Helping Your Patients With CKD

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CKD is classified based on:
- Cause (C)
- GFR (G)
- Albuminuria (A)

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73m²) Description and range</th>
<th>Albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 Normal or high ≥90</td>
<td>A1 Normal to mildly increased</td>
<td></td>
</tr>
<tr>
<td>G2 Mildly decreased 60-89</td>
<td>A2 Moderately increased</td>
<td></td>
</tr>
<tr>
<td>G3a Mildly to moderately decreased 45-59</td>
<td>A3 Severely increased</td>
<td></td>
</tr>
<tr>
<td>G3b Moderately to severely decreased 30-44</td>
<td>≥30 mg/g &lt;3 mg/mmol</td>
<td></td>
</tr>
<tr>
<td>G4 Severely decreased 15-29</td>
<td>30-299 mg/g 3-29 mg/mmol</td>
<td></td>
</tr>
<tr>
<td>G5 Kidney failure &lt;15</td>
<td>≥300 mg/g ≥30 mg/mmol</td>
<td></td>
</tr>
</tbody>
</table>

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Disclosure of Financial Relationships

Joseph A. Vassalotti, MD

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

**Consultantship**
- Merck, Inc. (CKD and Hepatitis C)
- Janssen, Inc. (CKD and T2DM)

**Honoraria**
- As above

**Research Grants/Contracts**
- No Commercial Grants

**Speaker’s Bureau**
- None
- No speaking roles in any consultantship
Questions to be Addressed

1. What steps can be taken to slow the progression of kidney disease?
2. How do new therapies for diabetes impact the care of the patient with CKD?
3. What are the data on continuing or stopping ACEi or ARB in kidney function and outcomes in advanced CKD?
4. What is the best management strategy for anemia related to CKD?
5. What conditions occur commonly in CKD patients that affect quality of life, and how should these be managed?
6. When should patients be referred to a nephrologist?
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1. **What steps can be taken to slow the progression of kidney disease?**

2. How do new therapies for diabetes impact the care of the patient with CKD?

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4. What is the best management strategy for anemia related to CKD?

5. What conditions occur commonly in CKD patients that affect quality of life, and how should these be managed?

6. When should patients be referred to a nephrologist?
A 68-year-old woman presents with CKD and HTN. Labs are eGFR 45 ml/min/1.73m² and urine UACR 1,800 mg/g. She feels well and lives independently. Her BP is 152/84 mm Hg and P 70 and regular. Exam is otherwise unremarkable. Total cholesterol 180 mg/dL, LDL 102 and HDL 60 mg/dL.

She takes lisinopril 40 mg, atorvastatin 20 mg daily and is a non-smoker with excellent lifestyle modification.

Would you advise her to add an anti-hypertensive medication?

A. Yes

B. No
Diagnosis and Classification

- Evaluation of eGFR
- Evaluation of Albuminuria
- Evaluation of Cause

- Diabetic kidney disease
- Hypertensive kidney disease
- Other etiology – additional testing

Establishes CKD Stage
## Different Categories for Albuminuria

<table>
<thead>
<tr>
<th>Albuminuria Terminology</th>
<th>Albumin Excretion mg/day</th>
<th>UACR mg/g</th>
<th>UPCR mg/g</th>
<th>Dipstick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal – mildly increased (A1)</td>
<td>&lt;30</td>
<td>&lt;30</td>
<td>&lt;150</td>
<td>negative</td>
</tr>
<tr>
<td>Moderately increased (A2)</td>
<td>30-&lt;300</td>
<td>30-&lt;300</td>
<td>150-&lt;500</td>
<td>+1</td>
</tr>
<tr>
<td>Severely Increased (A3)</td>
<td>&gt;300</td>
<td>&gt;300</td>
<td>&gt;500</td>
<td>+2 or greater</td>
</tr>
</tbody>
</table>

These categories incorporate approximations and inaccuracies depending on gender, age and other factors, but is useful as a pragmatic approach when ACR is not available.

These categories are adapted from KDIGO; Kidney Disease Improving Global Outcomes.
Management of Modifiable Risk Factors & Complications of CKD

- Hypertension
- Diabetes Mellitus
- CKD Metabolic acidosis
- Gout & Hyperuricemia (?)
- CKD Anemia
- CKD Bone and Mineral Disorder
- Dyslipidemia

Impacts CKD progression & morbidity

Impacts morbidity
## Categories of BP in Adults*

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130–139 mm Hg</td>
<td>80–89 mm Hg</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥140 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
</tbody>
</table>

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.)

Circulation. 2018;138(17):e595-e616
Methods of BP Measurement

- Office BP Monitoring (OBPM)
- Home BP Monitoring (HBPM)
- Ambulatory BP Monitoring (ABPM)
Randomization to Intensive BP Control in SPRINT Reduced CV Events Overall and in Prevalent CKD Population

Composite: MI, ACS, stroke, CHF, CV death

CKD Subgroup

Entire Cohort

Hazard ratio with intensive treatment, 0.75 (95% CI, 0.64–0.89)

Standard treatment

Intensive treatment

Routine Clinic BP vs the SPRINT BP Methodology: Subgroup Analysis in CKD Population

N= 275 with CKD and same day Clinic BP without specified rest

Systolic
-12.7 mmHg in research vs. clinic
-46 to +20.7 mmHg

Diastolic
-12.0 mmHg in research vs. clinic
-33.2 to +17.4 mmHg

BP Measurement Methodology Matters!

Bland–Altman plot showing the mean differences between various blood pressure (BP) recordings and their limits of agreement. SPRINT Trial

Agarwal R. J Am Heart Assoc 2017;6:e004536
7 SIMPLE TIPS TO GET AN ACCURATE BLOOD PRESSURE READING

The common positioning errors can result in inaccurate blood pressure measurement. Figures shown are estimates of how improper positioning can potentially impact blood pressure readings.

Sources:
2. Handler, J: The importance of accurate blood pressure measurement. The Hypertensive Journal/Summer 2009;Volume 15 No. 3 51

This 7 simple tips to get an accurate blood pressure reading was adapted with permission of the American Medical Association and The Johns Hopkins University. The original copyrighted content can be found at: https://www.ama-assn.org/ama-johns-hopkins-blood-pressure-measurement

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Factors to consider in the implementation of individualized blood pressure targets in CKD

- Method of blood pressure assessment (office, home, 24-hour ambulatory)
- Cardiovascular Risk
- Albuminuria
- Age (life expectancy)
- Risk of adverse effects of low BP target (hemodynamic AKI, falls, syncope)
- Orthostatic blood pressure (seniors, diabetic neuropathy)
- Shared decision making (motivation, frequent visits titration phase)

Commit to a specific target for each patient: <130/80, <140/90, or <150/90 (mm Hg)
Management of Hypertension in Patients With CKD

Treatment of hypertension in patients with CKD

BP goal <130/80 mm Hg (Class I)

Albuminuria (≥300 mg/d or ≥300 mg/g creatinine)

Yes

ACE inhibitor (Class IIa)

No

Usual “first-line” medication choices

ACE inhibitor intolerant

Yes

ARB* (Class IIb)

No

ACE inhibitor* (Class IIa)

- Colors correspond to Class of Recommendation in Table 1.
- *CKD stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d or ≥300 mg/g creatinine.
- ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; and CKD, chronic kidney disease.
Slowing CKD Progression: ACEi or ARB

- Check labs within two weeks after initiation (opinion).
  - Potassium
  - If less than 30% serum creatinine (SCr) increase, continue and monitor.
  - If more than 30% SCr increase, stop drug and evaluate for renal artery stenosis (RAS) and volume contraction.

