Joslin Diabetes Center's
Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes
From the Adult Diabetes and Clinical Research Sections, Joslin Diabetes Center. Approved February 13th, 2020

The objectives of the *Joslin Diabetes Center Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes* are to support and influence clinical practice to improve outcomes and to assure that the quality of care meets accepted standards. This guideline
Was established after careful review of current evidence, literature and clinical practice. It will be reviewed periodically and modified to reflect changes in clinical practice, evolving evidence-based data, and the impact of ongoing pharmacological treatment tool development.

This clinical guideline is not intended to serve as a mandatory standard, but rather to provide a set of recommendations for the treatment of people with type 2 diabetes. These recommendations are not a substitute for reasonable clinical judgment or patient-based decision-making and do not exclude other options. Clinical care must be individualized and tailored to the specific needs and self-care abilities of each person. This guideline has been created to address initial presentations and treatment strategies in the adult non-pregnant patient population. It is not a substitution for full sounds good prescribing information. Refer to Joslin's *clinical guideline for adults with diabetes* as well as *Joslin's guideline for the care of older adults with diabetes* for additional, more comprehensive information on the care of people with diabetes.

Table 1a Diabetes Mellitus – Diagnostic Criteria (Non-Pregnant Adults)

- Random plasma glucose ≥ 200 mg/dl and symptoms or signs of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) ***OR***
- Glycated hemoglobin (A1C) ≥ 6.5%[a] **OR**
- Fasting plasma glucose (FPG)≥126 mg/dl OR
- Results of a 2-hour 75-g Oral Glucose Tolerance Test (OGTT) ≥ 200 mg/dl at 2 hours

These tests should be confirmed by a repeat test, unless unequivocally high. The repeat test could be done on the same day and on the same sample for convenience, but in that case 2 different abnormal tests are required for diagnosis.

[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.

Table 1b: Goals of Glycemic Control for People with Diabetes		
Biochemical Index	**Normal glucose**	**Goal**
Fasting plasma glucose or preprandial glucose (mg/dl)	**< 100**	**80 – 130**
2 hours post-prandial (mg/dl)	**< 140**	**< 180**
Bedtime glucose (mg/dl)	**< 120**	**90 – 150**
A1C (%) sustained	**< 6%**	**< 7%** A1C target goal should be individualized for each patient. Suggested goals listed above including A1C < 7% have been chosen as practical targets for most patients to reduce the risk of complications. Achieving normal blood glucose and A1C is recommended only if it can be done practically and safely. Aiming for less stringent goals than are listed above may be considered for older adults or those with advanced comorbidities (see Joslin's guideline for older adults with diabetes).

5.3.0 TREATMENT STRATEGY (FIGURE 1)

5.3.1 Start with metformin unless contraindicated or severe presentation (Figure 1) [1B]

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

- eGFR should be assessed 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. Metformin is contraindicated in people with an estimated glomerular filtration rate (eGFR) below 30 mL/minute/1.73 m^2.
- Starting metformin in people with an eGFR <45 mL/minute/1.73 m^2.is not recommended.
- If eGFR later falls below 45 mL/minute/1.73 m^2 while patient is on metformin, assess benefits and risks of continuing treatment. Discontinue metformin if eGFR later falls below 30 mL/minute/1.73 m^2
- If eGFR is over 45 mL/minute/1.73 m^2 and later falls between 30- 45 mL/minute/1.73 m^2.while on metformin, dose can be lowered to 50%.

- Discontinue metformin if eGFR later falls below 30 mL/minute/1.73 m^2.
- Discontinue metformin at time of or before an iodinated contrast imaging procedure if eGFR is 30-60 mL/minute/1.73 m^2.; in patients with a history of liver disease, alcoholism, or who will undergo intra-arterial iodinated contrast. Re-assess eGFR 48 hours after the imaging procedure; restart metformin if renal function is back to baseline level
- With long-term use, assess patients for signs and symptoms of vitamin B 12 deficiency such as: weakness, fatigue, shortness of breath or paresthesias; consider laboratory assessment, and supplementation, if necessary.

5.3.2 Considerations for Selecting Noninsulin Glucose-Lowering Medications when advancing therapy

5.3.2.1 PREFERRED CONSIDERATIONS IN PERSONS WITH T2D AND ESTABLISHED CARDIOVASCULAR DISEASE (Table 2)

TABLE 2: **PREFERRED CONSIDERATIONS IN PATIENTS WITH T2D AND ESTABLISHED CARDIOVASCULAR DISEASE**

Clinical Setting	History (or high risk) of ASCVD	History (or high risk) of HF
Consider agents with CV safety and superiority (regardless of A1c)	A GLP-1 RA with evidence to reduce CVD events [1B], (e.g. liraglutide, dulaglutide ,injectable semaglutide)* If GLP-1 RA is not tolerated or contraindicated, use SGLT2 inhibitors [2A]	SGLT2 inhibitors with evidence to reduce HF and/or CV mortality [1B], (e.g. empagliflozin, canagliflozin, dapagliflozin) If SGLT2 inhibitors not tolerated or contraindicated, use GLP1 RA with proven CVD benefit [2B]
Other considerations and caveats	Avoid GLP-1 RA use with CKD stage 4 There is a slight increase in biliary disease and need for cholecystectomy with GLP-1 RA Increased risk of worsening retinopathy with semaglutide and pre-existing DR with poor glycemic control	Avoid use of drugs promoting HF; e.g. TZD Avoid using SU. If needed, use later generation SU Use metformin with caution, if eGFR < 45 mL/minute/1.73 m^2 Can use DPP -4 inhibitors except saxagliptin Avoid use of SGLT2 inhibitor perioperatively and/or in the presence of risk factors for DKA (e.g., prolonged fasting, dehydration, infection, major trauma, ketogenic diet) Distal lower limb amputations with canagliflozin Fournier Gangrene (very rare)

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; T2D, type 2 diabetes; SGLT2, sodium glucose co-transporter 2.

