Diabetes ECHO

Patient Case Discussion &

Introduction to Insulin Therapy series

November 9, 2023

Basal (fasting) Hyperglycemia

- Most medications impact
  - Metformin
  - **Longer acting (Basal) insulins**
    - Insulin direct effect on liver & on adipose tissue to reduce FFA = reduce hepatic glucose output
  - Sulfonyl-urea medications
  - TZDs
  - DPP4-inhibitors
  - **SGLT-2 inhibitors**
  - **Long-acting GLP-1 Receptor agonists**
    - increase insulin (direct effect on liver/ reduce FFA from adipocytes) & reduce glucagon = reduced hepatic glucose output)

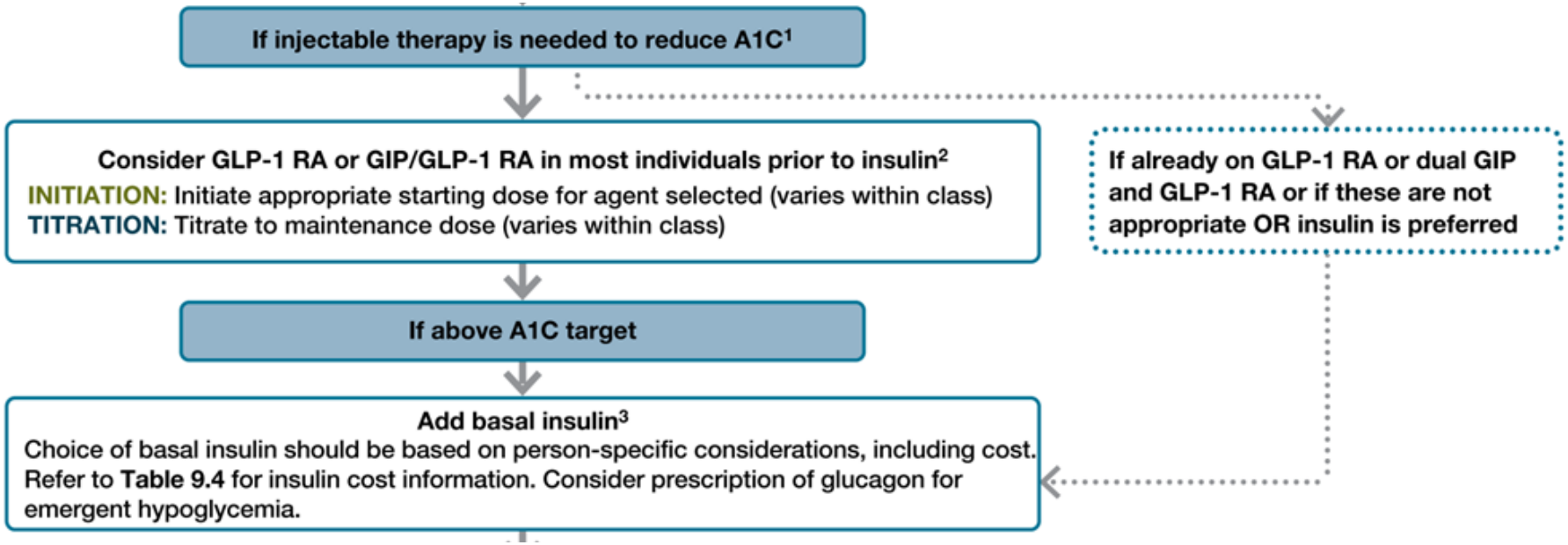
Postprandial Hyperglycemia

- Fewer medications impact
  - Alpha- Glucosidase Inhibitors (Precose, Glyset)
  - Glinides (Starlix, Prandin)
  - Stepwise addition of **prandial insulin** (mealtime [bolus] insulin)
    - More rapidly absorbed prandial insulin
  - Amylin receptor agonist (Symlin (pramlintide))
  - **SGLT2i** helps reduce height of postprandial rise
  - **GLP-1 receptor agonists**
    - GLP-1 receptor agonists provide improvements in both PPG and FPG levels because they
      - stimulate glucose-dependent insulin secretion
      - inhibit glucose-dependent glucagon secretion
      - slow gastric emptying
      - increase satiety

