Glycemic Management of Type 2 Diabetes

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Disclosures

• None
Learning Objectives

• Understand the importance of lifestyle therapy in diabetes management

• Know the classes of antihyperglycemic agents, mechanism of action, benefits and side effects of these agents

• Recognize the importance of individualized treatment goals for diabetic patients
AACE Comprehensive Care Plan

- Disease management from a multidisciplinary team
- Antihyperglycemic pharmacotherapy
- Comprehensive diabetes self-education for the patient
- Therapeutic lifestyle change

Glycemic Management of Type 2 Diabetes
Components of Therapeutic Lifestyle Change

- Healthful eating
- Sufficient physical activity
- Sufficient sleep
- Avoidance of tobacco products
- Limited alcohol consumption
- Stress reduction

Glycemic Management of Type 2 Diabetes

ANTIHYPERGLYCEMIC THERAPY
Cardiovascular Outcomes Trials: A Brief History

• 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  – Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    • Some study designs tested for superiority if noninferiority criteria were met
  – Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    • Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

## Noninsulin Agents Available for T2D

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary Mechanism of Action</th>
<th>Agent(s)</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>• Delay carbohydrate absorption from intestine</td>
<td>Acarbose</td>
<td>Precose or generic Glyset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miglitol</td>
<td></td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>• Decrease glucagon secretion</td>
<td>Pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td></td>
<td>• Slow gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase satiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td>• Decrease HGP</td>
<td>Metformin</td>
<td>Glucophage or generic</td>
</tr>
<tr>
<td></td>
<td>• Increase glucose uptake in muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>• Decrease HGP?</td>
<td>Colesevelam</td>
<td>WelChol</td>
</tr>
<tr>
<td></td>
<td>• Increase incretin levels?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>• Increase glucose-dependent insulin secretion</td>
<td>Alogliptin</td>
<td>Nesina</td>
</tr>
<tr>
<td></td>
<td>• Decrease glucagon secretion</td>
<td>Linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>Dopamine-2 agonist</td>
<td>• Activates dopaminergic receptors</td>
<td>Bromocriptine</td>
<td>Cycloset</td>
</tr>
<tr>
<td>Glinides</td>
<td>• Increase insulin secretion</td>
<td>Nateglinide</td>
<td>Starlix or generic Prandin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repaglinide</td>
<td></td>
</tr>
</tbody>
</table>

DPP4, dipeptidyl peptidase; HGP, hepatic glucose production.
ADA. *Diabetes Care.* 2017;40:S64-S74.

Continued on next slide
<table>
<thead>
<tr>
<th>Class</th>
<th>Primary Mechanism of Action</th>
<th>Agent(s)</th>
<th>Available as</th>
</tr>
</thead>
</table>
| GLP1 receptor agonists        | • Increase glucose-dependent insulin secretion  
• Decrease glucagon secretion  
• Slow gastric emptying  
• Increase satiety            | Albiglutide  
Dulaglutide  
Exenatide  
Exenatide XR  
Liraglutide              | Tanzeum  
Trulicity  
Byetta  
Bydureon  
Victoza              |
| SGLT2 inhibitors              | • Increase urinary excretion of glucose                                                  | Canagliflozin  
Dapagliflozin  
Empagliflozin               | Invokana  
Farxiga  
Jardiance               |
| Sulfonylureas                 | • Increase insulin secretion                                                            | Glimepiride  
Glipizide  
Glyburide               | Amaryl or generic  
Glucotrol or generic  
Diaβeta, Glynase,  
Micronase, or generic              |
| Thiazolidinediones            | • Increase glucose uptake in muscle and fat  
• Decrease HGP                          | Pioglitazone  
Rosiglitazone               | Actos  
Avandia               |

GLP1, glucagon-like peptide; HGP, hepatic glucose production; SGLT2, sodium glucose cotransporter 2.