Notes:
DDP-4 inhibitors: In several recent trials in patients with CVD, DPP-4 inhibitors were found to be safe (non inferior to) but also non-superior to other antihyperglycemic drugs from CV point of view; a secondary outcome, heart failure, was significantly increased with saxagliptin.

*GLP-1 RA: oral semaglutide (PIONEER-6), but not injectable semaglutide (SUSTAIN-6) showed a reduction in CV mortality [**1B**], only injectable semaglutide has received FDA indication for cardiovascular risk reduction in type 2 diabetes and CVD.
SGLT2-inhibitors: canagliflozin, empagliflozin and dapagliflozin showed reduction in heart failure. Empagliflozin has an indication to reduce cardiovascular mortality [1B], canagliflozin has indication to decrease cardiovascular risk in type 2 diabetes and CVD and dapagliflozin has an indication to reduce heart failure hospitalization [1B]

5.3.2.2Preferred considerations in patients with diabetic kidney disease (Table 3).

TABLE 3. Preferred considerations in patients with chronic kidney disease (CKD) or high risk of hypoglycemia

History of CKD	High risk of hypoglycemia
SGLT-2 inhibitors with evidence for reduction of ASCVD (see Table 2) [1B] or of CKD progression (a) [1B] Glucose-lowering efficacy of SGLT-2 inhibitors is: -diminished for eGFR 45-60 mL/minute/1.73 m^2 -modest when eGFR <45 mL/minute/1.73 m^2 Avoid use for GFR < 45 mL/minute/1.73 m^2, (< 30 mL/minute/1.73 m^2 for Canagliflozin) GLP-1RA with evidence for reduction of CVD (Table 2) and potential benefits on CKD outcomes (b) [2B]	DDP-4 inhibitors, GLP-1RA, SGLT2 –inhibitors are overall associated with low risk of hypoglycemia. Considerations: -saxagliptin, sitagliptin require dose adjustment for GFR <50 mL/minute/1.73 m^2; -aloglipitin requires dose adjustment for GFR <60 mL/minute/1.73 m^2; -linaglipitin is not renally cleared and does not require dose adjustment. -See Table 2 for GLP-1RA and SGLT2-ihibitors. Pioglitazone carries a low risk hypoglycemia. Considerations: risk of heart failure, which is a common co-morbidity in patients with T2D and CKD. If cost is a major issue, may also consider a later-generation sulfonylurea (except glyburide or glibenclamide) or repaglinide, which is excreted primarily in the bile, despite their moderate risk of hypoglycemia.

Notes:

(a) In patients with T2D enrolled in the CREDENCE trial, canaglifozin demonstrated a statistically (and clinically relevant) decrease in the composite of kidney outcomes, including reduction in end-stage kidney disease (ESKD), and death from renal and CV disease. Approximately, 60% of participants in CREDENCE had GFR 30-60 mL/minute/1.73 m^2 at baseline. The FDA has recently approved a new indication for canaglifozin to reduce the risk of ESKD in patients with GFR >30 mL/minute/1.73 m^2 and macroalbuminuria, defined as albumin-to- creatinine ratio (ACR) >300 mg/g.
Several ongoing trials are addressing the effects of other SGLT-2 inhibitors on kidney outcomes in patients with T2D.

(b) LEADER (using liraglutide) and SUSTAIN-6 (using injectable semaglutide) trials showed a reduction in the pre-specified secondary analysis of renal end-points. In both studies, this effect was mainly driven by a decrease in new onset of macroalbuminuria.

5.3.2.3Preferred considerations in patients with excess weight.

Consider GLP-1 RA or SGLT-2 inhibitor. Reassess in 1-3 months. If A1C remains above target, use both agents in addition to metformin. If unable to use GLP-1 RA or SGLT-2 inhibitor or if A1C remains above target, use DPP-4 inhibitor (if not on GLP-1 RA) or consider alpha-glucose inhibitor, or add insulin, or SU with further management of weight.

5.3.2.4 Preferred considerations in patients with hypoglycemia (Table 3)

Consider DPP-4 inhibitors, GLP-1 RA, SGLT 2-inhibitors or TZD. Assess within 2-3 months, if A1C remains above goal and consider add-on agents as needed. Do not combine GLP-1 RA and DPP-4 inhibitor. If A1C remains above goal on four medications, consider adding a basal insulin with lower risk of hypoglycemia or a new generation SU.

