REAL-WORLD CLINICAL OUTCOMES ASSOCIATED WITH CANAGLIFLOZIN IN PATIENTS AGED 65 YEARS AND OLDER WITH TYPE 2 DIABETES MELLITUS IN SPAIN: THE OLD REAL-WECAN STUDY.

Short running title: CANAGLIFLOZIN IN PATIENTS 65 YEARS AND OLDER

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Disclosures

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Abstract

Objectives

The observational REAL WECAN study showed that canagliflozin 100 mg (CANA100) as add-on therapy, and canagliflozin 300 mg (CANA300), switching from prior SGLT-2i therapy, significantly improved several cardiometabolic parameters in patients with T2DM. The aim of this sub-analysis was to assess the effectiveness and safety of canagliflozin in patients aged ≥65 years. The primary outcome of the study was the mean change in HbA1c over the follow-up time.

Materials and Methods

583 patients met the inclusion criteria (39.5% ≥ 65 years), 279 in the CANA100 cohort (36.9 % ≥ 65 years, mean HbA1c 8.05%) and 304 in the CANA300 cohort (41.8 % ≥ 65 years, mean HbA1c 7.51%).

Results

In the CANA100 cohort, older patients showed significant reductions in HbA1c (-0.78%) and weight (-4.5 kg). Patients aged ≥65 years switching to CANA300 experienced a significant decrease in HbA1c (-0.27%) and weight (-2.1 kg). There were no significant differences in HbA1c and weight reductions when the cohorts of patients <65 and ≥65 years were compared in a multiple linear regression model. The safety profile of canagliflozin was similar in both age groups.

Conclusion

These findings support canagliflozin as an effective therapeutic option for older adults with T2DM

What's known?

- We have previously shown the effectiveness of canagliflozin 100 and the switch to canagliflozin 300 from a prior SGLT-2i in patients with T2DM in a real world setting
- There is scarce data regarding the effectiveness and safety of canagliflozin comparing younger and older patients, and no data on intensification of SGLT-2is therapy by switching to canagliflozin 300 in elderly patients with T2DM.

What's new?

- Canagliflozin 100 (as add-on therapy) in patients with T2DM in a real-world setting, showed similar effectiveness and safety irrespective of age
- Canagliflozin 300 (switching from canagliflozin 100 or other SGLT-2is) is a safe and efficacious therapeutic option for the increasingly frequent patients with T2DM older than 65 years

KEYWORDS: 1 Canagliflozin; 2 SGLT-2 inhibitor; 3 Elderly patients; 4 Type 2 diabetes mellitus; 5 Real World Study

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INTRODUCTION

Diabetes, particularly type 2 diabetes mellitus (T2DM), is becoming more prevalent in the general population, especially in individuals over the age of 65 years. Older patients with T2DM typically have a longer disease duration, contributing to reduced pancreatic function, more comorbidities and greater medication complexity than those seen in younger people with T2DM. Hence treatment of T2DM in older patients requires careful consideration of the increased risk of hypoglycaemia, cardiovascular (CV) and renal complications, frailty, and more serious drug-related adverse events (AE). Therefore, selection of any antihyperglycaemic agents (AHA) for treating these patients should consider the benefit/risk ratio. In fact, there are several current guidelines that specifically address management of T2DM in this population to achieve glycaemic control with minimal risks [1-5].

Canagliflozin is one of the new therapies introduced in T2DM treatment in recent years. It belongs to the sodium-glucose co-transporter type 2 inhibitors (SGLT-2is) class of AHA drugs that reduce tubular reabsorption of filtered glucose, inducing urinary glucose excretion in individuals with hyperglycaemia, which leads to decreased plasma glucose as well as an osmotic diuresis and net caloric loss [6-9]. In Phase 3 studies canagliflozin has been shown, in patients with T2DM, to improve glycaemic control and reduce body weight and blood pressure (BP) in combination with different AHA therapies [10-14]. Additionally, canagliflozin has demonstrated CV and renal benefits in patients with T2DM and high CV risk or chronic kidney disease (CKD) [15-16].

