New Cardioprotective Medications for Diabetes

Thursday, October 10, 2019

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Objectives

At the conclusion of this program, the audience participant will be able to:

1. Understand which cardioprotective medications are most useful for their patients with diabetes.
2. Understand when these medications should not be used, or used with great caution, in patients with diabetes.
3. Understand the side effects of these cardioprotective medications.
Declaration of Interests:

- No conflicts of interest
Diabetes and Cardiovascular Disease

• Patients with diabetes are at significantly greater risk for cardiovascular disease than those without diabetes
• In addition, for nearly every cardiovascular event, those with diabetes have higher rates of mortality and morbidity than without diabetes
• The related risk for those with diabetes increases as they get older
Figure 2. Cardiovascular complications among adults age ≥65 y, by diabetes status, United States, 2007–2010. Data are self reported. Error bars represent 95% CIs.

LeRoith et al Diabetes in Older Adults Guidelines, J Clin Endo Metab, May 2019
Figure 4. Incidence (per 1000) of major diabetes complications according to age among adults with diabetes, 2009 (6). ER, emergency room; ESRD, end-stage renal disease; IHD, ischemic heart disease.
Case for Discussion –
Should we change this patient’s diabetes regimen?

- R.S. is a 84 y/o w/m who had had diabetes for 24 years
- He has a 30 year history of hypertension
- He had two cardiac stents placed 11 years ago
- He is obese at 224 lbs. with a BMI of 36.8
- He is taking carvedilol, losartan, glipizide, and 46 units of Lantus daily
- His HbA1c has been between 8.2 and 9% for most years
- He has some decrease in kidney function and complains of numbness of his feet and frequent falls
- He also has morning hypoglycemia
- He would like a second opinion
Cardiovascular Outcome Trials (CVOT’s) are a surprisingly recent development

- Prior to 2008, most drug testing of diabetes medications relied on 6 – 12 month Phase 2 and 3 trials which generally focused on glucose lowering efficacy.
- In 1997, troglitazone was withdrawn after multiple patients died of liver failure.
- In 2001, cerivastatin (Baycol) was withdrawn after 31 deaths from rhabdomyolysis.
- In 2005, Nissen et al published data showing that recently approved muraglitazar was associated with increased CV mortality. But, little changed.
In 2007, concerns about rosiglitazone were raised following a NEJM article by Nissen et al which showed a 43% increased risk of MI and a 64% increased risk of CV death vs comparators.

Many doctors who were speakers who regularly spoke glowingly about rosiglitazone, fought back.
In 2007, I was asked to write a commentary about the controversy for the official journal of the American Association of Clinical Endocrinologists, Endocrine Practice. It was published that year. A firestorm ensued.
A series of articles appeared in the New York Times which quoted Dr. Nissen and two of them contained quotes from me. I was now part of a national discussion on drug safety.
• The controversy resulted in the drug being withdrawn in 2010 and the first cardiovascular outcome trial (CVOT) was begun.
• Today, there are a proliferation of these articles. The original plan was to just demonstrate non-inferiority of the medications before a drug was approved but several surprising results emerged.
• Four CVOT’s showed strongly positive results
Figure 1—Completed and ongoing CVOTs.
Heart failure (HF) outcomes with select glucose-lowering therapies

CARMELINA, Cardiovascular and Renal Microvascular Outcome Study with Linagliptin;

ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome;

EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care;

EXSCEL, Exenatide Study of Cardiovascular Event Lowering;

ORIGIN, Outcome Reduction With Initial Glargine Intervention;

PROactive, PROspective Pioglitazone Clinical Trial In Macrovascular Events;

RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes;

SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>LEADER (10)</th>
<th>SUSTAIN-6 (11)</th>
<th>EMPA-REG OUTCOME (13, 60)</th>
<th>CANVAS Program (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>9,340</td>
<td>3,297</td>
<td>7,020</td>
<td>10,142</td>
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<tr>
<td>Mean age (years)</td>
<td>64.3</td>
<td>64.6</td>
<td>63.1</td>
<td>63.3</td>
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<tr>
<td>Diabetes duration (years)*</td>
<td>12.8</td>
<td>13.9</td>
<td>57% &gt;10</td>
<td>13.5</td>
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<tr>
<td>Mean baseline A1C (%)</td>
<td>8.7</td>
<td>8.7</td>
<td>8.1</td>
<td>8.2</td>
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<tr>
<td>Mean placebo-corrected A1C difference (%)†</td>
<td>−0.4</td>
<td>−0.7 (0.5 mg dose)</td>
<td>−0.24 (10 mg dose)</td>
<td>−0.36 (25 mg dose)</td>
</tr>
<tr>
<td>Median follow-up duration (years)</td>
<td>3.8</td>
<td>2.1</td>
<td>3.1</td>
<td>2.4</td>
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<tr>
<td>3-point MACE RRR (%)</td>
<td><strong>13</strong></td>
<td><strong>26</strong></td>
<td><strong>14</strong></td>
<td><strong>14</strong></td>
</tr>
<tr>
<td>3-point MACE ARR (%)</td>
<td>1.9</td>
<td>2.3</td>
<td>1.6</td>
<td>—†</td>
</tr>
<tr>
<td>CV death RRR (%)</td>
<td><strong>22</strong></td>
<td>2</td>
<td><strong>38</strong></td>
<td>4§; 13</td>
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<tr>
<td>Nonfatal MI RRR (%)</td>
<td>12</td>
<td>26</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Nonfatal stroke RRR (%)</td>
<td><strong>11</strong></td>
<td><strong>39</strong></td>
<td>+24</td>
<td>10</td>
</tr>
<tr>
<td>All-cause mortality RRR (%)</td>
<td><strong>15</strong></td>
<td>+5</td>
<td><strong>32</strong></td>
<td>13§; 10</td>
</tr>
<tr>
<td>HF hospitalization RRR (%)</td>
<td>13</td>
<td>+11</td>
<td><strong>35</strong></td>
<td><strong>33</strong></td>
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<tr>
<td>Worsening nephropathy RRR (%)†</td>
<td><strong>22</strong></td>
<td><strong>36</strong></td>
<td><strong>39</strong></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

Cefalu, W et al, Diabetes Care Volume 41, January 2018
The cardiovascular benefits with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) in participants with and without a history of heart failure

**EMPA-REG OUTCOME**

- No history of heart failure: HR 0.63 (0.51, 0.78)
- History of heart failure: HR 0.72 (0.50, 1.04)

**CANVAS Program**

- No history of heart failure: HR 0.87 (0.72, 1.06)
- History of heart failure: HR 0.61 (0.46, 0.80)
Renal outcomes in the EMPA-REG OUTCOME trial and CANVAS

Verma and McMurray (2018) Diabetologia
DOI 10.1007/s00125-018-4670-7
• The most striking results and the first major positive study was the EMPA-REG Outcome study in 2015, followed by the LEADER Trial in 2016, the SUSTAIN trial also in 2016 and the CANVAS trial in 2017.

• The EMPA-REG outcome trial showed the benefit of empagliflozin (sodium-glucose cotransporter inhibitor) on SGLT-2 inhibitors, primarily in the reduction of heart failure and later in preserving renal function. Both were a surprise to many.

• After all, the initial interest in the drug was due to the effect on inhibiting the reabsorption of glucose, causing glucosuria.
  
  • Why should they be so protective?
Cardiovascular protection by SGLT2 inhibitors

Diabetes-associated ventricular remodelling

- Left ventricle hypertrophy
- ↑ Cytokines and inflammation
- ECM remodeling
- Impaired cardiac metabolism
- CMC apoptosis

Healthy heart

Verma and McMurray (2018) Diabetologia
DOI 10.1007/s00125-018-4670-7
SGLT2 inhibitors improve ventricular loading conditions

Verma and McMurray (2018) Diabetologia
DOI 10.1007/s00125-018-4670-7
SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics.
The nexus of metabolic changes contributing to reduced plasma glucose and adiposity following inhibition of SGLT2
Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2

Fig. 1 Recognized major risks and benefits of SGLT2 inhibitors.
Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors).

• Reduce HbA1c by ~0.8%, can reduce weight, and do not cause hypoglycemia.

