Therapeutic Class Overview
Incretin Mimetics

Therapeutic Class

- **Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®) are Food and Drug Administration-approved as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-3] This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.[4,5] The incretin mimetics are most commonly associated with gastrointestinal-related adverse events, and all agents are associated with the risk of developing pancreatitis. Only exenatide extended-release (ER) and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Exenatide (Byetta®) is administered twice-daily, liraglutide (Victoza®) is administered once-daily, and exenatide ER (Bydureon®) is administered once weekly.[1-3] There are currently no generic incretin mimetics available.

Table 1. Current Medications Available in Therapeutic Class[1-3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Exenatide (Bydureon®, Byetta®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release injection (Bydureon®): 2 mg/vial* Injection (Byetta®): 250 µg/mL†	-
Liraglutide (Victoza®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Injection: 6 mg/mL‡	-

*Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide [as a white to off-white powder], one pre-filled syringe [0.65 mL diluents], one vial connector, and two custom needles).
†Supplied as a 5 µg/dose pre-filled syringe (1.2 mL, 60 doses) and 10 µg/dose pre-filled syringe (2.4 mL, 60 doses).
‡Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.[6-49]
- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[6-49]
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release (ER) significantly decreased HbA_{1c}, and achieved similar decreases in

body weight.[25,31] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[39]

- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide ER (-0.21%; 95% CI, -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7% compared to patients treated with exenatide ER (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[32]
- Overall, safety data demonstrate that incretin mimetics are commonly associated with gastrointestinal-related adverse events.[6-49] Exenatide ER appears to be associated with less nausea and vomiting, but more constipation, diarrhea, and injection site-related adverse events compared to exenatide.[25,31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Type 2 diabetes:[50-54]
    - Metformin remains the cornerstone to most antidiabetic treatment regimens.[50-54]
    - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.[50-54]
    - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.[51,53]
      - A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents.[51,53]
      - No one incretin mimetic is recommended or preferred over another.[50-54]
- Other Key Facts:
  - Exenatide (Byetta®) is administered twice-daily (60 minutes prior to food).[1]
  - Exenatide extended-release (ER) (Bydureon®) is administered once weekly (independent of meals).[2]
    - The extended effect was achieved by adding the biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide. As a result, microspheres are formed and after administered, continued infiltration of water into the microspheres causes them to swell and release exenatide in a slow predictable fashion.[55]
    - Patients who administer exenatide ER will have a palpable subcutaneous nodule at the injection site that dissipates as the medication is released.[55]
  - Liraglutide (Victoza®) is administered once-daily (independent of meals).[3]
  - No generic incretin mimetics are available.

References

1. Byetta® [package insert]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2011 Dec.
2. Bydureon® [package insert]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2013 Feb.
3. Victoza® [package insert]. Princeton (NJ): Novo Nordisk Inc.; 2013 Apr.
4. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011 Mar;96(3):737-45.
5. Drab SR. Clinical studies of liraglutide, a novel, once-daily human glucagon-like peptide-1 analog for improved management of type 2 diabetes mellitus. Pharmacotherapy. 2009;29(12 Pt 2):S43-54.
6. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1092-100.
7. Ratner RE, Maggs D, Nielson LL, Stonehouse AH, Poon T, Zhang B, et al. Long-term effects of exenatide therapy over 82 weeks on glycemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2006 Jul;8(4):419-28.
8. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005 May;28(5):1083-91.

9. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004 Nov;27(11):2628-35.
10. Riddle MC, Henry RR, Poon TH, Zhang B, Mac SM, Holcombe JH, et al. Exenatide elicits sustained glycemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulfonylureas with or without metformin. Diabetes Metab Res Rev. 2006 Nov-Dec;22:483-91.
11. Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, et al. Interim analysis of the effects of exenatide treatment on A1C, weight, and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006 Jul;8(4):436-47.
12. Buse JB, Klonoff DC, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. Clin Ther. 2007;29(1):139-53.
13. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least three years. Curr Med Res Opin. 2008 Jan;24(1):275-86.
14. Viswanathan P, Chaudhuri A, Bhatia R, Al-Atrash F, Mohanty P, Dandona P. Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. Endocr Pract. 2007;13:444-50.
15. Zinman B, Hoogwerf BJ, Duran Garcia S, Milton DR, Giaconia JM, Kim DD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes. Ann Intern Med. 2007;146:477-85.
16. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011 Jan 18;154(2):103-12.
17. Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. Am J Hypertens. 2010;23:334-9.
18. Derosa G, Maffioli P, Salvadeo SAT, Ferrari I, Ragonesi PD, Querci F, et al. Exenatide vs glibenclamide in patients with diabetes. Diabetes Technol Ther. 2010;12(3):233-40.
19. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide vs insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143(8):559-69.
20. Secnik Boye K, Matza LS, Oglesby A, Malley K, Kim S, Hayes RP, et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. Health Qual Life Outcomes. 2006 Oct 11;4:80.
21. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared to long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared to Long-Acting insulin (HEELA) study. Diabetes Obes Metab. 2009 Dec;11(12):1153-62.
22. Bunck MC, Diamant M, Corner A, Eliasson B, Malloy J, Shaginian RM, et al. One-year treatment with exenatide improves β-cell function, compared to insulin glargine, in metformin-treated type 2 diabetic patients. Diabetes Care. 2009;32:762-8.
23. Bunck MC, Corner A, Eliasson B, Heine RJ, Shaginian RM, Wu Y, et al. One-year treatment with exenatide vs insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress. Atherosclerosis. 2010 Sep;212(1):223-9.
24. Nauck MA, Duran S, Kim D, Johns D, Northrup J, Festa A, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia. 2007;50(2):259-67.
25. Drucker D, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al. Exenatide once weekly vs twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet. 2008;372:1240-50.
26. Buse JB, Drucker DJ, Taylor KL, Kim T, Walsh B, Hu H, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care. 2010;33:1255-61.
27. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010;376:431-9.
28. Wysham C, Bergenstal R, Malloy J, Yan P, Walsh B, Malone J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. Diabet Met. 2011;28:705-14.
29. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al. Once weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010;375:2234-43.
30. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4). Diabetes Care. 2012;35:252-8.
31. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared to exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:1301-10.
32. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013 Jan 12;381(9861):117-24.
33. Marre M, Shaw J, Brandle M, Bebakar WMW, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26:268-78.
34. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IS, et al. Efficacy and safety comparison of liraglutide glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. Diabetes Care. 2009;32:84-90.
35. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373:473-81.
36. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for two years as monotherapy compared to glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):348-56.

37. Bode BW, Testa MA, Magwire M, Hale PM, Hammer M, Blonde L, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:604-12.
38. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009;32:1,224-30.
39. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. Diabetologia. 2009;52:2046-55.
40. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day vs exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374:39-47.
41. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010;33:1,300-3.
42. Kaku K, Rasmussen MF, Clauson P, Seino Y. Improved glycemic control with minimal hypoglycemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 patients. Diabetes Obes Metab. 2010;12:341-7.
43. Seino Y, Rasmussen MF, Nishida T, Kaku K. Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. Curr Med Res Opin. 2010;26(5):1013-22.
44. Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, et al. Liraglutide vs sitagliptin for patients with type 2 diabetes who did not have adequate glycemic control with metformin: a 26-week, randomized, parallel-group, open-label trial. Lancet. 2010;375:1447-56.
45. Fakhoury WKH, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44-57.
46. Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res. 2011;2011:215764.
47. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. JAMA. 2007;298(2):194-206.
48. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared to exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother. 2011;45:850-60.
49. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
50. The American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2012 Jan;36(Suppl 1):S11-66.
51. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009 Jan;32(1):193-203.
52. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012;156:218-31.
53. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA et al. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. 2013;19(2):327-36.
54. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007 May-Jun;13(Suppl 1):S1-68.
55. Bischoff LA, Jabbour SA, Miller JL. Exenatide once weekly in type 2 diabetes mellitus. Expert Opin Pharmacother. 2011;128(8):1297-303.

Therapeutic Class Review
Incretin Mimetics

Overview/Summary

A significant advancement in the management of type 2 diabetes has been the development of incretin-based therapies. This novel therapeutic approach is important as type 2 diabetics have been shown to have an impaired incretin response.[1] Currently there are two classes of incretin-based therapies available; the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics. The incretin mimetics, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®), were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adult type 2 diabetics.[2-4] According to a press release from the manufacturer, exenatide (Byetta®) is approved for use as an add-on therapy to insulin glargine, with or without metformin and/or a thiazolidinedione (TZD), in conjunction with diet and exercise for adults with type 2 diabetes who are not achieving adequate glycemic control on insulin glargine alone.[5] Of note, according to the currently approved package labeling of exenatide, concurrent use with prandial insulin has not been studied and cannot be recommended.[2]

GLP-1 is an endogenous hormone that maintains glucose homeostasis by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. The endogenous hormone also increases insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. The actions of GLP-1 mainly affect fasting and post-prandial glucose levels as the hormone works in a glucose-dependent manner. Due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia. Furthermore, the use of incretin mimetics in the management of type 2 diabetes has also demonstrated a positive benefit on weight reduction, β cell function, glycemic control, and systolic blood pressure.[1,6]

