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Delaying Progression

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Disclosure

- **Paul Drawz, MD, MHS, MS** has no financial relationships with commercial interest(s).

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Learning Objective

- Identify strategies for delaying the progression of CKD in at-risk patients.

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Session Outline

- Recognize evidence-based management strategies that will help delay CKD progression in at-risk patients and improve outcomes.
  - ACEI/ARBs
  - DM control
- Recognize that BP lowering does not slow progression of CKD
- Recognize unconventional treatment strategies to slow progression of CKD

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Self Assessment Questions

- 1. Target blood pressure in non-dialysis diabetic CKD with a albumin-to-creatinine ratio of <30mg/g should be:
  - <120/80mmHg
  - <140/90mmHg
  - <150/90mmHg
  - <130/80mmHg

- 2. A 55 year-old Caucasian-American man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m^2 and an ACR of 38 mg/g. Which of the following should be avoided?
  - ACE and ARB in combination
  - Daily low-dose aspirin
  - NSAIDs
  - Statins
  - A and C

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Steps to CKD Patient Care

1. Does the patient have CKD?
2. Assess GFR, albuminuria
3. Determine etiology
4. Assess for evidence of progression
5. Assess for associated complications
6. Patient education
7. Assess life expectancy and patient wishes for dialysis/transplantation

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Delaying Progression of CKD

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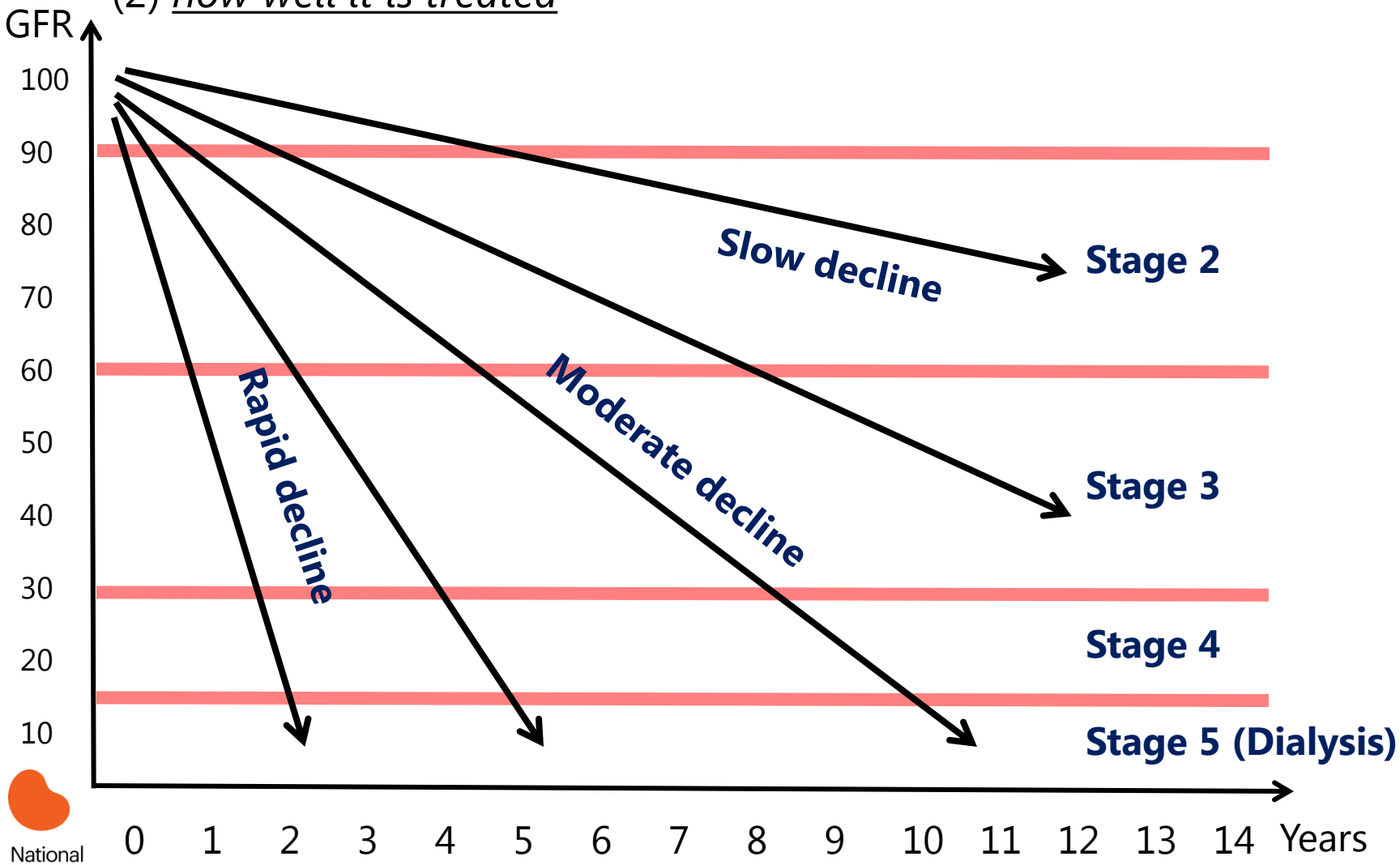
CKD- Progression of Kidney Failure Concept

Variable depending on several factors including (1) type of disease and (2) *how well it is treated*



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ACEI/ARBs to Slow CKD Progression

