GLYCEMIC MANAGEMENT STRATEGIES FOR THE INPATIENT AND AMBULATORY SETTING

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September 16th, 2022
Objectives:

1. Review ACP Guidance statements & ADA standards of care for glycemic management
2. Review strategies for evaluating baseline glycemic control
3. Identify appropriate glucose goals based on individualized care plan
4. Identify basic strategies for glycemic management in the inpatient settings
5. Identify basic strategies for glycemic management in the ambulatory setting
ACP Guidance Statements:

- HbA1c goal 7-8% in most patients with Type 2 diabetes (T2D)

- De-intensify pharmacologic therapy if HbA1c < 6.5%

- Treat patients with T2D to minimize symptoms related to hyperglycemia and avoid targeting a HbA1c level in patients with
  - Life expectancy < 10 years
  - Advanced age (80+)
  - Reside in nursing home
  - Chronic conditions (dementia, cancer, ESRD, severe COPD, CHF, etc.)
  - WHY? Harm outweighs benefit

ADA:

- HbA1c goal <7% for non pregnant adults with T2D
- Individualized HbA1c target to guide reduction in hypoglycemia

American Diabetes Association (ADA), (2018); Qaseem et al. (2018)
There is significant overlap between all interested parties...

- INDIVIDUALIZE glycemic target based on care goals for each patient, and multiple factors:
  - Risk of hypoglycemia
  - Modifiable and nonmodifiable risk factors
    - Pill / injection burden
    - Life Expectancy
  - Microvascular & macrovascular complication
  - COST!
GOALS FOR GLYCEMIC CONTROL
Blood sugar goals

**Ambulatory Targets (general population):**

- Fasting/pre-meal: 80 - 130 mg/dL
- Random: < 180 mg/dL

**Hospital Targets:**

- Floor status:
  - Fasting/pre-meal (general): 140-180 mg/dL
  - Fasting/pre-meal (select pts): 100 (110) - 140 mg/dL
  - Random: < 180 mg/dL
- Intensive Care:
  - 140 - 180 mg/dL

**Avoidance of hypoglycemia:**

- < 70 mg/dL = Hypoglycemia
- < 54 mg/dL = SEVERE Hypoglycemia

American Diabetes Association (2018); Korytkowski, et al. (2022); Finfer et. al (2009)
Evaluating Glycemic Control:

**Time in Range (TIR):**
- Continuous glucose monitoring systems
- Time spent in target glucose range, set by provider (70-180 mg/dL)
- Goal is **> 70% TIR** for most patients
  - Aligns with an A1c ~ 7%
- Consider **>50% TIR** for elderly patients or those with many risk factors
  - < 25% at levels > 180 mg/dL
  - < 5% at levels > 250 mg/dL
  - < 4% at levels < 70 mg/dL
  - < 1% at levels < 54 mg/dL

**Hb A1c:**
- Data on ~ 90 days
- Doesn’t identify variability
- Accuracy impeded by altered Hb levels:
  - Anemias (CKD, ETOH, etc.)
  - High doses of Vitamin C / E
  - Race & ethnicity

**Serum Fructosamine:**
- Lab draw → send out?
- Data on previous ~ 2-3 weeks
- Translate to Hb A1c
- Accuracy impeded by altered albumin metabolism

Endocrine Society (2022); Henderson, Parker, Batch (2021)
NUTRITIONAL & STEROID INDUCED HYPERGLYCEMIA
Nutritional Therapies: TPN

**BG goal 140-180 mg/dL (post-prandial state)**

**AVOID increasing Basal insulin to treat TPN related highs**

**Without Diabetes, high risk patient → correctional insulin q4-6 hrs**
- Total 24 hr correctional needs, if > 10 units add as IV Regular to TPN bag

**With diabetes, insulin sensitive**
- Continue basal insulin (~0.1 unit/kg if unknown)
- Continue normal correctional bolus insulin at q 4-6 hrs (1:50 mg/dL)
- Add IV Regular insulin to TPN bag, starting at 1 unit:15-20 gram carb (dextrose) ratio

**With diabetes, insulin resistant**
- Continue normal basal insulin (~0.2 units/kg if unknown)
- Continue normal correctional bolus insulin at q 4-6 hrs (2:50 mg/dL)
- Add IV regular insulin to TPN bag, starting at 1 unit :12-15 gram carb (dextrose) ratio
Nutritional Therapies: EN

