Non-Insulin Medications for Hyperglycemia Treatment in Type 2 Diabetes

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Nothing to Disclose
Objectives

• Discuss pathophysiologic approach to hyperglycemia treatment
• Review Diabetes Audit glycemia and treatment trends
• Assess medication treatment guidelines with emphasis on SGLT-2 inhibitors and GLP-1 Receptor Agonists
Progression of DM Type 2

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Pathophysiologic Approach to the Treatment of Hyperglycemia in Type 2 Diabetes

Hyperglycemic Stress and Need for More Insulin
- Increased insulin resistance: obesity, other causes
- Increased gastric emptying, glucose absorption
- Increased glucagon secretion
  - Increased hepatic glucose output
- Increased renal tubular reabsorption

Beta-cell Failure
- Decreased insulin secretion to high glucose
- Decreased first-phase insulin response

Agents for Reduction
- Weight loss, exercise, TZDs, dopamine agonist
- Decrease calorie, GLP-1 RA, a-Gl, colesevelam
- DPP-4 Inhibitor; GLP-1 RA
  - Metformin
- SGLT-2 Inhibitor

Agents for Stimulation/Replacement
- Sulfonylurea; glinide; insulin
- GLP-1 RA; DPP-4 Inhibitor
Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present and Future

Questions

• Do non-insulin medications prevent and/or delay beta-cell failure?
  • Which medications?
  • What about combinations or more aggressive treatment?

• Do these agents decrease complications independent of hyperglycemia reduction?
  • Microvascular and macrovascular?
  • What are the mechanisms?
Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

- What medications maintain long-term glycemic control in type 2 diabetes?
- 5-year, randomized, double-blind clinical trial involving 4,360 treatment-naïve, newly diagnosed type 2 DM subjects (96%–97% were < 2 years of Dx)
  - Randomized to metformin 1,000 mg BID (N = 1,454), glyburide 7.5 mg BID (N = 1,441), or rosiglitazone 4 mg BID (N = 1,456)
  - Mean age 56–57 years old; male 55%–59%; mean BMI 32; mean weight 91–92 kg
  - Average FPG 151 mg/dL, A1c 7.4%, HOMA-B was used to measure beta-cell function (%)
  - Primary Outcome: Time to Fasting Plasma Glucose > 140 mg/dL

- Side Effects
  - Hypoglycemia and weight gain with glyburide
  - Edema and weight gain with rosiglitazone
  - Rates of CHF were similar between metformin and rosiglitazone
  - More GI side effects were seen with metformin

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy (1)

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy (2)

Management of Hyperglycemia in Type 2 Diabetes, 2018 Recommendations

- Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes.
- The stepwise addition of glucose-lowering medication is generally preferred to initial combinations therapy.
- Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications.
- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medication.
- Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- The selection of medications added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific adverse medication effects, particularly hypoglycemia and weight gain; as well as safety, tolerability and cost.

Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes (VERIFY Study)

- Can early combination treatment versus stepwise approach lead to sustained good glycemic control in early type 2 diabetes?
- 5-year, multicenter, randomized, double-blind clinical trial in recently-diagnosed type 2 DM subjects (< two years diagnosis; N = 2,001 patients)
  - Eligibility: treatment-naïve subjects with A1c level between 6.5–7.5%
  - Design: Period 1: metformin (500–1,000 mg BID) versus metformin + vildagliptin* (50–500 mg or 50–1000 mg BID) or maximally tolerated doses. Period 2: vildagliptin added to metformin treatment failure group from Period 1.
  - Outcome: treatment failure A1c > 7.0% at two consecutive visits (13 weeks)
- Results and Summary
  - Less treatment failure over five years with dual therapy initiation than stepwise approach; a relative risk reduction of 49%.
  - Longer durability within treatment goal (A1c < 7%) with initial combination therapy.


*Vildagliptin is a DPP-4 Inhibitor similar to sitagliptin, saxagliptin, linagliptin, and alogliptin; available in Europe but not in the U.S.
Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

• 36-center, randomized, unmasked, parallel treatment group controlled clinical trial comparing the effectiveness of commonly used second medications in metformin-treated patients with type 2 diabetes.

