Interventions to reduce progression of CKD – what is the evidence?

John Feehally
Interventions to reduce progression of CKD – what is the evidence?

**CHALLENGES**

- Understanding what we know... **NOT**...what we think we know
- Disappointing that we are still debating long-established therapies
- Disappointing that mechanistic studies have been slow to yield new targeted therapy
- Designing high quality trials
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**CHALLENGES IN DESIGNING CLINICAL TRIALS**

- Definitive end-points (e.g. preventing ESRD) need long trials
- Acceptable surrogate end-points
- Identify those at low risk of progression
### Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR categories (ml/min/1.73 m²)</th>
<th>Description and range</th>
<th>Persistent albuminuria categories Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>A1: Normal to mildly increased</td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>A2: Moderately increased</td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>A3: Severely increased</td>
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<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
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<tr>
<td>G5</td>
<td>Kidney failure</td>
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- **A1**: Normal to mildly increased
- **A2**: Moderately increased
- **A3**: Severely increased

- <30 mg/g
- <3 mg/mmol
- 30-300 mg/g
- 3-30 mg/mmol
- >300 mg/g
- >30 mg/mmol
Interventions to reduce progression of CKD – what is the evidence?

CHALLENGES IN DESIGNING CLINICAL TRIALS

• Definitive end-points (e.g. preventing ESRD) need long trials
• Acceptable surrogate end-points
• Identify those at low risk of progression
• Trials versus ‘real life’
  • office, home, or ambulatory BP monitoring?
  • albuminuria or proteinuria?
  • spot or timed urine collections?
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Interventions to reduce progression

INTERVENTIONS WITH EVIDENCE OF HARM

BARDOXOLONE
An oral anti-oxidant inflammation modulator
NRF2 activator
Interventions to reduce progression

INTERVENTIONS WITH EVIDENCE OF HARM

BARDOXOLOONE

An oral anti-oxidant inflammation modulator
NrF2 activator

BEAM
Phase 2, double-blind RCT

Type 2 diabetes  n = 227
Stage 3b-4 CKD

eGFR increased up to 52 weeks

Minor adverse effects

Pergola PE et al. NEJM 2011;365:327
Interventions to reduce progression

INTERVENTIONS WITH EVIDENCE OF HARM

BARDOXOLONE
An oral anti-oxidant inflammation modulator
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BEAM
Phase 2, double-blind RCT
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Stage 3b-4 CKD

eGFR increased up to 52 weeks
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Pergola PE et al. NEJM 2011;365:327

BEACON
Double blind RCT
Type 2 diabetes  n=2185
Stage 4 CKD

Study terminated at  9 months
Excess mortality
Excess hospitalisation for heart failure
de Zeeuw D et al. NEJM 2013;369:2492
# Interventions to reduce progression of CKD – what is the evidence?

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INTERVENTIONS WITH INSUFFICIENT EVIDENCE OF BENEFIT

Correction of anaemia

Statins

Weight loss

High fluid intake
Interventions to reduce progression

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Correction of anaemia

Statins

Weight loss

High fluid intake
WEIGHT LOSS

Morbid obesity & segmental sclerosis
Interventions to reduce progression

INTERVENTIONS WITH INSUFFICIENT EVIDENCE OF BENEFIT

WEIGHT LOSS

Morbid obesity & segmental sclerosis

Moderate obesity with CKD: weight loss reduces proteinuria
WEIGHT LOSS

Morbid obesity & segmental sclerosis

Moderate obesity with CKD: weight loss reduces proteinuria

What is the ideal body weight?
Association of BMI with Outcomes in CKD

453,596 US veterans - eGFR < 60, mean age 73yrs, 87% White

MORTALITY

Lu JL et al. JASN 2014; 25: 2088
**Association of BMI with Outcomes in CKD**

453,596 US veterans - eGFR < 60, mean age 73yrs, 87% White

Lu JL et al. JASN 2014; 25: 2088
What is the ideal body weight in CKD?

453,596 US veterans, eGFR < 60 - mean age 73 yrs - 87% White

U-shaped curve

Worst renal outcomes: BMI < 25 & BMI > 35

Best outcomes: BMI 30-35

Lu JL et al. JASN 2014 Epub Mar 20
Interventions to reduce progression

INTERVENTIONS WITH INSUFFICIENT EVIDENCE OF BENEFIT

Correction of anaemia

Statins

Weight loss

High fluid intake
Is there a right amount of fluid to drink if you have CKD?

Drinking eight glasses of water each day (~ 2.5L)

is widely believed to improve kidney health

– in the USA ‘8 by 8’
Is there a right amount of fluid to drink if you have CKD?

