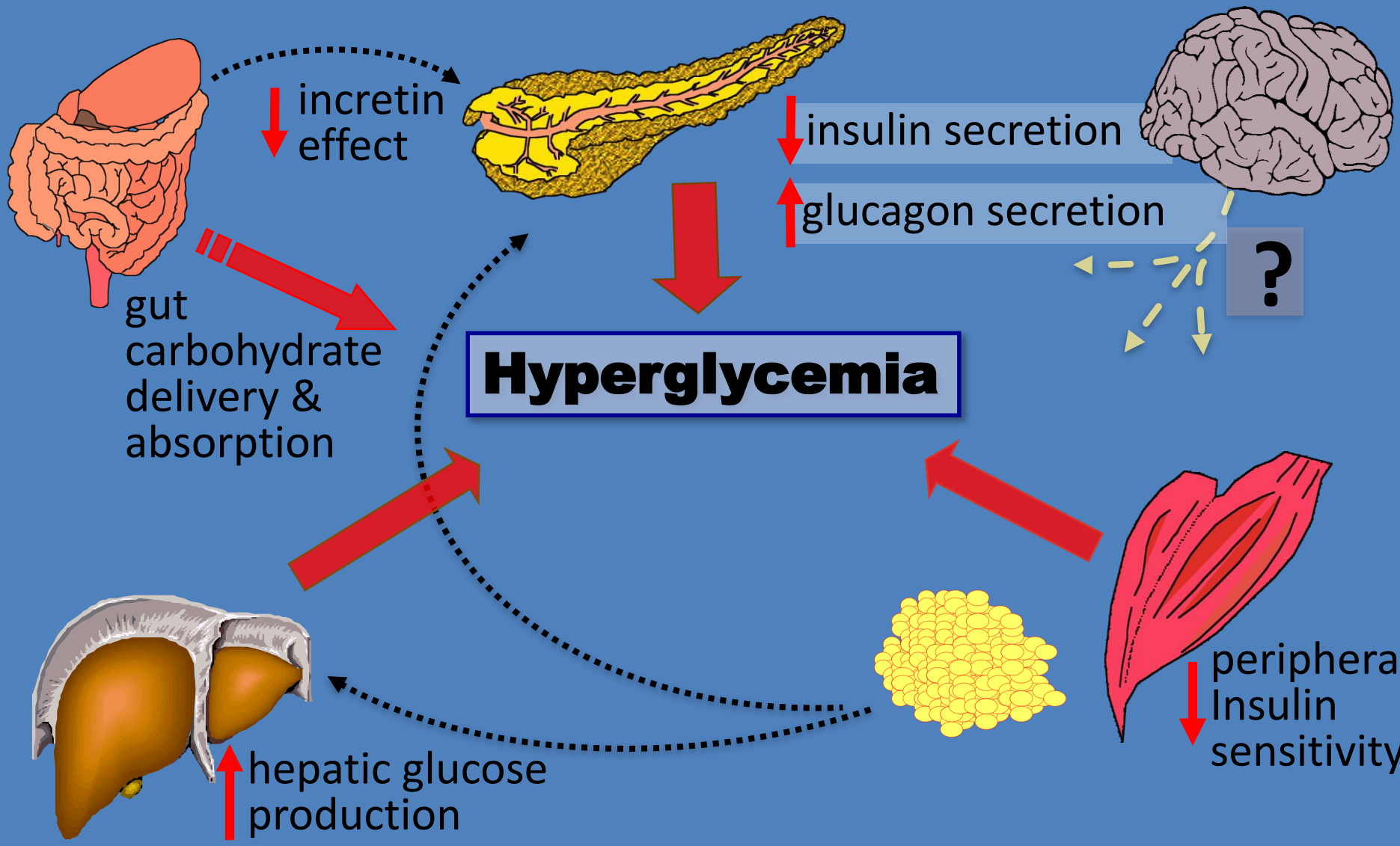
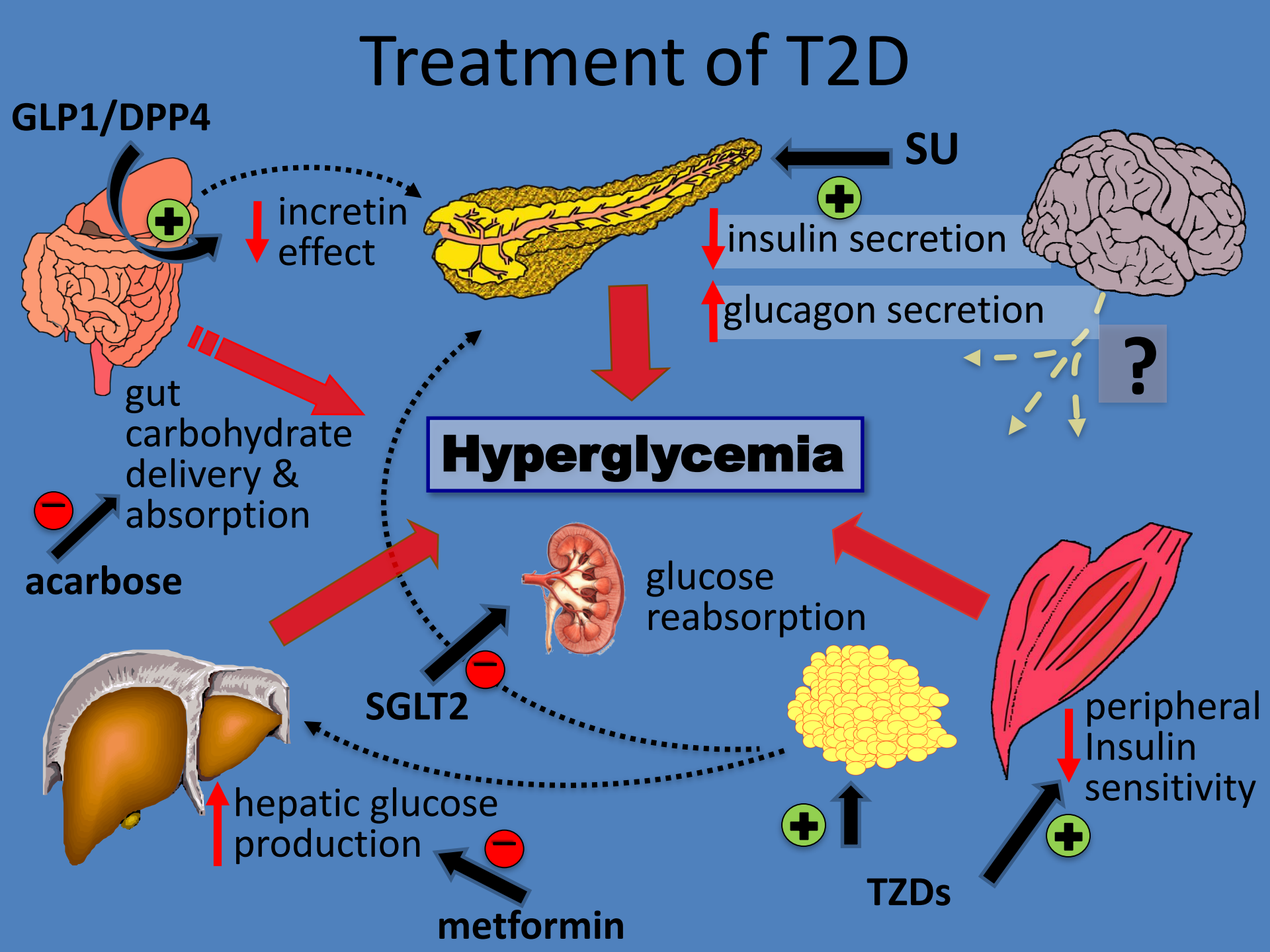
# Oral Agents in Type 2 Diabetes

**Robin Goland, MD**
**J. Merrill Professor of Medicine and Pediatrics**
**Co-Director, Naomi Berrie Diabetes Center**
**Columbia University, New York, USA**

# Pathophysiological Defects in T2D

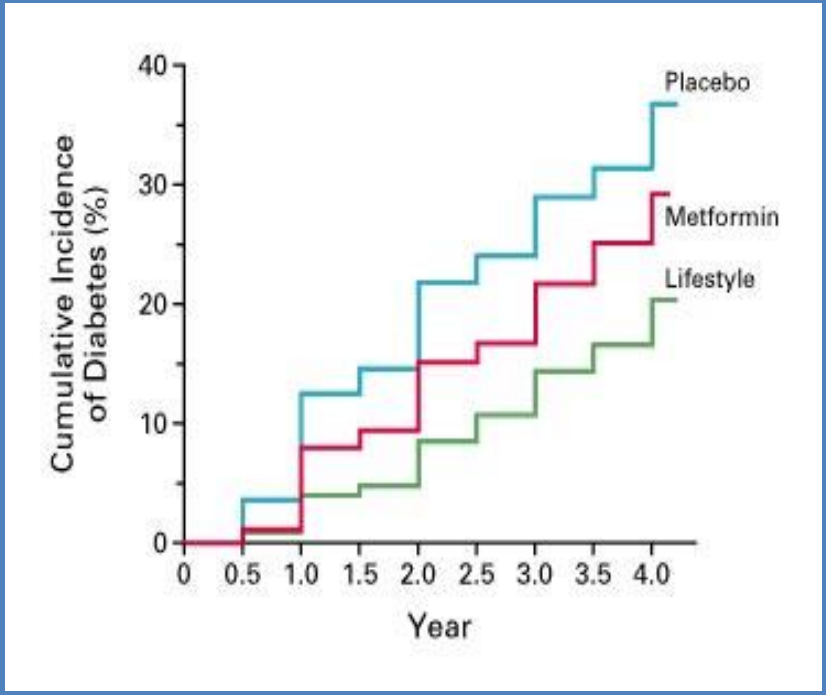


# Treatment of T2D



# Don’t forget about diet/exercise

Lessons from the Diabetes Prevention Program (DPP): 5-10% weight loss reduces development of diabetes by 58% in subjects with IGT (and improves control in patients with T2D)




