ECHO Diabetes

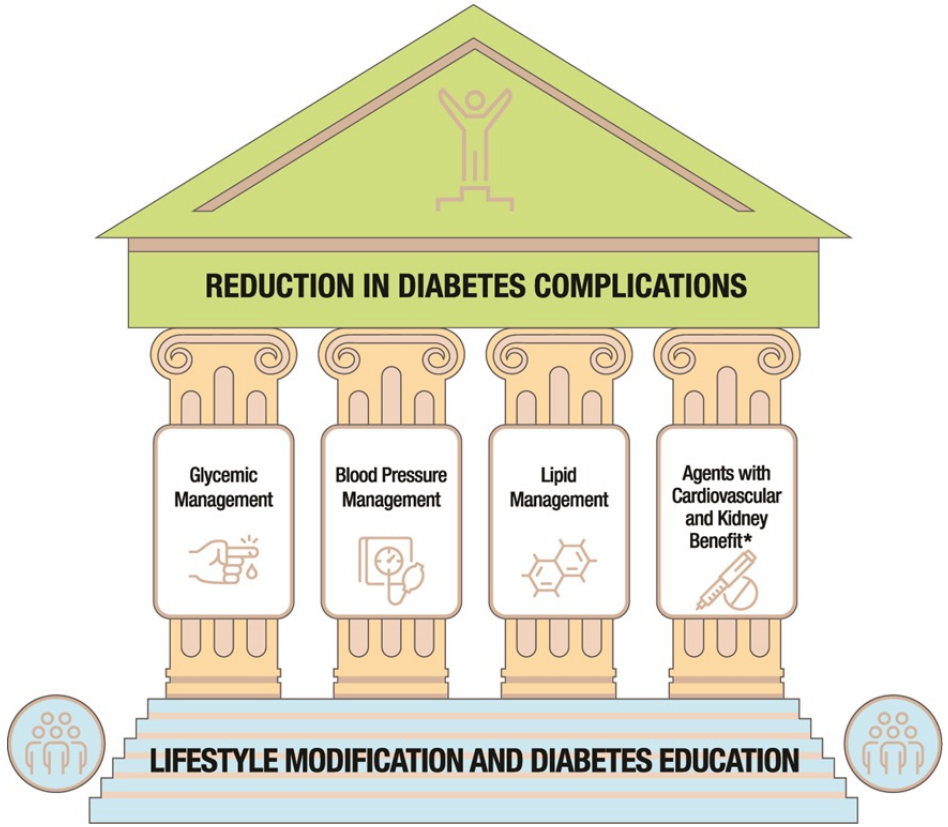
Case Discussion

May 12, 2022

Carol Greenlee MD

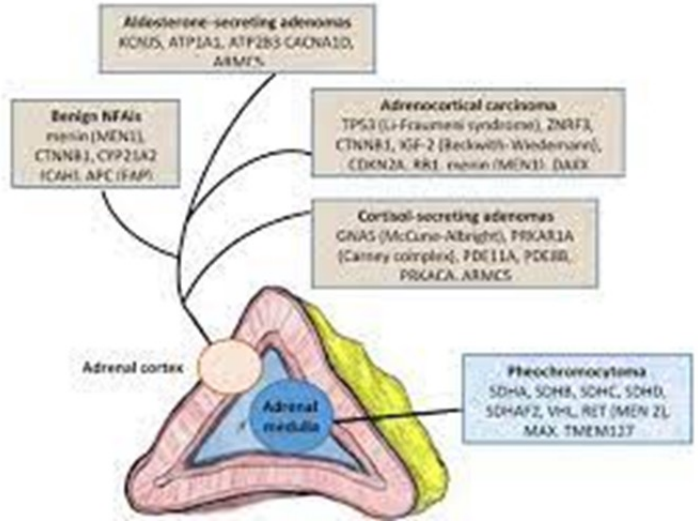
Goals

- Prevent bad outcomes
  - CVD event – risk higher in people with diabetes + PAD
    - GLP-1RA treatment effect in patients with T2DM and PAD - PACE-CME
  - Stroke
  - Heart Failure decompensation
  - Foot ulcer/LEA (lower extremity amputation)
    - PAD + DPN
  - Vision loss/ diabetic eye disease
  - DKD
  - ESLD (obesity + T2D = very high % NAFLD)
  - Other conditions
    - COPD, low BMD, Diverticular disease
- Improve quality of life
  - Reduce burden (time, cost, etc.)
  - Utilize “double duty” Rx /Avoid Rx that exacerbates

