Update in Diabetes Care & Role of Novel Agents

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Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Robert Hal Scofield, MD

I have no relevant financial relationships or affiliations with commercial interests to disclose.
Questions

1. What is the role of medication, such as metformin, for prevention of diabetes?
2. How does one choose an HbA1c target for patients with type 2 diabetes mellitus?
3. What should blood glucose goals be for hospitalized patients?
4. What are the optimal choices and sequence of novel oral and injectable therapies after metformin in type 2 diabetes mellitus?
1. What are the recommendations for prevention of diabetes?
Pre-Diabetes - Diagnosis

• A1C 5.7–6.4%

• Impaired glucose tolerance
  • random blood sugar between 140 mg% and 200 mg%.

• Impaired fasting glucose
  • fasting blood glucose between 100 and 125 mg%
Risks of Developing Prediabetes

- Physically inactive
- FH of diabetes
- Certain ethnic groups
  - Asian American, African-American, Hispanic American, and Native American
- Hx of gestational diabetes or have given birth to a child weighing more than 9 pounds
- Hypertension
- HDL cholesterol level $\leq 35$ mg/dl and/or triglyceride level $\geq 250$ mg/dl
- PCOS
- History of PVD
- IFG (impaired fasting glucose)
- IGT (impaired glucose tolerance)
Diabetes Prevention Program

- Metformin less effective than lifestyle modification
  - differences declining over time
- Metformin may be cost-saving over 10 years
  - As effective as lifestyle modification in BMI >35 kg/m2
  - Not better than placebo in patients over >60 years
- In Gestational DM
  - Metformin and intensive lifestyle modification
    - Equivalent 50% reduction in diabetes risk.
  - Both remained highly effective at 10-year follow-up

N Engl J Med 2002;346:393–403
Lancet Diabetes Endocrinol 2015;3:866–875
Diabetes Care 2012;35:723–730
J Clin Endocrinol Metab 2008;93:4774–4779
Pharmacological Interventions

- Pharmacologic agents
  - decrease incident diabetes to various degrees
    - Prediabetes research
- None are FDA approved
- Risk/benefit of each medication must be balanced
- Metformin
  - strongest evidence
  - long-term safety

Diabetes Care 2018;41:S55-S54
General Recommendations - Prediabetes

• Annual screening for diabetes

• Intensive behavioral lifestyle intervention
  • modeled on the Diabetes Prevention Program
  • 7% loss of initial body weight
  • increase moderate-intensity physical activity (walking 30 minutes a day).

• Technology-assisted tools
  • social networks, distance learning, and mobile apps
    • bidirectional communication
  • augment lifestyle modification to prevent diabetes.
Pre-Diabetes and CV Disease Prevention

• Prediabetics
  • increased risk for CV disease

• CV risk factors frequently present in pre-diabetes
  • Hypertension
  • Dyslipidemia

• Treatment goals
  • same as general population
  • Increased vigilance warranted
    • identify and treat cardiovascular risks (e.g., smoking)

J Am Coll Cardiol 2010;55: 1310–1317
Diabetes Care 2017;40:1401– 1408
2. How does one choose an HbA1c target for patients with type 2 diabetes mellitus?
A1C Goals in Adults: Recommendations - ADA

- Most non-pregnant adults
  - <7.0% is a reasonable goal
- More stringent A1C goals (such as <6.5%)
  - without significant hypoglycemia
  - other adverse effects of treatment (i.e., polypharmacy).
- Short duration of diabetes
- T2DM treated with lifestyle or metformin only
- Long life expectancy
- No significant cardiovascular disease.
A1C Goals in Adults: Recommendations - ADA

• Less stringent goals <8%
  • Severe hypoglycemia
  • Limited life expectancy
  • Advanced microvascular or macrovascular complications
  • Long-standing diabetes where glycemic goals are difficult to achieve
    • ACCORD trial

The American Diabetes Association “Standards of medical care in diabetes” 2018
A1C Goals in Adults: VA/DoD

- HbA1c 6.0%–7.0%
  - life expectancy >10–15 y
  - no or mild microvascular complications.
- HbA1c 7.0%–8.5%
  - established microvascular or macrovascular disease
  - comorbid conditions
  - life expectancy of 5–10 y