Diabetes Prevention Program Research Group, . N Engl J Med 2002;346:393-403

DPP *NEJM* 2002

# Biguanides

| Agent | Efficacy Δ%HbA1c | Mechanism of Action | Benefits | Risks/ Concerns |
|---|---|---|---|---|
| **Metformin**<br>**Metformin ER** | **-1 to 2%** | **Decreases hepatic glucose production** | **Weight neutral/mild weight loss, no hypoglycemia** | **Diarrhea, lactic acidosis** |

# T2D treatment
# 1st line = metformin

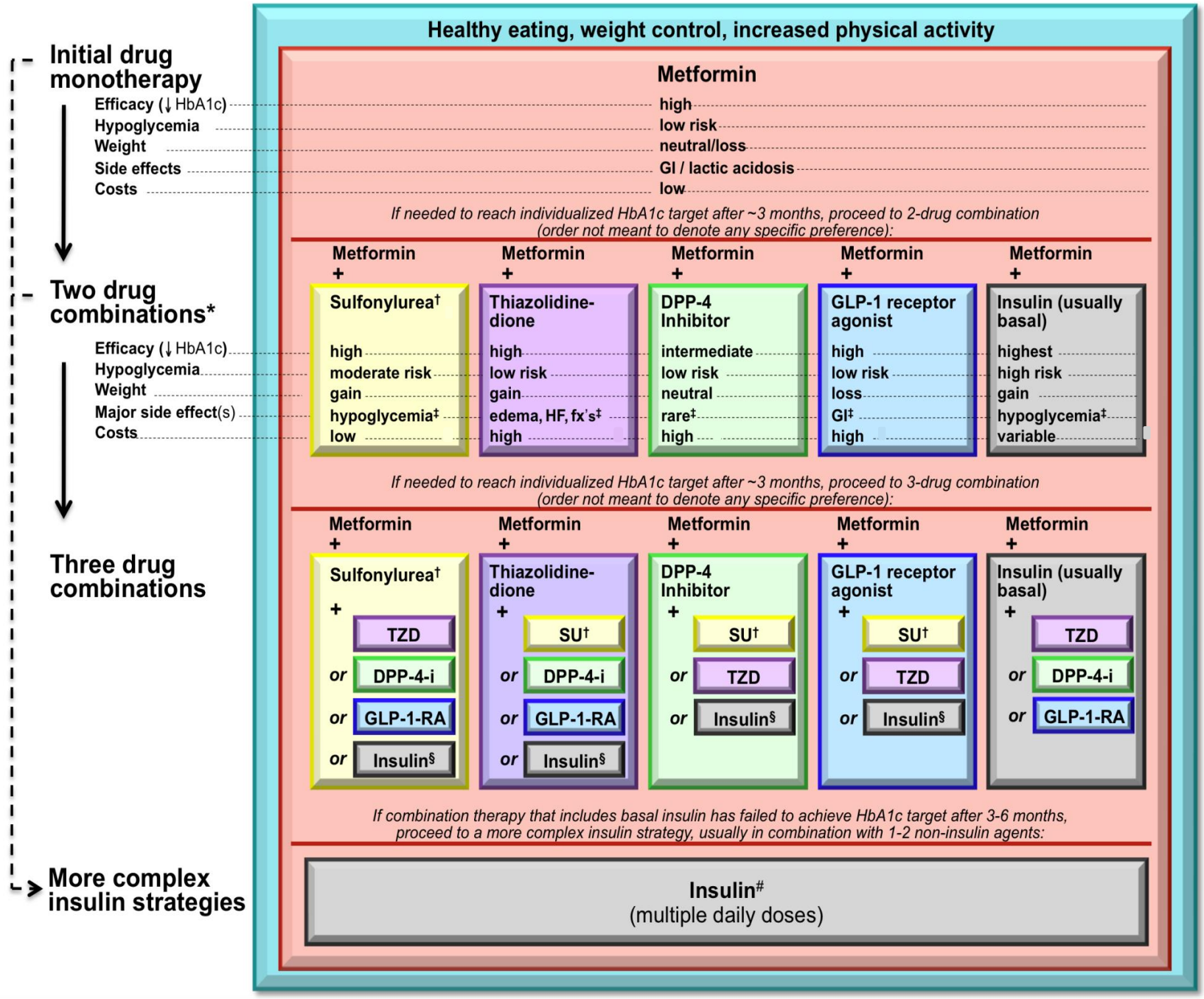
- Contraindications to metformin are very few
  - Severe dehydration, hemodynamic instability, metabolic acidosis, hepatic dysfunction/ alcoholism, unstable CHF/COPD
  - **Old guideline:** renal insufficiency (Cr≥1.5 mg/dL in men, 1.4 mg/dL in women)
  - **New guideline:**
    - Contraindicated in patients with eGFR <30
    - Not recommended in patients with eGFR 30-45
    - Recommended for all patients GFR 45+. If eGFR later falls to <45, assess benefits/risks of continuation; discontinue if eGFR later falls to <30.

# How to minimize metformin's GI side effects

- Many patients state that they had GI intolerance to metformin when prescribed by their PCPs, and refuse to take it again. This is a huge problem, as metformin is the best treatment option for patients with T2D, offering the best benefit/risk ratio, excellent durability, etc.
- If you are starting metformin, start low and go slow:
  - Patients may have heard about GI issues with metformin – tell them that with your approach, the likelihood of this is near-zero.
  - Start metformin 500mg daily x 3 days (with food); this is a homeopathic dose, but tolerates the patient to the drug.
  - After 3 days, increase to 500mg twice daily (with food).
  - Stay at this dose for 3 months, and assess HbA1c response. In meta-analyses, a total daily dose of 1000mg = 0.9% HbA1c reduction; 2000mg = 1.2% reduction.
  - If your patient has side-effects, consider an extended-release generic metformin (metformin ER). Only if this fails, try branded metformin (Glucophage, Glumetza, etc).

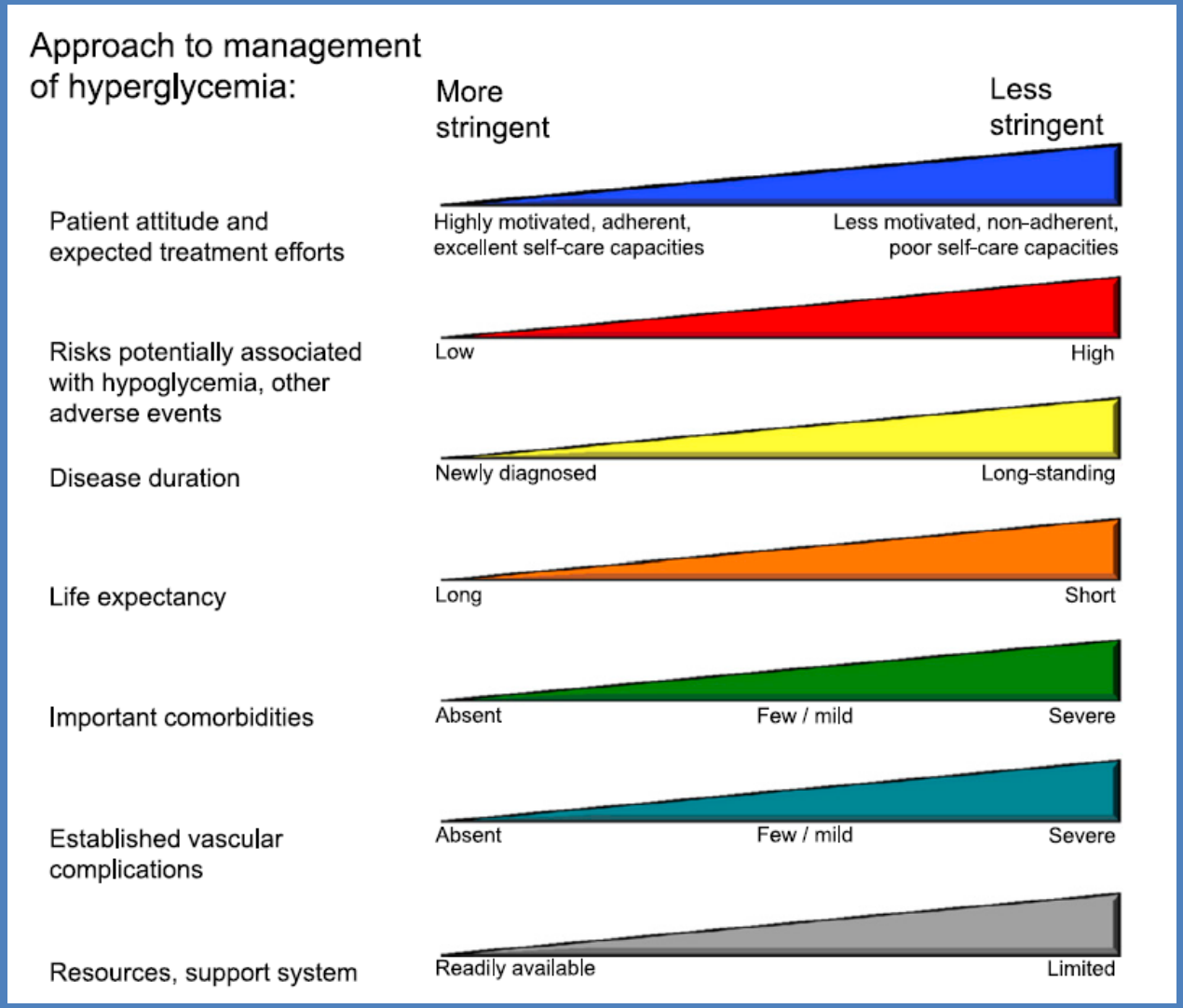
# T2D treatment – 2nd line

- Although there is clear consensus for 1st line therapy (metformin), there remains a black box for optimal 2nd and 3rd line therapy:
  - insulin-secretagogues (sulfonylureas/meglitinides)
  - DPP4 antagonists
  - GLP1 agonists
  - basal insulin
  - others (TZDs, SGLT2 inhibitors, prandial insulin)




