Hot Topics in Nephrology

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Question

• Which of these side effects can be seen with SGLT-2 inhibitors?

1) Fluid overload
2) Hyperkalemia
3) Hyponatremia
4) All of the above
5) None of the above
6) What is an SGLT2 inhibitor?
Question

• Vaptans can be used to slow the rate of progression of which kidney disease?
  1) Diabetic Nephropathy
  2) HTN nephrosclerosis
  3) Polycystic Kidney Disease
  4) FSGS
  5) None of the above – Everyone knows Vaptans are used only to treat hyponatremia
  6) What is a Vaptan?
**Question**

- What is the target blood pressure for patients with CKD based on the new AHA guidelines and what is the first line drug therapy for the treatment of HTN in CKD patients?

<table>
<thead>
<tr>
<th>Choice</th>
<th>Target BP</th>
<th>Drug of Choice (CKD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;140/90</td>
<td>Loop Diuretic</td>
</tr>
<tr>
<td>B</td>
<td>&lt;140/90</td>
<td>ACEI</td>
</tr>
<tr>
<td>C</td>
<td>&lt;130/80</td>
<td>ACEI</td>
</tr>
<tr>
<td>D</td>
<td>&lt;130/80</td>
<td>Thiazide</td>
</tr>
<tr>
<td>E</td>
<td>&lt;120/80</td>
<td>ACEI</td>
</tr>
<tr>
<td>F</td>
<td>&lt;120/80</td>
<td>Loop Diuretic</td>
</tr>
</tbody>
</table>
Worldwide Incidence of Kidney Disease

- CKD in the U.S.
  - 13% (26 million adults)
  - 65% with Stages 3/4
- ESRD
  - 500,000 people
- Cost of Kidney Disease
  - Medicare budget
  - 26 billion dollars
Worldwide Prevalence of CKD

- U.S.: 13.4%
- Europe: 11%
- Australia: 16%
- Japan: 20%
- China: 13%
But....The U.S. is not #1 in the Incidence of ESRD

Current Incidence rate of ESRD
U.S. - #3

Change in the Incidence of ESRD over time
Diabetes is the Primary Cause of ESRD Worldwide

U.S. – 44%
Racial Differences in the Incidence of CKD / ESRD

At every age group, the incidence of CKD and ESRD are significantly higher in people of black race ancestry.

Black Race 13% of U.S. population but 32% of ESRD population
Racial Predisposition for CKD / ESRD

Access to Health Care

Socioeconomic

Cultural Barriers

Compliance
What is this?
Does This Help?

TseTse Fly

Trypanosomiasis: "African Sleeping Sickness"
Trypanosomiasis

African

Sleeping Sickness

American

Chagas Disease

Trypanosomiasis

Gambienses

Rhododiense

Trypanosomiasis

Cruzii
African Trypanosomiasis

70 million people at risk within 36 African countries

7000 cases a year

During epidemics – death rate of > 50,000 / yr
Genetic Mutations called G1 or G2 must be homozygous in order to cause lysis of the parasite. Humans developed a method of inactivating the parasite through ApoL1 located on HDL3. Then, the trypanosoma acquired a way to deactivate the ApoL1 on HDL3. Finally, by natural selection, mutated ApoL1 variants renewed the capacity of humans to eliminate any Trypanosoma infection.
APOL1

• ApoL1 is a secreted lipoprotein and circulates on HDL3 complexes – major role in protection from Trypanosomiasis

• Lead to death of Trypanosomiasis by lysing the parasite’s lysosomes
  • Trypanosomal acquired resistance to ApoL1 resulting in a selection bias for Mutations G1 and G2
    • Represent an improved mutation from the wild type APOL1 due to ability to overcome Trypanosomal resistance

• ApoL1 constitutively expressed in podocytes, proximal tubular cells and endothelial cells
  • transport of lipids and cholesterol, formation of ion channels in lipid bilayers, innate immune responses, cytolysis and autophagic cell death
Trypanosomiasis

