

A Shot in the Dark: A Guide to Adjunctive Therapies for Diabetes

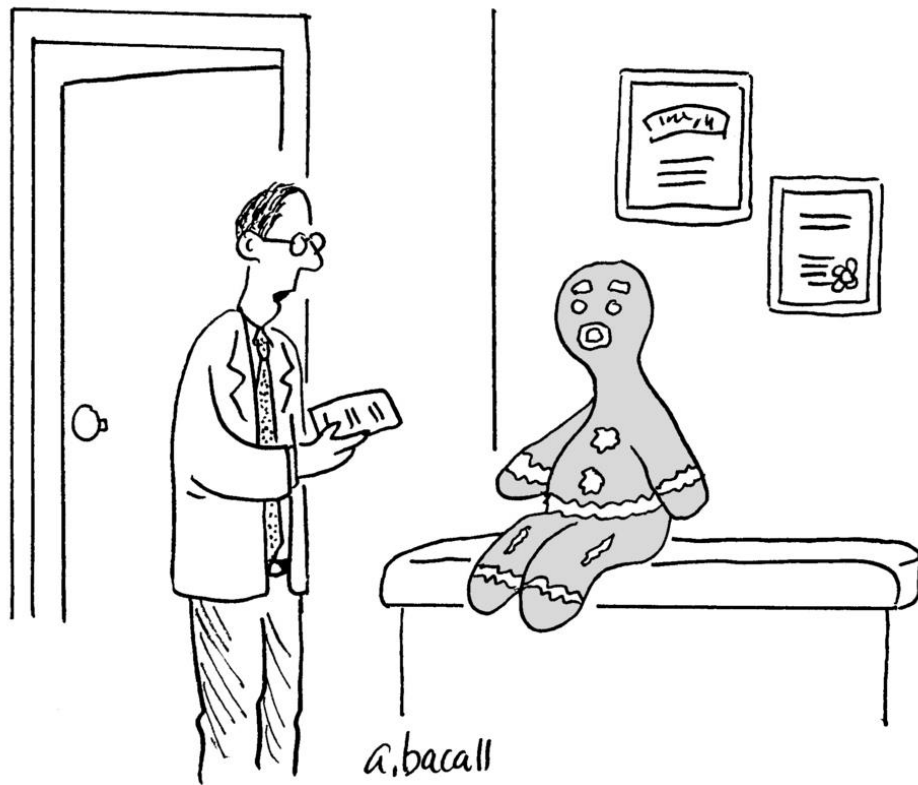
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"I have your test results. Your sugar is too high."

Disclosures

We have no financial disclosures

A1C

- **Use in combination with self-monitoring of blood glucose or CGM**
- **Assess Accuracy:**
 - Increased RBC turnover (hemolysis, G6PD, EPO, ESRD, pregnancy)
 - Assay Variability
- **Assess A1C goals:**
 - If controlled: Every 6 months
 - If uncontrolled or change in therapy: every 3 months (quarterly)

Estimated average glucose (eAG)

A1C (%)	mg/dL*	mmol/L
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CI. A calculator for converting A1C results into eAG, in either mg/dL or mmol/L, is available at professional.diabetes.org/eAG.

