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Cardiovascular Risks and Benefits of Oral Antidiabetic Drugs — An Update

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Abstract Diabetes mellitus is one of the known important risk factor for cardiovascular (CV) disease; CV events being the most important causes of morbidity and mortality in patients with diabetes. Among multifactorial approach, optimum blood sugar control is one of the intervention to prevent CV events. For optimum glycaemic control antidiabetic drugs are usually indicated; some having adverse, while others are neutral or with potential beneficial effects on the CV outcome. Therefore, careful selection of antidiabetic drugs is important for optimizing diabetic therapy in patient with CV disease. The role of this review paper is to explore the cardio-protective effects and CV risks of oral antidiabetic drugs used in patients with diabetes. Recently, new oral drugs have become good options in the management of diabetes with CV disease. Among the novel class, sodium-glucose cotransporter 2 inhibitors were found to be useful in a patient with chronic heart failure. Empagliflozin and canagliflozin was found to reduce the risk of CV mortality, nonfatal myocardial infarction and stroke in patient with diabetes and CV disease. Among the older drugs metformin was found to have excellent CV safety profile; CV mortality was lower for metformin compared with sulfonylureas.

Keywords Antidiabetic Drugs, Cardiovascular Outcomes, Cardiovascular risks, Cardiovascular benefits, Diabetes Mellitus

1. Introduction

Diabetes is an established high risk for the development of cardiovascular (CV) events (angina, myocardial infarction, hypertension, stroke or death); other risk factors include hypertension, dyslipidaemia, obesity, cigarette smoking, and sedentary life style. The leading cause of death in patients with type 2 diabetes mellitus (T2DM) is CV disease [1, 2]. Studies have shown that multifactorial interventions including lifestyle changes, weight loss, use of antiplatelet agents, control of blood pressure, hyperglycaemia, and dyslipidaemia reduce the risk of CV disease [2, 3]. In patients with T2DM, optimum blood sugar control is one of the most important intervention to reduce the risk of CV events. For optimum glycaemic control, most of the patient having diabetes will require anti-diabetic drugs; the glucose-lowering benefits of oral antidiabetic drugs (OAD) have been well established. But all the drugs are not absolutely safe in a patient having CV disease; some of these drugs have been associated with an increased risks of CV events. Therefore, CV outcomes should be considered when selecting antidiabetic medications for individual patients with diabetes. Numerous oral anti-diabetic drugs are now available, their potential CV effects, overall benefits and risks for CV disease needs to be defined.

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2. Aim

This review paper focuses on the updates of cardio-protective effects and CV risks of OAD used in patients with T2DM. Neither the approaches for the treatment of other risk factors responsible for CV disease, nor the efficacy on glycaemic control of OAD will be described in this paper.

3. Methods

Related original studies and review articles were explored that were published through Jan 2001 to Jan 2018 on the CV outcomes of OAD used for the management of T2DM; they were identified in google search including PubMed by using keywords like CV outcomes, CV risk, CV benefits, Adverse CV events, T2DM and Antidiabetic drugs.

4. Antidiabetic Drugs

Currently, 12 unique classes of drugs are available for the treatment of patients with T2DM in most countries of which

9 are oral agents. The glycaemic control in T2DM is achieved with some agents that predominantly lower the fasting plasma glucose level (metformin, sulfonylureas and basal insulins); with others that primarily lower postprandial plasma glucose excursions (meglitinides, α-glucosidase inhibitors, pramlintide, exenatide and prandial insulins); and with still others that do both (thiazolidinediones, dipeptidyl peptidase-4 inhibitors, liraglutide and premixed insulins) [4]. The glucose-lowering effectiveness of noninsulin pharmacological agents is said to be high for metformin, sulfonylureas (SUs), thiazolidinediones (TZDs), and glucagon like peptide-1 (GLP-1) receptor agonists; and generally lower for meglitinides, α-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors, colesevelam, and bromocriptin [5].

