HHP Care Model and Disease Management Webinar Series

Chronic Kidney Disease (CKD) #2

Thursday, April 08, 2021
5:30pm – 6:30pm

HAWAIʻI PACIFIC HEALTH | HAWAIʻI HEALTH PARTNERS

Moderator – 04/08/21

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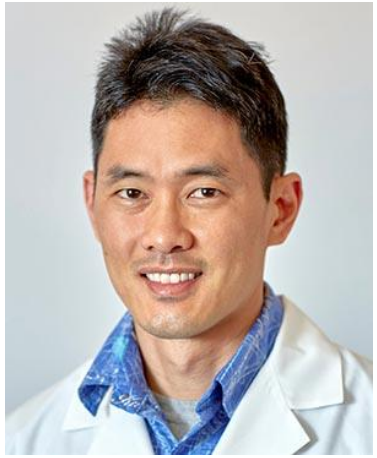
The Management of Chronic Kidney Disease



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Introduction to Chronic Kidney Disease (CKD)

- Epidemiology of CKD
- Identifying CKD
- Accurately assess kidney function and estimate risk for progression
- Determine cause of CKD
- **Take measures to slow down progression of CKD**
- Identify and treat secondary complications of CKD
- Select and prepare for renal replacement therapy

Summary of Last Presentation

- CKD is common, more than 1 in 7 (~15%) of adults have CKD 1-5 (>37 million in US). Native Hawaiian/Pacific
- Islander have the highest rate of ESRD in the US
- Verify Cr based eGFR using 24 hour Cr + urea clearance and/or Cystatin C Cr eGFR equation
- Quantify albuminuria
- Hematuria can indicate glomerular disease

CDC Website on CKD: https://nccd.cdc.gov/ckd/

Slowing Down CKD

- Managing hypertension
- Managing diabetes
- Use sodium glucose transporter-2 (SGLT-2) inhibitor therapy
- Treat metabolic acidosis
- Dietary and lifestyle management of CKD
- Update on disease specific CKD management

CDC Website on CKD: https://nccd.cdc.gov/ckd/

Hypertension and CKD Progression

- Target BP 125-130/<80mmHg
  - Reduces risk of ESRD in patients with albuminuria
  - Reduces CV risk and mortality in all patients
- ACE-I/ARBS (RAS blockade) first line in patients with albuminuria
  - High salt diet (>6 g/day) and volume expansion impair RAS blockade benefit
  - No benefit in combining ACE-I + ARB
- Diuretics
  - Use long-acting thiazide diuretic such as chlorthalidone

AASK Trial. JAMA. 2001;285(21):2719
MDRD Trial. NEJM. 1994;330(13):877

Managing Diabetes Mellitus

- Target hgba1c should be individualized. Improved control reduces microvascular complications of DM (nephropathy, neuropathy and retinopathy)
  - <7% for most patients
  - <8% in patients with limited life expectancy, advance CKD, co-morbid conditions and advanced age