Exenatide and liraglutide are administered by subcutaneous (SC) injection and are available as branded products. There are currently two formulations of exenatide available. The immediate-release formulation (Byetta®) is administered twice daily and should be given within 60 minutes prior to a meal, while the extended-release (ER) formulation (Bydureon®) is administered once weekly and can be administered without regard to meals.[2,3] The extended effect of exenatide ER results from the addition of a biodegradable polymer poly D, L-lactic-co-glycolic acid to the active component, exenatide, which forms microspheres. After exenatide ER is administered, continued infiltration of water into the microspheres causes them to swell and release the medication in a slow predictable fashion. Of note, patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[7] Liraglutide is administered once daily and can also be administered without regard to meals.[4] Overall, the safety profiles of exenatide and liraglutide appear similar; however, exenatide ER and liraglutide are associated with a Boxed Warning regarding the risk of thyroid C-cell tumors. Gastrointestinal-related adverse events are commonly reported with the use of incretin mimetics, but these generally subside with continued treatment. In addition, a risk for the development of pancreatitis is associated with the use of these agents.[2-4]

The incretin mimetics have been evaluated in combination with and in comparison to a variety of antidiabetic therapies. Overall, the medication class is significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, and body weight. Efficacy data comparing the incretin mimetics to other antidiabetic agents are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents. A limited number of head-to-head clinical trials have been conducted within the class.[8-47]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The incretin mimetics are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a DDP-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one incretin mimetic over another is not stated.[48-53]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Exenatide (Bydureon®, Byetta®)	Incretin mimetics	-
Liraglutide (Victoza®)	Incretin mimetics	-

Indications

Table 2. Food and Drug Administration-Approved Indications[2-4]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Exenatide	✔
Liraglutide	✔

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis. The incretin mimetics would not be effective in these situations.[2-4] According to Food and Drug Administration-approved package labeling, due to the uncertain relevance of the rat thyroid C-cell tumor findings to humans, exenatide extended-release and liraglutide are not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.[3,4]

Pharmacokinetics

Pharmacokinetic data for exenatide extended-release are not extensively reported. According to Food and Drug Administration-approved package labeling, following a single dose of exenatide extended-release, exenatide is released from microspheres over approximately 10 weeks. Two peaks of exenatide in the plasma after approximately two and six to seven weeks, respectively, are observed due to an initial period of release of surface-bound exenatide, and followed by a gradual release of exenatide from the microspheres.[3]

Table 3. Pharmacokinetics[54]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Exenatide*	65 to 76†	Not reported	Not reported	2.4
Liraglutide	55	0 to 6	Not reported	13

*Immediate-release.
†Animal data.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the incretin mimetics in the management of type 2 diabetes are outlined in Table 4.[8-47]

Moretto et al demonstrated that monotherapy with exenatide in treatment-naïve type 2 diabetics significantly improved glycosylated hemoglobin (HbA_{1c}), fasting and postprandial glucose control (PPG), and weight compared to placebo. Additional benefits of exenatide over placebo include achievement of HbA_{1c} goals (≤6.5 and ≤7.0%), and improvements of β-cell function and blood pressure. Nausea was the most commonly reported adverse events, and no cases of severe hypoglycemia were reported.[8]

The efficacy of exenatide as add-on therapy to metformin, a sulfonylurea, or existing antidiabetic regimen (metformin or a sulfonylurea) was evaluated in three, placebo-controlled, 30 week, randomized-controlled trials.[9,11,12] In all trials, there were significant decreases in HbA_{1c} with exenatide compared to placebo (P<0.002, P<0.001, and P<0.0002). Exenatide also resulted in significant decreases in fasting plasma glucose (FPG), body weight, and PPG compared to placebo. When administered as add-on therapy to a sulfonylurea, exenatide significantly decreased fasting proinsulin concentrations compared to placebo (P<0.01), but no difference between exenatide and placebo was observed in the decrease in fasting insulin concentrations.[12] There were also no differences in the decreases in fasting proinsulin or insulin concentrations between exenatide and placebo when added on to metformin therapy.[8] The most common adverse events were gastrointestinal in nature, and the incidence of hypoglycemia ranged from 19.2 to 36.0% (reported in two trials).[9,11,12]

Extensions of these 30 week trials demonstrate that the benefits of exenatide are sustained for up to three years.[10,13-16] Specifically, two open-label, one year extension trials (82 weeks total treatment) demonstrated that further decreases in HbA_{1c}, FPG, and body weight are achieved with long-term exenatide treatment. In addition, after 82 weeks 59 and 44% of patients with baseline HbA_{1c} >7.0% achieved a HbA_{1c} ≤7.0% when exenatide was added to metformin or a sulfonylurea.[10,13] An interim analysis of these two one-year extension trials supported these results.[14] Two additional interim analyses of patients receiving exenatide for two and three years noted sustained significant decreases in baseline HbA_{1c}. Regarding safety data, significant reductions from baseline in alanine aminotransferase and aspartate aminotransferase occurred, and nausea was the most commonly reported adverse event.[15,16]

Exenatide as add-on therapy in type 2 diabetics receiving a thiazolidinedione has also been evaluated. After 16 weeks, exenatide significantly decreased HbA_{1c} (P<0.001), FPG (P<0.001), and body weight (P<0.001) compared to placebo. Gastrointestinal adverse events were more common in patients receiving exenatide.[18]

Approval of exenatide extended-release (ER) in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in four of the five trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy.[22,24,26,28,29] Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA_{1c} compared to exenatide (P=0.0023), sitagliptin (P<0.0001), pioglitazone (P=0.0165), and insulin therapy (P=0.017), with no increased risk of hypoglycemia. Furthermore, significantly greater proportions of patients receiving exenatide ER achieved HbA_{1c} goals compared to these treatments.[22,24,26,29] In terms of decreases in body weight, exenatide ER was “superior” compared to sitagliptin (P=0.0002) and pioglitazone (P<0.0001), and similar compared to exenatide (P=0.89).[22,24,29] As expected, gastrointestinal-related adverse events were reported more commonly with the incretin-based therapies.[22,24,26,29] When compared to exenatide, extended ER was associated with lower incidences of nausea (26.4 vs 34.5% and 14 vs 35%) and vomiting (10.8 vs 18.6%), and higher incidences of diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), and injection site-related adverse events (22.3 vs 11.7% and 13 vs 10%).[22,29] As mentioned previously, DURATION-4 evaluated the safety and efficacy of exenatide ER as monotherapy in type 2 diabetics. As monotherapy, the decreases in HbA_{1c} achieved with exenatide ER were “superior” compared to sitagliptin (P<0.001), and similar compared to metformin

(*P*=0.620) and pioglitazone (*P*=0.328). In this trial, exenatide ER and metformin resulted in a similar proportion of patients achieving an HbA_{1c} goal of <7.0% (*P* value not reported), with exenatide ER being "superior" to sitagliptin (*P*<0.001). However, significantly more patients receiving exenatide ER achieved a goal of ≤6.5% compared to patients receiving metformin (*P*=0.004). Exenatide ER and metformin were also similar in terms of associated decreases in bodyweight, with exenatide ER achieving "superiority" compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more gastrointestinal-related adverse events, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin.[28] In the open-label DURATION-6 trial patients were randomized to receive exenatide ER or liraglutide for 26 weeks. There was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide ER (-0.21%; 95% CI, -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7% compared to patients treated with exenatide ER (60 vs 53%; *P*=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[30]

Approval of liraglutide in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to a sulfonylurea (LEAD-1), metformin (LEAD-2), metformin plus a thiazolidinedione (LEAD-4), metformin plus a sulfonylurea (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).[31-33,36-38]

In LEAD-1 liraglutide was compared to placebo or rosiglitazone as add-on therapy to a sulfonylurea. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg/day) significantly decreased HbA_{1c} compared to placebo (*P*<0.0001 for all), with only higher doses achieving "superiority" compared to rosiglitazone (*P*<0.001 for both). Similar results were observed for the proportion of patients achieving HbA_{1c}, FPG, and PPG goals, as well as improvements in β cell function. Additionally, compared to rosiglitazone, liraglutide significantly decreased body weight (*P*<0.0001). This trial did not demonstrate a difference in the decrease in systolic blood pressure between treatments.[31]

In LEAD-2 liraglutide was compared to placebo and a sulfonylurea as add-on therapy to metformin. Again, liraglutide significantly decreased HbA_{1c} compared to placebo; however, similar decreases were observed with liraglutide compared to the sulfonylurea. Liraglutide was associated with significant decreases in body weight compared to placebo (*P*<0.01) and the sulfonylurea (*P*<0.001). Other secondary outcomes, such as decreases in FPG and PPG and improvements in β cell function, were significant for liraglutide compared to placebo, and similar compared to a sulfonylurea.[32]

In LEAD-3 liraglutide was compared to a sulfonylurea as monotherapy, and liraglutide was "superior" in decreasing HbA_{1c} (*P* value not reported). In addition, increases in body weight were reported with the sulfonylurea, while liraglutide significantly decreased body weight (*P*=0.027). Other secondary outcomes that reached significance with liraglutide compared to the sulfonylurea included decreases in FPG and PPG, improvements in β cell function, and decreases in systolic blood pressure (liraglutide 1.8 mg/day only). Patients receiving liraglutide also reported improved quality of life scores (*P*=0.02 vs sulfonylurea), mainly as a result of improvements in weight image and concern (*P*<0.01).[33] In a one year extension trial, patients continuing liraglutide for a total of two years maintained significant improvements in HbA_{1c} compared to patients receiving sulfonylurea.[34] A post-hoc analysis revealed that based on the patient reported-outcomes, enhanced glycemic control and decreased body weight achieved with liraglutide improved psychological and emotional well-being, and health perceptions by reducing anxiety and worry associated with weight gain.[35]

In LEAD-4 and LEAD-5 liraglutide was compared to placebo as add-on therapy to metformin plus a sulfonylurea and to a thiazolidinedione. LEAD-5 also had an open-label arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA_{1c}, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials.[36,37] When compared to insulin therapy, decreases in HbA_{1c} (*P*=0.0015) and body weight (*P*<0.001) and improvements in β cell function (*P*=0.0019) were

significantly greater with liraglutide. It was noted that decreases in PPG were not different between the two treatments, and the likelihood of patients achieving FPG goals were also similar.[37]

