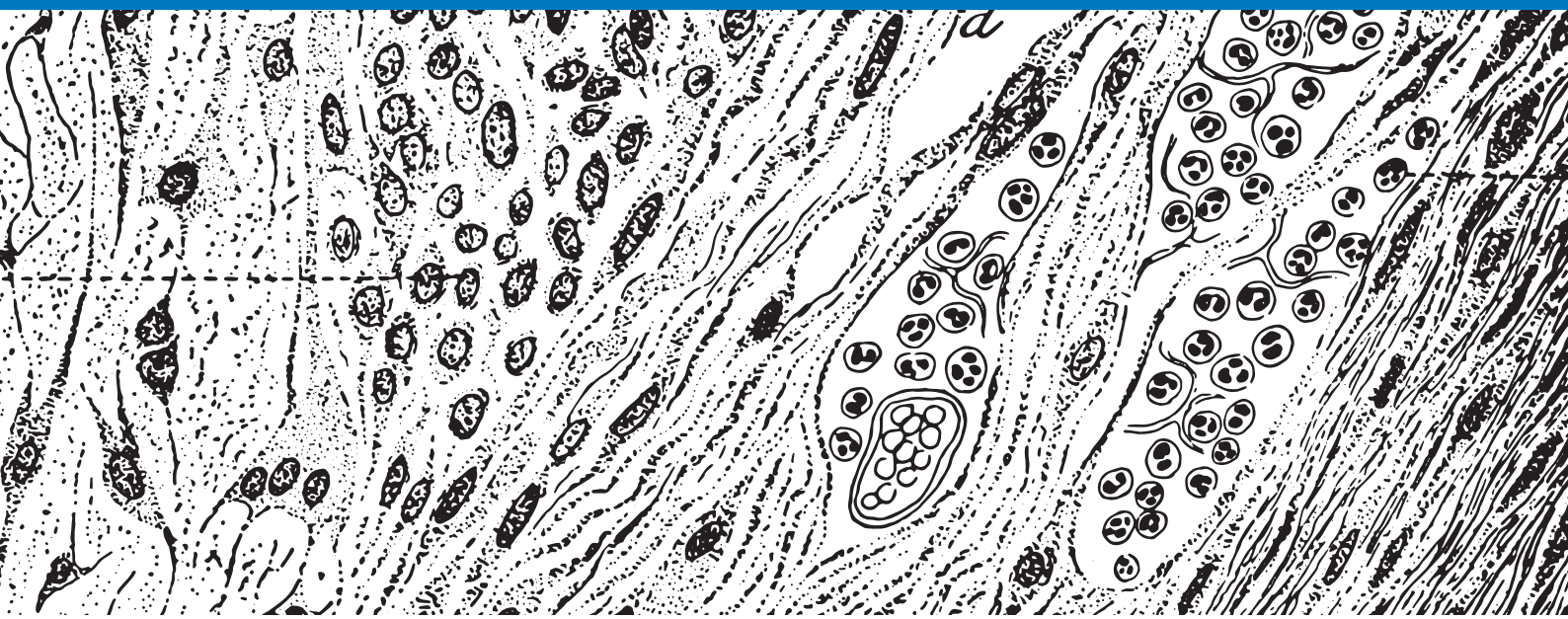
EXPERT MONOGRAPH ISSUE 37

Combining SGLT2 and DPP-4 Inhibition in Type 2 Diabetes



PROFESSOR MERLIN THOMAS MBChB, PhD, FRACP

Prof Merlin Thomas is a Professor of Medicine at Monash University, Melbourne. Professor Thomas is both a physician and a research scientist. He has published over 300 articles in many of the world's leading medical journals, as well as several books including The Longevity List and Fast Living, Slow Ageing. He is internationally recognised as a speaker, opinion-leader, teacher and medical storyteller. His research focuses on discovering new ways to prevent and treat the complications of diabetes.

This article discusses the evidence for using a combination of SGLT2 inhibitors & DPP-4 inhibitors in addition to standard care for the management of type 2 diabetes and its complications.

Most patients with type 2 diabetes will need more than monotherapy to achieve appropriate targets for glucose control. Dual therapy may begin early in their management, when it is clear that monotherapy is insufficient (primary failure), or later as the initial efficacy wanes (secondary failure). But, in the absence of significant weight loss or major lifestyle change, additional glucose-lowering agents will eventually be required in over 90% of patients with type 2 diabetes.