4.1. Metformin

The only drug of biguanide class available now is metformin; it mainly inhibits hepatic gluconeogenesis thereby decreasing glucose production; it also increases insulin-mediated glucose uptake in peripheral tissues [6]. It has neutral effect on weight, minimal risk of hypoglycaemia, and favourable safety profile. Gastrointestinal adverse events are considerable with metformin. Lactic acidosis is a rare but potentially fatal adverse effect that occurs in the setting of severe renal insufficiency [7]. Metformin was found to have an excellent CV safety profile, even with long-term use. A recent systematic review has supported the use of metformin as first line antidiabetic drug given its low cost, relative safety and beneficial effects on haemoglobin A1c, weight and CV mortality in patient with T2DM [8]. The review revealed that CV mortality was lower for metformin compared with sulfonylureas. Metformin, previously contraindicated in heart failure, can now be used if the ventricular dysfunction is not severe, if patient's CV status is stable, and if renal function is normal [9]. Observational studies have demonstrated that metformin use in patients with heart failure is associated with a lower risk of cardiovascular morbidity and mortality [9]. Metformin has also been shown to significantly reduce plasma total cholesterol levels; reducing serum triglyceride levels and slightly increasing serum high-density-lipoprotein (HDL) cholesterol levels [10].

4.2. Sulfonylureas

The SUs exert their hypoglycaemic effects by stimulating insulin secretion from the pancreatic beta-cell [11]. They are old and widely prescribed OADs. The problems of unwanted hypoglycaemia, weight gain, and beta cell failure are now limiting the use of SUs after availability of modern drugs [12]. First-generation SUs such as tolbutamide and chlorpropamide are no longer used due to high incidence of adverse reactions [13]. Examples of 2nd generation SUs are glibenclamide (in United States known as glyburide), glipizide and gliclazide. The adverse side effects are weight gain and hypoglycaemia; hypoglycaemia can be prolonged and life threatening, and are relatively more frequent in the elderly [13]. Glimepiride, a third-generation agent is less associated with both weight gain and hypoglycaemia [14]. The SUs are contraindicated in moderate to severe liver dysfunction due to increased risk of hypoglycaemia and should not be used during acute CV events. Glibenclamide which has a prolonged duration of action should not be used in renal failure [15]. A systematic review of 18 randomized trials showed that gliclazide was associated with a lowest risk of CV-related mortality compared with glimepiride, glipizide and glibenclamide [16]. However, a study on patients with prior CV events showed a clear superiority of metformin over gliclazide [17].

4.3. Meglitinides

Meglitinides, such as repaglinide or nateglinide, are sulfonylurea-like agents that stimulate insulin secretion and control postprandial hyperglycaemia [18]. The meglitinides have a very short onset of action and a short half-life. Meglitinides are associated with less hypoglycaemia and weight gain compared with sulfonylureas [19]. There are currently no long-term studies of meglitinides to assess cardiovascular outcomes or mortality in T2DM.

4.4. Thiazolidinediones

TZDs (pioglitazone and rosiglitazone) increase insulin sensitivity in the adipose tissue, skeletal muscle, and liver and do not cause hypoglycaemia [20]. Risk of hypoglycaemia is low; weight gain, fluid retention and peripheral oedema are major side effects and these drugs should be avoided in a patient with symptomatic heart failure and in those with advanced chronic kidney disease [21]. In addition, both the drugs have increased risk of fracture particularly in women. TZDs use causes redistribution of visceral fat to subcutaneous adipose tissue [22]. Pioglitazone is associated with improvements in cholesterol profiles decreasing triglycerides and increasing HDL cholesterols [23]; while rosiglitazone is associated with increase in low density lipoprotein (LDL) cholesterol [24]. There is evidence that patients with non-alcoholic fatty liver (steatohepatitis) may benefit from treatment with pioglitazone [15]. Pioglitazone was found to be associated with a possible increased risk of bladder cancer and has drawn attention [25]. The United States Food and Drug Administration (US FDA) recommends that T2DM patients with current bladder cancer should not be prescribed pioglitazone, and to use it with caution in patients with a past history of bladder cancer. US FDA has not concluded that pioglitazone increases the risk of bladder cancer; the agency is reviewing its safety concern [26].