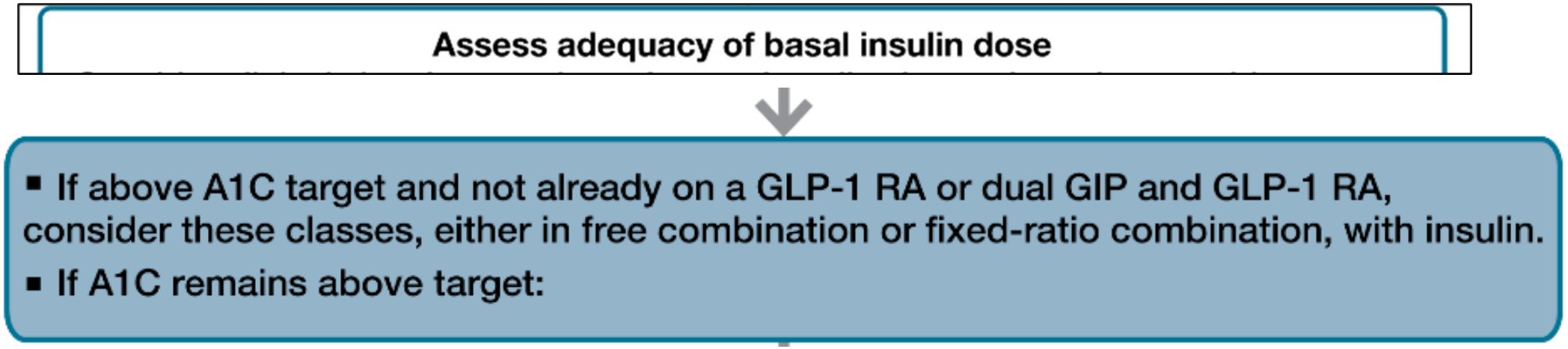
ADA 2023 Standards of Care

EASD & AACE/ACE

- 9.10 In adults with type 2 diabetes, a ***glucagon-like peptide 1 receptor agonist (GLP1 RA)*** is *preferred to insulin* when possible. A
- AACE/ACE: For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a *GLP-1 RA or GIP/GLP-1 RA* should be the *initial choice*, if not already in use



From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023**
https://diabetesjournals.org/care/article/46/Supplement_1/S140/148057/9-Pharmacologic-Approaches-to-Glycemic-Treatment



9.11 If insulin is used, *combination therapy* with a GLP1 RA is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. A ADA/EASD

Figure Legend: Intensifying to injectable therapies in type 2 diabetes. DSMES, diabetes self-management education and support; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide 1 receptor agonist; max, maximum; PPG, postprandial glucose. Adapted from Davies et al. (43).

Clin Diabetes. 2020 Jul; 38(3): 304–310. doi: 10.2337/cd19-0061

Overbasalization: Addressing Hesitancy in Treatment Intensification Beyond Basal Insulin

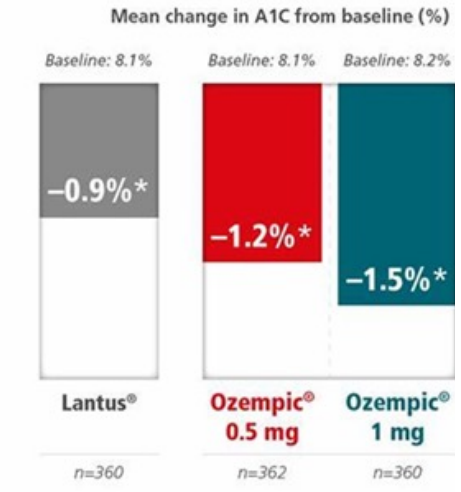
Kevin Cowart

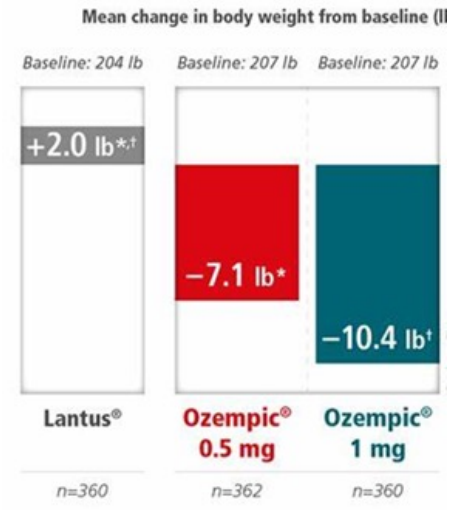
- The addition of **prandial insulin** is associated with a *higher incidence of weight gain and hypoglycemia* than the addition of a glucagon-like peptide 1 (GLP-1) receptor agonist to basal insulin
- A GLP-1 receptor agonist should be considered
  - before basal insulin therapy for most patients
  - as add-on therapy in patients needing treatment intensification beyond basal insulin.
- This recommendation is based on evidence demonstrating ***high efficacy***, ***lower risk of hypoglycemia***, and ***greater weight reduction*** of GLP-1 receptor agonists compared with insulin.
  - Additionally, GLP-1 receptor agonists have been found to **decrease major adverse cardiovascular (CV) events and mortality i**n patients with atherosclerotic cardiovascular disease (ASCVD) and those with increased ASCVD risk.