Study	Baseline Proteinuria	ACEI/ARB	Reduction in Renal Events
Diabetic			
RENAAL	UACR ~1250mg/g	losartan	21 (5 to 34)[A]
IDNT	Uprot 2.9g/24hr	irbesartan	33 (13 to 48)[D]
Lewis, et al.	Uprot 2.7g/24hr	captopril	48 (16 to 69)[D]
HOPE	32% microalbuminuria	ramipril	24 (3 to 40)[B]
Non-diabetic			
REIN 2	Uprot 5.3g/24hr	ramipril	48 (9 to 70)[A]
AIPRI	Uprot 1.8g/24hr	benazepril	53 (27 to 70)[A]
REIN 1	Uprot 1.7g/24hr	ramipril	63 (18 to 84)[C]
AASK	Uprot/Cr 0.5g/24hr	ramipril	38 (10 to 58)[E]
Hou, et al.	Uprot 1.7g/24hr	Benazepril	40 (P=0.02)[C]

Outcomes: A: doubling of serum creatinine or ESRD; B: overt nephropathy defined by 24 h urine albumin ≥300mg, 24 h urine protein ≥500mg, or urine albumin/creatinine ratio >36mg/mmol; C: ESRD; D: doubling of serum creatinine; E: 50% decline in GFR or ESRD

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ACEI/ARBs to Slow CKD Progression

- With proteinuria
  - ACEi or ARB +/- diuretic
- No proteinuria
  - ACEi or ARB preferred

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Fujisaki K, et al. Impact of combined losartan/hydrochlorothiazide on proteinuria in patients with CKD and hypertension. *Hypertens Res*. 2014;37:993-998.

Delaying CKD Progression: ACEi/ARB

- Check labs after initiation
  - If less than 25% SCr increase, continue and monitor
  - If more than 25% SCr increase, stop ACEi and evaluate for RAS
- Continue until contraindication arises, no absolute eGFR cutoff
- Better proteinuria suppression with low Na diet (<2 g of sodium; or <5 g sodium chloride per day) and diuretics
- Avoid volume depletion and NSAIDs

QUESTION- TRUE OR FALSE-

ACEI-ARBs have been shown to slow progression of CKD in patients with proteinuria?

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Managing Hyperglycemia

- Hyperglycemia is a fundamental cause of vascular complications, including CKD
- Poor glycemic control has been associated with albuminuria in type 2 diabetes.
- Risk of hypoglycemia increases as kidney function becomes impaired.
- Declining kidney function may necessitate changes to diabetes medications and renally-cleared drugs.
- Target HbA1c ~7.0%
  - Can be extended above 7.0% with comorbidities or limited life expectancy, and risk of hypoglycemia.

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NKF KDOQI. Diabetes and CKD: 2012 Update. *Am J Kidney Dis*. 2012 60:850-856.

Role of Intensive Glucose Control in Development of Renal End Points in Type 2 Diabetes Mellitus

Systematic Review and Meta-analysis

Steven G. Coca, DO, MS; Faramarz Ismail-Beigi, MD, PhD; Nowreen Haq, MD, MPH; Harlan M. Krumholz, MD, SM; Chirag R. Parikh, MD, PhD

Arch Intern Med. 2012;172(10):761-769

- 7 studies
- 28,065 participants
- Conventional control versus intensive control
  - A1c 7.3 to 9.1 versus 6.4 to 7.4

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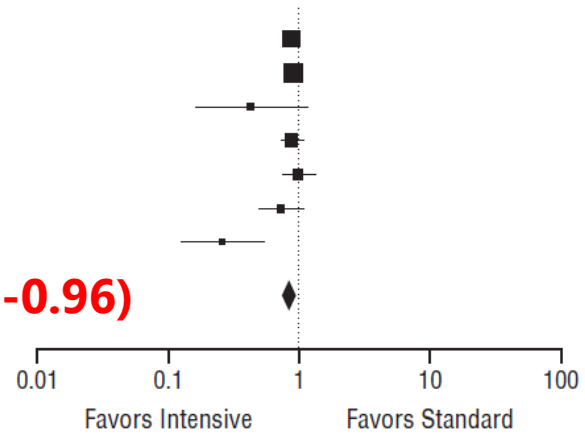
A Microalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	720	3250	828	3273	27.3	0.88 (0.80-0.96)
ADVANCE[12]	1318	5571	1434	5569	29.3	0.92 (0.86-0.98)
Kumamoto[4,15]	5	52	11	50	1.3	0.44 (0.16-1.17)
UKPDS 33[16]	368	2277	172	938	19.6	0.88 (0.75-1.04)
UKPDS 34[17]	79	342	95	411	12.2	1.00 (0.77-1.30)
VADT[11]	43	442	61	463	7.6	0.74 (0.51-1.07)
VA Feasibility Trial[5]	7	42	30	46	2.5	0.26 (0.13-0.52)
Total (95% CI)		**11 976**		**10 750**	**100.0**	**0.86 (0.76-0.96)**
Total events	**2540**		**2631**			

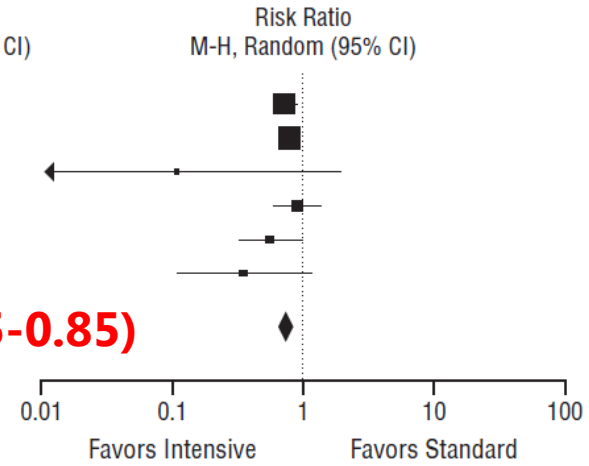
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_6 = 16.71$; $P = .01$; $I^2 = 64\%$
Test for overall effect: $z = 2.60$; $P = .009$