A1C Goals in Adults: VA/DoD

- HbA1c range of 8.0%–9.0%
  - life expectancy < 5 y
  - significant comorbid conditions; advanced complications
  - difficulties with self-management
    - mental status
    - Disability
    - other factors (such as food insecurity or insufficient social support)

HbA$_{1C}$ Targets for Type 2 Nonpregnant Adults - ACP

- Personalize goals for glycemic control
  - benefits and harms of pharmacotherapy
  - patients' preferences
  - patients' general health
  - life expectancy
  - treatment burden
  - costs of care

HbA$_{1C}$ Targets for Type 2 Nonpregnant Adults - ACP

• HbA1c level between 7% and 8%
  • in most patients
• HbA1c levels less than 6.5%.
  • deintensifying pharmacologic therapy
• Avoid hypoglycemia minimize hyperglycemic symptoms
  • life expectancy less than 10 years
  • advanced age (80 years or older)
  • residence in a nursing home
  • chronic conditions (dementia, cancer, ESRD, COPD or CHF)

No A1c target
A Firestorm Broke Out


General Concerns

• Four diabetes/endocrine societies
  • expressed immediate concern and ADA release a detailed critique

• Public disagreements
  • do not have a calming effect on patients.

• Before release
  • generalists and specialists working together on these guidelines
  • Confusion could have been avoided

Comparing the three guidelines

- Not as much controversy.
- Guiding principle
  - Minimize
    - Hypoglycemia
    - patient burden
    - cost of drugs.
- Shared decision making
  - patient centered approach
Glycemic Targets

• For most patients:
  • \(\text{HbA1c} < 7\%\)

• For *younger* patients
  • \(\text{HbA1c} < 6.5\%\)

• Frail adults
  • Complications
  • Co-morbidities
  • high risk for hypoglycemia
  • \(\text{HbA1c} \sim 8\%\)

• Fasting BGs
  • 80 to 130 mg/dL

• Peak post meal
  • 180 mg/dL
3. What should blood glucose goals be for hospitalized patients?
Moderate Versus Tight Glycemic Control

- Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, meta-analysis of 26 studies - increased rates of severe hypoglycemia (defined as glucose < 40 mg/dL) and mortality in tightly versus moderately controlled cohorts
  

- Recent randomized controlled studies and meta-analyses in surgical patients have also reported that targeting moderate perioperative blood glucose levels to 180 mg/dL is associated with lower rates of mortality and stroke compared with a liberal target glucose 200 mg/dL, whereas no significant additional benefit was found with more strict glycemic control 140 mg/dL
  
  Umpierrez et al. Diabetes Care 2015;38:1665–1672

- Clinical judgment combined with ongoing assessment of clinical status, including changes in the trends of glucose measures, illness severity, nutritional status, or concomitant medications that might affect glucose levels (e.g., glucocorticoids), should be incorporated into the day-to-day decisions regarding insulin doses.
  

The American Diabetes Association “Standards of medical care in diabetes” 2018
Glycemic Control in the Hospital

• Both hyperglycemia and hypoglycemia
  • associated with adverse outcomes, including death
• Inpatient goals
  • prevention of both hyperglycemia (>180 mg/dl) and hypoglycemia.
• Effective transition out of the hospital
• Non-insulin diabetic agents
  • appropriate in most hospitalized patients

The American Diabetes Association “Standards of medical care in diabetes” 2018
Hospital Care Standards

• Insulin therapy for persistent hyperglycemia > 180 mg/dL.
• Once insulin therapy started, glucose target 140–180 mg/dL
  • critically ill patients and non-critically ill patients.
• Higher glucose ranges acceptable
  • terminal illnesses
  • severe comorbidities
  • frequent glucose monitoring or close nursing supervision is not feasible
• More stringent goals, such as 110–140 mg/dl
  • selected patients – TPN?
  • without significant hypoglycemia

The American Diabetes Association “Standards of medical care in diabetes” 2018
Glycemic Control in the Hospital

• Basal plus mealtime and correction insulin regimen
  • Non-critically ill patients.

• Decisions must be made everyday

• Caution is required in interpreting results of POC glucose
  • anemia, polycythemia, hypoperfusion, or some medications.