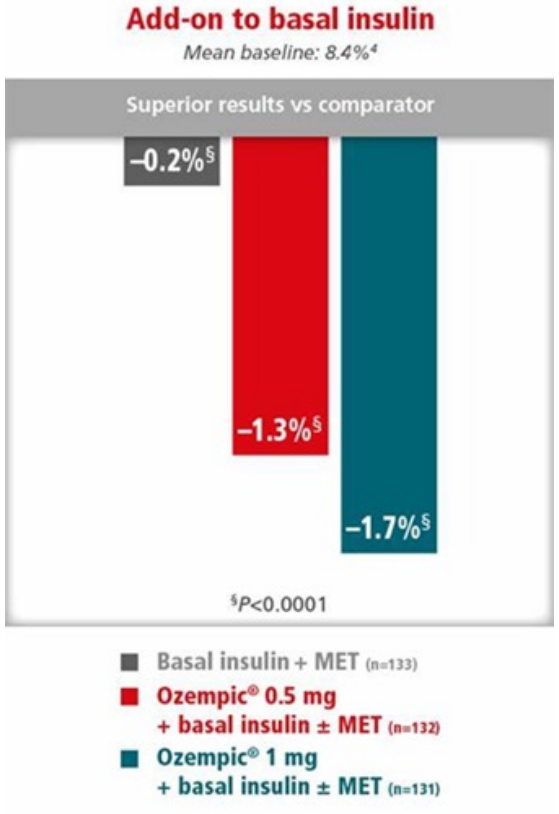
ADA 2023 Standards of Care
Pharmacologic Therapy for Adults with T2D

9.10 In patients with T2D, a GLP1 RA is preferred to insulin when possible. A

9.11 If insulin is used, combination with a GLP1 RA is recommended for greater efficacy and durability of treatment. A







Insulin titrated to target - limited by hypoglycemia

Adding Tirzepatide to Basal Insulin Cuts HbA1c in Poorly Controlled T2D — Results with the GIP/GLP-1 receptor agonist were statistically superior to added insulin lispro

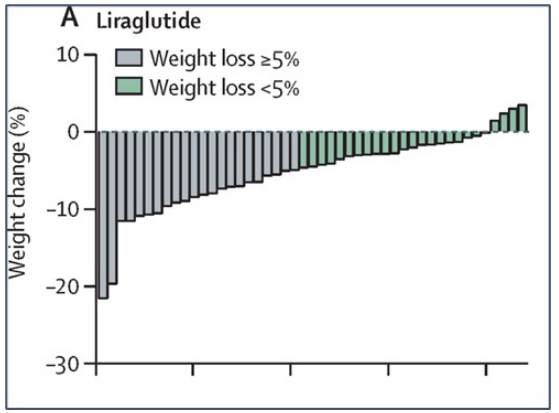
European Association for the Study of Diabetes (EASD) meeting

- In patients on an insulin glargine regimen (glargine + metformin), the estimated mean change from baseline in HbA1c at week 52 was
  - -2.1% for those assigned to one of three different doses of **tirzepatide**
    - 68% achieved A1c <7% (resulted in Mean HbA1c of 6.7%)
    - Mean weight change - loss of 9 kg (19.9 lb)
    - Hypoglycemia/severe hypoglycemia – 0.4 events/patient-year
    - Ave 46u/d Insulin → average 13u/d Insulin [20% able to dc Insulin]
  - -1.1% for those randomized to **insulin lispro**
    - 36% achieved A1c <7% (resultant Mean HbA1c 7.7%)
    - Mean weight change – gain of 3.2kg (7.1 lb)
    - Hypoglycemia/severe hypoglycemia – 4.4 events/patient-year
    - Ave 46u/d Insulin → 62u/d insulin lispro + 42u/d insulin glargine (104u/d)

Insulin dose adjustments with add-on glucagon-like peptide-1 receptor (GLP-1R) agonists in clinical practice

2017 Expert Opinion on Pharmacotherapy Volume 16, 2015 - Issue 10

- Looked at Byetta and Liraglutide added to insulin (mainly basal insulin) - *Review*
- In general, reduction in HbA1c was 1.2%, on average, accompanied by body weight loss of up to 7.3 kg
- However, individual responses are ***highly variable*** -
  - 67% experience reduction in both HbA1c and body weight
  - 14% show reduction in body weight alone
  - 12% show reduction in HbA1c alone
  - 7% both body weight and HbA1c were increased



- When starting a GLP-1RA, a concomitant decrease in insulin dose has been documented in almost every trial.
  - However, the reduction in insulin dose varies widely and ranges from **0 to 65% from baseline –** based on overall results when add a GLP1 RA recommend reducing:
    - **basal insulin by 10%**
    - **prandial insulin by 30 -- 40%**

Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist, Albiglutide, on Glycemic Control and on Reducing Prandial Insulin Use in Type 2 Diabetes Inadequately Controlled on Multiple Insulin Therapy: A Randomized Trial

Julio Rosenstock et al Diabetes Care 2020;43(10):2509–2518

Prospective Approach

- In the albiglutide + glargine group
  - At randomization (30 mg/wk starting dose albiglutide) lispro doses were ***halved***
  - At week 4 (albiglutide titrated up to 50 mg/wk) lispro injections were ***completely discontinued.***
  - Lispro could be systematically ***reintroduced*** by investigators based on postprandial plasma glucose excursions >180 mg/dL, based on mean measurements taken before lunch, dinner, or bedtime.
- Participants in the lispro + glargine group adjusted the lispro dose according to a dose titration algorithm
- Both groups could adjust glargine dose based on titration algorithm