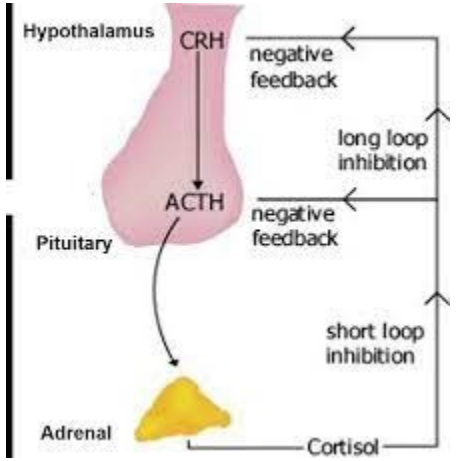


Any concern regarding Left Adrenal Adenoma?

- Malignant vs Benign/ Functioning vs Nonfunctioning
  - Adrenal Medulla - pheochromocytoma
  - Adrenal Cortex
    - Aldosterone-secreting adenoma (patient negative)
    - Sex-steroid secreting
    - Adrenal Cushing Syndrome (overt)
    - Nonfunctioning (benign)
      - Mild Autonomous Cortisol Secretion (MACS)
      - Previously called “subclinical CS”



- Dexamethasone suppression test
  - Detect autonomous secretion
    - Lack of negative feedback
  - Normal response = shut off cortisol
    - Negative feedback



Mild Autonomous Cortisol Secretion (MACS) (2022 Annals article)

- Benign adrenal adenomas – 1 mg Dex suppression test
  - Nonfunctioning adrenal tumors (NFATs) - <50 nmol/L (<1.8 mg/dl)
  - MACS-1 (possible MACS) – 50-138 nmol/L (1.8-5 mg/dl)
  - MACS-2 (definite MACS) - >138 nmol/L (>5 mg/dl)
  - Overt adrenal Cushing Syndrome >138 nmol/L (>5 mg/dl) + overt signs & symptoms

- Comorbidities possibly associated with adrenal incidentalomas with 'autonomous cortisol secretion' (also overt Cushing Syndrome)
  - Hypertension
  - Glucose intolerance/type 2 diabetes mellitus
  - Obesity
  - Dyslipidemia
  - Osteoporosis

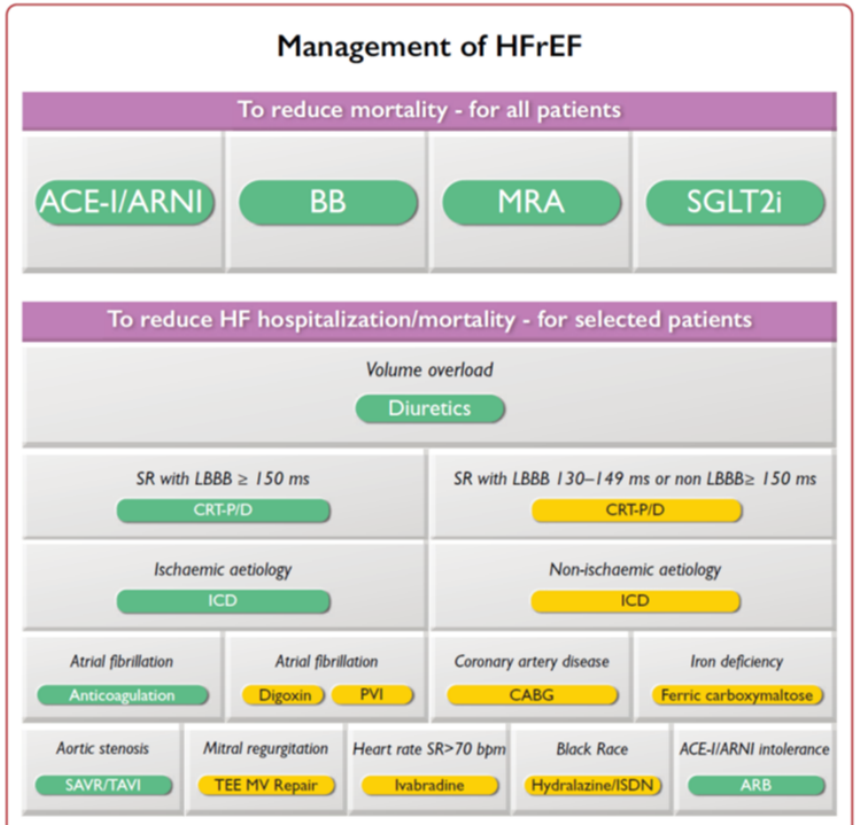
Considerations for patient
- Any overt CS signs – purple stria
- Effect of spironolactone on cortisol
- Hypermetabolism of dex (BMI, meds)
- Surgical candidate or not
- Glucocorticoid Rx of COPD (??)
- Need for new meds to block