B Macroalbuminuria

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	195	4397	272	4424	39.3	0.72 (0.60-0.86)
ADVANCE[12]	230	5571	292	5569	42.5	0.79 (0.67-0.93)
Kumamoto[4,15]	0	52	4	50	0.2	0.11 (0.01-1.94)
UKPDS 33[16]	72	2277	33	938	10.4	0.90 (0.60-1.35)
VADT[11]	20	693	36	703	6.2	0.56 (0.33-0.96)
VA Feasibility Trial[5]	3	24	10	28	1.4	0.35 (0.11-1.13)
Total (95% CI)		**13 014**		**11 712**	**100.0**	**0.74 (0.65-0.85)**
Total events	**520**		**647**			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_5 = 5.73$; $P = .33$; $I^2 = 13\%$
Test for overall effect: $z = 4.24$; $P = .001$



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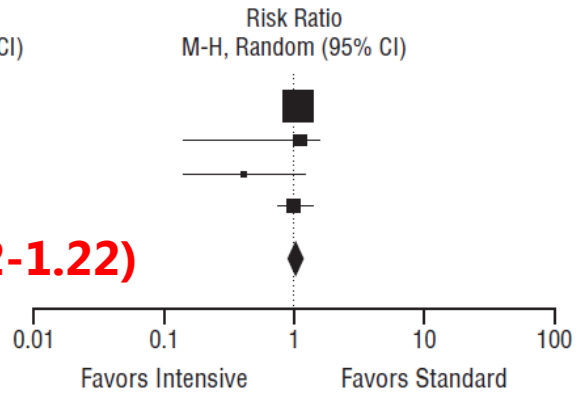
A Doubling of Serum Creatinine

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	392	5041	357	5035	62.5	1.10 (0.96-1.26)
ADVANCE[12]	67	5571	61	5569	15.6	1.10 (0.78-1.55)
UKPDS 33[16]	7	2150	7	895	1.9	0.42 (0.15-1.18)
VADT[11]	78	882	78	884	20.0	1.00 (0.74-1.35)
Total (95% CI)		**13 644**		**12 383**	**100.0**	**1.06 (0.92-1.22)**
Total events	**544**		**503**			

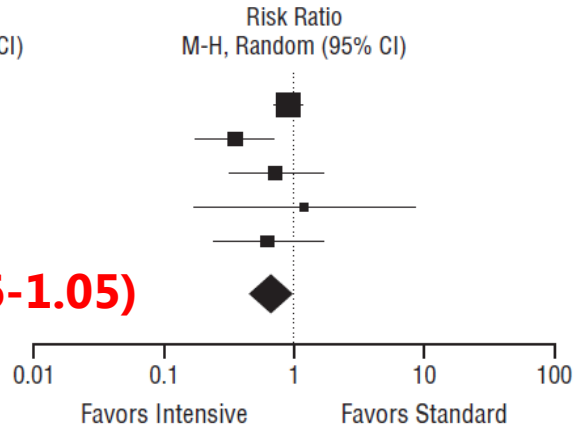
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 3.46$; $P = .33$; $I^2 = 13\%$
Test for overall effect: $Z = 0.76$; $P = .44$



B ESRD

Study or Subgroup	Intensive Therapy Events	Intensive Therapy Total	Standard Therapy Events	Standard Therapy Total	Weight, %	Risk Ratio M-H, Random (95% CI)
ACCORD[8,14]	138	5119	151	5115	43.2	0.91 (0.73-1.15)
ADVANCE[12]	11	5571	31	5569	21.2	0.35 (0.18-0.70)
UKPDS 33[16]	16	2729	9	1138	17.3	0.74 (0.33-1.67)
UKPDS 34[17]	2	342	2	411	4.2	1.20 (0.17-8.49)
VADT[11]	7	882	11	884	14.1	0.64 (0.25-1.64)
Total (95% CI)		**14 643**		**13 117**	**100.0**	**0.69 (0.46-1.05)**
Total events	**174**		**204**			

Heterogeneity: $\tau^2 = 0.09$; $\chi^2_4 = 7.08$; $P = .13$; $I^2 = 43\%$
Test for overall effect: $Z = 1.72$; $P = .09$



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Intensive Diabetes Therapy and Glomerular Filtration Rate in Type 1 Diabetes

The DCCT/EDIC Research Group*

Table 2. Incidence of an Impaired Glomerular Filtration Rate (GFR) and Secondary Outcomes.*

Outcome	Intensive Diabetes Therapy		Conventional Diabetes Therapy		Risk Reduction with Intensive Therapy†	P Value
	No. of Events	Incidence Rate/ 1000 Person-Yr	No. of Events	Incidence Rate/ 1000 Person-Yr	% (95% CI)	
Impaired GFR‡	24	1.6	46	3.0	50 (18 to 69)	0.006
Onset during DCCT	1		3			
Onset during EDIC	23		43			
Estimated GFR <45 ml/min/ 1.73 m^2	24	1.6	39	2.5	40 (1 to 64)	0.045
Estimated GFR <30 ml/min/ 1.73 m^2§	13	0.8	23	1.5	44 (–9 to 72)	0.09
End-stage renal disease§	8	0.5	16	1.1	51 (–14 to 79)	0.10
Combined outcome of impaired GFR or death¶	53	3.4	80	5.2	37 (10 to 55)	0.01

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Low BP targets and renal outcomes

- Toto et al.
- Lewis – collaborative study group
- REIN-2
- MDRD
- AASK

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Toto et al. – 1995

- CKD patients (GFR < 70), normal urine sediment, Uprot < 2g/d
- Randomized
  - Strict (DBP 65 to 80, n = 42)
  - Conventional (DBP 85 to 95, n = 35)
- Follow up ~40mo, mean DBP 81.1 and 87.1
- GFR decline
  - -0.31 vs -0.050 (P > 0.25)
- Secondary outcome – 50% decline GFR, doubling Cr, ESRD or death
  - 12 vs 7 (P > 0.25)

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Toto RD, KI, 1995, pg 851.

