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Economic evaluation of canagliflozin versus glimepiride and sitagliptin in dual therapy with metformin for the treatment of type 2 diabetes in Italy

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ABSTRACT

Purpose: To assess the treatment costs (direct medical costs) of canagliflozin versus glimepiride or sitagliptin 100 mg in patients with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin from the perspective of the Italian National Health Service.

Methods: A cost-minimization analysis (CMA) was conducted to compare the mean annual costs for a patient with T2DM treated with canagliflozin 100 or 300 mg, glimepiride (mean dose of 5.6 mg), or sitagliptin 100 mg. Two models were constructed to compare canagliflozin versus glimepiride and canagliflozin versus sitagliptin. Both models estimated annual patient costs using data from two clinical trials. In both models, only direct medical costs (antidiabetic drugs, concomitant drugs, hospitalizations, hypoglycemic events, glycemic control, genital mycotic infections, and weight) were considered. Italian costs were drawn from the literature and local sources. Uncertainty was assessed by deterministic sensitivity analyses and threshold analyses.

Results: Canagliflozin 100 and 300 mg were associated with lower expected costs (€2,785.46 and €2,979.52, respectively) versus glimepiride (€3,167.90). In the second comparison, canagliflozin 100 or 300 mg were also associated with lower expected costs (€2,820.05 and €3,013.96, respectively) versus sitagliptin 100 mg (€3,030.38). Sensitivity analyses generally supported the base case findings.

Conclusions: This CMA showed that treatment with canagliflozin 100 or 300 mg is a cost-saving strategy compared with glimepiride or sitagliptin 100 mg in patients with T2DM inadequately controlled with metformin from the perspective of the Italian National Health Service.

Keywords: Canagliflozin, Cost-minimization analysis, Glimepiride, Italy, Sitagliptin, Type 2 diabetes mellitus

Introduction

Surging obesity, an aging population, and increasingly sedentary lifestyles have led to a progressive worldwide increase in the observed prevalence of diabetes mellitus (1). Data from the 2013 Italian National Institute of Statistics (ISTAT) statistical yearbook indicated that >3 million people, or 5.4% of the Italian population (women, 5.3%; men, 5.6%), have diabetes (2). The prevalence of diabetes increases with age; at least 1 in 5 people ≥75 years of age has diabetes. Compared with the previous decade, in the past 10 years the number of people with diabetes has grown by 800,000 (3); in fact, from 2000 to 2011, the prevalence of diabetes in Italy increased from 3.9% to 4.6% (3). While the prevalence of diabetes in the adult population (≥18 years of age) in Italy was 5.8% between 2000 and 2011, it reached 15.2% among obese adults (3).

Approximately 90% of people with diabetes have type 2 diabetes mellitus (T2DM) (3). Hyperglycemia treatment in T2DM starts with education on eating habits, physical exercise, and a balanced diet aiming at reducing body weight, particularly in obese individuals. Lifestyle changes remain the backbone of therapy, even after pharmacological intervention is initiated (4, 5). International guidelines recommend starting pharmacological treatment with metformin from 500 to 2,500 mg per day (4). Other medications can be added to metformin when additional glycemic control is needed (5-8). However, some of these medications may have negative effects, such as weight gain and increased hypoglycemia risk (5).

Therefore, there is a need for medications capable of providing adequate control of glycemia and body weight, as well as low risk of hypoglycemia episodes. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of medications for the treatment of adults with T2DM that lower blood

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glucose by increasing urinary glucose excretion (UGE) via an insulin-independent mechanism that is complementary to other classes of diabetes medications (9). Increased UGE also results in a mild osmotic diuresis and a net loss of calories, thus resulting in weight loss and blood pressure reduction (9). In contrast, dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, sitagliptin) lower blood glucose but are not associated with weight loss or blood pressure reduction, and sulfonylureas (eg, glimepiride) are associated with weight gain and hypoglycemia (5).

Canagliflozin is an SGLT2 inhibitor developed for the treatment of T2DM (10). In patients with T2DM inadequately controlled with metformin, canagliflozin has demonstrated significant reductions in glycated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), body weight, and blood pressure, with a low frequency of hypoglycemia (10). Canagliflozin 100 mg demonstrated non-inferiority in HbA_{1c} lowering and canagliflozin 300 mg demonstrated superiority in HbA_{1c} lowering as add-on to metformin versus either glimepiride or sitagliptin 100 mg at 52 weeks (11, 12). Canagliflozin 100 and 300 mg were generally well tolerated compared with either glimepiride or sitagliptin 100 mg, with similar incidence of overall adverse events (AEs) and AE-related discontinuations observed across groups (11, 12).

The objective of this analysis is to evaluate whether treatment of a patient with T2DM with canagliflozin 100 or 300 mg compared with either a sulfonylurea (glimepiride) or a DPP-4 inhibitor (sitagliptin) as dual therapy add-on to metformin, would lead to a more efficient allocation of the resources available to the Italian National Health Service.

