Update on Diabetes Drugs
Diabetes Update and Advances in Endocrinology and Metabolism

Lisa Kroon, PharmD, CDE
Chair and Professor of Clinical Pharmacy
UCSF School of Pharmacy

Disclosure
No conflict of interest to disclose
Learning Objectives

♦ Describe the mechanism of action and unique characteristics of the various (new) classes of medications used in type 2 diabetes that are recommended as 2nd line agents.

♦ Discuss contraindications, precautions for use, and side effect profiles of these medications.

♦ Select among the classes of medications to develop appropriate and effective medication regimens to improve glycemic control for an individual patient.

Diabetes: U.S. Impact


Diabetes (A1C ≥6.5%)

(12-14% in 2012)

JAMA

29.1 Million
(9.3%)

~1-1.5 Million
Type 1

~28 Million
Type 2

2/3
Diagnosed

1/3
Undiagnosed
(8.1 Million)

Pre-Diabetes
(A1C 5.7-6.4%)

86 Million
(37%; people age 20 and older)

50% of U.S. population has either prediabetes or diabetes
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

**Obesity (BMI ≥ 30 kg/m²)**

1994

![Obesity Map 1994](image)

2000

![Obesity Map 2000](image)

2013

![Obesity Map 2013](image)

Diabetes

1994

![Diabetes Map 1994](image)

2000

![Diabetes Map 2000](image)

2013

![Diabetes Map 2013](image)


**Medication Treatments (%) 2010-2012**

Medication Treatment Options To 2000

♦ Insulin (human and analogs)
♦ Sulfonylureas (1950’s)
♦ Biguanides (metformin; 12/94)
♦ Alpha-glucosidase inhibitors (Acarbose 9/95)
♦ Meglitinides (Repaglinide 12/97; Nateglinide 12/00)
♦ Thiazolidinediones (Rosiglitazone 5/99; Pioglitazone 7/99)

Medication Treatment Options Since 2005

♦ Amylin (pramlintide)
♦ Glucagon-like peptide receptors agonists (GLP-1 RAs)
♦ Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)
♦ Bile acid sequestrants (colesevelam)
♦ Dopamine agonist (bromocriptine)
♦ Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors)
Diabetes-Related Complications among U.S. Adults with and without Diagnosed Diabetes (1990–2010)

A Population with Diabetes

- Acute myocardial infarction
- Stroke
- Amputation
- ESRD
- Death from hyperglycemic crisis

Events per 10,000 Adult Population with Diagnosed Diabetes


B Population with or without Diabetes

- Acute myocardial infarction
- Stroke
- Amputation
- ESRD
- Death from hyperglycemic crisis

Events per 10,000 Overall Adult Population


DCCT: Cumulative Incidence of First Occurrence of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Disease

57% ↓ risk

UKPDS 10-year Cohort Data: Reductions with Intensive Vs. Conventional Therapy

A1C results: 7.0% vs 7.9%

For every 1% ↓ A1C, a 35% ↓ in risk of microvascular complications

UKPDS-10 year Follow-Up
Glucose Control
Holman RR et al. NEJM 2008;359:1577 [UKPDS 80]
3,277 patients (of 4,209) entered post-trial monitoring; seen annually for 5 years

Mean Glycated Hemoglobin: Difference between conventional and control groups lost within 1 year after study ended
**UKPDS-10 year Follow-Up**

**Clinical Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SFU and Insulin Groups Relative Risk (p-value)</th>
<th>Metformin Group Relative Risk (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DM-related endpoint</td>
<td>↓ 9% (0.04)</td>
<td>↓ 21% (0.01)</td>
</tr>
<tr>
<td>MI</td>
<td>↓ 15% (0.01)</td>
<td>↓ 33% (0.005)</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>↓ 24% (0.001)</td>
<td>↓ 16% (0.31)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>↓ 13% (0.007)</td>
<td>↓ 27% (0.002)</td>
</tr>
</tbody>
</table>

---

Holman RR et al. NEJM 2008;359:1577 [UKPDS 80]

---

**Antihyperglycemic Therapy in Type 2 Diabetes**

ADA. Standards of Medical Care-2016. Diabetes Care 2016;39;Suppl 1
Glycemic Goals

✓ HbA1c < 7.0% (mean PG ~150-160 mg/dl)
✓ Pre-prandial PG 80-130 mg/dl
✓ Post-prandial PG <180 mg/dl
✓ Individualization is key:
  - Tighter targets (<6.5%) – short duration of diabetes, long life expectancy, no significant CVD
  - Looser targets (<8.0%) – long-standing diabetes, limited life expectancy, advanced micro/macro complications, comorbidities, hypoglycemia prone, etc.

