Turkish Journal of Internal Medicine
http://www.tjim.org
ISSN: 2687-4245
Editorial

Oral Glucose-Lowering Agent Treatments in Type 2 Diabetes Mellitus

Sazi IMAMOGLU[1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Bursa Uludag University Faculty of Medicine, Bursa, Turkey

Turk J Int Med 2021;3(1):1-5
DOI: 10.46310/tjim.815794

Keywords: *oral treatment, anti-diabetics, type 2 diabetes mellitus,*

Type 2 diabetes is manifested by impaired insulin secretion in pancreatic beta cells, increased glucagon secretion in alpha cells, and generally has a history of insulin resistance.[1,2] The treatment of glucose metabolism disorder and the resulting hyperglycemia constitute an important part of the treatment of type 2 diabetes.[3-5] Glycemic targets can be targeted with A1C <7% to reduce the risk of micro and macrovascular complications in eligible patients, and A1C <6.5% to reduce the risk of diabetic chronic renal failure and retinopathy in those with low risk of hypoglycemia.[5-8] We can consider the treatment of hyperglycemia in two components; lifestyle changes and glucose lowering agent therapy.[5]

Lifestyle Changes

All type 2 diabetics should be given adequate training on lifestyle changes (nutrition therapy, physical activity and weight maintenance, no smoking, improvement of lifestyle) and self-monitoring of their diabetes, and these trainings should be reinforced as the patient comes to control.[5-11]

Glucose-Lowering Agent Treatments

We can consider the glucose-lowering agent therapies necessary for the regulation of glycemia in type 2 diabetes as glucose-lowering oral agent and injection therapies and insulin therapy. Glucose-lowering oral agents are indicated for patients with noninsulin-dependent stage of type 2 diabetes.[5]

In this article, I will review the glucose lowering oral agent therapy used in the treatment of type 2 diabetes *(Table 1)*.

Glucose-Lowering Oral Agent Treatments

The glucose lowering oral agent treatment to be applied should be personalized according to the medical conditions (age, duration of diabetes, risk of hypoglycemia, co-morbidities and life expectancy) and other risk factors of the patients.[4-7]

Monotherapy

- **Biguanide (Metformin)**

Metformin enhances insulin sensitivity in liver and peripheral tissues by activation of AMP-activated protein kinase.[12,13] With the diagnosis of type 2 diabetes, lifestyle changes and

Received: October 24, 2020; Accepted: November 4, 2020; Published Online: January 29, 2021

Address for Correspondence:
Sazi Imamoglu, MD
Division of Endocrinology and Metabolism, Department of Internal Medicine, Uludag University Faculty of Medicine, Bursa, Turkey
E-mail: drsazi@gmail.com

Table 1. The characteristics of the glucose lowering oral agents

	Metformin	SGLT-2 Inhibitors	DDP-4 Inhibitors	Oral GLP-1 Receptor Agonist (*Semaglutide*)	Thiazolidinedione (*Pioglitazone*)	Sulphonylurea / Glinide
Efficacy on glycemia	High	Intermediate	Intermediate	High	High	High
Risk of hypoglycemia	No	No	No	No	No	Yes
Atherosclerotic Cardiovascular Disease	Potential benefits	Benefit *(Empagliflozine, Canagliflozine)*	Neutral	Benefit	Potential benefits *(Pioglitazone)*	Neutral
Heart Failure	Neutral	Benefit *(Empagliflozine, Canagliflozine, Dapagliflozine)*	Potential risk *(Saxagliptin)*	Neutral	Increased risk	Neutral
Effects on Progression of Diabetic Kidney Disease	Neutral	Benefit *(Empagliflozine, Canagliflozine, Dapagliflozine)*	Neutral	Benefit	Neutral	Neutral
Weight change	Neutral/Potential for modest loss	Loss	Neutral	Loss	Gain	Gain
Dosing for Renal function/Contraindications	• Contraindicated with eGFR<30 ml/min/1.73 m2	• Dose adjustment required *(Empagliflozine Canagliflozine Dapagliflozine)*	• Renal dose adjustment required *(sitagliptin, saxagliptin, allogliptine):* can be used in renal impairment • No dose adjustment required for *(linagliptine)*	• Caution: *When initiating or increasing dose due to potential risk of acute kidney injury*	• No dose adjustment required • Generally, not recommended in renal impairment due to for fluid retention	• Risk of hypoglycemia *Glipizide and Glimepiride initiate conservatively to avoid hypoglycemia*
Additional consideration	• Gastrointestinal side effects *(diarrhea, nausea)* • B12 deficiency	• FDA blacklist Risk of amputation *(canagliflozine)*	• Potential risk acute pancreatitis • Joint pain	• Gastrointestinal side effects *(nausea, vomiting, abdominal pain)* • Amylase, lipase increase • Acute pancreatitis risk • Thyroid C-cell cancer risk	• Fluid retention • Congestive heart failure • Risk for bone fracture • Bladder cancer • Benefit for NASH	• FDA specially warning on risk of cardiovascular mortality based on studies of an older sulphonylurea *(tolbutamide)*

initiation of metformin treatment in the absence of any contraindications [allergy to metformin, renal failure (eGFR <30%)] is the first step.[4,9,14]

