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Use of Dapagliflozin in Uncontrolled Type 2 Diabetes Patients: Non-Interventional Cohort Study at Outpatient Hospital Departments in Portugal

Utilização de Dapagliflozina em Doentes com Diabetes Tipo 2 Não Controlada: Estudo de Coorte Não Interventivo em Consultas Hospitalares Externas em Portugal

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Abstract

Introduction: Dapagliflozin improved glycemic control and cardiorenal endpoints in clinical trials in patients with and without type 2 diabetes *mellitus* (T2DM), but its real-world effect in Portuguese T2DM patients was not characterized.
Objectives: To describe the dapagliflozin effect over 12 months on HbA1c, body weight, and other cardiovascular (CV) risk outcomes.
Methods: Retrospective cohort study with T2DM adults followed at 10 Internal Medicine hospital departments, with HbA1c ≥ 6.5% and prescribed dapagliflozin as per clinical practice for at least 1 year. Changes in HbA1c, body weight, and other parameters were evaluated at 6 and 12 months, with paired t-test or Wilcoxon test ($\alpha = 0.05$).
Results: Eligible patients (n = 150) initiated dapagliflozin from Dec 2014–Nov 2019, were 61.2 ± 8.9 years, mostly male (59%) and non-smokers (60%). Most had T2DM for > 10 years (66%), hypertension (86%) and dyslipidemia (91%). About 30% of the patients had CV disease. Dapagliflozin was prescribed more frequently as ≥ 3rd antidiabetic agent (75%) and with other antidiabetics (91%), namely insulin (55%). At 12 months, statis-

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tically significant reductions were observed in HbA1c (-0.87%; 95%CI [-1.20, -0.55]) and body weight (-2.6kg; 95%CI [-3.4, -1.7]). Fasting glycemia, BMI, waist circumference, systolic BP, and HDL-C levels were also improved, with no adverse outcomes.
Conclusions: In a Portuguese real-world hospital setting, in T2DM patients with a high burden of disease and inadequate glycemic control, dapagliflozin was effective in the multifactorial management of T2D. Dapagliflozin was well tolerated and consistent with the well-established safety profile.

Keywords: type 2 diabetes *mellitus*; dapagliflozin; SGLT-2 inhibitors; heart failure; chronic kidney disease; cohort study; real-world

Resumo

Introdução: A dapagliflozina melhorou o controlo glicémico e os parâmetros cardiorrenais em estudos clínicos em doentes com e sem diabetes *mellitus* tipo 2 (DMT2), mas o seu efeito real em doentes portugueses com DMT2 não foi caracterizado.
Objetivos: Descrever o efeito da dapagliflozina, ao longo de 12 meses, sobre a HbA1c, peso corporal e outros fatores de risco cardiovascular (CV).
Métodos: Estudo de coorte retrospetivo em adultos com DMT2 seguidos em 10 departamentos hospitalares de Medicina Interna, com HbA1c ≥ 6,5% e tratados com dapagliflozina, prescrita de acordo com a prática clínica, há pelo menos 1 ano. Alterações da HbA1c, peso corporal e outros parâmetros foram avaliados aos 6 e aos 12 meses, com o teste- t emparelhado ou o teste de Wilcoxon (α = 0,05).
Resultados: Os doentes elegíveis (n = 150) iniciaram dapagliflozina entre dezembro de 2014 e novembro de 2019, tinham 61,2 ± 8,9 anos, a maioria eram do sexo masculino (59%) e não fumadores (60%). A maioria tinha DMT2 há > 10 anos (66%), hipertensão (86%) e dislipidemia (91%). Cerca de 30% dos doentes apresentavam doença CV. A dapagliflozina foi prescrita com maior frequência como ≥ 3º agente antidiabético (75%) e com outros antidiabéticos (91%), nomeadamente insulina (55%). Aos 12 meses, foram observadas reduções estatisticamente significativas da HbA1c (-0,87%; IC 95% [-1,20, -0,55]) e do peso corporal (-2,6kg; IC 95% [-3,4, -1,7]). A glicemia em jejum, o IMC, o perímetro abdominal, a PA sistólica e os níveis de C-HDL também melhoraram, sem resultados adversos.
Conclusões: Num ambiente português do mundo real (consultas hospitalares externas), em doentes com DMT2 com carga elevada de doença e controlo glicémico inadequado, a dapagliflozina foi eficaz no tratamento multifatorial da DMT2. A dapagliflozina foi bem tolerada e consistente com o seu perfil de segurança bem estabelecido.

Palavras-chave: diabetes *mellitus* tipo 2; dapagliflozina; inibidores do SGLT-2; insuficiência cardíaca; doença renal crónica; estudo de coorte; mundo real

> INTRODUCTION

Type 2 diabetes *mellitus* (T2DM) is a multifactorial chronic disease that results in hyperglycemia and increased cardiovascular (CV) risk. [1,2] T2DM patients frequently present additional risk factors, including overweight or obesity, thus requiring a management approach beyond glycemic control and centered on the reduction of overall CV risk. [1,3] T2DM patients frequently present CV complications, such as heart failure, stable angina, non-fatal myocardial infarction, peripheral arterial disease, and renal complications that all together may account for increased mortality. [4,5] Additionally, a recent retrospective cohort study, from a Portuguese Health Local Unit encompassing primary care units assisted by the same hospital, showed that the coexistence of heart failure or chronic kidney disease is associated with increased premature mortality as well as non-fatal CV events in T2DM patients under 65 years old. [6]

Diabetes *mellitus* affected 13.0% of Portuguese people aged between 20 and 79 years, in 2021, corresponding to an age-standardized prevalence of 9.1%, higher than the adjusted prevalence of the European region (7.0%) and the fourth highest after Turkey, Spain, and Andorra. [7] A national survey has estimated that 21.6% of adults were overweight and 36.5% were obese. [8]

Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) are oral blood glucose-lowering drugs that decrease renal glucose reabsorption. The increased urinary glucose excretion and subsequent loss of calories may contribute to the weight reduction that is not observed with other antidiabetic oral drugs such as dipeptidyl peptidase 4 inhibitors (DPP-4i). [2,9] SGLT-2i may also contribute to modest reductions in systolic blood pressure (BP) and potential improvement in the progression of renal disease. [10] Several meta-analyses of randomized clinical trials (RCT) suggested a protective effect of SGLT-2i against cardiovascular and kidney outcomes. [11–13] Moreover, several observational studies have examined the association between SGLT-2i and CV and renal outcomes, with most of these studies showing a reduced risk in comparison with other antidiabetic drugs. [14–18] Dapagliflozin is an SGLT-2i indicated in adults and children aged ≥ 10 years for the treatment of insufficiently controlled T2DM, as an adjunct to diet and exercise both as monotherapy (when metformin is considered inappropriate due to intolerance), or in addition to other glucose-lowering medicinal products (i.e., add-on combination therapy). Beyond diabetes treatment, this drug is also indicated for the treatment of heart failure with reduced ejection fraction and chronic kidney disease in patients with or without T2DM. [19,20] In recent years, real-

-world evidence is particularly useful as a complement to RCT data. To our best knowledge, no observational study of dapagliflozin use was conducted in Portugal, where T2DM control is an important outcome. [21] We aimed to describe the real-world use of dapagliflozin over 12 months in patients with T2DM, with a focus on the effect on glycated hemoglobin (HbA1c), body weight (BW), and other CV risk outcomes.

> MATERIALS AND METHODS

Study Design

This was a non-interventional, retrospective cohort study, to describe changes in HbA1c, BW, and other CV risk and laboratory outcomes in adult subjects with T2DM, at 6 months and 12 months after treatment initiation (index date) with dapagliflozin or dapagliflozin + metformin (fixed-dose combination). Study data were collected from medical records of outpatient diabetes clinics of the Internal Medicine departments among 10 public hospitals geographically distributed in mainland Portugal (6 in the North, 1 in the Center and 3 in Lisbon region) from Group I and II. The study was approved by the Ethics Committees of the participating hospital centers and complied with the Helsinki Declaration and European Legislation of Data Protection. All patients provided written informed consent before data collection.

Study Population

The study included T2DM patients aged ≥ 18 years followed at Portuguese hospitals, presenting inadequate glycemic control (defined as HbA1c ≥ 6.5%) at dapagliflozin initiation, and the latter must have occurred at least 12 months before recruitment (as per routine care and in compliance with the locally approved prescribing information). The study excluded patients: with type 1 or gestational diabetes, pregnant/breastfeeding women, with prior history of SGLT-2i use, with eGFR ≤ 60 mL/min/1.73 m2 or no documentation of eGFR > 60 mL/min/1.73 m2 at the index date, without medical visits at 6 [±1.5] months or 12 [±1.5] months after the index date, prescribed for weight loss medication (defined as any medication approved for the treatment of obesity/prescribed with the intent to promote weight loss at investigator discretion), or taking investigational drugs. Subjects were invited consecutively during routine diabetes medical visits. According to clinical practice and international recommendations it was expected that, after dapagliflozin initiation, each subject had at least one face-to-face medical appointment at 12 months and that most subjects had at least one additional assessment at 6 months.

Study Variables

Study variables included anthropometrics and sociodemographic characteristics, diabetes characteristics, other CV risk factors of interest (systolic and diastolic BP, smoking status, total cholesterol, HDL-C, LDL-C, triglycerides, first-degree family history of premature coronary heart disease), laboratory parameters (albumin excretion rate, eGFR, serum creatinine, uricemia), history of CV disease (i.e., coronary artery disease, cerebrovascular disease, peripheral vascular disease or heart failure), dapagliflozin treatment characteristics and safety, previous blood-glucose lowering drugs and concomitant medication. Study data were collected retrospectively for medical appointments occurring 6 [±1.5] months or 12 [±1.5] months after the index date. We considered the most recent laboratory results until 120 days before study visits.

Sample Size

Based on previous observational studies, [22–28] the most conservative estimates were related to change of BW, namely, a mean change ranging between -1.5 kg and -4.3 kg and a standard deviation (sd) up to 7.1 kg. Hence, assuming a mean change of -1.5 ± 7.1 kg, a total of 178 subjects with complete information at baseline and after 12 months of treatment would be required to reject the null hypothesis of response difference equals zero, with a power higher than 0.8 and a type I error probability of 0.05. Assuming that loss to follow-up / missing data would be up to 30%, a final sample of 254 subjects was determined.

Statistical Analysis

Descriptive analysis was performed for all study variables of the eligible dataset, i.e., patients who meet all inclusion criteria, did not meet any of the exclusion criteria, and signed informed consent. Changes from baseline were evaluated for HbA1c and BW, at 12 months (primary endpoints) and 6 months, as well as for BMI, waist circumference, fasting glycemia, systolic and diastolic BP, lipid profile, eGFR, and serum creatinine (secondary endpoints). Within-person absolute and percentual mean changes were evaluated with paired t-tests or Wilcoxon signed-rank tests when the normality assump-

tion was not verified. Sensitivity analyses on 12 months changes of HbA1c and BW were performed after imputation of missing data with the last observation carried forward (LOCF) method. The percentage and 95% confidence intervals (CI) of patients with HbA1c < 6.5% at 6 and 12 months were estimated, as well as the percentage of patients with simultaneous controlled HbA1c and any BW reduction. Bivariable analysis of HbA1c and BW percentual changes and baseline variables was performed with the t-test or the Mann-Whitney test (regarding dichotomous baseline variables), ANOVA or non-parametric Kruskal-Wallis test (if 3 or more categories) or the Pearson's r coefficient or the Spearman's coefficient (baseline numerical variables). To identify independent variables associated with percentual changes of HbA1c and BW from baseline to 12 months, multivariable linear regression models were performed including all variables with $p < 0.2$ in the bivariable analyses with optimization model done by the backward selection method. All tests were two-sided considering a significance level of 5%, and statistical analysis was performed in SAS® (version 9.4; SAS Institute Inc, Cary, USA).

> RESULTS

Patient Characteristics

A total of 238 patients from 10 centers were recruited between July 2020 and August 2021. The eligible dataset included 150 patients, with index dates between December 2014 and November 2019, of whom 107 had the 6-month visit and 124 had the 12-month visit (Figure 1). The primary analysis was performed for 114 patients regarding HbA1c change at 12 months and 109 patients for the change of BW at 12 months.

Eligible patients were aged between 40 and 81 years old, and 37.3% were 65 years or older; 58.7% were male, 60.2% never smoked and 66.2% had T2DM for more than 10 years (Table I). On average, patients had 1.0 ± 1.4 diabetic complications (ranging between 0 and 8). The most frequent were retinopathy (19.3%) and diabetic nephropathy (16.7%), followed by cerebrovascular disease (13.3%), neuropathy (11.3%), and coronary artery disease (10.7%). Approximately 9% of patients had heart failure. Most patients had other comorbidities 91.3% had dyslipidemia, 86.0% had hypertension and 30.0% had cardiovascular disease; six patients had a first-degree family history of premature coronary heart disease.

