REVIEW PAPER

JMS Journal of Medical Science

Bexagliflozin – evaluation of the clinical efficacy, safety profile and potential new applications of the SGLT2 inhibitor: a review of the literature

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https://doi.org/10.20883/medical.e1226

Keywords: flozin, bexagliflozin, EGT1442

Received 2025-02-07
Accepted 2025-05-30
Published 2025-06-30

How to Cite: Muszyński J. Bexagliflozin – evaluation of the clinical efficacy, safety profile and potential new applications of the SGLT2 inhibitor: a review of the literature. Journal of Medical Science. 2025 June;94(2);e1226. doi:10.20883/medical.e1226

ABSTRACT

Introduction. Type 2 diabetes (T2DM) is a growing global health, social, and economic problem. T2DM is often accompanied by other diseases and is associated with complications such as kidney damage and cardiovascular diseases. The 21st century has seen a breakthrough in treating T2DM, including incretins and flozins. This review focuses on bexagliflozin, a new SGLT-2 inhibitor approved by the FDA for treating T2DM. The efficacy, safety, and potential benefits of new uses are analysed.

Materials and methods. Sources were obtained using PubMed and Google Scholar, as well as Medline, with the keywords: bexagliflozin, EGT1442, new indications for bexagliflozin, and bexagliflozin trials.

Results. Unlike other SGLT-2 inhibitors, bexagliflozin has a different molecular structure, which may increase its selectivity and efficacy. Preliminary results suggest that the drug may offer additional therapeutic benefits over other drugs in this group, particularly in the treatment of hypertension and cardiac arrhythmias. Studies are currently underway to investigate its potential use in the treatment of chronic kidney disease in children and sleep apnoea.

Conclusions. Bexagliflozin shows promise as a treatment for type 2 diabetes, with additional potential benefits in treating other conditions. Although the drug is relatively new to the market, preliminary studies indicate that it may offer advantages over other SGLT-2 inhibitors in some areas. Nevertheless, further clinical trials are needed to further evaluate its efficacy compared to other therapies and its potential in a broader range of applications

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease, the main feature of which is elevated blood glucose levels due to impaired insulin production or response [1,2]. Symptoms of the disease were known in antiquity, and since the 17th century, it has been reported in Europe, Asia and South America [3]. According to the WHO, there are currently about 537 million adults struggling with T2DM, and an additional 541 million people have impaired glucose tolerance, which sig-

nificantly increases the risk of developing T2DM [4]. Moreover, the number of cases of T2DM is steadily increasing. Data show that the incidence rate has increased by 157.63% between 1990 and 2019 [5]. It is estimated that the number of adults with T2DM will reach 643 million by 2030 and 783 million by 2045 [6]. Although the peak incidence in both sexes is between the ages of 60 and 64, men are diagnosed earlier than women [5]. Moreover, it is believed that up to half of patients with T2DM may be unaware of their disease. T2DM is associated with numerous complications, both macrovascular and microvascular, which significantly affect mortality. It is estimated that as much as 12% of global health care spending goes to treating complications of the disease [7]. In 1990, the DALY (disability-adjusted life years) rate was 628.33 per 100,000 people, while in 2019 it had increased to 801.55 per 100,000 people [5]. In 2021, T2DM accounted for more than 12.2% of deaths in the 20–79 age group [2]. Over the past 30 years, the number of T2DM-related deaths has increased by 142.90% [5]. For this reason, new therapeutic options are constantly being sought [6]. A relatively new group of drugs used in the treatment of diabetes mellitus are inhibitors of the sodium-glucose cotransporter SGLT2. Their mechanism of action is through the induction of sugar metabolism, which leads to a reduction in serum glucose levels [8]. These drugs have been shown to have beneficial cardio- and nephroprotective effects [1]. In addition, SGLT2 inhibitors appear promising as adjunctive therapy for conditions such as hypertension, asthma, and chronic obstructive pulmonary disease. They may also have beneficial effects on the central nervous system, non-alcoholic steatohepatitis and the treatment of obesity [8]. In clinical practice, SGLT-2 inhibitors are used as second-line drugs in the treatment of type 2 diabetes when glycemic control with metformin is inadequate, or as first-line drugs in high-risk patients with cardiovascular disease, heart failure (HF) or chronic kidney disease [9]. It is indicated that only 8.3% of patients who could benefit are taking SGLT2 inhibitors [10]. The first drug in this group, approved by the Food and Drug Administration (FDA) in 2013, was canagliflozin [8]. Subsequent flozines, such as empagliflozin and dapagliflozin, gained approval a year later, while ertugliflozin was approved in 2017 [1]. The fifth flozin, approved in 2023 for the treatment of type 2 diabetes, is bexagliflozin [6,10]. It was registered as a drug to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise. However, the drug is not currently approved in Europe [11]. Although bexagliflozin belongs to the SGLT2 inhibitors, it is distinguished by its molecular structure, which translates into its high selectivity [2,3]. Its potential use in veterinary medicine has been recognised [12].