Drinking eight glasses of water each day (~ 2.5L) – in the USA ‘8 by 8’

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*Three cross-sectional epidemiological studies*
Is there a right amount of fluid to drink if you have CKD?

Drinking eight glasses of water each day (~ 2.5L) – in the USA ‘8 by 8’ is widely believed to improve kidney health.

*Three cross-sectional epidemiological studies*

**USA - NHANES**

*Total water intake*

Prevalence of CKD significantly higher among those with lowest (< 2 litres/day) *versus* highest (> 4.3 litres/day)

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- Total water intake
  - Prevalence of CKD significantly higher among those with lowest (< 2 litres/day) versus highest (> 4.3 litres/day)


**AUSTRALIA**
- Nutrition questionnaires
  - Highest quintile of fluid intake (3.2 L/day) - significantly lower risk of CKD

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**AUSTRALIA**
**Nutrition questionnaires**
Highest quintile of fluid intake (3.2 L/day) - significantly lower risk of CKD


**CANADA**
**Urine volume**
Urine volume ≥3 L/d ... significantly less likely to have rapid GFR decline .... compared to 1 to 1.9 L/d

*Clark WF et al. CJASN 2011; 6:2634*
Is there a right amount of fluid to drink if you have CKD?

**BUT**

*One longitudinal study*

**AUSTRALIA**
Prospective, population-based cohort study  \( n = 3858 \)

Median follow up 13 years

Daily fluid intake *not* associated with all-cause or cardiovascular mortality.

Rate of eGFR reduction *not* associated with fluid intake

Palmer SC et al. NDT 2014 Jan 6. [Epub ahead of print]
## Interventions to reduce progression of CKD – what is the evidence?

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Interventions to reduce progression

Widely-used interventions

Often have other potential benefits - e.g. reducing CV risk

But do they delay progression?

- Uric acid reduction
- Alkali therapy
- Physical exercise
- Dietary protein restriction
- Smoking cessation
- Dietary salt restriction
Interventions to reduce progression

INTERVENTIONS WITH MODERATE EVIDENCE

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Uric acid reduction

Alkali therapy

Physical exercise

Dietary protein restriction

Smoking cessation

Dietary salt restriction
Interventions to reduce progression
INTERVENTIONS WITH MODERATE EVIDENCE

Uric acid reduction
   Rationale
      uric acid is proinflammatory and vasculotoxic
      allopurinol is antinflammatory and cardioprotective
Uric acid reduction

Rationale

uric acid is proinflammatory and vasculotoxic
allopurinol is antinflammatory and cardioprotective

But does reducing uric acid delay progression?

Primary gout n = 59

Colchicine + Allopurinol 2 years

Allopurinol delayed progression

Gibson T et al. Ann Rheum Dis 1982; 41: 59
Effect of Uric Acid lowering therapy on renal outcomes

Effect of allopurinol on change in GFR from baseline

“... adequately powered randomised trials are needed ...”

Bose B et al. NDT 2014; 29: 406
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Interventions to reduce progression
INTERVENTIONS WITH MODERATE EVIDENCE

RATIONALE for ALKALI THERAPY
Interventions to reduce progression

INTERVENTIONS WITH MODERATE EVIDENCE

RATIONALE for ALKALI THERAPY
Interventions to reduce progression
INTERVENTIONS WITH MODERATE EVIDENCE

RATIONALE for ALKALI THERAPY
# Interventions to reduce progression

## INTERVENTIONS WITH MODERATE EVIDENCE

### ALKALI THERAPY

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>n</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Brito-Ashurst 2009</td>
<td>UK</td>
<td>134</td>
<td>CKD4 HCO$_3$ 16-20 mmol/l</td>
<td>NaHCO$_3$ mean 1.82 +0.8 g/d</td>
<td>Reduced ESRD Delayed eGFR decline</td>
</tr>
<tr>
<td>Phisitkul 2010</td>
<td>USA</td>
<td>59</td>
<td>eGFR 20-60 HCO$_3$ &gt;22 mmol/l</td>
<td>Na citrate equivalent to 1 mmol/kg/d NaHCO$_3$</td>
<td>Delayed eGFR decline</td>
</tr>
<tr>
<td>Goraya 2012</td>
<td>USA</td>
<td>76</td>
<td>CKD4 HCO$_3$ &lt;22 mmol/l</td>
<td>NaHCO$_3$ 1 mmol/kg/d</td>
<td>eGFR decline = comparator (fruit &amp; veg diet)</td>
</tr>
<tr>
<td>Mahajan 2010</td>
<td>USA</td>
<td>120</td>
<td>CKD2 HCO$_3$ &gt;24.5 mmol/l</td>
<td>NaHCO$_3$ 0.5 mmol/kg/d</td>
<td>Delayed eGFR decline</td>
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**Interventions to reduce progression**