Description of Dapagliflozin Treatment and Concomitant Medication

More than half of the patients (56.7%) received dapagliflozin and 43.3% were on fixed-dose combination dapagliflozin + metformin (Table II). Most patients received dapagliflozin for at least 12 months after the index date

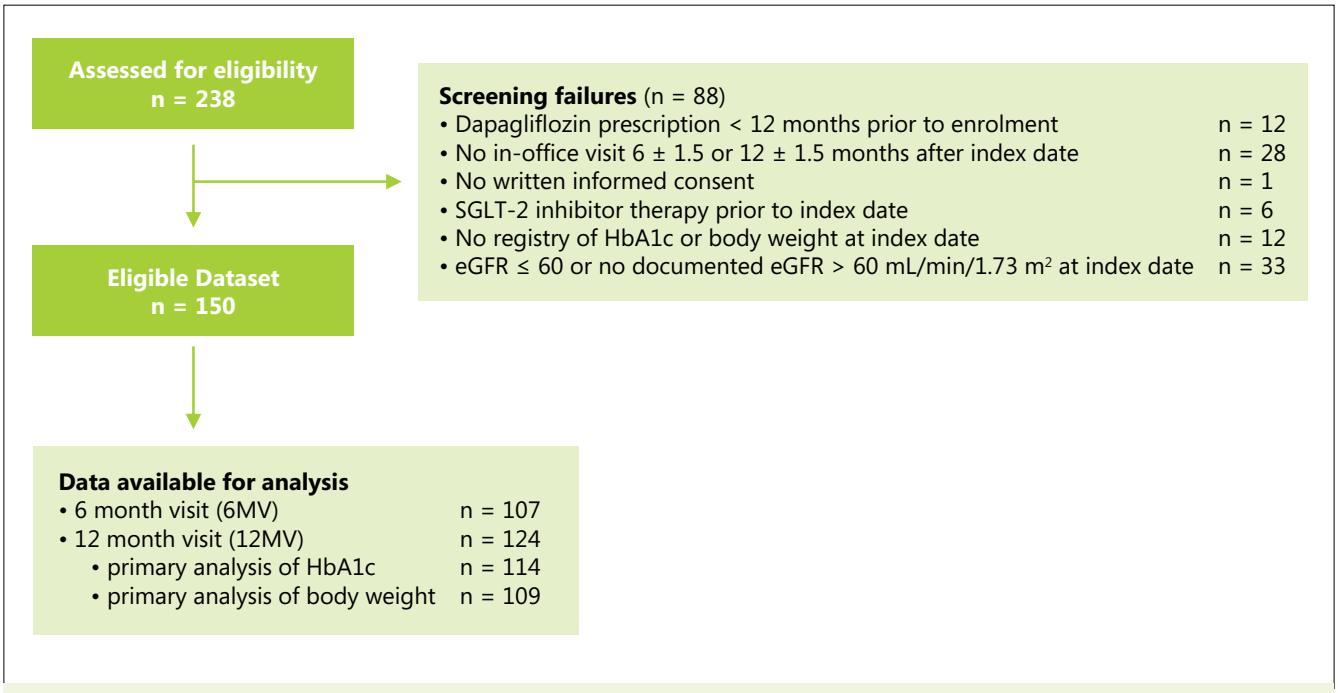

Figure 1 - Study flowchart.

Table I - Sociodemographic and clinical characteristics at baseline.

	Total (n=150)
Age at baseline (years), mean ± sd	61.2 ± 8.9
Male sex	88 (58.7%)
Smoking status [n=133]	
Never	80 (60.1%)
Former	40 (30.1%)
Current	13 (9.8%)
Diabetes duration [n=148]	[n=148]
<5 years	20 (13.5%)
≥5 and <10 years	30 (20.3%)
≥10 and <15 years	30 (20.3%)
≥15 and <20 years	31 (20.9%)
≥20 years	37 (25.0%)
Diabetes complications, mean ± sd	1.0 ±1.4
Retinopathy	29 (19.3%)
Diabetic nephropathy	25 (16.7%)
Neuropathy	17 (11.3%)
Cerebrovascular disease	20 (13.3%)
Coronary artery disease	16 (10.7%)
Heart failure	13 (8.7%)
Peripheral vascular disease	12 (8.0%)
Cardiovascular disease [a]	45 (30.0%)
Hypertension	129 (86.0%)
Dyslipidemia	137 (91.3%)
First-degree family members with a history of premature coronary heart disease [n=140]	6 (4.3%)

Values are the number (%) of patients, except otherwise mentioned.
[a] coronary artery disease, cerebrovascular disease, peripheral vascular disease, or heart failure

(n = 143, 95.3%). Treatment discontinuation was due to AEs (n = 4), physician indication (n = 2), and patient decision (n = 1). Seven patients switched between dapagliflozin options (of whom six changed to fixed combination dapagliflozin + metformin) and all had ongoing treatment for 12 months.

More than half of patients had prior treatment with insulin (56.0%) or metformin (54.0%). Prior use of DPP-4i combined with metformin (28.7% of the patients) or DPP-4i alone (28.0%), sulfonylurea (23.3%), glucagon-like peptide-1 receptor (GLP-1) agonist (18.0%) and

Table II - Medication history and changes during follow-up.

