

INVITED ARTICLE

Evidence Update

Update on newer antidiabetic drugs in clinical practice

Chandanie Wanigatunge¹

¹ Department of Pharmacology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka

Keywords: diabetes mellitus, insulin analogues, incretins, SGLT-2 inhibitors

Corresponding Author: Chandanie Wanigatunge E-mail: <caw@sjp.ac.lk>  <https://orcid.org/0000-0002-4477-8979>
Competing Interests: Author has declared that no competing interests exist

This is an open-access article distributed under a Creative Commons Attribution-Share Alike 4.0 International License (CC BY-SA 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are attributed and materials are shared under the same license.



Introduction

Diabetes mellitus is a metabolic disorder that occurs due to lack of insulin, resistance to the action of insulin in peripheral tissues or a combination of both. The hallmark of diabetes mellitus is elevated plasma glucose which is related to the development of long term complications. Optimal blood glucose control is essential to reduce complications and insulin and other antidiabetic drugs are prescribed to achieve this treatment goal.

Despite many new additions over the years, insulin, metformin and the sulfonylureas remain the most widely used antidiabetic medications. Many drug classes targeting different aspects of glucose absorption and metabolism have been developed over the last few decades and have become important when target blood glucose control is not achieved with the older and relatively cheaper antidiabetic medications. The increasing availability of a wide variety of drugs gives a wide choice to clinicians when selecting an appropriate drug for individual patients. This article reviews some of the recent additions to the antidiabetic medicines, their modes of action and indications and limitations for use.

Insulins and Insulin analogues

The discovery of insulin, almost a century ago, is considered one of the most dramatic and important medical milestones which revolutionized the management of both type 1 and type 2 diabetes mellitus. While insulins are essential for those with type 1 diabetes mellitus, they are increasingly being used to achieve good glycaemic control in those with type 2 diabetes mellitus. Insulin replacement consists of prandial (bolus) insulin, basal insulin and a correction-dose insulin supplement. The last is given to address pre-meal or between-meal hyperglycemia, independently of the prandial insulin [1].

The pharmacokinetic (PK) and pharmacodynamic (PD) features of standard insulins frequently lead to hypoglycemia as glycosylated hemoglobin (HbA1c) values approach the normal range. This resulted in the development of insulin formulations that more closely mimic basal and mealtime (prandial) endogenous insulin secretion. These recombinant human insulin analogues have action profiles that allow for more flexible

treatment regimens with a lower risk of hypoglycaemia and target to replace prandial and basal components of insulin secretions independently.

There are two groups of recombinant human insulin analogues.

1. Rapid-acting recombinant insulin analogues – e.g. insulin aspart, insulin glulisine, and insulin lispro. These are effective in managing postprandial hyperglycaemia.
2. Long acting analogues with slower onset of action which lasts for long periods, e.g. insulin detemir, insulin glargine, and insulin degludec. These provide the basal insulin requirements.

Rapid acting recombinant human insulin analogues

e.g. insulin lispro, insulin aspart, insulin glulisine

The molecular structures of insulin lispro, insulin aspart and insulin glulisine, differ only slightly from human insulin, with two amino acid changes for insulin lispro and insulin glulisine and one for insulin aspart [2,3]. This allows them to be absorbed more quickly than unmodified (regular/soluble) human insulin [2].

The rapid acting insulin analogues have a PK profile similar to that of meal time insulin secretion and allows for better control of post meal blood glucose surges [2,3]. Compared to soluble/regular insulin (onset of action 30-60 minutes, duration of action 8-10 hours), the rapid-acting insulin analogues have a faster onset (5-15 minutes) and shorter duration (4-6 hours) of action [2]. This is due to their capacity to dissociate quickly into dimers or monomers in subcutaneous tissue which in turn, diffuse rapidly into circulation [3]. The PD profile of the rapid-acting insulin analogues is also more similar to the physiological effect of endogenous insulin than subcutaneous soluble (regular) insulin and causes smaller postprandial blood glucose rises [3]. Thus, it is recommended that rapid acting insulin analogues be administered shortly before or immediately after meals [2,3].

