Basal Insulin

- Glargine (Lantus) U100
  - QD approved but used BID
- Glargine U300 (Toujeo)
  - Dose QD Use same units as U100
  - 3 times concentrated U100; the pen makes the volume adjustment
  - PK/PD flatter than U100
- Detemir (Levemir)
  - Dosed QD and BID
  - Bound to Albumin, Fairly flat basal
- NPH (Neutral Protamine Hagedorn)
  - Dose BID
  - Duration 12 hours Peak at 6-8 hrs
- Degludec (Tresiba) U100/U200
  - 48-72 hours activity but dosed QD

Basal only; advantages and disadvantages

Yeas

- Ideal for *needle scared* patients
- Less brain cell usage to administer
- Overall Less Hypo than Prandial Insulin

Nays

- Frequently relied upon for too long
- Difficult to titrate Fasting Glucose is limiting factor
- Not quite physiologic, after all it is a basal
- No meal time or post prandial coverage

Premixed Insulin Preparations

Lispro(Humalog) 75/25 Aspart(Novolog) 70/30

- 70%-75% 12 hour long acting and 25%-30% rapid meal time insulin.
- Better total day coverage and can be given initially once daily or increased to two times daily.
- *A more physiologic (better fit) than older 70/30 with Regular. Don't be stuck in the time warp of the past.*

Lispro (Humalog) 50/50

- 50% long 50% rapid Dosed QD-TID
- *Basal/Bolus in a Pen*
- "High Mix"

Dosing Low Premix

- QD initiation begin with Dinner 15-20 units
- Monitor Pre meals or 2 hour post prandial for titration
- AM fasting elevation will also indicate need for increase dinner dose and PM pre Dinner Blood sugar to increase Breakfast Dose
- Augment with rapid with Lunch if Gaps in insulin coverage or transition to 50/50 or Basal/Bolus

High Mix Insulin

- Lispro (Humalog 50/50)
  - Only high mix available in US
  - Dose calculations based on TDD if reasonable or .5-.8 unit Kg/Day
  - Can be dosed QD-TID
  - Limitations Over Night Basal Units Frequently not sufficient
  - Basal Bolus in a Pen
  - Limited by fixed dose
  - Titration based on Premeal CBG adjustment made to Insulin dose preceding the CBG

Scope of Premix Insulin

- Advantages
  - More physiologic in addressing meal time as well as basal
  - Can start as once daily and work up from there
  - Titration is possible
  - Augmenting with rapid acting at lunch for Low Mix

- Disadvantages
  - Fixed Dosing
  - More awareness needed due to rapid acting
  - Lunch time can be uncovered in patients who need more comprehensive insulin coverage
  - Addition of Basal to High Mix users

Rapid Acting Insulin

- Lispro (Humalog)

DOSED MEALS AND HIGHS

- Aspart (Novolog)

VERY SIMILAR PK/PD

- Glulisine (Apidra)
- Insulin Human (Afrezza)
  - Inhaled
  - PFT required
  - Bolus Unit packets 4, 8, 12 unit
  - Very Rapid Onset 30 mins
  - Sanofi Recently Returned Drug to Mankind

Basal Bolus

More Advanced Insulin Plan

- QD or BID long-acting Basal
- Short-acting Prandial insulin for Meals and Highs

1. Calculate using CBG levels: start at 1 unit per 50 blood sugar greater than 100 (glucose correction factor)
2. Grams of carbohydrate: begin with 1 unit per 15 gram of carb. (insulin to carbohydrate ratio)
3. Testing is the key to being successful
4. Get assistance from your local CDE's they are invaluable

Insulin Delivery Systems

- Insulin Infusion Pumps
  - Omni pod, T-Slim, Animas, Medtronic, and Accu-chek

Parting thoughts

- The treatment of diabetes is changing rapidly, with new information and insights yearly.
- Its a struggle for even the most enthusiastic of providers to stay current on treatment options.
- Remember this is a team approach, your education and input is critical for effective treatment.

Clinical Diabetes Basic Training

Eden Miller D.O.

A changing Landscape?

- Obesity Rates in the United States Among Children are starting to plateau
- Recent announcement that in 2014 the incidence of Diabetes declined for the first time in 10 years
- Still the Vast Majority of Americans and those world wide have not met targets for glucose management, and several unaware they have diabetes
- The message is getting out but there is still a long way to go

What is Diabetes?