- Avoid ACEi and ARB in combination\(^1-3\)
  - Risk of adverse events (hemodynamic AKI, hyperkalemia)

- ACEi better outcomes data vs ARB better tolerability data

Hypertension in CKD: Hot Potato
ARB FDA Recalls for Trace Carcinogens

The first phase of recalls involved the genotoxic impurity NDMA (in blue), the second involved NDEA (in green), and the most recent involved NMBA (in orange). Company names refer to the manufacturer and are not always the same as the distributor. HCTZ denotes hydrochlorothiazide.¹

2) FDA’s Assessment of Currently Marketed ARB drug products
https://www.fda.gov/Drugs/DrugSafety/ucm634620.htm

¹
Hypertension in CKD: Hot Potato
ARB FDA Recalls for Trace Carcinogens

- Risks of CV events short term and CKD progression long term are important to review to avoid self discontinuation of ARB.
- FDA estimate risk is 1 new malignancy for 8,000 patients treated at the highest contaminated ARB dose for 4 years continuously.

- Educate patients to work with pharmacy to use generic ARB brands that have not been recalled.
- If you prefer to switch ARB, what about future FDA recalls?
- FDA is currently in the process of evaluating all ARB drugs for nitrosamine contamination, see weblink below

2) FDA's Assessment of Currently Marketed ARB drug products
3 or More BP Medications to Achieve Target: RCT with CKD

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACCORD, Action to Control Cardiovascular Disease in Diabetes; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CKD, chronic kidney disease; IDNT, Irbesartan Diabetic Nephropathy Trial; MDRD, Modification of Diet in Renal Disease; RENAAL, Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan, SPRINT, Systolic Blood Pressure Intervention Trial; UKPKDS, United Kingdom Prospective Kidney Disease Study.

BP Medication Combinations:
Conceptual Diagram

Abbreviations

Green lines = preferred
Green dashes = useful
Black dashes = possible
Red line = not recommended

2013 ESH/ESC Guidelines
J Hypertens 2013
Causes of Secondary Hypertension

Drug-induced or Other Causes
- Renovascular hypertension (atherosclerotic, fibromuscular dysplasia)
- Primary aldosteronism
- Pheochromocytoma
- Cushing syndrome
- Hyperthyroidism
- Hypothyroidism
- Obstructive sleep apnea

Drug-induced or Other Causes
- Chemical or medication induced
- Caffeine, coffee (short term)
- Alcohol
- Nonsteroidal anti-inflammatory drugs
- Cyclooxygenase 2 inhibitors
- Cocaine, amphetamines, other illicit drugs
- Sympathomimetics (pseudoephedrine)
- Oral contraceptives
- Steroids
- Calcineurin Inhibitors (Cyclosporine and tacrolimus)
- Chemotherapeutic Agents (gemcitabine, VEGF receptor inhibitors)
- Illicit drugs (amphetamines, cocaine)

Monogenic Disorders
- Liddle Syndrome
- Syndrome of apparent mineralocorticoid excess
- Glucocorticoid-remediable hypertension
- Familial hyperaldosteronism Type III
- Gordon syndrome
Prescribing Steps in CKD
One Approach

1. ACEi or ARB if albuminuria or proteinuria
2. Diuretic or CCB
3. CCB or Diuretic
4. Mineralocorticoid Receptor Blocker (MRB)*

*MRB effective in Resistant HTN based the PATHWAY-2 trial that excluded CKD G3b+

ACEi Angiotensin Converting Enzyme Inhibitor
ARB Angiotensin Receptor Blocker
CCB Calcium Channel Blocker
A 60-year-old man presents with CKD G4, A2 and HTN
On exam, BP 126/74 mmHg, P 78 and regular
Medications: olmesartan 40 mg, pravastatin 40 mg (both daily)

Labs are eGFR 28 ml/min/1.73m² and urine UACR 80 mg/g. Lipid panel results are optimal

<table>
<thead>
<tr>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>tCO₂</th>
<th>BUN</th>
<th>SCr</th>
<th>GLU</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>4.7</td>
<td>108</td>
<td>17</td>
<td>44</td>
<td>2.4</td>
<td>84</td>
</tr>
</tbody>
</table>

Do you add an additional medication?

A. Yes
B. No
CKD Metabolic Acidosis

- Low Serum tCO$_2$? Confirm CKD metabolic acidosis.

- Prevalence increases as eGFR falls -37% CKD G4 in CRIC cohort

- Influenced by the balance of acid vs alkali producing foods

- Alkali protects loss of kidney function.
Acidosis and CKD Progression

Metabolic Acidosis
\[\uparrow \text{H}^+ \text{ Retention} \]
\[\downarrow \text{pH Interstitial Fluid} \]

- \[\uparrow \text{Endothelin} \]
- \[\uparrow \text{Pro-inflammatory Cytokines} \]

- \[\uparrow \text{NH}_4^+ \]
  - \[\uparrow \text{Activation of Complement} \]

- \[\uparrow \text{Angiotensin II} \]
  - \[\uparrow \text{Aldosterone} \]

Kidney Fibrosis

CKD Metabolic Acidosis: Prospective RCTs
Reduction in Kidney Event Rates

Reduction in kidney events in CKD with metabolic acidosis (tCO3 <22 mEq/l) treated with NaHCO3 vs control.
## Alkali Replacement Therapies

<table>
<thead>
<tr>
<th>Typical Daily Dose</th>
<th>Formulation*</th>
<th>Typical Dose Unit</th>
<th>HCO₃&lt;sub&gt;3&lt;/sub&gt; mEq/Dose</th>
<th>Typical Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>~ 0.5 – 1 mEq/kg/day</td>
<td>Sodium Bicarbonate NaHCO₃</td>
<td>650 mg</td>
<td>7.7 mEq</td>
<td>1 - 2 tabs 2-3 x day</td>
</tr>
<tr>
<td></td>
<td>Bicitra+ Sodium Citrate</td>
<td>30 ml</td>
<td>30 mEq</td>
<td>30 ml 1-2 x day</td>
</tr>
<tr>
<td></td>
<td>Baking soda Sodium Bicarbonate</td>
<td>30 ml</td>
<td>54 mEq</td>
<td>15-30 ml day mixed in Water</td>
</tr>
</tbody>
</table>