• Empagliflozin and canagliflozin
  – decrease major adverse cardiovascular events (MACE), heart failure, and the progression of CKD.

• SGLT2 inhibitors increase urine volume and increase urogenital candida infections.
  – Because adverse effects related to volume depletion were more frequent in older patients treated with canagliflozin, recommendations limit the dosage to 100 mg/d in such patients.

• Canagliflozin is associated with a decrease in bone mineral density at the hip, but not the femoral neck, lumbar spine, or distal radius.
  – Significant increase in fractures of arms and legs but not the spine.

• Very rare cases of diabetic ketoacidosis have been reported in patients with T2D taking SGLT2 inhibitors, including patients over the age of 65 years.
Adverse Effects of SGLT-2 Inhibitors

- Genitourinary infections
- Diabetic ketoacidosis: Most frequent in Type 1 diabetes but may occur in Type 2
- Amputations: Only noted with canagliflozin
- Skeletal fractures: Only noted with canagliflozin
- Volume depletion: May cause falls. More hazardous in the elderly or those with autonomic neuropathy and renal disease
- Acute kidney injury: Particularly with canagliflozin and dapagliflozin
- Risk of cancer: Possibly with bladder cancer and empagliflozin
GLP-1 receptor agonists

Glucagon-like peptide 1 in health and disease

Andreas Andersen, Asger Lund, Filip K. Knop, and Tina Vilsbøll

Published online: 04 May 2018
<table>
<thead>
<tr>
<th>Drug</th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EXSCEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design and salient features</td>
<td>Enrolled 6068 patients with T2DM and recent coronary event within 180 d; Median DM duration 9.2 yr; Median follow up 25 mo</td>
<td>Enrolled 9340 patients with T2DM and with high CV risks; Median DM duration 12.8 yr; Median follow up 3.8 yr</td>
<td>Enrolled 3297 patients with T2DM and established CV disease or with high CV risks; Median DM duration 13.2 yr and 14.1 yr in low dose and high dose treatment group, respectively; Median follow up 104 wk</td>
<td>Enrolled 14752 patients with T2DM at a wide range of CV risk; Approximately 27% of patients without known CV disease; Median DM duration 12 yr; Median follow up 3.2 yr; 43% subjects prematurely discontinued exenatide</td>
</tr>
<tr>
<td>Primary endpoint/MACE</td>
<td>No significant difference in MACE-4</td>
<td>13% reduction in MACE</td>
<td>26% reduction in MACE</td>
<td>9% reduction in MACE&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>No significant difference in death from CV causes; No significant differences in rate of hospitalization for heart failure</td>
<td>22% reduction in death from CV causes&lt;sup&gt;2&lt;/sup&gt;; 15% reduction in all-cause mortality&lt;sup&gt;2&lt;/sup&gt;</td>
<td>39% reduction in nonfatal stroke; 26% reduction in nonfatal myocardial infarction&lt;sup&gt;3&lt;/sup&gt;; No significant difference in CV death or all-cause mortality</td>
<td>14% reduction in all-cause mortality&lt;sup&gt;4&lt;/sup&gt;; No significant differences in death from CV causes</td>
</tr>
</tbody>
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**Table 1** Summary of cardiovascular outcome trials of glucagon-like peptide-1 receptor agonists