Materials and methods

In preparing the manuscript, a literature review was conducted from October 2024 to January 2025. The search for relevant sources was performed using PubMed, Google Scholar, and Medline databases. The following keywords were used in the search: bexagliflozin, EGT1442, new indications for bexagliflozin, and bexagliflozin trial. Inclusion criteria included original papers, systematic reviews, meta-analyses, and narrative reviews published in English, with a particular focus on clinical studies addressing the efficacy, safety, and new potential uses of bexagliflozin. However, works of low methodological quality and articles that did not provide relevant scientific data were excluded. The search process is summarised in **Figure 1**.

Structure and mechanism of action

Bexagliflozin, also known as EGT1442, has the IUPAC name: (2S,3R,4R,5S,6R)-[4-chloro-2-(4-((2-(cyclopropoxy)ethoxy)phenyl)methyl)-3-(phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol. Its chemical formula is $C_{24}H_{29}ClO_7$, and its molecular weight is 464.16018 g/mol [13]. The structural formula of bexagliflozin is presented in **Figure 2**. The bexagliflozin molecule consists of a glycone fragment, an aglycone fragment, a central phenyl ring and a peripheral phenyl ring. The glycone and aglycone fragments are linked by a C-glycosidic bond, which is more metabolically stable compared to an O-glycosidic bond. Bexagliflozin is a derivative of dapagliflozin, and the main difference between the two is the R2 group on the phenyl ring. Bexagliflozin contains a cyclopropyl ethoxy group, which gives it grea-

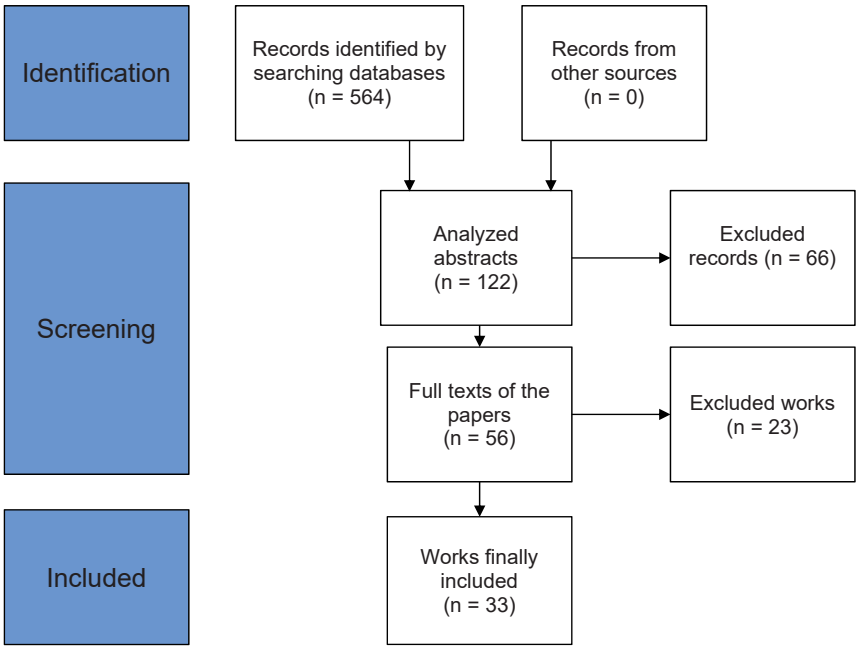

Figure 1. Scheme of review and identification of works.

