CAN CKD BE PREVENTED OR REVERSED?

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Can CKD be Prevented or Reversed?

- Yes - maintaining kidney function
- Yes - restoring kidney function

Today's nomenclature: conceptionally different - definition of (primary) prevention vs secondary prevention (halting progression).

The new lexicon
Considerations while preparing the presentation

**Nephrology:** The main focus today is/was retarding the progression of a diagnosed/established disease and the treatment of kidney failure with replacement therapy.

There was, so far, no focus on preservation or salvage of Kidney Health (among Nephrologists, GPs, Internists, Endocrinologists and Cardiologists). Excuse: no or little research data on early prevention is available.

Guidelines (KDIGO, ADA) focus on individuals with an eGFR less than 60 ml/min/1.73m² or with albuminuria categories A2 or A3 (established disease, secondary prevention).
4 Foundational Therapies for Kidney Outcomes: approaches to reduce the Cardio-Renal Risk in individuals with …….
# Maintaining or Restoring Kidney Health

## Albuminuria

<table>
<thead>
<tr>
<th>Albuminuria stages, description and range (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
</tr>
<tr>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>≤30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR categories, description and range (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
</tr>
<tr>
<td>G2</td>
</tr>
<tr>
<td>G3a</td>
</tr>
<tr>
<td>G3b</td>
</tr>
<tr>
<td>G4</td>
</tr>
<tr>
<td>G5</td>
</tr>
</tbody>
</table>

**KDIGO CKD-Guideline Kidney Int Suppl.**
2013;3:1-150
2024 in press

**JAMA 2023;330:** 1266-1277
Kidney-Heart Risk Factor Management

Comprehensive Care

Practice point 1.1.1.

Kidney Int 2020;98:849-859
Kidney Int 2022;102:990-999
GLP-1RA have the potential to maintain Kidney Health

worsening kidney function: 40% or 57% eGFR, ESKD, renal death

Composite including albuminuria

<table>
<thead>
<tr>
<th>Trial</th>
<th>N1/N2</th>
<th>I1/I2</th>
<th>Hedges g</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>172/2647 (6%)</td>
<td>203/2639 (8%)</td>
<td>0.84 (0.68 to 1.02)</td>
<td>0.083</td>
</tr>
<tr>
<td>LEADER</td>
<td>268/4668 (6%)</td>
<td>337/4672 (7%)</td>
<td>0.78 (0.67 to 0.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>62/1648 (4%)</td>
<td>100/1649 (6%)</td>
<td>0.64 (0.46 to 0.88)</td>
<td>0.005</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>366/6256 (6%)</td>
<td>407/6222 (7%)</td>
<td>0.88 (0.76 to 1.01)</td>
<td>0.065</td>
</tr>
<tr>
<td>REWIND</td>
<td>848/4949 (17%)</td>
<td>970/4952 (20%)</td>
<td>0.85 (0.77 to 0.93)</td>
<td>0.0004</td>
</tr>
<tr>
<td>AMPLITUDE-O</td>
<td>353/2717 (13%)</td>
<td>250/1359 (18%)</td>
<td>0.68 (0.57 to 0.79)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Subtotal (I²=47.5%, p=0.090)

Favours GLP-1 receptor agonists Favours placebo
No need to have UACR measured

Patient 55 y T2DM

Speed: moderately accelerated

3 month additional loss of lifespan per 1 year due to T2DM alone

eGFR 90 60

The Emerging Risk Factors Collaboration, JAMA 2015;314:52
**EMPAREG-OUTCOME:** Distribution of individual eGFR slopes in the total cohort (baseline to follow-up)

Adjusted mean (95% CI).

-1.8 (-2.0; -1.6)*

Proportion of patients, % (95% CI)

Placebo

N=7020

Wanner et al
JASN 2018;29:2755-2769
NEJM 2016;375:323-334
**EMPAREG-OUTCOME:** Distribution of individual eGFR slopes in the total cohort (baseline to follow-up)

*Adjusted mean (95% CI).*
Shifting in KDIGO CKD risk groups with empagliflozin: Kidney-protection from SGLT2 inhibition across the spectrum of risk

Robert Weingold, Bernard Zinman, Michaela Mattheus, Anne Pernille Ofstad, Dominik Steubli, Christoph Wanner, Silvio E. Inzucchi.

Table 1
Proportions of patients who experienced change in UACR and/or eGFR category among all patients who experienced the corresponding change (i.e., worsening or improvement) in KDIGO risk category.