- BG goal **140-180 mg/dL** (post prandial state)
- AVOID increasing basal insulin to treat
- Collaborate with RD
- Tend to see MUCH higher insulin needs

**Without Diabetes**, but high risk ➔ start correctional insulin q 4-6 hrs (2:50 mg/dL)

Draznin (2016) ; American Diabetes Association (2022)
Continuous EN: Underlying DM

**Basal + bolus:**

**Basal Insulin:**
- Use Baseline dosing, safe in NPO state
- IS: ~ 0.1 unit/kg
- IR: ~ 0.2 unit/kg

**Bolus Insulin (correctional + Nutritional):**
- Q 4h Correctional, treat > 150 or 200 mg/dL:
  - IS: 1:50 mg/dL
  - IR: 2:50 mg/dL
- Q 4h Nutritional:
  - IS: start 1u:15 grams
  - IR: start 1u:10-12 grams

**NPH (or mixed 70/30) + bolus:**
- NPH (or Mixed insulin 70/30) + Bolus insulin correction
  - **Up to TID** based on carb ratio
    - IS: start 1:15-20 grams
    - IR: start 1:10-12 grams
  - Q 4 hrs correctional, treat > 150-200 mg/dL:
    - IS: start 1:50 mg/dL
    - IR: start 2:50 mg/dL

Draznin (2016); American Diabetes Association (2020)
Example:

- IP: 50-y/o male (BMI 36), T2DM, **A1c 10%** on dual oral therapies (metformin + SU), intubated post MI, requiring Tube Feeds

- **Basal** → 0.2 -0.4 unit /kg

- **Bolus Plan** →
  1. Correctional lispro q 4, 2:50 mg/dl

- RD note: **Continuous TF, Peptamen Intense VHP**
  - Goal rate 80 mL/hr, start at 20 mL/hr, up by 20 mL q 8 hrs
  - Calculate total CHO delivered based on rate:
    - Goal rate → 80 mL/hr
      - 80 mL/hr x **22 hrs** = 1760 mL
      - 1760 mL x **0.076 grams/mL** = 134 grams
      - 134 grams / **24 hrs** = 5.58 grams / hr
        - 5.58 grm/hr x 4 hrs → 22 grams
        - 1 unit : 8 grams → 22 grm x 1 u /8 grm = 2.75 units → 3 units q 4 hrs
    - 60 mL/hr → 2 units q 4 hrs
    - 40 mL/hr → 1 units q 4 hrs
    - 20 mL/hr → 1 unit vs correction only?
Cyclic EN: Underlying DM

### Basal + Bolus:

**Basal Insulin:**
- Use Baseline dosing, safe in NPO state
- IS: ~ 0.1 unit/kg
- IR: ~ 0.2 unit/kg

**Bolus Insulin (correctional + Nutritional):**
- Q 4h correctional
  - IS: 1:50 mg/dL
  - IR: 2:50 mg/dL
- Q 4h nutritional, based on carb ratio:
  - IS: start 1u:15 gram
  - IR: start 1u:10-12 gram

### NPH (or mixed 70/30) + bolus:

- NPH (or mixed 70/30) + Bolus insulin correction
  - Up to BID based on carb ratio → give at START of EN and ½ way through if run > 10-12 hrs
    - IS: start 1:15-20 grams
    - IR: start 1:10-12 grams
  - Q 4 correctional DURING TF run, treat > 150-200 mg/dL:
    - IS: start 1:50 mg/dL
    - IR: start 2:50 mg/dL

Draznin (2016); American Diabetes Association (2020)
AB: 75-year-old female (BMI 18), hx of T1DM, A1c 7.5% on MDI of insulin at home, now requiring Tube feeds at home

RD note: **Nocturnal TF, Isosource 1.5**
- Rate 120 mL/hr, 12 hr run 8 P to 8 A

**Basal → Continue baseline dosing**

**Nutritional → Continue baseline dosing during DAY (1:50 mg/dL SF, 1:15 CR)**
- DURING TUBE FEED RUN:
  - Correction q 4 (if reasonable)?
  - Nocturnal Nutritional Coverage....