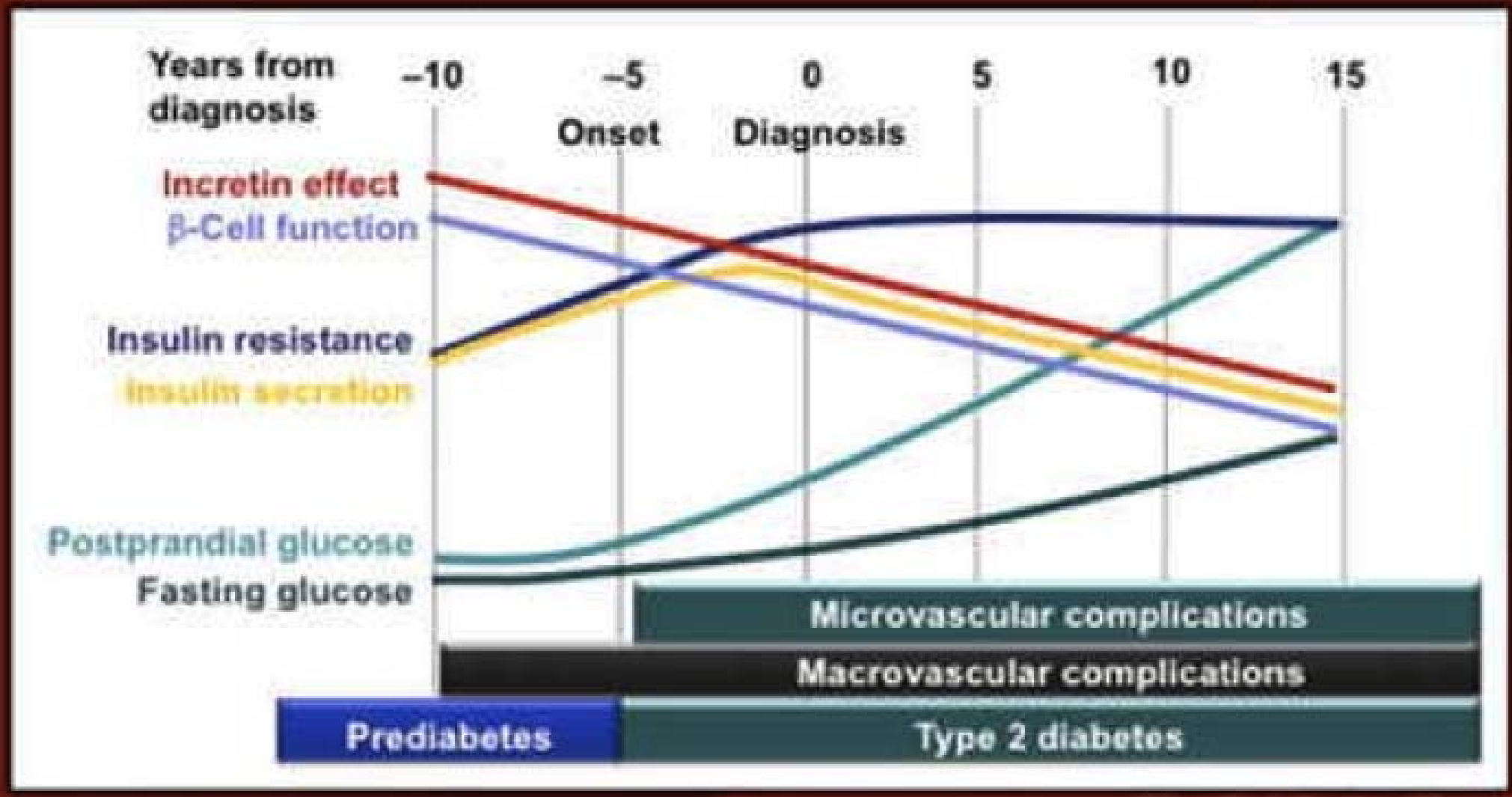
An impairment of the body's ability to effectively transport glucose into the cell so it may be utilized for fuel.

Diabetes is a Dual Hormone Disease

Insulin, the body hormone responsible for the transport of glucose, is either less potent, decreased, or absent in a diabetic individual.

Glucagon, the counter regulatory hormone to insulin is increased and often unopposed.

