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# **GLP-1 Receptor Agonists: Therapeutic Benefits in Real Function, Cardiovascular Risk, and Physical Activity – A Systematic Review**

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# ABSTRACT

**Introduction:** Type 2 diabetes is one of the greatest challenges of modern medicine. Its growing prevalence and numerous complications, especially cardiovascular ones, demand constant improvement of treatment strategies. Cardiovascular disease remains the leading cause of death in these patients, highlighting the importance of therapies that address both glycaemic control and cardiovascular risk.

**Aim of the study:** This paper discusses the effects of GLP-1 receptor agonists (GLP-1 RA) and analyses recent data on their impact on cardiovascular risk, renal function, and interaction with physical activity. Key clinical trials and practical applications in daily practice are also presented.

State of knowledge: GLP-1 RAs are well-established in the treatment of type 2 diabetes and obesity. They effectively lower glucose levels and reduce body weight while offering

cardiovascular and nephroprotective benefits. Their role is particularly significant in patients with chronic kidney disease. Emerging data also suggest possible applications beyond diabetology, including neurology and cardiology.

**Material and methods:** A PubMed search was conducted using relevant keywords for studies available up to March 2025. Only English-language publications were included. After title and abstract screening, full texts of eligible articles were analysed.

**Conclusions:** GLP-1 RAs are a valuable part of therapy for patients with type 2 diabetes and obesity. They improve glycaemic control, support weight loss, and reduce cardiovascular and renal risk. Their safety profile allows for combination with other drugs. When used alongside physical activity, they can significantly enhance health outcomes and quality of life.

Keywords: GLP-1 RA, semaglutide, type 2 diabetes, cardiovascular risk, macroalbuminuria

#### 1. INTRODUCTION

**1.1 Mechanisms of action of GLP-1 RA on natiuretic effect and blood pressure regulation** The use of GLP1-RAs significantly clinically reduces blood pressure via various, effects such as increased natriuresis, effects on the RAAS, weight loss, or more independent effects of NOdependent vasorelaxation and changes in endothelial cell function. A 2021 study showed that, via sodium-hydrogen exchanger 3 (NHE3) inhibition, GLP1-RAs induce sodium excretion and improve renal urinary flow in both healthy subjects and type II diabetics. They have also been shown to act indirectly by affecting the renin-angiotensin-aldosterone system through lowering renin and angiotensin II levels [1]. They also affect natriuresis and diuresis through modulation of tubular exchange of ions such as calcium, sodium, potassium. In a study performed on patients with type II diabetes, the authors were able to demonstrate a significant increase in brachial artery diameter, which was mediated through GLP1 receptor expression in endothelial cells [1].

#### 1.2 Mechanisms of action of GLP-1 RA for anti-inflammatory and antifibrotic effects

The GLP-1 receptor is present in cardiomyocytes and endothelial cells. It can directly and indirectly affect the cardiovascular system. It increases endothelial function and microvascular

perfusion, thereby improving microvascular blood flow and lowering blood pressure [2]. Studies have shown that GLP-1 RAs through protein kinase activation and cyclic AMP production inhibit inflammatory signalling pathways. This leads to reduced albuminuria and improved histopathological features in inflammation. This effect may be attenuated by nuclear factor Kappa B (NF-kB), which is induced by hyperglycaemia. This factor affects endothelial nitric oxide synthase and TNF-alpha expression in podocytes. Downregulation of NF-kB will increase endothelial nitric oxide synthase levels and decrease TNF-alpha expression, which will modulate the beneficial effects of GLP-1R [1].

#### 1.3 Mechanisms of action of GLP-1 RA on cholesterol modulation

GLP-1 RAs can affect cholesterol metabolism by increasing ABCA-1 expression and decreasing miR19b expression in isolated hepatocytes. They also show statin-like effects by inhibiting HMG-CoA reductase and sterol regulatory element binding protein 1C (SREBP-1C) [3].

#### 2. MATERIALS AND METHODS

PubMed databases were searched using appropriate keywords for accessible studies published until April 2025. Only articles written in English were included. Titles and abstracts were screened first, followed by an evaluation of relevant full-text publications.