Type 1 DM with nephropathy

- 129 subjects – Cr <4
- Randomized
  - Low MAP of 92 to 100 mmHg
  - High MAP of 100 to 107 mmHg
- Follow up >2yrs, avg MAP difference 6 mmHg
- All treated with ramipril
- Primary outcome – absolute change in iGFR
  - Low MAP – 62 to 54
  - High MAP – 64 to 58
- Secondary outcome – 24hr Uprot lower in low MAP group

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Lewis JB, AJKD, 1999, pg 809.

REIN-2

- 335 non-DM patients receiving ramipril
  - 1-3gm/24hr with CrCl <45
  - ≥ 3gm/24hr with CrCl <70
- Randomized
  - DBP <90
  - Intensified BP control (< 130/80)
- Median f/u 19mo; difference in BP: 4.1/2.8 mmHg
- ESRD
  - 20% in conventional arm
  - 23% in intensified arm (P = 0.99)
- No difference in rate of GFR decline or Uprot

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Ruggenenti P, Lancet, 2005, pg 939.

MDRD

- Usual BP – MAP 107 mmHg (140/90)
- Low BP – MAP 92 mmHg (125/75)
- Study 1 – 585 subjects GFR 25 to 55
  - Mean decline in GFR (ml/min/3yrs)
    - 12.3 in usual vs 10.8 in low BP target (P = 0.18)
- Study 2 – 255 subjects GFR 13 to 24
  - Mean decline in GFR (ml/min/yr)
    - 4.2 in usual vs 3.7 in low BP target (P = 0.28)

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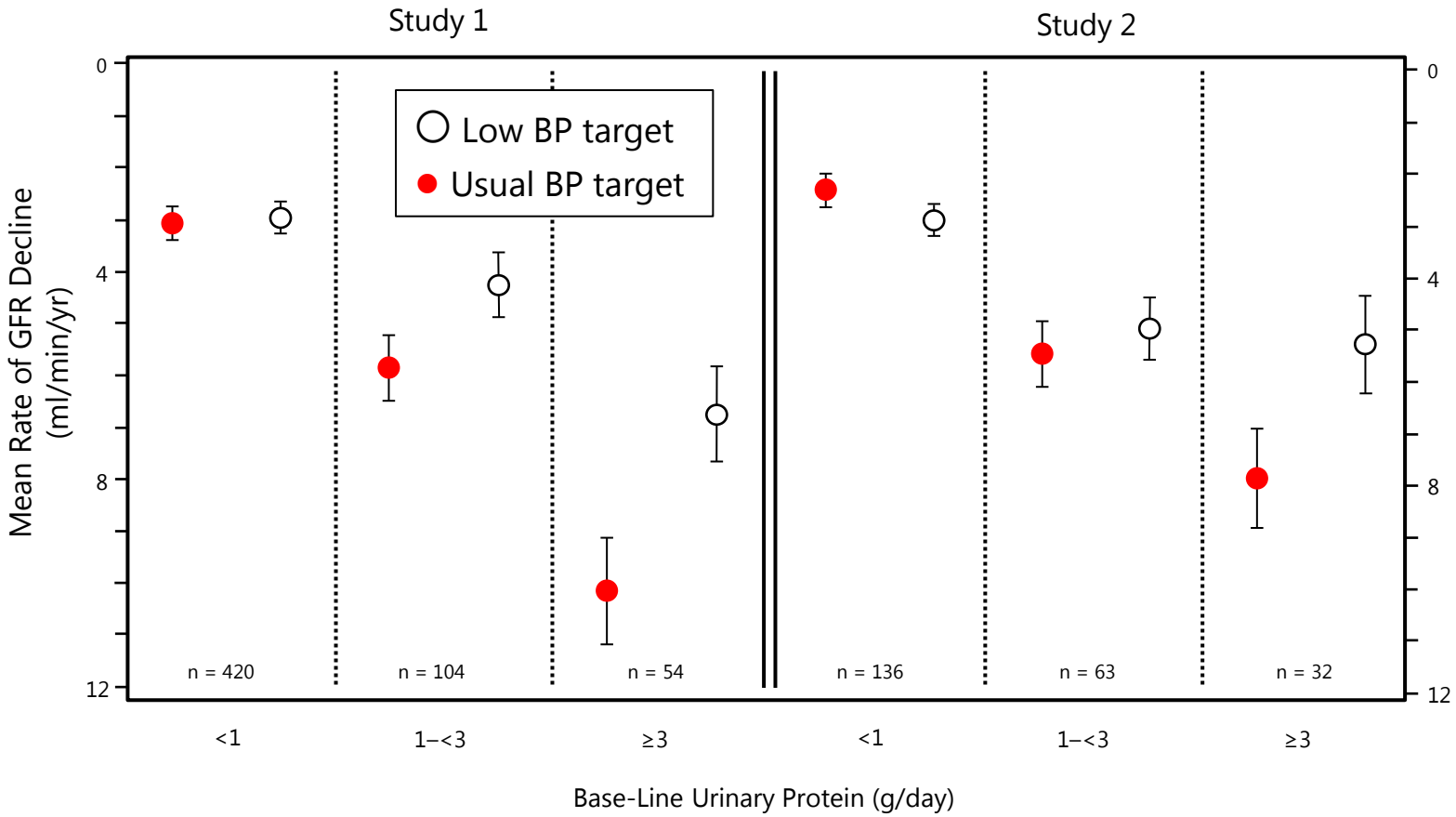
Klahr S, NEJM, 1994, pg 877.