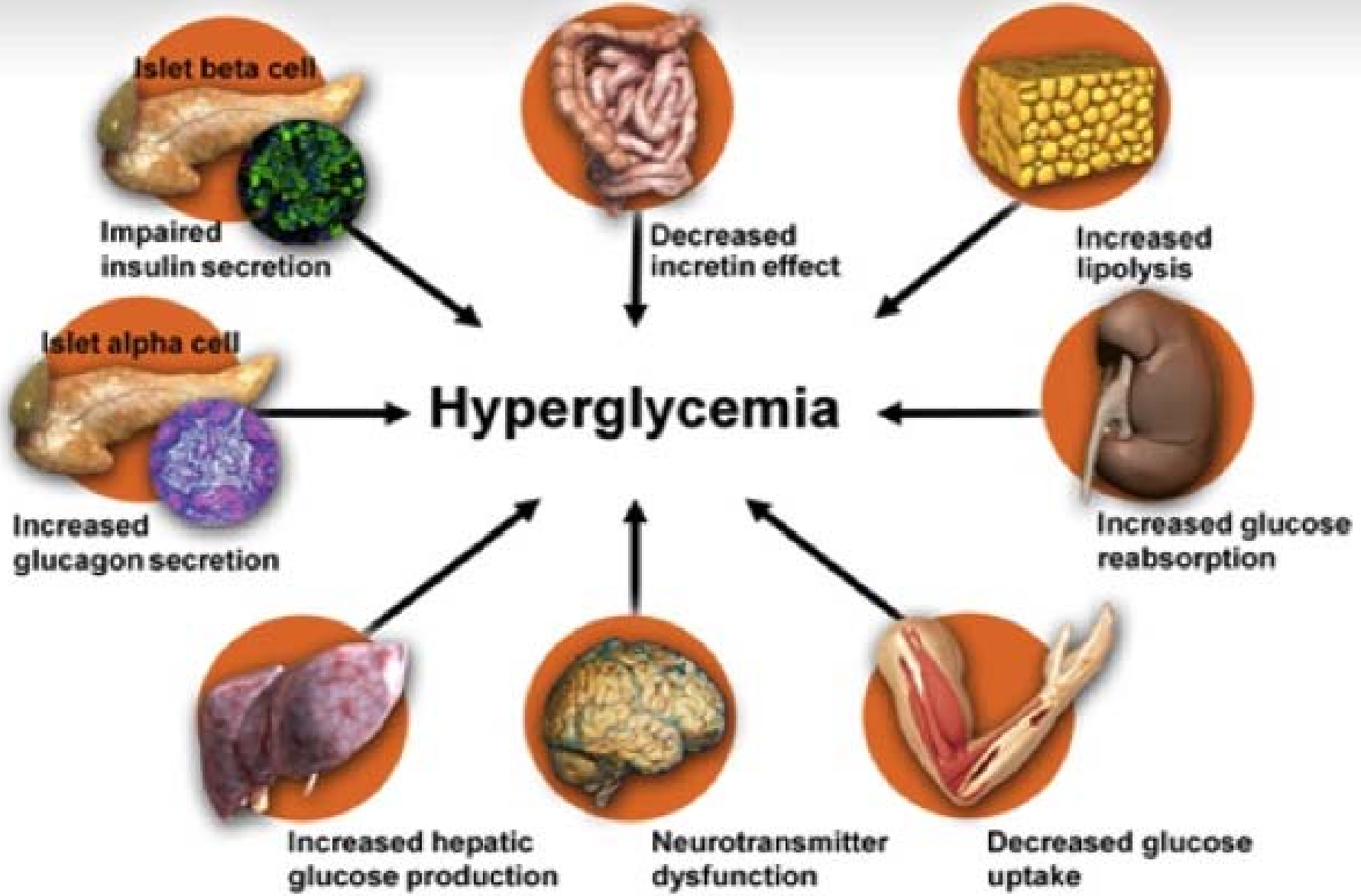
Natural History of Type 2 Diabetes



A Touch of Sugar
(fasting serum)

- Glucose intolerance: 105-113
- Pre diabetes: 114-125 *(annually 5-10% of individuals progress to diabetes)*
- Diabetes: 126 or greater

Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58:773-795.

A1C what should it be?

- A.D.A.- less than 7%
- A.C.E.- less than 6.5%

What does that percentage mean in terms of numbers.

