Type 2 Diabetes Mellitus: GLP1 Receptor Agonists and SGLT2 Inhibitors in Patients Referred to Ambulatory Consultant Cardiology Clinics

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ABSTRACT **Background:** Sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA) are new antidiabetic drugs that are recommended by current guidelines as a class I novel glucose-lowering treatment that improves cardiovascular outcome in type 2 diabetes mellitus (T2DM), particularly in patients with cardiovascular disease.
Objectives: To evaluate adherence to the current guidelines for treatment with SGLT2i and GLP1-RA drugs in patients referred to ambulatory consultant cardiology clinics with pre-existing T2DM.
Methods: We studied consecutive new patients with a pre-existing diagnosis of T2DM who were referred to the Clalit Health Services ambulatory consultant cardiology clinic over a 6-month period. The recorded information included demographics, co-morbidities, and prescribed drugs at patient admission.
Results: During the study period, 1782 patients visited our outpatient cardiology clinic. At screening, T2DM was present in 428 patients (24%); 77 (18%) were being treated with SGLT2i, and 39 (9.1%) with GLP1-RA. Patients receiving SGLT2i and GLP1-RA were younger and had more coronary artery disease, lower mean left ventricular ejection fraction, and higher mean estimated glomerular filtration rates than those who were not receiving these drugs. HbA1C was > 7 in 205 (47.9%) patients and > 7.5 in 136 patients (31.8%). Body mass index was > 30 kg/m^2 in 231 (54%) patients.
Conclusions: GLP1-RA and SGLT2i drugs were found to be administered more frequently than previously reported, but they are not yet satisfactorily prescribed.

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KEY WORDS: ambulatory consultant cardiology clinic, cardiovascular disease, glucagon-like peptide-1 receptor agonist (GLP1-RA) drugs, sodium-glucose cotransporter-2 inhibitor (SGLT2i) drugs, type 2 diabetes mellitus

Cardiovascular disease (CVD) is a common co-morbidity in patients diagnosed with type 2 diabetes mellitus (T2DM) and is a major cause of death or disability among these patients [1]. People with T2DM are more affected by CVD than non-diabetic patients [2]. The continued increase in the prevalence of T2DM is likely to lead to an increased burden of CVD. The relationship between T2DM and CVD highlights the usefulness of joint management of these diseases.

Specific antidiabetic drugs have different risks and benefits for CVD. Recent cardiovascular outcome trials have shown cardiovascular benefit of some glucose-lowering drugs in patients with CVD [4-8]. Glucagon-like peptide-1 receptor agonist (GLP1-RA) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) are new antidiabetic drugs that have been recommended by the European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) guidelines as a class I novel approach for glucose-lowering treatment [9] that improves cardiovascular outcome in T2DM, particularly in patients with CVD [10].

The aim of our study was to evaluate adherence to the current guidelines for treatment by GLP1-RA and SGLT2i drugs in patients referred to ambulatory consultant cardiology clinics with pre-existing T2DM.

PATIENTS AND METHODS

Study approval was obtained from the Ethics Review Committee on Human Research, Emek Medical Center, Afula (No. EMC-0216-20).

We studied consecutive new patients referred to the ambulatory consultant cardiology clinic of Clalit Health Services during the period 1 August 2020 to 1 February 2021 with a pre-existing diagnosis of T2DM and established CVD, or in a high-risk category for CVD, according to the ESC–EASD guidelines [9].

The recorded information included demographics, co-morbidities, and the drugs being prescribed at the time of the patient's visit to the clinic. SGLT2i and GLP1-RA drugs were prescribed by the family physician after consultation with a diabetic specialist. The prescribed SGLT2i drugs were dapagliflozin and empagliflozin, and the GLP1-RA drugs were liraglutide and dulaglutide.

DEFINITIONS

Obesity is defined as body mass index (BMI) ≥ 30 kg/m^2. In our study, we considered chronic renal failure as severe when estimated glomerular filtration rate (eGFR) was ≤ 45ml/min per

1.73m^2, moderate when eGFR was 45–60 ml/min per 1.73 m^2, and mild when eGFR was 60–90 ml/min per 1.73m^2. Coronary artery disease included prior myocardial infarction, coronary artery bypass graft, and percutaneous cardiovascular intervention.