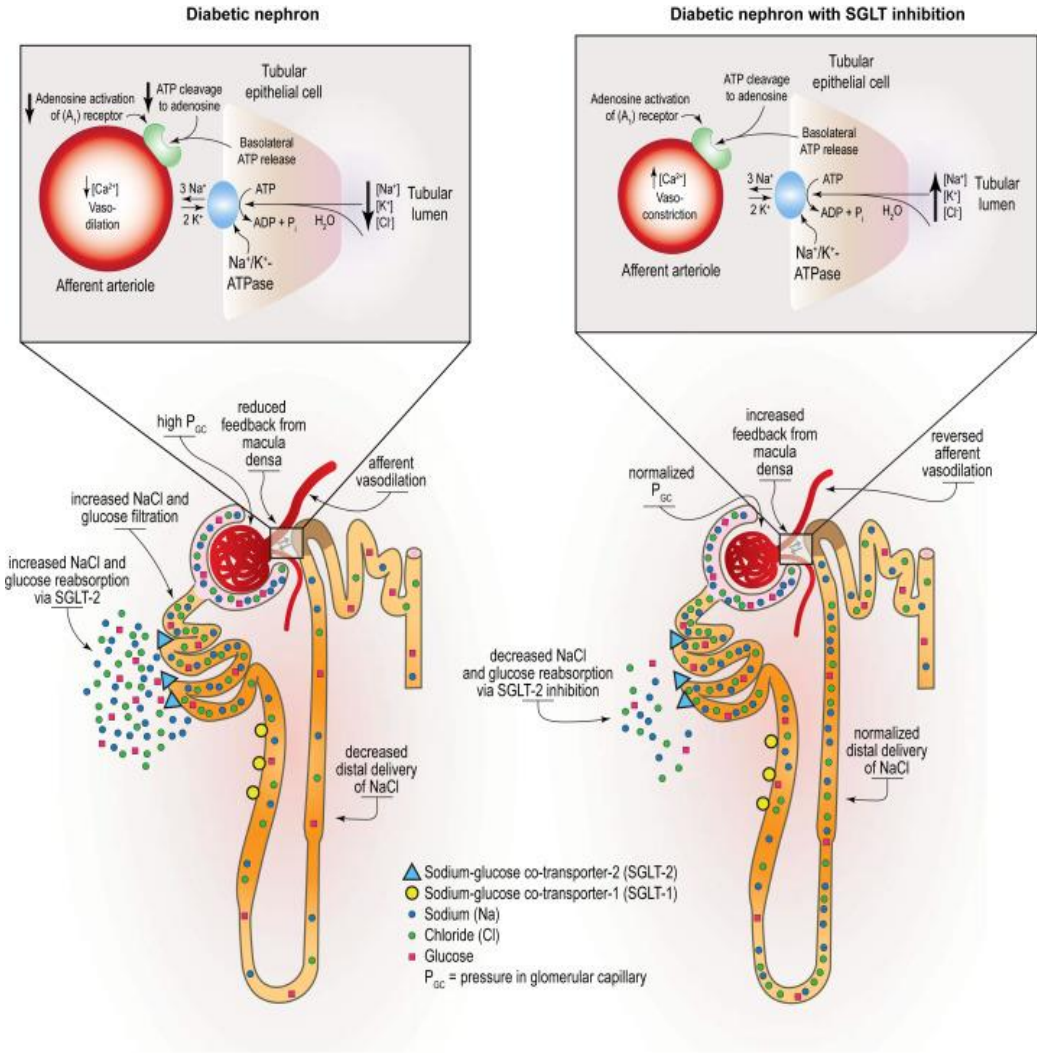
- Implement known multifaceted interventions to reduce CKD progression in adults with DM
  - Smoking cessation
  - Intensive BP control (<130/80)

UKPDS. Lancet 1998
ACCORD. Lancet 2010

Prescribe SGLT-2 Inhibitor

- 4 SGLT-2 inhibitors
  - Cangliflozin
  - Empagliflozin
  - Dapagliflozin
  - Ertugliflozin

- Mechanism
  - Inhibit sodium and glucose reabsorption in the proximal tubule



AJKD: January 1, 2021

Evidence Supporting SGLT-2 Inhibitor Therapy

- EMPA-REG (NEJM 11/2015)
  - Reduced CV events and death (32% risk reduction)
- CANVAS (NEJM 8/2017): CV and renal outcomes
  - Reduced CV events (26.9 vs 31.5/1000, p <0.001)
  - Trend towards improved renal outcomes but NOT statistically significant
  - Increase risk of amputation (6.3% vs 3.4%)
- DAPA-HF (NEJM 11/2019)
  - Dapagliflozin reduce risk of worsening heart failure, death and heart failure associated hospitalizations in both diabetics and non-diabetics
- CREDENCE (NEJM 6/2019)
- DAPA-CKD (NEJM 10/2020)

AJKD: January 1, 2021

Evidence Supporting SGLT-2 Inhibitor Therapy

- CREDENCE (NEJM 11/2019)
  - 4401 patient with albuminuric CKD (eGFR 30-90mL/min) received canagliflozin 100mg or placebo.
  - 30% lower risk of ESRD, doubling of serum Cr and death from renal or CV causes
  - No increased risk of amputation or fractures

- DAPA-CKD (NEJM 10/2020)
  - 4304 patients with CKD (with or w/o DM) received dapagliflozin 10mg or placebo. 14.5% eGFR <30mL/min
  - Dapagliflozin reduced risk for GFR by <50%, ESRD or death from renal causes (HR 0.61, P <0.001)
  - No significant increase in hypoglycemia or ketoacidosis

