CHAPTER 5
TABLE OF CONTENTS

CHAPTER 5.

Clinical Guideline for Pharmacological Management of Adults With Type 2 Diabetes

Om P. Ganda, MD, Chair, Clinical Oversight Committee; Alissa Segal, PharmD, CDE, CDTC; Elizabeth Blair, MS, ANP-BC, CDE, CDTC; Richard Beaser, MD; Jason Gaglia, MD; Elizabeth Halprin, MD; Robert A. Gabbay, MD, PhD, FACP; and the members of the Joslin Clinical Oversight Committee

From the Adult Diabetes and Clinical Research Sections, Joslin Diabetes Center, Harvard Medical School. ***Approved May 10, 2016; updated April 24, 2018.***

Objective: The objective of the Joslin Diabetes Center Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes is to support clinical practice, influence clinical behavior to improve outcomes, and to assure quality of care according to accepted standards. The guideline was established after careful review of current evidence, literature, and clinical practice. This guideline is reviewed periodically and modified to reflect changes in clinical practice and available pharmacological information.

This guideline is not intended to serve as a mandatory standard, but rather to provide a set of recommendations for patient care management. These recommendations are not a substitute for sound and reasonable clinical judgment or decision making and do not exclude other options. Clinical care must be individualized to the specific needs of each patient and interventions must be tailored accordingly. The guideline has been created to address initial presentations and treatment strategies in the adult nonpregnant patient population. The guideline is not a substitution for full prescribing information. Refer to Joslin's Clinical Guideline for Adults with Diabetes (Chapter 1) as well as Joslin's Guideline for the Care of Older Adults With Diabetes (Chapter 4) for additional, more comprehensive information on diabetes care and management.

5.1.0 DIABETES MELLITUS: DIAGNOSTIC CRITERIA (NONPREGNANT ADULTS)

- Random plasma glucose (PG) ≥200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) **or**
- Glycated hemoglobin (A1C) ≥6.5%[a] **or**
- Fasting plasma glucoseb ≥126 mg/dl **or**
- Results of a 2-hour 75-g oral glucose tolerance test ≥200 mg/dL at 2 hours

[a]Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes. Consider evaluation for hemoglobin variant if A1C is discordant from PG values.
[b]These tests should be confirmed by a repeat test, on a different day, unless unequivocally high.

5.2.0 GOALS OF GLYCEMIC CONTROL FOR INDIVIDUALS WITH DIABETES (TABLE 1)

TABLE 1.

Biochemical Index	Normal	Goal[1]
FPG or preprandial glucose (mg/dL)	<100	80-130
2 hours postprandial glucose (mg/dL)	<140	<180 [**2C**]
Bedtime glucose (mg/dL)	<120	90-150
A1C (%) sustained	<6%	<7% [**1A**] A1C target goal should be individualized for each patient. A goal of <7% is chosen as a practical level for most patients to reduce the risk of complications. Achieving normal blood glucose and A1C is recommended, if it can be done practically and safely. Less stringent goals may be considered for older adults or those with advanced comorbidities (see Joslin's Guideline for Older Adults With Diabetes, Chapter 4).

See notes to table on SP259
A1C indicates glycated hemoglobin; FPG, fasting plasma glucose. mg/dL

5.3.0 INITIAL TREATMENT STRATEGY (FIGURE)

5.3.1 Advancing antidiabetes medications:

TABLE 2. Considerations for Selecting Noninsulin Glucose-Lowering Medications

Start With Metformin Unless Contraindicated [1B]

Action: Decreases hepatic glucose production, increases GLP-1 secretion. Use as initial therapy unless contraindicated.
Adverse effects: Gas, diarrhea, lactic acidosis; B-12 deficiency (long-term). Initiate at low dose, increase dose slowly and take with food to decrease gas, diarrhea. Extended release formulation may decrease gastrointestinal symptoms.
Dosing:

- Metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Starting metformin in patients with an eGFR <45 mL/min is not recommended.
- Obtain eGFR at least annually in all patients taking metformin. In patients at increased risk for renal impairment, such as the elderly, assess renal function more frequently.
- If eGFR later falls below 45 mL/min, assess benefits and risks of continuing treatment. Discontinue metformin if eGFR later falls below 30 mL/min.
- Discontinue metformin at time of or before an iodinated contrast imaging procedure if eGFR is 30-60 mL/min; in patients with a history of liver disease, alcoholism, or heart failure; or who will undergo intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is back to baseline level.

table continued SP256

5.4.0 CONSIDERATIONS FOR SELECTING NONINSULIN GLUCOSE-LOWERING MEDICATIONS

5.4.1 First-line add-on to metformin or use as monotherapy if metformin is contraindicated: *see table SP256*

5.5.0 PREFERRED CONSIDERATIONS IN PATIENTS WITH T2D AND ESTABLISHED CARDIOVASCULAR DISEASE

TABLE 3. Preferred Considerations in Patients With T2D and Established Cardiovascular Disease

Clinical Setting	History of ASCVD	History of HF
Consider drugs with CV safety and superiority	GLP-1 RA with evidence to reduce CVD events (eg, liraglutide **[1B],** semaglutide)	SGLT2 inhibitors with evidence to reduce HF and mortality, (eg, empagliflozin **[1B],** canagliflozin)
Other considerations and caveats	Avoid use with advancing CKD Recent data indicate a small increase in biliary disease and need for cholecystectomy Increased risk of retinopathy progression with semaglutide	Avoid use perioperatively and/or in the presence of risk factors for DKA (eg, LADA, dehydration, infection, major trauma) Avoid use with advancing CKD Distal lower limb amputations increased with canagliflozin

ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; LADA, latent autoimmune diabetes of adults; T2D, type 2 diabetes.
Notes:
In several recent trials in patients with CVD, DPP-4 inhibitors were found to be safe (noninferior to) but also nonsuperior to other antihyperglycemic drugs from CV point of view; a secondary outcome, heart failure, was significantly increased with saxagliptin. In clinical trials, liraglutide and empagliflozin reduced CV mortality. [**1B**]

See **Table 2** for additional details on various classes of noninsulin drugs.

5.6.0 ORAL GLUCOSE-LOWERING MEDICATIONS (TABLE 4)

5.6.1 Examples of fixed-dose medications (TABLE 4):

5.7.0 INJECTABLE ANTIDIABETES MEDICATIONS (INCRETIN MIMETICS AND NONINSULIN ANALOGUES) (TABLE 5)

5.8.0 INSULIN PRODUCTS (TABLE 6)

5.8.1 Premixed insulin combinations:

TABLE 7. Premixed Insulin Combinations

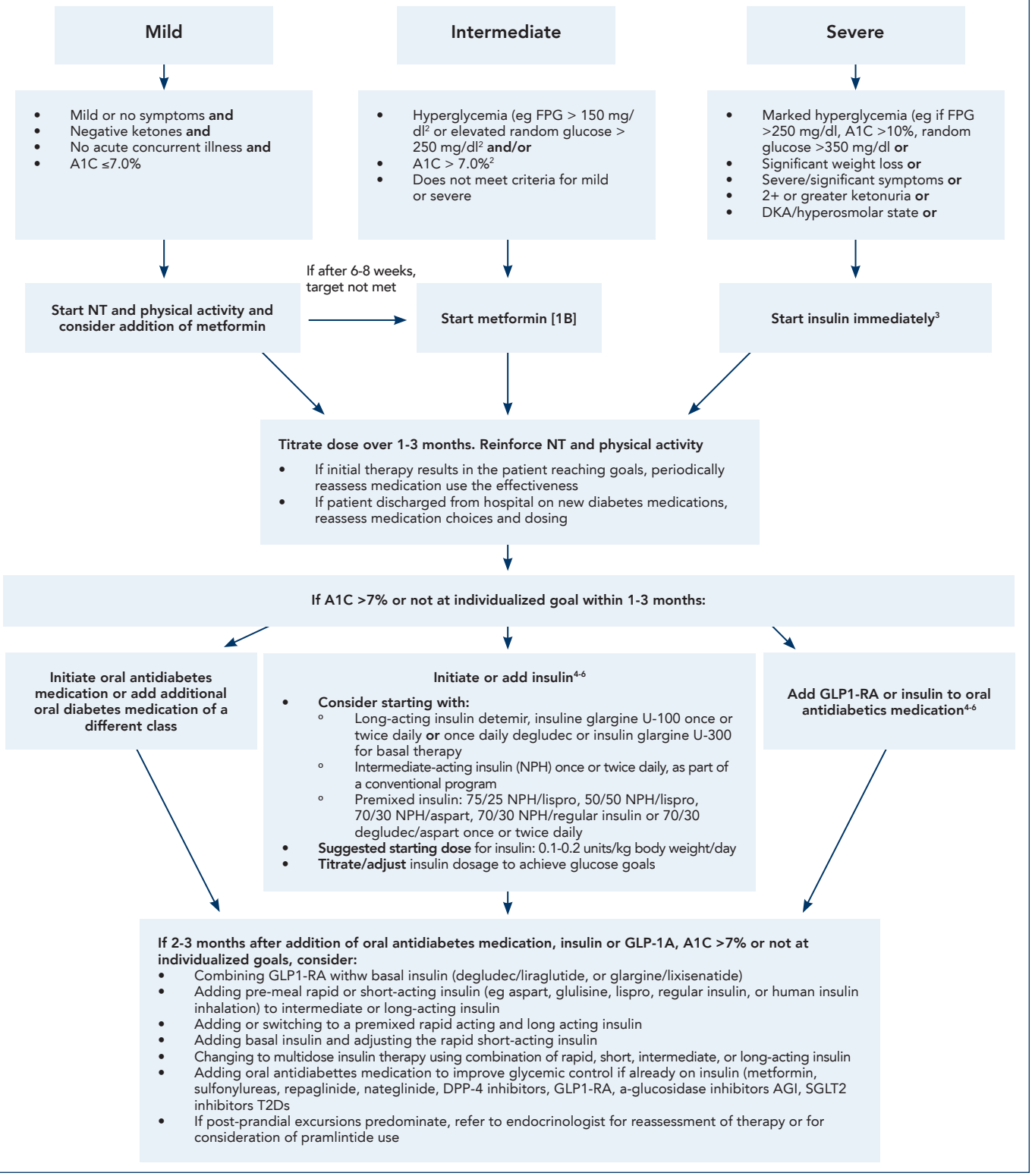
Insulin Type	Product
70% NPH, 30% regular	Humulin 70/30
70% NPH, 30% regular	Novolin 70/30
50% lispro protamine suspension, 50% lispro	Humalog Mix 50/50
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25
70% aspart protamine suspension, 30% aspart	Novolog Mix 70/30
70% degludec, 30% insulin aspart	Ryzodeg 70/30 (approved by FDA, but not yet available)

NPH indicates neutral protamine Hagedorn.

