NMQF

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ACE/AACE Treatment Algorithm
Jaime Davidson, MD
Disclosure Information

- Consultant, and/or an Advisory or Speaker’s Board member: AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Bayer Pharmaceuticals, Eli Lilly & Co., Janssen, Roche Diagnostic, Johnson & Johnson, Merck-Sharp and Dome, Novo Nordisk and Sanofi.

- Dr. Davidson intends to reference unlabeled/unapproved uses of SGLT2 inhibitors in his presentation.
Relationship between Glycemia and Complications

DCCT and UKPDS

43% reduction in risk for every 10% decrease in HbA1c

37% reduction in risk for every 1% decrease in HbA1c
Why Does Diabetes Cost Us So Much?

1. Complications due to poor control
2. Litigious societies adding unnecessary cost to doctors visits, hospitals, pharmacies, medications, etc.
3. Access to care
4. Health education
5. Chronic and complex condition
Diabetes: worst treated US illness

Percentage NOT receiving recommended care¹

Patients NOT receiving recommended care

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage NOT receiving recommended care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>55%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>46%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>36%</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>35%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>32%</td>
</tr>
</tbody>
</table>

A1c ≤ 6.5%
For healthy patients without concurrent illness and at low hypoglycemic risk

A1c > 6.5%
Individualize goals for patients with concurrent illness and at risk for hypoglycemia
Pathogenesis of Type 2 Diabetes
An Evolving Concept

- Increased Lipolysis
- Increased Glucagon Secretion
- Impaired Insulin Secretion
- Increased Glucose Uptake
- Decreased Glucagon Secretion
- Increased HGP
- Decreased Incretin Effect
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
Considerations for Therapy Selection

- Baseline HbA1c
- Efficacy profile
- Risk for hypoglycemia
- Risk for fractures
- Weight effects
- Adverse event profile
  - Edema
  - GI side effects (nausea, vomiting, diarrhea)
- Comorbidities
  - Cardiovascular disease
  - Renal impairment
- Costs and formulary availability
Properties of the Ideal Drug

- Robust ↓ HbA1c
- No hypoglycemia
- No weight gain
- Complimentary actions
- Durability
- Well tolerated
- Long-term safety
- Simple administration
- Added value
  - e.g., ↓BP, lipids, β cell function, CVD protection, etc.
Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

GLP-1 RA
DPP4-i
TZD
SGLT-2
Basal insulin
Colesevelam
Bromocriptine QR
AG-i
SU/GLN

* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data

If not at goal in 3 months proceed to triple therapy

LEGEND

= Few adverse events or possible benefits
= Use with caution
Glycemic Control Algorithm

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DUAL THERAPY*

- GLP-1 RA
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- Basal insulin
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MET or other first-line agent

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

- GLP-1 RA
- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

MET or other first-line agent

If not at goal in 3 months proceed to or intensify insulin therapy

* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data

LEGEND

☑ = Few adverse events or possible benefits
⚠ = Use with caution
AACE / ACE Diabetes Algorithm: Principles

- Prioritize medication choices according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence and cost of medications.
- Stratify treatment choices based on A1C level.
- Recommend only combinations of medications approved by the FDA that provide complementary mechanisms of action.
AACE / ACE Diabetes Algorithm: Principles

- Monitor therapy with A1C and SMBG.
- Adjust or advance therapy frequently (every 2 to 3 months) if appropriate goal has not been achieved.
- Provide a flowchart and table summarizing major considerations.
Approach to management of hyperglycemia:

<table>
<thead>
<tr>
<th>Patient attitude and expected treatment efforts</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, non-adherent, poor self-care capacities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risks potentially associated with hypoglycemia, other adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Newly diagnosed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease duration</th>
</tr>
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<tbody>
<tr>
<td>Long</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Established vascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resources, support system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readily available</td>
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</tbody>
</table>
Minimize risk of hypoglycemia and weight gain

When other agents fail to achieve goal, advance to insulin therapy ± oral agents. Starting insulin with an A1c in the 7% range, AM prandial insulin may be best choice
Individualize therapy for each patient

Major cost of diabetes is due to complications, including hypoglycemia.