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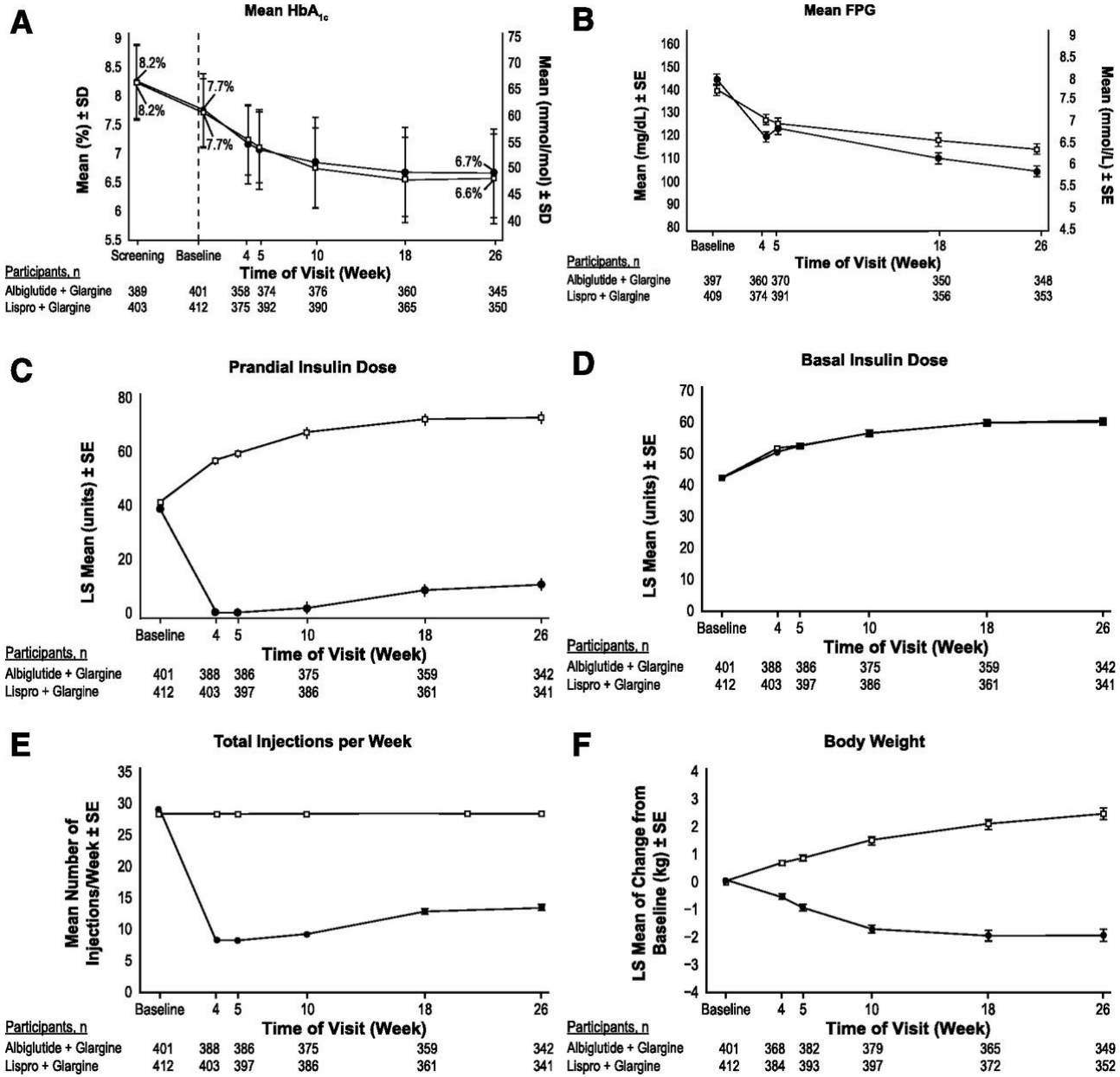
- Conclusion: ***Replacing prandial insulin*** with a **weekly GLP-1RA** can ***simplify*** treatments and ***achieve better outcomes*** in type 2 diabetes.
- In the albiglutide + glargine group
  - 54% replaced all prandial insulin without reintroducing lispro up to week 26.
  - Total daily prandial insulin dose was similar at baseline (~40u) but was lower by 62 units/day at week 26 (down to average of 9.8u vs increase to average of 71.9u)
  - Total number of weekly injections was also reduced from 29 to 13 per week.
  - Less severe/documented symptomatic hypoglycemia (57.2% vs. 75.0%)
  - Weight loss (−2.0 ± 0.2 kg) vs. vs. lispro + glargine (+2.4 ± 0.2 kg)
  - Gastrointestinal adverse events were higher with albiglutide (26% vs. 13%)

