# AN UPDATE ON FIXED-DOSE COMBINATION OF SGLT-2 AND DPP-4 INHIBITORS IN THE MANAGEMENT OF TYPE-2 DIABETES

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**Abstract**

**Background:** Type2 Diabetes mellitus is a progressive disease with multiple pathophysiological defects. If tolerated and not contraindicated metformin as monotherapy is the drug of choice in the diabetic patient. Dual or triple therapy can be considered if glycemic control is not achieved in the three months. Combination drug with complimentary mechanism of action and with lesser adverse events (hypoglycemia, weight gain, cardio-renalevents) can be consider in patients with type 2diabetesmellitus.

**Methodology:** A thorough literature search was performed using PubMed, Google Scholar and Embase. The authors selected the articles based on relevance. T2DM, SGLT2 inhibitors, SGLT2 antagonist, DPP-4 antagonist, DPP-4 inhibitors, dual therapy, add-on therapy were the major searched key words.

**Result:** Through the literature we observed that diabetic patients on monotherapy are at high risk of developing micro and macrovascular complication. Two oral hypoglycemic drugs i.e., sodium glucose cotransporter 2 inhibitor (SGLT2i) and dipeptidyl peptidase 4 inhibitor (DPP-4i) were identified with complementary mechanism of action. Dual (SGLT2i and DPP-4i) therapy or add on therapy to metformin can be used at any phase of diabetes mellitus and are usually well tolerated with lesser side effects.

**Conclusion:** Combination use of SGLT2 inhibitors and DPP-4 inhibitors is attractive because of their complementary mode of action. Dual therapy or add on to metformin should be consider from the initial point of prescribing. Though the precise positioning of a DPP-4i-SGLT2i combination should be better outlined by supplementary studies, this process seems to be a novel choice for the management of patients with T2DM, with a good efficacy/safety ratio but at a higher cost.

**Keywords:** Diabetes, Fixed dose combination, DPP4inhibitor,SGLT2inhibitor

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## Introduction

Type2diabetesmellitus, is a gradual illness with several pathophysiological defects [1,2].Mono drug therapy cannot address these multiple pathophysiological blemishes and often leads to drug failure or failure to uphold targeted glycaemic control. American Diabetes Association (ADA) and American Association of Clinical Embryology (AACE) proposed sequential addition of T2DM treatments from routine alterations to combination therapy[3,4]. However, high HbA1c level varies in both the guidelines (≥7.5% AACE or ≥9.0%ADA]. If tolerated and not contraindicated, metformin is recommended choice of drug in diabetes. If glycaemic control is not attained in three months, then the addition of a second drugis considered. Triple therapy is indorsed if dual therapy failed to attain the target glycaemic control. Prolonged exposure to hyperglycaemia can lead to micro and macrovascular complications. Therefore, combination therapy can be initiated early to improve long term complications and to avert progressive beta cell damage [2,5]. An ideal combination of an oral hypoglycaemic drug should have a complementary mechanism of action and should target all phases of diabetes without increased risk for hypoglycaemia, weight gain, cardio-renal events as well as provide patient drug compliance by providing oral medication, once a day single pill administration. Two classes of oral hypoglycaemic agents that meet the above criteria are sodium-glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase 4 (DPP-4) inhibitors. At extant, SGLT-2i and DDP-4i are the second or third line of treatment to add on to dual or triple therapy [3,4]. Patients or individuals with metformin contraindication, DPP4i and SGLT2i are the drugs that can be used at any stage of diabetes. The present review will discuss the possible complementary mechanism of SGLT2i and DPP4iindetail [6].

## SLT2 inhibitor and DPP4 inhibitor combination with other oral hypoglycemic agent on the market

There are numerous possible combinations of diabetes medications. Since metformin is a prescription that the majority of diabetic peoples take, it is included in nearly half of the combination products available today [7,8]. Table. 1 summarises the FDA-approved dose combinations of metformin, SGLT2 inhibitors, and DPP-4 inhibitors, as well as metformin, DPP-4 inhibitor, and SGLT2 inhibitor. The majority of recently authorised mono therapies known as novel molecular entities (NMEs) target established molecular pathways that most recently approved NMEs that are monotherapies target proven molecular pathways that have been verified by other approved antihyperglycemic drugs. For instance, sodium-glucose co transporter type 2 (SGLT2), which received approval in 2014, is the newest molecular target. However, combination therapies that target various routes for the treatment of diabetes mellitus have also been getting more approvals [9-14].

