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Commentary

Type 2 diabetes: Why should diabetologists and cardiologists work more closely together?

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Commentary

The incidence of type 2 diabetes (T2D) is increasing worldwide, and diabetes complications represent tremendous human and economic burdens. Cardiovascular disease (CVD) affects around one out of three patients with T2D, and accounts for approximately half the mortality.

It has extensively been shown that glucose-lowering medications decrease the risk of microangiopathic complications, although the search for tighter glucose control was associated with increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [1]. In addition, new drug classes have shown both glucose-lowering and CVD protective effects, and sometimes even additional nephroprotective properties [2]. The recent American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus statement [3] clearly identified the presence/absence of CVD and/or chronic kidney disease (CKD) as a major trigger for the use of second-line treatment (after metformin) in T2D management.

CVD here includes not only coronary artery disease (CAD), stroke and peripheral vascular disease (PVD), but also chronic heart failure (HF). However, the clinical diagnosis of CVD in patients with T2D may be difficult in everyday practice. Secondary prevention can easily be defined as referring to patients with a history of CV events although, in recently published cardiovascular outcome trials (CVOTs), inclusion criteria were slightly different, combining both patients with previous CVD events and those with established CVD. Primary prevention is more complicated to define in diabetes patients, as CAD can often be silent in such patients [4]. In a landmark study such as the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) [5], 20% of patients were in primary prevention with high CVD risk, defined as having an age $\geq$ 60 years and $\geq$ 1 cardiovascular (CV) risk factor and potential end-organ damage. Thus, if guidelines highlight specific indications for patients in secondary prevention [3], then some patients considered as being in 'primary' prevention but having a high CV risk profile, especially those with silent CAD, might also benefit from the treatment.

CV risk assessment in asymptomatic patients with no history of CVD usually includes electrocardiography (ECG) and echocardiography, and often a stress test (ECG and/or myocardial scintigraphy and/or echography) as well, with subsequent coronary angiography in patients with clear evidence of silent myocardial ischaemia. More recently, the coronary artery calcium (CAC) score was shown to predict CVD mortality [6], although the management of asymptomatic patients with elevated CAC scores still raises questions. The CAC score may be considered a risk modifier and used as a first-line screening test for CAD. A high CAC score can help to further stratify risk through the use of selected tests to assess patients for silent myocardial ischaemia [7].

CKD is associated with increased CVD risk and also has interactions with HF. It has been shown that subjects with the highest risk for HF-related hospitalization had either previous HF, an estimated glomerular filtration rate (eGFR) $\leq$ 60 mL/min/1.73 m^2 or elevated baseline levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) [8]. In fact, HF has emerged in the last 20 years as a serious CV complication in patients with T2D. Indeed, a recent cohort study suggested that patients with T2D and five risk-factor variables within target ranges had little or no excess risk of death, myocardial infarction or stroke compared with the general population, but nevertheless retained an excess risk of HF [9]. A meta-analysis of randomized trials of intensive glucose treatment showed no benefit for the reduction of HF-related events [10]. Moreover, when aiming for tight glucose control, hypoglycaemia may be detrimental due to sympathetic activation and the subsequent risk of arrhythmia [11] or recurrent congestive episodes [12] in some patients.

Therefore, new treatments with limited or no risk of hypoglycaemia are of particular interest, and specific treatment choices are now available for patients with T2D and HF. Whereas most diabetologists may not be familiar with chronic HF, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) study [13] and then the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 [14] found increased rates of hospitalization for HF in patients treated

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with pioglitazone, a thiazolidinedione, and saxagliptin, a dipeptidyl peptidase-4 inhibitor, respectively. Given this sign, subsequent CVOTs looked specifically for this issue. However, with the sodium–glucose cotransporter-2 inhibitors (SGLT2is), not only were there no further reports of HF increases, but there was even a significant decrease in hospitalizations for HF, making this drug group the first-line treatment for patients with HF [3]. Nevertheless, HF is a progressive condition in diabetes and the diagnosis may sometimes be complicated, as the ejection fraction (EF) is not always reduced and natriuretic peptide measurements may be normal, especially in obese patients. Indeed, up to 50% of patients with T2D and HF have a preserved EF with essentially the same signs, symptoms and prognosis as patients with HF and reduced EF [15].

Before the publication of these CVOTs, there was no specific treatment available to improve outcomes in patients with HF and preserved EF. A recent meta-analysis of CVOTs carried out to test the safety of SGLT2is revealed that these drugs are able to reduce the risk of hospitalization for HF independently of the presence of atherosclerotic CVD or HF at inclusion [16]. A recently published post-hoc analysis of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME) showed that, with empagliflozin, risk reduction for the composite CV outcome (CV death, non-fatal myocardial infarction or stroke) was greater in patients with than without left ventricular (LV) hypertrophy on ECG [17]. However, whether SGLT2is can reduce LV mass and improve its function is currently being studied in patients with either preserved or reduced EF [18]. The findings will likely lead to additional considerations of subclinical HF stages as detected by echocardiography or elevated natriuretic peptide levels. Nevertheless, it should be emphasized that canagliflozin was recently found, in a subgroup of patients included in the Canagliflozin Cardiovascular Assessment Study (CANVAS), to reduce the overall risk of HF events in patients with T2D and high CVD risk whatever their EF status (preserved, reduced or unknown) [19]. Furthermore, empagliflozin was shown to reduce hospitalizations for HF and CVD mortality regardless of whether HF was present or not at baseline, suggesting that the drug might prevent new-onset HF [20].