Medications that can may potentially interfere with overnight dexamethasone suppression test

Class	Medications
SSRI/SNRI (33)	Sertraline, fluoxetine, paroxetine, trazodone, citalopram, bupropion, venlafaxine
Lipid-lowering agents (10)	Atorvastatin, simvastatin
Calcium channel blockers (12)	Verapamil, diltiazem, amlodipine, nifedipine, felodipine
Angiotensin (AT1type) receptor antagonists (3)	Irbesartan, Losartan
Atypical antipsychotics (5)	Olanzapine, quetiapine
Proton pump inhibitors (6)	Pantoprazole, lansoprazole, omeprazole
PPARγ antagonists (3)	Pioglitazone, rosiglitazone
Antiarrhythmics (2)	Quinidine
β−Adrenoceptor blockers (2)	Propranolol
Benzodiazepine sedatives (2)	Clonazepam
Anticonvulsants (2)	Tiagabine, topiramate

Current medications

- Glycemia
  - Glargine U300 (172 u- 86x2) QD + Novolog 40u TID
  - Empagliflozin 25 mg QD (CVD & Renal nonglycemic benefit)
- Heart Failure/ Hypertension
  - Furosemide 40 mg QD (short half-life)
  - Hydralazine 25 mg QD (short half-life)
  - Carvedilol 6.25 mg BID
  - Empagliflozin 25 mg QD
  - Spironolactone 25 mg QD
- ? ACEI/ARB in past



#321 Hypertension FAQ: Common Outpatient Cases with Dr. Jordy Cohen (The Curbsiders podcast)

Exacerbation/ Risk Concerns regarding NSAIDs

- Counteract antihypertensive meds/diuretics
- Increased BP
- Increased fluid retention – Heart Failure
- Renal damage – AKI, especially in diabetes
- Increased risk of acute MI, stroke
- Increased risk of diverticulitis
  - Increased bleeding risk

Diverticulitis

- Risk factors of diverticulitis
  - Overweight/obesity
  - Red meat, fatty, processed foods (vs high fiber, limited red meat diet)
  - Smoking
  - **NSAIDs**
  - Lack of exercise
- No evidence of GLP1 RA causing or exacerbating diverticulitis

- Annals On Call - Diverticulitis: Myth Versus Evidence | Annals of Internal Medicine (acpjournals.org)
- Annals On Call - Evidence-Based Care of Patients With Diverticulitis | Annals of Internal Medicine (acpjournals.org)
- https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00259-5/fulltext#:~:text=In%20patients%20with%20IBD%20and,the%20disease%20course%20of%20IBD.
  Use of GLP1 RA to treat/improve intestinal disorders

Pharmacologic Therapy for Adults with T2D

ADA Standards of Care 2022

- 9.9 Among individuals with T2D who have *established ASCVD* or *indicators of high cardiovascular risk, established kidney disease* or heart failure a **SGLT2i** and/or **GLP1 RA** *with demonstrated CVD benefit** is recommended as part of the glucose-lowering regimen and the comprehensive CV risk reduction, independent of A1c and in consideration of patient-specific factors. A
- 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

- *liraglutide, semaglutide (SQ) & dulaglutide
- Demonstrated CVD benefit, some renal benefit (albuminuria) – trials ongoing
- No dose adjustment for renal impairment
- Glycemic benefit even at reduced GFR (unlike SGLT2i)
- Limited by cost & tolerability
- Combination therapy with SLGT2i & GLP1 RA appears to have additive CVD protection

Adding GLP1 RA to Basal Bolus Insulin

- Study showed >50% of patients were able stop bolus insulin when added albiglutide to basal-bolus insulin – suspect newer, stronger GLP1 RA agents even more effective

- 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**.
- These findings highlight the potential to achieve glycemic control with a **simplified treatment regimen** by adding a weekly GLP-1RA to mitigate the common unwanted effects associated with insulin therapy.

Diabetes Spectr. 2021 May;34(2):175-183. doi: 10.2337/ds20-0025. Epub 2021 Feb 2.