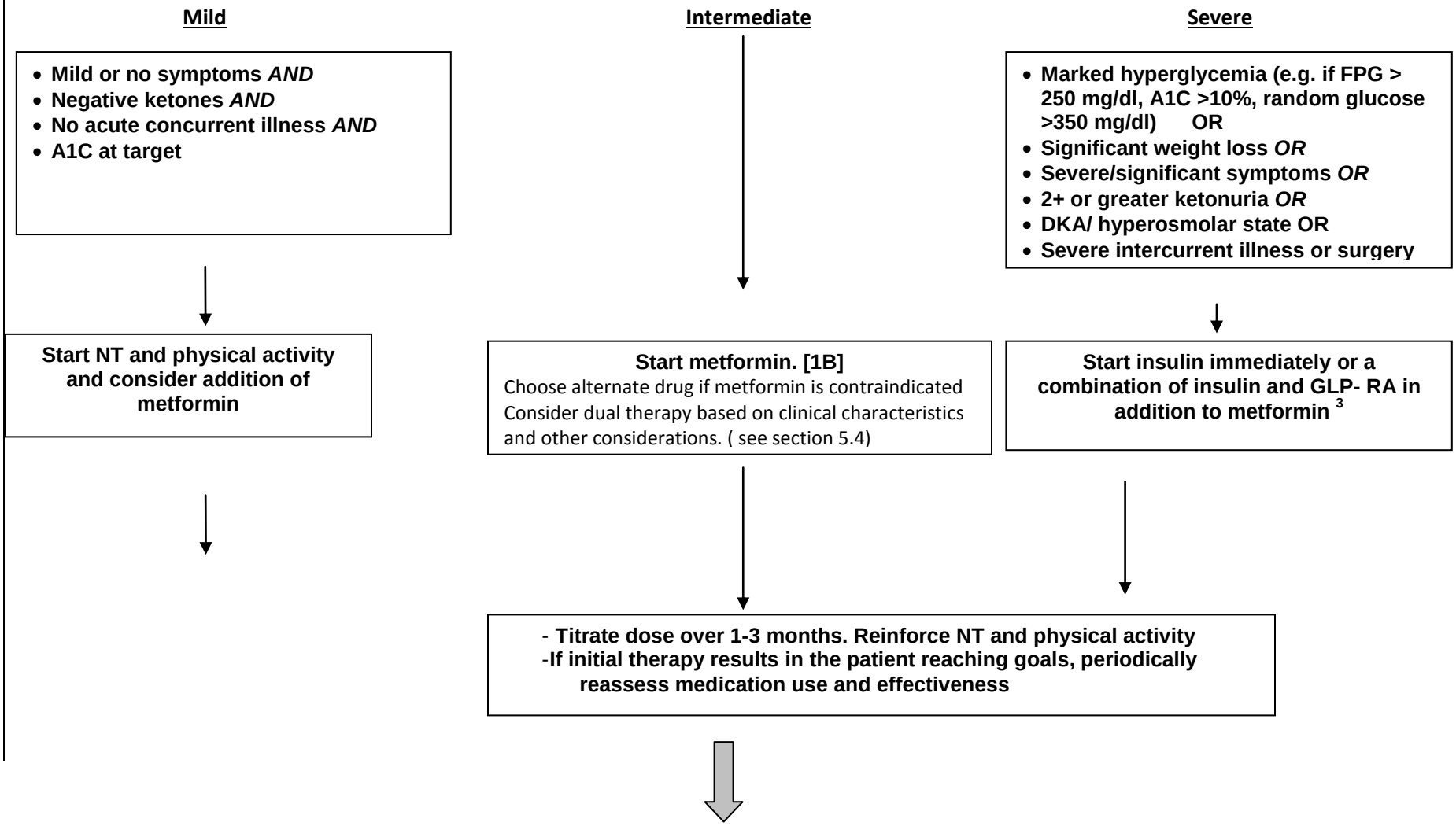
5.3.2.5 Preferred considerations in patients with low resources
Consider sulfonylureas or thiazolidinedione first. If A1C remains above goal, consider non analogue human insulin

5.4 Oral Glucose Lowering Agents (Table 4a)
5.4.1 Oral Glucose Lowering Agents: Fixed-dose medications (Table 4b)
5.5 Injectable anti-diabetes medications (incretin mimetics and noninsulin analogs): Table 5
5.6 Insulin Products (Table 6)
5.6.1 Insulin Products: Premixed insulin combinations: Table 7

Figure 1: INITIAL TREATMENT STRATEGY (also see preferred considerations, Table 2,3)

Nutrition therapy (NT), physical activity, blood glucose monitoring, continued follow up 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. A1C goals should be individualized.

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



If A1C >7% or not at individualized goals within 1-3 months:

- **Hyperglycemia AND/OR**
- **A1C > not at goal [2] AND/OR**

Add a medication from a different class, oral or injectable based on clinical characteristics and other considerations (GLP-RA preferred) (see section 5.3.2)

INITIATE OR ADD INSULIN [4,5,6] (see Tables 2, 3 forr preferred considerations)

- **Consider initiating:**
  - Long-acting insulin detemir, insulin glargine U-100, Basaglar U-100 once or twice daily **or** once daily degludec or insulin glargine U-300 for basal therapy
  - Intermediate-acting insulin (NPH) once or twice daily, as part of a conventional insulin program
  - Premixed insulin: 75/25 NPH/lispro, 50/50 NPH/lispro, 70/30 NPH/aspart, 70/30 NPH/regular insulin or 70/30 degludec/aspart once or twice daily
- **Suggested starting dose** for insulin: 0.1-0.2 units/kg body weight/day
- **Titrate/adjust** insulin dosage to achieve glucose goals

If A1C > 7% or not at individualized goals within 2 - 3 months, or not at goal on 3 medications consider: [4,5,6]

- Combining GLP-1 with basal insulin (separate injections or combination formulations: degludec/liraglutide, or glargine/lixisenatide).
- Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro, regular insulin, or human insulin inhalation) at one, two or all three meals to the pre-existing intermediate or long-acting insulin
- Adding or switching to a premixed rapid acting and long acting insulin.
- Adding oral anti-hyperglycemic medication to improve glycemic control if already on insulin (metformin, sulfonylureas, meglitinide, D-phenylalanine, DPP-4 inhibitors, GLP-1 agonist, α-glucosidase inhibitors, SGLT-2 inhibitors, TZDs[6] and colesevelam are approved for use in combination with insulin)
- If post-prandial excursions predominate, refer to endocrinologist for reassessment of therapy or for consideration of pramlintide use.

More information on next page….