ADA. Diabetes Care. *Diabetes Care* 2015;38(suppl 1):S43

# ADA-EASD (2016) Management of T2DM

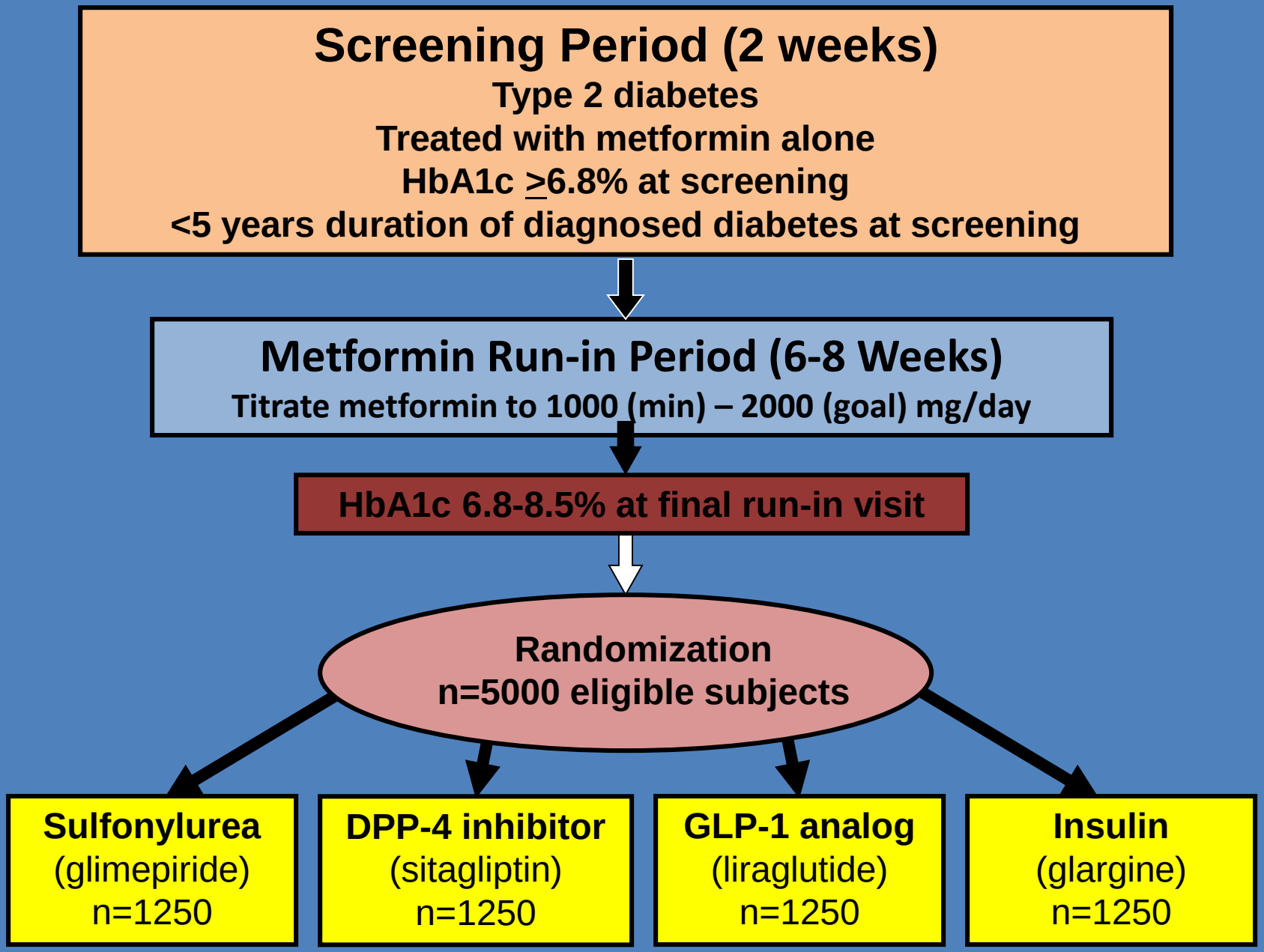



ADA. Diabetes Care. *Diabetes Care* 2016;39(suppl 1):S43

# GRADE Study: The Glycemia Reduction Approaches in Diabetes: a comparative Effectiveness Study

- RCT in recent-onset (<10 years) type 2 diabetes
- Compare the metabolic effects of 4 common anti-diabetic drugs when combined with metformin
    - SU: glimepiride
    - DPP-4: sitagliptin
    - GLP-1: liraglutide
    - Basal insulin: Glargine

GRADE
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)


Screening Period (2 weeks)
Type 2 diabetes
Treated with metformin alone
HbA1c ≥6.8% at screening
<5 years duration of diagnosed diabetes at screening
Metformin Run-in Period (6-8 Weeks)
Titrate metformin to 1000 (min) – 2000 (goal) mg/day
HbA1c 6.8-8.5% at final run-in visit
Randomization
n=5000 eligible subjects
Sulfonylurea
(glimepiride)
n=1250
DPP-4 inhibitor
(sitagliptin)
n=1250
GLP-1 analog
(liraglutide)
n=1250
Insulin
(glargine)
n=1250

# Outline

- 2nd-line antidiabetic agents
  - Sulfonlyureas
  - DPP4 inhibitors
  - GLP1r agonists (injectable)
  - basal insulin (injectable)
- 3rd-line oral antidiabetic agents
  - Alpha-glucosidase inhibitors
  - Thiazolidinediones (TZDs)
  - SGLT2 inhibitors
- Cases

# Insulin secretagogues: Sulfonylureas (and Meglitinides)

| Agent | Efficacy Δ%HbA1c | Mechanism of Action | Benefits | Risks/ Concerns |
|---|---|---|---|---|
| **Sulfonylureas**<br>Glyburide<br>Glipizide<br>Glimepiride | -1% | Binds sulfonylurea receptor on β-cells, stimulates insulin secretion | Extensive experience | Hypoglycemia, weight gain |
| **Meglitinides**<br>Repaglinide (Prandin)<br>Nateglinide (Starlix) | -1% | Binds sulfonylurea receptor on β-cells, stimulates insulin secretion | Rapid-acting version of SUs | Hypoglycemia, weight gain |

- Short acting: target post-prandial hyperglycemia
- Longer acting: target fasting hyperglycemia

# Do I use these meds?

Sulfonylureas/meglitinides are good options as 2nd line therapy. They work quickly (so can reduce glucose toxicity) and are inexpensive. Thus, sulfonylureas are the WHO recommendation for patients with T2D. These drugs also have significant downsides, including weight gain and hypoglycemia – especially problematic for long-acting agents (i.e. glyburide) – and effects are not durable (more on that later).

# Incretins: Overview

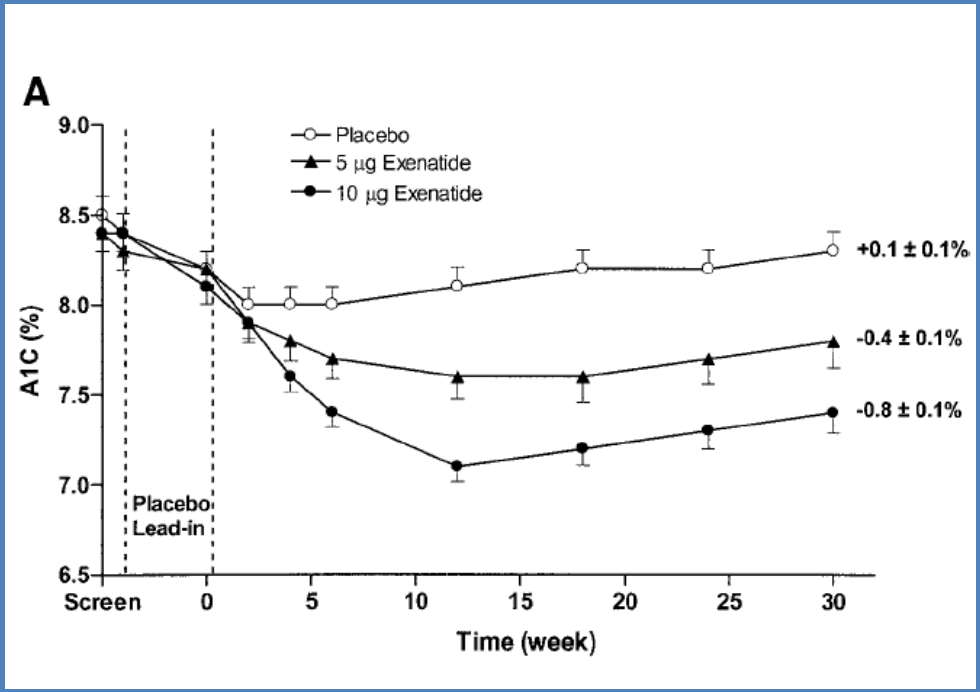
- Oral nutrition provides more potent insulin stimulus compared with isoglycemic IV challenge
- Enteroendocrine cells regulate energy intake and glucose homeostasis
- 2 major bioactive incretins:
  - Glucagon-like-peptide 1: GLP-1
  - Glucose-dependent-insulinotropic peptide: GIP

Nauck, Drucker *Lancet* 2006

# GLP-1 Receptor Agonists

| Agent | Dose | Adjustment renal failure | | |
|---|---|---|---|---|
| **GLP-1 R Agonists** | **CrCl >50** | **CrCl 30-50** | **CrCl <30** | **HD** |
| **Exenatide (Byetta)** | **10mcg bid** | **Caution titrating from 5 to 10mcg dose** | **Not recommended** | **Not recommended** |
| **Liraglutide (Victoza)** | **0.6mg daily x 1 week 1.2mg daily x 1 week 1.8mg daily** | **Caution** | **Caution Likely not recommended** | **Not recommended** |
| **Exenatide ER (Bydureon)** | **2mg weekly** | **Caution** | **Not recommended** | **Not recommended** |
| **Albiglutide (Tanzeum)** | **30mg, 50mg weekly** | **Caution** | **Not recommended** | **Not recommended** |
| **Dulaglutide (Trulicity)** | **0.75mg, 1.5mg weekly (no mixing required)** | **Caution** | **Not recommended** | **Not recommended** |

# GLP1r agonists + Metformin: range in 0.8-1.5% HbA1c Reduction




- Above is data from Byetta; newer GLP-1 agonists are more potent (1-1.2% reduction; higher in patients with A1c >9% where you can expect 1.5-2% reduction).
- Dosing schedules are also more convenient with newer agents: daily (Victoza) or weekly (Bydureon, Trulicity) dosing