Exploring Why People With Type 2 Diabetes Do or Do Not Persist With Glucagon-Like Peptide-1 Receptor Agonist Therapy: A Qualitative Study William Polonsky, Cory Gamble, Neeraj Iyer, Mona Martin, Carol Hamersky

- Results: Among continuers (n = 16), the most commonly identified **facilitators supporting the decision to continue** were the observations of improved glucose control (50%) and weight loss (55%). [*treatment efficacy*]
- Among discontinuers (n = 20), the most commonly identified **challenges leading to treatment discontinuation** were side effects (55%) and high cost (50%).
- **Continuers were more likely** than discontinuers to **receive clinically relevant information from their health care team**, including facts about GLP-1 receptor agonist medications, likely treatment benefits, the importance of gradual dose titration, and the need to adjust diet after initiation.
- Conclusion: Although **cost** is a major obstacle to treatment continuation, it can only be resolved through changes in ongoing reimbursement coverage and policies.
- However**, many other obstacles could potentially be addressed through more collaborative patient-clinician interactions before initiating therapy.**

GLP1 receptor agonist therapy

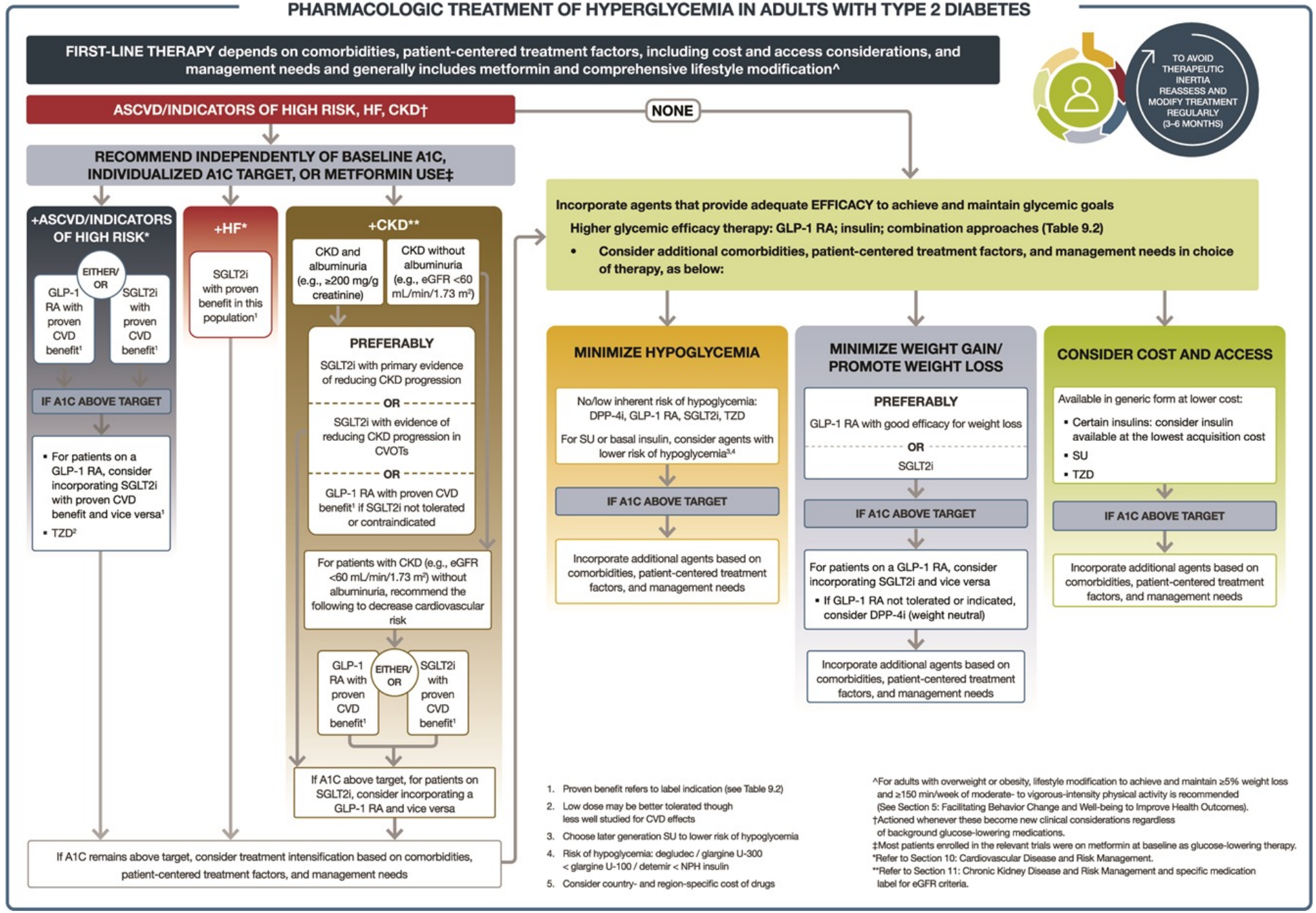
Continuers

- Perceived treatment efficacy
  - Glycemia
  - Weight loss
  - *"The knowledge of the cardiovascular benefit helped me stay on the GLP-1 [receptor agonist]."*
- Perceived treatment burden
  - Cost/insurance coverage
  - Ease of use
- Relevant information from healthcare team
  - explained that GLP-1 receptor agonist therapy would improve my blood glucose control [and other benefits]
  - explained the importance of **gradual dosage titration**
  - explained **how to manage food volume and fats**
    - [stop eating when feel full/ satiety – also bland foods, avoid carbonation & fatty or greasy foods]
  - my questions were answered by my health care team when I started on GLP-1 receptor agonist therapy.
  - I was provided information about GLP-1 receptor agonist medications.
  - my physician's office called to check on my progress and ask if I had any additional questions.

Discontinuers

- Side Effects (GI, injection site)
- Cost
- Lack of benefit