+ Polycitra as potassium citrate is also available, but should be avoided with hyperkalemia risk

* Some Alka-Seltzer products contain potassium bicarbonate, e.g. Alka Selzer Gold
Avoid or Minimize Exposure to Drugs that Cause AKI or CKD progression

- Prolonged NSAIDS or Cox-2 inhibitors
- Sodium phosphate colonoscopy preps (Visicol and Osmoprep)
- Iodinated contrast media (intra-arterial > intravenous)
- Proton pump inhibitors (interstitial nephritis, AKI, CKD progression)
- High dose acyclovir
- Tenofovir disoproxil > Tenofovir alafenamide
- Lithium (especially in combination with NSAID or ACEi or ARB)

- Other drugs need to be dose adjusted or avoided for systemic toxicity based on low eGFR.
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Diabetes and CKD: Glycemic Target

KDIGO + KDOQI Clinical Practice Guidelines
Target HbA1c ~ 7.0% (1A)

RCT: Hyperglycemia associated with incident & worsening albuminuria and loss of eGFR

HbA1c less precise in CKD (shortened RBC survival), but is generally recommended for monitoring.

Hypoglycemia is the most common patient safety hazard for diabetes with impaired eGFR.
Pathophysiologic Defects and Sites of Action of Medications for T2DM

HYPERGLYCEMIA

Liver: ↑↑ ↑↑ Hepatic glucose secretion

Muscle and adipose tissue: ↓↓ ↓↓ Glucose uptake

CNS: Delayed satiety Neurotransmitter dysfunction

Kidney: ↑↑ ↑ ↑ Glucose reabsorption

Gut: Diminished incretin effect
Altered intestinal glucose absorption

Adipose tissue: ↑ Lipolysis

Pancreas
↓ Insulin secretion
↑ Glucagon secretion

DPP-4i
GLP-1RA

GLP-1RA

SGLT-2i

Metformin

Liver: ↑ Hepatic glucose secretion

Metformin

Insulin
SU
Meglitinide

Metformin-containing Medicines FDA Labeling Revisions
4/08/16

<table>
<thead>
<tr>
<th>Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m².</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m² is not recommended</td>
</tr>
</tbody>
</table>

The Goal is to Decrease Intraglomerular Pressure
EMPA-REG OUTCOME Trial: Kidney Function Over Time

Empagliflozin 10 mg & 25 mg arms combined vs Placebo

Primary Outcome (not shown) 14% ↓ 3 Point MACE (13% ↓ MI, 24% ↓ CVA, 36% ↓ CV Death)

Wanner C, et al. JASN 2018;29:2755
SGLT-2i: Intermediate Markers of Cardiovascular Risk


Modest mean A1C -0.58% reduction compared to placebo.
SGLT2 Inhibitor RCT Primary Cardiovascular Outcomes: Secondary Analysis of Kidney Outcomes

Composite of worsening of eGFR, ESKD, or kidney death

<table>
<thead>
<tr>
<th>eGFR &lt;60 mL/min per m²</th>
<th>Patients</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>1196</td>
<td>605</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>CANVAS Program</td>
<td>NA</td>
<td>NA</td>
<td>83</td>
<td>11.4</td>
<td>15.1</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>606</td>
<td>659</td>
<td>59</td>
<td>8.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Fixed effects model for eGFR &lt;60 (p=0.0054)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR 60 to &lt;90 mL/min per m²</td>
<td>EMPA-REG OUTCOME</td>
<td>2406</td>
<td>1232</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>NA</td>
<td>NA</td>
<td>118</td>
<td>4.6</td>
<td>7.4</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3838</td>
<td>3894</td>
<td>186</td>
<td>4.2</td>
<td>7.8</td>
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<tr>
<td>Fixed effects model for eGFR 60 to &lt;90 (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥90 mL/min per m²</td>
<td>EMPA-REG OUTCOME</td>
<td>1043</td>
<td>486</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>NA</td>
<td>NA</td>
<td>48</td>
<td>3.8</td>
<td>8.1</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>4137</td>
<td>4025</td>
<td>120</td>
<td>25</td>
<td>4.9</td>
</tr>
<tr>
<td>Fixed effects model for eGFR ≥90 (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Glucose-lowering medication in T2DM: overall approach

Metformin is the preferred initial drug for T2DM. (A)

Among patients with ASCVD at high risk of heart failure or in whom heart failure coexists, SGLT-2i are preferred. (C)

For patients with T2DM and CKD, consider use of an SGLT-2i or GLP-1 RA shown to reduce risk of DKD progression, cardiovascular events, or both. (C)

FDA avoid all if eGFR < 45 ml/min/1.73m²
EMP A REG Outcome (Empagliflozin)
CANVAS-R (Canagliflozin)
DECLARE (Dapagliflozin)

American Diabetes Association Clin Diabetes 2019;37:11-34
SGLT2-Inhibitors: Benefits and Risks

- Heart Failure
- CKD*
- CV Death
- ↓ Weight
- ↓ BP
- ↓ CV events
- Hypertension
- Ketoacidosis
- Insulin-Treated
- Genito-urinary Infections
- Peripheral Arterial Disease

Adapted: Curr Opin Cardiol 2018; 33:676–682
*FDA only if eGFR ≥ 45 ml/min/1.73m²
Questions to be Addressed

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2. How do new therapies for diabetes impact the care of the patient with CKD?

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6. When should patients be referred to a nephrologist?
Do you routinely discontinue ACEi or ARB in CKD G4+ (eGFR < 30 ml/min/1.73m²)?

A. Yes

B. No

Predictors of Hyperkalemia before Starting Therapy Derived from Trials

- eGFR <45 mL/min/1.73m²
- Serum potassium >4.5 mEq/L
- eGFR <45 mL/min/1.73m² + serum K >4.5 mEq/L (Strongest Predictor)
- eGFR <30 mL/min/1.73m² often have both of the above.
- In general continue ACEi or ARB for eGFR <30 mL/min/1.73m², discontinuing only for intractable hyperkalemia or concerns about low eGFR.

