Tanaka and Node *Cardiovasc Diabetol* (2020) 19:206
https://doi.org/10.1186/s12933-020-01191-5

Cardiovascular Diabetology

COMMENTARY Open Access

How should we monitor the cardiovascular benefit of sodium–glucose cotransporter 2 inhibition?

Atsushi Tanaka* and Koichi Node

Abstract

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are increasingly prescribed for the treatment of patients with type 2 diabetes to reduce the risk of cardiovascular events, including heart failure (HF). The mechanisms by which SGLT2 inhibitors reduce such risk are likely to be independent of diabetes status and improvement of glycemic control. In this commentary, based on recent mediation analyses of cardiovascular outcome trials with SGLT2 inhibitors, we discuss the prognostic role of a well-known HF-related biomarker, amino-terminal pro-B-type natriuretic peptide (NT-proBNP), in patients receiving SGLT2 inhibitors. Interestingly, the NT-proBNP concentration had a relatively small impact on the SGLT2 inhibitor-associated benefit on HF events, suggesting a limited value in measuring NT-proBNP concentrations to monitor effects on cardiovascular outcomes after initiation of SGLT2 inhibitor therapy. Instead, clinical factors, such as body weight and volume status, were prognostic for cardiovascular outcomes. As shown in some biomarker studies, short-term SGLT2 inhibitor treatment significantly improved volume and HF-related health status, despite the absence of a significant change in NT-proBNP concentration. Given the early and continuous risk reduction in HF events seen in the cardiovascular outcome trials with SGLT2 inhibitors, changes in these fundamental clinical parameters after initiation of SGLT2 inhibitor therapy, independent of NT-proBNP, could be more prognostic and could represent key determinants to identify responders or non-responders to SGLT2 inhibitors for cardiovascular outcomes. Thus, this commentary highlights the clinical importance of establishing how clinicians should monitor patients initiating SGLT2 inhibitor therapy to predict the expected cardiovascular benefit. Further detailed investigations and discussion to better understand this "black box" are urgently warranted.

Keywords: Sodium glucose co-transporter 2 inhibitor, Heart failure, Cardiovascular benefit, Biomarker

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have a protective effect on the cardiovascular system beyond their glucose-lowering effect [1] and are increasingly prescribed for the treatment of patients with type 2 diabetes (T2D) to reduce the risk of cardiovascular events, including heart failure (HF) [2, 3]. Although the magnitude of the treatment effect of SGLT2 inhibitors on such cardiorenal outcomes varied among the large-scale outcome trials, no explanation for the statistical evidence of heterogeneity in the treatment effects on such outcomes could be clearly identified [4]. This suggests that SGLT2 inhibitors have plausible class effects on cardiorenal outcomes [5, 6]. Indeed, some large-scale observational cohort studies also demonstrated that initiation of SGLT2 inhibitors compared with other glucose-lowering drugs, such as dipeptidyl peptidase-4 inhibitors, was associated with a decreased risk of cardiorenal events among patients with T2D in clinical practice [7–10].

Importantly, results of recent studies indicated that the mechanisms by which SGLT2 inhibitors reduce the risk of adverse cardiorenal events are likely to be independent of diabetes status and improvement of glycemic

*Correspondence: tanakaa2@cc.saga-u.ac.jp
Department of Cardiovascular Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

control [11], and baseline renal filtration function and degree of albuminuria were the most significant indicators of risk for those events [5]. However, it is still uncertain how clinicians should monitor patients who have started SGLT2 inhibitor therapy to predict the expected cardiovascular benefit (Fig. 1).

Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) is an established biomarker that is useful in the diagnosis of HF and can predict the risk for adverse cardiovascular events [12]. Furthermore, natriuretic peptide-guided treatment is known to be able to improve clinical outcomes and reduce HF-related events irrespective of history of HF [13, 14]. Recently, Januzzi et al. [15] reported concentrations of NT-proBNP over six years using data obtained from the CANVAS program and found that a substantial proportion of patients had elevated levels of NT-proBNP, irrespective of prior history of HF, contributing to a greater risk of cardiovascular events. In addition, canagliflozin, relative to placebo, attenuated the rise in NT-proBNP concentrations over time, and this was consistent with results of a previous study in older adults with T2D [16]. These findings suggest that the reduction in NT-proBNP concentrations with canagliflozin was associated with better cardiovascular outcomes. However, a mediation analysis demonstrated that NT-proBNP lowering had a relatively small effect on the canagliflozin-associated benefit on HF events, suggesting a limited value in measuring NT-proBNP concentrations to monitor effects on cardiovascular outcomes after initiation of SGLT2 inhibitor therapy. Regarding potential mediators associated with improvement of outcomes in another clinical trial with SGLT2 inhibitor therapy, a previous mediation analysis of the EMPA-REG OUTCOME trial showed that hematocrit and hemoglobin, indicative of a hemodynamic effect, were the most important mediators of the reduction in the risk of cardiovascular death [17].

Interestingly, recent small studies investigating clinical surrogate markers, including NT-proBNP, in patients with established HF showed that short-term SGLT2 inhibitor intervention did not decrease the NT-proBNP level compared with glimepiride [18] or placebo [19]. Instead, a 6-month course of canagliflozin decreased body weight and altered volume status, as assessed by hemoconcentration and plasma volume [18]. Furthermore, a 12-week course of dapagliflozin significantly improved HF-related health status, as assessed by the Kansas City Cardiomyopathy Questionnaire [19]. Similarly, a 6-month course of empagliflozin in patients with T2D and known coronary artery disease was associated with a significant reduction in left ventricular mass, as measured by cardiac magnetic resonance imaging, although no significant effect of empagliflozin, compared to placebo, on NT-proBNP concentration was observed [20].

Given the early and continuous risk reduction in HF events seen in the previous outcomes trials with SGLT2 inhibitors, changes in these clinical parameters after initiation of an SGLT2 inhibitor, independent of NT-proBNP concentration, could be more prognostic and could represent key determinants to identify responders or non-responders to SGLT2 inhibitors for cardiovascular outcomes. Thus, it is urgently required to establish how clinicians should monitor patients who have initiated SGLT2 inhibitor therapy to predict its cardiovascular benefit (Fig. 1).

Acknowledgements
This work was supported in part by the Uehara Memorial Foundation.