Defronzo et al *Diabetes Care*, 2005

# DPP4 inhibitors

| Agent | Dose | Adjustment renal failure | | |
|---|---|---|---|---|
| | CrCl >60 | CrCl 30-60 | CrCl <30 | HD |
| Sitagliptin (Januvia) | 100mg | 50mg | | 25mg |
| Saxagliptin (Onglyza) | 5mg | | 2.5mg | 2.5mg |
| Alogliptin (Nesina) | 25mg | 12.5mg | 6.25mg | 6.25mg |
| Linagliptin (Tradjenta) | 5mg | No adjustment (hepatically cleared) | | |

*Vildagliptin (Galvus) approved by European markets, but not by FDA

# DPP4 inhibitors + metformin: ~0.6% HbA1c Reduction

| Treatment | Weighted mean change in $HbA_{1c}$ (95% CrI) |
|---|---|
| Alogliptin + metformin | −0.68 (−0.96 to −0.40)* |
| Linagliptin + metformin | −0.57 (−0.75 to −0.40)* |
| Saxagliptin + metformin | −0.61 (−0.79 to −0.44)* |
| Sitagliptin + metformin | −0.64 (−0.79 to −0.50)* |
| Vildagliptin + metformin | −0.59 (−0.75 to −0.44)* |

DPP4 (dipeptidyl peptidase 4) degrades GLP-1; inhibiting this enzyme increases endogenous GLP-1 levels, but not nearly to the levels of pharmacologic GLP-1, which likely accounts for its relatively milder effect on A1c

Craddy et al *Diabetes Ther*, 2014

# Do I use these meds?

Yes, these are my usual 2nd line therapy, as they are weight-neutral (DPP4 inhibitors) or –reducing (GLP-1 agonists), with negligible hypoglycemia. In addition, Liraglutide (Victoza) has proven CV outcome benefits – unknown if this is a class effect.

Both also have downsides, including high cost for the uninsured, relatively weak efficacy for DPP4 inhibitors, and the potential fear of injections for GLP-1 agonists, as well as several over-reported fears (pancreatitis, medullary thyroid cancer, etc).

# Basal insulin

- A mainstay of T2D treatment – not necessarily a medication of last-resort, and can be used as 2nd line
- Multiple options that can be used once daily:
  - traditional glargine (Lantus or Basaglar)
  - U200 glargine (Toujeo)
  - degludec (Tresiba)
- How to titrate – for most, a "treat to target" algorithm based on fasting blood sugars will work as long as the insulin is taken at the same time daily. Most TTT algorithms target fasting FSG <100mg/dl, but adjust for your particular patient.

| Start with 10 IU/day bedtime basal insulin and adjust weekly | |
|---|---|
| Mean of self-monitored FPG values from preceding 2 days | Increase of insulin dosage (IU/day) |
| ≥180 mg/dl (10 mmol/l) | 8 |
| 140–180 mg/dl (7.8–10.0 mmol/l) | 6 |
| 120–140 mg/dl (6.7–7.8 mmol/l) | 4 |
| 100–120 mg/dl (5.6–6.7 mmol/l) | 2 |

Riddle et al *Diabetes Care*, 2003

# Do I use these meds?

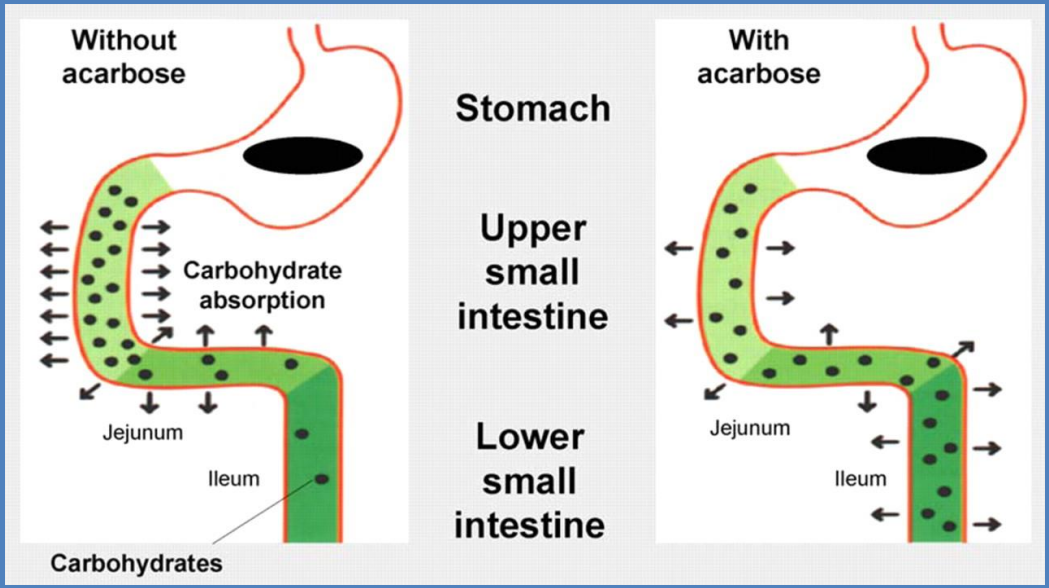
Yes, especially in patients who want a “natural” option as 2nd line, or for patients with T2D who have low insulin production. This may happen in patients with long-standing disease, but may happen sooner in specific patient populations. There are down-sides as well, including weight gain and hypoglycemia (and fear of injections, often physician>patient), which preclude basal insulin as the preferred 2nd line option.

# Outline

- 2nd-line antidiabetic agents
  - Sulfonlyureas
  - DPP4 inhibitors
  - GLP1r agonists (injectable)
  - basal insulin (injectable)
- 3rd-line oral antidiabetic agents
  - Alpha-glucosidase inhibitors
  - Thiazolidinediones (TZDs)
  - SGLT2 inhibitors
- Cases

# Alpha-glucosidase inhibitors

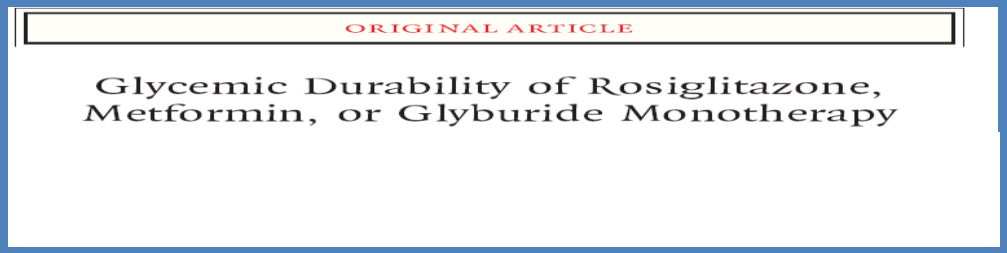
| Agent | Efficacy Δ%HbA1c | Mechanism of Action | Benefits | Risks/ Concerns |
|---|---|---|---|---|
| **Acarbose (Precose)**<br>**Miglitol (Glyset)** | **-0.5-0.8%** | **Delays complex carbohydrate absorption** | **Weight neutral** | **Flatulence, diarrhea and abdominal pain** |




Standl and Schnell, *Diab Vasc Dis Res,* 2012

# Thiazolidinediones (TZDs)

| Agent | Efficacy Δ%HbA1c | Mechanism of Action | Benefits | Risks/ Concerns |
|---|---|---|---|---|
| **Rosiglitazone (Avandia)**<br>**Pioglitazone (Actos)** | **-1 to 2%** | **Activates PPAR-γ, increase peripheral insulin sensitivity** | **Addresses one of the primary defects of T2DM, no hypoglycemia, ?β-cell sparing** | **Edema, heart failure, ?MI, weight gain, fractures, monitor LFTs**<br><br>**Rosiglitazone: Black Box Warning**<br><br>**Pioglitazone: ?bladder cancer risk** |

