Hot Topics in Nephrology

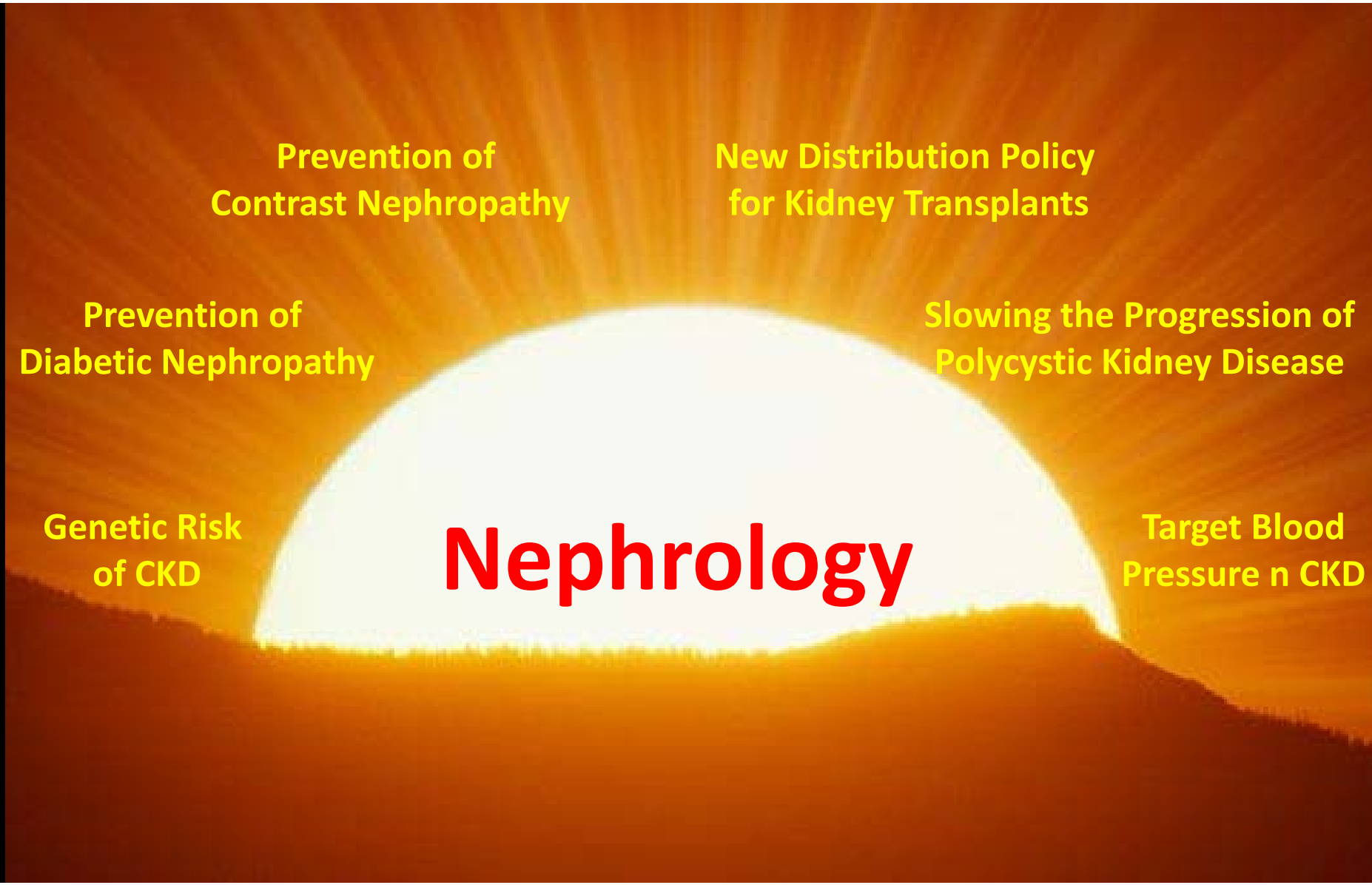
Warren Kupin MD FACP

Professor of Medicine

Miami Transplant Institute

Katz Family Division of Nephrology and Hypertension

University of Miami Miller School of Medicine


Prevention of
Contrast Nephropathy
New Distribution Policy
for Kidney Transplants
Prevention of
Diabetic Nephropathy
Slowing the Progression of
Polycystic Kidney Disease
Genetic Risk
of CKD
Nephrology
Target Blood
Pressure n CKD

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 ?

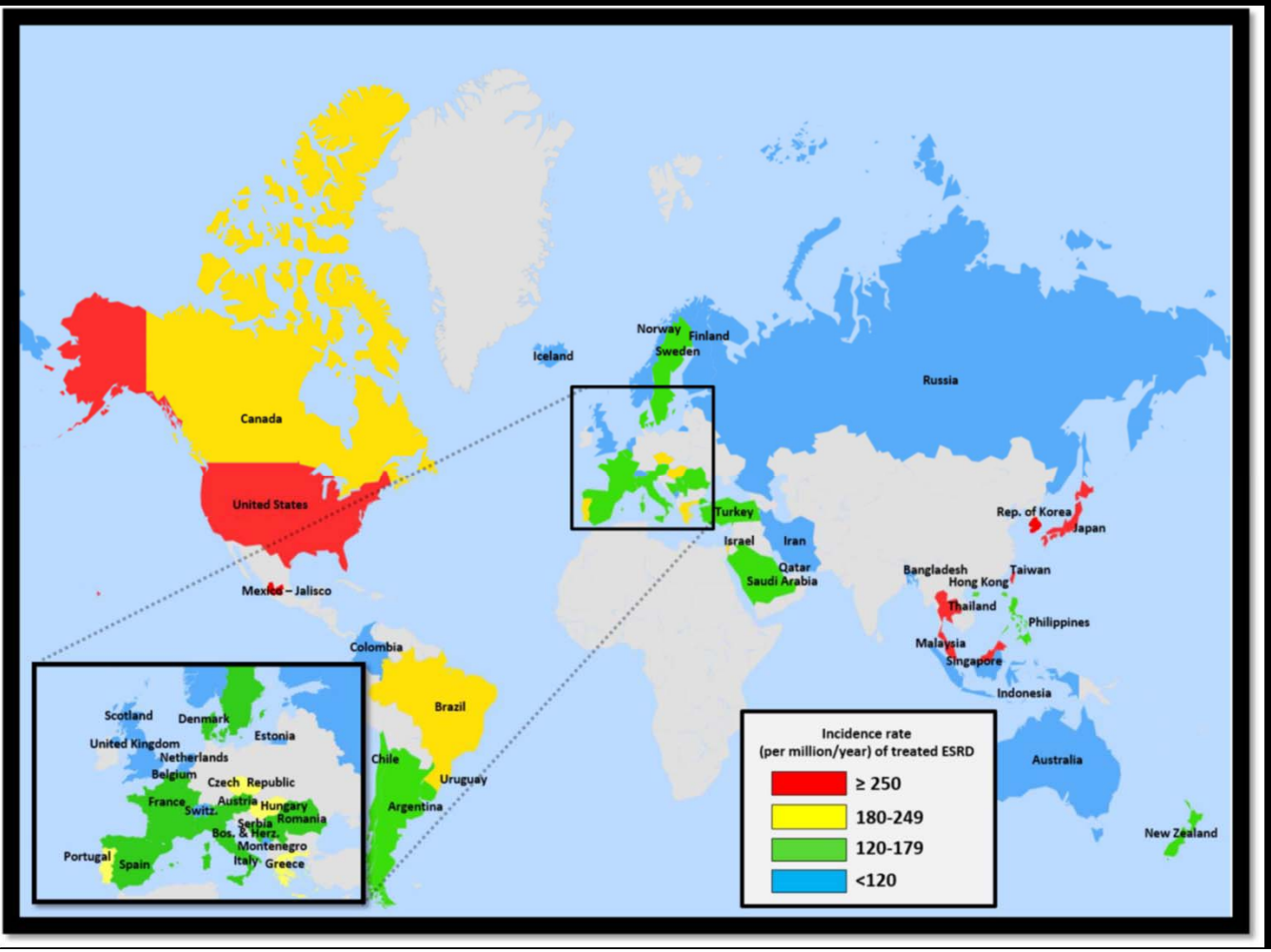
1) Diabetic Nephropathy
2) HTN nephrosclerosis
3) Polycystic Kidney Disease
4) FSGS
5) None of the above – Everyone knows Vaptans are used only to treat hyponatremia
6) What is a Vaptan?

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 ?**

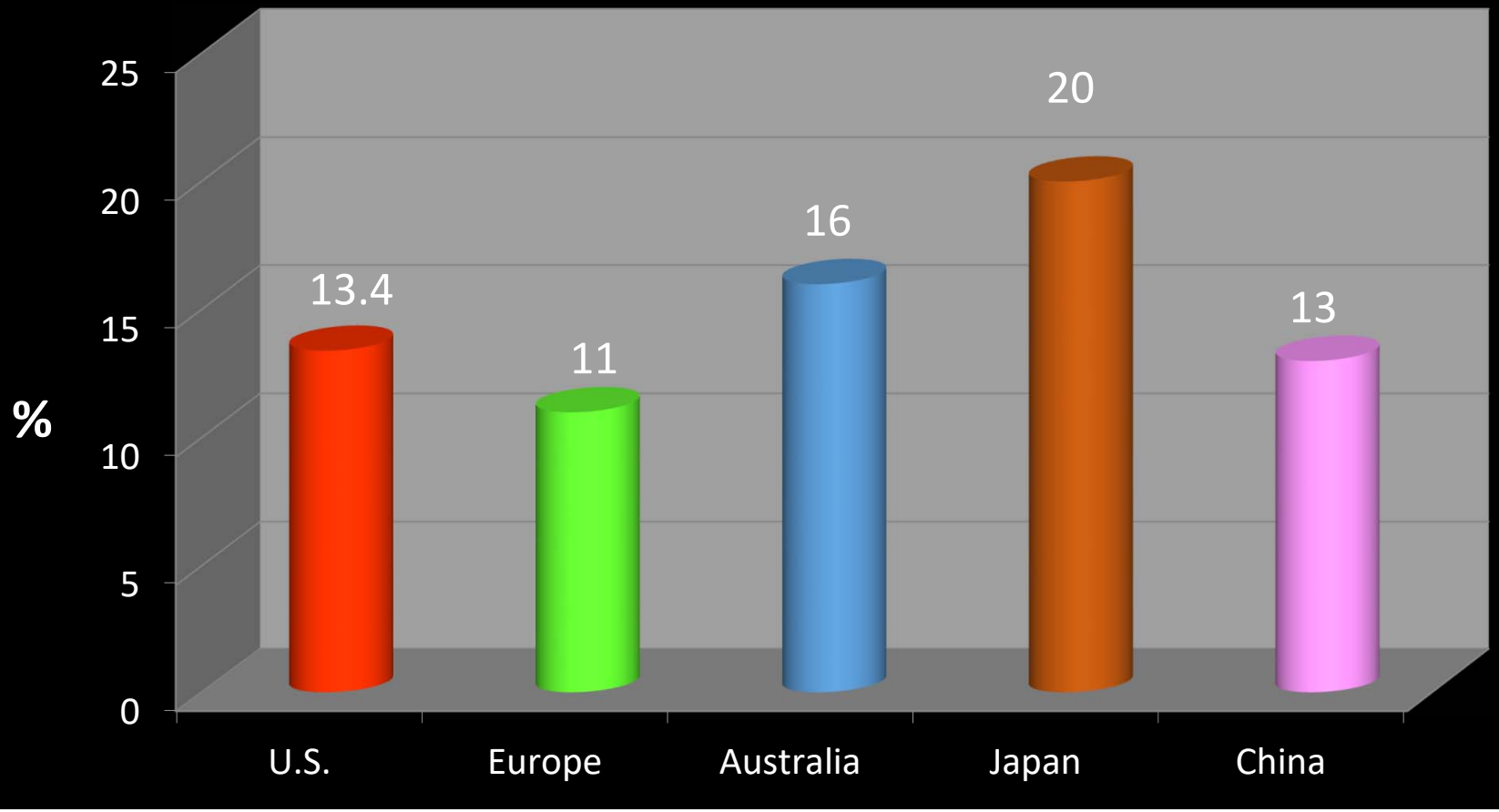
Choice	Target BP	Drug of Choice (CKD)
A	<140/90	Loop Diuretic
B	<140/90	ACEI
C	<130/80	ACEI
D	<130/80	Thiazide
E	<120/80	ACEI
F	<120/80	Loop Diuretic

Worldwide Incidence of Kidney Disease

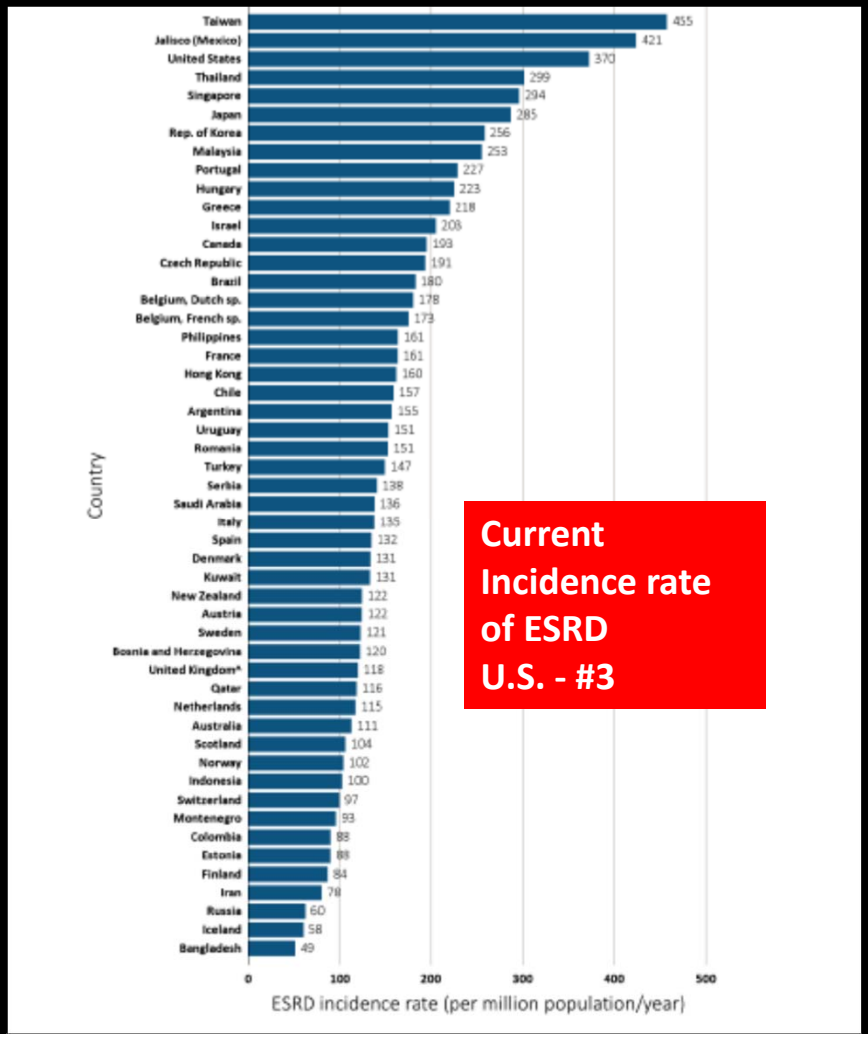


- **CKD in the U.S.**
  - 13% (26 million adults)
    - 65% with Stages 3/4
- **ESRD**
  - 500,000 people
- **Cost of Kidney Disease**
  - Medicare budget
    - 26 billion dollars

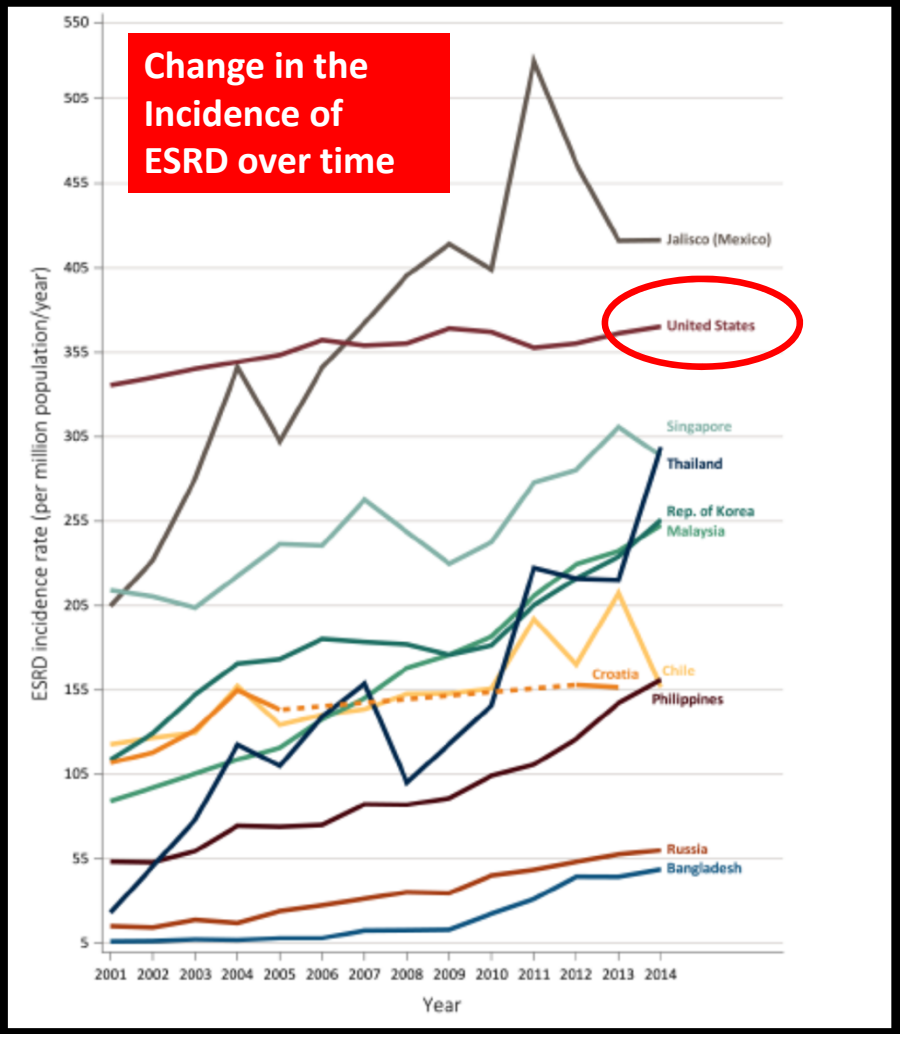
Worldwide Prevalence of CKD

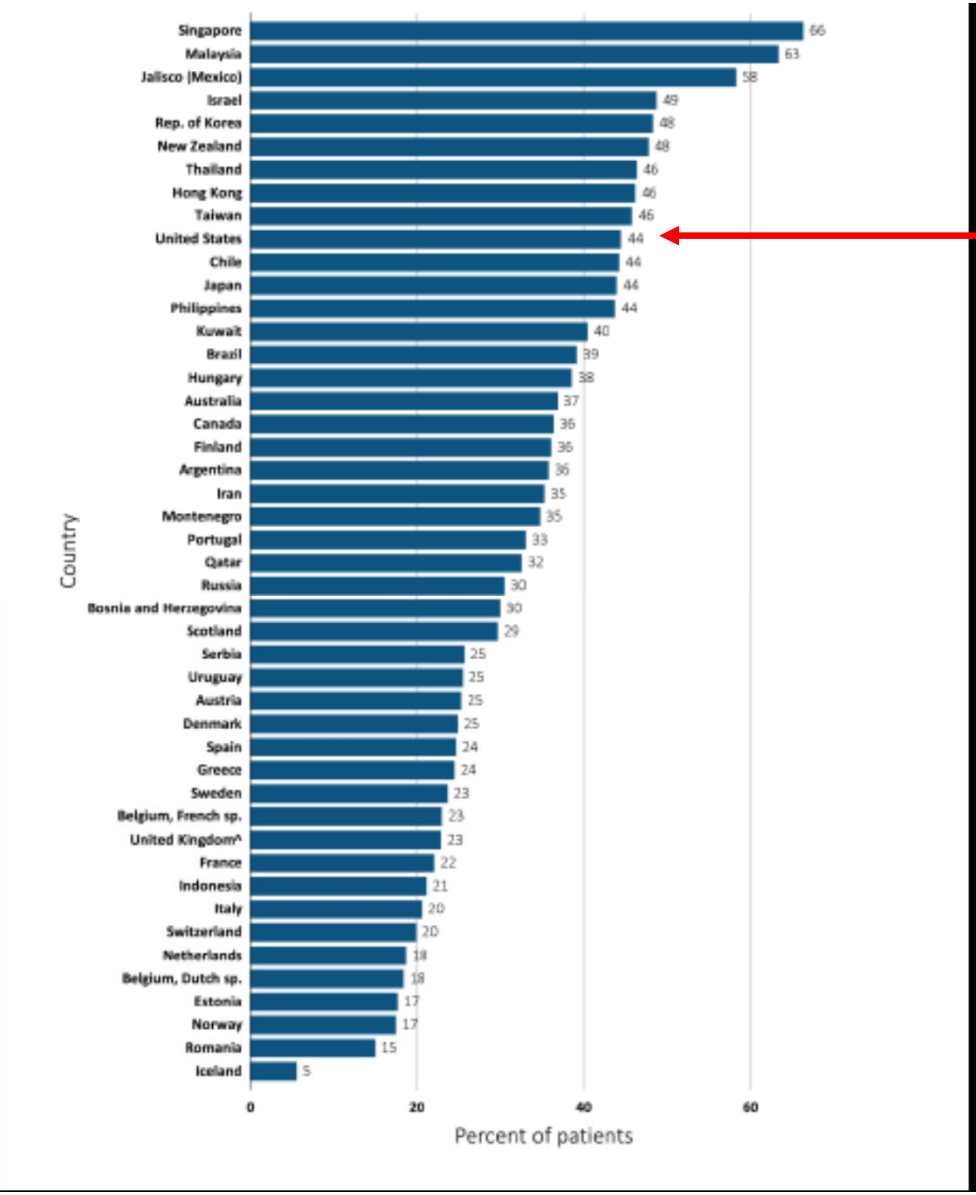


But….The U.S. is not #1 in the Incidence of ESRD



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

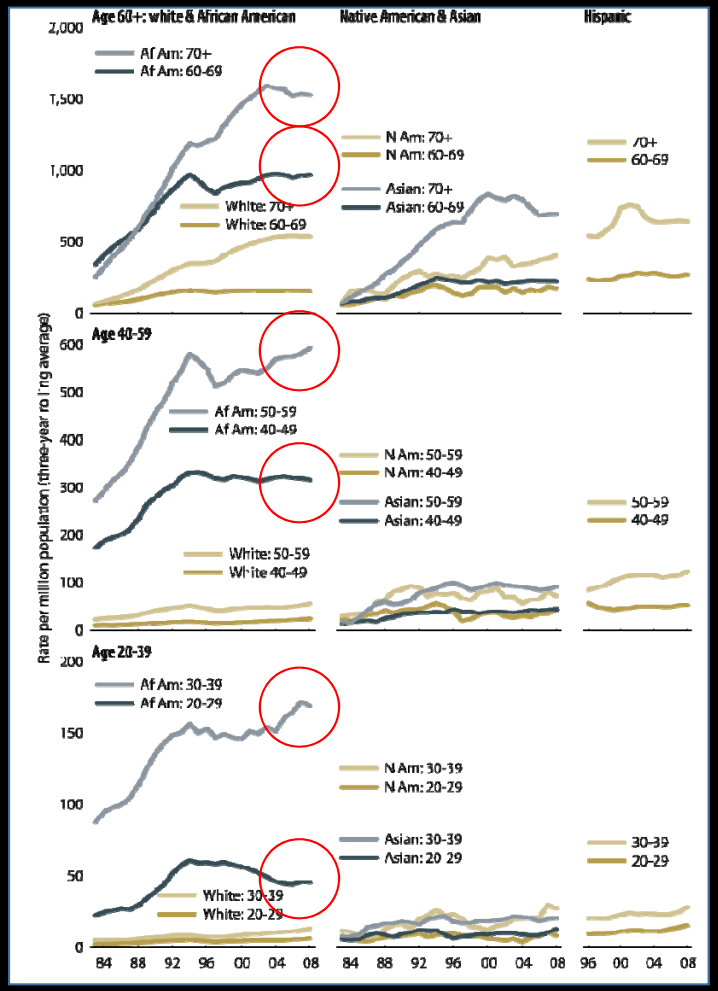




Diabetes is the Primary Cause of ESRD Worldwide

U.S. – 44%

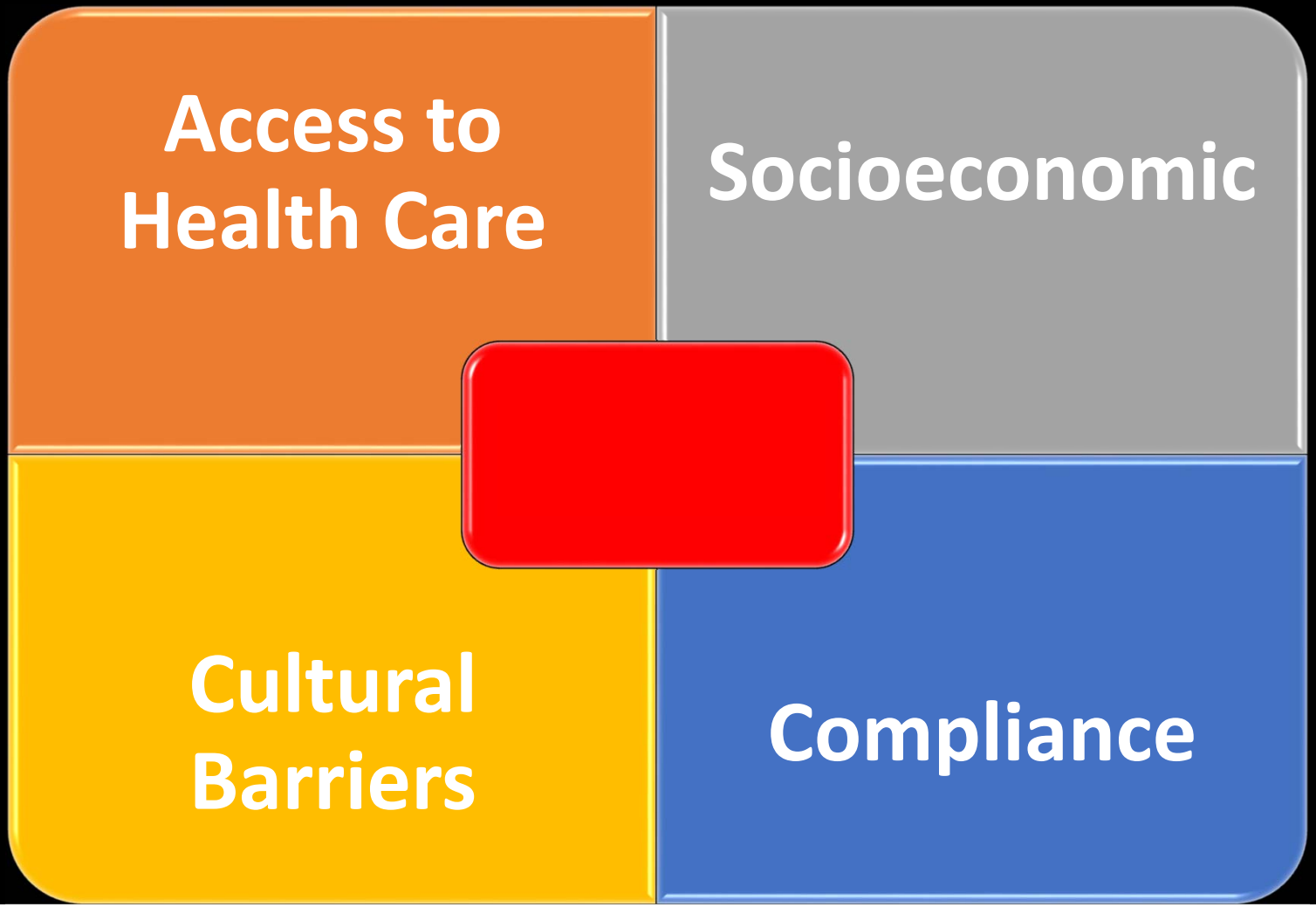
Racial Differences in the Incidence of CKD / ESRD



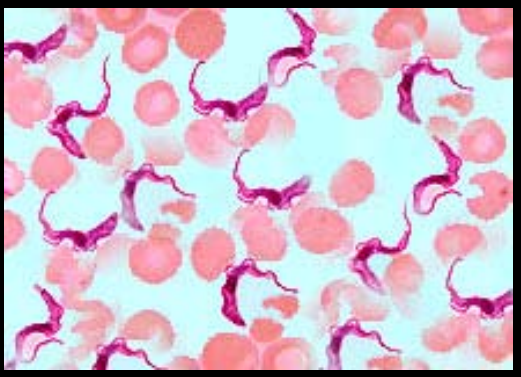
Black Race 13% of U.S. population but 32% of ESRD population