Avoidance of hypoglycemia

Diagram: Glycemic Control Algorithm

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>≤</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>≤</td>
<td>≤</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>≤</td>
<td>≤</td>
</tr>
</tbody>
</table>

Kendall DM, Bergenstal RM. © International Diabetes Center 2009


Tailored Approach to the Management of Hyperglycemia

Why Metformin as 1st Line?

♦ Demonstrated long-term impact on macrovasular complications
♦ Stimulates AMP-activated protein kinase, which ↓ hepatic glucose output
  – Inhibits mitochondrial respiratory chain, causing shift towards anaerobic metabolism (lactate is by-product) resulting in ↓ energy for gluconeogenesis
♦ +CV effects: ↓ TG, ↓ LDL-C, ↑ HDL-C; improves endothelial function
♦ Other effects: ? anticancer properties
♦ SE: GI (diarrhea, nausea, anorexia, metallic taste), lactic acidosis, vit B₁₂ deficiency
♦ No weight gain; no hypoglycemia (except when used in combo therapy)
♦ Affordable

Case Study

♦ MK, a 52 year old male, was diagnosed with type 2 diabetes. [A1C 8.1%; LDL-C 66; TG 148; HDL-C 53; BMI 32; BP 136/80]. Other medical problems include hypertension (on HCTZ 25 mg daily, benazepril 40 mg daily) and dyslipidemia (on atorvastatin 40 mg daily). He was started on metformin and over the next 2 months, the metformin is titrated to 1000 mg BID. His A1C is now 7.1%.

➢ What is your assessment of his glycemic control? Is he at goal?
Case Study, cont’d

♦ It is now 2 years later and MK still is taking metformin 1000 mg po BID.
♦ Labs: A1C 8.2% (was as low as 6.5% 1 year after starting metformin); eGFR 80; LFT’s wnl; BMI 28.
♦ What is your assessment?
  - What is his A1C goal?
  - What do you recommend?

Advancing to Dual Therapy

Combination Therapy:
Combine Agents with Different Mechanisms of Action
Incretin-Based Therapies

♦ Gut hormones released postprandially
♦ 2 main gut incretins
  - Glucose-dependent insulinotropic polypeptide (GIP)
    • Released by K cells in duodenum
  - Glucagon-like peptide-1 (GLP-1)
    • Released by L cells in small intestines
    • Levels are diminished in type 2 DM post-meal; $t_{1/2} < 2$ minutes
    • Rapidly degraded by dipeptidyl peptidase IV (DPP-IV)
      • GLP-1 analogs (injectable)
      • DPP-IV inhibitors (oral, daily)
“Incretin Effect” in Healthy Subjects


Actions of GLP-1

GLP-1: Secreted upon the ingestion of food

Promotes satiety and inhibits appetite

Alpha cells:
↓ Postprandial glucagon secretion

Beta cells:
- Enhances glucose-dependent insulin secretion
- ↑ Beta cell mass
  ↓ apoptosis

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Slows gastric emptying

Stomach:
- Slows gastric emptying
- Enhances glucose-dependent insulin secretion
- ↓ Beta cell mass
  ↓ apoptosis

Nauck MA, et al, Diabetologia. 1986;39:1546-1553; Data from Drucker DJ, Diabetes. 1998;47:159-169
Plasma GLP-1
Plasma Exenatide

Postprandial Plasma Levels of Exenatide Exceeded Physiologic Levels of GLP-1

Patients with T2D; Evaluable population, n = 61 for all treatment groups; Mean ± SE

Baseline  Exenatide  Sitagliptin

2-h Postprandial Plasma GLP-1 (pM)

<table>
<thead>
<tr>
<th>GLP-1 RAs: Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta)</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>FDA Approved</td>
</tr>
<tr>
<td>Glucose profile target</td>
</tr>
<tr>
<td>Admin</td>
</tr>
<tr>
<td>Delivery</td>
</tr>
<tr>
<td>Renal dosing</td>
</tr>
</tbody>
</table>

* Requires reconstitution
GLP-1 RAs: Nausea

While nausea declines after 3 weeks, it persists in some patients.