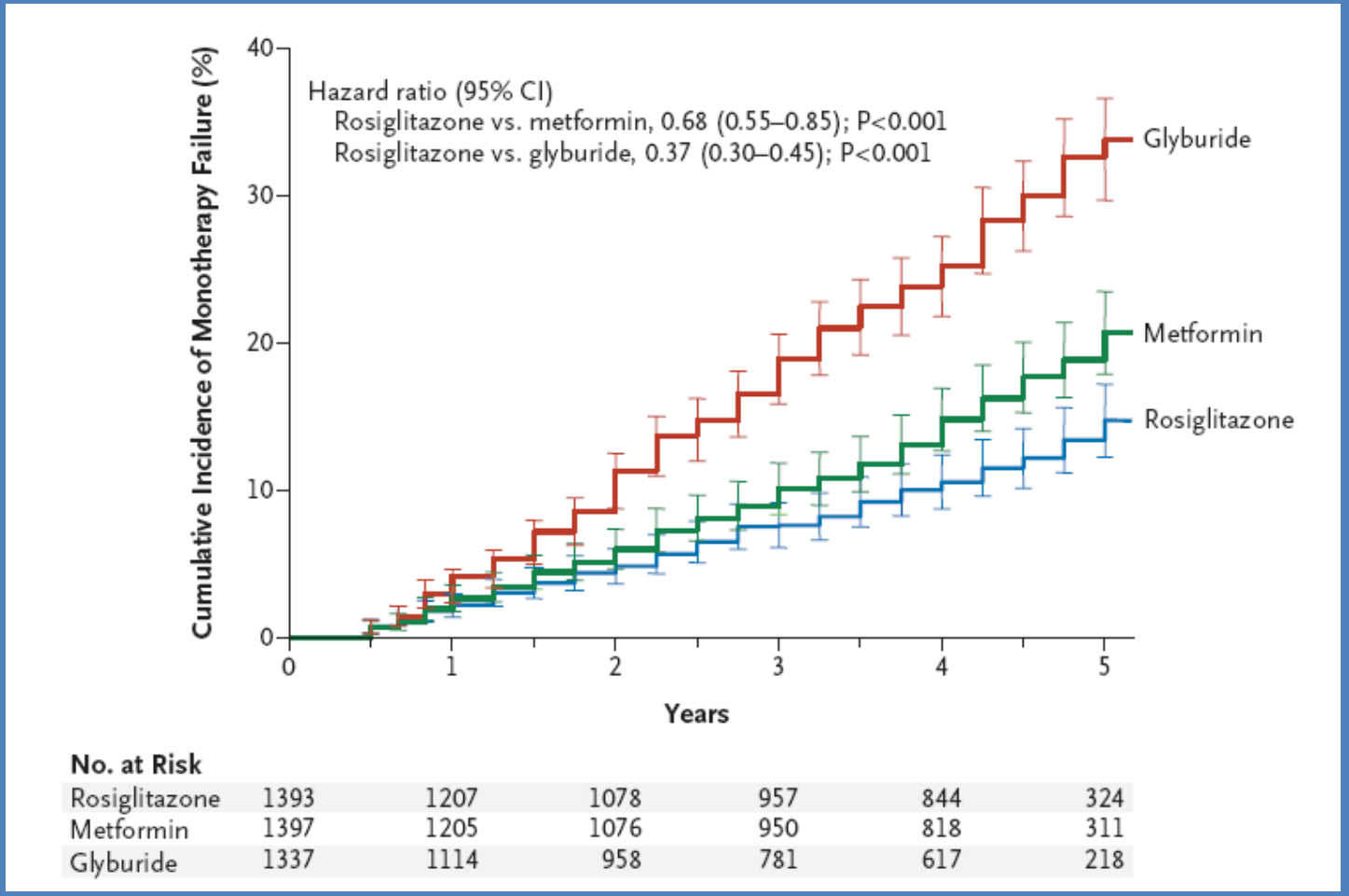

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

- **Trial participants:**
  - mean age 56yo, 58% male, BMI ~32
  - DM2 patients, 97% <2yrs duration, HbA1c 7.3%, no previous treatment for DM2
  - 50% on anti-HTN therapy
  - no history of coronary disease/CHF
- **Intervention**
  - rosiglitazone 8mg daily vs. metformin or glyburide
- **Primary outcome**
  - time to need for second antidiabetic medication

Kahn SE et al, *NEJM*, 2006

# Increased glycemic durability with rosiglitazone as opposed to either metformin or glyburide




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Rosiglitazone | 1393 | 1207 | 1078 | 957 | 844 | 324 |
| Metformin | 1397 | 1205 | 1076 | 950 | 818 | 311 |
| Glyburide | 1337 | 1114 | 958 | 781 | 617 | 218 |

Kahn SE et al, *NEJM*, 2006

# Alerts/Considerations: Rosiglitazone

- **FDA Alert 5/2011: Based on meta-analysis data, suggesting an elevated risk of heart attacks in patients treated with rosiglitazone**

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

| Study | Rosiglitazone Group | Control Group | Odds Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events/total no. (%)* | | | |
| **Myocardial infarction** | | | | |
| Small trials combined | 44/10,285 (0.43) | 22/6106 (0.36) | 1.45 (0.88–2.39) | 0.15 |
| DREAM | 15/2,635 (0.57) | 9/2634 (0.34) | 1.65 (0.74–3.68) | 0.22 |
| ADOPT | 27/1,456 (1.85) | 41/2895 (1.42) | 1.33 (0.80–2.21) | 0.27 |
| Overall | | | 1.43 (1.03–1.98) | 0.03 |
| **Death from cardiovascular causes** | | | | |
| Small trials combined | 25/6,845 (0.36) | 7/3980 (0.18) | 2.40 (1.17–4.91) | 0.02 |
| DREAM | 12/2,635 (0.46) | 10/2634 (0.38) | 1.20 (0.52–2.78) | 0.67 |
| ADOPT | 2/1,456 (0.14) | 5/2895 (0.17) | 0.80 (0.17–3.86) | 0.78 |
| Overall | | | 1.64 (0.98–2.74) | 0.06 |

- **Subsequent studies have not demonstrated increased risk, but has not affected the "black box" warning**

Nissen and Wolski, *NEJM*, 2007

# Do I use these meds?

In most patients, TZDs should probably be avoided. Despite the lack of evidence of causation to bladder cancer and cardiovascular harm – and in fact, recent results from the IRIS study suggest pioglitazone may show benefit post-CVA (IRIS trial), confirming potential CV benefit seen in PROActive – TZDs have significant risks, including weight gain, fluid retention, CHF and bone loss with increased risk of fracture.

As a result, I use TZDs specifically in patients who have T2D and Non-Alcoholic Steatohepatitis (NASH), based on results from the PIVENS trial which showed that Pioglitazone may ameliorate NASH.

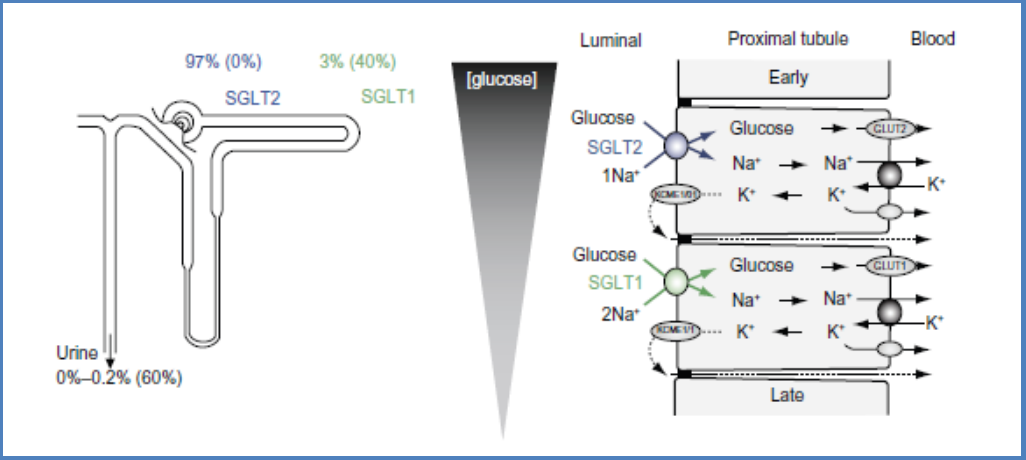
Sanyal et al, *NEJM*, 2010

# Sodium-glucose cotransporter 2 inhibitors (SGTL2s)

| Agent | Efficacy Δ%HbA1c | Mechanism of Action | Benefits | Risks/ Concerns |
|---|---|---|---|---|
| **Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)** | **-1 to 2%** | **Causes urinary elimination of glucose** | **Weight loss, rapid effects, additive with other therapies** | **UTIs/yeast infections, ?dehydration, ?risk of DKA** |

# SGLTs - background

- SGLT family of transmembrane proteins is responsible for transport of glucose across the brush-border membrane of renal tubules (SGLT2) and intestinal epithelium (SGLT1)
- SGLTs bind $Na^+$, then glucose, and the electrochemical Na+ gradient generated by the $Na^+/K^+$-ATPase is the driving force for the symporter activity




Kim and Babu, Diabetes, Met Syndrome and Obesity, 2012

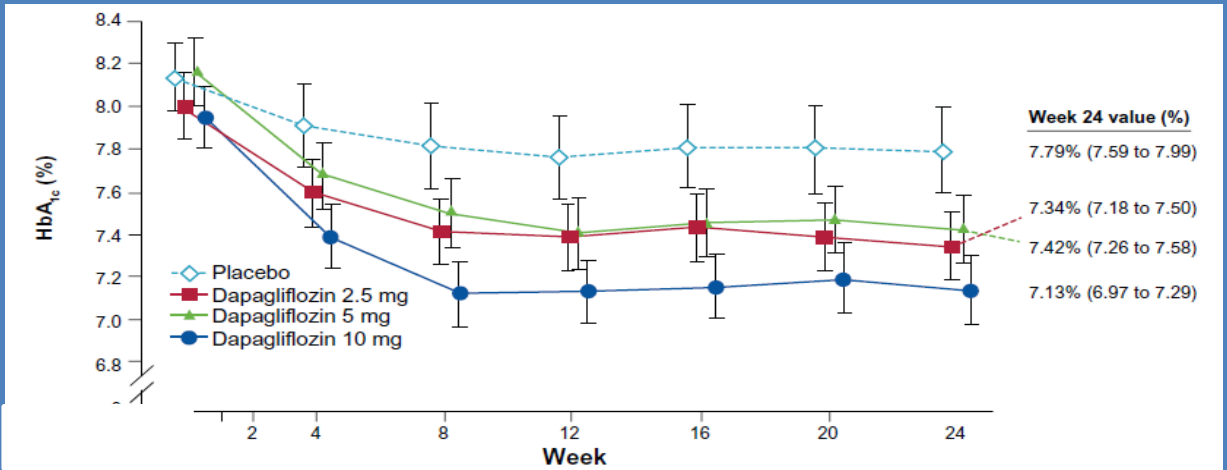
# SGLTs - purpose

- Approximately 180g of glucose is filtered daily in a non-diabetic adult; most reabsorbed by SGLT action (SGLT2 >> SGLT1) with <1% (0.03-0.3g/day) excreted in urine when renal function is normal.
- Sequential action of SGLTs prevent glucose-wasting (generally does not occur until plasma glucose >180mg/dl), and is evolutionarily conserved from yeast to retain nutrients
  - SGLT2 (proximal) = low-affinity, high-capacity
  - SGLT1 (distal) = high-affinity, low-capacity

# SGLT2 inhibitors now available

- Canagliflozin (INVOKANA) – approved 3/2013
  - Dosage: Start at 100mg with breakfast, can be increased to 300mg daily
  - Contraindications: GFR <45 for 100mg dose, <60 for higher doses
- Dapagliflozin (FARXIGA) – approved 1/2014
  - Dosage: Start at 5mg daily, can be increased to 10mg daily
  - Contraindications: GFR < 60
- Empagliflozin (JARDIANCE) – approved 8/2014
  - Dosage: Start at 10mg daily, can be increased to 25mg daily
  - Contraindications: GFR <45

