CHOICES OF AGENTS AND INTERVENTIONAL THERAPIES FOR HTN IN CKD

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Disclosure of Interests

• Akebia-Consultant
• Amgen-Consultant
• Astra-Zeneca-Consultant
• Boehringer-Ingelheim-Consultant
• Novo Nordisk-Consultant
• Relypsa-Consultant
• ZS Pharma-Consultant
Take Home: Management of Hypertension in Chronic Kidney Disease

- RAAS blockade-based drug regimens
  - Vs placebo and other comparators improve renal outcomes especially in those with proteinuria
  - Systematic review: reduce mortality in DM

- Combined RAAS blockade based drug regimens compared to single RAAS blockade
  - do not improve renal or cardiovascular or all-cause mortality

- Tight vs Standard BP target: similar improvement in CV Disease and slightly lower all-cause mortality (SPRINT)

- Dietary intervention and Devices not tested/proven to improve renal or CV outcomes or all cause mortality

- Role of SGLT-2 and K binding agents on renal and CV outcomes unknown-stay tuned
Pathophysiologic Basis of Treatment of Hypertensive Kidney Disease

**Na Reabsorption**
- Angiotensin II
- Sympathetic nerves
- NOS inhibitors
- Impaired pressure natriuresis
- ↓ Glomerular surface area
- Decreased PGs

**Volume Expansion**

**Vasoconstrictors**
- Angiotensin II
- Endothelin
- Sympathetic Nerves
- NOS inhibitors
- Decreased PGs
- Digoxin-like factors

**Peripheral Resistance**

**Diuretic** → HYPERTENSION

**Vasodilator**
Approaches to Lowering BP in Hypertensive Patients with CKD

RAAS blockade

Lifestyle
Dietary Sodium
Restriction
Weight Loss

Novel Agents
K lowering agents
SGLT-2 Inhibition

Non-RAAS Antihypertensives
Diuretics

Other: CCB, BB, Vasodilators, etc.

Devices
Renal Denervation
Baroreceptor Activation

Other: CCB, BB, Vasodilators, etc.
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<th>Trial</th>
<th>Year Journal</th>
<th>Drug</th>
<th>Outcome</th>
<th>Benefit</th>
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AASK: Composite Clinical Events: Declining GFR Event, ESRD or Death by Drug Group

- Metoprolol vs. Amlodipine: RR = 20%, (p=0.17)
- Ramipril vs. Amlodipine: RR = 38%, (p=0.004)

Ramipril vs. Metoprolol: RR = 22%, p = 0.042

Follow-up Month

% with Events

RR = Risk Reduction
Conclusions from SPRINT

• Among non-diabetics Systolic Blood Pressure < 120 mmHg vs < 140 mmHg improves cardiovascular disease events and mortality among high-risk hypertensive populations.

• SBP of <120 mm Hg resulted in lower rates of CV events and death, without evidence of effect modifications by CKD, or a deleterious effect on the main kidney outcome.

• Longer follow up is needed to confirm benefit of lower SBP on CV and renal outcome, meanwhile,

• Based on these data one can make it seems reasonable to target SBP of < 120 mmHg for people with non-diabetic CKD and hypertension.

Irbesartan in Diabetic Nephropathy Trial:
Time to Doubling of Serum Creatinine, ESRD, or Death

1,715 Type 2 Diabetics with Nephropathy

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Irbesartan: RRR 23% \[P = .006\]
Amlodipine: RRR 20% \[P = .02\]
Placebo: RRR NS

Effectiveness of ACEi or ARBs in patients with early CKD
- ACEi had little or no effect on all-cause mortality, cardiovascular events and end-stage kidney disease in people with stage 3 CKD.

Effectiveness of MRAs with or without ACEi or ARB in patients with CKD
- Decrease proteinuria and lower blood pressure.
- Insufficient data on mortality, ESKD and cardiovascular events.

Effectiveness of ACEi or ARB in patients with IgA nephropathy
- Reduced proteinuria.
- No evidence that treatment with decreased mortality, cardiovascular events or adverse renal outcomes.
RAAS blockade in CKD with DM: Cochrane Systematic Review (26 trials, N=61,264)

• ACEi vs placebo reduced
  – risk of mortality (6 studies, 11,350): RR 0.84,
  – new onset of micro and macroalbuminuria, (8 studies, N=11,906) RR 0.71.