• Structured discharge plan
  • Individualized

The American Diabetes Association “Standards of medical care in diabetes” 2018
Glycemic Control in the Hospital - Logistics

• Initiating insulin
  • 0.5 units/kg divided equal as basal and mealtime
  • Lower dose (0.25-0.3 units/kg)
    • Older
    • Renal failure
    • Sicker

• Titrate up to 20% a day

Umpierrez GE et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diab Care 30:2181-6, 2007
Umpierrez GE, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diab Care. 34:256-61, 2011
Therapy with SSI is proven to be harmful, discouraged.

- Never speak of SSI in front of an endocrinologist.

In randomized trials associated with:
- Hypoglycemia
- Hyperglycemia
- Iatrogenic DKA in hospitalized type 1 diabetes
- Longer hospital stays

Do not confuse with "correction" insulin, given in conjunction with scheduled preprandial insulin to correct for preprandial hyperglycemia.

Endocr Pract. 2004;10:77-82
Umpierrez GE et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial). Diab Care. 30:2181-6, 2007
Umpierrez GE, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diab Care. 34:256-61, 2011
## Hypoglycemia

<table>
<thead>
<tr>
<th>Level</th>
<th>Glycemic criteria/description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Glucose &lt;70 mg/dL and glucose ≥54 mg/dL - hospital alert level</td>
</tr>
<tr>
<td>Level 2</td>
<td>Glucose &lt;54 mg/dL - Level at which neuroglycopenic symptoms begin to occur and immediate action is needed</td>
</tr>
<tr>
<td>Level 3</td>
<td>A severe event characterized by altered mental and/or physical status requiring assistance from another person</td>
</tr>
</tbody>
</table>

The American Diabetes Association “Standards of medical care in diabetes” 2018
Hypoglycemia Treatment

• For alert patients with blood sugar less than 70 mg/dl give “Fast Fifteen” carbohydrates
  • 3 glucose tablets
  • 120 ml regular soda
  • 120 ml juice

• For patients with decreased sensorium, administer D$_{50}$W
  • BS 60-69 – 15 ml
  • BS 50-59 - 20 ml
  • BS 30-49 – 25 ml
  • BS <30 - 30 ml

• For obtunded patients, give glucagon 1 mg IM while assessing for the ABC’s

• Check blood sugars every 15 minutes
  • until BS > 70
  • patient is awake.
4. What are the optimal choices and sequence of oral and injectable therapies after metformin in type 2 diabetes mellitus?
<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>generic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miglitol</td>
<td></td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>• Decrease glucagon secretion&lt;br&gt;• Slow gastric emptying&lt;br&gt;• Increase satiety</td>
<td>Pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td>Biguanide</td>
<td>• Decrease HGP&lt;br&gt;• Increase glucose uptake in muscle</td>
<td>Metformin</td>
<td>generic</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>• Decrease HGP?&lt;br&gt;• Increase incretin levels?</td>
<td>Colesevelam</td>
<td>WelChol</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>• Increase glucose-dependent insulin secretion&lt;br&gt;• Decrease glucagon secretion</td>
<td>Alogliptin</td>
<td>Nesina</td>
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<tr>
<td></td>
<td></td>
<td>Linagliptin</td>
<td>Tradjenta</td>
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<td>Saxagliptin</td>
<td>Onglyza</td>
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<td></td>
<td></td>
<td>Sitagliptin</td>
<td>Januvia</td>
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<tr>
<td>Dopamine-2 agonist</td>
<td>• Activates dopaminergic receptors</td>
<td>Bromocriptine</td>
<td>Cycloset</td>
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<tr>
<td>Glinides</td>
<td>• Increase insulin secretion</td>
<td>Nateglinide</td>
<td>Starlix</td>
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<tr>
<td></td>
<td></td>
<td>Repaglinide</td>
<td>Prandin</td>
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</table>