Table 4a NON-INSULIN GLUCOSE LOWERING MEDICATIONS

Insulin Secretagogues (sulfonylurea, meglitinide or D-phenylalanine derivative)	Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)	Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists)	Sodium-glucose co-transporter 2 (SGLT-2 Inhibitors)[11]	α-Glucosidase Inhibitors (AGIs)	Thiazolidinediones[7,8,9] (TZDs)
Action: Stimulates beta cell insulin secretion. **Side effects**: Hypoglycemia **Contraindications:** Hypersensitivity and DKA **Precautions:** Severe liver or renal disease for 2nd generation SUs, meglinitides, or d-phenylalanine derivatives **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	**Action:** In a glucose dependent manner, slow inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels. **Side effects:** URI- like symptoms. Angioedema (reported with vildagliptin) and bullous pemphigoid reported with DDP-4's **Notes**: Reduce dose in renal disease with all members of the class except linagliptin. -Post marketing 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] The risk of acute pancreatitis or pancreatic cancer has not been confirmed in clinical trials. The FDA is currently monitoring the clinical reports via AERS	**Action:** In a glucose dependent manner increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety. **Side effects:** Nausea, vomiting, diarrhea, AKI that occurs when associated with dehydration **Contraindications:** 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, injectable semaglutide, and dulaglutide reduced the major CV outcomes in 3 large clinical trial in patients with CVD or high risk of CVD. -It is unknown if GLP-1 agonists increase the risk for pancreatitis. The risk of acute pancreatitis or pancreatic cancer has not been confirmed in clinical trials. The FDA is currently monitoring the clinical reports via AERS	**Action**: Block reabsorption of glucose by the kidney thereby increasing excretion of glucose in the urine. **Side effects:** Hypotension, genital mycotic infections, UTI, dehydration, hyperkalemia, increased LDL cholesterol, ketoacidosis in the absence of severe hyperglycemia[11] **Contraindications**: Do not use in: -eGFR < 30 mL/minute /1.73 m^2 with canagliflozin and -eGFR < 45 mL/minute /1.73 m^2 for other SGLT-2 inhibitors **Notes**: - Use may be associated with modest decrease in BP and in weight. - Adjust dose in moderate renal disease. -Associated with a	**Action:** Delay absorption and breakdown of carbohydrates **Side effects:** Gas, diarrhea. modest weight loss **Contraindications:** Chronic intestinal disorders or obstructions, DKA acarbose in cirrhosis **Notes**: Use if postprandial hyperglycemia predominates. Acarbose and miglitol not indicated in renal impairment (creatinine >2.0 mg/dl) -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	**Action**: Improves glucose transport and decreases hepatic glucose production. **Side effects**: Weight gain, fluid retention **Contraindications:** Liver disease, NYHA III or IV heart failure. **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. -Do not use pioglitazone in setting of bladder cancer, see footnote

		-Oral semaglutide requires strict adherence to administration instructions for absorption and avoidance of drug interactions. -Use with caution in setting of gastroparesis, especially if requiring treatment with metoclopramide.	transient worsening of renal function. - May slow progression of renal function decline & nephropathy - Empagliflozin and Canagliflozin reduced major CV events and heart failure in clinical trials, in those with pre-existing CVD as well as risk of renal disease progression (see table #2,3) - Dapagliflozin reduced heart failure hospitalization in those at high risk for CVD **Precautions:** **-**Use dapagliflozin with caution in setting of personal history of bladder cancer -Cases of acute kidney injury have been reported with canagliflozin and dapagliflozin. Promptly discontinue these drugs if this occurs and treat the renal impairment.		

			-A small increase in fracture rate & lower limb amputations have been reported with canagliflozin -Risk of euglycemic 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 - Rare cases of Fournier gangrene		

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 triglyceride > 500mg/dl • History of hypertriglyceridemia-induced pancreatitis	**Centrally Acting Agent (bromocriptine mesylate)** • Mechanism of action for glucose lowering is unclear • Most effective when used in combination with other antidiabetes medications • Modest effect on A1C **Contraindications:** • Should not be taken by nursing mothers, or by patients who take ergot medicines or have syncopal migraines

TABLE 4B. ORAL GLUCOSE LOWERING MEDICATIONS

Biguanides	Insulin Secretagogues	DPP-4 Inhibitors	SGLT-2 inhibitors	AGI	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 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 USA. See appendix for additional drug combinations		
• 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 (Kozano)	• 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*) • dapagliflozin, saxagliptin and metformin HCl extended-release (*QternMet XR)*
Others		
Bile Acid Sequestrant • colesevelam (*Welchol*) ; cholestyramine		
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.

Table 5. INJECTABLE DIABETES MEDICATIONS AVAILABLE IN THE USA

INCRETIN MIMETICS AND NON-INSULIN SYNTHETIC ANALOGS			
Product	**Mechanism of Action**	**Diabetes Type**	**Administration Frequency**
exenatide (*Byetta*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.	2	2 injections/day
extended release exenatide (*Bydureon*)		2	1 injection/week
dulaglutide (*Trulicity*)		2	1 injection/week
liraglutide (*Victoza*)		2	1 injection/day
lixisenatide (*Adlyxin*)		2	1 injection/day
semaglutide (*Ozempic*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with basal insulins	2	1 injection/week
semaglitude (*Rybelsus*)		2	1 tablet/day
pramlintide (*Symlin*)	Synthetic analog 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 injections/day (with meals)

Table 6. INSULINS (U-100 except where noted)				
Insulin Type	**Product**	**Onset**	**Peak**	**Duration**
Rapid-Acting *				
Insulin aspart analog	Fiasp	10 – 20 minutes	30 minutes – 2 hours	3 – 7 hours
Insulin human inhalation	Afrezza	12 – 15 minutes	30 – 90 minutes	3 hours
Insulin aspart analog Insulin glulisine analog Insulin lispro analog	Novolog Apidra Humalog U-100 and U-200, Admelog	10 – 30 minutes	30 minutes – 3 hours	3 – 7 hours
Short-Acting				
Human Regular	Humulin R Novolin R	30 – 60 minutes	2 – 5 hours	up to 12 hours**
Intermediate-Acting				
Human NPH insulin	Humulin N Novolin N	90 minutes – 4 hours	4 – 12 hours	up to 24 hours***
Long-Acting				
Insulin detemir	Levemir	45 minutes – 4 hours	Minimal peak	up to 24 hours ****
Insulin glargine	Lantus	45 minutes – 4 hours	Minimal peak	up to 24 hours ****
Insulin glargine concentrated	Toujeo U-300	6 hours	Minimal peak	up to 36 hours
Insulin degludec	Tresiba	1 hour	Minimal peak	up to 42 hours
Insulin degludec concentrated	Tresiba U-200	1 hour	Minimal peak	up to 42 hours
U-500 insulin				
Human regular insulin concentrated	Humulin R U-500	<15 minutes	4 -8 hours	13 - 24 hours

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

***The onset of activity for Fiasp and insulin human inhalation are faster than the other rapid acting insulin formulations. These differences may allow for changes in timing of administration in reference to a meal and may cause different glucose responses to a meal depending on the macronutrient composition of the meal.**

****Usual clinical relevance can be less than 12 hours**

***** Usual clinical relevance can be less than 24 hours. Often requires twice daily dosing**

****** Individual response may require twice daily dosing**

SEE APPENDIX FOR ADDITIONAL INFORMATION ON STORAGE FOR INSULIN AND OTHER INJECTABLES

Footnotes:

[1] Goals should be individualized based on the following, including: co-morbidity, age, duration of diabetes, hypoglycemic awareness.