	n (%)	n
Study treatment		
Dapagliflozin	85 (56.7%)	
Dapagliflozin + Metformin	65 (43.3%)	
Study treatment line [n=149]		
1st line	1 (0.7%)	
2nd line	37 (24.8%)	
3rd line	63 (42.3%)	
>3rd line	48 (32.2%)	
Prior antidiabetic regimen [a]		Discontinued at index
Insulin	84 (56.0%)	15
Metformin alone	81 (54.0%)	23
DPP-4 inhibitor	42 (28.0%)	16
Sulfonylurea	35 (23.3%)	11
GLP-1 receptor agonist ± metformin	27 (18.0%)	7
Thiazolidinediones (glitazones)	3 (2.0%)	3
Other OADs	47 (31.3%)	12
DPP-4i + metformin	43 (28.7%)	10
Other OADs	6 (4.0%)	2
Monotherapy vs. Combined therapy for T2DM		
Monotherapy	16 (10.7%)	
Combination with other T2DM treatments	134 (89.3%)	
Concomitant medication during follow-up [a]	148 (98.7%)	
Blood glucose-lowering drugs	136 (90.7%)	Added / Stopped
Insulin	83 (55.3%)	6 / 7
Metformin alone	63 (42.0%)	2 / 2
GLP-1 receptor agonist	35 (23.3%)	9 / 3
DPP-4 inhibitor	31 (20.7%)	3 / 2
Fixed-Dose Combination	44 (29.3%)	
DPP-4 inhibitor + metformin	43 (28.7%)	2 / 4
Metformin, Other OAD	1 (0.7%)	1 / 2
Sulfonylurea	29 (19.3%)	5 / 6
Other OADs	2 (1.3%)	0 / 2
Antihypertensive drugs	123 (82.0%)	
Antidyslipidemic drugs	113 (75.3%)	
Both antihypertensive + antidyslipidemic drugs	91 (60.7%)	

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	n (%)	n
Changes to concomitant antidiabetics during follow-up [a]	54 (36.0%)	
Treatment intensification	36 (24.0%)	
Dose increased	22 (14.7%)	Insulin: 18 pts
Added another blood glucose-lowering drug(s)	19 (12.7%)	
Dose reduction	20 (13.3%)	Insulin: 14 pts
Discontinued concomitant blood glucose-lowering drug(s)	16 (10.7%)	
Switch of concomitant blood glucose-lowering drug(s)	7 (4.7%)	
Changes to dapagliflozin treatment		
Discontinued dapagliflozin	7 (4.7%)	
Switch between study treatments	7 (4.7%)	

n, number of patients. DPP-4, dipeptidyl peptidase 4. GLP-1, glucagon-like peptide-1. T2DM, type 2 diabetes mellitus. OADs, oral antidiabetic drugs (i.e., blood glucose-lowering drugs excluding insulin)
Percentages were calculated for the total of patients (n=150)
[a] More than one possible option.

thiazolidinediones (2.0%) were also reported, besides other options (4.0%).
Most patients received dapagliflozin treatment as 3rd line antidiabetic (42.3%) or > 3rd line options (32.2%).

Almost all patients (98.7%) were prescribed concomitant medication during follow-up, namely blood glucose-lowering drugs (90.7%), antihypertensives (82.0%), and antidyslipidemic agents (75.3%). Having only metformin as concomitant antidiabetic was observed in 10 (6.7%) patients. Changes to the antidiabetic regimen prescribed at the index date occurred in 36.0% of the patients, and 24.0% had a treatment intensification. Most changes were related to insulin treatment, which was added in 6 patients (7.2% of insulin users) and 18 (21.7%) had dose increases while being reduced in 14 patients (16.9%) and stopped in 7 (8.4%). Initiation of GLP-1 agonists was observed in 6% of total patients.

Treatment Outcomes During Follow-up

HbA1c and Fasting Plasma Glucose

The HbA1c values showed statistically significant mean reductions of -0.92% (95% CI [-1.25, -0.60]) at 6 months and -0.87% (95% CI [-1.20, -0.55]) at 12 months (Table III). These absolute reductions corresponded to changes of -9.1 percentual points (95%CI [-12.2, -5.9]; $p < 0.0001$) and -8.5 percentual points (95% CI [-11.7, -5.3]; $p < 0.0001$) at 12 months (Figure 2). The LOCF sensitivity analysis estimated a mean percentual reduction of -9.2% (95% CI [-11.9, -6.5]; $p < 0.0001$). The proportion

Table III - Changes in clinical outcomes, from baseline to 6 and 12 months of treatment.

		N	Mean ± sd	Percentual change from baseline: Mean [95%CI]	p-value
HbA1c (%)	baseline	150	8.5 ± 1.5	--	--
	Δ 6M	102	-0.9 ± 1.7	-9.06 [-12.21; -5.91]	PT: <0.0001
	Δ 12M	114	-0.9 ± 1.8	-8.50 [-11.68; -5.32]	PT: <0.0001
	Δ 12M*	147	-0.9 ± 1.7	-9.17 [-11.86; -6.48]	PT: <0.0001
Body weight (kg)	baseline	150	85.7 ± 17.6	--	--
	Δ 6M	99	-3.0 ± 3.8	-3.31 [-4.13; -2.49]	WC: <0.0001
	Δ 12M	109	-2.6 ± 4.5	-2.80 [-3.75; -1.85]	WC: <0.0001
	Δ 12M*	138	-2.6 ± 4.3	-2.84 [-3.64; -2.04]	WC: <0.0001
BMI (kg/m^2)	baseline	130	31.6 ± 5.1	--	--
	Δ 6M	89	-1.1 ± 1.4	-3.34 [-4.20; -2.48]	WC: <0.0001
	Δ 12M	97	-1.0 ± 1.7	-3.04 [-4.05; -2.02]	PT: <0.0001
waist circumference (cm)	baseline	54	107.0 ± 12.1	--	--
	Δ 6M	24	-3.8 ± 6.8	-3.35 [-5.63; -1.07]	WC: 0.001
	Δ 12M	26	-3.0 ± 4.3	-2.84 [-4.52; -1.16]	PT: 0.002

