Interventions to delay progression of kidney disease and minimize risk of adverse events or complications

A/Prof Ivor Katz | Nephrologist
St George Hospital
Understanding CKD ‘Kidney Failure’

Proteinuria
Albuminuria
= kidney leakage = Vascular damage
Kidney disease

Start Here

GFR = 30mls/min

CKD = CRF, CRI, PRF

RRT – Renal Replacement Therapy
e.g. Dialysis and transplantation
RSC – Renal Supportive Care
Non dialysis pathway

HD - Haemodialysis

ESRD

• Anaemia
• Nutrition
• Bone
• CVS
disease

• Adequacy e.g. anaemia
• Nutrition
• Bone
• Cardiovascular protection

PD – Peritoneal Dialysis

KDOQI – NKF USA Eknoyan
Risk Factors Are Complex and Heterogeneous

Adapted from KDIGO and Cuban conceptual models (Levey et al., 2007a, Almaguer et al., 2005).

CKD – chronic kidney disease, GFR – glomerular filtration rate ml/min; ESRD – End Stage Kidney Disease or CKD stage 5
Conceptual Model of CKD Progression

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16)
Glomerular filtration rate (GFR) decline... the facts

Herbert et al *Kidney International* 59 (4) p1211

**NORMAL**

**DISEASE**
- Hypertension
- Diabetes
- Glomerulonephritis
- APKD
The prevalence of chronic renal disease is increasing worldwide. Most chronic nephropathies lack a specific treatment and progress relentlessly to end-stage renal disease. However, research in animals and people has helped our understanding of the mechanisms of this progression and has indicated possible preventive methods. The notion of renoprotection is developing into a combined approach to renal diseases, the main measures being pharmacological control of blood pressure and reduction of proteinuria. Lowering of blood lipids, smoking cessation, and tight glucose control for diabetes also form part of the multimodal protocol for management of renal patients. With available treatments, dialysis can be postponed for many patients with chronic nephropathies, but the real goal has to be less dialysis—in other words remission of disease and regression of structural damage to the kidney. Experimental and clinical data lend support to the notion that less dialysis (and maybe none for some patients) is at least possible.
## Modifying the Risk Factors

**Definitions of progression, remission, and regression**

Remuzzi NEJM 1998 339;20

1448-56

<table>
<thead>
<tr>
<th>Variable</th>
<th>Progression</th>
<th>Remission</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>1 g/24 h</td>
<td>&lt;1 g/24 h</td>
<td>&lt;0.3 g/24 h</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Declining*</td>
<td>Stable</td>
<td>Increasing</td>
</tr>
<tr>
<td>Renal structural changes</td>
<td>Worsening</td>
<td>Stable</td>
<td>Improving</td>
</tr>
</tbody>
</table>

*Faster than physiological decline associated with aging (1 mL/min/1.73 m² per month).
# Targets of the multidrug approach to reduce decline in GFR

Lancet vol 357 p1601 Ruggenenti

<table>
<thead>
<tr>
<th>Variable</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic or diastolic blood pressure (mm Hg)</td>
<td>&lt;125/75*</td>
</tr>
<tr>
<td>24 h urinary protein excretion rate (g)</td>
<td>&lt;0.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>&lt;2.6</td>
</tr>
<tr>
<td>LDL and VLDL cholesterol (mmol/L)</td>
<td>&lt;3.4</td>
</tr>
<tr>
<td>Proportion HbA$_1^c$ †</td>
<td>&lt;7.5%</td>
</tr>
</tbody>
</table>

*Morning, pretreatment value; †In diabetics.
Effects of increased glomerular permeability to proteins on progressive renal injury

Remuzzi
NEJM
1998 339;20
1448-56
The nephron

Vulnerability of the kidney

- Important blood flow (1/4 of cardiac output)
- High metabolic activity
- Largest endothelial surface by weight
- Multiple enzyme systems
- Transcellular transport
- Concentration of substances
- Protein unbinding
- High $O_2$ consumption/delivery ratio in outer medulla

Site of renal damage

- ACE inhibitors
- NSAID
- Aminoglycosides
- Aciclovir
- Cisplatinum
- HgCl2
- Lithium
- Ischemia
AKI and CKD as an Interconnected Syndrome