Metformin is a safe drug that is considered to reduce the cardiovascular events and related deaths that can be caused by diabetes.[4,5] Besides the vitamin B12 deficiency, metformin has rare side effects such as nausea, vomiting and diarrhea.[15,16] If the glycemic goal is not achieved within 3-6 months with metformin treatment and life changes, metformin treatment and life changes should be questioned, if there is no deficiency in their application, the addition of a second drug should be considered.[5,17]

Combination Treatments

When a second oral agent is added to the treatment, a patient-centered assessment should be made. In this evaluation; clinical characteristics such as the presence of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), diabetic kidney disease (DKD), diabetic retinopathy, diabetic neuropathy and other co-morbidities, as well as the effect of the second drug on glycemia, the risk of hypoglycemia, the effect of weight change and diabetes complications, and the side effects of the drug should be considered.[5,18,20]

- **Sodium Glucose Co-Transporter-2 (SGLT-2) Inhibitors**

Glucose excretion from the kidneys is decreased in patients with type 2 diabetes. SGLT-2's is effective in the reabsorption of glucose in the proximal renal tubule in the kidneys. SGLT2 inhibitors inhibit glucose reabsorption in the kidney and promote urinary glucose excretion, thus improve glycemic control independently of insulin-mediated mechanisms.[9,20]

SGLT-2 inhibitors are quite safe, well tolerated and do not cause hypoglycemia.[20] SGLT-2 inhibitors significantly reduce cardiovascular death or hospitalization and heart failure in patients with cardiovascular problems or pre-existing heart failure problems.[21-23] This effect is not statistically significant in patients without cardiovascular problems.[21-23]

SGLT-2 inhibitors in use today significantly reduce the deterioration of kidney function due to diabetes, end-stage renal failure and kidney-related deaths.[24-26] This effect appears to be present in both groups with and without atherosclerotic cardiovascular disease.[24-26]

Side effects of SGLT-2 inhibitors such as vaginal fungal infections, urinary infections, volume depletion, low blood pressure, increased risk of

diabetic ketoacidosis, increased LDL-cholesterol can be seen.[24-26]

Canagliflozin studies have reported an increase in bone fractures and leg amputations, although not in other SGLT-2 inhibitors.[25]

- **Dipeptidyl Peptidase-4 (DPP-4) Inhibitors**

DPP-4 inhibitors maintain the effects of incretin hormones (GLP-1, GIP) for a long time by inhibiting the DPP-4 enzyme that enzymatically degrades incretin hormones.[27] Incretin hormones increase insulin secretion in pancreatic beta cells according to serum glucose concentration, inhibit glucagon secretion in alpha cells and delay gastric emptying.[27] In this group of drugs with neutral cardiovascular effects and some weight reduction, the risk of heart failure was found to only be high in saxagliptin studies.[27-30] Pancreatitis and joint pain may rarely be seen in patients using DPP-4 inhibitors.[27]

- **Oral Glucagon Like Peptid-1 (GLP-1) Receptor Agonist (Semaglutide)**

Semaglutide is an oral GLP-1 receptor agonist. Semaglutide stimulates GLP-1 receptors and promote insulin secretion in a glucose dependent manner while at the same time inhibiting glucagon secretion and delay gastric emptying.[31] Studies with Semaglutide reported that it reduced cardiovascular death and all-cause death compared to placebo.[32,33] In a study comparing the efficacy and tolerability oral semaglutide with empagliflozin and sitagliptin, it was reported that the capacity of oral semaglutide to lower A1C was superior to empagliflozin and sitagliptin, and this superiority in weight reduction was not observed with empagliflozin.[34] Semaglutide may show side effects such as gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), increased amylase and lipase, risk of acute pancreatitis, risk of thyroid c cell cancer (not seen in human studies), risk of acute renal failure.[32] Semaglutide is to be initiated at a low dose, with its dose titrated upwards as appropriate.[32,33]

- **Thiazolidinedione (TZD)'s (Pioglitazone)**

TZDs activate one of the nuclear receptors, peroxisome proliferator-activated receptors gamma (PPAR-gamma), increase specific genes and also increase the synthesis of certain proteins involved in fat and glucose metabolism, which reduces levels of certain types of lipids, and circulating free fatty acids.[35,36] TZDs are shown to improve glycemic control by promoting peripheral insulin sensitivity and inhibiting hepatic glucose release. TZDs generally decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).[37,38]

TZDs are also often associated with weight gain due to their ability to promote fluid retention and they also carry risks such as the development of edema, congestive heart failure, anemia, bladder cancer, and bone fracture.[39-43] Patients should also be monitored in these aspects.

