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CLINICAL COMMENTARY

Combination therapy in type 2 diabetes mellitus: adding empagliflozin to basal insulin

Evaluation of Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle H-J; on behalf of the EMPA-REG BASAL™ trial investigators. *Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015 doi: 10.1111/dom.12503. 2015; 17(10): 936–48.*

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Abstract

Type 2 diabetes mellitus (T2DM) management is complex, with few patients successfully achieving recommended glycemic targets with monotherapy, most progressing to combination therapy, and many eventually requiring insulin. Sodium glucose cotransporter 2 (SGLT2) inhibitors are an emerging class of antidiabetes agents with an insulin-independent mechanism of action, making them suitable for use in combination with any other class of antidiabetes agents, including insulin. This review evaluates a 78-week, randomized, double-blind, placebo-controlled trial investigating the impact of empagliflozin, an SGLT2 inhibitor, as add-on to basal insulin in patients with inadequate glycemic control on basal insulin, with or without metformin and/or a sulfonylurea. Empagliflozin added on to basal insulin resulted in significant and sustained reductions in glycated hemoglobin (HbA1c) levels compared with placebo. Empagliflozin has previously been shown to induce weight loss, and was associated with sustained weight loss in this study. This combination therapy was well tolerated, with similar levels of hypoglycemic adverse events in the empagliflozin and placebo groups over the 78-week treatment period. Urinary tract infections and genital infections, side effects associated with SGLT2 inhibitors, were reported more commonly in the empagliflozin group; however, such events led to treatment discontinuation in very few patients. These findings suggest that, with their complementary mechanisms of action, empagliflozin added on to basal insulin may be a useful treatment option in patients on basal insulin who need additional glycemic control without weight gain.

Keywords: type 2 diabetes mellitus, sodium glucose cotransporter 2, empagliflozin, blood glucose, body weight, insulin, combination therapy, hypoglycemic agents.

Abbreviations: ADA, American Diabetes Association; ANCOVA, analysis of covariance; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FDA, US Food and Drug Administration; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; MDI, multiple daily injection; NPH, neutral protamine Hagedorn; OAD, oral antidiabetes drug; SBP, systolic blood pressure; SE, standard error of mean; SGLT2, sodium glucose cotransporter 2; T2DM, type 2 diabetes mellitus; US, United States.

Citation

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Introduction

Glycemic management in type 2 diabetes mellitus (T2DM) is complex, challenging, and progressive. Increased insulin resistance and decreased pancreatic insulin secretion represent the core defects in T2DM [1]. As the disease progresses, pancreatic β-cell function deteriorates, and the increasing insulin resistance in peripheral tissues can no longer be compensated for by increased insulin secretion by the β-cells [1]. Thus, increasing insulin resistance and progressive loss of β-cell

function necessitate treatment intensification [1]. In addition, impaired lipolysis in adipocytes, gastrointestinal incretin defects, increased glucose reabsorption in the kidneys, pancreatic α-cell hyperglucagonemia, and neurotransmitter dysfunction contribute to hyperglycemia [1]. Disease management is further complicated in many patients by difficulties in adhering to increasingly complex multiple-drug regimens [2], from a wide array of antidiabetic agents with varied efficacy and safety profiles/adverse effects [3]. In addition, individual patients have unique needs, preferences, and levels of tolerance to the different pharmacological agents [3].

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) position statement acknowledges these difficulties and recommends an individualized approach to patient care, with metformin the preferred initial antidiabetic agent at or soon after diagnosis if it is not contraindicated and if it is tolerated [3]. If metformin monotherapy at maximum tolerated dose fails to achieve or maintain glycated hemoglobin (HbA1c) target (<7.0% in most patients) over 3 months, the addition of a second agent is recommended. These include sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), sodium glucose cotransporter 2 (SGLT2) inhibitors, or basal insulin [3]. In addition, initial combination therapy with two noninsulin agents or insulin in combination with another agent may be appropriate in individuals with high baseline HbA1c (≥9.0%) with a low likelihood of achieving glycemic target (HbA1c <7.0%) with metformin monotherapy [3]. If the combination of metformin plus a second glucose-lowering drug fails to achieve or maintain target HbA1c over 3 months, treatment can be escalated to a three-drug combination. With the progressive loss of β-cell function, many patients will ultimately require insulin therapy to maintain glucose control because insulin is efficacious throughout the continuum of diabetes [4]. In a proportion of patients, insulin therapy will be needed earlier: the ADA/EASD statement also recommends the use of insulin therapy, with or without additional agents, from the outset in newly diagnosed individuals with symptomatic T2DM and/or highly elevated blood glucose levels (HbA1c ≥10.0–12.0%) [3]. Therefore, a significant proportion of patients will be candidates for insulin therapy over their lifetime; however, fear of hypoglycemia and concern about adverse effects, including weight gain, have been identified as barriers to initiation or intensification of insulin therapy [5].