In July 2007 a study published in New England Journal of Medicine showed 40% increase risk of CV events and death among users of rosiglitazone [27]. In 2008, US FDA issued a guidance to pharmaceutical industry on the conduct of clinical studies to prove the CV safety of the antidiabetic drugs at acceptable levels prior to drug approval [28]. In

September 2010, FDA significantly restricts access to rosiglitazone in US to patients with T2DM who were not effectively treated with other medications [29]. In 2013, the FDA has withdrawn their restriction on the basis of the results from the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trial, which failed to reproduce the results from the 2007 meta-analysis and indicated no elevated risk of CV events or death in patients being treated with rosiglitazone as compared with other antidiabetic drugs [30]. Pioglitazone may have beneficial CV effects. Recently a large trial was performed to evaluate the effects of pioglitazone on CV morbidity and mortality in high-risk patients with T2DM; pioglitazone was found to reduce all-cause mortality, nonfatal myocardial infarction, and stroke [31].

4.5. Alpha-Glucosidase Inhibitors

The AGIs control postprandial hyperglycaemia by inhibiting small intestine brush-border alpha-glucosidases, thereby slowing degradation of complex carbohydrates into glucose as well as reducing the rate of glucose absorption [32]. Acarbose, miglitol and voglibose are the drugs in this group. The risk of hypoglycaemia is low but these drugs may have significant gastrointestinal side effects like cramping and flatulence. They have no effect on body weight. A randomized comparable study has shown that miglitol reduces waist circumference, and in particular visceral fat, in patients with metabolic syndrome [33]. There are no long-term studies examining the effect of AGIs on CV disease or mortality in T2DM and therefore at present these are not recommended over the other available agents.

4.6. Colesevelam

The bile acid sequestrant colesevelam is used as an adjunctive therapy to improve glycaemic control in adults with T2DM. It binds to intestinal bile acids/cholesterols, and by unknown mechanism it lowers blood glucose in those with T2DM. It has minimum effect in reducing blood glucose, but it was found to be very effective in lowering LDL cholesterol. Colesevelam is a useful adjunctive therapy to reduce overall CV risk in patients with T2DM. [34]. One study revealed that colesevelam was associated with lower risk of major CV events (acute myocardial infarction and stroke) among patients with hyperlipidaemia and T2DM [35].

4.7. Bromocriptin

The dopamine-2 agonist bromocriptin is available in the US as an anti-diabetic agent. It activates brain dopamine D2 receptors to lower plasma levels of glucose. The findings of a large placebo controlled clinical study suggest that in T2DM subjects on metformin, bromocriptin therapy may represent an effective strategy for reducing CVD risk [36].

4.8. Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors are novel class oral anti-diabetic drugs that reduce metabolism of glucagon-like peptide-1 (GLP-1) prolonging its action [37]. GLP-1 is a hormone released by the small intestine in response to meals which in turn potentiates the release of insulin and reduces the postprandial rise in blood glucose. The available DPP-4 inhibitors (also known as gliptins) are sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin. The DPP-4 inhibitors are weight neutral antidiabetic agents with a low risk for hypoglycaemia [38]. The major side effects of these drugs appeared to be gastrointestinal; and there are safety concerns with pancreatitis and pancreatic neoplasia [39].

The DPP4 inhibitors were proven to be neutral with regard to CV outcomes [40, 41]. However, concerns on the safety of heart failure have been raised with increase in the risk for heart failure hospitalization in diabetic patients treated with DPP4 inhibitor saxagliptin and alogliptin [40-42]. In 2016, the US FDA has added warnings about heart failure risk to label antidiabetic drugs, saxagliptin and alogliptin particularly with heart disease. [43]. The most recent large-scale TECOS (Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin) findings did not confirm the findings of increased risk of hospitalization for heart failure [44]. Further studies are required to come to a conclusion on whether DPP4 inhibitors result in increased risk of heart failure. However, TECOS revealed a particularly favourable CV profile for sitagliptin; sitagliptin appears to be safe in terms of CV events in patient with CV risk and may have potential positive effects on the CV outcomes. Recently, other CV safety studies with OADs including DPP-4 inhibitor have shown only neutrality, not superiority, with regard to CV outcome [40, 41, 45, 46]. In one recent study involving data analysis from large cohorts of patients with diabetes, DPP-4 inhibitors were not associated with an increased risk of hospitalization for heart failure, as compared with commonly used combinations of OADs [47].