- Calculate total CHO delivered based on rate:
  - 120 mL/hr x 12 hrs = 1440 mL
  - 1440 mL x 0.156 grams/mL = 225 grams CHO
  - 225 grams x 1 unit/15 grm (home CR) = 15 units NPH given at START of tube Feeds

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**Example:**

<table>
<thead>
<tr>
<th>Tube Feeding Per 1000 mL</th>
<th>REPLETE®</th>
<th>ISOQUICK®</th>
<th>FIBERSOURCE®</th>
<th>ISOQUICK® 1.5 CAL</th>
<th>NUTRIN® 2.0</th>
<th>NOVASOURCE® RENAL</th>
<th>IMPACT® PEPTIDE 1.5</th>
<th>PEPTAMEN® A/F®</th>
<th>PEPTAMEN® INTENSE VHP</th>
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<tbody>
<tr>
<td><strong>Type of Diet</strong></td>
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<td>High Protein Tube Feeding</td>
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<td>Standard Tube Feeding</td>
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<td>Fiber-Containing Tube Feeding</td>
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<tr>
<td>Calorically Dense Fiber-Containing Tube Feeding</td>
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<td>Calorically Dense Tube Feeding</td>
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<tr>
<td>Acute or Chronic Kidney Disease Tube Feeding or Oral Supplement</td>
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<tr>
<td>Immunonutrition Peptide-Based Calorically Dense Tube Feeding</td>
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<tr>
<td>Peptide-Based Advanced Formula Critical Illness Tube Feeding</td>
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<tr>
<td>Peptide-Based Very High-Protein Tube Feeding</td>
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<td><strong>Prefilled System</strong></td>
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<td>1000 mL</td>
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<td>1000 mL</td>
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<tr>
<td>Calories per mL</td>
<td>1.0</td>
<td>1.2</td>
<td>1.2</td>
<td>1.5</td>
<td>2.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>64</td>
<td>54</td>
<td>54</td>
<td>88</td>
<td>84</td>
<td>90.7</td>
<td>94</td>
<td>76</td>
<td>92</td>
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<tr>
<td>Fat (g)</td>
<td>34</td>
<td>40</td>
<td>40</td>
<td>55.2</td>
<td>92</td>
<td>100</td>
<td>63.6</td>
<td>54</td>
<td>38</td>
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<tr>
<td>Carbohydrate (g)</td>
<td>112</td>
<td>156</td>
<td>164</td>
<td>176</td>
<td>216</td>
<td>163</td>
<td>140</td>
<td>112</td>
<td>76</td>
</tr>
<tr>
<td>Osmolality (mOsM/kg)</td>
<td>300</td>
<td>510</td>
<td>480</td>
<td>650</td>
<td>780</td>
<td>800</td>
<td>510</td>
<td>390</td>
<td>345</td>
</tr>
<tr>
<td>Water (%)</td>
<td>84%</td>
<td>81%</td>
<td>81%</td>
<td>76%</td>
<td>69%</td>
<td>72%</td>
<td>77%</td>
<td>81%</td>
<td>84%</td>
</tr>
</tbody>
</table>
## Nutritional Therapies: Bolus EN

### Basal Insulin:
- Use Baseline dosing, safe in NPO state
- **IS:** ~ 0.1 unit/kg
- **IR:** ~ 0.2 unit/kg

### Bolus Insulin (correctional + Nutritional):
- Correctional dosing at same frequency as EN bolus
  - **IS:** 1:50 mg/dL
  - **IR:** 2:50 mg/dL
- Nutritional, at time of bolus:
  - **IS:** start 1:15 grams
  - **IR:** start 1:10-12 grams

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Draznin (2016); American Diabetes Association (2020)
Corticosteroids

- Patients receiving steroids developed hyperglycemia (~20%), and DM (~30%) (ambulatory)

- Treatment with high dose steroids (>40 mg/day prednisone equivalent) for at least 2 days resulted in 64% developing steroid induced hyperglycemia (IP)
  - Usually see BG > 180 mg/dL within first 48 hrs of treatment

- Steroids increase glycemic response to CHO’s more than underlying (basal) insulin needs

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Equivalent dose (mg)</th>
<th>Estimated duration of biological action (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>12-16</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>12-16</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>12-16</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-36</td>
</tr>
</tbody>
</table>
Steroids: No Known Diabetes

- Watch /wait 48hrs
  - > 140 mg/dL, start correction

- >20 units/day or BG >180 mg/dL:
  - **NPH:**
    - Give AT THE SAME TIME as prednisone
    - Suspect DM: NPH: Pred, 1:1 first 20 mg, 1:2 next 20 mg, 1:4 next 20 mg
  - **Basal-Bolus:**
    - TDD = 0.4 units/kg/day
    - 70% bolus + 30% basal