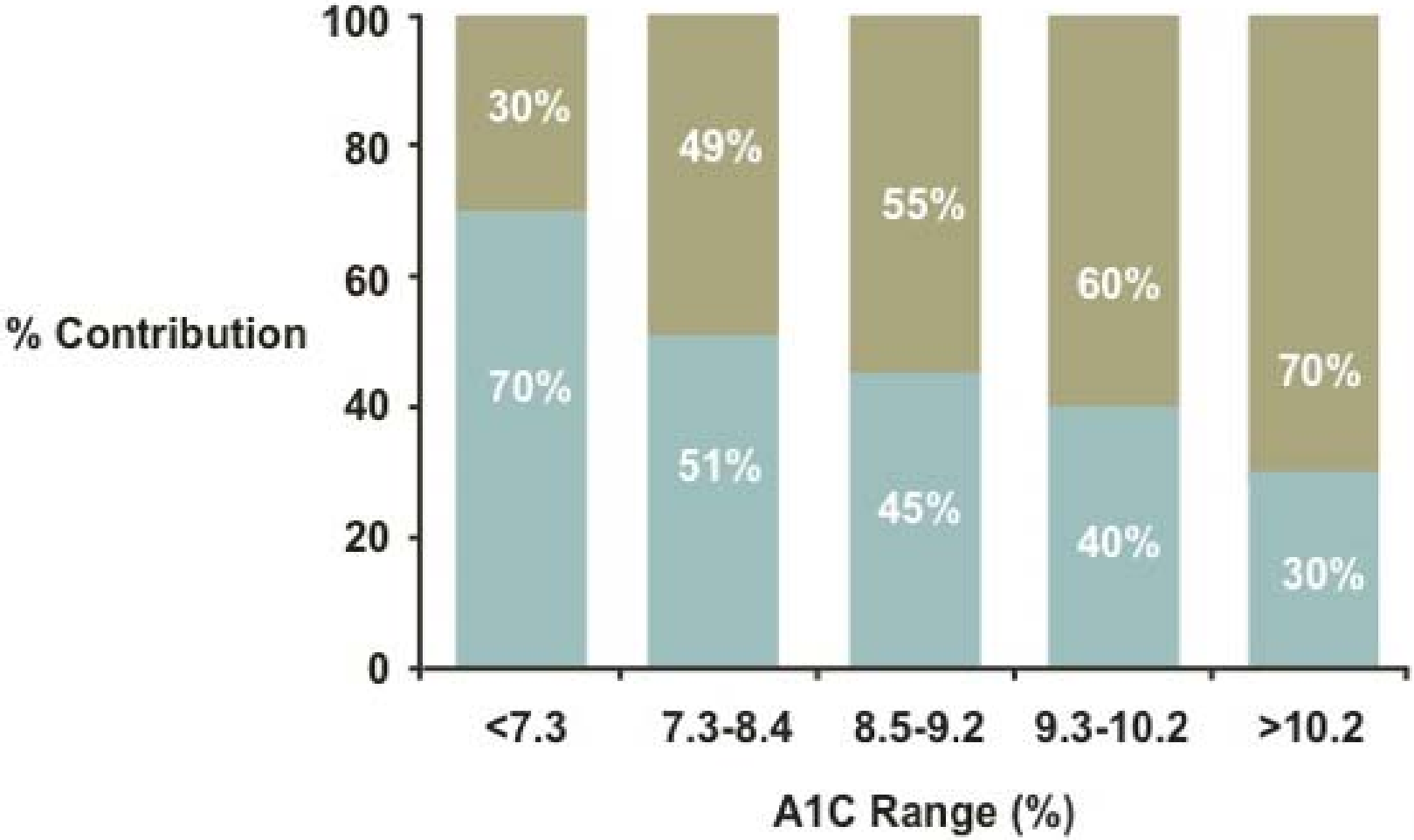
6%-135 7%-170

8%-205 9%-240

10%-275 11%-310

12%-345

Relative Contribution of Postprandial Glucose Increases as A1C Approaches Target

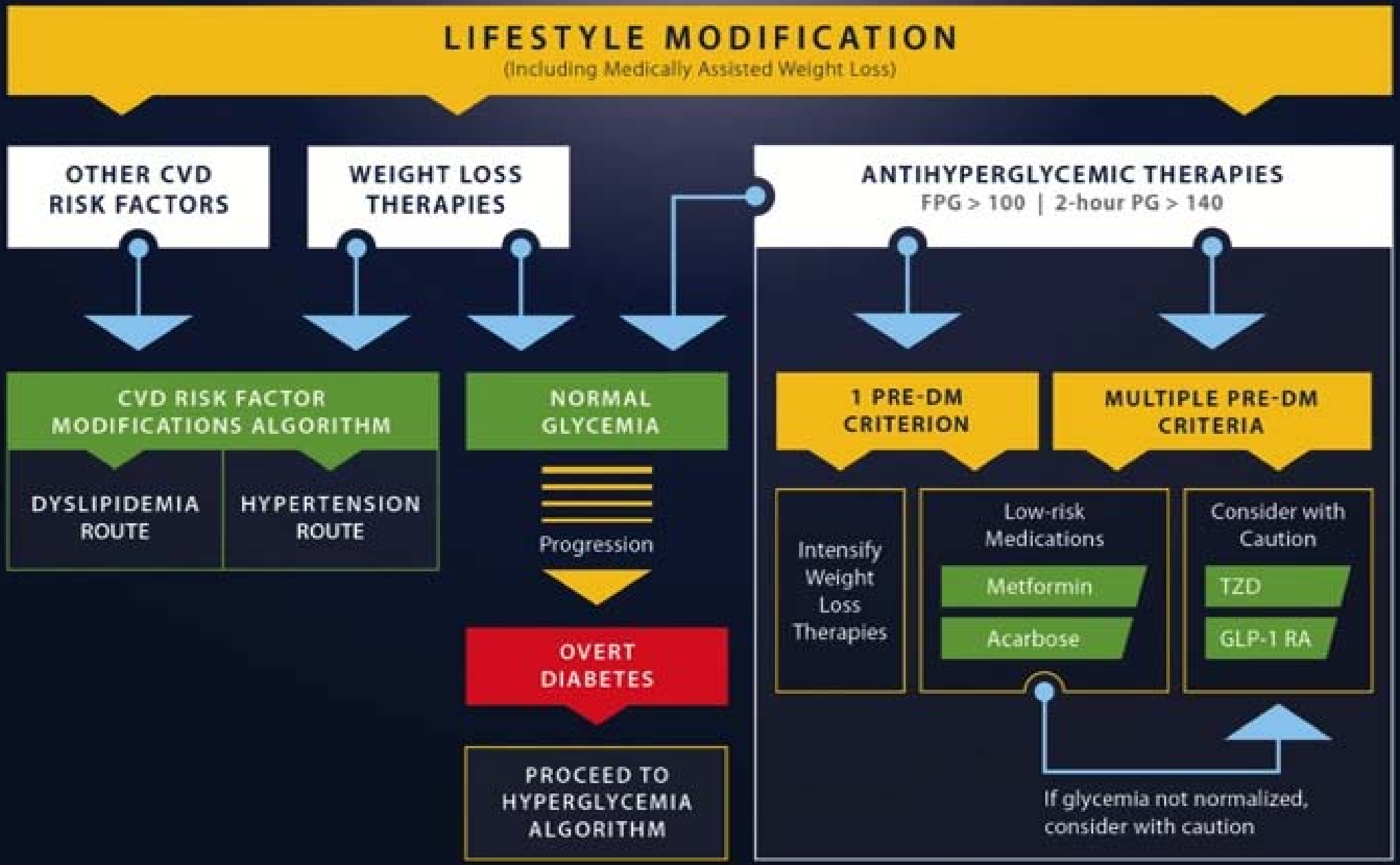


N = 290; Percentages are approximations

Adapted from Monnier L, et al. *Diabetes Care* 2003; 26:881-885

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2005)



Medication used for DM II

- Glucophage (Metformin)
  Action is on the liver to decrease extra glucose
- Sulfonylureas (Glipizide, Glyburide,Glimiperide)
  release of insulin
- SGLT2 Inhibitors (Invokana,Jardiance, Farxiga,Steglatro)
  Glucouretic, Kidney release of glucose
- Glitizones (Actos and Avandia) mRNA propagation of insulin receptors on cellular surface
- GLP1 Incretin Family – (Byetta,Bydureon,Victoza, Tanzium, Trulicity, Ozempic mimics hormone naturally found in the body
- DPP4 inhibitors (Januvia, Tradjenta, Onglyza) prevent native GLP 1 breakdown.

Metformin (Glucophage)

- Biguanide
- Dosed 500mg – 1000mg Dosed QD or BID
- Prevents the conversion of glycogen to glucose in the liver
- First Line Treatment for Diabetes