Effect of low BP target depends on baseline level of proteinuria



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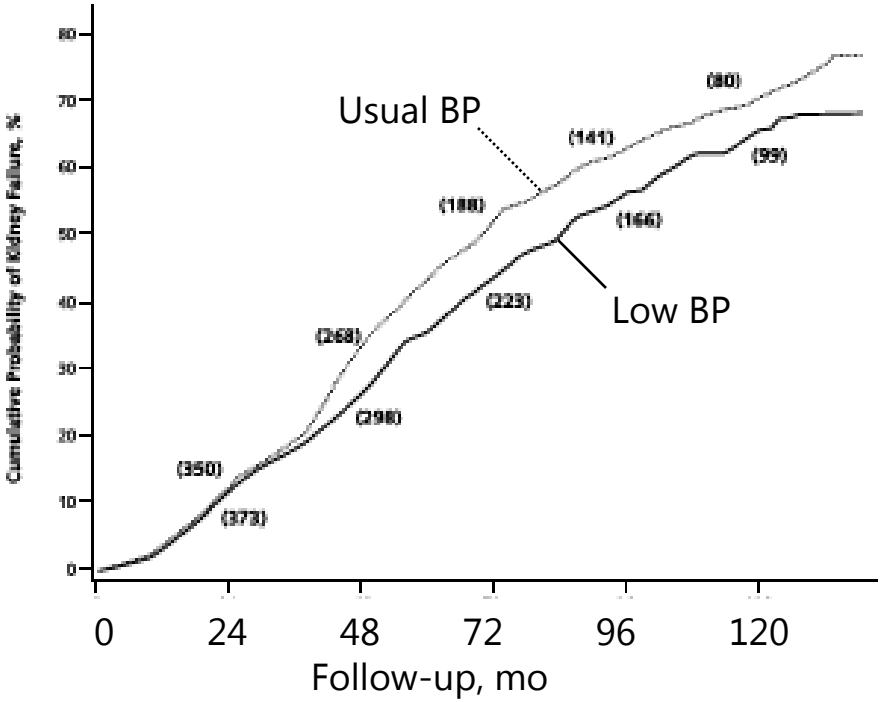
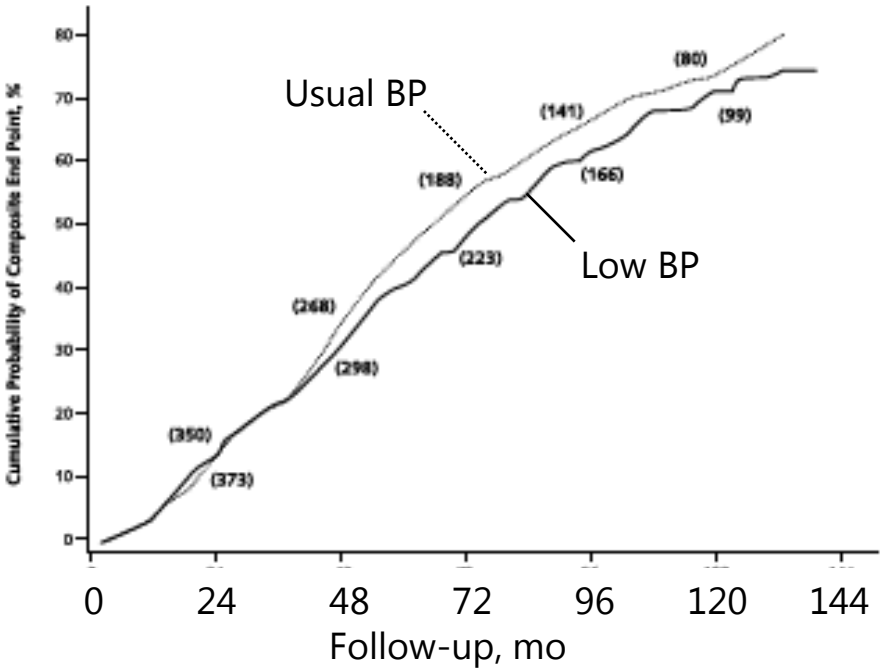
Klahr S et al. N Engl J Med 1994;330:877-884.

MDRD – long term outcomes

Kidney failure



Kidney failure or all-cause mortality



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Sarnak MJ, Ann Int Med, 2005, pg 342.

AASK

- African American, non-DM, GFR 20-65
- Randomized
  - Usual MAP (102 to 107 mmHg)
  - Low MAP (92 mmHg)
- Achieved BP 141/85 vs 128/78
- GFR decline (ml/min/1.73m^2/yr)
  - Usual: 1.95
  - Low: 2.21 (P = 0.24)
- No difference in 50% decline GFR, death, ESRD or composite