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		N	Mean ± sd	Percentual change from baseline: Mean [95%CI]	p-value
FPG (mg/dl)	baseline	128	177.6 ± 59.8	--	--
	Δ 6M	77	-38.2 ± 76.5	-13.35 [-21.47; -5.22]	PT: 0.002
	Δ 12M	88	-29.3 ± 61.2	-10.64 [-17.38; -3.91]	PT: 0.002
systolic BP (mmHg)	baseline	141	143.5 ± 20.4	--	--
	Δ 6M	94	-6.1 ± 20.4	-3.11 [-5.90; -0.32]	WC: 0.008
	Δ 12M	101	-5.2 ± 21.0	-2.36 [-5.19; 0.46]	WC: 0.029
diastolic BP (mmHg)	baseline	141	78.2 ± 11.0	--	--
	Δ 6M	94	-1.0 ± 11.7	-0.19 [-3.35; 2.97]	WC: 0.358
	Δ 12M	101	-1.6 ± 12.3	-0.82 [-3.92; 2.27]	PT: 0.599
HDL-C (mg/dl)	baseline	124	44.7 ± 12.9	--	--
	Δ 6M	67	0.4 ± 8.1	2.73 [-1.51; 6.98]	WC: 0.366
	Δ 12M	81	1.5 ± 8.6	6.09 [1.57; 10.61]	WC: 0.043
LDL-C (mg/dl)	baseline	121	93.8 ± 36.7	--	--
	Δ 6M	66	-1.3 ± 31.8	1.31 [-6.18; 8.79]	PT: 0.729
	Δ 12M	78	-2.9 ± 34.6	3.29 [-3.77; 10.34]	PT: 0.356
total cholesterol (mg/dl)	baseline	123	166.7 ± 42.5	--	--
	Δ 6M	71	-2.8 ± 40.0	0.38 [-4.82; 5.58]	WC: 0.923
	Δ 12M	81	-4.2 ± 41.3	0.09 [-4.54; 4.71]	PT: 0.970
triglycerides (mg/dl)	baseline	123	165.5 ± 103.4	--	--
	Δ 6M	70	-2.3 ± 115.1	7.94 [-5.95; 21.83]	WC: 0.928
	Δ 12M	80	-5.9 ± 79.6	5.92 [-7.42; 19.25]	WC: 0.559
eGFR (mL/min/1.73 m²)	baseline	150	91.2 ± 23.0	--	--
	Δ 6M	82	-3.7 ± 15.5	-3.06 [-6.60; 0.47]	WC: 0.016
	Δ 12M	96	-2.6 ± 15.3	-1.88 [-5.48; 1.72]	WC: 0.105
serum creatinine (mg/dl)	baseline	144	0.8 ± 0.2	--	--
	Δ 6M	79	0.0 ± 0.1	4.42 [1.28; 7.57]	WC: 0.011
	Δ 12M	94	0.0 ± 0.2	2.09 [-1.73; 5.91]	PT: 0.281

sd, standard deviation. 95%CI, 95% confidence interval. BMI, Body Mass Index. BP, blood pressure. WC, Wilcoxon signed-rank test. PT, Paired t-test.Δ 6 (12) M, change at 6 (12) months. * After imputation of missing data (last observation carried forward).

of patients with HbA1c ≥ 9% also decreased from 33.3% at baseline to 12.7% and 9.6% at 6 and 12 months, respectively (Figure 3). The proportion of patients with HbA1c < 6.5% was 15.7% (95% CI [9.2, 24.2]; n = 16) at 6 months and 13.2% (95% CI [7.6, 20.8]; n = 15) at 12 months. Fasting glycemia had a statistically significant change of -10.6 percentual points (95% CI [-17.4, -3.9]; *p* = 0.002) at 12 months.

The HbA1c percentual change at 12 months was statistically associated with baseline variables (Table IV), namely: smoking habits (current smokers showed a mean increase of 3.2%, compared to the mean reduction of -10.3% among non-smokers ever and of -8.9% for former smokers), previous use of GLP-1 agonists (-1.0% *vs.* -9.9% for no previous users), and previous use of metformin alone (mean reduction of -5.5% *vs.* -12.2% for

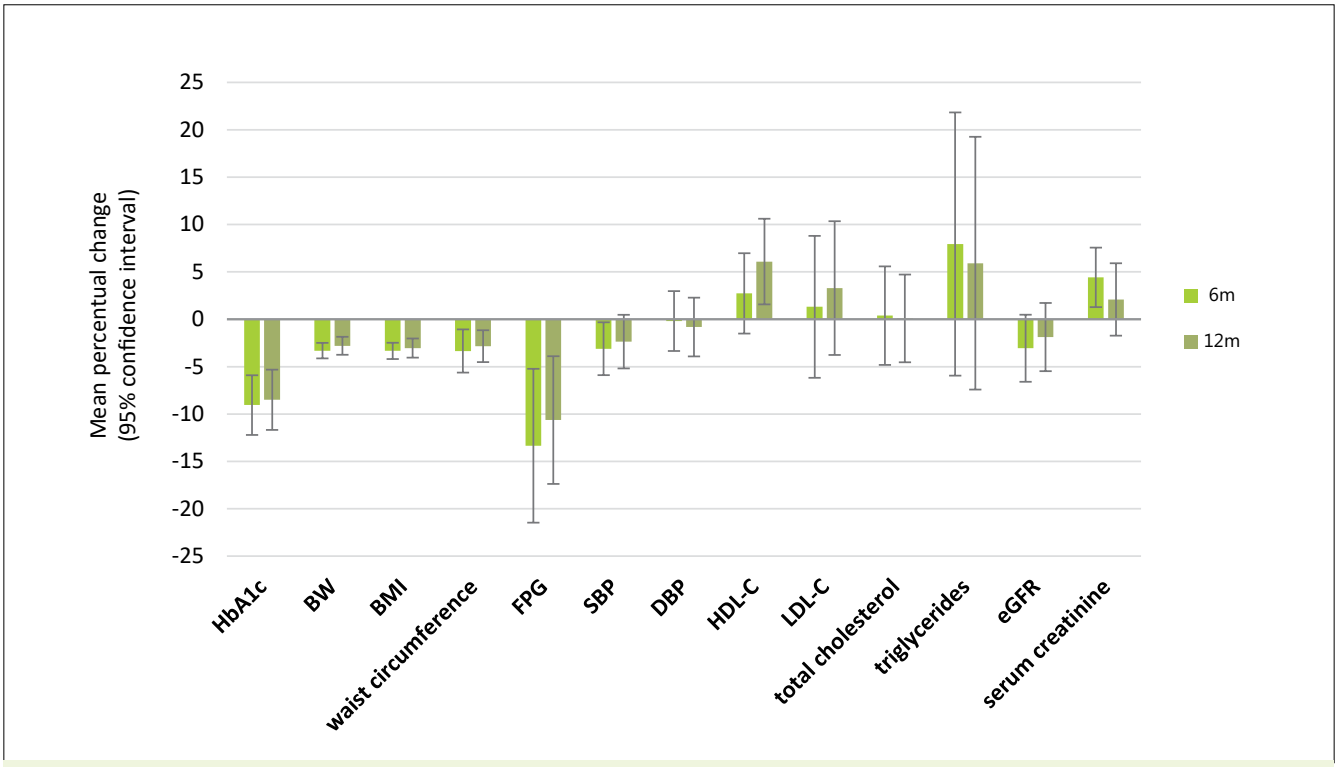

Figure 2 - Mean percentual change from baseline, at 6-month and 12-month visits.

non-users/users of fixed-dose combinations). Higher baseline values of LDL-C and triglycerides were statistically correlated with lower percentual changes of HbA1c from baseline to 12 months (r_s = -0.19 and r_s = -0.23, both weak correlations). After adjustment, patients who had previously taken metformin alone had a statistically lower reduction of HbA1c at 12 months by 8.4 percentual points (95% CI [1.5, 15.3]; p = 0.016) compared to non-users/users of fixed-dose combinations.