  - **therapeutic heterogeneity**: *"lack of glycemic improvement, lack of weight loss, and/or intolerability of side effects may simply be an unmodifiable class effect in some participants, which could explain why 25.0% of discontinuers reported 'numbers did not improve' as their primary reason for discontinuation"*
- Less likely to receive relevant information from healthcare team

GI side effects:
Nausea less with once weekly
But **diarrhea** more common


PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
GLP-1 RA with proven CVD benefit[1]
EITHER/ OR
SGLT2i with proven CVD benefit[1]
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia[3,4]
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
Certain insulins: consider insulin available at the lowest acquisition cost
SU
TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs
^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.
*Refer to Section 10: Cardiovascular Disease and Risk Management.
**Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

“What other medication can we consider for patient? “

- Metformin – past abdominal pain
- TZD –
  - HF, osteoporosis, weight gain
  - NAFLD, CVD benefit with pioglitazone
- DPP4i –
  - HF risk with 2 agents, minimal glycemic benefit especially for the cost
  - no CVD/renal benefit
- SU –
  - likely minimal benefit with basal-bolus insulin but increased risk of hypoglycemia/weight gain
  - no CVD or renal benefit
- Optimize insulin
  - U500 Regular Insulin (absorption/duration like NPH)
  - CSII
  - Insulin degludec

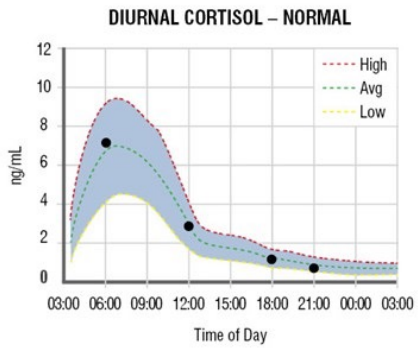
Comparison of Long-acting Insulin options

- Toujeo (glargine 300 u/ml) Solostar pen:
  - Maximum dose: 80 units per injection
  - Adjust dose in 1-unit increments
  - Units per pen: 450
- Toujeo (glargine 300 u/ml) Maximum Solostar pen:
  - Maximum dose: 160 units per injection
  - Adjust dose in 2-unit increments
  - Units per pen: 900
- In clinical trials, many people switching from Lantus to Toujeo required a ***higher dose of Toujeo*** compared with their previous Lantus dose.
- Tresiba (insulin degludec injection) U-100 FlexTouch pen (100 U/mL)
  - Maximum dose per injection: 80 units
  - Adjust dose in 1-unit increments
  - Units per pen: 300 ml
- Tresiba (insulin degludec injection) FlexTouch pen 200 U/mL
  - Maximum dose per injection: 160 units
  - Adjust dose in 2-unit increments
  - Units per pen: 600 ml
- In clinical trials, people switching from Lantus to Tresiba usually required a ***lower dose of Tresiba*** compared to their previous Lantus dose.