**Table1.**List of oral antidiabetic Fixed Dose Combination

| **DPP4 inhibitors & Metformin** | | | | |
|---|---|---|---|---|
| **Generic name** | | **Brand** | **Machenism of Action** | **FDA Approval** |
| Sitagliptin + Metformin | 50/500mg<br>50/1000mg | Janumet, Janumet XR | Prevent the breakdown of Glp-1 and GIP, Stimulate insulin and decrease the glucagon release from the pancreas | 2007 |
| Saxagliptin + Metformin | 5/500mg<br>5/1000mg<br>2.5/1000mg | Kombiglyze XR | | 2010 |
| Linagliptin + Metformin | 2.5/500mg, 2.5/1000mg | Jentadueto | | 2012 |
| Alogliptin + Metformin | 12.5/500mg | Kazano | | 2013 |
| **SGLT2 inhibitors & Metformin** | | | | |
| Canagliflozin + Metformin | 50/500 mg | Invokamet, | Reduced the blood glucose by blocking the glucose reabsorption in the kidney | 2014 |
| Canagliflozin + Metformin | 50/500mg | Invokamet XR | | 2016 |
| Ertugliflozin + | 2.5/500mg | Segluromet | | 2017 |

| | | | | |
|---|---|---|---|---|
| Metformin | | | | |
| Empagliflozin + Metformin | 5/500mg,5/1000mg 12.5/500mg, 12.5/1000mg | Synjardy, Synjardy XR | | 2015 |
| Dapagliflozin + Metformin | 5/500mg, 10/500mg 5/1000mg/10/1000mg | Xigduo XR | | 2014 |
| **SGLT2 Inhibitor & DPP-4 Inhibitor** | | | | |
| Empagliflozin + Linagliptin | 10/5mg | Glyxambi | SGLT2 and DPP-4 inhibitors lower blood glucose separately by blocking the glucose reabsorption in the kidney and Prevent the breakdown of Glp-1 and GIP, Stimulate insulin | 2015 |
| Dapagliflozin + Saxagliptin | 10/5mg | Qtern | | 2017 |
| Ertugliflozin + Sitagliptin | 5/100mg | Steglujan | | 2017 |
| **Biguanide, DPP-4 Inhibitor & SGLT2 Inhibitor** | | | | |
| Empagliflozin + Linagliptin + Metformin | Tardy XR | 5/2.5/1000mg, 10/5/1000mg, 12.5/2.5/1000mg, 25/5/1000mg | | 2019 |
| Dapagliflozin + Saxagliptin + Metformin | Qternmet XR | 2.5/2.5/1000mg 5/5/1000mg 10/5/2000mg | | 2020 |

**SGLT2 inhibitor and DPP4 inhibitor: A possible complementary mechanism of action**

Several complementary modes of activity By different, complimentary processes, SGLT2 inhibitors and DPP-4 inhibitors both reduce blood sugar levels. Both depend on glucose, which explains why there is little chance of hypoglycemia when receiving medication. Within minutes of eating, the hormones known as incretins, including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are secreted into the bloodstream where, among other things, they control pancreatic secretion of insulin and glucagon. The enzyme DPP-4 quickly renders them both inactive. Of the two incretins, GLP-1 is more crucial for glucose control in persons with type 2 diabetes. Inhibition of DPP-4 stops GLP-1 from being broken down, increasing insulin secretion while decreasing glucagon release and suppressing the generation of endogenous glucose. [15-18].The enzyme SGLT2 controls the reabsorption of glucose in the renal tubules. Therefore, SGLT2 inhibition increases urine glucose excretion, which immediately affects blood sugar levels.5, the entire implications of these characteristics are not yet fully known, however SGLT2 inhibitors significantly boost endogenous glucose synthesis 6 and glucagon secretion [19-21]. Combining these methods of action should therefore increase their ability to decrease blood sugar levels; a DPP-4 inhibitor may even work to offset the effects of an SGLT2 inhibitor on glucagon secretion and endogenous glucose synthesis. In people on metformin, their combined effects on blood glucose are less than additive [22-29]. Fig. 1, illustrates the complementary positive effect of this combination [30].

**Pathophysiological effect**

SGLT1 and SGLT2 are transporter proteins, located at early proximal tubules which facilitate glucose reabsorption. SGLT2 alone is responsible for 70-90% of the glucose reabsorption [6,31]. In diabetes, expression of SGLT2 increased, causative to enhance glucose reabsorption [31]. Inhibitions of SGLT2 results in decreased renal glucose reabsorption up to 50% and therefore reduce hyperglycaemia in type 2 diabetes mellitus. Drugs of the SGLT2i class are now becoming the most commonly prescribed drug, as the mechanism of SGLT2i is sovereign to pancreatic beta-cell function and insulin sensitivity [32].