However, in most of these studies, the mean age of the population was below 65 years, extending these results to older patients is questionable. Additionally, no randomized clinical trials (RCTs) or real world studies (RWS) have evaluated possible outcome differences between these two age groups with the strategy of intensification of SGLT-2i therapy by switching to CANA300, either from CANA100 or other SGLT-2is.

In summary, there is scarce data from RWS regarding the effectiveness and safety of canagliflozin comparing younger and older patients and no data on intensification of SGLT-2is therapy by switching to CANA300 in elderly patients with T2DM.

We have previously studied the effectiveness of CANA100 and the switch to CANA300 from a prior SGLT-2i in patients with T2DM in a real world setting [17]. In that study we found a significant improvement in several cardiometabolic parameters, with a low incidence of AEs and a high rate of persistence. Our findings confirmed the results from phase 3 RCTs with CANA100 and obtained real-life evidence on the effectiveness and safety of switching to CANA300 from prior SGLT-2i therapy in patients with suboptimal metabolic control. We

performed a sub-analysis of this RWS, the OLDer age patients Real World Evidence with CANagliflozin (OLD Real-WECAN), to assess the effectiveness and safety of CANA100 daily as add-on to the background antihyperglycaemic therapy and to evaluate the intensification of SGLT-2i therapy, by switching to CANA300 daily, either from CANA100 or other SGLT-2is, in patients of 65 years and older compared to younger individuals.

METHODS

Study design and patient population

This subgroup analysis was based on data from the previously reported Real-Wecan Study [17]. Briefly, The Real-Wecan Study is a multicentre retrospective study whose aims were to assess the effectiveness and safety of canagliflozin 100 mg/d (CANA100) as add-on to the background AHAs in a real-world setting, and to evaluate the intensification of prior SGLT-2i therapy by switching to canagliflozin 300 mg/d (CANA300) in patients with T2DM. The patients were consecutively selected from the diabetes clinic databases between May 2015 and July 2019 if they were older than 18 years, were diagnosed with T2DM according to the American Diabetes Association criteria, had received initial and regular follow-up diabetes care from endocrinologists at the diabetes clinic, started treatment with CANA100 or CANA300 as a part of their diabetes care at least 6 months before the data collection and received at least 1 dose of the drug. Treatment decisions were in accordance with clinical practice and at the discretion of the treating physician. Switching to CANA300 was indicated in patients with suboptimal HbA1c or weight response to prior SGLT-2is

The study was approved by the Ethical Review Board (ethic code 19/56) of the centres which took part in the study and was done in compliance with the ethical guidelines for research in humans. All the procedures were in accordance with the requirements set out in the international standards for epidemiological studies, as recorded in the International Guidelines for Ethical Review of Epidemiological Studies and with the Helsinki Declaration of 1964, as revised in 2013. For this type of study individual consent was not required.

Outcomes and study measures

Demographic, clinical and laboratory data were extracted from electronic medical records by the investigators at each centre, defining 3 data capture visits: V1, baseline 1 (CANA100 mg) or switch (CANA300); V2, 6 +2 months after the start of CANA100 or after switching to CANA300;

and V3, last visit of the follow-up period. Electronic databases from Primary Care, Laboratory Departments, and Emergency Departments were also reviewed to collect unreported AEs.