#### **3. DISCUSSION**

#### 3.1 Effects of GLP-1 agonists on renal function - a review of clinical trials

## 3.1.1 Effects on urinary albumin excretion - literature review

GLP-1 receptor agonists significantly reduce urinary albumin excretion. The authors of the 2022 meta-analysis in data collected from 18 randomised controlled clinical trials showed that treatment with GLP-1 RA significantly reduced urinary albumin excretion (WMD: -18.01 mg/day, 95% CI: -31.20, -4.82, P = .007, I2 = 23%). At the same time, the authors concluded that GLP-1 agonists did not significantly affect changes in creatinine levels and glomerular filtration rate. The agonists showed nephroprotective effects, including a reduction in the development of microalbuminuria in patients with type 2 diabetes mellitus. The authors noted that the mechanisms by which GLP-1 Ar affects the reduction of albumin excretion are not fully understood and further research is needed [4]. In a 2017 review article, the authors using the available literature and their own research also concluded that GLP-1 RAs reduce urinary albumin excretion. The authors suggest that analogues may play a role in reducing kidney damage and the incidence of albuminuria [5] A meta-analysis of 22 articles involving 39714

patients indicated that the use of analogues was associated with a reduction in albuminuria in patients with type two diabetes by (weighted mean difference -16.14%, 95% CI -18.42 to -13.86%; p < .0001) compared to the control group. The authors noted that most GLP-1Ra showed a significant reduction in albuminuria compared to the control group exenatide (WMD -11.74%, 95% CI -15.93 to -7.55%; p < .00001), liraglutide (WMD -16.52%, 95% CI -21.28 to -11.75%; p < .0001), dulaglutide (WMD -18.45%, 95% CI -22.67 to -11.75%; p < .00001), efpeglenatide (WMD -18.00%, 95% CI -20.87 to -15.13%; p < .00001), subcutaneous semaglutide (WMD -15.70%, 95% CI -28.93 to -2.48%; p = .02) and oral semaglutide (WMD -33.00%, 95% CI -65.83 to -0.17; p = .05). Only with lixisenatide was there no significant reduction in albuminuria compared with the control group (WMD -9.42%, 95% CI -22.59 to 3.75%; p = .16). Compared with antidiabetic drugs, agonists noticeably reduced albuminuria, excluding insulins (similar effect) (WMD -11.93%, 95% CI -16.22 to -7.64%; p < .00001) [6] Often their effect on reducing urinary albumin excretion is presented as the main benefit of GLP-1 RA therapy. Comparing the LEADER study (liraglutide 1.8mg compared to placebo), SUSTAIN-6 (semaglutide 0.5/1mg compared to placebo) and REWIND (dulaglutide 1.5mg compared to placebo) showed a reduction in new-onset macroalbuminuria, which was associated with a reduced risk of nephropathy. Dulaglutide also reduced albuminuria in the REWIND study. Another study showed that in patients with G3 chronic kidney disease, the use of liraglutide resulted in reduced albuminuria and improved glomerular filtration rate. Some studies also showed the effect of liraglutide and lixisenatide on the urine albumin/creatinine ratio (UACR). Both studies showed that after the use of the analogue, the UACR decreased compared to placebo, in the case of lixisenatide slightly. To summarise the work, it can be concluded that a reduction in urinary albumin excretion can be observed when using GLP-1 RA. These analogues become a key element of renal protection in diabetes [7]. Other authors also used the LEADER, SUSTAIN-6, ELIXA, and REWIND studies. They reached similar conclusions to their predecessors, but added a post hoc analysis of the SUSTAIN 1-5 and 7 studies, where semaglutide showed a 30% reduction in albuminuria and regression to micro- or normoalbuminuria, regardless of previous degrees of albuminuria. In addition, post hoc analysis of the ELIXA trial showed a reduced risk of a first macroalbuminuria event in patients without macroalbuminuria at baseline and a lower rate of change in UACR in patients with micro- or macroalbuminuria. At the same time, the authors indicate that further studies are underway to assess the effect of GLP-1 RA on renal outcomes [1]. At the same time, it is worth noting that the AWARD-7 study did not find significant differences between dulagdite and insulin glargine with type 2 diabetes and moderate to severe ckd and moderate to severe CKD. (LSM -22.5%

(95% CI -35.1 to -7.5) with dulaglutide 1.5 mg; -20.1% (-33.1 to -4.6) with dulaglutide 0.75 mg; -13.0% (-27.1-3.9) with insulin glargine) [8]. In animal models of diabetic kidney disease, GLP-1 R analogues show the ability to reduce albuminuria independently of the effect on glucose levels. In a rat model of streptozotocin-induced type 1 diabetes, exenatide and liraglitide were able to reduce albuminuria and renal inflammation without concomitantly lowering blood glucose levels [9].