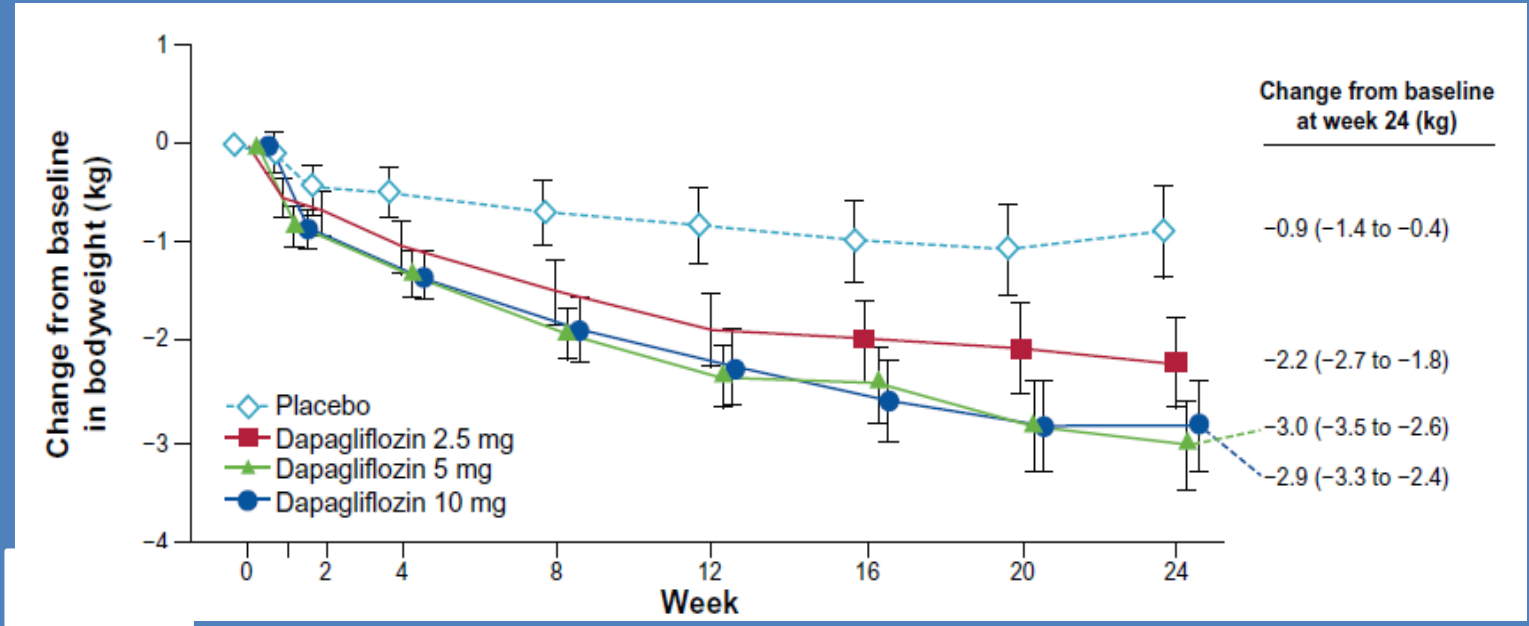
# In metformin-treated patients with b/l HbA1c 8% → relatively mild decrease in A1c




- But, in patients who were poorly-controlled (HbA1c >9%), SGLT2 inhibitor treatment improved HbA1c by 1.5-2.5%. This is somewhat predictable, since SGLT2i target renal threshold for glucose excretion (~180mg/dl) which should produce an A1c ~7.5%.

Bailey et al, Lancet, 2010; Ferrannini et al, Diabetes Care, 2010

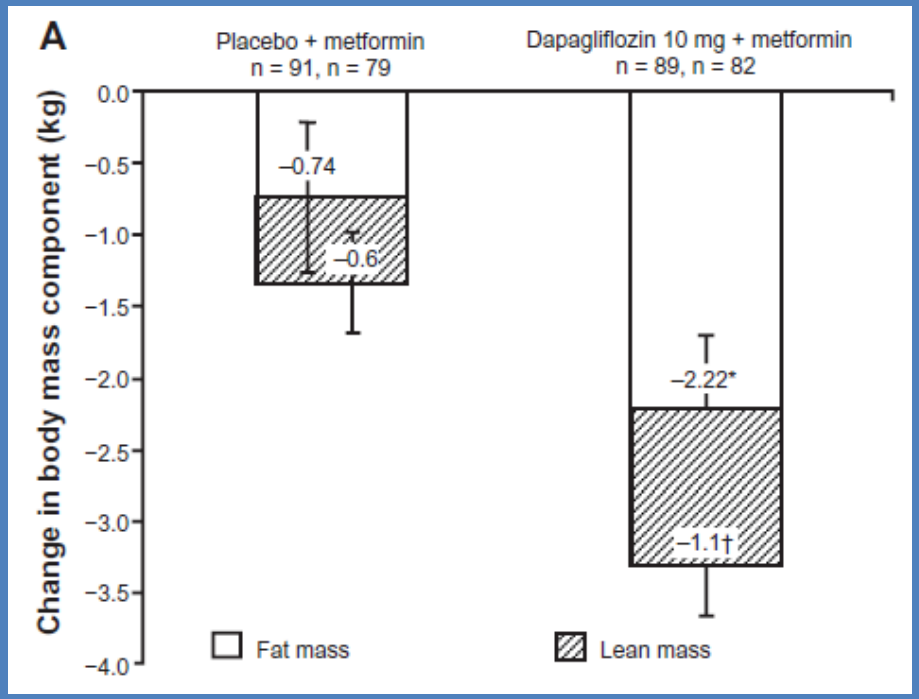
# An added benefit of SGLT2i treatment – reduced body weight

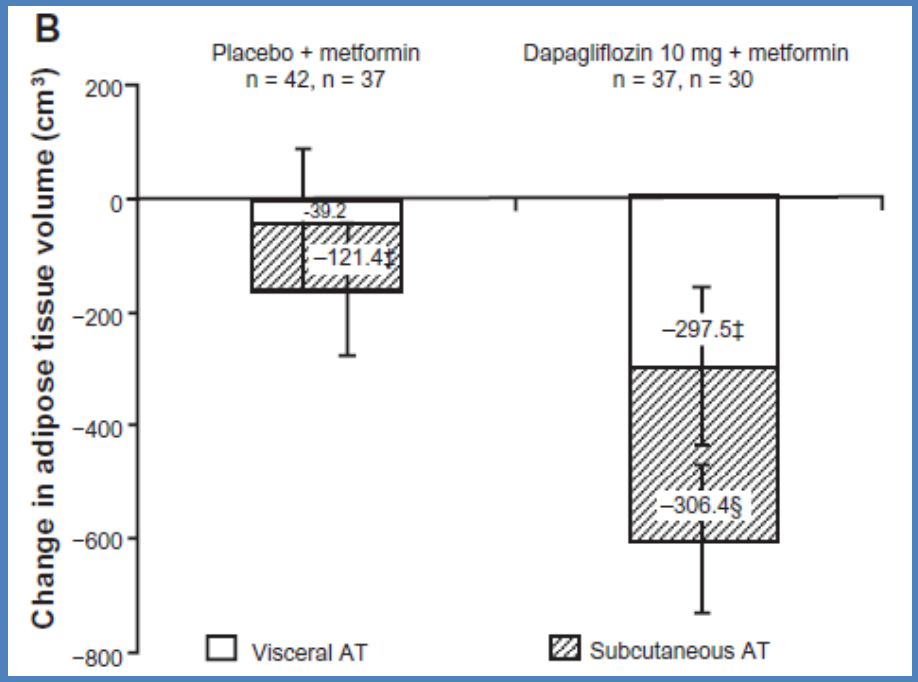



- As compared to glipizide add-on to metformin, adjusted weight difference of 5kg in the 1st year of treatment (-3.2kg for dapa, +1.9kg for glipizide)

Bolinder, et al, JCEM, 2012
Nauck, et al, Diabetes Care, 2011
Kahn, et al, NEJM, 2006

# Preferential loss of fat mass, especially in visceral compartment




Bolinder, et al, JCEM, 2012

# Side effects of SGLT2 inhibitors?

- genital and lower urinary tract infections
  - patients with DM2 are at higher risk of fungal genital infections and UTIs compared with general population
  - dapaglifozin-treated patients, especially women, reported an increase in genital and lower UTIs (not pyelo) as compared to control treatments (metformin or glipizide)
  - genital infections
    - men: 5.3% vs 0.4%
    - women 21.1% vs 5.4%
  - UTIs:
    - men: 8% vs 4%
    - women 14.4% vs 9.2%