Baseline clinical parameters included gender, age, duration of T2DM, microvascular and macrovascular complications, other CV risk factors (hypertension, hypercholesterolaemia, hypertriglyceridemia), heart failure, arrhythmias, and background AHAs, anti-hypertensive and lipid-lowering drugs. In the cohort of patients switching from other SGLT-2is to CANA300, clinical parameters before initiating the prior SGLT-2i were also registered. HbA1c, fasting plasma glucose (FPG), weight, Body Mass Index (BMI), systolic BP (SBP) and diastolic BP (DBP), were collected at V1, V2 and V3. Causes of withdraws (WDs) and deaths were registered. AEs associated in clinical trials to SGLT-2is (genital mycotic infections [GMIs], urinary tract infections [UTIs], fractures, polycythemia, volume depletion, diabetic ketoacidosis [DKA], atraumatic lower extremity amputations) were collected by the investigators at each visit. GMIs and UTIs were diagnosed in those patients with positive cultures or patients reporting genital or urinary symptoms who received antifungal agents or antibiotics. Polycythemia was defined as increased haematocrit higher than 49% in men or higher than 48% in women. AEs related to volume depletion were diagnosed in patients with hospital or emergency department admissions due to episodes of postural dizziness, hypotension, dehydration or falls. DKA was defined as an anion-gap acidosis with increased plasma or urine ketones even in the presence of normoglycaemia. Hypoglycaemia episodes were defined as biochemically documented (≤70 mg/dl) and severe episodes as those requiring the assistance of another individual or resulting in seizure or loss of consciousness.

The main outcome measures were to assess changes in HbA1c at V2 and V3 from V1 in both cohorts of CANA100 and CANA300 and to compare these results between subgroups of participants younger than 65 and aged 65 and older. Secondary outcomes were changes in weight and BP in both age groups.

Statistical methods

Categorical data are shown in percentages. Continuous variables that follow a normal distribution are expressed as a mean (standard deviation [SD]) and those that do not meet normality criteria are shown as a median (interquartile range [IQR]). Analyses were carried out using the available data without any imputation of missing data. Paired t-tests (for parametrically distributed data), Wilcoxon tests (for non-parametrically distributed data) and McNemar tests (for categorical variables) were performed to compare baseline data to that at

follow-up A multiple linear regression analysis was performed to assess adjusted mean differences between older and younger patients, controlling for those baseline variables with statistically significant differences between the age groups

All analyses were conducted with the Statistical Package for the Social Sciences (SPSS) version 15.0.1 (IBM Corp., Armonk, NY) by using 2-sided tests and a significance level of 0.05.

RESULTS

Demographic and baseline characteristics

583 patients met the inclusion criteria (230 (60.5%) ≥65 years, 33 (5.7%) ≥75 years), 279 in the CANA100 cohort (men 54.8%, mean age 59.7 years, 36.9 % ≥65 years, mean HbA1c 8.05%, mean BMI 34.8 kg/m2) and 304 in the CANA300 cohort (men 55.9%, mean age 61.1 years, 41.8 % ≥65 years, mean HbA1c 7.51%, mean BMI 34.5 kg/m2). Baseline characteristics of the patients stratified by age and canagliflozin dose are shown in Table 1.

In both cohorts, patients aged ≥65 years showed a longer duration of T2DM, lower BMI, higher prevalence of high BP (in CANA100 cohort) and hyperlipidaemia, and more advanced CKD.

Analyses of effectiveness

In the CANA100 cohort (median follow up 9.2 months) patients aged ≥65 years showed significant reductions in HbA1c at V2 and V3 (- 0.70 % [95% CI -0.93 to -0.44] and – 0.78% [95% CI -1.0 to -0.55] respectively, both p<0.0001), and the percentage of patients with HbA1c below 7% significantly increased from 23.8% at V1 to 49.5% at V3 (p <0.0001). Patients younger than 65 years showed significant reductions in HbA1c at V2 and V3 (- 1.06 % [95% CI – 1.39 to -0.73] and -0.97 % [95% CI – 1.21 to -0.72] respectively, both p<0.0001) and the percentage of patients with HbA1c below 7% significantly increased from 26 % at V1 to 51.2 % at V3 (p <0.0001).

In the subgroup of patients aged ≥65 years with suboptimal glycaemic control, defined as baseline HbA1c >7% (mean HbA1c 8.48%), CANA100 decreased HbA1c at V2 and V3 (- 0.83 % [95% CI -1.1 to -0.53] and – 1.0 % [95% CI -1.2 to -0.73] respectively, both p<0.0001). In those patients with poor glycaemic control, defined as baseline HbA1c >8 (mean HbA1c 9.1 %) CANA100 decreased HbA1c at V2 and V3 (- 1.0 % [95% CI -1.5 to -0.62] and – 1.3% [95% CI -1.7 to -0.91] respectively, both p<0.0001).