**INTERVENTIONS WITH MODERATE EVIDENCE**

**ALKALI THERAPY - meta-analysis**

4 long term studies – follow up 1-5 yr, n = 295

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<tr>
<th>INCREASED</th>
<th>REDUCED</th>
<th>NOT CHANGED</th>
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<td>Serum bicarbonate</td>
<td>Fall in GFR</td>
<td>Systolic BP</td>
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<tr>
<td></td>
<td>Serum potassium</td>
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</tr>
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<td>Serum chloride</td>
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Interventions to reduce progression
INTERVENTIONS WITH MODERATE EVIDENCE

ALKALI THERAPY

Current guidelines recommend sodium bicarbonate when serum $\text{HCO}_3^- < 22 \text{ mmol/l}$
Interventions to reduce progression

INTERVENTIONS WITH MODERATE EVIDENCE

ALKALI THERAPY

Current guidelines recommend sodium bicarbonate when serum $\text{HCO}_3^- < 22$ mmol/l

3 RCTs recruiting

USA: CKD 3b-4, age > 18 yrs - normal and low serum $\text{HCO}_3^-$

USA: Diabetes CKD2-4, age > 18 yrs - normal serum $\text{HCO}_3^-$

UK: CKD4-5, age > 65 yrs, low serum $\text{HCO}_3^-$
Interventions to reduce progression

INTERVENTIONS WITH MODERATE EVIDENCE

Widely-used interventions
Often have other potential benefits - e.g. reducing CV risk

But do they delay progression?

Uric acid reduction

Alkali therapy

Physical exercise

Dietary protein restriction

Smoking cessation

Dietary salt restriction
Low cost
Low risk
Available

Exercise as Medicine
Physical exercise and CKD progression

Aerobic exercise in CKD
- Reduces systemic inflammation
- Improves BP control
- Improves exercise capacity
- Improves quality of life

Resistance exercise in CKD
- Increases muscle mass

Three RCTS of aerobic exercise in CKD have **not** shown alterations in rate of progression

... **but** were not designed to test this
Physical exercise and CKD progression
Physical exercise and CKD progression

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Physical exercise and CKD progression

Community-based cohort study
Greater physical activity exercise associated with lower rates of decline of kidney function
Physical exercise and CKD progression

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Greater physical activity exercise associated with lower rates of decline of kidney function

**Longitudinal cohort study**
n = 256  CKD stages 3 & 4
Validated questionnaire - 3.7 yrs follow up

Robinson-Cohen C et al. CJASN 2014; 25: 390
Physical exercise and CKD progression

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Each 60 min increment in exercise
0.5% slower GFR decline per yr

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Greater physical activity is associated with lower rates of decline of kidney function.


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>150 min activity per week = slowest GFR decline
Each 60 min increment in exercise = 0.5% slower GFR decline per yr

Large RCTs with hard renal endpoints are now justified
Interventions to reduce progression

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INTERVENTIONS WITH GOOD EVIDENCE

BLOOD PRESSURE CONTROL

RAS BLOCKADE
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

EVIDENCE

Trials with hard renal endpoints

Trials with surrogate renal endpoints

Subgroup analysis of trials with a primary cardiovascular focus

Observational association studies
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

There are two RCTs with hard renal endpoints

- Usual BP: < 140/90
- Low BP: < 125/75

Long follow up
3 yr trial
10 yr total

ESRD reduced by low BP target
only if
uP > 1g/d
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

There are two RCTs with hard renal endpoints

MDRD

Long follow up
3 yr trial
10 yr total

ESRD reduced by low BP target
only if uP > 1g/d

Usual BP < 140/90
Low BP < 125/75
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

There are two RCTs with hard renal endpoints

AASK

Primary end point: **no difference**

Subgroup analysis, prolonged follow up: **differences emerge**

Achieved...
- Low BP 128/78
- Normal BP 141/85
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

There are two RCTs with hard renal endpoints

AASK

Primary end point: 

*no difference*

Subgroup analysis, prolonged follow up:

differences emerge

Achieved...

