ECHO Diabetes

case discussion

December 14, 2023

Clinical Questions

- High Novolog use. Would you deescalate Novolog in favor or titrating metformin/Toujeo? This may be dependent on Ozempic toleration.
- What about Jardiance in regard to toe amputations and known infection risk?

- Novolog 50u TID
- Toujeo 98u QD

248u Insulin/day
1.5u/kg total insulin (not yet optimized)
0.6 U/Kg basal insulin

- *FBS ~300**
  - *high FBS suggests inadequate basal insulin
- Wt 164.65 Kg

Severe Insulin Resistance

- Patients with **severe insulin resistance** require >2 units/kg of body weight or 200 units/day of insulin.

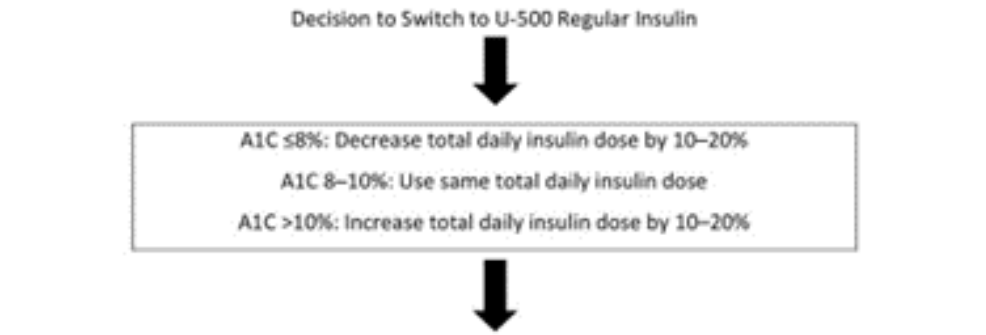
- Medications contributing to severe IR (In patients with severe insulin resistance, an effort should be made to discontinue such agents or switch to alternative medications if possible)
  - Glucocorticoids
  - Atypical antipsychotics
    - Abilify (aripiprazole) – lower risk than Zyprexa, etc.
    - Abilify can increase IR independent of increasing weight gain
  - Calcineurin inhibitors
  - Protease inhibitors
  - Oral contraceptives

Also associated with Weight Gain
- mirtazapine (Remeron) (tetracyclic antidepressant)
- paroxetine (Paxil) (SSRI)
- +/- gabapentin

- Assuming diabetes not induced by AA – just exacerbated??

One option is to utilize U500 Insulin

Clin Diabetes. 2016;34(2):97-104. doi:10.2337/diaclin.34.2.97



U-500 regular insulin initial dosing recommendations (6,55).

Current Total Daily Dose of U-100 Insulin	U-500 Regular Insulin Dosing Options
200–299 units	1. Two daily injections given as 60% of total daily dose before morning meal and 40% of total daily dose before evening meal 2. Three daily injections given in the following percentage distribution of total daily dose before meals: a. 40%/30%/30% b. 45%/35%/20% c. 40%/40%/20%
300–600 units	1. Three daily injections given in the following percentage distribution of total daily insulin dose before meals: a. 40%/30%/30% b. 45%/35%/20% c. 40%/40%/20% 2. Consider adding a bedtime dose—not to exceed 10% of total daily insulin dose—for a total of four daily injections 3. CSII with total basal insulin infusion delivering ~50% of total daily insulin dose and prandial insulin doses given as 20%/15%/15% of total daily insulin dose before meals
>600 units	1. Four daily injections given in the following percentage distribution of total daily dose before meals: a. 25%/25%/25%/25% b. 30%/30%/30%/10% 2. CSII with total basal insulin infusion delivering ~50% of total daily insulin dose and prandial insulin doses given 20%/15%/15% of total daily insulin dose before meals

But I would favor attempting to utilize Ozempic (semaglutide) or tirzepatide

Atypical Antipsychotic Medication Metabolic Issues

- **Metformin** has been the main agent added to help offset AAWG (atypical antipsychotic weight gain) and diabetes
  - Despite safety profile, and established weight loss properties of metformin in AAWG, published data from a multisite randomized control trial (RCT) show that ***only approximately 17% of patients lose ⩾5% body weight with metformin***, leaving a large majority of patients with unclear subsequent options.
- Increasing evidence for & use of **GLP1 RA** medications for AAWG and diabetes.
  - “Initial evidence from our real-world clinical setting suggests that semaglutide may be effective in ***reducing AAWG*** in patients not responding to metformin.”
  - “Our analysis revealed that GLP-1 RA treatment is safe and effective on ***cardio-metabolic parameters*** over control in antipsychotic-treated patients with schizophrenia.”

