Joslin Diabetes Center & Joslin Clinic
Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes
10/08/2016

The objectives of the *Joslin Diabetes Center & Joslin Clinic Clinical Guideline for Pharmacological Management of Adults with Type 2 Diabetes* are 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 will be reviewed periodically and modified to reflect changes in clinical practice and available pharmacological information.

This Clinical 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 non-pregnant patient population. The Guideline is not a substitution for full 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 diabetes care and management.

Diabetes Mellitus – Diagnostic Criteria (Non-Pregnant Adults)

- Random plasma glucose ≥ 200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) ***OR***
- Glycated Hemoglobin (A1C) ≥ 6.5%** **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, on a different day, unless unequivocally high*

*** Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes*

Goals of Glycemic Control for People with Diabetes

Biochemical Index	Normal	Goal[1]
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. 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).

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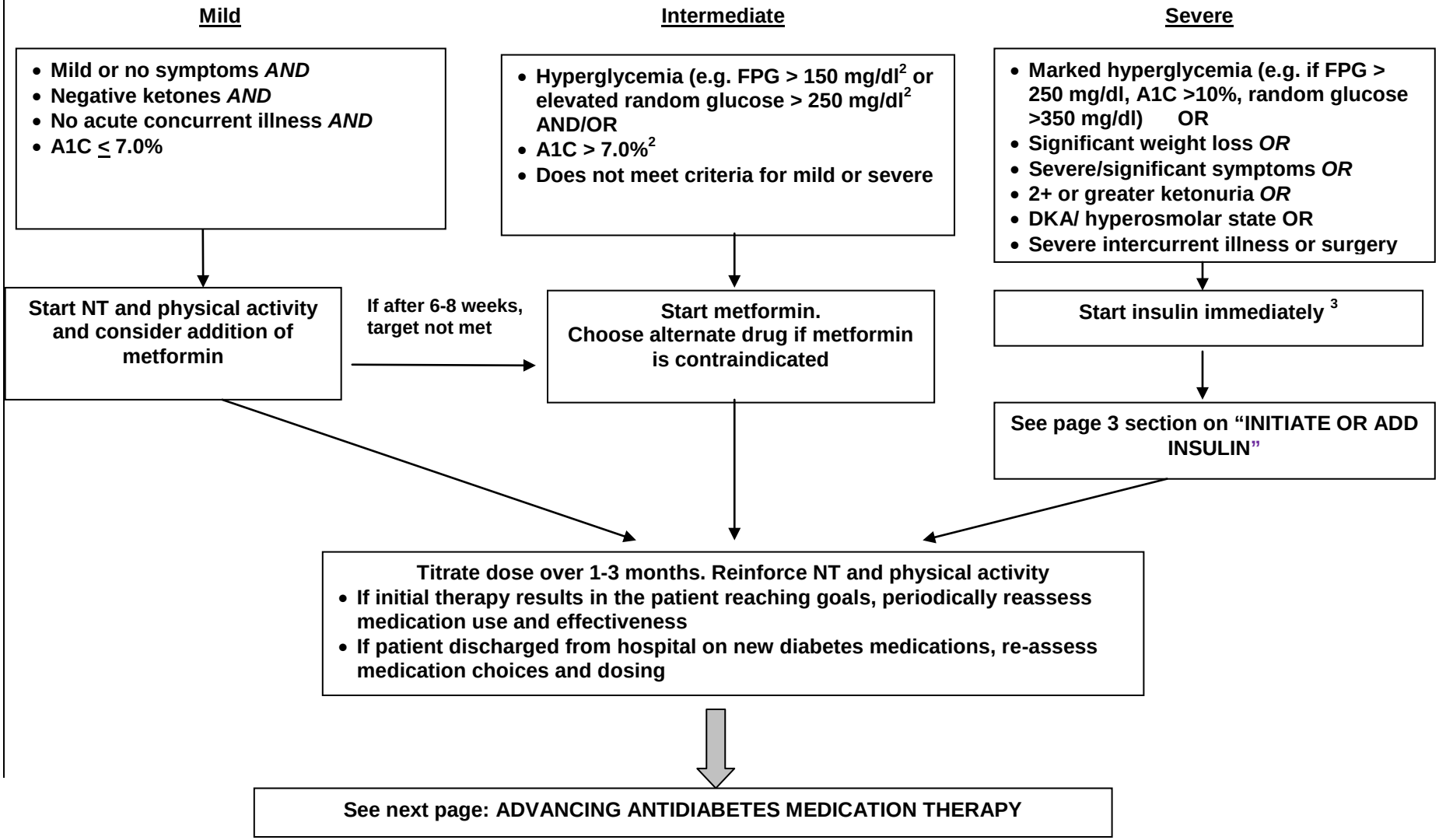
INITIAL TREATMENT STRATEGY