- Limitations Side effects GI and renal function/clearance
- Rarely Metabolic Acidosis since not metabolized in the liver

Sulfonylureas

- Glipizide 2nd Generation (Glucotrol) 2.5m-10mg
- Glyburide 2nd Generation (Micronase)
- Glimiperide *3rd Generation Pancreatic Specific* (Amaryl) 2mg, 4mg and 8mg only in US

By Blocking potassium channels the opening of voltage dependent gates causing calcium influx and insulin degranulation and release. Also may inhibit glucagon and potentiate insulin action at peripheral tissue. Mainly fasting glycemic effect.

Meglitinides

- Starlix –*nateglinide 60-120mg daily*
- Prandin-*repeglinide .5mg,1mg and 2mg once daily*
- Secretagog like but less affinity with the ATP channels and thus a greater disassociation with the receptor when may lessen the rapid out flow of pro-insulin
- Both Fasting and PPG effect

Glitizones (Sensitizers)

- Pioglitizone (Actos)
- Dosed 15-45 mg QD
- Beneficial CV and Lipid effects
- Non-hypoglycemic
- Edema due to sodium reabsorption in Nephron

- Rosiglitizon (Avandia)
- Dosed 2-8 mg QD
- Data Conflicting on CV effects
- Non-hypoglycemic
- Edema sodium reabsorption