As an alternative to intensifying to ever-more aggressive insulin regimens, clinical studies have confirmed that glycemic control can be improved when noninsulin agents are continued when basal insulin is started, or when they are added to established insulin treatment [6]. This strategy is aimed at minimizing the adverse effects of insulin treatment known to affect adherence, such as hypoglycemia and weight gain, or avoiding an increase in the number of injections [5–8].

Combination therapy with insulin

Evidence that insulin in combination with metformin can provide better glycemic control with less risk of hypoglycemia, lower insulin dosage, and less weight gain, compared with insulin alone, supports the use of this combination for treating T2DM [6]. Sulfonylureas, on the other hand, have similar, if not increased, risk of weight gain when used in combination with insulin [6], and the combination may increase risk of hypoglycemia [9]. DPP-4 inhibitors are weight neutral and are not associated with increased risk of hypoglycemia [10]. Adding DPP-4 inhibitors to insulin results in moderate reductions in HbA1c while maintaining weight neutrality [9].

There is also extensive evidence that supports the use of GLP-1 RAs in combination with insulin [11,12]. With significant reduction in body weight when administered in combination with insulin, GLP-1 RAs have been shown to result in significant reductions in insulin dose, improved glucose control, and low rates of hypoglycemia (in some cases at placebo levels). Like insulin, however, GLP-1 RAs are injectable, which may have a bearing on patient adherence/comfort. The updated ADA/EASD algorithm recommends the addition of either a GLP-1 RA or prandial bolus injections of insulin when HbA1c targets are not achieved on basal insulin alone after 3–6 months, with GLP-1 RAs preferred in obese patients or those unable to follow complex regimens [3]. However, basal-bolus treatment may be associated with reduced adherence due to increased number of injections [8], and is associated with weight gain and increased risk of hypoglycemia [13].

SGLT2 inhibitors

Inhibitors of the SGLT2 protein are an emerging class of glucose-lowering agents that have an insulin-independent mechanism of action [14]. SGLT2 inhibitors act by reducing glucose reabsorption in the kidney, leading to increased urinary glucose excretion and lowered blood-glucose levels. SGLT2 inhibitors promote weight loss by reducing the available calories as a result of urinary glucose excretion and are associated with low risk of hypoglycemia [14]. In addition, SGLT2 inhibitors have also been demonstrated to significantly reduce systolic and diastolic blood pressure (BP), likely due to their osmotic diuretic effect [15]. Currently, three SGLT2 inhibitors, empagliflozin, dapagliflozin, and canagliflozin, are approved for treatment of T2DM in the United States (US) [16–18].

Owing to their unique mechanism of action, independent of insulin secretion or insulin action, SGLT2 inhibitors may be especially suitable for use as a second-line therapy option in combination with insulin. Here, we discuss the findings of a study evaluating empagliflozin added on to basal insulin in patients with T2DM.

Results from Rosenstock et al.

Rosenstock and colleagues recently reported the results of a 78-week randomized, placebo-controlled, double-blind study undertaken to evaluate the efficacy, safety, and tolerability of empagliflozin 10 or 25 mg once daily compared with placebo as add-on to basal insulin in patients with T2DM [19].