Homozygous mutation of APOL1 gene
Chromosome 22

Survival: Clearance of Trypanosomiasis

Increased Risk of CKD / FSGS / HIV Nephropathy
Genetic Mal-adaptation for Survival in Africa

- **Malaria**
  - Sickle Cell Mutation
  - Resistance to Infection
  - Systemic Complications of SS Disease

- **Trypanosomiasis**
  - APOL1 Mutation
  - Resistance to Infection
  - Increased Risk of CKD/ESRD
APOL1 variants:
APAN: Apolipoprotein Associated Nephropathy

36% of Black race individuals in the U.S. carry a mutation either G1 or G2 of the APOL1 allele.
AASK Trial: African American Study Kidney Disease

APOL1 mutation influenced the outcome of the study regardless of BP or anti-hypertensive agent used.

Caveat: future studies in black race patients on the development of CKD/ESRD need to stratify treatment groups by APOL1 allele status.
Donor APOL1 Status Affects the Outcome of Kidney Transplantation

Donor Kidney APOL1 Status

Recipient APOL1 Status does not influence graft outcome
Risk of ESRD after Living Kidney Donation

- **White Men**: 0.06%
- **Black Men**: 0.24%
- **White Women**: 0.04%
- **Black Women**: 0.15%

APOL1 Status – Unknown
Requires further research on whether ApoL1 carriers should be living donors
Future Use of APOL1 measurement in Selected Black Race Patient Populations

- Kidney Donation
- Research Trials
- HTN management
- FSGS
APOL1 Polymorphism and Renal Disease

The single most important discovery regarding the ethnic disparity in the development of CKD within the Black Race population
Kidney Failure Is Increasing in the U.S.

Per million population, 2000

Per million population, 2010

HSA=CDC health service area.
United States Renal Data System 2010 Annual Report
Causes of CKD in the U.S.

72% of all cases of CKD are potentially avoidable by proper treatment of Diabetes and HTN
Prevention of Diabetic Nephropathy

- Glycemic Control
- BP Control
- RAAS Inhibition
- ?????????????????
**Diabetes** = *diabainein* = a siphon = **excessive urination**

Mellitus = “like honey”

**Old Paradigm**
- Decrease glucose production
- Increase glucose utilization

**New Paradigm**
- Increase urinary glucose excretion

**Therapeutic Intervention**
Glucose Handling by the Nephron

SGLT = Sodium GLucose Transporter

At blood sugars < 180 mg/dl there is usually no glucose in the urine with complete reabsorption

Glucose is absorbed with Na+
SGLT-2 Inhibitors

Marked increase in urinary glucose excretion (Solute diuresis - increased osmolality)

Increased urinary volume

Increased Na+ loss

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invokana</td>
<td>canagliflozin</td>
</tr>
<tr>
<td>Invokamet</td>
<td>canagliflozin and metformin</td>
</tr>
<tr>
<td>Farxiga</td>
<td>dapagliflozin</td>
</tr>
<tr>
<td>Xigduo XR</td>
<td>dapagliflozin and metformin extended-release</td>
</tr>
<tr>
<td>Jardiance</td>
<td>empagliflozin</td>
</tr>
<tr>
<td>Glyxambi</td>
<td>empagliflozin and linagliptin</td>
</tr>
<tr>
<td>Synjardy</td>
<td>empagliflozin and metformin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral Antidiabetic Medications</th>
<th>A1C Reduction (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2 inhibitors</td>
<td>0.7 to 1.0</td>
</tr>
<tr>
<td>Biguanides</td>
<td>1.0 to 1.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.0 to 1.5</td>
</tr>
<tr>
<td>Meglinides</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td>0.5 to 1.0</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1.0 to 1.5</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>0.5 to 1.0</td>
</tr>
</tbody>
</table>
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erodotu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*
EMPA

- 7020 Type 2 Diabetic patients at 590 sites in 42 countries
  - 80% of patients were on RAAS inhibition
  - GFR > 30 cc/min
  - Established CV disease

Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, death from renal disease and incident albuminuria
<table>
<thead>
<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2) 60.7</td>
<td>497/2102 (23.6) 95.9</td>
<td>0.61 (0.55–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124 (12.7) 47.8</td>
<td>388/2061 (18.8) 76.0</td>
<td>0.61 (0.53–0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
<td>459/4091 (11.2) 41.8</td>
<td>330/2033 (16.2) 64.9</td>
<td>0.62 (0.54–0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²</td>
<td>70/4645 (1.5) 5.5</td>
<td>60/2323 (2.6) 9.7</td>
<td>0.56 (0.39–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3) 1.0</td>
<td>14/2333 (0.6) 2.1</td>
<td>0.45 (0.21–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7) 6.3</td>
<td>71/2323 (3.1) 11.5</td>
<td>0.54 (0.40–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria in patients with a normal albumin level at baseline</td>
<td>1430/2779 (51.5) 252.5</td>
<td>703/1374 (51.2) 266.0</td>
<td>0.95 (0.87–1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Delayed Progression of Renal Disease in Patients with Established Diabetic renal Disease :
GFR < 60 cc/min and Macroalbuminuria

![Graph showing cumulative probability of event over time with Kaplan-Meier curves for Placebo and Empagliflozin. The hazard ratio (HR) is 0.58 with a 95% confidence interval (CI) of 0.47 to 0.71. The p-value is <0.001.](image-url)
EMPA was effective as an add on to RAAS inhibition

Hypothesis –
  • Natriuresis
    • Activates tubulo-glomerular feedback and decreases intraglomerular pressure
Canagliflozin Cardiovascular Assessment Study (CANVAS) and Renal Assessment Study (CANVAS-R)

- 10,142 participants, 4330 in CANVAS and 5812 in CANVAS-R
- 667 centers in 30 countries
- Type 2 Diabetes with CV disease or age 50 with > 2 CV risk factors
Canagliflozin Cardiovascular Assessment Study (CANVAS) and Renal Assessment Study (CANVAS-R)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of participants per 1000 patient-yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>
Decreased Progression of Renal Disease with SGLT-2 Inhibition
Potential Side Effects of SGLT-2 Inhibition

- Volume Depletion
  - Osmotic diuresis
  - Natriuresis
- Hypotension
  - Natriuresis
  - Dehydration
- UTI
  - Increased urinary glucose
- Mycotic Genital Infections
  - Glycosuria
- Ketosis
  - Glycosuria
- Weight Loss
  - Glycosuria
  - Volume depletion
Increased Amputation Risk with Canagliflozin

- Highest risk was in pts with a previous history of amputation
- Possibly related to decreased BP and hypovolemia
Increased Fracture Risk with Canagliflozin

Table S9. Effects of canagliflozin versus placebo on fracture in CANVAS, CANVAS-R, and the CANVAS Program

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin Per 1000 patient-years</th>
<th>Placebo Per 1000 patient-years</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-trauma fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS</td>
<td>12.98</td>
<td>8.31</td>
<td>1.56 (1.18–2.06)</td>
<td></td>
</tr>
<tr>
<td>CANVAS-R</td>
<td>7.87</td>
<td>10.30</td>
<td>0.76 (0.52–1.12)</td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>11.58</td>
<td>9.17</td>
<td>1.23 (0.99–1.52)</td>
<td>0.003</td>
</tr>
<tr>
<td>All fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS</td>
<td>16.92</td>
<td>10.94</td>
<td>1.55 (1.21–1.97)</td>
<td></td>
</tr>
<tr>
<td>CANVAS-R</td>
<td>11.42</td>
<td>13.23</td>
<td>0.86 (0.62–1.19)</td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>15.40</td>
<td>11.93</td>
<td>1.26 (1.04–1.52)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitors and Diabetic Renal Disease

• These agents represent a **novel therapeutic class** that have been shown in Diabetics to
  • Reduce CV disease including CHF and death
  • Slow the rate of progression of diabetic kidney disease