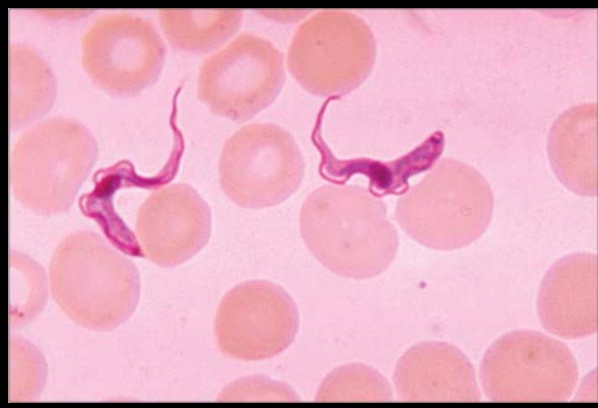
At every age group, the incidence of CKD and ESRD are significantly higher in people of black race ancestry

Racial Predisposition for CKD / ESRD

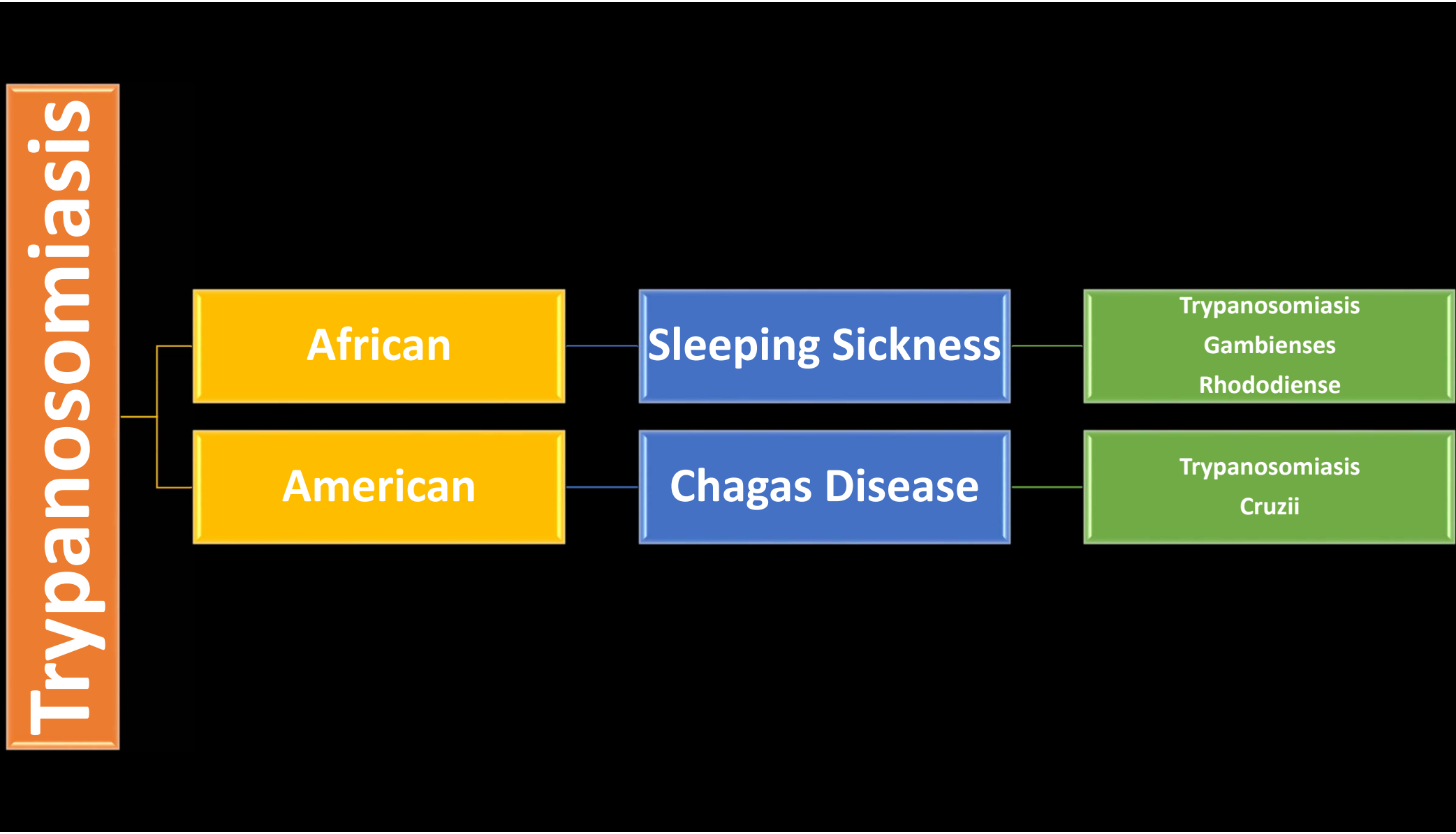


What is this ?





Does This Help ?

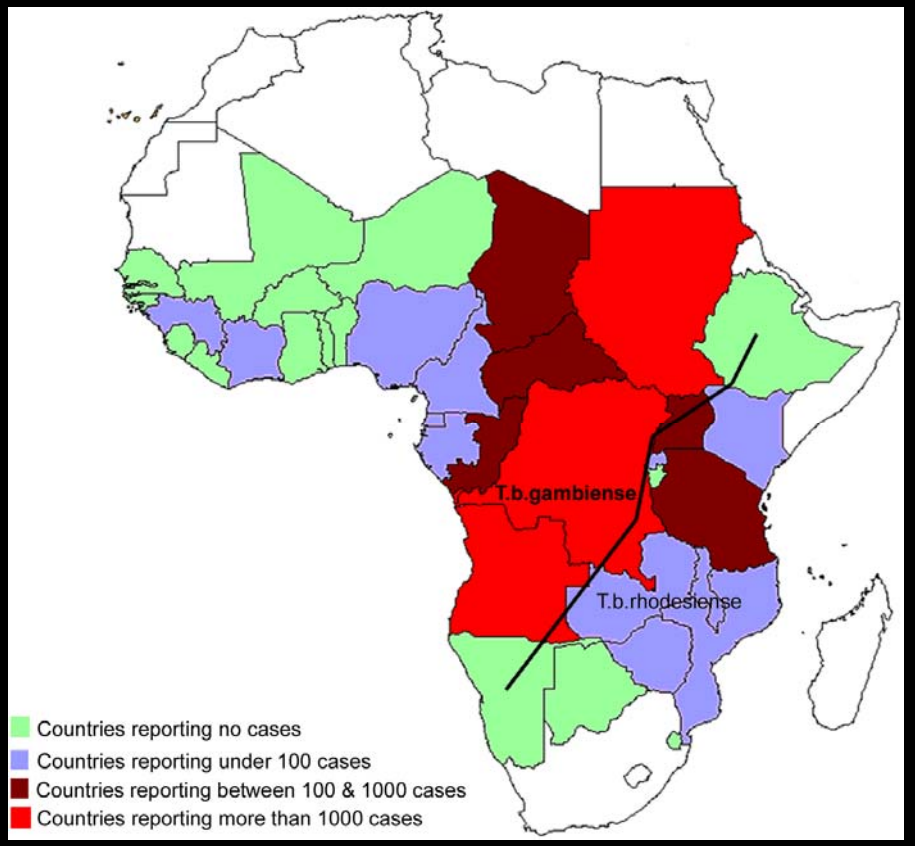

Trypanosomiasis
African
Sleeping Sickness
Trypanosomiasis
Gambienses
Rhododiense
American
Chagas Disease
Trypanosomiasis
Cruzii

African Trypanosomiasis

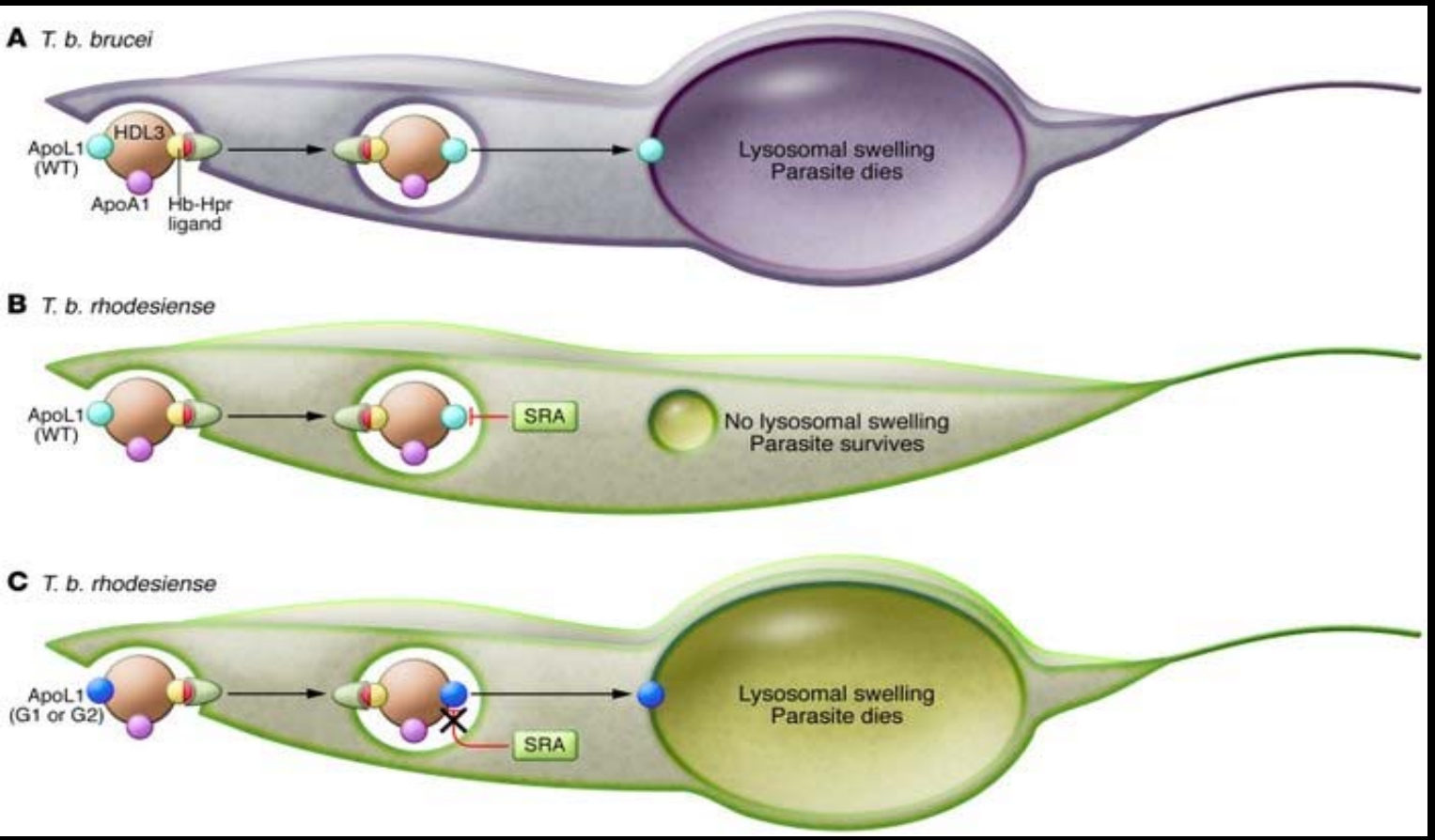
70 million people at risk within 36 African countries

7000 cases a year

During epidemics – death rate of > 50,000 / yr



Trypanosomiasis and Natural Selection



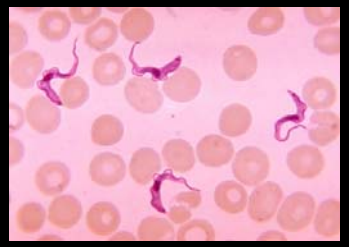
Humans developed a method of inactivating the parasite through Apol1 located on HDL3

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

D'Agati V. Curr Opin Nephrol Hypertens 2012 March 1

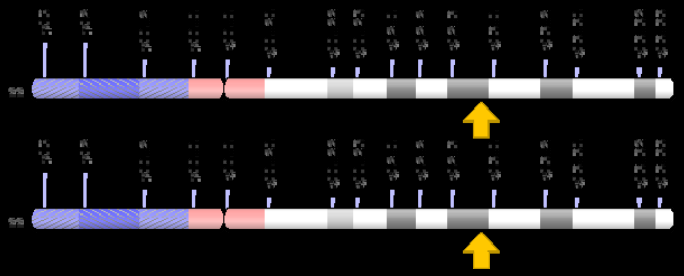
APOL1



- **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

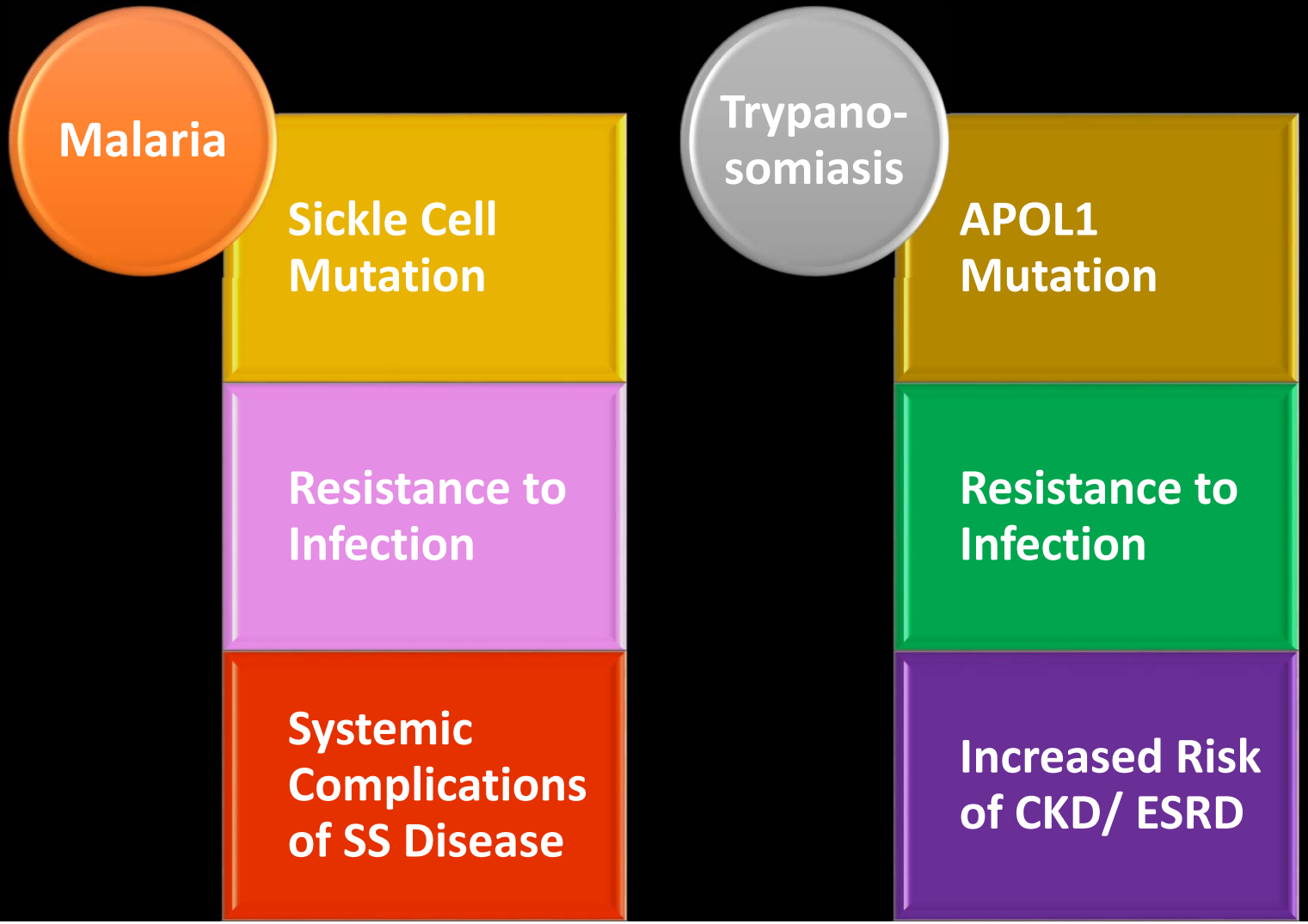
Homozygous mutation of APOL1 gene Chromosome 22



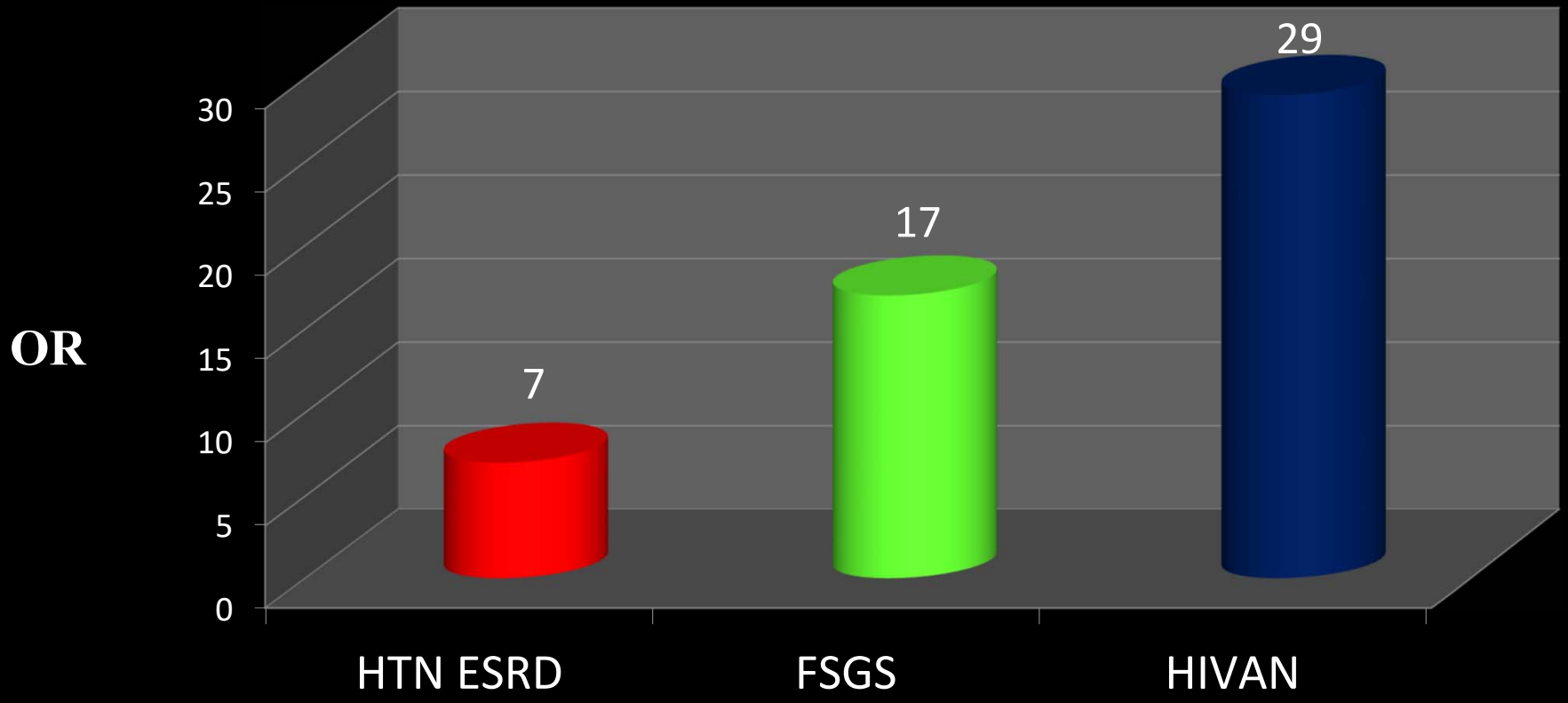
Survival : Clearance of Trypanosomiasis

Increased Risk of CKD / FSGS / HIV Nephropathy

Genetic Mal-adaption for Survival in Africa



APOL1 variants :
APAN : Apolipoprotein Associated Nephropathy



Genovese G, Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010; 329: 841–845

African-Americans, Kidney Failure and APOL1

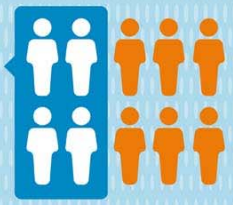
African-Americans are **13%** of the **US** population but account for **32%** of **kidney failure** in the US[1]

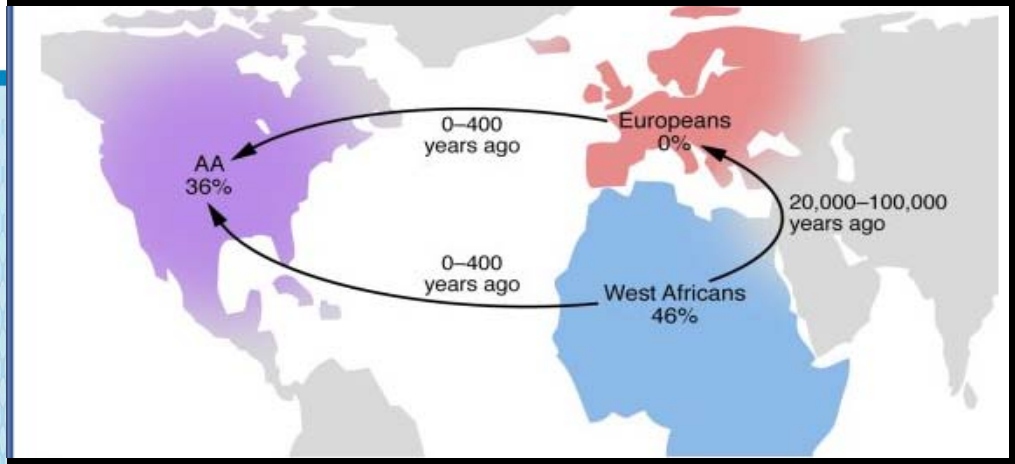
African-Americans are almost **4 times** **more likely** to develop **kidney failure** than caucasians.[1]

About **1 in 5** **people** with two copies of **APOL1 renal risk variants** will develop **kidney disease**[2]

These **APOL1 variants** account for **70%** of non-diabetic **kidney failure** in **African-Americans**[2]

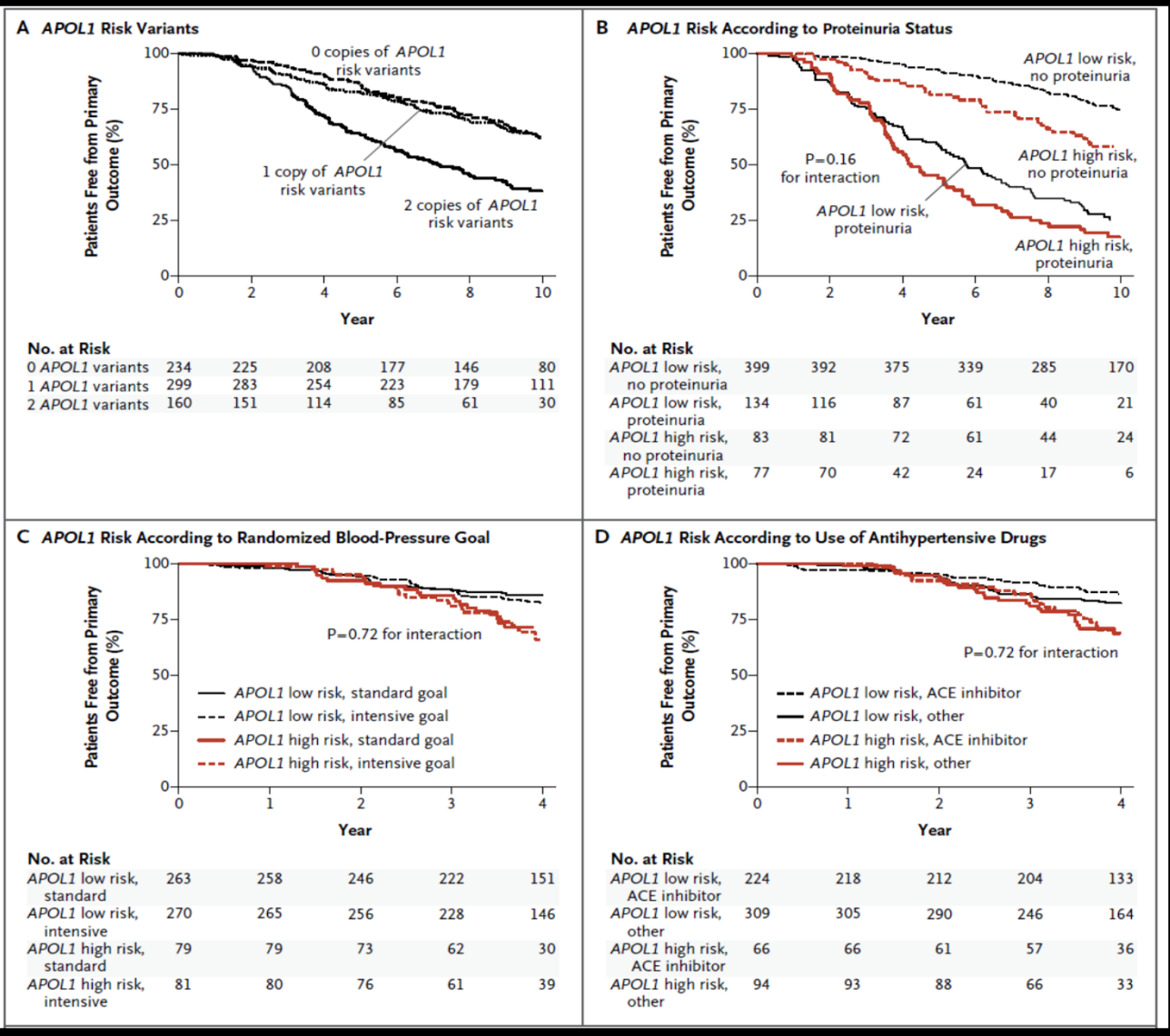
About **4 in 10** **African-Americans** on dialysis have **kidney failure** caused by **APOL1**[2]





36% of Black race individuals in the U.S. carry a mutation either G1 or G2 of the APOL1 allele

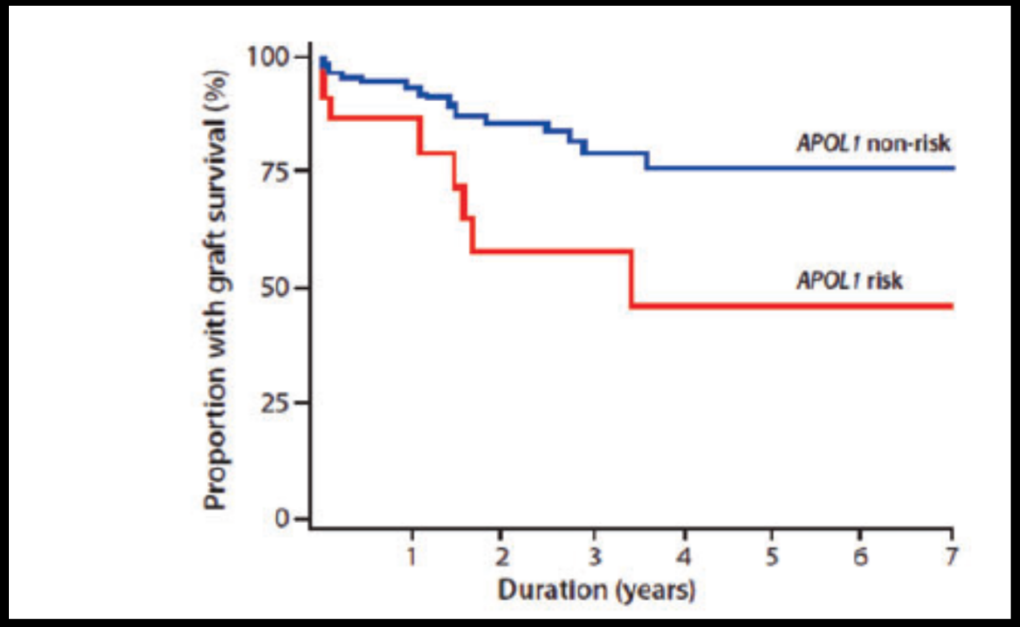
AASK Trial : African American Study Kidney Disease