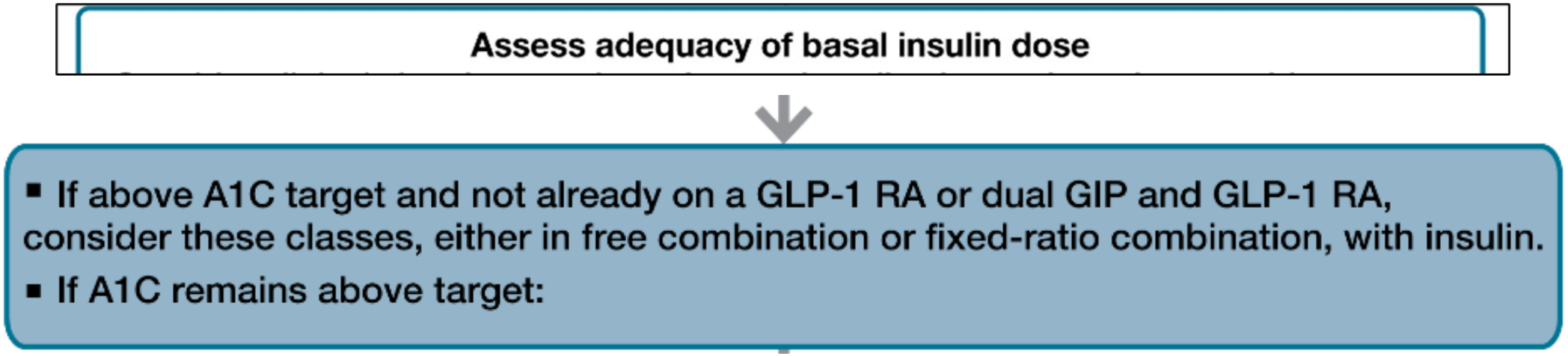
GRADE recommendations based on the reviewed papers.

2023 systemic analysis [for Second-generation antipsychotic med- induced IR, etc.]

Pharmacological agents	GRADE recommendations	Observations
GLP-1RAs (as a pharmacological class)	C: These agents may be used **as add-ons to metformin** in patients diagnosed with severe mental disorders undergoing AP treatment, especially OLZ/CLZ, for the purpose **of controlling BW changes**	Based on the favorable results of a therapeutic guideline, two meta- analyses, and one retrospective review
	C: **For improvement of glucose metabolism dysfunctions (as add-ons)**	
	C: For the treatment of lipid metabolism dysfunctions (as add-ons)	

In Support of Encouraging Semaglutide vs just increasing Insulin

ADA 2023 Standards of Care (EASD & AACE/ACE)



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

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

American Diabetes Association®

Rationale for adding GLP1 RA

- The addition of prandial insulin
  - adds complexity – more challenges to adherence
  - 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
- GLP1 RA therapy has evidence demonstrating ***high efficacy, lower risk of hypoglycemia, and greater weight reduction*** compared with insulin.
  - reduce insulin requirements through multiple mechanisms
  - large effect on prandial glycemia as well as overall & basal glycemia
    - Can add mealtime (prandial) insulin to meal(s) with persistent postprandial high BG
- GLP-1 receptor agonists have been found to **decrease major adverse cardiovascular (CV) events and mortality** in patients with atherosclerotic cardiovascular disease (ASCVD) and those with increased ASCVD risk.
- Increasing evidence for renal protection (& reduced HFpEF) for semaglutide

Whether to titrate metformin instead of or along with titrating semaglutide?

- What was patient's previous difficulty with Ozempic?
- Metformin intolerance (GI) often exacerbated by GLP1 RA meds –

- My suggestion would be to attempt titration of GLP1 RA med first, then see if can titrate up metformin (there is potential added benefit).
  - The GLP1 RA may require an extra slow titration, longer to see effect
  - Remember therapeutic heterogeneity

BP/ Renal Considerations

- Guidelines suggest addition of a ***RAAS agent*** (ACEI or ARB)*
  - Evaluate for AKI first
- SGLT2i would be helpful here –
  - Renal Protection (also reduce HF and CVD risk)
  - BP reduction
  - Possibly eliminate loop diuretic (potential renal toxicity & contribution to hyperglycemia)
  - More rapid reduction in severe hyperglycemia/ glucotoxicity
- GLP1 RA med
  - Naturetic effect
  - BP reduction
  - FLOW ended early - an independent data monitoring panel found that Ozempic lowered the risk of a drop in GFR, end-stage kidney disease or death from either kidney disease or cardiovascular disease – results still blinded but met pre-planned criteria
  - Usually slower response to reduce hyperglycemia/glucotoxicity – titration required

Acute Kinney Injury Concerns

- Is loop diuretic for CCB-induce edema? – increased risk of **AKI*** when use diuretic for this –
- If edema is issue, could also be related to **gabapentin** (&/or weight-related venous stasis)
  - Increased fluid retention – “gabapentinoids significantly decreased the myogenic tone to the same extent as verapamil and nifedipine” [peripheral effect - vasodilatory edema secondary to altered myogenic tone]
  - Gabapentin induced edema, “just like calcium channel blockers induced edema, is not associated with salt and water retention and hence diuretics are ineffective”- case reports of **AKI with diuretic use (**intravascular volume depletion – prerenal)