Materials and methods

Treatments

For this financial evaluation, 1 sulfonylurea (glimepiride) and 1 DPP-4 inhibitor (sitagliptin) were chosen based on the availability of clinical trials directly comparing these medications to canagliflozin and because they are more commonly used in Italian clinical practice.

Clinical data

A search of the medical literature was conducted to identify all clinical studies that had directly (head-to-head) compared canagliflozin with glimepiride and/or sitagliptin. This PubMed search was limited to works published in English between January 2012 and September 2015, and used the following keyword combinations: 1) "canagliflozin" and "glimepiride" and "type 2 diabetes" and "inadequately controlled with metformin"; 2) "canagliflozin" and "sitagliptin" and "type 2 diabetes" and "inadequately controlled with metformin".

According to these criteria, 2 articles comparing canagliflozin with glimepiride (12, 13) and 7 articles comparing canagliflozin with sitagliptin (11, 14-19) were identified. Of the 2 articles comparing canagliflozin versus glimepiride, only the study conducted by Cefalu et al (12) was included in the analysis since the second article reviewed the results from the Cefalu et al study (13). Of the 7 articles comparing canagliflozin versus sitagliptin, only the study by Lavalle-González et al was included in the analysis (11). The other 6 articles were not considered since 2 were economic analyses (17, 18), 2 provided an analysis based only on the quality of outcome indicators related to diabetes (15, 19), 1 evaluated the quality-of-life associated with body weight changes (16), and 1 showed results from a comparison of sitagliptin with canagliflozin 300 mg only and in triple therapy (out of scope of the analysis) (14).

Canagliflozin versus glimepiride (12)

A phase III, multicenter, randomized, double-blind study was carried out in 157 centers in 19 Countries between August 2009 and December 2011 (12). The study evaluated 1,450 patients aged 18 to 80 years with T2DM inadequately controlled with metformin (HbA_{1c} ≥7.0% and ≤9.5%) (12). Patients were randomized (1:1:1) to receive maximally tolerated glimepiride (n = 482), canagliflozin 100 mg (n = 483), or canagliflozin 300 mg (n = 485). Change in HbA_{1c} over 52 weeks was the primary endpoint. Secondary endpoints included the percentage of patients with hypoglycemic episodes (with a distinction between mild to moderate and severe), the incidence of genital mycotic infections, and change in body weight. Table I shows baseline patient characteristics and a summary of the key results at 52 weeks. Patients treated with canagliflozin had decreased HbA_{1c} compared with those treated with glimepiride; at Week 52, canagliflozin 300 mg demonstrated superiority in HbA_{1c} lowering (differences vs glimepiride [95% confidence interval (CI)] of -0.12% [-0.22, -0.02]) and canagliflozin 100 mg demonstrated non-inferiority in HbA_{1c} lowering (difference vs glimepiride [95% CI] of -0.01% [-0.11, 0.09]) (12).

Canagliflozin versus sitagliptin (11)

A phase III, multicenter, randomized, double-blind study was carried out in 169 centers in 22 Countries between April 2010 and August 2012 (11). The study evaluated 1,284 patients aged 18 to 80 years with T2DM inadequately controlled with metformin (HbA_{1c} ≥7.0% and ≤10.5%) (11). The patients were randomized (2:2:2:1) to receive canagliflozin 100 mg (n = 368), canagliflozin 300 mg (n = 367), sitagliptin (n = 366), or placebo (n = 183). Patients who completed the 26-week core treatment period entered a 26-week extension treatment period, during which the patients randomized to canagliflozin 100 or 300 mg or sitagliptin 100 mg continued with the initial treatment, while those initially randomized to placebo switched to sitagliptin 100 mg.

Change in HbA_{1c} over 26 weeks was the primary endpoint and change in HbA_{1c} over 52 weeks was a secondary endpoint. Other secondary endpoints at 52 weeks were change in FPG, the percentage of patients with hypoglycemic episodes, the incidence of genital mycotic infections, and change in body weight. Table II shows baseline patient characteristics and a summary of the key results at 52 weeks. Canagliflozin improved glycemic control and reduced body weight at 26 weeks compared with placebo. Results at 52 weeks showed that compared to sitagliptin 100 mg, glucose-lowering was superior with canagliflozin 300 mg (difference [95% CI] of -0.15% [-0.27, -0.03]) and non-inferior with canagliflozin 100 mg (difference [95% CI] of 0.0% [-0.12, 0.12]). Findings from

TABLE I - Baseline characteristics and key results from the canagliflozin versus glimepiride study (12)

	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride
Baseline characteristics			
Number of patients	483	485	482
Age, yrs	56.4	55.8	56.3
Female, %	48	50	45.0
Weight, kg	86.9	86.6	86.5
BMI, kg/m^2	31.0	31.2	30.9
HbA_{1c}, %	7.8	7.8	7.8
Duration of T2DM, yrs	6.5	6.7	6.6
Results at week 52			
Change in HbA_{1c}, %	-0.82*	-0.93*	-0.81
Total hypoglycemia episodes†, %	5.6	4.9	34.2
Mild to moderate hypoglycemia‡	5.2	4.3	31.1
Severe episodes	0.4	0.6	3.1
Genital mycotic infections, %	8.9	11.1	1.7
Change in weight			
%	-4.2	-4.7	1.0
kg	-3.7	-4.0	0.7