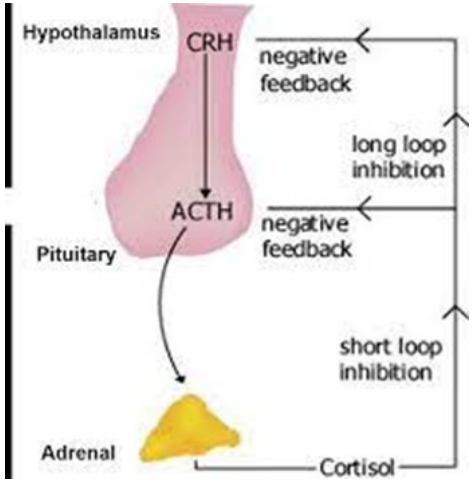
Considerations

- Emphasize diet/lifestyle changes with benefits for many aspects of her health & many of her medical conditions
- Stop NSAIDs (perhaps replace with Acetaminophen)
  - Strong link to diverticulitis and complex diverticulitis + other concerns
- Prioritize repeat trial on GLP1 RA (glycemic & non-glycemic benefits)
  - If refuses semaglutide, consider dulaglutide (not on formulary)
  - Emphasize benefits – talk through adjusting diet, etc., provide phone call support
  - Hopefully, reduce insulin requirements
- Consider trial on insulin degludec to see if can give one injection basal insulin
  - Consider CSII linked to Dexcom G6 (often lower insulin doses required)
- Optimize HTN/HF meds –
  - ? ACEI or ARB instead of hydralazine/ ? long-acting thiazide
- Consider evaluation for cortisol excess (can start with AM ACTH, cortisol & DHEA-S)*
  - Able/willing to go to surgery (can often be laparoscopic but check with her BMI)

Evaluation for autonomous cortisol secretion*



- ACTH and Cortisol are highest in the morning when first wake up
- As adrenal adenoma secretes increasing amounts of cortisol the pituitary detects excessive cortisol, and the negative feedback causes ACTH to be suppressed – morning ***ACTH usually <10*** if cortisol excess – (want to check ACTH before giving dexamethasone because dex itself will cause low ACTH)
- As adrenal adenoma secretes more cortisol, DHEA-S levels are increasingly suppressed
- After 1 mg dexamethasone at bedtime, normal response is suppression of cortisol – if not suppressed, suggests autonomous production from the adenoma (? Get dex level with cortisol)



Be sure no recent exogenous steroids

MACS resources

- https://www.healio.com/news/endocrinology/20220126/mild-autonomous-cortisol-secretion-in-benign-adrenal-tumors-increases-cardiometabolic-risk
- Annals On Call - Are Adrenal Incidentalomas Clinically Important? | Annals of Internal Medicine (acpjournals.org)

- Annals of Internal Medicine March 2022 Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors A Cross-Sectional Multicenter Study Alessandro Prete, MD, Anuradhaa Subramanian, MSc, Irina Bancos, MD, … https://doi.org/10.7326/M21-1737

Other Resources

- #321 Hypertension FAQ: Common Outpatient Cases with Dr. Jordy Cohen (The Curbsiders podcast)
- GLP-1RA treatment effect in patients with T2DM and PAD - PACE-CME
- Annals On Call - Diverticulitis: Myth Versus Evidence | Annals of Internal Medicine (acpjournals.org)
- Annals On Call - Evidence-Based Care of Patients With Diverticulitis | Annals of Internal Medicine (acpjournals.org)
- https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00259-5/fulltext#:~:text=In%20patients%20with%20IBD%20and,the%20disease%20course%20of%20IBD . Use of GLP1 RA to treat/improve intestinal disorders

Review Curr Med Res Opin 2018 Jan;34(1):1-10

Adding Prandial GLP-1 Receptor Agonists to Basal Insulin: A Promising Option for Type 2 Diabetes Therapy

Ronald M Goldenberg, Lori Berard

Abstract

- Results: Most of the studies presented in this review show that **the addition of a prandial GLP-1 RA to basal insulin** results in **equal or slightly superior efficacy** compared to the addition of prandial insulin**, together with weight loss and less hypoglycemia.**
- Conclusions: The results of the studies suggest that a prandial GLP-1 RA as an add-on to basal insulin may be a safe and effective treatment intensification option (vs basal-plus or basal-bolus insulin).

Diabetes Care. 2020 Oct; 43(10): 2509–2518. Published online 2020 Jul 21. doi: 10.2337/dc19-2316

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

STUDY – looked at **patients already on Basal-Bolus insulin +/- metformin**; replaced bolus insulin with GLP1 RA Albiglutide in one group vs adjusting basal-bolus insulin in the other group

RESULTS – noninferiority for A1c reduction

- Mean ± SD HbA1c at baseline,
  - 7.8 % in the albiglutide + glargine group→ 6.7% at 26 weeks
  - 7.7 % in the lispro + glargine group → 6.6% at 26 weeks
- In the albiglutide + glargine group,
  - **Over 50% of participants replaced all prandial insulin** without reintroducing lispro up to week 26
  - **Less severe/documented symptomatic hypoglycemia** (57.2% vs. 75.0%)
  - Meaningful **weight** differences (LS mean ± SE **−2.0 ± 0.2 vs. +2.4 ± 0.2 kg**) vs. lispro + glargine.