CANA100 was associated with a significant weight loss (WL) in the older group at V2 and V3 (- 3.9 kg [95% CI -2.6 to -0.67] and -4.5 kg [95% CI -6.0 to -2.9] respectively, both p<0.0001). In younger patients, CANA100 was associated with a significant WL at V2 and V3 (- 3.62 kg [95% CI -4.63 to -2.62] and -3.79 kg [95% CI -4.7 to -2.87] respectively, both p<0.0001).
In addition, in the CANA100 cohort, older patients showed and a non-significant reduction in SBP (-4.6 mmHg) and a significant decrease in DBP at V3 (- 2.4 mm Hg [95% CI -4.5 to -0.23] p< 0.05).
In those individuals with SBP > 140 mmHg at V1 (mean SBP 155 mmHg), CANA100 lowered SBP levels at V3 by -16.1 and -14.1 mmHg in older and younger patients respectively (both p<0.0001).
In the multivariate analysis, after controlling for duration of T2DM, estimated Glomerular Filtration Rate (eGFR), weight, A1c, HTA and dyslipidaemia, adjusted differences in HbA1c reduction, WL and BP changes between the age groups were not statistically significant.

In the CANA300 cohort (median follow up 14 months) patients aged ≥65 years showed, starting from a median HbA1c 7.58 % at V1, significant reductions in HbA1c at V2 and V3 (- 0.36 % [95% CI -0.17 to -0.04] and – 0.27 % [95% CI -0.11 to -0.07] respectively, both p<0.0001) The percentage of patients with HbA1c below 7% significantly increased from 23.6 % at V1 to 40.7 % at V3 (p <0.0001). Patients younger than 65 years showed, starting from a median HbA1c 7.48 % at V1, significant reductions in HbA1c at V2 and V3 (- 0.51 % [95% CI -0.68 to -0.34] and – 0.40 % [95% CI -0.58 to -0.22] respectively, both p<0.0001). The percentage of patients with HbA1c below 7% significantly increased from 32.8 % at V1 to 50.9 % at V3 (p <0.0001).

In the subgroup of patients aged ≥65 years with suboptimal glycaemic control, defined as baseline HbA1c >7% (mean HbA1c 8.1 %), CANA300 significantly decreased HbA1c at V2 and V3 (- 0.42 % [95% CI -0.64 to -0.20] and – 0.39 % [95% CI -0.58 to -0.20] respectively, both p<0.0001). In those patients with poor glycaemic control, defined as baseline HbA1c >8% (mean HbA1c 9.13 %) CANA300 significantly lowered HbA1c at V2 and V3 (- 0.92 % [95% CI -1.3 to -0.51] and - 0.91 % [95% CI -1.3 to -0.53] respectively, both p<0.0001). In the multivariate analysis, adjusted differences in HbA1c reduction between the age groups were not statistically significant.

CANA300 was associated to significant WL in the older group at V2 and V3 (- 2 kg [95% CI -2.8 to -1.1] and 2.1 kg [95% CI -3 to -1.1] respectively, both p<0.0001). In younger patients,

CANA300 significantly lowered the body weight at V2 and V3 (- 2.14 kg [95% CI -2.87 to -1.41] and -2.15 kg [95% CI -3.13 to -1-18] respectively, both p<0.0001).

There was a numerical reduction in SBP (-3.0 mmHg) and DBP (-1.8 mmHg) at the end of the follow-up in older patients, without reaching statistical significance. In those patients with SBP > 140 mmHg at V1 (mean SBP 153 mmHg), CANA300 lowered SBP levels at V3 by -15.4 and -16.2 mmHg in older and younger patients respectively (both p<0.0001).

In the multivariate analysis, after controlling for duration of T2DM, eGFR, weight, A1c, HTA and dyslipidaemia, smoking and coronary heart disease, adjusted differences in HbA1c reduction, WL and BP changes between the age groups were not statistically significant.