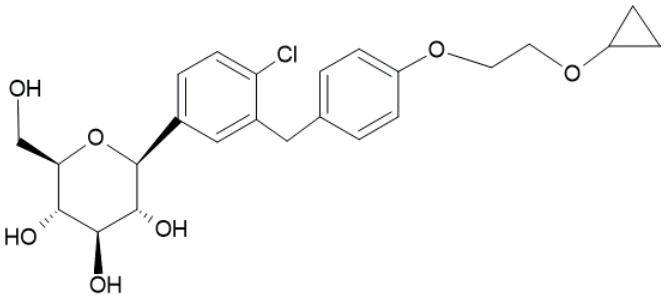

Figure 2. Structural formula of bexagliflozin.

ter SGLT2 inhibitory potency and higher selectivity to SGLT1 compared to dapagliflozin, which has an ethoxy group. Due to this unique molecular structure, bexagliflozin exhibits a more potent action and greater potency than dapagliflozin, and its selectivity against SGLT2 is almost twice as high. In addition, compared to canagliflozin, bexagliflozin has greater selectivity, even though both drugs have similar SGLT2 inhibitory potency [2]. Also, a study by Celik et al. showed that bexagliflozin binds more weakly to DPPIV compared to the other drugs tested, confirming that its efficacy in the treatment of type 2 diabetes is primarily due to SGLT2 inhibition rather than a direct effect on DPPIV [3]. Bexagliflozin belongs to the SGLT-2 inhibitor group. They are oral drugs that are absorbed from the gastrointestinal tract into the blood and then filtered through the kidneys, where they reach the glomeruli [2]. There are two types of sodium-glucose cotransporters: SGLT1 and SGLT2, which play a key role in glucose reabsorption [3]. It is estimated that SGLT2 is responsible for 90% of glucose reabsorption, while SGLT1 is responsible for the remaining 10% [2]. The mechanism of action of flozins involves inhibition of sodium-glucose cotransporter subtype 2, located in the proximal ileal tubule of the kidney. Inhibition of SGLT2 leads to inhibition of reabsorption of filtered glucose and sodium, resulting in sugaruria and natriuresis. This mechanism, by lowering blood glucose levels, reduces the need for insulin, which is particularly important in the context of impaired insulin secretion or action in type 2 diabetes mellitus (T2DM).In addition, the loss of glucose and sodium produces a diuretic effect, leading to a reduction in plasma volume,

which is essential in the treatment of heart failure or hypertension. In addition, the loss of glucose is associated with a loss of calories, which can be beneficial in the treatment of obesity [14].

Dosage

Bexagliflozin is a drug intended for oral administration [15]. It is recommended to be taken at a dose of 20 mg once a day. [16]. It should be taken in the morning, regardless of meals [17]. The maximum concentration of bexagliflozin in the blood appears within 2–4 hours after oral administration, and its half-life is about 13 hours [13]. Before initiating therapy, it is recommended to assess renal function. A dose of 30 ml/min/17.3 m2 is the same as in patients with normal renal function [17].