## Agents Used for Chronic Hyperkalemia

<table>
<thead>
<tr>
<th></th>
<th>SPS</th>
<th>Patiromer</th>
<th>SZC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>15g 1–4 times daily</td>
<td>8.4–25.2g daily</td>
<td>Initial (for up to 48 hours):</td>
</tr>
<tr>
<td></td>
<td>Maintenance: once daily</td>
<td>Titrate by 8.4 g increments</td>
<td>10g 3 times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 10g once daily</td>
</tr>
<tr>
<td><strong>Electrolyte</strong></td>
<td>Hypocalcemia, Hypomagnesemia</td>
<td>Hypomagnesemia (5.3%)-</td>
<td>None</td>
</tr>
<tr>
<td><strong>disturbances</strong></td>
<td></td>
<td>reduction 0.15-0.2 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td>Cation-donating antacids/laxatives, avoid</td>
<td>Binds oral 3 medications</td>
<td>Not formally tested—label says</td>
</tr>
<tr>
<td><strong>interactions</strong></td>
<td>sorbitol, lithium, thyroxine</td>
<td>(cipro, metformin, levothyroxine)</td>
<td>oral meds should be spaced by</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administer 3 hours apart</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

**Adverse Effects**

- **SPS** – Sodium polystyrene sulfonate - constipation, diarrhea, nausea, intestinal necrosis (sorbitol formulation – published post-marketing reports)
- **Patiromer**—constipation, diarrhea, nausea, abdominal discomfort/flatulence, hypomagnesemia
- **SZC**- Sodium Zirconium Cyclosilicate – edema 16.1% with 10 g dosing, constipation, diarrhea, nausea

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STOP-ACEi Trial in CKD G4+

- International, multicenter trial of 410 participants with advanced CKD stage (G4 or 5) treated with ACEi, ARB or both. Patients will be randomized 1:1 ratio to either discontinue (experimental arm) or continue therapy (control arm).
- Study visits at 3 monthly intervals for 3 years
- Primary outcome is eGFR at 3 years.

- Secondary outcomes
  - Renal events
  - Quality of life and physical functioning
  - Hospitalization rates
  - BP and laboratory measures, including serum cystatin-C
  - Safety
    - Mortality
    - Cardiovascular events (heart failure, myocardial infarction or stroke)
Questions to be Addressed

1. What steps can be taken to slow the progression of kidney disease?
2. How do new therapies for diabetes impact the care of the patient with CKD?
3. What are the data on continuing or stopping ACEi or ARB in kidney function and outcomes in advanced CKD?
4. What is the best management strategy for anemia related to CKD?
5. What conditions occur commonly in CKD patients that affect quality of life, and how should these be managed?
6. When should patients be referred to a nephrologist?
CKD Anemia in 2019

- **Diagnosis:**
  - Hemoglobin
  - CKD anemia or another etiology?

- **Treatment:**
  - Iron administration
  - Erythropoiesis Stimulating Agent (ESA) administration
  - Blood transfusions

- **ESA Risks**
  - RCT Hb targets showed increased risk of thrombotic events with normalized Hb (CHOIR, CREATE and TREAT)
Anemia in CKD

Prevalence of anemia by CKD stage in Kidney Early Evaluation Program
Abbreviations: WHO, World Health Organization
KDOQI, Kidney Disease Outcomes Quality Initiative

Anemia associated with poorer QOL, LVH, increased risk of blood transfusion
Especially for CKD G1-3, consider other anemia etiologies

Erythropoiesis Stimulating Agent (ESA) Therapy in CKD Anemia

- Initiate iron therapy if TSAT ≤30% and ferritin ≤500 ng/mL (IV iron for dialysis, oral or IV for non-dialysis CKD).
- Individualize erythropoiesis stimulating agent (ESA) therapy: avoid transfusion.
  
  Start ESA if Hb <10 g/dl, and maintain Hb 9-11.5 g/dl.
- Ensure no contraindications: active malignancy, uncontrolled hypertension.

<table>
<thead>
<tr>
<th>ESA</th>
<th>Subcutaneous Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alpha</td>
<td>50-100 U/kg every 1-2 week</td>
</tr>
<tr>
<td>Darbepoetin alpha</td>
<td>0.45 μg/kg every 2-4 week</td>
</tr>
</tbody>
</table>

- Appropriate iron supplementation is needed for ESA to be effective.

Questions to be Addressed

1. What steps can be taken to slow the progression of kidney disease?
2. How do new therapies for diabetes impact the care of the patient with CKD?
3. What are the data on continuing or stopping ACEi or ARB in kidney function and outcomes in advanced CKD?
4. What is the best management strategy for anemia related to CKD?
5. What conditions occur commonly in CKD patients that affect quality of life, and how should these be managed?
6. When should patients be referred to a nephrologist?
Conditions Affecting Quality of Life in CKD

- Pain - about 50% prevalence with multiple causes identified 18%
  - prevalence increases as eGFR falls
- Peripheral edema
- Pruritis
- Depression
- Fatigue

## Analgesia with Reduced Kidney Function

<table>
<thead>
<tr>
<th>Pain Severity</th>
<th>Analgesic</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1 mild</strong></td>
<td>Acetaminophen</td>
<td>650 mg q4-6 h</td>
<td>1 - 2 tabs 4-6 x day maximum</td>
</tr>
<tr>
<td>(1-3/10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 mild</td>
<td>NSAIDs</td>
<td>Topically</td>
<td>Topical NSAIDs, short-acting sulindac, or short-course with monitoring</td>
</tr>
<tr>
<td>(1-3/10)</td>
<td>Cox-2 inhibitors</td>
<td>(hands and knees) Variable</td>
<td></td>
</tr>
<tr>
<td>Stage 2 moderate</td>
<td>Tramadol</td>
<td>50-100 mg q 4-12 h</td>
<td>q12 for CKD G4+ Short course, adjuvants</td>
</tr>
<tr>
<td>(4-6/10)</td>
<td>Oxycodone</td>
<td>10-30 mg q 4-6 h</td>
<td></td>
</tr>
<tr>
<td>Stage 3 severe</td>
<td>Hydromorphone</td>
<td>1-4 mg every 4-6 h</td>
<td>Adjuvants, short course, combination analgesia</td>
</tr>
<tr>
<td>(7-10/10)</td>
<td>Fentanyl</td>
<td>Oral equivalent Referral</td>
<td>Referral Palliative Care or Pain Management</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
<td>Required</td>
<td></td>
</tr>
</tbody>
</table>

Adjuvant Therapy: Physical Therapy, Cognitive Behavioral Therapy; Neuropathic pain options: gabapentin, pregabalin

Questions to be Addressed

1. What steps can be taken to slow the progression of kidney disease?
2. How do new therapies for diabetes impact the care of the patient with CKD?
3. What are the data on continuing or stopping ACEi or ARB in kidney function and outcomes in advanced CKD?
4. What is the best management strategy for anemia related to CKD?
5. What conditions occur commonly in CKD patients that affect quality of life, and how should these be managed?
6. When should patients be referred to a nephrologist?
Why Refer to Nephrology