4.9. Sodium-Glucose Co-Transporter 2 Inhibitors

The sodium-glucose cotransporter 2 (SGLT2) inhibitors are another novel class of antidiabetic drugs that can effectively control blood sugar level without producing weight gain or hypoglycaemia. The available SGLT2 inhibitors are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. The SGLT2, expressed in the renal proximal tubules, accounts for 98% of the glucose reabsorption filtered through the glomeruli [48]. The SGLT2 inhibitors selectively inhibit SGLT2, increase urinary excretion of glucose in patients with hyperglycaemia and lower plasma glucose levels in an insulin-independent manner [49]. They produce osmotic diuresis in diabetes with hyperglycaemia and are accompanied by modest blood pressure reduction, some weight loss and improved glycaemic control [50]. Side effects of SGLT2 inhibitors include significant increase of

genitalia and urinary tract infection. A small increase in LDL cholesterol levels have been observed for this class [51]. A modest increase in HDL cholesterol and decrease in triglycerides has also been observed [52]. Euglycaemic diabetic ketoacidosis (DKA) have been reported in patients having diabetes with all SGLT2 inhibitors [53]. These drugs should be prescribed carefully in those patients with severe beta-cell insufficiency, latent autoimmune diabetes and in postsurgical patients [54]. The US FDA issued a warning about the risk of euglycaemic DKA occurring in the absence of significant hyperglycaemia in patients with diabetes treated with SGLT2 inhibitors. The US FDA has also issued a warning for canagliflozin related to reduced bone mineral density and increased risk of bone fracture [55]. Final results from two large recent clinical trials – the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus) – showed that leg and foot amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo [56]. Based on new data from those two large clinical trials, the US FDA in May 2017, concluded that canagliflozin causes an increased risk of leg and foot amputations and issued a boxed warning to the label of canagliflozin to be added to describe this risk [57]. The same risk has not been seen in studies of the other SGLT2 inhibitors, empagliflozin and dapagliflozin; thus, US FDA has not extended the label warning about amputations to these drugs.

Some SGLT2 inhibitors (canagliflozin and empagliflozin) have demonstrated CV benefits in patients with T2DM and established CV disease. Recent trials have revealed CV benefits of empagliflozin by reducing the risk of CV death, non-fatal MI, or non-fatal stroke compared with placebo in patients having diabetes and CV disease [58, 59]. Reduction of body weight and blood pressure are also involved in favourable CV outcomes in a patient with T2DM and CV disease [60]. Empagliflozin was found to have an excellent long term safety and tolerability profile [61]. Empagliflozin was not only proven safe in a population of type 2 diabetic patients at high CV risk, but was also shown to reduce CV risk. In 2016, Dec 2, the US FDA added a new indication for empagliflozin, to reduce the risk of CV death in adults with T2DM and CVD [62] based on data from the EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial [59]. Several large trials have also revealed similar CV benefits of canagliflozin among participants with and without kidney disease at baseline [56, 58]. In T2DM patients with chronic heart failure, SGLT2 inhibitor therapy may be considered, because part of the SGLT2 inhibitor mechanism includes diuresis, which leads to a preload reduction [63].