Patients with inadequate glycemic control (HbA1c >7.0–10.0%) despite treatment with stable basal insulin glargine or insulin detemir (≥20 IU/day) or neutral protamine Hagedorn (NPH) insulin (≥14 IU/day) with or without concomitant metformin and/or sulfonylurea were randomized (1:1:1) to empagliflozin 10 mg once daily, empagliflozin 25 mg once daily, or placebo after a 2-week, open-label placebo run-in period. During the first 18 weeks, basal insulin dose remained fixed. Over the next 60 weeks of the study, insulin dose adjustment at the treating investigator's discretion was permitted provided the patient's fasting plasma glucose (FPG) was >110 mg/dL; metformin and sulfonylurea regimens were to remain unchanged.

Background antidiabetes treatment at baseline included insulin plus metformin in 40% of patients, insulin plus metformin and sulfonylurea in 39% of patients, insulin plus sulfonylurea in 10% of patients, and insulin only in 10% of patients. At baseline, 58% of patients were on glargine, 19% were on detemir, and 14% were on NPH insulin. A total of 494 patients were randomized and treated with empagliflozin 10 mg (n=169), empagliflozin 25 mg (n=155), or placebo (n=170).

Primary outcome measure

As shown in Table 1, the change in HbA1c levels from baseline to week 18 was greater with empagliflozin plus insulin than with placebo plus insulin. The adjusted mean changes (±SE) in HbA1c from baseline at week 18 in the empagliflozin 10- and 25-mg groups were −0.6±0.1% (difference *vs* placebo, −0.6±0.1%; p<0.001) and −0.7±0.1% (difference *vs* placebo, −0.7±0.1%; p<0.001), respectively.

Key secondary outcome measures

At week 78, the adjusted mean changes (±SE) in HbA1c levels from baseline in the empagliflozin 10- and 25-mg groups were −0.5±0.1% (difference *vs* placebo, −0.5±0.1%; p<0.001) and −0.6±0.1% (difference *vs* placebo, −0.6±0.1%; p<0.001), respectively (Table 1). Among patients with HbA1c ≥7.0% at baseline, a greater proportion of patients in the empagliflozin 10- and 25-mg groups (18.0 and 19.5%, respectively) reached HbA1c <7.0% at week 18 compared with those in the placebo group (5.5%). At week 78, a significantly greater proportion of patients on empagliflozin 25 mg (18.0%), but not empagliflozin 10 mg (12.0%), achieved HbA1c <7.0% compared with placebo (7.0%). The mean insulin doses (±SE) at baseline in patients in the empagliflozin 10-mg, empagliflozin 25-mg, and placebo groups were 45.1±2.6, 48.4±2.8, and 47.8±3.1 IU, respectively. The adjusted mean changes (±SE) in basal insulin dose from baseline were −1.2±1.5 IU with empagliflozin 10 mg (difference *vs* placebo, −6.7±2.2 IU; p=0.002) and −0.5±1.6 IU with empagliflozin 25 mg (difference *vs* placebo, −5.9±2.3 IU; p=0.009).

Other secondary endpoints

For FPG, adjusted mean (±SE) changes from baseline at 78 weeks were −10.1±3.2 mg/dL in the empagliflozin 10-mg group (difference *vs* placebo, −12.9 mg/dL; p=0.005) and −15.2±3.4 mg/dL in the empagliflozin 25-mg group

Table 1. Summary of changes in HbA1c at week 18 (primary endpoint) and week 78 (key secondary endpoint).

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA1c at baseline (±SE), %	8.1±0.1	8.3±0.1	8.3±0.1
HbA1c at week 18 (±SE), %	8.1±0.1	7.7±0.1	7.6±0.1
Change from baseline (±SE), %	0.0±0.1	−0.6±0.1	−0.7±0.1
Difference *vs* placebo (95% CI), %; p-value		−0.6±0.1 (−0.8, −0.4); <0.001	−0.7±0.1 (−0.9, −0.5); <0.001
HbA1c at week 78 (±SE), %	8.1±0.1	7.8±0.1	7.6±0.1
Change from baseline (±SE), %	0.0±0.1	−0.5±0.1	−0.6±0.1
Difference *vs* placebo (95% CI), %; p-value		−0.5±0.1 (−0.7, −0.2); <0.001	−0.6±0.1 (−0.9, −0.4); <0.001