LEAD-6 is a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA_{1c} compared to exenatide (1.12 vs 0.79%; *P* value not reported), and a significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} goals (HbA_{1c} <7.0%, 54 vs 43%; odds ratio, 2.02; 95% confidence interval, 1.31 to 3.11; *P* value not reported, and HbA_{1c} ≤6.5%, 35 vs 21%; odds ratio, 2.73; 95% confidence interval, 1.68 to 4.43; *P* value not reported). Significant decreases in FPG were also achieved with liraglutide (*P*<0.0001); however, exenatide significantly decreased PPG after breakfast and dinner (*P*<0.0001 and *P*=0.0005). Both treatments were associated with similar decreases in body weight and systolic blood pressure.[38] A 14 week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits.[39]

Meta-analyses and Cochrane Reviews evaluating incretin-based therapies (dipeptidyl peptidase-4 inhibitors and incretin mimetics) have been conducted and demonstrate similar decreases in HbA_{1c} and significant decreases in body weight compared to other antidiabetic agents.[41-47] A recent meta-analysis revealed that incretin-based therapies are not associated with an increased risk of cardiovascular events compared to placebo or other antidiabetic agents.[43]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moretto et al[8] (2008) Exenatide 5 µg SC BID vs exenatide 10 µg SC BID vs placebo	DB, PG, RCT Patients ≥18 years of age with type 2 diabetes who were drug naïve and whose diabetes was inadequately controlled on diet and exercise alone	N=232 24 weeks	Primary: HbA_{1c}, fasting serum glucose, six-point self-monitored blood glucose, proportions of patients achieving HbA_{1c} values ≤6.5 and ≤7.0%, weight; HOMA-B, safety Secondary: Not reported	Primary: Mean changes in HbA_{1c} from baseline (LSM) were significantly greater with exenatide 5 and 10 µg compared to placebo (-0.7 and -0.9 vs -0.2%, respectively; *P*=0.003 and *P*<0.001 vs placebo). Mean changes in fasting serum glucose from baseline were significantly greater with exenatide 5 and 10 µg compared to placebo (-17.5 and -18.7 vs -5.2 mg/dL, respectively; *P*=0.029 and *P*=0.016 vs placebo). Changes in daily mean PPG excursions from baseline to end point were significantly greater with exenatide 5 and 10 µg compared to placebo (-21.3 and -24.7 vs -8.3 mg/dL, respectively; *P*<0.001 vs placebo for both). With exenatide 5 and 10 µg, 31 and 35% of patients achieved HbA_{1c} ≤6.5% at end point vs 19% of patients receiving placebo (*P* value not significant and *P*=0.026, respectively), while 48 and 46 vs 29% of patients achieved HbA_{1c} ≤7.0% (*P*=0.024 and *P*=0.036, respectively). Changes in weight at 24 weeks were greater with exenatide 5 and 10 µg compared to placebo (-2.8 and -3.1 vs -1.4 kg, respectively; *P*=0.004 and *P*<0.001). HOMA-B values increased from baseline to end point by 32 and 28% with exenatide 5 and 10 µg, respectively, compared to 6% with placebo. Improvements from baseline to end point in HOMA-B were significantly greater with exenatide 5 and 10 µg compared to placebo (*P*=0.002 and *P*=0.010, respectively). Significant improvements in mean SBP and DBP from baseline to end point were also observed with exenatide (SBP: exenatide 5 and 10 µg, -3.7 mm Hg; *P*=0.037, DBP: exenatide 10 µg, -2.3 mm Hg; *P*=0.046) compared to placebo (SBP: -0.3 mm Hg and DBP: -0.3 mm Hg). Overall, 25% of patients reported at least one treatment-emergent adverse event. Nausea was reported with the greatest incidence (exenatide 5 µg,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				3%; exenatide 10 µg, 13%; placebo, 0%; *P*=0.010 for the combined exenatide group vs placebo). Most (88%) treatment-emergent adverse events were mild or moderate in intensity. Hypoglycemia was reported in five, four, and one percent of patients receiving exenatide 5 and 10 µg and placebo groups, respectively (*P* value not significant), with no incidents of severe hypoglycemia reported.
DeFronzo et al[9] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing metformin therapy.	MC, PC, PG, RCT, TB Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=336 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids	Primary: Significantly greater decreases in HbA_{1c} were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; *P*<0.002 for pairwise comparison). Secondary: A significantly greater proportion of patients achieved HbA_{1c}≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; *P*<0.01 for pairwise comparison). Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; *P*<0.005) and 10 µg (-10.1 mg/dL; *P*<0.0001) compared to placebo (14.4 mg/dL). Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; *P*<0.05) and 10 µg (-2.8 kg; *P*<0.001) compared to placebo (-0.3 kg). There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (*P* values not reported). No differences in lipid profiles were observed between any of the treatments (*P* value not reported). Gastrointestinal side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (*P* values not reported). The incidence of hypoglycemia was similar with all treatments. Withdrawals

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported).
Ratner et al[10] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin therapy.	ES, MC, OL (DeFronzo et al[9]) Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=150 52 weeks (82 weeks total)	Primary: Changes in baseline HbA_{1c}, body weight, and lipid profile of the completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population) Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c} >7.0% who achieved an HbA_{1c} ≤7.0%, reduction of weight after stratification by baseline BMI, safety	Primary: At week 30, the completer cohort had significant decreases in HbA_{1c} from baseline of -1.0±0.1%. At week 82, the decrease was -1.3±0.1% (95% CI, -1.5 to -1.0; *P*<0.05). For the total cohort, the decrease at week 30 was -0.7±0.1% (95% CI, -0.8 to -0.5; *P*<0.05) and at week 82 was -0.8±0.1% (95% CI, -1.0 to -0.6; *P*<0.05). At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0±0.6 kg. At week 82, the decrease from baseline was -5.3±0.8 kg (95% CI, -7.0 to -3.7; *P*<0.05). For the total cohort, the decrease at week 30 was -2.3±0.4 kg and at week 82 was -4.3±0.6 kg (95% CI, -5.5 to -3.2; *P*<0.05). At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; *P* value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; *P* value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; *P* value not reported). Secondary: At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7.0% and who achieved an HbA_{1c} ≤7.0% was 46 and 59% (*P* values were not reported). Patients in the completer cohort whose baseline BMI ≥30 kg/m^2 experienced a greater decrease of weight (-6.9±1.1 kg) compared to those whose baseline BMI was <30 kg/m^2 (-2.3±0.8 kg; *P* values were not reported). The following adverse events were experienced by patients in the total cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%), diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (*P* values were not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kendall et al[11] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing diabetes regimens. All patients continued pre-trial metformin regimen. To standardize sulfonylurea use, patients were randomized to either maximally effective or minimum recommended sulfonylurea dose.	DB, MC, PC, PG, RCT Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m^2, HbA_{1c} 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=733 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, and body weight	Primary: Significantly greater decreases in HbA_{1c} were achieved with exenatide 5 (-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; *P*<0.001 for pairwise comparison). Secondary: Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo (0.8±0.2 mmol/L; *P*<0.0001 for pairwise comparison). Significantly greater decreases in PPG were achieved with exenatide 5 (*P*=0.009) and 10 µg (*P*=0.0004) compared to placebo. Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; *P*≤0.01). Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (*P* values not reported).
Buse et al[12] Exenatide 5 µg SC BID	MC, PC, PG, RCT, TB Type 2 diabetic patients 22 to 76	N=377 30 weeks	Primary: Change in baseline HbA_{1c}	Primary: Significantly greater decreases in HbA_{1c} were noted with exenatide 10 (-0.86%) and 5 µg (-0.46%) compared to placebo (0.12%; *P*<0.0002 for pairwise comparison).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing sulfonylurea therapy.	years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		Secondary: Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins	Secondary: A significantly greater decreases in FPG was reported with exenatide 10 µg at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; *P*<0.05). There was no difference between exenatide 5 µg and placebo (*P* value not reported). A significantly greater decrease in body weight was noted with exenatide 10 µg at week 30 compared placebo (-1.6 vs -0.6 kg; *P*<0.05). There was no difference between exenatide 5 µg and placebo (*P* value not reported). There were no differences in fasting insulin concentrations between any of the treatments (*P* value not reported). A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 compared to placebo (-16 mmol/L; *P*<0.01). A similar trend was reported with exenatide 5 µg compared to placebo, but no significance was reported (*P* value not reported). There was a small decrease in LDL-C and apo B (*P*<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (*P* values not reported). Side effects reported by patients receiving exenatide 10 µg included nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (*P* values not reported). There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%) withdrawals with placebo (*P* values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Riddle et al[13] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	ES, MC, OL (Kendall et al[11] and Buse et al[12]) Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) or maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value	N=401 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline weight, change in baseline HbA_{1c} and weight stratified by baseline HbA_{1c} and BMI	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.8±0.1% for the original exenatide 5 µg arm and -1.0±0.1% for the original 10 µg arm. At week 82, the decrease was -1.0±0.1% (95% CI, -0.9 to -1.2; *P* value not reported). For the total cohort group, the decrease at week 82 was -0.7±0.1% (95% CI, -0.8 to -0.5; *P* value not reported). Results from week 30 week were not reported. At week 30, the completer cohort observed a decrease in FPG of -0.52±0.16 mmol/L (*P* value not reported). At week 82, the decrease was -0.62±0.19 mmol/L (*P* value not reported). FPG data for the total cohort were not reported. Secondary: At week 30, the completer cohort group experienced a decrease in body weight of -1.4±0.3 kg for the original exenatide 5 µg arm and -2.1±0.3 kg for the original 10 µg arm. At week 82, the decrease was -4.0±0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3±0.2 kg (95% CI, -2.8 to -3.7; *P* value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m^2 experienced a greater decrease in mean weight from baseline of -4.4±0.4 kg compared to -3.2±0.5 kg in patients with a baseline BMI <30 kg/m^2 (*P* values not reported). Of the patients in the completer cohort who had a baseline HbA_{1c} >7.0%, 44% achieved an HbA_{1c} ≤7.0% at week 82. Patients with a baseline HbA_{1c} ≥9.0% experienced a greater decrease (-1.9±0.2%) compared to those with a baseline HbA_{1c}<9.0% (-0.7±0.1%) (*P* values were not reported). The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (*P* values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Blonde et al[14] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, MC, OL (Ratner et al[10] and Riddle et al[13]) Type 2 diabetics	N=551 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline FPG and weight, change in baseline weight and HbA_{1c} stratified by baseline BMI and HbA_{1c}, change in lipid profile	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.9±0.1%, and this decrease was maintained at week 82, with a decrease of -1.1±0.1% (95% CI, -1.0 to -1.3; *P* value not reported). The total cohort experienced a decrease at week 82 of -0.8±0.1% (95% CI, -0.6 to -0.9; *P* value not reported). Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (*P* values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (*P* values not reported). Secondary: At week 30, the completer cohort experienced a decrease in FPG of -0.7±0.1 mmol/L (*P* value not reported). At week 82, the decrease was -0.9±0.2 mmol/L (*P* value not reported). The total cohort FPG levels were not reported. At week 30, the completer cohort group experienced a decrease in body weight of -2.1±0.2 kg and at week 82 the decrease was -4.4±0.3 kg (95% CI, -3.8 to -5.1; *P* value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5±0.2 kg (95% CI, -3.1 to -4.0; *P* value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥40 kg/m^2 experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI <25 kg/m^2 (*P* values not reported). In the completer cohort, of those patients whose baseline HbA_{1c} was >7.0%, 39 and 48% achieved HbA_{1c} ≤7.0% at weeks 30 and 82, respectively. At week 82, a greater decrease in HbA_{1c} was achieved in patients who had a baseline HbA_{1c} ≥9.0% (-2.0±0.2) compared to those with a baseline HbA_{1c} <9.0% (-0.8±0.1) (*P* values were not reported). In the completer cohort, of the lipid levels measured, significant benefits