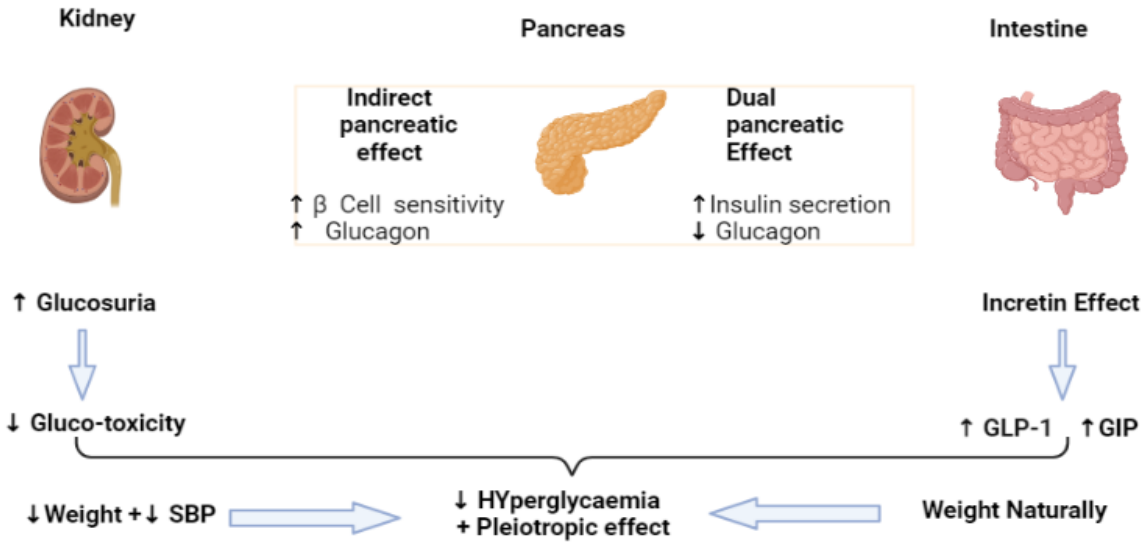


**Fig 1.** An example of type 2 diabetes mellitus and the complementing glucose-lowering effects of DPP4i and SGLT2i. Systolic blood pressure, GIP glucose-dependent insulinotropic polypeptide.

DPP-4 inhibitors, inhibit the enzymatic degradation of incretin hormone consequently increase the half-life of incretin which in turn augment the insulin secretion and decrease glucagon secretion from pancreatic beta and alpha cells respectively, thus reduce endogenous glucose production[33].

**Efficacy of SGLT2 and DPP-4 inhibitors in type2 diabetes mellitus**

The majority of the meta-analysis showed that treatment with SGLT2i as monotherapy improved HbA1c level by 0.5-1.0%, reduced weight by approx 2kg and reduced systolic blood pressure by 2-5mmHg [34-37]. A possible mechanism behind weight loss is due to loss of calories through augmented glucose excretion in the urine [38, 39]. Drop in systolic blood pressure is not known but can be due to weight loss, and reduced arterial stiffness [40-42]. Some meta-analyses showed a reduction of up to3%in patients with baseline HbA1c of more than 10% [43-45]. The following mechanism can be explained by the drug mode of action, where the amount of urinary glucose purging is moderately reliant on the patient's glycaemic level and will up surge with increasing plasma glucose concentrations [6].

Placebo-control trials showed reduction of 0.6-0.7% of HbA1c with DPP-4i from the baseline of 7.8-8.0% [42,46,47]. Besides greater reduction in HbA1c (upto1.5%) is seen in a patient with HbA1c baseline of more than 9% [42,48]. Increased level of GLP-1, no significant weight loss and small change in blood pressure was found to be associated with DPP-4i [4,48-51]. The use of SGLT2 inhibitor and DDP-4 inhibitor to additional oral antidiabetic medications is advised as a second- or third-line therapy option our subgroup meta-analysis showed that combination therapy with SGLT2 inhibitor/DPP-4 inhibitor could give patients receiving metformin or naive therapy optimal efficacy without raising the risk of side effects. This demonstrated that a variety of patients at various stages, such as those who were first treated with metformin but were unable to tolerate it, could benefit from the combined strategy [52]. Safety Profile of SGLT2 inhibitors and DPP-4inhibitors

SGLT2i are well tolerated and one of the safe drugs concerning their mechanism of action. In the absence of insulin or insulin secretagogue, the risk of hypoglycaemia is very low [53-55]. However, some authors reported, SGLT2i induced genital mycotic infection and urinary tract infection. The genitourinary related infection is thought to be related to an increased level of glucose in urine [56]. In 2008, FDA revised the SGLT2i drug label with a possible complication of urosepsis and pyelonephritis [57]. In elderly patients or patients with impaired renal function or patients on a diuretic or ACE inhibitor, the use of SGLT2i should be monitor due to possible complications of hypotension [53,54,58]. Glycaemic efficacy of SGLT2 inhibitors reduced with reduction in renal functions, therefore, these classes of drugs are contra-indicated in patients with end-stage renal disease (ESRD) or on dialysis. In the fourth phase of a clinical trial, diabetic ketoacidosis was found to be associated with SGLT2i [58]. Surgical procedures, infection and extensive exercise were found to be

predisposing factors for diabetic ketoacidosis in patients with SGLT2i [59]. Canagliflozin was found to be allied with the peril of bone fracture and fractures were detected within 12 weeks of therapy initiation [58].

