Pathophysiological mechanisms and benefits of SGLT-2 inhibitors in a patient with cerebral artery aneurysm: A case report

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Abstract. The present study described the case of a 50-year-old male patient. The patient had type 2 diabetes since the age of 38 years (in 2013) with an initial elevated glycated hemoglobin A1c of 7.2%, with a significant cardiovascular (CV) history consisting of an aneurysm of the anterior communicating artery that had been operated on in 1998 and a ruptured basilar artery tip aneurysm embolized with a stent in 2013; the case was also associated with bronchiectasis (since 2020), non-alcoholic fatty liver disease (since 2018), diabetic neuropathy (since 2023) and obesity with a body mass index of 31.72 kg/m^2 (since 2010). Over the years the patient exhibited good metabolic control, initially treated with Metformin and managed through a change of diet. However, due to intolerance to Metformin, the patient stopped receiving treatments and only managed his diet. Since diabetes is by definition a condition that implies a high CV risk by itself, the primary focus with this patient was to provide additional CV protection, particularly secondary protection against any other potential future, and possibly fatal, CV events. After a brief introduction regarding the available therapeutic options, the case is presented along with the medical history, concomitant medications and evolution after 1 year. In the discussion section, similar documented cases in the literature were compared with the present case, and the potential effects of the therapeutic intervention in the present study were compared.

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Introduction

Large clinical trials have shown that sodium-glucose co-transporter (SGLT-2) inhibitors provide good metabolic control and cardiovascular (CV) benefits, such as reductions in overall CV risk, hospitalization rates for heart failure and CV, and all-cause mortality rates, with renoprotective effects as well. Large investigational trials have demonstrated that representative drugs from this class, such as empagliflozin or dapagliflozin, exhibited beneficial primary and secondary effects regarding CV and cerebrovascular (CVB) protection. These drugs act by blocking glucose and sodium reabsorption in the kidneys, resulting in its excretion through urine, and therefore, lowering blood glucose levels and arterial hypertension (1). This medication has other effects, such as reducing inflammation and oxidative stress, and assuming these are the basis for the onset of CV or CVB events, it is hypothesized that the use of SGLT-2 inhibitors may have additional CV and CVB protective effects (1).

Cerebral artery aneurysm (CAA) is a condition that can cause severe neurological deficits and potentially death. CAA is characterized by abnormal dilatation of a portion of an artery in the brain; due to this enlargement in volume, there is a consequent high risk of rupture and subarachnoid hemorrhage (2).

The symptoms of a ruptured CAA include double vision, nausea, vomiting, stiff neck, sensitivity to light, seizures, loss of consciousness and even cardiac arrest (3). Although not all patients who develop a CAA require treatment, the ruptured aneurysms require prompt intervention to save the patient's life. Interventions include surgery (microvascular clipping), endovascular treatment (platinum coil embolization) or implantation of flow diversion devices. Other treatments may include anti-seizure drugs, calcium channel-blocking drugs, the insertion of a shunt or rehabilitative therapy (3). The long-term management of CAA focuses on reducing the risk factors and they emphasize the necessity of lowering high blood pressure to a normal value such as by reducing the use of alcohol and giving up smoking (3).

Causes and risk factors for CAA include a genetic predisposition, smoking, arterial hypertension, diabetes and atherosclerosis. Previously and at present, the primary method of treatment for CAA is surgery, with the intention of preventing the rupture. However, more recently, novel treatments have shown CV benefits and are increasingly being used (4). Several genes have been described in the literature as being implicated in the development of CAA, with effects on vascular wall structure, extracellular matrix homeostasis or inflammatory response. One such gene is COL3A1, located on chromosome 2q32.2, which encodes type III collagen. Mutations in this gene can disrupt collagen production, leading to vascular wall weakening and predisposition to the formation of an aneurysm (5).

Another gene associated with aneurysm development is ELN, located on chromosome 7q11.23, which encodes elastin. Mutations affecting elastin production result in increased vascular rigidity, contributing to aneurysm susceptibility (6).

A different mechanism involves the degradation of the extracellular matrix, which weakens arterial wall resistance. This process can be exacerbated by increased expression of matrix metalloproteinase (MMP)9 in smooth muscle cells and endothelium. MMP9, located on chromosome 20q13.12, encodes an enzyme involved in the degradation of collagen and elastin (7).

