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Review of Diabetes Pharmacotherapy in the Older Adult

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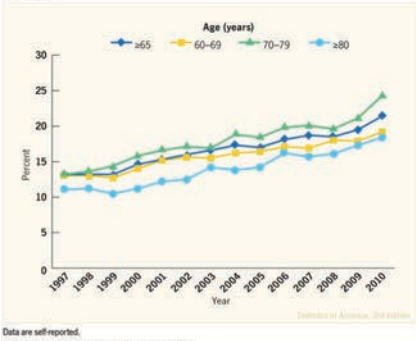
March 7,2020

Trends in the Percent of Diagnosed Diabetes Among Adults Age ≥60 Years, by Age, U.S., 1997–2010



Data are self-reported.
SOURCE: National Health Interview Surveys 1997–2010

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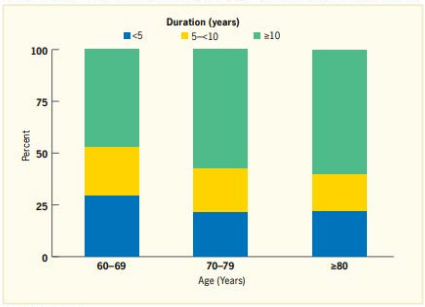
FIGURE 16.3. Duration of Diabetes Among Adults Age ≥60 Years, by Age, U.S., 2009–2010



Data are self-reported.
SOURCE: National Health Interview Surveys 2009–2010

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Approach to Diabetes Management in Older Adults

- Establish goals of therapy
- Evaluate Interventions
  - Lifestyle
  - Pharmacologic
- Minimize risks
  - Hypoglycemia
  - BP
  - Lipids

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Establish Goals of Therapy

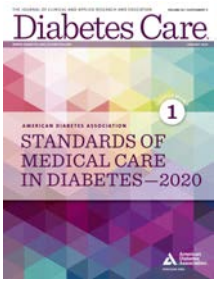
Case

- 74 year old male, T2D x 20 years
- A1c had been 7.2%, recently 9.0%
- Glyburide, metformin- doses recently increased to 20 mg glyburide and 1000 mg bid
- More forgetful and disoriented recently
- Blurry vision, nocturia
- PMH HTN, HLD
- No SMBG
- PE remarkable for older than stated age, oriented to person and place only, BMI 27.4, BP 165/95, absent pedal pulses and monofilament sensation
- eGFR 36 ml/min/1.73m2, urine alb/Cr 279 mg/g

What would be your target HbA1c for this patient ?

- A. Less than 9% and ≥8.5%
- B. Less than 8.5%
- C. Less than 8.0% and ≥7.5%
- D. Less than 7.5%

Which Target??



ADA-Recommended Glucose Goals

Parameter	Treatment Goal for Nonpregnant Adults
A1C (%)	Individualize • <7.0% for most nonpregnant adults • <6.5 if it can be achieved without significant hypoglycemia or other adverse effects of treatment* • <8% for those at risk†
Preprandial glucose (mg/dL)	80-130
Peak postprandial glucose (mg/dL)	<180

*Appropriate patients
- Short duration of diabetes
- T2D treated only with lifestyle or metformin
- Long life expectancy
- No significant cardiovascular disease

†At risk patients
- History of severe hypoglycemia
- Limited life expectancy
- Advanced micro- or macrovascular complications
- Extensive comorbid conditions
- Long-standing T2D in which A1C goal has been difficult to attain despite intensive efforts

ADA. *Diabetes Care*. 2018;41:S55-S64.

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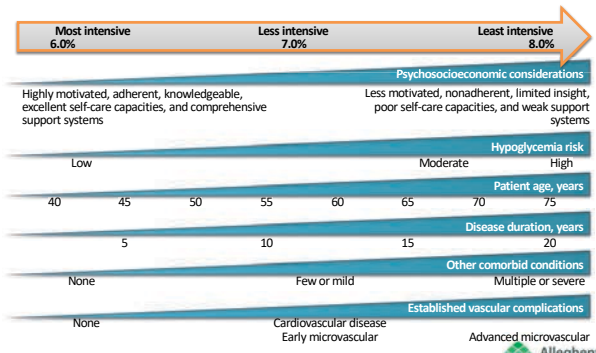
Algorithm for Individualizing Glycemic Targets



Ismail-Beigi F, Moghissi E, et al. *Ann Intern Med*. 2011;154:554-559.