• Benefits must be weighed against the risks of
  • Hypovolemia / hypotension
  • Increased potential for amputations (???)
  • Increased fracture risk (???)
  • Increased cutaneous genital infections
Prevention of Contrast Nephropathy: The Final Word

PRESERVE TRIAL

Prevention of Serious Adverse Events Following Angiography

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine


New England Journal of Medicine November 12, 2017
Prevent Contrast Nephropathy
Dinner Menu

Appetizer (Choose one or more)

N Acetyl Cysteine
Theophylline
Mannitol
Furosemide
Statin

Entrée (choose one)

0.9 Normal Saline
IV Bicarbonate
PRESERVE Trial
5000 patients

Patient Population
GFR 15 – 45 cc/min
or
GFR 45 – 60 cc/min with Diabetes

End Point
A) 50% increase in creatinine at 90 days
B) Dialysis
C) Death

Normal Saline
1 – 3 cc/kg minimum 1 hour prior and 6-12 hrs post

Bicarbonate

Normal Saline + Acetylcysteine
1200 mg 1 hour prior and BID afterward for 96 hours

Bicarbonate + Acetylcysteine
### PRESERVE Trial

**NO BENEFIT !!!**

Bicarbonate or N-Acetylcysteine did not provide any benefit to prevent contrast nephrotoxicity
PRESERVE Trial

• In conclusion, in patients with impaired kidney function who were undergoing angiography, we found that periprocedural intravenous isotonic sodium bicarbonate showed no benefit over intravenous isotonic sodium chloride with respect to the risk of major adverse kidney events, death, or acute kidney injury. In addition, we found no benefit for the oral administration of acetylcysteine over placebo in decreasing the same risks.
Prevent Contrast Nephropathy
Dinner Menu

Appetizer

0.9 Normal Saline

Entrée

0.9 Normal Saline

Dessert

0.9 Normal Saline
Autosomal Dominant Polycystic Kidney Disease

10% of all cases of ESRD
50% ESRD by age 50
600,000 affected people in the U.S.
12 million worldwide

ADPCKD is always bilateral
Football placed for comparison – there are no footballs in the abdomen
ADPCKD is a hereditary but not a congenital disease – the cysts are not present at birth and develop over time.
Strategies to Reduce the Progression of ADPCKD

- Hypertension Control
- Na Restriction
- Strategies to Reduce the Progression of ADPCKD
The Vaptans

• Blocks the V2 receptor in the collecting ducts preventing ADH from binding
  • Water diuresis
  • Approved treatment for hyponatremia

Aquaretics

• Arginine vasopressin (AVP) V2 receptor antagonists
  • “Vaptans”
    • Conivaptan
    • Tolvaptan
    • Lixivaptan
Mechanism of Action of Tolvaptan in ADPKD

Impair AQP2 Generation

Reduce Intracellular cAMP
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes: TEMPO

- 1445 patients with Stage 1-3 CKD and ADPCKD
- Phase 3, multicenter, double-blind, placebo-controlled, 3-year trial

Significant reduction in the rate of kidney growth with Tolvaptan independent of the Stage of CKD 1-3
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes: TEMPO

Significant reduction in the rate of kidney growth with Tolvaptan occurs immediately in the first 12 months and continued through the 2nd and 3rd years.
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes: TEMPO

Rate of decline in GFR with Tolvaptan was significantly slower starting in Stage 2-3 CKD and fewer patients progressed to the next Stage of CKD.
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes: TEMPO

Slower cyst growth translates to fewer episodes of cyst rupture
Elevated LFTs all returned to baseline with drug cessation.
Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO)

Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial,
Tolvaptan significantly slowed the rate of decline in kidney function in all age groups and degree of CKD. Delay in the need for dialysis / Transplant > 3 years.
A total of 31 patients (4.6%) receiving tolvaptan had serious hepatic adverse events, as compared with 4 (0.6%) receiving placebo.