Additionally, genes such as RNF213 (chromosome 17q25.3) play a role in the development of cerebral arteries. Mutations in RNF213 have been linked to an increased risk of CAA due to fragile cerebral vessels prone to rupture (8).

In the present case study, the potential beneficial effects of using SGLT-2 inhibitors in a patient with prior CAA and at high risk for a CV event are described.

Case report

In March 2022, at the Diabetes Department of Marius Nasta Institute of Pneumology (Bucharest, Romania), a 50-year-old white/Caucasian male from an urban environment, with no history of smoking, alcohol consumption or recreational drug use, was admitted. The patient stated that he works in agriculture and runs a grain farm. The patient's family history included a sister with type 1 diabetes, but no known CV diseases were present in the family. The patient was diagnosed with type 2 diabetes in 2013, at the age of 38, with an initial glycated hemoglobin A1c (HbA1c) of 7.2% (normal range, 0-5.6%) without any signs and typical symptoms of diabetes onset. For the treatment of diabetes, the patient initially received medical nutritional therapy (diet and exercise) and oral antidiabetics: First line of treatment with Metformin according to the guidelines (9) with an initial dose of 2,000 mg per day, a dose at which the patient experienced gastrointestinal symptoms. Although lower doses of metformin were tried, the patient could not tolerate this treatment. After several attempts with the lowest possible dose and several commercial preparations, Metformin treatment was ceased due to the intolerance. The patient continued his treatment with diet and exercise only, and over the years glycemic control was good, with an HbA1c ≤6.0%.

The patient's medical history included type 2 diabetes, arterial hypertension (since 2013), dyslipidemia (since 2013), a surgically repaired aneurysm of the anterior communicating artery (in 1998), a ruptured basilar artery tip aneurysm that was subsequently embolized with a stent (in 2013), obesity [from the age of 35 in 2010; a body mass index (BMI) of 31.72 kg/m^2], bronchiectasis (since 2020) diagnosed by a CT scan, non-alcoholic fatty liver disease (NAFLD; since 2018) diagnosed by abdominal ultrasound and diabetic neuropathy (since 2023) diagnosed by peripheral sensitivity tests.

The onset of both CAAs was sudden and the primary clinical symptoms for both were a severe headache along with dizziness and nausea. Since this condition posed a threat to the patient's life, an urgent surgical intervention was performed both in 1998 and in 2013; in 1998, the CAA was surgically repaired and in 2013 a stent was used for embolization.

Fig. 1 shows the stent that was used to repair the basilary artery tip aneurysm (left image, arrow pointing at the lower side of the picture, middle and right images, arrow pointing at the lower side of the picture) and the metallic artifacts from pieces that were used for the surgical repair of the CAA of the anterior communicating artery (left and right side: arrows pointing in the upper side of the picture). A computed tomography scan was used to acquire these images.

The patient was treated with a long-acting angiotensin-converting enzyme inhibitor-Perindopril, 5 mg once a day (qd) (since February 2016), this being the first line of treatment for arterial hypertension in diabetic patients based on international guidelines (10); β-blockers-Nebivololum 5 mg qd (since February 2016); antiplatelet medication-acetylsalicylic acid, 75 mg qd since (since February 2020); and statins-Atorvastatin, 20 mg qd since (since February 2020) (Table I).

In March 2022, the patient came to the hospital with symptoms of shortness of breath, bilateral lower limb edema, fatigue and a noticeable decline in quality of life; these symptoms are consistent with the clinical symptomatology of heart failure. The symptoms started ~2 weeks prior and got progressively worse up to the point that the patient sought medical support. Given the worsening of the symptoms, the patient's daily activities were perturbed; he was no longer able to perform his daily tasks as he did previously. At that time the patient was undergoing chronic treatments for his pathologies, as aforementioned (detailed in Table I).

Physical examination revealed a high blood pressure of 144/82 mmHg, Grade I obesity, a BMI of 31.72 kg/m^2 and abdominal obesity with a waist circumference of 112 cm and bilateral lower limb edema.

The only available clinical examination for this patient in 2022 was an electrocardiogram that did not reveal any abnormal findings; the patient had a normal regular sinus rhythm and a heart rate of 82 bpm. Other clinical examinations were not available as, at that time, accessibility of the patient's medical information was hampered by the COVID-19 pandemic.