- **If Torsemide is being used for edema – consider tapering / discontinuing**
  - **especially before adding ACEI or ARB**
  - **taper or stop before adding SGLT2i med**

Recommended dose adjustments of gabapentin based on varying degrees of renal impairment to avoid gabapentin toxicity

CrCl cutoff	Maximum recommended dosing	
	Gabapentin[1]	Pregabalin[2]
30–59 mL/min	700 mg BID	150 mg BID
		100 mg TID
15–29 mL/min	700 mg once a day	75 mg BID
		50 mg TID
<15 mL/min	300 mg once a day	75 mg once a day
Supplemental doses in hemodialysis	100–300 mg post dialysis	75–150 mg post dialysis

Considering SGLT2i medication

- SGLT2i – significant, rapid drop in BG levels/ “break ***glucotoxicity***” (vs high-dose insulin)
  - Insulin sparing
  - Diuretic sparing
  - BP lowering
  - Benefit of rapid BG lowering
  - but ?? increased risk of amputation - new data suggest not increased but…
  - DKA risk?? (DKA can be associated with Atypical Antipsychotic medication use -usually at onset of diabetes)

High glucose levels increases infection & impairs wound healing

Zhou K, Lansang MC. Diabetes Mellitus and Infections. [Updated 2021 Mar 16]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK569326/

- Glycemic Control and Diabetes Therapies
- There is good evidence that glycemic control is correlated with infection.
  - A study of 69,318 patients with type 2 DM in Denmark revealed an association between increased risk for community- and hospital-treated infection in those **with higher HbA1c ≥10.5%** compared with HbA1c 5.5-<6.4% .
  - Similarly, in a large English cohort there was an **increasing risk of infection in parallel with HbA1c for patients with both type 1 and type 2**.
  - In a Taiwanese study looking at outcomes from a community-based health screening program, the authors found that **fasting plasma glucose >200 mg/dL** and DM was associated with the ***highest risk of infection and also a 3-fold higher risk of death*** than those without DM.
  - Looking at an older population, the risk of certain infections was significantly higher in those with **poor glycemic control HbA1c >8.5%** compared with good glycemic control (relative risk infections ranging from 1.28-2.38).

Infections in People with Diabetes – Increased by higher glycemia

- Diabetes Research and Clinical Practice VOLUME 207, 111023, JANUARY 2024 **A matched cohort study evaluating the risks of infections in people with type 1 diabetes and their associations with glycated haemoglobin** Umar A.R. Chaudhry
- ***Higher HbA1c levels*** and a ***greater variability in blood sugar*** levels were strongly associated with a ***higher risk of infections***.

- Indian J Endocrinol Metab. 2012 Mar; 16(Suppl1): S27–S36. **Infections in patients with diabetes mellitus: A review of pathogenesis** Juliana Casqueiro, et al
- In general, infectious diseases are more frequent and/or serious in patients with diabetes mellitus, which potentially increases their morbimortality. The greater frequency of infections in diabetic patients is caused by the ***hyperglycemic environment that favors immune dysfunction*** (e.g., damage to the neutrophil function, depression of the antioxidant system, and humoral immunity)

Decreasing Concern regarding SGLT2i & LEA

- PLOS ONE June 5, 2020
  Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: A systematic review and meta-analysis James Heyward, Omar Mansour, Lily Olson, Sonal Singh, G. Caleb Alexander

- Conclusions: Overall, there was ***no consistent evidence of SGLT2i exposure and increased risk of amputation***.
  - The increased risk of amputation seen in the large, long-term Canagliflozin Cardiovascular Assessment Study (CANVAS) trial for canagliflozin, and select observational studies, merits continued exploration.

Meta-Analysis Diabetes Res Clin Pract
. 2020 May:163:108136. doi: 10.1016/j.diabres.2020.108136. Epub 2020 Apr 6.

Risk of amputation associated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of five randomized controlled trials

- Use of ***SGLT2 inhibitors was not associated with significant increase in the risk of amputation as compared with controls*** (OR: 1.31, 95% CI: 0.92-1.87, I2 = 75%).
  - Subgroup analysis showed that neither canagliflozin, empagliflozin, nor dapagliflozin was associated with increased risk of amputation.
- In conclusion, our ***meta-analysis showed that neither canagliflozin nor other SGLT2 inhibitors increase the risk of amputation***.

Diabetes Epidemiology and Management Volume 6, April–June 2022, 100054

Lower-limb amputations in patients treated with SGLT2 inhibitors versus DPP-4 inhibitors: A meta-analysis of observational studies

Andre J. Scheen

- The incidence rate expressed as a number of LLA events per 1000 patient-years was almost ***similar among SGLT2i users and DPP-4i users*** (2.48±1.45 versus 2.67±3.09, p=0.849).
- Conclusion
- Physicians should not fear an increased risk of LLA with SGLT2is compared with DPP-4is in daily clinical practice, *even if caution may be advised in some patients exposed to special conditions*.

FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) Drug Safety Communication (PDF - 58KB) **8-26-2020** FDA Drug Safety Communication

- Safety information from recent clinical trials also suggests that the risk of amputation, while still increased with canagliflozin, is lower than previously described, particularly when appropriately monitored.
- Based upon these considerations, we have concluded that the Boxed Warning should be removed. The amputation risk with canagliflozin remains and is still described in the Warnings and Precautions section of the prescribing information.
- Health care professionals and patients should continue to recognize the importance of preventative foot care and monitor for new pain, tenderness, sores, ulcers, and infections in the legs and feet.
- *Risk factors that may predispose patients to the need for amputation should be considered when choosing antidiabetic medicines.*

Journal of Diabetes Nursing Issue: Vol:23 | No:04

CARDIOVASCULAR DISEASE, MICROVASCULAR COMPLICATIONS, NEWER THERAPIES SGLT2 inhibitors – moving on with the evidence

David Morris

17 Jul **2019 [newer data since then….]**

- NICE (2015) and MHRA (2017) have provided advice on reducing the risk of lower limb amputation when using SGLT2 inhibitors in type 2 diabetes:
  - Check feet regularly and follow preventative care.
  - Report any foot infection or ulceration.
  - ***Avoid initiation of SGLT2 inhibitors if active foot ulceration or if previous lower limb amputation***.
  - Be cautious about initiating SGLT2 inhibitors in people with peripheral vascular disease. [more recent studies showed improved outcomes]
  - ***Consider stopping SGLT2 inhibitors in cases of foot ulceration, osteomyelitis or gangrene.***

A “Non-evidence-based” thought….

- Marked hyperglycemia (prolonged > 250) results in ***glucotoxicity***
- Glucotoxicity leads to
  - markedly reduced Beta-cell function (endogenous insulin release)
  - increased insulin resistance
  - impaired response to diabetes meds
- Traditionally use aggressive insulin therapy to achieve & maintain BG <240 (250)
  - Increased/restored responsiveness to lower doses of insulin and to other diabetes meds
- SGLT2i improve glycemia (reduce hyperglycemia) by non-Beta cell mechanism
  - More marked response with higher BG levels/ reduce glucotoxicity
- Could SGLT2i be used *temporarily* to reduce BG/reduce glucotoxicity (improve IR & endogenous insulin response to GLP1RA, exogenous insulin, etc.) & then dc SGLT2i and rely on other meds long term – infection* & other benefits ????
  - * articles on increased infection risk with SGLT2i focus on GMI, Fournier gangrene – do not include other soft tissue or foot infections as being increased

Case Considerations

- Evaluate for pre-renal volume depletion ("AKI" - reduction in eGFR)
  - Reduce/discontinue loop diuretic
  - Consider adding RAAS inhibitor (AACEI, ARB)
- Educate/assist patient to effectively use CGM
- If possible, reduce obesogenic medications
- Explore lifestyle, native cultural/spiritual options, etc.
  - one thing has multiple effects
  - explore Diabetes Distress (hopelessness, futility, fear, etc.) (result from & in epigenetic changes – inflammation, etc.)
- Continue to titrate semaglutide (or trial on tirzepatide (greater weight, BG, BP reduction with ~milder GI))
- Titrate basal insulin (glargine U300) to achieve FBS closer to target
- Re-evaluate prandial insulin requirements – CGM valuable
  - Optimizing basal insulin & use of GLP1 RA can reduce need for prandial insulin
- Consider temporary SGLT2i (? 2-4 weeks) therapy to break glucotoxicity (no data)

Extra Slides

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2738809/#:~:text=Increase%20in%20insulin%20resistance%20caused,skeletal%20muscle%2C%20and%20adipose%20tissue.

- While the incidence of antipsychotic-induced diabetic ketoacidosis (DKA) is uncommon, the risk is noted to be the highest with medications such as olanzapine and clozapine, risk factors of which include underlying type 1 diabetes, pre-diabetes, non-Caucasian ethnicity, acute physical illness, male gender, and middle age.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10265718/

- Exp Ther Med. 2023 Jul; 26(1): 355.
- Published online 2023 Jun 1. doi: 10.3892/etm.2023.12054
- PMCID: PMC10265718
- PMID: 37324512
- Therapeutic management of atypical antipsychotic-related metabolic dysfunctions using GLP-1 receptor agonists: A systematic review
- Octavian Vasiliucorresponding author
- Author information Article notes Copyright and License information PMC Disclaimer

- SYSTEMATIC REVIEW article
- Front. Psychiatry, 05 May 2023
  Sec. Schizophrenia
  Volume 14 - 2023 | https://doi.org/10.3389/fpsyt.2023.1153648
- Glucagon-like peptide-1 receptor-agonists treatment for cardio-metabolic parameters in schizophrenia patients: a systematic review and meta-analysis
- Conclusion: Our analysis revealed that GLP-1 RA treatment is safe and effective on cardio-metabolic parameters over control in antipsychotic-treated patients with schizophrenia. Nevertheless, the present evidence is not sufficient to confirm the safety and efficacy of GLP-1RA treatment on insulin and respiratory adverse events. Therefore, further studies are recommended.