FIGURE 1. Advancing Antidiabetes Medication Therapy

Nutrition therapy (NT), physical activity, blood glucose monitoring and patient education are the cornerstones of diabetes management for all patients. Pharmacological management should be used in combination with nutrition therapy and physical activity. Current weight status and lifestyle should be considered when choosing initial pharmacological therapy.

Initial Presentation (Based on characteristics listed within each box) —



A1C indicates glycated hemoglobin; AGI, α-glucosidase inhibitor; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; SGLT2, sodium glucose co-transporter-2; TZDs, thiazolidinediones. See notes to table on SP259.

TABLE 2 (cont.). Considerations for Selecting Noninsulin Glucose-Lowering Medications

First-Line Add-On To Metformin Or Use As Monotherapy If Metformin Is Contraindicated

Insulin Secretagogues (sulfonylurea, repaglinide, nateglinide)

Action: Stimulates beta cell insulin secretion.

Adverse effects: Potential for hypoglycemia.

Contraindications: Sulfonylurea use is contraindicated in severe liver or renal disease.

Notes: Metabolites of glipizide are less active than other sulfonylureas. Consider the use of short-acting sulfonylureas, such as glipizide or glimepiride, in setting of renal disease.

Glyburide is not preferred due to the increased risk of hypoglycemia.

Repaglinide or nateglinide may be useful for those with postprandial hyperglycemia or with hypoglycemia on a sulfonylurea.

DPP-4 Inhibitors

Action: In a glucose-dependent manner, slows inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels.

Adverse effects: UTI-like symptoms.

Notes: Reduce dose in renal disease with all members of the class except linagliptin.

- Postmarketing reports of hepatic failure with alogliptin.

- Clinical trials reported no adverse CV outcomes, except increased secondary outcome of heart failure with saxagliptin.

-It is unknown if DPP-4 inhibitors increase the risk for pancreatitis.[10]

GLP-1 RAs

Action: In a glucose-dependent manner, increases insulin secretion, decreases glucagon secretion, slows gastric emptying, and increases satiety.

Adverse effects: Nausea, diarrhea, renal impairment if low eGFR.

Contraindications: Gastroparesis requiring treatment with metoclopramide.

Personal or family history of medullary thyroid cancer or patients with MEN2.

Notes: Use may be associated with weight loss. To avoid hypoglycemia when using a GLP-1 RA with a sulfonylurea or insulin, consider initially decreasing sulfonylurea or insulin dose.

- Increased risk of biliary disease and gallstones.

- Liraglutide reduced major CV events in 2 large clinical trials in patients with CVD or high risk of CVD.

- It is unknown if GLP-1 RAs increase the risk for pancreatitis.[10]

SGLT2 Inhibitors[11]

Action: Blocks reabsorption of glucose by the kidney, thereby increasing excretion of glucose in the urine.

Adverse effects: Hypotension, genital mycotic infections, UTI, dehydration, hyperkalemia, increased LDL cholesterol, ketoacidosis in the absence of severe hyperglycemia.[11]

Contraindications: Do not use in moderate to severe renal disease as it may worsen renal function.[12]

Notes: Use may be associated with modest decreases in BP and in weight.

Adjust dose in mild renal disease.

Mechanism of action results in positive test for urine glucose.

- Dapagliflozin is contraindicated in setting of bladder cancer; use with caution if there is a history of bladder cancer.

- A small increase in fracture rate has been reported with canagliflozin and dapagliflozin.

- Cases of acute kidney injury have been reported with canagliflozin and dapagliflozin. Promptly discontinue these drugs if this occurs and treat the renal impairment.

- Empagliflozin and canagliflozin reduced major CV events and heart failure in clinical trials, in those with preexisting CVD as well as risk of renal disease progression (**see Table 3**).

AGIs

Action: Delays absorption and breakdown of carbohydrates.

Adverse effects: Gas, diarrhea.

Contraindications: Chronic intestinal disorders, acarbose in cirrhosis, acarbose and miglitol in renal impairment (creatinine >2.0).

Notes: Use if postprandial hyperglycemia predominates.

Ideally use pure glucose to treat hypoglycemia when used in combination therapy as the drug decreases absorption of other forms of carbohydrate.

Initiate at low dose and increase slowly to decrease flatulence.

TZDs[7-9]

Action: Improves glucose transport and decreases hepatic glucose production.

Adverse effects: Weight gain, fluid retention.

Contraindications: Liver disease, severe LV dysfunction at risk for CHF.

Do not use pioglitazone in setting of bladder cancer (**see footnotes**)

Notes: Full effect of initiation or titration of therapy may take 2-4 weeks.

May increase risk for macular edema.

Increases bone loss and risk for bone fracture.

Can be used in renal impairment but may increase fluid retention.

A recent trial with pioglitazone showed reduced CVD events in nondiabetic patients with insulin resistance.

Other Therapy

Bile Acid Sequestrant (colesevelam)

- Mechanism of action re: glucose lowering is unclear
- Modest effect on A1C. Also lowers LDL-C.