### Current Insulin Options

<table>
<thead>
<tr>
<th>Type</th>
<th>Basal Insulins</th>
<th>Prandial Insulins</th>
<th>Premixed Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>U-100 NPH</td>
<td>U-100 regular human insulin</td>
<td>U-100 70/30 RHI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U-500 regular human insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Technosphere inhaled insulin</td>
<td></td>
</tr>
<tr>
<td>Analog</td>
<td>U-100 glargine</td>
<td>U-100 lispro</td>
<td>U-100 50/50 lispro</td>
</tr>
<tr>
<td></td>
<td>U-100 glargine equivalent*</td>
<td>U-100 aspart</td>
<td>U-100 70/30 aspart</td>
</tr>
<tr>
<td></td>
<td>U-100 detemir</td>
<td>U-100 glulisine</td>
<td>U-100 75/25 lispro</td>
</tr>
<tr>
<td></td>
<td>U-100 degludec</td>
<td>U-200 lispro</td>
<td>U-100 70/30 degludec/aspart</td>
</tr>
<tr>
<td></td>
<td>U-200 degludec</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>U-300 glargine</td>
<td>U-200 lispro</td>
<td></td>
</tr>
</tbody>
</table>

- Analogue insulins are associated with less hypoglycemia than human insulins, although these differences are not always statistically significant.

*In the US, U-100 glargine equivalent is not approved as a biosimilar product.

## Fixed-Dose Oral Combination Agents for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Class</th>
<th>Added Agent</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 inhibitor + SGLT-2 inhibitor</td>
<td>Linagliptin + empagliflozin</td>
<td>Glyxambi</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin + dapagliflozin</td>
<td>Qtern</td>
</tr>
<tr>
<td>Metformin + DPP4 inhibitor</td>
<td>Alogliptin</td>
<td>Kazano</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Jentadueto</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Janumet</td>
</tr>
<tr>
<td>Metformin + glinide</td>
<td>Repaglinide</td>
<td>Prandimet</td>
</tr>
<tr>
<td>Metformin + SGLT2 inhibitor</td>
<td>Canagliflozin</td>
<td>Invokamet</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>Xigduo XR</td>
</tr>
<tr>
<td>Metformin + sulfonylurea</td>
<td>Glipizide</td>
<td>Metaglip and generic</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Glucovance and generic</td>
</tr>
<tr>
<td>Metformin + thiazolidinedione</td>
<td>Pioglitazone</td>
<td>ACTOplus Met</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone*</td>
<td>Avandamet</td>
</tr>
<tr>
<td>Thiazolidinedione + DPP4 inhibitor</td>
<td>Pioglitazone + alogliptin</td>
<td>Oseni</td>
</tr>
<tr>
<td>Thiazolidinedione + sulfonylurea</td>
<td>Pioglitazone</td>
<td>Duetact</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td>Avandaryl</td>
</tr>
</tbody>
</table>
## Fixed-Ratio Injectable Combination Agents Available for Type 2 Diabetes

<table>
<thead>
<tr>
<th>GLP1 receptor agonist +</th>
<th>Basal insulin</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide +</td>
<td>Degludec</td>
<td>Xultophy</td>
</tr>
<tr>
<td>Lixisenatide +</td>
<td>Glargine</td>
<td>Soliqua</td>
</tr>
</tbody>
</table>

ADA. *Diabetes Care.* 2017;40:S64-S74.
Antihyperglycemic Agent Considerations

- **SE**
  - Hypoglycemia, Weight, Renal/GU, GI Sx, Cardiac, Bone, Ketoacidosis

- **A1c**
  - Reduction

- **Individualize**
  - Elderly
  - Serious Illness

- **Cost**
  - Insurance formulary
  - Medicare
  - Uninsured
<table>
<thead>
<tr>
<th>Profiles of Antidiabetic Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MET</strong></td>
</tr>
<tr>
<td>HYPO</td>
</tr>
<tr>
<td>WEIGHT</td>
</tr>
<tr>
<td>RENAL / GU</td>
</tr>
<tr>
<td>GI Sx</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>CARDIAC*</td>
</tr>
<tr>
<td>ASCVD</td>
</tr>
<tr>
<td>BONE</td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
</tr>
</tbody>
</table>

**Legend:**
- Green: Few adverse events or possible benefits
- Yellow: Use with caution
- Orange: Likelihood of adverse effects
- Question Mark: Uncertain effect

* FDA indication to prevent CVD death in diabetes plus prior CVD events

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Metformin

Neutral
- Hypoglycemia
- Cardiac
- Bone
- Ketoacidosis

Possible Benefits
- Weight loss

Adverse Effects
- Gastrointestinal

Contraindications
- eGFR <30 ml/min/1.73m²
Glucagon-like Peptide 1 Receptor Agonists (GLP1 Ras)

Neutral
- Hypoglycemia
- Bone
- Ketoacidosis

Possible Benefits
- Weight loss
- Renal/Genitourinary (liraglutide)
- CHF (liraglutide)
- ASCVD