Low BP 
128/78

Normal BP 
141/85
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

Proteinuria < 1g/24hr 130/80

Proteinuria > 1g/24hr 125/75

JNC7
European Task Force
KDOQI
etc.
BP TREATMENT RECOMMENDATIONS FOR DIABETIC KIDNEY DISEASE

No RCTs with hard renal endpoints

*Post hoc* analyses – diabetes with *overt* nephropathy

Cooperative Study Group 1999

Achieved SBP 130 =

GFR loss only 2ml/min/yr

RENAAL 2003

Every 10 mm Hg rise in systolic BP

*increased* risk for ESRD or death by 6.7%

IDNT 2005

SBP < 120 mm Hg

all-cause mortality *increased*
BP TREATMENT RECOMMENDATIONS FOR DIABETIC KIDNEY DISEASE

No RCTs with hard renal endpoints

Post hoc analyses – diabetes with overt nephropathy

Achieved SBP 130 = GFR loss only 2ml/min/yr

IDNT 2005
RENAAL 2003
SBP < 120 mm Hg all-cause mortality increased

Cooperative Study Group 1999
Every 10 mm Hg rise in systolic BP increased risk for ESRD or death by 6.7%

These data led to guideline recommendations of SBP < 130 for overt diabetic nephropathy

How achievable is this?
Multiple drugs, multiple visits

< 120 mm Hg
BP TREATMENT RECOMMENDATIONS FOR DIABETIC KIDNEY DISEASE

No RCTs with hard renal endpoints

Post hoc analyses in patients with overt nephropathy

Cooperative Study Group 1999
Achieved SBP 130
GFR loss only 2ml/min/yr
IDNT 2005
RENAAL 2003
SBP < 120 mm Hg all-cause mortality increased

But what about the majority of diabetics who do not have overt diabetic nephropathy?

We know that:

- Only 10% of diabetics have overt nephropathy YET
- 25% of diabetics age > 65yrs have eGFR<60

Every 10 mm Hg increase in systolic BP increased risk for ESRD or death by 6.7%

YET > 120 mm Hg
Rely on *post hoc* analysis of large (4000+) trials addressing cardiovascular endpoints.

These trials include:
- few > 70 yrs
- few with microalbuminuria
- even fewer with overt diabetic nephropathy
BP TREATMENT RECOMMENDATIONS FOR DIABETIC KIDNEY DISEASE WITHOUT PROTEINURIA

Rely on post hoc analysis of large (4000+) trials addressing cardiovascular endpoints

These trials include:
• few > 70 yrs
• few with microalbuminuria
• even fewer with overt diabetic nephropathy

Target BP? ...... or achieved BP?

3 different meta-analyses

....... debate about methodology .......
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

BLOOD PRESSURE CONTROL

RAS BLOCKADE
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

RAS BLOCKADE

OVERT DIABETIC NEPHROPATHY

Cooperative Study Group, RENAAL, IDNT

• ACEi or ARB reduce double sCr & ESRD

• Post hoc – proteinuria is a legitimate intermediate outcome measure
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

RAS BLOCKADE

OVERT DIABETIC NEPHROPATHY

Cooperative Study Group, RENAAL, IDNT

- ACEi or ARB reduce double sCr & ESRD

- *Post hoc* – proteinuria is a legitimate intermediate outcome measure

NON-DIABETIC PROTEINURIC CKD

REIN-2, AASK, Benazapril

- ACEi or ARB reduce double sCr & ESRD

- More proteinuria = greater benefit

- Proteinuria <0.5 g/d - *no* benefit
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

RAS BLOCKADE

OVERT DIABETIC NEPHRITIS
Cooperative Study Group, RENAAL, IDNT
• ACEi or ARB reduce double sCr & ESRD
• Post hoc – proteinuria is a legitimate intermediate outcome measure

NON-DIABETIC PROTEINURIC CKD
REIN-2, AASK, Benazapril
• ACEi or ARB reduce double sCr & ESRD
• More proteinuria = greater benefit
• Proteinuria <0.5 g/d - no benefit

ACEi or ARB?
No difference in renal outcomes
DETAIL Study

ARB better tolerated?

COST
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

RAS BLOCKADE

NON-PROTEINURIC CKD

Adults > 70yrs & eGFR<60: only 5% have proteinuria >0.5g/d

Rely on subanalyses of large CV trials

75% of the studies did not include >70yr
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

RAS BLOCKADE

NON-PROTEINURIC CKD

Adults > 70yrs & eGFR<60:
only 5% have proteinuria >0.5g/d

Rely on subanalyses of large CV trials

75% of the studies did not include >70yr

- NO evidence that renal endpoints are improved by RAS blockade in non-proteinuric CKD
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