Semaglutide for the treatment of antipsychotic-associated weight gain in patients not responding to metformin – a case series

Femin Prasad https://orcid.org/0000-0002-5445-2489, Riddhita De, **[…]**, and Sri Mahavir Agarwal https://orcid.org/0000-0002-2705-5146 mahavir.agarwal@camh.ca

https://doi.org/10.1177/20451253231165169

- Abstract
- Metformin is the currently accepted first-line treatment for antipsychotic-associated weight gain (AAWG). However, not all patients benefit from metformin. Glucagon-like peptide-1 receptor agonists (GLP1-RA) have shown promise in the management of obesity in the general population, with preliminary evidence supporting efficacy in AAWG. Semaglutide is a weekly injectable GLP-1RA which received recent approval for obesity management and noted superiority over other GLP-1RAs. This study explored the efficacy and tolerability of semaglutide in AAWG among individuals with severe mental illness.
- A retrospective chart review of patients treated with semaglutide in the Metabolic Clinic at the Center for Addiction and Mental Health (CAMH) between 2019 and 2021 was conducted. Patients failing a trial of metformin (<5% weight loss or continuing to meet criteria for metabolic syndrome) after 3 months at the maximum tolerated dose (1500–2000 mg/day) were initiated on semaglutide up to 2 mg/week. The primary outcome measure was a change in weight at 3, 6, and 12 months. Twelve patients on weekly semaglutide injections of 0.71 ± 0.47 mg/week were included in the analysis. About 50% were female; the average age was 36.09 ± 13.32 years. At baseline, mean weight was 111.4 ± 31.7 kg, BMI was 36.7 ± 8.2 kg/m2, with a mean waist circumference of 118.1 ± 19.3 cm. A weight loss of 4.56 ± 3.15 kg ($p < 0.001$), 5.16 ± 6.27 kg ($p = 0.04$) and 8.67 ± 9 kg ($p = 0.04$) was seen at 3, 6, and 12 months, respectively, after initiation of semaglutide with relatively well-tolerated side-effects.
- Initial evidence from our real-world clinical setting suggests that semaglutide may be effective in reducing AAWG in patients not responding to metformin. Randomized control trials investigating semaglutide for AAWG are needed to corroborate these findings.

- PHARMACOLOGY AND THERAPEUTICS| AUGUST 15 2013
- Antipsychotic-Induced Insulin Resistance and Postprandial Hormonal Dysregulation Independent of Weight Gain or Psychiatric Disease
- Karen L. Teff; Michael R. Rickels; Joanna Grudziak; Carissa Fuller; Huong-Lan Nguyen; Karl Rickels
- Diabetes 2013;62(9):3232–3240
- https://doi.org/10.2337/db13-0430 PubMed: 23835329
- Atypical antipsychotic (AAP) medications that have revolutionized the treatment of mental illness have become stigmatized by metabolic side effects, including obesity and diabetes. It remains controversial whether the defects are treatment induced or disease related. Although the mechanisms underlying these metabolic defects are not understood, it is assumed that the initiating pathophysiology is weight gain, secondary to centrally mediated increases in appetite. To determine if the AAPs have detrimental metabolic effects independent of weight gain or psychiatric disease, we administered olanzapine, aripiprazole, or placebo for 9 days to healthy subjects (n = 10, each group) under controlled in-patient conditions while maintaining activity levels. Prior to and after the interventions, we conducted a meal challenge and a euglycemic-hyperinsulinemic clamp to evaluate insulin sensitivity and glucose disposal. We found that olanzapine, an AAP highly associated with weight gain, causes significant elevations in postprandial insulin, glucagon-like peptide 1 (GLP-1), and glucagon coincident with insulin resistance compared with placebo. Aripiprazole, an AAP considered metabolically sparing, induces insulin resistance but has no effect on postprandial hormones. Importantly, the metabolic changes occur in the absence of weight gain, increases in food intake and hunger, or psychiatric disease, suggesting that AAPs exert direct effects on tissues independent of mechanisms regulating eating behavior.