There are now many different agents that can be added on to standard therapy to improve glucose control in type 2 diabetes.[1] Traditionally, metformin has been considered first-line therapy with sulphonylureas used as second-line. However, sulphonylurea use, as a percentage of total patients, has fallen by more than half over the last decade, chiefly due to concerns over hypoglycaemia and weight gain and the need for dose-titration in patients who are increasingly old, frail and/or complicated. At the same time, new glucose-lowering agents without these limitations have emerged as attractive alternatives to sulphonylureas, including DPP-4 inhibitors (so-called 'gliptins') and more recently, SGLT2 inhibitors.

Take Home Messages

- In the absence of major lifestyle changes and weight loss, 90% of patients with type 2 diabetes will eventually require more than monotherapy to achieve glycaemic targets
- Key differences in glucose-lowering mechanisms of DPP-4 inhibitors and SGLT2 inhibitors mean that combining them offers a broad range of treatment coverage.
- Recent changes in PBS subsidies mean that practitioners can now access the utility of DPP-4 inhibitors and the benefits of SGLT2 inhibitors together in the same patient

Although, in 2013, Australia was one of the first countries in the world to licence SGLT2 inhibitors in type 2 diabetes, and DPP-4 inhibitors have also been subsidised for over 10 years in Australia, before 2018 practitioners were required to choose between these drug strategies. Each path had its own unique advantages and disadvantages that may be individually relevant to different patients and different settings. But a choice had to be made. There was no opportunity (inside the PBS) for any one patient the share the advantages of both, even if suboptimal glucose control necessitated additional therapy. However, in April 2018 this changed, as Australians with type 2 diabetes were now provided a subsidy by the PBS for the simultaneous prescription of two 'new' agents for controlling blood glucose levels (HbA1c >7%) using a DPP-4 inhibitor together with an SGLT2 inhibitor, in addition to standard therapy. In addition, fixed-dose combination formulations containing both SGLT2 and DPP-4 inhibitors (e.g. Glyxambi and Qtern) have also been made available on the PBS. This review will look at the potential utility and limitations of this new combination treatment strategy for the management of type 2 diabetes.

What does DPP-4/SGLT2 inhibitor combination do for glucose control?

Across many clinical trials, SGLT2 inhibitors lower the HbA1c by between 0.6 to 0.9%, regardless of background therapy.[2] Similar results have also been reported with DPP-4 inhibitors, meaning that, on average, there is little difference in glycaemic control achieved by using either strategy alone as an add-on therapy.[3] However, as treatment with SGLT2i reduces plasma glucose levels in type 2 diabetes proportional to the ambient glucose concentration and the glomerular filtration of this glucose, greater glucose-lowering may be seen in patients with poor glycaemic control and/or hyperfiltration, potentially more than with other agents in the same setting.[2] Equally, lesser reductions in HbA1c following treatment with SGLT2 inhibition may be observed in patients with better control at baseline,[4-8] especially at low-dose, and potentially less than with other agents, like DPP-4i, whose mechanism of action is not glucose-dependent. Equally, the glucose-lowering effects of SGLT2 inhibitors are attenuated in patients with eGFR<60ml/min/1.73m^2 and non-significant below 30ml/min/1.73m^2.[9] This is unlike DPP-4 inhibitors that retain their glucose-lowering efficacy across all levels of renal function.

One potential advantage of combining a DPP-4 inhibitor together with an SGLT2 inhibitor in an individual patient, is that these key differences in glucose-lowering offer an opportunity for broader coverage. For example, in a patient with poor glucose control, treatment with an SGLT2 inhibitor reduces plasma glucose levels effectively, but their glycosuria wanes the closer they get to target. Subsequently adding in a DPP-4 inhibitor in patients who are not far off target who just need a little more, then takes them the rest of the way. Equally, in patients with an eGFR below 60ml/min/1.73m^2, using a DPP-4 inhibitor ensures glucose-lowering efficacy while the cardiovascular and renal benefits of SGLT2 inhibition are retained (see below).