CONCLUSIONS

- **Replacing *prandial insulin with a weekly GLP-1RA can* simplify *basal plus prandial insulin treatments and* achieve better outcomes *in type 2 diabetes***.

How they did the adjustments of adding GLP1 RA to Basal-Bolus Insulin

- At baseline
  - A1c range 7.0% to 9.5% and Insulin dose </= 140u/day
  - Run-in phase of study was insulin optimization – brought average A1c to 7.8% range
  - +/- metformin – no other diabetes meds except insulin
- All participants were taking glargine QD + lispro TID
- Started with 30 mg of albiglutide weekly and reduced lispro insulin doses to ½ at same time
- At 4 weeks increased albiglutide to 50 mg weekly & discontinued lispro insulin injections
- At 8 weeks – could add back in lispro if postprandial BGs were averaging >180

Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist continued

- Difficult to predict who will respond:
- At study end, participants who completed the study in the albiglutide + glargine group
  - 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.

Reduction in # of injections/week
29 → 13

- There were ***no differences between individuals*** who did or did not require the reintroduction of lispro in terms of duration of diabetes, age, weight, BMI, baseline HbA1c, and baseline total insulin dose

- Mean prescribed daily **prandial insulin** dose
  - decreased from **38.7** +/- 19.0 u → **9.8** +/- 17.3 u at week 26 in the albiglutide + glargine group
  - increased from **41.3** +/- 21.6 u → **71.9** +/- 40.1 u in the lispro + glargine group.
- Daily basal insulin dose increased to a similar degree in both groups from baseline to week 26
  - 41.6 +/- 17.3 u for albiglutide + glargine to 59.3 +/- 24.1u (total insulin 80.3 +/- 29.1 u → 69 +/- 33.2 u)
    - only 28% were on the same or higher dose
  - 41.6 +/-17.1 u for lispro + glargine to 58.6 =/- 25.9 u (total insulin 82.9 +/- 32.1 u →130.4 +/- 61.1 u)

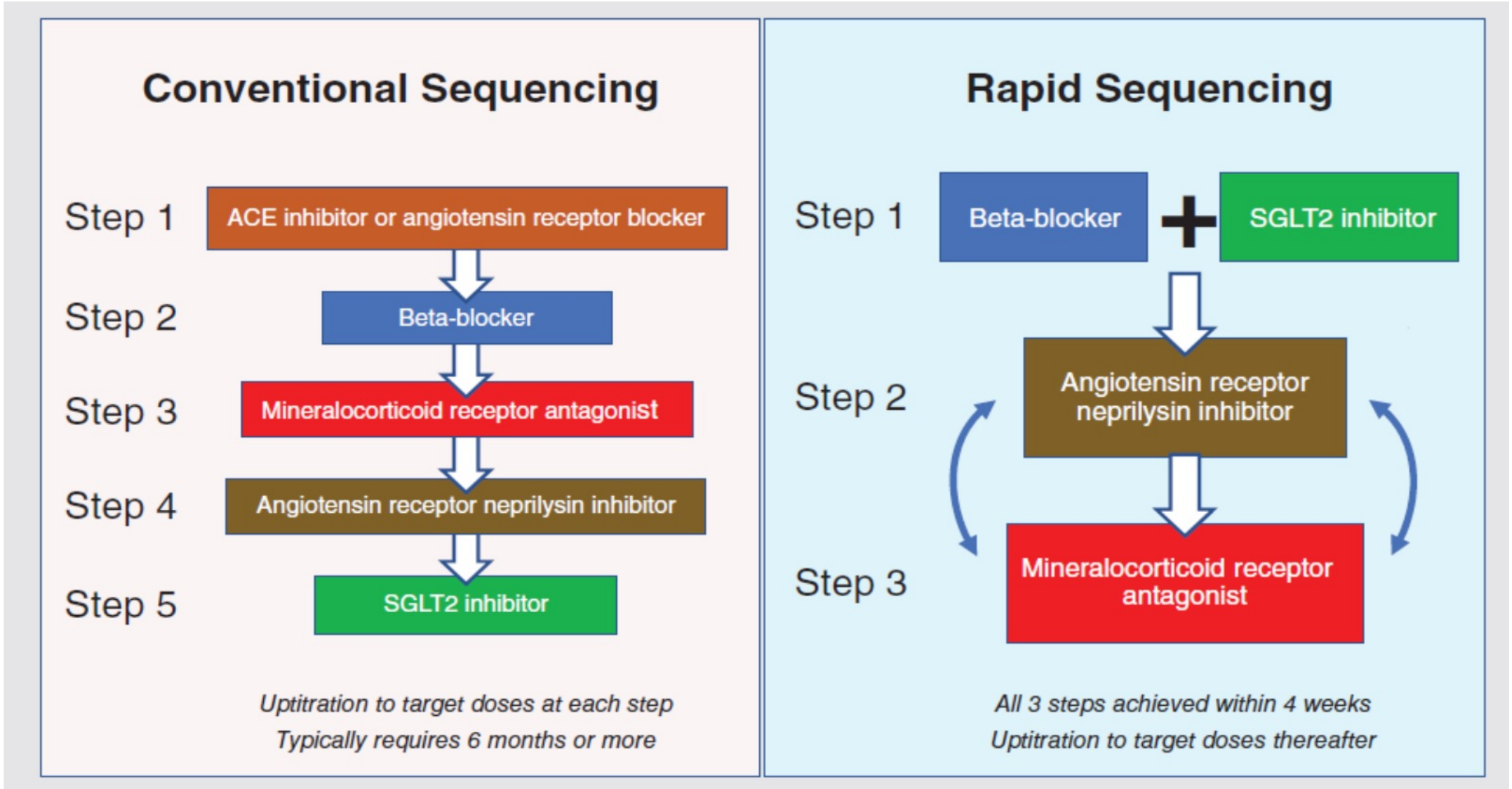
Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist continued