DPP-4 Inhibitors

Dipeptidyl peptidase-4 inhibitor

Sitagliptin – *Januvia*

Typical Dose 100mg daily with or without food

Secondary doses of 50mg GFR 30-50 and 25mg for GFR<30

Saxtagliptin- *Onglyza*

Dosing 2.5mg and 5mg if GFR <50 then 2.5mg

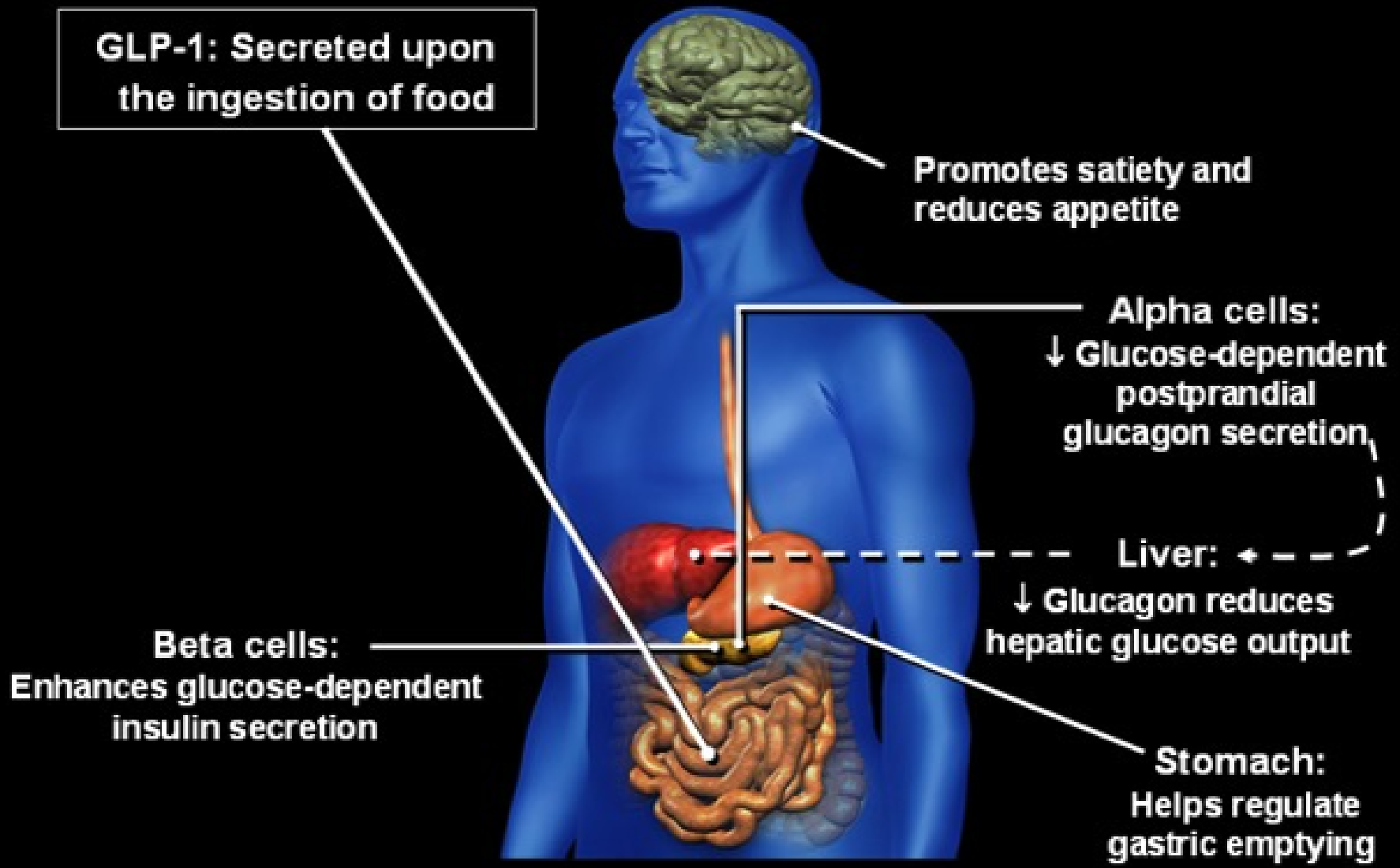
Linagliptin-*Tradjenta*

5mg single dosing irrespective of GFR

GLP1-Incretins

- Byetta (Exenatide) BID dosing 5mcg and 10mcg
- Victoza (Liraglutide) QD Dosing .6mcg-1.8mcg
- Bydureon(Exenatide LAR) Q weekly Dosing 2mg GFR>30
- Tanzium **ON HOLD** (Albiglutide) Q weekly Dosing 30mg and 50mg
- Trulicity (Dulaglutide) Q weekly Dosing .75mg and 1.5mg
- Ozempic (Simaglutide) Q weekly .25mg-1mg