Note: Reduces gastric absorption of some drugs. If known interaction or unknown interaction with narrow therapeutic index drug, administer 1 hour prior or 4 hours after colesevelam.

Contraindications:

- Bowel obstruction
- Serum triglycerides >500mg/dl
- History of hypertriglyceridemia-induced pancreatitis

Centrally Acting Agent (bromocriptine mesylate)

- Mechanism of action re: glucose lowering is unclear
- Most effective when used in combination with other antidiabetes medications
- Modest effect on A1C

Contraindications:

- Should not be taken by patients who are nursing mothers, take ergot medicines, or have syncopal migraines

Source: American Diabetes Association

A1C indicates glycated hemoglobin; AGI, α-glucosidase inhibitor; BP, blood pressure; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; MEN2, multiple endocrine neoplasia type 2; SGLT2, sodium glucose co-transporter 2; UTI, urinary tract infection, TZD, thiazolidinedione.

See notes to tables on SP259.

TABLE 4. Oral Glucose-Lowering Medications

Biguanides	Insulin Secretagogues	DPP-4 Inhibitors	SGLT2 Inhibitors	AGIs	TZDs[9]
• liquid metformin* (Riomet) • metformin (Glucophage) • metformin extended release (Glucophage XR, Fortamet, Glumetza) Glucophage, Glucophage XR, and Fortamet are available as generic medications *Liquid metformin formulation can be used for patients unable to swallow large tablets and/or who are post gastric bypass.	**Sulfonylureas** • glimepiride (Amaryl) • glipizide (Glucotrol) • glipizide extended • release (Glucotrol XL) • glyburide (Micronase, Diabeta) • micronized glyburide • (Glynase) *Glimepiride, glipizide, and glyburide are available as generic medications. **Meglitinides** • repaglinide (Prandin) **D-phenylalanine Derivatives** • nateglinide (Starlix) *Repaglinide and nataglinide are available as generic medications.	• sitagliptin (Januvia) • saxagliptin (Onglyza) • linagliptin (Tradjenta) • alogliptin (Nesina) • vildagliptin (Galvus; not available in the United States)	• canagliflozin (Invokana) • dapagliflozin (Farxiga) • empagliflozin (Jardiance) • ertugliflozin (Steglatro)	• acarbose (Precose) • miglitol (Glyset) *Acarbose is available as a generic medication.	• pioglitazone (Actos) • rosiglitazone (Avandia) *Pioglitazone and rosiglitazone are available as generic medications.

Examples of fixed-dose combination medications in the United States

- metformin and glipizide (Metaglip)
- metformin and glyburide (Glucovance)
- sitagliptin and metformin (Janumet)
- sitagliptin and metformin ER (Janumet XR)
- saxagliptin and metformin ER (Kombiglyze XR)
- alogliptin and metformin (Kazano)
- linagliptin and metformin (Jentadueto)
- linagliptin and metformin ER (Jentadueto XR)
- alogliptin and pioglitazone (Oseni)
- dapagliflozin and metformin (Xigduo)
- empagliflozin and metformin (Synjardy)
- empagliflozin and linagliptin (Glyxambi))
- dapagliflozin and saxagliptin (Qtern)
- canagliflozin and metformin (Invokamet)
- ertugliflozin and metformin (Stegluromet)
- ertugliflozin and sitagliptin (Steglujan)

Others

Bile Acid Sequestrants
- colesevelam (Welchol) ; cholestyramine (Questran)

Centrally Acting
- bromocriptine (Cycloset)

AGI indicates a-glucosidase Inhibitor; DPP-4, dipeptidyl peptidase-4; ER, extended release; SGLT2, sodium-glucose co-transporter 2; TZDs, thiazolidinediones.
See notes to tables on SP259.

TABLE 5. Injectable Noninsulin Antidiabetes Medications Available in the United States

Incretin Mimetics And Synthetic Analogues			
Product	**Mechanism of Action**	**Diabetes Type**	**Injection Frequency**
exenatide (Byetta)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	2/day
lixisenatide (Adlyxin)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with short-acting insulins	2	1/day
liraglutide (Victoza)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/day
extended release exenatide (Bydureon)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Not approved for use with insulin	2	1/week
dulaglutide (Trulicity)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/week
semaglutide (Ozempic)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1/week
pramlintide (Symlin)	Synthetic analogue of human amylin, a naturally occurring hormone made in the beta cells, which slows gastric emptying, suppresses glucagon secretion, and regulates food intake. A significant reduction in insulin dose may be required when insulin is used in conjunction with pramlintide	1 and 2	1-4/day (with meals)