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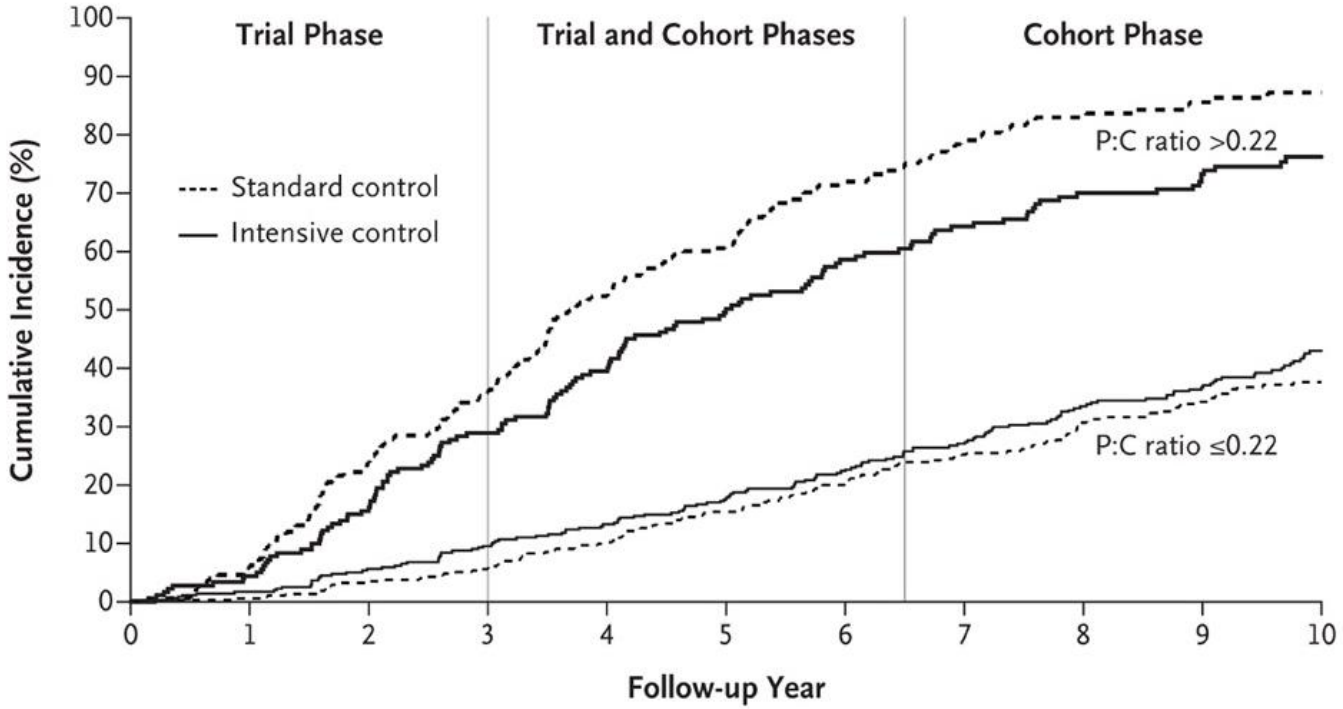
Wright JT Jr, JAMA, 2002, pg 2421.

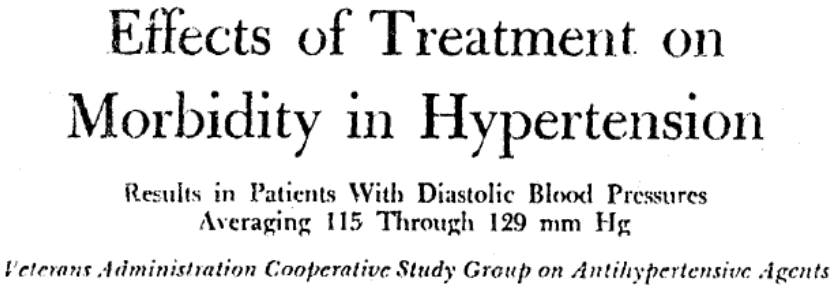
AASK – Doubling of Cr, ESRD or Death According to Baseline Proteinuria Status



P:C Ratio >0.22											
Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25
P:C Ratio ≤0.22											
Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128

The NEW ENGLAND JOURNAL of MEDICINE

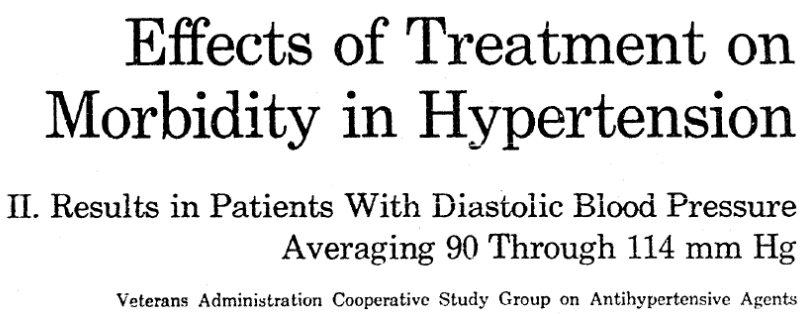
Appel LJ, NEJM, 2010, pg 918.



Effects of Treatment on Morbidity in Hypertension

Results in Patients With Diastolic Blood Pressures Averaging 115 Through 129 mm Hg

Veterans Administration Cooperative Study Group on Antihypertensive Agents



Effects of Treatment on Morbidity in Hypertension

II. Results in Patients With Diastolic Blood Pressure Averaging 90 Through 114 mm Hg

Veterans Administration Cooperative Study Group on Antihypertensive Agents

- Renal Outcomes

	Placebo	Active treatment	*P* value
DBP 115 to 129 mmHg	2/70	0/73	0.146
DBP 90 to 114 mmHg	3/191	0/186	0.089

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UKPDS 38

- 1148 subjects – type 2 DM, median fu 8.4yrs
- At 9 years
  - No difference in Cr or proportion of patients with a doubling of Cr

Outcome	Tight control	Less tight control	RR
Ualb > 50mg/l	28.8%	33.1%	0.87 (0.60 to 1.26)
Ualb > 300mg/l	7.0%	6.6%	1.06 (0.42 to 2.67)

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UK Prospective Diabetes Study Group, BMJ, 1998, pg 703.

Systolic Hypertension in the Elderly Study (SHEP)

- 4736 men and women
- Randomized
  - Active tx – target SBP < 160 mmHg (or decrease 20 mmHg if baseline < 180 mmHg)
  - Placebo

Outcome	Group	Active	Placebo
Cr ≥ 2mg/dl	DM	4.5%	4.1%
	Non-DM	2.6%	2.1%
≥ 1+ UProt	DM	32.3%	34.6%
	Non-DM	17.2%	19.8%

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Curb JD et al, JAMA, 1996, pg 1886.

The NEW ENGLAND JOURNAL of MEDICINE N Engl J Med 2010;362:1575-85.