• ACEi vs CCB, reduced onset of micro and macroalbuminuria (5 studies, N=1,253): RR 0.60.

• ARB vs placebo no difference
  – mortality (5 studies, N=7,653: RR 1.12, 95%CI 0.88 to 1.41)
  – onset of microalbuminuria, macroalbuminuria or both (5 studies, N=7,653): RR 0.90.

• Combination of ACEi and ARB vs ACEi alone no difference in onset of micro or macroalbuminuria (2 studies, N=4171): RR 0.88.
Conclusion

ACE inhibitors or Angiotensin Receptor Blockers should be first line agents in patients with hypertensive CKD.
WHEN IS the GFR TOO LOW TO SEE BENEFIT OF ACEi in CKD?

Controversy
ACE inhibition in Non-Diabetic Nephropathy (N = 317)

Baseline Scr
- Gp 1: 1.5-3.0 mg/dl
- Gp 2: 3.1-5.0

BP Control in Non-Diabetic Nephropathy (N = 317)

Baseline Serum Creatinine
Group 1: 1.5-3.0 mg/dl
Group 2: 3.1-5.0 mg/dl

WHAT IS EFFECT OF PROTEINURIA ON RENAL OUTCOME?
ARB (losartan) Reduces Risk of ESRD in Diabetic Nephropathy

Reduction in Endpoints in NIDDM with Angiotensin Antagonist Losartan (RENAAL) Trial: 1513 type 2 Diabetics with Nephropathy

Placebo
BP 142 / 74

Losartan
BP 140 / 74

Risk Reduction: 28%
p = 0.002

Change in Proteinuria

- Avg: 3.5 BP drug/pt
- 90% in both groups received a CCB

1860 patients from 11 RCTS with non-diabetic kidney disease
- Anti-hypertensive regimens with ACE inhibitors vs. regimens without ACE inhibitors on progression of kidney disease.
  - Minimum follow-up of one year

Objectives:
1) Determine whether antihypertensive regimens with ACE inhibitors are superior to those without ACE inhibitors
2) Assess the relationship of BP with progression of kidney disease across a wide range of urine protein excretion

Relative Risk for Kidney Disease Progression with ACEi vs. non-ACE based regimen in Non-Diabetic Nephropathies

Relative Risk for ESRD: ACEi vs No ACEi in Non-Diabetic CKD (N=1860)

AASK: Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status.

Conclusion

Proteinuria modulates the effect of blood pressure lowering in hypertensive patients with CKD
ARE ACEi and ARB SUPERIOR TO NON-ACEi/ARB IN CKD WITH MICROALBUMINURIA?

Controversy
Irbesartan in Microalbuminuria (IRMA 2): Development of Overt Nephropathy

BP 144/83

Placebo

Irbesartan 150 mg/d

Irbesartan 300 mg/d

↓39%
P=NS

↓70%
P=0.004

NNT: 10 patients over 2 years to prevent 1 case of overt nephropathy

Conclusion

No long-term Outcomes Trials of Renal or Cardiovascular Endpoints
WHEN SHOULD YOU CONSIDER STOPPING ACEI/ARB IN CKD?

Controversy
When to Stop RAAS blockade in CKD

- Hyperkalemia
- When the GFR is low?
- In my opinion NO
Continuation of Losartan After Serum Creatinine Doubles AND Incident ESRD

Risk Reduction: 30%

P (+CT) 198 111 48 11 4
L (+CT) 162 104 43 19 3

Basis for Discontinuing ACEi in Advanced CKD: Observational Study

- 52 patients (1/2 DM) stages 4 and 5 CKD observed year before and year after stopping ACEi/ARB mean eGFR ~ 16

- 12 months after discontinuation
  - eGFR increased about 10 ml and decline in the eGFR slope was reversed +0.48 ± 0.1 (p = 0.0001).
  - BP increased about 5 mmHg

- Discontinuation of ACEi/ARB delayed the onset of RRT

Conclusion

We do not yet know whether stopping RAAS blockade in stage 4 or 5 CKD improves outcomes, so...
STOP ACEi Trial

CKD patients stage 4-5
ACEi/ARB treatments

Eligible for STOP-ACEi study?