Adjusted mean change from baseline in HbA1c was assessed using an analysis of covariance (ANCOVA) model, with treatment and region as fixed effects and baseline HbA1c as a linear covariate, in the full analysis set (FAS)-completers for week 18 and week 78 using last observation carried forward. The FAS-completers included randomized patients treated with ≥1 dose of study drug who had a baseline HbA1c value, did not discontinue the trial prior to week 18 (or week 78), had a treatment duration of ≥119 days (or ≥532 days), and had an on-treatment HbA1c value available in that visit window.
FAS-completers week 18: placebo (n=125), empagliflozin 10 mg (n=132), empagliflozin 25 mg (n=117).
FAS-completers week 78: placebo (n=112), empagliflozin 10 mg (n=127), empagliflozin 25 mg (n=110).
CI, confidence interval; HbA1c, glycated hemoglobin; SE, standard error of mean.

(difference *vs* placebo, –17.9 mg/dL; $p<0.001$). The adjusted mean (±SE) changes in body weight at 78 weeks were –2.2±0.5 and –2.0±0.5 kg with empagliflozin 10 and 25 mg, respectively (both $p<0.001$ *vs* placebo, with an increase in the placebo group of 0.7±0.5 kg).

Exploratory endpoints

Adjusted mean (±SE) changes from baseline in systolic blood pressure (SBP) were –3.7±0.9 mmHg with empagliflozin 10 mg (difference *vs* placebo, –3.4 mmHg; $p=0.011$) and –3.3±1.0 mmHg with empagliflozin 25 mg (difference *vs* placebo, –3.0 mmHg; $p=0.027$) at week 18. At week 78, mean (±SE) change from baseline in SBP was greater with empagliflozin 10 mg than placebo (difference *vs* placebo, –4.2 mmHg; $p=0.004$), but the change with empagliflozin 25 mg did not reach significance compared with placebo (difference *vs* placebo, –2.4 mmHg; $p=0.099$).

Safety

For the key safety outcome of confirmed hypoglycemic events, the incidence was similar between treatment groups at week 18, with events reported in 20% of patients on empagliflozin 10 mg, 28% of patients on empagliflozin 25 mg, and 21% of patients on placebo. At week 78, confirmed hypoglycemic events occurred in 36% of patients receiving empagliflozin 10 and 25 mg, and 35% of patients on placebo. Over 78 weeks, events consistent with urinary tract infections were reported in a lower proportion of patients receiving placebo (9%) than empagliflozin 10 mg (15%) or empagliflozin 25 mg (12%); most events were mild or moderate, with one patient in each group having a severe event. One patient in the empagliflozin 25-mg group experienced an event consistent with urinary tract infection, leading to discontinuation of study drug. Another patient in the same group also experienced an event consistent with urinary tract infection that required hospitalization, but did not lead to study-drug discontinuation. Events consistent with genital infection were reported in a smaller proportion of patients on placebo (2%), compared with empagliflozin 10 mg (8%) and empagliflozin 25 mg (5%). All events were of mild or moderate intensity, with discontinuation due to genital infection reported in one patient in each empagliflozin group. One of these patients, receiving empagliflozin 10 mg, experienced a scrotal abscess considered unrelated to study medication that required hospitalization and surgery. No diabetic ketoacidosis (DKA) or ketonuria was reported as an adverse event in any of the patients. At the end of treatment, small decreases in mean estimated glomerular filtration rate (eGFR) (±SD) from baseline were observed in all groups of patients (–6.3±13.0, –4.8±12.1, and –5.7±13.4 mL/min/1.73 m^2 with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively). At follow-up (2 weeks after the end of treatment), mean eGFR (±SD) values returned to near baseline levels in the empagliflozin groups (change from baseline –1.9±13.0 and –0.8±12.0 mL/min/1.73 m^2 with empagliflozin 10 and 25 mg, respectively), but not the placebo group. At week 78, no significant differences in mean changes from baseline in total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglycerides were observed in patients receiving placebo or either dose of empagliflozin.

Significance and practical implications

The National Diabetes Statistics Report (2014) determined that 2.9 million of the estimated 21 million adults in the United States who are diagnosed with diabetes are treated with insulin only, and 11.9 million are on oral medication only [20]. The patients on insulin-only treatment are likely to contend with escalating doses and unwanted side effects such as weight gain, whereas patients on oral antidiabetes drugs (OADs) will likely progress to a treatment strategy involving initiation of insulin as their disease progresses.