Adverse Effects
- Gastrointestinal

Contraindications
- eGFR <30 ml/min/1.73m² (exenatide)
Sodium Glucose Cotransporter 2 Inhibitors (SGLT2is)

Neutral
- Hypoglycemia
- Gastrointestinal

Possible Benefits
- Weight loss
- Renal (empagliflozin)
- CHF
- ASCVD (empagliflozin)

Adverse Effects
- Bone (canagliflozin)
- DKA
- Genital mycotic infections

Contraindications
- eGFR <45 ml/min/1.73m²
Dipeptidyl Peptidase 4 Inhibitors (DPP4is)

**Neutral**
- Hypoglycemia
- Weight loss
- ASCVD
- Bone
- Ketoacidosis
- Gastrointestinal

**Possible Benefits**
- Reducing albuminuria

**Adverse Effects**
- Renal dose adjustment (except linagliptin)
- CHF (possible saxagliptin and alogliptin)
- Possible pancreatitis

**Contraindications**
### Secretagogues (SU, GLN)

<table>
<thead>
<tr>
<th>Category</th>
<th>Possible Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
<td>- Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>- Bone</td>
</tr>
<tr>
<td></td>
<td>- Ketoacidosis</td>
</tr>
<tr>
<td>Possible Benefits</td>
<td>- Reduced microvascular and macrovascular complications*</td>
</tr>
<tr>
<td></td>
<td>- Inexpensive</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>- Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>- Weight gain</td>
</tr>
<tr>
<td></td>
<td>- CHF</td>
</tr>
</tbody>
</table>

*PloS Med 2016;13;13:e1001992*
Thiazolidinediones (TZDs)

Neutral
- Hypoglycemia
- Renal
- Gastrointestinal
- Ketoacidosis

Possible Benefits
- May reduce stroke risk

Adverse Effects
- Moderate fracture risk
- Weight gain
- CHF

Contraindications
Alpha Glucosidase Inhibitors (AGIs)

Neutral:
- Hypoglycemia
- Cardiac
- Bone
- Ketoacidosis
- Weight loss
- Renal

Possible Benefits:

Adverse Effects:
- Gastrointestinal

Contraindications:
Colesevelam and Bromocriptine Mesylate

**Neutral**
- Hypoglycemia
- Weight
- Bone
- Ketoacidosis
- CHF

**Possible Benefits**
- ASCVD

**Adverse Effects**
- Gastrointestinal

**Contraindications**
Insulin

Neutral
- GI
- ASCVD
- Bone
- Ketoacidosis

Possible Benefits

Adverse Effects
- Hypoglycemia
- Weight gain
- CHF risk

Contraindications
Glycemic Management of Type 2 Diabetes

REDUCING COMPLICATIONS

BLINDNESS
HEART ATTACK
KIDNEY FAILURE
AMPUTATION
A1C and Mortality in Clinical Practice

Retrospective Cohort Study
(N=27,965)

Macrovascular Benefits of Glycemic Control Depend on Duration of Diabetes

Veterans Affairs Diabetes Trial

**Effect of intensive glycemic control**

- Neutral
- Reduced risk
- Neutral
- Elevated risk

Microvascular Complications Increase With Increasing A1C

Diabetes Control and Complications Trial

Reducing A1C Reduces Microvascular Risk

United Kingdom Prospective Diabetes Study

- 37% Decrease per 1% reduction in A1C
- Hazard Ratio

Effects of Intensive Glucose Control on Macrovascular Risk in T2D

Meta-analysis of 5 Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes

(ACCORD, ADVANCE, PROactive, UKPDS, VADT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds ratio</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>0.83 (0.75-0.93)</td>
<td>-17%</td>
</tr>
<tr>
<td>Any CHD event</td>
<td>0.85 (0.77-0.93)</td>
<td>-15%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.93 (0.81-1.06)</td>
<td>-7% (NS)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.02 (0.87-1.19)</td>
<td>+2% (NS)</td>
</tr>
</tbody>
</table>

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; NS, not significant; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

CV Risk Increases With Comorbid Diabetes and CKD

AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PVD, peripheral vascular disease.

*ASVD was defined as the first occurrence of AMI, CVA/TIA, or PVD.

