SLOWING PROGRESSION OF CHRONIC KIDNEY DISEASE

ASPN/HKSN CME COURSE
SEPTEMBER 28, 2019
# Prognosis of CKD by GFR and albuminuria category

**Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012**

| Persistent albuminuria categories | A1                        | A2                        | A3                        |
|----------------------------------|---------------------------|---------------------------|---------------------------|
| Description and range            | Normal to mildly increased| Moderately increased      | Severely increased        |
|                                 | <30 mg/g                  | 30-300 mg/g               | >300 mg/g                 |
|                                 | <3 mg/mmol                | 3-30 mg/mmol              | >30 mg/mmol               |

| GFR categories (ml/min 1.73 m²) | Description and range |
|----------------------------------|-----------------------|
| G1                               | Normal or high ≥90    |
| G2                               | Mildly decreased 60-89|
| G3a                              | Mildly to moderately decreased 45-59 |
| G3b                              | Moderately to severely decreased 30-44 |
| G4                               | Severely decreased 15-29|
| G5                               | Kidney failure ≤15     |

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
Timing of clinical outcomes in CKD with severely decreased GFR

Age (30-85 yrs) 60
Sex Male
Race (White or Black) White
eGFR (mL/min/1.73m²) 25
Systolic Blood Pressure (mmHg) 140
History of Cardiovascular Disease Yes
Diabetes Diabetes
Urine Albumin to Creatinine (mg/g) Click to change between mg/g and mg/mmol 2000
Smoking History Current Smoker

Risk at 4 Years

| Outcome | Risk  |
|---------|-------|
| Any Kidney Replacement Therapy (KRT a.k.a. ESRD) | 37.1% |
| Any Cardiovascular Disease (CVD) | 45.2% |
| Any Death | 40.1% |

- CKD G4+ - no event 19.8%
- KRT Only 15.3%
- KRT After CVD 2.4%
- CVD After KRT 4.7%
- Death After KRT 7.9%
- Death After KRT and CVD 6.7%
- Death After CVD 13.7%
- Death Only 11.8%
- CVD Only 17.7%

Grams ME, et al: Kidney Int 2018; 93:1442
Why identify patients with early CKD?

- Manage complications
  - Anemia
  - Mineral and bone disorders
  - Hypertension
  - Cardiovascular **
- Slow progression
- Plan for renal replacement therapy
PATHOPHYSIOLOGY OF PROGRESSION

- Hyperfiltration
- Renin-angiotensin-aldosterone
- Inflammation/oxidant stress
- Genetic susceptibility
• 1388 living kidney donors
  • CT scan kidney
  • Iothalamate-based GFR
  • Kidney biopsy at donation
• SNGFR = GFR/number of nephrons
  (#nephrons: cortical volume on CT x biopsy determined glomerular density)
Mean number of nephrons = 860,000 ± 370,000
Mean GFR = 115 ± 24 ml/min
Mean SNGFR = 80 ± 40 nl/minute
Higher SNGFR associated with risk factors for CKD:
  ▪ Larger nephrons
  ▪ More glomerulosclerosis and arteriosclerosis
  ▪ Obesity
  ▪ Family history of ESRD
Nephron number and GFR progressively decrease even with healthy aging.

Aleksandar Denic et al. JASN 2017;28:313-320

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N=9361 SBP >130
Intensive: SBP<120
Standard: SBP<140
• **Primary outcome:** composite of MI, acute coronary syndrome, stroke, HF, death
| Outcome                                           | Intensive Treatment | Standard Treatment | Hazard Ratio (95% CI) | P Value |
|--------------------------------------------------|---------------------|--------------------|-----------------------|---------|
|                                                  | no. of patients (%) | % per year         | no. of patients (%)   | % per year | (N=1330) | (N=1316) |                          |         |
| Participants with CKD at baseline                |                     |                    |                       |         |
| Composite renal outcome‡                         | 14 (1.1)            | 0.33               | 15 (1.1)              | 0.36    | 0.89 (0.42–1.87) | 0.76 |
| ≥50% reduction in estimated GFR§                 | 10 (0.8)            | 0.23               | 11 (0.8)              | 0.26    | 0.87 (0.36–2.07) | 0.75 |
| Long-term dialysis                               | 6 (0.5)             | 0.14               | 10 (0.8)              | 0.24    | 0.57 (0.19–1.54) | 0.27 |
| Kidney transplantation                           | 0                   | 0                  |                       |         |         |         |
| Incident albuminuria¶                            | 49/526 (9.3)        | 3.02               | 59/500 (11.8)         | 3.90    | 0.72 (0.48–1.07) | 0.11 |
| Participants without CKD at baseline            | (N=3332)            |                    | (N=3345)              |         |
| ≥30% reduction in estimated GFR to <60 ml/min/ min/1.73 m²§ | 127 (3.8)          | 1.21               | 37 (1.1)              | 0.35    | 3.49 (2.44–5.10) | <0.001 |
| Incident albuminuria¶                            | 110/1769 (6.2)      | 2.00               | 135/1831 (7.4)        | 2.41    | 0.81 (0.63–1.04) | 0.10 |

Renal outcome: decrease eGFR 50% or more, ESRD requiring dialysis or transplant
ADVERSE EFFECTS OF ANGIOTENSIN II

Afferent arteriole

Efferent arteriole

glomerular capillary hypertension

proteinuria

Loss of podocytes

↑ mesangial matrix and proliferation

Pro-fibrotic

proinflammatory

mesangial matrix and proliferation
The renin-angiotensin-aldosterone system

- Angiotensinogen
  - Renin
    - Renin Inhibitor
    - Angiotensin I
      - ACE
        - ACE-I
        - Angiotensin II
          - Angiotensin II receptor
            - Aldosterone antagonist
              - Aldosterone
                - Aldosterone receptor
Diabetic patients:
- Normoalbuminuric normotensive
- Microalbuminuric normotensive
- Diabetic nephropathy
- Non-diabetic kidney disease