TABLE 6. Insulin Pharmacodynamics

Insulin Type/Generic	Brand Name	Onset	Peak	Duration
Ultra–Rapid-Acting				
Faster insulin aspart	Fiasp	10-20 minutes	30 minutes-2 hours	3-5 hours
Insulin human inhalation	Afrezza	12-30 minutes	30-90 minutes	3 hours
Rapid Acting				
Insulin aspart	Novolog	15-30 minutes	30 minutes-3 hours	3-5 hours
Insulin glulisine	Apidra			
Insulin lispro U-100 Insulin lispro U-200	Humalog/Admelog Humalog			
Short-Acting				
Insulin human regular	Humulin/Novolin R	30-60 minutes	2-5 hours	up to 12 hours
Insulin human regular concentrated	Humulin R U-500	30-60 minutes	2-5 hours	6.5-10 hours
Intermediate-Acting				
Human NPH (neutral protamine Hagedorn) insulin	Humulin/Novolin N	90 minutes-4 hours	4-12 hours	up to 24 hours
Long-Acting				
Insulin detemir	Levemir	45 minutes-4 hours	Minimal peak (depending on dose)	up to 22 hours
Insulin glargine	Lantus/Basaglar			
Insulin glargine U-300	Toujeo	6 hours		>24 hours
Insulin degludec U-100 or U-200	Tresiba	1 hour		>42 hours

Notes for Figure and Tables

1. Goals should be individualized based on factors that include the following: comorbidities, age, duration of diabetes, hypoglycemic awareness.
2. If diet history reveals markedly excessive carbohydrate intake, consider initial trial of nutrition therapy and physical activity before initiating oral antidiabetes medications, even if glucose levels are above the thresholds listed.
3. Some patients with T2D initially stabilized on insulin may be considered for transition to noninsulin antidiabetes medications as blood glucose control permits.
4. May need to taper and discontinue some or all oral antidiabetes medications as insulin is initiated and adjusted, particularly if using short- or rapid-acting and basal insulins.
5. Pre- *and* postprandial blood glucose should be checked. Frequency of checking may vary; it can be 1 to 4 times/day depending on individual patient and status of glycemic control.
6. There is an increased risk for edema when insulin and a thiazolidinedione are used together. Rosiglitazone should not be used in combination with insulin.
7. FDA requirements for LFT monitoring for thiazolidinediones (TZDs): If initial alanine aminotransferase (ALT) is >2.5 times normal, do not start this medication. If ALT is >2.5 times normal during treatment, check weekly. If rise persists or becomes >3 times normal, discontinue TZD.
8. Thiazolidinediones cause or exacerbate congestive heart failure in some patients. After initiation of TZDs and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive or rapid weight gain; dyspnea; and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of the TZD must be considered. TZDs are not recommended in patients with symptomatic heart failure or in patients with established NYHA Class III or IV heart failure.

9a. On September 23, 2010, the FDA announced regulatory actions with respect to products containing rosiglitazone: Avandia (rosiglitazone maleate) tablets, Avandamet (rosiglitazone maleate and metformin hydrochloride) tablets, and Avandaryl (rosiglitazone maleate and glimepiride) tablets. These FDA actions required GlaxoSmithKline to implement restrictions on the use of these products through a Risk Evaluation and Mitigation Strategy (REMS) program to assure their safe use and through additional safety labeling changes in response to the agency's review of data that suggested an elevated risk of cardiovascular events. However, based on additional data review, the REMS program was removed as of December 16, 2015. Rosiglitazone now has the same indications for prescribing as pioglitazone.

9b. According to the FDA advisory issued on June 15, 2011, regarding potential increased risk of bladder cancer with pioglitazone use: (1) Do not use pioglitazone in patients with active bladder cancer. (2) Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

10. Risks of acute pancreatitis or pancreatic cancer have not been confirmed in clinical trials. The FDA is currently monitoring clinical reports via the Adverse Event Reporting System
11. Diabetic ketoacidosis (DKA) with SGLT-2 inhibitors: Rare but sometimes serious cases have been reported. Check for DKA if symptoms develop, even if glucose levels are not elevated
12. The potential benefits of SGLT-2 inhibitors in preventing progression of early renal disease are being investigated.

REFERENCES

Diagnosis

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2011;34(suppl 1):S62-S69. doi: 10.2337/dc11-S062**.**
2. Nathan DM, Kuenen J, Borg R, Zheung H, Schoenfield D, Heine RJ; A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. *Diabetes Care.* 2008;31(8):1473-1478. doi: 10.2337/dc08-0545.

Goals Of Glycemic Control And Pharmacotherapy

3. American Diabetes Association. 8. Pharmacological approaches to glycemic treatment: *Standards of Medical Care in Diabetes–2018. Diabetes Care.* 2018;41(suppl 1):S73-S85. doi: 10.2337/dc18-S008.
4. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. *Ann Intern Med.* 2018;168(8):569-576. doi: 10.7326/M17-0939.
5. Beaser RS, Staff of Joslin Diabetes Center. *Joslin's Diabetes Deskbook: A Guide for Primary Care Providers.* 3rd ed. Boston, MA: Joslin Diabetes Center; 2014.
6. Massachusetts Department of Public Health's Diabetes Prevention and Control Program. Massachusetts guidelines for adult diabetes care. Boston, MA: Massachusetts Department of Public Health; 2011.
7. 7. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2018 executive summary. *Endocr Pract.* 2018;24(1):91-120.