Injection of these rapidly acting analogues results in twice the maximal concentration, in half the time (30-90 minutes) equivalent doses of soluble (regular) insulin (2-3 hours) [3, 4, 5, 6, 7]. This results in better control of postprandial blood-glucose concentration and less frequent occurrence of post prandial hypoglycaemia compared to soluble insulin. A better control of postprandial hyperglycaemia will result in more patients achieving target HbA1c, which will result in a reduction of vascular complications [2]. Compared with regular/soluble insulin, the use of rapid acting analogues is also associated with less snacking as the risk of postprandial hypoglycaemia is less [3]. This results in a less caloric intake which would also be beneficial.

Although the site of subcutaneous injections has an influence on the PK of rapid acting insulin analogues, this does not affect the overall blood glucose lowering effect [3]. Subcutaneous injection of insulin analogues would also be convenient for those who wish to inject shortly before, or shortly after a meal. This would improve compliance as it allows for greater flexibility of meal times in relation to an active lifestyle. Both insulin

aspart and insulin lispro can be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery [8].

There is considerable patient to patient variation in the duration of action of a particular type of insulin and this needs to be assessed individually during use [8]. This variability is less with short acting insulin analogues [3]. All three currently marketed short acting analogues are equally efficacious and safe and the glycaemic control achieved is comparable to that provided by soluble insulin when the same basal insulin is used [3]. They can all be administered easily with insulin pens and make control of prandial glucose easier, especially in those with erratic meal times.

Long acting recombinant human insulin analogues

e.g. Insulin glargine, insulin detemir and insulin degludec

Insulin glargine is produced by substitution of amino acids of the original insulin molecule which leads to a shift in the isoelectric point to a neutral pH [2]. This makes it less soluble at the injection site, resulting in precipitation of insulin in subcutaneous tissue which forms a depot from which insulin is slowly released. The slow absorption results in very little peak activity and a duration of action of 22 ± 4 hours [9]. Insulin detemir has a covalently bound C14 fatty acid chain and removal of an amino acid from the original insulin structure [10]. Compared with glargine, detemir has a shorter time-action profile and may be used as once or twice daily dosing. In contrast, neutral protamine Hagedorn (NPH) insulin reaches a peak between 4-8 hours after injection and then falls off rapidly and has a duration of action between 12-14 hours [2].

The longer duration of action of the basal analogues provide a better coverage during the between meal (basal) period [10]. The minimal/absent peak activity seen with these analogues, their slow and continuous absorption into systemic circulation and prolonged duration of action, compared to NPH, are more similar to that of endogenous basal insulin and are associated with lower incidence of hypoglycaemia [2,10]. In randomized control trials in both type 1 and 2 diabetics, there were marginal or no differences in reduction in HbA1c between the analogues and the NPH insulin group [11,12]. However, there appear to be benefits in terms of reduced episodes of hypoglycemia, and also reduced inter- and intra-individual variability and small benefits in fasting blood glucose [10,12]. The smoother profiles of basal insulin analogues and absence of a pronounced peak has the potential to allow larger doses than NPH insulin which would lead to improved fasting glycaemic control, without an increased risk of nocturnal hypoglycemia [10]. These analogues also cause less weight gain compared to NPH with no significant difference between insulin glargine or detemir [10].

Insulin degludec (IDeg) is an ultra-long-acting basal insulin analogue with a longer duration of action (measured beyond 42 h) compared with currently available analogues [10,13]. IDeg has a much lower day-to-day within-subject variability in glucose-lowering effect than insulin glargine and a stable and consistent PK and PD properties that are preserved across various patient populations including children, adolescents, elderly,

patients from different race and ethnic backgrounds and those with renal or hepatic impairment [13]. Compared to insulin glargine, it has a lower risk of hypoglycaemia, especially nocturnal hypoglycaemia, and offers the potential for a more flexible dosing interval and a simpler titration algorithm [13]. All these could lead to improved patient compliance and an overall better glycaemic control.

Biosimilar insulins

“A biosimilar medicinal product is a ‘copy version’ of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise” [14]. Biosimilars will also display a certain degree of variability (‘microheterogeneity’) to the reference biological product as the biological systems used in the manufacturing process are different [14]. Therefore, unlike generics, the biosimilars are not identical to the reference product. The comparatively reduced cost when compared to the reference products, and their “similar” therapeutic efficacy, makes biosimilars an attractive therapeutic option [14].