Initial laboratory results for this patient, in 2022, are shown in Table II. The patient had well-controlled type 2 diabetes; HbA1c was 5.2% (normal range, 0-5.6%), but was outside the range regarding secondary prevention of CV events, his total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides were outside treatment targets for him; as a consequence, his overall CV risk was very high (a score of SCORE 2 RISK=14.2%). SCORE 2 RISK is an online risk

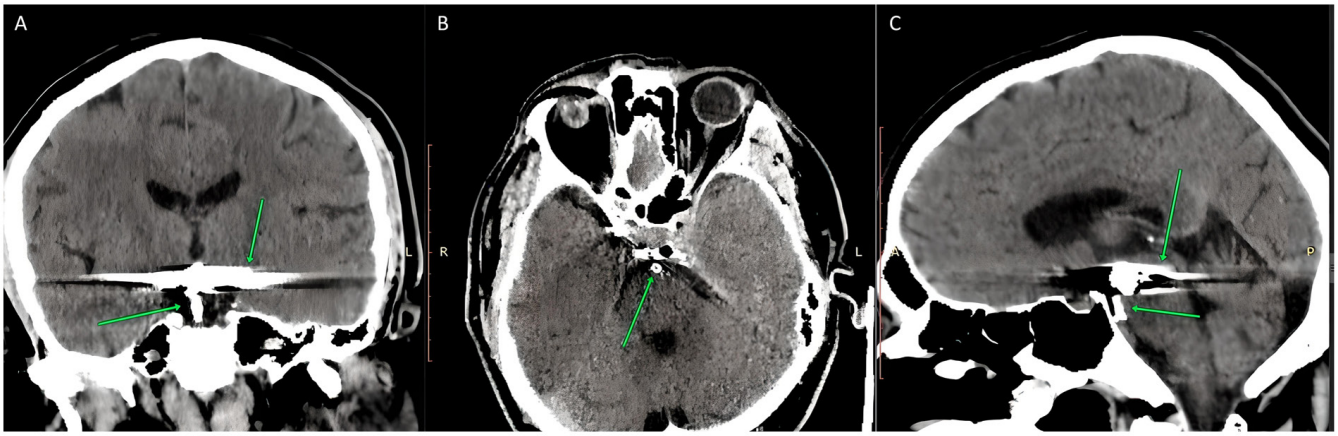

Figure 1. Computed tomography scans of the brain. (A) A posterior view of the stent, the arrow in the lower side of the picture shows the stent and the arrow from the upper side of this image shows the metallic artifacts from pieces that were used for the surgical repair of the cerebral artery aneurysm of the anterior communicating artery. (B) An axial view of the stent that was used to repair the basilary artery tip aneurysm, the arrow points to the stent. (C) A sagittal view of the stent that was used to repair the basilary artery tip aneurysm and it is indicated by the arrow from the lower part of the image. In addition, a sagittal view of the metallic artifacts from pieces that were used for the surgical repair of the cerebral artery aneurysm of the anterior communicating artery, which are indicated by the arrow from the upper part of this image.

assessment model that estimates the 10-year risk of CV disease used in Europe; it is an algorithm that uses simple data such as age, sex, tobacco use, systolic blood pressure, total cholesterol and high-density lipoprotein to produce a numeric value that translates into low risk, medium risk or high risk (<2%, low risk; 2-4.9%, moderate risk; 5-9.9%, high risk; and ≥10%, very high risk) (11).

Due to the uncontrolled LDL levels, a change in statin treatment was suggested to the patient; in February 2020, rosuvastatin 20 mg qd was switched to atorvastatin 20 mg qd and the patient did not experience any side effects of atorvastatin; however, the patient refused to increase the dose of atorvastatin due to the side effects he suffered with rosuvastatin [myalgias and elevated creatine kinase levels when taking high doses of rosuvastatin (20 mg)]. The patient did not experience any side effects from atorvastatin.

In addition, the patient's blood pressure was not adequately controlled, since the guidelines for a diabetic patient suggests that blood pressure values should be <130/70 mmHg (12). At this point, the patient was referred to a cardiologist for a check-up and adjustment of his antihypertensive treatment, but could not get an appointment since the urgency of his condition was still low in the context of the overall pandemic.

After reviewing the patient's case, it was decided that the best course of action was the use of medication with proven CV protective effects. Out of the available classes of drugs for the treatment of diabetes, SGLT-2 inhibitors have shown CV protective effects, and in clinical studies, SGLT-2 inhibitors have shown that they can prolong the life of patients when given early in the course of the disease (1).