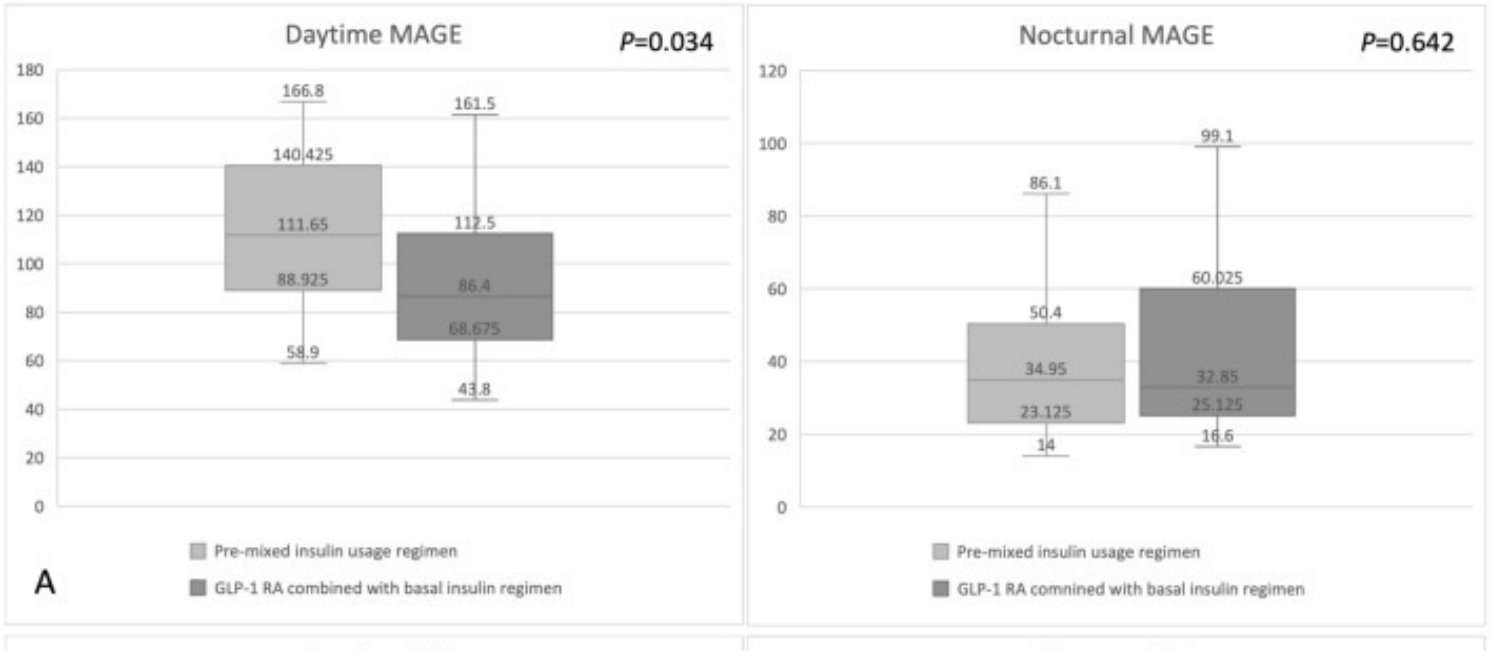

A
Mean HbA1c
Mean (%) ± SD
Mean (mmol/mol) ± SD
8.2%
8.2%
7.7%
7.7%
6.7%
6.6%
Screening
Baseline
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 389 401 358 374 376 360 345
Lispro + Glargine 403 412 375 392 390 365 350
B
Mean FPG
Mean (mg/dL) ± SE
Mean (mmol/L) ± SE
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 397 360 370 350 348
Lispro + Glargine 409 374 391 356 353
C
Prandial Insulin Dose
LS Mean (units) ± SE
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 401 388 386 375 359 342
Lispro + Glargine 412 403 397 386 361 341
D
Basal Insulin Dose
LS Mean (units) ± SE
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 401 388 386 375 359 342
Lispro + Glargine 412 403 397 386 361 341
E
Total Injections per Week
Mean Number of Injections/Week ± SE
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 401 388 386 375 359 342
Lispro + Glargine 412 403 397 386 361 341
F
Body Weight
LS Mean of Change from Baseline (kg) ± SE
Time of Visit (Week)
Participants, n
Albiglutide + Glargine 401 368 382 379 365 349
Lispro + Glargine 412 384 393 397 372 352

Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist, Albiglutide, on Glycemic Control and on Reducing Prandial Insulin Use in Type 2 Diabetes

- In conclusion, introduction of a once-weekly GLP-1RA with planned cessation of prandial insulin can *improve glucose control* to near normoglycemia with *substantially less insulin* and *fewer prandial injections*, *less hypoglycemia*, and *reduced body weight*.
- More than 50% of people who were previously treated with basal plus prandial insulin were able to achieve glycemic control with continued use of basal insulin alone. At study end
  - 62% required no injections of lispro
  - 9% required one injection of lispro per day,
  - 12% required two injections of lispro per day
  - 16% required three injections of lispro per day
- It is conceivable, based on available data, that other weekly GLP-1RAs (i.e., dulaglutide, semaglutide) might have a greater effect than albiglutide.