Body Weight, Body Mass Index, and Waist Circumference

Body weight showed statistically significant mean reductions of -3.0kg (95% CI [-3.7, -2.2]) at 6 months, and -2.6kg (95% CI [-3.4, -1.7]) at 12 months (Table III). These absolute reductions corresponded to changes of -3.3 percentual points (95% CI [-4.1, -2.5]; p < 0.0001) at 6 months and -2.8 percentual points (95% CI [-3.8, -1.9]; p < 0.0001) at 12 months (Figure 2). A similar result was obtained with LOCF sensitivity analysis, of -2.8 percentual points (95% CI [-3.6, -2.0]). Additionally, combined BW reduction and HbA1c < 6.5% were observed for 13.5% of patients (95% CI [7.4, 22.0]; n = 13) at 6 months and 11.9% (95%CI [6.3, 19.8]; n = 12) at 12 months. At baseline, 61.5% of the patients were obese and 32.3% were overweight, while at 12 months, these proportions were 46.4% and 47.4%, respectively (Figure 3). At 12 months, statistically significant mean changes were observed for BMI (-3.0 percentual points) and waist circumference (-2.9 percentual points).

Blood Pressure and Lipid Profile

At baseline, the systolic/diastolic BP mean values were 143.5/78.2 mmHg. Systolic BP presented statistically significant reductions of -6.1mmHg (95% CI [-10.3, -1.9]; p = 0.008) at 6 months and -5.2mmHg (95% CI [-9.4, -1.1]; p=0.029) at 12 months (Table III). Diastolic BP showed no statistically significant changes during follow-up.
The mean lipid values at baseline were 44.7 mg/dl (HDL-C), 93.8 mg/dl (LDL-C), 166.7 mg/dl (total cholesterol), and 165.5 mg/dl (triglycerides). A statistically significant increase of 6.1% in HDL-C values was observed from baseline to 12 months. In all study time points, the majority of patients reported normal values for lipid profile, namely at 12 months: 61.8% (HDL-C), 68.6% (LDL-C), 71.1% (total cholesterol), and 63.3% (triglycerides) – Figure 3. No changes on antihypertensive and antidyslipidemic drugs were observed during follow-up period.

Figure 3 - Distribution of patients by categories of HbA1c (A), BMI (B), and laboratory parameters (C), at baseline and during follow-up.

Table IV - Baseline variables associated with the percentual change of HbA1c at 12 months.

		n	Percentual change: mean ± sd	p-value [a]	Linear Regression: initial model	
					β [95%CI]	p-value
Sex	Male	65	-7.4 ± 16.9	0.419		
	Female	49	-10.0 ± 17.5			
Smoking status	Never	60	-10.9 ± 15.8	**0.040** *	Ref.	-
	Former	29	-5.9 ± 19.4		5.24 [-2.78; 13.26]	0.185
	Current	10	2.0 ± 13.9		11.63 [-1.19; 24.46]	0.046
Diabetes duration	<5 years	19	-14.7 ± 23.3	0.166‡	-12.96 [-24.52; -1.41]	0.020
	[5-10[years	21	-7.3 ± 11.6		-7.88 [-19.01; 3.26]	0.142
	[10-15[years	23	-9.4 ± 16.7		-7.97 [-18.92; 2.97]	0.132
	[15-20[years	23	-10.8 ± 14.5		-9.97 [-20.96; 1.02]	0.062
	≥20 years	28	-2.5 ± 17.4		Ref.	-
Retinopathy	Yes	20	-11.3 ± 15.7	0.428		
	No	94	-7.9 ± 17.5			
Neuropathy	Yes	13	-4.8 ± 18.0	0.413		
	No	101	-9.0 ± 17.1			
Peripheral vascular disease	Yes	9	-0.3 ± 9.0	na		
	No	105	-9.2 ± 17.5			
Cerebrovascular disease	Yes	15	-11.2 ± 24.6	0.645		
	No	99	-8.1 ± 15.8			
Coronary artery disease	Yes	15	-5.4 ± 21.2	0.452		
	No	99	-9.0 ± 16.5			
Heart failure	Yes	12	-9.0 ± 17.8	0.592†		
	No	102	-8.4 ± 17.1			
Diabetic nephropathy	Yes	20	-10.9 ± 17.5	0.486		
	No	94	-8.0 ± 17.1			
Cardiovascular disease	Yes	36	-9.0 ± 17.8	0.830		
	No	78	-8.3 ± 16.9			
Hypertension	Yes	99	-7.9 ± 17.3	0.332		
	No	15	-12.5 ± 16.0			
Dyslipidemia	Yes	104	-8.9 ± 16.0	0.610		
	No	10	-4.3 ± 26.9			
Prior Insulin	Yes	64	-8.8 ± 17.4	0.820		
	No	50	-8.1 ± 17.0			
Prior DPP-4i	Yes	37	-4.9 ± 17.3	0.216†		
	No	77	-10.2 ± 16.9			

(continues)