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (*P* values not reported).
Buse et al[15] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OL (Ratner et al[10], Riddle et al[13], and Blonde et al[14]) Type 2 diabetics	N=521 104 weeks (2 years total)	Primary: Change in baseline HbA_{1c}, weight, and hepatic biomarkers; safety Secondary: Not reported	Primary: At week 104, exenatide significantly decreased HbA_{1c} by -1.1% (95% CI, -1.3 to -1.0; *P*<0.001). At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; *P*<0.001). At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -7.1 to -3.5; *P*<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; *P*<0.05). Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected: nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (*P* values were not reported). Secondary: Not reported
Klonoff et al[16] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OE, OL (Ratner et al[10], Riddle et al[13], and Blonde et al[14]) Type 2 diabetics	N=217 156 weeks (3 years total)	Primary: Change in baseline HbA_{1c}, weight, and ALT; safety Secondary: Not reported	Primary: At Week 156, exenatide significantly decreased HbA_{1c} by -1.0±0.1% (*P*<0.0001). At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (*P*<0.0001). At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (*P*<0.0001). The most frequently reported adverse event was mild to moderate nausea. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Viswanathan et al[17] Exenatide 5 µg SC BID vs control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal or economic reasons) The dosages of rapid-acting and mixed insulin were reduced by 10% in patients with HbA_{1c} <7.5%. Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.	RETRO Obese type 2 diabetic patients not adequately controlled despite treatment with oral hypoglycemic agents and insulin and HbA_{1c} >7.0%	N=52 26 weeks	Primary: Change in baseline body weight, HbA_{1c}, and insulin dose Secondary: Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety	Primary: Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (*P*<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (*P*<0.001). Exenatide-treated patients experienced a decrease in HbA_{1c} (-0.60±0.21%; *P*=0.007). The patients in the control group also experienced a decrease in HbA_{1c} (-8.4±0.5%; *P* value not reported). Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (*P*<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (*P*<0.02). Insulin requirements for the control group were not reported. Secondary: Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (*P*=0.03) compared to the patients in the control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (*P*=0.08). Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (*P*=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (*P*=0.91). Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (*P*=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP. Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (*P*=0.05). Data for the control group were not reported. Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed.
Zinman et al[18] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing TZD therapy (with or without metformin).	MC, PC, RCT Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) for ≥4 months before screening, alone or in combination with a stable dose of metformin for 30 days, HbA_{1c} 7.1 to 10.0%, BMI 25 to 45 kg/m^2, and a history of stable body weight (≤10% variation) for ≥3 months before screening	N=233 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, body weight, self-monitored blood glucose concentrations, safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-0.89±0.09 vs 0.09±0.10%; *P*<0.001). Secondary: Exenatide significantly decreased FPG compared to placebo (-1.59±0.22 vs 0.10±0.21 mmol/L; *P*<0.001). Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; *P*<0.001). Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared to baseline (*P*<0.001) and placebo treated patients (*P*<0.001). Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4).
Buse et al[19] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing	DB, MC, PC, RCT Type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3	N=261 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0 or ≤6.5%; seven-point self-monitored glucose concentrations; change in baseline body weight, waist circumference, and insulin dose; safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-1.74 vs -1.04%; *P*<0.001). Secondary: A significantly greater proportion of patients receiving exenatide achieved an HbA_{1c} ≤7.0% (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; *P*<0.001). Similar results were observed with HbA_{1c} ≤6.5% (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; *P*<0.001). With regards to seven-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo (*P*<0.001), but not at midday (*P*=0.320).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m^2, and stable body weight over past 3 months			Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; *P*<0.001), but no difference between treatments was observed in waist circumference (*P*=0.23). The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo (*P*=0.49).
Rosenstock et al[20] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0%	Exploratory analysis of Buse et al[19] Baseline factors associated with glycemic control and weight loss in type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45	N=259 30 weeks	Primary: Change in baseline HbA_{1c}, weight Secondary: Not reported	Primary: Patients receiving exenatide had achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo, irrespective of baseline HbA_{1c} (*P*<0.001). Patients receiving exenatide with longer duration of diabetes and those with lower BMI achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo (*P*<0.01). Patients receiving exenatide lost significantly more weight, regardless of baseline HbA_{1c} or BMI compared to patients receiving placebo (*P*<0.05). Patients receiving exenatide with longer duration of diabetes lost the most weight compared to patients receiving placebo (*P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	kg/m^2, and stable body weight over past 3 months			
Okerson et al[21] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo or insulin All patients also received existing antidiabetic treatment regimens.	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; *P*=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; *P*<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; *P*=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; *P*=0.16). No differences in the proportions of patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; *P*=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; *P*<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (*P* values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; *P*<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; *P*<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference, 19%; *P*=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of "abnormal DBP" to "normal DBP" compared to placebo (treatment difference, 41.4 vs 32.4%; *P*=0.02). Secondary: Not reported
Drucker et al[22] DURATION-1 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 28 days, followed by 10 µg BID	AC, OL, non-inferiority, RCT Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents	N=303 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Safety and tolerability; FPG and PPG; body weight; fasting glucagon; fasting lipids; BP; proportion of patients achieving HbA_{1c} ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies	Primary: Both treatments achieved significant decreases in HbA_{1c}, with a decrease at week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; *P*=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall, decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years). Secondary: Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritis (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). Gastrointestinal complaints were the most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (*P* value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritis with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (*P* value not reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment. Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; *P*<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles. Body weight decreased progressively with both treatments (-3.7±0.5 vs -3.6±0.5 kg; 95% CI, -1.3 to 1.1; *P*=0.89). At week 30, the mean percentage of weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (*P*>0.05). Both treatments significantly decreased FPG and PPG (*P* values not reported). Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (*P* values not reported). TG decreased with both treatments (-15 vs -11%; *P* value not reported). Both treatments achieved significant improvements in SBP and DBP (*P* values not reported). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} ≤7.0% compared to patients receiving exenatide (77 vs 61%; *P*=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved HbA_{1c} ≤6.5 and ≤6.0%. Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (*P*=0.0002), but most antibodies were either not detectable or of low titer.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Buse et al[23] DURATION-1 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-1 who were randomized to exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period.	ES (DURATION-1[22]) Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents	N=258 22 weeks (52 weeks total)	Primary: Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability Secondary: Not reported	Primary: During the 22 weeks, patients who continued exenatide ER maintained improvements in HbA_{1c}, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 HbA_{1c} decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean HbA_{1c} (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an HbA_{1c} ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline HbA_{1c} <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in HbA_{1c} were observed in patients with a baseline HbA_{1c} ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]). Body weight decreased similarly with both treatments. At week 52, the decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who switched to exenatide ER. In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment. Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9). Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritis was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported. Secondary: Not reported
Bergenstal et al[24] DURATION-2 Exenatide ER 2 mg SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	DB, DD, MC, PG, RCT Type 2 diabetics ≥18 years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=514 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; *P*<0.0001) and pioglitazone (-1.2% [95% CI, -1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; *P*=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (*P*<0.0001 and *P*=0.0120) or ≤7.0% (*P*<0.0001 and *P*=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; *P*=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; *P*=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; *P*<0.0001), but no difference was observed between patients receiving pioglitazone (52%; *P*=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to sitagliptin, but not pioglitazone (*P* values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; *P*=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; *P*<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0). Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; *P*=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; *P*<0.0001). Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (*P* values not reported). All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; *P*=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; *P*=0.0406). The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Wyshman et al[25] DURATION-2 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg SC once weekly after the initial 26 week trial period.	ES (DURATION-2[24]) Type 2 diabetics ≥18 years of age, receiving stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2	N=319 26 weeks (52 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, proportion of patients achieving an HbA_{1c} <7.0 or ≤6.5%, proportion of patients achieving FPG <7 mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety Secondary: Not reported	Primary: Patients who continued exenatide ER demonstrated significant 52 week improvements in HbA_{1c} (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body weight (-1.8±0.5 kg; *P*=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in HbA_{1c} (-0.3±0.1%; *P*=0.0010), FPG (-0.7±0.2 mmol/L; *P*=0.0017), and body weight (-1.1±0.3 kg; *P*=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained HbA_{1c} and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; *P*<0.0001). No differences in the proportions of patients achieving target HbA_{1c} <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (*P*<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (*P*=0.0002). Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables were not different from baseline. Patients switched to exenatide ER from sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and plasminogen activator inhibitor-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER. Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event (continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported. Secondary: Not reported