BMI = body mass index; HbA_{1c} = glycated hemoglobin; T2DM = type 2 diabetes mellitus.
* Canagliflozin 100 mg demonstrated non-inferiority in HbA_{1c} lowering and canagliflozin 300 mg demonstrated superiority in HbA_{1c} lowering versus glimepiride at Week 52.
† Includes documented hypoglycemia episodes from the clinical trial, defined as biochemically documented episodes (ie, glucose levels ≤3.9 mmol/L) with or without symptoms, and severe episodes (ie, those requiring the assistance of another individual or resulting in seizure or loss of consciousness).
‡ Includes documented hypoglycemia episodes from the clinical trial that were not considered severe.

TABLE II - Baseline characteristics and key results from the canagliflozin versus sitagliptin study (11)

	Canagliflozin 100 mg	Canagliflozin 300 mg	Sitagliptin 100 mg
Baseline characteristics			
Number of patients	368	367	366
Age, yrs	55.5	55.3	55.5
Female, %	52.7	55	53.0
Weight, kg	88.8	85.4	87.7
BMI, kg/m^2	32.4	31.4	32
HbA_{1c}, %	7.9	7.9	7.9
Duration of T2DM, yrs	6.7	7.1	6.8
Results at week 52			
Change in HbA_{1c}, %	-0.73*	-0.88*	-0.73
Total hypoglycemia episodes†, %	6.8	6.8	4.1
Mild to moderate episodes‡	6.5	6.8	3.8
Severe episodes	0.3	0.0	0.3
Genital mycotic infections, %	8.4	6.5	1.9
Change in weight			
%	-3.8	-4.2	-1.3
kg	-3.3	-3.7	-1.2

BMI = body mass index; HbA_{1c} = glycated hemoglobin; T2DM = type 2 diabetes mellitus.
* Canagliflozin 100 mg demonstrated non-inferiority in HbA_{1c} lowering and canagliflozin 300 mg demonstrated superiority in HbA_{1c} lowering versus sitagliptin 100 mg at Week 52.
† Includes documented hypoglycemia episodes from the clinical trial, defined as biochemically documented episodes (ie, glucose levels ≤3.9 mmol/L) with or without symptoms, and severe episodes (ie, those requiring the assistance of another individual or resulting in seizure or loss of consciousness).
‡ Includes documented hypoglycemia episodes from the clinical trial that were not considered severe.

this study also demonstrate that canagliflozin has an acceptable tolerability profile.

Study design

The comparison of canagliflozin versus glimepiride or sitagliptin 100 mg was assessed in the context of a cost-minimization analysis (CMA) that considered only the direct health care costs (eg, medicinal products, hospitalizations, specialist medical care, glycemic self-monitoring, hypoglycemic events) associated with the treatment of T2DM and body weight changes in patients with T2DM (20). A conservative hypothesis of therapeutic equivalence was used in the CMA, even though canagliflozin 300 mg demonstrated superiority versus both sitagliptin and glimepiride.

Use of health care resources and value analysis

Weight changes

Results from a 12-month study that monitored changes in weight and associated health care costs in adults with T2DM indicated that, on an annual basis, each 1% loss in body weight corresponds to a significant decrease in health care costs associated with the T2DM management (3.6%; $P<0.05$) (20). Conversely, each 1% of weight gain was not related to a statistically significant increase in treatment costs (20).

Diabetes medication costs

The cost of diabetes medications in the 2 comparisons was calculated based on the dosages indicated in the respective clinical trials for the related ex-factory prices, net of the mandatory discount pursuant to the law (21). The average daily costs for canagliflozin 100 and 300 mg were €1.34 and €1.99, respectively. The daily average cost of sitagliptin 100 mg was €1.28. In order to make the price of sitagliptin uniform with the price of other drugs included in the present analysis, we considered an additional discount of 5% as Pay-Back procedure. The daily average cost for glimepiride was €0.118, which was derived from the average dosage of 5.6 mg (from the clinical trial) multiplied by the mean reference price per milligram (€0.0211) obtained from the Italian Medicines Agency (AIFA) transparency list of 17/11/2014 applicable to the marketed packages.

Patient costs

The average annual cost incurred by a patient with T2DM while being treated with one of the medications included in this comparison study was obtained from the national survey conducted by Osservatorio ARNO Diabete (22). This study showed that the average annual cost for a patient with T2DM (not differentiated according to the administered pharmacological treatment regimen) was €2,756, of which €814 was spent on medications, €1,569 for hospitalizations, and €373 for specialist medical care. For this analysis, a total cost of €2,585 per patient was used, with the costs for antidiabetic medications (€171) excluded to avoid a double-counting. All costs for the administered antihyperglicemic pharmacological treatment (canagliflozin, glimepiride, or sitagliptin), management of a hypoglycemic event, self-monitoring of blood glucose (SMBG), and treatment of an episode of genital mycotic infection (described below) were added to the "baseline" cost.