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

- 4,733 participants with type 2 DM
- SBP target <120mmHg vs. <140mmHg
- Achieved SBP 119mmHg vs. 133.5mmHg

Outcome	Intense	Standard	HR	P value
Primary*	1.87 %/yr	2.09 %/yr	0.88 (0.73-1.06)	0.20
Stroke	0.32 %/yr	0.53 %/yr	0.59 (0.39-0.89)	0.01
Death	1.28 %/yr	1.19 %/yr	1.07 (0.85-1.35)	0.55
eGFR <30	**4.2 %**	**2.2 %**		**<0.001**
Macroalbuminuria	**6.6 %**	**8.7 %**		**0.009**

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* Nonfatal MI, nonfatal stroke, or death from CV causes.

ACCORD, NEJM, 2010, p1575.

BP targets in CKD – **CV risk reduction**

- Target blood pressure in non-dialysis CKD:[1]
  - ACR <30 mg/g: ≤140/90 mm Hg
  - ACR 30-300 mg/g: ≤140/90 mm Hg*
  - ACR >300 mg/g: ≤140/90 mm Hg*
  - Individualize targets and agents according to age, coexistent CVD, and other comorbidities
- Avoid ACEi and ARB in combination[3,4]
  - Risk of adverse events (impaired kidney function, hyperkalemia)

QUESTION – True or False –

Intense BP lowering slows progression of CKD?

*Reasonable to select a goal of 140/90 mm Hg, especially for moderate albuminuria (ACR 30-300 mg/g.)[2]

1) 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults - Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8), JAMA. 2014;311(5):507-520
2) Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. *Kidney Int Suppl.* (2012);2:341-342.
3) KDOQI Commentary on KDIGO Blood Pressure Guidelines. *Am J Kidney Dis*. 2013;62:201-213.
4) Kunz R, et al. *Ann Intern Med*. 2008;148:30-48.
5) Mann J, et al. ONTARGET study. *Lancet*. 2008;372:547-553.

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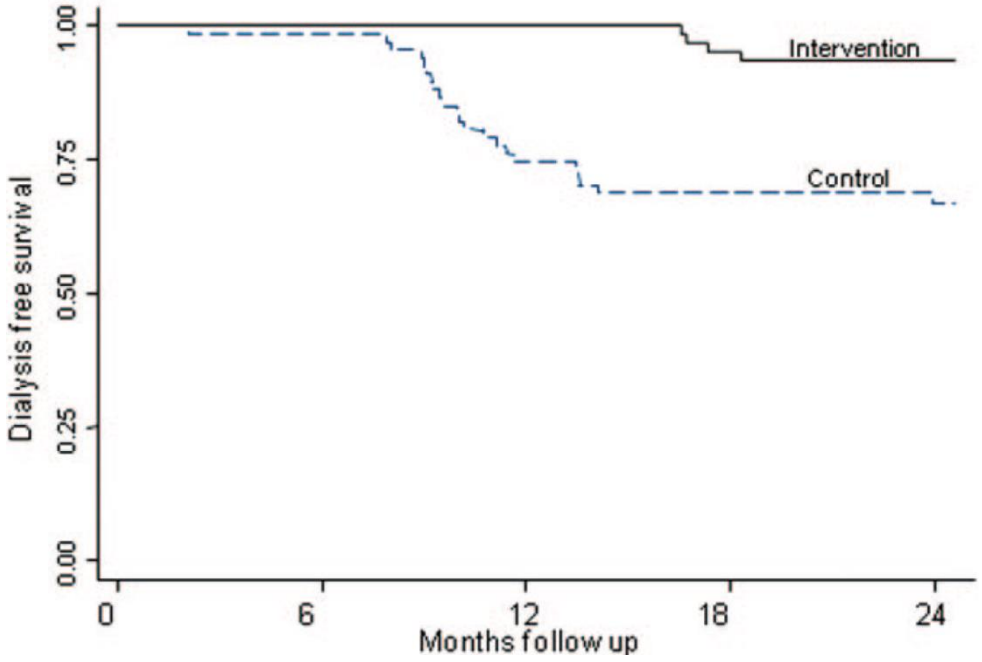
Metabolic Acidosis

- Often becomes apparent at GFR < 25-30 ml/min
  - More severe with higher protein intake
- May contribute to bone disease, protein catabolism, and progression of CKD
- Correction of metabolic acidosis may slow CKD progression and improve patients functional status[1,2]

Adults with CKD (eGFR 15-30 ml/min/1.73m^2) with bicarbonate 16-20 mmol/L; treated with sodium bicarbonate for 2 years to normalize serum bicarbonate concentration[2]



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1) Mahajan, et al. *Kidney Int*. 2010;78:303-309.
2) de Brito-Ashurst I, et al. *J Am Soc Nephrol*. 2009;20:2075-2084.

Metabolic Acidosis

- Maintain serum bicarbonate ≥ 22 mmol/L
  - Start with 0.5-1 mEq/kg per day
  - Sodium bicarbonate tablets
    - 325mg, 625 mg tablets; 1 g = 12 mEq
  - Sodium citrate solution
    - 1 mEq/ml
    - Avoid if on aluminum phosphate binders
  - Baking soda
    - 54 mmol/level tsp

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Allopurinol?

- Randomized controlled trial
- 54 patients with either Uprot > 0.5g/24hr or Cr >1.35mg/dL (but <4.5)
  - Uric acid >7.6mg/dL
- Allopurinol 100mg/d versus placebo
  - Cr 1.64 to 1.99 versus 1.86 to 2.89 (P=0.08)
  - Deterioration in renal function: 16% versus 46% (P=0.02)

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Siu et al, AJKD, 2006, p51.