Macrovascular Risk Reduction in Type 2 Diabetes

- Individualized glucose control
- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Aspirin therapy
- Diagnosis and management of:
  - Autonomic cardiac neuropathy
  - Kidney disease

## Vaccinations for Patients with Diabetes

<table>
<thead>
<tr>
<th>Vaccine, frequency of administration</th>
<th>Patient age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine childhood immunizations, according to standard schedule (e.g., measles, mumps, rubella, varicella, polio, tetanus-diphtheria)</td>
<td>6 months to 18 years</td>
</tr>
<tr>
<td>Influenza, annually</td>
<td>≥6 months</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide vaccine</td>
<td>≥2 years</td>
</tr>
<tr>
<td>PVC13, 1-2 injections</td>
<td>2-18 years</td>
</tr>
<tr>
<td>PPSV23, 1 injection</td>
<td>19-64 years</td>
</tr>
<tr>
<td>PVC13 plus PPSV23, 1 injection each, in series</td>
<td>≥65 years</td>
</tr>
<tr>
<td>Hepatitis B, 1 injection</td>
<td>20-59 years*</td>
</tr>
<tr>
<td>Tetanus-diphtheria booster, every 10 years in adults</td>
<td>≥19 years</td>
</tr>
<tr>
<td>Individuals not already immunized for childhood diseases and those requiring vaccines for endemic diseases should be immunized as required by individual patient needs</td>
<td>Any age</td>
</tr>
</tbody>
</table>

*Consider for patients ≥60 based on assessment of risk and likelihood of adequate immune response.

Glycemic Management of Type 2 Diabetes

SPECIAL DISEASE MANAGEMENT CONSIDERATIONS
Management of Diabetic Nephropathy

• Optimal control of blood pressure, glucose, and lipids
• Smoking cessation
• RAAS blockade
  – ACE inhibitor, ARB, or renin inhibitor
  – Do not combine RAAS blocking agents
  – Monitor serum potassium
• Nephrologist referral
  – Atypical presentation
  – Rapid decline in eGFR or albuminuria progression
  – Stage 4 CKD

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin angiotensin aldosterone system.
## DKD Risk Factor Management

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
<th>Management Recommendation</th>
</tr>
</thead>
</table>
| Hyperglycemia | Individualized A1C goals ≤6.5% for most (AACE) ~7.0% (NKF)          | Avoid metformin in moderate to severe CKD  
Consider need for dose reductions and/or risk of hypoglycemia and other renal-related AEs with other antidiabetic agents  
Do not target A1C <7% in patients at risk of hypoglycemia |
| Hypertension  | BP ~130/80 mmHg                                                      | Use ACE inhibitor or ARB in combination with other antihypertensive agents as needed       |
| Proteinuria   |                                                                     | Use ACE inhibitor or ARB as directed                                                      |
| Dyslipidemia  | LDL-C <100 mg/dL, <70 mg/dL an option for high risk                 | Statin +/- ezetimibe therapy recommended for all patients except those on dialysis (NKF)  
Fibrate dose reduction may be required |

## Use of Antihyperglycemic Agents in Kidney Disease

<table>
<thead>
<tr>
<th>Class: Agent(s)</th>
<th>Kidney Disease Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin analog: pramlintide</td>
<td>Not recommended for CKD stage ≥4</td>
</tr>
<tr>
<td>Biguanide: metformin</td>
<td>Contraindicated if SCr &gt;1.5 (men) or 1.4 (women) mg/dL</td>
</tr>
<tr>
<td>Bile acid sequestrant: colesevelam</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Dopamine-2 agonist: bromocriptine</td>
<td>Use with caution</td>
</tr>
<tr>
<td>DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin</td>
<td>Reduce dosage for alogliptin, saxagliptin and sitagliptin if CrCl &lt;50 mg/dL</td>
</tr>
<tr>
<td>Glinides: nateglinide, repaglinide</td>
<td>Start at lowest effective dose if GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>GLP-1 receptor agonists: albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide</td>
<td>Exenatide and liraglutide not recommended with GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors: acarbose, miglitol</td>
<td>Avoid if GFR &lt;25 (miglitol) or &lt;30 (acarbose) mL/min/1.73 m²</td>
</tr>
<tr>
<td>Insulin: aspart, detemir, glargine, glulisine, inhaled, lispro, NPH, regular</td>
<td>Adjust dose based on patient response</td>
</tr>
<tr>
<td>SGLT inhibitors: canagliflozin, dapagliflozin, empagliflozin</td>
<td>Ineffective if GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Sulfonylureas: glimepiride, glipizide, glyburide</td>
<td>No dose adjustment for glipizide; start glimepiride conservatively; avoid glyburide and all other SUs</td>
</tr>
<tr>
<td>Thiazolidinediones: pioglitazone, rosiglitazone</td>
<td>No dosage adjustment</td>
</tr>
</tbody>
</table>