Hypoglycemia costs

The percentages of patients with ≥1 episode of hypoglycemia were obtained from the clinical trials. Episodes of hypoglycemia were classified as either mild to moderate, defined as biochemically documented episodes (ie, glucose levels ≤3.9 mmol/L) with or without symptoms, or severe (ie, those requiring the assistance of another individual or resulting in seizure or loss of consciousness) (Tabs. II and III) (11, 12).

Based on the literature and opinions of diabetes experts, it was assumed that a hypoglycemic episode could be treated at home, with access to emergency care or hospitalization, if needed. In the case of a severe hypoglycemic episode, 70.2% of the patients needed hospitalization to resolve the event, while for the remaining 29.8%, emergency care was sufficient; no severe events were managed at home (23). Conversely, in the case of a mild to moderate hypoglycemic episode, 86% of the patients resolved the event at home, while the remaining 14% needed to be treated in an emergency care facility; no patients were hospitalized for a mild to moderate hypoglycemic episode.

In the event of hospitalization, the hypoglycemic episode was given a value according to the diagnosis-related group (DRG) tariffs, as identified in a study conducted by Fondazione Mario Negri Sud (24). These DRG tariffs were based on the presence in SDO (Scheda Dimissione Ospedaliera [ie, hospital discharge form]) of codes 250.3 and 250.8 from *The International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) for hypoglycemia as the main diagnosis; the average (weighted) cost per hospitalization was €2,833. The cost for accessing an emergency care facility of €133.89 was determined by giving a value, based on the respective national fees, to the health care services provided to the patient in this context. These health services were identified on the basis of an estimate provided by an expert and are included in Table III. Finally, note that a hypoglycemic episode treated at home was assumed to not result in any direct cost for the Italian National Health Service.

TABLE III - Costs per glycemic episode treated in emergency care facilities

Emergency services	N	ICD-9-CM code	Unit cost	Total cost
Physical examination	3	89.7	€20.66	€61.98
Chest X-ray	1	87.44/1	€15.49	€15.49
ECG	1	89.50	€11.61	€11.61
Hemochrome	1	90.62/2	€3.17	€3.17
Glycemia	3	90.26/5	€3.33	€9.99
Azotemia	1	90.44/1	€1.13	€1.13
Creatinine	1	90.16/3	€1.13	€1.13
Transaminases	1	90.04/5	€1.00	€1.00
CPK	1	90.15/4	€1.44	€1.44
LDH	1	90.29/2	€1.13	€1.13
Troponine	1	90.82/3	€11.46	€11.46
Sodium	1	90.40/4	€1.02	€1.02
Potassium	1	90.37/4	€1.02	€1.02
Blood gas test	1	89.65/1	€12.32	€12.32
Total cost				**€133.89**

ECG = electrocardiogram; CPK = creatinine phosphokinase; ICD-9-CM = *The International Classification of Diseases, 9th Revision, Clinical Modification;* LDH = lactate dehydrogenase.

SMBG costs

The costs associated with SMBG were calculated by attributing a value to the daily average usage of reaction strips and finger pricks. An average national cost was calculated by using the respective regional reimbursement prices (Tab. IV). The average daily frequency of SMBG associated with the regimens analyzed was estimated by referencing the new recommendations of the Società Italiana di Diabetologia (SID) and Associazione Medici Diabetologi (AMD) (8). The SID/AMD recommends at least 25 to 100 controls per month (an average of 2 per day) in patients treated with oral hypoglycemic secretagogues (glimepiride). For patients under a diet treatment, treated with insulin sensitizer medications, incretin mimetics, and/or antihyperglycemic medicinal products (sitagliptin and canagliflozin), at least 25 to 50 controls per quarter are recommended (an average of 3 per week).

Genital mycotic infection costs

Genital mycotic infections were more frequent in patients treated with canagliflozin 100 or 300 mg compared with those treated with glimepiride or sitagliptin (Tabs. I and II) (11, 12). Because genital mycotic infections in the clinical studies were normally of mild to moderate severity and were self-managed with over-the-counter, antimycotic medications (eg, Canacid®), in the base case they were not considered to be costs borne by the Italian National Health Service (11, 12).

Projection period

The projected period for this analysis was 12 months (ie, 52 weeks of treatment), consistent with the duration of the 2 clinical studies (11, 12).