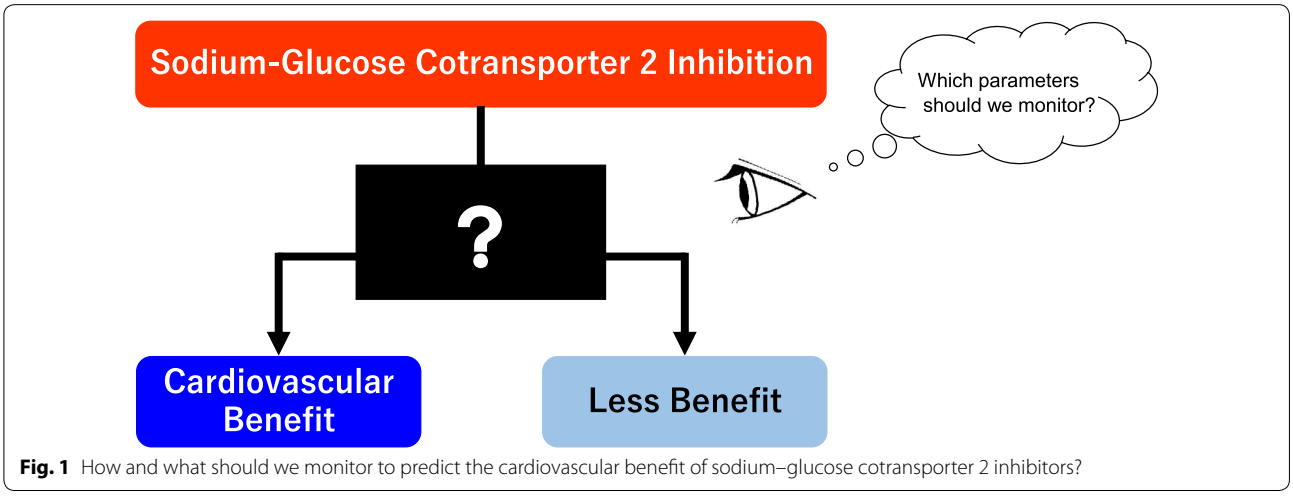

Fig. 1 How and what should we monitor to predict the cardiovascular benefit of sodium–glucose cotransporter 2 inhibitors?

Authors' contributions
AT drafted the article, which was then critically reviewed by KN. Both authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
AT has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Fukuda Denshi, Kowa, MSD, Mitsubishi Tanabe, Mochida, Novo Nordisk, Ono, Taisho Toyama, Takeda, and Teijin and research funding from GlaxoSmithKline. KN has received research grants from Asahi Kasei, Astellas, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe, Teijin, and Terumo; scholarships from Astellas, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Takeda, and Teijin; and personal fees from Astellas, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Mitsubishi Tanabe, MSD, Ono, Otsuka, and Takeda.

Received: 19 November 2020 Accepted: 2 December 2020
Published online: 07 December 2020