- Identify Cause – Kidney Biopsy in selected cases
- Slow Progression of CKD
- CKD Complications Management
  - CKD Anemia
  - CKD Hyperkalemia
  - CKD Mineral and Bone Disease
  - CKD Metabolic Acidosis
- Medication management
- Kidney Replacement Therapy Decision Making and Planning
**Indications for Nephrology Referral for People with CKD**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &lt; 30 ml/min/1.73 m² (GFR categories G4-G5)</td>
</tr>
<tr>
<td>A 25% or greater drop in eGFR</td>
</tr>
<tr>
<td>CKD Progression with a sustained decline in eGFR &gt; 5 ml/min/1.73 m² per year</td>
</tr>
<tr>
<td>A consistent finding of significant albuminuria (category A3)</td>
</tr>
<tr>
<td>Persistent unexplained hematuria</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism, persistent anion gap acidosis, non-iron deficiency anemia</td>
</tr>
<tr>
<td>CKD and hypertension refractory to treatment with 4 or more antihypertensive agents</td>
</tr>
<tr>
<td>Persistent abnormalities of serum potassium</td>
</tr>
<tr>
<td>Recurrent or extensive nephrolithiasis</td>
</tr>
<tr>
<td>Hereditary kidney disease or unknown cause of CKD</td>
</tr>
</tbody>
</table>

*Significant albuminuria is defined as ACR ≥300 mg/g (≥30 mg/mmol) or AER ≥300 mg/24 hours, approximately equivalent to PCR ≥500 mg/g (≥50 mg/mmol) or PER ≥500 mg/24 hours*

KDOQI US Commentary on the 2012 KDIGO Evaluation and Management of CKD.
Kidney Replacement Therapy

- In-center or Home Hemodialysis
- Kidney Transplant
- Peritoneal Dialysis
- Kidney Failure
- Maximal Medical Care Palliation
Questions?

Joseph A. Vassalotti, MD
Chief Medical Officer
National Kidney Foundation
Associate Clinical Professor of Medicine,
Icahn School of Medicine at Mount Sinai
@Joe_Vassalotti
josephv@kidney.org
joseph.vassalotti@mssm.edu

Internal Medicine Meeting 2019
Saturday 13 April 4:00 – 5:00pm
Bonus Slides for Questions as Needed
<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| OBPM   | Most commonly used in RCTs and outcomes trials | - Highly variable  
- Observer bias  
- May be inaccurate in masked and white coat hypertension |
|        | Wide availability and low cost | |
| HBPM   | Stronger predictor of hypertensive end-organ damage than CBPM | - Requires training and device calibration  
- Out of pocket patient expense  
- Unreliable in atrial fibrillation  
- May exacerbate anxiety disorder and obsessive compulsive behavior |
|        | Improves adherence and BP control | |
|        | Detects white coat and masked hypertension | |
|        | Wide availability and low cost | |
| ABPM   | Stronger predictor of hypertensive end-organ damage than CBPM | - Expensive  
- Cumbersome for the user  
- Strict criteria for reimbursement  
- Limited availability (academic centers) |
|        | Most reliable way to assess non-dipping and reverse dipping | |
|        | Detects white coat and masked hypertension | |
### BP Categories based on Office and Ambulatory BPM

<table>
<thead>
<tr>
<th>BP Category</th>
<th>Office BPM</th>
<th>Ambulatory BPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>White-coat HTN</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Masked HTN</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Sustained HTN</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>


Relationship Between Achieved BP and Decline in Kidney Function From Primary Renal Endpoint Trials

Nondiabetes
- REIN. *Lancet.* 1997
- AASK. *JAMA.* 2002

Diabetes

Ode to Chlorthalidone

- No head-to-head trials of Thiazides in CKD
- General population: Chlorthalidone is superior to HCTZ with limited data
  - Approximately 3 x as potent and 2-3 times longer half-life
  - Superior to HCTZ for LVH regression in post hoc analysis of the Multiple Risk Factor Intervention Trial (Mr. FIT)
  - Superior to HCTZ for CV event reduction in a retrospective cohort analysis.
- Diuretic Comparison Project VA – first Chlorthalidone vs HCTZ trial
  - Approximately 1 million Veterans prescribed thiazide each year
    - 95% HCTZ vs 2-3% Chlorthalidone
  - 13,500 Veterans age 65 or older on HCTZ randomized between 2016 to 2020
  - CKD will be included
  - Primary Outcome: CV events

4. www.clinicaltrials.gov
Always switch Diuretic therapy from Thiazide alone to Loop Diuretic for CKD with eGFR < 30 ml/min/1.73m²?

A. Yes
B. No
Chlorthalidone in Chronic Kidney Disease (CLICK) Study

• Pilot Study\(^1\) eGFR 20-45 (n = 11) suggests efficacy

• Double-blind RCT of Chlorthalidone vs Placebo
  – 160 adults with CKD stage G4
  – 12 weeks
  – Primary Outcome: Ambulatory BP Monitoring
  – Secondary Outcomes
    • Albumin-creatinine ratio
    • Aldosterone-renin ratio
    • B-Naturetic peptide
    • Total body volume
  – Study completion anticipated 2022


Systolic & Diastolic HBPM Pilot Data\(^1\)
ABPM data similar trend (not shown)
What About Diabetes?
**ACCORD-BP**

- 4733 participants
- Type-2 Diabetes

**Standard**
- SBP <140 mm Hg

**Intensive**
- SBP <120 mm Hg

Neither Accord nor SPRINT are primary CKD studies. Both are Hypertension trials that included CKD subjects. Unlike SPRINT, ACCORD excluded SCr > 1.5 mg/dL. Unlike SPRINT, ACCORD also included Intensive vs Standard Glycemia arms (A1c <6% vs <7-7.9%, respectively).
Diabetes: ACCORD – Major CV Events

A Primary Outcome

![Graph showing systolic pressure and proportion with event over years since randomization.]