GLP-1 Modulates Numerous Functions in Humans



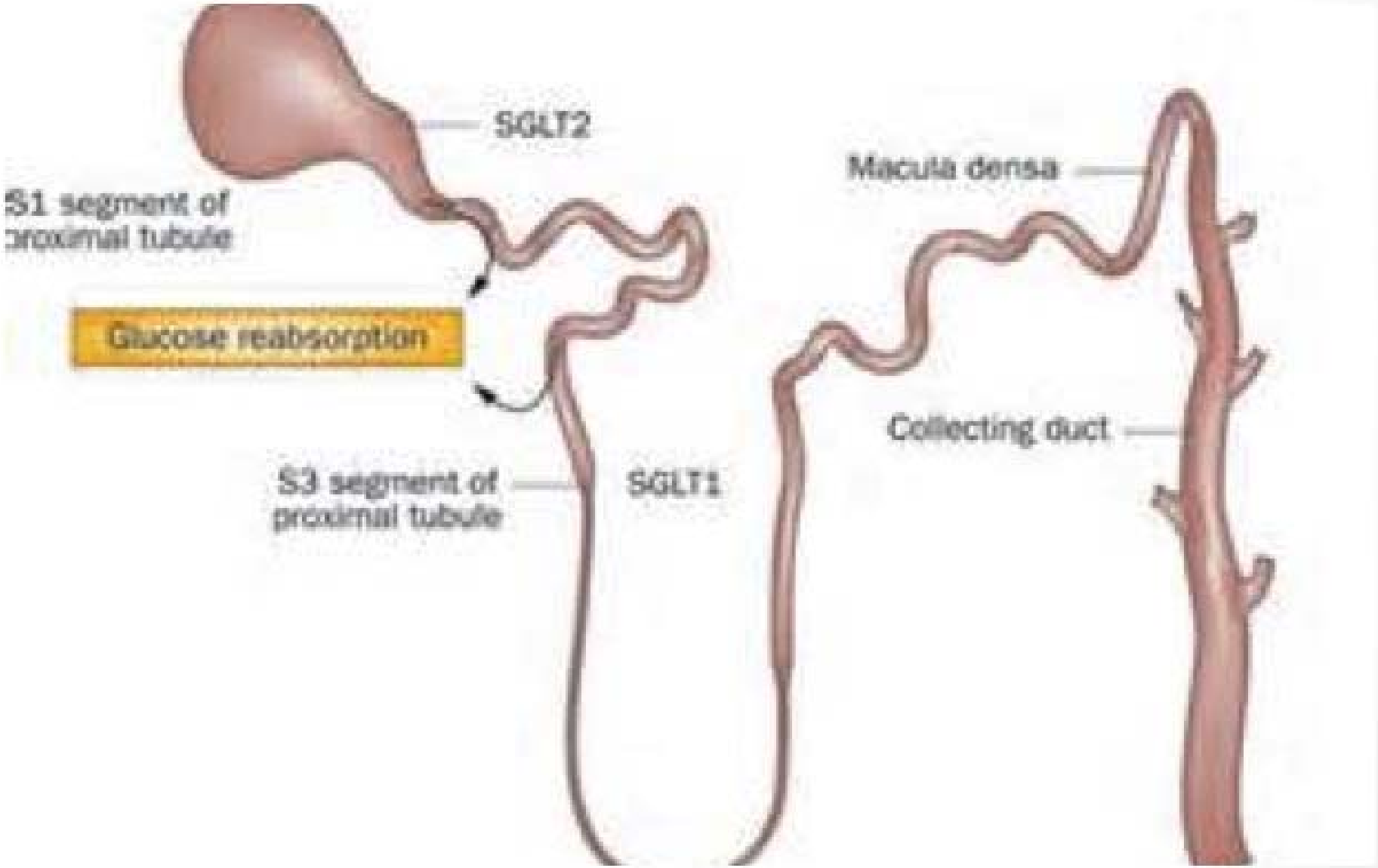
Data from Flint A, et al. *J Clin Invest.* 1998;101:515-520; Data from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422
Data from Nauck MA, et al. *Diabetologia.* 1996;39:1546-1553; Data from Drucker DJ. *Diabetes.* 1998;47:159-169

SGLT2 (Glucouretics)

- Invokana-(Canagliflozin) 150mg GFR≥45 300mg GFR≥60
- Farxiga-(Dapagliflozin) 5mg or 10mg GFR≥60
- Jardiance-(Empagliflozin) 10mg or 25mg GFR≥45
- Steglatra (Ertugliflozin) 5mg and 15mg GRF≥60

Lower the renal glucose threshold by inhibiting SGLT2 receptors in the Kidney causing renal glucose excretion up to 120 grams of glucose. Recent CV data for Empagliflozin