Risk Factors
- Age
- Race or ethnic group
- Genetic factors
- Hypertension
- Diabetes mellitus
- Metabolic syndrome

Disease Modifiers
- Severity of acute kidney injury
- Stage of chronic kidney disease
- No. of episodes
- Duration of acute kidney injury
- Proteinuria

Outcomes
- Cardiovascular events
- Kidney events
- ESRD
- Disability
- Diminished quality of life
- Death

Acute Kidney Injury

Chronic Kidney Disease
Mechanisms of Kidney Injury and subsequent repair after AKI
AKI progressing to ESKD

• Distinction between AKI and CKD may be artificial.

• The integrated clinical syndrome of diminished GFR, with acute & chronic stages.

• Patients should be provided long-term follow-up even with first episodes of AKI or even if they presented with normal renal function.

Effect of acute kidney injury (AKI) frequency on outcomes.
Thakar et al.DM pts with >2 episodes of AKI were much more likely to progress to stage 4 CKD than patients who experienced only one episode of AKI.

Stages in the Progression of CKD and Therapeutic Strategies

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16)
## Nurse role in CKD

### Reduce the impact of CKD

<table>
<thead>
<tr>
<th>Screen for risks</th>
<th>Manage disease</th>
<th>Monitor patient progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Kidney Health Check</td>
<td>Using care plans and item numbers</td>
<td>Using item numbers</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Promote self management</td>
<td>Adherence to treatment</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Diabetes</td>
<td>Nephrotoxic medications</td>
</tr>
<tr>
<td>Cardiovascular using Absolute CVD Risk Calculator*</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Other CKD risk factors</td>
<td>CKD</td>
<td></td>
</tr>
<tr>
<td>Using health checks &amp; item numbers</td>
<td>Symptoms</td>
<td></td>
</tr>
</tbody>
</table>

*Refer to slide 20
Increased Risk - CKD Screening

CKD Screening Recommendations in Australia?

Mike G screening is done by checking:

- urine albumin/creatinine ratio (ACR)
- estimated glomerular filtration rate (eGFR)
- blood pressure

All 3 screening tests should be performed in high risk patients to maximise the likelihood of CKD detection as there is variable overlap of indicators of kidney damage.

- In AusDiab study, 92% of patients with eGFR < 60 mL/min/1.73 m² did not have albuminuria/proteinuria
- 57% of subjects with albuminuria/proteinuria did not have an eGFR < 60 mL/min/1.73 m²
## Screening for CKD

<table>
<thead>
<tr>
<th>Indications for assessment*</th>
<th>Recommended assessments</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Urine ACR, eGFR, blood pressure</td>
<td>Every 1-2 years†</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established cardiovascular disease**</td>
<td>If urine ACR positive repeat twice over 3 months (preferably first morning void)</td>
<td></td>
</tr>
<tr>
<td>Family history of kidney failure</td>
<td>If eGFR &lt; 60mL/min/1.73m² repeat within 7 days</td>
<td></td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander origin aged ≥ 30 years*</td>
<td>See recommendations in handbook</td>
<td></td>
</tr>
<tr>
<td>History of acute kidney injury</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Whilst being aged 60 years of age or over is considered to be a risk factor for CKD, in the absence of other risk factors it is not necessary to routinely assess these individuals for kidney disease.

**Established cardiovascular disease is defined as a previous diagnosis of coronary heart disease, cerebrovascular disease or peripheral vascular disease.

† Annually for individuals with diabetes or hypertension.

‡ Refer to booklet for more details regarding recommendations for testing in Aboriginal and Torres Strait Islander peoples.
GFR and ageing

Estimated GFR (MDRD)
Median and interquartile range

Prevalence of eGFR < 60 mL/min in population

GFR declines by 5-8mL/min/1.73m² each decade

NOTE* Current Recommendations - PEAK

Whilst being aged 60 years of age or over is considered to be a risk factor for CKD, in the absence of other risk factors it is not necessary to routinely assess these individuals for kidney disease.
### Guidelines for Referral and Goals of management