Mechanisms for reducing albuminuria:

These are numerous and include, but are not limited to, improved glycaemic control, reduction of oxidative stress, increased sodium excretion, and altered glomerular haemodyma [1]. At the same time, it is thought that the reduction in albuminuria may be influenced by the effect of GLP-1RA on traditional DKD factors, namely hyperglycaemia, obesity or hypertension [8]. Combining this with the satisfactory effects of albuminuria reduction and the fact that albuminuria is a strong predictor of worsening renal function, a reduction in albuminuria may indicate a reduction in nephrological risk [8].

#### 3.1.2 Changes in GFR (glomerular filtration rate) - literature review

The beneficial effects of GLP-1 RA on the kidney are thought to be due to their antiinflammatory, antioxidant and vasodilator properties, as well as blood pressure reduction and weight reduction. Numerous studies indicate that they contribute to slowing eGFR decline [10]. The 2023 observational study compares the effects of GLP-1 and basal insulin on renal function in adult patients with type 2 diabetes taking GLP-1R analogues or basal insulin from 2010 to 2019. Patients were matched according to propensity-score matching in a 1:1 ratio and observed until October 2021 (intention-to-treat [ITT] analysis). In the intention-to-treat analysis (astreated [AT]), the analysis was completed when the study drug was discontinued or treatment with the comparator drug was initiated. In the AT analysis, GLP-1 RA treatment is associated with a less steep decline in eGFR compared with basal insulin. The mean annual difference between groups was  $0.42 \text{ mL/min}/1.73 \text{ m}^2/\text{year}$ . [95% CI 0.11-0.73]; p = 0.008). The difference in eGFR decline was evident in patients with baseline eGRF <90 mL/min/1.73 m2, but was not seen in those with eGRF >90 (0.95 mL/min/1.73 m2/year [95% CI 0.38-1.52] and 0.09 mL/min/1.73 m2/year [-0.26-0.43], respectively). The difference in decline between GLP-1 RA and basal insulin was 0.53 mL/min/1.73 m2/year in patients using SGLT2i at the start of the study and 0.41 mL/min/1.73 m2/year in patients not using SGLT2i. At the same time, there were no significant differences in the change in eGFR in the overall study population (0.08

mL/min/1.73 m2/year [-0.06 to 0.23]; p = 0.258) or ITT-48mo analyses (0.14 mL/min/1.73 m2/year [-0.03 to 0.30]; p = 0.103) [11].

Another study - AWARD-7 published in 2018 involving 577 patients with type 2 diabetes and chronic kidney disease - found that dulaglutide 1.5 mg was associated with a significantly lower decrease in eGFR compared with insulin glargine over 52 weeks, by an average of about 10% (-0.5 mL/min/1.73 m<sup>2</sup> vs -5.5 mL/min/1.73 m<sup>2</sup>), an effect that was more pronounced in those with macroalbuminuria. The 2021 AMPLITUDE-O trial, where patients with type two diabetes and a history of renal failure were studied, showed that efpeglenatide use resulted in a lower risk of a sustained decrease in eGRF by up to 40% compared to the group taking placebo. Unfortunately, not all studies indicated significant differences in eGFr decline between groups. In the ELIXA study, which evaluated lixisenatide, no significant differences in eGFR decline were found after a median follow-up of 108 weeks. Also, the HARMONY study with 9463 participants with a mean HbA1c of 8.7%, which evaluated abiglutide in patients with type 2 diabetes and cardiovascular disease, showed no significant benefit in slowing eGFR decline after 1.6 years of follow-up. Other researchers attempted to affect eGFR with twice-daily exenatide - also with no noticeable difference to insulin glargine [12].

The induction of an initial, small decrease in eGFR by GLP-1 RA may suggest a reduction in intraglomerular pressure and glomerular hyperfiltration. It was also noted that the initial decline in eGFR was milder with GLP-1 RA than with SGLT2i formulations, with similar baseline eGFR values.