Following such treatment parameters as surrogate CVD risk markers would need to be shared between cardiologists and diabetologists. Moreover, as a potentially increased risk for lower-limb amputation was reported with canagliflozin in CANVAS [21], careful evaluation of PVD should be discussed among specialists before the prescription of any SGLT2i.

Since the 2008 US Food and Drug Administration (FDA) guidelines, most CVOTs have demonstrated CV safety based on the non-inferiority of new antidiabetic drugs *vs* placebo. However, some CVOTs showed significant superiority in CV outcomes, thereby leading to the new ADA/EASD consensus [3]. Other professional societies have likewise published reports going into the same direction [22,23]. All of these position statements have focused on the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and SGLT2is in patients with T2D and a high CV risk profile, especially those with atherosclerotic CVD. Yet, as a detailed review of the CVOTs with these two antidiabetic drug classes is beyond the scope of this commentary and, in fact, has already been done [3,22,23], a summary of the published trials reporting both CV and non-CV outcomes with the two classes is presented in Table 1; a complete review of renal outcomes is available elsewhere [24]. The worsening of diabetic retinopathy reported with semaglutide in the Trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes (SUSTAIN-6) happened very early on in the trial and was probably related to the rapid improvement in glucose control in insulin-treated patients with preexisting retinopathy [25]. Nevertheless, whether the CVD effects of GLP-1RAs and SGLT2is are drug-dependent or a class effect remains unclear.

Thus, the expertise of both diabetologists and cardiologists is necessary when treating patients with T2D. This implies to control blood glucose levels to reach the individualized HbA1c target value [3] and according to the recent European guidelines to be more aggressive in terms of blood pressure (BP) control (in patients aged < 65 years, systolic BP can be 120–130 mmHg, if tolerated,

Table 1
Cardiovascular (CV) outcome trials with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT2is): primary outcome results [3-point major adverse CV events (MACEs): CV death, non-fatal myocardial infarction, non-fatal stroke] and non-CV outcomes.

Drug	Trial	Mean follow-up (years)	Primary CV outcome (HR)	Hospital admissions for HF (HR)	Non-CV outcomes (HR)
SGLT2is					
Canagliflozin	Canvas	2.4	0.86 (0.75–0.97)	0.67 (0.52–0.87)	Progression of albuminuria: 0.73 (0.67–0.79)
	Credence[a]	2.6	0.80 (0.67–0.95)	0.61 (0.47–0.80)	Primary outcome[a]: 0.70 (0.59–0.82)
Dapagliflozin	Declare–timi	4.2 (median)	0.93 (0.84–1.03)	0.73 (0.61–0.88)	Composite renal endpoint[b]: 0.76 (0.67–0.87)
Empagliflozin	Empa reg outcome	3.1	0.86 (0.74–0.99)	0.65 (0.50–0.85)	Progression to macroalbuminuria: 0.61 (0.53–0.70) Prespecified secondary composite outcome[c]: 0.61 (0.53–0.70)
GLP-1RAs					
Albiglutide	Harmony	1.6	0.78 (0.68–0.90)	Not available	Not available
Dulaglutide	Rewind	5.4	0.88 (0.79–0.99)	No difference	Exploratory composite outcome[d]: 0.85 (0.77–0.93)
Exenatide QW	Exscel	3.2	0.91 (0.83–1.00)	0.94 (0.78–1.13)	No difference in new macroalbuminuria
Liraglutide	Leader	3.8	0.87 (0.78–0.97)	0.87 (0.73–1.05)	New macroalbuminuria: 0.74 (0.60–0.91) Secondary composite endpoint[e]: 0.78 (0.67–0.92)
Lixisenatide	Elixa	2.1	1.02 (0.89–1.17)[f]	0.96 (0.75–1.23)	New macroalbuminuria: 0.81 (0.66–0.99)
Semaglutide	Sustain-6	2.1	0.74 (0.58–0.95)	1.11 (0.77–1.61)	New or worsening nephropathy: 0.64 (0.46–0.88) Diabetic retinopathy: 1.76 (1.11–2.78)