- Severe or documented symptomatic hypoglycemia
  - lower in the albiglutide + glargine group at 57.2%
    - on-therapy documented symptomatic hypoglycemic event = 46.8% (daytime) and 25.3% (nocturnal)
    - the **odds ratio for risk** of one **hypoglycemic event** and the hypoglycemia event rate **were more than halved with the albiglutide substitution**
  - than the lispro + glargine group at 75%
    - on-therapy documented symptomatic hypoglycemic event = 70.9% (daytime) and 36.8% (nocturnal)
- Body weight changes from baseline to week 26 differed in direction between
  - albiglutide + glargine = - 2.0 +/- 0.2 kg
  - lispro + glargine = +2.4 +/- 0.2 kg
- A + G group: Improvements were seen for all five domains of the TRIM-Diabetes questionnaire (*treatment burden, daily life, diabetes management, compliance, and psychological health*)
- More adverse events (GI) in A + G group –some leading to discontinuation (3.5% vs 2.2%) –
  - GI/nausea vs hypoglycemia

Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist continued

- These findings provide **scientific evidence for a role for GLP-1RAs as a replacement for prandial insulin** in patients with type 2 diabetes requiring multiple daily insulin injections to achieve glycemic control
  - **HbA1c reductions with albiglutide in the 0.8%–0.9% r**ange, while **dulaglutide and semaglutide achieved HbA1c reductions in the 1.1%–1.8%** range and with **greater weight loss** in most studies.
  - it is ***conceivable that other weekly GLP-1RAs (i.e., dulaglutide, semaglutide) might have a greater effect*** *than albiglutide for reducing HbA1c and body weight when replacing prandial insulin in patients with type 2 diabetes on multiple daily insulin therapy.*

- 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**.
  - These findings highlight **the potential to achieve glycemic control with a simplified treatment regimen by adding a weekly GLP-1RA** to mitigate the common unwanted effects associated with insulin therapy.


Conventional Sequencing
Step 1
ACE inhibitor or angiotensin receptor blocker
Step 2
Beta-blocker
Step 3
Mineralocorticoid receptor antagonist
Step 4
Angiotensin receptor neprilysin inhibitor
Step 5
SGLT2 inhibitor
Uptitration to target doses at each step
Typically requires 6 months or more
Rapid Sequencing
Step 1
Beta-blocker
SGLT2 inhibitor
Step 2
Angiotensin receptor neprilysin inhibitor
Step 3
Mineralocorticoid receptor antagonist
All 3 steps achieved within 4 weeks
Uptitration to target doses thereafter

Cumulative Impact of Evidence-based HFrEF Medical Therapies on All-Cause Mortality

	Relative Risk	2 yr Mortality
None		35.0%
ARNI	↓ 28%	25.2%
Beta blocker	↓ 35%	16.4%
Aldosterone antagonist	↓ 30%	11.5%
SGLT2 inhibitor	↓ 17%	9.5%

Cumulative risk reduction if all evidence based medical therapies used:
Relative risk reduction of 72.9%, Absolute risk reduction: 25.5%. **NNT = 4**

Butler, Javed. "Optimizing Heart Failure Therapy: Selection, Sequences, Substitution?" New York Academy of Medicine and Icahn School of Medicine Mount Sinai. 8 Oct. 2021, New York Academy of Medicine. Lecture.