A number of studies have confirmed the efficacy of combining a DPP-4 inhibitor together with an SGLT2 inhibitor, or *vice versa*, in addition to standard therapy in patients with sub-optimally controlled type 2 diabetes. For example, in one meta-analysis adding an SGLT2 inhibitor onto background therapy with a DPP-4 inhibitor reduced HbA1c by –0.62%, [95% CI: –0.73 to –0.51%; P < 0.001] on average compared to DPP-4i with placebo.[7,8] However, the magnitude of this effect is highly dependent on baseline glucose control and maybe more modest in patients with good control (HbA1c<8%) at baseline.

By contrast, the effect of adding a DPP-4 inhibitor onto background therapy with an SGLT2 inhibitor appears slightly smaller (weighted mean difference –0.37% [95% CI: –0.50 to –0.25%; P < 0.001]) though still significant at all levels of glucose control. This observed difference in HbA1c reduction likely reflects differences in baseline glucose control and the glucose-dependence of lowering with SGLT2 inhibition. This is also why the glucose-lowering effects of simultaneously combining a DPP-4 inhibitor together with an SGLT2 inhibitor, are not additive and/or synergistic with respect to HbA1c reduction, as each agent reduced the baseline glucose for the other to work off. Importantly, the likelihood of achieving a target HbA1c <7% was increased to the same extent whether adding a DPP-4 inhibitor to an SGLT2 inhibitor, or SGLT2 inhibitor to a DPP-4 inhibitor.[7,8]

What does a DPP-4/SGLT2 inhibitor combination do for tolerability?

The key advantage of using DPP-4 inhibitors is their highly favourable tolerability.[10,11] This is critical, given that the most patients with type 2 diabetes in Australian general practice are over 65, in whom polypharmacy, inconstant health and comorbidity are frequent companions. Recent studies have confirmed a real but small risk of pancreatitis with DPP-4 inhibitors.[12] But generally DPP-4 inhibitors are tolerated as well any placebo in clinical trials.[10,11]

By contrast, about one in 12 women with diabetes using a SGLT2 inhibitor will develop genital thrush (*candidiasis*), usually in the first 3-4 months of treatment,[13] especially older women with urinary incontinence and/or poor genital hygiene. Although thrush is easy to recognise and treat with short courses of standard antifungal therapies (topical creams, suppositories or oral 'azoles') it is painful, distressing and characterised by

- Acute genital itchiness
- White vaginal discharge
- Vaginal soreness, irritation, vulvar burning, pain with sex or urination
- Odour, if present, is slight and inoffensive.

Symptoms are often worse in the week before menses. In

uncircumcised men, thrush can cause balanitis (painful swelling of the end of the penis). Because of this issue, women and uncircumcised men should be tactfully educated about the importance of genital hygiene (e.g. pad changes, washing) and what to look out for as well as encouraged to treat themselves early in the event of any symptoms. They should also be reminded that genital mycotic infection does not mean a sexually transmitted disease (STD) as the terms are frequently confused on the internet (with awkward implications).

Candidiasis arising from SGLT2 inhibition is dependent on glycosuria. This means that the lesser glycosuria achieved using combination therapy (as glucose is lower with the DPP-4 inhibitor) may be associated with fewer side effects. Consistent with this notion as recent study reported that SGLT2/DPP-4 inhibitor combination resulted in a lower relative risk of genital infection compared with SGLT2 inhibitor alone (RR: 0.42, 95% CI: 0.18 to 0.99; P = 0.046).[7]

SGLT2 inhibition is also associated with increased hepatic ketogenesis and rarely ketoacidosis in some metabolically stressful settings (e.g. catabolism, starvation, after surgery, excess alcohol intake or major inter-current illness). Inappropriate and excessive reductions of insulin may also induce excess ketone production. As DPP-4 inhibition may prevent the rise in glucagon following SGLT2 inhibition, it is conceivable that a resulting higher insulin/glucagon ratio may attenuate ketogenesis. However, the effects of SGLT2/DPP-4 inhibitor combination on ketoacidosis remain unclear, and elevated glucagon alone is probably not enough to trigger ketoacidosis.

What does a DPP-4/SGLT2 inhibitor combination do for weight control?