TABLE IV - Unit cost for glycemia self-monitoring

Region	Cost of test strips*	Costs of finger pricks*	Source
Lombardy	€0.49	€0.09	Regional Decree n. 888 of 10/13
Piedmont	€0.46	n.d.	Regional Decree 15-5526 of 3/13; Regional Decree 61-895 of 10/10
Marche	€0.41	€0.08	Regional Decree n. 94 of 06/05/10
Puglia	€0.53	€0.13	Regional Decree n. 1714 of 26/7/11
Lazio	€0.82	€0.17	Regional Decree n.1055 of 12/07
Veneto	€0.46	€0.10	Regional Decree n. 43 of 1/14; Regional Decree n. 1067 of 28/6/13
Tuscany	€0.38	€0.05	Regional Decree n. 647 of 8/08
Sicily	€0.64	€0.12	Regional Decree of 16/9/05
Sardinia	€0.49	€0.06	Regional Decree n. 17/4 of 24/4/12
Basilicata	€0.23	€0.19	Regional Decree n. 565 of 10/12
Calabria	n.d.	n.d.	Regional Decree n. 4 of 01/12
Friuli	€0.65	€0.13	Regional Decree n. 1134 of 06/11
Trento	n.d.	n.d.	Regional data not available (used the national average data)
Bolzano	n.d.	n.d.	Regional data not available (used the national average data)
Umbria	€0.69	€0.12	Regional Decree n. 1093 of 7/10
Abruzzo	n.d.	n.d.	Regional data not available (used the national average data)
Campania	n.d.	n.d.	Regional data not available (used the national average data)
Emilia Romagna	€0.32	n.d.	Parliamentary question regarding act s.3/02303 available at www.parlamento16.openpolis.it (last accessed March 2013)
Liguria	n.d.	n.d.	Regional data not available (used the national average data)
Molise	n.d.	n.d.	Regional data not available (used the national average data)
VdA	n.d.	n.d.	Regional data not available (used the national average data)
Italy	**€0.51**	**€0.11**	

n.d. = not disclosed.
* The prices are before value added tax (VAT).

Sensitivity analyses

Sensitivity analyses were conducted to examine the uncertainty of the results of the base case, consistent with guidelines from the Associazione Italiana di Economia Sanitaria for the conduct of health care–related financial evaluations (25). Univariate analyses were conducted that varied the costs for the treatment of a genital mycotic infection and costs and treatment setting of a hypoglycemia episode, as follows:

- Cost of treatment of a genital mycotic infection borne by the Italian National Health Service of €17.87, and corresponding purchase cost of a Canacid® (fluconazole) package (7 tablets of 200 mg).
- Average cost of hypoglycemia hospitalization of €3,677 (associated with ICD-9-CM 250.3 and 250.8 codes in the secondary diagnosis position) using the results of the study conducted by Fondazione Mario Negri Sud (24).
- Average cost of hypoglycemia hospitalization of €3,374 (assuming ICD-9-CM 250.3 and 250.8, in the position of both primary and secondary diagnosis positions) using the results of the study conducted by Fondazione Mario Negri Sud (24).
- Cost for the treatment of a hypoglycemic episode in an emergency care facility ±25% change compared to the baseline cost.
- All mild to moderate hypoglycemic episodes treated in emergency care facilities.
- All severe episodes required hospitalization.

A threshold analysis was also carried out on the parameters that could affect the CMA results; that is, a reduction in weight loss efficacy with canagliflozin, a decrease in treatment costs for a patient with T2DM (from the study by Osservatorio ARNO Diabete), and a reduction in the number of SMBG measurements associated with glimepiride.

Results

Canagliflozin versus glimepiride

Canagliflozin 100 and 300 mg were associated with a lower annual cost per patient (€2,785.14 and €2,979.20, respectively)

compared with glimepiride (€3,166.13) and, therefore, resulted in cost savings (Tab. V). Based on a higher daily cost for canagliflozin versus glimepiride, costs for diabetes medications were higher with canagliflozin compared with glimepiride (canagliflozin 100 mg, €487.76; canagliflozin 300 mg, €724.36; glimepiride, €43.05). However, these higher costs were completely offset by the cost differences related to a reduction in body weight (ie, other medications, hospitalizations, specialist medical care; canagliflozin 100 mg, -€390.85; canagliflozin 300 mg, -€437.38) and a reduction in costs associated with the management of SMBG (canagliflozin 100 or 300 mg, -€375.44).

Canagliflozin versus sitagliptin

Canagliflozin 100 or 300 mg were associated with a lower annual cost per patient than sitagliptin 100 mg (Tab. VI). The cost savings with canagliflozin 100 and 300 mg (-€210.33 and -€16.42, respectively) were due primarily to the differences in costs related to a greater reduction in body weight (ie, other medications, hospitalizations, specialist medical care). Cost differences associated with other components (eg, management of hypoglycemia, SMBG) were negligible (Tab. VI).