In all cases, the elevated liver-enzyme levels returned to normal after the interruption or discontinuation of treatment. No reports of persistent sequelae have been received, and no patients had concurrent elevations in the bilirubin level to more than two times the upper limit of the normal range.
First Drug Ever Approved for ADPCKD
Guidelines for the use of Tolvaptan in ADPCKD

• Rapid disease progression
  • annual eGFR decline of at least 5 mL/min/1.73 m² in 1 year, and/or at least 2.5 mL/min/1.73 m² per year over a period of 5 years
  • greater than 5% increase in total kidney volume per year by repeated measurements (preferably 3 or more, each at least 6 months apart and by magnetic resonance imaging)
  • ultrasound (US) kidney length (KL) >16.5 cm

Starting dose of 45 mg in the morning and 15 mg in the evening, uptitrating the dose to 50/30 and 90/30 when tolerated, and discontinuing tolvaptan when patients approach end-stage renal disease
Worldwide Approval for Tolvaptan in Rapidly Progressive ADPKD

- Japan 2014
- Canada 2015
- European Commission 2015
- USA: Pending FDA Approval
Tolvaptan and ADPKD

• **The first drug approved with supporting evidence for slowing the rate of cyst growth and reducing the degree of GFR loss**

• Recommended for the subset of PCKD patients with rapidly progressive disease

• **The FDA has not yet approved this drug in the U.S. pending the completion of additional safety studies**

• Canadian and European physicians have guidelines on the use of this agent for Stage 1-3 CKD
Famous People with A Kidney Transplant

- George Lopez, Sarah Hyland
- Natalie Cole
- Ivan Klasnic, Lucy Davis
- Sean Elliott
- Alonzo Mourning
- Tracy Morgan, Gary Coleman
- Jimmy Little
- Ron Springs – Everson Walls
- Ken Howard
- Jennifer Harman
- Steve Cojocaru
- Neil Simon

Note: Diabetic individuals are highlighted.
And just recently ..........a Baltimore Raven gave a Kidney to a Pittsburgh Steeler

“Ma’ake Kemoeatu was probably the largest normal kidney I’ve ever seen,” Dr Bartlett

“Ma’ake Kemoeatu

“He couldn't play anymore, and I didn't want to be in a position where he couldn't play but I'd keep playing- so I quit football and gave him my kidney “
Expected Remaining Lifetimes in ESRD Patients, Transplant Patients and U.S. Population

Transplantation significantly prolongs survival even up to 80 years old but still remains 20-30% lower than the normal population.
Influence of Donor Source on Renal Allograft Survival

- **Living Related 2 Haplotype Match**: > 25 years
- **Living Related 1 Haplotype Match**: 15-17 years
- **Living Related 0 Haplotype Match or Living Un-Related**: 13-15 years
- **Cadaver donor**: 9 years
Organ TP 2000 - 2016

UNOS reports NEW record!

More than 33,600 U.S. organ transplants in 2016

20% increase in transplants over 5 years*

*Based on OPTN | UNOS data as of January 9, 2017. Data subject to change between future data releases or revisions.

Matching organs. Saving lives.
Transplant Waiting List: December 1, 2017

- Kidney: 109,136
- Liver: 16,601
- Heart: 4,240
- Kidney-Pancreas: 2016
- Lung: 1,408
- Intestines: 277

129,005 Candidates for a Solid Organ Transplant
Patients are Waiting Longer and Longer for a Kidney Transplant

Average waiting time 3-4 years
15% of patients are on the list > 5 years
Wide variation in Cadaveric Donation Rates in the U.S.

Cadaveric Kidney Donation rates (per 1000 deaths)
How are Kidneys Allocated to Recipients on the List?
Who Gets the Next Kidney from the List?

It used to be this.....

Now it is like this.....