HR: hazard ratio; HF: heart failure.
[a] Composite of end-stage renal disease [ESRD: dialysis, transplantation, sustained estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2, doubling of creatinine, death from renal or CV causes].
[b] $> 40\%$ decrease in eGFR, new ESRD, death from renal or CV causes.
[c] Incident or worsening nephropathy [progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy (RRT), death from renal disease].
[d] First occurrence of new macroalbuminuria (urine albumin-to-creatinine ratio: > 33.9 mg/mmol), sustained $\geq 30\%$ decline in eGFR from baseline, chronic RRT.
[e] New-onset persistent macroalbuminuria, persistent doubling of serum creatinine, ESRD, death due to renal disease.
[f] Primary CV outcome was 4-point MACE (3-point MACE plus hospitalization for unstable angina).

and diastolic BP < 80 mmHg) and low-density lipoprotein (LDL) levels (< 100 mg/dL or 70 mg/dL in patients with high or very high risk, respectively). In addition, GLP-1RAs and SGLT2is improve not only glucose control and body weight, but also CV outcomes–mostly, if not totally, independently of their effect on HbA_{1c} levels.

Recent guidelines help to position each drug in the therapeutic choice according to the presence of CAD, HF or CKD [3]. More specifically, it is time to favour the use of antihyperglycaemic drugs, such as SGLT2is, that have demonstrated clear benefits in decreasing the risk of HF and CV outcomes, and GLP-1RAs, which reduce mostly CV outcomes in patients with atherosclerotic CVD [5,26]. The LEADER study showed a 13% reduction [hazard ratio (HR): 0.87, 95% confidence interval (CI): 0.78–0.97] at 3.8 years in primary efficacy outcome (death from CVD, non-fatal myocardial infarction or stroke) with liraglutide vs. placebo. Similarly, SUSTAIN-6 showed, at 2 years, a 26% reduction (HR: 0.74, 95% CI: 0.58–0.95) in this same composite outcome in high-risk patients (aged ≥ 50 years with secondary prevention, HF or CKD, or aged ≥ 60 years with ≥ 1 additional CV risk factor) and a 39% reduction in stroke incidence (HR: 0.61, 95% CI: 0.38–0.99) with semaglutide vs. placebo. Most recently, albiglutide was also found, after only 1.6 years of follow-up, to be superior to placebo in terms of major CV events (HR: 0.78, 95% CI: 0.68–0.90) in the Harmony Outcomes trial [27], while the results of the REWIND study showed that major CV events happened less frequently during a 5.4-year follow-up of dulaglutide vs. placebo (HR: 0.88, 95% CI: 0.79–0.99) [28].

The patient's opinion and participation in medical decision-making should also be an essential part of an individualized treatment choice [3]. However, despite the remarkable results with liraglutide in LEADER [5], a T2D patient may still be extremely reluctant and refuse daily injections for a condition that has no apparent ill effects. Weekly injections might, in this case, offer an acceptable alternative although, sometimes, any injectable treatment may be totally refused and has to be replaced by oral treatment with another class of drug. Thus, to guide the patient's decision, the physician has to be able to accurately estimate CVD risk, and clearly know and explain the expected benefit–risk balance of each treatment choice.

The second-line drug choice after metformin in a patient with T2D presupposes both an accurate characterization of the patient's condition (primary prevention, CVD including HF, CKD) and a discussion with the patient of the various treatment choices, including drug presentation (oral, daily injections, weekly injections), drug effects on blood glucose, weight loss, CV and non-CV outcomes, and any potential adverse effects. This would require close collaboration between diabetologists and cardiologists along with evolution of the role of each specialist, which could therefore mean that each specialist in the field has to be trained in 'cardio-diabetology'. Furthermore, antihypertensive treatment might need to be adjusted when a GLP-1RA or SGLT2i is introduced and, as rare side-effects such as hypovolaemia can arise with SGLT2is, this would require, here again, close collaboration between these specialists. Finally, nephrologists may also have to be included in the team, as SGLT2is may be the first treatment of established CKD, as revealed with canagliflozin in the Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial [29].

In addition to the new specialty of cardio-diabetology, a further objective might be the requirement for the young endocrinologists and cardiologists to be trained in the two fields to create or enhance links between specialists and to achieve the expertise necessary for the management of patients with both T2D and CVD risk. To achieve greater acceptance and adherence to treatment, but also to avoid both clinical inertia and poor compliance, it would also be essential for the patient to be part of the decision-making process and to therefore understand the reason for the choice while participating in the decision [3]. Thus, it becomes crucial that both cardiologists and diabetologists 'speak the same language' to the patient, and communicate with each other as well as with the primary-care practitioner [22]. This would be comparable to other specialty crossings, such as onco-cardiology and obesity management, and presupposes frequent communications and exchanges between specialists both in daily practice and at meetings.

In conclusion, T2D management needs to be patient-centred not only in the setting of treatment targets, but also in the choice of pharmacological agents. While the role of the general practitioner is essential in everyday patient management, any treatment decisions now require more and more specialized expertise for evaluation of the CV risk and associated conditions, such as silent CAD and CKD. Indeed, accurate characterization of the T2D patient's profile can greatly influence the choice of antidiabetic treatment as well as targets for lipid parameters, adjustment of antihypertensive therapies and aspirin prescription.

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