The FLOW study, which involved 3534 people with type 2 diabetes and chronic kidney disease treated with semaglutide 1mg/week [HR 0.76 (95% CI 0.66-0.88)], showed that the mean annual rate of eGFR decline was 35% lower in the semaglutide group (difference 1.16 ml/min/1.73 m2, P < .001). Similar findings were obtained in the SELECT study in overweight or obese subjects without type 2 diabetes, with 2.4 mg/week of semaglutide administered among 17604 participants. Compared to the placebo group, use of the drug was associated with a beneficial effect on eGFR after 104 weeks of follow-up, a difference of 0.75 ml/min/1.73 m2; P < .001, over a loss of 1.61 ml/min/1.73 m2 on placebo. The rate of annual decline in eGFR was also lower by 0.29 ml/min/1.73 m2. The researchers also considered those with an eGRF <60 ml/min/1.73 m2. Interestingly, an increase in eGFR values was seen in both groups. However, this increase was greater in the semaglutide treatment group (difference 2.19 ml/min/1.73 m2; ).

A combined analysis of the SUSTAIN-6 and PIONEER 6 studies showed that semaglutide use was associated with an average 0.59 ml/min/1.73 m2 (95% CI 0.29-0.89) lower annual rate of

eGFR decline [10]. The effect of slowing eGFR decline was more pronounced in patients with baseline eGFR <60 ml/min/1.73 m2. Furthermore, a post hox EXSCEL analysis found that the rate of eGFR decline was reduced in the exenatide group in patients with UACR>100 mg/g (treatment effect 0.79 mL/min/1.73 m2 per year, p = 0.005) and UACR>200 mg/g (treatment effect 1.32 mL/min/1.73 m2 per year, p = 0.0005), while there was no reduction in decline in the group with lower UACR [10].

#### 3.2 Effect of GLP-1 agonists on cardiovascular risk - a review of clinical trials

# **3.2.1** Reduction in risk of cardiovascular events (e.g. myocardial infarction, stroke, hospitalisations for heart failure) literature review

According to the collected literature, GLP-1 receptor agonists show a positive effect on the risk of cardiovascular events. A 2018 meta-analysis found that treatment with GLP-1 RA compared to placebo led to a significant 10% relative risk reduction in the primary composite endpoint of MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; HR 0.90, 95% CI 0.82-0.99; p=0.033). There was also a 13% relative reduction in the risk of death from cardiovascular causes and a 12% relative reduction in the risk of death from any cause. It should be noted, however, that this meta-analysis showed no significant effect of GLP-1 RA on the risk of non-fatal and fatal myocardial infarction, non-fatal and fatal stroke, hospitalisation for unstable angina, or hospitalisation for heart failure [14] Subsequent articles provide similar results of the effect of analogues on cardiovascular risk. A 2021 meta-analysis considering four trials with albiglutide, dulaglitide, exentide and liraglutide (43456 patients, including metformin users) showed a significant reduction in MACE of 13 % (HR 0.87, 95% CI 0.82-0.93). The risk of death from any cause was reduced by 12%, regardless of whether patients had previously used metformin [15].

In a double-blind study, the authors selected patients with type 2 diabetes and high cardiovascular risk who were given either liraglutide or placebo. With the primary hypothesis that liraglutide would be no worse than placebo for the primary endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, with an assumed upper limit of 1.3 and a confidence interval of 95% hazard ratio. 9340 patients were followed up for a mean of 3.8 years. In the analogue group, the adverse event occurred at a lower rate (13%) than in the placebo group (14.0%). In addition, the number of deaths from cardiovascular causes was lower in the liraglutide group (219 patients, or 4.7%) than in the placebo group (278 patients, or 6%). The risk of death from any cause was also lower with liraglutide (8.2%) than with placebo (9.6%). The researchers also showed that liraglutide administration had a statistically

insignificant effect on hospitalisations for heart failure or the risk of non-fatal myocardial infarction compared with placebo [16]. Similar conclusions were reached in the dulaglutide REWIND study, a double-blind randomised placebo-controlled trial. Compared with the control group, dulaglutide significantly reduced the risk of the first occurrence of a composite endpoint, which included non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes. This event occurred in 12% of those in the dulaglutide group and 13.4% of those in the placebo group. This corresponds to a risk reduction of 12% (hazard ratio [HR] 0.88, 95% CI 0.79-0.99; p=0.026) As with liraglutide, the risk of death from any cause was lower in the dulaglutide group, but this was statistically insignificant. The researchers did not separately analyse the effect of the formulation on hospitalisations for heart failure as a primary endpoint, but it was taken into account in the cardiovascular events studied [17].