[2]If diet history reveals markedly excessive carbohydrate intake, may consider initial trial of nutrition therapy and physical activity before initiating oral antidiabetes medications even though glucose levels are above the thresholds listed.

[3]Some patients with type 2 diabetes initially stabilized on insulin may be considered for transition to non-insulin 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 between 1-4 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 ALT is > 2.5 times normal, do not start this medication

Once TZD is started, monitor ALT periodically thereafter according to clinical judgement.

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, 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. Discontinuation or dose reduction of the TZD must be considered. TZDs are not contraindicated in patients with symptomatic heart failure or in patients with established NYHA Class III or IV heart failure.

[9 i] On September 23, 2010, the Food and Drug Administration (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 (GSK) to implement restrictions on the use of these products through a REMS program (Risk Evaluation and Mitigation Strategy) 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 Dec 16, 2015. Rosiglitazone now has the same indications for prescribing as pioglitazone.

[9 ii] According to FDA advisory issued on June 15, 2011 re: potential increased risk of bladder cancer with pioglitazone use: a. Do not use pioglitazone in patients with active bladder cancer. b. 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.

Glossary and Common Abbreviations

A1C: glycohemoglobin A1C (hemoglobin A1C)
AERS: Adverse Event Reporting System of the FDA
AGI: alpha glucosidase inhibitors
ALT: alanine aminotransferase
CHF: congestive heart failure
CV: cardiovascular
DKA: diabetic ketoacidosis
DPP-4: dipeptidyl peptidase IV inhibitors
eGFR: estimated glomerular filtration rate
FDA: Food and Drug Administration
FPG: fasting plasma glucose
G: gram
GI: gastrointestinal
GLP-1: glucagon-like peptide-1is secreted by the intestinal L cell in response to food intake, impacting glucose regulation.
HS: bedtime
Incretin: hormone produced by the gastrointestinal tract in response to food intake and necessary for glucose homeostasis
Incretin mimetics: a class of agents used for managing type 2 diabetes that mimics the enhancement of glucose-dependent insulin secretion and other glucoregulatory actions of naturally occurring incretins
IV: intravenous
kg: kilogram
LDL-C: low density lipoprotein, cholesterol
LFT: liver function tests
LV: left ventricular
MEN2: multiple endocrine neoplasia type 2
Mg: milligram
Mg/dl: milligram per deciliter
mL/minute/1.73 m^2: milliliter per minute per 1.73m^2
NPH: Neutral Protamine Hagedorn
NT (Nutrition Therapy): Begins with assessment of overall nutrition status, followed by individualized prescription for treatment. Registered dietitian considers food intake, physical activity, course of any medical therapy, individual preferences and other factors.
OGTT: oral glucose tolerance test
Rx: treatment
SGLT-2: sodium-glucose co-transporter 2
TZDs: thiazolidinediones
URI: upper respiratory infection
UTI: urinary tract infection

Working group members: Joanna Mitri, MD, MS, Om P.Ganda, MD, Alissa R. Segal, Pharm D, CDE, CDTC; Richard Beaser, MD, Jason Gaglia, MD; Giulio Romeo, MD

References for Joslin's Pharmacological Management of Type 2 Diabetes Guideline

Diagnosis

1. ADA Position Statement: Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2020; 43 (suppl 1): S 14- S31

2 Wei, N., et al.. Empirically establishing blood glucose targets to achieve HbA1c goals. Diabetes Care 2014: 37(4): 1048-1051.

Goals of Glycemic Control and Pharmacotherapy

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2020; 43 (suppl 1): S 98-S110
2. Beaser, RS and Staff of Joslin Diabetes Center. Joslin's Diabetes Deskbook for Primary Care Providers. Updated Third edition. Joslin Diabetes Center, Boston; 2014
3. Diabetes Prevention and Control Program, Diabetes Guidelines Work Group. Massachusetts guidelines for adult diabetes care. Boston (MA): Massachusetts Department of Public Health; 2011 June
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
5. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists/ American College of Endocrinology' comprehensive diabetes management algorithm 2015. Endocr Pract. 2015; 21: e1-e10
6. NICE guideline. Type 2 diabetes in adults: management. http://nice.org.uk/guidance/ng28; 1-57

Antihyperglycemic Therapy (Reviews)

1. Home, P. (2019). "Cardiovascular outcome trials of glucose-lowering medications: an update." Diabetologia 62(3): 357-369.
2. Bajaj, H. S. and B. Zinman (2018). "Glucose Lowering Strategies for Cardiac Benefits: Pathophysiological Mechanisms." Physiology (Bethesda, Md.) 33(3): 197-210.
3. Carbone, S., et al. (2018). "Glucose-Lowering Therapies for Cardiovascular Risk Reduction in Type 2 Diabetes Mellitus: State-of-the-Art Review." Mayo Clinic Proceedings 93(11): 1629-1647.
4. 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): 127-138
5. Kahn SE, Haffner SM, Heise MA, et. al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. New England Journal of Medicine 2006; 355: 2427-2443
6. Currie, CC, Poole, CD, Evans, M et al. Mortality and Other Important Diabetes-Related Outcomes With Insulin vs Other Antihyperglycemic Therapies in Type 2 Diabetes J Clin Endocrinol Metab 2013; 98: 668-677
7. Garvey, WT Use of Available Glucose-lowering Agents in Patients with Different Levels of Renal Impairment. Endocrine Practice 2013; 19, suppl1: 14-18
8. Berkowitz, SA, Krumme, RA, Avron, J et al. Initial Choice of Oral Glucose-Lowering Medication for Diabetes Mellitus A Patient-Centered Comparative Effectiveness Study. Ann Intern Med 2014; 174: 1955-1962
9. Bailey, CJ Interpreting Adverse Signals in Diabetes Drug Development Programs. Diabetes Care 2013; 36: 20198-2106
10. Murthur, 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; April 19; on- line.