Analyses of safety

In the CANA100 cohort, drug discontinuation was 36.9 % and 48.9% in older and younger patients, respectively, over the entire follow-up period (Table 2). The main reasons leading to CANA100 discontinuation in patients aged ≥65 years (other than switching to CANA300, 28.2%) were GMIs (2.9%), UTIs (1.0%) and worsening of kidney function (1.0%). No significant differences in WD were observed between the age groups.

In the older age group, the most common AEs with CANA100 were GMI (9.7%), UTI (4.9 %), mild hypoglycaemia (9.7 %), intravascular volume-related AEs (1.9 %) and fractures (1.9 %) without significant differences with younger patients. No amputations, polyglobulia or ketoacidosis were reported.

In the CANA300 cohort, drug discontinuation rates were similar in both age groups (9.4% and 9.0% in older and younger patients respectively) (Table 2). The main AEs leading to WD of CANA300 in patients aged ≥65 years were UTIs (2.4%), GMIs (0.8%) and worsening of kidney function (0.8%).

7.9% of patients ≥65 years experienced GMIs, 9.4% UTI, 13.4% mild hypoglycaemia, 0.8% polycythemia, and 0.8% intravascular volume-related AEs, without significant differences with younger patients except a higher frequency of hypoglycaemias. No fractures, ketoacidosis or amputations were reported.

DISCUSSION

Findings from this observational, retrospective, multicentre study show that CANA100 improved glycaemic control and reduced body weight and BP in patients with T2DM younger than 65 and aged 65 and older, without statistically significant differences between the age groups. In addition, switching to CANA 300 from prior CANA100 or other SGLT-2is, was associated with a statistically significant reduction in HbA1c and weight regardless of age group.

The efficacy and safety of canagliflozin in older adults with T2DM were assessed in a randomized placebo-controlled trial in patients aged 55 to 80 years [18] and in a 78-week extension report of same study [19]. In this trial canagliflozin improved glycaemic control, reduced body weight and SBP and was generally well tolerated. However, there were no data about potential differences with younger patients.

There are also some pooled analyses of 26-week, placebo-controlled phase 3 RCTs with canagliflozin comparing individuals aged 65 years and older with younger patients [20, 21], showing similar reductions in HbA1c and BMI, except with smaller HbA1c reductions in older participants with baseline eGFR 45 to <60 ml/min/m^2. A pooled analysis of placebo-controlled randomized Phase 3 studies of 18-26 weeks of duration found a lower numerical reduction in HbA1c in in patients aged 75 and older with canagliflozin [22], possibly related to their lower mean baseline eGFR and a higher incidence of AE.

While RCTs report clinical outcomes in controlled settings, such results may not be generalizable to patients seen in clinical practice, and RWS, although statistically less rigorous, can provide valuable insight into how AHA perform within specific subgroups (such as older patients), often excluded in RCTs. We have identified some retrospective RWS with canagliflozin in older patients (≥ 65 years) [23-26], but in most of them the study design does not allow the comparison of clinical outcomes with those from younger patients, except the study by Johnson et al [25], which found smaller HbA1c reductions in older patients. Those results need to be interpreted with caution due to the small sample size in the older subgroup (66 patients) and the short follow-up period (mean time to last visit 215 days).

Some sub-analyses from CV outcome trials with empagliflozin (EMPAREG-OUTCOME) and dapagliflozin (DECLARE) [27,28] have shown similar cardio-renal benefits and safety with both SGLT-2is independent of age.

The sub-analysis of our study shows that improvements with CANA100 therapy in glycaemic control, BP and weight previously described in the entire cohort were also found in older patients [17]. The observation of a greater reduction in HbA1c seen among those patients who had higher baseline HbA1c, is also a feature independent of age.

HbA1c decrease in our study with CANA100 (- 0.78 %) is similar to that reported with this drug in RWS and pooled analyses in older patients with canagliflozin therapy [20-26]. Although younger patients showed numerically greater reductions in HbA1c than the older subgroup, the difference was not statistically significant, in contrast to the report by Johnson et al [25].