Minimize total cost of care, not cost of medications per se
Association of severe hypoglycaemia and risk of mortality in ACCORD

HR 1.41

HR 2.30

UK Study Group: Proportion experiencing at least 1 episode of severe hypoglycaemia over 9–12 months

UK Hypoglycaemia Study Group. Diabetologia 2007
Lifestyle modification, diabetes education, and dietary consultation are essential, have major benefits, and should be initiated with medical therapy.

Delay of pharmacotherapy is inappropriate because lifestyle interventions are usually not sufficient.
An A1C of 6.5% is recommended as the primary goal. This level must be customized for each patient considering: co-morbidities, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, life expectancy and other medications.
Rapid-acting insulin analogues are superior to “regular human insulin” and provide a better, safer alternative.

- yield better reproducibility and consistency between patients and within patients
- reduce risk of hypoglycemia

Insulin regimens such as basal, basal-bolus, prandial, pre-mixed and CSII can be combined with a variety of oral agents.

Basal analogues preferred
Rapid Acting Analogues vs Regular Human Insulin

Woodworth, et al. Diabetes. 1993;42(suppl 1):54A.
Rapid Analogues vs Regular Human Insulin

<table>
<thead>
<tr>
<th></th>
<th>Analogues</th>
<th>Regular human</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (hours)*</td>
<td>1.0</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* 0.2 U/kg SC.

Basal Insulin Variability
Same Patient

Major Advantages of the AACE Algorithm

1. Includes all major classes of medications
2. Does not relegate important agents to a “second tier”
3. Incretin analogs and DPP-4 inhibitors are not relegated to a category of “too new”. SGLT-2 inhibitors are also included
4. Suggested agents based on A1C level and targeted agent activity
5. Attempts to reduce total costs of care including costs related to hypoglycemia and complications
6. Simple graphical layout with emphasis on early intervention and A1c at presentation
7. Simplified table of Benefits and Risks of each medication
Early vs Late Intervention in Type 2 Diabetes

Early diagnosis and intensive glucose control therapy from the start are the key to long-term risk reduction in diabetes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Goal: FPG &lt;108 mg/dL</th>
<th>Intervention endpoint: 7.0%</th>
<th>Follow-up: 7.0%</th>
<th>Macrovascular Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 80</td>
<td>N=4209</td>
<td>17 yr</td>
<td>Newly diagnosed with T2DM</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Elevated Mealtime Glucose is a Concern at All Levels of HbA$_{1c}$

<table>
<thead>
<tr>
<th>HbA$_{1c}$</th>
<th>Mean FPG</th>
<th>% Patients With FPG &gt;140 mg/dL</th>
<th>Mean 2-h Glucose</th>
<th>% Patients With 2-h Glucose &gt;200 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>116</td>
<td>7</td>
<td>208</td>
<td>67</td>
</tr>
<tr>
<td>6-6.9</td>
<td>132</td>
<td>28</td>
<td>233</td>
<td>77</td>
</tr>
<tr>
<td>7-7.9</td>
<td>172</td>
<td>83</td>
<td>315</td>
<td>94</td>
</tr>
<tr>
<td>8-8.9</td>
<td>205</td>
<td>94</td>
<td>371</td>
<td>100</td>
</tr>
<tr>
<td>&gt;9</td>
<td>278</td>
<td>100</td>
<td>432</td>
<td>100</td>
</tr>
</tbody>
</table>

Clinical Inertia: Standard Therapeutic Approaches Lead to Prolonged Hyperglycemia

At insulin initiation, the average patient had:
- 5 years with HbA$_1c$ >8%
- 10 years with HbA$_1c$ >7%

Glucose control:

4 years of data in managed care (N 9376)

First Step- Metformin + Lifestyle

- Recognizes failure of life-style alone
- Inhibits hepatic glucose output- predominantly lowers fasting glycemia
- Lowers HbA1c by ~1.5%
- No hypoglycemia
- Effective in obese and non-obese patients and in preventing diabetes in pre-diabetics (DPP)
- “Glucophage” off-patent, very inexpensive
Daily glycemic variation (mmol/L) by A1c levels in type 2 diabetes

Initial Treatment: Insulin plus Metformin in Type 2 Diabetes


HbA1c Results

Baseline 3-month HbA1c (%)