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)**



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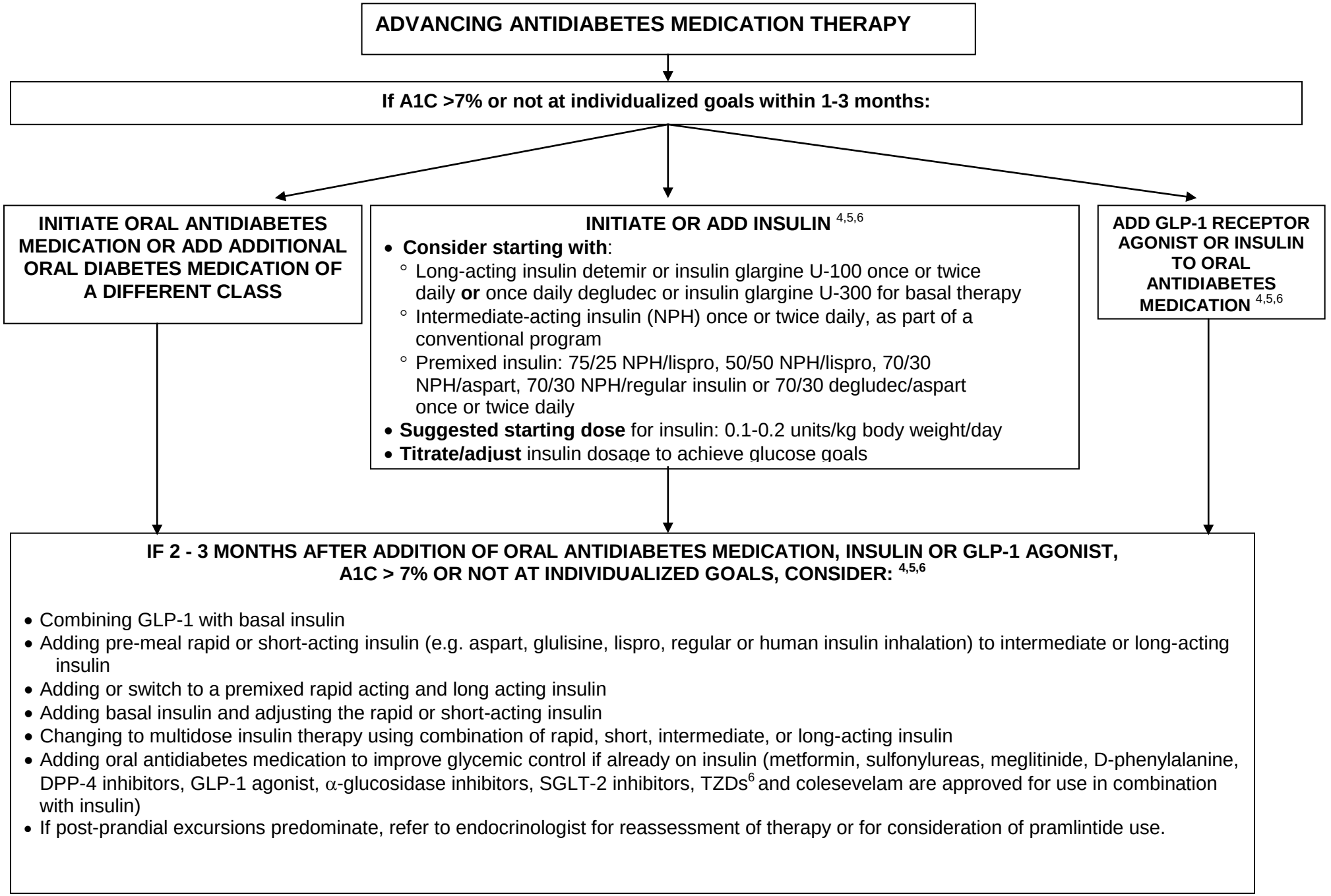

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CONSIDERATIONS FOR SELECTING NON-INSULIN GLUCOSE LOWERING MEDICATIONS

START WITH METFORMIN UNLESS CONTRAINDICATED

Action: Decreases hepatic glucose production, increases GLP-1 secretion. Use as initial therapy unless contraindicated.
Side 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 GI symptoms.
Dosing:

- Metformin is contraindicated in patients with an 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 between 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 stable.