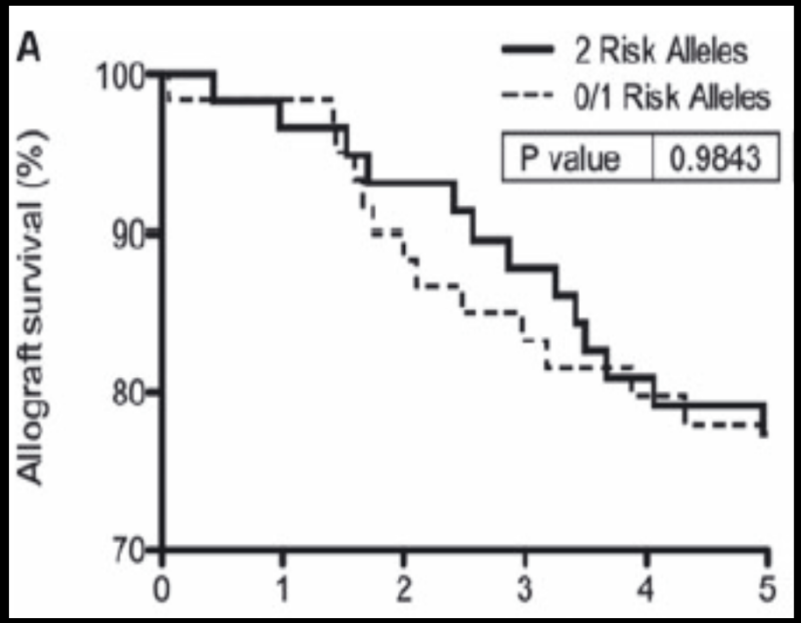
APOL1 mutation influenced the outcome of the study regardless of BP or anti-hypertensive agent used

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

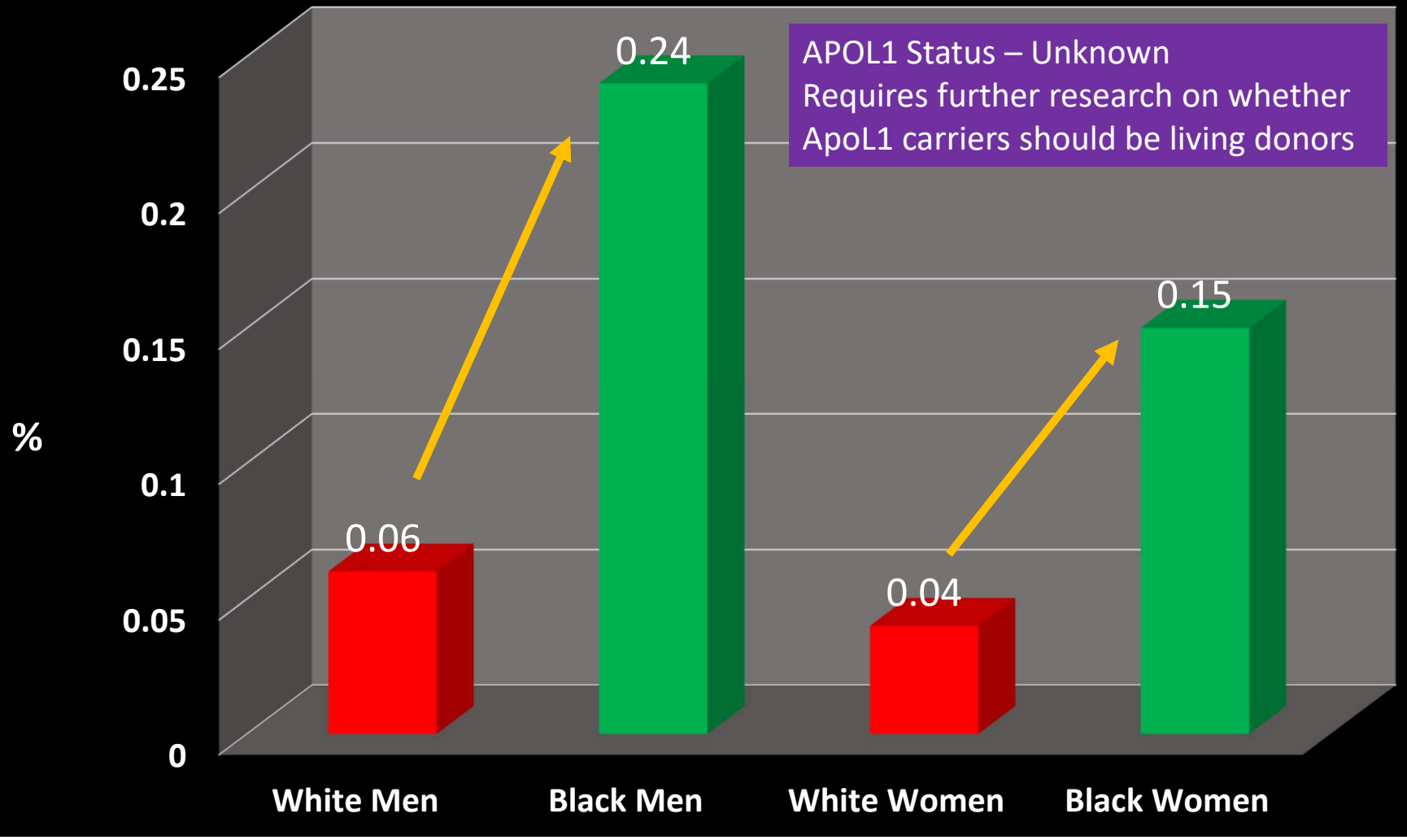


Donor Kidney APOL1 Status

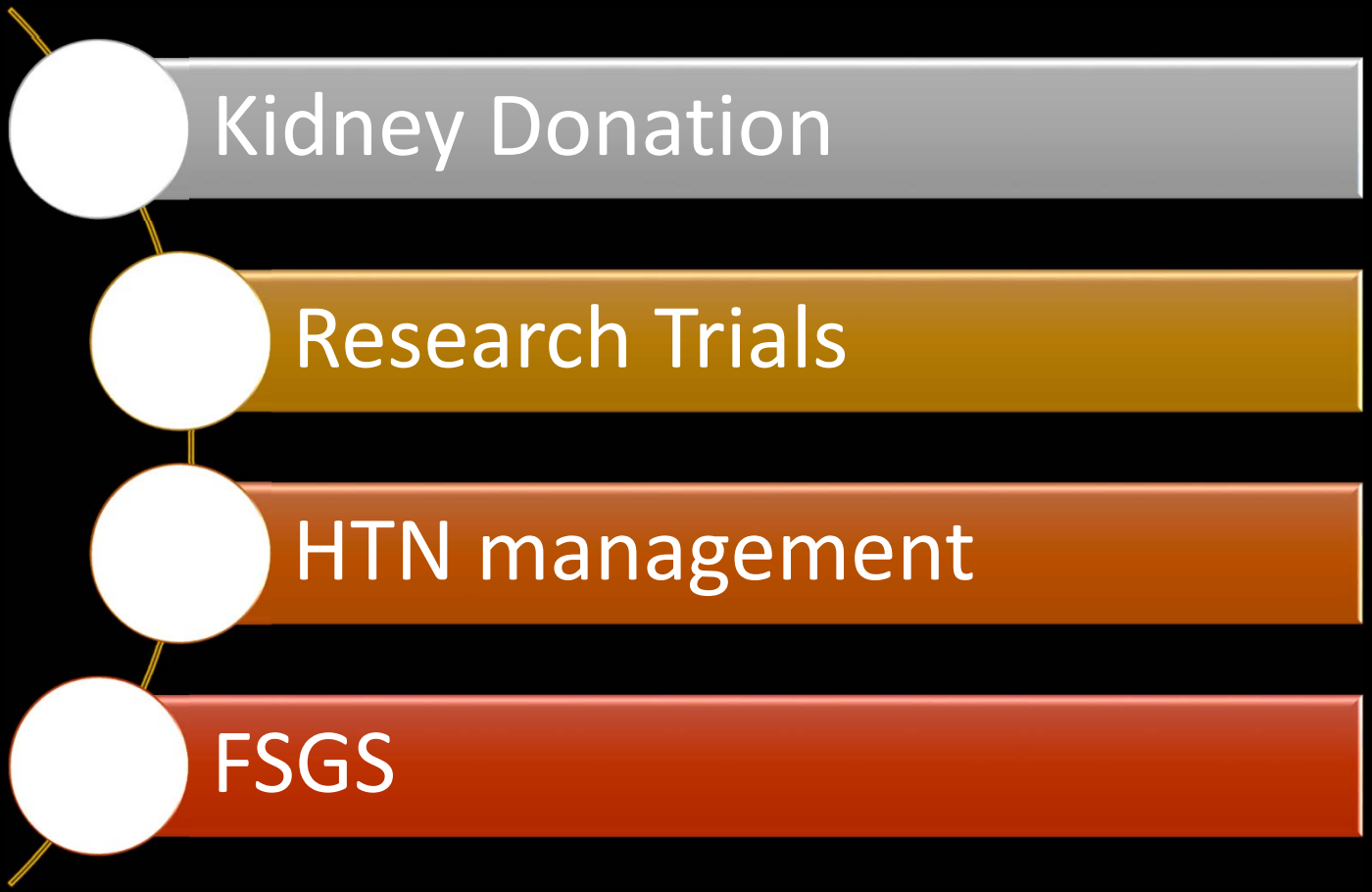


Recipient APOL1 Status does not influence graft outcome

Risk of ESRD after Living Kidney Donation



Future Use of APOL1 measurement in Selected Black Race Patient Populations

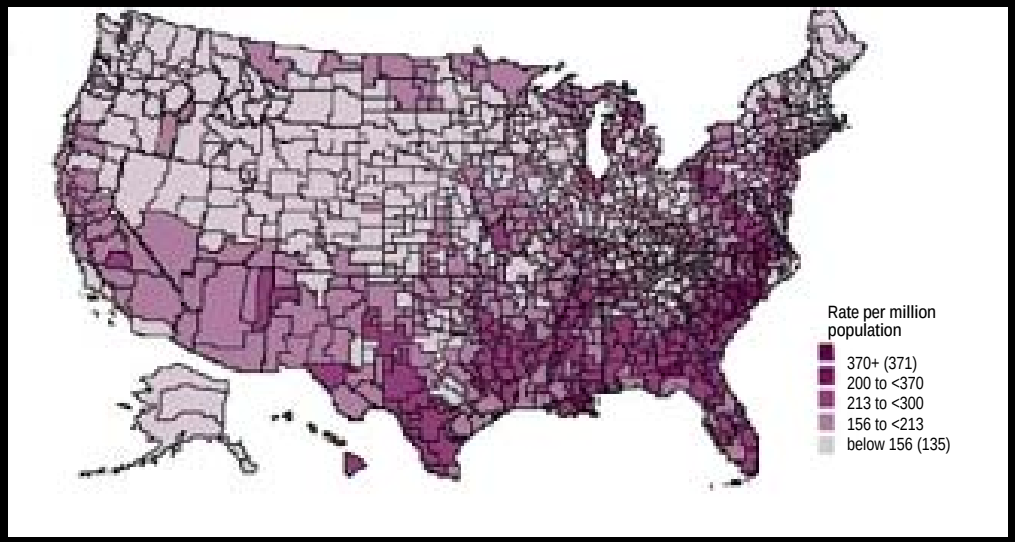


APOL1 Polymorphism and Renal Disease

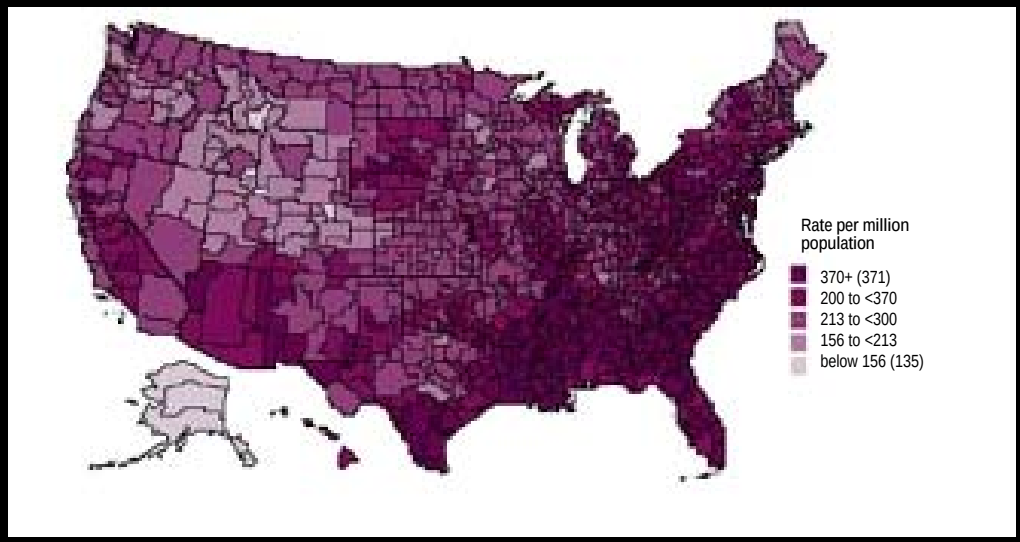
The single most important discovery

regarding the ethnic disparity in the development of CKD within the Black Race population

Kidney Failure Is Increasing in the U.S.



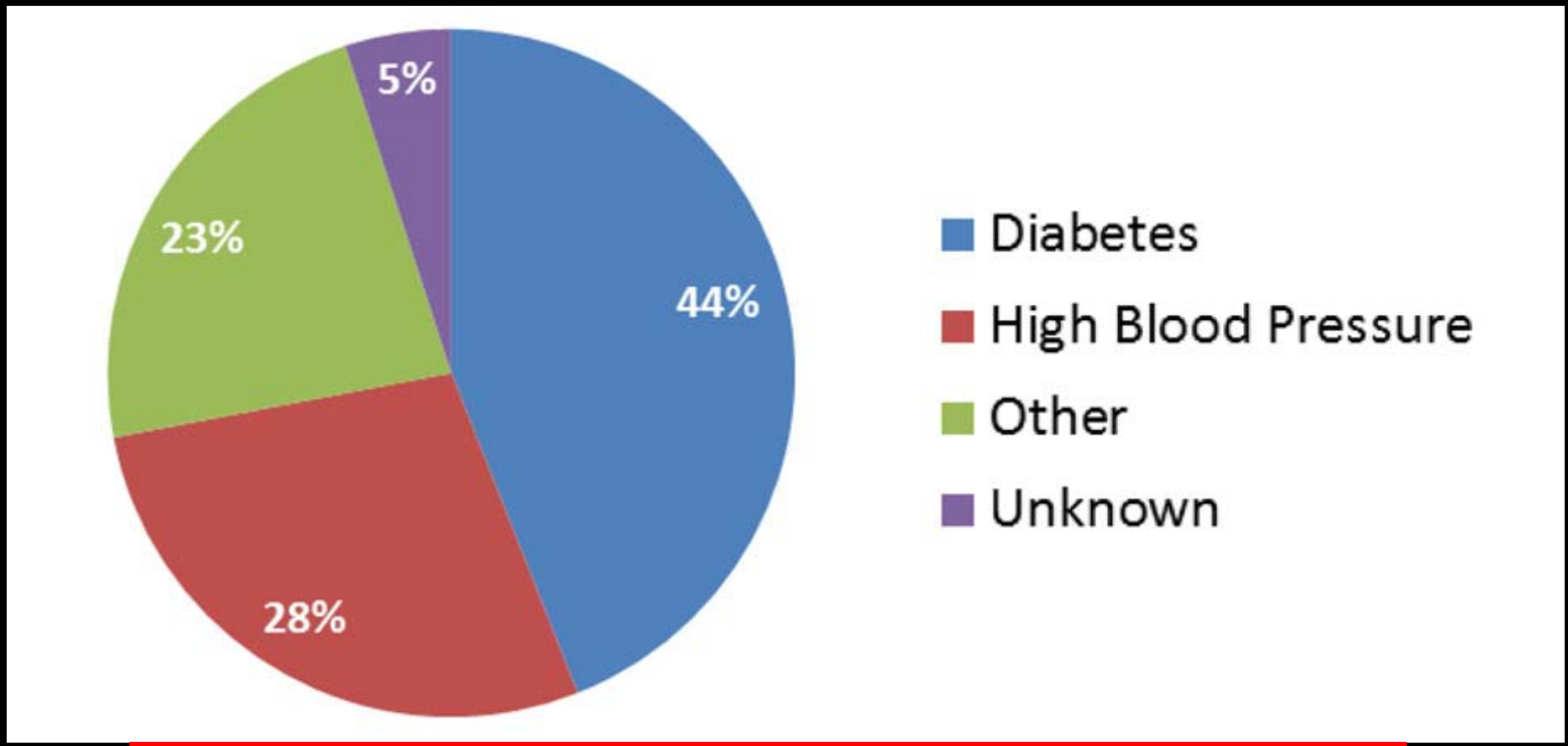
Per million population, 2000



Per million population, 2010

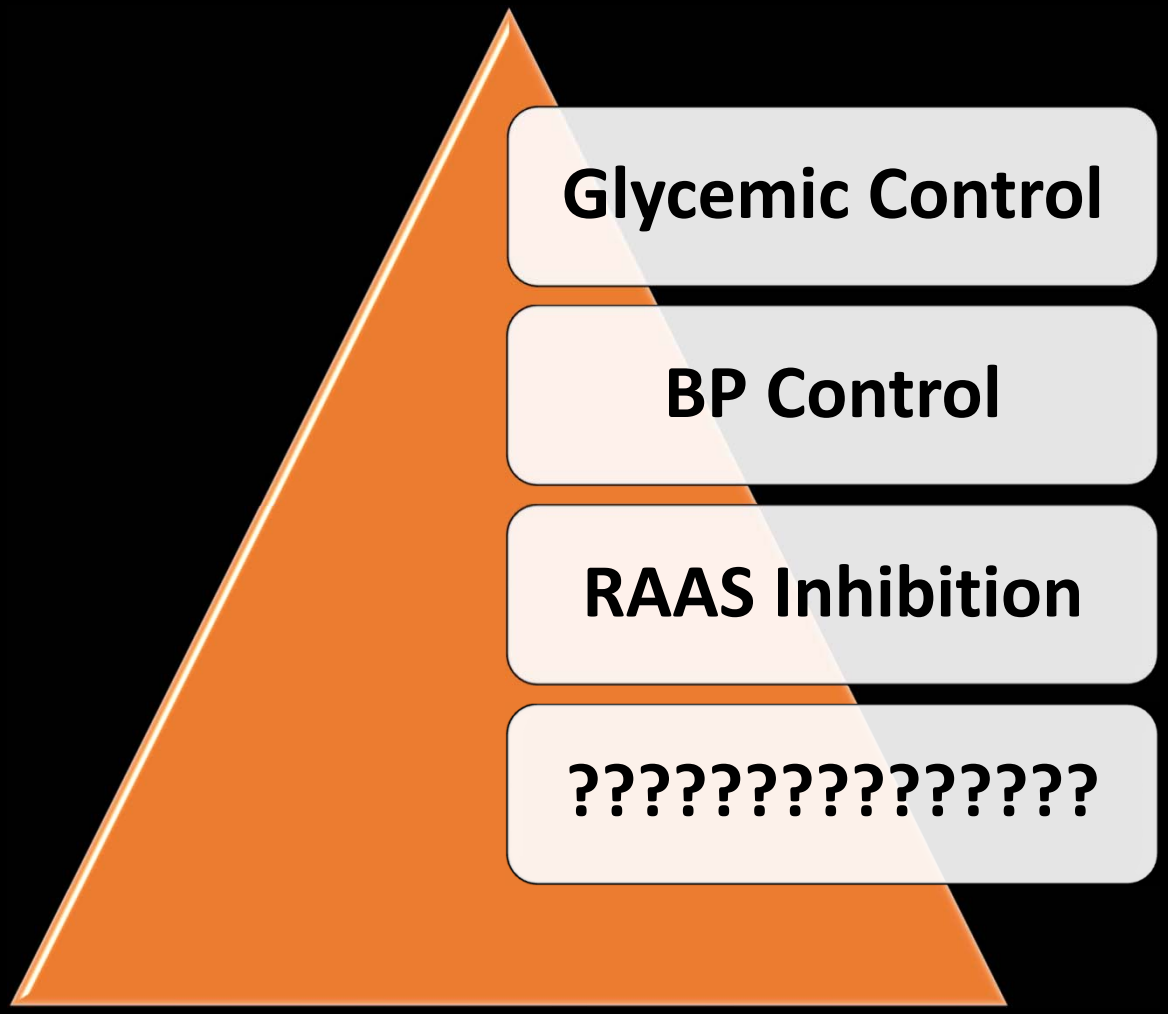
HSA=CDC health service area.
United States Renal Data System 2010 Annual Report

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

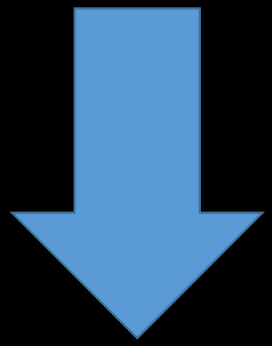


Diabetes = **diabainein** = a siphon = **excessive urination**

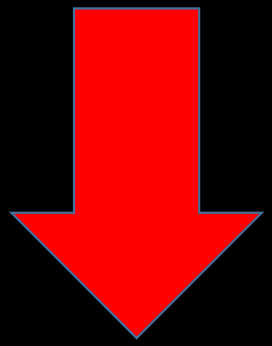
Mellitus = **"like honey"**

Old Paradigm

New Paradigm



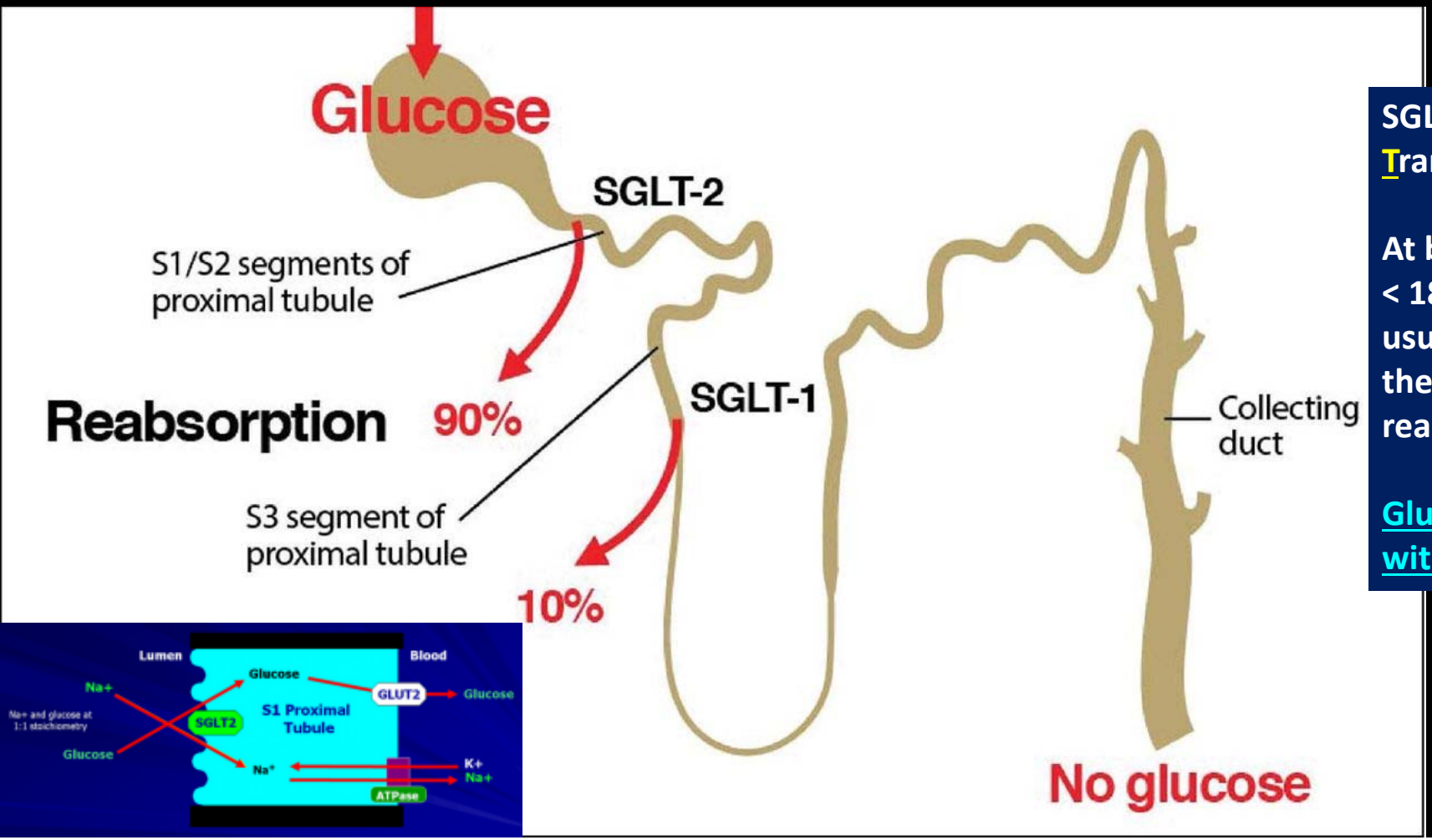
Therapeutic Intervention



Decrease glucose production
Increase glucose utilization

Increase urinary glucose excretion

Glucose Handling by the Nephron

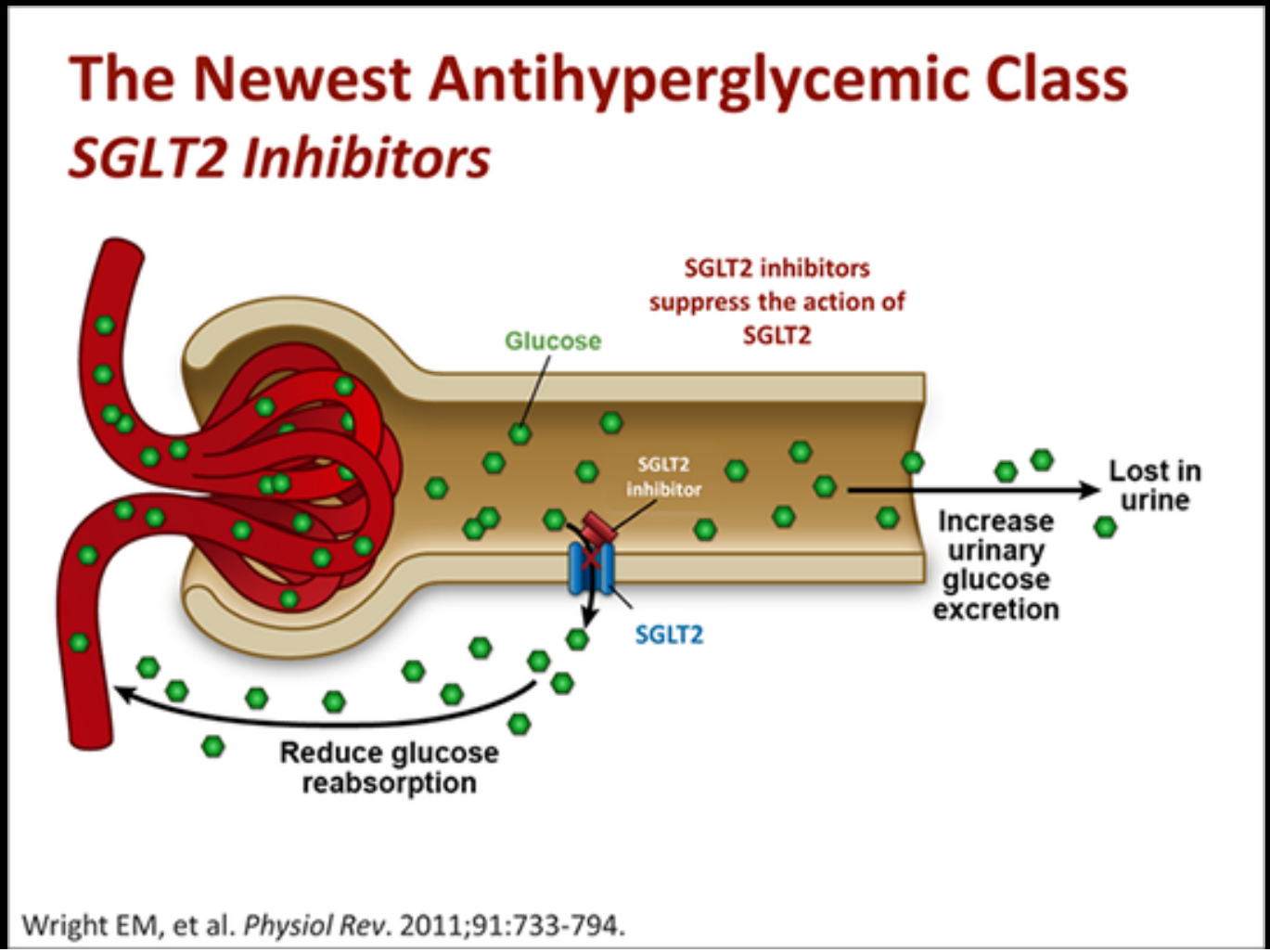


SGLT = Sodium GLucose Transporter

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

Brand name	Generic name
Invokana	canagliflozin
Invokamet	canagliflozin and metformin
Farxiga	dapagliflozin
Xigduo XR	dapagliflozin and metformin extended-release
Jardiance	empagliflozin
Glyxambi	empagliflozin and linagliptin
Synjardy	empagliflozin and metformin

Oral Antidiabetic Medications	A1C Reduction (%)*
SGLT2 inhibitors	**0.7 to 1.0**
Biguanides	1.0 to 1.5
Sulfonylureas	1.0 to 1.5
Meglintides	0.5 to 1.0
Dipeptidyl peptidase-4 inhibitors	0.5 to 1.0
Thiazolidinediones	1.0 to 1.5
Alpha-glucosidase inhibitors	0.5 to 1.0

ORIGINAL ARTICLE

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*

N Engl J Med - June 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

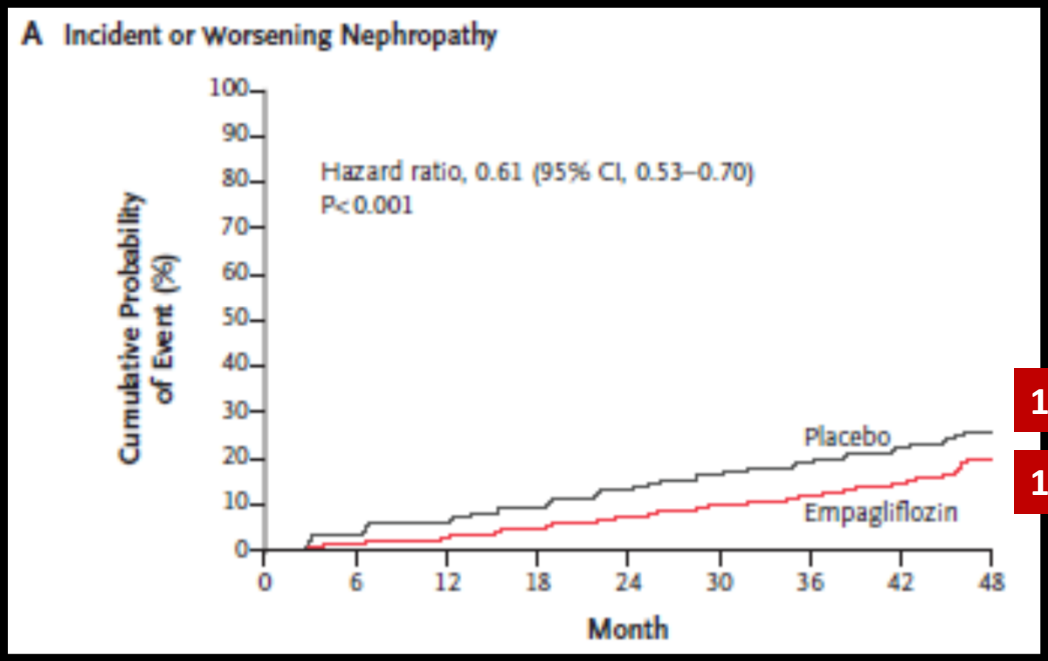
Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative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

N Engl J Med - June 2017

Wanner C. N Engl J Med 2016;375:323-34.