Antihyperglycemic Therapy (Reviews)

8. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA.* 2002;287(3):360-372.
9. Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs.* 2005;65(3):385-411.
10. DeFronzo RA, Eldor RE, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care.* 2013;36(suppl 2):S127-S138. doi: 10.2337/dcS13-2011**.**
11. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy [published correction appears in *N Engl J Med.* 2007;356(13):1387-1388]. *N Engl J Med.* 2006;355(23):2427-2443. doi: 10.1056/NEJMoa066224.
12. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for the Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes mellitus: 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;32(1):193-203. doi: 10.2337/dc08-9025.
13. Currie CC, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab.* 2013;98(2):668-677. doi: 10.1210/jc.2012-3042.
14. Garvey WT. Use of available glucose-lowering agents in patients with different levels of renal impairment. *Endocr Pract.* 2013;19(suppl 1):14-18. doi: 10.4158/EP12362.OR.
15. Berkowitz SA, Krumme AA, Avorn J, et al. Initial choice of oral glucose-lowering medication for diabetes mellitus: a patient-centered comparative effectiveness study. *JAMA Intern Med.* 2014;174(12):1955-1962. doi: 10.1001/jamainternmed.2014.5294.
16. Bailey CJ. Interpreting adverse signals in diabetes drug development programs. *Diabetes Care.* 2013;36(7):2098-2106. doi: 10.2337/dc13-0182.
17. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med.* 2016;164(11):740-751. doi: 10.7326/M15-2650.

Metformin

18. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach: the COSMIC Approach Study. *Diabetes Care.* 2005;28(3):539-543.
19. Grant PJ. The effects of high- and medium-dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. *Diabetes Care.* 1996;19(1):64-66.
20. Inzucchi SE. Metformin and heart failure: innocent until proven guilty. *Diabetes Care.* 2005;28(10):2585-2587. doi: 10.2337/diacare.28.10.2585.
21. Johansen K. Efficacy of metformin in the treatment of NIDDM. meta-analysis. *Diabetes Care.* 1999;22(1):33-37.
22. Eppenga WL, Lalmohamed A, Geerts AF, et al. Risk of lactic acidosis or elevated lactate concentrations in metformin users with renal impairment: a population-based cohort study. *Diabetes Care.* 2014;37(8):2218-2224. doi: 10.2337/dc13-3023.
23. UK Prospective Diabetes Study (UKPDS 34) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet.* 1998;352(9139):1558]. *Lancet.* 1998;352(9131):854-865.

24. Salpeter SR, Greyber E, Pasternak GA, Salpeter Posthumous EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus [update in *Cochrane Database Syst Rev.* 2010;(4):CD002967]. *Cochrane Database Syst Rev.* 2010;(1):CD002967. doi: 10.1002/14651858.CD002967.pub3.
25. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA.* 2010;303(14):1410-1418. doi: 10.1001/jama.2010.405.
26. Stevens RJ, Ali R, Bankhead CR, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomized clinical trials. *Diabetologia.* 2012;55(10):2593-2603. doi: 10.1007/s00125-012-2653-7.
27. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA.* 2014;312(24):2668-2675. doi: 10.1001/jama.2014.15298.

Thiazolidinediones

28. Charbonnel B, Roden M, Urquhart R, et al. Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with gliclazide-based regimens. *Diabetologia.* 2005;48(3):553-560. doi: 10.1007/s00125-004-1651-9.
29. Davidson JA, Perez A, Zhang J; the Pioglitazone 343 Study Group. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. *Diabetes Obes Metab.* 2006;8(2):164-174.
30. Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA.* 2006;296(21):2572-2581.
31. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med.* 2004;351(11):1106-1118.
32. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med.* 2007;357(1):100]. *N Engl J Med.* 2007;356(24):2457-2471. doi: 10.1056/NEJMoa072761.
33. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366(9493):1279-1289.
34. Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet.* 2009;373(9493):2125-2135. doi: 10.1016/S0140-6736(09)60953-3.
35. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care.* 2011;34(6):1369-1371. doi: 10.2337/dc10-2412.
36. FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines. FDA website. fda.gov/downloads/drugs/drugsafety/ucm477575.pdf. Updated December 16, 2015. Accessed December 16, 2015.
37. Lewis JD, Habel LA, Quesenberry CP, et al. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA.* 2015;314(3):265-277. doi: 10.1001/jama.2015.7996.

Insulin Secretagogues

38. Bailey CJ, Day C. Antidiabetic drugs. *Br J Cardiol.* 2003;10:128-136.
39. Del Prato S, Heine RJ, Keilson L, Guitard C, Shen SG, Emmons RP. Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care.* 2003;26(7):2075-2080.
40. Dornhorst M. Insulotropic meglitinide analogues. *Lancet.* 2001;358(9294):1709-1715.
41. Hazama Y, Matsuhisa M, Ohtoshi K, et al. Beneficial effects of nateglinide on insulin resistance in type 2 diabetes. *Diabetes Res Clin Pract.* 2006;71(3):251-255. doi: 10. 1016/j.diabres.2005.08.004.
42. Plosker Gl, Figgitt DP. Repaglinide: a pharmacoeconomic review of its use in type 2 diabetes mellitus. *Pharmacoeconomics.* 2004;22(6):389-411.

Alpha-Glucosidase Inhibitors

43. Balfour JA, McTavish D. Acarbose. an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs.* 1993;46(6):1025-1054.
44. Carlson RF. Miglitol and hepatotoxicity in type 2 diabetes mellitus. *Am Fam Physician.* 2000;62(2):315-318.
45. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J.* 2004:25(1):10-16. doi: 10.1016/S0195-668X(03)00468-8.
46. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005;(2):CD003639. doi: 10.1002/14651858.CD003639.pub2.