FIRST LINE ADD ON TO METFORMIN OR USE AS MONOTHERAPY IF METFORMIN IS CONTRAINDICATED

Insulin Secretagogue (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**: Potential for hypoglycemia **Contraindications:** Sulfonylureas 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	**Action:** In a glucose dependent manner, slow inactivation of incretin hormones, resulting in increased insulin secretion and decreased glucagon levels . **Side effects:** URI symptoms. **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]	**Action:** In a glucose dependent manner increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety. **Side effects:** nausea, diarrhea, renal impairment **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 basal insulin, consider initially decreasing sulfonylurea or insulin dose. - increased risk of biliary disease and gallstones -liraglutide reduced the major CV outcomes in a large clinical trial in patients with CVD or high risk of CVD. -It is unknown if GLP-1 agonists increase the risk for pancreatitis[10]	**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 moderate to severe renal disease as it may worsen renal function. **Notes**: Use may be associated with modest decrease 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's 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 reduced CV mortality, CHF, and heart failure in one trial, in those with pre-existing CVD as well as risk of renal disease progression	**Action:** Delay absorption and breakdown of carbohydrates **Side 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	**Action**: Improves glucose transport, and decreases hepatic glucose production. **Side 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 footnote **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.

OTHER THERAPY

Bile Acid Sequestrant (colesevelam)	Centrally Acting Agent (bromocriptine mesylate)
• 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*	• Mechanism of action re glucose lowering is unclear • Most effective when used in combination with other antidiabetes medications • Modest effect on A1C

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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	**Contraindications:** • Should not be taken by nursing mothers, or by patients who take ergot medicines or have syncopal migraines

ORAL GLUCOSE LOWERING MEDICATIONS

Biguanides	Insulin Secretagogues	Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)	Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)	α-Glucosidase Inhibitors	TZDs[9] (Thiazolidinediones)
• 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*)	•acarbose (*Precose*) •miglitol (*Glyset*) (acarbose is available as a generic medication)	• pioglitazone *(Actos)* • rosiglitazone *(Avandia)* (pioglitazone and rosiglitazone are available as generic medications)

FIXED DOSE COMBINATION MEDICATIONS

• 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*) • repaglinide and metformin (PrandiMet) • pioglitazone and metformin *(Actoplus MET)* [9] • pioglitazone and glimepiride (Duetact) [9]	• rosiglitazone and glimepiride *(Avandaryl)* [9] • rosiglitazone and metformin (*Avandamet*) • dapagliflozin and metformin (*Xigduo*) • empagliflozin and metformin (*Synjardy*) • empagliflozin and linagliptin (*Glyxambi)*) • canagliflozin and metformin (*Invokamet)*

Others

Bile Acid Sequestrant
• colesevelam (*Welchol*)

Centrally Acting
•bromocriptine (*Cycloset*)

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INJECTABLE DIABETES MEDICATIONS AVAILABLE IN THE USA

INCRETIN MIMETICS AND NON-INSULIN SYNTHETIC ANALOGS			
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
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
albiglitude (*Tanzeum*)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins. Has not been studied in use with prandial insulins	2	1/week
dulaglutide (*Trulicity*)	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/week
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 /day (with meals)

INSULINS (U-100 except where noted)				
Insulin Type	**Product**	**Onset**	**Peak**	**Duration**
Rapid-Acting				
Insulin aspart analog Insulin glulisine analog Insulin lispro analog	Novolog Apidra Humalog U-100 and U-200	10 – 30 minutes	30 minutes – 3 hours	3 – 5 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 U-100,	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 U-100	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 500 units per mL	U-500 concentrated Humulin R	<15 minutes	4 -8 hours	13 - 24 hours
Inhaled insulin				
Insulin human inhalation	Afrezza	12 – 30 minutes	30 – 90 minutes	3 hours

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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

***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. 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.

[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.

[10] Risk of acute pancreatitis or pancreatic cancer has not been confirmed in clinical trials. The FDA is currently monitoring the clinical reports via AERS

[11] 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.

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Glossary and Common Abbreviations

A1C: glycohemoglobin (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/min: milliliter per minute
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

Guideline Working Group: Om Ganda, MD, Richard Beaser, MD, Jason Gaglia, MD, Sethu Reddy, MD, Alissa Segal Pharm D, CDE, CDTC, Elizabeth Blair, MSN, ANP-BC, CDE

Joslin Clinical Oversight Committee

Om Ganda, MD – Chairperson	Sethu Reddy, MD
Richard Beaser, MD	Jo-Anne Rizzotto, MEd, RD, CDE
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Approved by Joslin Clinical Oversight Committee on 05/10/2016

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Thiazolidinediones

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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** •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 •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 •**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.

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Inhaled insulin	How to store this insulin
Afreeza sealed (unopened) foil packages not in use	Store in the refrigerator until the expiration date. **DO NOT FREEZE**
Afreeza sealed (unopened) foil package, blister cards and strips **in use**	Keep at room temperature for **10 days** then throw away
Afreeza (opened) strips **in use**	Keep at room temperature for **3 days** then throw away
Byetta, Bydureon, Symlin, Tanzeum, 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.**
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.
Tanzeum pen	Store in the refrigerator until the expiration date. **DO NOT FREEZE.** Can store at room temp (below 86 degrees), in the box, for **28 days before use,** 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.

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