<table>
<thead>
<tr>
<th>Sequence A</th>
<th>Sequence B</th>
<th>Sequence C</th>
<th>Sequence D</th>
</tr>
</thead>
<tbody>
<tr>
<td>KDPI &lt;=20%</td>
<td>KDPI &gt;20% but &lt;=35%</td>
<td>KDPI &gt;=35% but &lt;=85%</td>
<td>KDPI &gt;85%</td>
</tr>
<tr>
<td>Highly Sensitized 0-ABDRmm (top 20% EPTS)</td>
<td>Highly Sensitized 0-ABDRmm Prior living donor Local pediatrics Local adults Regional pediatrics Regional adults National pediatrics National adults</td>
<td>Highly Sensitized 0-ABDRmm Prior living donor Local Regional National</td>
<td>Highly Sensitized 0-ABDRmm Local + Regional National</td>
</tr>
</tbody>
</table>

OPTN

Next in LINE!
Allocation of Cadaveric Kidneys: Maximizing the Outcomes

- December 4, 2014 marked a turning point in the distribution of cadaveric kidneys with the creation of 2 new indices – EPTS / KPDI

- **Donor KDPI (Kidney donor Prognostic Index)**
  - Age
  - Height
  - Weight
  - Ethnicity
  - History of Hypertension
  - History of Diabetes
  - Cause of Death
  - Serum Creatinine
  - Hepatitis C Virus (HCV) Status
  - Donation after Circulatory Death (DCD) Status
Estimated Post Transplant Survival

- Current diagnosis of diabetes
- Any prior solid organ transplant
- Duration on dialysis
- Candidate’s age

OPTN

EPTS score range 0%-100%

Figure 1: Kaplan-Meier Patient Survival Curves by EPTS Score
Deceased Donor, Adult, Solitary Kidney Transplants from 2003-2010
Based on OPTN data as of Feb 7, 2014
The best kidneys are mandated to go to the best recipients
Potential Source of Cadaveric Allografts: HCV+

- 1.0% of the U.S. population
- 30,000 new cases/year
- Choices of what to do with an HCV+ donor

Previous Policy:
- Discard
- Research
- TP HCV+ Recipient

New Policy:
- TP HCV- Recipient

Graph showing estimated persons infected with HCV (in millions):
- NHANES III 1988-1994: 3.9 (Anti-HCV) and 2.7 (HCV RNA)
- NHANES 1999-2002: 4.1 (Anti-HCV) and 3.2 (HCV RNA)
- NHANES 2003-2010: 3.6 (Anti-HCV) and 2.7 (HCV RNA)
Transplant HCV+ Donor Kidney into an HCV+ Recipient

- **Recipient must be actively replicating HCV** and treatment naïve
- Direct Acting Anti-virals (DAA) are usually started 2 months after transplantation
- Allows an HCV+ patient to get cadaveric kidney transplant much faster than the standard waiting list

Caveat:

- Many hepatologists prematurely treat the HCV+ dialysis patient and once they are in a SVR – this REDUCES their chance for a timely transplant – it is important to educate the hepatology specialists NOT to treat HCV+ CKD patients unless there is significant liver fibrosis present
Comparable Outcome of HCV+ donors into HCV+ recipients compared to HCV- Donors

Jawa P, Am J Transplant. 2013; 13 (suppl 5)
HCV+ Donors for HCV- Recipients

- Recipients will all acquire HCV+ status
- Direct Acting Acting Antivirals (DAA) started as soon as possible posttransplant

- Although graft survival is inferior to HCV- donors/HCV- recipients, the patient survival is still superior compared to remaining on dialysis therapy
- Currently being done under NIH protocols in selected centers
HCV+ Donors for HCV- Recipients : Ethical Issues

- Directly infecting a patient with a potentially lethal virus
  - 2-4% of HCV genotypes will not respond with an SVR to DAA