<table>
<thead>
<tr>
<th>Prednisone Equivalent (mg/day)</th>
<th>NPH dose (units/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40</td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>0.3</td>
</tr>
<tr>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Draznin (2016); M. McDermott, personal communication, 2017
Steroids: Pre-Existing Diabetes

- **T1DM:**
  - Keep basal at baseline
  - (1) Increase Bolus (nutritional) by 10-20% \( \text{up to 50%} \)
  - (2) NPH \( \rightarrow \) Consider in higher steroids / obesity
  - NPH: Pred, 1:2 first 20 mg, 1:4 next 20 mg, 1:8 next 20 mg

- **T2DM:**
  - Well controlled (orals):
    - (1) Add Bolus (correction + CHO)
    - (2) Add NPH if > 20 units/day or bgs > 180 mg/dL
  - Uncontrolled (or insulin at baseline):
    - (1) + NPH w/ steroid
    - NPH: Pred, 1:1 first 20 mg, 1:2 next 20 mg, 1:4 next 20 mg
    - Start / Adjust current Basal - Bolus regimen
      - (2) + bolus \( \sim 20\% \) \( \text{up to 50\%} \)
      - (3) Modified home dosing, TDD: 30% basal, 70% bolus

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<tr>
<td>10</td>
<td>0.1</td>
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<table>
<thead>
<tr>
<th>Weight</th>
<th>TDD of insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean, Type 1 DM</td>
<td>0.4 units/kg/day</td>
</tr>
<tr>
<td>Overweight, (BMI 25-30) Type 1 or Type 2</td>
<td>0.5 units/kg/day</td>
</tr>
<tr>
<td>Obese, (BMI &gt;30), Type 2</td>
<td>0.6 units/kg/day, or &gt;</td>
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</tbody>
</table>

Draznin (2016), M. McDermott, personal communication, 2017
Compare?

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<tr>
<td>10</td>
<td>0.1</td>
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</table>

<table>
<thead>
<tr>
<th>Prednisone (mg)</th>
<th>T1 DM (IS) - Insulin (units)</th>
<th>T2 DM (IR) - Insulin (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>5 units</td>
<td>10 units</td>
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<tr>
<td>15 mg</td>
<td>7 units</td>
<td>15 units</td>
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<td>20 mg</td>
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<td>20 units</td>
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<td>30 mg</td>
<td>12 units</td>
<td>25 units</td>
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<td>40 mg</td>
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<td>50 mg</td>
<td>16 units</td>
<td>32 units</td>
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<tr>
<td>60 mg</td>
<td>17 units</td>
<td>35 units</td>
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</table>

Draznin (2016); M. McDermott, personal communication (2017)
Example:

60-year-old male, obese (102 kg) T2DM, A1c = 9% on metformin + Jardiance, COPD starting prednisone 40 mg daily

**Hospital:**
- Stop orals
- Start basal at 0.2 unit/kg = 20 q HS
- Start bolus at 2:50 mg/dL correction, 1:8 gram CHO
- NPH dosing:
  - 0.4 unit/kg x 102 kg = 40.8 units
  - NPH: Pred, 1:1 first 20 mg, 1:2 next 20 mg, 1:4 next 20 mg
    - 20 units (20 mg) + 10 (20 mg) = 30 units
- Alternative:
  - Keep basal at 0.2 unit / kg
  - Increase Bolus → 1:15-20 CF mg/dL , 1: 5-6 gram CR

**Discharge:**
- Continue home meds
  - Tolerating higher metformin?
  - Jardiance at 25 mg ?
- Insulin an option?
  - NPH (low cost, once daily)
  - Lispro correction 3:50 mg/dL (higher cost / burden)
- Insulin NOT realistic?
  - SU through steroid course
  - Glipizide qAM (low cost, effective)
  - Glimepiride q AM (longer lasting)

**FOLLOW UP ! ! ! ! !**
Transition off Insulin drip to SC

- **USE BASAL INSULIN**
  - Average insulin drip rate for ~ 4-6 hrs during NPO state (nocturnal)
    - Drip rate (units/hr) x 20 hrs (20% dose reduction)
      - Ex. Avg rate ~ 2 units/hr in NPO state, 2 x 20 = 40 unit basal
      - Ex. Avg rate ~ 2 units/hr WHILE eating (w/o coverage), 2 x 20 = 40 unit TDD, 20 unit basal + 2:50 SF, 1:8 CR
  - DKA/ HHS:
    - Higher insulin requirements (glucose toxic)
    - High rate of Dextrose IVF
    - Triggering Event (MI, infection, etc.)
  - Acute Hyperglycemia:
    - Consider transition when rate drops < 2 units/ hr

Draznin (2016); American Diabetes Association (2020); CMS (2022)
AMBULATORY TREATMENT STRATEGIES
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.