In March 2022, SGLT-2 inhibitor (Empagliflozin, 10 mg qd) treatment was launched. This treatment was started despite good glycemic control with a HbA1c of 5.2%, due to the CV benefits of this class of drugs (1). The patient's symptoms on presentation were more indicative of a heart failure. However, it was not possible to run specific tests for confirmation of heart failure (echocardiography and N-terminal pro b-type natriuretic peptide levels) due to the low accessibility to medical services during the pandemic. Based on clinical judgment, a diagnosis of heart failure was assumed and it was decided to administer treatment as a means of performing a therapeutic test.

The patient returned for a follow-up evaluation in March 2023, after 1 year of treatment, when he declared better tolerance for exerting effort, lack of lower limb edema (also revealed at the physical exam), a better quality of life and no more shortness of breath.

At the follow-up physical examination, the patient had a normal blood pressure of 128/70 mmHg, a heart rate of 75 bpm and a lack of peripheral edema; however, the patient was still classed as Grade I obesity (BMI, 30.25 kg/m) and the abdominal obesity persisted (waist circumference, 109 cm). The patient managed to lower his blood pressure and also managed to lose 3 kg of body weight over the year from the initiation of SGLT2 inhibitor treatment.

The patient was evaluated from a biological perspective and the lab values showed a significant improvement in the lipid profile with a slight decline in renal function, a known temporary effect of initiation of SGLT-2 inhibitors. The results of the lipid panel analysis improved with the normalization of cholesterol and triglycerides values, but the patient was still outside the normal range for LDL target for a diabetic patient with a prior CV event; the target for him being <55 mg/dl (Table III).

The patient was evaluated by echocardiography in March 2023. The left ventricular ejection fraction was 55%, diastolic function was normal, left ventricular hypertrophy was present and systolic function was normal; the patient was diagnosed with heart failure with preserved ventricular ejection fraction (data not available).

Additionally, in March 2023, the patient underwent a CT scan of the brain that showed no new onsets of aneurysmal dilations, no new metal clip artifacts, no new aneurysms post-embolization and no acute changes. The SCORE 2 RISK was 11%, which was a reduction of

Table I. Medical history of the patient.

Condition	Baseline treatment	Start/end dates	Switch to other treatments	Start/end dates
Type 2 diabetes	Metformin 2000 mg/day	December 2013-February 2014	Empagliflozin 10 mg/day	March 2022-ongoing
Arterial hypertension	Perindopril 5 mg/day	February 2016-ongoing	-	-
Arterial hypertension	Nebivololum 5 mg/day	February 2016-ongoing	-	-
Dyslipidemia/secondary CV prevention	Rosuvastatin 20 mg/day	November 2013-February 2020	Atorvastatin 20 mg/day	February 2020-ongoing
Secondary CV prevention	Clopidogrel 75 mg/day	November 2013-February 2020	Acetylsalicylic acid 75 mg/day	February 2020-ongoing

UN, unknown; CV, cardiovascular.

Table II. Blood test results from 2022.

Parameter	Value	Normal range
HbA1c, %	5.2	0-5.6
Cholesterol, mg/dl	229	120-200
High-density lipoprotein cholesterol, mg/dl	50	>40 in male subjects
Low-density lipoprotein cholesterol	138	<100 in a diabetic patient and <55 in a patient with prior CV events (5)
Triglycerides, mg/dl	207	40-149
Alanine aminotransferase, UI/l	17	<37
Aspartate transaminase, UI/l	29	<40
Creatinine, mg/dl	0.94	0.6-1.1
eGFR, ml/min/1.73 m^2	91	>90 ml/min

HbA1C, glycated hemoglobin A1c; eGFR, estimated glomerular filtration rate; CV, cardiovascular.

Table III. Blood test results from March 2023.

Parameter	Value	Normal range
HbA1c, %	4.9	0-5.6
Cholesterol, mg/dl	164	120-200
High-density lipoprotein cholesterol, mg/dl	49	>40 in male subjects
Low-density lipoprotein cholesterol, mg/dl	91	<100 in a diabetic patient and <55 in a patient with prior CV events
Triglycerides, mg/dl	119	40-149
Alanine aminotransferase, UI/l	22	<37
Aspartate transaminase, UI/l	34	<40
Creatinine, mg/dl	0.98	0.6-1.1
eGFR, ml/min/1.73 m^2	86	>90

eGFR, estimated glomerular filtration rate; CV, cardiovascular.

3.2% from the initial score registered in 2022; the patient continued with the treatment as part of his further management since this treatment demonstrated improvement of his clinical variables.