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



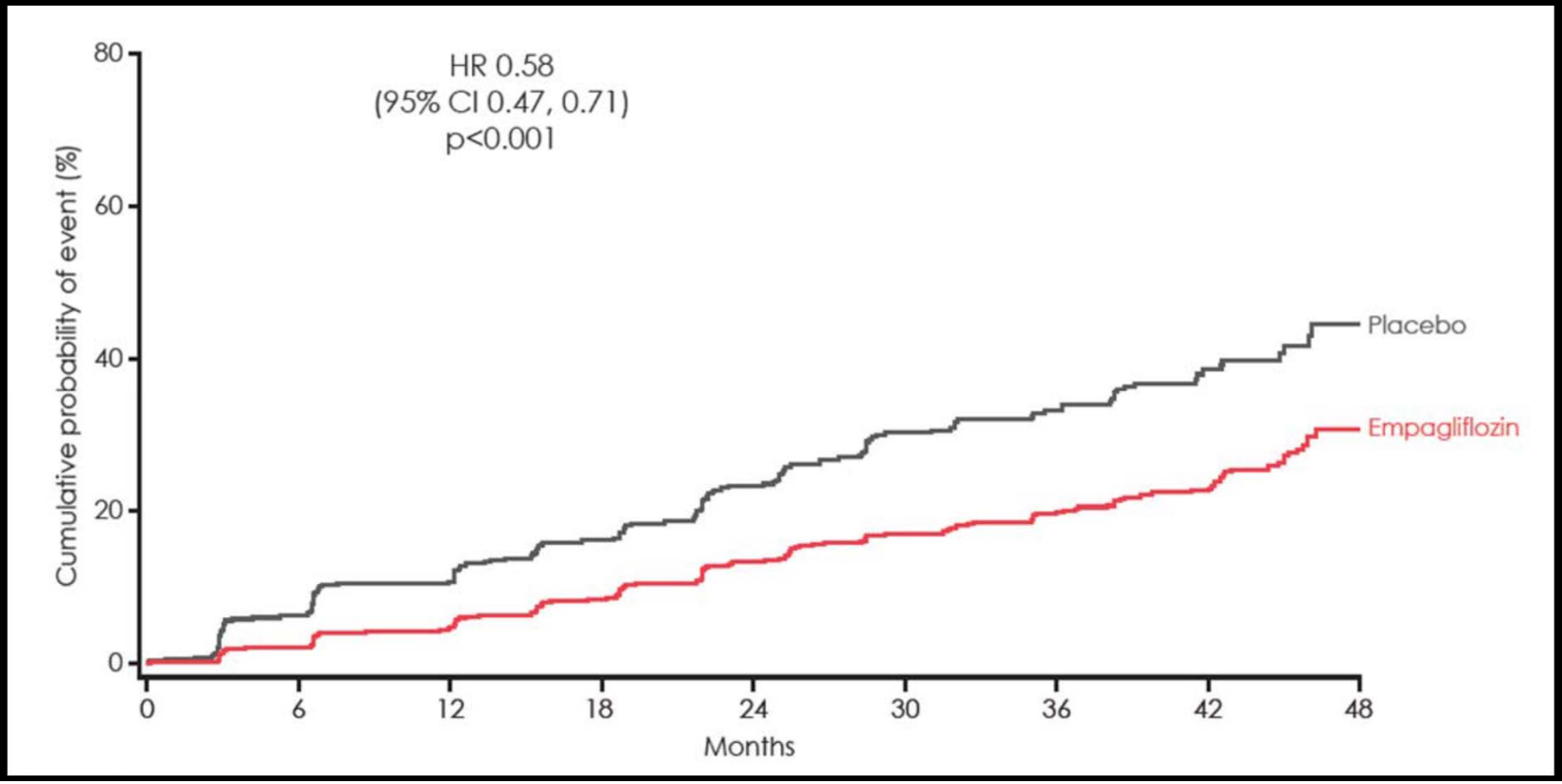
Progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, death from renal disease and incident albuminuria

Wanner C. N Engl J Med 2016;375:323-34.

Renal Outcome Measure	Empagliflozin no. with event/ no. analyzed (%)	Empagliflozin rate/1000 patient-yr	Placebo no. with event/ no. analyzed (%)	Placebo rate/1000 patient-yr	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

Wanner C. N Engl J Med 2016;375:323-34.

Delayed Progression of Renal Disease in Patients with Established Diabetic renal Disease : GFR < 60 cc/min and Macroalbuminuria



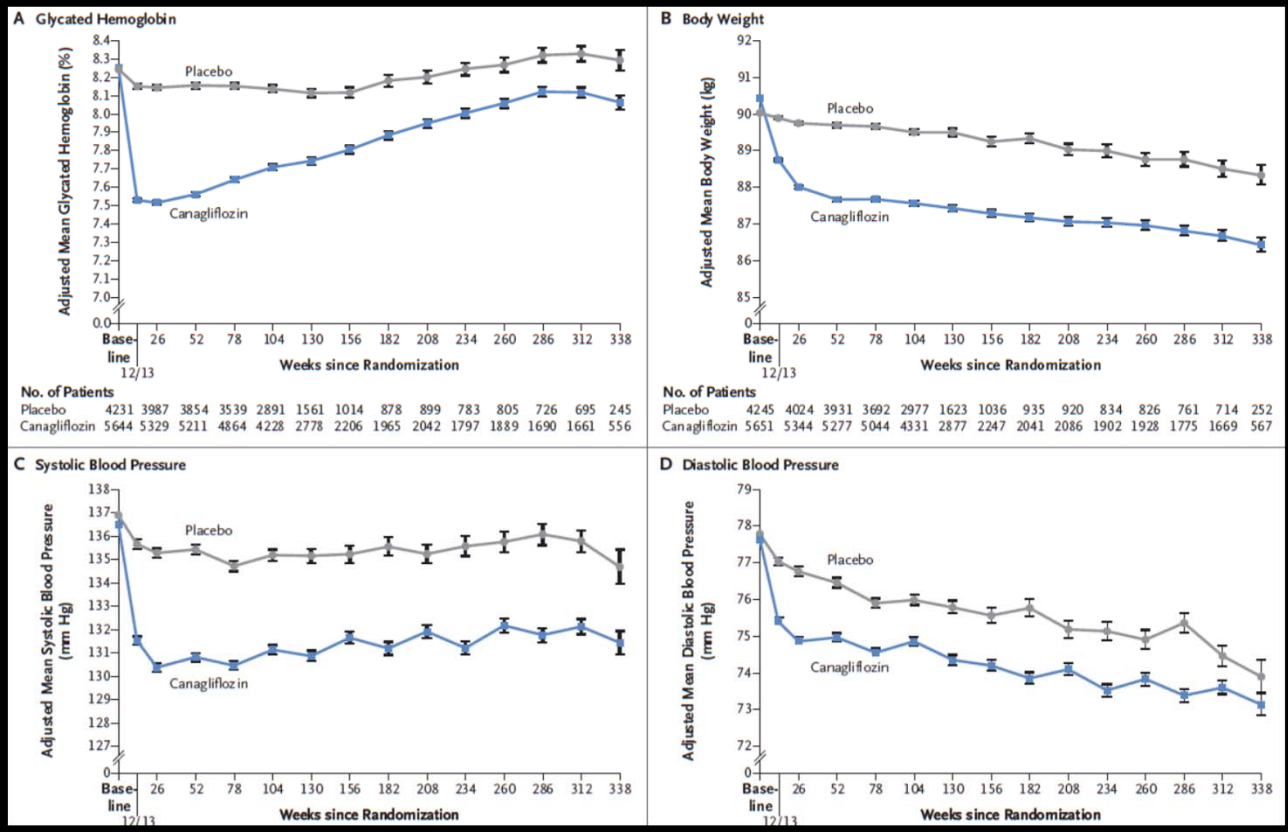
In conclusion, among patients with type 2 diabetes who were at high risk for cardiovascular events, the use of empagliflozin was associated with slower progression of kidney disease than was placebo when added to standard care. Empagliflozin was also associated with a significantly lower risk of clinically relevant renal events.

- **EMPA was effective as an add on to RAAS inhibition**
- **Hypothesis –**
  - **Natriuresis**
    - **Activates tubulo-glomerular feedback and decreases intraglomerular pressure**

Neal B. N Engl J Med 2017 June 12

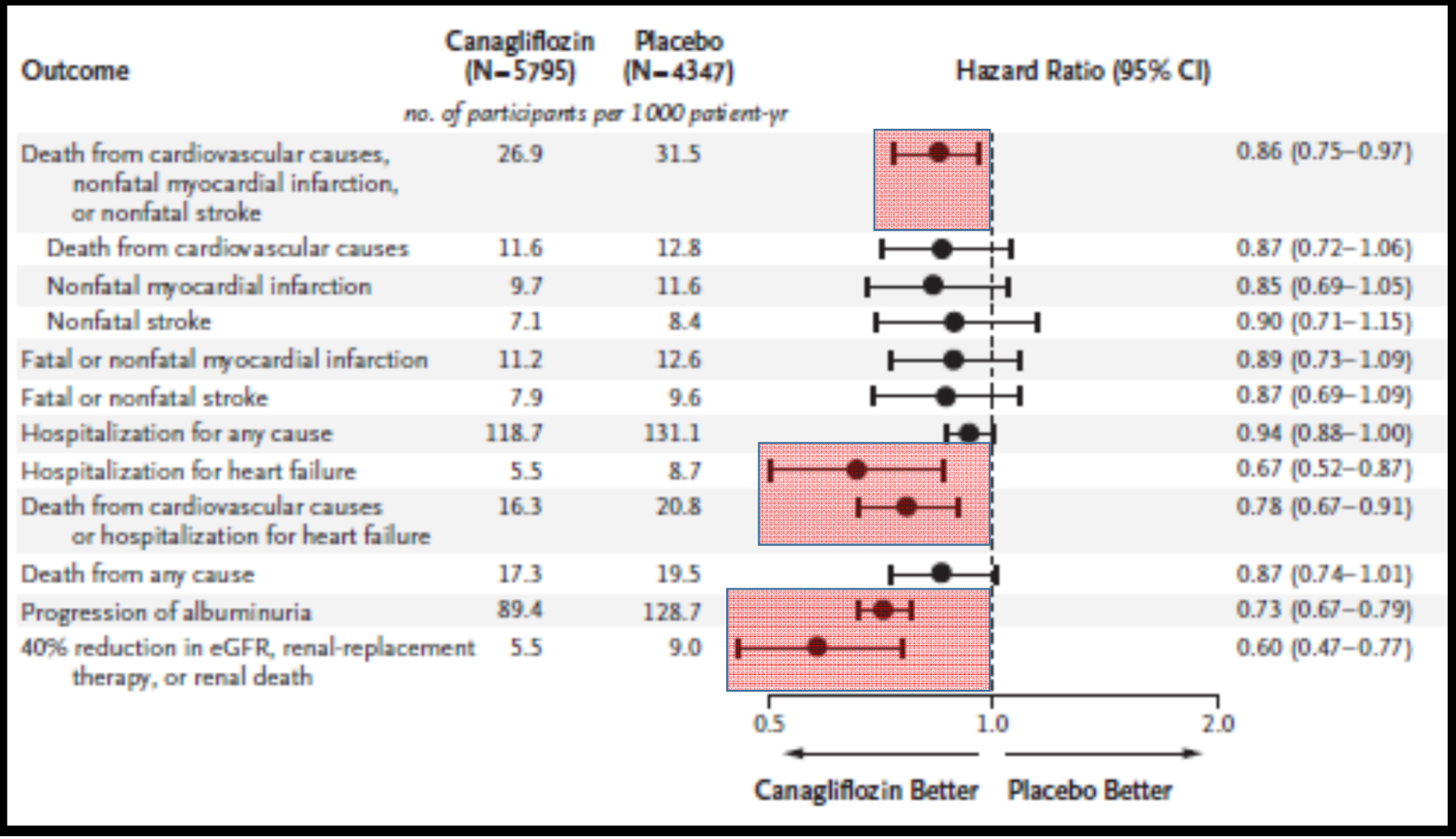
Canagliflozin Cardiovascular Assessment Study (CANVAS) and Renal Assessment Study (CANVAS-R)

- 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



Neal B. N Engl J Med 2017 June 12

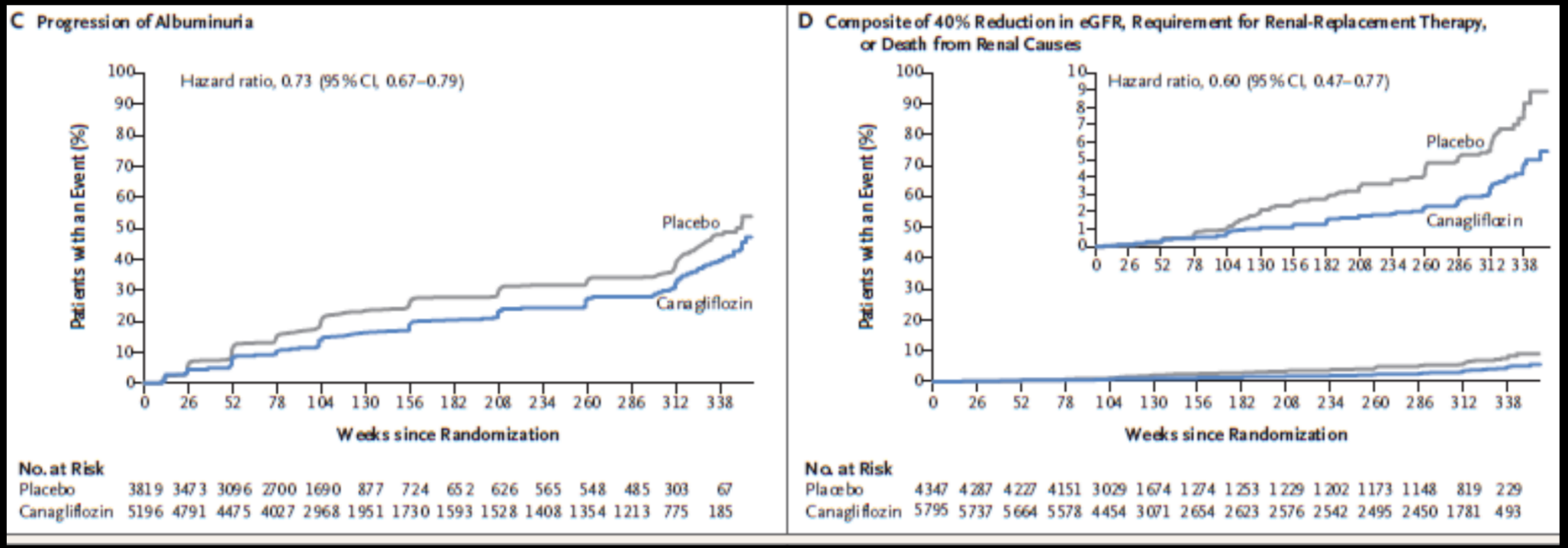
Canagliflozin Cardiovascular Assessment Study (CANVAS) and Renal Assessment Study (CANVAS-R)



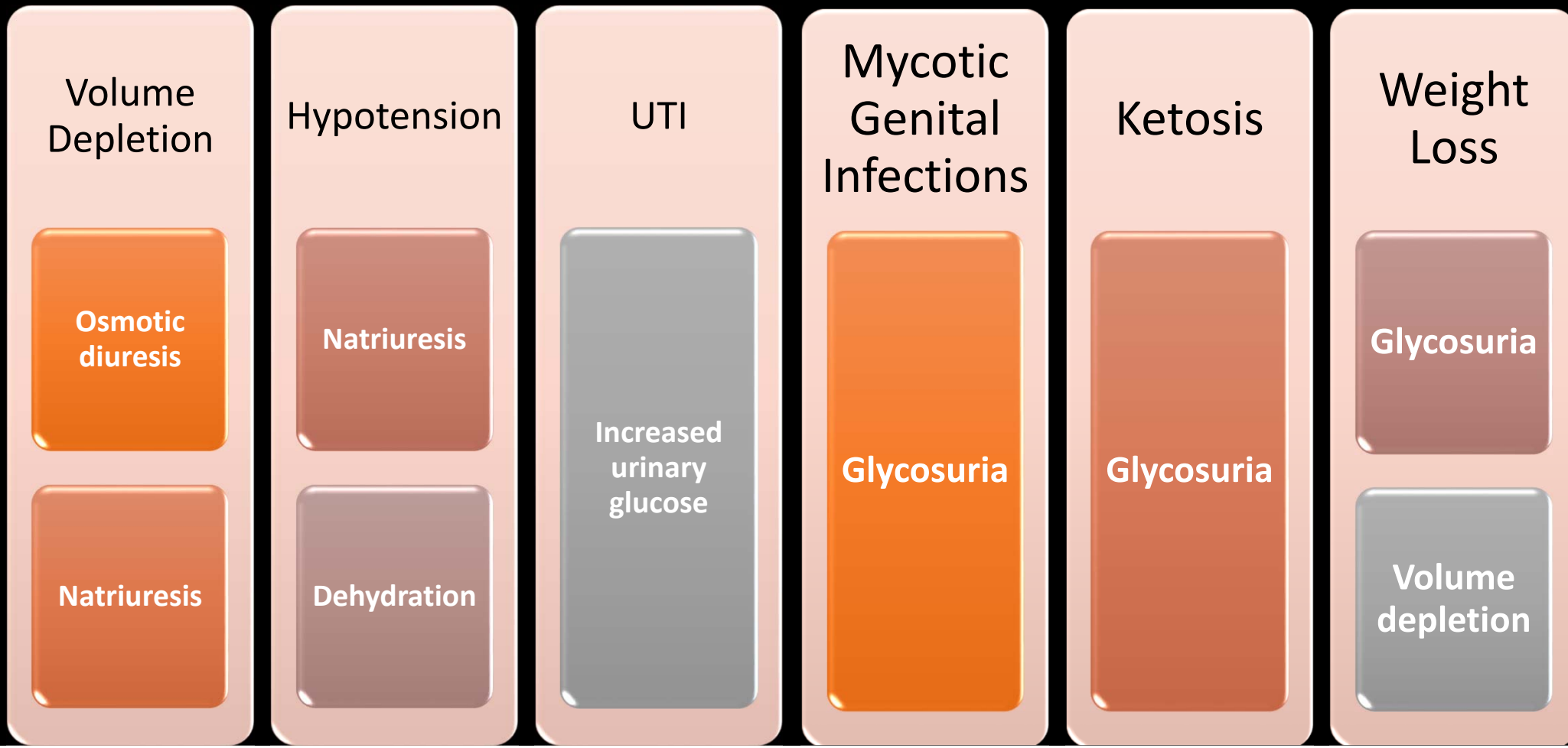
Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial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

Neal B. N Engl J Med 2017 June 12

Decreased Progression of Renal Disease with SGLT-2 Inhibition



Potential Side Effects of SGLT-2 Inhibition



Increased Amputation Risk with Canagliflozin

Figure S5. Highest-level atraumatic lower-limb amputations experienced by participants in the CANVAS Program

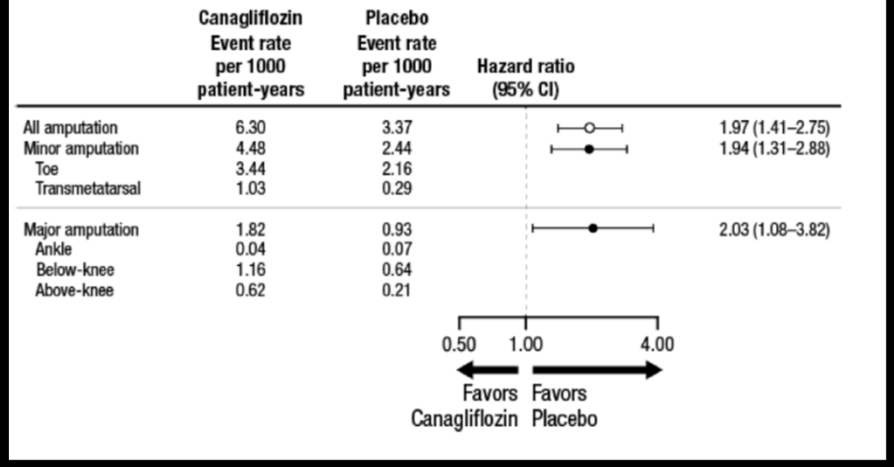


Table S8. Effects of canagliflozin versus placebo on atraumatic lower limb amputation in key subgroups in the CANVAS Program

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)
History of amputation			
Yes	96.30	59.16	2.15 (1.11–4.19)
No	4.68	2.48	1.88 (1.27–2.78)
History of peripheral vascular disease			
Yes	12.09	8.16	1.39 (0.80–2.40)
No	5.20	2.41	2.34 (1.53–3.58)

- 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

	Canagliflozin Per 1000 patient-years	Placebo Per 1000 patient-years	Hazard ratio (95% confidence interval)	P value*
Low-trauma fracture (primary outcome)				
CANVAS	12.98	8.31	1.56 (1.18–2.06)	
CANVAS-R	7.87	10.30	0.76 (0.52–1.12)	
CANVAS Program	11.58	9.17	1.23 (0.99–1.52)	0.003
All fracture (secondary outcome)				
CANVAS	16.92	10.94	1.55 (1.21–1.97)	
CANVAS-R	11.42	13.23	0.86 (0.62–1.19)	
CANVAS Program	15.40	11.93	1.26 (1.04–1.52)	0.005

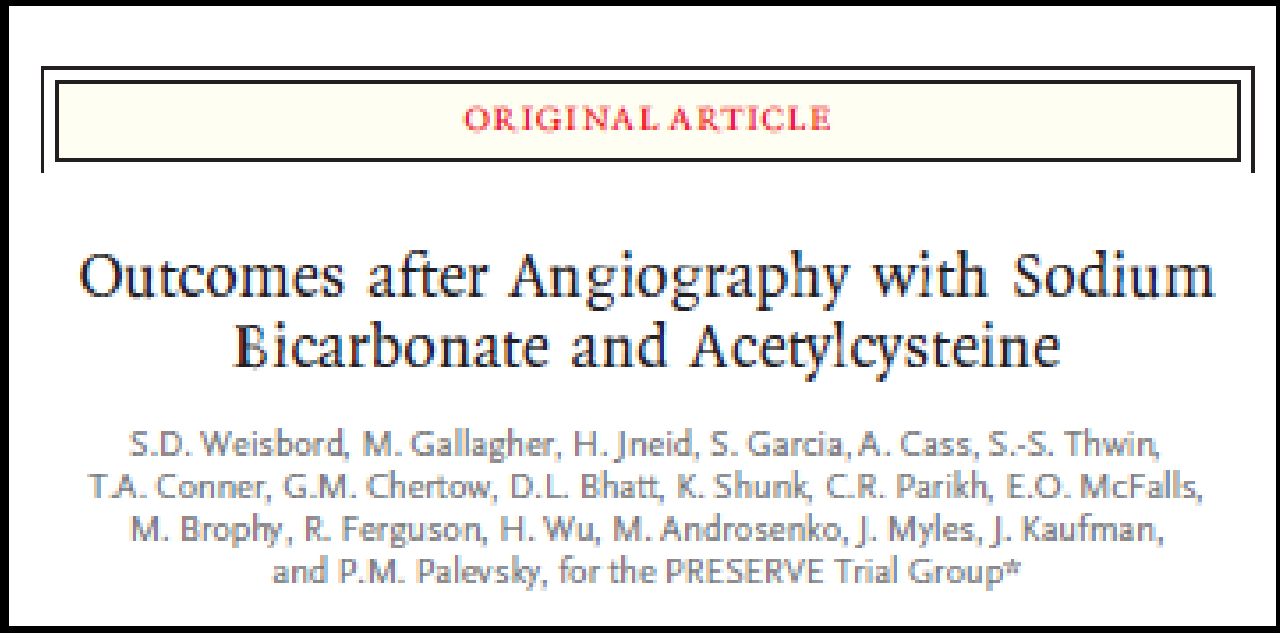
SGLT-2 Inhibitors and Diabetic Renal Disease

- **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



ORIGINAL ARTICLE

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

S.D. Weisbord, M. Gallagher, H. Jneid, S. Garcia, A. Cass, S.-S. Thwin, T.A. Conner, G.M. Chertow, D.L. Bhatt, K. Shunk, C.R. Parikh, E.O. McFalls, M. Brophy, R. Ferguson, H. Wu, M. Androsenko, J. Myles, J. Kaufman, and P.M. Palevsky, for the PRESERVE Trial Group*