Most people with type 2 diabetes are obese or overweight. Weight/fat control is critical for their management, especially in early diabetes when weight loss is a high priority, and can be hard to achieve, reinforce or sustain with standard therapies such as sulfonylureas, insulin and thiazolidinediones that promote weight gain in exactly the same patients in whom we are encouraging weight loss. A key advantage of DPP-4 inhibitors is that they do not cause weight gain. By contrast, SGLT2 inhibitors are often associated with weight loss of between 2-3 kg over six months of treatment,[2] regardless of background therapy. For example, adding an SGLT2 inhibitor onto background therapy with a DPP-4 inhibitor reduced body weight by –1.75 kg [95% CI: –2.02 to –1.49 kg; P < 0.001) on average, compared to DPP-4i with placebo.[7,8] Weight reduction is modestly greater in subjects with the highest baseline HbA1c and attenuated in those with good glucose control at initiation of therapy.[14] This is partly due to the magnitude of glycosuria resulting from SGLT2i and its impact on overall energy balance. But even in the absence of significant glycosuria (e.g. those with renal impairment) weight loss may still be observed.

What does a DPP-4/SGLT2 inhibitor combination do for CVD?

Cardiovascular disease (CVD) is the most important complication of type 2 diabetes. CVD accounts for not only the greatest financial costs, but also the largest proportion of the reduced health- and life-expectancy in those with the type 2 diabetes. The majority of patients with type 2 diabetes attending primary care are at high risk of cardiovascular event (>15% over 5 years) either because of established/prior CVD or because of the conglomeration of type 2 diabetes with one or more other high-CVD-risk states (e.g. obesity, hypertension, dyslipidaemia, age >60 years, Indigenous Australians, chronic kidney disease). Recognising this, interventions to reduce CVD risk have been prioritised for the management of type 2 diabetes, including statins and blockade of the renin angiotensin aldosterone system (RAAS), as these strategies have both demonstrated CVD benefits in large randomised cardiovascular outcome trials (CVOT).

In addition, the EMPA-REG and CANVAS trials with empagliflozin (Jardiance) and canagliflozin (not available in Australia) respectively, both reported a significant reduction in the primary composite outcome of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death (known as 3P-MACE). This effect appeared to be independent and additional to glucose-lowering. In addition, the EMPA-REG Outcomes trial also reported a reduced cardiovascular and total mortality rates by 38% and 32%, respectively.[15] The size of this effect translates into treating 39 individuals with type 2 diabetes and established CVD for three years would prevent one death, similar in magnitude to results reported with ACE inhibition or statin therapy in patients with type 2 diabetes.

By comparison, while CVOT trials with DPP-4 inhibitors have clearly demonstrated safety,[16,17] the kind of cardiovascular benefits reported with SGLT2i have not been observed. Not surprisingly, given the heightened cardiovascular risk in patients with diabetes, practitioners have been keen to add SGLT2 inhibitors to their therapy over DPP-4i. However, it should be noted that formal studies in high-risk patients without established CVD have yet to be performed and cardiovascular outcomes with dapagliflozin (Forxiga) are due to reported later this year. Moreover, the long-term cardiovascular benefits arising from good glucose control achieved with DPP-4 inhibitors in the absence of weight gain and hypoglycaemia cannot be ignored.

What does a DPP-4/SGLT2 inhibitor combination do for HF?

Heart failure is a common finding in patients with type 2 diabetes. Patients with type 2 diabetes have over twice the risk of incident heart failure than people without diabetes.[18-20] Given the high prevalent rate of heart failure in patients with type 2 diabetes, its generally greater severity and complexity, associated comorbidity relative resistance to treatment, type 2 diabetes is an increasingly

common factor for admission to hospital in patients with heart failure.

DPP-4 inhibitors are associated with a small increased risk of hospitalisation from heart failure.[21] Whether this is a class-effect or limited to only some DPP-4 inhibitors is still unclear.[21] By contrast, treatment with SGLT2 inhibitors is associated with a substantial reduction in hospitalisation for heart failure in patients with established heart disease. It is likely that this action partly reflects the approximately 8% reduction in plasma volume achieved when using agents of this class. However, additional actions on rate control, cardiac metabolism and neurogenic signalling cannot be excluded. Notably this effect is observed rapidly, within a few months of commencing therapy and persists with ongoing therapy, suggesting that this therapy may be effective in preventing both early and late admission in patients with heart failure.

Moreover, patients with a low risk of heart failure experienced the same relative risk reduction as those with high risk (ABCD) heart disease, suggesting SGLT2 inhibitors are not fixing a failing heart (at least in the short term), rather they are taking everyone a little further away from a point of volume overload/decompensation. It should also be noted, however, that heart failure was not the primary outcome of these safety studies, and specific trials testing the utility of SGLT2 inhibitors in patients with fully characterised cardiac status still need to be performed, including ones specifically in patients with HFpEF.