- Meta-Analysis Diabetes Res Clin Pract
- . 2020 May:163:108136. doi: 10.1016/j.diabres.2020.108136. Epub 2020 Apr 6.
- Risk of amputation associated with sodium-glucose co-transporter 2 inhibitors: A meta-analysis of five randomized controlled trials
- Satoshi Miyashita 1, Toshiki Kuno 2, Hisato Takagi 3, Takehiro Sugiyama 4, Tomo Ando 5, Nelson Valentin 1, Yuichi J Shimada 6, Masaki Kodaira 7, Yohei Numasawa 7, Yumiko Kanei 8, Sripal Bangalore 9
- Affiliations expand
- PMID: 32272190 DOI: 10.1016/j.diabres.2020.108136
- Abstract
- Amputation has been known to be a rare adverse event of sodium glucose co-transporter-2 (SGLT2) inhibitors. It remains unclear whether the SGLT2 inhibitor as a class or specific categories of the SGLT2 inhibitors are linked with an increased risk of amputation. The objective of this meta-analysis was to investigate the association between the amputation risk and the use of SGLT2 inhibitors. The main outcome measure was the risk of amputation. Multiple databases were searched up to February 2020 and data extraction was performed. Inclusion criteria were randomized controlled trials (RCTs) which reported risk of amputation with SGLT2 inhibitors over non-SGLT2 inhibitors or placebo. The risk of bias was assessed by Cochrane bias tool. The initial search yielded 1,873 citations and a total of five RCTs were included in the meta-analysis. The five included studies evaluated a total of 39,067 patients with diabetes mellitus, including 21,395 patients on SGLT2 inhibitors. The incidence rate of amputation ranged from 0.36 to 3.18% in the SGLT2 inhibitor group and from 0% to 2.87% in the control group. Follow up duration ranged from 24 weeks to 4.2 years. Use of SGLT2 inhibitors was not associated with significant increase in the risk of amputation as compared with controls (OR: 1.31, 95% CI: 0.92-1.87, I2 = 75%). Subgroup analysis showed that neither canagliflozin, empagliflozin, nor dapagliflozin was associated with increased risk of amputation. In conclusion, our meta-analysis showed that neither canagliflozin nor other SGLT2 inhibitors increase the risk of amputation.

- Diabetes Epidemiology and Management
- Volume 6, April–June 2022, 100054
- Diabetes Epidemiology and Management
- Review
- Lower-limb amputations in patients treated with SGLT2 inhibitors versus DPP-4 inhibitors: A meta-analysis of observational studies
- Background
- An increased risk of lower limb amputations (LLA) has been suspected with the use of sodium-glucose cotransporter type 2 inhibitors (SGLT2is) in the CANVAS programme with canagliflozin and in pharmacovigilance reports with all SGLT2is. Even if reassuring observations were reported in several large prospective placebo-controlled cardiovascular outcome trials, real-life conditions in more frailty patients might be associated with a higher risk.

- Methods
- This work analyses the incidence of LLA events in retrospective observational studies that compared SGLT2i users with patients treated with dipeptidyl peptidase-4 inhibitors (DPP-4is), a pharmacological class with an excellent safety profile. A meta-analysis of 12 comparative cohort studies (9 of them using a propensity score matching) worldwide has been performed.

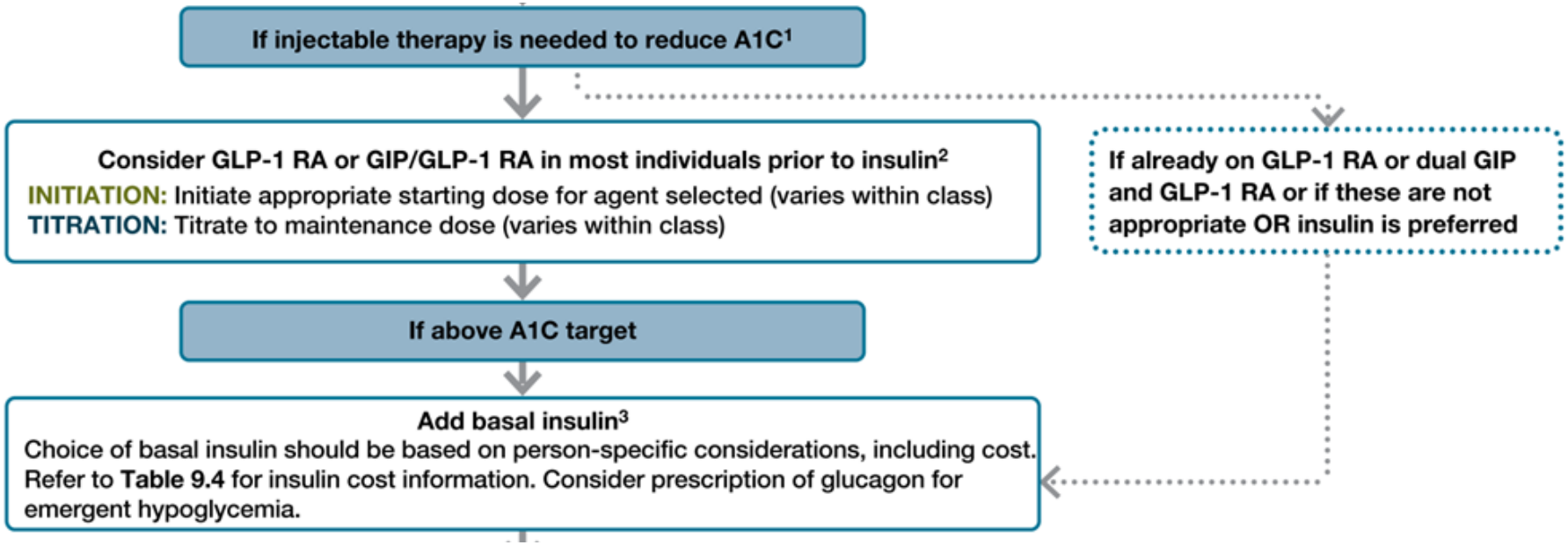
- Results
- The relative risk of LLA tended to be slightly lower in SGLT2i users (1228 LLA events/711159 patients) versus DPP-4i users: 2167 LLA events/1121914 patients, with a hazard ratio 0.91, 95% CI 0.85-0.98, p=0.01). However, a high between-study heterogeneity was observed (I^2 = 79%, P<0.00001), which could not be explained by differences across countries, between studies with/without propensity score matching, between cohorts treated with/without canagliflozin or between patients with/without peripheral artery disease. The incidence rate expressed as a number of LLA events per 1000 patient.years was almost similar among SGLT2i users and DPP-4i users (2.48±1.45 versus 2.67±3.09, p=0.849).