Angiotensin II receptor blockade = Angiotensin converting enzyme inhibition

20% risk reduction
### Table 3. Summary of the Effects of Glycemic Control on Renal Disease

| Event                                      | Effect                  |
|--------------------------------------------|-------------------------|
| Development of albuminuria                 | +                       |
| Progression of microalbuminuria to overt proteinuria | +                       |
| GFR loss in type 2 diabetes                | −                       |
| GFR loss in type 1 diabetes                | +, long-term effect     |

_Seminars in Nephrology, Vol 36, No 4, July 2016, pp 331–342_
The diagram illustrates the transport of glucose in the kidney. Glucose is absorbed in the proximal tubule via SGLT2, with approximately 90% reabsorption. In the distal S2/S3 segment of the proximal tubule, SGLT1 is involved in the transport of glucose, with about 10% reabsorption. There is no glucose detected in the collecting duct.
• N=4401, DM2, eGFR=30 to <90, max RAAS blockade
• Median follow-up = 2.62 years
• Primary outcome: composite of ESRD, doubling S[Cr], death from renal cause
• Main results: primary outcome 30% lower in canagliflozin group
• Also: lower risk of CV death, MI, or stroke, hospitalization for heart failure
• No differences in rates of amputation or fracture
Nephron Protection in Diabetic Kidney Disease

Hans-Joachim Anders, M.D., John M. Davis, Ph.D., and Klaus Thurau, M.D.
- Endothelin A receptor antagonist
- Type 2 diabetic patients:
  - Age 18-85 years (5117 enrichment; 2648 responders)
  - eGFR – 25-75 mL/min/1.73m²
  - UACR – 300-5000 mg/g
- Maximal RAAS blockade for 4 weeks
- Median follow up 2.2 years
Primary renal outcome - composite of:
• Doubling of SCr
• ESRD
• Death

Primary endpoint:
• 6% atrasentan vs 7.9% placebo (p=0.0047)
Liraglutide and Renal Outcomes in Type 2 Diabetes

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Neil R. Poulter, F.Med.Sci., Søren Rasmussen, Ph.D., Karen Tornøe, M.D., Ph.D.,
Bernard Zinman, M.D., and John B. Buse, M.D., Ph.D.,
for the LEADER Steering Committee and Investigators

Liraglutide: glucagon-like peptide-1 (GLP-1) analogue – stimulates insulin release

- 9340 DM2 patients at high risk for CV disease
- Secondary renal outcome: new onset persistent macroalbuminuria, persistent doubling of serum Cr, need for renal replacement therapy, or death due to renal cause
A Composite Renal Outcome

Hazard ratio, 0.78 (95% CI, 0.67–0.92)
P=0.003

No. at Risk
Placebo 4672 4643 4540 4428 4316 4196 4094 3990 3901 3331 1613 433
Liraglutide 4688 4635 4561 4492 4400 4304 4210 4114 3132 1632 454

B New Onset of Persistent Macroalbuminuria

Hazard ratio, 0.74 (95% CI, 0.60–0.91)
P=0.004

No. at Risk
Placebo 4672 4646 4551 4455 4359 4252 4162 4073 1642 442
Liraglutide 4688 4638 4570 4508 4437 4353 4268 4182 1662 461

C Persistent Doubling of Serum Creatinine Level

Hazard ratio, 0.89 (95% CI, 0.67–1.19)
P=0.43

No. at Risk
Placebo 4672 4647 4596 4529 4447 4367 4282 4196 1682 456
Liraglutide 4688 4639 4591 4544 4476 4403 4332 4264 1692 475

D Continuous Renal-Replacement Therapy

Hazard ratio, 0.87 (95% CI, 0.61–1.24)
P=0.44

No. at Risk
Placebo 4672 4645 4590 4527 4454 4370 4299 4227 1699 461
Liraglutide 4688 4640 4596 4547 4484 4416 4349 4282 1710 483
| Trial         | Target                                             |
|--------------|----------------------------------------------------|
| FIDELIO-DKD  | Finerenone (nonsteroidal MRA)                      |
| PERL         | Allopurinol                                        |
| BASE         | Bicarbonate (high and low dose)                    |
| SONAR        | Atrasentan (endothelin antagonist)                 |
| Many         | Linagliptin (DPP-4 inhibitor)                      |
| Many         | SGLT2 inhibitors (DN and non-DN)                   |
| NCT01377285  | Pentoxifylline (antifibrotic)                      |
| PROCEED      | Paricalcitol (Vit D receptor agonist)              |
| VALID        | Dual RAAS blockade                                 |
EXECUTIVE ORDERS

Executive Order on Advancing American Kidney Health

HEALTHCARE | Issued on: July 10, 2019

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

HEALTH AND SCIENCE

Trump signs executive order overhauling kidney transplant, dialysis market

PUBLISHED WED. JUL 10 2019 - 9:48 AM EDT | UPDATED WED. JUL 10 2019 - 6:26 PM EDT

Brockley Lovelace Jr. | UAHKXEL1YR

SHARE  

Press

Executive order provides more options for people with kidney disease
CONCLUSIONS

- Lower BP – <130/80 (more aggressive in those patients with >proteinuria)
- Use RAAS blockade but only single agent
- SGLT2 inhibitors and liraglutide can prevent DN
- Keep HCO₃ >22; consider low protein diets
- Early nephrology referral and coordinated CKD care
- The future: endothelin antagonists, antifibrotic agents, antioxidants, cellular therapy
- Many ongoing trials
- White House Executive Order