STATISTICS

Baseline patient characteristics were analyzed for their association in patients with SGLT-2i or GLP1-RA treatment and without SGLT2i or GLP1-RA treatment. Continuous variables were expressed as means ± standard deviation and compared using Student's *t*-test. Categorical variables were expressed as total number and percentages and compared using chi-square test. A *P*-value < 0.05 was considered significant. Statistical analysis was performed using R Statistical Software, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 1782 patients visited our outpatient cardiology clinic. At screening, 428 patients (24%) had been diagnosed with T2DM. They constituted our study population, which was divided into group 1 (patients taking SGLT2i or GLP1-RA) and group 2 (patients not taking SGLT2i or GLP1-RA). Their clinical characteristics, according to treatment group, are reported in Table 1.

Overall, 77 (18%) patients were treated with SGLT2i, and 39 (9.1%) with GLP1-RA. SGLT2i drugs were prescribed to 13 patients (3%) as a monotherapy, and GLP1-RA to only 1 patient (0.2%) as a monotherapy. Group 1 patients were younger than those in group 2 [Table 1]. Women received therapy with SGLT2i or GLP1-RA drugs less frequently than men (33.6% vs. 52.6%, $P = 0.01$). Group 1 had more patients with coronary artery disease, hypertension and smokers than Group 2. Group 1 patients had a lower left ventricular ejection fraction than group 2 patients [Table 1].

No significant difference was noted between the groups in the number of patients with prior CVD, peripheral vascular disease, atrial fibrillation, thyroid disease, obesity, or mild or moderate chronic renal failure, or in length of time with T2DM. There were 231 (54%) patients with BMI > 30 kg/m^2; 57 had severe chronic renal failure; in 38 patients, eGFR ranged between 30 and 44 ml/min per 1.73 m^2, and in 10 patients, eGFR was < 30 ml/min per 1.73 m^2. Mean eGFR was significantly higher in patients who received SGLT2i or GLP1-RA drugs (group 1) than in those who did not (group 2; $P < 0.001$).

Of the 205 patients with HbA1c > 7, 28 had eGFR < 45 mL/min per 1.73 m^2. As a result, for 177 patients (41.4%), SGLT2i drugs were included the health insurance healthcare basket. Of the 136 patients with HbA1c > 7.5, 21 had eGFR < 45 ml/min per 1.73 m^2. As a result, for 115 patients (26.9%) GLP1-RA drugs were included the health insurance healthcare basket. However, 38 of the 223 patients with HbA1c < 7 (17%), which also in-

Table 1. Characteristics of the 428 patients with type 2 diabetes mellitus at the screening visit, divided into two groups: those being treated with SGLT2i or GLP1-RA antidiabetic drugs and controls