From 2002 to 2005, approximately 3,600 people younger than 20 years of age were newly diagnosed with T2DM annually in the US [21]. From 2008 to 2009, this number increased to around 5,100 annually [20], indicating a trend of increased incidence of T2DM in younger individuals. In addition, in 2012, around 371,000 new cases of diabetes (including type 1 as well as T2DM) were diagnosed in US individuals who were 20–44 years of age [20]. Together, these younger patient groups represent a growing population of patients who may require combination therapy, including insulin, in the long term.

In this context, this study by Rosenstock and colleagues is relevant. The researchers conclude that adding empagliflozin to basal insulin therapy provided improvements in glycemic control, with concomitant reduction in body weight and insulin dose. The results of this study suggest that empagliflozin in combination with basal insulin may be a viable treatment alternative in this patient population, improving glycemic control and minimizing the drawbacks of insulin by reducing insulin dose. This could potentially result in preventing and/or delaying progression to a basal-bolus insulin regimen involving multiple daily injections (MDIs). There is evidence for an inverse correlation between the number of insulin injections and patient adherence to insulin therapy [22]. Thus, preventing and/or delaying progression from the once-daily basal insulin regimen to the MDI schedule of the basal-bolus regimen would be expected to have a bearing on patient adherence.

One of the major obstacles to achieving treatment goals in patients with T2DM is the lack of adherence to the treatment regimen [23]. Fear of hypoglycemia and insulin-induced weight gain are frequently cited as key barriers to insulin adherence or intensification [5]. In the study reported by

Rosenstock and colleagues, the percentage of patients with confirmed hypoglycemic events over the complete 78-week treatment period was similar between treatment groups, despite a significant decrease in HbA1c in the empagliflozin groups. Furthermore, empagliflozin as add-on to basal insulin resulted in sustained weight loss over 78 weeks, suggesting that empagliflozin in combination with basal insulin may help improve treatment adherence. A recent 52-week study showed that empagliflozin in combination with MDI insulin also resulted in improved glycemic control and reduced weight in obese, difficult-to-treat patients with T2DM [24]. Overall, these results suggest that empagliflozin as add-on to basal insulin may improve adherence by alleviating the two major undesirable side effects of insulin.

In the study by Rosenstock and colleagues, the proportion of patients reporting adverse events consistent with urinary tract and genital infections was higher in the empagliflozin-treated groups compared with placebo. These observations are consistent with the findings of other placebo-controlled trials of empagliflozin as monotherapy, as combination therapy with other OADs, and as add-on to MDI insulin, although not every empagliflozin study has shown an increase in urinary tract infections [25]. This increase is also consistent with observations in clinical studies with other SGLT2 inhibitors, in which these infections have been shown to respond to standard therapy [26]. Although an increase in genitourinary infections has been observed in the clinical trial programs of canagliflozin, dapagliflozin, and empagliflozin, discontinuation from treatment due to these infections has been found to be consistently low [18,27].

Similar results have been reported in studies of other SGLT2 inhibitors as add-on to insulin. A study evaluating the efficacy of dapagliflozin in patients with T2DM inadequately controlled with high doses of insulin (≥30 IU/day) with or without other OADs over 104 weeks has demonstrated improvements in glycemic control and reduced weight without increase in risk of hypoglycemia compared with placebo [28]. This study also showed that dapagliflozin stabilized insulin dosing in these patients, with up-titration limited to clinical necessity based on predefined glycemic criteria, whereas mean insulin dose increased in the placebo group [28]. Canagliflozin as add-on to insulin with or without other OADs has also demonstrated improvements in glycemic control and body-weight reductions over 52 weeks [29]. In this study, rates of documented hypoglycemia with canagliflozin treatment were not significantly greater than with placebo [29]. In both of these studies, genital mycotic infections and urinary tract infections, adverse events typical of SGLT2 inhibitors in patients with T2DM [30], occurred more frequently in patients receiving study drug (dapagliflozin or canagliflozin) than in those receiving placebo [28,29]. Whereas in the study by Rosenstock and colleagues only patients on basal insulin were enrolled and a flexible insulin dose period was included, the reported studies of canagliflozin and dapagliflozin were conducted in patients on different insulin regimens at unchanged insulin doses [19,28,29].