Biosimilar insulins (BIs) are available for clinical use and clinicians should be mindful that they are not identical to the reference product and hence not interchangeable [15]. The use of BIs is challenging because of the complex structure and a narrow therapeutic window of insulin [15]. It is also important to note that the dosing accuracy of BIs depends on the formulation of the product and quality of the administration device [15].

Incretin mimetics and incretin enhancers

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are intestinal peptide hormones released in response to ingestion of meals.

GLP-1 acts on GLP-1 receptors on the β -cells of pancreas and stimulate insulin secretion in a glucose dependent manner, which is known as the “incretin effect”. In healthy subjects the incretin effect accounts for up to 70% of the insulin secreted in response to glucose ingestion [16]. The incretin effect is reduced in those with type 2 diabetes mellitus (T2DM) [17]. GLP-1 also reduce glucagon secretion, slows gastric emptying and, by acting on brain GLP-1 receptors, reduces appetite and induce early satiety [16]. GLP-1 is rapidly inactivated by dipeptidyl peptidase IV (DPP-4) [16]. DPP-4 is an ectoenzyme located on the luminal side of capillary endothelial cells that metabolizes incretins such as GLP-1 [16]. This makes natural GLP-1 useless as a therapeutic agent. Therapeutic agents, therefore, act by enhancing the activity of endogenous GLP-1 by reducing its breakdown by DPP-4 enzyme (incretin enhancer e.g. sitagliptin) or by acting as longer acting agonists of GLP-1 receptors (incretin mimetics, e.g. exenatide). Both these modalities also cause significant and clinically relevant improvement in glycemic control with regard to fasting plasma glucose, postprandial glucose, and HbA1C [16]. Improvements in glucose control can be achieved with minimal risk of hypoglycemia even when combined with metformin or thiazolidinedione but when combined with sulfonylureas, the risk of hypoglycemia appears to be similar to that of sulfonylureas alone [16].

Incretin based therapies have the added advantage of either preventing weight gain or being weight neutral [16,17]. This is useful in T2DM which is usually associated with obesity, which contributes to peripheral insulin resistance.

Incretin mimetics: Glucagon-like peptide-1 (GLP-1) receptor agonists

e.g. exenatide, liraglutide, albiglutide, dulaglutide

Exenatide and liraglutide have the physiological and pharmacological properties of GLP-1 but are not metabolized by DPP-4 [16]. Therefore, they are able to interact with GLP-1 receptors and mimic all aspects of the antidiabetic activity of GLP-1, with an action that lasts for a longer duration than that of native GLP-1 [16]. They are approved for use as monotherapy and as adjunctive therapy for patients with T2DM not achieving glycemic targets with other drugs [8]. Given as weekly subcutaneous injections, incretin mimetics have the advantage of not promoting weight gain, which is seen with sulfonylureas and insulins [16].

NICE has recommended that treatment with standard release exenatide should be continued only if HbA1c is reduced by at least 1% and a weight loss of at least 3% is achieved within 6 months of starting treatment [8].

Incretin enhancers: Dipeptidylpeptidase-4 inhibitors (Gliptins)

e.g. sitagliptin, vildagliptin, linagliptin

Gliptins act by inhibiting DPP-4 and thereby promoting a longer duration of action of GLP-1 which results in an increased insulin secretion [16,17]. They also lower glucagon secretion [16,17] but have no effect on gastric emptying [16]. Given orally, they are indicated for T2DM as monotherapy when metformin is contraindicated, as dual therapy in combination with either metformin, pioglitazone, a sulfonylurea, or insulin (when treatment with these drugs alone fails to achieve adequate glycaemic control), or as triple therapy in combination with metformin and either pioglitazone or insulin [8].

Since gliptins have no insulinotropic activity at lower glucose concentrations, the risk of hypoglycemia is low [16]. The dose of concomitant insulin or drugs that stimulate insulin secretion may need to be reduced to prevent hypoglycaemia [17]. DPP-4 inhibitors are weight neutral [16].