Patient characteristics	With SGLT2i or GLP1-RA, n=116	Without SGLT2i or GLP1-RA, n=312	*P*-value
Mean age, years	66.6 ± 8.7	71.4 ± 9.1	< 0.001
Male (%)	164 (52.6)	77 (66.4)	0.01
Female (%)	39 (33.6)	148 (47.4)	
Co-morbidities			
Smoking (%)	43 (37.1)	84 (26.9)	0.041
Obesity (mean ± SD)	31.4 ± 6.1	30.7 ±5.4	0.226
Prior coronary artery bypass graft (%)	31 (26.7)	43 (13.8)	0.002
Prior cerebrovascular disease (%)	12 (10.3)	55 (17.6)	0.065
Prior myocardial infarction (%)	44 (37.9)	84 (26.9)	0.027
Prior percutaneous cardiovascular intervention (%)	54 (46.6)	108 (34.6)	0.024
Peripheral vascular disease (%)	10 (8.6)	33 (10.6)	0.550
Atrial fibrillation (paroxysmal or permanent) (%)	14 (12.1)	57 (18.3)	0.125
Mean diabetes mellitus duration (years)	14.3 ± 7	12.9 ± 7.6	0.078
Hypertension (%)	83 (71.6)	253 (81.1)	0.033
Hyperlipidemia (%)	104 (89.7)	250 (80.1)	0.021
Thyroid disease (%)	37 (11.9)	11 (9.5)	0.489
HbA1c > 7	76 (66.7)	129 (42.6)	0.001
Mild chronic renal failure (%)	55 (47.4)	141 (45.2)	0.682
Moderate chronic renal failure (%)	13 (11.2)	49 (15.7)	0.240
Severe chronic renal failure (%)	4 (3.4)	53 (17)	0.001
Mean eGFR (ml/min per 1.73 m^2)	81.7 ± 19.4	70.7 ± 22.4	< 0.001
Mean LVEF	55.2 ± 10.6	58.4 ± 9.7	0.005
LVEF < 45	17 (14.7)	22 (7.1)	0.015
Medications			
β-blockers (%)	31 (26.7)	102 (32.7)	0.236
ACE inhibitors and angiotensin II receptor blockers (%)	81 (69.8)	212 (67.9)	0.710
Statins (%)	101 (87.1)	243 (77.9)	0.033
Anticoagulants (%)	15 (12.9)	57 (18.3)	0.189
Aspirin (%)	91 (78.4)	201 (64.4)	0.006
Diuretics (%)	26 (22.4)	75 (24)	0.725

ACE = angiotensin-converting-enzyme, BMI = body mass index, eGFR = estimated glomerular filtration rate, GLP1-RA = glucagon-like peptide-1 receptor agonists, LVEF = left ventricular ejection fraction, SGLT2i = sodium-glucose cotransporter-2 inhibitors

cluded 4 patients with eGFR < 45 ml/min per 1.73 m^2, were also receiving these drugs even though they did not fall into the correct category for inclusion of these drugs in the healthcare basket.

The number of antidiabetic drugs prescribed as single drugs and combined as antidiabetic drug-associated therapies is reported in Table 2.

DISCUSSION

All Israeli citizens are covered by the National Health Insurance Law that provides general health coverage as specified by the *Healthcare Basket*. SGLT2i therapy for T2DM is covered for the following indications: patients with HbA1c > 7 and patients with eGFR > 45 ml/min per 1.73 m^2. For GLP1-RA drugs, HbA1c must be > 7.5.

Current SGLT2i drug (empagliflozin, canagliflozin, and dapagliflozin) labeling does not recommend these drugs in patients with eGFR < 45 mL/min per 1.73 m^2 (13), but ESC–EASD guidelines [9] report that, "treatment with SGLT2i is associated with a lower risk of renal endpoints and is recommended if eGFR is >30 to 90 ml/min per 1.73 m^2." These guidelines are supported by findings of the EMPA-REG OUTCOME [14], CREDENCE [15], and DAPA-CKD [16] studies.

Although GLP1-RA use has been suggested to have a positive renal effect, no GLP1-RA trial has yet been published that assesses renal safety. Therefore, this class of drugs has licensing limitations based on chronic kidney disease stages [17].

According to current guidelines, SGLT2i and GLP1-RA therapy should have been prescribed in 418 of our patients (97.7%), but under healthcare basket restrictions, only 177 patients (41.4%) were allowed to get SGLT2i therapy and 115 patients (26.9%) GLP1-RA drugs. In real-world cardiology, endocrinology, and primary care practices, SGLT2i and GLP1-RA drugs are prescribed for only 5.2% and 6.0% of diabetic patients, respectively [11]. Similar results were obtained by Vaduganathan et al. [12], who reported that concurrent prescriptions were initiated by cardiologists in 5.1% of cases, despite the accumulating data supporting the use of these drug classes for CVD prevention in T2DM patients. We saw more frequent prescription of SGLT2i and GLP1-RA drugs (18% and 9.1%, respectively) in CVD patients than previously reported; however, their use is not yet satisfactory. These antidiabetic drugs were prescribed in 27.1**%** of our patients, that is, less than one-half of those allowed by the healthcare basket restrictions. SGLT2i and GLP1-RA drugs could have been prescribed by the physician to more patients, but they are expensive and the patients did not agree to pay for them. Nevertheless, 17% of our patients who were not allowed these drugs according to healthcare basket restrictions did receive them. Most of the SGLT2i and GLP1-RA agents were prescribed in association with other antidiabetic drugs. They were prescribed as a monotherapy in only 3% of the cases.