Kidney Health Australia

GP guidelines

#### Stages of CKD

<table>
<thead>
<tr>
<th>Kidney Function Stage</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Albuminuria Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal (urine ACR mg/mmol)</td>
</tr>
<tr>
<td>1</td>
<td>≥90</td>
<td>Not CKD unless haematuria, structural or pathological abnormalities present</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>45-59</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>30-44</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td></td>
</tr>
</tbody>
</table>

#### Goals of management

<table>
<thead>
<tr>
<th>Investigations to exclude treatable kidney disease Reduce progression of kidney disease Assessment of absolute cardiovascular risk Avoidance of nephrotoxic medications or volume depletion</th>
<th>Investigations to exclude treatable kidney disease Reduce progression of kidney disease Reduce cardiovascular risk Avoidance of nephrotoxic medications or volume depletion</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Early detection and management of complications Adjustment of medication doses to levels appropriate for kidney function Appropriate referral to a Nephrologist when indicated</td>
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<td>Early detection and management of complications Adjustment of medication doses to levels appropriate for kidney function</td>
</tr>
<tr>
<td>Prepare for dialysis or preemptive transplant if eGFR &lt;30 mL/min/1.73m² Discuss advanced care directive if dialysis inappropriate Multidisciplinary team involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Case study – Mike G

### Mike’s results:

<table>
<thead>
<tr>
<th>Test</th>
<th>Results 4 months ago</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td>155/90 mmHg (seated)</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td></td>
<td>100 μmol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td>74 mL/min/1.73m²</td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td>8.4% / 68 mmol/mol</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td>6.1 mmol/L</td>
</tr>
<tr>
<td>Urine ACR</td>
<td>4.6 mg/mmol (random spot)</td>
<td>10 mg/mmol (first void)</td>
</tr>
<tr>
<td>Urate</td>
<td></td>
<td>0.55 mmol/L</td>
</tr>
</tbody>
</table>

**Ht** 179cm  
**Wt** 98kg  
**BMI** 30.58kg/m²
Staging CKD

Combine eGFR stage, albuminuria stage and underlying diagnosis to specify CKD stage e.g. stage 3b CKD with microalbuminuria secondary to diabetic kidney disease

<table>
<thead>
<tr>
<th>GFR Stage</th>
<th>GFR mL/min/1.73m²</th>
<th>Normal urine ACR mg/mmol</th>
<th>Microalbuminuria urine ACR mg/mmol</th>
<th>Macroalbuminuria urine ACR mg/mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥90</td>
<td>Not CKD unless haematuria, structural or pathological abnormalities present</td>
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</table>

Colour-coded Clinical Action Plans in handbook and on CKD-Go! App
Stage 2 CKD with microalbuminuria, probably secondary to diabetic kidney disease

Goals of management

• Investigations to exclude treatable disease
• Assessment of absolute cardiovascular risk
• Reduce cardiovascular risk
• Early detection and management of complications
• Avoidance of nephrotoxic medications or volume depletion
CKD and the risk of death, CV events and hospitalisation


Kaiser Permanente Renal Registry

N = 1,120,295
Proteinuria is related to life expectancy*

*Observational study of 375,325 men without end stage kidney disease followed for up to 7 years

Kidney & cardiovascular outcomes in patients with CKD

Kaiser Permanente Longitudinal Study

Patients with CKD are 20 times more likely to die from cardiovascular events than survive to reach dialysis

Keith et al; Arch Int Med 2004
# Yellow Clinical Action Plan

## Monitoring

- ✓ 12 monthly clinical review

## Clinical Assessment

- ✓ Blood pressure
- ✓ Weight

## Laboratory Assessment

- ✓ urine ACR
- ✓ Biochemical profile including urea, creatinine, electrolytes
- ✓ eGFR
- ✓ HbA1c (for people with diabetes)
- ✓ Fasting lipids
Adequate BP management delays the progression of CKD

If a patient's blood pressure was consistently below target, the GFR loss per year would be reduced by 80%

Bakris et al., Am J Kid Disease, 2000
CKD risk factors: High blood pressure

High BP damages small blood vessels in the kidneys. Starts the process described earlier causing fibrosis.