Diamant et al[26] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported quality of life, safety	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; *P*=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; *P*=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; *P*=0.010) and <6.5% (35 vs 23%; *P*=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; *P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (*P*<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (*P*=0.022) and before breakfast (*P*<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (*P*=0.004). Exenatide ER resulted in significantly greater reductions in post-prandial glucose excursions compared to insulin glargine after morning (*P*=0.001) and evening meals (*P*=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; *P*<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to 0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; *P*<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; *P*<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). Gastrointestinal events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. Gastrointestinal events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Diamant et al[27] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	ES of Diamant et al[26] (MC, OL, PG, RCT) Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=390 84 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety	Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (*P*=0.029). Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (*P*=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (*P*=0.009), respectively. Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (*P*<0.001). Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (*P*<0.001). Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (*P*<0.05) with exenatide ER compared to insulin glargine.
Russell-Jones et al[28] DURATION-4 Exenatide ER 2 mg SC once weekly vs	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (*P*=0.620 vs exenatide ER), pioglitazone (*P*=0.328 vs exenatide ER), and sitagliptin (*P*<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight		and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported quality of life	Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; *P* value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; *P*<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; *P*=0.004) and sitagliptin, respectively (49 vs 26%; *P*<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (*P*<0.001 for both). There were no differences observed with exenatide ER compared to metformin (*P*=0.155 at week 26) and pioglitazone (*P*=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments. Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (*P*≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; *P*=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (*P*<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (*P*<0.001 for both), and the change with exenatide ER was similar to sitagliptin (*P*=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to pioglitazone (*P* values not reported).
Blevins et al[29] DURATION-5 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	AC, MC, OL, RCT Type 2 diabetics ≥18 years of age treated for ≥2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 kg/m^2	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, HbA_{1c} was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide. Secondary: A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0 (58.1 vs 30.1%; *P*<0.0001) and <6.5% (41.1 vs 16.3%; *P*<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; *P*=0.0008). Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				weight loss and a decrease in HbA_{1c}. Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; *P*=0.0008). Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment. Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide. Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritis. There were no major hypoglycemic episodes. The incidence of serious adverse events were low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including gastrointestinal symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point.
Buse et al[30] DURATION-6 Exenatide ER 2 mg SC once weekly vs liraglutide 1.8 mg SC QD Liraglutide was titrated	AC, MC, OL, PG, RCT Type 2 diabetics ≥18 with suboptimal glycemic control with diet and exercise and a maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0% and BMI	N=912 26 weeks	Primary: Change in baseline Hb_{A1c} Secondary: Proportion of patients reaching HbA_{1c} ≤7%, changes in bodyweight, FPG, BP, lipid concentrations, hypoglycemia and safety	Primary: The change from baseline in HbA_{1c} was significantly greater for patients treated with liraglutide compared to exenatide ER (-0.21%; 95% CI, -0.08 to -0.33). Secondary: Overall, significantly more patients receiving liraglutide achieved an HbA_{1c} of less than 7% compared to patients treated with exenatide ER (271 [60%] vs 243 [53%]; *P*=0.0011). Changes in bodyweight were significantly greater with liraglutide compared to exenatide ER at 26 weeks (-0.90 kg; 95% CI, -0.39 to -1.40).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
from 0.6 mg per day to 1.2 mg per day, then to 1.8 mg per day. Each titration was completed after at least 1 week, but could be delayed if the patient had severe nausea or vomiting as established by the investigator.	≤45 kg/m^2			At 26 weeks, FPG was significantly decreased in both groups (*P*<0.0001); however, there was a greater decrease in patients in the liraglutide group compared to those in the exenatide ER group (-0.36; 95% CI, -0.05 to -0.66; *P*=0.02). Patients in both groups had similar decreases in systolic (-0.97; 95% CI, -0.53 to 2.47) and diastolic BP (-0.01; 95% CI, -0.96 to 0.98). Improvements in other cardiovascular biomarkers (lipids, CRP, and BNP) were similar between the treatment groups. The most common adverse events were gastrointestinal in nature and a greater frequency of nausea, diarrhea, and vomiting occurred in the liraglutide group. Nausea, diarrhea and vomiting occurred more frequently at the start of treatment in both groups, with incidence decreasing over time. Twenty four (5%) patients in the liraglutide group discontinued treatment due to treatment-emergent adverse events compared to 12 (3%) in the exenatide ER group. Four patients (two in each group) died; three died after they had completed the 26 week treatment period (suicide, cerebrovascular accident, and pulmonary embolism), and one died (sudden death) 10 weeks following discontinuation for a protocol violation. Concentrations of pancreatic lipase and total amylase varied in both groups and were not predictive of gastrointestinal symptoms. Mean calcitonin concentrations were unchanged in both groups. One patient in the exenatide ER group had acute pancreatitis for which ultra sonography showed cholelithiasis. One patient in the exenatide ER group had a nonserious, asymptomatic case of pancreatitis that led to discontinuation; however, a CT scan showed no evidence of acute pancreatitis. No episodes of major hypoglycemia were reported. In patients taking concomitant sulfonylurea, 36 (12%) of those in the liraglutide group and 45 (15%) in the exenatide ER group had minor hypoglycemia. In those not taking concomitant sulfonylurea, minor hypoglycemia occurred in four (3%) patients receiving liraglutide and in six (4%) receiving exenatide ER.
Marre et al[31]	AC, DB, DD, MC, PG,	N=1,041	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	26 weeks	Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; *P*<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; *P*<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; *P*<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; *P*<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were "superior" compared to treatment with rosiglitazone (*P*<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (*P*<0.0001) and rosiglitazone (*P*<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg (*P*=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; *P*=0.002), 1.2 mg (37%; *P*<0.001), and 1.8 mg (38%; *P*=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (*P*=0.007 and *P*=0.01, respectively). The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (*P*<0.05), but not rosiglitazone (*P* value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (*P*<0.0001), although there were no differences compared to placebo (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).
Nauck et al[32] LEAD-2 Liraglutide 0.6, 1.2, and 1.8 mg SC QD vs placebo vs glimepiride 4 mg/day All patients also received metformin 1,500 to 2,000 mg/day.	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m^2	N=1,091 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline body weight, FPG, seven-point self-monitored glucose concentrations, and β cell function	Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had "superior" glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride demonstrated that liraglutide 1.2 and 1.8 mg were noninferior to treatment with glimepiride. Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01). Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported). Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; *P*<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (*P* values not reported). No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (*P* values not reported). Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (*P* value not reported), and were significantly greater compared to placebo (0.1; *P*<0.0001). Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (*P* values not reported).
Garber et al[33] LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous	N=746 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported quality of life	Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; *P*<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; *P*=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; *P*=0.0046). Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (*P* values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks. Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; *P*=0.027 and 1.8 mg, -1.42 mmol/L; *P*=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L). Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			glimepiride; *P*=0.1616, liraglutide 1.8 mg vs glimepiride; *P*=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; *P*=0.1319). Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (*P*=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (*P*<0.0118). Mean DBP decreased but not significantly with any treatment. HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (*P*=0.0249 and *P*=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride). Patients receiving liraglutide 1.8 mg reported improved quality of life scoring for physical and emotional domains compared to glimepiride (*P*=0.02). Improvements were largely as a result of improvements in weight image and weight concern (*P*<0.01).
Garber et al[34] LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day	ES (LEAD-3[32]) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c}	N=440 52 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP	Primary: The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; *P*=0.0376) and 1.8 mg (-1.1 vs -0.6%; *P*=0.0016) compared to glimepiride over two years of treatment. Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; *P*<0.001 for both comparisons). Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (*P*=0.0015 and *P*=0.0001, respectively). In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (*P*=0.0451 for liraglutide