<table>
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<th>Drug</th>
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<tr>
<td></td>
<td>Lixisenatide</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Exenatide</td>
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</tr>
</tbody>
</table>
Fig. 1 | Effects of GLP1 and GLP1RAs on various tissues.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Approval year</th>
<th>Structure based on exendin 4 or GLP1</th>
<th>Administration</th>
<th>Dose</th>
<th>Half-life</th>
<th>Elimination</th>
<th>Antibody development (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting GLP1RAs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Exenatide twice daily</td>
<td>2005</td>
<td>Exendin 4</td>
<td>Twice daily</td>
<td>5–10 μg</td>
<td>2.4 hours</td>
<td>Mainly renal</td>
<td>35 (REF. 51)</td>
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<tr>
<td>Lixisenatide</td>
<td>2016</td>
<td>Exendin 4</td>
<td>Once daily</td>
<td>10–20 μg</td>
<td>3 hours</td>
<td>Mainly renal</td>
<td>56–70 (REFS 50,56)</td>
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<tr>
<td><strong>Long-acting GLP1RAs</strong></td>
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<tr>
<td>Liraglutide</td>
<td>2010</td>
<td>GLP1</td>
<td>Once daily</td>
<td>0.6–1.8 mg</td>
<td>13 hours</td>
<td>Peptidases, renal (6%) and faecal (5%)</td>
<td>8.6 (REF. 68)</td>
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<tr>
<td>Exenatide once weekly</td>
<td>2012</td>
<td>Exendin 4</td>
<td>Once weekly</td>
<td>2 mg</td>
<td>NA</td>
<td>Mainly renal</td>
<td>57 (REF. 55)</td>
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<td>Albilglutide</td>
<td>2014</td>
<td>GLP1</td>
<td>Once weekly</td>
<td>30–50 mg</td>
<td>5 days</td>
<td>Peptidases and renal</td>
<td>5.5 (REF. 69)</td>
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<tr>
<td>Dulaglutide</td>
<td>2014</td>
<td>GLP1</td>
<td>Once weekly</td>
<td>0.75–1.5 mg</td>
<td>4.7 days</td>
<td>Peptidases and renal</td>
<td>1.6 (REF. 59)</td>
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<td><strong>Emerging GLP1RAs</strong></td>
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<tr>
<td>Semaglutide</td>
<td>2017&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GLP1</td>
<td>Once weekly</td>
<td>0.5–1.0 mg</td>
<td>165 hours</td>
<td>Peptidases and renal</td>
<td>0.01–3.50 (REFS 83,130,131)</td>
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<tr>
<td>Efpeglenatide</td>
<td>Phase III initiated Oct 2017</td>
<td>Exendin 4</td>
<td>Once monthly</td>
<td>NA</td>
<td>NA</td>
<td>Mainly renal</td>
<td>20–31 (REF. 132)</td>
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<tr>
<td>ITCA 650 (Subdermal release of exenatide)</td>
<td>Awaiting approval</td>
<td>Exendin 4</td>
<td>Up to 12 months after implantation</td>
<td>20–60 μg daily</td>
<td>NA</td>
<td>Mainly renal</td>
<td>NA</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; GLP1, glucagon-like peptide 1; GLP1RA, GLP1 receptor agonist; NA, not available. *Currently not marketed.
Figure 1.
(a) Chronic administration of glucagon-like protein-1 receptor (GLP-1R) agonists has been shown to affect renal hemodynamics through decreasing the estimated glomerular filtration rate (eGFR).

(b) The antialbuminuric actions of GLP-1R agonists on kidneys involve effects on multiple mechanisms of diabetic nephropathy.

Greco, EV, et al. Medicina 2019, 55,233; doi:10.3390
Side Effects of GLP-1 Receptor Agonists

- Nausea, vomiting, diarrhea
- Gastroparesis (reversible)
- Antibody development (limiting efficiency)
- Injection site reaction
- Headaches
- Sinus tachycardia
- Abdominal pain and distension
- Possible pancreatitis
- Rarely hypersensitivity reaction
- Contraindicated in
  - MEA-2 (multiple endocrine adenomatosis type 2)
  - Medullary thyroid cancer
Insulin

• Endocrine Society uses insulin when oral agents do not work.
• I usually begin it if HbA1c >9% or diagnostic CGM shows glucose >200 often despite current Rx
• The ES points out that insulin glargine U-300 and insulin degludec, which both are longer duration than glargine U-100, are less likely to cause hypoglycemia and less variability with similar glucose control.
• The ES also notes that a more complex insulin regimen may be hard to follow correctly. I agree. It needs to be frequently reevaluated.
Insulin Therapy:

- Insulin therapy should be given with great care and oversight
- Check for nocturnal hypoglycemia with CGMS at any significant change and at the outset
- Re-examine insulin requirements frequently
- Basal insulin is safer than basal bolus but may not be sufficient
- Declining renal function, worsening CHF, decreasing weight, increased cognitive dysfunction should increase risk of insulin therapy without significant change
Summary:

• SGLT-2 inhibitors are very useful in heart failure where some renal function is preserved, but not used if creatinine clearance is <45cc/min