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

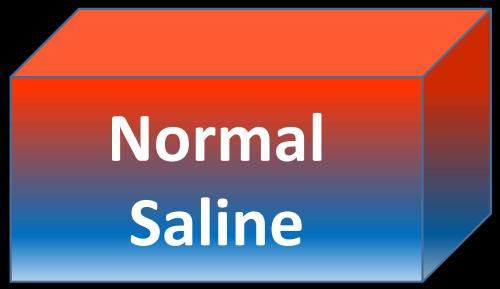
GFR 45 – 60 cc/min with Diabetes

End Point

A) 50% increase in creatinine at 90 days

B) Dialysis

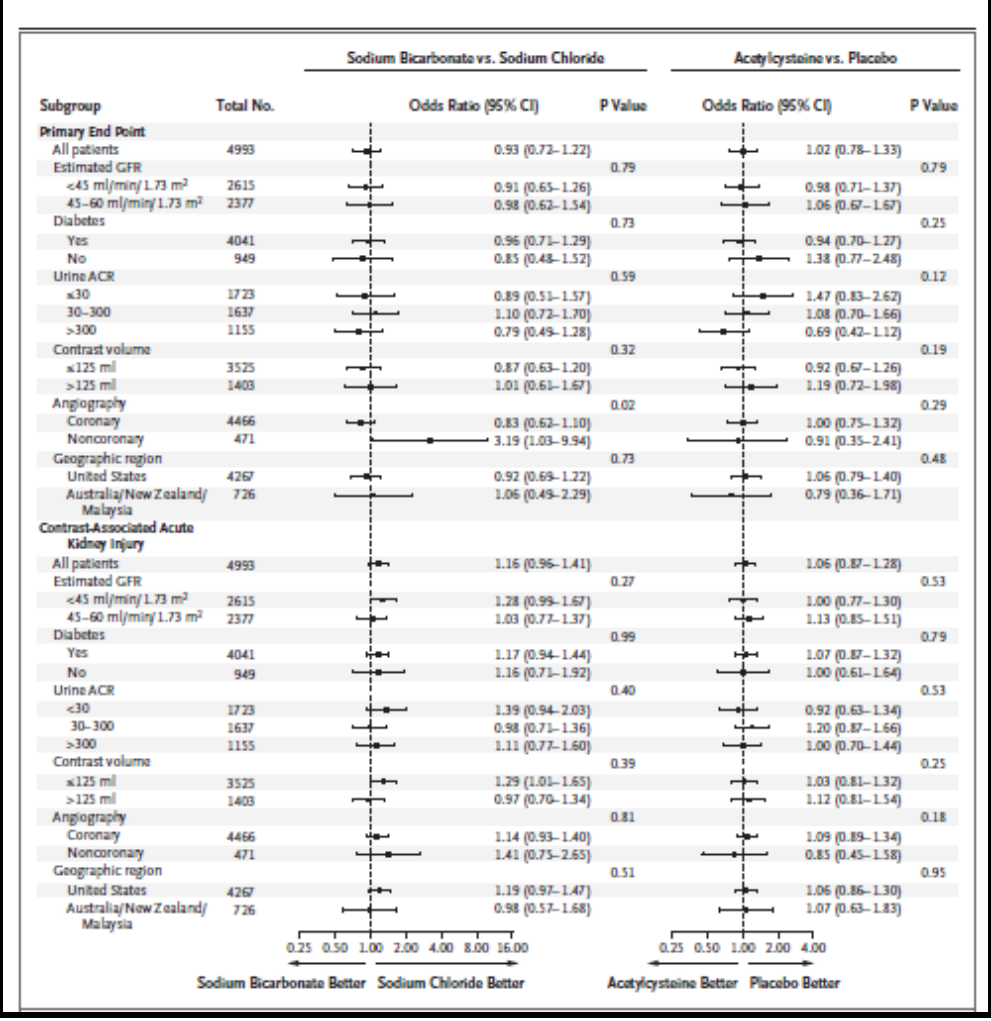
C) Death



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

1200 mg 1 hour prior and BID afterward for 96 hours

PRESERVE Trial



Subgroup	Total No.	Sodium Bicarbonate vs. Sodium Chloride: Odds Ratio (95% CI)	P Value	Acetylcysteine vs. Placebo: Odds Ratio (95% CI)	P Value
Primary End Point					
All patients	4993	0.93 (0.72–1.22)		1.02 (0.78–1.33)	
Estimated GFR			0.79		0.79
<45 ml/min/1.73 m²	2615	0.91 (0.65–1.26)		0.98 (0.71–1.37)	
45–60 ml/min/1.73 m²	2377	0.98 (0.62–1.54)		1.06 (0.67–1.67)	
Diabetes			0.73		0.25
Yes	4041	0.96 (0.71–1.29)		0.94 (0.70–1.27)	
No	949	0.85 (0.48–1.52)		1.38 (0.77–2.48)	
Urine ACR			0.59		0.12
≤30	1723	0.89 (0.51–1.57)		1.47 (0.83–2.62)	
30–300	1637	1.10 (0.72–1.70)		1.08 (0.70–1.66)	
>300	1155	0.79 (0.49–1.28)		0.69 (0.42–1.12)	
Contrast volume			0.32		0.19
≤125 ml	3525	0.87 (0.63–1.20)		0.92 (0.67–1.26)	
>125 ml	1403	1.01 (0.61–1.67)		1.19 (0.72–1.98)	
Angiography			0.02		0.29
Coronary	4466	0.83 (0.62–1.10)		1.00 (0.75–1.32)	
Noncoronary	471	3.19 (1.03–9.94)		0.91 (0.35–2.41)	
Geographic region			0.73		0.48
United States	4267	0.92 (0.69–1.22)		1.06 (0.79–1.40)	
Australia/New Zealand/ Malaysia	726	1.06 (0.49–2.29)		0.79 (0.36–1.71)	
Contrast-Associated Acute Kidney Injury					
All patients	4993	1.16 (0.96–1.41)		1.06 (0.87–1.28)	
Estimated GFR			0.27		0.53
<45 ml/min/1.73 m²	2615	1.28 (0.99–1.67)		1.00 (0.77–1.30)	
45–60 ml/min/1.73 m²	2377	1.03 (0.77–1.37)		1.13 (0.85–1.51)	
Diabetes			0.99		0.79
Yes	4041	1.17 (0.94–1.44)		1.07 (0.87–1.32)	
No	949	1.16 (0.71–1.92)		1.00 (0.61–1.64)	
Urine ACR			0.40		0.53
<30	1723	1.39 (0.94–2.03)		0.92 (0.63–1.34)	
30–300	1637	0.98 (0.71–1.36)		1.20 (0.87–1.66)	
>300	1155	1.11 (0.77–1.60)		1.00 (0.70–1.44)	
Contrast volume			0.39		0.25
≤125 ml	3525	1.29 (1.01–1.65)		1.03 (0.81–1.32)	
>125 ml	1403	0.97 (0.70–1.34)		1.12 (0.81–1.54)	
Angiography			0.81		0.18
Coronary	4466	1.14 (0.93–1.40)		1.09 (0.89–1.34)	
Noncoronary	471	1.41 (0.75–2.65)		0.85 (0.45–1.58)	
Geographic region			0.51		0.95
United States	4267	1.19 (0.97–1.47)		1.06 (0.86–1.30)	
Australia/New Zealand/ Malaysia	726	0.98 (0.57–1.68)		1.07 (0.63–1.83)	

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

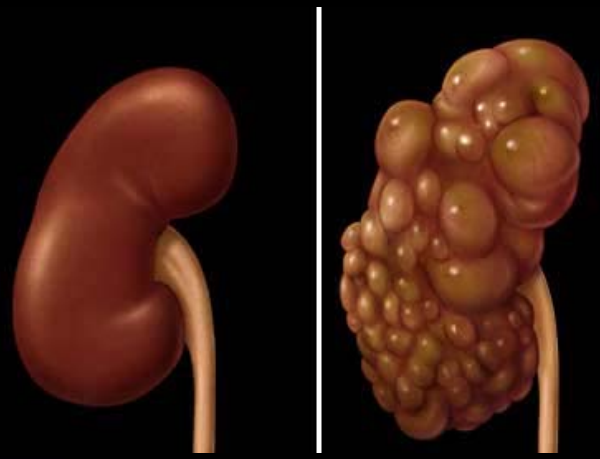
Entrée

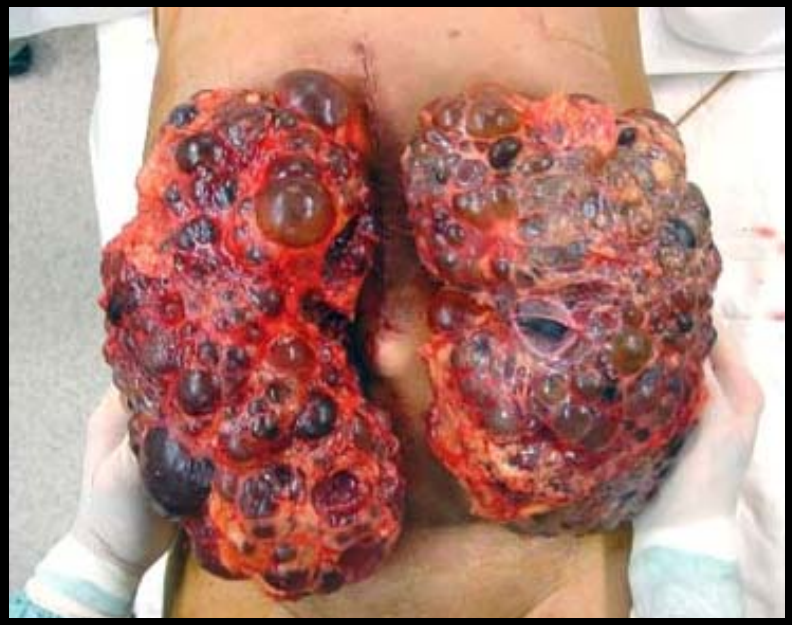
0.9 Normal Saline

Dessert

0.9 Normal Saline

Autosomal Dominant Polycystic Kidney Disease

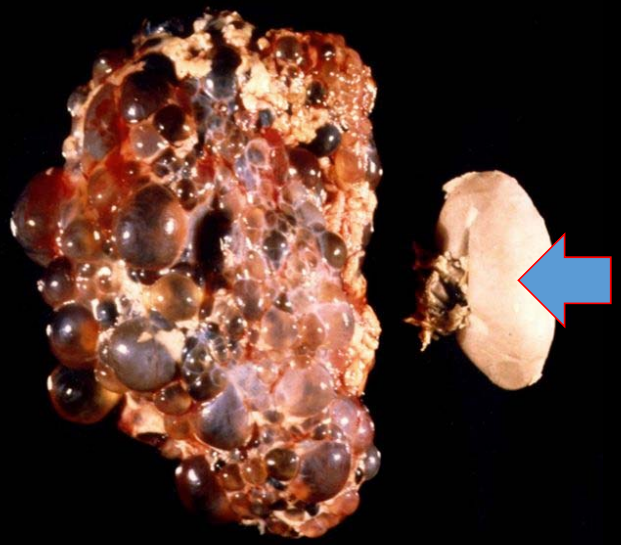




10% of all cases of ESRD

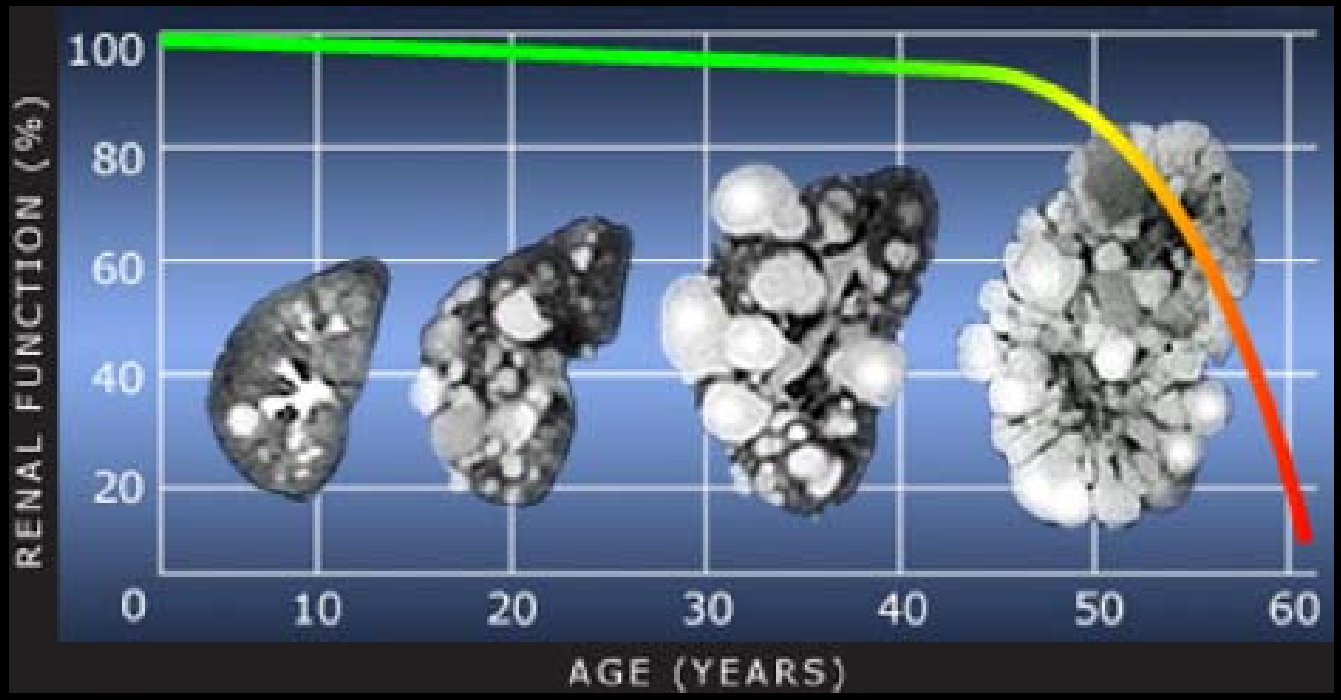
50% ESRD by age 50

600,000 affected people in the U.S.
12 million worldwide



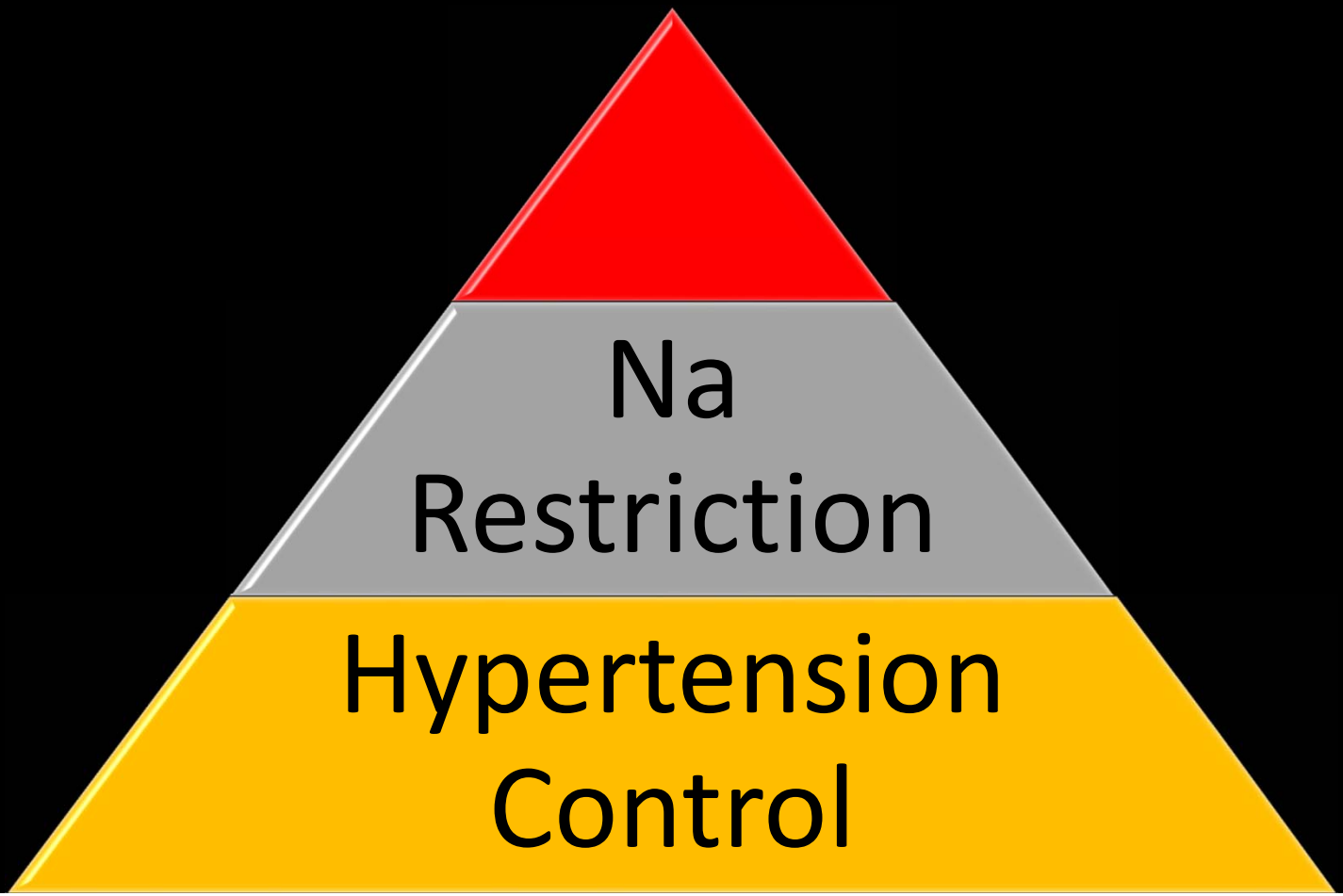
for comparison only - ADPCKD is **always bilateral**
Football placed for comparison – there are no footballs in the abdomen

Autosomal Dominant Polycystic Kidney Disease



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

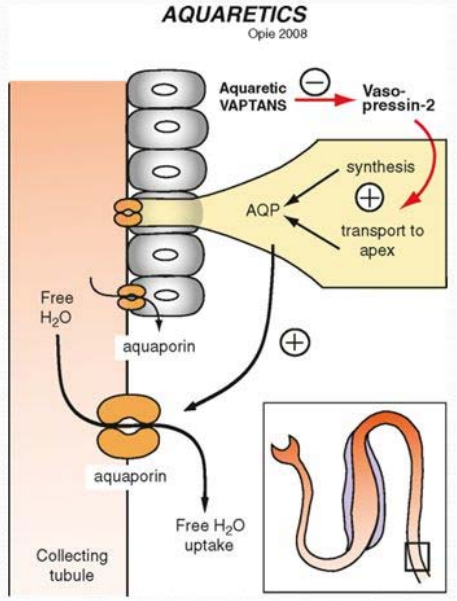


The Vaptans

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

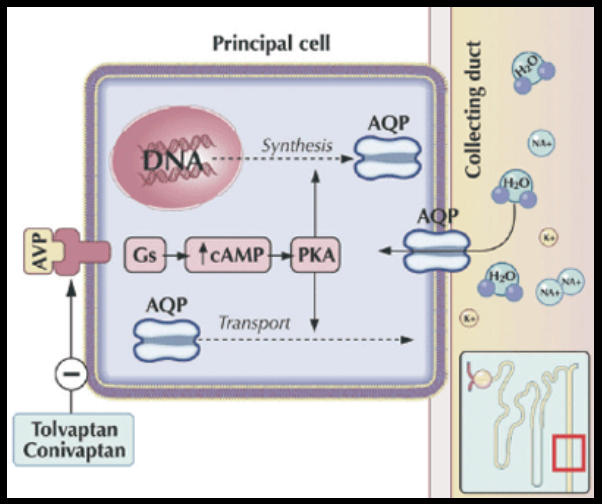
Aquaretics

- Arginine vasopressin (AVP) V2 receptor antogonists
- "Vaptans"
  - Conivaptan
  - Tolvaptan
  - Lixivaptan



Mechanism of Action of Tolvaptan in ADPCKD

Impair AQP2 Generation

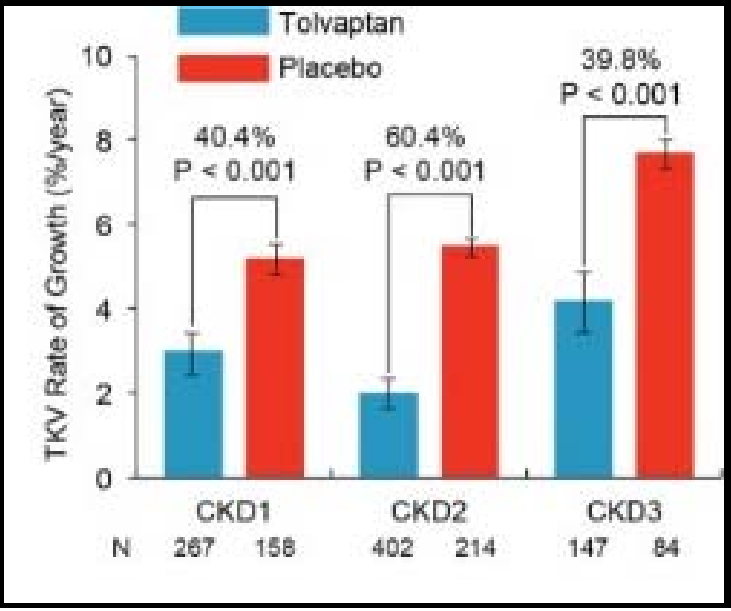


Reduce Intracellular cAMP

Torres VE, CJASN. 2016;11(5):803-811.

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

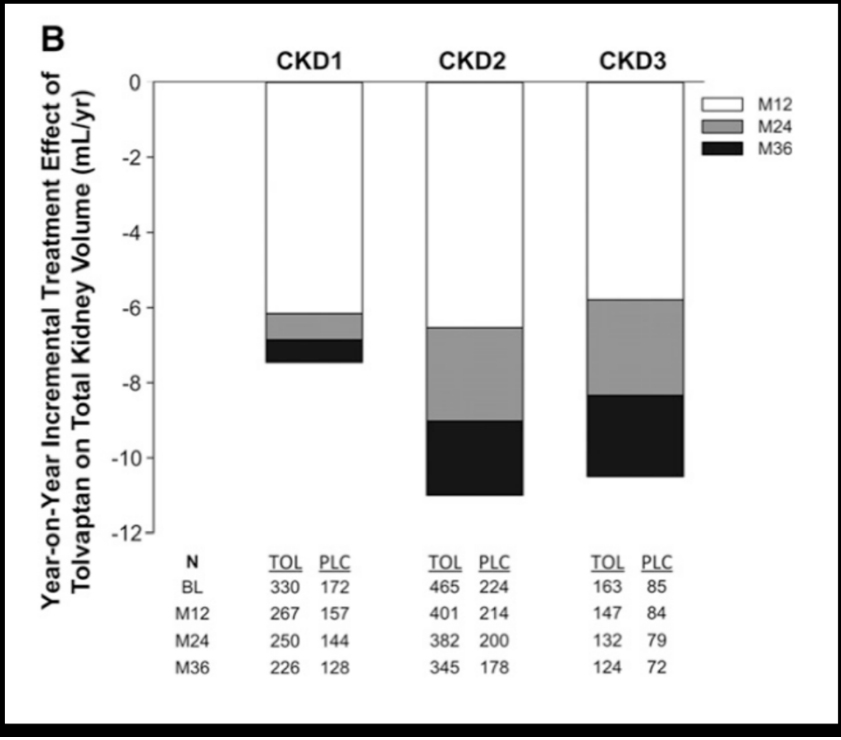
- 1445 patients with Stage 1-3 CKD and ADPCKD
- Phase 3, multicenter, double-blind, placebo-controlled, 3-year trial



Significant reduction in the rate of kidney growth with Tolvaptan independent of the Stage of CKD 1-3

Torres VE, CJASN. 2016;11(5):803-811.

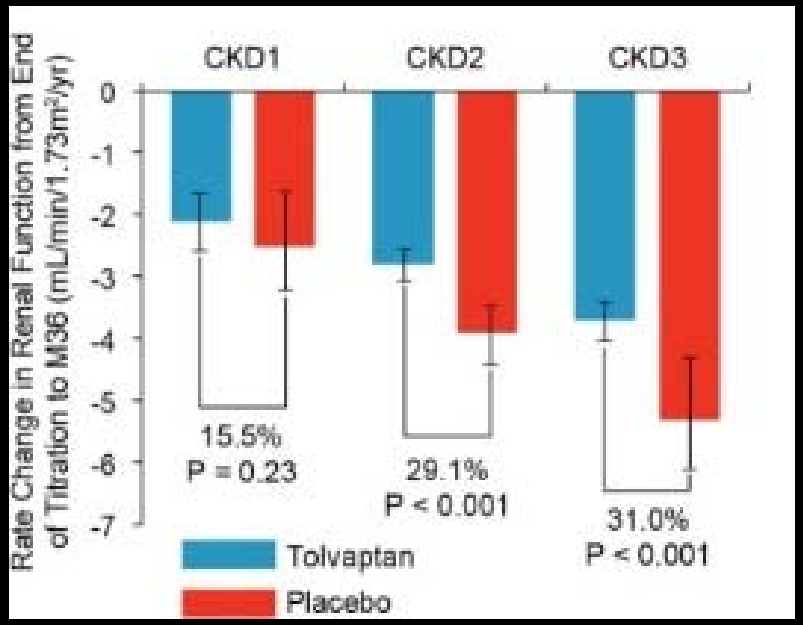
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes : TEMPO

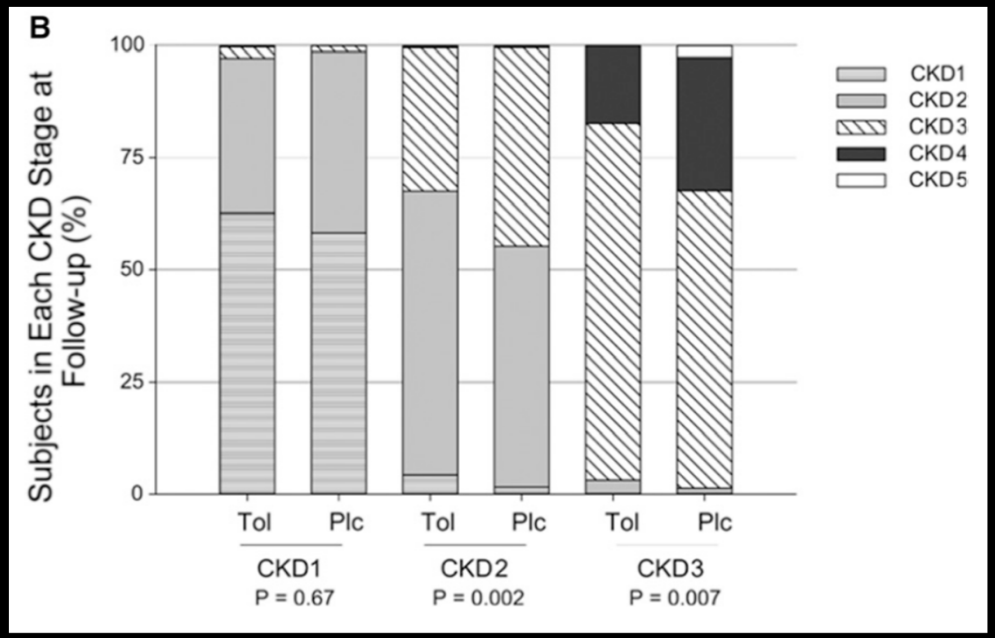


Significant reduction in the rate of kidney growth with Tolvaptan occurs immediately in the first 12 months and continued through the 2nd and 3rd years

Torres VE, CJASN. 2016;11(5):803-811.

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

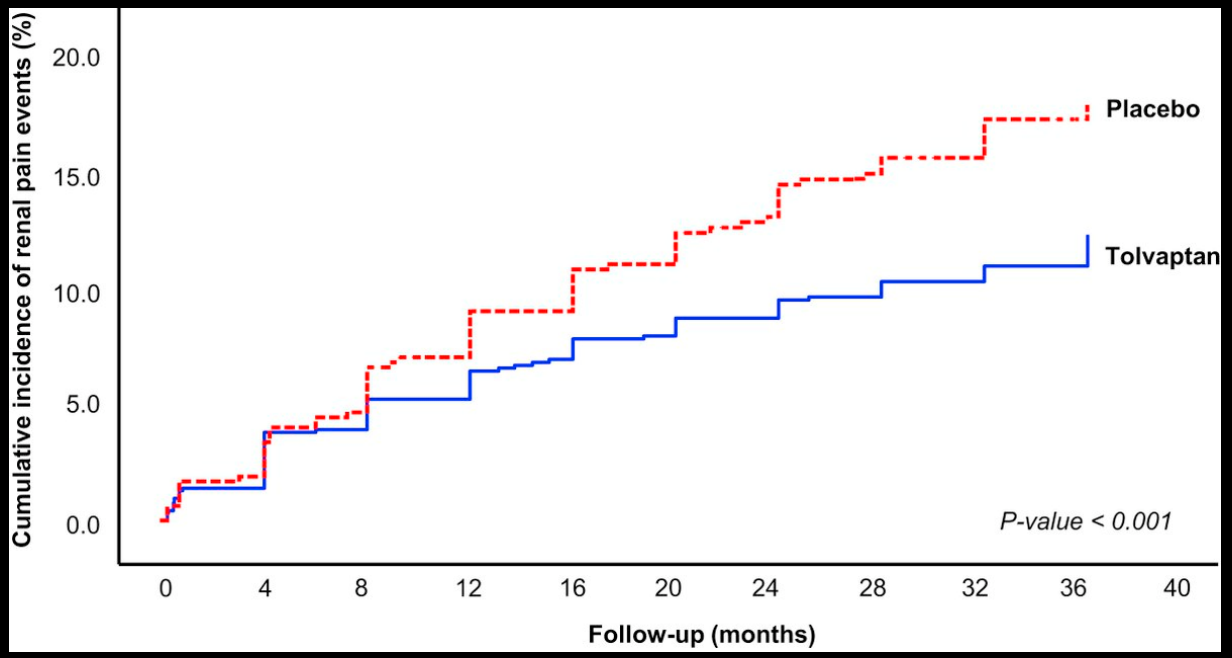




Rate of decline in GFR with Tolvaptan was significantly slower starting in Stage 2-3 CKD and fewer patients progressed to the next Stage of CKD

Torres VE, CJASN. 2016;11(5):803-811.