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)			1.2 mg vs glimepiride). The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (*P* values not reported). After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (*P* values not reported). No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.
Bode et al[35] LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	Post-hoc analysis (LEAD-3[32]) Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)	N=746 52 weeks	Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being and distress, cognitive functioning and health Secondary: Not reported	Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point “my weight is just right” was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (*P*=0.002). Furthermore, weight concern decreased markedly with liraglutide, with mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; *P*<0.0001 and liraglutide 1.8 mg; *P*<0.001). Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either “somewhat” or “very overweight” vs “just right”, “somewhat underweight,” or “very overweight” during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; *P* value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being “somewhat worried”, “very worried,” or “extremely worried” vs “a little concerned” or “not concerned at all” about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; *P* value not reported). There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P* values not reported). The health-related quality of life composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (*P*=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (*P*<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (*P* values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (*P*=0.006). Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (*P*<0.0001 for both), indicating that patients' reports were valid representations of actual weight losses. Decreases in HbA_{1c} corresponded to improvements in general perceived health (*P*<0.0001), cognitive functioning composite score (*P*=0.006), and cognitive performance (*P*=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg. Secondary: Not reported
Zinman et al[36] LEAD-4 Liraglutide 1.2 and 1.8 mg SC QD vs placebo	DB, MC, PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3	N=533 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, seven-point self-monitored glucose	Primary: The mean baseline HbA_{1c} for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; *P* value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; *P* value not reported) compared to -0.5±0.1% with placebo. Secondary: Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients also received metformin 2,000 mg/day and rosiglitazone 8 mg/day.	months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy for ≥3 months), and BMI ≤45 kg/m^2		concentrations, β cell function, and lipids	*P*<0.0001 for both). Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to placebo (-0.4 mmol/L; *P*<0.0001 for both). Decreases in mean PPG were significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; *P*<0.001 for both). The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; *P*<0.05 for both). The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; *P*<0.05 for both). Increases in HOMA-B with liraglutide were significantly greater compared to placebo (*P*<0.05), but decreases with HOMA-IR were not different between treatments (*P* values not reported). Decreases in FFA were significantly greater with liraglutide 1.2 mg (-0.03±0.02 mmol/L; *P*<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; *P*<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; *P*<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; *P*<0.05).
Russell-Jones et al[37] LEAD-5 Liraglutide 1.8 mg SC QD vs	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before screening,	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body weight, waist circumference, FPG,	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; *P*<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; *P*=0.0015). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo vs insulin glargine (OL) All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2		eight-point self-monitored glucose concentrations, β cell function, and BP	The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; *P*=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; *P*<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; *P*<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; *P*=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; *P*<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported). Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin (-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; *P*<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; *P*=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; *P*<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; *P*=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; *P*=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.
Buse et al[38]	AC, MC, OL, PG, RCT	N=464	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LEAD-6 Liraglutide 1.8 mg SC QD vs exenatide 10 µg SC BID Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea doses could be reduced to no less than 50% of the starting dose.	Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	26 weeks	Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} targets (<7.0 and ≤6.5%); change in baseline FPG, seven-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles	Decreases in HbA_{1c} with liraglutide were "superior" compared to exenatide (-1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -0.18; *P* value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; *P*<0.0001). Secondary: The proportion of patients achieving target HbA_{1c} was significantly greater with liraglutide compared to exenatide (HbA_{1c} <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; *P* value not reported and HbA_{1c} ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; *P* value not reported). Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; *P*<0.0001). In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; *P*<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI, 0.44 to 1.57; *P*=0.0005). After lunch differences between the two treatments were not significant (data not reported). Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; *P*=0.2235). Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; *P*<0.0001). Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; *P*=0.1436). No differences were observed between the two treatments in terms of decreases in SBP (*P*=0.6409) or DBP (*P*=0.1610).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (*P*=0.0277), TG (*P*=0.0485), and FFA (*P*=0.0014). All other lipid parameters were similar between the two treatments.
Buse et al[39] Liraglutide 1.8 mg SC QD (continued liraglutide) vs liraglutide 1.8 mg SC QD (switched to liraglutide) Patients enrolled in LEAD-6 who were randomized to exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period.	ES (LEAD-6[37]) Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	N=376 14 weeks (40 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, and SBP; adverse events Secondary: Not reported	Primary: HbA_{1c} decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (*P*<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; *P*=0.1222). Additional patients reached HbA_{1c} targets after switching from exenatide to liraglutide. After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; *P*<0.0001), body weight (-0.9±0.15 kg; *P*<0.0001), and SBP (-3.8±0.84 mmHg; *P*<0.0001) occurred, while HOMA-B increased (14.5±4.4%; *P*=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; *P*=0.0973), body weight (-0.4±0.15 kg; *P*=0.0089), and SBP (-2.2±0.88 mmHg; *P*=0.0128) occurred. No significant changes in PPG occurred in either treatment group (*P* value not reported). Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; *P* value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported. Secondary: Not reported
Kaku et al[40] Liraglutide 0.6 and 0.9 mg SC QD vs placebo All patients received existing sulfonylurea therapy.	DB, MC, PG, RCT Japanese type 2 diabetics ≥20 years of age currently treated with a sulfonylurea for ≥8 weeks, HbA_{1c} 7.0 to <10.0%, and BMI <35 kg/m^2	N=264 52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)	Primary: Change in baseline HbA_{1c} at 24 weeks Secondary: seven-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an HbA_{1c} <7.0 or <6.5% (post-hoc analysis)	Primary: Liraglutide significantly decreased and sustained HbA_{1c} compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56±0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46±0.95% and placebo, -0.40±0.93%). HbA_{1c} at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg. Secondary: Improvements in metabolic controls were apparent in the seven-point self monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with liraglutide compared to placebo (*P*<0.0001). Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (*P* values not reported). Weight decreased with placebo (-1.12 kg). Full impact on FPG levels was achieved at the first two visits at week four, and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; *P*<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (*P* values not reported). The means of AUC_{0-3hr} at week 24 were also significantly lower with liraglutide compared to placebo (*P*<0.0001). No significant treatment effects were observed in any of the parameters of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; *P*=0.0018 and liraglutide 0.9 mg vs placebo; *P*=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (*P*=0.0218), but no difference was observed between liraglutide 0.9 mg and placebo (*P*=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (*P* values not reported). A significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} values <7.0 and <6.5% compared to placebo (*P* values not reported).
Pinelli et al[41] Exenatide plus other antidiabetic agents vs TZD plus other antidiabetic agents	MA (22 RCTs) Patients with type 2 diabetes receiving combination therapy	N=9,325 ≥24 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} <7.0%, mean change from baseline in FPG and body weight, hypoglycemia, gastrointestinal adverse events	Primary: There were small reductions in HbA_{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide. When only PC trials were analyzed, there were greater reductions in HbA_{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83). When only TZD AC trials were analyzed, there was a significant difference in HbA_{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01). There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, non-inferiority trials. Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%. FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32). In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64). The most commonly reported adverse effects were gastrointestinal disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients receiving comparator.
Fakhoury et al[42] Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs placebo	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin) Type 2 diabetics ≥18 years of age	N=Not reported Duration varied (4 to 52 weeks	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia Secondary: Not reported	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; *P*<0.001) significantly decrease HbA_{1c} compared to placebo. Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; *P*<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; *P*<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; *P*<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to 0.87; *P*<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; *P*<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; *P*=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; *P*=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; *P*=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; *P*=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; *P*=0.050). Secondary: Not reported
Monami et al[43] GLP-1 receptor agonist based therapies (albiglutide*, exenatide, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs other classes of antidiabetic medications or placebo	MA Type 2 diabetics	N=10,485 Up to 52 weeks	Primary: Major cardiovascular events Secondary: Not reported	Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; *P*=0.12). Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; *P*=0.55). Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; *P*=0.20). In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular events (OR, 0.46; 95% CI, 0.25 to 0.83; *P*=0.009). In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; *P*=0.84). Secondary: Not reported
Amori et al[44]	MA (29 RCTs)	N=12,996	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	Type 2 diabetics	Duration varied (12 to 52 weeks)	Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Pinelli et al[45] GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*) vs exenatide and sitagliptin	MA, SR (5 RCTs) Adult type 2 diabetics	N=not reported Duration varied (not reported)	Primary: Change in baseline HbA_{1c}, FPG, PPG, weight , BP, and lipid profile; safety Secondary: Not reported	Primary: Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31). Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04). In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; *P*=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(treatment difference, -24 mg/dL; *P*<0.0001) and dinner (-18 mg/dL; *P*=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (*P*<0.05). Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44). In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; *P*=0.006), but results were not significant in the three other trials (*P* values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; *P*=0.02). Between-group differences were not significant in the other three trials (*P* values not reported). Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; *P* value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; *P*=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; *P*=0.05). No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were gastrointestinal-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritis in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment. Secondary: Not reported
Shyangdan et al[46] GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell function	Primary: *Change in baseline HbA_{1c}* Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; *P*=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; *P*<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; *P*=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; *P*=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; *P*<0.0001) and patients receiving insulin glargine (60 vs 48%; *P*=0.03). Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; *P*<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; *P*<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; *P* value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; *P* value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; *P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; *P*=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; *P*<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; *P*<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; *P* value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; *P* value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; *P* value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; *P*=0.27). Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; *P* value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; *P* value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; *P*=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (*P*=0.92). *Incidence of hypoglycemia* The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (*P*=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; *P*=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (*P*=0.048), and similar rates compared to DPP-4 inhibitors (*P* values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (*P*<0.00001). *Weight loss* Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; *P*<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; *P*=0.0009), and insulin glargine (-2.6 vs 1.4 kg; *P*<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; *P*=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg; 95% CI, -4.31 to -2.49; *P* value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; *P* value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; *P* value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; *P* value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; *P*=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; *P* value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; *P* value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; *P* value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Data on mortality and morbidity were not reported for any treatment. *Quality of life* Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; *P*=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; *P*=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. *Safety* Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more gastrointestinal adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. *BP* There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to -1; *P*=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (*P*=0.15) compared to placebo (*P*=0.15) and DPP-4 inhibitors (*P*=0.76). Liraglutide 1.8 mg significantly decreased SBP (*P*=0.05) compared to placebo, but not DPP-4 inhibitors (*P*=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (*P*=0.0001) and sulfonylureas (*P* value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (*P* value not reported). Data comparing liraglutide and TZDs were not reported. *FPG* There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; *P*=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; *P*=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; *P*=0.01). Liraglutide significantly decreased FPG compared to placebo (1.2 mg; *P*<0.0001 and 1.8 mg; *P*<0.00001), TZDs (*P*≤0.006), and DPP-4 inhibitors (*P*<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (*P* value not reported). *PPG* There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (*P*<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (*P*=0.004) and insulin glargine at 03000 hour (*P*=0.022) and before breakfast (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Liraglutide significantly decreased PPG compared to placebo (*P* value not reported), TZDs (*P*<0.05), and sulfonylureas (liraglutide 1.8 mg; *P*<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (*P* value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. *Lipid profile* TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (*P*<0.05) and LDL-C (*P*<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. *β cell function* Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (*P* value not reported), TZDs (*P*<0.05), and DPP-4 inhibitors (*P* value not reported); and proinsulin:insulin ratio compared to placebo (*P* value not reported), insulin glargine (*P*=0.0019), and TZDs (*P*≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Monami et al[47] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides,	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different placebo-controlled trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; *P*<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GLP-1 agonists				Secondary: Not reported