DPP-4 inhibitors are generally well tolerated as incretin associated insulin excretion occurs in retort to food intake. The risk of hypoglycaemia with DPP4i is very low. However, the risk of hypoglycemia is increased when taken with insulin or with insulin secretagogue [60-62]. Dose adjustment is required in patients with moderate to severe renal impairment but linagliptin does not require dose adjustment [60-63]. In phase four of clinical trials, moderate to incapacitating arthralgia, anaphylaxis, angioedema and skin disorders have been reported.

Concerning bone fracture, one meta-analysis of randomized control trials reported that general risk was comparable to that of controls [64]. In patients with DPP4i, acute pancreatitis has been observed. However, it is not identified whether patients with a medical history of pancreatitis are at augmented risk of developing pancreatitis during the treatment [65].

**Cardiovascular safety of SGLT2 inhibitors and DPP-4 inhibitors**

EMPA_REG trial conscripted patients with T2DM with a past medical-history of cardiovascular disease and was treated with empagliflozin. The trial reported a lower rate of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke [66]. The trial also reported a reduction of cardiovascular mortality by 35%, all-cause mortality by 32% and relative risk by 35% in hospitalized patients with heart failure [56]. Thrillingly, empagliflozin was also allied with better renal functions or outcomes [67]. Three trials with DPP-4i were conducted: SAVOR-TIMI 53 [68,69], EXAMINE [70] and TECOS [71]. All three trials reported better cardiovascular outcomes (cardiovascular death, non-fatal myocardial infarction and stroke). However, unlike EXAMINE and TECOS, SAVOR-TIMI 53 reported an increased risk of hospitalization with saxagliptin. Agents with demonstrated CV advantages, as SGLT2i and GLP1-RAs, in patients with high CV risk, followed by agents with established CV safety if more glycemic control is needed. Therefore, in patients with high CV risk and/or heart failure risk who have HbA1c [1.5% above the individualized target], the combination of an SGLT2i and DPP4i may become more important. Targeting manifold pathophysiological mechanism for T2DM with SGLT2i and DPP4i combination treatment is a unambiguous advantage and also supports the application of this combination early in T2DM management [72].

**Combining SGLT2 inhibitors and DPP-4 inhibitors**

To target different pathophysiological defects allied with T2DM, combination of SGLT2i and DPP4i mechanism of action are found to be valuable [3,46]. Metabolic studies with SGLT2i confirmed that falling of plasma glucose by means of an agent that acts through renal, improves peripheral insulin sensitivity as well as beta cell functions, in spite of an increase in endogenous glucose production [8,9]. Hansen L et al., reported beneficial effect of saxagliptin plus dapagliflozin on pancreatic alpha and beta cell's function [47]. Furthermore, both the drug classes have better tolerability and have no risk of hypoglycemia when used with other drugs except with insulin or insulin secretagogue. Another potential benefits weight loss with SGLT2 inhibitors while DPP4i are weight neutral. As discussed before, empagliflozin (SGLT2i) have cardio protective effect mean while more research is obligatory for DPP4i. Not one case of heart failure was stated in clinical trial with empagliflozin-linagliptin as combination or as add-on to metformin [48,49]. At present two pill choice are available, these medicines are not retested in analogous clinical trial program to the discrete drug since agents are bioequivalent[50].

**Empagliflozin and Linagliptin Combination Therapy**

Efficacy and safety of empagliflozin plus linagliptin was determined in the randomised, double blind parallel group trial [49]. Result directed toward the benefits of empagliflozin as add-on to linagliptin-metformin [51] as well as linagliptin to add on to metformin-empagliflozin [52]. The use of empagliflozin and linagliptin as a single pill is approved by FDA [53], and by the European Medicine Agency [54]. The bioequivalence of the empagliflozin 25mg-linagliptin 5mg single pill combination stranded on the overall associate like area under the curve, time to the maximum plasma concentration [55].