(continuation)

		n	Percentual change: mean ± sd	p-value [a]	Linear Regression: initial model	
					β [95%CI]	p-value
Prior Sulfonylurea	Yes	27	-12.5 ± 13.8	0.065†	-2.31 [-10.60; 5.99]	0.568
	No	87	-7.3 ± 17.9		Ref.	-
Prior GLP-1 agonist	Yes	19	-1.0 ± 15.5	**0.047†**	5.18 [-4.71; 15.07]	0.274
	No	95	-10.0 ± 17.1		Ref.	-
Prior Metformin alone	Yes	63	-5.5 ± 16.2	**0.036**	6.29 [-0.98; 13.56]	0.087
	No	51	-12.2 ± 17.7		Ref.	-
Dapagliflozin		69	-10.1 ± 16.4	0.182†	1.84 [-5.29; 8.96]	0.608
Dapagliflozin + Metformin		45	-6.1 ± 18.1		Ref.	-
		n	**Correlation coefficient**	**p-value [b]**	**β [95%CI]**	**p-value**
Age at baseline (years)		114	0.04	0.703*		
Duration of prior antidiabetic (months)	14	0.15	0.604			
Body weight		114	0.14	0.146	0.07 [-0.12; 0.26]	0.481
Body Mass Index		99	0.05	0.604		
Waist circumference	39	0.07	0.674			
Systolic Blood Pressure		105	0.11	0.278		
Diastolic Blood Pressure		105	-0.02	0.815		
HDL-C		114	0.09	0.359		
LDL-C		114	-0.19	**0.040**	0.00 [-0.01; 0.02]	0.882
Total cholesterol		114	-0.13	0.169		
Triglycerides		114	-0.23	**0.016**	-0.01 [-0.02; 0.01]	0.464
eGFR		114	-0.01	0.925		
Serum creatinine		109	0.04	0.709		

na, not applicable. 95%CI, 95% confidence interval. sd, standard deviation. Ref., reference category
[a] p-values are from t-test except for * Kruskal-Wallis, ‡ ANOVA, and †Mann-Whitney test
[b] p-values of correlation coefficients are from Spearman correlation, except * Pearson correlation

Renal Function

Statistically significant changes were observed from baseline to 6 months for eGRF (-3.1 percentual points) and serum creatinine (4.4 percentual points) but not from baseline to 12 months (Table III). During the study, most patients reported normal values of eGRF (baseline mean value of 91.2 mL/min/1.73m^2), serum creatinine, albumin excretion rate, and uricemia (Figure 3).

Safety of Dapagliflozin Treatment

The present study showed a safety profile generally consistent with what was observed in clinical trials. A total of 74 adverse events (AE) were registered for approximately one-quarter of patients (n = 37; 24.7%). The most common AEs (i.e., reported for ≥ 2.0% of patients) were dyslipidemia worsening [4 AEs reported in 4 (2.7%) patients] and genital fungal infection [3 AEs reported in 3 (2.0%) patients]. Thirteen patients (8.7%) experienced 17 AEs related to treatment, of whom 4 patients (2.7%) were discontinued from treatment with 6 AEs (genital infection, vulvovaginitis, asthenia, hematuria, suprapubic pain, and intolerance/undefined). Genital fungal infection was the most common AE related to treatment [3 AEs reported by 3 (2.0%) patients]. ST-elevation myo-

cardial infarction was the only serious adverse event reported in one patient, not related to treatment and without requiring treatment discontinuation.

> DISCUSSION

At 12 months after initiation of dapagliflozin treatment, we observed a statistically significant improvement in HbA1c and fasting glycemia, BW, BMI, and waist circumference, as well as systolic BP and HDL-C levels. The results of our retrospective cohort study at the hospital level are in line with previous RCTs, which demonstrate dapagliflozin efficacy in patients with T2DM with inadequate glycemic control both in monotherapy and while taking other blood glucose-lowering drugs. [29–33] We observed a mean reduction of HbA1c at both 6 and 12 months of approximately -0.9%, within the range of other observational studies (between -0.7% and -1.1%). [22–28] The results at 12 months seem to indicate a stable effect of dapagliflozin over time, independent of baseline sociodemographic characteristics, complications, and CV risk factors variables, although a lower reduction was observed among users of prior metformin alone, compared to non-users of metformin or users of fixed-dose combinations. The mean reduction in BW (approximately -2.6 kg) was also within the range reported by RCTs (between 2 and 3 kg), and other observational results. [22–28]

The target of controlled T2DM should be defined on a case basis, considering factors like risk of hypoglycemia, life expectancy, comorbidities, CV disease, and patient's preference. [34–36] Guidelines now recommend the use of at least one GLP-1 or SGLT-2i drug in diabetic patients with high CV risk, regardless of the glycemic target. [34–36] Dapagliflozin have demonstrate to reduce the rates of cardiovascular death or hospitalization for heart failure in T2DM patients at risk for atherosclerotic disease or established cardiovascular disease. [17,38–40] We observed a reduction of patients with very poor glycemic control (HbA1c > 9.0%), from 33% at baseline to less than 10% after 12 months. In addition, 16% of the patients achieved HbA1c < 6.5%, suggesting better glycemic control.

In our cohort, most patients have been prescribed dapagliflozin as a third-line therapy or higher, which can be partially explained by barriers to access, since dapagliflozin was a newer treatment at that time and only approved for the treatment of T2DM during the observation period. However, we also acknowledge that our cohort, selected from internal medicine departments, comprises patients with a higher burden of disease and CV risk, and poorer glycemic control despite prior use of other blood glucose-lowering drugs, which justified their referral from primary care. Most of the patients presented dyslipidemia, the vast majority were hypertensive and almost a third of patients presented CV disease, defined as a history of coronary artery disease, cerebrovascular disease, peripheral vascular disease, or heart failure. We observed reductions in systolic BP similar to what has been reported. [24,26,28] A network meta-analysis indicated that SGLT-2i conferred reductions both in BW and BP which remain sustainable after one year of treatment. [9] There were no statistically significant changes in LDL-C, total cholesterol, or triglycerides, probably due to the vast majority of patients (about 75%) having concomitant antidyslipidemic drugs. Nevertheless, an improvement in HDL-C was observed, which can be related to BW reduction.

Dapagliflozin is a highly selective and reversible SGLT-2i, reducing glucose reabsorption in the proximal renal tubule with a subsequent increase in glycosuria. [29] This mechanism explains its association with urinary tract infections and genital infections, [39,40] the latter being the most frequent AEs attributed to dapagliflozin in our study which is consistent with RCTs' findings. [22–28] Of notice, only four patients had treatment interruption due to AEs, highlighting the good safety profile of dapagliflozin.