The US Food and Drug Administration (FDA) has issued a warning that the risk of DKA may be increased with the use of SGLT2 inhibitors [31]. Rosenstock and colleagues report that DKA was not identified as an adverse event in any of the patient groups in their study [19]. This finding is consistent with findings of a low frequency of reported DKA, and no difference between empagliflozin and placebo treatment groups in a retrospective analysis of results from Phase II and Phase III trials of empagliflozin [32]. These results are also similar to those reported from the clinical trial programs for canagliflozin and dapagliflozin [32,33]. It is worth noting that DKA events reported under the FDA Adverse Events Reporting System, following treatment with SGLT2 inhibitors, were uncharacteristic in that they were mostly euglycemic (mild to moderately elevated blood glucose) [31,32]. Consideration must also be given to the fact that some of the patients in whom DKA has been reported were individuals with type 1 diabetes mellitus, for whom SGLT2 inhibitors are not currently indicated [31,32]. Furthermore, concurrent major illness, reduced food and fluid intake, and reduced insulin doses in insulin-treated patients could be potentiating factors in DKA [31,32]. While the FDA is continuing to investigate this safety issue, patients are encouraged to pay close attention to any symptoms of acidosis as informed by their caregiver, and physicians are encouraged to evaluate for the presence of acidosis, including ketoacidosis.

Rosenstock and colleagues did not report on clinical cardiovascular events in their trial, and the study was not designed to examine these long-term outcomes. However, it has recently been shown that empagliflozin is associated with cardiovascular benefits compared with placebo in patients at high risk of cardiovascular events, of whom about half (2,252 patients of 4,687 randomized to receive empagliflozin) were on background insulin (median daily dose of 54 IU) at baseline [34]. This suggests that the results of the study by Rosenstock and colleagues in patients treated with empagliflozin as add-on to basal insulin may translate to improved cardiovascular outcomes in the long term. It is also worth noting that hypertension is common in patients with T2DM and is a significant risk factor for cardiovascular disease (CVD). Treatment with empagliflozin and other SGLT2 inhibitors was associated with significant reductions of BP [35]. Empagliflozin has also been associated with significant reductions of BP in patients with T2DM and hypertension [36]. The improvements in SBP that were observed in the current study also suggest empagliflozin may have the potential to reduce CVD risk in patients with T2DM, beyond the benefits of glycemic control.

The unique mechanism of action of SGLT2 inhibitors and the oral delivery route, taken together with the results of this study and studies on other SGLT2 inhibitors, suggest that empagliflozin and other SGLT2 inhibitors may provide physicians with a viable choice as add-on therapy in patients with inadequate glycemic control despite basal insulin therapy.

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References

1. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95. http://dx.doi.org/10.2337/db09-9028
2. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008;31:213–24. http://dx.doi.org/10.1007/s10865-007-9147-y
3. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. 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;38:140–9. http://dx.doi.org/10.2337/dc14-2441
4. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. 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;35:1364–79. http://dx.doi.org/10.2337/dc12-0413
5. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. Diabet Med. 2012;29:682–9. http://dx.doi.org/10.1111/j.1464-5491.2012.03605.x
6. Yki-Jarvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care. 2001;24:758–67. http://dx.doi.org/10.2337/diacare.24.4.758
7. Riddle MC. Combined therapy with insulin plus oral agents: is there any advantage? An argument in favor. Diabetes Care. 2008;31 Suppl 2:S125–30. http://dx.doi.org/10.2337/dc08-s231
8. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. Diabetes Care. 2010;33:240–5. http://dx.doi.org/10.2337/dc09-1348
9. Frandsen CS, Madsbad S. Efficacy and safety of dipeptidyl peptidase-4 inhibitors as an add-on to insulin treatment in patients with type 2 diabetes: a review. Diabet Med. 2014;31:1293–300. http://dx.doi.org/10.1111/dme.12561
10. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes Metab. 2012;38:89–101. http://dx.doi.org/10.1016/j.diabet.2011.11.001
11. Gerich J. Pathogenesis and management of postprandial hyperglycemia: role of incretin-based therapies. Int J Gen Med. 2013;6:877–95. http://dx.doi.org/10.2147/IJGM.S51665