Management Considerations for Elderly Patients with Diabetes

Increased risk of and from falling
- Impaired vision
- Reduced strength and stamina
- Sensitivity to medication side effects
- Frailty
- Susceptibility to hypoglycemia

Hypoglycemia unawareness and recurrent hypoglycemia
- Impaired counter-regulatory mechanisms

Other complicating factors
- Diminished kidney function
- Urinary incontinence
- Status of social support and/or caregiver
- Drug-drug interactions

Impaired capacity, understanding, and/or motivation for proper self-care
- Cognitive decline and dementia
- Depression
- Impaired vision

Consider risks before prescribing:
- Sulfonylureas and glinides (hypoglycemia risk)
- Thiazolidinediones (fracture risk)
- Metformin (risk of lactic acidosis with decreased kidney function)

Consider when establishing treatment goals
- Patient overall health and well-being
- Self-care capacities
- Social/family support
Glycemic Management of Type 2 Diabetes

OTHER DIABETES TREATMENT MODALITIES
Inhaled Insulin

- Inhaled administration
- Rapid-acting insulin
  - Peak levels achieved in ~15 minutes

### Safety Considerations with Inhaled Insulin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung disease</strong></td>
<td>- Contraindicated in asthma, COPD, and other chronic lung diseases&lt;br&gt;- Perform spirometry to assess lung function before initiating inhaled insulin, after 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms&lt;br&gt;- Do not use in patients with active lung cancer and use with caution in patients with a history of lung cancer or those at risk for lung cancer</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>- Observe for signs and symptoms of fluid retention or heart failure, especially when used with TZDs</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>- Increase frequency of glucose monitoring</td>
</tr>
</tbody>
</table>

Afrezza (insulin human) inhalation powder prescribing information. Danbury, CT: MannKind Corporation; 2014.
Insulin Pumps and Continuous Glucose Sensors
CSII in Type 2 Diabetes: Patient Candidates

- Absolutely insulin-deficient
- Take 4 or more insulin injections a day
- Assess blood glucose levels 4 or more times daily
- Motivated to achieve tighter glucose control

- Mastery of carbohydrate counting, insulin correction, and adjustment formulas
- Ability to troubleshoot problems related to pump operation and plasma glucose levels
- Stable life situation
- Frequent contact with members of their healthcare team, in particular their pump-supervising physician

CSII, continuous subcutaneous insulin infusion.
TREATMENT APPROACH

Glycemic Management of Type 2 Diabetes
Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - More stringent: highly motivated, adherent, excellent self-care capacities
  - Less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - Low
  - High

- **Disease duration**
  - Newly diagnosed
  - Long-standing

- **Life expectancy**
  - Long
  - Short

- **Important comorbidities**
  - Absent
  - Few/mild
  - Severe

- **Established vascular complications**
  - Absent
  - Few/mild
  - Severe

- **Resources, support system**
  - Readily available
  - Limited

*Figure 1*

### Guidelines for Glycemic, BP, & Lipid Control

<table>
<thead>
<tr>
<th></th>
<th>American Diabetes Association Standard of Care 2017 Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7.0% (Individualization)</td>
</tr>
<tr>
<td>Pre-prandial glucose</td>
<td>70-130 mg/dl</td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td>&lt;180 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;140/90 mmHg</td>
</tr>
<tr>
<td>Lipids</td>
<td>LDL: &lt;100 mg/dl</td>
</tr>
<tr>
<td></td>
<td>&lt;70 (overt CVD)</td>
</tr>
<tr>
<td></td>
<td>HDL: &gt;40 mg/dl (males)</td>
</tr>
<tr>
<td></td>
<td>HDL: &gt;50 mg/dl (females)</td>
</tr>
<tr>
<td></td>
<td>TG: &lt;150 mg/dl</td>
</tr>
<tr>
<td>Drug</td>
<td>A1C Reduction</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Biguanide</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1-1.5%</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Alpha-glucosidase Inhibitors</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5%</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>0.5%</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Entry A1C

**A1c < 7.5%**
- Metformin
- Recheck 3 months

**A1c > 7.5%**
- Metformin + OA
- Recheck 3 months

**A1c > 9%**
- Metformin + 2 agents
- Recheck 3 months

**A1c not at goal**
- Start Insulin
Entry A1C

Life Style

A1C > 9% (Symptomatic)