Or......*damaged kidneys cause high blood pressure and high blood pressure damages kidneys*
BP control

The cumulative incidence of end stage kidney disease is higher with more severe BP category

Tozawaw et al, Hypertension 2003;41:1341-1345
Treatment of blood pressure in CKD
Which agent and how many?

- RAAS Blockade - ACEi or ARB
  - Independent effect (tissue effects) over BP alone
- CKD patients often need multiple medications to achieve BP control
- Achieving below target BP is essential
ACE inhibitors in Type 2 Diabetes with hypertension

The BENEDICT Trial

Adjusted HRs for major cardiovascular events according to baseline albuminuria

Risk of CVD is significantly reduced

Ruggenenti et al; JASN 2012
Case study – Pt with DKD

If you started an ACEi or ARB, when would you recheck his chemistry & how much reduction in eGFR would you tolerate?

Check eGFR at 1 week and 1 month after starting

- ACEi & ARBs can cause reversible reduction in GFR at initiation of treatment

Tolerate a 25% decrease in eGFR*

- Continue ACEi or ARB if reduction is less than 25% and stabilises within two months of starting therapy
- Cease ACEi or ARB if reduction >25% below baseline
- In ceasing ACEi or ARB, consider referral to Nephrologist for bilateral renal artery stenosis
- All reductions in GFR with ACEi or ARB are reversible

RAS Blockade

- Loss of renal efferent arteriolar vasoconstriction:
  - Acute decrease in intra-glomerular pressure $\rightarrow$ **fall in GFR**
**CKD risk factors: Obesity**

Being overweight (BMI 25-29 kg/m$^2$) did not increase CKD risk, but all classes of obesity (BMI $\geq$ 30kg/m$^2$) increased risk.

*CKD with eGFR <45mL/min/1.73m$^2$*

Hallan et al, Am J Kid Dis 2006
Risk factors - obesity

- Overweight (BMI 25.1-30) – 40% risk
- Obese (BMI >30) → 80% more likely to develop CKD compared to normal weight individuals*
- **Central obesity** more important than generalised
- Although not as powerful as diabetes or hypertension as a risk factor, obese subjects may be *more likely to develop albuminuria* and proteinuria
- Obesity = **greater difficulty** in achieving glycaemic & BP control

Risk of ESKD related to baseline proteinuria (dipstick) over 18 year period

N= 106,000

Iseki et al, Kidney Int 2003;63:1468-1476
Macroalbuminuria is a better marker than GFR in predicting loss of kidney function

N=8952 – F/U 4yrs

PREVEND Study; J Am Soc Nephrol 2006
Proteinuria

Blue – normal ACR
Green – microalbuminuria
Red - macroalbuminuria

Clockwise from top left:
Cardiovascular mortality
End stage renal disease

Note log scale on Y axis for Hazard Ratio

Adapted from Levey et al, 2010, Kidney International
LIPID REDUCTION

SHARP results: 17% reduction in major atherosclerotic events

Risk ratio 0.83 (0.74 – 0.94)
Log rank p=0.0022

17% reduction in risk

Proportion suffering event* (%)

Years of follow-up

* Major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke, or any revascularization)

Baigent et al, Lancet 2011
SHARP results: consistent with results from previous cholesterol lowering trials

SHARP results compared with Cholesterol Lowering Treatment Triallists Collaboration

Mean LDL cholesterol difference between treatment groups (mg/dL)

Proportional reduction in atherosclerotic event rate (95% CI)

SHARP results: 17% risk reduction

Statin vs control (21 trials)

More vs Less (5 trials)

SHARP 32 mg/dL (0.83 mmol/l)
Mike Gs Medication list

Medications
• ACE/ARB
• HTN medication (more than two)
• Anti-lipid agents
• Allopurinol
• DM medication

Risks
• eGFR decline ↑K+
• Multiple medications and side effects
• CK Muscle cramps
• Rash or TEN
• Hypoglycaemia, lactic acidosis, worsening renal function
Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

American Journal of Kidney Diseases, Volume 47, Issue 1, January 2006, Pages 51-59
Yui-Pong Siu, Kay-Tai Leung, Matthew Ka-Hang Tong, Tze-Hoi Kwan

Mean percentage of change in creatinine levels in treatment and Control Groups *p<0.05 compared with baseline