Incretin mimetics and enhancers have been shown to be associated with beneficial effects on cardiovascular risk factors such as weight loss, decrease in blood pressure and changes in lipid profile [16]. An increased risk of acute pancreatitis is a reported rare side effect of gliptins but at present, a definite causal relationship has not been found [18,19]. However, patients should be educated about signs and symptoms of pancreatitis such as the development of severe, persistent abdominal pain and advised to seek medical advice if they develop such symptoms [8]. Permanent discontinuation of treatment is recommended if pancreatitis occurs [8].

Sodium glucose co-transporter 2 (SGLT-2) inhibitors (Gliflozins)

e.g. canagliflozin, dapagliflozin

The adult kidney filters approximately 180g of glucose per day. Almost all of this filtered glucose is reabsorbed by the sodium glucose cotransporter (SGLT) proteins – SGLT-1 and SGLT-2 in the proximal convoluted tubule [20]. Despite elevated plasma glucose in T2DM, the kidneys continue this glucose reabsorption. SGLT-2 is a low-affinity, high-capacity transporter found exclusively in the proximal renal tubule. It is responsible for the reabsorption of 90% of glucose filtered by the kidney [20].

SGLT-2 inhibitors act by reversible inhibition of this SGLT-2 cotransporter to reduce glucose reabsorption and increase urinary glucose excretion (UGE) [20,21]. This results in a reduction of hyperglycaemia without inducing hypoglycaemia [20]. SGLT-2 inhibitors promote weight loss by increased glycosuria and exert a modest diuretic effect due to osmotic diuresis [20] with blood pressure reduction [21]. Due to their mechanism of action, the level of hyperglycaemia and the state of renal function will directly affect the efficacy of SGLT-2 inhibitors [21].

The primary action of SGLT-2 inhibitors is independent of insulin, but secondary indirect effects on insulin secretion and action may occur due to reduced glucose toxicity [20]. They have an excellent oral bioavailability, a long elimination half-life which allows for once-daily administration, a low accumulation index, no active metabolites and a limited renal excretion [21]. These agents have a negligible risk of drug–drug interactions [20] and are given orally, preferably before breakfast [8].

SGLT-2 inhibitors may be used as monotherapy in diet treated patients if metformin is inappropriate [8, 21] or in combination with any other glucose lowering agents in those with T2DM [8, 20, 21]. Despite the low risk of hypoglycaemia, the dose of concomitant insulin or other insulin secretagogues may need to be reduced when given with SGLT-2 inhibitors [8,21]. The class lowers HbA1c by about 0.5% to 1% and is potentially useful for patients with an HbA1c <9% [20].

Increased urinary excretion of glucose by SGLT-2 inhibitors may lead to urinary tract infections and genital mycotic infections [20]. With increasing use, newer side effects have been identified, and serious and potentially life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients taking the SGLT2 inhibitor canagliflozin for T2DM [8]. To minimise the risk of such effects when treating patients with a SGLT-2 inhibitor, the European Medicines Agency has issued the following advice [8]:

1. Test for raised ketones in patients presenting with symptoms of DKA, even if plasma glucose levels are near-normal; omitting this test could delay diagnosis of DKA.
2. Discontinue treatment if DKA is suspected.
3. If DKA is confirmed, take appropriate measures to correct the DKA and monitor glucose levels.
4. Patients should be advised on how to recognize the signs and symptoms of DKA and to seek prompt medical attention if symptoms of DKA develop.

Place of newer antidiabetics in therapy

Optimal drug therapy for diabetes mellitus would depend on [22, 23]

- the effectiveness of the drug treatment in terms of metabolic response
- safety and tolerability of the drug treatment
- the person's individual clinical circumstances, for example, comorbidities, risks from polypharmacy
- the person's individual preferences and needs – for example, side effects, ease of administration
- the licensed indications or combinations available
- cost and availability, especially in the state sector

Selection of appropriate medicines should therefore be individualized and “patient centered”. The threshold targets that needs to be achieved, should be decided upon by the physician in consultation with the patient to ensure optimum outcomes.