The 2024 meta-analysis also provided similar findings. GLP-1 RA significantly reduced the risk of major cardiovascular events in patients with type 2 diabetes, including myocardial infarction (HR: 0.90, 95% CI: 0.82-0.98), stroke HR: 0.85, 95% CI: 0.77-0.95), and hospitalisation for heart failure (HR: 0.90, 95% CI: 0.83-0.97). This study showed:

- A significant reduction in the risk of a composite primary endpoint (including myocardial infarction, stroke and cardiovascular death) (HR: 0.86, 95% CI: 0.80-0.92).
- Reduction in the risk of death from cardiovascular causes (HR: 0.85, 95% CI: 0.78-0.93).
- Reduction in the risk of all-cause death (HR: 0.87, 95% CI: 0.82-0.93).

In addition, the authors were able to analyse that the effects of analogues were better with combination therapy and in patients with chronic kidney disease. A longer follow-up of more than two years showed that the therapy reduces the risk of death from all causes and hospitalisation for heart failure and stroke. The quality of evidence was classified as high in the GRADE system [18].

#### 3.2.2 Effects on blood pressure and lipid profile literature review

Systematic reviews show that GLP-1 RAs contribute to lower blood pressure and consequently reduce the risk of major adverse cardiovascular events. This is associated with improved vascular endothelial function and reduced ANP production [3]. Zhang et al, compared 66 patients with type 2 diabetes given either exenatide or insulin. They concluded that the GLP-1 analogue reduced lipoprotein and cholesterol-LDL levels to a greater extent at weeks 16 and 40. they also noted that exenatide therapy could prevent the progression of atherosclerosis better than insulin therapy [19]. Hasegawa et al. In their study, they showed that GLP-1 administration improves dyslipidaemia by inhibiting HMG-CoA reductase in patients with type 2 diabetes,

demonstrating that analogues can beneficially modulate cholesterol metabolism independently of their antidiabetic effect [20].

The results confirm that GLP-1r analogues may have a positive effect on the lipid profile in patients with type 2 diabetes and co-morbid dyslipidaemia. A retrospective cohort study investigated the effect of GLP-1 RA (dulaglutide) on lipid profile in people with type 2 diabetes in whom treatment with statins was unsuccessful. Three months of dulaglutide therapy was shown to result in significant reductions in triglyceride levels (median level decreased by 20 mg/dL, a 20.2 per cent reduction) and LDL cholesterol (median level decreased by 25.5 mg/dL, a 22.76 per cent reduction) in study patients [21]

There are also reviews that show conflicting results. The 2024 review noted that some studies report significant reductions in LDL-C levels after liraglutide 1.2 mg daily or 1.8 mg daily (-0.28 and -0.23 mmol/L) and exenatide once weekly (-0.13 and -0.17 mmol/L). Tuttolomondo et al, observed that patients taking dulaglutide 1.5 mg daily had significantly better metabolic profiles. Positive effects on arterial stiffness and markers of endothelial function were demonstrated [22]. For HDL cholesterol, studies with liraglutide and exenatide also show negligible changes (-0.04 to 0.00 mmol/L). However, a meta-analysis has emerged, according to which five studies found significant increases in HDL cholesterol and 29 studies found non-significant increases in cholesterol [23]. These studies indicate that further research and analysis may be needed in the future.

Data from large-scale cardiovascular outcome trials (CVOTs) show that all available GLP\_1 RA have an effect on cardiovascular risk factors. It has been shown that systolic blood pressure can be lowered by up to 2-6 mmHg, leading to a reduction in MACE [24]. An analysis by Quin et al., 2022 also confirms an improvement in systolic blood pressure. At the same time, they indicate that they do not affect the incidence of fatal or simple myocardial infarction compared to placebo [25].