10.8
5.9

Phase 2b/3 Pooled Population
Time to Onset of First Primary MACE

Patients at Risk | Control | All SAXA
---|---|---
BL | 1251 | 3356
24 Weeks | 935 | 2615
37 Weeks | 860 | 2419
50 Weeks | 774 | 2209
63 Weeks | 545 | 1638
76 Weeks | 288 | 994
89 Weeks | 144 | 498
102 Weeks | 123 | 436
115 Weeks | 102 | 373
128 Weeks | 57 | 197

HR 0.45 (95%CI 0.24-0.83)
Control n=1251
All SAXA (n=3356)

### Hypoglycemic Events & Change in Weight from Baseline

<table>
<thead>
<tr>
<th></th>
<th><strong>SAXA + MET</strong> (N=428)</th>
<th><strong>GLIP + MET</strong> (N=430)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (%) of subjects with a hypoglycemic event</strong></td>
<td>13 (3.0%)</td>
<td>156 (36.3%)</td>
</tr>
<tr>
<td><strong>Difference in proportions vs. glipizide + metformin [95%CI]</strong></td>
<td>-33.2% [-38.1%, -28.5%]</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Adjusted change in weight from baseline, mean (%)</strong></td>
<td>-1.1 kg (0.17%)</td>
<td>+1.1 kg (0.17%)</td>
</tr>
<tr>
<td><strong>Mean difference vs. glipizide + metformin [95%CI]</strong></td>
<td>-2.2 kg [-2.7, -1.7]</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Between group comparison significant after controlling overall alpha of the study

Liraglutide resulted in weight loss – SU resulted in weight gain
Japanese study

Analysis population: all subjects with baseline and week 24 measurements (LOCF)
Statistical analysis: ANOVA model with treatment group and pre-trial treatment as fixed effects and baseline value as a covariate
Trial ID: NN2211-1700
## GLP and DPP4 Inhibitors

<table>
<thead>
<tr>
<th>GLP and its Analogues</th>
<th>DPP 4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stimulate insulin secretion</td>
<td>1. Inhibit breakdown of endogenous GLP, raising levels by ~2-fold</td>
</tr>
<tr>
<td>2. Suppress glucagon</td>
<td>2. Decrease A1c by ~0.6%</td>
</tr>
<tr>
<td>4. Lower A1c by ~1.0%/1.5%</td>
<td>4. No weight loss</td>
</tr>
<tr>
<td>5. 1-2 injections per day or once weekly</td>
<td>5. No GI side-effects</td>
</tr>
<tr>
<td>6. Weight loss of ~ 5 lb</td>
<td>6. Expensive</td>
</tr>
<tr>
<td>7. Associated with nausea, vomiting, diarrhea in ~40%</td>
<td></td>
</tr>
<tr>
<td>8. Expensive</td>
<td></td>
</tr>
</tbody>
</table>
Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes are likely to respond

SGLT2 = sodium-glucose cotransporter 2.
Glomerulus

Proximal Convoluted Tubule

Early

Distal

Glucose reabsorption into systemic circulation

Glucose

SGLT1

SGLT2

Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose co-transporter.
Type 2 diabetes + SGLT-2 Inhibitor (70-90 mg/dL)

Non-diabetic (180 mg/dL)

Type 2 diabetes (240 mg/dL)

Adapted with permission from Abdul-Ghani MA, DeFronzo RA.

$RT_G$ = renal threshold for glucose excretion.

Treatment with SGLT-2 Inhibitor

Glomerulus

Proximal Convoluted Tubule

Early

Distal

Decreased glucose reabsorption into systemic circulation

Glucose in urine

Glucose SGLT2 SGLT2 inhibitor SGLT1

Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose co-transporter.
Change in HbA1c in 12-Week Add-on to Metformin Studies of SGLT2 Inhibitors


Canagliflozin & Empagliflozin not FDA approved
Caveats

• Although the algorithm should apply to most people with type 2 diabetes, it does not apply to all
• Individualize therapy is a must
• May select different glycemic goals
  - Elderly
  - Persons with projected life span too short to benefit
  - Persons in whom side-effects outweigh benefits
• May select different medications based on
  - Patient acceptance, tolerance
  - Specific risk factors
• Don’t forget other interventions - lipids, blood pressure, CVD prevention