All FDA-approved medicines for treating hyperglycemia in type 2 diabetes mellitus lower HbA1c levels by 0.6% to 1.5%. Despite the availability of newer antidiabetics as treatment options, metformin remains the drug of choice for type 2 diabetes mellitus, unless there are compelling contraindications for its use [22, 23]. This is based its glucose-lowering efficacy, safety profile, weight neutrality, and reasonable cost. Combination therapy is recommended to achieve glycaemic targets when required or as initial therapy if the blood glucose values are very high.

When metformin alone is inadequate in achieving control, any of the other agents, including basal insulin, may be added to obtain the desired control [22]. Adding a second agent should not be delayed until the patient's glycaemic control has deteriorated. The best blood glucose reduction, assessed with HbA1c, is seen with basal insulins, metformin and sulfonylureas [22, 23]. The newer additions, despite a better adverse effect profile, do not offer a greater advantage than the older agents with regard to glycaemic control [8, 20, 25]. In the absence of a clear advantage in respect to glycaemic control, the selection would depend on the cost, side effect profile and patient preferences. The addition of any oral glucose-lowering agents in people with type 2 diabetes mellitus and inadequate glycaemic control despite being on insulin therapy, has positive effects on glycaemic control and insulin requirements [24].

Insulin is the mainstay treatment for those with type 1 diabetes mellitus. Both prandial and basal insulins are required to achieve optimal glycaemic control. Education regarding matching prandial insulin doses to carbohydrate intake, pre-meal glucose levels, and anticipated activity should be considered when planning insulin regimens for those with type 1 diabetes mellitus. The glycaemic control achieved is comparable between regular (soluble) insulin and the newer rapid acting analogues [3, 26] and between NPH insulin and the newer long acting analogues [11, 12].

The recommendation that most individuals with type 1 diabetes mellitus should use rapid-acting insulin analogs to reduce hypoglycemia risk [22], should be weighed against

the cost and the lack of a significant difference in terms of glycaemic control [3, 26] when compared with regular (soluble) insulin, which is cheaper.

Conclusions

Despite a vast array of medicines available to treat diabetes mellitus, glycaemic control remains suboptimal in a significant number of diabetic patients. Side effects such as weight gain and hypoglycaemia limit the use of most of the older insulins and sulfonylureas. It is in this background that insulin analogues and drugs such as incretin mimetics and enhancers and gliflozins appear as attractive options. However, compared to the older insulins, metformin and sulfonylureas, these do not offer a greater advantage in therapeutic efficacy and are recommended to be used when older antidiabetic medicines are not tolerated or as add on therapy for better glycaemic control. Ease of administration and patient satisfaction should be weighed against the higher cost of these drugs. Experience with most of the newer drugs is short. With wider use, more evidence enabling systematic reviews and cost analysis will inform the role of these newer antidiabetic drugs in day to day clinical practice. The key to successful treatment of diabetes mellitus remains in individualizing therapy to suite the patient's needs.

Competing interests – None.

References

1. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA* 2003; 289:2254-64.
<https://doi.org/10.1001/jama.289.17.2254> PMID:12734137
2. Hirsch BI. Insulin analogues. *N Engl J Med* 2005; 352:174-83.
<https://doi.org/10.1056/NEJMra040832> PMID:15647580
3. Homes PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab.* 2012;14:780-8
<https://doi.org/10.1111/j.1463-1326.2012.01580.x> PMID:22321739
4. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin: a rapidly absorbed analogue of human insulin. *Diabetes* 1994; 43:396-402.
<https://doi.org/10.2337/diab.43.3.396> <https://doi.org/10.2337/diabetes.43.3.396> PMID:8314011
5. Mudaliar S, Lindberg FA, Joyce M, et al. Insulin aspart (B28 Asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 1999; 22:1501-6. <https://doi.org/10.2337/diacare.22.9.1501> PMID:10480516
6. Heinemann L, Heise T, Wahl LC et al. Prandial glycaemia after a carbohydrate-rich meal in type I diabetic patients: using the rapid acting insulin analogue [Lys(B28), Pro(B29)] human insulin. *Diabet Med* 1996;13: 625–629.
[https://doi.org/10.1002/\(SICI\)1096-9136\(199607\)13:7<625::AID-DIA134>3.0.CO;2-2](https://doi.org/10.1002/(SICI)1096-9136(199607)13:7<625::AID-DIA134>3.0.CO;2-2)
7. Lindholm A, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes.