- Question
  - Who is going to pay for the DAA therapy ($80,000) which is an intentional iatrogenic infection
  - Current payment allocation for kidney transplantation will not be enough to cover this therapy
What is the Target BP for Patients with CKD?
<table>
<thead>
<tr>
<th>JNC/ACC/AHA</th>
<th>Year</th>
<th>BP Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1977</td>
<td>&lt; 169/90 mmHg</td>
</tr>
<tr>
<td>2</td>
<td>1980</td>
<td>Diastolic &lt; 90 mmHg</td>
</tr>
<tr>
<td>3</td>
<td>1984</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td>6</td>
<td>1997</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;130/85 for high risk</td>
</tr>
<tr>
<td>7</td>
<td>2003</td>
<td>&lt; 140/90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 130/80 for high risk</td>
</tr>
<tr>
<td>8</td>
<td>2014</td>
<td>&lt; 140/90 for &lt; 60 yrs old</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;150/90 for &gt; 60 yrs old</td>
</tr>
<tr>
<td>ACC/AHA</td>
<td>2017</td>
<td>130/80</td>
</tr>
</tbody>
</table>
Worldwide Prevalence of Hypertension Based on 140/90

- 1 billion people worldwide
- 30% of the adult population
- 80 Million in the USA
- 7.5 million deaths
- 94 billion dollars cost

Poland 70%
Germany 55%
Japan 45%
Spain 45%
England 38%
Italy 37%
USA 30%
Canada 22%

New Revised Goal (130/80) 46%
New BP Targets Increase the Percentage of HTN Patients in all Age groups, Genders and Ethnicities

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>SBP/DBP ≥130/80 mm Hg or Self-Reported Antihypertensive Medication‡</th>
<th>SBP/DBP ≥140/90 mm Hg or Self-Reported Antihypertensive Medication‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall, crude</td>
<td>46%</td>
<td>32%</td>
</tr>
<tr>
<td>Men (n=4717)</td>
<td>Women (n=4906)</td>
<td>Men (n=4717)</td>
</tr>
<tr>
<td>Overall, age-sex adjusted</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–44</td>
<td>30%</td>
<td>19%</td>
</tr>
<tr>
<td>45–54</td>
<td>50%</td>
<td>44%</td>
</tr>
<tr>
<td>55–64</td>
<td>70%</td>
<td>63%</td>
</tr>
<tr>
<td>65–74</td>
<td>77%</td>
<td>75%</td>
</tr>
<tr>
<td>75+</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>Race-ethnicity§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>47%</td>
<td>41%</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>59%</td>
<td>56%</td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>44%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Average increase in the HTN Population based on the new classification of HTN

Men – 16%
Women – 11%
Progress is impossible without change, and those who cannot change their minds cannot change anything.

George Bernard Shaw
The SPRINT Trial
Systolic Blood Pressure Intervention Trial

A Randomized Trial of Intensive versus Standard Blood-Pressure Control
The SPRINT Trial
Systolic Blood Pressure Intervention Trial

Systolic BP < 120 mmHg

Primary Outcome
CVD - CHF

Secondary Outcome
CKD – Albuminuria
Dementia

Systolic BP < 140 mmHg
The SPRINT Trial
Systolic Blood Pressure Intervention Trial

• Final Study
  • 102 centers in the U.S.
  • 9361 patients randomized into 2 groups
    • 31% Black race
    • 10% Hispanic race
    • 30% Stage 3 CKD (baseline GFR 72 cc/min)
  • Age 68 yrs
  • Age > 75: 28%
  • 3.2 years followup
  • Blood pressure measured 3 times per visit
    • Automated (Omron) system
The SPRINT Trial
Systolic Blood Pressure Intervention Trial

BP meds : 1.8
134 mmHg

BP meds : 2.8
121 mmHg
SPRINT : CVD Outcome

NIH Safety Board stopped the Trial after 3.3 yrs
43% reduction in CVD in Intensive Tx arm
Important Critique of SPRINT BP Target: Method of Measurement

• Study patients were placed in a quiet room for 5 minutes
  • Blood pressure was recorded 3 times
  • Average of the readings was used for analysis

• This is NOT TYPICAL of office based BP

SPRINT target of 120/80 is more likely a “real world” blood pressure of 130/85
SPRINT Trial: CKD Group

Intensive BP Control resulted in .....