*Agent is not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, QD=once-daily, SC=subcutaneous, XL=extended-release
Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, ITT=intention-to-treat, LSM, least square mean, MC=multicenter, OE=open-ended, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, SR=systematic review, TB=triple-blind, WMD=weighted mean difference
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, IWQOL=Impact of Weight on Quality of life Questionnaire, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, PGWP=Psychological General Well-being index, PPG=post-prandial glucose, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, VLDL-C=very low density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[2-4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Exenatide	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children have not been established.	Not recommended with end-stage renal disease or severe renal dysfunction (creatinine clearance <30 mL/minute). Use with caution in patients with renal transplantation. No dosage adjustment required with moderate renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Liraglutide	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children have not been established.	Use with caution.*	Not studied with hepatic dysfunction.	C	Unknown; use with caution.

*There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease.

Adverse Drug Events

Table 6. Adverse Drug Events* (%)[2-4]

Adverse Event	Exenatide/Exenatide Extended-Release	Liraglutide
Anorexia	-	9
Asthenia	4	-
Back pain	-	5
Constipation	-/6.3 to 10.1	5.1 to 9.9
Decreased appetite	1 to 2/5	9.3
Diarrhea	1 to 13/9.3 to 20.0	7.2 to 17.1
Dizziness	1 to 9	5.2
Dyspepsia	3 to 7/5.0 to 7.4	5.2 to 6.5
Fatigue	-/5.6 to 6.1	5.1
Feeling jittery	9	-
Gastroenteritis viral	-/8.8	-
Gastroesophageal reflux disease	3/7.4	-
Headache	9/6.1 to 9.9	8.2 to 9.6
Hyperhidrosis	3	-
Hypertension	-	3
Hypoglycemia	3.8 to 35.7/0 to 20	0.1 to 27.4

Adverse Event	Exenatide/Exenatide Extended-Release	Liraglutide
Influenza	-	7.4
Injection site erythema	-/5.4 to 7.4	-
Injection site hematoma	-/5.4	-
Injection site nodule	-/6.0 to 10.5	-
Injection site pruritis	-/5.0 to 18.2	-
Nasopharyngitis	-	5.2
Nausea	8 to 44/11.3 to 27.0	7.5 to 34.6
Sinusitis	-	5.6
Upper respiratory tract infection	-	9.5
Urinary tract infection	-	6
Vomiting	4 to 13/10.8 to 11.3	6.5 to 12.4

*Corresponds to monotherapy or combination therapy with other antidiabetic therapies.
-Event not reported.

Contraindications/Precautions

Table 7. Contraindications[2-4]

Contraindication(s)	Exenatide/Exenatide Extended-Release	Liraglutide
Hypersensitivity	✔	✔
Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2	✔ (extended-release)	✔

Table 8. Warnings and Precautions[2-4]

Warning(s)/Precaution(s)	Exenatide/Exenatide Extended-Release	Liraglutide
Gastrointestinal disease; therapy has not been studied in patients with severe gastrointestinal disease, including gastroparesis, and therapy is not recommended in patients with severe gastrointestinal disease	✔	-
Hypersensitivity reactions; there have been postmarketing reports of serious hypersensitivity reactions with therapy and angioedema has also been reported with other glucagon-like peptide-1 receptor agonists	✔	✔
Immunogenicity; patients may develop antibodies to therapy following treatment	✔	-
Macrovascular outcomes; there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with therapy or any other antidiabetic drug	✔	✔
Pancreatitis; in clinical trials, cases of pancreatitis were observed	✔	✔
Renal impairment; there have been postmarketing reports of altered renal function with therapy	-	✔
Risk of thyroid C-cell tumors; therapy causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice	✔ (extended-release)	✔ *
Use of medications known to cause hypoglycemia; patients receiving therapy in combination with an insulin secretagogue or insulin may have an increased risk of hypoglycemia	✔	✔

***** Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe liraglutide only to patients for whom the potential benefits are considered to outweigh the potential risk. Luraglutide is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Black Box Warning for Bydureon® (exenatide extended-release)[3]

WARNING
Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be determined by clinical or nonclinical studies. Exenatide extended-release is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with exenatide extended-release. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Black Box Warning for Victoza® (liraglutide)[4]

WARNING
Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Drug Interactions

No clinical significant drug interactions have been reported for either exenatide or liraglutide.[2-4,54,55]

Dosing and Administration

The incretin mimetics are administered as a subcutaneous injection in the abdomen, thigh, or upper arm. Exenatide is administered twice-daily (60 minutes before meals), liraglutide is administered once-daily (independent of meals), and exenatide extended-release is administered once weekly (independent of meals).[2-4]

Table 9. Dosing and Administration[2-4]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Exenatide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Extended-release injection: initial, 2 mg SC once weekly Injection: initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy	Safety and efficacy in children have not been established.	Extended-release injection (Bydureon®): 2 mg/vial* Injection (Byetta®): 250 µg/mL†
Liraglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Safety and efficacy in children have not been established.	Injection: 6 mg/mL‡

BID=twice-daily, QD=once-daily, SC=subcutaneous

*Supplied in cartons of four single-dose trays (one vial containing 2 mg exenatide [as a white to off-white powder], one pre-filled syringe [0.65 mL diluents], one vial connector, and two custom needles).

†Supplied as a 5 µg/dose pre-filled syringe (1.2 mL, 60 doses) and 10 µg/dose pre-filled syringe (2.4 mL, 60 doses).

‡Supplied as 0.6 (30 doses), 1.2 (15 doses), and 1.8 mg (10 doses) pre-filled, multi-dose pens (3 mL) available in a package of two or three pens.

Clinical Guidelines

Current clinical guidelines are summarized in Table 10. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2013)**[48]	Current criteria for the diagnosis of diabetes • The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention/delay of type 2 diabetes • An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. • Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus. Glycemic goals in adults • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. • Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For many patients, use of insulin analogs to reduce hypoglycemic risk.

Clinical Guideline	Recommendations
	Pharmacologic and overall approaches to treatment-type 2 diabetes • At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. • In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. • Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[49]	Key points • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. Initial drug therapy • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. • Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less

Clinical Guideline	Recommendations

attractive candidates.

- Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.

Advancing to dual combination therapy

- If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required.
- On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%.
- If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
- Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
- It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
- For all medications, consideration should also be given to overall tolerability.

Advancing to triple combination therapy

- Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
- Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
- In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
- Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations

Initial Drug Monotherapy	Metformin				
Efficacy (↓HbA_{1c})	High				
Hypoglycemia	Low risk				
Weight	Neutral/loss				
Side Effects	Gastrointestinal/lactic acidosis				
If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)					
Two Drug Combin-ations	Metformin + sulfonylurea	Metformin + thia-zolidinedione (TZD)	Metformin + DPP-4 inhibitor	Metformin + GLP-1 receptor agonist	Metformin + insulin (usually basal)
Efficacy (↓HbA_{1c})	High	High	Inter-mediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Gain

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Oedema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td></td><td>TZD, DDP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[50]</td><td>
• Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.
• Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.
• It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.
</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[5]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>
• The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[24]
• Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
• Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.
• TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.
• When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.
• The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.
</td></tr>
</table>

Clinical Guideline	Recommendations
	• When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[52]	Principles underlying the algorithm • Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to

Clinical Guideline	Recommendations
	2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> • Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors.

Clinical Guideline	Recommendations
	o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides Insulin therapy algorithm • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.

Clinical Guideline	Recommendations
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[53]	Glycemic management-all patients with diabetes • Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. • Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. • Initiate self-monitoring blood glucose levels. Glycemic management-patients with type 2 diabetes • Aggressively implement all appropriate components of care at the time of diagnosis. • Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who have not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous SC insulin infusion in insulin-treated patients. • Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. • Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. • Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients.

Clinical Guideline	Recommendations
	• Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. • Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. • Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. • Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. • Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> • Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. • Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. • Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. • Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. • Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. • Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. • Individualize insulin regimens to accommodate patient exercise patterns. • Treat hypoglycemic reactions with simple carbohydrates. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> • Combining therapeutic agents with different modes of action may be advantageous. • Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated.

Clinical Guideline	Recommendations
	• Insulin is the therapy of choice in patients with advanced chronic kidney disease. • Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. • The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. • Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. • Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. • Individualize treatment regimens to accommodate patient exercise patterns. • Administer basal insulin in the evening if fasting glucose is elevated. • Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin.