Regimen comprising GLP-1 receptor agonist and basal insulin can decrease the effect of food on glycemic variability compared to a pre-mixed insulin regimen

Eur J Med Res. 2022 Dec 3;27(1):273. doi: 10.1186/s40001-022-00892-9.



MAGE = mean amplitude of glucose excursion

https://pubmed.ncbi.nlm.nih.gov/36463197/

Guidance on Adding A GLP1/Dual Receptor Agonist Medication to Insulin

- Adding a GLP1 or Dual RA medication to Basal Insulin:
  - Reduce the dose of basal insulin by 20 % in patients with an HbA1c ≤8 %.

- Adding a GLP1 or Dual RA medication to Basal-Bolus Insulin:
  - Reduce Bolus insulin dose by ½ with initial dose of the GLP1/ Dual RA
  - Stop Bolus insulin as increase GLP1 Dual RA dose –
  - Titrate GLP1/Dual RA to max tolerated dose, adjust Basal insulin as needed
  - Add back bolus insulin to meals with high pp BG

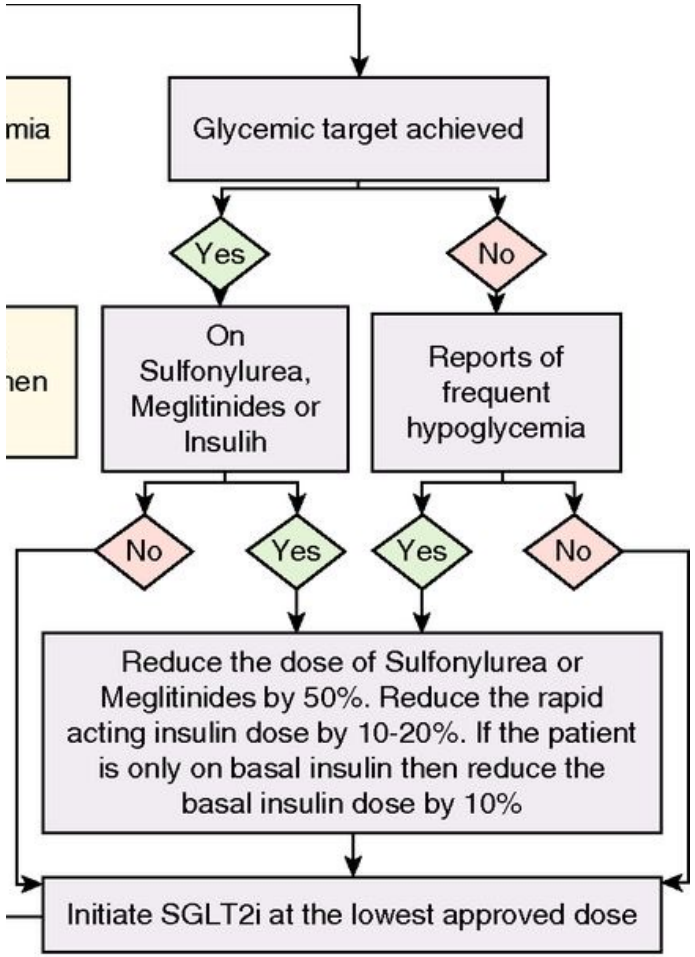
What about SGLT2 inhibitors & insulin?

- SGLT2i effect on glucose lowering depends on level of glycemia & GFR
- SGLT2 inhibitors reduce glucose variability (“spikes”)

- Studies looking at SGLT2i added to insulin
- Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes - PMC (nih.gov)
  - Insulin dosage change: mean $-4.85\,\mathrm{U/24hours}$, 95%CI [−7.42 to −2.29]
  - Minimal risk of mild hypoglycemia
- Benefits of Combining SGLT-2 Inhibitors to Insulin (diabetesincontrol.com)
  - Average decrease in Insulin 8.79 units
  - Minimal risk of hypoglycemia (“without a risk of hypoglycemia”)

- Other studies showed more of a risk of hypoglycemia when SGLT2i medications added to insulin therapy

