD	For patients with T2DM and established atherosclerotic CV disease) where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists.	Patients with atherosclerotic cardiovascular disease (ASCVD) should be treated with an SGLT2 inhibitor or a GLP-1 RA
T2DM without established CVD	To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with T2DM without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid, or lower extremity artery stenosis >50%, left ventricular hypertrophy, eGFR <60 mL min ⁻¹ [1.73 m] ⁻² , or albuminuria.	Patients) at high risk (DM duration ≥10 years without target organ damage plus any other additional risk factor; no ASCVD) should be treated with an SGLT2 inhibitor or a GLP-1 RA
Metformin use	Metformin should be baseline therapy in all patients	In patients at moderate risk metformin be should be considered as first line therapy (Class IIa C recommendation).

Conflict of Interest

NM has given lectures for Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk; has received unrestricted research grants from Boehringer Ingelheim, and has served as an advisor for Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, NovoNordisk. In addition, served in trial leadership for Boehringer Ingelheim and NovoNordisk. NM declines all personal compensation from pharma or device companies.

MD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, an advisory board member for Servier and Gilead Sciences Ltd and as a speaker for NAPP, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis, Lilly, Boehringer Ingelheim, AstraZeneca and Janssen.

CM serves or has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche, Medtronic, ActoBio Therapeutics, Pfizer and UCB. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for CM from Medtronic, Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Roche, Abbott, ActoBio Therapeutics and Novartis; CM serves or has served on the speakers bureau for Novo Nordisk, Sanofi, Merck Sharp and Dohme, Eli Lilly and Company, Boehringer Ingelheim, AstraZeneca and Novartis. Financial compensation for these activities has been received by KU Leuven.

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PJG Co-chair ESC guidelines on CV disease in diabetes and prediabetes, Diabetes Advisor to Synexus, Editor in Chief, Diabetes and Vascular Disease Research. Presentations and advisory board Boehringer Ingelheim, Bayer, Astrazeneca, Lilly, Merck, Janssen Pharmaceutica and NovoNordisk.

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References

References

1. Mulnier HE Seaman HE Raleigh VS et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. *Diabetologia*. 2008; 51: 1639-1645
2. Bell S Fletcher EH Brady I et al. End-stage renal disease and survival in people with diabetes: a national database linkage study. *QJM*. 2015; 108: 127-134
3. McAllister DA Read SH Kerssens J et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. *Circulation*. 2018; 138: 2774-2786
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *lancet*. 1998; 352: 837-853
5. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008; 358: 2560-2572
6. Udell JA Cavender MA Bhatt DL Chatterjee S Farkouh ME Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *lancet Diabetes Endocrinol*. 2015; 3: 356-366
7. Davies MJ D'Alessio DA Fradkin J et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) *Diabetes Care*. 2018; 41: 2669-2701
8. Buse JB Wexler DJ Tsapas A et al. 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA)

and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2020; 43: 487-493

9. Cosentino F, Grant PJ, Aboyans V et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020; 41: 255-323

10. Dennis JM, Henley WE, McGovern AP et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010–2017. *Diabetes Obes Metab*. 2019; 21: 1576-1584

11. Dave CV, Schneeweiss S, Wexler DJ, Brill G, Patorno E. Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013–2018. *Diabetes Care*. 2020; 43: 921-924

12. Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373: 2117-2128

13. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017; 377: 644-657

14. Perkovic V, Jardine MJ, Neal B et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; 380: 2295-2306

15. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2018; 380: 347-357

16. Cannon CP, Pratley R, Dagogo-Jack S et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020; 383: 1425-1435

17. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019; 381: 1995-2008

18. Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020; 383: 1413-1424
19. Heerspink HJL, Stefánsson BV, Correa-Rotter R et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020; 383: 1436-1446
20. Marso SP, Daniels GH, Brown-Frandsen K et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016; 375: 311-322
21. Marso SP, Bain SC, Consoli A et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016; 375: 1834-1844
22. Hernandez AF, Green JB, Janmohamed S et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018; 392: 1519-1529
23. Gerstein HC, Colhoun HM, Dagenais GR et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019; 394: 121-130
24. Holman RR, Bethel MA, Mentz RJ et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017; 377: 1228-1239
25. Husain M, Birkenfeld AL, Donsmark M et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2019; 381: 841-851
26. Pfeffer MA, Claggett B, Diaz R et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med.* 2015; 373: 2247-2257
27. Kristensen SL, Rørth R, Jhund PS et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol.* 2019; 7: 776-785

28.Marsico F Paolillo S Gargiulo P et al. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2020; 41: 3346-3358

29.Piepoli MF Hoes AW Agewall S et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016; 37: 2315-2381

30.Caparrotta TM Blackbourn LAK McGurnaghan SJ et al. Prescribing paradigm shift? Applying the 2019 European Society of Cardiology-led guidelines on diabetes, prediabetes, and cardiovascular disease to assess eligibility for sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists as first-line monotherapy (or add-on to metformin monotherapy) in type 2 diabetes in Scotland. *Diabetes Care.* 2020; 43: 2034-2041

31.Inzucchi SE Fitchett D Jurišić-Eržen D et al.

Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy?. *Diabetes Obes Metab.* 2020; 22: 631-639

32.McCoy RG Dykhoff HJ Sangaralingham L et al. Adoption of new glucose-lowering medications in the US—the case of SGLT2 inhibitors: nationwide cohort study. *Diabetes Technol Ther.* 2019; 21: 702-712

33.Vaduganathan M Patel RB Singh A et al. Prescription of glucagon-like peptide-1 receptor agonists by cardiologists. *J Am Coll Cardiol.* 2019; 73: 1596-1598

34. Goldner MG Knatterud GL Prout TE Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III. Clinical implications of UGDP results. JAMA. 1971; 218: 1400-1410