Conclusions

The glucagon-like peptide-1 receptor agonists, or incretin mimetics, exenatide (Bydureon®, Byetta®) and liraglutide (Victoza®), are incretin-based antidiabetic therapies that are Food and Drug Administration-approved as adjunctive therapy to diet and exercise in adult type 2 diabetics.[2-4] These agents work in a glucose-dependent manner and maintain glucose homeostasis through several different mechanisms. Incretin mimetics enhance insulin secretion from the pancreatic β cell in the presence of elevated glucose, suppress inappropriately elevated glucagon secretion, and slow gastric emptying, all of which result in improved fasting plasma glucose.[1-4,6]

The incretin mimetics are available as subcutaneous (SC) injections to be administered in the abdomen, thigh, or upper arm. Specifically, exenatide (Byetta®) is administered twice-daily (60 minutes prior to meals), liraglutide (Victoza®) is administered once-daily (independent of meals), and exenatide extended-release (ER) (Bydureon®) is administered once weekly (independent of meals).[2-4] The ER formulation of exenatide (Bydureon®), was developed by adding the biodegradable polymer poly D, L-lactic-co-glycolic acid to exenatide. As a result, microspheres are formed and after administered, continued infiltration of water into the microspheres causes them to swell and release exenatide in a slow predictable fashion. Patients who administer exenatide ER will have a palpable SC nodule at the injection site that dissipates as the medication is released.[7] In terms, of adverse events, the most commonly reported with the incretin mimetics are gastrointestinal-related, and all of the agents are associated with risk of developing pancreatitis.[2-4] Exenatide ER and liraglutide are associated with a Boxed Warning regarding the risk for thyroid C-cell tumors.[3,4]

The incretin mimetics have been evaluated in clinical trials and have consistently demonstrated positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, body weight, and blood pressure. In general, the incretin mimetics have been evaluated as add-on therapy to treatment regimens of established antidiabetic agents. The most commonly reported adverse events associated with the incretin mimetics within clinical trials were gastrointestinal-related. Overall, there is insufficient evidence to suggest that one incretin mimetic is more efficacious than another.[8-47]

According to current clinical guidelines, metformin remains the cornerstone of most type 2 diabetes treatment regimens. Patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals, and at this time, there are no uniform recommendations regarding the best agent to be combined with metformin. Incretin mimetics are recommended as a potential second line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and

the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. The incretin mimetics may also be useful as initial therapy in patients who cannot receive metformin, and in whom weight loss is seen as an essential aspect of therapy. Among all current clinical guidelines, no one incretin mimetic is recommended or preferred over another.[48-53]

References

1. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011 Mar;96(3):737-45.
2. Byetta® [package insert]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2011 Dec.
3. Bydureon® [package insert]. San Diego (CA): Amylin Pharmaceuticals, Inc.; 2013 Feb.
4. Victoza® [package insert]. Princeton (NJ): Novo Nordisk Inc.; 2013 Apr.
5. Byetta® approved for use with insulin glargine in the U.S. [press release on the Internet]. San Diego (CA) and Indianapolis (IN): Amylin Pharmaceuticals and Eli Lilly and Co; 2011 Oct 19 [cited 2013 Aug 02]. Available from: http://phx.corporate-ir.net/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1619235.
6. Drab SR. Clinical studies of liraglutide, a novel, once-daily human glucagon-like peptide-1 analog for improved management of type 2 diabetes mellitus. Pharmacotherapy. 2009;29(12 Pt 2):S43-54.
7. Bischoff LA, Jabbour SA, Miller JL. Exenatide once weekly in type 2 diabetes mellitus. Expert Opin Pharmacother. 2011;128(8):1927-303.
8. Moretto TJ, Milton DR, Ridge TD, Macconell LA, Okerson T, Wolka AM, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2008;30(8):1448-60.
9. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1092-100.
10. Ratner RE, Maggs D, Nielson LL, Stonehouse AH, Poon T, Zhang B, et al. Long-term effects of exenatide therapy over 82 weeks on glycemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2006 Jul;8(4):419-28.
11. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005 May;28(5):1083-91.
12. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004 Nov;27(11):2628-35.
13. Riddle MC, Henry RR, Poon TH, Zhang B, Mac SM, Holcombe JH, et al. Exenatide elicits sustained glycemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulfonylureas with or without metformin. Diabetes Metab Res Rev. 2006 Nov-Dec;22:483-91.
14. Blonde L, Klein EJ, Han J, Zhang B, Mac SM, Poon TH, et al. Interim analysis of the effects of exenatide treatment on A1C, weight, and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006 Jul;8(4):436-47.
15. Buse JB, Klonoff DC, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. Clin Ther. 2007;29(1):139-53.
16. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least three years. Curr Med Res Opin. 2008 Jan;24(1):275-86.
17. Viswanathan P, Chaudhuri A, Bhatia R, Al-Atrash F, Mohanty P, Dandona P. Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. Endocr Pract. 2007;13:444-50.
18. Zinman B, Hoogwerf BJ, Duran Garcia S, Milton DR, Giaconia JM, Kim DD, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes. Ann Intern Med. 2007;146:477-85.
19. Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, Kwan AY, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011 Jan 18;154(2):103-12.
20. Rosenstock J, Shenouda SK, Bergenstal RM, Buse JB, Glass LC, Heilmann CR, et al. Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. Diabetes Care. 2012;35:955-8.

21. Okerson T, Yan P, Stonehouse A, Brodows R. Effects of exenatide on systolic blood pressure in subjects with type 2 diabetes. Am J Hypertens. 2010;23:334-9.
22. Drucker D, Buse JB, Taylor K, Kendall DM, Trautmann M, Zhuang D, et al. Exenatide once weekly vs twice daily for the treatment of type 2 diabetes: a randomized, open-label, non-inferiority study. Lancet. 2008;372:1240-50.
23. Buse JB, Drucker DJ, Taylor KL, Kim T, Walsh B, Hu H, et al. DURATION-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. Diabetes Care. 2010;33:1255-61.
24. Bergenstal RM, Wysham C, MacConell L, Malloy J, Walsh B, Yan P, et al. Efficacy and safety of exenatide once weekly vs sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomized trial. Lancet. 2010;376:431-9.
25. Wysham C, Bergenstal R, Malloy J, Yan P, Walsh B, Malone J, et al. DURATION-2: efficacy and safety of switching from maximum daily sitagliptin or pioglitazone to once-weekly exenatide. Diabet Met. 2011;28:705-14.
26. Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, et al. Once weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomized trial. Lancet. 2010;375:2234-43.
27. Diamant M, Van Gaal L, Stranks S, Guerci B, MacConell L, Haber H, et al. Safety and efficacy of once-weekly exenatide compared to insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care. 2012;35:683-9.
28. Russell-Jones D, Cuddihy RM, Hanefeld M, Kumar A, Gonzolez JG, Chan M, et al. Efficacy and safety of exenatide once weekly vs metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4). Diabetes Care. 2012;35:252-8.
29. Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared to exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:1301-10.
30. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013 Jan 12;381(9861):117-24.
31. Marre M, Shaw J, Brandle M, Bebakar WMW, Kamaruddin NA, Strand J, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared to adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med. 2009;26:268-78.
32. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IS, et al. Efficacy and safety comparison of liraglutide glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. Diabetes Care. 2009;32:84-90.
33. Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, et al. Liraglutide vs glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-weeks, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373:473-81.
34. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycemic control and weight for two years as monotherapy compared to glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011 Apr;13(4):348-56.
35. Bode BW, Testa MA, Magwire M, Hale PM, Hammer M, Blonde L, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. Diabetes Obes Metab. 2010;12:604-12.
36. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009 Jul;32(7):1224-30.
37. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomized controlled trial. Diabetologia. 2009;52:2046-55.

38. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day vs exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374:39-47.
39. Buse JB, Sesti G, Schmidt WE, Montanya E, Chang CT, Xu Y, et al. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. Diabetes Care. 2010;33:1,300-3.
40. Kaku K, Rasmussen MF, Clauson P, Seino Y. Improved glycemic control with minimal hypoglycemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 patients. Diabetes Obes Metab. 2010;12:341-7.
41. Pinelli NR, Cha R, Brown MB, Jaber LA. Addition of thiazolidinedione or exenatide to oral agents in type 2 diabetes: a meta-analysis. Ann Pharmacother. 2008;42(11):1541-51.
42. Fakhoury WKH, LeReun C, Wright D. A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretin-based medications in patients with type 2 diabetes. Pharmacology. 2010;86(1):44-57.
43. Monami M, Cremasco F, Lamanna C, Colombi C, Desideri CM, Iacomelli I, et al. Glucagon-like peptide-1 receptor agonists and cardiovascular events: a meta-analysis of randomized clinical trials. Exp Diabetes Res. 2011;2011:215764.
44. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes. JAMA. 2007;298(2):194-206.
45. Pinelli NR, Hurren KM. Efficacy and safety of long-acting glucagon-like peptide-1 receptor agonists compared to exenatide twice daily and sitagliptin in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Pharmacother. 2011;45:850-60.
46. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD006423. DOI: 10.1002/14651858.CD006423.pub2.
47. Monami M, Lamanna C, Marchionni N, Mannucci E. Comparison of different drugs as add-on treatments to metformin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008 Feb;79(2):196-203.
48. The American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2012 Jan;36(Suppl 1):S11-66.
49. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364-79.
50. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2012;156:218-31.
51. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. Endocr Pract. 2011;17:287-302.
52. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA et al. American Association of Clinical Endocrinologists Comprehensive Diabetes Management Algorithm 2013. Endocr Pract. 2013;19(2):327-36.
53. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007 May-Jun;13(Suppl 1):S1-68.
54. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Aug 02]. Available from: http://www.thomsonhc.com/.
55. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2010 [cited 2013 Aug 02]. Available from: http://online.factsandcomparisons.com.