A lower efficacy with SGLT2, occasionally reported in the elderly, may be a consequence of an age-dependent decline in the eGFR rather than ageing per se [22, 29]. Pooled analysis by Gilbert et al [21] only observed differences in HbA1c reductions between age groups in the subset of participants with baseline eGFR 45 to <60 mL/min/1.73m2. In our study, despite a lower baseline eGFR in older patients, we did not observe significant differences in glycaemic control between age groups. However, our study was not statistically weighted to detect differences by CKD stages and results were adjusted by eGFR, so a potential influence of renal function on canagliflozin effectiveness in our study cannot be ruled out.

In relation to the strategy of intensification to CANA300 from other SGLT-2is, not previously tested in older patients, we observed further HbA1c and weight reductions, increasing the percentage of patients with good control (HbA1c below 7%) from 23.6 % to 40.7 %, without age-related differences. In this cohort, improvements in HbA1c and weight were modest compared to those observed in the CANA100 cohort, but we should take into account that significant reductions in HbA1c and weight had already been attained with prior SGLT-2is therapy before the switch. In fact, HbA1c in the CANA300 cohort before the switch was 7.58%.
Significant improvement in SBP has been previously reported in elderly patients treated with canagliflozin [15-16,18-22]. In our study this effect was more relevant in the subset of patients with suboptimal control (SBP > 140 mm Hg). In this setting, both cohorts (CANA 100 and CANA 300) showed clinically relevant reductions above 15 mm Hg in older patients, contributing to an adequate BP control.
Safety analysis was consistent with findings observed in RCTs [30] and other RWS [31] including elderly patients with T2DM [26]. The overall incidence of AEs with canagliflozin in our study was low, most of them being mild or moderate in severity, but without differences between the age groups. In fact, drug discontinuation rates were numerically higher in younger than in older patients in the CANA100 cohort. A higher rate of non-severe hypoglycaemia in older patients in the CANA300 cohort may be related to numerically more individuals being treated with insulin in this group. Notwithstanding, special attention is needed to prevent severe hypoglycaemia in elderly patients. An appropriate dose adjustment of insulin or secretagogue doses should be considered in order to prevent hypoglycaemia when using these drugs in combination with SGLT-2is.

Limitations of this study include the retrospective study design, which did not allow for control of sample bias, but we have compared the results with the younger patients from the same sample. The study design was not weighted to find differences between age subgroups. Information on some variables was not recorded at each office visit, which resulted in missing data in some analyses. There is a potential recall bias in the frequency of AEs, as they were collected retrospectively. However, systematic research through electronic databases from Primary Care, Laboratory Departments and Emergency Departments was conducted to collect unreported AEs. Additionally, since some AHAs were modified (either increased or decreased) over the follow-up, especially in the CANA100 cohort, some influence of these changes on the final outcomes cannot be excluded.

It is also important to acknowledge that the results from this study may not be generalizable to broader populations because the sample in this study was selected from Endocrinology clinics with generally more advanced T2DM than those from a Primary Care setting.

Despite these limitations, findings from the present study supplement the evidence on real-world outcomes with canagliflozin in the population with T2DM over 65 years.

In summary, CANA100 (as add-on therapy) and CANA300 (switching from CANA100 or other SGLT-2is) in patients with T2DM in a real-world setting, showed similar effectiveness and safety irrespective of age. This sub-analysis confirms results of previous RCTs and RWS in older patients and adds real-life evidence on the strategy of switching to CANA300 from prior SGLT-2 therapy in that age group. Together, these findings support canagliflozin (as add-on therapy of CANA 100 or switching to CANA300 from other ISGLT-2is) as an effective and safe therapeutic option for the increasingly greater subgroup of elderly patients with T2DM.

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AUTHOR CONTRIBUTIONS

All authors participated in the design, data collection, data interpretation, and critical review of the article. Juan J Gorgojo-Martínez performed the statistical analysis. Manuel Gargallo-Fernandez wrote the manuscript.

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