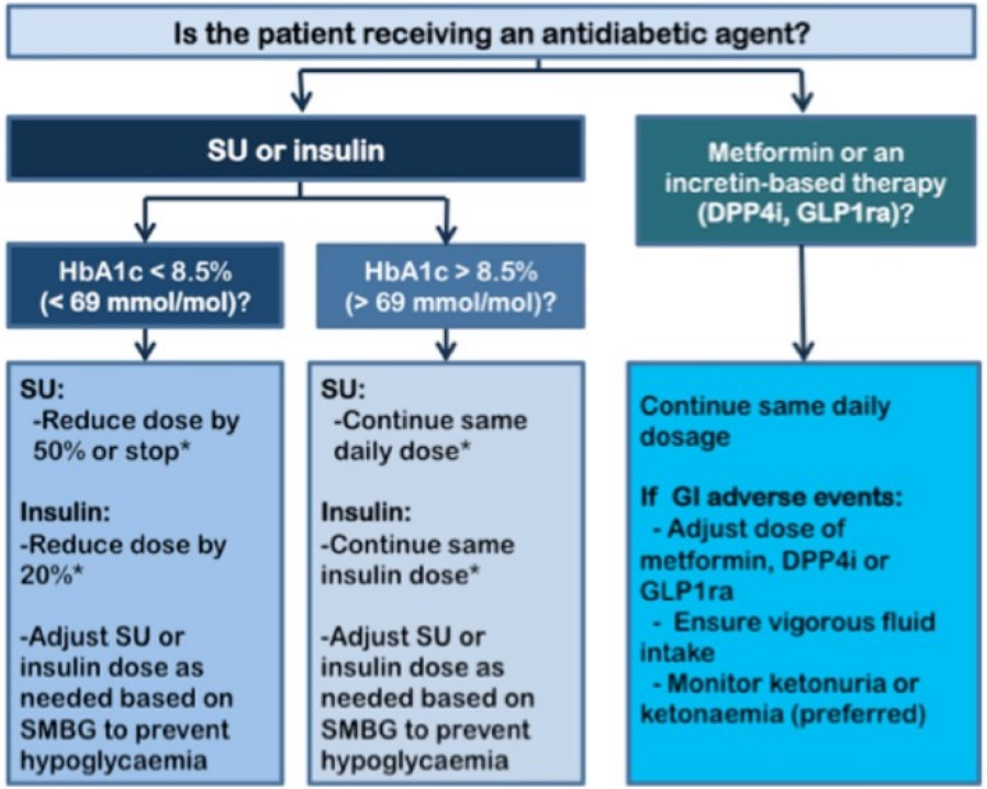
Algorithm to assess BP, volume status and glycemic control at the time of sodium-glucose cotransporter-2 inhibitor (SGLT2i) initiation.



Kidney360

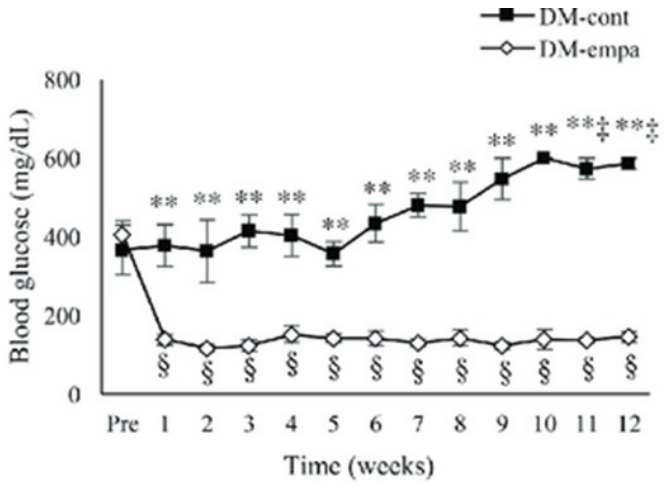
David Lam, and Aisha Shaikh Kidney360 2021;2:742-746

Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes
Diabetes Ther. 2017 Oct; 8(5): 953–962.

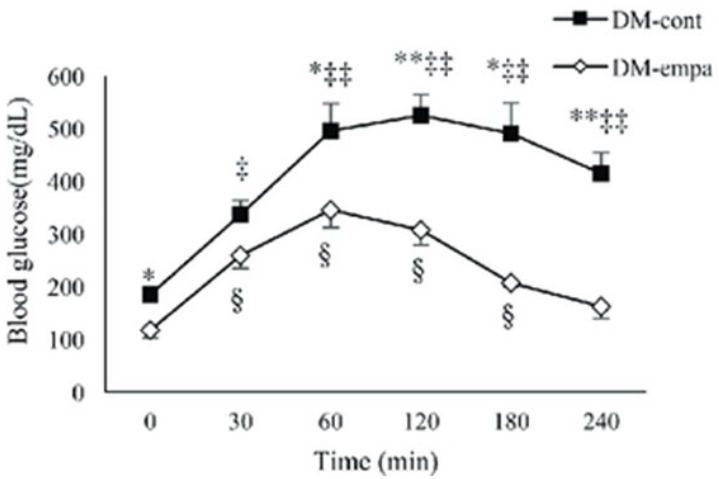


In some patients, I have witnessed a large reduction in need for Prandial Insulin – any of you noted this?