- Conclusion
- Physicians should not fear an increased risk of LLA with SGLT2is compared with DPP-4is in daily clinical practice, even if caution may be advised in some patients exposed to special conditions.

In Support of Encouraging Semaglutide vs just increasing Insulin

ADA 2023 Standards of Care (EASD & AACE/ACE)

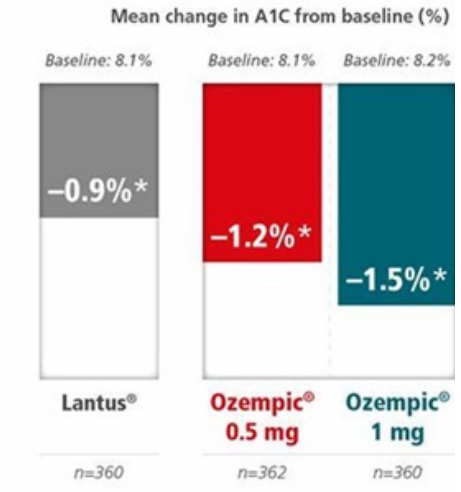
- 9.10 In adults with type 2 diabetes, a ***glucagon-like peptide 1 receptor agonist (GLP1 RA)*** is *preferred to insulin* when possible. A
- AACE/ACE: For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a *GLP-1 RA or GIP/GLP-1 RA* should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

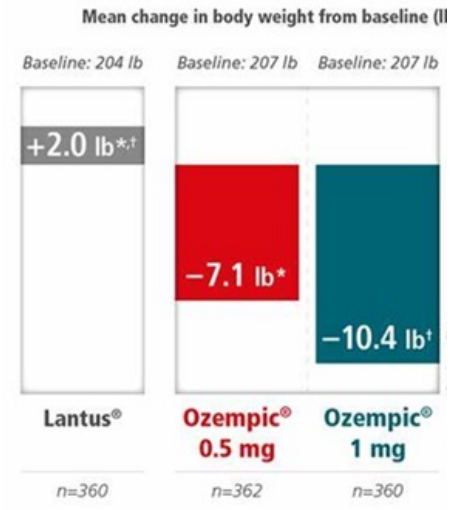


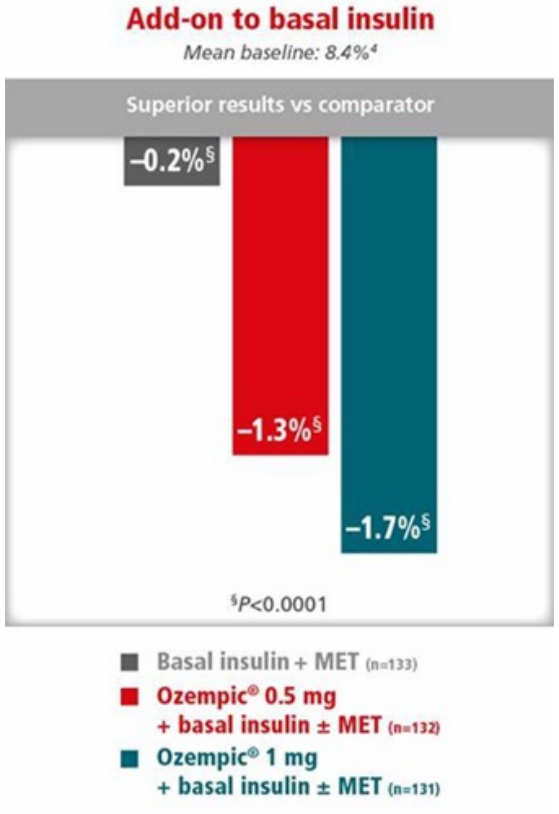
ADA 2023 Standards of Care
Pharmacologic Therapy for Adults with T2D