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Factors to Consider When Choosing Goals of Therapy

- Few long term studies in older adults demonstrating benefits of intensive glycemic, BP, and lipid control.
- Poor diabetes control is associated with decline in cognitive function.
- Cognitive impairment makes it challenging to help patients reach individualized glycemic, BP, and lipid targets.
- Polypharmacy/pill burden/complexity of regimen
- COST!!!

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Case, Medication Selection

- 72 yo M with Type 2 DM and mild cognitive impairment taking glyburide 20 mg daily and metformin 1000 mg bid . A1c 9.0% and eGFR 36 ml/min/1.73 m² . Patient was asked to do home glucose monitoring, which he did erratically. 3 times over the past 4 weeks he had what appeared to be “random” mid-day glucoses.
- He also complained of waking up sweating at night, but never checked his glucose levels.

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Which approach would most safely and effectively reduce his risk of hypoglycemia?

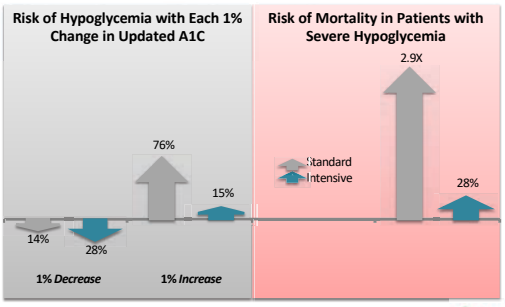
- A. Reduce dose of glyburide to 10 mg daily.
- B. Switch glyburide to glimepiride
- C. Switch glyburide to linagliptin
- D. Switch metformin to linagliptin
- E. None of the above

Hypoglycemia

- Neuroglycopenic symptoms predominate with aging

Hypoglycemia and Mortality

ACCORD Posthoc Analysis



Miller ME, et al. *BMJ*. 2010;340:b5444-b5444.

Hypoglycemia: Risk Factors

Patient Characteristics

- Older age
- Female gender
- African American ethnicity
- Longer duration of diabetes
- Neuropathy
- Renal impairment
- Previous hypoglycemia

Behavioral and Treatment Factors

- Missed meals
- Elevated A1C

Miller ME, et al. *BMJ*. 2010 Jan 8;340:b5444. doi: 10.1136/bmj.b5444.

Consequences of Hypoglycemia

- Cognitive, psychological changes (eg, confusion, irritability)
- Accidents
- Falls
- Recurrent hypoglycemia and hypoglycemia unawareness
- Refractory diabetes
- Dementia
- CV events
  - Cardiac autonomic neuropathy
  - Cardiac ischemia
  - Angina
  - Fatal arrhythmia

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

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Treatment Options

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Lifestyle Interventions

- Weight loss should be approached with caution
- Reduce sedentary activity
- Assess nutritional status
- Avoid restrictive diets and limit consumption of simple sugars

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Metformin

Recommended for All Patients, Unless Contraindicated or Not Tolerated

Hypoglycemia	Neutral
Weight	Slight loss
Renal / Genitourinary	Contraindicated if eGFR <30 mL/min/1.73 m^2
Gastrointestinal adverse effects	Moderate
Cardiac	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

eGFR = estimated glomerular filtration rate.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

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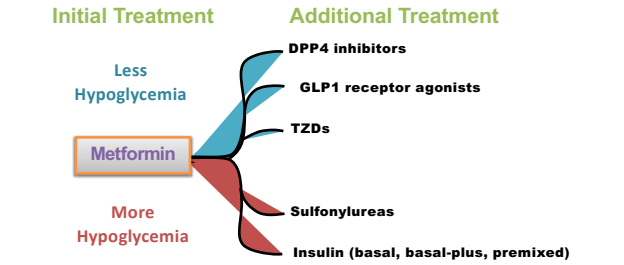
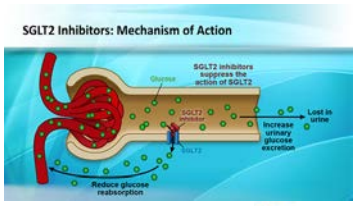
Hypoglycemia Risk With Antihyperglycemic Agents Added to Metformin



Moghissi E, et al. *Endocr Pract.* 2013;19:526-535.