ASCVD/INDICATORS OF HIGH RISK, HF, CKD†

RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡

IF A1C ABOVE TARGET

+ASCVD/INDICATORS OF HIGH RISK* OR +HF*

GLP-1 RA with proven CVD benefit†

SGTL2i with proven benefit in this population†

PREFERABLY

SGTL2i with primary evidence of reducing CKD progression

OR

SGTL2i with evidence of reducing CKD progression in CVOTs

OR

GLP-1 RA with proven CVD benefit† if SGTL2i 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†

SGTL2i with proven CVD benefit†

If A1C above target, for patients on SGTL2i, consider incorporating a GLP-1 RA and vice versa

IF A1C ABOVE TARGET

MINIMIZE HYPOGLYCEMIA

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:

For patients on GLP-1 RA, consider incorporating SGTL2i and vice versa

MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS

IF A1C ABOVE TARGET

CONSIDER COST AND ACCESS

Available in generic form at lower cost:

- Certain insulins: consider insulin available at the lowest acquisition cost

- SU

- TZD

For patients on a GLP-1 RA, consider incorporating SGTL2i and vice versa

IF A1C ABOVE TARGET

Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs

If A1C remains above target, consider treatment intensification 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 ≥7% weight loss and a ≥10 min/wk of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well being to Improve Health Outcomes).
†Adopted whenever these became 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.
**Recommend Independently of Baseline A1C, Individualized A1C Target, or Metformin Use**

**ASCVD/INDICATORS OF HIGH RISK, HF, CKD†**

- For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa
- TZD²

**IF A1C ABOVE TARGET**

- If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs

**Metformin:**
- ASCVD: Potential benefits
- HF: Neutral
- DKD: Neutral, dose adjustments

**SGLT2i:**
- ASCVD: Jardiance, Invokana, (Farxiga)
- HF: Jardiance, Farxiga, Invokana, Steglatro
- DKD: Invokana, Farxiga, (Jardiance)

**GLP1 RA:**
- ASCVD: Ozempic, Victoza, Trulicity, Tanzeum
- HF: neutral ? hospitalization ?
- DKD: Ozempic, Victoza, Trulicity

**Actos:**
- ASCVD: Potential benefit ?
- HF: High risk
- DKD: Neutral

**DPP4i:**
- ASCVD: neutral
- HF: hospitalization saxagliptin & alogliptin
- DKD: Neutral

**Basal Insulin:**
- ASCVD/ HF/ DKD: neutral ? HF risk?

**SU:**
- ASCVD: controversial, Glimepiride
- HF: Neutral ?
- DKD: Glipizide, low dose Glimepiride
SGLT2i

- **Contraindications:** Euglycemic DKA
  - Acute care?
    - Jardiance for acute HF
      - EMPULSE trial
  - Planned surgery (2-3 days prior)
  - **Risk of amputation (Invokana)**
    - Fournier’s gangrene risk
    - Pregnancy & breast feeding
- **Caution:**
  - DKA hx (T1D / pancreatogenic/ LADA)
    - Europe: Farxiga / Invokana in obese
  - Complicated / frequent UTI -risk is 10%
  - Severe PAD
  - High Fracture risk (Invokana)
  - ETOH abuse / malnourished / disordered eating
  - Elderly / thin
  - Volume Depletion / Hypotension
  - High A1c at initiation

GLP1-RA

- **Contraindications:**
  - MEN2
  - Medullary Thyroid Cancer (rodent study)
  - Pregnancy & breast feeding
- **Caution:**
  - Gallbladder disease
  - Pancreatitis Hx
  - Proliferative retinopathy, SUSTAIN 6, PIONEER 6
    - FOCUS trial to evaluate
  - Gastroparesis / Chronic GI upset
  - Underweight
  - ETOH abuse?
<table>
<thead>
<tr>
<th>Primary Goal</th>
<th>Consider SGLT2i First</th>
<th>Consider GLP1 RA first</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE reduction</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HF outcomes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Kidney disease</td>
<td>X (“harder” outcomes, reduction in creatinine, renal replacement therapy, etc.)</td>
<td>x (“softer” outcomes, reduction in albuminuria)</td>
</tr>
<tr>
<td>Reduce A1c</td>
<td>x</td>
<td>X</td>
</tr>
<tr>
<td>Obesity</td>
<td>x</td>
<td>X</td>
</tr>
</tbody>
</table>