• Eligibility: Patients with type 2; < 10 years of diagnosis (initial < 5 years), age 30 years and older (except AI/AN > 20 years), and A1c level 6.8%–8.5%

• Medications (background metformin dose 2000 mg daily)
  • Sulfonylurea (glimepiride), N = 1,254
  • Dipeptidyl Peptidase-4 Inhibitor (sitagliptin), N = 1,268
  • Glucagon-Like Peptide-1 Receptor Agonist (liraglutide), N = 1,262
  • Basal Insulin (glargine), N = 1,254

• Primary Outcome: Time to initial treatment failure, A1c > 7 %

• Baseline Characteristics
  • Mean age 57.2 years (41.6% > 60 years old); 63.6% males; 65.7% white, 19.8% black, 18.4% Hispanic
  • Duration of diabetes 4.2 years; mean BMI 34.3; % BP < 140/90, 75.3%; cigarette smoking 13.8%
  • History: family with DM 69.8%, MI/Stroke 6.5%, retinopathy 1.0%, neuropathy 21.5%, HTN 66.6%
  • Medications: BP medication 69.2%, statin 63.6%, ASA 45.3%, depression/anxiety 18.9%

Lowering the Risk of Diabetes Complications

- Foremost: Hyperglycemia management, A1C < 7 (individualize)
- Addressing other co-morbid conditions
  - Blood pressure < 140/90
  - Statin therapy for high risk; targeting LDL cholesterol
  - RAS Inhibitor
  - Anti-platelet treatment
  - Smoking cessation
  - Lifestyle changes for weight loss
  - Recommended screenings and early treatment
## Approach to Individualization of Glycemic Targets

**Glycemic Targets: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43 (Suppl. 1): S66–S76**

### Approach to Individualization of Glycemic Targets

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Patient preference</td>
<td>highly motivated, excellent self-care capabilities</td>
<td>preference for less burdensome therapy</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
</table>


What glucose-lowering medications are patients using?
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Efficacy (Decreased A1c)</th>
<th>Other Benefits</th>
<th>Side effects; Caution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (biguanide)</td>
<td>Decrease Hepatic glucose production</td>
<td>1.0–2.0% Decrease</td>
<td>CVD; Dementia; Cost</td>
<td>GI symptoms; Need eGFR &gt; 30 ml/min</td>
<td>B12 deficiency Lactic Acidosis</td>
</tr>
<tr>
<td>Sulfonylurea/Glinides</td>
<td>Stimulate insulin secretion-SUR/K+ATPase</td>
<td>1.0–2.0% Decrease</td>
<td>CVD neutral/worsening; Cost</td>
<td>Hypoglycemia; Weight Gain</td>
<td>Accelerates beta-cell failure?</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Inhibit degradation of GLP-1; increase insulin/decrease glucagon</td>
<td>0.5–1.0% Decrease</td>
<td>CVD neutral; Weight neutral</td>
<td>Pharyngitis, pemphigous; HF hospitalization – saxagliptin, alogliptin</td>
<td>All indications; renal dose adjustment (not linagliptin)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin receptor activation</td>
<td>Unlimited decrease (&gt; 2.5%)</td>
<td>Inpatient, surgical, and pregnancy use; Weight gain</td>
<td>Hypoglycemia; Weight Gain</td>
<td>Many options</td>
</tr>
</tbody>
</table>

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43 (Suppl. 1): S99–S110
Question

• Do non-insulin medications decrease complications, independent of hyperglycemia reduction?
  • Microvascular and macrovascular?
  • What are the mechanisms?
ADA Standards of Medical Care in Diabetes – 2020

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020. Diabetes Care 2020; 43 (Suppl. 1): S99–S110
### Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) and Sodium Glucose CoTransporter-2 (SGLT-2) Inhibitor Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Efficacy (Decreased A1c)</th>
<th>Other Benefits</th>
<th>Side effects; Caution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Stimulate GLP-1 receptors; Increase insulin/decrease glucagon, delay gastric emptying, decrease appetite</td>
<td>Decreased 1.0–2.0%</td>
<td>Decreased CVD (liraglutide, semaglutide, dulaglutide) CKD Weight loss</td>
<td>GI problems; Injection site issues; Pancreatitis; Medullary Thyroid CA; Renal assessment for exenatide, lixisenatide</td>
<td>Cost; Injectable; Nausea/vomiting major side effect</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>(exenatide, liraglutide, semaglutide*, dulaglutide, lixisenatide)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>Inhibit Sodium Glucose Co-transporter 2; increase glycosuria</td>
<td>Decreased 0.5–1.0%</td>
<td>Decreased CVD, CVD Mortality, HF Hospitalization, CKD, SBP Weight loss</td>
<td>Need eGFR &gt; 45 ml/min UTI &amp; genital mycotic; amputation (cana); bone fracture (cana); acute kidney injury; DKA; Fournier’s gangrene</td>
<td>Cost; Monitor renal function</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>(empagliflozin, canagliflozin, dapagliflozin, ertugliflozin^)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(semaglutide, oral and injectable formulations are FDA approved; ^ertugliflozin without CVD outcomes studies)*