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

- canagliflozin (Invokana)
- dapagliflozin (Farxiqa)
- empagliflozin (Jardiance)
- ertugliflozin (Steglatro)



Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

Hypoglycemia	Neutral
Weight	Loss
Renal / Genitourinary	Not indicated for eGFR <45 mL/min/1.73 m^2 Genital mycotic infections
	Possible benefit of empagliflozin
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Possible benefit of empagliflozin
Cardiac--ASCVD	Possible cardiovascular benefit
Bone	Canagliflozin warning
Ketoacidosis	DKA occurring in T2D in various stress settings

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

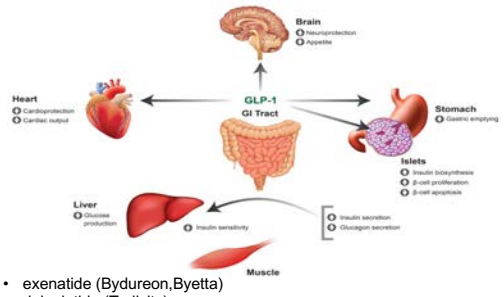
AACE/ACE Position Statement on Association of SGLT2 Inhibitors With DKA

- DKA occurs infrequently
- Risk-benefit ratio favors continued use of SGLT2 inhibitors with no changes in current recommendations
- DKA diagnosis may be missed or delayed due to atypical presentation involving lower-than-anticipated glucose levels or other misleading laboratory values
  - This atypical presentation has been seen with other antihyperglycemic agents long before the introduction of SGLT2 inhibitors

DKA = diabetic ketoacidosis; SGLT2 = sodium glucose cotransporter 2.

Handelsman Y, et al. *Endocr Pract.* 2016;22:753-762.

Glucagon-like Peptide 1 Receptor Agonists (GLP1 RAs)



- exenatide (Bydureon,Byetta)
- dulaglutide (Trulicity)
- liraglutide (Victoza)
- lixisenatide (Lyxumia)
- Pasemaglutide (Ozempic, Rybelsus (oral))

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Glucagon-like Peptide 1 Receptor Agonists (GLP1 RAs)

Hypoglycemia	Neutral
Weight	Loss
Renal / Genitourinary	Exenatide not indicated if CrCl <30 mL/min
	Possible benefit of liraglutide
Gastrointestinal adverse effects	Moderate
Cardiac—CHF	Possible benefit of liraglutide
Cardiac--ASCVD	Possible cardiovascular benefit
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Dipeptidyl Peptidase 4 Inhibitors (DPP4is)

- linagliptin (Tradjenta)
- saxagliptin (Onglyza)
- sitagliptin (Januvia)

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Dipeptidyl Peptidase 4 Inhibitors (DPP4is)

Hypoglycemia	Neutral
Weight	Neutral
Renal / Genitourinary	Dose adjustment necessary (except linagliptin) Effective in reducing albuminuria
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Possible risk for saxagliptin and alogliptin
Cardiac--ASCVD	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.

Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Secretagogues (glimepiride, glipizide, glyburide, repaglinide, nateglinide)

	SU	GLN
Hypoglycemia	Moderate / severe	Mild
Weight	Gain	
Renal / Genitourinary	More hypoglycemia risk	
Gastrointestinal adverse effects	Neutral	
Cardiac—CHF	More CHF risk	
Cardiac--ASCVD	?	
Bone	Neutral	
Ketoacidosis	Neutral	

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; GLN = glinide; SU = sulfonylurea.
Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Alpha Glucosidase Inhibitors (AGis) (acarbose)

Hypoglycemia	Neutral
Weight	Neutral
Renal / Genitourinary	Neutral
Gastrointestinal adverse effects	Moderate
Cardiac	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.
Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Thiazolidinediones (TZDs)* (pioglitazone)

Hypoglycemia	Neutral
Weight	Gain
Renal / Genitourinary	Neutral
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	Moderate
Cardiac--ASCVD	May reduce stroke risk
Bone	Moderate fracture risk
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | Uncertain effect

*Moderate dose (pioglitazone 30 mg).
ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.
Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Colesevelam and Bromocriptine Mesylate

	Colesevelam	BCR-QR
Hypoglycemia	Neutral	Neutral
Weight	Neutral	Neutral
Renal / Genitourinary	Neutral	Neutral
Gastrointestinal adverse effects	Mild	Moderate
Cardiac—CHF	Neutral	Neutral
Cardiac--ASCVD	Benefit	Safe
Bone	Neutral	Neutral
Ketoacidosis	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; BCR-QR = bromocriptine mesylate quick release; CHF = congestive heart failure.
Garber AJ, et al. *Endocr Pract.* 2017;23:207-238.