Comparison of GLP-1 RAs (A1C)

Comparison of GLP-1 RAs (Weight)

![Comparison of GLP-1 RAs](image)


DPP-4 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (Januvia)</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approved</td>
<td>2006</td>
<td>2009</td>
<td>2011</td>
<td>2013</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>100 mg daily</td>
<td>5 mg daily</td>
<td>5 mg daily</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>Efficacy (↓ A1C monotherapy)</td>
<td>↓ 0.6%</td>
<td>↓ 0.7%</td>
<td>↓ 0.4%</td>
<td>↓ 0.8%</td>
</tr>
<tr>
<td>Efficacy (↓ A1C combination therapy)</td>
<td>↓ 0.7%</td>
<td>↓ 1.2%</td>
<td>↓ 0.7%</td>
<td>↓ 0.9%</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>50 mg daily (30-50) 25 mg (&lt;30)</td>
<td>2.5 mg daily (&lt;50)*</td>
<td>No dosage adjustment</td>
<td>12.5 mg (30-60) 6.25 mg (&lt;30)</td>
</tr>
</tbody>
</table>

GLP-1 RAs vs. DPP-4 Inhibitors (not head-to-head)

Aroda VR et al. Clinical Therapeutics. 2012

DPP4-Inhibitors: head-to-head with other oral agents

AJ Scheen, Diabetes & Metabolism. 2012
Incretin Agents: Safety Issues

♦ Thyroid cancer and neoplasia
  - Thyroid C-cell tumors in rodent models
  - CI/not recommended for use in patients with personal or family history of MTC (medullary thyroid cancer) or MEN 2
  - Black box warning for liraglutide, exenatide XR, albiglutide, dulaglutide

♦ Pancreas
  - In pancreata of age-matched organ donors, DM treated with incretins had ~40% ↑ pancreatic mass (exocrine cell proliferation and dysplasia (intraepithelial neoplasia). [Butler et al. Diabetes. 2013]
  - Pancreatitis

Incretin Therapy and Pancreatitis

♦ Risk of pancreatitis difficult to determine due to:
  - Extremely low event rate
  - Type 2 DM associated with 3-fold increased risk

♦ Incidence of acute pancreatitis in liraglutide RCTs (n=18) was 1.6 cases/1000 PYE vs. 0.7 cases/1000 PYE for active comparators (Jensen T. Diabetes Care. 2015:1058-66)
  - Not all cases met diagnostic criteria
  - 75% had confounding variables present
Risk of Hospitalization for Acute Pancreatitis

Crude Odds Ratio: 1.44 (95% CI, 1.34-1.54)

Pancreatitis: General Guidance

♦ FDA and EMA independent reviews of patient and animal data: no evidence of causal relationship, but recommend risk to be disclosed and further investigation (Egan et al, NEJM 2014)
♦ Avoid if history of pancreatitis, gallstones, alcoholism, hypertriglyceridemia
♦ Patient education: abdominal pain (persistent, severe, radiating to back, N/V, anorexia) to contact provider

DPP-4 Inhibitors & Joint Pain

♦ FDA safety alert (08.28.15) indicating DPP-4 inhibitors may cause severe joint pain/arthralgia
♦ 33 cases from 2006-2013 identified from FAERS and published literature
  - Onset from 1 day to years (22 cases within 1 month)
  - 10 cases hospitalized
  - 8 cases documented a positive rechallenge with different DPP-4 inhibitor
  - 21 cases were being treated with meds for arthritis
  - Reversible

SGLT-2 inhibitors

♦ SGLT-2 inhibitor class: inhibit sodium glucose cotransporter-2 in proximal tubules, where ~90% of glucose filtered through nephron is reabsorbed

SGLT-2 Mediates Glucose Reabsorption in Kidney


Renal Glucose Handling

SGLT-2 Inhibitors lower Tmax

SGLT-2 Inhibitors: Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (Invokana)</th>
<th>Dapagliflozin (Farxiga)</th>
<th>Empagliflozin (Jardiance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Approved</td>
<td>2013</td>
<td>2014</td>
<td>2014</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>100-300 mg daily</td>
<td>5-10 mg daily</td>
<td>10-25 mg daily</td>
</tr>
<tr>
<td>Efficacy (↓ A1C) monotherapy</td>
<td>↓ 0.77-1.03%</td>
<td>↓ 0.8-0.9%</td>
<td>↓ 0.7-0.8%</td>
</tr>
<tr>
<td>Efficacy (↓ A1C) combination therapy</td>
<td>↓ 0.79-0.94%</td>
<td>↓ 0.7-0.8%</td>
<td>↓ 0.7-0.8%</td>
</tr>
<tr>
<td>Weight lowering (kg)</td>
<td>-2.3 to -4.0</td>
<td>-3.22</td>
<td>-2.4 to -2.8</td>
</tr>
<tr>
<td>Renal dosing</td>
<td>45-59: 100 mg max</td>
<td>Do not use &lt;60</td>
<td>Do not use &lt;45</td>
</tr>
<tr>
<td></td>
<td>Do not use &lt;45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT-2 Inhibitors: Safety Issues