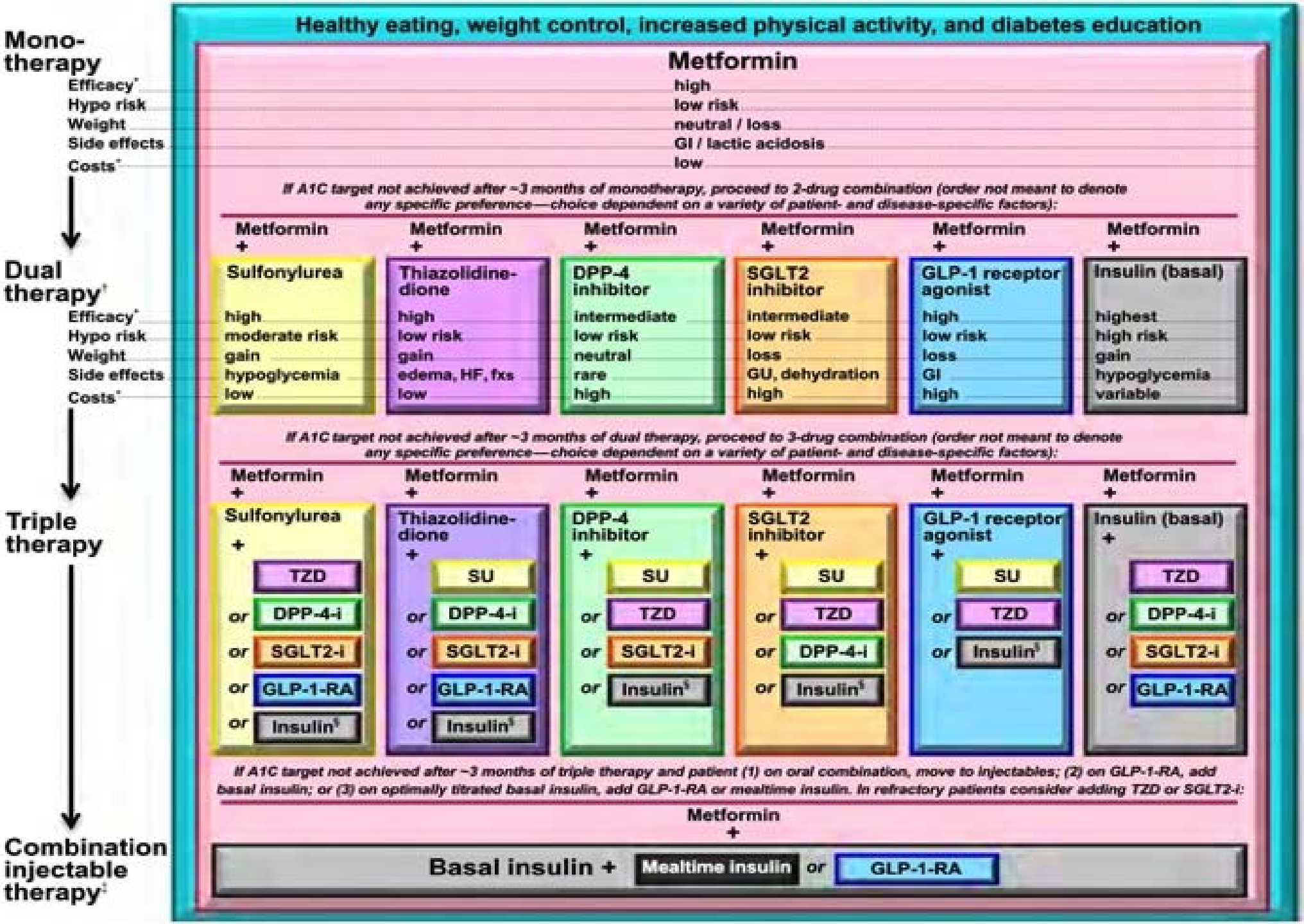
SGLT2 Blockade



Atypical Orals

- Precose- *Acarbose* alpha glucosidase inhibitor 25-100mg TID prior to meals
- Bromocriptine-*Parlodel* dopamine agonist 1.6mg-4.8mg daily
- Welchol-*Colesevelam bile acid sequestrant doses 6 tablets daily or one packet daily*

ADA 2016


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin
high
low risk
neutral / loss
GI / lactic acidosis
low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Efficacy*
Hypo risk
Weight
Side effects
Costs*
Metformin + Sulfonylurea
high
moderate risk
gain
hypoglycemia
low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

MONOTHERAPY*
- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ✓ AGi
- ⚠ TZD
- ⚠ SU/GLN

If not at goal in 3 months proceed to Double Therapy

Entry A1c ≥ 7.5%

DUAL THERAPY*
MET or other 1st-line agent +
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*
MET or other 1st-line agent + 2nd-line agent +
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1c > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- ✓ Few adverse events or possible benefits
- ⚠ Use with caution

* Order of medications listed represents a suggested hierarchy of usage

PROGRESSION OF DISEASE

When to cross over to insulin.

- No more non-insulin medication to add.
- Rising post-meal blood sugars
- Increasing hemoglobin A1C (this occurs later)
- Very high blood sugars either early on in the disease or later in the advanced disease.
- A large percentage of diabetics will require Insulin within 10-15 years after diagnosis.
- Insulin Deficiency by laboratory or Disease progression

DON'T BE AFRAID OF INSULIN

It's natural!

Modification of Oral when transitioning to Insulin

- No need for secretagogs (Sulfonylureas) personal opinion
- May continue sensitizers but may increase risk of edema
- Metformin may always be continued as long as appropriate (pts. still have livers)
- GLP1 should always be considered if possible (Fortified with Insulin in Europe)
- SGLT2 (Kidney dependent) able to be added at any time to insulin

Types of Insulin Commonly Used

- Once-a-day long-acting Lantus U100/U300 Toujeo or Levemir or BID NPH Tresiba (Degludec) U100/U200
- 75/25 mix insulin, Novolog 70/30, or Humalog 50/50
- Short-acting at meal time Bolus (Humalog, Novolog, Apidra, or Inhaled Afrezza)
- Complete transition to insulin using long-acting/short-acting with multiple injections termed *Basal/Bolus*
- Continuous Insulin Infusion using Pumps