TABLE V - Base case results: canagliflozin versus glimepiride

Cost items	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride 5.6 mg
Medications for diabetes	€487.76	€724.36	€43.05
Other medications	€545.78	€534.20	€643.00
Hospitalizations	€1,331.77	€1,303.53	€1,569.00
Specialist medical care	€316.60	€309.89	€373.00
Hypoglycemia (mild to moderate)	€0.97	€0.81	€5.83
Hypoglycemia (severe)	€8.40	€12.55	€63.13
Hypoglycemia self-monitoring	€93.86	€93.86	€469.30
Total per treated patient	**€2,785.14**	**€2,979.20**	**€3,166.13**

TABLE VI - Base case results: canagliflozin versus sitagliptin

Cost items	Canagliflozin 100 mg	Canagliflozin 300 mg	Sitagliptin 100 mg
Medications for diabetes	€487.76	€724.36	€465.92
Other medications	€555.04	€545.78	€612.91
Hospitalizations	€1,354.36	€1,331.77	€1,495.57
Specialist medical care	€321.97	€316.60	€355.54
Hypoglycemia (mild to moderate)	€1.22	€1.27	€0.72
Hypoglycemia (severe)	€5.51	€0.00	€5.54
Hypoglycemia self-monitoring	€93.86	€93.86	€93.86
Total per treated patient	**€2,819.73**	**€3,013.64**	**€3,030.06**

Sensitivity analyses

Sensitivity analyses that varied the costs of treatment of genital mycotic infections or the costs and treatment setting of hypoglycemia confirmed the base case results, which indicated that canagliflozin 100 and 300 mg were associated with lower costs versus glimepiride (Tab. VII) and sitagliptin 100 mg (Tab. VIII).

Threshold analyses showed that canagliflozin 100 or 300 mg and glimepiride continued to represent a cost-saving option versus glimepiride even when there was a reduction in weight loss efficacy (Fig. 1A) or a reduction in patient treatment costs (Fig. 1B) with canagliflozin versus glimepiride. Canagliflozin 100 and 300 mg also remained cost-saving versus glimepiride, unless the number of SMBG measurements with glimepiride was reduced substantially (>39.8%; Fig. 1C).

Threshold analyses confirmed the base case results that canagliflozin 100 mg was associated with cost savings versus sitagliptin 100 mg at all values for reduction in weight loss efficacy with canagliflozin (Fig. 2A) and reduction in costs for managing a patient with T2DM (Fig. 2B), while the uncertainty was greater for the comparison of canagliflozin 300 mg versus sitagliptin 100 mg. Canagliflozin 300 mg provided cost savings compared with sitagliptin 100 mg unless weight loss efficacy with canagliflozin was reduced by >4.2% or patient treatment costs were reduced by >6.1%.

Discussion and conclusions

This CMA identifies canagliflozin 100 or 300 mg as a cost-saving treatment option compared with glimepiride and sitagliptin 100 mg for the treatment of patients with T2DM inadequately controlled with metformin in Italy.

Cost savings per patient treated with canagliflozin versus glimepiride were attributable to all cost items being considered in this analysis (ie, weight loss, reduced risk of hypoglycemia, lower number of SMBG measurements). The difference in treatment costs associated with canagliflozin 100 mg compared with glimepiride (-€381.17) is greater than the difference generated by canagliflozin 300 mg (-€187.11). Note the estimated cost savings associated with canagliflozin 300 mg are conservative since the HbA_{1c} lowering efficacy was greater with canagliflozin 300 mg compared with canagliflozin 100 mg in the trial (12).

These results may underestimate the real cost savings due to the reduction of hypoglycemia with canagliflozin versus glimepiride. This analysis considers the costs associated with the number of patients with ≥1 hypoglycemia episode, as reported in the study, and not the total number of episodes. Only 2.3% and 3.5% of patients treated with canagliflozin 100 and 300 mg, respectively, experienced only 1 hypoglycemia episode, while 5.6% and 4.9% reported ≥1 episode; in the glimepiride arm, 34.2% of patients experienced ≥1 episode, and 18.3% of patients experienced ≥3 episodes, showing that the total number of episodes in the clinical trial was substantially higher with glimepiride versus canagliflozin, and was greater than considered in the analysis (data on file).

Finally, the sensitivity analyses conducted on key clinical and cost variables suggested that these base case results are robust; canagliflozin 100 and 300 mg were cost-saving

TABLE VII - Sensitivity analysis results: canagliflozin versus glimepiride

Univariate analysis	Canagliflozin 100 mg	Canagliflozin 300 mg	Glimepiride 5.6 mg
Base case	€2,785.14	€2,979.20	€3,166.13
Costs for genital mycotic infection treatment			
One Canacid® package, Italian National Health Service	€2,786.73	€2,981.19	€3,166.61
Costs for hypoglycemia hospitalization			
ICD-9-CM 250.3 and 250.8 secondary diagnosis	€2,787.59	€2,982.86	€3,184.75
ICD-9-CM 250.3 and 250.8 main and secondary diagnosis	€2,786.71	€2,981.55	€3,178.13
Costs for emergency care of hypoglycemia			
-25%	€2,784.85	€2,978.93	€3,164.54
+25%	€2,785.42	€2,979.46	€3,168.08
Hypoglycemia setting			
Mild to moderate: 100% treated in emergency care facilities	€2,791.10	€2,984.18	€3,202.14
Severe: 100% required hospitalization	€2,788.47	€2,984.17	€3,191.34

ICD-9-CM = *The International Classification of Diseases, 9th Revision, Clinical Modification.*