**Empagliflozin and Linagliptin: Treatment naïve patient and Add on to metformin**

Treatment naïve or metformin treated patients were sub-divided into 5sets: empagliflozin 25mg-linagliptin 5mg; empagliflozin10mg-linagliptin 5mg; empagliflozin 25mg; empagliflozin10mg; or

linagliptin 5mg for 12 months. At 24 weeks, in treatment naïve patients, significant reductionin HbA1c was noticed in patients with both empagliflozin and linagliptin as compared to patients with linagliptin; empagliflozin10mg-linagliptin5mg showeda significant drop in HbA1c as related to empagliflozin10mg [49]. At 24 weeks of treatment with metformin, significant reduction of HbA1c was noticed as compared to the both doses of empagliflozin and linagliptin [48]. At 24 and 52 weeks of treatment with empagliflozin plus linagliptin, significant weight reduction was found when compared to linagliptin but not compared with either empagliflozin dose [48,49]. With respect to blood pressure, at 52 week no difference was determined between monotherapy and empagliflozin plus linagliptin [49]. In metformin group, significant blood pressure reduction was found when compared to empagliflozin plus linagliptin [48]. With respect to safety profile, no difference was found in patients with empagliflozin plus linagliptin and in patients with monotherapy. [48,49]. Similar extents of genital infection and UTI were reported in both the studies group. One case of pancreatitis was reported in empagliflozin plus linagliptin and in linagliptin plus metformin group respectively.

**Dapagliflozin and Saxagliptin Combination therapy**

EMA and FDA approved single pill use of dapagliflozin plus saxagliptin for use in patients with T2DM [56]. Both saxagliptin 2.5 mg plus dapagliflozin 5mg and saxagliptin 5mg plus dapagliflozin10mg found to be bioequivalent to the strength of monotherapy [57]. Rosenstock et al [58], Mathieu et al [59], and Matthaei et al assed safety profile of saxagliptin-dapagliflozin combination therapy as add-on to metformin in control-placebo, double blinded randomized control trial.

**Dapagliflozin plus saxagliptin as add on to metformin**

Randomized control trial by Rosenstock et al., equated combination of dapagliflozin 10mg and saxagliptin 5mg with monotherapy or as add-on to extended-release formulation of metformin [58]. Patients with T2DM treated with Metformin (≥1.5g/day) who had anHbA1c of 8–12% and a BMI of ≤45 kg/m2 were randomized to dapagliflozin 10 mg andsaxagliptin 5 mg, dapagliflozin 10mg and placebo, or saxagliptin 5mg and placebo. At 6months, the trial reported significant reduction of HbA1C from the baseline in patient with saxagliptin and dapagliflozin combination pill as compared to monotherapy add on to metformin. Similarly, reduction of fasting blood glucose was found to be significant in saxagliptin and dapagliflozin combination group when compared to saxagliptin monotherapy but not against dapagliflozin at 24 weeks. Significant loss of weight was observed in patients with saxagliptin plus dapagliflozin when compared to saxagliptin but not with dapagliflozin. Safety profiles were similar in all the treatment groups and no maj or hypoglycaemic event or heart failure event was observed in thet rial. As compare to saxagliptin and combination therapy patients on dapagliflozin monotherapy, were reported with urinary tract infection. Single case of pancreatitis was observed in combination therapy group.

**Conclusion**

Diabetic patients on monotherapy often require additional agent to achieve targeted glycaemic values. Combination of SGLT2 inhibitors and DPP4 inhibitors as add on to metformin therapy effectively improves the glycaemic control. In addition to glycaemic control, SGLT2 inhibitors and DPP-4 inhibitors provide significant reduction in blood pressure and weight. Use of SGLT2 inhibitors and DPP-4 inhibitors as a single pill is well tolerated and very few adverse events were observed. Rather than using stepwise treatment plan, physician can directly consider triple therapy in T2DM patients to achieve desired glycaemic control.

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**References:**

1. Tönnies, Thaddäus, et al. "Projections of type 1 and type 2 diabetes burden in the US population aged< 20 years through 2060: the SEARCH for Diabetes in Youth study." Diabetes Care 46.2 (2023): 313-320.
2. DefronzoRA.BantingLecture.Fromthetriumvi ratetotheominousoctet:anewparadigmforthe treatment oftype2 diabetesmellitus.Diabetes2009;58:773–95
3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the AmericanAssociationofClinicalEndocrinolog istsandAmericanCollegeofEndocrinologyont he comprehensive type 2 diabetes