Decrease in CVD by 28% similar to non CKD population

Decrease in all cause mortality similar to non CKD population

No change in the rate of ESRD or a 50% decline in GFR
SPRINT Trial: CKD Group

Persistent decrease in microalbuminuria

Intensive BP Control resulted in.....
Sprint Trial : CKD Group

- The benefits of intensive BP control on reducing CVD and all cause mortality are the same in non-diabetic patients with or without CKD.
- Intensive BP control did not worsen the degree of CKD (no J curve) but did reduce the degree of microalbuminuria.
- The small risk of AKI / electrolyte disorders is superceded by the clinical benefit of CV protection.
ACC/AHA 2017 HTN Guidelines and CKD

RAAS inhibition slows the rate of progression of any form of kidney disease and must be used preferentially as first line therapy regardless of blood pressure.

The presence of proteinuria mandates RAAS inhibition therapy.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>SBP: B-R&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg (1-6).</td>
</tr>
<tr>
<td>Ila</td>
<td>B-R</td>
<td>2. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression (3, 7-12).</td>
</tr>
<tr>
<td>IIb</td>
<td>C-E0</td>
<td>3. In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]) (7, 8), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.</td>
</tr>
</tbody>
</table>
### Drug Classes – ARB / ACEI

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Benazepril</th>
<th>10–40</th>
<th>1 or 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>12.5–150</td>
<td>2 or 3</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>5–40</td>
<td>1 or 2</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10–40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10–40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moexipril</td>
<td>7.5–30</td>
<td>1 or 2</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td>4–16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>10–80</td>
<td>1 or 2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARBs</th>
<th>Azilsartan</th>
<th>40–80</th>
<th>1</th>
<th>• Do not use in combination with ARBs or direct renin inhibitor.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candesartan</td>
<td>8–32</td>
<td>1</td>
<td>• There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K⁺ supplements or K⁺-sparking drugs.</td>
</tr>
<tr>
<td></td>
<td>Eprosartan</td>
<td>600–800</td>
<td>1 or 2</td>
<td>• There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis.</td>
</tr>
<tr>
<td></td>
<td>Irbesartan</td>
<td>150–300</td>
<td>1</td>
<td>• Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued.</td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>50–100</td>
<td>1 or 2</td>
<td>• Avoid in pregnancy.</td>
</tr>
<tr>
<td></td>
<td>Olmesartan</td>
<td>20–40</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telmisartan</td>
<td>20–80</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
<td>80–320</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Question

Which of these side effects can be seen with SGLT-2 inhibitors?

1) Fluid overload
2) Hyperkalemia
3) Hyponatremia
4) All of the above
5) None of the above
Question

- Vaptans can be used to slow the rate of progression of which kidney disease?
  1) Diabetic Nephropathy
  2) HTN nephrosclerosis
  3) Polycystic Kidney Disease
  4) FSGS
  5) None of the above – Everyone knows Vaptans are used to treat hyponatremia only
Question
• What is the target blood pressure for patients with Stage 3 CKD based on the new AHA guidelines and what is the first line drug therapy for the treatment of HTN?

<table>
<thead>
<tr>
<th>Choice</th>
<th>Target BP</th>
<th>Drug of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt;140/90</td>
<td>Loop Diuretic</td>
</tr>
<tr>
<td>B</td>
<td>&lt;140/90</td>
<td>ACEI</td>
</tr>
<tr>
<td>C</td>
<td>&lt;130/80</td>
<td>ACEI</td>
</tr>
<tr>
<td>D</td>
<td>&lt;130/80</td>
<td>Thiazide</td>
</tr>
<tr>
<td>E</td>
<td>&lt;120/80</td>
<td>ACEI</td>
</tr>
<tr>
<td>F</td>
<td>&lt;120/80</td>
<td>Thiazide</td>
</tr>
</tbody>
</table>
Genetic Risk of CKD

Prevention of Contrast Nephropathy

Prevention of Diabetic Nephropathy

New Distribution Policy for Kidney Transplants

Slowing the Progression of Polycystic Kidney Disease

Target Blood Pressure in CKD

Thank You!