CKD Fix Study
RCT Allopurinol vs Placebo
Sunil Badve
Hypertension <130/80
Proteinuria <1g/d
Lipids
HIV
Alcohol
Uric Acid
Weight
AKI
Prevent
Smoking
STOP

M el Nahas Bellagio 2004
Modified 2018
Renoprotection

ACEI/ARB
NDCCB
BB

ART

STATIN

ACEI/ARB
NDCCB
b-blocker

AKI
prevent

STOP

Cardioprotection

M el Nahas Bellagio 2004
Modified
What about future screening and determining risk of progression and follow up?
Using Predictive Models

• Multivariate equations derived with the goal of predicting absolute risk at a given time frame

• Not an association study of a single risk factor or biomarker

• Emphasis on prediction over biological association

• Navdeep Tangri MD PhD FRPC
• A/Prof Division of Nephrology, University of Manitoba, Canada
• ASN New Orleans 2017
• Publications
Why do we need models in CKD
Tangri et al. Curr Opinion Nephrology Hypertionsion 2013

1. Early and appropriate nephrology care – Nephrologist vs GP
2. Prognostic Information for patient and provider
3. Decision regarding intensity of care and timing of dialysis/transplantation education
4. Planning of vascular access
5. Planning Renal Supportive Care
Patient and Physician Tools – www.kidneyfailurerisk.com
Kidney Failure Risk Equation (KFRE)

Tangri et al JAMA 2011

- Developed lab based prediction models that accurately predicted progression of CKD (C stastics 0.84-0.91)
- Models used routine lab data

- 4 variable KFRE – Age , Gender, eGFR, ACR
- 8 variable KFRE - + calcium, phosphate, bicarbonate and serum albumin
## Risk Thresholds – KFRE vs eGFR

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KFRE Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3% over 5 years</td>
<td>0.97</td>
<td>0.62</td>
<td>0.22</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>eGFR&lt;45</strong></td>
<td>0.84</td>
<td>0.54</td>
<td>0.17</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>KFRE Threshold</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% over 5 years</td>
<td>0.86</td>
<td>0.80</td>
<td>0.33</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>eGFR&lt;30</strong></td>
<td>0.62</td>
<td>0.84</td>
<td>0.30</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>C-Statistic for KFRE</strong></td>
<td>0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C-Statistic for eGFR</strong></td>
<td></td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tangri 2017, ASN
KFRE St George Hospital

eGFR, 2 Year %, 5 Year % by ESRD Outcome

n=302

Marina Wainstein, Manaul van Deventer et al

ESRD Outcome | n
---|---
No | 188
Yes | 114

<table>
<thead>
<tr>
<th>Test</th>
<th>Area</th>
</tr>
</thead>
</table>
eGFR      | 0.88 |
2 Year %  | 0.93 |
5 Year %  | 0.93 |

Abstract submitted to ASN 2018
Risk-Based Triage for Nephrology Referrals Using the Kidney Failure Risk Equation

Hingwala et al; Can J Kidney Health and Dis, 2017
Median wait time in pre-triage and post-triage periods.

Note. Intervention resulted in statistically significant change in wait time ($P < .001$) and change in wait time trend (slope) post intervention ($P = .029$).
So, the value of KFRE?

1. KFRE is still simple, highly accurate and validated across diverse populations
2. Implementations can reduce wait times, improve pre-dialysis care and align resources with risk!
3. Consider implementation KFRE in CKD care
4. More research in particular situations is required
   • When best to refer to ROC
   • When best to place an AVF

• How and when should it be used?
Implementation?
Recommended (not evidence based)

• Triage of new nephrology referrals - (3% risk over 5 years)
  • >3% book in 6 months
  • >10% see within 4 weeks
• Entry into interdisciplinary care - (10% over 2 years)
• Modality education and preliminary planning - (20% over 2 years)
• Dialysis access insertion - (40% over 2 years)
FUTURE CKD SURVEILLANCE

Primary Health Clinic

Virtual Medical Consultation VMC

RENAL TERTIARY CARE

Cardiology Clinic

Diabetes clinic

Renal clinic

LAB RESULTS

DATA Warehouse

KFRE

Other scores, AI...