Mean No. of Medications Prescribed

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>3.2 3.4</td>
<td>1.9 2.1</td>
</tr>
<tr>
<td>Standard</td>
<td>3.4 3.5</td>
<td>2.2 2.3</td>
</tr>
</tbody>
</table>

No. of Patients

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>2174 2071</td>
<td>1973 1792</td>
</tr>
<tr>
<td>Standard</td>
<td>2208 2136</td>
<td>2077 1860</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>2362 2273</td>
<td>2182 2117</td>
</tr>
<tr>
<td>Standard</td>
<td>2371 2274</td>
<td>2196 2120</td>
</tr>
</tbody>
</table>

P=0.20

ACCORD Study Group. NEJM 2010
SPRINT and ACCORD: Combined Data

Pooled data mostly driven by SPRINT cohort

The Interaction Between Intensive BP Lowering and Intensive Glycemic Control Masked Beneficial Effects of BP Lowering in ACCORD BP

### Composite CVD endpoint

<table>
<thead>
<tr>
<th></th>
<th>Intensive SBP</th>
<th>Standard SBP</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT (N=9381)</td>
<td>243(1.65)</td>
<td>319(2.19)</td>
<td>0.75(0.64–0.89)</td>
</tr>
<tr>
<td>ACCORD BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard glycemia arm (N=2362)</td>
<td>162(2.98)</td>
<td>205(3.85)</td>
<td>0.77(0.63–0.95)</td>
</tr>
<tr>
<td>Intensive glycemia arm (N=2371)</td>
<td>161(3.02)</td>
<td>183(2.91)</td>
<td>1.04(0.83–1.29)</td>
</tr>
<tr>
<td>Combined glycemia arms (N=4733)</td>
<td>323(3.00)</td>
<td>368(3.36)</td>
<td>0.89(0.76–1.03)</td>
</tr>
</tbody>
</table>

### All-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Intensive SBP</th>
<th>Standard SBP</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT (N=9381)</td>
<td>155(1.03)</td>
<td>210(1.39)</td>
<td>0.73(0.60–0.90)</td>
</tr>
<tr>
<td>ACCORD BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard glycemia arm (N=2362)</td>
<td>64(1.08)</td>
<td>77(1.29)</td>
<td>0.85(0.61–1.19)</td>
</tr>
<tr>
<td>Intensive glycemia arm (N=2371)</td>
<td>86(1.48)</td>
<td>67(1.10)</td>
<td>1.34(0.98–1.85)</td>
</tr>
<tr>
<td>Combined glycemia arms (N=4733)</td>
<td>150(1.28)</td>
<td>144(1.19)</td>
<td>1.08(0.86–1.36)</td>
</tr>
</tbody>
</table>

Interaction p-values for comparisons of the effects of intensive SBP versus standard SBP

<table>
<thead>
<tr>
<th>For composite CVD endpoint</th>
<th>For all-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT vs. ACCORD BP standard glycemia arm</td>
<td>0.87</td>
</tr>
<tr>
<td>SPRINT vs. ACCORD BP intensive glycemia arm</td>
<td>0.023</td>
</tr>
<tr>
<td>ACCORD BP intensive vs. standard glycemia arm</td>
<td>0.053</td>
</tr>
<tr>
<td>SPRINT vs. ACCORD BP combined glycemia arms</td>
<td>0.16</td>
</tr>
</tbody>
</table>

## Unfortunate Pharmacoepidemiology

### ACEi Observational Data and Lung Cancer

#### Baseline Characteristics by Antihypertensive Drug

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire cohort</th>
<th>Antihypertensive drug use at cohort entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>ACEIs</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>55.6 (15.6)</td>
<td>57.8 (13.3)</td>
</tr>
<tr>
<td>Male sex</td>
<td>459064 (46.3)</td>
<td>133091 (63.9)</td>
</tr>
<tr>
<td>Alcohol related disorders</td>
<td>716064 (19.9)</td>
<td>181995 (8.7)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>215098 (21.7)</td>
<td>41595 (20.0)</td>
</tr>
<tr>
<td>Past</td>
<td>227504 (22.9)</td>
<td>58683 (28.2)</td>
</tr>
<tr>
<td>Never</td>
<td>484831 (48.9)</td>
<td>99820 (47.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>64628 (6.5)</td>
<td>8255 (4.0)</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>303311 (30.6)</td>
<td>45164 (21.7)</td>
</tr>
<tr>
<td>25-30</td>
<td>304699 (30.7)</td>
<td>71655 (34.4)</td>
</tr>
<tr>
<td>≥30.0</td>
<td>224888 (22.7)</td>
<td>67353 (32.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13220 (1.3)</td>
<td>15928 (0.8)</td>
</tr>
<tr>
<td>Mean (SD) duration of treated hypertension, years</td>
<td>0.2 (1.5)</td>
<td>0.3 (1.8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22403 (2.3)</td>
<td>5027 (2.4)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2399 (0.2)</td>
<td>474 (0.2)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>78669 (7.9)</td>
<td>16152 (7.8)</td>
</tr>
<tr>
<td>Statins</td>
<td>164891 (16.6)</td>
<td>73510 (35.3)</td>
</tr>
<tr>
<td>Mean (SD) total No of unique drug classes</td>
<td>4.1 (4.1)</td>
<td>4.1 (4.1)</td>
</tr>
<tr>
<td>0</td>
<td>150293 (15.2)</td>
<td>35284 (17.0)</td>
</tr>
<tr>
<td>1</td>
<td>147609 (14.9)</td>
<td>31022 (14.9)</td>
</tr>
<tr>
<td>2</td>
<td>135085 (13.6)</td>
<td>27027 (13.0)</td>
</tr>
<tr>
<td>3</td>
<td>115121 (11.6)</td>
<td>22157 (10.6)</td>
</tr>
<tr>
<td>≥4</td>
<td>443953 (44.8)</td>
<td>92763 (44.5)</td>
</tr>
</tbody>
</table>

14 % hazard ratio for lung CA with ACEi vs ARB only after 5 years ACEi

Unadjusted Absolute risk ~0.4 per 1000 pt years
1.6 ACEi vs 1.2 ARB with NNH ~2,500

#### Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>1.14 (1.01 to 1.29)</td>
<td>1.13 (0.99 to 1.29)</td>
</tr>
<tr>
<td>Two year lag period</td>
<td>1.18 (1.02 to 1.35)</td>
<td>1.22 (1.03 to 1.44)</td>
</tr>
<tr>
<td>Three year lag period</td>
<td>1.20 (1.06 to 1.36)</td>
<td></td>
</tr>
</tbody>
</table>

#### Forest plot

**Residual Confounding**

Lower Socioeconomic Status with ACEi?

Detection bias: ↑Thoracic Imaging with ACEi?

Smoking duration & intensity was not assessed.

Bottom Line: Don’t change your prescription practice. Inform high risk patients about study.

1) Hicks BM, et al. BMJ. 2018 Oct 24;363:k4209
2) Cronin-Fenton D. BMJ. 2018 Oct 24;363:k4337
3) BMJ [https://www.bmj.com/content/363/bmj.k4209/rapid-responses](https://www.bmj.com/content/363/bmj.k4209/rapid-responses)
CKD and Atrial Fibrillation

Efficacy and safety of DOACs vs. warfarin in the subgroup of patients with CKD

## CKD categories lacking RCT data on anticoagulation

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Endoxaban</th>
<th>Ribaroxiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-30</td>
<td>Adjusted dose for INR 2–3 could be considered</td>
<td>2.5 twice daily</td>
<td>75 mg twice daily</td>
<td>30mg daily?</td>
<td>15mg daily</td>
</tr>
<tr>
<td>&lt;15 not on dialysis</td>
<td>Equipoise: observational data and meta-analysis</td>
<td>2.5 twice daily</td>
<td>NR</td>
<td>NR</td>
<td>15mg daily?</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Equipoise: observational data and meta-analysis</td>
<td>2.5 twice daily</td>
<td>NR</td>
<td>NR</td>
<td>15mg daily?</td>
</tr>
</tbody>
</table>

NR – not recommended

APOL1 risk alleles are associated with CKD progression in AASK

HR 1.88 (1.46-2.41); p<0.001

Parsa et al. NEJM 2013; 369(23):2183-96
Why are alleles present?