management algorithm – 2016 executive summary.EndocrPract2016;22:84–113
4. MilliganS.Combinationtherapyfortheimprovementoflong-termmacrovascularandmicrovascular outcomes in type 2 diabetes: Rationale and evidence for early initiation. J Diabetes Complications 2016;30:1177–85
5. Abdul-Ghani MA, De Fronzo RA, Norton L. NovelhypothesistoexplainwhySGLT2inhibitors inhibit only 30-50% of filtered glucose load in humans. Diabetes2013;62:3324–8
6. Laffel, Lori M., et al. "Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised , double-blind, parallel group, phase 3 trial." The Lancet Diabetes & Endocrinology 11.3 (2023): 169-181.
7. Shults A. Drug facts: Combination medications [Internet]. AMS Nutrition. 2020 [cited 2023 Jun 20]. Available from: https://www.amsnutritioncounseling.com/post/drug-facts-combination-medications
8. Dahlén, Amelia D., et al. "Trends in antidiabetic drug discovery: FDA approved drugs, new drugs in clinical trials and global sales." Frontiers in Pharmacology 12 (2022): 807548.
9. Trijardy XR - A New 3-Drug Combination for Type 2 Diabetes | The Medical Letter Inc. (n.d.-c). https://secure.medicalletter.org/TML-article-1599e
10. Qternmet XR Dosage Guide. (n.d.-b). Drugs.com. https://www.drugs.com/dosage/qternmetxr.html
11. Qtern - Search results. Page 1 of about 44 results. (n.d.). Drugs.com. https://www.drugs.com/search.php?searchterm=Qtern
12. Steglujan - Search results. Page 1 of about 44 results. (n.d.). Drugs.com. https://www.drugs.com/search.php?searchterm=Steglujan
13. Glyxambi - Search results. Page 1 of about 54 results. (n.d.). Drugs.com. https://www.drugs.com/search.php?searchterm=Glyxambi&a=1
14. Jentadueto Dosage Guide. (n.d.). Drugs.com. https://www.drugs.com/dosage/jentadueto.html
15. Shah, Najeeb, et al. "Therapeutics for type-2 diabetes mellitus: a glance at the recent inclusions and novel agents under development for use in clinical practice." Therapeutic Advances in Endocrinology and Metabolism 12 (2021): 20420188211042145.
16. Álvarez-Almazán, Samuel, et al. "Current molecular aspects in the development and treatment of diabetes." Journal of physiology and biochemistry 76.1 (2020): 13-35.
17. Walker, John T. New Insights into the Molecular Mechanisms of Islet Dysfunction in Human Diabetes. Diss. 2021.
18. Evans, Elizabeth. The Skin: A Novel Regulator of Whole-body Glucose Metabolism. Diss. King's College London, 2020.
19. Gonzalez, Claudio D., et al. "Autophagy dysregulation in diabetic kidney disease: from pathophysiology to pharmacological interventions." Cells 10.9 (2021): 2497.
20. Hsu, Chih-Neng, et al. "Anti-Diabetic Therapy and Heart Failure: Recent Advances in Clinical Evidence and Molecular Mechanism." Life 13.4 (2023): 1024.
21. Guo, Yanying, et al. "Metabolic disorder-related hypertension." Secondary Hypertension: Screening, Diagnosis and Treatment (2020): 507-545.
22. Chaplin S. DPP-4/SGLT2 inhibitor combined therapy for type 2 diabetes. Prescriber. 2017 Nov;28(11):32-8.
23. Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, Kovil R, Kumar S, Misra A, Mohan V. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i+ DPP4i in the Indian Diabetes Setting. Diabetes Therapy. 2022 May;13(5):1097-114.
24. Taylor SI, Yazdi ZS, Beitelshees AL. Pharmacological treatment of hyperglycemia in type 2 diabetes. The Journal of Clinical Investigation. 2021 Jan 19;131(2).
25. The management of diabetes mellitus-imperative role of natural products against dipeptidyl peptidase-4, α-glucosidase and sodium-dependent glucose co-transporter 2 (SGLT2)
26. Brown, Emily, et al. "The expanding role of SGLT2 inhibitors beyond glucose-lowering to cardiorenal protection." Annals of Medicine 53.1 (2021): 2072-2089.
27. Kale, Ajinath, et al. "Klotho: A possible mechanism of action of SGLT2 inhibitors preventing episodes of acute kidney injury and cardiorenal complications of diabetes."