TABLE VIII - Sensitivity analysis results: canagliflozin versus sitagliptin

Univariate analysis	Canagliflozin 100 mg	Canagliflozin 300 mg	Sitagliptin 100 mg
Base case	€2,819.73	€3,013.64	€3,030.06
Costs for genital mycotic infection treatment			
One Canacid® package, Italian National Health Service	€2,821.23	€3,014.81	€3,030.40
Costs for hypoglycemia hospitalization			
ICD-9-CM 250.3 and 250.8 secondary diagnosis	€2,821.34	€3,013.64	€3,031.68
ICD-9-CM 250.3 and 250.8 main and secondary diagnosis	€2,820.76	€3,013.64	€3,031.10
Costs for emergency care of hypoglycemia			
-25%	€2,819.39	€3,013.32	€3,029.86
+25%	€2,820.06	€3,013.96	€3,030.27
Hypoglycemia setting			
Mild to moderate: 100% treated in emergency care facilities	€2,827.24	€3,021.47	€3,034.47
Severe: 100% required hospitalization	€2,821.91	€3,013.64	€3,032.26

ICD-9-CM = *The International Classification of Diseases, 9th Revision, Clinical Modification.*

versus glimepiride in all but one case. Specifically, canagliflozin 300 mg was estimated to have higher treatment costs only if the number of times glycemic self-monitoring was performed for glimepiride was reduced more than 40% (compared with the base case).

Cost savings per patient with canagliflozin 100 and 300 mg versus sitagliptin 100 mg primarily resulted from lower treatment costs associated with body weight reduction. The difference in the treatment costs associated with canagliflozin 100 mg compared with sitagliptin (-€210.34) was greater than the difference generated by canagliflozin 300 mg (-€16.42). As in the previous comparison, this must be considered in light of the clinical results, which showed that HbA_{1c} lowering was greater with canagliflozin 300 mg than canagliflozin 100 mg (11). Considering the results of the sensitivity analyses that considered variation in the key clinical and cost parameters, canagliflozin 100 mg was always associated with a lower treatment cost compared with sitagliptin 100 mg. In the sensitivity analyses comparing canagliflozin 300 mg with sitagliptin 100 mg, sitagliptin 100 mg was cost-saving when there was a >4.2% reduction in weight loss efficacy with canagliflozin 300 mg or a >6.1% reduction in T2DM treatment costs (ie, other medicinal products, hospitalizations, specialist medical care). It would probably be more appropriate to refer to a neutral effect in treatment costs between a patient receiving sitagliptin 100 mg or canagliflozin 300 mg, while underlining the significantly greater glycemic efficacy of canagliflozin 300 mg (11).

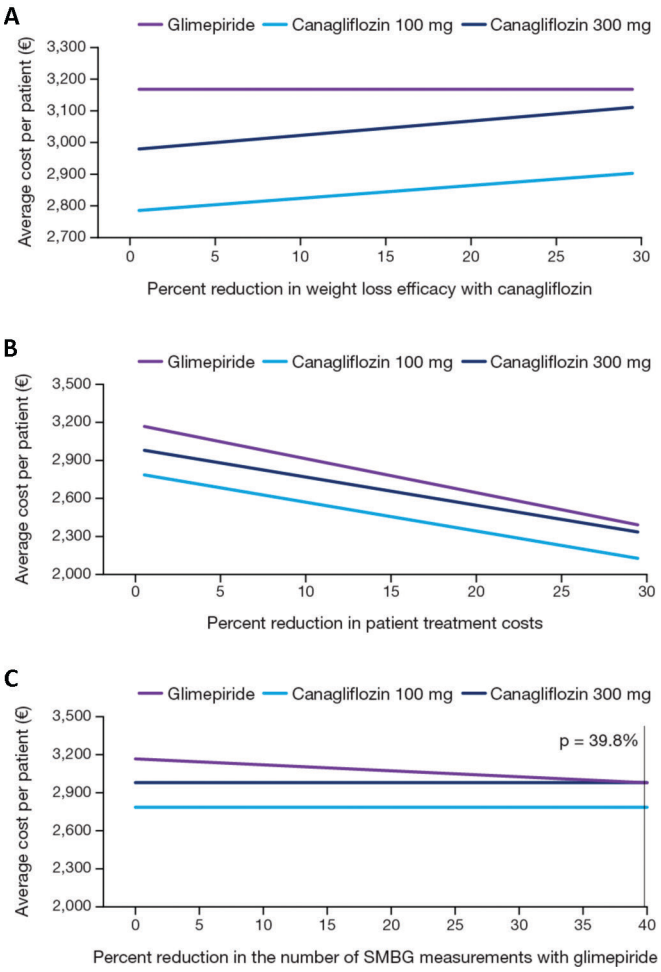

Fig. 1 - Threshold analysis results for canagliflozin versus glimepiride assuming (**A**) reduction in weight loss efficacy with canagliflozin, (**B**) reduction in patient treatment costs, and (**C**) reduction in the number of SMBG measurements with glimepiride. Note that p represents the percent reduction at which canagliflozin is no longer cost-saving versus glimepiride.