Randomize 1:1 ratio, N=410

Control Arm: Continue ACEi/ARB
N=205

Experimental Arm: Discontinue ACEi/ARB
N=205

3-year follow-up

3-monthly visits:
Routine tests (eGFR, FBC, BCP, urinary PCR), BP, documentation of ESA dose, adverse events, compliance and changes in medication
Extra tests at annual visits:
QOL questionnaire, weight and BMI, 6-minute walk test, ECG, bloods for C-reactive protein, cystatin-C, NT-proBNP, ACE/renin levels and biomarkers

Analysis

Interim analysis of efficacy and safety carried out for data monitoring and ethics committee
First analysis once the last randomized participant completes the 3-year follow-up.

A LITTLE BIT ABOUT BP CONTROL LEVEL
Long-term risk of ESRD in AASK: Strict vs Usual BP Control

Long-term risk of All Cause Mortality in AASK: Strict vs Usual BP Control

HR = 0.92 [95% CI 0.77-1.10]
### SPRINT: Primary Outcome Experience in 6 Pre-specified Subgroups

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<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>P*</th>
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<td>Overall</td>
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<tr>
<td>No Prior CKD</td>
<td>0.70 (0.56, 0.87)</td>
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<tr>
<td>Prior CKD</td>
<td>0.82 (0.63, 1.07)</td>
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<td>Age &lt; 75</td>
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<td>Age ≥ 75</td>
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<td>Male</td>
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<td>No Prior CVD</td>
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<td>Prior CVD</td>
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<td>SBP ≤ 132</td>
<td>0.70 (0.51, 0.95)</td>
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<td>132 &lt; SBP &lt; 145</td>
<td>0.77 (0.57, 1.03)</td>
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<td>SBP ≥ 145</td>
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*Unadjusted for multiplicity

*Treatment by subgroup interaction
SPRINT CKD (baseline eGFR < 60) Cohort: Blood Pressure Control

Renal Outcome Decrease in eGFR > 50% or ESRD in SPRINT Participants with CKD at Baseline

HR (95% CI)
0.81 (0.63-1.05)

All Cause Mortality in SPRINT Participants with CKD at Baseline

Cardiovascular Outcome in SPRINT Participants with CKD at Baseline (eGFR < 60 ml/min/1.73 m²)

HR (95% CI)
0.90 (0.44-1.83)

Change in eGFR in non-CKD (eGFR ≥ 60) in SPRINT Participants (N=6405)

Beddhu et al. *Annals of Internal Medicine* Sept 2017
Outcomes in SPRINT Participants without Baseline CKD

Incident CKD
 (>30% dec. in eGFR to < 60 ml/min/1.73 m$^2$)

Incident CVD

Beddhu et al. *Annals of Internal Medicine* Sept 2017
All Cause Mortality in SPRINT Participants without Baseline CKD

Beddu et al. Annals of Internal Medicine Sept 2017
Conclusions

AASK
• Strict BP control strategy may lead to a mortality benefit consistent with SPRINT.

SPRINT
• Targeting an SBP of 120 compared with 140 reduced rates of MACE and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.
• Intensive SBP lowering increased risk for incident CKD, but this was outweighed by cardiovascular and all cause mortality benefits
KDIGO
DIETARY INTERVENTIONS
Dietary Interventions in CKD: Systematic Review (17 studies, N=1639)

• 3 enrolled dialysis pt, 4 enrolled transplant recipients, and 10 enrolled CKD stages 1 to 5.
• Follow up median of 12 months (range 1 to 46.8).
• Conclusions:
  – uncertain effects on mortality, cardiovascular events and ESKD (rarely reported).
  – may increase HRQOL, eGFR, serum albumin, and reduce blood pressure and cholesterol levels.
  – large-scale pragmatic RCTs to test the effects of dietary interventions on patient outcomes are required.
MANAGING HYPERTENSION IN CKD

