# Understanding the restrictions in the prescription and use of potentially beneficial diabetes medications associated with low socio-economic status

*Michael A. Nauck,* and Johannes W. Dietrich*

Diabetes, Endocrinology and Metabolism Section, Department of Medicine I, St. Josef Hospital, Katholisches Klinikum Bochum gGmbH, Ruhr-University Bochum, Bochum, Germany

**The Lancet Regional Health - Europe 2022;14: 100318**
Published online xxx
https://doi.org/10.1016/j.lanepe.2022.100318

After decades of treating type 2 diabetes mainly by lowering plasma glucose and glycated haemoglobin, in 2015[1] and 2016,[2] evidence was published that inhibitors of sodium-glucose co-transporter-2 (SGLT-2 Is) and glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) lower the risk for cardiovascular events, mainly in patients with pre-existing cardiovascular disease. Consequently, guidelines issued by learned societies in the diabetes[3] and cardiovascular[4] field after 2018 recommended the use of SGLT-2 Is and GLP-1 RAs with a high level of evidence and a high class of recommendation for such patients.

Falkentoft et al.[5] now provide evidence that the likelihood for a prescription of SGLT-2 Is or GLP-1 RAs as a second glucose-lowering medication added to pre-existing metformin treatment depends on disposable income (a surrogate parameter for the socioeconomic status). They find that in Denmark, the use of SGLT-2 Is or GLP-1 RAs has increased from periods 2012-2014 (these classes were approved, but evidence for CV benefits was lacking), 2015-2017 (scientific evidence for CV benefits were first published), and 2018-2020 (strong guideline recommendations were available), but that the probability ratio was approximately 20% higher for those in the highest (compared to the lowest) income quartile. This pattern was similar for patients with and without CV disease.[5]

The present results can be interpreted in light of the concept of an "allostatic load" as a predictor of negative health outcomes. *Allostasis* describes the attempt of organisms to appropriately adapt to environmental changes. *Allostatic load* is the cumulative biological burden resulting from attempts to adapt to life's stressful demands, mediated and assessed by measures of chronic distress (corticosteroids, catecholamines, sympathetic nervous activity, blood pressure, atherogenic lipoproteins, impaired glucose regulation).[6] Indeed, allostatic load scores are significant predictors of diabetes mellitus,[7] arterial hypertension,[7] cardiovascular disease,[7,8] and mortality.[8] Relevant to the present study, a low socioeconomic status has a lasting impact on allostatic load indices.[6] Health-related behavior has been identified as a mediator of this association.[6] It is, therefore, not surprising that in the present study, a diagnosis of coronary, cerebrovascular or peripheral vascular disease, heart failure or chronic kidney disease was higher in those with a low disposable income,[5] providing more convincing reasons for a use of medications addressing these risks in those with a lower socioeconomic status, but the opposite was observed.

Falkentoft et al.[5] stress that in the public Danish health care system, medication costs are mainly public expenses, with a co-payment of up to 574 € per patient. This amount appears to be low, but this may be perceived in a different way by patients, considering that this represents 1.2 % of the yearly income for those in the highest, but 2.8 % in the lowest income quartile. The initial 135 € spent on medications are fully paid for by patients, so the highest burden comes as an immediate consequence of the decision to initiate medications.

The initiation of any pharmacological treatment should be the result of shared decision making between patients and health care professionals.[3] The results by Falkentoft et al.[5] seem to indicate that the relation of perceived benefits versus costs or potential harms of initiating SGLT-2 Is or GLP-1 RAs is different between those with high vs. low disposable incomes.

For patients, this judgement may be influenced by health literacy[9] in more general terms, the willingness and efforts to gather information relevant to the change in diabetes medications, the individually perceived value associated with a potentially reduced risk for major CV events, and the acceptance of costs for co-payments.

For physicians, the degree of exposure to current evidence (scientific or educational meetings, printed publications) and individual beliefs regarding the value of an approximately 15 % reduction in MACE events with SGLT-2 Is or GLP-1 RAs (e.g., a 1.9 % absolute risk reduction over 3.5 years with the GLP-1 RA liraglutide[2] [number needed to treat: 53]; 1.6 % absolute risk reduction over 3.1 years with the SGLT-2 I empagliflozin[1]

DOI of original article: http://dx.doi.org/10.1016/j.lanepe.2022.100308

*Corresponding author at: Diabetes, Endocrinology and Metabolism Section, Department of Medicine I, St. Josef Hospital, Katholisches Klinikum Bochum gGmbH, Ruhr-University Bochum, Gudrunstr. 56, 44791 Bochum, Germany.
*E-mail address:* Michael.nauck@rub.de (M.A. Nauck).