• Three GLP-1 receptor agonists (liraglutide, semaglutide, long-acting exenatide) have demonstrated efficacy in CVOT’s in reducing adverse CV outcomes, primarily in ischemic heart disease

• Insulin is generally neutral with respect to heart failure outcomes and long-term may be useful in reducing coronary heart disease. However, hypoglycemia in vulnerable patients may worsen ischemic heart disease and precipitate an event.
Overtreatment & Undertreatment of Older Patients with Diabetes

- The medications most often associated with hypoglycemia are insulin and sulfonylurias.
- The factors that predispose to hypoglycemia in elderly patients are:
  - Decreased renal function
  - Decreased hepatic function
  - Sarcopenia
  - Defective counterregulatory mechanisms
  - Decreased cognitive function
  - Decreased vision
  - Polypharmacy
  - Decreased appetite
  - Decreased caloric intake
  - Non-adherence to medication
  - Poverty
  - Social isolation
How do we assess effectiveness of therapy?

• Is HbA1c a good marker for safe glycemic control in the elderly?
  • The answer is probably no.
  • Munshi showed in 2017 that in nursing homes, patients with HbA1c ≥9% frequently had severe hypoglycemia revealed by CGMS
  • Poor glycemic control in elderly increases the risk from infections, dehydration, delirium and falls, as well as higher risk of CHF and worsening microvascular complications
• HbA1c in the elderly is affected by factors (non-glycemic) that alter HbA1c levels
• Examples:
  – Iron deficiency
  – B12 deficiency
  – Hemolysis
  – Infections – shortens RBC survival
  – Renal failure
  – Erythropoiten usage

Increases HbA1c

Decreases HbA1c
Strengths and Weaknesses of Other Commonly Used Medications in Diabetes Care
Metformin

- Metformin remains the mainstay of treatment of type 2 diabetes in patients with cardiovascular disease
- It is a first line drug because the drug:
  - Effect is neutral regarding heart failure
  - Does not cause hypoglycemia
  - Does not cause weight gain
  - Excellent safety profile
  - Few drug interactions
  - Safe in pregnancy
  - Very rarely if ever causes lactic acidosis
  - May reduce risk of cancer
  - May have cardiovascular benefit
Limitations of Metformin

- Contraindicated if creatinine clearance <15mL/min or patient is on dialysis
- GI intolerance is common and is dose related
- Elderly patients may develop GI intolerance later in the course of therapy, often long-acting preparation in lower dosage is effective (e.g. metformin XR 500 mg daily)
- CRF stage 3 requires a dose reduction
- Usually not used with creatinine clearance <30ml/min
- B12 deficiency is common
- Often needs careful titration
Sulfonylureas and glinides.

- Inexpensive, most useful in new onset younger patients with mild hyperglycemia
- SUs, repaglinide, and nateglinide can cause hypoglycemia and weight gain.
- Glyburide should be avoided in older individuals because of a substantially increased risk of hypoglycemia compared with that of glimepiride and glipizide
Thiazolidinediones.

- Excellent choice for young, non-obese males with fatty liver disease
- Not safe in pregnancy
- Pioglitazone and rosiglitazone can cause fluid retention and may precipitate or worsen heart failure; indeed, these drugs are contraindicated in patients with class III and IV heart failure
- Furthermore, these medications are associated with increased fracture rates and bone loss in women; thus, use in older women with underlying bone disease, such as osteoporosis, could potentially be problematic.
Dipeptidyl peptidase-4 inhibitors.

• Excellent choice for patients with no heart disease, generally well controlled diabetes in whom injectables are not wanted and hypoglycemia risk is high

• Dipeptidyl peptidase-4 (DPP-4) inhibitors are generally well tolerated.

• Importantly, early concerns regarding an increased risk of pancreatitis have not been borne out

• Some DPP-4 inhibitors have been associated with heart failure

• Avoid use with moderate to severe renal disease

LeRoith et al Diabetes in Older Adults Guidelines, J Clin Endo Metab, May 2019
a-Glucosidase inhibitors.