♦ Side Effects
- Common side effects: genital fungal infections and UTIs (due to increased glucose in urine)
- Increased risk of dehydration, hypovolemia, hypotension, dizziness in 1st few months (diuretic effect)

♦ FDA safety alert (12.05.15): for 19 cases of urosepsis and pyelonephritis

♦ FDA safety alert (09.10.15) for bone fracture risk/decreased bone density with canagliflozin

♦ Dapagliflozin: Previously rejected approval 1/2012 due to breast & bladder cancer concerns; Do not use in patients with bladder cancer
SGLT-2 Inhibitors: Safety Issues, cont’d

♦ Euglycemic DKA: FDA safety alert (05.15.15, 20 reports); updated 12.04.15: 73 case reports
♦ Potential triggers include intercurrent illness, reduced food and fluid intake, reduced insulin doses and history of alcohol intake; use in T1 DM/LADA (insulin deficiency).
♦ “Artificially” lowers plasma glucose
♦ Patients who develop N/V, malaise, SOB on SGLT-2 should evaluate urine/blood ketones even if BG normal.
♦ AACE held 10.2015 meeting: stop prior to surgery; consider ½ dose.

Peters A. Diabetes Care. DOI:10.2337/dc15-0843

TZDs & CVD Risk: Rosiglitazone

♦ On 09.22.10, rosiglitazone become available through restricted access only (meta-analysis in NEJM, 05.21.07 & redone in 2010 - significant ↑d risk of MI by 28% [OR 1.28])
♦ June 5-6, 2013, readjudicated results of RECORD were discussed by FDA; committee members voted to eliminate REMS or lessen restrictions.
♦ FDA announced (11.25.13) to remove restrictions on Avandia.
♦ FDA announced (12.16.15) to remove REMS (Risk Evaluation and Mitigation Strategy) requirement
FDA CV Guidelines (2008): CI Bars


CV Risk Outcome Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>REWIND</td>
<td>NCT01394952</td>
</tr>
<tr>
<td>Exenatide</td>
<td>EXSCEL</td>
<td>NCT01144338</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>LEADER</td>
<td>NCT01179048</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>NCT01032629</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DECLARE-TIMI58</td>
<td>NCT01730534</td>
</tr>
<tr>
<td>Multiple oral agents</td>
<td>BMS</td>
<td>NCT01086280</td>
</tr>
<tr>
<td>TZDs vs. SFUs</td>
<td>TOSCA-IT</td>
<td>NCT00700856</td>
</tr>
<tr>
<td>Linagliptin vs. Glimepiride</td>
<td>CAROLINA</td>
<td>NCT01243424</td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (U-100)</td>
<td>ORIGIN</td>
<td>NCT00069784</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>SAVOR-TIMI53</td>
<td>NCT01107886</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>NCT00790205</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>NCT00968708</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG OUTCOME</td>
<td>NCT01131676</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>NCT01147250</td>
</tr>
</tbody>
</table>
Saxagliptin & CV Outcomes

**A Primary End Point**

Hazard ratio, 1.00 (95% CI, 0.89–1.12)  
P=0.80 for non-inferiority  
P=0.99 for superiority

- Patients with End Point (%)
  - Saxagliptin
  - Placebo

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Saxagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>8212</td>
<td>7983</td>
<td>7761</td>
</tr>
<tr>
<td>7267</td>
<td>4855</td>
<td>851</td>
</tr>
</tbody>
</table>

**B Secondary End Point**

2-yr Kaplan-Meier rate:  
- Saxagliptin, 12.8%  
- Placebo, 12.4%

Hazard ratio, 1.02 (95% CI, 0.94–1.11)  
P=0.68 for non-inferiority  
P=0.00 for superiority

Note: rate of hospitalization for HF increased

Scirica BM et al. NEJM, 2013

---

Sitagliptin & CV Outcomes

**A Primary Cardiovascular Outcome**

Hazard rate, 0.98 (95% CI, 0.98–1.00)  
P=0.44

- Patients with Event (%)
  - Saxagliptin
  - Placebo

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Saxagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3700</td>
<td>3701</td>
<td>3698</td>
</tr>
<tr>
<td>3701</td>
<td>3698</td>
<td>3700</td>
</tr>
</tbody>
</table>