AJKD: January 1, 2021

Prescribe SGLT-2 Inhibitor

- Complications
  - Increased risk of genital infections (candidiasis, Fournier's gangrene)
  - Possible increased risk of lower extremity amputations
  - Volume depletion
  - Increased risk of fracture
  - Euglycemic diabetic ketoacidosis (DKA)
    - RFs: Insufficient insulin, reduced carbohydrate intake, excessive alcohol, volume depletion, concomitant infections

CJASN. November 2020

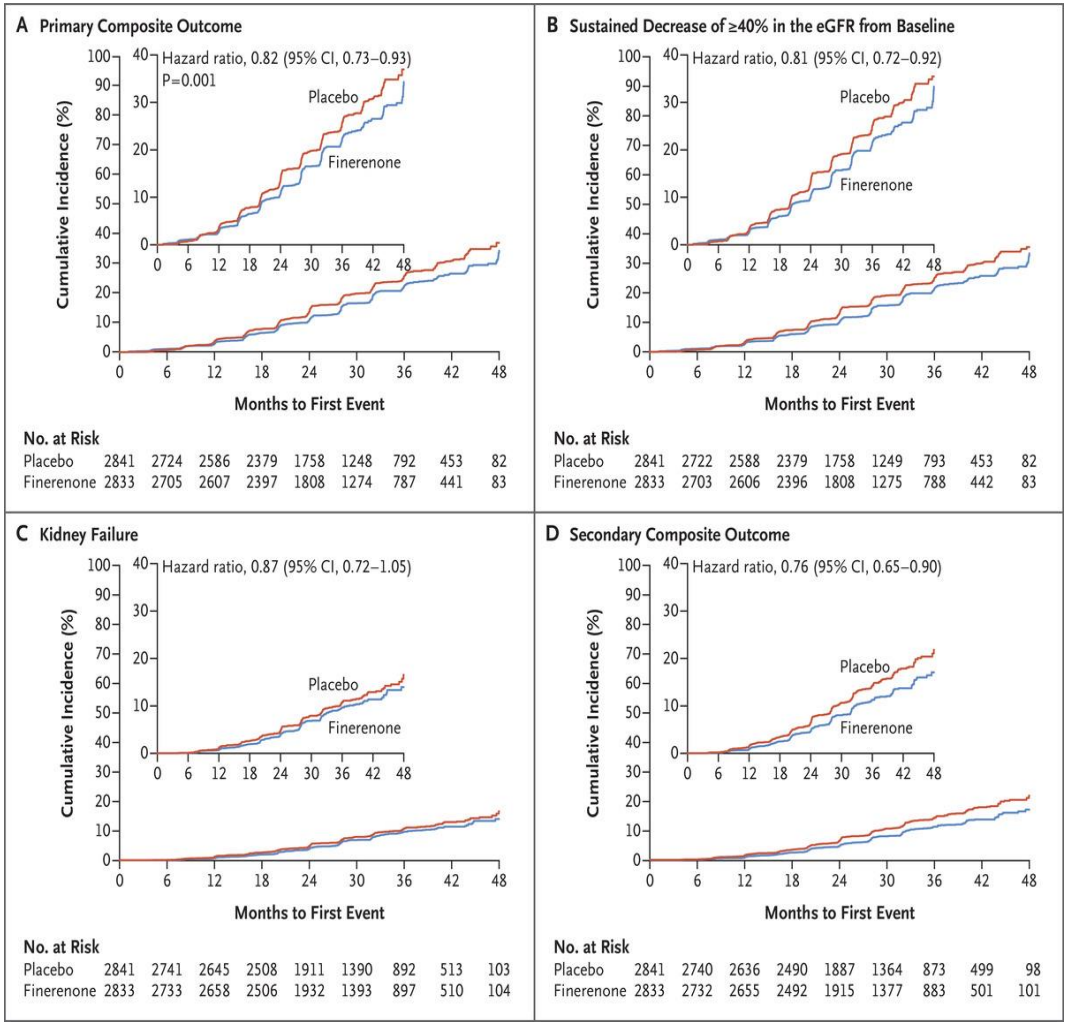
Finerenone for Diabetic Kidney Disease

- Selective mineralcorticoid receptor antagonist
- Short term trials showed reduction in albuminuria but. Trial assess long-term outcomes of finerenone.
- 5743 patients with type 2 DM and CKD randomized to finerenone (10mg – 20mg daily) versus placebo
- All patients on maximal dose ACE or ARB