Metformin

1. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach. Diabetes Care 28:539-543, 2005.
2. Inzucchi SE. Metformin and heart failure: innocent until proven guilty. Diabetes Care 28:2585-2587, 2005.
3. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. Diabetes Care 22:33-7, 1999.
4. 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: 2218-2224
5. UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352: 854-865, 1998.
6. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2006 Issue 4.
7. Salpeter S., Greyber E, Paternak G., Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Sys Rev 2006 Issue 4.
8. 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: 1410-1418
9. 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: 2593-2603
10. Inzucchi, SE, Lipska, KJ, Mayo, H et al Metformin in patients with type 2 diabetes and kidney disease a systematic review JAMA 2014; 312: 2668-2675.

11. Desai, U., et al. (2018). Time to Treatment Intensification After Monotherapy Failure and Its Association With Subsequent Glycemic Control Among 93,515 Patients With Type 2 Diabetes. Diabetes Care 41(10): 2096-2104.

Thiazolidinediones

1. Charbonnel1B, Roden M, Urquhart , Mariz S, Johns D, Mihm M, Wide M, Tan M. Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with glipazide-based regimens. Diabetologia 48:553-60, 2005.
2. 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 8:164-74, 2006.
3. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R. American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 108:2941-8, 2003.
4. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB, Sr. 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.
5. Yki-Jarvinen, H. Thiazolidinediones. New England Journal of Medicine 2004; 351: 1106-1118.
6. Nissen, SE, Wolski, K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine 2007; 356: 2457-2471.
7. 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 randomized controlled trial. Lancet 2005; 366:1279–1289.
8. 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; 373:2125–2135.
9. U.S. Food and Drug Administration. Postmarketing drug safety information for patients and providers. Q&A: Avandia (rosiglitazone). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226976.htm. Accessed September 2010.
10. Piccinni, C, Motola, D, Marchesini,D, Poluzzi, E Assessing the association of pioglitazone use and bladder cancer through drug adverse reporting. Diabetes Care 2011; 34: 1369-1371
11. FDA News Release: FDA Eliminates the Risk Evaluation and Mitigation Strategy (REMS). Accessed Dec 16, 2015
12. Lewis, JD et al. PIoglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. JAMA 2015;314: 265-277
13. Kahn SE, Haffner SM, Heise MA, et. al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. New England Journal of Medicine 2006; 355: 2427-2443
14. Kernan WN, Viscoli CM, Furie KL et al IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;374:1321–1331

15. Vaccaro O, Masulli M, Nicolucci A, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomized multicentre trial. *Lancet Diabetes Endocrinol*. 2017;5(11):887-897

Insulin Secretagogues

1. Bailey CJ, Day C. Antidiabetic drugs. Br J Cardiol 10:128-36, 2003.

2. 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 26:2075-80, 2003.
3. Dornhorst M. Insulotropic meglitinide analogues. Lancet 358:1709-15, 2001.
4. Hazama Y, Matsuhisa M, Ohtoshi K, Gorogawa S, Kato K, Kawamori D, Yoshiuchi K, Nakamura Y, Shiraiwa T, Kaneto H, Yamasaki Y, Hori M. Beneficial effects of nateglinide on insulin resistance in type 2 diabetes. Diabetes Res Clin Pract 71:251-5, 2006.
5. Plosker, Gl, Figgitt, DP.Repaglinide: A pharmacoeconomic review of its use in type 2 diabetes mellitus. PharmacoEconomics 22:389-411, 2004.

Alpha-Glucosidase Inhibitors

1. Balfour JA, McTavish D. Acarbose. An update of its pharmacology and therapeutic use in diabetes mellitus. Drugs 46:1025-54, 1993.
2. Carlson RF. Miglitol and hepatotoxicity in type 2 diabetes mellitus. Am Fam Physician 62:315 -318, 2000.
3. 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 25:10-6, 2004.
4. 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 18; (2):CD003639, 2005.
5. Holman, R. R., et al.. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2017; 5(11): 877-886.

GLP-1 Receptor Agonists

1. DeFronzo RA et al. Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 28:1092-1100, 2005.
2. 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 27:2628-35, 2004.
3. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. Diabetes Care 26:2370-7, 2003.
4. 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 143:559-69, 2005.
5. Iltz JL, Baker DE, Setter SM, Keith Campbell R. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus. Clin Ther 28:652-65, 2006.
6. Kendall, DM 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 28:1083-1091, 2005.
7. Russell-Jones D, Vaag A, Schmitz O, 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 randomised controlled trial. Diabetologia 2009; 52: 2046–55.
8. Garber A, Henry R, Ratner R, et al. 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: 473–81.
9. Vilsbøll T, Christensen M, Junker AE, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771
10. Buse JB1, Nauck M, Forst T et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a raDiamant 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;375:2234–43

11. 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: 2228–2234
12. Abdul-Ghani, MA et al. Initial combination therapy with metformin, pioglitazone, and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes, Diab Ob and Metab 2015; 17: 268-275
13. Egan AG et al Pancreatic safety of incretin-based drugs--FDA and EMA assessment. N Engl J Med. 2014 Feb 27;370(9):794-7
14. H. W. Rodbard et al., GREATER COMBINED REDUCTIONS IN HbA1C ≥1.0% AND WEIGHT ≥5.0% WITH SEMAGLUTIDE VERSUS COMPARATORS IN TYPE 2 DIABETES. Endocr. Pract. 25, 589-597 (2019).

DPP-IV Inhibitors

1. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. J Clin Endocrinol Metab 2008; 93(10):3703-3716.