12. Vora J. Combining incretin-based therapies with insulin: realizing the potential in type 2 diabetes. Diabetes Care. 2013;36 Suppl 2:S226–32. http://dx.doi.org/10.2337/dcS13-2036
13. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, Paul SK. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med. 2009;361:1736–47. http://dx.doi.org/10.1056/NEJMoa0905479
14. Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev. 2011;32:515–31. http://dx.doi.org/10.1210/er.2010-0029
15. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014;8:262–75 e9. http://dx.doi.org/10.1016/j.jash.2014.01.007
16. Janssen Pharmaceuticals Inc. Prescribing Information: INVOKANA (canagliflozin), tablets, for oral use, March 2015 [cited 2015 Apr 1]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204042s005lbl.pdf.
17. AstraZeneca Pharmaceuticals LP. March 2015, Prescribing Information: FARXIGA (dapagliflozin) tablets, for oral use [cited 2015 Apr 1]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202293s002lbl.pdf.
18. Boehringer Ingelheim Pharmaceuticals Inc. Prescribing information: JARDIANCE (empagliflozin) tablets, for oral use, August 2014 [cited 2014 Aug 8]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204629s000lbl.pdf.
19. Rosenstock J, Jelaska A, Zeller C, Kim G, Broedl UC, Woerle HJ. Impact of empagliflozin added-on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2015;17(10):936–48. http://dx.doi.org/10.1111/dom.12503
20. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report: estimates of diabetes and its burden in the United States, 2014 [cited 2014 Aug 8]. Available from: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
21. Centers for Disease Control and Prevention (CDC). National Diabetes Fact Sheet, 2011 [cited 2014 Aug 8]. Available from: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
22. Donnelly LA, Morris AD, Evans JM. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes. QJM. 2007;100:345–50. http://dx.doi.org/10.1093/qjmed/hcm031
23. Doggrell SA, Warot S. The association between the measurement of adherence to anti-diabetes medicine and the HbA1c. Int J Clin Pharm. 2014;36:488–97. http://dx.doi.org/10.1007/s11096-014-9929-6
24. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care. 2014;37:1815–23. http://dx.doi.org/10.2337/dc13-3055
25. Dailey G. Empagliflozin for the treatment of type 2 diabetes mellitus: an overview of safety and efficacy based on Phase 3 trials. J Diabetes. 2015;7:448–61. http://dx.doi.org/10.1111/1753-0407.12278
26. Geerlings S, Fonseca V, Castro-Diaz D, List J, Parikh S. Genital and urinary tract infections in diabetes: impact of pharmacologically-induced glucosuria. Diabetes Res Clin Pract. 2014;103:373–81. http://dx.doi.org/10.1016/j.diabres.2013.12.052
27. Moses RG, Colagiuri S, Pollock C. SGLT2 inhibitors: new medicines for addressing unmet needs in type 2 diabetes. Australas Med J. 2014;7:405–15. http://dx.doi.org/10.4066/AMJ.2014.2181
28. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab. 2014;16:124–36. http://dx.doi.org/10.1111/dom.12187
29. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Ways K, Desai M, Shaw W, Capuano G, Alba M, Jiang J, Vercruysse F, Meininger G, Matthews D. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care. 2015;38:403–11. http://dx.doi.org/10.2337/dc14-1237
30. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335–80. http://dx.doi.org/10.2147/DDDT.S50773
31. Food and Drug Administration. Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood, 2015 [cited 2015 Sep 22]. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf.
32. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care. 2015;38:1638–42. http://dx.doi.org/10.2337/dc15-1380
33. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care. 2015;38:1680–6. http://dx.doi.org/10.2337/dc15-1251
34. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. Epub 2015 Sep 17. http://dx.doi.org/10.1056/NEJMoa1504720
35. Oliva RV, Bakris GL. Blood pressure effects of sodium-glucose co-transport 2 (SGLT2) inhibitors. J Am Soc Hypertens 2014;8:330–9. http://dx.doi.org/10.1016/j.jash.2014.02.003
36. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, Woerle HJ. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care. 2015;38:420–8. http://dx.doi.org/10.2337/dc14-1096