FIDELO-DKD. NEJM. Dec 2020; 383 2219-2229

Finerenone for Diabetic Kidney Disease

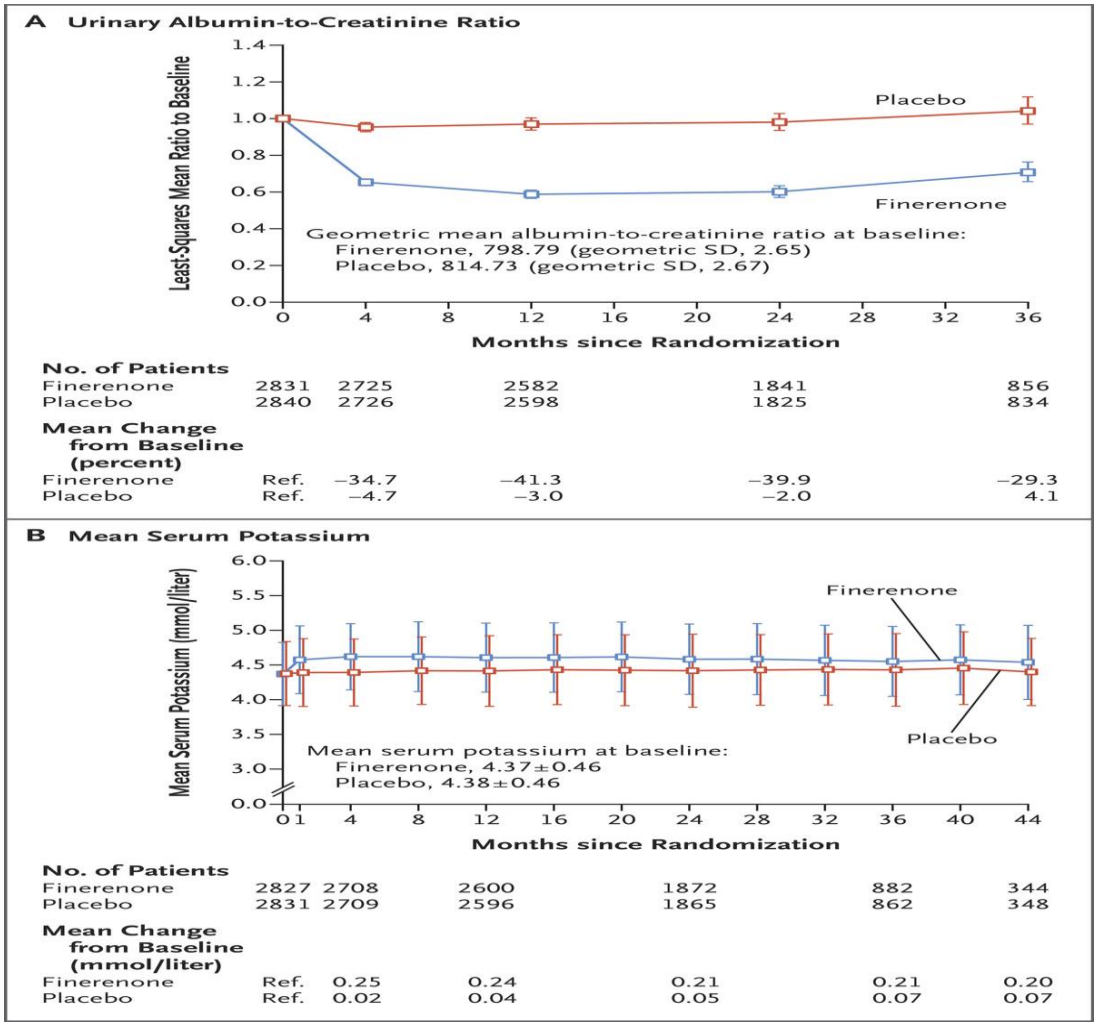
- Primary outcomes:
  - Time to kidney failure
  - Sustain decrease in eGFR by >40%
  - Death from kidney related causes
- Secondary outcomes:
  - Death from CV causes
  - Non-fatal MI
  - Non-fatal CVA
  - Hospitalization for HF



FIDELO-DKD. NEJM. Dec 2020; 383 2219-2229

Finerenone for Diabetic Kidney Disease

- Albuminuria
  - 31% greater reduction in albuminuria versus placebo
- Hyperkalemia
  - Finerenone 2.3%
  - Placebo 0.9%