Analysis

High Risk
Encourages tracking and early referral

PATIENT CLINICAL DATA

PATIENT CLINICAL DATA AND INFORMATION AVAILABLE

- Data already analysed
- Decision to refer made automatically

‘FIGS’ and Apps
Prevention Strategies & Education

Patient
Smoking
Lifestyle factors
Family History
and
Biomarkers
Smokers with a 25-49 pack-year history had an increased risk of 42% compared with non-smokers and those with >50 pack years had 105% increased risk.
## Lifestyle effects on BP

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Change in BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>BMI 18-24.9 kg/m²</td>
<td>4.4mmHg (for 5.1kg weight lost)</td>
</tr>
<tr>
<td>Dietary sodium restriction</td>
<td>Reduce dietary sodium intake to no more than 2.4g sodium (or 6g salt)</td>
<td>4-7mmHg (for reduction by 6g in daily salt intake)</td>
</tr>
<tr>
<td>DASH diet</td>
<td>Fruit, vegies, low saturated and total fat</td>
<td>5.5-11.4mmHg (5.5 for normotensives 11.4 for hypertensives)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Aerobic activity for 30-60mins/day, 3-5 days/week</td>
<td>5mmHg</td>
</tr>
<tr>
<td>Moderate alcohol consumption</td>
<td>No more than 2 drinks per day (men) or 1 drink per day (women)</td>
<td>3mmHg (for 67% reduction from baseline of 3-6 drinks per day)</td>
</tr>
</tbody>
</table>
CKD risk factors: Family history

- Caucasian men: 14.4%
- Caucasian women: 14.6%
- African-American men: 22.9%
- African-American women: 23.9%

Freedman et al., JASN 1997
CKD risk factors: Aboriginal or Torres Strait Islander Origin

Indigenous Australians starting treatment for ESKD

Source: AIHW analysis of ANZDATA Registry data.

Figure 2.3: Incidence of treated ESKD, by Indigenous status, age and sex, 2007–2008

Australian Institute of Health and Welfare, 2011
Biomarkers of Chronic Kidney Disease

• Serum creatinine and albuminuria form the core of most predictive models of CKD and risk of progression BUT alterations relatively late in the disease trajectory and thus are NOT suitable for very early diagnosis of CKD.

• New Biomarkers – more predictive early disease
  • Cystatin C
  • β-trace protein (BTP)
  • Neutrophil gelatinase-associated lipocalin (NGAL)
  • Kidney injury molecule 1 (KIM-1)
  • Liver-type fatty acid–binding protein (L-FABP)
  • Asymmetric dimethylarginine (ADMA)
  • Uromodulin
  • micro RNA
# Schema for Discussion Novel Biomarkers

<table>
<thead>
<tr>
<th>Group</th>
<th>Biomarker</th>
<th>Sample</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FILTRATION</td>
<td>BTP – β trace protein</td>
<td>Blood / Urine</td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>B2M - β 2microglobulin</td>
<td>Image</td>
<td>CVD / Death</td>
</tr>
<tr>
<td>EXCRETION</td>
<td>Na + – sodium K+ - Potassium</td>
<td>Blood / Urine</td>
<td>Renal</td>
</tr>
<tr>
<td>TUBULAR INJURY</td>
<td>NGAL/KIM-1/L-FAB/ NAG</td>
<td>Image</td>
<td>CVD / Death</td>
</tr>
<tr>
<td>INFLAMMATION</td>
<td>suPAR FLC</td>
<td>Blood / Urine</td>
<td>Renal</td>
</tr>
<tr>
<td>MINERAL METABOLISM</td>
<td></td>
<td>Blood / Urine</td>
<td>CVD / Death</td>
</tr>
<tr>
<td>ARTERIAL DISEASE</td>
<td></td>
<td>Blood / Urine</td>
<td>Renal</td>
</tr>
<tr>
<td>GENTETICS</td>
<td></td>
<td>Blood / Urine</td>
<td>CVD / Death</td>
</tr>
</tbody>
</table>
suPAR (Soluble Urokinase-type Plasminogen Activator receptor) and CKD Progression