Adapted from Chang, L. (2022, May 2). Choosing SGLT2 Inhibitors vs GLP-1 Receptor Agonist, and Das SR (2020) Expert Consensus Decision Pathway on Novel Therapies for CV risk reduction in patients with T2D.
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 hypoglycemia1-4

**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)

**IF A1C ABOVE TARGET**

- 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

**Metformin**
- **Weight**: Modest, to neutral
- **Hypo**: Low risk

**SGLT2i**
- **Weight**: Loss (all)
- **Hypo**: Low risk (all)

**GLP1 RA**
- **Weight**: Significant loss (Ozempic > Victoza > Trulicity > Bydureon > Adlyxin)
- **Hypo**: Low risk (all)

**DPP4i**
- **Weight**: Neutral (all)
- **Hypo**: Low risk (all)

**TZD**
- **Weight**: Gain (all)
- **Hypo**: Low (all)

**SU**
- **Weight**: Gain (all)
- **Hypo**: High risk (all)

**Basal Insulin**
- **Weight**: Gain
- **Hypo**: High risk (Degludec & Toujeo preferred)
INSULIN ...

When you must go there 😊
Highlights...

- **Consider GLP1RA therapy prior to insulin**
- **Start Basal 10 units OR weight based (0.1-0.2 units/kg)**
- **Titration Algorithm**
  - Increase by 2 units q 3 days to get FPG to goal
  - Lower by 10-20% for hypo
  - “Do not exceed” dose
- **Consider adding Prandial once basal > 0.5 units/kg**
  - Or BID NPH
- **Stepwise addition of Prandial (biggest meal, 2 meals, etc.)**

---

**Consider GLP1 RA**

If not already in regimen

- For addition of GLP1 RA, consider lowering insulin dose dependent on current glycemic assessment and patient factors

**Add basal insulin**

Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.4 for insulin cost information.

**Add prandial insulin**

Usually one dose with the largest meal or meal with greatest FPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

**Consider self-mixed/split insulin regimen**

Can adjust NPH and short/rapid-acting insulin separately

**Consider twice daily premixed insulin regimen**

Usually unit per unit at the same total insulin dose, but may require adjustment to individual needs

---

**Titration Algorithm**

- Increase by 2 units q 3 days to get FPG to goal
- Lower by 10-20% for hypo
- “Do not exceed” dose

**Consider adding Prandial once basal > 0.5 units/kg**

- Or BID NPH

---

**If already on GLP1 RA or if GLP1 RA not appropriate OR insulin preferred**

- **If injectable therapy is needed to reduce A1C**
  - **INITIATION**: Initiate appropriate starting dose for agent selected (varies within class)
  - **TITRATION**: Titrate to maintenance dose (varies within class)

**If above A1C target**

- **Add basal insulin**
  - **INITIATION**: Start 10 units per day OR 0.1-0.2 units/kg per day
  - **TITRATION**: Set FPG target (see Section 6: Glycemic Targets)
  - Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
  - For hypoglycemia determine cause, if no clear reason lower dose by 10-20%

**Assess adequacy of basal insulin dose**

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose more than ~0.5 units/kg/day, elevated bedtime morning and/or post-prandial differential, hypoglycemia (aware or unaware), high variability)

**If on bedtime NPH, consider converting to twice-daily NPH regimen**

Conversion based on individual needs and current glycemic control. The following is one possible approach

- **INITIATION**: Total dose = 80% of current bedtime NPH dose
  - 2/3 given in the morning
  - 1/3 given at bedtime
  - **TITRATION**: Titrate based on individualized needs

---

**Stepwise addition of prandial insulin**

(i.e., basal insulin and prandial insulin with each meal)

Proceed to full basal-bolus regimen (i.e., basal insulin and prandial insulin with each meal)
Basal insulin Choices

**High dosing?**
- Toujeo (Glargine U 300), Solostar MAX = 160 units/injection
- Tresiba (Degludec U 200) = 160 units/injection