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

Torres VE, CJASN. 2016;11(5):803-811.

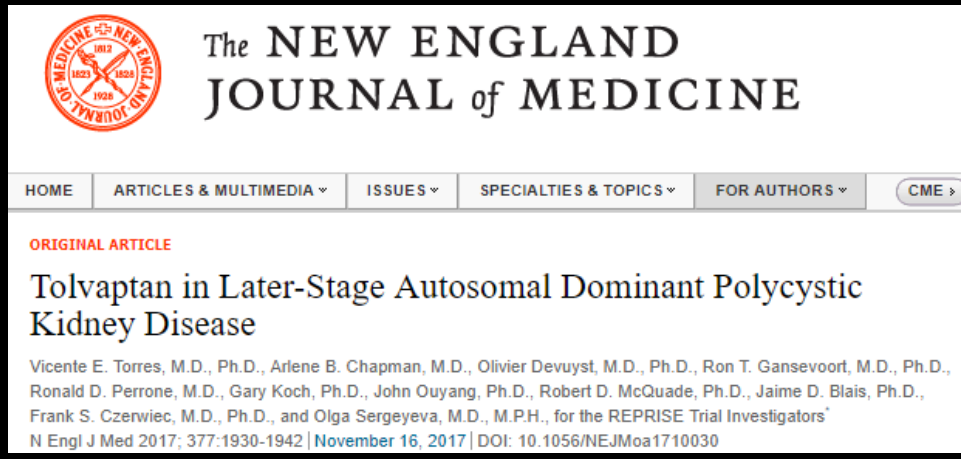
Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes : TEMPO

Variable	CKD Stage 1 (*n*=502)		CKD Stage 2 (*n*=689)		CKD Stage 3 (*n*=248)	
	Tolvaptan (*n*=330)	Placebo (*n*=172)	Tolvaptan (*n*=465)	Placebo (*n*=224)	Tolvaptan (*n*=163)	Placebo (*n*=85)
AEs (% of patients with at least one event)						
Thirst	53.6	20.9	57.2	19.2	53.4	23.5
Polyuria	44.8	18.6	35.5	16.5	33.7	16.5
Nocturia	28.5	12.2	29.5	12.9	30.1	15.3
Pollakiuria	16.1	6.4	27.5	5.4	25.2	2.4
Serum sodium >150 mEq/L, %	2.4	2.9	4.1	1.3	6.7	0
Serum uric acid >7.5 mg/dl, %	20.7	12.9	38.7	24.7	71.8	49.4
Serum ALT >2.5 times ULN	5.2 (2.18)[a]	1.7 (0.66)[a]	5.6 (2.21)[a]	1.3 (0.48)[a]	7.4 (2.87)[a]	2.4 (0.82)[a]
Serum AST >2.5 times ULN	3.9 (1.66)[a]	0.6 (0.22)[a]	3.7 (1.45)[a]	0.9 (0.32)[a]	4.9 (1.91)[a]	1.2 (0.41)[a]

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,



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

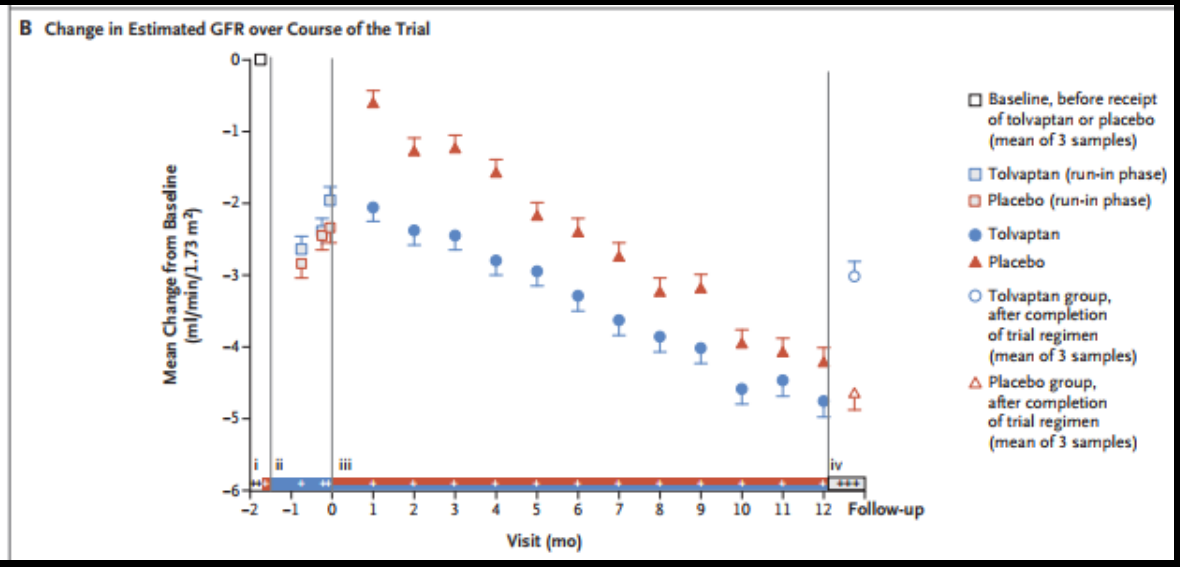
Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

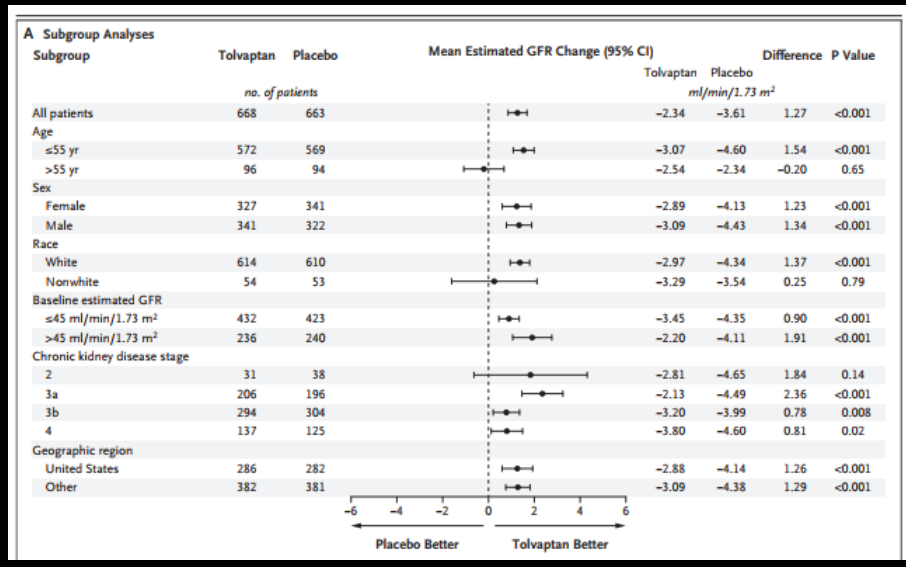
Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*

N Engl J Med 2017; 377:1930-1942 | November 16, 2017 | DOI: 10.1056/NEJMoa1710030

N Engl J Med 2017; 377:1930-1942

REPRISE Trial

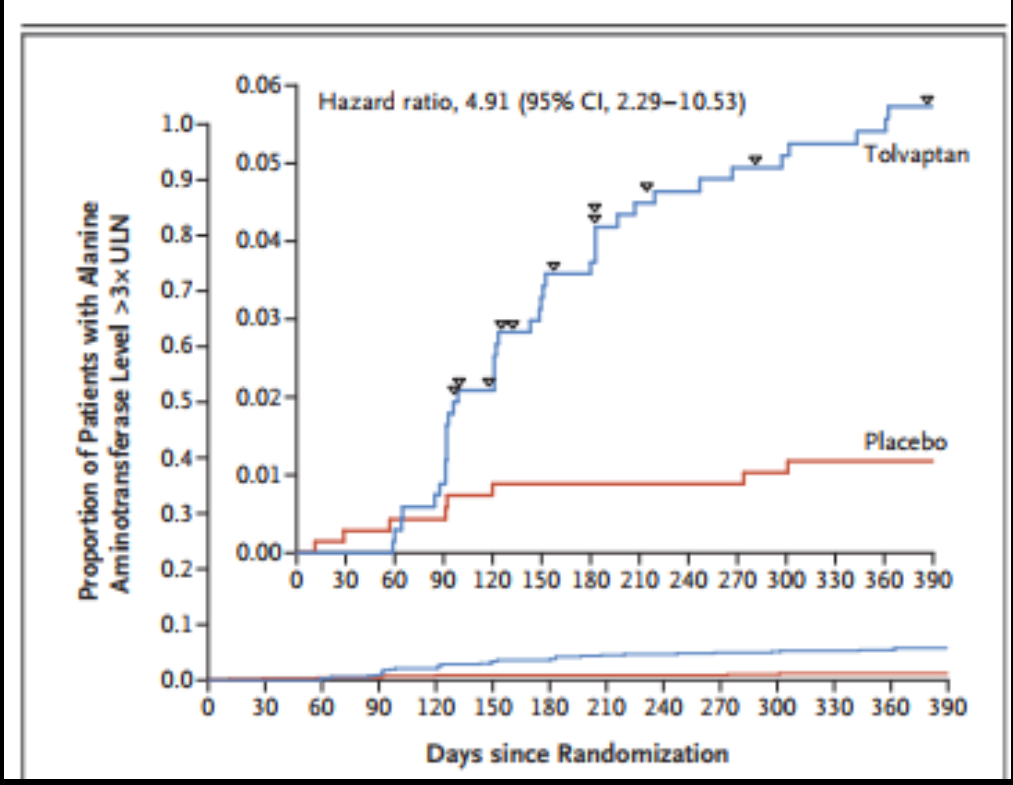




Tolvaptan significantly slowed the rate of decline in kidney function in all age groups and degree of CKD

Delay in the need for dialysis / Transplant > 3 years

REPRISE Trial
Adverse Side Effects of Tolvaptan



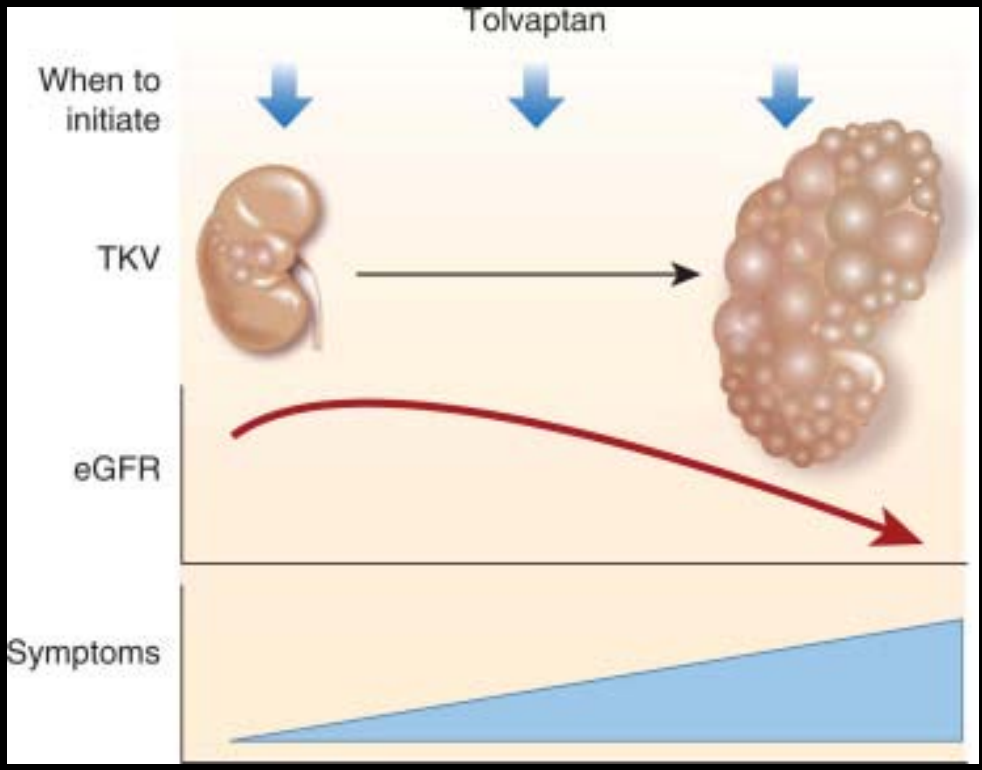
A total of 31 patients (4.6%) receiving tolvaptan had serious hepatic adverse events, as compared with 4 (0.6%) receiving placebo.

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.

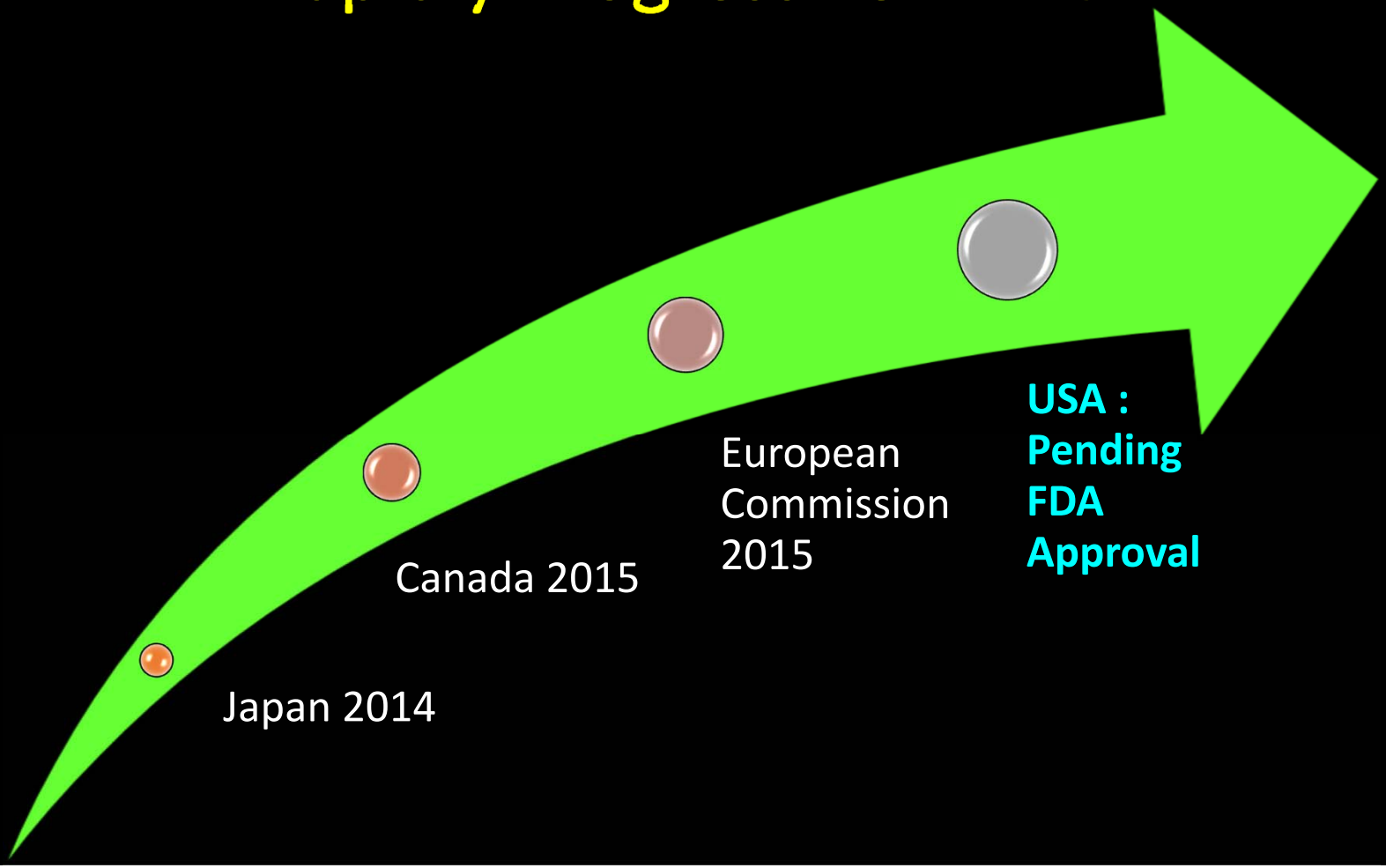
First Drug Ever Approved for ADPCKD
Guidelines for the use of Tolvaptan in ADPCKD

- **Rapid disease progression**
  - annual eGFR decline of at least 5 mL/min/1.73 m^2 in 1 year, and/or at least 2.5 mL/min/1.73 m^2 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 ADPCKD



Tolvaptan and ADPCKD

- **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

Alonzo Mourning

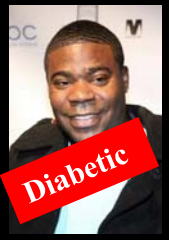
Natalie Cole

Ivan Klasnic

Lucy Davis

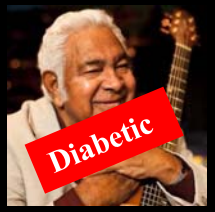
Sean Elliott

Ron Springs – Everson Walls



Tracy Morgan

Gary Coleman



Jimmy Ilttle

Ken Howard

Jennifer Harman

Steve Cojocaru

Neil Simon

And just recently ……..a Baltimore Raven gave a Kidney to a Pittsburgh Steeler

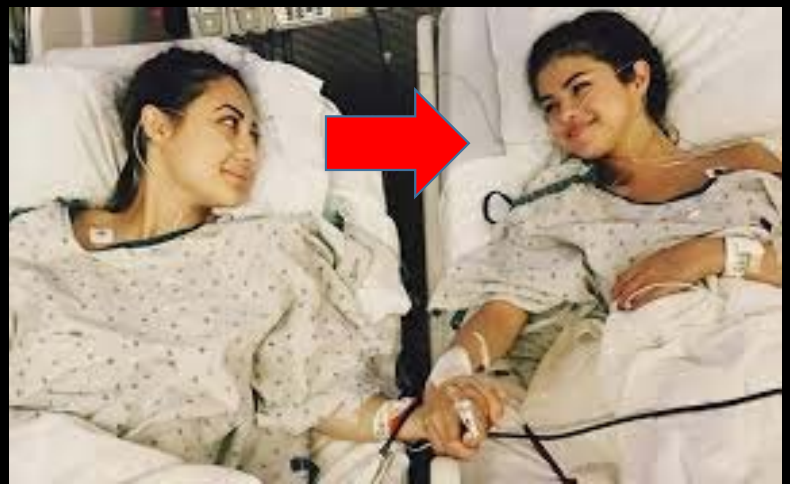
“The kidney we got from Ma’ake was probably the largest normal kidney I’ve ever seen,” Dr Bartlett

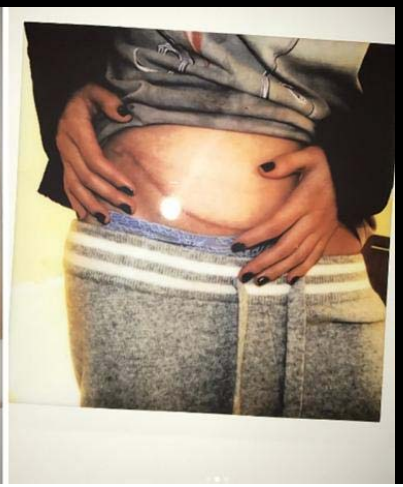
Chris Kemoeatu

Ma'ake Kemoeatu

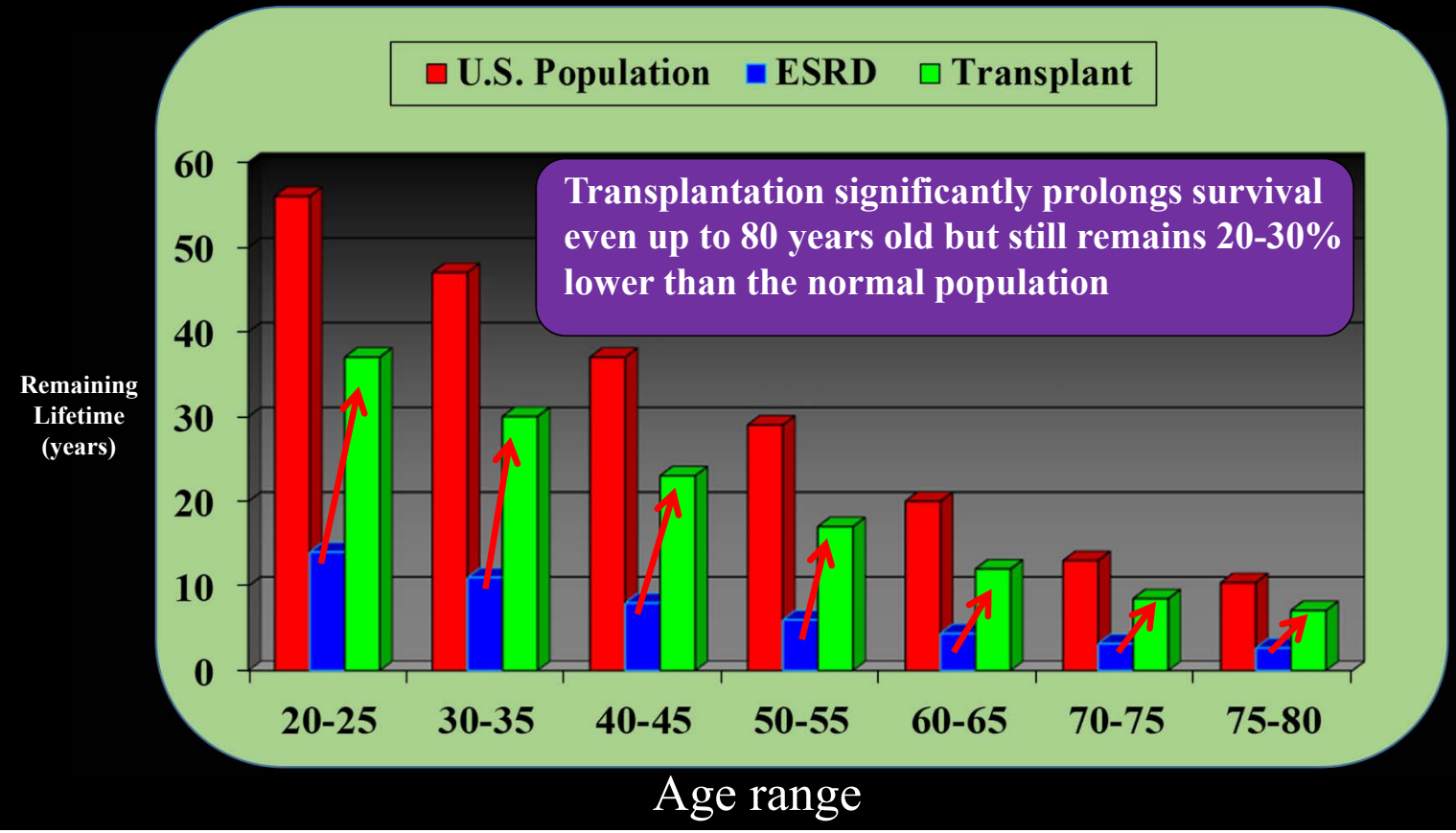
"He couldn't play anymore, and I didn't want to be in a position where he couldn't play but I'd keep playing- so I quit football and gave him my kidney “

Selena Gomez

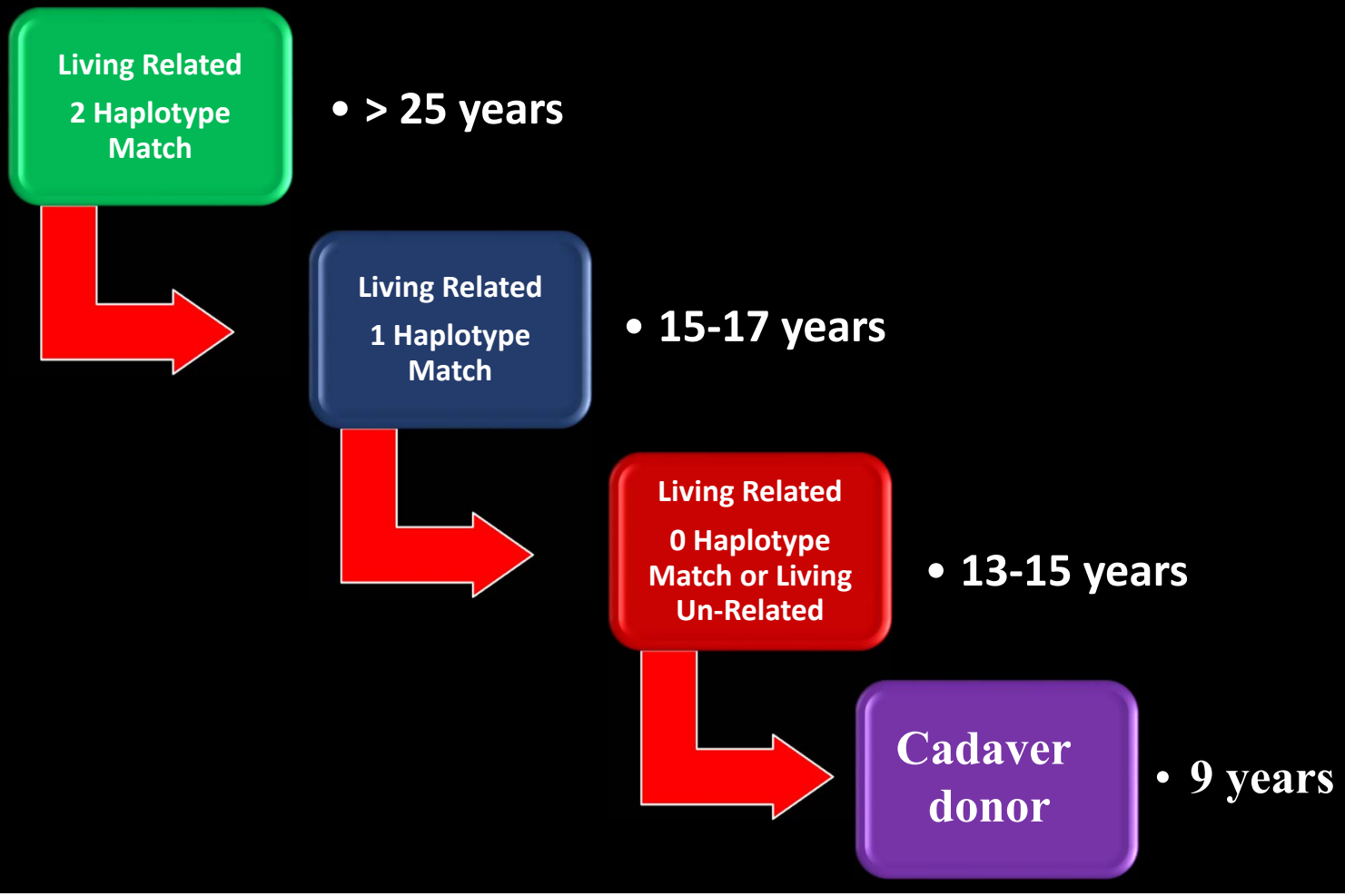




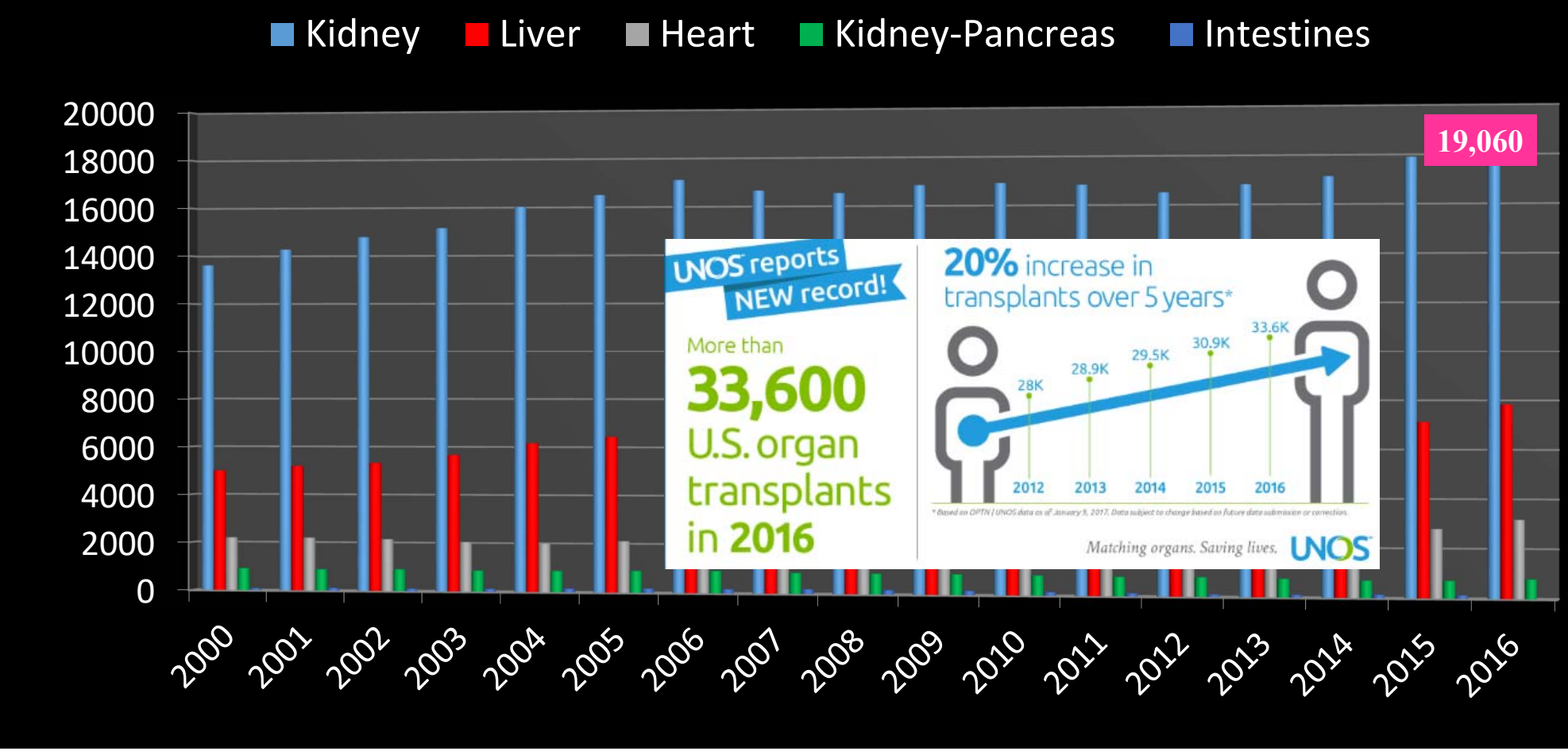
Expected Remaining Lifetimes in ESRD Patients, Transplant Patients and U.S. Population