2. DeFronzo RA, Hissa MN, Garber AJ, et al. 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; 32:1649–55.
3. Scott, LJ Linagliptin in type 2 diabetes mellitus . Drugs 2011; 71: 611-624.
4. Gibbs JP, Fredrickson J, Barbee T, Correa I, Smith B, Lin S-L, Gibbs MA. 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; 52:1494-1505.
5. Scheen AJ. DPP-4 inhibitors in the management of type 2 diabetes: a critical review of head-to-head trials. Diabetes & Metabol 2012;38:89-101.
6. Egan AG et al Pancreatic safety of incretin-based drugs--FDA and EMA assessment. N Engl J Med. 2014 Feb 27;370(9):794-7.
7. Filion, KB et al A multicenter observational study of incretin-based drugs and heart failure. N Engl J Med 2016; *374: 1145-1154.*

Sodium Glucose Co-Transporter-2 Inhibitors

1. Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2:e001007. doi:10.1136/bmjopen-2012-001007
2. Stenlof K, Cefalu WT, Kim KA, Abla M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obesity and Metabolism 2013; 15:372-382.
3. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K,, Capuano G, Canovatchel W, 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;35:1232-1238.
4. Sha, S, Devineni D, Ghosh A, Polidori D, Chen S, Wexler D, Shalayda K, Demarest K, Rothenberg P. Canagliflozin, a novel inhibitor of sodium glucose co-transporter-2, dose dependently reduces calculated renal threshold for glucose excretion and increases urinary glucose excretion in healthy subjects. Diabetes Obesity and Metabolism 2011;13:669-672.
5. 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):740-50.
6. 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.
7. Ridderstråle M, Andersen KR, Zeller C et al . 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. Lancet Diabetes and Endocrinol 2014, 2: 691-700
8. Tahrani AA. Barnett AH. Bailey CJ. SGLT inhibitors in management of diabetes.The Lancet Diabetes & Endocrinology. 2013;1(2):140-51.

9. FDA advisory, Canagliflozin (Invokana, Invokamet) and Dapagliflozi (Farxiga, Xigduo XR): Drug Safety Communication-Strengthened Kidney Warning)
10. G. P. Fadini, M. Sarangdhar, F. De Ponti, A. Avogaro, E. Raschi, Pharmacovigilance assessment of the association between Fournier's gangrene and other severe genital adverse events with SGLT-2 inhibitors. BMJ open diabetes research & care 7, e000725 (2019).
11. Watts, NB et al Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. J Clin Endocrin Metab 2015; doi: 10.1210/jc.2015-3167
12. Garg, S. K., et al. (2018). "Strategy for Mitigating DKA Risk in Patients with Type 1 Diabetes on Adjunctive Treatment with SGLT Inhibitors: A STICH Protocol Diabetes Technology and Therapeutics 2018; 20: 571-575

Recent Cardiovascular Clinical Trials with Incretin–based agents and SGLT-2 inhibitor:

1. 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; 369:1327–1335
2. 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; 369:1317–1326
3. 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 Jul 16;373(3):232-42
4. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med 2015;373:2247-57
5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.\
6. Marso, P. Daniels,GH, Brown-Frandsen, K et al Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016, doi:10.1056/NEJMoa1603827
7. Wanner, C, Inzucci, SE, Lachin, JM et al Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes N Engl J Med 2016 doi:10.1056/NEJMoa1515920
8. Rosenstock, J., et al. "Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial." JAMA 2019; sept 19; on line .
9. Rosenstock, J., et al. (2019). "Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial." JAMA 321(1): 69-79.
10. Wiviott, S. D., et al. (2019). "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med 380(4): 347-357.
11. Home, P. Cardiovascular outcome trials of glucose-lowering medications: an update Diabetologia 2019; 62(3): 357-369.
12. Kristensen, S. L., et al Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. 2019; The Lancet Diabetes & Endocrinology 2019; 7: 765-785
13. Zelniker, T. A., et al. (2018). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials." The Lancet. 2019; 393: 31-39
14. McMurray, J. J. V., et al. (2019). Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction." New England Journal of Medicine., 2019; Sept 20; on- line.
15. Perkovic, V., et al. (2019). "Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy." N Engl J Med 380(24): 2295-2306.
16. Neuen, B. L., et al. (2019). SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. The Lancet Diabetes & Endocrinology. 2019; 7: 845-854

17. Matthews, D. R., et al."Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial." Lancet 2019; 394(10208): 1519-1529.
18. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394:121-30.
19. The VERTIS-CV Trial. Cardiovascular Outcomes Following Ertugliflozin Treatment in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease. Presented during American Diabetes Association (ADA) Virtual 88th Scientific Sessions, June16,2020

Bile Acid Sequestrants

1. 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.
2. 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.
3. 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.
4. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. Diabetes Obes Metab 2010;12:384–392

Combination Therapy with Insulin

1. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled insulin-treated type 2 diabetes mellitus. Ann Intern Med 131:182-88, 1999.
2. Belcher G, Lambert C, Goh1 KL, Edwards G, Valbuena1 M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and glipazide. Int J Clin Pract 58:833-7, 2004.
3. Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Sys Rev 2006 Issue 4.
4. 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 5:163-70, 2003.
5. 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 27:1535-47, 2005.
6. 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 29:554-9, 2006.
7. Yki-Jarvinen H et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 3:1-10, 2006.
8. Buse, JB et al Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With Type 2 Diabetes Ann Intern Med 2011; 154: 103-112.