5. Conclusions

The leading cause of death in patients with T2DM is CV disease; optimum glycaemic control is one of the important intervention to reduce the risk of CV events in patients with diabetes. In addition to diabetes management, the interventions to treat other risk factors of CV disease should be taken into consideration. The OAD should be chosen with care for patients with T2DM at high CV risk, considering their glucose-lowering effects as well as overall benefits and risks for CV disease. Recent trials indicate that metformin has demonstrated excellent CV safety even with long term use. Among the sulfonylureas gliclazide has a comparatively more favourable CV profile, but not superior to metformin. DPP-4 inhibitors have overall neutral CV effect, but saxagliptin was seen to be associated with increased risk of heart failure. The SGLT2 inhibitors canagliflozin and empagliflozin have demonstrated promising CV benefits in patients with T2DM and established CV disease. Among the TZDs, pioglitazone was seen to be associated with improvements in cholesterol profiles decreasing triglycerides and increasing HDL cholesterols. The TZDs should be avoided in patients with symptomatic heart failure and in those with advanced chronic kidney disease. Pioglitazone was found to reduce all-cause mortality, nonfatal myocardial infarction, and stroke. Clinical trials are going on and will provide further evidences about the CV risks and benefits of OAD in near future.

REFERENCES

[1] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013 Jan; 127(1): 143-52.

[2] Rosenstock J, Marx N, Kahn SE, Zinman B, Kastelein JJ, Lachin JM, et al. Cardiovascular outcome trials in type 2 diabetes and the sulphonylurea controversy: rationale for the active-comparator CAROLINA trial. Diab Vasc Dis Res. 2013; 10: 289–301.

[3] Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. Diabetes Care. 2008 Aug; 31(8): 1672-78.

[4] Lebovitz HE. Type 2 diabetes mellitus—current therapies and the emergence of surgical options. Nat Rev Endocrinol 2011 Jul; 7: 408-419.

[5] Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011; 154: 602–613.

[6] Pernicova I, Korbonits M. Metformin–mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014; 10(3): 143–56.

[7] Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996; 334(9): 574–79.

[8] Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016; 164: 740–51.

[9] Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ. 2007; 335: 508–12.

[10] DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995; 333: 541-49.

[11] Ashcroft FM. Mechanisms of the glycaemic effects of sulfonylureas. Horm Metab Res. 1996 Sep; 28(9): 456-63.

[12] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006; 355: 2427–43.

[13] Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015; 11(4): 840–48.

[14] Massi-Benedetti M. Glimerpiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. Clin Ther. 2003; 25(3): 799–816.

[15] Inzucchi, SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach. Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 June; 35(6): 1364-79.

[16] Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. Lancet Diabetes Endocrinol. 2015; 3(1): 43–51.

[17] Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab. 2013; 15(10): 938–53.

[18] Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial. 2004; 17(5): 365–70.

[19] Ferrannini E, DeFronzo RA. Impact of glucose-lowering drugs on cardiovascular disease in type 2 diabetes. Eur Heart J. 2015; 36(34): 2288–96.

[20] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009; 32: 193– 203.

[21] Williams ME, Garg R. Glycemic management in ESRD and earlier stages of CKD. Am J Kidney Dis. 2014; 63((2 Suppl 2)): S22–38.

[22] Yki-Jarvinen H. Thiazolidinediones. N Engl J Med. 2004; 351(11): 1106–18.

[23] Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005; 28(7): 1547–54.

[24] American Diabetes Association. Diabetes Care 2018 Jan; 41 (Supplement 1): S73-S85. https://doi.org/10.2337/dc18-S008.

[25] Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care. 2011; 34: 916–22.

[26] U. S. Food and Drug Administration. FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

[27] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356: 2457-71.

[28] US Food and Drug Administration Guidance for industry: Diabetes mellitus — Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Available from: http://www.fda.gov/downloads/drugs/guidancecompliancere gulatoryinformation/guidances/ucm071627.pdf.

[29] Woodcock J, Sharfstein JM, Hamburg M. Regulatory action on rosiglitazone by US Food and Drug Administration. N Engl J Med. 2010; 363: 1489–91.

[30] Mahaffey KW, Hafley G, Dickerson S, Burns S, Tourt-Uhlig S, White J, et al. Results of a reevaluation of cardiovascular outcomes in the RECORD trial. Am Heart J. 2013;166:240 –49.

[31] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglit Azone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005; 366: 1279–89.