Effectiveness

The 12-week study evaluated the efficacy of bexagliflozin in monotherapy in adult patients, comparing it with placebo. The treatment effects in placebo-adjusted HbA1c reduction for the 5 mg, 10 mg, and 20 mg groups were shown to be -0.55%, -0.68%, and -0.80%, respectively. In addition, a dose-dependent lowering effect on fasting plasma glucose levels was observed. In terms of weight reduction, decreases of 1.44 kg, 1.59 kg, and 1.75 kg were noted for the 5 mg, 10 mg and 20 mg doses of bexagliflozin. In addition, a mean decrease of -3.83 mmHg in systolic blood pressure (SBP) and -2.04 mmHg in diastolic blood pressure (DBP) was recorded in patients taking the drug at the 20 mg dose [18]. In a prolonged 96-week study using only the 20 mg dose of the drug, a reduction in HbA1c by -0.53%, systolic blood pressure (SBP) by -4.9 mmHg, and diastolic blood pressure (DBP) by -1.43 mmHg was achieved. In addition, a weight loss of -2.41 kg was noted. Treatment with bexagliflozin for 96 weeks was shown to have a lasting effect [19]. Halvorsen et al. studied the impact of baxogliflozin compared to placebo in combination with metformin in adult patients with T2DM. After 24 weeks of treatment, they showed that bexagliflozin was more effective in reducing HbA1c by 0.7% compared to placebo plus metformin. The adjusted weight loss in the bexagliflozin group was 3.6 kg, compared with only 1.1 kg in the placebo group, a difference of 2.5 kg. In addition, there was a decrease in systolic blood pressure in the flozins group, in contrast to the placebo group, where blood pressure increased. [20] In 2024, the efficacy of bexagliflozin was compared to that of dapagliflozin. The results showed that the difference in HbA1c reduction between the bexagliflozin and dapagliflozin groups was 0.03%, in favour of dapagliflozin. The difference in mean weight change from baseline to week 24 was -0.30 kg in favour of bexagliflozin. After 24 weeks, HbA1c < 7% was achieved by 32.3% of patients in the bexagliflozin group and 31.6% in the dapagliflozin group, while HbA1c < 6.5% was achieved by 12.2% and 11.2% of patients, respectively. [21] In another study in patients taking metformin, the addition of bexagliflozin compared to glimepiride at week 96 resulted in a difference in HbA1c -2.30 mmol/mol (-0.21%), confirming the greater efficacy of bexagliflozin. It should be noted, however, that at the beginning of the study, it was glimepiride that resulted in a greater average reduction in HbA1c, but ultimately bexagliflozin proved more effective. In addition, the percentage of patients experiencing severe or documented symptomatic hypoglycemia was found to be 20.8% in the glimepiride group compared to 3.3% in the bexagliflozin group. Bexagliflozin showed better efficacy than glimepiride in reducing body weight, with the added benefit of lowering fasting glucose levels and reducing the rate of eGFR decline [22]. Another study compared the efficacy of bexagliflozin to sitagliflozin, an oral dipeptidylpeptidase (DPP-4) inhibitor drug, as an adjunct to metformin treatment. Bexagliflozin was not inferior to sitagliflozin in terms of reducing % HbA1c and provided a significantly greater reduction in fasting glucose. Among overweight and obese participants, significant weight loss was observed, with adjusted weight losses of 3.35 kg in the bexagliflozin group and 0.81 kg in the sitagliflozin group, resulting in a difference of 2.54 kg. In addition, patients in the bexagliflozin group had a decrease in SBP of 4.23 mmHg, compared to 1.90 mmHg in the sitagliflozin group [23]. It is noteworthy that the reduction in HbA1C compared to placebo in maximum bexagliflozin was higher (0.80%) than with maximum empagliflozin at 0.68%.[18] To date, no randomised controlled trial has been published that directly compared bexagliflozin with other SGLT-2 inhibitors in the treatment of type 2 diabetes. Therefore, further investigation is needed to determine whether bexagliflozin is more or less

effective than other common SGLT-2 inhibitors used in clinical practice [6]. Some researchers note that in indirect comparisons, bexagliflozin's HbA1c reduction was higher (0.80%) compared to empagliflozin (0.68%) at maximal doses. [18]