Discussion

The mechanism underlying the development of CAA involves endothelial dysfunction, smooth muscle cell apoptosis and

vascular remodeling, and it typically occurs at the bifurcations of cerebral arteries where, due to the high blood flow, a weakening of the vessel wall can occur; this can also be exacerbated due to endothelial injury (13). The patient of the present study had a history of arterial hypertension, an aneurysm of the anterior communicating artery that had been operated on and a ruptured basilar artery aneurysm that was embolized with a stent.

Another potential cause of an emerging aneurysm is an imbalance in the actions of proteolytic enzymes, which can cause a defect in the arterial wall matrix and exacerbate the brittleness of a vessel (14). CAA may be induced by inflammation and oxidative stress; inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), have a well-established role in vascular remodeling. The dysregulated action of inflammatory cytokines is one of the core reasons for the onset of atherosclerosis, and atherosclerosis along with the damage during remodeling of the arterial wall are considered to be the main causes of the onset of CAA (15). Oxidative stress can also increase endothelial dysfunction, and along with inflammatory cytokines, the damage to the arterial wall is exacerbated (16).

Obesity results in the presence of a pro-inflammatory state, characterized by high levels of inflammatory cytokines such as TNF-α and IL-6. The patient was classed as obese since 2010, when at the age of 35 years, he was classed as Grade 1 obese. Obesity is an additional risk factor for the patient's history of CVB events, along with the arterial hypertension mentioned previously (17).

SLGT-2 inhibitors have shown CV benefits in diabetic and non-diabetic patients, with a significant reduction in hospitalizations due to heart failure and also a significant reduction in the onset of stroke in these patients (18). This underlined the choice to use empagliflozin in the present case, and since the patient was a very high-risk CV patient, it would be beneficial to suggest a treatment for improved protection, particularly secondary prevention against another CAA event.

SGLT2 inhibitors have been shown to reduce arterial hypertension, and systolic and diastolic blood pressure, in addition to the reduction in blood glucose levels; and these are hypothesized to be key elements underlying the CV protective effects of these drugs (4,19). Thus, it was hypothesized that empagliflozin may potentially prevent another CAA event, since lowering the blood pressure is known to help with the stabilization of a pre-existing aneurysm and/or the onset of a new one, considering that in the present case, the patient had hypertension since 2013.

Another reason an SGLT-2 inhibitor was used in this patient was the anti-inflammatory effect that this class has shown; in large studies, SGLT-2 inhibitors lowered TNF-α and IL-6 levels (1). This can reduce the likelihood of CAA formation and prevent progression, as inflammation is one of the primary causes of the onset of CAA (5). Thus, empagliflozin was used to reduce inflammation and reduce the vascular remodeling process that leads to the formation of CAA.

Oxidative stress is also involved and plays a crucial role in the development of endothelial dysfunction that can lead to CAA through vascular disorders. SGLT-1 inhibitors have been shown to inhibit NADPH oxidase and reduce overall oxidative stress (20), and this was also considered in the choice of using this treatment.

Another pleiotropic effect of SGLT-2 inhibitors is reduced vascular stiffness and improved endothelial function (21). These effects could help prevent the onset of a CAA event and reduce the risk of rupture of an existing aneurysm.

The renal benefits of SGLT-2 inhibitors are well-established and are mediated by increased sodium excretion by reducing fluid retention, and along with the reduction of arterial hypertension, can lead to better CV hemodynamics (22). The use of SGLT2 inhibitors in a diabetic patient, at a high risk of developing secondary renal impairment from diabetes and hypertension, is a preventative strategy (1), and in the present case, considering the preexisting CAA, it was also a protective measure due to the improvement in CV hemodynamics.

Patients with metabolic syndrome and type 2 diabetes are at higher risk of liver dysfunction compared to the normal population (23). These drugs, SGLT-2 inhibitors, have a significant impact on blood glucose levels as well as insulin sensitivity in peripheral tissues. Furthermore, they are now recognized as effective agents in diabetic patients with CV and renal complications owing to their several pleiotropic effects. Recent evidence suggests that SGLT2 inhibitors interact with hepatic functions and SGLT2 inhibition modulates liver function in pathways that are not yet well defined.

NAFLD is a disorder that covers a spectrum of liver lesions [steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis] that appears in the lack of or minimal alcohol consumption, and in the absence of other causes of liver disease, and is associated with metabolic impairments, including type 2 diabetes (24).