<table>
<thead>
<tr>
<th>Reason for risk change</th>
<th>Worsening in KDIGO risk category</th>
<th>Improvement in KDIGO risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑UACR</td>
<td>↓eGFR</td>
</tr>
<tr>
<td>Placebo (N = 661)</td>
<td>47.5%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Empagliflozin (N = 1017)</td>
<td>44.2%</td>
<td>42.0%</td>
</tr>
<tr>
<td></td>
<td>↓UACR</td>
<td>↑eGFR</td>
</tr>
<tr>
<td>Placebo (N = 208)</td>
<td>58.2%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Empagliflozin (N = 576)</td>
<td>63.7%</td>
<td>29.9%</td>
</tr>
</tbody>
</table>
EMPAREG-OUTCOME

Lancet Diabetes Endocrinol 2017;5:610-621; NEJM 2016;375:323-334
Neuen BL et al JASN 2019;30:2229-2242
DECLARE included substantial numbers of participants with normal kidney function
EMPＡ-KIDNEY: loss of kidney function in relation to albuminuria

Compared to Placebo Empagliflozin reduces the decline in eGFR (ml per year) with and without albuminuria.

Average eGFR-decline per year absolute difference +1.37 (95% CI 1.16, 1.59)

Empagliflozin: -1.37
Placebo: -2.75

Empagliflozin vs Placebo:
- <30 mg/g UACR: -0.11 vs -0.89
- ≥30 to <300 mg/g UACR: -0.49 vs -1.69
- ≥300 mg/g UACR: -2.35 vs -4.11

Mean 37 ml/min/1.73m²
Analyses show that patients at lower risk - many of whom in their lifetime would otherwise develop kidney failure - could benefit in terms of preservation of kidney function. If widely implemented, use of SGLT2i could therefore have a substantial impact on the public health impacts of CKD.
Maintaining Kidney Health: How to identify?

Should we* go for population based screening to detect people at risk (the Thomas Study)?

* We = General Practitioners?
TOP 11 factors that define early risk for CKD and potential treatment target populations

1. T1D/T2D, SLD (steatotic liver disease), morbid obesity (in aging and aged societies)
2. Prediabetes, gestational diabetes
3. Adverse intrauterine child conditions (metabolic imprinting, epigenetic factors)
4. CKD in families (a high genetic risk score), ethnic minorities
5. Gestational age - preterm - low birth weight
6. High BP, preeclampsia
7. toxins (environmental, air pollution), NSAIDs
8. AKI, the risk at the ICU
9. Young rural males in central America
10. Gout arthritis, chemotherapy
11. CAKUT, unilateral nephrectomy and albuminuria
PRACTICE POINT 1.1.1.

Kidney Int 2020;98:849-859
Kidney Int 2022;102:990-999
TOP 11 factors that define early risk for CKD and potential treatment target populations

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3 categories that define early risk for CKD

A) Metabolic diseases
1. T1D/T2D, SLD (steatotic liver disease), morbid obesity (in aging and aged societies)
2. Prediabetes, gestational diabetes
3. Adverse intrauterine child conditions (metabolic imprinting, epigenetic factors)
4. Gout & arthritis

B) Familial, in-extrinsic, multifactorial
1. CKD in families (a high genetic risk score), Gestational age - preterm - low birth weight
2. High BP, preeclampsia, CAKUT, unilateral nephrectomy and albuminuria
3. Ethnic minorities

C) Environmental
1. Toxins (air pollution), NSAIDs, chemotherapy
2. ICU risks, AKI
3. Young rural males in central America
Monogenic risk justifying early adjunctive treatment?

Diagnosis of prevalent KRT patients 2019 on the basis of genetic nephropathies

Inherited kidney diseases
- Hereditary nephropathy (subtype unknown)
- Other rare genetic conditions
- Tubulopathies
- Thrombotic microangiopathy of (potentially) genetic origin
- Phakomatoses
- Lysosomal storage disorders
- Genetic nephrotic syndrome
- Alport syndrome
- Familial amyloidosis
- Genetic interstitial disease
- Other cystic diseases
- ADPKD
What is missing:

- Mechanisms of preventing CKD (tubular stress, address biomarkers, consumption of kidney functional reserve)
- More focus on nonCKD trials with SGLT2i, Inkretines and anti-inflammatory therapies to identify more subgroups who carry a risk for CKD development
- The healing process: personalized medicine in specific forms of kidney disease (IgAN, MN, Lupus Nephritis, FSGS etc) targeting causal pathomechanisms to stabilize nephron loss or kidney volume
The predictable Future

New approaches/studies are being developed to retard the progression of kidney disease in a broad population with established disease.

Subgroup analysis of such trials may also provide relevant data.

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The unpredictable future

- Demographie (Langlebigkeit)
- Klima, Hitze
- Umweltbelastung (Toxizität), Luftqualität
Therapy of CKD ± T2D

2021-2030

From all in to personalized medicine

2025 2026 2030

ACE-I / ARB  SGLT2 Inhibition  MRA-Finerenon  GLP1-RA  Endothelin RA  sGC-Activation Aldost Synth Inhibition

Residual Risk

Life style & Salt

Glucose and Blood pressure control
The unpredictable future

- Demography (longevity)
- Change in climate, heat waves (special populations)
- Environment (toxicity), pollution (air)