Allopurinol RCT #2

- 113 patients – eGFR <60 ml/min/1.73m2
- Allopurinol 100mg/day versus usual therapy
- After 24 months, treatment with allopurinol:
  - Lowered uric acid: 6.0 vs 7.5 (P<0.001)
  - Stabilized eGFR: 42.2 vs. 35.9 (P<0.001)
- No effect on albuminuria
- No effect on blood pressure
- HR for new CV events: 0.29 (0.09 to 0.86)

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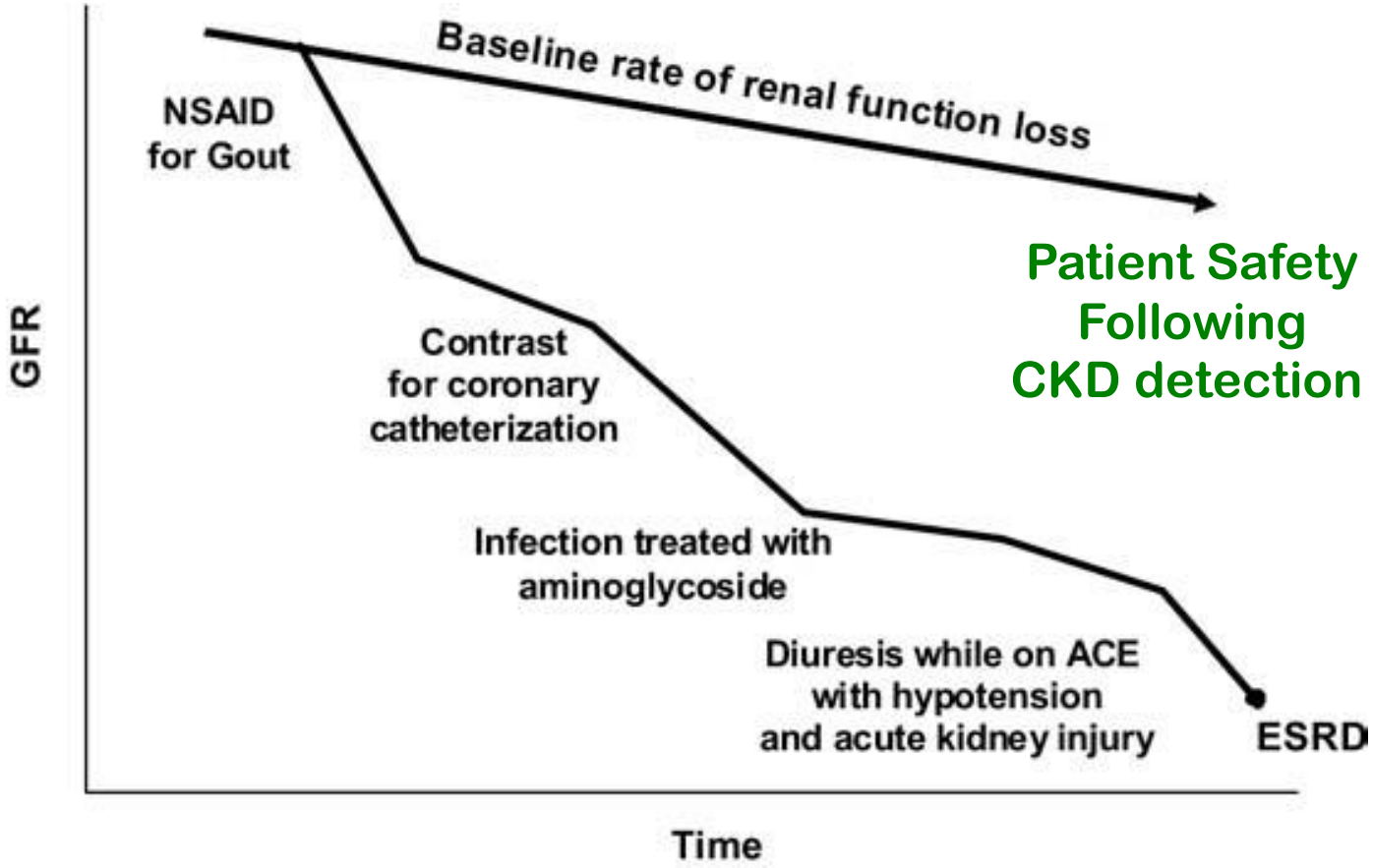
Goicoechea et al, cJASN, 2010, p1388.

Impact of primary care CKD detection with a patient safety approach



Improved diagnosis creates opportunity for strategic preservation of kidney function

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Fink et al. *Am J Kidney Dis*. 2009,53:681-668

Discuss Take Home Points

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Self Assessment Questions

- 1. Target blood pressure in non-dialysis diabetic CKD with a albumin-to-creatinine ratio of <30mg/g should be:
  - A. 120/80mmHg
  - B. *140/90mmHg*
  - C. 150/90mmHg
  - D. 130/80mmHg

  B Rationale: Comparison of Guideline Recommendations for CKD Blood Pressure Targets among reliable sources, including JAMA2014 and KDIGO2012, contain similar recommendations as less than 140/90 mm Hg in CKD

- 2. A 55 year-old Caucasian-American man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m^2 and an ACR of 38 mg/g. Which of the following should be avoided?
  - A. ACE and ARB in combination
  - B. Daily low-dose aspirin
  - C. NSAIDs
  - D. Statins
  - E. *A and C*

  E. Rationale: ACE and ARBs used in combination have been shown to increase adverse events, particularly impaired kidney function and hyperkalemia. NSAIDs have been shown to cause kidney damage and increase CKD progression. Statins are indicated based on KDIGO guidelines and a daily low-dose aspirin is not contraindicated in CKD.

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Questions and Answers

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Additional Resources

- KDOQI Clinical Practice Guideline For Diabetes: Update 2012

https://www.kidney.org/professionals/guidelines/guidelines_commentaries

- Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)

http://www2.kidney.org/professionals/KDOQI/guidelines_bp/

- National Kidney Foundation Tool: *Self-Management, Diabetes and CKD*

https://www.kidney.org/sites/default/files/12_10_2095_SelfManagement.pdf

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