GLP-1 Receptor Agonists

47. 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;28(5):1092-1100. doi: 10.2337/diacare.28.5.1092.
48. 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;27(11):2628-2635. doi: 10.2337/diacare.27.11.2628.
49. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med.* 2005;143(8)559-569. doi: 10.7326/0003-4819-143-8-200510180-00006.
50. Iltz JL, Baker DE, Setter SM, Keith Campbell R. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus. *Clin Ther.* 2006;28(5):652-665. doi: 10.1016/j.clinthera.2006.05.006.
51. Kendall DM, Riddle MC, Rosenstock J, 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;28(5):1083-1091.
52. Russell-Jones D, Vaag A, Schmitz O, et al; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia.* 2009;52(10):2046-2055. doi: 10.1007/s00125-009-1472-y.
53. Garber A, Henry R, Ratner R, et al; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet.* 2009;373(9662):473-481. doi: 10.1016/S0140-6736(08)61246-5.
54. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ.* 2012;344:d7771. doi: 10.1136/bmj.d7771.
55. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2011;96(5):1301-1310. doi: 10.1210/jc.2010-2081.
56. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in

patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381(9861):117-124. doi: 10.1016/S0140-6736(12)61267-7.

57. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. *Lancet*. 2010;375(9733):2234-2243. doi: 10.1016/S0140-6736(10)60406-0.
58. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384(9961):2228-2234. doi: 10.1016/S0140-6736(14)61335-0.
59. Abdul-Ghani MA, Puckett C, Triplitt C, et al. Initial combination therapy with metformin, pioglitazone, and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial. *Diabetes Obes Metab*. 2015;17(3):268-275. doi: 10.1111/dom.12417.
60. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med*. 2014;370(9):794-797. doi: 10.1056/NEJMp1314078.

DPP-4 Inhibitors

61. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2008;93(10):3703-3716. doi: 10.1210/jc.2007-2109.
62. Miller S, St Onge EL. Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Ann Pharmacother*. 2006;40(7-8):1336-1343.
63. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE; Sitagliptin 036 Study Group. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2007;30(8):1979-1987. doi: 10.2337/dc07-0627.
64. DeFronzo RA, Hissa MN, Garber AJ, et al; Saxagliptin 014 Study Group. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care*. 2009;32(9):1649-1655. doi: 10.2337/dc08-1984.
65. Scott LJ. Linagliptin: in type 2 diabetes mellitus. *Drugs*. 2011;71(5):611-624. doi: 10.2165/11207400-000000000-00000.
66. Gibbs JP, Fredrickson J, Barbee T, et al. Quantitative model of the relationship between dipeptidyl peptidase-4 (DPP-4) inhibition and response: meta-analysis of alogliptin, saxagliptin, sitagliptin, and vildagliptin efficacy results. *J Clin Pharmacol*. 2012;52(10):1494-1505. doi: 10.1177/0091270011420153.
67. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. *Diabetes Metab*. 2012;38(2):89-101. doi: 10.1016/j.diabet.2011.11.001.
68. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med*. 2014;370(9):794-797. doi: 10.1056/NEJMp1314078.
69. Filion KB, Azoulay L, Platt RW, et al; CNODES Investigators. A multicenter observational study of incretin-based drugs and heart failure. *N Engl J Med*. 2016;*374(12):1145-1154*. doi: 10.1056/NEJMoa1506115.
70. Sodium glucose co-transporter 2 inhibitors
71. Clar C, Gill JA, Court R, Waugh N. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. *BMJ Open*. 2012;2(5). pii: e001007. doi: 10.1136/bmjopen-2012-001007.
72. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382. doi: 10.1111/dom.12054.
73. Rosenstock J, Aggarwal N, Polidori D, et al; Canagliflozin DIA 2001 Study Group. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care*. 2012;35(6):1232-1238. doi: 10.2337/dc11-1926.
74. Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapaglifozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2014;37(3):740-750. doi: 10.2337/dc13-0467.
75. Zhang M, Zhang L, Wu B, Song H, An Z, Li S. Dapaglifozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Metab Res Rev*. 2014;30(3):204-221. doi: 10.1002/dmrr.2479.
76. Sun YN, Zhou Y, Chen X, Che WS, Leung SW. The efficacy of dapaglifozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *BMJ Open*. 2014;4(4):e004619. doi: 10.1136/bmjopen-2013-004619.
77. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU Trial Investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial [published correction appears in *Lancet Diabetes Endocrinol*. 2015;3(9):e7]. *Lancet Diabetes Endocrinol*. 2014;2(9):691-700. doi: 10.1016/S2213-8587(14)70120-2.
78. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medications canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). FDA website. www.fda.gov/Drugs/DrugSafety/ucm505860.htm. Updated June 17, 2016.
79. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrin Metab*. 2016;101(1):157-166. doi: 10.1210/jc.2015-3167.
80. Recent cardiovascular clinical trials with Incretin-based agents and SGLT-2 inhibitors
81. White WB, Cannon CP, Heller SR, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335. doi: 10.1056/NEJMoa1305889.
82. Scirica BM, Bhatt DL, Braunwald E, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326. doi: 10.1056/NEJMoa1307684.
83. Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232-242. doi: 10.1056/NEJMoa1501352.
84. Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi: 10.1056/NEJMoa1509225.
85. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720.
86. Marso P, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322. doi: 10.1056/NEJMoa1603827.
87. Wanner C, Inzucci SE, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. doi: 10.1056/NEJMoa1515920.
88. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 agonists, and dipeptidyl peptidase-4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319(15):1580-1591. doi: 10.1001/jama.2018.3024.
89. Kernan WN, Viscoli CM, Furie KL, et al; IRIS Trial Investigators. Pioglitazone after

ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374(14):1321-1331. doi: 10.1056/NEJMoa1506930.