COMBINATION RAS BLOCKADE
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

COMBINATION RAS BLOCKADE

... in proteinuric CKD

COOPERATE Study
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

COMBINATION RAS BLOCKADE

... in proteinuric CKD

COOPERATE Study
META-ANALYSIS OF COMBINATION ACEi & ARB IN PROTEINURIC IgA NEPHROPATHY

PROTEINURIA REDUCED

No effect on:
- GFR
- BP
- Serum K

Interventions to reduce progression

INTERVENTIONS WITH GOOD EVIDENCE

COMBINATION RAS BLOCKADE

NON-PROTEINURIC CKD
&
CKD with CV disease

ONTARGET

ALTITUDE
A cardiovascular secondary prevention study (n=25,620)
Combination RAS Blockade

| Study population | Mean age 66yr  
69% hypertension  
37% DM  
13% microalbuminuria  
4% macroalbuminuria |
|------------------|-----------------------------------------------|
| **Worse renal outcomes in combination group** | More hypotension  
More hyperkalaemia  
More doubling sCr  
More dialysis for AKI |
### High risk type 2 diabetes (n=8,561)
Combination RAS Blockade using direct renin inhibitor

<table>
<thead>
<tr>
<th>Study population</th>
<th>Mean age 64.5yr 95% hypertension 100% DM 26% microalbuminuria 58% macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worse renal outcomes in combination group</strong></td>
<td>More hypotension</td>
</tr>
<tr>
<td></td>
<td>More hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>More AKI</td>
</tr>
<tr>
<td><strong>Renal outcome not different</strong></td>
<td>ESRD</td>
</tr>
</tbody>
</table>
Interventions to reduce progression
INTerventions with Good Evidence

Combination RAS Blockade

VA NEPHRON-D

Type 2 DM > 18yr

Stage 2-3 CKD
Albuminuria > 0.3g/g

Data collection finishing Sept 2014
BP TREATMENT RECOMMENDATIONS FOR CHRONIC KIDNEY DISEASE

RAS BLOCKADE

First line therapy for BP in proteinuric CKD

Little or no benefit in non-proteinuric CKD

... except in diabetes where they delay progression through microalbuminuria to overt diabetic nephropathy

Combination RAS blockade: safe and effective in young proteinurics .... but not in older vasculopathics
Interventions to reduce progression
INTERVENTIONS WITH GOOD EVIDENCE

BLOOD PRESSURE CONTROL

RAS BLOCKADE
<table>
<thead>
<tr>
<th>Proteinuria</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.3g/d</td>
<td>0.3-1g/d</td>
<td>&gt; 1g/d</td>
</tr>
<tr>
<td><strong>Non-diabetic</strong></td>
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</tr>
<tr>
<td>&lt; 140/90</td>
<td>&lt;130/80</td>
<td>&lt;130/80 or &lt;125/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>if young and heavy proteinuria</td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td><strong>Diabetic</strong></td>
<td><strong>Diabetic</strong></td>
</tr>
<tr>
<td>SBP&lt; 130-140</td>
<td>&lt;130/80</td>
<td>&lt; 130/80 or &lt;125/75</td>
</tr>
<tr>
<td>DBP &lt; 80</td>
<td></td>
<td>if young and heavy proteinuria</td>
</tr>
<tr>
<td></td>
<td>Proteinuria &lt;0.3g/d</td>
<td>Proteinuria 0.3-1g/d</td>
</tr>
<tr>
<td>----------------</td>
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<td>----------------------</td>
</tr>
<tr>
<td><strong>Non-diabetic</strong></td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Agent</td>
<td>None preferred</td>
<td>ACEi or ARB</td>
</tr>
<tr>
<td><strong>Diabetic</strong></td>
<td>SBP&lt;130-140 DBP&lt;80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Agent</td>
<td>ACEi or ARB</td>
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</table>
# ‘CONSENSUS’ BP TARGETS & PREFERRED FIRST LINE AGENTS

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<th>Diabetic</th>
<th>Agent</th>
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</tr>
</tbody>
</table>

**BUT - use clinical common sense**

In older people...
**titrate carefully with close attention for adverse events**
## Interventions to reduce progression of CKD – what is the evidence?

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Intervention(s)</th>
</tr>
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<tbody>
<tr>
<td>GOOD</td>
<td>BP control</td>
</tr>
<tr>
<td></td>
<td>RAS blockade</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Uric acid lowering</td>
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<tr>
<td></td>
<td>Alkali</td>
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<tr>
<td></td>
<td>Physical exercise</td>
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<tr>
<td></td>
<td>Dietary protein restriction</td>
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<td>Smoking cessation</td>
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<td></td>
<td>Salt restriction</td>
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<tr>
<td>INSUFFICIENT</td>
<td>Anemia correction</td>
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<td></td>
<td>Statins</td>
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<tr>
<td></td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>High fluid intake</td>
</tr>
<tr>
<td>Evidence of HARM</td>
<td>Bardoxolone</td>
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</table>