- **Sulphonylurea (SU)s / Glinides**

SUs and glinides binding a channel protein in the ATP-sensitive potassium channels on the membrane of pancreatic beta cells, they promote the secretion of insulin from pancreatic beta-cell.[44] SUs are not recommended for people who are overweight or obese, as their mode of action (increase in insulin secretion) means that weight gain can be a relatively common side effect.[45-47] Their effect on insulin levels also means users are at increased risk of hypoglycemia, although this risk is reduced with newer sulphonylureas.[47]

- ***α*-Glucosidase inhibitors (AGIs)**

AGIs inhibit intestinal glycolysis and delay intestinal glucose absorption and suppress postprandial hyperglycemia and hyperinsulinemia.[48,49] AGIs are also often associated with flatulans and diarrhea.[48,49]

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S14-S31. doi: 10.2337/dc20-S002.
2. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia. 2003 Jan;46(1):3-19. doi: 10.1007/s00125-002-1009-0.
3. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N

Engl J Med. 1976 Aug 19;295(8):417-20. doi: 10.1056/NEJM197608192950804.
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1577-89. doi: 10.1056/NEJMoa0806470.
5. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of medical care in diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S98-S110. doi: 10.2337/dc20-S009.
6. Vijan S, Sussman JB, Yudkin JS, Hayward RA. Effect of patients' risks and preferences on health gains with plasma glucose level lowering in type 2 diabetes mellitus. JAMA Intern Med. 2014 Aug;174(8):1227-34. doi: 10.1001/jamainternmed.2014.2894.
7. Vaag AA. Glycemic control and prevention of microvascular and macrovascular disease in the Steno 2 study. Endocr Pract. 2006 Jan-Feb;12 Suppl 1:89-92. doi: 10.4158/EP.12.S1.89.
8. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B, Horowitz KR, Savage PJ, Seaquist ER, Simmons DL, Sivitz WI, Speril-Hillen JM, Sweeney ME. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010 Jan 8;340:b4909. doi: 10.1136/bmj.b4909.
9. Chong S, Ding D, Byun R, Comino E, Bauman A, Jalaludin B. Lifestyle changes after a diagnosis of type 2 diabetes. Diabetes Spectr. 2017 Feb;30(1):43-50. doi: 10.2337/ds15-0044.
10. Zinman B, Ruderman N, Campaigne BN, Devlin JT, Schneider SH; American Diabetes Association. Physical activity/exercise and diabetes mellitus. Diabetes Care. 2003 Jan;26 Suppl 1:S73-7. doi: 10.2337/diacare.26.2007.s73.
11. Mulcahy K, Maryniuk M, Peeples M, Peyrot M, Tomky D, Weaver T, Yarborough P. Diabetes self-management education core outcomes measures. Diabetes Educ. 2003 Sep-Oct;29(5):768-70, 773-84, 787-8 passim. doi: 10.1177/014572170302900509.
12. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001 Oct;108(8):1167-74. doi: 10.1172/JCI13505.
13. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR, Shulman GI. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes. 2000 Dec;49(12):2063-9. doi: 10.2337/diabetes.49.12.2063.
14. Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care. 2011 Jun;34(6):1431-7. doi: 10.2337/dc10-2361.
15. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181.
16. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, Bray GA, Schade DS, Temprosa MG, White NH, Crandall JP; Diabetes Prevention Program Research Group. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016 Apr;101(4):1754-61. doi: 10.1210/jc.2015-3754.
17. Cahn A, Cefalu WT. Clinical considerations for use of initial combination therapy in type 2 diabetes. Diabetes Care. 2016 Aug;39 Suppl 2(Suppl 2):S137-45. doi: 10.2337/dcS15-3007.
18. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes Obes Metab. 2014 May;16(5):410-7. doi: 10.1111/dom.12233.
19. Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL Jr, Kalyani RR, Kosiborod M, Magwire ML, Morris PB, Sperling LS. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018 Dec 18;72(24):3200-23. doi: 10.1016/j.jacc.2018.09.020.
20. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, Feldman L, Vassy J, Wilson R, Bass EB, Brancati FL. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med. 2008 Oct 27;168(19):2070-80. doi: 10.1001/archinte.168.19.2070.
21. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720.
22. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017 Aug 17;377(7):644-57. doi: 10.1056/NEJMoa1611925.
23. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diabetes Metab Syndr Obes. 2012;5:313-27. doi: 10.2147/DMSO.S22545.
24. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, Woerle HJ, Broedl UC, von Eynatten M, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus, established cardiovascular disease, and chronic kidney disease. Circulation. 2018 Jan 9;137(2):119-29. doi: 10.1161/CIRCULATIONAHA.117.028268.
25. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol. 2018 Sep;6(9):691-704. doi: 10.1016/S2213-8587(18)30141-4.
26. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2