What does a DPP-4/SGLT2 inhibitor combination do for CKD?

At least half of all patients with type 2 diabetes in Australian general practice have chronic kidney disease (CKD) denoted by the presence of elevated albuminuria and/or a reduced estimated GFR. Patients with CKD are at increased risk for poor health outcomes including adverse drug reactions, CVD, heart failure, and premature mortality. This makes their management not only challenging but also urgent.

DPP-4 inhibitors improve and simplify glycaemic control in patients with renal impairment, with efficacy comparable to that observed in patients with normal renal function and a low incidence of adverse drug reactions including hypoglycaemia.[6] Although the glucose-lowering effects of SGLT2 inhibitors are negligible in patients with renal impairment, because of reduced glycosuria, fewer participants treated with empagliflozin in the EMPA-REG study reported renal failure or needing dialysis.[22] In absolute terms, this reduction was particularly marked in those with established CKD (e.g. a low GFR or elevated albuminuria). However, even in participants without CKD a slowing in the rate of decline of GFR and reduction in albuminuria was observed. In so far as renoprotection is a treatment priority such SGLT2 inhibition may be considered valuable. However, only the combination with DPP-4 inhibition allows for safe and effective glucose control at the same time.

What comes first, DPP-4 or SGLT2 inhibitor?

Most patients with type 2 diabetes will need dual or triple therapy to achieve and maintain glucose control. This can be achieved by many different agents now available, with little difference between them in terms of achieved glucose levels. However, there are certainly significant differences between them in terms of the other things that they do.

In those in whom early weight loss and immediate vasculo-protection are important, SGLT2 inhibitors are a valuable and effective second-line agent. As glucosuria declines with improving control, DPP-4 inhibition can then be added in as next agent to safely reach the desired target without hypoglycaemia or weight gain. Using a fixed dose combination of DPP-4 and SGLT2 inhibitors also means no additional pill burden.

Equally, in the patient with more comorbidity, DPP-4 inhibition is safest, best-tolerated second line agent. Providing the HbA1c remains above 7%, SGLT2 inhibition can then be added for its additional (glucose-independent) vasculo-protective benefits in appropriate patients at highest absolute risk of complications, who stand to get the highest absolute benefits from SGLT2 inhibition. The disadvantage of initiating SGLT2 inhibition in a patient with an HbA1c 7-8% is that glucose lowering may be minimal, especially at low dose. But if the real reasons for initiating the therapy are the potential cardiovascular, renal and mortality benefits that have been observed in clinical trials and observational studies, then glucose lowering doesn't matter. Moreover, polyuria, frequency and candidiasis are all less common when starting SGLT2 inhibition at a lower HbA1c.

In the future it may be that early multi-modal approach to comprehensive glucose control will become the norm for managing diabetes rather than relying on clinical decision points to precipitate a delayed change in therapy. We are already seeing a move away from a traditional glucose-centric approach to type 2 diabetes, to assessing the risks from comorbidities and complications which influence the choice of a particular glucose-lowering medication or medications.

The real advantage is that with recent changes in PBS subsidies in Australia, practitioners can now access the utility of DPP-4 inhibitors and the benefits of inhibitors together in the same patient.

Competing interests

Prof Merlin Thomas was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author.

The author's competing interests statement can be viewed at www.healthed.com.au/monographs.

References

1. The Royal Australian College of General Practitioners and Diabetes Australia. *General practice management of type 2 diabetes – 2014–15.* Melbourne: RACGP; 2014. 174 p.

2. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. *Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis.* Diabetes Obes Metab. 2016 Aug; 18(8): 783-94. DOI: [10.1111/dom.12670]

3. Goring S, Hawkins N, Wygant G, Roudaut M, Townsend R, Wood I, et al. *Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis*. Diabetes Obes Metab. 2014 May; 16(5): 433-42. DOI: [10.1111/dom.12239]

4. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. *Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial*. Lancet Diabetes Endocrinol. 2013 Nov; 1(3): 208-19. DOI: [10.1016/S2213-8587(13)70084-6]

5. Bujac S, Del Parigi A, Sugg J, Grandy S, Liptrot T, Karpefors M, et al. *Patient Characteristics are not Associated with Clinically Important Differential Response to Dapagliflozin: a Staged Analysis of Phase 3 Data*. Diabetes Ther. 2014 Dec; 5(2): 471-82. DOI: [10.1007/s13300-014-0090-y]