Bile Acid Sequestrants

90. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch Intern Med*. 2008;168(18):1975-1983. doi: 10.1001/archinte.168.18.1975.
91. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care*. 2008;31(8):1479-1484. doi: 10.2337/dc08-0283.
92. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med*. 2008;168(14):1531-1540. doi: 10.1001/archinte.168.14.1531.
93. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab*. 2010;12(5):384-392. doi: 10.1111/j.1463-1326.2009.01181.x.

Combination Therapy With Insulin

94. Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled insulin-treated type 2 diabetes mellitus. a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1999;131(3):182-188.
95. Belcher G, Lambert C, Goh KL, Edwards G, Valbuena M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. *Int J Clin Pract*. 2004;58(9):833-837.
96. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database Sys Rev*. 2004;(4):CD003418.
97. Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diabetes Obes Metab*. 2003;5(3):163-170.
98. Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*. 2005;27(10):1535-1547.
99. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. *Diabetes Care*. 2006;29(3):554-559. doi: 10.2337/diacare.29.03.06.dc05-0695**.**
100. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006;49(3):442-451.
101. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin–treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med*. 2011;154(2):103-112. doi: 10.7326/0003-4819-154-2-201101180-00300.

Insulin

102. Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. *Clin Ther*. 2005;27(suppl B):S75-S88.
103. Hirsch IB, Bergenstal RM, Parkin CG, Wright E, Buse JB. A real-world approach to insulin therapy in primary care practice. *Clin Diabetes*. 2005;23(2):78-86. doi: 10.2337/diaclin.23.2.78.
104. Kennedy L, Herman WH, Strange P, Harris A; GOAL A1C Team. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Points of Care (GOAL A1C) Trial. *Diabetes Care*. 2006;29(1):1-8. doi: 10.2337/diacare.29.01.06.dc05-1058**.**
105. Riddle MC. The Treat-to-Target trial and related studies. *Endocr Pract*. 2006;12(suppl 1):71-79. doi: 10.4158/EP.12.S1.71.
106. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev*. 2006;(2):CD003287.
107. Valensi P, Cosson E. Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects? *Diabetes Metab*. 2005;31(4 Pt 2):4S34-4S39.
108. Davidson MB, Raskin P, Tanenberg RJ, Vlajnic A, Hollander P. A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. *Endocr Pract*. 2011;17(3):395-403. doi: 10.4158/EP10323.OR.
109. Rossetti P, Ampudia-Blasco FJ, Ascaso JF. Old and new basal insulin formulations: understanding pharmacodynamics is still relevant in clinical practice. *Diabetes Obes Metab*. 2014;16(8):695-706. doi: 10.1111/dom.12256.
110. de la Peña A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. *Diabetes Care*. 2011;34(12):2496-2501. doi: 10.2337/dc11-0721.
111. Segal AR, Vootla T, Beaser RS. Insulin: making sense of current options. *Endocrinol Metab Clin North Am*. 2016;45(4):845-874. doi: 10.1016/j.ecl.2016.06.009.

Inhaled Insulin

112. Pittas AG, Westcott GP, Balk EM. Efficacy, safety, and patient acceptability of Technosphere inhaled insulin for people with diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(11):886-894. doi: 10.1016/S2213-8587(15)00280-6.
113. Leahy JL. Technosphere inhaled insulin: is faster better? *Diabetes Care*. 2015;38(12):2282-2284. doi: 10.2337/dci15-0002.

Pramlintide

114. Hollander P, Ratner R, Fineman M, et al. Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab*. 2003;5(6):408-414. doi: 10.1046/j.1463-1326.2003.00295.x.
115. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care*. 2003;26(3):784-790. doi: 10.2337/diacare.26.3.784.
116. Weyer C, Gottlieb A, Kim DD, et al. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. *Diabetes Care*. 2003;26(11):3074-3079. doi: 10.2337/diacare.26.11.3074**.**
117. Whitehouse F, Kruger DF, Fineman M, et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care*. 2002;25(4):724-730. doi: 10.2337/diacare.25.4.724**.**

Bromocriptine

118. Holt RI, Barnett AH, Bailey CJ. Bromocriptine: old drug, new formulation and new indication. *Diabetes Obes Metab*. 2010;12(12):1048-1057. doi: 10.1111/j.1463-1326.2010.01304.x.
119. DeFronzo R. Bromocriptine: a sympatholytic, d2-dopamine agonist for the treatment of type 2 diabetes. *Diabetes Care*. 2011:34(4):789-794. doi: 10.2337/dc11-0064.
120. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care*. 2010;33(7):1503-1508. doi: 10.2337/dc09-2009.
121. Scranton R, Cincotta A. Bromocriptine—unique formulation of a dopamine agonist for the treatment of type 2 diabetes. *Expert Opin Pharmacother*. 2010;11(2):269-279. doi: 10.1517/14656560903501544.