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020. Diabetes Care 2020; 43 (Suppl. 1): S99-S110
## CVD Intervention Trials: GLP-1 RA Medications

<table>
<thead>
<tr>
<th>Medication (Study, N)</th>
<th>Type of Patients</th>
<th>Mean Duration</th>
<th>MACE Hazard Ratio</th>
<th>Secondary Outcomes (HR)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (daily) (LEADER 9340)</td>
<td>Known CVD 81%</td>
<td>3.8 years</td>
<td>0.87 (p=0.01) 13% vs. 14.9%</td>
<td>CV Mortality (0.85) 4.7% vs 6.0%</td>
<td>MACE = 53 Death = 71</td>
</tr>
<tr>
<td>Semaglutide (weekly) (SUSTAIN 3297)</td>
<td>Known CVD 83%</td>
<td>2.1 years</td>
<td>0.74 (p=0.02) 6.6% vs. 8.9%</td>
<td>CV Mortality (0.98) 2.7% vs 2.8%</td>
<td>MACE = 43</td>
</tr>
<tr>
<td>Exenatide Weekly (EXSCEL 14,752)</td>
<td>Known CVD 70%</td>
<td>3.2 years</td>
<td>0.91 (p=0.061) 11.4% vs. 12.2%</td>
<td>CV Mortality (0.86) 4.6% vs 5.2%</td>
<td>~100 Death=~150</td>
</tr>
<tr>
<td>Lixisenatide (daily) (ELIXA 6068)</td>
<td>Acute Coronary Syndrome Hx</td>
<td>2.1 years</td>
<td>1.02 13.4% vs. 13.2%</td>
<td>Mortality (0.96) lower Albuminuria</td>
<td>NA</td>
</tr>
<tr>
<td>Dulaglutide (weekly) (REWIND 9,901)</td>
<td>Known CVD 31.5%</td>
<td>5.4 years</td>
<td>0.88 (p=0.02) 12.0% vs. 13.4%</td>
<td>CV Mortality (0.90)</td>
<td>MACE = 60 CVD Hx 18</td>
</tr>
<tr>
<td>Oral Semaglutide (daily) (PIONEER 3183)</td>
<td>Known CVD 85%</td>
<td>1.4 years</td>
<td>0.79 (p=0.01) 3.8% vs. 4.8%</td>
<td>CV Mortality (0.49) 0.9% vs. 1.9%</td>
<td>MACE = 100</td>
</tr>
</tbody>
</table>

MACE: CVD death, Nonfatal MI, Nonfatal stroke
## CVD Intervention Trials: SGLT-2 Inhibitor

<table>
<thead>
<tr>
<th>Medication (Study, N)</th>
<th>Type of Patients</th>
<th>Mean Duration</th>
<th>MACE Hazard Ratio</th>
<th>Secondary Outcomes (HR)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empagliflozin</strong></td>
<td>Known CVD 99%</td>
<td>3.1 years</td>
<td>0.86 (p=0.04)</td>
<td>CV Death 0.62 3.7% vs. 5.9% HF 0.65, 2.7% vs. 4.1%</td>
<td>MACE = 59 CV Death = 45 HF = 71</td>
</tr>
<tr>
<td>(EMPA-REG 7020)</td>
<td></td>
<td></td>
<td>10.5% vs. 12.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canagliflozin</strong></td>
<td>Known CVD 71%</td>
<td>3.6 years</td>
<td>0.86 (p=&lt;0.02)</td>
<td>HF 0.67, 1.5% vs 3.0%</td>
<td>MACE = 80–100</td>
</tr>
<tr>
<td>(CANVAS 4,330; CANVAS-R 5,812)</td>
<td></td>
<td></td>
<td>9.5% vs. 10.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dapagliflozin</strong></td>
<td>Known CVD 40%</td>
<td>4.2 years</td>
<td>0.93 (p=0.17)</td>
<td>HF 0.73 (p=0.005) 2.5% vs 3.3%</td>
<td>MACE= NA HF= 111</td>
</tr>
<tr>
<td>(DECLARE 17,160)</td>
<td>CVD Risk Factors 60%</td>
<td></td>
<td>8.8% vs 9.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MACE:** CVD death, Nonfatal MI, Nonfatal stroke
Association of Heart Failure with Anti-Diabetes Medications