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

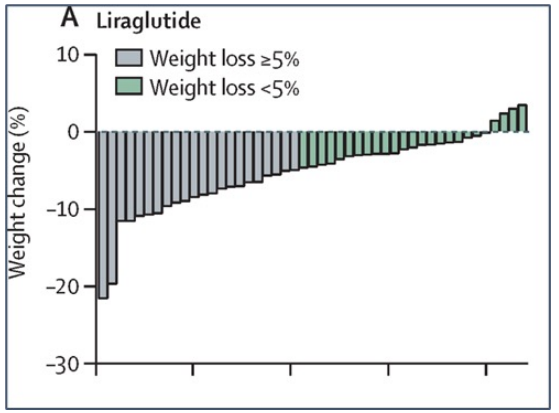
European Association for the Study of Diabetes (EASD) meeting

- In patients on an insulin glargine regimen, 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

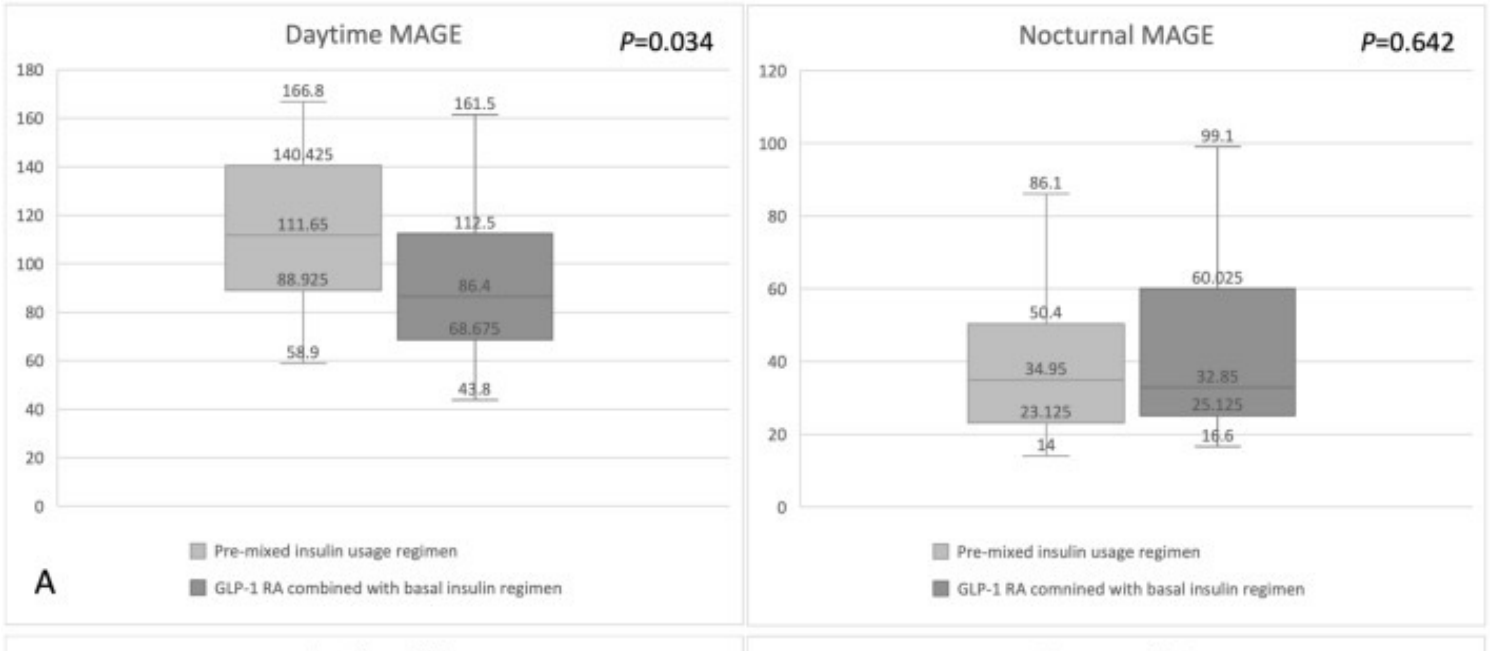
- Looked at Byetta and Liraglutide added to insulin (mainly basal insulin) - Review
- In general, reduction in HbA1c was 1.2%, on average, accompanied by body weight loss of up to 7.3 kg
- However, individual responses are ***highly variable*** -
  - 67% experience reduction in both HbA1c and body weight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

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