<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>GLP1 receptor agonists</td>
<td>• Increase glucose-dependent insulin secretion</td>
<td>Albiglutide, Dulaglutide</td>
<td>Tanzeum, Trulicity</td>
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<tr>
<td></td>
<td>• Decrease glucagon secretion</td>
<td>Exenatide, Exenatide XR</td>
<td>Byetta, Bydureon</td>
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<tr>
<td></td>
<td>• Slow gastric emptying</td>
<td>Liraglutide, Semaglutide</td>
<td>Victoza, Ozempic</td>
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<td></td>
<td>• Increase satiety</td>
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<td></td>
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<tr>
<td>SGLT2 inhibitors</td>
<td>• Increase urinary excretion of glucose</td>
<td>Canagliflozin, Dapagliflozin</td>
<td>Invokana, Farxiga, Jardiance</td>
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<tr>
<td>Sulfonylureas</td>
<td>• Increase insulin secretion</td>
<td>Glimepiride, Glipizide, Glyburide</td>
<td>Amaryl or generic, Glucotrol or generic, Diaβeta, Glynase, Micronase, or generic</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>• Increase glucose uptake in muscle/fat</td>
<td>Pioglitazone, Rosiglitazone</td>
<td>Actos, Avandia</td>
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<td>Class</td>
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<td>Available as</td>
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<tr>
<td>-------------------------------------------</td>
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<tr>
<td>DPP4 inhibitor + SGLT-2 inhibitor</td>
<td>Linagliptin + empagliflozin</td>
<td>Glyxambi</td>
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<tr>
<td></td>
<td>Saxagliptin + dapagliflozin</td>
<td>Qtern</td>
<td></td>
</tr>
<tr>
<td>Metformin + DPP4 inhibitor</td>
<td>Alogliptin</td>
<td>Kazano</td>
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<td>Linagliptin</td>
<td>Jentadueto</td>
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</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Janumet</td>
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<tr>
<td>Metformin + glinide</td>
<td>Repaglinide</td>
<td>Prandimet</td>
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<tr>
<td>Metformin + SGLT2 inhibitor</td>
<td>Canagliflozin</td>
<td>Invokamet</td>
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<tr>
<td></td>
<td>Dapagliflozin</td>
<td>Xigduo XR</td>
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<tr>
<td>Metformin + sulfonylurea</td>
<td>Glipizide</td>
<td>Metaglip and generic</td>
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<tr>
<td></td>
<td>Glyburide</td>
<td>Glucovance and generic</td>
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<tr>
<td>Metformin + thiazolidinedione</td>
<td>Pioglitazone</td>
<td>ACTOplus Met</td>
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<tr>
<td></td>
<td>Rosiglitazone*</td>
<td>Avandamet</td>
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<td>Thiazolidinedione + DPP4 inhibitor</td>
<td>Pioglitazone + alogliptin</td>
<td>Oseni</td>
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<td>Thiazolidinedione + sulfonylurea</td>
<td>Pioglitazone</td>
<td>Duetact</td>
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<tr>
<td></td>
<td>Rosiglitazone</td>
<td>Avandaryl</td>
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</table>
Medications and Weight Loss

• Metformin
  • Modest

• Sodium–glucose cotransporter 2 inhibitors

• Glucagon-like peptide 1 agonists
A1C and CVD Outcomes

• DCCT (Type 1)
  • Trend toward lower risk of CVD events with intensive control
  • Long term follow up – significant decrease

• EDIC (type 1)
  • 57% reduction in risk of nonfatal MI, stroke, or CVD death

• UKPDS (type 2)
  • Non-significant reduction in CVD events (T2DM)

• ACCORD, ADVANCE, VADT (type 2)
  • no significant reduction in CVD outcomes
# Post-FDA CV Outcomes in Diabetes

## DPP4-i

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
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<td>alogliptin</td>
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<td>Comparator</td>
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<td>glimepiride (SU)</td>
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<td>14,671</td>
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<tr>
<td>Results</td>
<td>2013</td>
<td>2015</td>
<td>2015</td>
<td>2019</td>
<td>2018</td>
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</table>

- CHF

## GLP1-RA

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
<th>HARMONY</th>
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<tbody>
<tr>
<td>GLP1-RA</td>
<td>lixisenatide</td>
<td>liraglutide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
<td>albiglutide</td>
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<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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<tr>
<td>N</td>
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<td>9,10</td>
<td>3,997</td>
<td>14,000</td>
<td>9,622</td>
<td>9,400</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2016</td>
<td>2016</td>
<td>2018</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

- stroke
- retinopathy

## SGLT2-i

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS (&amp; ‘R’)</th>
<th>(CREDENCE)</th>
<th>DECLARE</th>
<th>VERTIS CV</th>
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<tbody>
<tr>
<td>SGLT2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
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<td>Comparator</td>
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<td>N</td>
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<td>4,323 (‘+813, ‘-R’)</td>
<td>4,200</td>
<td>17,150</td>
<td>8,000</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2019</td>
<td>2019</td>
</tr>
</tbody>
</table>