Side effects

In studies evaluating the safety of bexagliflozin versus placebo, the percentage of patients experiencing at least one adverse event was 42.3% in the bexagliflozin group and 40.3% in the placebo group. Most reported adverse events were mild to moderate [18]. In the 96-week extension study, although genital fungal infections are frequently observed with some drugs, their incidence was low, and differences from placebo were not noticeable. In addition, there was no increased risk of hypoglycemia in the bexagliflozin group compared to placebo. Severe adverse reactions occurred less frequently in the bexagliflozin group (2.8%) than in the placebo group (8.5%) [24]. In the study comparing bexagliflozin with dapagliflozin, the most common adverse reactions were urinary tract infections (6.4% in the bexagliflozin group vs. 8.4% in the dapagliflozin group) and hypoglycemia (3.5% vs. 3.9%). In addition, major cardiovascular incidents (1.48% vs. 0.99%) and falls and fractures (0.49% vs. 1.48%) were reported. The incidence of urinary ketone bodies was higher in the bexagliflozin group (9.85% vs. 4.43%) [21, 24]. In another study, bexagliflozin increased HDL and LDL cholesterol levels, but improved the LDL to HDL ratio, which is beneficial for cardiovascular health [16, 20]. In a study comparing bexagliflozin with glimepiride, 80.8% of patients (172 patients) taking bexagliflozin experienced at least one treatment-related adverse event (AE), compared with 81.2% (173 patients) in the glimepiride group. Urinary tract infections and joint pain were more frequently observed in the bexagliflozin group compared to the glimepiride group [22]. In another study comparing bexagliflozin with sitagliptin, adverse events occurred in 47.1% of patients in the bexagliflozin group and 56.0% of patients taking sitagliptin. Serious adverse events were reported in 3.7% of patients in the bexagliflozin group and 2.1% in the sitagliptin group [23]. The meta-analysis did not show that bexagliflozin increased the risk of Major Adverse Cardiovascular Events (MACE) in patients with T2DM compared to placebo or active control. [25] Another meta-analysis showed that bexagliflozin (20 mg) significantly lowered eGFR compared to other SGLT2 inhibitors, with a probability of 77.8%. In addition, the risk of urinary tract infections was higher with bexagliflozin (20 mg) than with ertugliflozin (5 mg) [26]. The C-476 study showed a higher incidence of amputation in patients treated with bexagliflozin compared to placebo [27]. The drug's effects may further be associated with fluid loss, which can lead to dehydration [17]. Registration studies of the drug showed that the most common adverse effects during bexagliflozin use were more frequent urination, fungal infections in the genital area and urinary tract infections. Such effects are also characteristic of other SGLT-2 inhibitors, due to the process of glucosuria [6].

Contraindications and interactions

Before initiating bexagliflozin therapy, it is necessary to assess renal function, as well as analyse the patient's history for factors that increase the risk of amputation. It should be noted that bexagliflozin may potentiate the hypoglycemic effects of other drugs, such as acarbose, GLP-1 receptor agonists, dipeptidylpeptidase-4 (DPP-4) inhibitors, sulfonylurea derivatives, and insulin [13,17]. In addition, bexagliflozin is contraindicated in patients with type 1 diabetes, as it may increase the risk of developing ketoacidosis. The drug is contraindicated in patients with end-stage chronic kidney disease who are receiving dialysis and in those with an estimated glomerular filtration rate (eGFR) of ≤30 ml/min/1.73 m² [6]. It should not be administered to pregnant women or nursing mothers. The use of the drug is also not recommended in patients with severe liver failure [17]. Attention should be paid to patients with type 2 diabetes who have been given SGLT2 inhibitors (including bexagliflozin), who have been reported to develop ketoacidosis, a serious, life-threatening condition requiring emergency hospitalisation. Adult patients with type 2 diabetes treated with bexagliflozin who show clinical signs of dehydration and severe metabolic acidosis (with associated symptoms such as nausea, vomiting, abdominal pain, general malaise, or shortness of breath) should be tested for ketoacidosis, regardless of blood glucose levels. It has been observed that bexagliflozin-associated ketoacidosis, although rare, can occur even at glucose levels below 250 mg/dl [6].

New research directions and applications of bexagliflozin

In animals

It is the first gliflozin registered for the treatment of diabetes in animals, specifically in cats [12]. It has shown glucose-lowering potential in dogs, suggesting its potential use in other animals as well [28].

In humans

Due to the relatively recent FDA approval of bexagliflozin and its short time on the market, available trial data on this drug are still limited [2]. In 2021, a study on the use of bexagliflozin for the treatment of spontaneous hypertension was completed with promising results [29]. A meta-analysis showed that bexagliflozin may have borderline tachycardia-reducing effects [30]. The results of these studies are included in **Table 1**. In 2027, a trial is scheduled to be completed to evaluate the impact of bexagliflozin on the severity of sleep apnoea in overweight or obese adults, compared with placebo [31]. The potential is seen for the use of bexagliflozin in pediatric patients for the treatment of type 2 diabetes between the ages of 10 and 17, with a projected completion date of 2031 [27]. It is described that bexagliflozin is the cheapest SGLT2 inhibitor available on the market in the US [32]. Its introduction may increase competition among antidiabetic therapies, which is likely to translate into lower prices for other drugs in this group [33]. However, it is noted that future cost-effectiveness analyses will be needed to determine whether bexagliflozin is more cost-effective than other SGLT2 inhibitors for the treatment of type 2 diabetes [6].