SGLT2 inhibitors have been shown to provide therapeutic benefits for NAFLD, as they can reduce the mass of stored fat in the liver and normalize its composition. Studies have shown that SGLT2 inhibition using empagliflozin attenuates inflammatory responses.

A clinical study has shown that long-term therapy with SGLT2 inhibitors provides histological benefits for the livers of patients with T2DM and NAFLD by significantly reducing steatosis and normalizing liver tissue composition. Empagliflozin was found to improve lobular inflammation, steatosis, bloating and fibrosis (25).

SGLT2 inhibitors may serve as promising therapeutic agents for patients with NASH. Current evidence strongly suggests that SGLT2 inhibitors may improve liver failure in patients with NAFLD either by promoting fat burning or by attenuating inflammatory processes (25).

In the present case, the patient was also diagnosed with NASH; therefore, based on the above, the use of SGLT-2 inhibitors may have improved hepatic function.

Studies have shown that the use of SGLT-2 inhibitors reduced cerebral ischemia and also improved cardiovascular outcomes following the modelling of a stroke in animals (26). This, together with the other beneficial effects of reducing CV risk, CV events, reducing arterial hypertension, reducing oxidative stress and improving endothelial function in diabetic patients (1), underlined the rationale for the use of empagliflozin in the patient of the present study.

In a study conducted by Jin *et al* (27), the effects of empagliflozin were assessed in patients with abdominal aortic aneurysms (AAA), and it was found that it could potentially benefit such patients. They described that SGLT-2 inhibitors

were present in the vascular wall and played a key role in reducing endothelial dysfunction and also in the remodeling of the arterial wall. Thus, empagliflozin can protect patients with AAA by lowering the blood pressure, in-turn reducing vascular wall stiffness, and therefore lower the risk of an AAA rupture. The same mechanism may also underlie the beneficial effects of empagliflozin in CAA, making it a drug that can benefit several types of aneurysms. Thus, this drug has promising results as a novel preventative and conservative treatment for AAA.

A study by Liu *et al* (28) showed that empagliflozin reduced lipid levels and reduced systemic inflammation in non-diabetic mouse models. By reducing oxidative stress in the vascular wall alongside the effect of reducing blood pressure, this medication may prevent damage to the vascular wall and therefore prevent the onset of an aneurysm or the rupture of a pre-existing aneurysm.

However, the last two studies mentioned were performed on non-diabetic populations, so it is unknown whether the effects that this drug has on patients without diabetes are replicated in diabetic patients; to the best of our knowledge, there are no studies on the effect of empagliflozin on lipid levels in diabetic patients.

The present study is limited by the fact that the findings pertain to only one patient and are therefore not universally applicable. In addition, the patient was a white/Caucasian male from Eastern Europe, and thus, the findings may not apply to individuals from other races, as genetic factors may be at play, which were not assessed here. Another limitation was the lack of cardiac ultrasound images given the limitations in clinical availability due to the pandemic at the time.

In conclusion, SGLT-2 inhibitors may be a suitable option for the prevention of CAA. To date, only a few cases have been reported; thus, there is a need for further study and potentially a clinical trial; however, the results do seem promising. The effects, which include reducing blood pressure, inflammation and oxidative stress, and improving endothelial function, are all beneficial for patients with CV impairment, so there is hope that these drugs will show benefits in patients with CAA.

It is not possible to say with certainty whether the use of SGLT-2 inhibitors in this patient definitively had a protective effect from a further potential instance of a CAA. However, the patient's quality of life was notably improved and CV risk was reduced by 3.2%.

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Availability of data and materials

The datasets generated in the present study may be requested from the corresponding author.

Authors' contributions

OAP conceived the study, wrote and revised the manuscript, and was in charge of Software and conducting the clinical investigation. DR was in charge of Software and collection of clinical data. MAB analyzed the data and was in charge of the methodology of this research. GG collected the data, analyzed the data, participated in the clinical investigation and was in charge of project administration. RMN and GG supervised the study and the corrections of the preliminary versions of the manuscript, also were involved in the conceptualization of the research and validated the manuscript. OAP, GG and MAB confirm the authenticity of all the raw data. All authors have read and confirmed the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of his data and images.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

ChatGPT was used to correct the spelling and grammar of the manuscript. During the preparation of this work, AI tools were used to improve the readability and language of the manuscript. The authors revised and edited the content produced by the AI tools as necessary, and take full responsibility for the final content presented in the manuscript.

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