[number needed to treat: 63]) may differ, and this may, perhaps, depend on socio-economic status as well.

It appears worth mentioning that Falkentoft et al.[5] only examined the situation when a second glucose-lowering medication was to be added to first-line metformin. In cardiovascular outcomes trials comparing novel glucose-lowering medications with placebo treatment, a much wider range of diabetes stages was studied, with a substantial proportion of patients using combinations of oral agents or even insulin.[1,2] Thus, focusing on the first step of intensification may not allow to estimate the full extent of missed chances for initiating potentially highly beneficial treatments. Furthermore, this approach may even introduce some bias, since the baseline burden of cardiovascular disease was higher in those with a lower income, despite a similar diabetes duration, suggesting more advanced and, perhaps, less well controlled type 2 diabetes, indicating a greater need for treatment intensification in those with lower socio-economic status. In addition, differences in income may not only be associated with disparities in the initiation of potentially beneficial medications, but also in adherence (regularly taking the medication at the dose and frequency as prescribed) and persistence (continuing treatment by refilling prescriptions as long as medically indicated).[10] Thus, the study by Falkentoft et al.[5] leaves some important questions to be answered in the future.

The impact of socioeconomic status described by Falkentoft et al.,[5] with the potential to aggravate health-related consequences for those with low incomes, who most likely have accumulated a greater allostatic load anyway,[6-8] underscores the need to identify mechanisms leading to this disparity, with the aim to offer equal treatments and benefits to everyone, independent from socioeconomic status.

## Declaration of interests

Dr. Nauck reports personal fees and non-financial support from Berlin-Chemie, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Eli Lilly & Co, grants, personal fees and non-financial support from Merck Sharp & Dohme, personal fees and non-financial support from Novo Nordisk, personal fees from Regor, personal fees from ShouTi, personal fees and non-financial support from Astra Zeneca, personal fees and non-financial support from Sun Pharma, personal fees and non-financial support from Medscape, outside the submitted work. JWD is co-owner of the intellectual property rights for the patent 'System and Method for Deriving Parameters for Homeostatic Feedback Control of an Individual' (Singapore Institute for Clinical Sciences, Biomedical Sciences Institutes, Application Number 201208940-5, WIPO number WO/2014/088516).

## Author contributions

MAN searched literature regarding diabetes medications and relevant guidelines, and drafted sections of the commentary dealing with these items. JWD contributed literature concerning the allostatic load concept and drafted the section related to this topic. MAN and JWD jointly finalized the manuscript and decided to submit for publication. Both are guarantors of the scientific accuracy of this commentary.

### References


1 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.

2 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.

3 Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2018;61:2461–2498.

4 Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41:255–323.

5 Falkentoft AC, Andersen J, Malik ME, et al. Socioeconomic position and initiation of SGLT-2 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes - a Danish nationwide observational study. *Lancet Region Health - Eur*. 2022;12. https://doi.org/10.1016/j.lanepe.2022.100308.

6 Misiak B, Stanczykiewicz B, Pawlak A, et al. Adverse childhood experiences and low socioeconomic status with respect to allostatic load in adulthood: a systematic review. *Psychoneuroendocrinology*. 2021;136: 105602.

7 Mattei J, Demissie S, Falcon LM, Ordovas JM, Tucker K. Allostatic load is associated with chronic conditions in the Boston Puerto Rican Health Study. *Soc Sci Med*. 2010;70:1988–1996.

8 Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci USA*. 2001;98:4770–4775.

9 Lastrucci V, Lorini C, Caini S, Health Literacy Florence, Research G, Bonaccorsi G. Health literacy as a mediator of the relationship between socioeconomic status and health: A cross-sectional study in a population-based sample in Florence. *PLoS One*. 2019;14: e0227007.

10 Uzoigwe C, Liang Y, Whitmire S, Paprocki Y. Semaglutide once-weekly persistence and adherence versus other GLP-1 RAs in patients with type 2 diabetes in a US real-world setting. *Diabetes Ther*. 2021;12:1475–1489.