FIDELO-DKD. NEJM. Dec 2020; 383 2219-2229

Treat Metabolic Acidosis

- Sulfuric acid is derived from metabolism of sulfur containing amino acids (animal protein)
- Acid accumulates with CKD due to decreased ammoniagenesis and bicarbonate wasting
- Benefits of bicarbonate therapy
  - Target CO2 >23 – 29
  - Lower risk of ESRD
  - Slower decline in eGFR
  - Lower all cause mortality
  - Improved nutritional status and decreased muscle catabolism
  - Improved bone parameters

De Brito-Ashurst et. Al. JASN. 2009; 20(9):2075
Mahajan et. Al. Kid Int. 2010: 78(3)L 303
Menon et Al. Am. J. Kidney Dis. 2010 Nov; 56(5):907-914

Dietary Management of CKD

- Dietary protein restriction (0.6 to 0.8g/kg/day)
  - Dietary protein increases glomerular hyperfiltration and pressure
  - Increased acid load (animal based proteins)
  - Reduction in uremic symptoms
  - Reduction in proteinuria

- Sodium restriction
  - J-shaped curve mortality <3 grams and >5 grams
  - Generally recommend <4 grams/day in patients with CKD and <3 grams per day is selected patients with fluid retention or hypertension

Nutritional management of CKD. NEJM. November 2017

Dietary Management of CKD

- Water Intake Trial
  - 631 adults with stage 3 CKD randomized to increased (mean 0.6L/day more) vs standard water intake
  - No significant change in CrCl, albuminuria and Quality of health
  - Conditions that benefit from increased water intake- PKD, UTI and kidney stones

Table 3. Primary Outcome: 1-Year Change in Estimated Glomerular Filtration Rate[a]

eGFR, mL/min per 1.73 m^2	Mean (95% CI)		Adjusted Between-Group Difference in Change[b] (95% CI)	*P* Value
	Hydration Group (n = 311)	Control Group (n = 308)		
Prerandomization	43.3 (42.1 to 44.4)	43.6 (42.6 to 44.7)		
12 Months	41.0 (39.5 to 42.6)	41.7 (40.3 to 43.1)		
Change	−2.2 (−3.3 to −1.1)[c]	−1.9 (−2.9 to −0.9)[c]	−0.3 (−1.8 to 1.2)	.74

Table 4. Secondary Outcomes: 1-Year Change in Plasma Copeptin, Creatinine Clearance, 24-Hour Urine Albumin, and Patient-Reported Overall Quality of Health[a]

	Hydration Group (n = 291)	Control Group (n = 299)	Between-Group Difference in Change[b] (95% CI)	*P* Value[b]
Plasma copeptin, mean (SD), pmol/L				
Prerandomization	17.4 (12.4)	17.5 (13.0)		
12 Month	16.1 (13.5)	18.3 (13.6)		
Change (95% CI)	−1.4 (−2.7 to −0.0)[c]	0.8 (−0.3 to 1.9)[c]	−2.2 (−3.9 to −0.5)	.01
Creatinine clearance, mean (SD), mL/min per 1.73 m^2				
Prerandomization	52.5 (17.1)	54.6 (15.6)		
12 Month	53.1 (19.7)	51.6 (18.9)		
Change (95% CI)	0.6 (−1.6 to 2.7)[c]	−3.0 (−4.9 to −1.2)[c]	3.6 (0.8 to 6.4)	.01
Urine albumin, mean (SD), mg/d				
Prerandomization	139 (49 to 425)	108 (32 to 606)		
12 Month	142 (38 to 509)	103 (32 to 497)		
Change (95% CI)	7 (−4.1 to 16.2)[c]	0.2 (−7.0 to 4.6)[c]	6.8 (−3.9 to 50.8)	.11
Quality of health[d]				
Prerandomization	7.3 (1.6)	7.3 (1.6)		
12 Month	7.2 (1.9)	7.1 (1.8)		
Change (95% CI)	−0.0 (−0.3 to 0.2)[c]	−0.2 (−0.4 to −0.0)[c]	0.2 (−0.3 to 0.3)	.22