Drug Discovery Today 26.8 (2021): 1963-1971.
28. Massimino, Elena, et al. "The impact of glucose-lowering drugs on sarcopenia in type 2 diabetes: current evidence and underlying mechanisms." Cells 10.8 (2021): 1958.
29. Miao, Lei, et al. "Old and new classes of glucose-lowering agents as treatments for non-alcoholic fatty liver disease: A narrative review." Clinical and Molecular Hepatology 28.4 (2022): 725.
30. Chadha, Manoj, et al. "Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i+ DPP4i in the Indian Diabetes Setting." Diabetes Therapy 13.5 (2022): 1097-1114.
31. De Fronzo RA, Davidson JA, DelPratoS. The role of the kidneys in glucose home ostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab2012;14:5–14
32. Liu JJ, Lee T, DeFronzo RA. Why do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? Diabetes 2012;61:2199–204
33. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonistsanddipeptidylpeptidase-4inhibitorsintype2 diabetes.Lancet2006;368:1696–705
34. Yang XP, Lai D, Zhong XY, etal. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol 2014;70: 1149–58
35. Zhang M, ZhangL, WuB,et al. Dapagliflozin treatmentfortype2diabetes:asystematicreview and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev2014;30:204–21
36. Tikkanen I, Narko K, Zeller C, etal. Empaglifloz in reduces blood pressure inpatients with type 2 diabetes and hypertension. Diabetes Care 2015;38:420–8
37. Liakos A, Karagiannis T, Athanasiadou E, etal. Efficacyandsafetyofempagliflozinfortype2diabetes:asystematic review andmeta-analysis.DiabetesObesMetab2014;16:984–93
38. Barnett AH. Impact of sodium glucose cotransporter 2 inhibitorson weight in patients with type 2 diabetes mellitus. Postgrad Med2013;125:92–100
39. Bolinder J, Ljunggren O, Kullberg J,etal. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with in adequate glycemic control on met form in. J Clin Endocrinol Me tab 2012;97:1020–31
40. Cherney DZ, Perkins BA, Soleymanlou N, etal. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol2014;13:28
41. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587–97
42. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptinas monotherapy on glycemic controlin patients with type 2 diabetes. Diabetes Care2006; 29:2632–7
43. Ferrannini E, Ramos SJ, Salsali A,etal. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217–24
44. Stenl of K, Cefalu WT, Kim KA, etal. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013; 15:372–82
45. Roden M, Weng J, Eilbracht J, etal. 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;1:208–19
46. Rosenstock J, Aguilar-Salinas C, Klein E, etal. Effect of saxagliptin monotherapy intreatment naïve patients with type 2 diabetes. Curr Med Res Opin 2009; 25:2401–11
47. De Fronzo RA, Fleck PR, Wilson CA, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor aloglipt in in patients with type 2 diabetes and in adequate glycemic control: arandomized, double-blind, placebo-controlled study. Diabetes Care 2008; 31:2315–7
48. Del Prato S, Barnett AH, Huisman H, etal. Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. Diabetes Obes Metab2011;13:258–67
49. Von Eynatten M, Gong Y, Emser A, et al.

Efficacy and safety of linagliptin in type 2 diabetes subjects at high risk for renal and cardiovascular disease: a pooled analysis of six phase III clinicaltrials. Cardiovasc Diabetol 2013;12:60

50. Tremblay AJ, Lamarche B, Deacon CF, etal. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes.DiabetesObesMetab2011;13:366–73
51. Zhang X, Zhao Q. Effects of dipeptidyl peptidase-4 inhibitors on blood pressure inpatients with type 2 diabetes: a systematic review and meta-analysis. J Hypertens2016;34:167–75
52. Li, Dandan, et al. "SGLT2 inhibitor plus DPP-4 inhibitor as combination therapy for type 2 diabetes: a systematic review and meta-analysis." Diabetes, Obesity and Metabolism 20.8 (2018): 1972-1976.
53. Farxiga (dapagliflozin), prescribing information. Astra Zeneca Pharmaceuticals LP, July2016. Available at http://www.azpicentral.com/farxiga/pi_farxiga.pdf#page=1[LastaccessedJanuary20]
54. Jardiance® (empagliflozin), prescribing information. Boehringer Ingelheim, December 2016. Available at http://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Jardiance/jardiance.pdf [Lastaccessed December 20]
55. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy ormet form in based combination therapy for type 2 diabetes: a systematic review and meta-analysis.AnnInternMed2016;164:740–51
56. Geerlings S, Fonseca V, Castro-Diaz D, et al. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. Diabetes Res Clin Pract2014;103:373–81
57. FD Arevises labels of SGLT2 inhibitors for diabetes to include warnings about too muchacid in the blood and serious urinary tract infections. US Food and Drug Administration, 2015. Available at http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm [Last accessedAugust29]
58. Invokana (canagliflozin), prescribing information. Janssen Pharmaceuticals Inc, February 2017. Available at https://www.invokana.com/prescribing-information.pdf [Last accessedMarch1]
59. Handelsman Y, Henry RR, Bloomgarden ZT, etal. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic keto acidosis. Endocr Pract 2016; 22:753–62
60. Tradjent a® (linagliptin), prescribing information. Boehringer Ingelheim, December 2016. Available at http://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Tradjenta/Tradjenta.pdf? DMW_FORMAT=pdf [Last accessed January 20]
61. Onglyza (saxagliptin), prescribing information. AstraZeneca Pharmaceuticals, Inc., February 2017. Available at http://www.azpicentral.com/onglyza/pi_onglyza.pdf#page=1 [Last accessed March1]
62. Nesina (alogliptin), prescribing information. Takeda Pharmaceuticals, Inc., December 2016. Available at http://general.takedapharm.com/content/file.aspx?applicationcode=5D2277FD-CFC0-423CB543811D41F4771E&filetypecode=NESINAPI&cacheRandomizer=ee9ea085- a270-41c0-8876-cb0b1d1a9931 [Last accessed January 10]
63. Januvia® (sitagliptin), prescribing information.. Merck, February 2017. Available at http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf [Last accessed March 1]
64. Fu J, Zhu J, Hao Y, et al. Dipeptidyl peptidase-4 inhibitors and fracture risk: an updated meta analysis of randomized clinicaltrials. Sci Rep2016;6:29104
65. Scheen AJ. Safety of dipeptidyl peptidase-4 inhibitors for treating type 2 diabetes. Expert Opin Drug Saf 2015;14:505–24
66. Zinman B, Wanner C, Lachin JM, etal. Empagliflozin, cardiovascular out comes, and mortality in type 2diabetes.N Engl J Med2015;373:2117–28
67. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. NEnglJ Med2016;375:323–34
68. Scirica BM, Bhatt DL, Braunwald E,etal. Saxagliptin and cardiovascular out comes in patients with type 2 diabetes mellitus. N Engl JMed2013;369:1317-26
69. Scirica BM, Braunwald E, Raz I, etal. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation2014;130:1579–88
70. Zannad F, Cannon CP, Cushman WC, etal. Heart failure and mortality out comes in

patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: amulti centre, randomised, double-blindtrial. Lancet 2015; 385: 2067–76
71. Green JB, Bethel MA, Armstrong PW, etal. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. NEnglJ Med 2015; 373: 232-42
72. Chadha, Manoj, et al. "Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i+ DPP4i in the Indian Diabetes Setting." Diabetes Therapy 13.5 (2022): 1097-1114.
73. Schwartz SS, Epstein S, Corkey BE, etal. The time is right for a new classification system for diabetes: rationale and implications of the beta-cell-centric classification schema. Diabetes Care 2016; 39:179–86
74. Hansen L, Iqbal N, Ekholm E, etal. Postprandial dynamics of plasma glucose, insulin, and glucagon in patients with type 2 diabetes treated with saxagliptin plus dapagliflozin add-on to met form in therapy. Endocr Pract 2014; 20:1187–97
75. De Fronzo RA, Lewin A, Patel S, etal. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes in adequately controlledon met form in. Diabetes Care 2015;38:384–93
76. Lewin A, De Fronzo RA, Patel S, etal. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care 2015;38:394–402
77. Scheen AJ. Pharmacokinetic Characteristics and Clinical EfficacyofanSGLT2Inhibitor Plus DPP-4 Inhibitor Combination Therapy inType2Diabetes.ClinPharmacokinet2016
78. Softel and E, Meier JJ, Vangen B, et al. Empagliflozin as Add-on therapy in patients withtype 2 diabetes inadequately controlled with linagliptin and metformin: a 24-week randomized, double-blind, parallel-grouptrial. Diabetes Care 2017; 40:201-09
79. Tinahones FJ, Gallwitz B, Nordaby M, etal. Linagliptinas add-on to empagliflozin and met form in in patients with type 2 diabetes: Two 24-week randomized, double-blind, double-dummy, parallel-grouptrials. Diabetes ObesMetab2017;19:266-74
80. Glyxambi® (empagliflozin and linagliptin), prescribing information.. Boehringer Ingelheim, December 2016. Available at http://docs.boehringeringelheim.com/Prescribing%20Information/PIs/Glyxambi/Glyxambi.pdf[LastaccessedJanuary9]
81. Glyxambi® (empagliflozin and linagliptin), summary of product characteristics. Boehringer In gelheim, November 2016. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Product_Information/human/003833/WC500216972.pdf[LastaccessedNovember27]
82. Glund S, Mattheus M, Runge F, et al. Relative bioavailability of an empagliflozin 25-mg/linagliptin 5-mg fixed-dose combination tablet. Int J Clin Pharmacol Ther 2017;55 [Epuba head of print]
83. QTERN® (dapagliflozin and saxaglipt in) tablets, for oraluse, prescribing information. AstraZeneca, February 2017. Available athttp://www.azpicentral.com/qtern/qtern.pdf#page=1[LastaccessedMarch1]
84. Vakkala gadda B, Vetter ML, Rana J,etal. Bioequivalence of saxagliptin/dapagliflozin fixed-dose combination tablets compared with co administration of the individual tablets to healthy subjects. Pharmacol Res Perspect 2015;3:e00201
85. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015; 38: 376–83
86. Mathieu C, Ranetti AE, LiD, etal. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care2015;38:2009–17