• Worsening and/or cause of heart failure hospitalization
  • Effect of Rosiglitazone on the frequency of diabetes inpatients with IGT or IFG: a randomized controlled trial. Lancet 2006; 368: 1096–1105.
  • EXAMINE; heart failure and mortality outcomes with alogliptin in patients with type 2 DM. Lancet 2015; 385: 2067–76.

• No effect on cardiac heart failure (CHF)
  • Linagliptin CARMELINA. JAMA 2019; 321: 69–79.

• Improvement of CHF and CHF mortality
  • Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in EMPA-REG OUTCOME Trial. Circulation 2019; 139: 1384–95. DOI: 10.1161/CIRCULATIONAHA.118.037778.
  • Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS); N Engl J Med 2017; 377: 644–657. DOI: 10.1056/NEJMoa1611925
## CKD Outcomes: SGLT-2 Inhibitor and GLP-1 RA Medications

<table>
<thead>
<tr>
<th>Medication (Study, N)</th>
<th>Type of Patients</th>
<th>Mean Duration</th>
<th>CKD Hazard Ratio</th>
<th>Secondary Outcomes (HR)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Empagliflozin</strong> (EMPA-REG 7020)</td>
<td>75% eGFR &gt;60, 60% w UACR&lt;30, High-Risk CVD (99%)</td>
<td>3.1 years</td>
<td>0.61&lt;br&gt;12.7% vs. 18.8%</td>
<td>Doubling Cr (0.66)&lt;br&gt;CVD death (0.71); HF (0.61)</td>
<td>CKD = 16 (CVD = 90)</td>
</tr>
<tr>
<td><strong>Canagliflozin</strong> (CREEDENCE 4,401)</td>
<td>CKD 2-3, eGFR ≥ 60 (1/3), 30- &lt;45 (1/3), 45 -&lt; 60 (1/3) UACR &gt;300, 50% w CVD</td>
<td>2.6 years</td>
<td>0.70&lt;br&gt;(ESRD-0.68)&lt;br&gt;11.1% vs. 15.5%</td>
<td>CVD (0.80)&lt;br&gt;8.1% vs 11.5%&lt;br&gt;HF (0.61), 4.0% vs. 6.4%</td>
<td>CKD = 23 (CVD = 30) (HF = 42)</td>
</tr>
<tr>
<td><strong>Dapagliflozin</strong> (DECLARE8,162)</td>
<td>95% eGFR &gt; 60, UACR &lt; 30 (71%), 40% CVD, 60% Risk</td>
<td>4.2 years</td>
<td>0.54, 4.3% vs 5.6% eGFR, 1.4% vs. 2.5%</td>
<td>ESRD/Death (0.41)&lt;br&gt;0.1% vs. 0.3%</td>
<td>CKD = 77</td>
</tr>
<tr>
<td><strong>Liraglutide</strong> (LEADER 9340)</td>
<td>Known CVD 81%</td>
<td>3.8 years</td>
<td>0.78&lt;br&gt;5.7% vs. 7.2%</td>
<td>CVD 0.87&lt;br&gt;13% vs. 14.9%</td>
<td>CKD = 71</td>
</tr>
<tr>
<td><strong>Dulaglutide</strong> (REWIND 9,901)</td>
<td>Known CVD 31.5%</td>
<td>5.4 years</td>
<td>Improved CKD 0.85</td>
<td>CV Mortality (0.90)</td>
<td></td>
</tr>
</tbody>
</table>

CKD: doubling creatinine, renal replacement, progressing or incident albuminuria, sustained eGFR decrease > 40% to < 60 ml/min
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF²

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower extremity artery stenosis ≥50%, or LVH)

PREFERABLY
- GLP-1 RA with proven CVD benefit¹
  OR
- SGLT2i with proven CVD benefit¹
    if eGFR adequate⁶

If A1C above target
- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹
  - DPP-4i if not on GLP-1 RA
  - Basal insulin⁴
  - TZD⁵
  - SU⁵