References

1. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose–lowering effect. Cardiovasc Diabetol. 2020;19:98.
2. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020;43:487–93.
3. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41:255–323.
4. Yu J, Zhou Z, Mahaffey KW, Matthews DR, Neuen BL, Heerspink HJL, Jardine MJ, Li J, Perkovic V, Neal B, Arnott C. An exploration of the heterogeneity in effects of SGLT2 inhibition on cardiovascular and all-cause mortality in the EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, and CREDENCE trials. Int J Cardiol. 2020 Sep 24:S0167-5273(20)33831-6.
5. Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, Cobble ME, McCullough PA. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol. 2019;18:99.
6. Carbone S, Dixon DL. The CANVAS Program: implications of canagliflozin on reducing cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2019;18:64.
7. Schernthaner G, Karasik A, Abraitienė A, Ametov AS, Gaàl Z, Gumprecht J, Janež A, Kaser S, Lalić K, Mankovsky BN, Moshkovich E, Past M, Prázný M, Radulian G, Smirčić Duvnjak L, Tkáč I, Trušinskis K. Evidence from routine clinical practice: EMPRISE provides a new perspective on CVOTs. Cardiovasc Diabetol. 2019;18:115.
8. Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, Schneeweiss S. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. Circulation. 2019;139:2822–30.
9. Kohsaka S, Lam CSP, Kim DJ, Cavender MA, Norhammar A, Jørgensen ME, Birkeland KI, Holl RW, Franch-Nadal J, Tangri N, Shaw JE, Ilomäki J, Karasik A, Goh SY, Chiang CE, Thuresson M, Chen H, Wittbrodt E, Bodegård J, Surmont F, Fenici P, Kosiborod M, CVD-REAL 2 Investigators and Study Group. Risk of cardiovascular events and death associated with initiation of SGLT2 inhibitors compared with DPP-4 inhibitors: an analysis from the CVD-REAL 2 multinational cohort study. Lancet Diabetes Endocrinol. 2020;8:606–15.
10. Heerspink HJL, Karasik A, Thuresson M, Melzer-Cohen C, Chodick G, Khunti K, Wilding JPH, Garcia Rodriguez LA, Cea-Soriano L, Kohsaka S, Nicolucci A, Lucisano G, Lin FJ, Wang CY, Wittbrodt E, Fenici P, Kosiborod M. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol. 2020;8:27–35.
11. Tuttle KR, Brosius FC 3rd, Cavender MA, Fioretto P, Fowler KJ, Heerspink HJL, Manley T, McGuire DK, Molitch ME, Mottl AK, Perreault L, Rosas SE, Rossing P, Sola L, Vallon V, Wanner C, Perkovic V. SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: Report of a scientific workshop sponsored by the National Kidney Foundation. Am J Kidney Dis. 2020 Oct 22:S0272-6386(20)30934-3.
12. Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, Erntell H, Persson H, O'Connor CM, Moertl D, Karlström P, Dahlström U, Gaggin HK, Januzzi JL, Berger R, Richards AM, Pinto YM, Nicholls MG. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J. 2014;35:1559–67.
13. Sweeney C, Ryan F, Ledwidge M, Ryan C, McDonald K, Watson C, Pharithi RB, Gallagher J. Natriuretic peptide-guided treatment for the prevention of cardiovascular events in patients without heart failure. Cochrane Database Syst Rev. 2019;10:CD013015.
14. Natriuretic Peptides Studies Collaboration. Willeit P, Kaptoge S, Welsh P, Butterworth AS, Chowdhury R, Spackman SA, Pennells L, Gao P, Burgess S, Freitag DF, Sweeting M, Wood AM, Cook NR, Judd S, Trompet S, Nambi V, Olsen MH, Everett BM, Kee F, Ärnlöv J, Salomaa V, Levy D, Kauhanen J, Laukkanen JA, Kavousi M, Ninomiya T, Casas JP, Daniels LB, Lind L, Kistorp CN, Rosenberg J, Mueller T, Rubattu S, Panagiotakos DB, Franco OH, de Lemos JA, Luchner A, Kizer JR, Kiechl S, Salonen JT, Goya Wannamethee S, de Boer RA, Nordestgaard BG, Andersson J, Jørgensen T, Melander O, Ballantyne ChM, DeFilippi Ch, Ridker PM, Cushman M, Rosamond WD, Thompson SG, Gudnason V, Sattar N, Danesh J, Di Angelantonio E. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. Lancet Diabetes Endocrinol 2016;4:840–9.
15. Januzzi JL Jr, Xu J, Li J, Shaw W, Oh R, Pfeifer M, Butler J, Sattar N, Mahaffey KW, Neal B, Hansen MK. Effects of canagliflozin on amino-terminal pro-B-type natriuretic peptide: implications for cardiovascular risk reduction. J Am Coll Cardiol. 2020;76:2076–85.
16. Januzzi JL Jr, Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M, Davies MJ. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. J Am Coll Cardiol. 2017;70:704–12.
17. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, Schmoor C, Ohneberg K, Johansen OE, George JT, Hantel S, Bluhmki E, Lachin JM. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. Diabetes Care. 2018;41:356–63.
18. Tanaka A, Hisauchi I, Taguchi I, Sezai A, Toyoda S, Tomiyama H, Sata M, Ueda S, Oyama JI, Kitakaze M, Murohara T, Node K. CANDLE Trial Investigators. Effects of canagliflozin in patients with type 2 diabetes and chronic heart failure: a randomized trial (CANDLE). ESC Heart Fail. 2020;7:1585–94.
19. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, Drazner MH, Fong MW, Givertz MM, Gordon RA, Jermyn R, Katz SD, Lamba S, Lanfear DE, LaRue SJ, Lindenfeld J, Malone M, Margulies K, Mentz RJ, Mutharasan RK, Pursley M, Umpierrez G, Kosiborod M. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019;140:1463–76.
20. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, Zuo F, Quan A, Farkouh ME, Fitchett DH, Goodman SG, Goldenberg RM, Al-Omran M, Gilbert RE, Bhatt DL, Leiter LA, Jüni P, Zinman B, Connelly KA. Effect of Empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation. 2019;140:1693–702.

Publisher's Note