Standards of Care

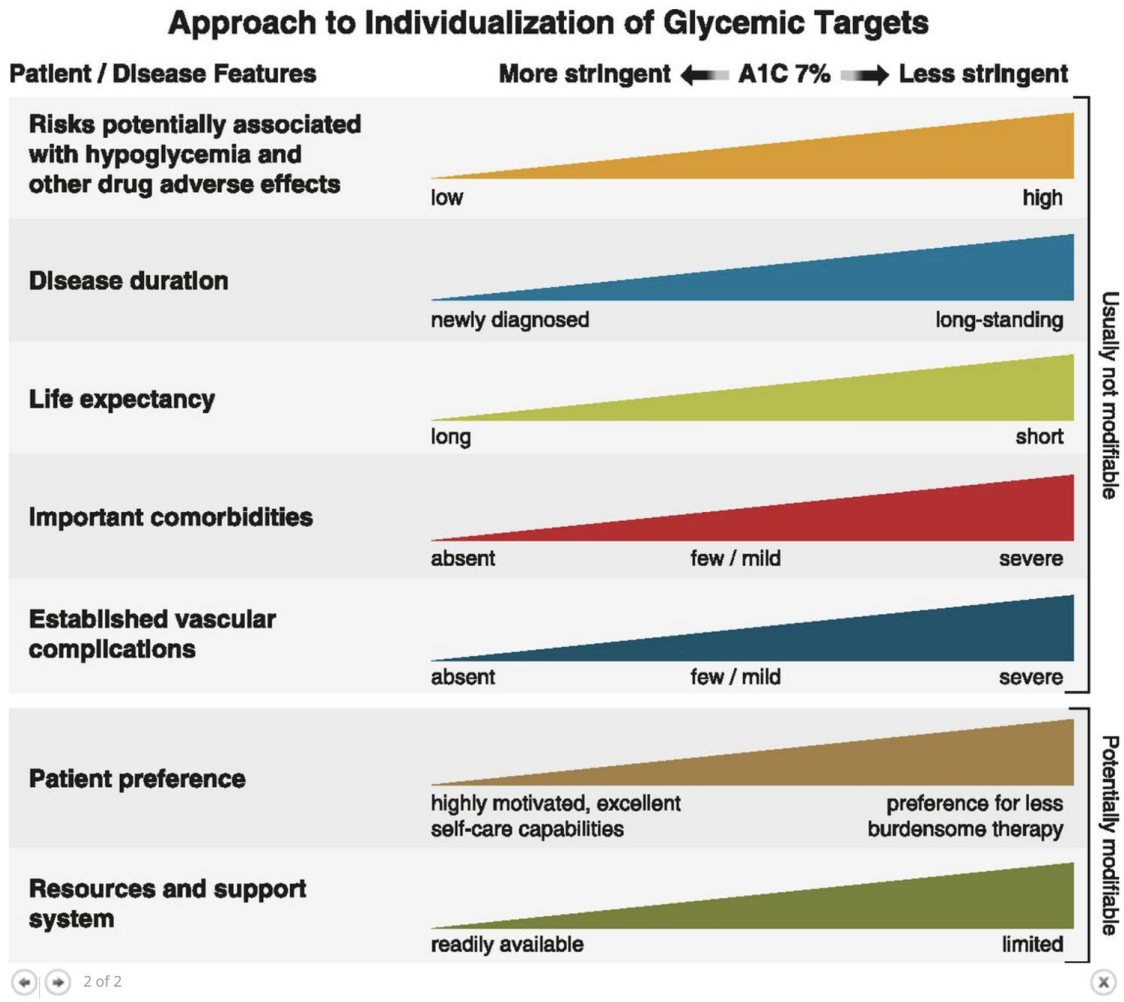
6. Glycemic Targets: *Standards of Medical Care in Diabetes—2021*

American Diabetes Association
Diabetes Care 2021 Jan; 44(Supplement 1): S73-S84.
<https://doi.org/10.2337/dc21-S006>



A1C Targets

- <7% for nonpregnant adults
- <8% if limited life expectancy or if risk outweighs benefit
- Goal is to decrease microvascular complications
- ACCORD, ADVANCE, VADT Trials - increased death by any cause with tighter control in those with CVD
- Kumamoto Study and UKPDS Study - decreased microvascular complications with intensive control for patients with newly diagnosed T1DM



Take Home Point

- Tighter HbA1c control is preferred in low-risk groups

First Line Therapy: Metformin

MOA: Not completely understood, many reported mechanisms

Non-FDA Approved Alternative Uses:

- **PCOS associated infertility**
- **Gestational Diabetes**
- **Prediabetes/Weight loss**

Adverse Effects

- **GI distress, B12 malabsorption**
- **Lactic acidosis**

Contraindications:

- **eGFR <30**
- **Hypersensitivity**
- **Hold prior to iodinated contrast administration (okay to resume 48 hrs later)**

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGI	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate to Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m ²	Exenatide Not Indicated CrCl <30 Possible Benefit of Liraglutide	Not Indicated for eGFR <45 mL/min/1.73 m ² Genital Mycotic Infections Possible CKD Benefit	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects

- Liraglutide—FDA approved for prevention of MACE events.
- Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
- Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

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Type 2 DM and Cardiovascular Disease

- **GLP1 Analogues**

- LEADER trial (2016): Liraglutide was associated with reduction in CV events compared to placebo in DM2 patients with high risk for CV events

- **SGLT-2 Inhibitors**

- EMPA-REG OUTCOME trial (2015): Empagliflozin reduced primary composite outcomes vs placebo in patients with DM2 + high risk for CV event
- CANVAS trial (2017): Similar benefit for canagliflozin
 - Higher risk of lower extremity amputation (toe, foot, or leg)

Type 2 DM and Congestive Heart Failure

- SGLT-2 Inhibitors
 - **Heart Failure w/ Reduced Ejection Fraction (HFrEF)**
 - DAPA-HF trial (2019): Dapagliflozin associated with reduced CV death, worsening HF, and all cause mortality in patients with HFrEF regardless of DM2.
 - **Heart Failure w/ Preserved Ejection Fraction (HFpEF)**
 - EMPEROR-Preserved Trial (2021): similar outcomes for Empagliflozin in HFpEF

Take Home Points

- Tighter HbA1c control is preferred in low-risk groups
- **For patients with HFrEF and HFpEF, recommend usage of SGLT2 inhibitors**
- **For patients with CAD, recommend usage of GLP1 analogues**

Type 2 DM and Chronic Kidney Disease

- General Guidance
 - **Weight loss > 5%**
 - **Protein intake 0.8g/kg/day; 1-1.2 g/kg/day if on RRT**
- Monitoring
 - **HbA1c goal same as without CKD, personalized**
 - **HbA1c measurements less accurate with more advanced CKD**
 - **Recommend monitoring HbA1c every 3-6 months**
 - **Recommend monitoring urine MA:Cr annually**
- KDIGO 2020:
 - **SGLT-2i should be used in DM with CKD**
 - **Reduce other glycemic agents, if needed, to make room for SGLT-2**
 - **Addition of GLP-1RA if eGFR<15 or additional control needed**

Type 2 DM and CKD

Recent studies SGLT-2:

- DAPA-CKD (2020): decreased rate of decline of eGFR with dapagliflozin vs placebo
- EMPEROR-Reduced (2020): lower rate of eGFR decline with empagliflozin vs placebo
- EMPA REG Outcome (2016): lower rate of new RRT, doubling of Cr with empagliflozin vs placebo
- EMPA REG (2020): lower rate of new/worsening nephropathy **regardless of KDIGO strata**

Recent studies GLP-1RA

- Liraglutide decreased new macroalbuminuria vs placebo (NEJM 2017)
- Semaglutide decreased rate of new/worsening nephropathy (NEJM 2016)
- Dulaglutide vs insulin glargine had similar A1c reduction and improved GFR, no change in urine MA:Cr ratio (Lancet 2018)

SGLT-2 preferred

- 2021 Meta-analysis of CKD pts found SGLT-2 reduced MACE and renal adverse events, GLP-1 RAs did not

Type 2 DM and CKD

Recent studies SGLT-2:

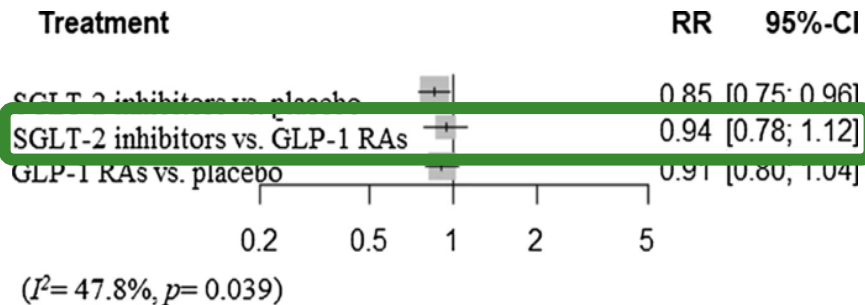
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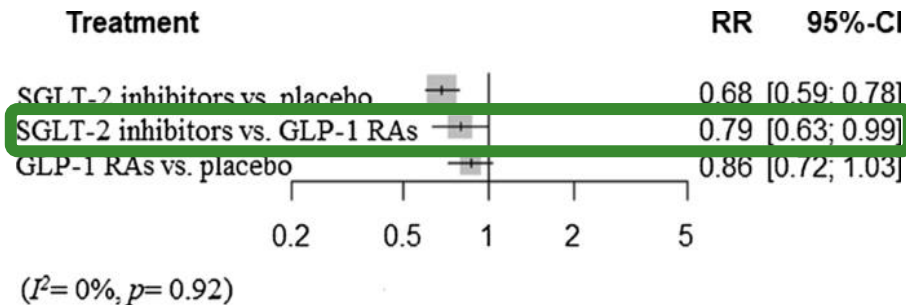
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Cardiac Events



Renal Events

Renal Dosing of Medications

- Metformin
 - Reduce dose to 500 BID at GFR 45
 - Stop at GFR < 30
- SGLT-2i
 - Do not start GFR < 30
 - Can be continued until side effect or RRT
 - DAPA-CKD included pts with GFR >25
 - EMPA-REG (2016) nephroprotection, CV benefits did not vary by KDIGO strata
- GLP-1
 - No Renal dose adjustment for most GLP-1RAs

Take Home Points

- Tighter HbA1c control is preferred in low-risk groups
- For patients with HFrEF and HFpEF, recommend usage of SGLT2 inhibitors
- For patients with CAD, recommend usage of GLP1 analogues
- **For patients with CKD and eGFR > 15, recommend use of SGLT-2 inhibitors**
- **For patients with CKD and eGFR < 15, recommend use of GLP-1 RA**