Conclusions

Bexagliflozin is the fifth flozin registered for the treatment of type 2 diabetes in the United States, marking an essential step in the development of treatments for the disease. As SGLT-2 inhibitors, flozines are playing an increasingly important role in the treatment of type 2 diabetes, not only for their ability to lower blood glucose levels, but also for their beneficial effects on other aspects of patients' health. Numerous clinical studies confirm that bexagliflozin effectively lowers glycated haemoglobin (HbA1c), a key indicator of long-term glycemic control. As a result, the drug shows high efficacy in the treatment of type 2 diabetes, especially in patients for whom previous therapies have not yielded satisfactory results. A critical aspect of bexagliflozin is its good safety profile. Studies indicate that the incidence of side effects, such as urinary or genital tract infections, is comparable to other drugs in the flozin group. These effects are well known and are related to the mechanism of action of the

Table 1. Summary of bexagliflozin studies in indications other than type 2 diabetes.

Name of study/Authors	Methodology	Results
THR-1442-C-603 [29]	The study evaluated the Effect of bexagliflozin 20 mg on the change in SBP and DBP values after 24 and 36 wks of cumulative exposure in 673 participants compared to placebo.	At the 24th week, a decrease in SBP of 9,262 mmHg and a decrease in DBP of 4,044 mmHg were observed. At the 36th week of treatment, there was a decrease in SBP of 12,454 mmHg and a decrease in DBP of 5,566 mmHg.
Xu et al. [30]	A study of the relationship between SGLT2 inhibitors and cardiac disorders conducted on a group of 35,432 patients using these drugs.	Bexagliflozin may have a borderline reducing effect on the incidence of ventricular tachycardia (RR 0.25; 95% CI 0.06–1.00; P = 0.05). Bexagliflozin did not clearly affect the incidence of cardiac arrest (RR 2.99; 95% CI 0.77–11.60; P = 0.11).
ADIPOSA [31]	The study will include overweight/obese adults (BMI 25–40 kg/m²) and moderate/severe OSA, evaluating whether bexagliflozin (20 mg/day) reduces AHI compared to placebo, as well as its effects on visceral fat/neck volume, closing pressure, fluid shift, and clinical indicators of OSA severity and sleep deprivation.	The study is scheduled to be completed in 2027.

AHI – apnea hypopnea index, SBP – Systolic Blood Pressure, DBP – Diastolic Blood Pressure, OSA – obstructive sleep apnoea, SGLT2 – Sodium-Glucose Co-Transporter 2.

flozines, which increase the excretion of glucose in the urine, which can promote the development of infections. However, it should be kept in mind that bexagliflozin is a relatively new drug on the market, and thus long-term studies evaluating its efficacy and safety, especially in the context of treating cardiovascular disease, are still lacking. Previous studies of bexagliflozin in the treatment of hypertension and cardiac arrhythmias indicate that the drug may have broader applications. If its multi-target effects are confirmed, it could reduce polypharmacy, increasing the safety of therapy and patient comfort. However, further studies are needed to determine in which patient groups it will provide the most significant benefit. Also hopeful are the planned studies on the use of bexagliflozin for the treatment of chronic kidney disease in children. If the results of these studies prove promising, it could open up new therapeutic options for young patients in whom currently available treatment options are limited. It is also worth noting a unique aspect of bexagliflozin – it is the first flozin registered not only for the treatment of diabetes in humans but also in animals. This shows how drugs developed for humans can find application in veterinary medicine, which can help improve animal health.

Acknowledgements

List of abbreviations: AHI: Apnea Hypopnea Index;; DBP: Diastolic Blood Pressure; FDA: Food and Drug Administration; HbA1c: Hemoglobin A1c; OSA: Obstructive Sleep Apnea; SBP: Systolic Blood Pressure; SGLT2: Sodium-Glucose Co-Transporter 2; T2DM: Type 2 Diabetes Mellitus.

Availability of Data and Materials
All data generated or analysed during this study are included in the published article.

Author's Contribution
JM (Józef Muszyński): Conceptualisation, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Supervision, Project Administration, Writing – Review & Editing. The author read and approved the final content.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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