Serum resistance associated binding domain

Limou et al. KI 2015; 88:28-34
**CKD Metabolic Acidosis: Open Label Prospective RCT**

**Study Population:**
Aged 18-75 years
eGFR 15-29 ml/min/1.73m² (Stage G4)
Bicarbonate 16-20 mEq/L (normal 22-26)

**Exclusion Criteria:**
Uncontrolled HTN (> 150/90 mm Hg)
CHF
Morbid Obesity

**Randomized Single Center:**
Unblinded
2 year follow up

---

Refused consent = 20
Not eligible = 30

Withdrew = 5 intervention arm only

---

Control

Bicarbonate (Oral NaHCO₃ 1–3 g/day)

---

CKD Metabolic Acidosis: Open Label Prospective RCT

Less Incident Dialysis

Preservation of kidney function above
No change in albuminuria
No change in Systolic and Diastolic BP
Non-significant increase overall BP drugs
bicarbonate group 61% vs 48%, $P=0.17$

Non-significant increase in loop diuretic use
bicarbonate group 39 vs 30%, $P=0.50$

CKD Metabolic Acidosis: Fruits & Vegetables vs Bicarbonate

- 108 patients with Stage G3 CKD
- No Acidosis: Serum TCO₂ 22 – 24
- Randomized to 3 arms:
  - No treatment
  - NaHCO₃ 1 mEq/kg/day
  - Fruits and vegetable diet
- 3 year follow-up
- Results
  - Serum TCO₂ 22 vs 24 with Rx
  - eGFR better preserved with Rx
  - BP decreased in all groups, but most in fruits and vegetables (F + V) arm (data not shown).

Hyperuricemia? If Gout treat, if not don’t

- KDIGO
  - There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. *(Not graded)*

- Uric acid lowering therapy if 2 or more gout flares per year and anyone with tophi. More aggressive in CKD?
Allopurinol in CKD: Observational Data
Slows Loss of eGFR

75 – 85% on ACEi or ARB.
35 – 40% DM

84 month follow-up data slower CKD Progression (ESRD/50%↓eGFR) in those receiving allopurinol

Goicoechea M et al. AJKD. 2015;65:543-549
Allopurinol for all CKD patients with Gout?

- **Allopurinol hypersensitivity syndrome**
  - Incidence ~ 0.3%,
  - Mortality rate ~ 20-25%
  - Initial dose is major risk
  - Start at 50 – 100 mg once daily (50 mg if CKD G4+)

- **Alternatives**
  - Febuxostat may slow loss of eGFR
  - Uricosuric agents (probenecid) are not effective at low eGFR & risk uric acid nephrolithiasis

Khanna D *et al*. Arthritis Care Res. 2012;64:1431-1446
Khanna D *et al*. Arthritis Care Res. 2012;64:1447-1461
Case Rep Dermatol 2017;9:1–7
Gout in CKD

- Uric Acid Lowering Therapy if 2 or more flares per year or any patient with tophi to target Uric acid less than 7 mg/dL
- Allopurinol associated with slower loss of eGFR in observational studies
- Allopurinol should be first line except
  - History of Allopurinol Allergy
  - HLA-B*5801 test Asians to predict risk for skin hypersensitivity
- Febuxostat 40 or 80 mg dose for others
- Febuxostat FDA black box warning 11/17 patients with established Cardiovascular disease – higher CV death in RCT vs allopurinol.

https://www.fda.gov/Drugs/DrugSafety/ucm631182.htm
Allopurinol: HLA-B*5810 predicts high risk for severe cutaneous adverse reaction

- Pretest Asians HLA-B*5801 if negative Allopurinol 50-100 mg daily and titrate
- Monitor eGFR, UACR, CBC, uric acid, transaminases, eosinophils
- Educate patient to discontinue for any skin reaction & ER for painful rash

<table>
<thead>
<tr>
<th>Population</th>
<th>Approximate HLA-B*5801 Allele Frequency, %</th>
<th>Guideline for HLA-B*5801 Testing Prior to Allopurinol Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han Chinese descent</td>
<td>6.0-8.0</td>
<td>Consider with any renal function</td>
</tr>
<tr>
<td>Thai descent</td>
<td>6.0-8.0</td>
<td>Consider with any renal function</td>
</tr>
<tr>
<td>Korean descent (CKD stage 3 or worse)</td>
<td>12.0</td>
<td>Consider in chronic kidney disease stage 3 or worse</td>
</tr>
<tr>
<td>African American</td>
<td>3.8</td>
<td>Not recommended</td>
</tr>
<tr>
<td>White/Hispanic</td>
<td>&lt;1.0</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Febuxostat Use in CKD

- Allopurinol should be first line except
  - History of Allopurinol Allergy
  - HLA-B*5801
- Febuxostat 40 or 80 mg dose
- Febuxostat FDA black box warning 2/21/19

“Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.”

https://www.fda.gov/Drugs/DrugSafety/ucm631182.htm
SGLT-2i data from EMPA REG OUTCOME: Heart Failure Hospitalization or CV death by eGFR

<table>
<thead>
<tr>
<th>Event n/n Analysed</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>Placebo</td>
</tr>
<tr>
<td>All patients</td>
<td>265/4687</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td></td>
</tr>
<tr>
<td>≥90</td>
<td>36/1050</td>
</tr>
<tr>
<td>60 to &lt;90</td>
<td>117/2423</td>
</tr>
<tr>
<td>45 to &lt;60</td>
<td>31/831</td>
</tr>
<tr>
<td>30 to &lt;45</td>
<td>20/381</td>
</tr>
</tbody>
</table>

Cox regression analysis in the treated set

Unpublished data from EMPA REG Outcome trial supports efficacy for eGFR 30 to 45 ml/min/1.73m²

 Courtesy of Christoph Wanner
Figure 1—Tubuloglomerular feedback system in normal physiology (A), diabetes (B), and diabetes after treatment with SGLT2 inhibition (C). TGF, tubuloglomerular feedback. Adapted from Cherney et al. (36).
Kidney Outcomes Significantly Reduced by SGLT-2i in EMPA-REG
Summary of potential mechanisms leading to kidney protection with SGLT-2i

Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR® Research to Practice project

Suzanne V Arnold¹, Silvio E Inzucchi², Fengming Tang¹, Darren K McGuire³, Sanjeev N Mehta⁴, Thomas M Maddox⁵, Abhinav Goyal⁶, Laurence S Sperling⁷, Daniel Einhorn⁷, Nathan D Wong⁸, Kamlesh Khunti⁹, Carolyn SP Lam¹⁰, and Mikhail Kosiborod¹

Abstract

Aims: Recent trials (EMPA-REG OUTCOME and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER]) have shown improved cardiovascular (CV) mortality with specific currently available glucose-lowering medications (empagliflozin and liraglutide, respectively), but were limited to selected patient populations. We sought to evaluate the current use and potential real-world impact of empagliflozin (and other sodium–glucose co-transporter 2 inhibitors [SGLT2i]) and liraglutide (and other glucagon-like peptide-1 receptor agonist [GLP-1 RA]) among patients in the Diabetes Collaborative Registry (DCR).

Methods and results: We evaluated 182,525 patients from the DCR – a large, US-based outpatient registry of individuals with type 2 diabetes from 313 sites that included cardiology, endocrinology and primary care practices. Among these patients, 26.2% met major eligibility criteria for EMPA-REG OUTCOME and 48.0% met major eligibility criteria for LEADER. Of these potentially eligible patients, only a small minority were actually prescribed these agents: 5.2% on an SGLT2i and 6.0% on a GLP-1 RA, respectively. Patients receiving these studied medications or medication
Sodium-glucose Cotransporter-2 Inhibitors (SGLT-2i): Gamechanger more than Overhyped

- **Gamechanger**
  - First drug class since ACEi or ARB to reduce eGFR progression
  - First drug class since ACEi or ARB to reduce incident/progression of albuminuria
  - Remarkable reduction in Heart Failure hospitalization that is enriched in CKD

- **Overhyped**
  - Morass of expert SGLT2i opinions & controversy over individual drug vs class effect
  - Canagliflozin, Dapagliflozin, and Empagliflozin currently approved by FDA only if eGFR 45 and above.
  - Adverse reactions
    - Amputations – CANVAS-R canagliflozin trial only – safety signal or not?
    - Genitourinary Infections
    - Ketoacidosis: insulin-treated DM
  - CREDENCE and DAPA-CKD trials are pending
CREDENCE trial stopped early for favorable CKD findings with canagliflozin

July 19, 2018

The steering committee behind the phase 3 CREDENCE clinical trial, evaluating the efficacy and safety of the SGLT2 inhibitor canagliflozin vs. placebo for adults with type 2 diabetes and chronic kidney disease, announced an early stop of the trial based on the achievement of prespecified efficacy criteria, according to a press release from Janssen.
Colonic Necrosis from Kayexalate in 70% Sorbitol

By 2005 the FDA had received 35 reports of serious bowel injuries associated with both oral and rectal administration of the mixture, many were fatal.

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Serum K+ Starting Dose (mEq/L) (Gms)
5.1 to 5.4 4.2 bid
5.5 to 6.4 8.4 bid

Patiromer Side Effects

- Hypomagnesemia
  - 8.6% Mg < 1.4 mg/dl
  - 4.3% Mg < 1.2 mg/dl
  - 9/13 had Mg <1.8 mg/dl on entry
  - 8/13 on diuretics or PPI’s

- Constipation 5-10%

- Calcium Load
  - No difference in serum calcium

- Black box warning issued about drug-drug interactions
  - 3 hours between Patiromer & other drugs
Anemia in CKD

- KDIGO and KDOQI
  - < 13.0 g/dL in males and < 12.0 g/dL in females
  - Non-anemic
    - Measure at least annually for Stage G3 CKD
    - Measure at least twice per year for Stage G4 – 5 CKD
  - Anemic
    - Measure every 3 months for Stages G3 – 5

- Evaluation: CBC, retic count, ferritin, Fe saturation, B12

- Stages CKD G3 – 5
  - ESA main indication is to avoid transfusion
  - Consider when Hb 9.0 – 10.0 g/dL to avoid Hb falling below 9 (2B)
Iron Management in CKD Anemia

- Consider iron if TSAT ≤ 30% and ferritin ≤ 500 ng/ml
  - Attempt oral repletion before considering ESA
- IV iron if oral ineffective or if receiving ESA
  - Better tolerated but potential for severe side-effects
- Oral iron (200 mg elemental iron daily)
  - Bioavailability: empty stomach if tolerated

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose / tablet</th>
<th>Elemental Fe / tablet</th>
<th>Typical Rx</th>
<th>Daily Elemental Fe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron polysaccharide</td>
<td>150 mg</td>
<td>150 mg</td>
<td>1 tab day</td>
<td>150 mg</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>324 mg</td>
<td>106 mg</td>
<td>1 tab 2xday</td>
<td>212 mg</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325 mg</td>
<td>65 mg</td>
<td>1 tab TID</td>
<td>195 mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>325 mg</td>
<td>39 mg</td>
<td>5 tabs</td>
<td>195 mg</td>
</tr>
</tbody>
</table>

Hypoxia Inducible Factor Inhibitors:
Future Potential Oral CKD Anemia Therapy
CKD Anemia Summary

- Anemia and iron deficiency are common in CKD, especially CKD G4+
- Effective erythropoiesis requires both EPO and iron
- Biosimilar ESAs offer the promise of lower cost and greater patient access with safety and efficacy similar to the reference products
- HIF inhibitors are not currently FDA approved, but are oral alternatives to ESA that hold promise.
Observational Studies of Early versus Late Nephrology Consultation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early referral mean (SD)</th>
<th>Late referral mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality, %</td>
<td>11 (3)</td>
<td>23 (4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year mortality, %</td>
<td>13 (4)</td>
<td>29 (5)</td>
<td>0.028</td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>13.5 (2.2)</td>
<td>25.3 (3.8)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serum albumin at RRT start, g/dl [g/l]</td>
<td>3.62 (0.05) [36.2 (0.5)]</td>
<td>3.40 (0.03) [34.0 (0.3)]</td>
<td>0.001</td>
</tr>
<tr>
<td>Hematocrit at RRT start, %</td>
<td>30.54 (0.18)</td>
<td>29.71 (0.10)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Abbreviation: RRT, renal replacement therapy.


**TESTING FOR CKD-MBD**

**3.2.1:** In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest bone mineral density (BMD) testing to assess fracture risk if results will impact treatment decisions (*2B*).

**3.2.2:** In patients with CKD G3a-G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).
DEXA-determined femoral BMD Predicts Fracture Risk in advanced CKD: Meta-Analysis