Aside from the healthcare basket restrictions, underuse in T2DM patients of SGLT2i and GLP1-RA drug classes is probably also because they are considered antidiabetic drugs by cardiologists and family physicians, who are reluctant to prescribe drugs that are not considered tools of their specialty. However, recent research has shown that, in addition to diabetic care, these drugs play an important role in reducing CVD in diabetic patients. Prevention and cure of CVD are part of a cardiologist's job. We do not hesitate to prescribe SGLT2i and GLP1-RA class drugs because they are also cardiac drugs.

SGLT2i drugs were used twice as frequently as GLP1-RA drugs, most probably due to patient preference for orally administered vs. injected medications and because they lower HbA1c values, as requested by the healthcare basket.

Table 2. Number of antidiabetic drugs prescribed as a single drug or in combination for antidiabetic drug-associated therapy

Drugs	Insulin	Metformin	DPP-4	GLP1	SGLT2i	S.urea	Repagl.	Acarb.	Pioglit.
Insulin	**31**	69	21	10	16	2	3	1	1
Metformin	69	**143**	69	13	27	18	3	2	3
DPP-4	21	69	**12**	2	7	4	1	1	2
GLP1	10	13	2	**1** (0.2%)	10	1	2	0	0
SGLT2i	16	27	7	10	**13** (3%)	2	0	1	1
S.urea	2	18	4	1	2	**2**	1	0	0
Repagl.	3	3	1	2	0	1	**9**	0	0
Acarb.	1	2	1	0	1	0	0	**1**	0
Pioglit.	1	3	2	0	1	0	0	0	**0**
Total	**154 (36%)**	**347 (81%)**	**119 (28%)**	**39 (9.1%)**	**77 (18%)**	**30 (7%)**	**19 (4.4%)**	**6 (1.4%)**	**7 (1.6%)**

Patient numbers are given with percentages in parentheses
Acarb. = acarbose, GLP1 = glucagon-like peptide-1, Pioglit. = pioglitazone A, Repagl. = repaglinide, SGLT2i = sodium-glucose cotransporter-2 inhibitor, S.urea = sulfonylurea Bold indicates antidiabetic drugs given as monotherapy

HbA1c ≤ 7 has been accepted as a reasonable goal for diabetic patients to decrease microvascular and prevent macrovascular complications [9]. HbA1c > 7 has been associated with severity of coronary artery disease [18]. Our results showed that T2DM was not adequately balanced in half of our patients.

Obesity is associated with an increased risk for T2DM [19] and it was reported in more than half of our patients. T2DM duration of > 10 years, which is known to be associated with subclinical atherosclerosis and left systolic and diastolic dysfunction in middle-aged patients [20], applied to more than half of our patients.

LIMITATIONS

Our study was confined to only our ambulatory clinics, and practices may vary at other ambulatory centers. Moreover, this study was retrospective, and some data were not available for analysis.

CONCLUSIONS

This snapshot of real-life contemporary clinical practice shows that GLP1-RA and SGLT2i drugs are administered more frequently than previously reported but are not yet sufficiently prescribed.

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Capsule

Autoantibodies help reveal cancer risk

Small-cell lung cancer (SCLC) is a major cause of cancer-related deaths. Effective early detection strategies for it are lacking. **Lastwika** and co-authors took advantage of a feature specific to SCLC to develop a candidate method for early detection. The authors developed a technique to identify targets of SCLC-associated autoantibodies, finding that many of the antibodies targeted disease-specific posttranslational modifications in extracellular proteins. The authors used these findings to generate a risk-prediction model using five autoantibody targets in combination with cigarette smoke consumption. This model was able to accurately predict disease in three independent cohorts, suggesting that circulating autoantibodies could provide an essential early detection method.

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