CKD Water Intake Trial. JAMA 319. 1870-1879, 2018

Dietary Management of CKD

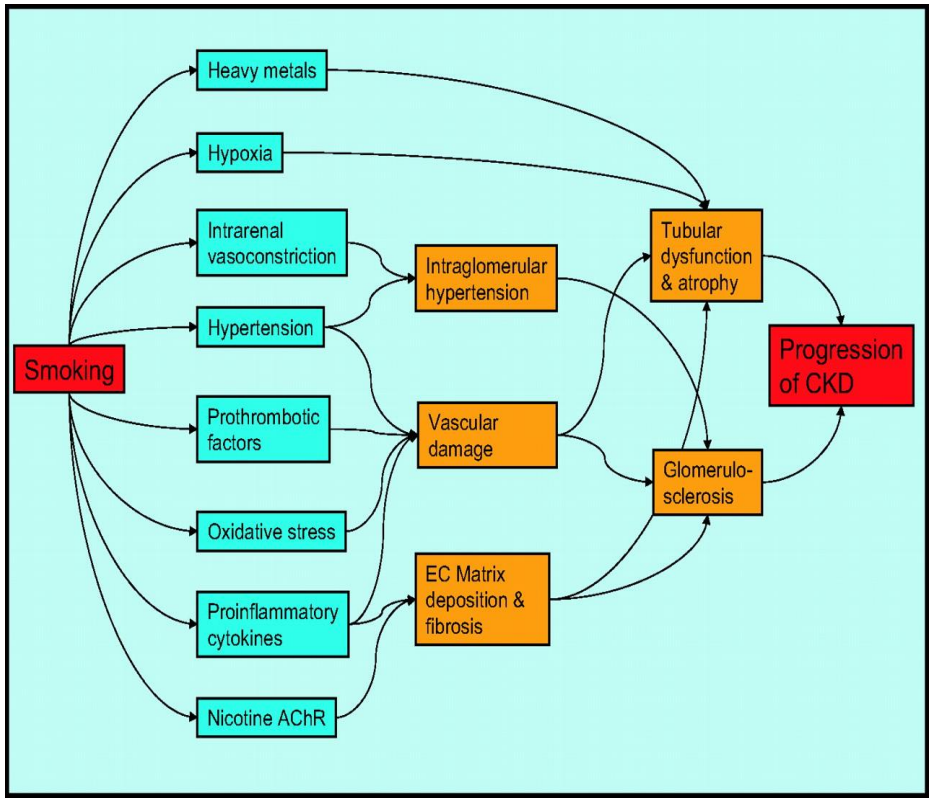
- Coffee may be protective
  - Polyphenols in coffee increase glutathione which reduces oxidative stress/ischemic injury to kidney tubules
  - Observational data showed consumption of >2 cups per day reduced ESRD risk (benefit greater in men)

- Diet soda
  - Phosphate containing preservatives can increase acid load
  - 5-7 cups/week increased ESRD risk by 1.33
  - >7 cups/week increased ESRD risk by 1.83

Coffee consumption and incident kidney disease. Am J Kidney Dis. March 2018
Diet soda consumption and risk of ESRD. CJASN. January 2017

Smoking Cessation

- Smoking associated with enhanced risk of both development and progression of CKD
- Stopping smoking is associated with slower rate of CKD progression



CJASN. January 2008

Manage Obesity

- Obesity can cause worsened metabolic syndrome parameters (blood glucose, hyperuricemia and hypertension) and renal hyperfiltration injury

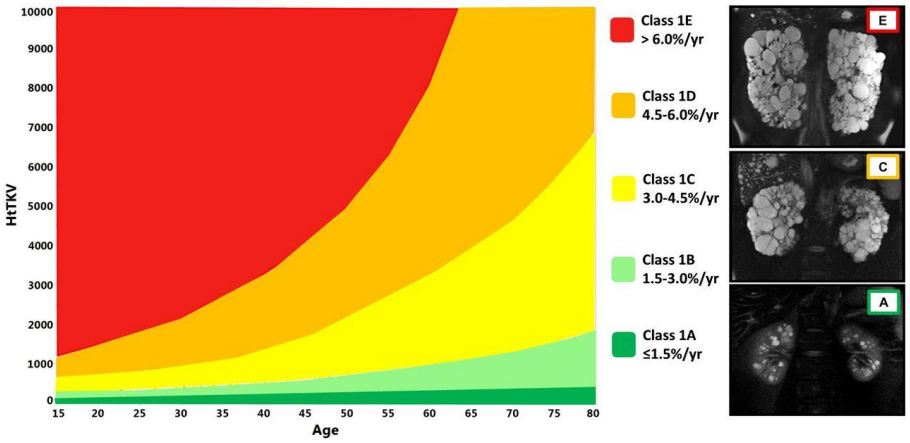
- Weight loss is associated with improved renal outcomes
  - Difficult to determine if improved outcomes are due to metabolic or hemodynamic improvements (probably both)