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Insulin

Hypoglycemia	Moderate to severe
Weight	Gain
Renal / Genitourinary	More hypoglycemia risk
Gastrointestinal adverse effects	Neutral
Cardiac—CHF	More CHF risk
Cardiac—ASCVD	Neutral
Bone	Neutral
Ketoacidosis	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | Uncertain effect

ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure.

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.

Pharmacokinetics of Available Insulins

	Agent	Onset (h)	Peak (h)	Duration (h)	Considerations
Basal	**NPH**	2-4	4-10	10-16	Greater risk of nocturnal hypoglycemia compared to insulin analogs
Basal	**Glargine Detemir Degludec**	~1-4	No pronounced peak*	Up to 24†	Less nocturnal hypoglycemia compared to NPH
Basal-Prandial	**Regular U-500**	≤0.5	~2-3	12-24	• Inject 30 min before a meal • Indicated for highly insulin resistant individuals • Use caution when measuring dosage to avoid inadvertent overdose
Prandial	**Regular**	~0.5-1	~2-3	Up to 8	• Must be injected 30-45 min before a meal • Injection with or after a meal could increase risk for hypoglycemia
Prandial	**Aspart/Fiasp Glulisine Lispro Inhaled insulin**	<0.5	~0.5-2.5	~3-5	• Can be administered 0-15 min before a meal • Less risk of postprandial hypoglycemia compared to regular insulin

* Exhibits a peak at higher dosages.

† Dose-dependent.

NPH, Neutral Protamine Hagedorn.

Moghissi E et al. *Endocr Pract*. 2013;19:526-535. Humulin R U-500 (concentrated) insulin prescribing information. Indianapolis: Lilly USA, LLC.

Insulin Concentrations

Concentration	Units/mL	Units/vial	Units/pen
U-100	100	1000 (10 units per vial)	300 (3 mL/pen)
U-200	200	Not available in vials	600 (3 mL/pen)
U-300	300	Not available in vials	450 (1.5 mL/pen)
U-500	500	10,000 (20 units/vial)	1500 (1.5 mL/pen)

- Insulin pens significantly reduce the risk of dosing errors and hypoglycemic events
- Pens completely eliminate the need for converting doses based on the volume of insulin injected
- Dosing errors with U-500 insulin vials are common and dangerous but can be avoided with newly available pens
  - 5-fold higher insulin dose relative to the same volume of a U-100 insulin

Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA. Newton C, et al. AACE Annual Meeting. 2013 [abstract 271]. Segal AR, et al. Am J Health Syst Pharm. 2010;67:1526-1535.

Antidiabetic Agents and Weight

Class	Agent(s)	Weight Effect
Amylin analog	Pramlintide	↓
Biguanide	Metformin	↓
GLP1 receptor agonists	dulaglutide, exenatide, exenatide XR, liraglutide	↓
SGLT-2 inhibitors	canagliflozin, dapagliflozin, empagliflozin	↓
α-Glucosidase inhibitors	Acarbose, miglitol	↔
Bile acid sequestrant	Colesevelam	↔
DPP4 inhibitors	linagliptin, saxagliptin, sitagliptin	↔
Dopamine-2 agonist	Bromocriptine	↔
Glinides	Nateglinide, repaglinide	↑
Sulfonylureas	Glimepiride, glipizide, glyburide	↑
Insulin	Aspart, detemir, glargine, glulisine, lispro, NPH, regular, inhaled	↑↑
Thiazolidinediones	Pioglitazone	↑↑

- Risk of additional weight gain must be balanced against the benefits of the agent
  - Sulfonylureas may negate weight loss benefits of GLP1 receptor agonists or metformin
  - Insulin should not be withheld because of the risk of weight gain

Garber AJ, et al. *Endocr Pract*. 2017;23:207-238.
ADA. *Diabetes Care*. 2017;40:S64-S74.
Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

Glycemic Management of Type 2 Diabetes

TECHNOLOGY FOR TYPE 2 DIABETES MANAGEMENT

SMBG in Type 2 Diabetes: AACE/ACE Recommendations

Noninsulin Users

- Introduce at diagnosis
- Personalize frequency of testing
- Use SMBG results to inform decisions about whether to target FPG or PPG for any individual patient