Obesity Management with Diabetes

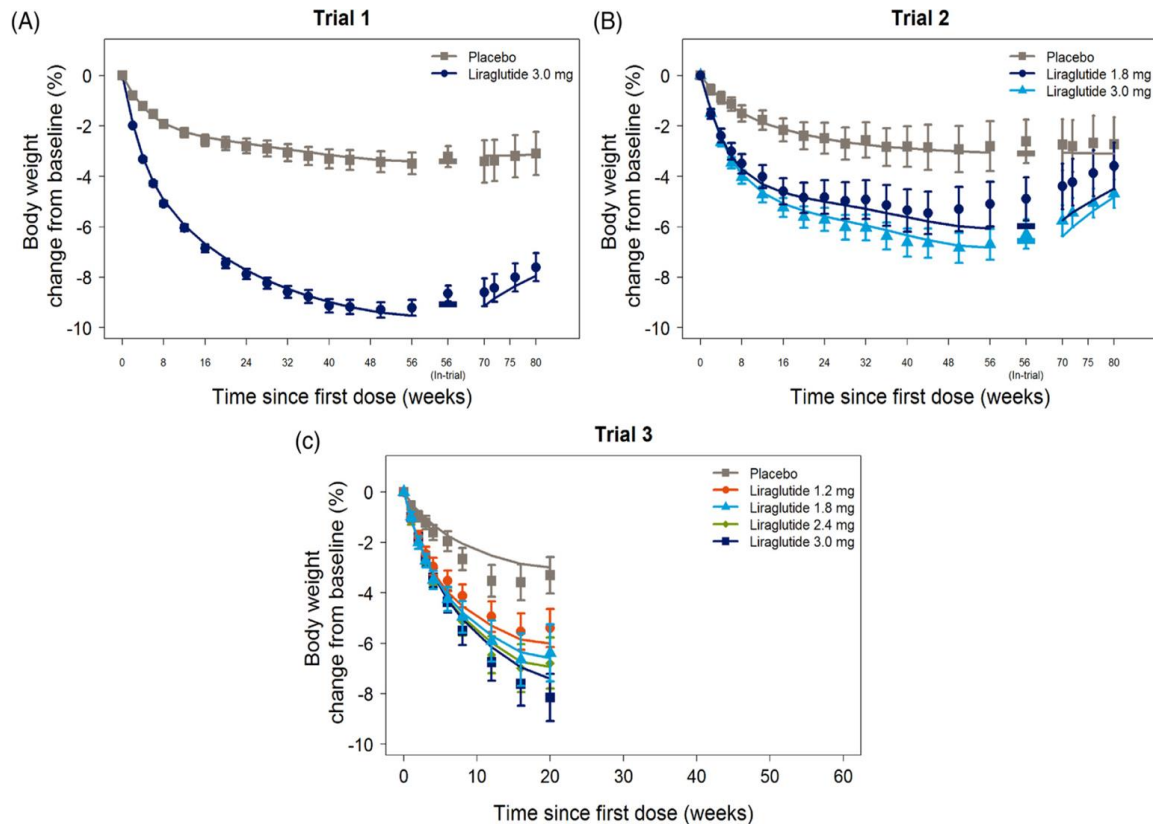
Obesity **ADA** standards of care 2021:

- Recommend lifestyle management for >5% drop in wt loss
- Recommend consideration of medication for weight loss
- Recommend discussing bariatric surgery for BMI > 40 or BMI >35 after failure to achieve "durable weight loss and improvement in comorbidities (hyperglycemia) with other management"
- Bariatric surgery may be considered for BMI > 30 with failure to achieve "durable weight loss and improvement in comorbidities"

Obesity Medications:

- Liraglutide (3.0mg daily dosing)
 - SCALE Diabetes and SCALE Obesity and Prediabetes trials
 - Additional weight loss benefit on top of low calorie diet
 - Early response (16wks) predicts 1-year response

Liraglutide versus placebo on body weight



Type 2 DM and NAFLD management

Risk factors for NAFLD include insulin resistance and elevated triglyceride levels

Treatments:

- NAFLD without fibrosis or NASH: Lifestyle interventions
- biopsy-proven NASH with fibrosis (\geq F2), or early stage fibrosis with high risk for progression: pharmacotherapy + lifestyle interventions
- Possible treatments: pioglitazone, semaglutide, liraglutide
- Not recommended: Metformin due to no histologic change

Bottom Line:

- Piaglitazone
- Semaglutide
- Liraglutide

Other agents to consider

Sulfonyureas

- **High hypoglycemia risk**
- **Cheap, but not preferred**
- **Good for steroid-associated hyperglycemia**

TZDs (Pioglitazone)

- **Cheap, low hypoglycemia risk**
- **Not for use in heart failure (water retention) or liver failure**
- **An option for NAFLD**

Take Home Points

- Tighter HbA1c control is preferred in low-risk groups
- Metformin continues to be first line therapy
- SGLT-2 inhibitors preferred
 - CKD
 - HFrEF
 - HFpEF
- GLP-1 RA preferred
 - eGFR < 15
 - Weight loss
 - CAD
- Incorporate patient preference and risk factors into medication choices
- Other meds as indicated by cost, method of delivery, insurance, etc.

Thank you

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