Most patients were already treated with other concomitant antidiabetics, with more than 50% having prior and concomitant treatment with insulin. Dapagliflozin can be safely initiated in combination with other oral agents or insulin, as the mechanism of action is not related to insulin secretion or resistance as other antidiabetic drugs. [29,32] Most of the treatment changes during follow-up were related to insulin treatment and, despite we did not collect insulin daily dose, we observed similar proportions of patients having insulin intensification and patients who stopped/reduced dose. RCTs have reported that dapagliflozin stabilizes insulin doses, reducing up to -13.3% of total daily dose by 12 months. [33,41] On the other hand, the number of patients with increased doses of insulin may be related to the improvement in glycemic lability which allowed for a more secure increase in basal insulin. In fact, an effect of SGLT-2i was observed in the improvement of β-cell response to glucose and incretin hormones in patients with inadequately controlled T2DM. [42,43]

Most patients were on dapagliflozin treatment at 12 months, a much higher proportion compared to other estimates which ranged between 44.3% and 72.1%. [44] This may be explained by the clinical context of included patients, with fewer factors associated with poorer persistence, e.g., female sex, higher baseline HbA1c, fasting glycemia, and eGFR, and less common use of metformin. [45]

The reduction of heart failure hospitalization risk reported in the DECLARE TIMI 54 study prompted additional RCTs to evaluate if this dapagliflozin effect. The DAPA--HF study was a phase 3 placebo-controlled trial with 4744 patients with heart failure and a reduced ejection fraction, with or without T2DM, followed for a median of 18.2 months. [46] The results showed that dapagliflozin reduced the risk of worsening heart failure or CV death by 26% compared to the placebo group (hazard ratio 0.74; 95% CI, 0.65 to 0.85). Supported by this evidence, dapagliflozin is approved for the treatment of symptomatic chronic heart failure with reduced ejection fraction. [19] It is also approved for the treatment of chronic kidney disease irrespective of diabetes diagnosis, based on the results of the DAPA-CKD trial which reported a lower risk of disease progression (hazard ratio 0.56; 95% CI, 0.45 to 0.68), as well as a smaller mean annual decrease in eGFR than the placebo group. [47] An initial eGRF statistically reduction of -3.1% at 6 months was observed, although we did not find a significant reduction of eGFR at 12 months.

Changes in Study Conduct due to COVID-19 Pandemic and Other Limitations

Each subject was expected to have at least one face-to--face medical appointment approximately 12 months after dapagliflozin initiation, and it was expected that most subjects would have had at least one additional assessment (at 6 months), according to clinical practice at the time of study initiation. However, the study was conducted during the COVID-19 pandemic which affected data availability (e.g., laboratory parameters) required for analysis of study outcomes. About 20% of the patients had their follow-up when lockout measures were implemented, which impacted the number of in-office medical appointments, as well as the availability of centers' staff to collect study data. Patient recruitment was also affected as the main reasons for screening failures were related to missing laboratory results to confirm eligibility and lack of routine medical visits up to 14 months after the index date. For that reason, a time window of study visits was allowed and complemented with an LOCF analysis of the primary endpoints, besides the decision to analyze only patients with at least one visit within the protocol-defined time windows. Missing information is a recognized limitation of retrospective studies, affecting mostly the availability of some laboratory and safety variables. In addition, the lack of a comparator arm does not allow a comparison with other antidiabetic drugs. Even so, observational studies are key to providing information about drug effectiveness, since RCTs include more selected populations than the real users.

> CONCLUSION

In Portuguese real-world hospital practice, after 12 months of treatment of T2DM patients with a high burden of disease and inadequate glycemic control followed in Internal Medicine Departments, dapagliflozin was effective in the multifactorial management of T2DM. HbA1c, BW, BMI, and systolic BP, significantly decreased and reported adverse events were consistent with the well-established safety profile of dapagliflozin. These findings and the RCT's evidence of benefit for patients with heart failure or chronic kidney disease highlight the relevancy of dapagliflozin as a cardio and renal protective agent in the context of T2DM management in Portugal. <

Conflicts of interests/*Conflitos de Interesses:*
J.C., M.C.R., C.C., J.B. and L.A. declares no conflicts of interest. P.C.G. declares speaker fees from AstraZeneca, Bayer, Bial and Novo Nordisk. S.H. declares speaker fees from Ascencia, AstraZeneca, Bayer, Bial, Boehringer-Ingelheim, Lilly, MSD, Novartis, Novo Nordisk, Pfizer, and Viartris and consulting fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Lilly, and Novo Nordisk. Z.L. declares speaker fees from AstraZeneca, and Novo Nordisk and has received research funding from AstraZeneca. P.S. declares speaker fees from AstraZeneca, Boehringer-Ingelheim, MSD, Novartis, Novo Nordisk, MEDINFAR, Bial, and LifeScan and declares consulting fees from AstraZeneca. E.P. declares speaker fees from Abbott, AstraZeneca, Boehringer--Ingelheim, Lilly, MSD, Novo Nordisk and Roche. R.M. declares speaker fees from AstraZeneca and Novo Nordisk. J.C., M.P., H.M., and F.B. are employees of AstraZeneca, Produtos Farmacêuticos SA. M.F. is an employee of CTI, a CRO that provides services for AstraZeneca and other pharmaceutical companies./*J.C., M.C.R., C.C., J.B. e L.A. declaram não haver conflitos de interesses. P.C.G. declara honorários de palestrante da AstraZeneca, Bayer, Bial e Novo Nordisk. S.H. declara honorários de palestrante da Ascencia, AstraZeneca, Bayer, Bial, Boehringer-Ingelheim, Lilly, MSD, Novartis, Novo Nordisk, Pfizer e Viartris e honorários de consultoria da AstraZeneca, Bayer, Boehringer-Ingelheim, Lilly e Novo Nordisk. Z.L. declara honorários de palestrante da AstraZeneca e Novo Nordisk e recebeu financiamento de pesquisa da AstraZeneca. PS declara honorários de palestrantes da AstraZeneca, Boehringer-Ingelheim, MSD, Novartis, Novo Nordisk, MEDINFAR, Bial e LifeScan e declara honorários de consultadoria da AstraZeneca. E.P. declara honorários de palestrantes da Abbott, AstraZeneca, Boehringer-Ingelheim, Lilly, MSD, Novo Nordisk e Roche. R.M.*

declara honorários de palestrante da AstraZeneca e Novo Nordisk. J.C., M.P., H.M. e F.B. são funcionários da AstraZeneca, Produtos Farmacêuticos SA. M.F. é funcionário da CTI, uma CRO que presta serviços para a AstraZeneca e outras empresas farmacêuticas.

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Author Contributions/*Contribuições dos Autores:*
All authors made significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation. All authors revised the article and gave final approval of the version to be submitted./*Todos os autores deram contribuição significativa para o trabalho relatado, seja na conceção, desenho do estudo, execução, aquisição de dados, análise e interpretação. Todos os autores reveram o artigo e aprovaram a versão final a ser submetida*

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