DOI: 10.1056/NEJMoa1506362

2292 Individuals undergoing heart Catheterisation
1335/2292 with eGFR >60 ml/min/1.73m²

RESULTS
A higher suPAR level at baseline was associated with a greater decline in the eGFR during follow-up

CONCLUSIONS
An elevated level of suPAR was associated with incident CKD and an accelerated decline in eGFR
872 Participants in the UK CRISIS study 
(Chronic Renal Insufficiency Standards Implementation Study)

A strong independent relationship between high FLCs Levels and ESKD Performance as a prognostic marker yet to be assessed

Conclusions
An elevated serum combined Ig free light chain level is an independent risk factor formortality and
Summary Biomarkers

- A number of biomarkers are emerging
- Many show relationships with kidney function and long term outcomes
- The ability of biomarkers to enhance our ability to diagnose, prognosticate progression of CKD beyond what is possible using existing measures of eGFR and albuminuria is uncertain
- suPAR and FLC appear promising but more testing is needed
Summarise!!
Conceptual Model of CKD and Therapeutic Strategies

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16

Screening for CKD risk factors
CKD risk reduction, Screening for CKD
Diagnosis & treatment, Treat comorbid conditions, Slow progression
Estimate progression, Treat complications, Prepare for replacement
Replacement by dialysis & transplant & Renal supportive care

Complications

Normal → Increased risk → Damage → ↓ GFR → Kidney failure → CKD death
Susceptibility Factors
Age & Family Hx CKD
kidney Mass or low birth weight
Hyperfiltration e.g. ↑ protein intake, sickle cell D, glycogen storage diseases.
Male, Race, income & Education
HTN in pregnancy

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16)
Risk Factors & CKD

**Initiation Factors**
Older age Male / DM/ Hypertension/ Obesity/ Metabolic syndrome/ dyslipidaemia/ $\uparrow$Ca2+/AI Disease/Systemic Infections / UTIs / stones / Obstruction / drug toxicity / endog toxins e.g myeloma / nephrotoxins /

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Tsai et al. Medicine
Volume 95, Number 11, March 2016

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16
Progression Perpetuating Factors

1. Higher levels of proteinuria
2. Systolic Blood Pressure
3. Poor glycaemic diabetic control
4. Smoking
5. High protein intake
6. Nephrotoxins
7. Anaemia
8. Hyperuricaemia
9. Emerging biomarkers
10. Gender Male ?older females (androgens)
11. Older age

Tsai et al. Medicine
Volume 95, Number 11, March 2016

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16
Progression Factors & CKD

End Stage Factors
1. Lower dialysis Dose (kt/v)
2. Temporary Vascular Access
3. Anaemia
4. Smoking
5. Lower serum albumin
6. LATE REFERRAL
7. RENAL SUPPORTIVE CARE

Levey et al. AJKD
2009-03-01, Volume 53, Issue 3, Pages S4-S16)
THANK YOU!

Available along with more kidney health fact sheets at www.kidney.org.au

Resources

CKD patient fact sheets
Resources

CKD management in General Practice
2015 guidelines handbook

Available at
www.kidney.org.au/health-professionals
Resources

CKD-GO! Phone App

Available on iTunes and Google Play app stores

All the best bits of the ‘CKD Management in General Practice’ handbook now in a handy app!

Rated a ‘must have’ App by Medical Observer
Resources
My Kidneys, My Health Handbook & App
Free resource for patients newly diagnosed with early stage CKD

App available on iTunes and Google Play app stores

Hardcopy books available to order visit www.kidney.org.au
Kidney Community...

**KIDNEY COMMUNITY** members receive a monthly newsletter from KHA allowing you to access:

- Information and invitations to KHA's education and support activities
- Updates on medical research in kidney disease
- Information on advocacy opportunities and government relations issues
- Information on community and corporate events held by Kidney Health Australia

To join the kidney community, email [community@kidney.org.au](mailto:community@kidney.org.au)
BASELINE PROTEINURIA AND GFR SLOPE IN THE MDRD STUDY

Study A
Mean Slope (±SE) Over 3 Years

Study B
Mean Slope (±SE)

GFR Slope (ml/min/yr)

Baseline Urine Protein (g/day)

Klahr, S, NEJM, 330:878, 1994