Ann Internal Medicine. January 2006
Kidney International. October 2017

Disease Specific CKD Management-ADPKD

- Autosomal dominant polycystic kidney disease
  - TEMPO and REPRISE Trials
    - Total kidney volume (TKV) predicts risk for CKD progression and ESRD
    - The vasopressin receptor 2 antagonist Tolvaptan reduced rate of increase in TKV and decline in eGFR
    - Extrapolation of trial data predicts extension of time to progression to ESRD by 6-9 years if started when eGFR is >60mL/min

Mayo Clinic Classification of TKV



TEMPO. NEJM. December 2012
REPRISE. NEJM. November 2017

Disease Specific CKD Management- Hyperuricemia

- Hyperuricemia and CKD
  - Definition of hyperuricemia
    - Uric acid >9.0 if Cr <1.5
    - Uric acid >10.0 if Cr between 1.5 and 2.0
    - Uric acid >12 if Cr >2.0
  - Consequence of hyperuricemia
    - Gout
    - Uric acid nephrolithiasis
    - Uric acid nephropathy
    - Association with hypertension, CKD, CV disease and insulin resistance syndrome (but causes relationships have not been established)

Reumatologia. October 2020

Disease Specific CKD Management- Hyperuricemia

- Treatment of hyperuricemia
  - Allopurinol preferred (Febuxostat associated with increased CV mortality)
  - Screen for HLA-B*5801 allele in Asian and African patients
- No benefit for CKD progression

- CKD-FIX (NEJM 10/2020)

Table 2. Effects of Allopurinol on Secondary Outcomes.

Outcome*	Allopurinol	Placebo	Risk Ratio (95% CI)†	Hazard Ratio (95% CI)‡
	no./total no. (%)			
40% decrease in eGFR, end-stage kidney disease, or death	63/182 (35)	51/181 (28)	1.23 (0.90–1.67)	1.34 (0.92–1.93)
30% decrease in eGFR, end-stage kidney disease, or death	82/182 (45)	72/181 (40)	1.13 (0.89–1.44)	1.23 (0.90–1.69)
40% decrease in eGFR	47/166 (28)	37/167 (22)	1.28 (0.88–1.86)	1.39 (0.90–2.13)
30% decrease in eGFR	70/170 (41)	63/172 (37)	1.12 (0.86–1.47)	1.21 (0.86–1.70)
End-stage kidney disease	25/171 (15)	19/175 (11)	1.35 (0.77–2.35)	1.38 (0.76–2.50)
Death from any cause	11/157 (7)	6/162 (4)	1.89 (0.72–4.99)	1.89 (0.70–5.11)
Fatal or nonfatal cardiovascular event	22/152 (14)	30/163 (18)	0.79 (0.48–1.30)	0.74 (0.43–1.29)
Hospitalization for any cause	83/171 (49)	77/172 (45)	1.08 (0.86–1.36)	1.17 (0.86–1.60)

* End-stage kidney disease was defined as receipt of dialysis for at least 30 days or kidney transplantation.
† Results were estimated from a prespecified analysis of log binomial regression models. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.
‡ Results were estimated from a post hoc analysis of Cox regression models. Confidence intervals have not been adjusted for multiplicity, and inferences drawn from the intervals may not be reproducible.

Conclusions

- Target BP and hgba1c values should be individualized but generally <130/80 and <7% to reduce risk of CKD progression
- Use SGLT2 inhibitors in patients with (and without?) diabetes mellitus to prevent CKD progression
- Identify and treat metabolic acidosis with sodium bicarbonate targeting serum bicarbonate >22
- Advise moderate dietary animal protein restriction, increase intake of fruits and vegetables
- Advise weight loss and smoking cessation
- Early nephrology referral for patient's with ADPKD for consideration of Tolvaptan
- Treatment of asymptomatic hyperuricemia for CKD prevention is controversial, but consider if serum uric acid levels are markedly elevated

Q&A

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Next Webinar:

HHP/HPH Community Webinar:

COVID-19: Updates and Recommendations*

Thursday, April 15, 2021

5:30pm – 6:30 pm

**Agenda is tentative and is subject to change*

Thank you!

- A recording of the meeting will be available afterwards.
- Unanswered question?
  - Contact us at info@hawaiihealthpartners.org

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