[32] Di Nicolantonio JJ, Bhutani J, O'Keefe JH. Acarbose: safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes. Open Heart. 2015; 2(1): e000327.

[33] Shimabukuro M, Higa M, Yamakawa K, Masuzaki H, Sata M. Miglitol, alpha-glycosidase inhibitor, reduces visceral fat accumulation and cardiovascular risk factors in subjects with the metabolic syndrome: a randomized comparable study. Int J Cardiol. 2013; 167(5): 2108–13.

[34] Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. Diabetes Obes Metab. 2010 May; 12(5): 384–92.

[35] Ye X, Qian C, Liu J, St Peter WL. Lower risk of major cardiovascular events associated with adherence to colesevelam HCI. Pharmacotherapy. 2013 Oct; 33(10): 1062-70.

[36] Chamarthi B, Ezrokhi M, Rutty D, Cincotta AH. Impact of bromocriptine-QR therapy on cardiovascular outcomes in type 2 diabetes mellitus subjects on metformin. Postgrad Med. 2016 Nov; 128(8): 761-69.

[37] Drucker DJ, Nauck MA. The incretin system: glucagon-like

peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006; 368: 1696-705.

[38] Davidson JA. Advances in therapy for type 2 diabetes: GLP-1 receptor agonists and DPP-4 inhibitors. Cleve Clin J Med. 2009; 76(Suppl 5): S28–38.

[39] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38: 140-49.

[40] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; 369: 1327-35.

[41] 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; 369: 1317–26.

[42] Xia C, Goud A, D'Souza J, Dahagam C, Rao X, Rajagopalan S, et al. DPP4 inhibitors and cardiovascular outcomes: safety on heart failure. Heart Fail Rev. 2017 May; 22(3): 299-304.

[43] FDA drug safety communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm486096.htm.

[44] McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, et al. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial. JAMA Cardiol. 2016; 1: 126–35.

[45] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373: 232–42.

[46] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015; 373: 2247–57.

[47] Filion KB, Azoulay L, Platt RW, Dahl M, Dormuth CR, Clemens KK, et al. A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med. 2016; 374(12): 1145–54.

[48] Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open. 2012; 2(5): e001007.

[49] Ghosh RK, Ghosh SM, Chawla S, Jasdanwala SA. SGLT2 inhibitors: a new emerging therapeutic class in the treatment of type 2 diabetes mellitus. J Clin Pharmacol. 2012; 52: 457–63.

[50] Brunton SA. The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. Int J Clin Pract. 2015; 69(10): 1071-87.

[51] Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res. 2015 Mar; 12(2): 90-100.

[52] Hasan FM, Alsahli M, Gerich JE. SGLT2 inhibitors in the treatment of type 2 diabetes. Diabetes Res Clin Pract. 2014; 104(3): 297–322.

[53] Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. Diabetes Care. 2015; 38:1687-93.

[54] Rosenstock J, Ferrannini E. Euglycaemic Diabetic Ketoacidosis: A Predictable, Detectable and Preventable Safety Concern with SGLT2 inhibitors. Diabetes Care. 2015; 38: 1638-42.

[55] US Food and Drug Administration. FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Safety Announcement 2015; http://www.fda.gov/Drugs/DrugSafety/ucm461449.htm.

[56] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017; 377: 644–57.

[57] US FDA Drug Safety Communication. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) issued on May 18 2017 available from:https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf.

[58] Wanner C, Inzucchi SE, Lachin JM, Lachin JM, Fitchett D, von Eynatten M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016; 375: 323–334. doi: 10.1056/NEJMoa1515920.

[59] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 2117–28.

[60] Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013; 159: 262-74.

[61] Roden M, Merker L, Christiansen AV, Roux F, Salsali A, Kim G, et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naive patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovasc Diabetol. 2015; 14: 154.

[62] US Food and Drug Administration. FDA News Release on Dec 02, 2016. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm.

[63] Braunwald E. Heart failure. JACC Heart Fail. 2013; 1: 1–20.