Nauck et al, Diabetes Care, 2011

# Is there a difference in safety between different SGLT2 inhibitors?

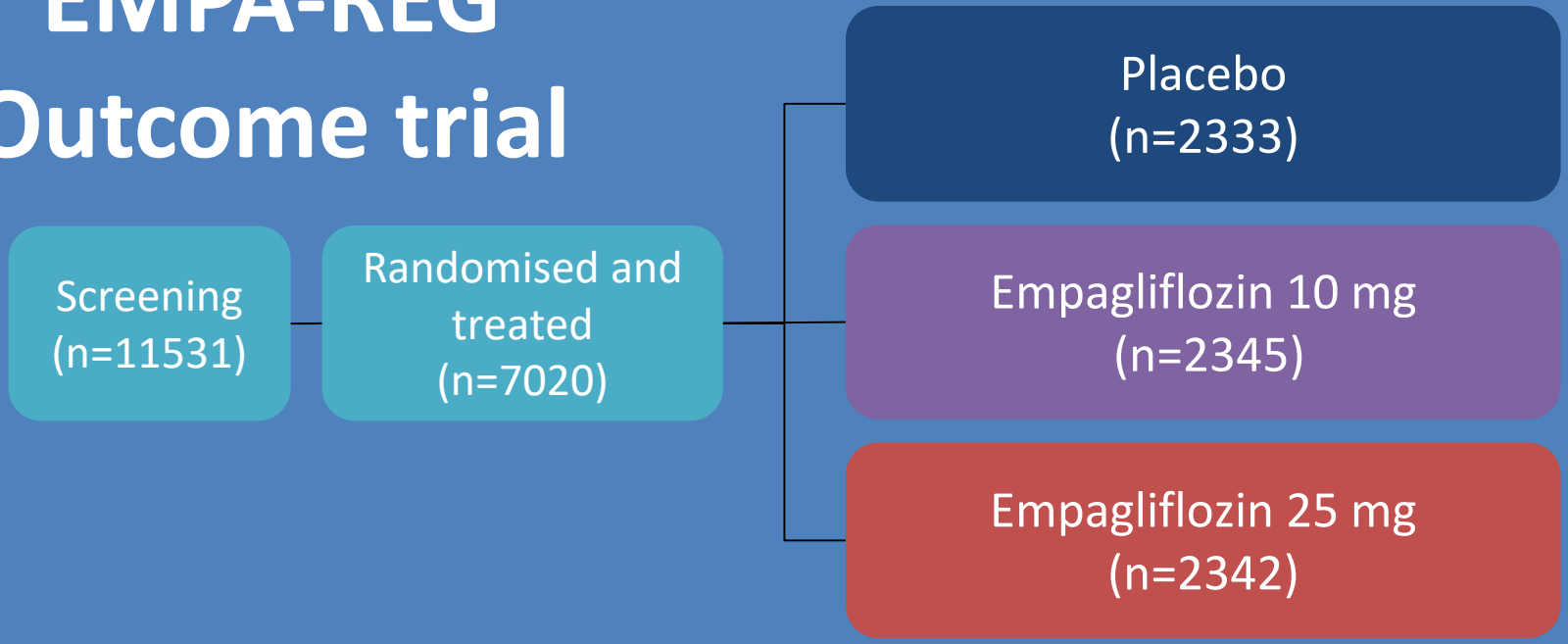
- UTI
  - dapa: RR 1.54 (5.7% vs. 3.7%)
  - cana: RR 1.45 (5.9% vs. 4.0%)
  - empag: RR 1.22 (9.3% vs. 7.6%)
- genital mycotic infection
  - dapa: F- RR 5.6 (8.4% vs. 1.5%), M- RR 9.0 (2.7% vs. 0.3% )
  - cana: F- RR 3.56 (11.4% vs. 3.2%), M- RR 7.0 (4.2% vs. 0.6%)
  - empag: F- RR 4.3 (6.4% vs. 1.5%), M- RR 4.0 (1.6% vs. 0.4%)

Clar et al, BMJ Open, 2012

# Is there a difference in efficacy between SGLT2 inhibitors?

- My guess is no, even between the selective SGLT2 and nonselective SGLT1/2 inhibitors
- In trials, all 3 approved drugs had ~0.8-1.2% reduction in A1c when added to metformin-treated patients
- That being said…

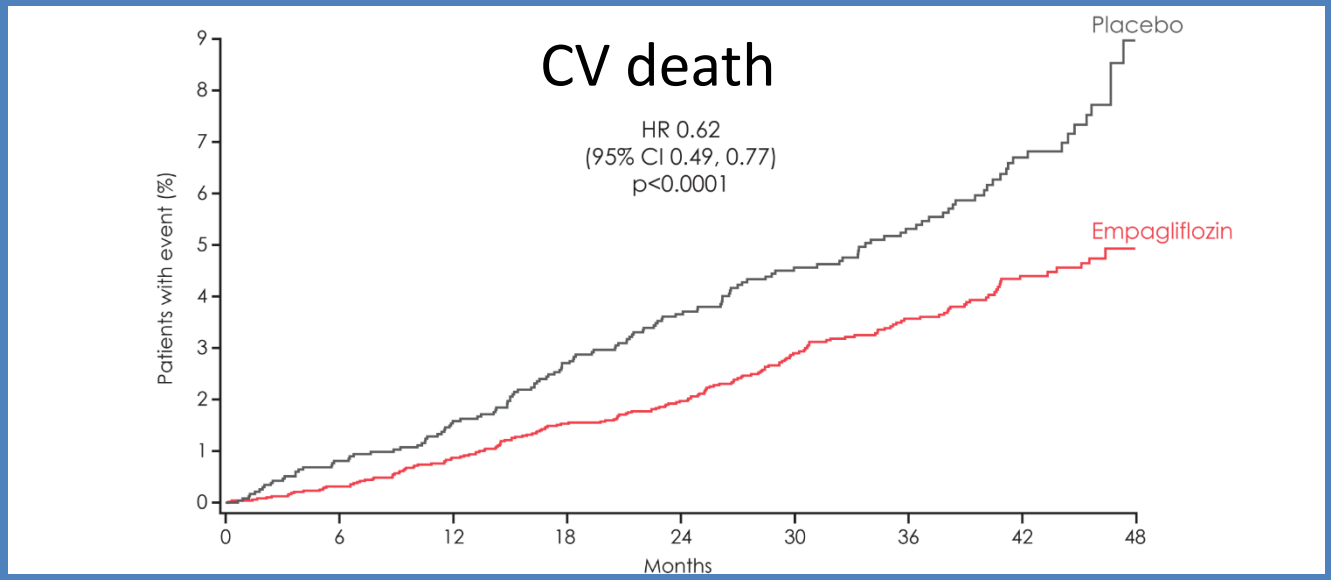
# EMPA-REG Outcome trial

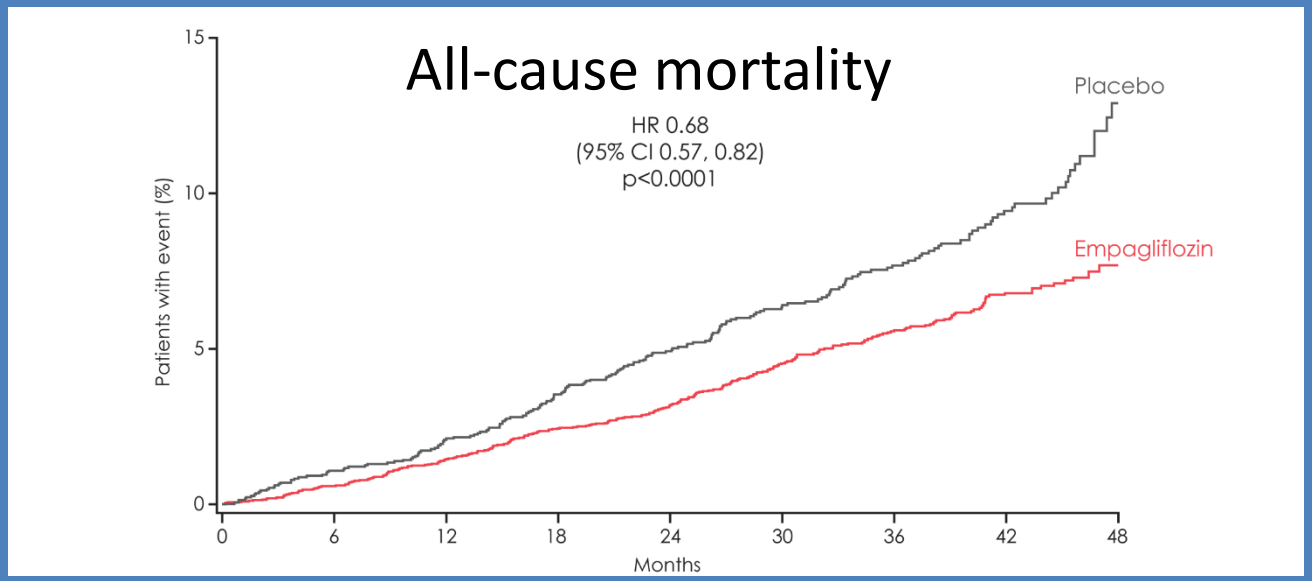



- **To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events**
- **Population studied: Adults with type 2 diabetes**
  - **BMI ≤45 kg/m²**
  - **HbA1c 7–10%**
  - **Established cardiovascular disease**
  - **CrCl > 30**

Zinman, et al, NEJM, 2015

# Empagliflozin reduces risk of death




Zinman, et al, *NEJM*, 2015

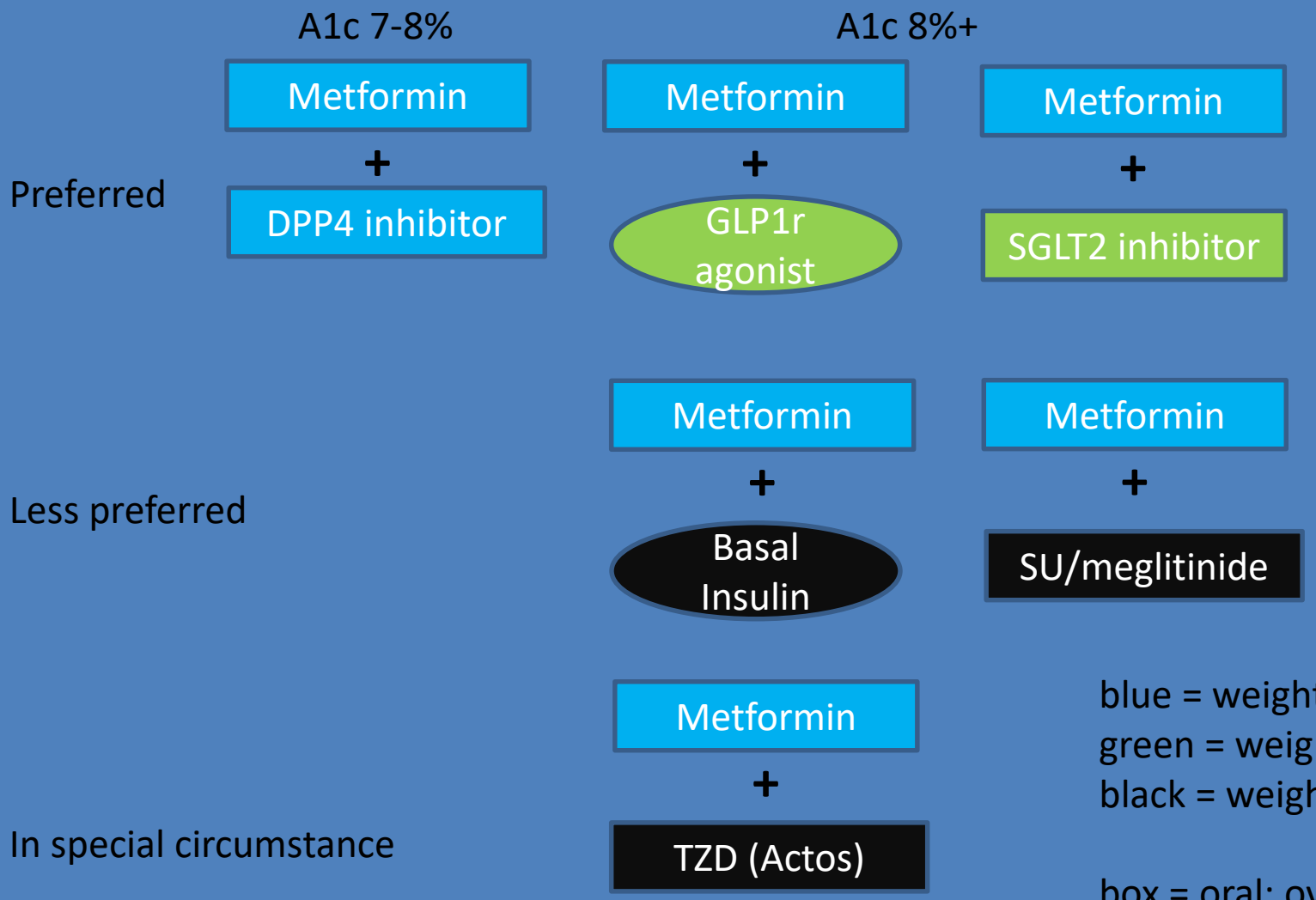
# Do I use these meds?