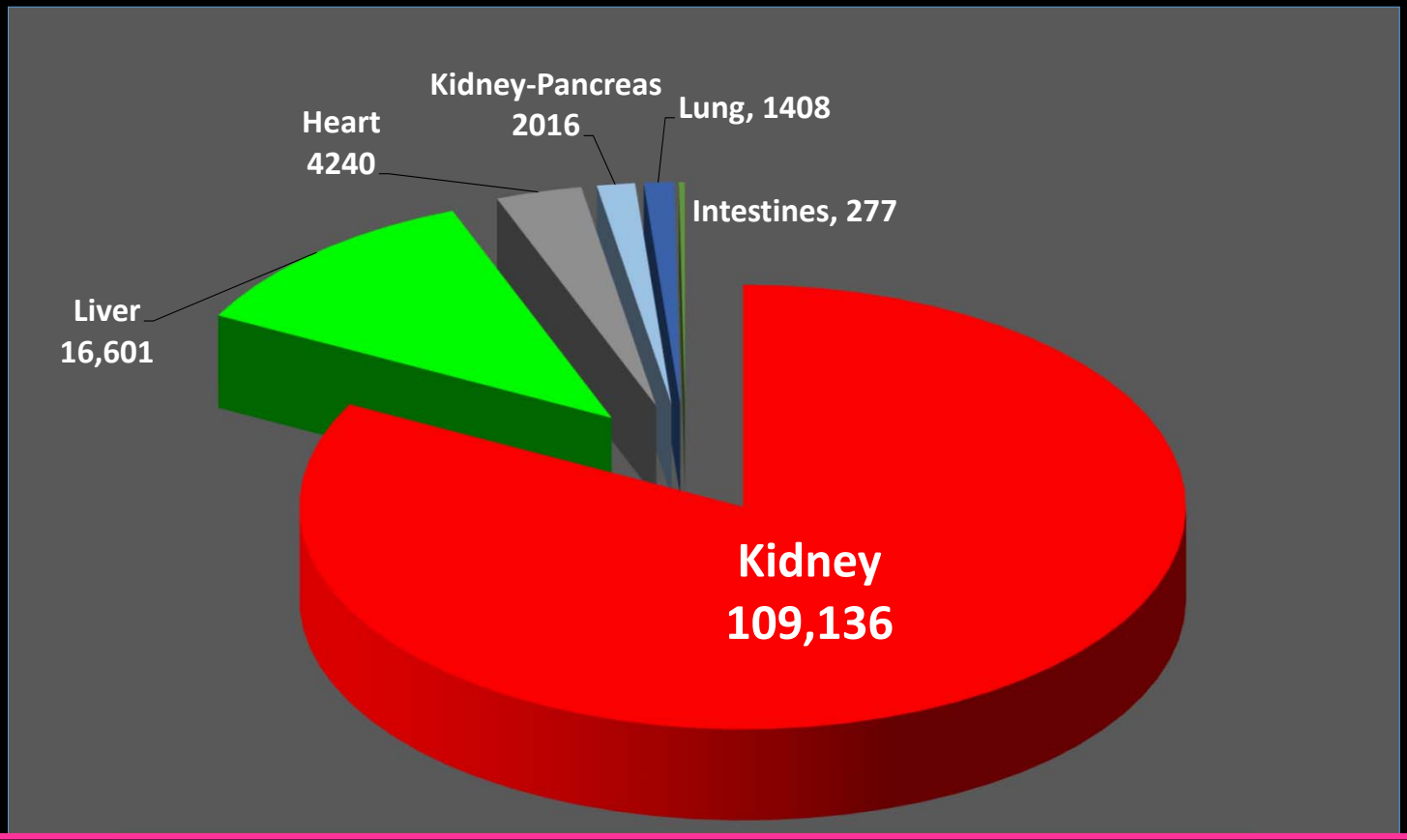
Influence of Donor Source on Renal Allograft Survival



Organ TP 2000 - 2016

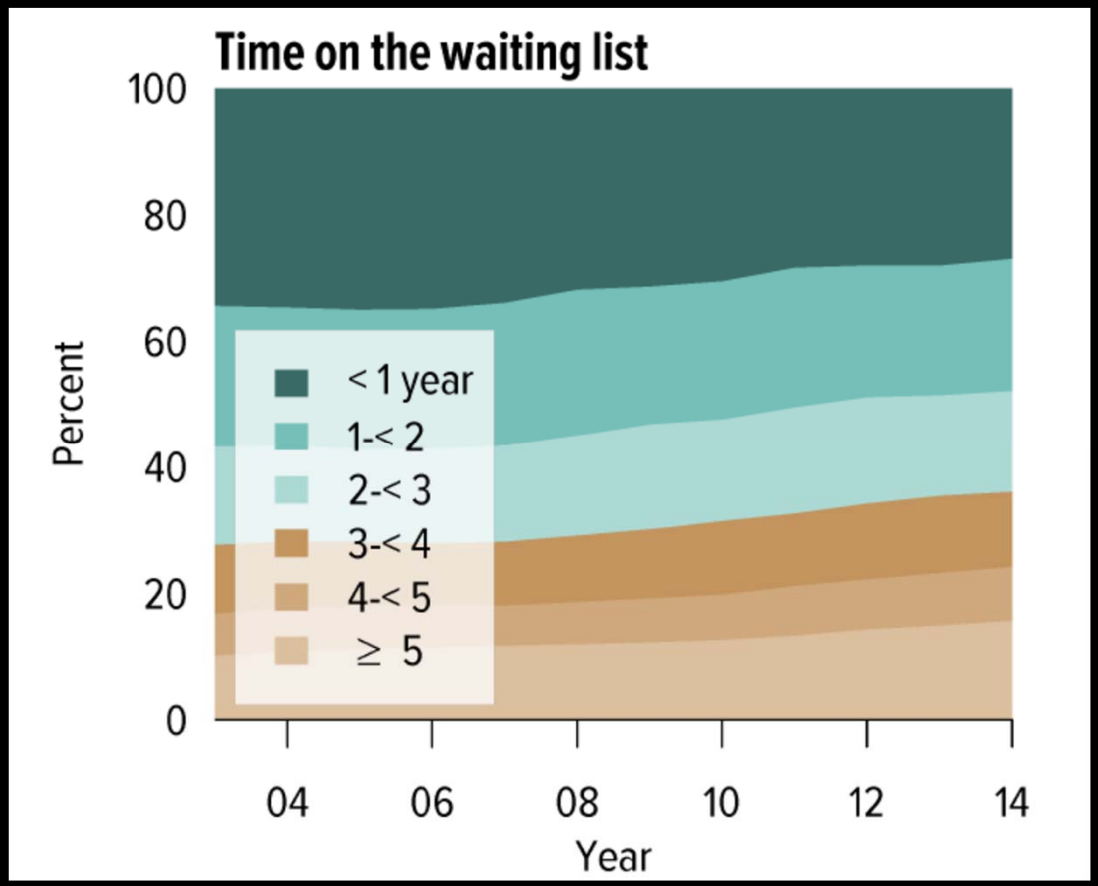


Transplant Waiting List : December 1, 2017



129,005 Candidates for a Solid Organ Transplant

Patients are Waiting Longer and Longer for a Kidney Transplant

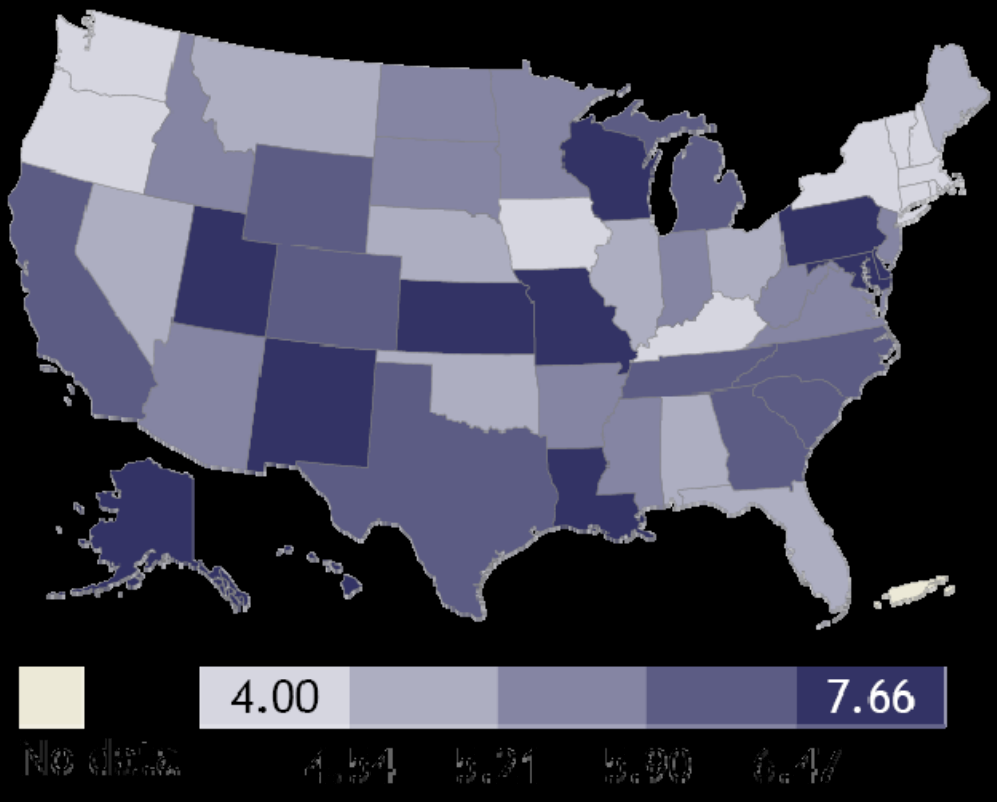


Average waiting time 3-4 years

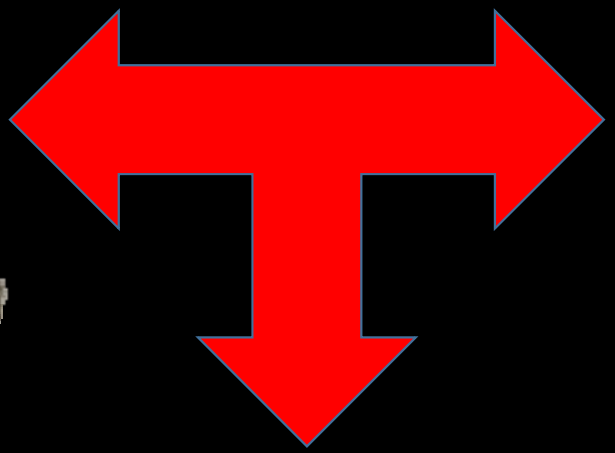
15% of patients are on the list > 5 years

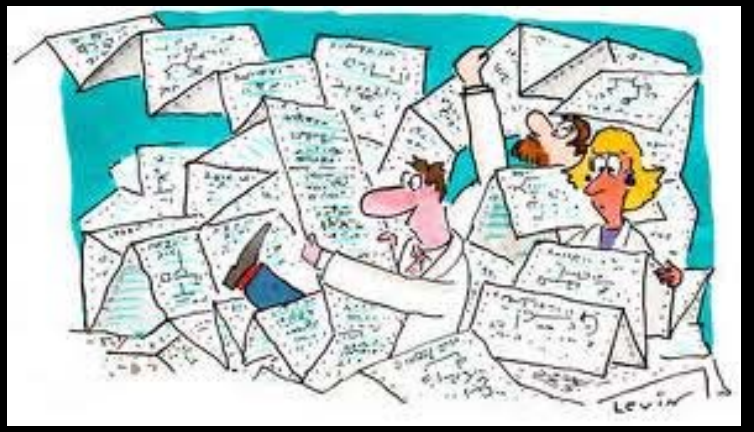
Wide variation in Cadaveric Donation Rates in the U.S.

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 …..

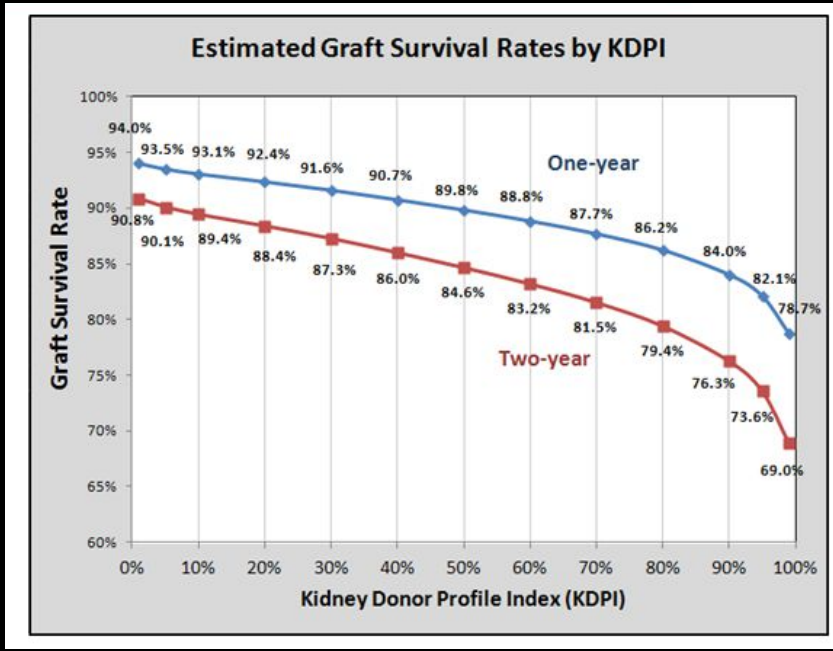
Now it is like this …..

Sequence A KDPI <=20%	Sequence B KDPI >20% but <35%	Sequence C KDPI >=35% but <=85%	Sequence D KDPI>85%
Highly Sensitized 0-ABDRmm (top 20% EPTS) Prior living donor Local pediatrics Local top 20% EPTS 0-ABDRmm (all) Local (all) Regional pediatrics Regional (top 20%) Regional (all) National pediatrics National (top 20%) National (all)	Highly Sensitized 0-ABDRmm Prior living donor Local pediatrics Local adults Regional pediatrics Regional adults National pediatrics National adults	Highly Sensitized 0-ABDRmm Prior living donor Local Regional National	Highly Sensitized 0-ABDRmm Local + Regional National

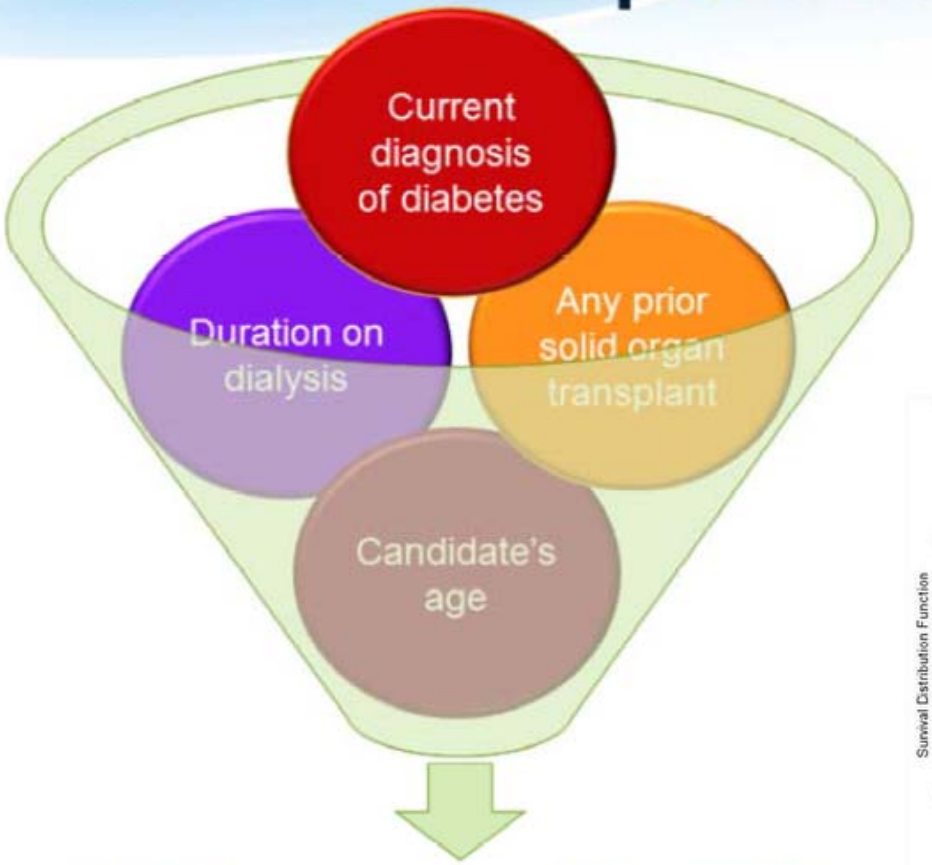
OPTN UNOS DONATE LIFE

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 KD**PI (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**



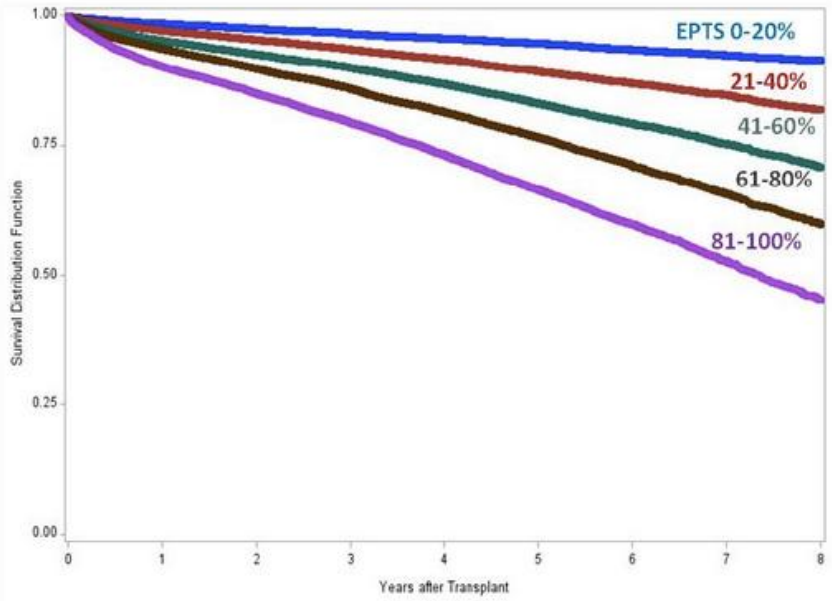
Estimated Post Transplant Survival



EPTS score range 0%-100%

OPTN

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



EPTS & KDPI in the New System

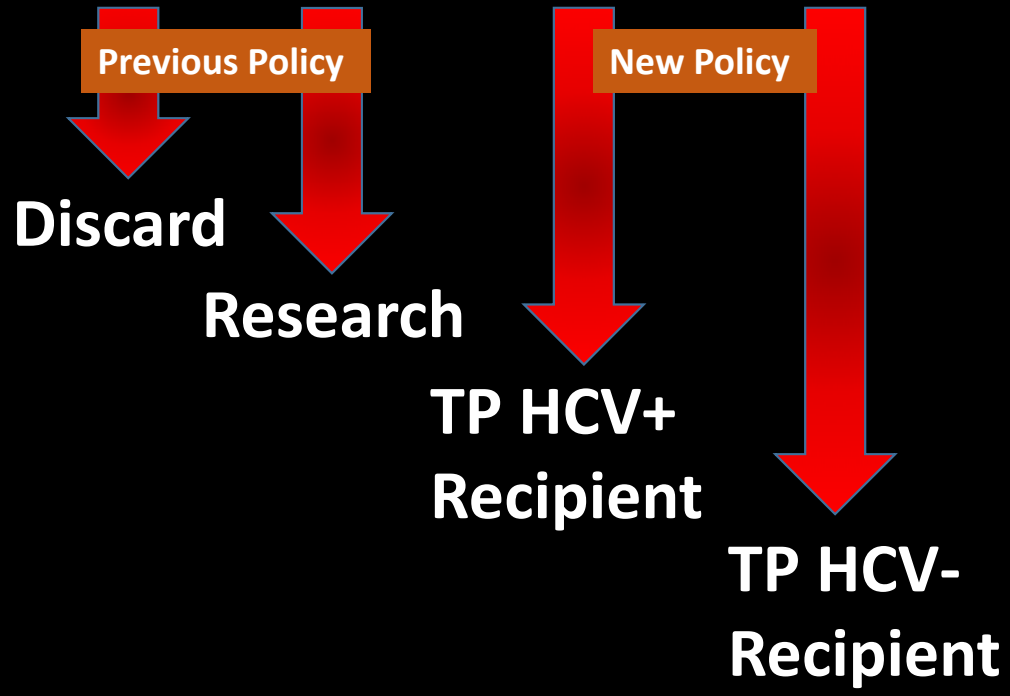
The best kidneys are mandated to go to the best recipients

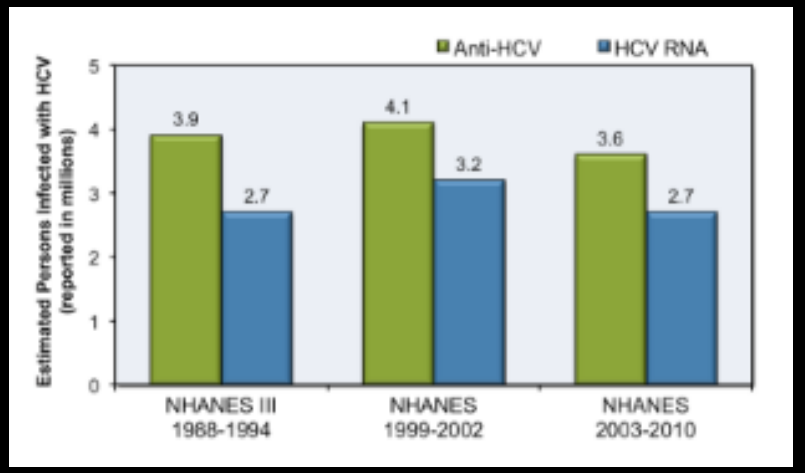
OPTN

UNOS DONATE LIFE
UNITED NETWORK FOR ORGAN SHARING

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





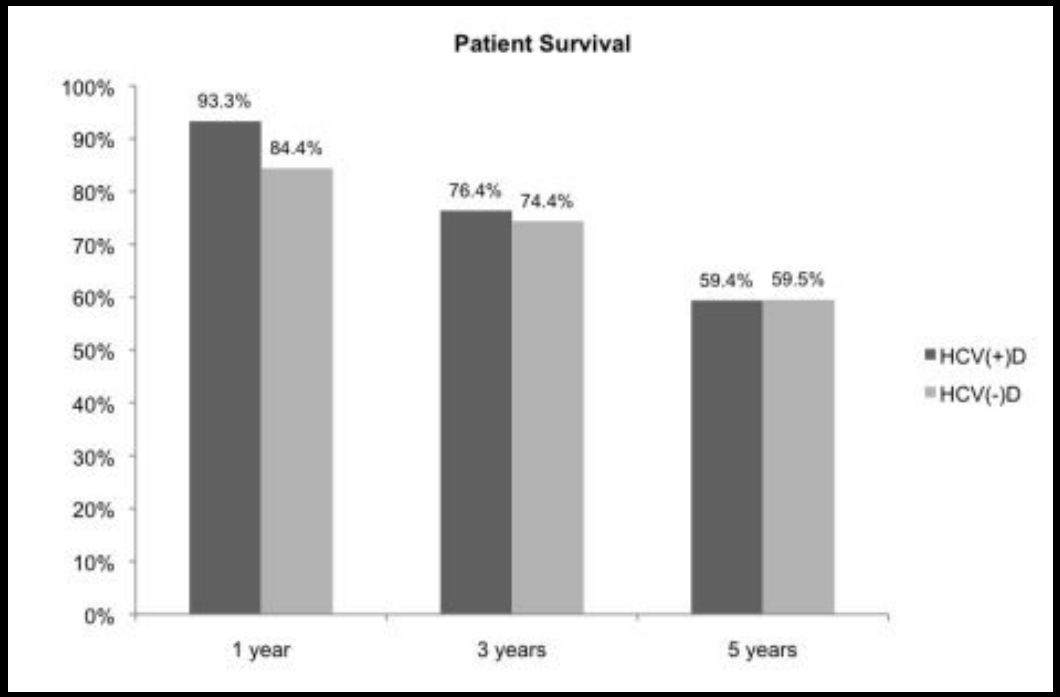
Transplant HCV+ Donor Kidney into an HCV+ Recipient

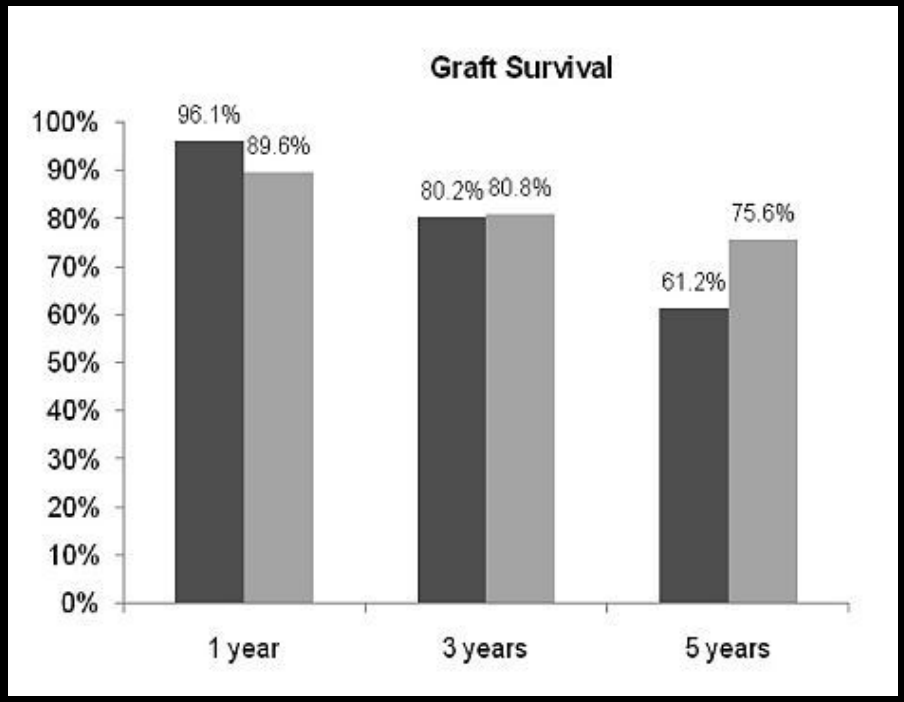
- **Recipient must be actively replicating HCV and treatment naïve**
- **Direct Acting Anti-virals (DAA) are usually started 2 months after transplantation**
- **Allows an HCV+ patient to get cadaveric kidney transplant much faster than the standard waiting list**