**B Secondary Cardiovascular Outcome**

Hazard rate, 0.99 (95% CI, 0.98–1.00)  
P=0.22

- Patients with Event (%)
  - Saxagliptin
  - Placebo

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Saxagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3700</td>
<td>3701</td>
<td>3698</td>
</tr>
<tr>
<td>3701</td>
<td>3698</td>
<td>3700</td>
</tr>
</tbody>
</table>

**C Hospitalization for Heart Failure**

Hazard ratio, 1.00 (95% CI, 0.83–1.20)  
P=0.98

- Patients with Event (%)
  - Saxagliptin
  - Placebo

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Saxagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3700</td>
<td>3701</td>
<td>3698</td>
</tr>
<tr>
<td>3701</td>
<td>3698</td>
<td>3700</td>
</tr>
</tbody>
</table>

**D Death from Any Cause**

Hazard ratio, 1.00 (95% CI, 0.94–1.16)  
P=0.68

- Patients with Event (%)
  - Saxagliptin
  - Placebo

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Saxagliptin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3700</td>
<td>3701</td>
<td>3698</td>
</tr>
<tr>
<td>3701</td>
<td>3698</td>
<td>3700</td>
</tr>
</tbody>
</table>

Green JB et al. NEJM, 2015
Empagliflozin & CV Outcomes


NNT to prevent 1 death in 3 years = 39

GLP-1RA (Liraglutide) & CV Outcomes

03.04.16: Press release on LEADER trial
- Primary endpoint: composite of 1st occurrence of CV death, nonfatal MI or nonfatal stroke
- Both noninferiority and superiority for all 3 endpoints
- Results at ADA 2016
Pioglitazone & CVD risk and other ADEs

♦ Pioglitazone does not appear to have MI risk, however does increase risk for heart failure (PROactive)
  - Observational study suggests rosi has HR for heart failure of 1.25 compared to pioglitazone in an elderly population (Graham DJ et al. JAMA 2010;304)

♦ On 08.04.11, FDA updated safety announcement indicated label changes to Actos to reflect that “use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer.”

♦ TZDs use due to ADEs (e.g., increases risk HR, edema, reduced bone density) have reduced use overall

Pioglitazone & Reduced Risk of Stroke in Non-DM Patients with Insulin Resistance as Secondary Prevention [IRIS Trial] (02.17.16)

Case Study, cont’d

♦ What 2nd agent would you add?
  - SFU
  - DPP-4 inhibitor
  - GLP-1 RA
  - SGLT-2 inhibitor
  - Insulin

Case Study, cont’d

♦ How would you modify his therapy if…
  - he developed renal dysfunction?
  - he was obese?
  - he had severe liver dysfunction?
  - this was a postmenopausal woman (or person with osteopenia/osteoporosis)?
  - he was elderly with a history of an MI?
  - his A1C was 10.4% on metformin only? Or on 2 (or 3) non-insulin therapies?
Metformin in Renal Dysfunction

- Incidence of lactic acidosis among metformin users is 3 to 10/100,000 person-years (almost indistinguishable from rate in people with diabetes not on metformin)

- Suggested approach:

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR, mL/min per 1.73 m²</th>
<th>Maximal Total Daily Dose, mg</th>
<th>Other Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>2550</td>
<td>Avoid if kidney function is or expected to become unstable</td>
</tr>
<tr>
<td>2</td>
<td>60-&lt;90</td>
<td>2550</td>
<td>Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>3A</td>
<td>45-&lt;60</td>
<td>2000</td>
<td>Avoid if kidney function is or expected to become unstable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider more cautious follow-up of kidney function</td>
</tr>
<tr>
<td>3B</td>
<td>30-&lt;45</td>
<td>1000</td>
<td>Do not initiate therapy at this stage but drug may be continued</td>
</tr>
<tr>
<td>4</td>
<td>15-&lt;30</td>
<td>Do not use</td>
<td>Avoid if kidney function is or expected to become unstable</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Do not use</td>
<td>Consider more cautious follow-up of kidney function</td>
</tr>
</tbody>
</table>

Inzucchi SE. JAMA, 2014;314:2668-75.