Yes, but not 1st (metformin) and only occasionally as 2nd (DPP4 inhibitors, GLP1 agonists) line therapy. In a patient failing metformin/2nd oral agent dual therapy, or who refuses to try an injectable, I do use them. In my practice thus far, fewer GU side-effects and better efficacy than reported. In addition, the results from EMPA-REG (despite the uncertain etiology of this finding) are quite remarkable. I do not know if this is a class effect, so Jardiance is my preferred med, but in combination with weight loss/efficacy, this is a class of meds that are increasing in popularity.

# My usual algorithm for 2nd line therapy

Caveats –

1) diet/lifestyle discussed at every titration
2) patient preference weighs heavy




blue = weight neutral
green = weight-reducing
black = weight gaining

box = oral; oval = injection

# My usual algorithm for 3rd line therapy

Caveats –

1) diet/lifestyle discussed at every titration
2) patient preference weighs heavy

Preferred: Metformin + DPP4 inhibitor or GLP1r agonist + SGLT2 inhibitor or Basal Insulin

Less preferred: Metformin + SU/meglitinide + SGLT2 inhibitor or Basal Insulin

I usually don't mix DPP4/GLP1 with SU as these all act the same way – to increase insulin secretion

Much less preferred: Metformin + Basal Insulin + Prandial Insulin

or pre-mixed insulin (similar to basal/prandial)

50yo white male, dx with Type 2 Diabetes ~3yo on routine labs which demonstrated HbA1c 7.5% (repeated, similar value). Initiated diet/exercise regimen, which decreased his HbA1c to 6.5-7% on multiple checks, but in the past year, his A1c has been consistently 7.5-8%.

T2D meds: none

Data:

Physical Exam: weight 80kg, BMI 28

FSG range 160-180 (fasting), 150-200 (pre-prandial)

HbA1c 8%, GFR 80

Which of the following options is the best management at this time?

A. Start metformin at 1000mg bid

B. Start glipizide XL at 5mg daily

C. Start metformin 500mg daily, increase to 500mg bid after 3 days.

D. Start liraglutide (Victoza) 0.6mg daily

E. Start pioglitazone (Actos) 15mg daily

F. Start SGLT2 inhibitor

G. Start sitagliptin (Januvia) 100mg daily

He started metformin, which was titrated as above, with improved A1c to 6.5% at next visit, with 1kg weight loss as well.

76yo Iranian male, filmmaker, patient w/ Type 2 Diabetes, dx ~15yrs ago on routine labs, recent control reportedly okay with A1c 7-7.5% on metformin 1000mg bid for years, but higher recently.

T2D meds: metformin 1000mg bid
Data:
Physical Exam: weight 78kg, BMI 28
FSG range: does not check FSG
HbA1c 8.9% (last 9.0% six months prior), GFR 75

Which of the following options is appropriate management at this time?

A. Increase metformin from 1000mg bid to 850mg tid
B. Start glimepiride 1mg daily
C. Start glargine (Lantus) 10 units daily
D. Start liraglutide (Victoza) 0.6mg daily
E. D/c metformin, start Janumet 50/1000mg bid
F. Start SGLT2 inhibitor

He refused any injectable, but accepted sulfonylurea therapy. Started glimepiride 1mg daily, titrated eventually to 4mg daily, with improved A1c to 6.9-7.1% at next 2 visits.

46yo Dominican male, unemployed, w/ morbid obesity, depression (on SSRI), anxiety d/o (on BZD) and chronic lower back pain. T2D dx several years prior on routine blood work w/ A1c 9.9%. Started metformin 2g daily by PMD, but patient complained of nausea and loose stools, prompting PMD to switch to glipizide 5mg daily. A1c decreased to 7.1%, but has since increased to 8.5% despite increase in dose to 10mg daily. Has been having hypoglycemia 2-3x/week and wants to come off glipizide.

T2D meds: glipizide 10mg daily

Data:

Physical Exam: weight 149kg, BMI 46; obese but non-Cushingoid

FSG range: does not check

HbA1c 8.5%, GFR 85

Which of the following options is appropriate management at this time?

A. Change glipizide to 20mg daily
B. D/c glipizide and start sitagliptin (Januvia) 100mg daily
C. D/c glipizide and start glargine (Lantus) 10units daily
D. D/c glipizide and start metformin 500mg daily, increase to 500mg bid after 3 days.
E. D/c glipizide and start liraglutide (Victoza) 0.6mg daily
F. Start SGLT2 inhibitor

D/c'd glipizide and started metformin 500mg daily, followed by 500mg bid. No GI upset. A1c decreased from 8.5% → 7.5%, but since has stabilized despite increase in metformin to 1000mg bid which patient now tolerates.

T2D meds: metformin 1000mg bid

Data:

Physical Exam: weight 148kg, BMI 45.8

FSG range: does not check

HbA1c 7.5%, GFR 85

Which of the following options is appropriate management at this time?

A. Start sitagliptin (Januvia) 100mg daily

B. Start glipizide 5mg daily

C. Start glargine (Lantus) 10units daily

D. Start liraglutide (Victoza) 0.6mg daily

E. Start SGLT2 inhibitor

F. Start pioglitazone (Actos) 15mg daily

22yo Asian male, college student, w/ NAFLD/NASH (b/l ALT 100-140) and Type 2 Diabetes, dx ~4yrs ago on routine labs. Strong FH of T2D (I take care of his father, who is lean and has T2D). Prior endocrinologist had attempted metformin at diagnosis, but ALT increased to 300, so d/c'd. Since then, has been on no meds, but A1c has increased from 6.8% → 7.2% → 7.7% → 8.5%.

T2D meds: none

Data:

Physical Exam: weight 83kg, BMI 29; no striae or supraclavicular fullness

FSG range: does not check

HbA1c 8.5%, fasting C-peptide 3.2 (nl 0.7-1.4) with glucose 180mg/dl, anti-GAD/anti-ICA/anti-insulin Ab negative

Which of the following options is appropriate management at this time?

A. Start metformin 500mg daily with instructions to titrate to 500mg bid at 3 days
B. Start glimepiride 1mg daily
C. Start glargine (Lantus) 10 units daily
D. Start liraglutide (Victoza) 0.6mg daily
E. Start pioglitazone 15mg daily
F. Start rosiglitazone 1mg daily
G. Start Januvia 100mg daily
H. Start SGLT2 inhibitor

Started pioglitazone 15mg daily and titrated up to 30mg bid, with progressive improvement in A1c from 8.5% to 7.3%. ALT decreased from 110 → 90.

73yo Peruvian male, retired chef, w/ HTN, hyperlipidemia and T2D dx 20+ yr ago, generally uncontrolled, leading to retinopathy dx 2012 now s/p laser, A1c range in the past year 12.6-14.0%.

T2D meds: metformin 1000mg daily, glargine (Lantus) 50units qAM and insulin aspart (Novolog) 15units qac (forgets ½ the time)

Data:

Physical Exam: weight 98kg, BMI 39; obese but non-Cushingoid

FSG range: 140-220 (fasting), 180-480 (pre-prandial)

HbA1c 14%, GFR 61

Which of the following options is appropriate management at this time?

A. Start sitagliptin (Januvia) 100mg daily

B. Start glimepiride 1mg daily

C. Increase and split glargine (Lantus) dose to 30units bid

D. Reinforce aspart (Novolog) use

E. D/c glargine and aspart, start Novolog 70/30 bid

F. Start liraglutide (Victoza) 0.6mg daily

G. Start SGLT2 inhibitor

Increased and split glargine dose to 30units bid and metformin to 1000mg bid; also reinforced a reduced carb diet and more regular Novolog use, with progressive improvement in A1c from 14% → 12.4% → 10.6%, but then stabilized in the 10-11% range. Still forgetting lunch and dinner Novolog doses.

T2D meds: metformin 2000mg daily, Lantus 35units bid, Novolog 15units (breakfast)
Data:
Physical Exam: weight 110kg, BMI 42; obese but non-Cushingoid
FSG range: 80-150 (fasting), 120-350 (pre-prandial)
HbA1c 10.5%, GFR 55

Which of the following options is appropriate management at this time?

A. Start sitagliptin (Januvia) 100mg daily
B. Start glimepiride 1mg daily
C. Increase glargine (Lantus) to 40units bid
D. Reinforce aspart (Novolog) use with lunch and dinner
E. D/c glargine (Lantus) and aspart (Novolog), start Novolog 70/30 bid
F. D/c aspart (Novolog), and start liraglutide (Victoza) 0.6mg daily
G. Start dapagliflozin (Farxiga) 5mg daily
H. Start canagliflozin (Invokana) 100mg daily

Started canagliflozin 100mg daily, A1c improved from 10.5% to 7.5%.