Testing positively affects glycemia in T2D when the results are used to:
- Modify behavior
- Modify pharmacologic treatment

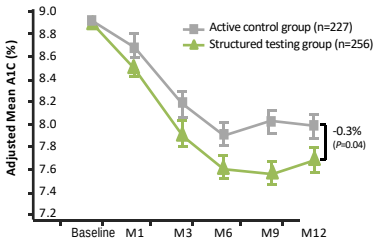
Insulin Users

- All patients using insulin should test glucose
  - ≥2 times daily
  - Before any injection of insulin
- More frequent SMBG (after meals or in the middle of the night) may be required
  - Frequent hypoglycemia
  - Not at A1C target

FPG, fasting plasma glucose; PPG, postprandial glucose; SMBG, self-monitoring of blood glucose; T2D, type 2 diabetes.

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

SMBG in Patients With T2D Not Using Insulin



	Baseline	M1	M3	M6	M9	M12
ACG	8.9% (0.08)	8.7% (0.1)	8.2% (0.1)	7.9% (0.1)	8.0% (0.1)	8.0% (0.1)
STG	8.9% (0.07)	8.5% (0.09)	7.9% (0.09)	7.9% (0.09)	7.6% (0.09)	7.7% (0.09)

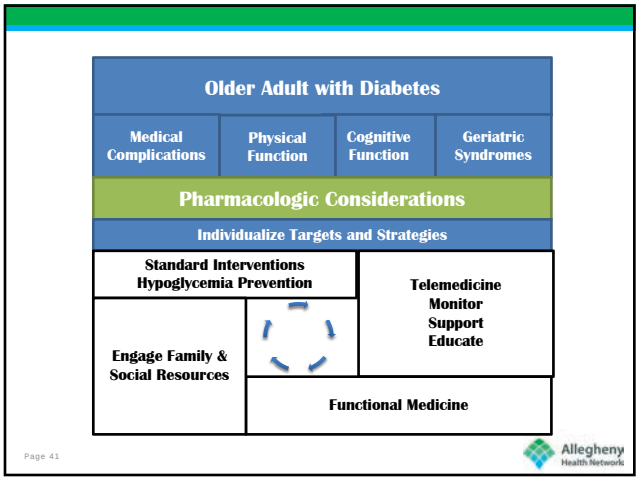
ACG, active control group; SMBG, self-monitoring of blood glucose; STG, structured testing group; T2D, type 2 diabetes.

Polonsky WH, et al. *Diabetes Care.* 2011;34:262-267.

The Future is Here: Remote Glucose Monitoring

Freestyle Libre

Dexcom G6


Older Adult with Diabetes
Medical Complications
Physical Function
Cognitive Function
Geriatric Syndromes
Pharmacologic Considerations
Individualize Targets and Strategies
Standard Interventions
Hypoglycemia Prevention
Telemedicine
Monitor
Support
Educate
Engage Family & Social Resources
Functional Medicine
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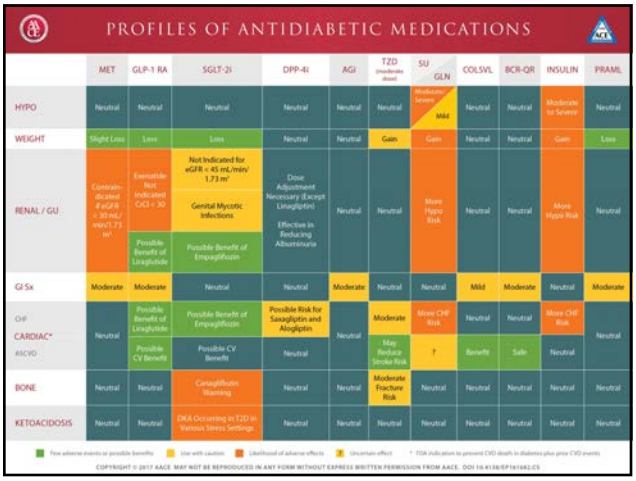
PROFILES OF ANTIDIABETIC MEDICATIONS
MET
GLP-1 RA
SGLT-2i
DPP-4i
AGi
TZD
SU
GLN
COLSVL
BCR-QR
INSULIN
PRAML
HYPO
WEIGHT
RENAL / GU
GI Sx
CARDIAC*
BONE
KETOACIDOSIS