HF OR CKD PREDOMINATES
- Particularly HFpEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate⁶
  OR
- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate⁶ add GLP-1 RA with proven CVD benefit¹

If A1C above target
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin⁴
  - SU⁵

ADA Standards of Medical Care in Diabetes–2020
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020. Diabetes Care 2020; 43 (Suppl. 1): S99–S110
Clinical Experience (Dr. Arakaki) with GLP-1 RAs and SGLT-2 Inhibitors: Summary

- GLP-1 RA, liraglutide is effective in obese AI/AN patients with type 2 diabetes and high A1c level (mean 9.87%; BMI 41; N=98)
  - 68% decreased A1c level; 84% decreased weight
  - A1c level reduced on average 0.73%; weight loss average of 14 lbs.
  - Treatment response independent of initial BMI
  - Mean duration of treatment 369 days; well tolerated
  - GI side effects are common; 1 case of pancreatitis over 3 years

- SGLT-2 inhibitor, empagliflozin offered mixed results but the database of patients treated is small (N=17)
  - Slightly increased average A1c level; no effect on BP
  - Average weight loss of 10 lbs.
  - Mean duration of treatment 242 days; well tolerated
  - UTI/balanitis side effects noted
A drug class review of the Sodium-Glucose CoTransporter-2 inhibitors (SGLT2s) was performed. Clinical practice guidelines from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), the ACC, and the National Institute for Health and Care Excellence (NICE) were shared in supporting the role and use of SGLT2s. Cardiovascular outcomes trial (CVOT) findings for each medication were reviewed in detail which offered valuable insight. Internal IHS data of pharmacoepidemiologic and drug utilization trends and cost utility were used to add perspective to the review. Ultimately, the NPTC voted to add empagliflozin to the NCF.

A drug class review of the Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) was also provided. Medical literature reviewed in the evaluation included findings from CVOTs, various published meta-analyses, and practical guidance from the American Diabetes Association, AACE/ACE, NICE and European Society of Cardiology. Agency-specific medication procurement, utilization and pharmacoepidemiologic data were also reviewed. Following the comprehensive analysis, the NPTC voted to add either subcutaneous dulaglutide, liraglutide or semaglutide to the NCF (listed alphabetically only, no preference).

• No national “Use Criteria” for SGLT-2 inhibitors or GLP-1 Receptor Agonists. However, local pharmacies may elect to establish their own “use criteria.”

• Agency-wide distribution of NPTC Formulary Briefs are available on NPTC website for reference:
  • https://www.ihs.gov/NPTC/
Thank you for your attention. Questions or comments?
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.
Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial

<table>
<thead>
<tr>
<th>Blood Glucose</th>
<th>eGFR</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hba₁₀ &lt;7%</td>
<td>9/773 (1.2%)</td>
<td>0.42 (0.19-0.91)</td>
</tr>
<tr>
<td>Hba₁₀ 7 to &lt;8%</td>
<td>38/3317 (1.1%)</td>
<td>0.45 (0.31-0.66)</td>
</tr>
<tr>
<td>Hba₁₀ 8 to &lt;9%</td>
<td>41/2193 (1.9%)</td>
<td>0.73 (0.49-1.09)</td>
</tr>
<tr>
<td>Hba₁₀ &gt;9%</td>
<td>39/2297 (1.7%)</td>
<td>0.48 (0.32-0.70)</td>
</tr>
<tr>
<td>eGFR &gt;90 ml/min per 1.73 m²</td>
<td>41/4137 (1.0%)</td>
<td>0.50 (0.34-0.73)</td>
</tr>
<tr>
<td>eGFR 60 to &lt;90 ml/min per 1.73 m²</td>
<td>65/3838 (1.7%)</td>
<td>0.54 (0.40-0.73)</td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min per 1.73 m²</td>
<td>21/606 (3.5%)</td>
<td>0.60 (0.35-1.02)</td>
</tr>
<tr>
<td>UACR &lt;30 mg/g</td>
<td>50/5819 (0.9%)</td>
<td>0.52 (0.37-0.74)</td>
</tr>
<tr>
<td>UACR 30-300 mg/g</td>
<td>39/2017 (1.9%)</td>
<td>0.59 (0.39-0.87)</td>
</tr>
<tr>
<td>UACR &gt;300 mg/g</td>
<td>31/594 (5.2%)</td>
<td>0.38 (0.25-0.58)</td>
</tr>
</tbody>
</table>

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