#### 3.3 Combining physical activity with GLP-1 RA

It is thought that physical activity may enhance GLP-1 RA therapy in patients with type 2 diabetes. It has been suggested that physical activity reduces cellular resistance to GLP-1 [26]. A study by Mensberg et al. showed that combining exercise with GLP-1RA was effective in patients with type 2 diabetes. HbA1c in the group combining exercise with ALP-1RA 2.0%  $\pm$  1.2% (from 8.2%  $\pm$  1.4%) fell more strongly than in the exercise + placebo group 0.3%  $\pm$  0.9% (from 8.0%  $\pm$  1.2%). A similar result was seen in weight reduction: (exercise plus liraglutide: - 2.5%  $\pm$  1.4% [ P < .001]; exercise plus placebo: -2.2%  $\pm$  1.9% [ P < .001]) and maximum

oxygen uptake (exercise plus liraglutide:  $0.5 \pm 0.5 \text{ L O}_2/\text{min}$  [ P < .001]; exercise plus placebo:  $0.4 \pm 0.4$  L O<sub>2</sub>/min [ P = .002]). Systolic blood pressure (-5.4 ± 7.4 mm Hg vs -0.6 ± 11.1 mm Hg, P < .01) and fasting glucose levels (-3.4  $\pm$  2.3 mM vs -0.3  $\pm$  2.6 mM, P < .001) also showed positive differences [27]. Physical activity furthermore increases the production of short-chain fatty acids (SCFAs) by the microbiota, which then interact with G-protein-coupled receptors on intestinal L cells and increase GLP-1 secretion. Additionally, the authors noted that myokines released during exercise may play a role in modulating GLP-1 function, although they note that more research is needed on this issue [26]. Studies show that aerobic training in combination with semaglutide improves pancreatic beta-cell secretory function to a greater extent than training alone in people with type 2 diabetes. It is further indicated that liranglutide with exercise further reduces the severity of the metabolic syndrome. The combination treatment additionally reduces CRP levels. The use of exercise alone or liranglutide alone does not have this effect. This indicates that the association of GLP-1 RA and physical activity is beneficial for the condition. Although the association is very beneficial, the timing of the inclusion of semaglutide alone also makes a difference. Pre-treatment with semaglutide promotes a reduction in hyperglycaemia, inflammation, oxidative stress and allows a better response to exercise. The authors note that studies should be performed to help determine the minimum amount of exercise needed to have an effect [28]. In a 2018 study among 703 men, we can read that routine moderate physical activity is associated with lower fasting GLP-1 levels and a greater response, up to 16% glucose-induced GLP-1 (after 30 and 120 minutes), regardless of BMI and insulin sensitivity. It has been observed that intestinal L cells become sensitised so that fasting GLP-1 levels are low, and with a meal the cells respond better to glucose ingestion by increasing GLP-1 secretion. This may enhance the effect of exogenous GLP-1 administered in GLP-1 RA therapy. Similar correlations were not observed in a group of less active women. [29]

# 4. CONCLUSIONS

GLP-1 receptor agonists (GLP-1 RA) play a key role in the treatment of type 2 diabetes and obesity. They effectively improve glycaemic control and reduce body weight. They exhibit multidirectional effects that are beneficial not only in terms of glycaemic control, but also in terms of cardiovascular protection through lowering blood pressure and beneficial effects on the lipid profile and renal protection. By stimulating insulin secretion, inhibiting glucagon secretion, delaying gastric emptying or influencing the gut microbiota, they help to better manage glucose levels in the body. They allow the metabolism to be controlled safely and

effectively. However, it is important to bear in mind that therapy with these drugs can lead to hypoglycaemia, especially in complex therapy. It is important to tailor the therapy to the patient individually and to monitor them closely to maximise the benefits. In light of current clinical trials, the use of GLP-1 receptor analogues is associated with a significant reduction in the risk of cardiovascular complications and progression of chronic kidney disease, particularly in high-risk patients. Their effect in combination with exercise also offers an interesting alternative to many other therapies. However, further research is needed, especially long-term studies, to fully understand their potential and safety, especially in different patient groups

#### **5. DISCLOSURE**

Authors do not report any disclosures.

#### **Author's contributions**

Conceptualisation: ŁK, TK; Methodology: ŁK; TK Software: n/a; check: ŁK, TK, MB; Formal analysis: TK, MB; Investigation: ŁK, TK, MB, MP, KM; Resources: ŁK; Data curation: ŁK, TK, MB, MP, KM, PZ, JM, AC, AJ, MK; Writing - rough preparation: ŁK, TK, MB; Writing - review and editing: ŁK, TK, MB, MP, KM, PZ, JM, AC, AJ, MK; Visualization: ŁK, TK, MP; Supervision: JM, PZ, AJ; Project administration: ŁK; Receiving funding: n/a.

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The authors declare no conflict of interest.

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