- CHF
- Amputations
Positive Effects
CV Outcome and GLP1 agonists

• Liraglutide
  • MACE outcome, 81% with CAD
  • 608/4668 versus 684/4672 (13.0% versus 14.9%)
  • All cause mortality statistically lower – 8.2% versus 9.6%

• Exenatide
  • MACE outcome, 73% with CAD
  • 839/7356 versus 905/7396 (11.4% versus 12.2%)

Negative Effects
Amputation and SGL2 inhibitors

• Canagliflozin
  • MACE outcome, 10,142 subjects, 72.2% with CAD
  • MACE
    • 26.9 versus 31.5 events per 1000 patient-years (p=0.02 for superiority)
  • Amputation
    • 6.3 versus 3.4 amputations per 1000 patient-years
  • Renal outcome
    • Trend for improvement but not statistically significant
• All cause mortality
  • Not different

Consideration of Medication Choice for T2DM

- Metformin
- GLP1 agonists

No shots

- No endogenous insulin

- CHF
  - Avoid – DPP4 inhibitor
  - GLP1 agonist
  - TZD
  - Neuropathy/PAD
  - Avoid - canagliflozin

- Renal disease
- Liver disease

- Everybody

- Impact on weight
- Patient preferences
- Efficacy
- Disease duration
- Comorbidities
- Age
- Hypoglycemia risk
- Cost
AACE/ACE and ADA/EASD T2D – Common Principles

• Individualize glycemic goals based on patient characteristics
• Promptly intensify antihyperglycemic therapy to maintain blood glucose at individual targets
  • Combination therapy necessary for most patients
  • Base choice of agent(s) on individual patient medical history, behaviors and risk factors, ethno-cultural background, and environment
• Insulin eventually necessary for many patients
• SMBG vital for day-to-day management of blood sugar
  • All patients using insulin
  • Many patients not using insulin

ADA vs AACE

• Both lead with Metformin as initial monotherapy
• ADA hierarchy – SU, TZD’s, DDP-4, SGLT2, GLP-1 agonist, insulin
• AACE hierarchy - GLP-1 agonist, SGLT-2, DPP-4, then (all to be used with caution) TZD, basal insulin and, lastly, SU.
Summary

• The underlying approach to the management of Type 2 Diabetes is a patient-centered using shared decision making.

• This applies to outpatient HgbA1c targets, inpatient glycemic goals and choice of anti-diabetic agents.
### Current Insulin Options

<table>
<thead>
<tr>
<th>Type</th>
<th>Basal Insulins</th>
<th>Prandial Insulins</th>
<th>Premixed Insulins</th>
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</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>
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<tr>
<td></td>
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<td>U-500 regular human insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Technosphere inhaled insulin</td>
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<tr>
<td>Analog</td>
<td>U-100 glargine</td>
<td>U-100 lispro</td>
<td>U-100 50/50 lispro</td>
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<tr>
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<td>U-100 glargine equivalent*</td>
<td>U-100 aspart</td>
<td>U-100 70/30 aspart</td>
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<td>U-100 detemir</td>
<td>U-100 glulisine</td>
<td>U-100 75/25 lispro</td>
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<tr>
<td></td>
<td>U-100 degludec</td>
<td>U-200 lispro</td>
<td>U-100 70/30 degludec/aspart</td>
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<td></td>
<td>U-200 degludec</td>
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<tr>
<td></td>
<td>U-300 glargine</td>
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- Humulin R U-500 for use with extreme insulin resistance
- Analogue insulins are associated with less hypoglycemia than human insulins, although these differences are not always statistically significant

Algorithm for Adding/Intensifying Insulin

START BASAL (Long-Acting Insulin)
- **A1C < 8%**
  - TDD: 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD: 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

*Glycemic Goal:
- <7% for most patients with T2D; fasting and premeal
  - BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

INTENSIFY (Prandial Control)
- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i

Basal Plus 1, Plus 2, Plus 3
- Start: 10% of basal dose or 5 units
- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

Basal Bolus
- Start: 50% of TDD in three doses before meals
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL.
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

*Glycemic Control Not at Goal*