6. Abe T, Matsubayashi Y, Yoshida A, Suganami H, Nojima T, Osawa T, et al. *Predictors of the response of HbA1c and body weight after SGLT2 inhibition*. Diabetes Metab. 2018 Mar; 44(2): 172-4. DOI: [10.1016/j.diabet.2017.10.003]

7. Min SH, Yoon JH, Moon SJ, Hahn S, Cho YM. *Combination of sodium-glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor in type 2 diabetes: a systematic review with meta-analysis*. Sci Rep. 2018 Mar 13; 8(1): 4466. DOI: [10.1038/s41598-018-22658-2]

8. Cho YK, Kang YM, Lee SE, Lee J, Park JY, Lee WJ, Kim YJ, et al. *Efficacy and safety of combination therapy with SGLT2 and DPP-4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis*. Diabetes Metab. 2018 Nov; 44(5): 393-401. DOI [10.1016/j.diabet.2018.01.011]

9. Cherney DZI, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, et al. *Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin*. Kidney Int. 2018 Jan; 93(1): 231-44. DOI: [10.1016/j.kint.2017.06.017]

10. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. *Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis*. BMJ. 2012 Mar 12; 344: e1369. DOI: [10.1136/bmj.e1369]

11. Kawalec P, Mikrut A, Lopuch S. *The safety of dipeptidyl peptidase-4 (DPP-4) inhibitors or sodium-glucose cotransporter 2 (SGLT-2) inhibitors added to metformin background therapy in patients with type 2 diabetes mellitus: a systematic review and meta-analysis*. Diabetes Metab Res Rev. 2014 May; 30(4): 269-83. DOI: [10.1002/dmrr.2494]

12. DeVries JH, Rosenstock J. *DPP-4 Inhibitor-Related Pancreatitis: Rare but Real!* Diabetes Care. 2017 Feb; 40(2): 161-3. DOI: [10.2337/dci16-0035]

13. Wilding JP. *The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors*. Metabolism. 2014 Oct; 63(10): 1228-37. DOI: [10.1016/j.metabol.2014.06.018]

14. Kurinami N, Sugiyama S, Nishimura H, Morita A, Yoshida A, Hieshima K, et al. *Clinical Factors Associated with Initial Decrease in Body-Fat Percentage Induced by Add-on Sodium-Glucose Co-transporter 2 Inhibitors in Patient with Type 2 Diabetes Mellitus*. Clin Drug Investig. 2018 Jan; 38(1): 19-27. DOI: [10.1007/s40261-017-0580-6]

15. Zinman B, Lachin JM, Inzucchi SE. *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes*. N Engl J Med. 2016 Mar 17; 374(11): 1094. DOI: [10.1056/NEJMc1600827]

16. Patil HR, Al Badarin FJ, Al Shami HA, Bhatti SK, Lavie CJ, Bell DS, et al. *Meta-analysis of effect of dipeptidyl peptidase-4 inhibitors on cardiovascular risk in type 2 diabetes mellitus*. Am J Cardiol. 2012 Sep 15; 110(6): 826-33. DOI: [10.1016/j.amjcard.2012.04.061]

17. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. *Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus*. N Engl J Med. 2013 Oct 3; 369(14): 1317-26. DOI: [10.1056/NEJMoa1307684]

18. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, et al. *The association between glucose abnormalities and heart failure in the population-based Reykjavik study*. Diabetes Care. 2005 Mar; 28(3): 612-6. DOI: [10.2337/diacare.28.3.612]

19. Kannel WB, Hjortland M, Castelli WP. *Role of diabetes in congestive heart failure: the Framingham study*. Am J Cardiol. 1974 Jul; 34(1): 29-34. DOI: [10.1016/0002-9149(74)90089-7]

20. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, et al. *Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure*. JACC Heart Fail. 2015 Feb; 3(2): 136-45. DOI: [10.1016/j.jchf.2014.08.004]

21. Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, et al. *Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies*. BMJ. 2016 Feb 17; 352: i610. DOI: [10.1136/bmj.i610]

22. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. *Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes*. N Engl J Med. 2016 Jul 28; 375(4): 323-34. DOI: [10.1056/NEJMoa1515920]