Individualizing Therapy: Examples

<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Avoid</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction</td>
<td>Metformin, certain SFUs</td>
<td>Glipizide, glinides, DPP-4 inhibitors (dose adjust)</td>
</tr>
<tr>
<td>Severe liver dysfunction</td>
<td>Most agents</td>
<td>Insulin, caution with others</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>TZD</td>
<td>Metformin, GLP-1 agonist, SGLT-2 inhibitor; DPP-4 inhibitor</td>
</tr>
<tr>
<td>Heart failure</td>
<td>TZD, metformin (only unstable/severe)</td>
<td>Most other agents</td>
</tr>
<tr>
<td>Reduced bone density or osteoporosis</td>
<td>TZD, Canagliflozin</td>
<td>Most other agents</td>
</tr>
<tr>
<td>History of pancreatitis</td>
<td>GLP-1 agonist, DPP-4 inhibitor</td>
<td>Most other agents</td>
</tr>
<tr>
<td>History of bladder cancer</td>
<td>Pioglitazone, Dapagliflozin</td>
<td>Most other agents</td>
</tr>
<tr>
<td>Pre-existing edema</td>
<td>TZD</td>
<td>Most other agents</td>
</tr>
<tr>
<td>Joint pain</td>
<td>DPP-4 inhibitors</td>
<td>Most other agents</td>
</tr>
</tbody>
</table>
New Insulins

♦ Rapid-acting
  - Humalog (insulin lispro) U-200 (5/2015)
  - Ultra rapid-acting
  - Biosimilar: insulin lispro

♦ Long-acting
  - Degludec (Tresiba); U-100, U-200 (9/2015)
  - Insulin glargine (Toujeo) U-300 (2/2015)
  - Biosimilar: insulin glargine (Basaglar; 12/2015; available 12/2016)

♦ Insulin mixtures
  - Degludec/insulin aspart (Ryzodeg 70/30; 9/2015)
Meta-analysis of the EDITION 1, 2 and 3 studies: Hypoglycemia with insulin glargine U-300 versus U-100 in T2DM

BG ≤ 70 mg/dl  ↓ 14%

Insulin Degludec vs. Insulin Glargine (U-100): Hypoglycemia

BG ≤ 70 mg/dl  ↓ 31%

Ritzel R. Diabetes, Obesity and Metabolism. 2015;17:859-67.

Zinman B. Dia Care. 2012;35:2464-2471
Cost Considerations

♦ Brand medications are now $275-$450+ monthly
♦ Recent price increases
  - 07.2015: Glutmetza (metformin XL) price ↑ 500%
    • For 1000 mg pill: $133.59
    • For generic metformin ER pill: $7.45
    • For generic metformin IR 500 mg (#100): $8.42
  - 06.2014: Humulin U-500 insulin vial increased from $220 to $1,200 a vial
♦ In comparison, generics
  - Glipizide 10 mg (#100): $8.42
  - $4 generic lists

Individualizing Care

1. Set A1C target
   ✓ Patient factors
   ✓ Provider considerations
2. Assess how close patient is to target
   ✓ Why or why not?
   ✓ Changes since last visit (improve/worsen/same)
   ✓ Assess adherence, medication SEs, lifestyle (exercise, meals); psychosocial factors
3. Create a patient-specific plan to reach target
   ✓ Is patient on submax/therapeutic dose of particular medication? Titrate
   ✓ Is patient on max/therapeutic dose of medication? Add-on? Insulin?

Adapted from Anne Peters, MD. February 9, 2014
Individualizing Care, cont’d

4. Goal setting

- Set Goals

  5 Characteristics for Effective Goal Settings

  Create S.M.A.R.T. Goals

  S - Specific
  M - Measurable
  A - Achievable
  R - Realistic
  T - Timely

  Example:
  "I will try to become more physically active" ✗
  "I will try to walk at a moderate pace for 30 minutes, 3 times per week for the next 4 weeks" ✓

  1) Specific: What activity, what intensity, for how long
  2) Measurable: The patient can monitor and measure this amount of physical activity
  3) Achievable: This amount and intensity of physical activity is appropriate for the current level of fitness for this patient
  4) Realistic: Finding time to walk for 30 minutes 3 times per week is what is feasible for this patient
  5) Timely: Deciding on a length of time for the patient to work on this goal allows for a time frame of when to reassess the goal and adjust if necessary before moving forward

http://guidelines.diabetes.ca/SelfManagementEducation/SMETools

Individualizing Care, cont’d

5. Summarize plans from visit

- Teach back
- Handouts

6. Follow-up

- Continual guidance/support