- Rat model
- Empagliflozin



- Required less insulin with glucose load

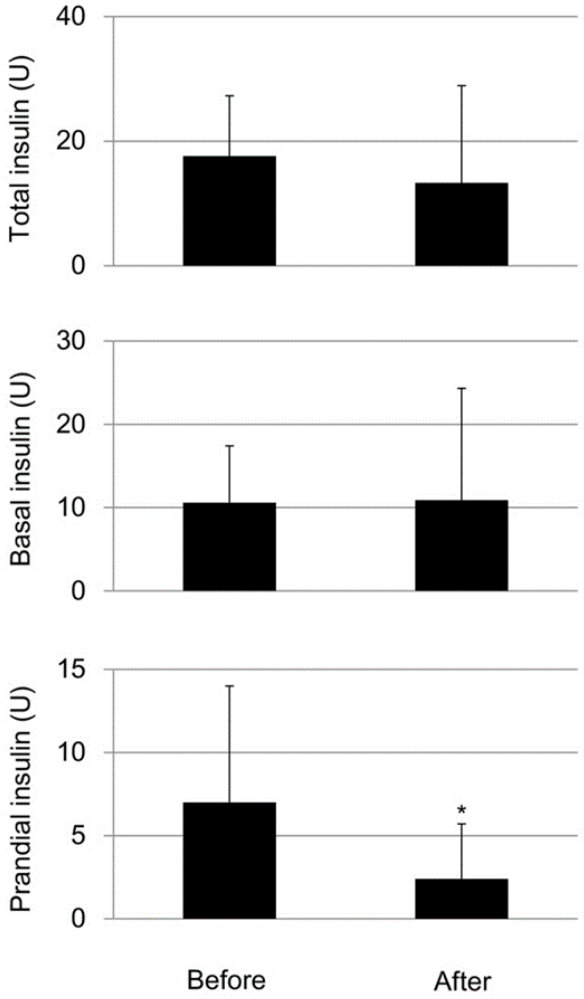


Could this be impacting our Case patient?

Sodium-Glucose Cotransporter 2 Inhibitors Reduce Prandial Insulin Doses in Type 2 Diabetic Patients Treated With the Intensive Insulin Therapy

J Clin Med Res. 2018 Jun; 10(6): 493–498.

- The SGLT2i addition did not show a significant difference in total insulin doses and daily basal insulin doses, however, significantly ***reduced daily prandial insulin doses***
- This result may be due to SGLT2i-mediated improvement of postprandial hyperglycemia *by increasing urinary glucose excretion* not via insulin secretion



Case Considerations

- Both the Semaglutide and Empagliflozin have strong impact on prandial glycemia & prandial insulin needs – combined with Lispro could result in hypoglycemia.
- He might not require prandial insulin at all meals now or might require lower doses at some meals or at least lower prandial doses on workdays.
  - CGM data will be helpful
  - With his physical activity at work – needs less insulin so that glucose uptake by muscle does not exceed glucose production by the liver (but adds complexity)
    - In general, moderate-intensity aerobic exercise that lasts approximately *30 minutes* requires a **25% to 50% meal bolus insulin reduction**,
    - whereas more prolonged activity *(~60–90 minutes)* requires a **50% to –75**% meal bolus insulin reduction
- Would increasing Ozempic from 1 mg/wk to 2 mg/wk further reduce need for prandial insulin & improve overall glycemia?
  - In comparison trial 2mg dose reduced A1c an average of 0.2% vs 1 mg (1.9% vs 2.1%)
  - Remember therapeutic heterogeneity – worth a try (he might respond above average)
- ***Simplification*** key consideration for this patient (reduce injection number)
- Could he be omitting several meds after or in concern about a hypoglycemic event?

Extra Slides

Adding Tirzepatide to Basal Insulin Cuts HbA1c in Poorly Controlled T2D — Results with the GIP/GLP-1 receptor agonist were statistically superior to added insulin lispro

European Association for the Study of Diabetes (EASD) meeting

- To be included, all participants had to have their **type 2 diabetes inadequately controlled with once- or twice-daily basal insulin**, including insulin NPH, insulin glargine, insulin detemir, or insulin degludec, with a maximum combination of two oral antidiabetics including metformin, sulfonylurea, or a DPP-4 inhibitor. ***Oral agents except for metformin were discontinued at baseline***
  - Mean baseline A1c 8.8%
  - Patients with type 1 diabetes, an eGFR under 30 mL/min/ 1.73 m2 or under 45 mL/min/1.73 m2 for those on metformin, and ***proliferative diabetic retinopathy, diabetic macular edema, or nonproliferative diabetic retinopathy requiring immediate treatment were excluded***.
- After randomization, 708 patients received prandial **thrice-daily insulin lispro** and 243, 238, and 236 patients received **5, 10, and 15 mg once-weekly tirzepatide injection**, respectively.
- There was a target fasting glucose of 100-125 mg/dL during the trial.
  - Most common adverse effects – GI adverse events were mild to moderate gastrointestinal symptoms, including nausea, diarrhea, and vomiting.

Sodium-Glucose Cotransporter 2 Inhibitors Reduce Prandial Insulin Doses in Type 2 Diabetic Patients Treated With the Intensive Insulin Therapy

J Clin Med Res. 2018 Jun; 10(6): 493–498.

- The addition of SGLT2i to the intensive insulin therapy tended to decrease fasting blood glucose and did not significantly change blood glucose levels before lunch, dinner and at bedtime.
- However, the addition of SGLT2i tended **to reduce insulin doses before breakfast and dinner, and also significantly reduced insulin dose before lunch** (Fig. 2).