• Rarely used because of side effects
• Modest efficacy, and in older individuals, the gastrointestinal adverse effects of flatulence and diarrhea tend to cause a relatively high rate of nonadherence.
Clinical Correlation

• Metformin is safe to use and continues to be a mainstay in CAD and CHF -
  – If renal function is at least marginal (creatinine clearance 30cc/min).
  – Dose should be adjusted if creatinine clearance is <45 cc/min
• Sulfonylureas are generally not helpful in lowering CV risks and events and may worsen the CV outcomes, particularly in the elderly.
• DPP-4’s are limited in efficacy and saxagliptin has been shown to increase the risk of heart failure
• α-glucosidase inhibitors such as acarbose may reduce CV risk but probably have no value in many patients
Individualization of therapy is best – match therapy to the patient

Examples:

– Empagliflozin for CHF patients who have only moderately decreased renal function

– Liraglutide for patients with established ischemic heart disease and morbid obesity

– Thiazolidines have multiple risks in the elderly and should be used in highly selective circumstances

– However, glyburide should never be used in elderly patients and sulfonylureas are to be discouraged

– DPP-4 inhibitors can be used in a patient not prone to CHF who has severe hypoglycemic unresponsiveness and cannot manage injectables
Therapy in older patients

• Individualize therapy in older patients
• Insulin requirements usually decrease
• Be sure that patient can afford the regimen
• Be sure you know who can provide help to the patient and avoid burdening patients with no social support by providing demanding and complicated therapies
• Use agents that have proven cardiovascular benefit in patients with established CVD
• Monitor for hypoglycemia
Case for Discussion –
Should we change this patient's diabetes regimen?

- R.S. is an 84 y/o w/m who had had diabetes for 24 years
- He has a 30 year history of hypertension
- He had two cardiac stents placed 11 years ago
- He is obese at 224 lbs. with a BMI of 36.8
- He is taking carvedilol, losartan, glipizide, and 46 units of Lantus daily
- His HbA1c has been between 8.2 and 9% for most years
- He has some decreased in kidney function and complains of numbness of his feet and frequent falls
- He also has morning hypoglycemia
- He would like a second opinion
Diagnostic continuous glucose monitoring data
Analysis

• His obesity suggests that medications that are either weight neutral or associated with weight loss would be preferable
  • Metformin
  • GLP-1 receptor agonist
  • SGLT-2 cotransporter inhibitor
  – Rather than
    • Insulin
    • Thiazolidinedione
    • Sulfonylureas
    • Glinids
• However, lifestyle changes remain key. Sustained weight loss requires a decrease in caloric intake.
Ischemic Heart Disease

Suggestions
- GLP-1 agents have positive value and agents that do not cause hypoglycemia are safer
- Metformin should be added
- DPP-4 can be considered but not if heart failure is likely

The history of shortness of breath led to an echocardiogram being performed which showed severe diastolic dysfunction which is a precursor to heart failure
- SGLT-2 agents are useful and should be considered, unless a contraindication exists
  - If creatinine clearance is <45 ml/min, they would not be used
  - Thiazolidinediones should not be used in this patient
- Saxagliptin is unwise
Frequent morning hypoglycemia

- Sulfonylureas should be stopped
- Insulin should be reduced
- CGMS should be considered
- Non-hypoglycemia causing agents are safer
Clinical Summary

- The patient was diagnosed with peripheral neuropathy.
- A bone density showed severe osteoporosis and a sleep study showed sleep apnea.
- CGMS was begun (personal Libre) and diet habits were changed.
- Patient began a supervised exercise program
- Educated about falls
- Mini-mental status exam revealed good score, patient considered regimen not too complex and diabetes educator agreed.
Clinical Summary

- Glipizide stopped
- GLP-1 receptor agonist once weekly begun and well tolerated
- Long acting insulin reduced

Later,
- Low dose SGLT-2 added
- HbA1c improved, hypoglycemia disappeared

Three years later,
- Suppertime insulin added when efficacy of GLP-1 receptor appeared to decline
Conclusion:

• There are new medications which have proven efficacy in patients with both diabetes and cardiovascular disease
• Treatment should be individualized
• Some medications should be narrowly targeted
• Co-morbid conditions should be used in the choice of therapy