**Hypoglycemia risk (renal disease, nocturnal lows, etc.)?**
- Toujeo (Glargine U300)
- Tresiba (Degludec)

**Compliance**
- Toujeo (Glargine U300)
- Tresiba (Degludec)

**Peak?**
- Levemir (Detemir)
- NPH (Humulin N, Novolin N, Relion N)

**Cost?**
- ReliOn NPH

Toujeo vs Lantus (n.d.); Billingsley, A. (2022); Injectable Insulin medications (2018).
# Bolus Insulin Choices

<table>
<thead>
<tr>
<th>Quicker onset?</th>
<th>Cost?</th>
<th>Strength</th>
<th>Pump</th>
</tr>
</thead>
</table>
| • Lyumjev (Lispro-aabc)  
• Fiasp (Aspart)  
• Apidra (Glulisine) | • ReliOn R | • Humalog (Lispro) U 200  
• Lyumjev (Lispro-aabc) U 200 | • Humalog (Lispro)  
• Novolog (Aspart)  
• Apidra (Glulisine)  
• Fiasp (Aspart) |
U500 Regular Insulin

- Onset: < 15 mins
- Peak: 4-8 hrs
- DOA: 13-24 hrs

- Consider in patients requiring > 200 units of insulin per day
  - Discontinue all other insulins
  - Dose at 80% of TDD of previous regimen (unless very poorly controlled → 100%)
- If BID → 60% with AM meal, 40% with PM meal
- If TID → 40% with AM meal, 30% with Lunch & 30% with Dinner
- 5-unit Increments

- PEN or Vial (Requires special syringe)
- Can be used in Insulin pump (off label)
Pre-Mixed Insulins (T2DM)

**NPH + Regular**

- 70/30 = 70% NPH + 30% R
- 50/50 = 50% NPH + 50% R
  - Onset = 0.5-1 hr
  - Peak = 2-12 hrs
  - DOA = 10-16 hrs
- 70/30 = Low Cost / OTC ReliOn

**NPL/Protamine + bolus analog**

- Humalog 75/25 = 75% NPL + 25% lispro
- Humalog 50/50 = 50% protamine + 50% Lispro
- Novolog 70/30 = 70% protamine + 30% Aspart
  - Onset = 5-20 m
  - Peak = 1-2 hr
  - DOA = 10-16 hrs
- Higher cost

Dose:

- 50% in AM + 50% in PM
- OR
- 2/3 in AM + 1/3 in PM

Draznin (2016); Injectable Insulin medications (2018)
<table>
<thead>
<tr>
<th>Class</th>
<th>Compound(s)</th>
<th>Dosage strength (if applicable)</th>
<th>Median AWP (min, max)</th>
<th>Median NADAC (min, max)</th>
<th>Maximum approved daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>500 mg (IR)</td>
<td>$84 ($4, $185)</td>
<td>$2</td>
<td>2000 mg</td>
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<tr>
<td></td>
<td></td>
<td>850 mg (IR)</td>
<td>$108 ($6, $309)</td>
<td>$3</td>
<td>2,550 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,000 mg (IR)</td>
<td>$87 ($4, $88)</td>
<td>$2</td>
<td>2,000 mg</td>
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<tr>
<td></td>
<td></td>
<td>500 mg (ER)</td>
<td>$89 ($67, $7412)</td>
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<td>5,000 mg</td>
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<tr>
<td></td>
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<td>750 mg (ER)</td>
<td>$74 ($60, $74)</td>
<td>$4</td>
<td>2,000 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,000 mg (IR)</td>
<td>$242 ($242, $7,214)</td>
<td>$224 ($224, $910)</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride</td>
<td>4 mg</td>
<td>$74 ($71, $138)</td>
<td>$4</td>
<td>8 mg</td>
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<tr>
<td></td>
<td>Glipizide</td>
<td>10 mg (IR)</td>
<td>$75 ($67, $97)</td>
<td>$5</td>
<td>40 mg (IR)</td>
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<tr>
<td></td>
<td></td>
<td>10 mg (XL)</td>
<td>$48</td>
<td>$5</td>
<td>20 mg (XL)</td>
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<tr>
<td></td>
<td>Glyburide</td>
<td>6 mg (micronized)</td>
<td>$50 ($48, $71)</td>
<td>$4</td>
<td>42 mg (micronized)</td>
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<tr>
<td></td>
<td></td>
<td>5 mg</td>
<td>$93 ($63, $103)</td>
<td>$11</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>45 mg</td>
<td>$948 ($283, $349)</td>
<td>$4</td>
<td>45 mg</td>
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<tr>
<td></td>
<td></td>
<td>4 mg</td>
<td>$407</td>
<td>$3</td>
<td>8 mg</td>
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<tr>
<td>α-Glucosidase</td>
<td>Acarbose</td>
<td>100 mg</td>
<td>$106 ($104, $116)</td>
<td>$23</td>
<td>100 mg</td>
</tr>
<tr>
<td>inhibitors</td>
<td>Miglitol</td>
<td>100 mg</td>
<td>$241</td>
<td>$311</td>
<td>100 mg</td>
</tr>
<tr>
<td>Meglitinides (glinides)</td>
<td>Nateglinide</td>
<td>120 mg</td>
<td>$155</td>
<td>$291</td>
<td>120 mg</td>
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<tr>
<td></td>
<td></td>
<td>2 mg</td>
<td>$878 ($162, $857)</td>
<td>$39</td>
<td>16 mg</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Alogliptin</td>
<td>25 mg</td>
<td>$284</td>
<td>$168</td>
<td>25 mg</td>
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<tr>
<td></td>
<td>Saxagliptin</td>
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<td>$505</td>
<td>$393</td>
<td>5 mg</td>
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<tr>
<td></td>
<td>Linagliptin</td>
<td>5 mg</td>
<td>$523</td>
<td>$419</td>
<td>5 mg</td>
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<tr>
<td></td>
<td>Sitagliptin</td>
<td>250 mg</td>
<td>$541</td>
<td>$700 mg</td>
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<tr>
<td>SGLT2 inhibitors</td>
<td>Empagliflozin</td>
<td>15 mg</td>
<td>$338</td>
<td>$271</td>
<td>15 mg</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>10 mg</td>
<td>$591</td>
<td>$473</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>25 mg</td>
<td>$591</td>
<td>$473</td>
<td>25 mg</td>
</tr>
<tr>
<td></td>
<td>Empagliflozin</td>
<td>25 mg</td>
<td>$591</td>
<td>$473</td>
<td>25 mg</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>Exenatide (extended release)</td>
<td>2 mg powder for suspension or pen</td>
<td>$640</td>
<td>$57/2</td>
<td>2 mg**</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>10 μg pen</td>
<td>$876</td>
<td>$730</td>
<td>20 μg</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>1.5/0.5 mL pen</td>
<td>$911</td>
<td>$730</td>
<td>1.5 mg**</td>
</tr>
<tr>
<td></td>
<td>Semaglutide</td>
<td>1 mg pen</td>
<td>$927</td>
<td>$745</td>
<td>1 mg**</td>
</tr>
<tr>
<td></td>
<td>Erasemglutide</td>
<td>18 mg (tablet)</td>
<td>$927</td>
<td>$868</td>
<td>18 mg</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>18 mg/3 mL pen</td>
<td>$1,106</td>
<td>$868</td>
<td>18 mg</td>
</tr>
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<td>Lixisenatide</td>
<td>300 μg/3 mL pen</td>
<td>$744</td>
<td>N/A</td>
<td>20 μg</td>
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<tr>
<td>bile acid sequestrant</td>
<td>Colesevelam</td>
<td>625 mg tabs</td>
<td>$712 ($674, $712)</td>
<td>$177</td>
<td>7.5 g</td>
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<tr>
<td></td>
<td></td>
<td>5.75 g suspension</td>
<td>$675</td>
<td>$415</td>
<td>7.5 g</td>
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<tr>
<td></td>
<td></td>
<td>$739</td>
<td></td>
<td></td>
<td>8.8 mg</td>
</tr>
<tr>
<td>Amylin mimetic</td>
<td>Exenatide</td>
<td>120 μg pen</td>
<td>$2,623</td>
<td>$2,097</td>
<td>220 μg/injection??</td>
</tr>
</tbody>
</table>

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium-glucose cotransporter 2. *Calculated for 30 days supply (AWP [54] or NADAC [55] unit price × number of doses required to provide maximum approved daily dose × 30 days); median AWP or NADAC listed alone when only one product and/or price.* Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ***AWP and NADAC calculated based on 120 μg three times daily.
References

References

- Eckel (April 2022). ACC 2022: An overview of SGLT2i and GLP1 RA use in Cardiovascular disease. As retrieved from: ACC 2022: An Overview of SGLT2i and GLP1 RA Use in Cardiovascular Disease | VuMedi
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◦ M. McDermott, personal communication (2017). University of Colorado Hospital, Training seminar for Glucose Management Team.