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



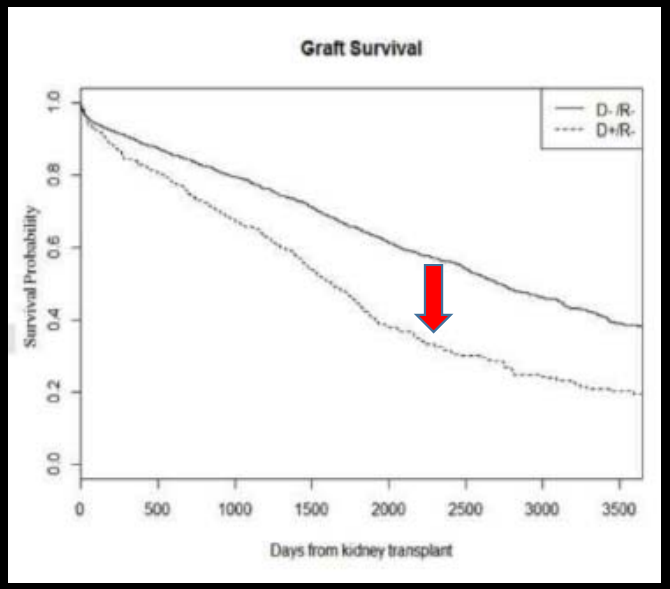


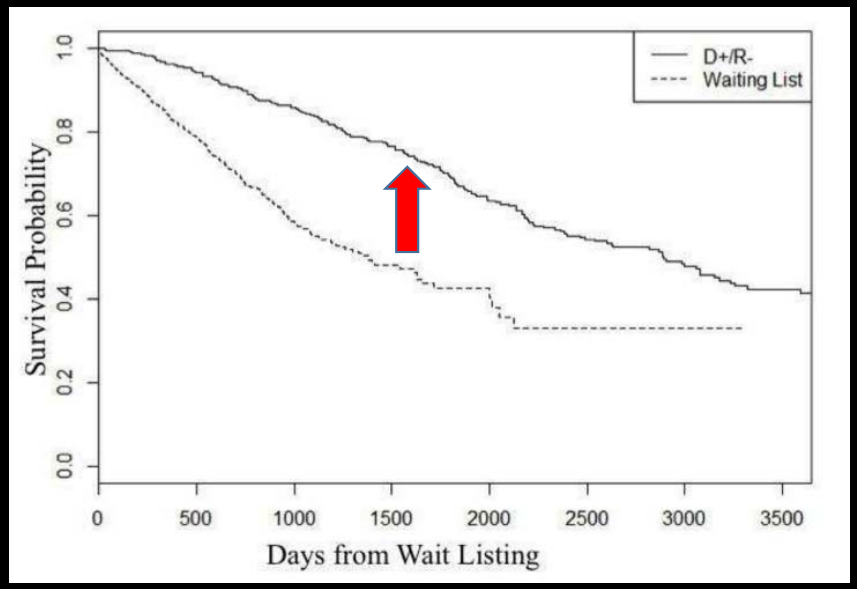
Jawa P, *Am J Transplant*. 2013; 13 (suppl 5)

G Gupta. Clinical transplantation , 2017

HCV+ Donors for HCV- Recipients

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





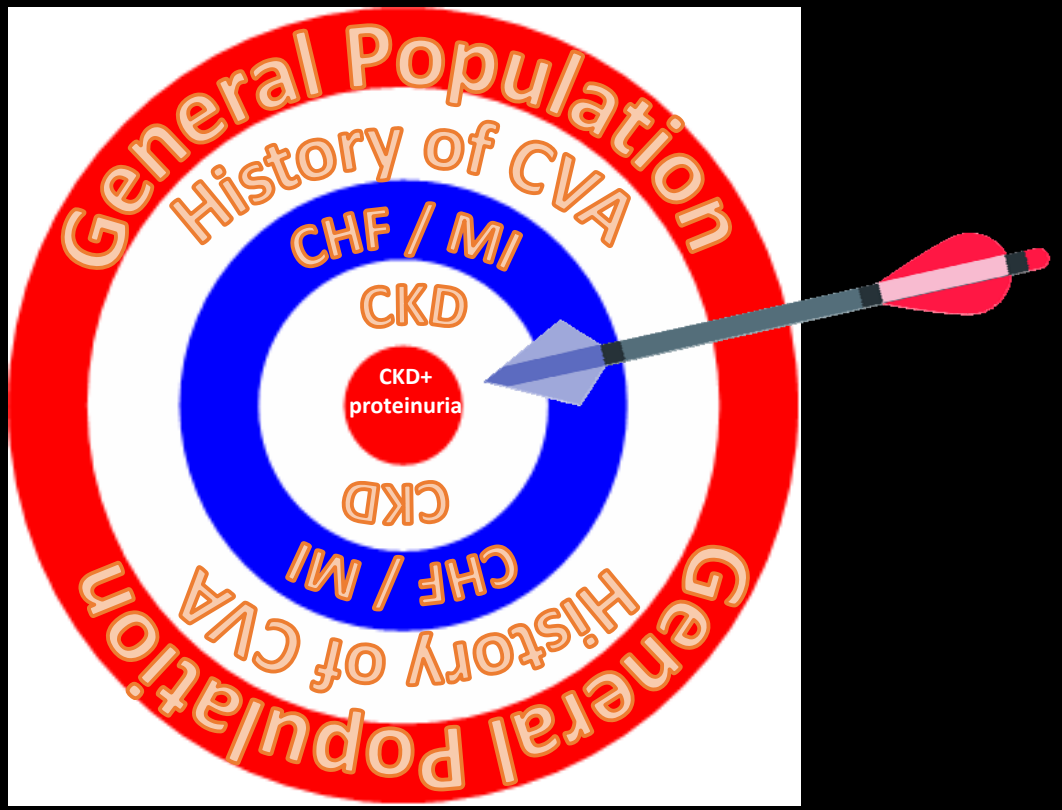
- **Although graft survival is inferior to HCV- donors/HCV- recipients , the patient survival is still superior compared to remaining on dialysis therapy**
- **Currently being done under NIH protocols in selected centers**

G Gupta. Clinical transplantation , 2017

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?

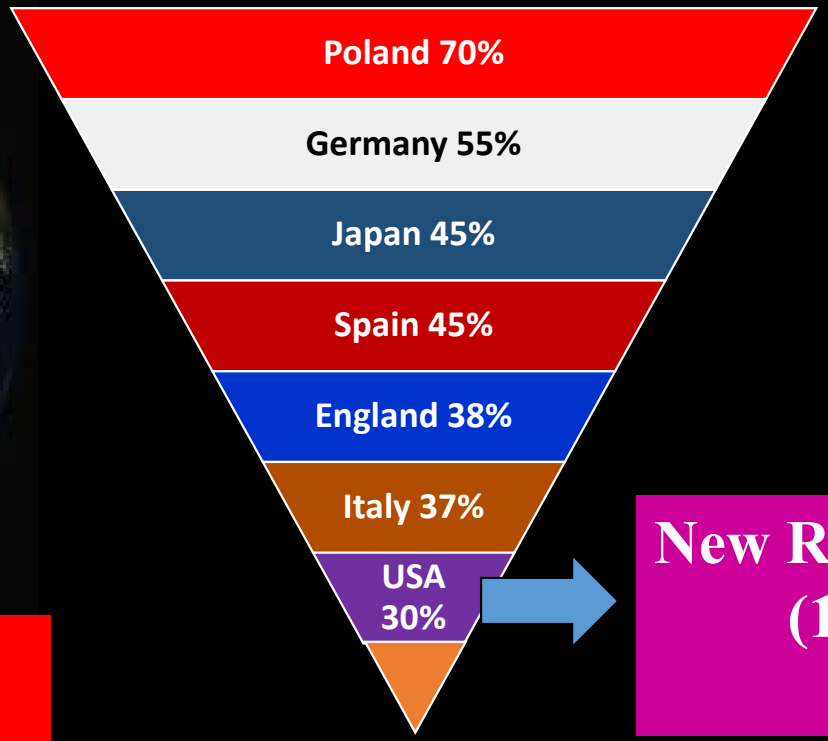


Evolving Target of Controlled BP

• JNC 1	1977	< 169/90 mmHg
• JNC 2	1980	Diastolic < 90 mmHg
• JNC 3	1984	< 140/90
• JNC 6	1997	< 140/90 <130/85 for high risk
• JNC 7	2003	< 140/90 < 130/80 for high risk
• JNC 8	2014	< 140/90 for < 60 yrs old <150/90 for > 60 yrs old
• ACC/AHA	2017	130/80

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



New Revised Goal (130/80) 46%

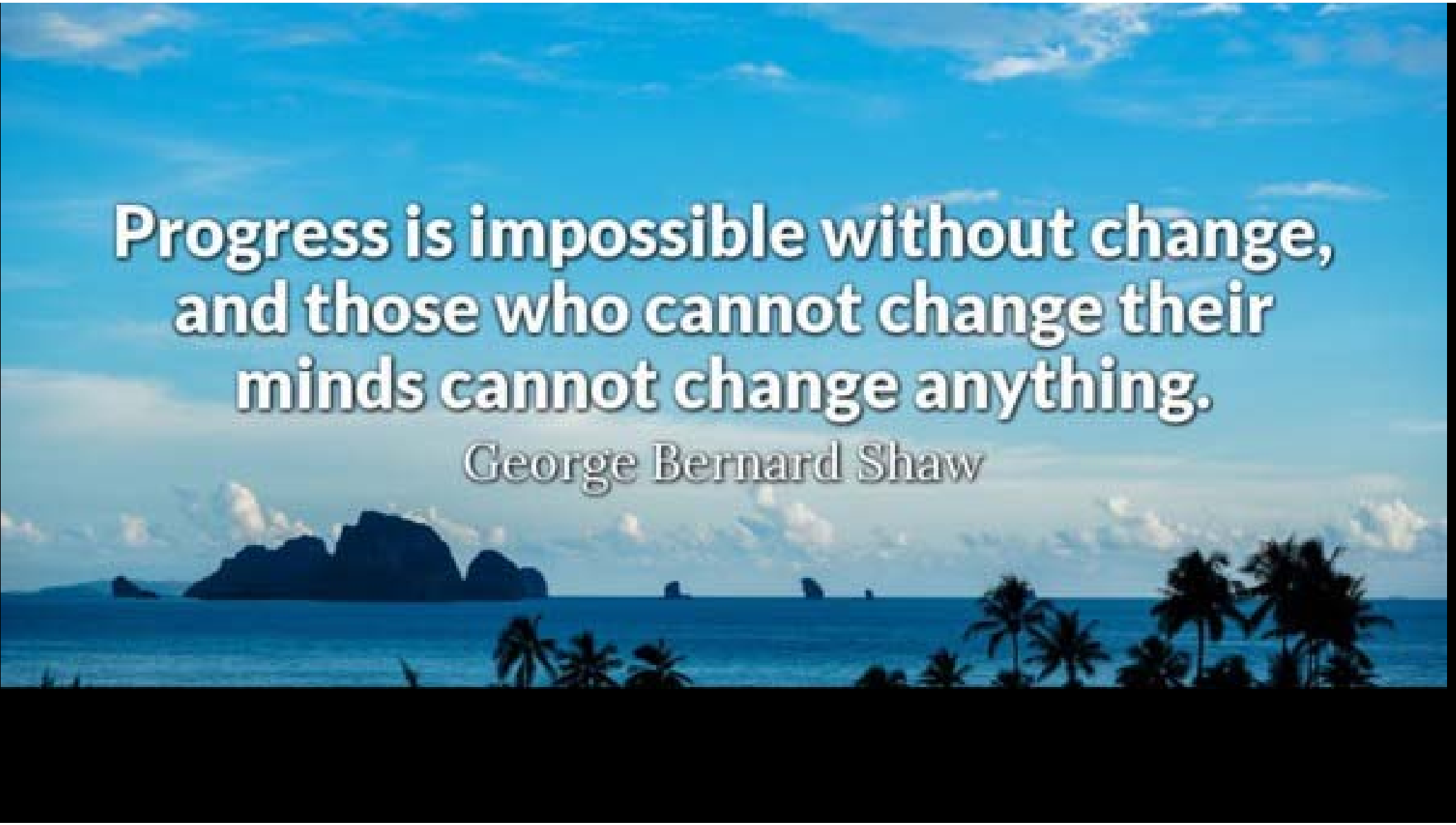
New BP Targets Increase the Percentage of HTN Patients in all Age groups, Genders and Ethnicities

	SBP/DBP ≥130/80 mm Hg or Self-Reported Antihypertensive Medication†		SBP/DBP ≥140/90 mm Hg or Self-Reported Antihypertensive Medication‡	
Overall, crude	46%		32%	
	Men (n=4717)	Women (n=4906)	Men (n=4717)	Women (n=4906)
Overall, age-sex adjusted	48%	43%	31%	32%
Age group, y				
20–44	30%	19%	11%	10%
45–54	50%	44%	33%	27%
55–64	70%	63%	53%	52%
65–74	77%	75%	64%	63%
75+	79%	85%	71%	78%
Race-ethnicity§				
Non-Hispanic white	47%	41%	31%	30%
Non-Hispanic black	59%	56%	42%	46%
Non-Hispanic Asian	45%	36%	29%	27%
Hispanic	44%	42%	27%	32%

<u>Average increase in the HTN Population based on the new classification of HTN</u>

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Trial
Systolic Blood Pressure Intervention Trial

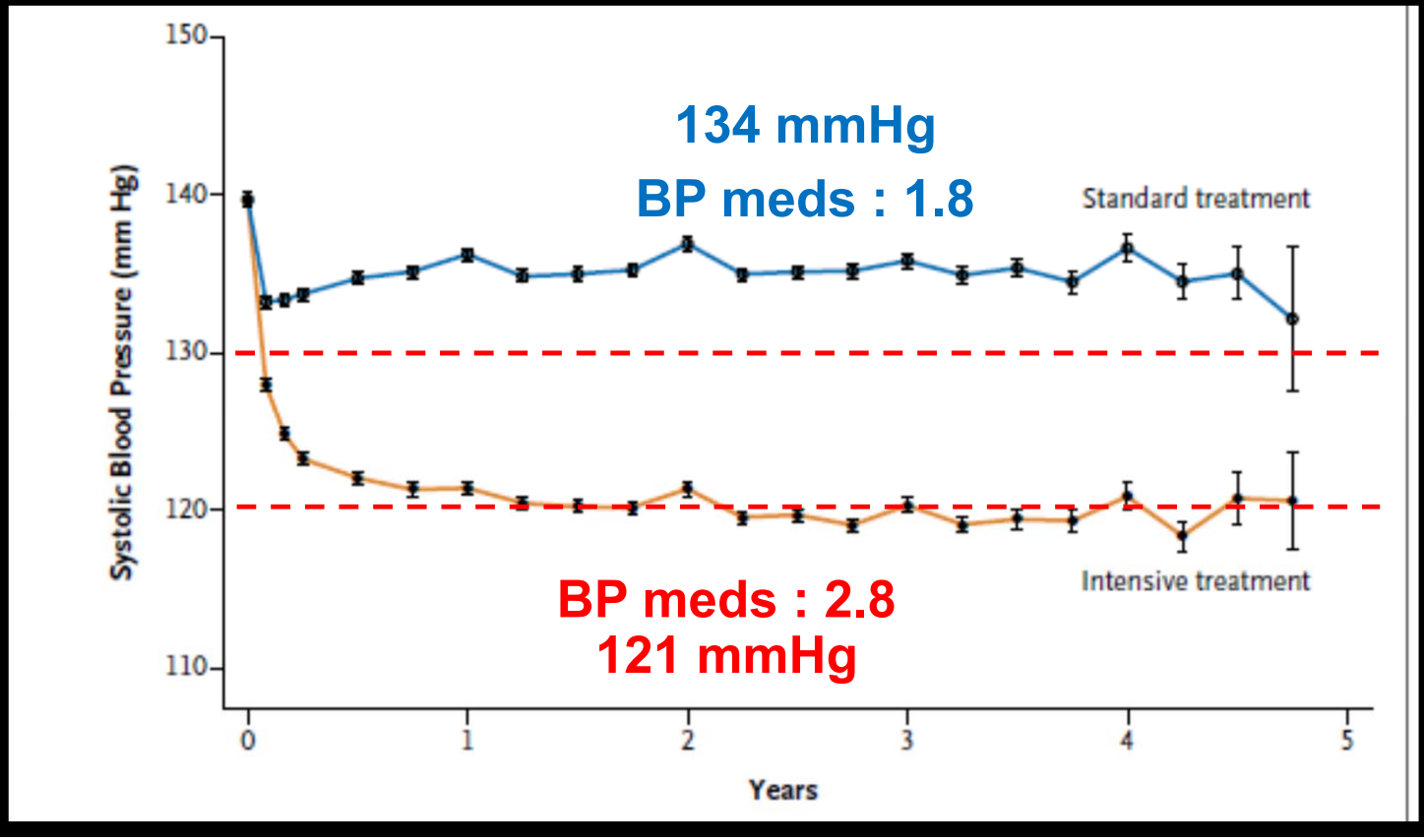
Primary Outcome
CVD - CHF

Secondary Outcome
CKD – Albuminuria
Dementia

The SPRINT Trial
Systolic Blood Pressure Intervention Trial

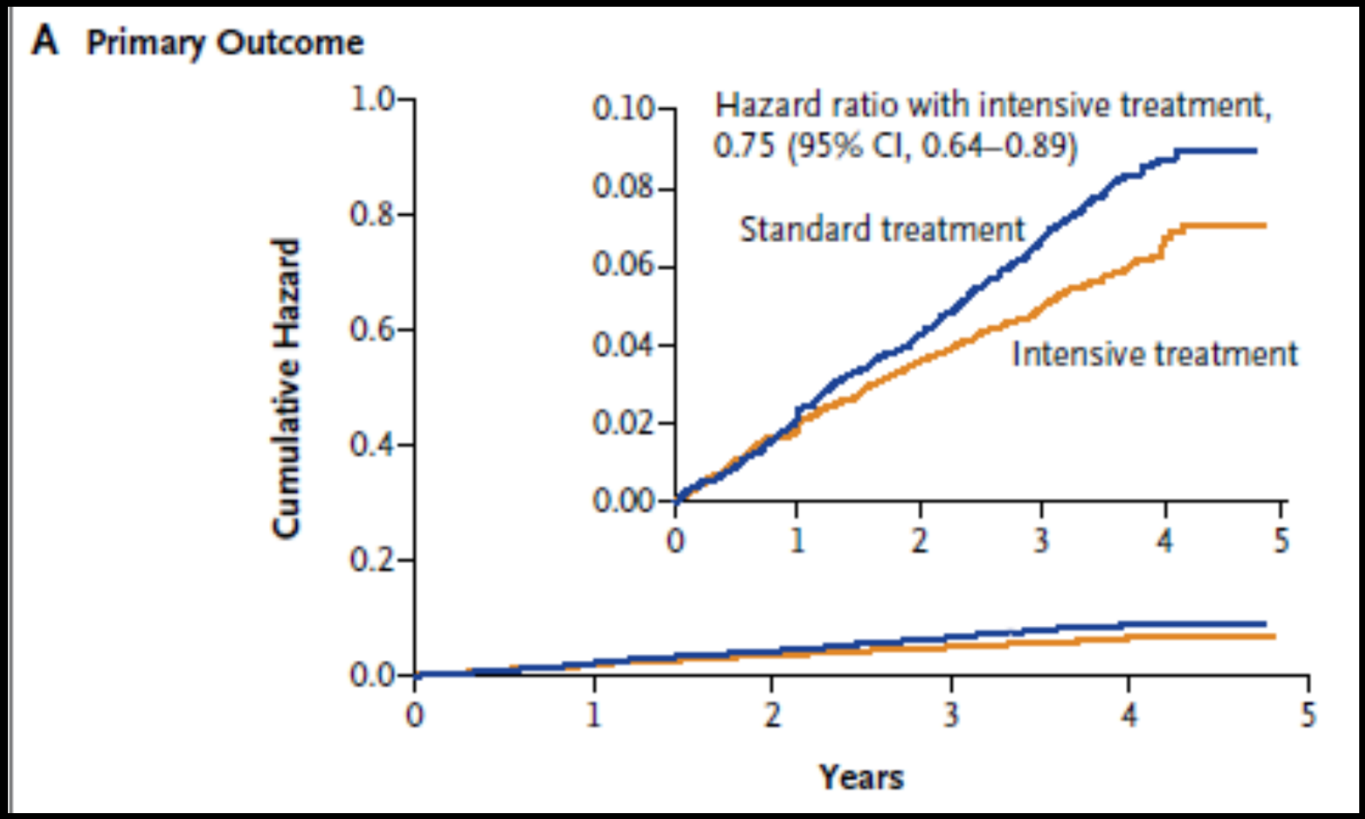
- **Final Study**
  - **102 centers in the U.S.**
  - **9361 patients randomized into 2 groups**
    - **31% Black race**
    - **10% Hispanic race**
    - **30% Stage 3 CKD (baseline GFR 72 cc/min)**
    - **Age 68 yrs**
    - **Age > 75 : 28%**
  - **3.2 years followup**
  - **Blood pressure measured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

The SPRINT Trial
Systolic Blood Pressure Intervention Trial



SPRINT : CVD Outcome

NIH Safety Board stopped the Trial after 3.3 yrs
43% reduction in CVD in Intensive Tx arm



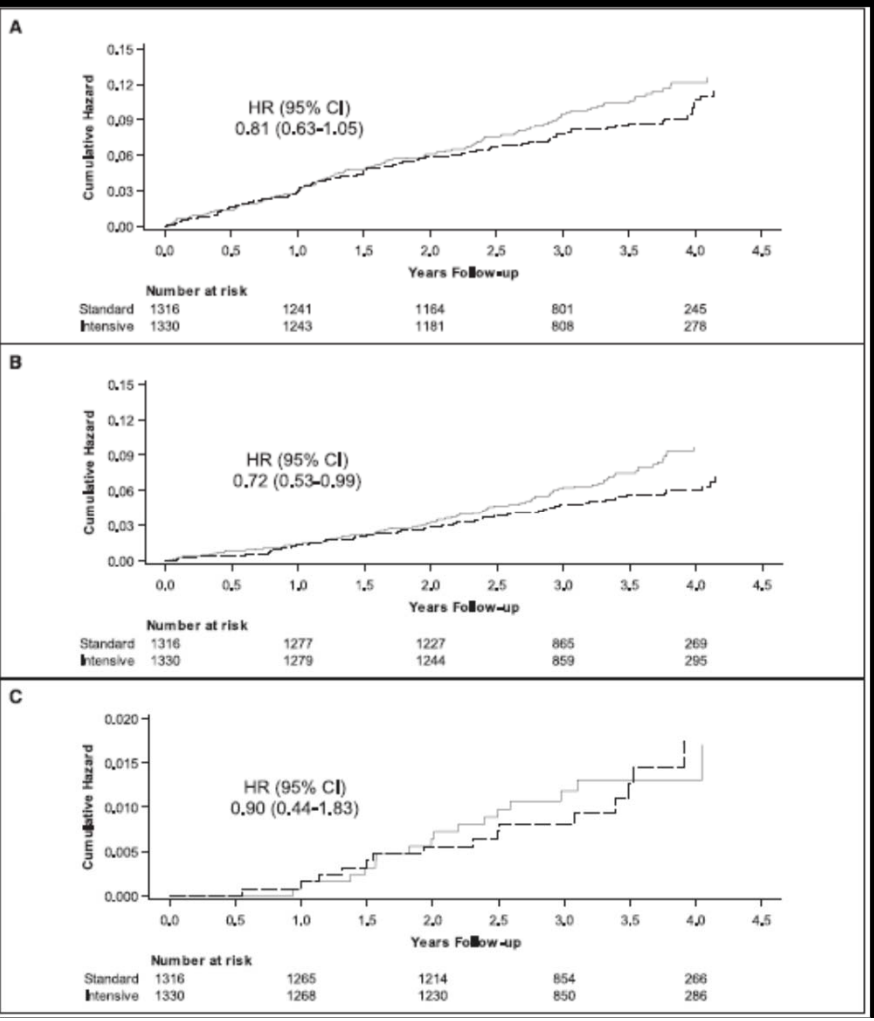
Important Critique of SPRINT BP Target : Method of Measurement

- **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

Cheung A. J Am Soc Nephrol 2017: 28

SPRINT Trial : CKD Group



Intensive BP Control resulted in …..

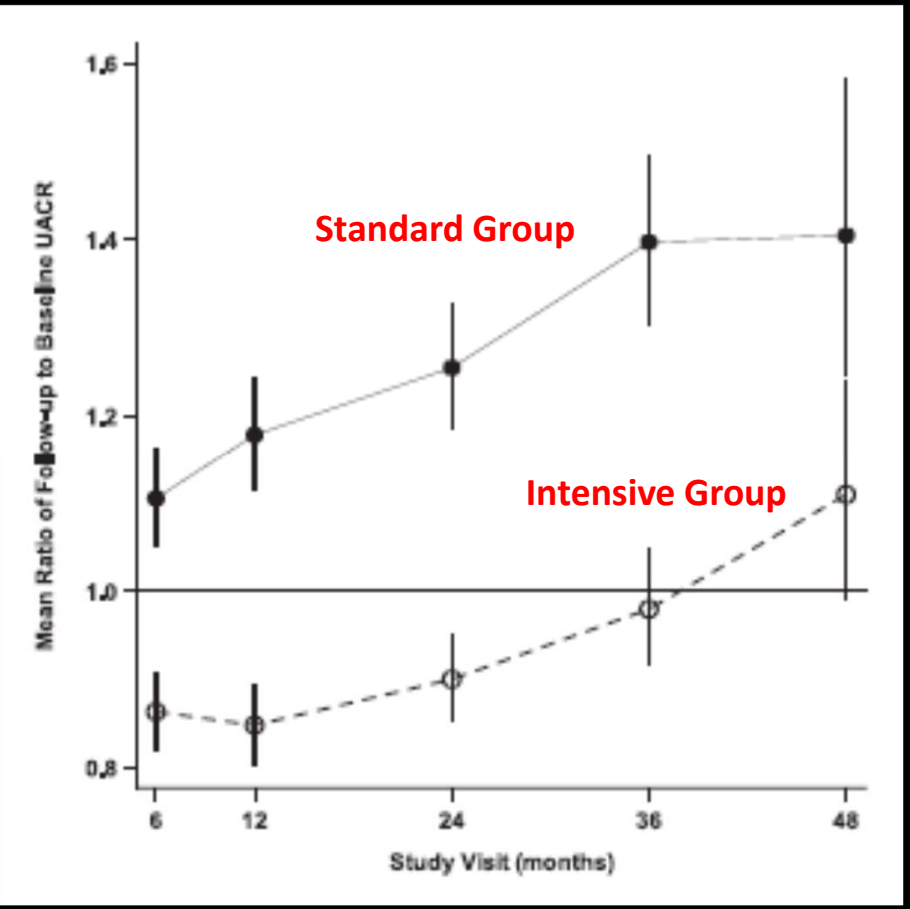
Decrease in CVD by 28%
similar to non CKD population

Decrease in all cause mortality
similar to non CKD population

No change in the rate of ESRD or a 50% decline in GFR

Cheung A. J Am Soc Nephrol 2017: 28

SPRINT Trial : CKD Group



Intensive BP Control resulted in …..

Persistent decrease in microalbuminuria

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

Recommendations for Treatment of Hypertension in Patients With CKD

COR	LOE	Recommendations
I	SBP: B-R[SR] DBP: C-EO	1. Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg (1-6).
IIa	B-R	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).
IIb	C-EO	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.

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

The presence of proteinuria mandates RAAS inhibition therapy

Drug Classes – ARB / ACEI

ACE inhibitors	Benazepril	10–40	1 or 2	• Do not use in combination with ARBs or direct renin inhibitor. • There is an increased risk of hyperkalemia, especially in patients with CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • Do not use if patient has history of angioedema with
	Captopril	12.5–150	2 or 3	
	Enalapril	5–40	1 or 2	
	Fosinopril	10–40	1	
	Lisinopril	10–40	1	
	Moexipril	7.5–30	1 or 2	
	Perindopril	4–16	1	
	Quinapril	10–80	1 or 2	
ARBs	Azilsartan	40–80	1	• Do not use in combination with ACE inhibitors or direct renin inhibitor. • There is an increased risk of hyperkalemia in CKD or in those on K^+ supplements or K^+-sparing drugs. • There is a risk of acute renal failure in patients with severe bilateral renal artery stenosis. • 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. • Avoid in pregnancy.
	Candesartan	8–32	1	
	Eprosartan	600–800	1 or 2	
	Irbesartan	150–300	1	
	Losartan	50–100	1 or 2	
	Olmesartan	20–40	1	
	Telmisartan	20–80	1	
	Valsartan	80–320	1	

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?**

Choice	Target BP	Drug of Choice
A	<140/90	Loop Diuretic
B	<140/90	ACEI
C	<130/80	ACEI
D	<130/80	Thiazide
E	<120/80	ACEI
F	<120/80	Thiazide


Prevention of
Contrast Nephropathy
New Distribution Policy
for Kidney Transplants
Prevention of
Diabetic Nephropathy
Slowing the Progression of
Polycystic Kidney Disease
Thank You !
Genetic Risk
of CKD
Target Blood
Pressure n CKD