MY RECIPE
How I do get Blood Pressure to 120 - 130 / 70 - 80 mmHg?: Part 1

• Dietary sodium restriction

• Once Daily ACE Inhibitor or ARB

• Diuretic
  – eGFR ≥ 50 ml/min thiazide or chlorthalidone
  – eGFR < 50 ml/min loop diuretic, or chlorthalidone
How I do get Blood Pressure to 120 - 130 / 70 - 80 mmHg?: Part 2

- $\alpha,\beta$-blocker, e.g. carvedilol
- Long-Acting CCB, e.g. Amlodipine
- Spironolactone
- Minoxidil/ Clonidine
Baroreceptor Activation and Renal Denervation
Baroreflex activation therapy bypasses intrinsic mechanical-electrical coupling by using an extrinsic electrical current to overdrive the carotid baroreceptor axons directly. This axonal input is interpreted as an increase in BP and is integrated centrally to elicit baroreflex responses.
Resistant Hypertension

Sustained Reduction of Blood Pressure With Baroreceptor Activation Therapy
Results of the 6-Year Open Follow-Up

Peter W. de Leeuw, John D. Bisognano, George L. Bakris, Mitra K. Nadim, Hermann Haller, Abraham A. Kroon; on behalf of the DEBuT-HT and Rheos Trial Investigators

Long-term follow-up data were analyzed from all patients who had been included in 1 of the 3 trials that focused on treatment-resistant hypertensive patients
Time course of blood pressure and heart rate after implantation

Follow-up entire cohort

Year since implant

SBP (mmHg)

DBP (mmHg)

HR (bpm)

Renal denervation in Resistant Hypertension

Effect of Renal Denervation in CKD

- 30 patients stage 2-4 CKD underwent Renal Denervation with "standard procedure" by single operator
- Office BP at baseline 185/107 Hg
- 24-month follow-up 131/87 mm Hg
- Mean eGFR increased from 61.9 to 88.0 mL/min/1.73 m² (P<.0001).
- UACR decreased from 99.8 mg/g to 11.0 mg/g
- CKD Stage decreased

Conclusion

BAT and Renal Denervation hold promise for management of HTN in CKD. Long-term larger scale studies with CV and Renal Outcomes—Stay tuned.
SGLT-2 INHIBITORS and Potassium Binders
Effect of SGLT2 inhibitors on daytime diastolic blood pressure.

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<th>SD</th>
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<tr>
<td>Heterogeneity: I-squared=0%, p=0.9927</td>
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Baker et al. J Am Heart Assoc. 2017
A Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

Cumulative Probability of Event (%)

Month

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
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<td>Empagliflozin</td>
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</table>

A Change in eGFR over 192 Wk

Adjusted Mean eGFR (ml/min/1.73 m²)

Week

Baseline 4 12 28 52 80 94 108 122 136 150 164 178 192

Yes. 4 12 28 52 80 94 108 122 136 150 164 178 192

Empaglifloz, 10 mg
Empagliflozin, 25 mg
Placebo

No. at Risk

Placebo 2323 2295 2267 2205 2121 2064 1927 1981 1763 1479 1262 1123 977 731 448
Empagliflozin, 10 mg 2322 2290 2264 2235 2162 2114 2012 2064 1839 1540 1314 1180 1024 785 513
Empagliflozin, 25 mg 2322 2288 2269 2216 2156 2111 2006 2067 1871 1563 1340 1207 1063 838 524

No. in Follow-up Analysis

Total 7020 7020 6996 6931 6864 6765 6696 6651 6068 5114 4443 3961 3488 2707 1703

Patiromer, Aldosterone Potassium and Blood Pressure in CKD

Randomized Placebo Controlled Trial
Patiromer N = 242 Type 2 DM and CKD On ACEi or ARB at baseline
Hyperkalemia

Take Home: Management of Hypertension in Chronic Kidney Disease

- RAAS blockade-based drug regimens
  - Vs placebo and other comparators improve renal outcomes
  - Systematic review: reduce mortality in DM
- Combined RAAS blockade based drug regimens compared to single RAAS blockade
  - Do not improve renal or cardiovascular or all-cause mortality
- Tight vs Standard BP control does not increase CV morbidity or mortality (SPRINT)
- Dietary intervention and Devices not tested/proven to improve renal or CV outcomes or all cause mortality
- Role of SGLT-2 and K binding agents on renal and CV outcomes unknown-stay tuned