inhibitors: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2017 Mar;19(3):348-55. doi: 10.1111/dom.12825.
27. Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). Best Pract Res Clin Endocrinol Metab. 2009 Aug;23(4):479-86. doi: 10.1016/j.beem.2009.03.004.
28. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42. doi: 10.1056/NEJMoa1501352.
29. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013 Oct 3;369(14):1327-35. doi: 10.1056/NEJMoa1305889.
30. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. 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.
31. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, Jeppesen OK, Christiansen E, Hertz CL, Haluzík M; PIONEER 1 Investigators. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Diabetes Care. 2019 Sep;42(9):1724-32. doi: 10.2337/dc19-0749.
32. Pieber TR, Bode B, Mertens A, Cho YM, Christiansen E, Hertz CL, Wallenstein SOR, Buse JB; PIONEER 7 investigators. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-39. doi: 10.1016/S2213-8587(19)30194-9.
33. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsbøll T, Warren ML, Bain SC; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019 Aug 29;381(9):841-851. doi: 10.1056/NEJMoa1901118.
34. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, Lingvay I, Søndergaard AL, Treppendahl MB, Montanya E; PIONEER 2 Investigators. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019 Dec;42(12):2272-81. doi: 10.2337/dc19-0883.
35. Kahn CR, Chen L, Cohen SE. Unraveling the mechanism of action of thiazolidinediones. J Clin Invest. 2000 Dec;106(11):1305-7. doi: 10.1172/JCI11705.
36. Smith U. Pioglitazone: mechanism of action. Int J Clin Pract Suppl. 2001 Sep;(121):13-8.
37. Al Majali K, Cooper MB, Staels B, Luc G, Taskinen MR, Betteridge DJ. The effect of sensitisation to insulin with pioglitazone on fasting and postprandial lipid metabolism, lipoprotein modification by lipases, and lipid transfer activities in type 2 diabetic patients. Diabetologia. 2006 Mar;49(3):527-37. doi: 10.1007/s00125-005-0092-4.
38. Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med. 2003 Dec 8;115 Suppl 8A:42S-48S. doi: 10.1016/j.amjmed.2003.09.005.
39. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007 Sep 12;298(10):1180-8. doi: 10.1001/jama.298.10.1180.
40. Scheen AJ. Outcomes and lessons from the PROactive study. Diabetes Res Clin Pract. 2012 Nov;98(2):175-86. doi: 10.1016/j.diabres.2012.09.001.
41. Filipova E, Uzunova K, Kalinov K, Vekov T. Pioglitazone and the risk of bladder cancer: a meta-analysis. Diabetes Ther. 2017 Aug;8(4):705-26. doi: 10.1007/s13300-017-0273-4.
42. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009 Jan 6;180(1):32-9. doi: 10.1503/cmaj.080486.
43. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008 Apr 28;168(8):820-5. doi: 10.1001/archinte.168.8.820.
44. Seino S. Cell signalling in insulin secretion: the molecular targets of ATP, cAMP and sulfonylurea. Diabetologia. 2012 Aug;55(8):2096-108. doi: 10.1007/s00125-012-2562-9.
45. 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):1672-8. doi: 10.2337/dc08-0167.
46. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997 Aug 11-25;157(15):1681-6.
47. Derosa G, Mugellini A, Ciccarelli L, Crescenzi G, Fogari R. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. Clin Ther. 2003 Feb;25(2):472-84. doi: 10.1016/s0149-2918(03)80090-5.
48. Hanefeld M, Fischer S, Schulze J, Spengler M, Wargenau M, Schollberg K, Fücker K. Therapeutic potentials of acarbose as first-line drug in NIDDM insufficiently treated with diet alone. Diabetes Care. 1991 Aug;14(8):732-7. doi: 10.2337/diacare.14.8.732.
49. Coniff RF, Shapiro JA, Seaton TB. Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus. Arch Intern Med. 1994 Nov 14;154(21):2442-8.