Start Insulin
- 0.3-0.5 units/kg/day
- 50% basal and 50% bolus
- ↑ basal by 10% if fasting BG > 110 mg% every 3 days
- ↑ prandial by 10% if pre meal BG > 140 mg% every 3 days
## Adverse Effects

| Renal | • Metformin < 30 ml/min/1.73 m²  
|       | • Exenatide < 30 ml/min/1.73 m²  
|       | • Insulin and sulfonylurea - ↑ hypoglycemic risk |
| Bone  | • Canagliflozin  
|       | • Thiazolidinediones |
| Diabetic Ketoacidosis | • SGLT2 Inhibitors |
Adverse Effects

**Cardiac**
- CHF risk
  - Saxagliptin, Alogliptin, TZD, Insulin, SU

**Weight Gain**
- TZD
- Insulin & SU

**GI**
- Metformin, GLP-1 RA, AGI
- Bromocriptine, Pramlin
Benefits

Renal
- Liraglutide
- Empagliflozin

Cardiac
- Liraglutide – CHF and ASCVD
- Empagliflozin – CHF
- TZD – may reduce stroke risk
- Colesevelam
- Bromocriptine

Weight loss
- GLP-1 RA
- Pramlintide
- SGLT2i
- Metformin
## Non-Insulin Costs

<table>
<thead>
<tr>
<th>Medication</th>
<th>$ Cost (30 day supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>2.30-8.70</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>9.00</td>
</tr>
<tr>
<td>Metformin</td>
<td>9.10-35.00</td>
</tr>
<tr>
<td>Alpha-Glucosidase Inhibitors</td>
<td>48.00-170.00</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>195.00-363.00</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>200.00</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>249.00-626.00</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>392.00</td>
</tr>
<tr>
<td>Combinations</td>
<td>41.00-576.00</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>885.00</td>
</tr>
</tbody>
</table>
## Insulin Costs

<table>
<thead>
<tr>
<th>Medication</th>
<th>$ Cost (per unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long Acting (10 ml vial, 3ml pen)</td>
<td>63.00-248.00</td>
</tr>
<tr>
<td>Pre-Mix (10 ml vial, 3ml pen)</td>
<td>98.00-265.00</td>
</tr>
<tr>
<td>Long Acting + GLP1 (3ml pen)</td>
<td>127.00 -191.00</td>
</tr>
<tr>
<td>NPH (10 ml vial, 3ml pen)</td>
<td>138.00</td>
</tr>
<tr>
<td>Regular insulin (10 ml vial)</td>
<td>138.00</td>
</tr>
<tr>
<td>Rapid Acting (10 ml vial, 3ml pen)</td>
<td>255.00</td>
</tr>
<tr>
<td>Inhaled Insulin</td>
<td>279.00</td>
</tr>
<tr>
<td>Device</td>
<td>$ Cost</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Glucose meter</td>
<td>20-80</td>
</tr>
<tr>
<td>Insulin pen needles</td>
<td>250/yr.</td>
</tr>
<tr>
<td>Glucose lancets</td>
<td>270/yr.</td>
</tr>
<tr>
<td>Insulin syringes</td>
<td>360/yr.</td>
</tr>
<tr>
<td>Glucose strips</td>
<td>1,500/year</td>
</tr>
<tr>
<td>Insulin pump</td>
<td>5,500</td>
</tr>
<tr>
<td>Insulin pump supplies</td>
<td>1,200/yr.</td>
</tr>
<tr>
<td>CGM monitor</td>
<td>1000-1400</td>
</tr>
<tr>
<td>CGM sensors</td>
<td>4,800/yr.</td>
</tr>
</tbody>
</table>
Average Diabetes Medical Costs

$13,700/Year
1. Lifestyle optimization
2. A1c target individualized
3. Choice of anti-hyperglycemic agents individualized
   a. Efficacy
   b. Mechanism of action
   c. Hypoglycemia risk
   d. Weight gain
   e. Adverse effects
   f. Tolerability
   g. Likely adherence
   h. Cost
   i. Heart, kidney safety
4. Comprehensive management of lipid and blood pressure
5. Therapy evaluated every 3 months, titrate as needed until stable
References

• AACE 2017 Consensus Statement Type 2 Diabetes Management – Endocrine Practice Vol 23 No. 2 February 2017

• Drugs for Type 2 Diabetes – Medical Letter Vol 59 January 16, 2107

• Standard of Medical Care in Diabetes 2017 – Vol 40 Supplement 1