Insulin

1. Baker A, Ahmed E, Mallias J, Home PD. Optimization of evening insulin dose in patients using the short-acting insulin analog lispro. Diabetes Care 21:1162-66, 1998.
2. Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. Clin Ther 27:S75-88, 2005.
3. Hirsch B, Bergenstal RM, Parkin CG, Wright E, Buse JB. A real-world approach to insulin therapy in primary care practice. Clin Diabetes 23: 78-86, 2005.
4. Kennedy L, Herman WH, Strange P, Harris A for the 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. Diabetes Care 29:1-8, 2006.
5. Riddle MC. The Treat-to-Target Trial and related studies. Endoc Pract. 37:495-501, 2006.
6. Scholtz HE, Pretorious SG, Wessels DH, Becker RH. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. Diabetologia 48:1988-95, 2005.
7. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003287.
8. Valensi P, Cosson E. Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects? Diabetes Metab 31:4S34-4S39, 2005
9. Davidson MB, Raskin P, Tanenberg RJ, Vlajnic A, et al A stepwise approach to insulin therapy in patients with type 2 diabetes mellitus and basal insulin treatment failure. Endocrine Practice 2011;17:395–403
10. Rosetti, P. Ampudia-Blasco, FJ, Ascaso, JF. Old and new basal insulin formulations: understanding pharmacodynamics is still relevant in clinical practice Diabetes, Obesity, Metaboloism 2014; doi:10.1111/dom.12256
11. De la Pena, A Riddle, M, Morrow, LA et alPharmacokinetics and pharmacodynamics of high-dose humanregular U-500 iInsulin versus human regular U-100 insulin in healthy obese subjects Diabetes Care 2011; 2496- 2501

Inhaled insulin

1. 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 Nov;3(11):886-94
2. Leahy, JL. Technosphere Inhaled Insulin: Is Faster Better? Diabetes Care. 2015 Dec;38(12):2282-4

Pramlintide

1. Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, Kolterman O, Weyer C. 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 5:408-14, 2003.
2. Hollander PA 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 26:784-790, 2003.
3. Weyer C, Gottlieb A, Kim DD, Lutz K, Schwartz S, Gutierrez M, Wang Y, Ruggles JA, Kolterman OG, Maggs DG. 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 26:3074-9, 2003.
4. Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG, Weyer C, Kolterman OG. 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 25:724-30, 2002.

Bromocriptine

1. Holt, RI et al Bromocriptine: old drug, new formulation, and new indication. Diabetes, Obesity, and Metabolism 2010; 12: 1048-1057.
2. DeFronzo R. Bromocriptine: A Sympatholytic, D2-Dopamine Agonist for the Treatment of Type 2 Diabetes. Diabetes Care 2011:34:789–794
3. 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;33:1503–8
4. Scranton R, Cincotta A. Bromocriptine--unique formulation of a dopamine agonist for the treatment of type 2 diabetes. Expert Opin Pharmacother 2010;11:269–79.

APPENDIX

Storage Chart for Insulin and Other Diabetes Injectable Medications

Insulin Available in Vials	How to store this insulin
Sanofi insulin in vials •Lantus •Apidra **Lilly insulin in vials** •Humalog •Humalog Mix 75/25 •Humalog mix 50/50 •Humulin N •Humulin R Humulin 70/30 •Humulin R U-500 **Novo Nordisk insulin in vials** •Fiasp •Novolog •Novolog Mix 70/30 •Levemir •Novolin R •Novolin N •Novolin 70/30	**Unopened vials** of insulin: (Lilly, Novo Nordisk, Sanofi) Store in the refrigerator until the expiration date. **DO NOT FREEZE.** **Opened vials** of insulin: (Lilly, Novo Nordisk, Sanofi) Keep open vials at room temperature or in the refrigerator for **28-30 days**, and then throw away, **except** for Levemir by Novo Nordisk. Levemir can be kept for **45 days**. Keep all away from heat and sunlight.
Insulin available in pens and cartridges	**How to store this insulin**
Novo Nordisk PenFill cartridge **not** in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Novo Nordisk PenFill cartridges **in use** •Novolog 3.0 ml •Novolog Mix 3.0	Keep at room temperature for: •**28 days** then throw away •**14 days** then throw away
Novo Nordisk FlexPen/FlexTouch not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Novo Nordisk FlexPen or **FlexTouch in use** •NovoLog Mix 70/30 •NovoLog •Fiasp •Ryzodeg 70/30 •Levemir •Tresiba U-100 or U-200	Keep at room temperature for: •**14 days** then throw away •**28 days** then throw away •**28 days** then throw away •**28 days** then throw away •**42 days** then throw away •**56 days** then throw away
Lilly cartridges not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Lilly cartridges in use •Humalog	Keep at room temperature for **28 days** then throw away
Lilly Kwik Pen not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**

Lilly Kwik Pen in use •Humulin N •Humalog or Humalog U-200 •Humalog Mix 75/25 •Humulin R U-500	Keep at room temperature for: •**14 days** then throw away •**28 days** then throw away •**10 days** then throw away •**28 days** then throw away
Sanofi Disposable SoloStar pen not in use •Lantus •Apidra •Toujeo	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Sanofi Disposable SoloStar pen in use •Lantus •Apidra •Toujeo	Keep at room temperature for **28 days** then throw away.

Inhaled insulin	How to store this insulin
Afrezza sealed (unopened) foil packages not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE**
Afrezza sealed (unopened) foil package, blister cards and strips **in use**	Keep at room temperature for **10 days** then throw away
Afrezza (opened) strips **in use**	Keep at room temperature for **3 days** then throw away
Byetta, Bydureon, Ozempic, Symlin, Trulicity, Victoza Storage Information	
Byetta pen not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Byetta pen in use	Store in refrigerator or room temperature (less than 77 degrees) for **30 days** then throw away.
Bydureon kit or pen	Store in the refrigerator until the expiration date. **DO NOT FREEZE.** May be stored at room temperature (less than 77 degrees) for up to **30 days.**
Ozempic pen not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Ozempic pen in use	Keep in the refrigerator or at room temperature (59 – 86 degrees) for **56 days** then throw away.
SymlinPen not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
SymlinPen in use	Keep in the refrigerator or at room temp for **30 days** then throw away.
Trulicity pen	Store in its original packaging in the refrigerator until the expiration date. **DO NOT FREEZE.** May be stored at room temperature for up to **14 days**, as long as it is protected from light**.**
Victoza pen not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE.**
Victoza pen in use	Keep in the refrigerator or at room temperature (59 – 86 degrees) for **30 days** then throw away.