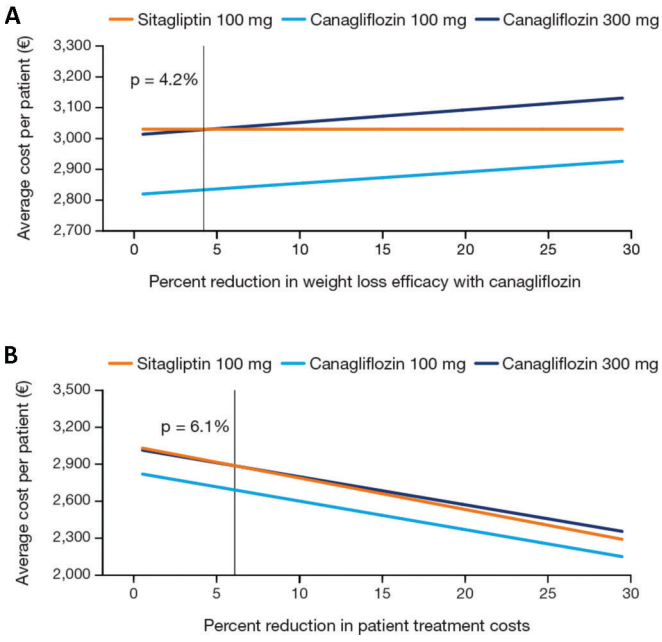

Fig. 2 - Threshold analysis results for canagliflozin versus sitagliptin assuming (**A**) reduction in weight loss efficacy with canagliflozin and (**B**) reduction in patient treatment costs. Note that p represents the percent reduction at which canagliflozin is no longer cost-saving versus sitagliptin.

To our knowledge, this is the first economic analysis conducted in Italy on canagliflozin; however, results from the present CMA conducted from the Italian National Health Service perspective are consistent with results of a "cost-efficiency" study from the United States, which demonstrated lower annual costs for treatment with canagliflozin 300 mg versus sitagliptin 100 mg (difference of US$215) (18) and a higher percentage of patients reaching a therapeutic target for HbA_{1c} with canagliflozin versus sitagliptin 100 mg.

A possible limitation of the current analysis is the use of efficacy data from 2 clinical trials that may not be representative of real-world clinical practice. However, data obtained through head-to-head, randomized, phase III studies represent a more preferred source for carrying out an economic evaluation versus indirect comparison data as a source, which is often all that is available to examine the costs between alternative treatments.

The assignment of an economic value to a reduction in body weight associated with the administered treatments could represent another limitation given the use of various assumptions described below. The benefits associated with weight loss in patients with T2DM, such as improvement in glycemic control and cardiovascular risk factor control, have been observed in previous clinical and epidemiological studies (26, 27). They represent aspects of T2DM treatment that, if managed correctly, could lead to significant differences in treatment costs. Therefore, in line with the data from Yu et al that revealed a correlation between weight loss and lower treatment costs (20), converting the weight loss resulting from the antidiabetic treatments being discussed here into an economic value was appropriate. The difference in cost resulting from weight loss only applied to medications, hospitalizations, and specialist medical care, while this adjustment was not applied to the costs associated with the medications for diabetes, hypoglycemia events, and SMBG.

Note that the results from the survey conducted by Osservatorio ARNO Diabete as a proxy of the average annual costs for patients with T2DM, is in line with a recent analysis conducted by Mario Negri Sud in the Marche Region, where the average costs for a person with diabetes amounted to €2,855.55 (of which €819.05 was for medications) (28).

The number of self-monitoring glucose tests (SMBG) for canagliflozin, sitagliptin, and glimepiride was estimated by referring to the data included in the recommendations provided by SID and AMD. These recommendations may not reflect actual clinical practice, especially for glimepiride (characterized by a greater average number of daily tests given the inherent risk of hypoglycemic episodes). As such, these simulation results likely understate the cost savings associated with using canagliflozin versus glimepiride.

Because the number of patients who developed genital mycotic infections was higher with canagliflozin compared with glimepiride and sitagliptin in both clinical studies, the expected economic impact of these infections was estimated. The severity of the genital mycotic infections reported in clinical studies was mild or moderate and treated with over-the-counter antimycotic medications (eg, Canacid®); therefore, in the base case the costs borne by the Italian National Health Service were not considered. In the sensitivity analysis, a scenario in which an episode of infection would be treated with a medication reimbursed by the Italian National Health Service was assumed; in this case, canagliflozin remained the best cost-saving option.

Finally, while the estimated average costs of treatment with canagliflozin based on the data obtained from the Cefalu et al study (canagliflozin versus glimepiride) (12) differ from the estimated costs that consider the results obtained in the Lavalle-González et al study (canagliflozin versus sitagliptin) (11), these differences are negligible.

This analysis demonstrates that canagliflozin 100 or 300 mg are likely to be the best cost-saving options compared with maximally-tolerated glimepiride and sitagliptin 100 mg in the treatment of patients with T2DM inadequately controlled with metformin in Italy, which may allow more efficient allocation of resources available to the Italian National Health Service.

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