- Diabetes Care 1999; 22: 801–805
<https://doi.org/10.2337/diacare.22.5.801> PMID:10332685
8. Joint Formulary Committee. British National Formulary 73. London: BMJ Group and Pharmaceutical Press; 2017
 9. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlack M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH and placebo. *Diabetes Care* 2000; 23:644-9. <https://doi.org/10.2337/diacare.23.5.644> PMID:10834424
 10. Mavrogiannaki AN, Migdalis IN. Long-acting basal insulin analogs: latest developments and clinical usefulness. *Ther Adv Chronic Dis* 2012; 3: 249–257 <https://doi.org/10.1177/2040622312454158> PMID:23342239 PMCID:PMC3539259
 11. Singh S, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ* 2009; 180: 385–397. <https://doi.org/10.1503/cmaj.081041> PMID:19221352 PMCID:PMC2638025
 12. Gough S. A review of human and analogue insulin trials. *Diabetes Res Clin Pract* 2007; 77: 1–15. <https://doi.org/10.1016/j.diabres.2006.10.015> PMID:17112621
 13. Haahr H, Heise T. A Review of the Pharmacological Properties of Insulin Degludec and Their Clinical Relevance. *Clin Pharmacokinet* 2014; 53:787–80 <https://doi.org/10.1007/s40262-014-0165-y> PMID:25179915 PMCID:PMC4156782
 14. Weise M, Bielsky MC, De SK, et al. Biosimilars-why terminology matters. *Nat Biotechnol.* 2011; 29:690-693. <https://doi.org/10.1038/nbt.1936> PMID:21822237
 15. Krämer I, Sauer T. The new world of biosimilars: what diabetologists need to know about biosimilar insulins. *British Journal of Diabetes & Vascular Disease* 2010; 10: 163-171 <https://doi.org/10.1177/1474651410369234>
 16. Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S. Incretin-Based Therapies. *Diabetes Care* Nov 2009; 32 (suppl 2) S223-S231 <https://doi.org/10.2337/dc09-S315> PMID:19875556 PMCID:PMC2811437
 17. Nori KE, Zalesin KC, Miller WM, McCullough PA. Treating type 2 diabetes: incretin mimetics and enhancers. *Ther Adv Cardiovasc Dis* 2009; 3:387-395 <https://doi.org/10.1177/1753944709341377> PMID:19808944
 18. Sheen A. Gliptins (dipeptidyl peptidase-4 inhibitors) and risk of acute pancreatitis Expert opinion on drug safety 2013; 12 545-557 <https://doi.org/10.1517/14740338.2013.793671> PMID:23621381
 19. Egan AG, Blind E, Dunder K, de Graeff P, Hummer BT, Bourcier T, Rosebraugh C. Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment. *N Engl J Med* 2014; 370:794-797 <https://doi.org/10.1056/NEJMp1314078> PMID:24571751
 20. Whalen K, Miller S, St. Onge E. The Role of Sodium-Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 Diabetes. *Clin Ther* 2015; 37:1150-66 <https://doi.org/10.1016/j.clinthera.2015.03.004> PMID:25891804
 21. Scheen AJ. Pharmacodynamics, Efficacy and Safety of Sodium–Glucose Co-Transporter Type 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes

- Mellitus. *Drugs*. 2015; 75:33–59 <https://doi.org/10.1007/s40265-014-0337-y>
PMid:25488697
22. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64–S74 <https://doi.org/10.2337/dc17-S011> PMid:27979895
23. Type 2 diabetes in adults: management. NICE guideline. Published: 2 Dec 2015
24. Vos RC, van Avendonk MJP, Jansen H, Goudswaard AN, van den Donk M, Gorter K, Kerssen A, Rutten GEHM. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. *Cochrane Database of Systematic Reviews* 2016, Issue 9. Art. No.: CD006992.
<https://doi.org/10.1002/14651858.CD006992.pub2> PMid:27640062
25. Chahal H. Comparative Review of Oral Hypoglycemic Agents in Adults. For WHO Secretariat.
26. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, Plank J, Pieber TR, Gerlach FM. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD012161.
<https://doi.org/10.1002/14651858.CD012161>