Hypertension in CKD-What Should be the BP Targets and With Which Drugs

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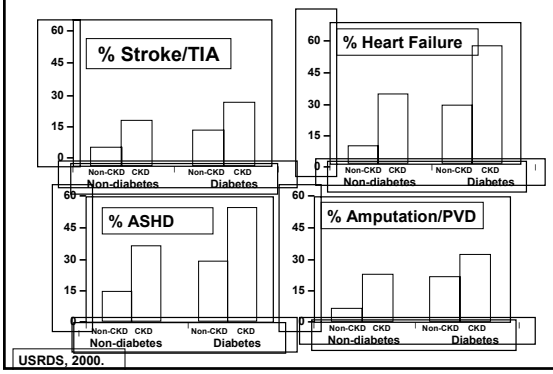
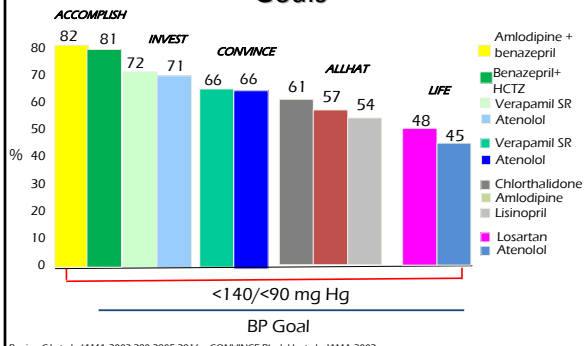
Cardiovascular Comorbidities,

5% Medicare Sample, by Diabetes and CKD Status 1999-2000



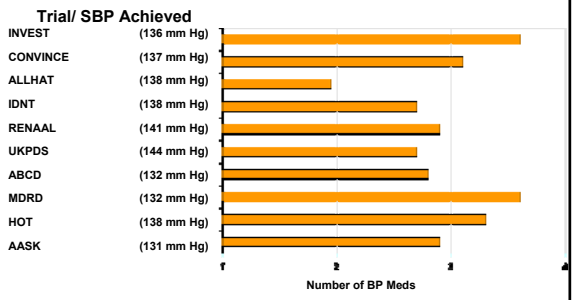
USRDS, 2000.

Percent of Patients Reaching JNC-7 BP Goals



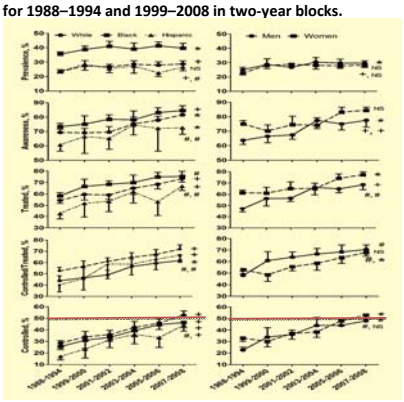
Pepine CJ et al. *JAMA.* 2003;290:2805-2816. CONVINCE Black H et.al. JAMA 2002
JAMA. 2002;288:2981-97. Dahlöf B et al. *Lancet.* 2002;359:995-1003. Jamerson K et.al. Blood Pressure 2007:16:78-86

Average Number of Antihypertensive Agents Needed per Patient to Achieve Target BP Goals



Updated from Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

Prevalence, Awareness, Treatment, controlled/treated, and control are provided for 1988–1994 and 1999–2008 in two-year blocks.



Egan B et.al. JAMA 2010;303(20):2043-2050

Current Guideline Recommendations for Managing Hypertension

JNC 7 Guideline Recommendations for Managing Hypertension

- Control BP to reduce cardiovascular and renal morbidity and mortality
- BP goal
  - **< 140/90 mm Hg**
  - **< 130/80 mm Hg for patients with diabetes or CKD**
- Therapy
  - **SBP 140-159 or DBP 90-99 mm Hg**
    - **Thiazide-type diuretic for most**
    - **May consider ACEI, ARB, BB, CCB, or combination**
  - **SBP ≥ 160 or DBP ≥ 100 mm Hg**
    - **Two-drug combination for most**
    - **Usually thiazide-type diuretic and ACEI or ARB or BB or CCB**
  - **Specific recommendations for compelling indications (heart failure, post-MI, high CAD risk, diabetes, CKD, recurrent stroke prevention)**

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JNC 7 Express. http://www.nhlbi.nih.gov/guidelines/hypertension/expresss.pdf

What is the Goal BP and Initial Therapy in Kidney Disease or Diabetes to Reduce CV Risk?

Group	Goal BP (mmHg)	Initial Therapy
ADA (2009)	<130/80	ACE Inhibitor/ARB*
KDOQI (NKF) (2007)	<130/80	ACE Inhibitor/ARB
ESH (2007)	<130/80	ACE Inhibitor/ARB*
KDOQI (NKF) (2004)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2002)	<130/80	ACE Inhibitor/ARB*
Natl. Kidney Foundation (2000)	<130/80	ACE Inhibitor*
British HTN Soc. (1999)	<140/80	ACE Inhibitor
WHO/ISH (1999)	<130/85	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

*** Indicates use with diuretic**

Questions Regarding Current Guidelines

- Should we be starting antihypertensive therapy with combination agents
- Can we truly support <130/80 mmHg
- Can we support albuminuria reduction as an indicator of slowed kidney disease progression

Recent Studies That May Impact Guideline Recommendations

Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension

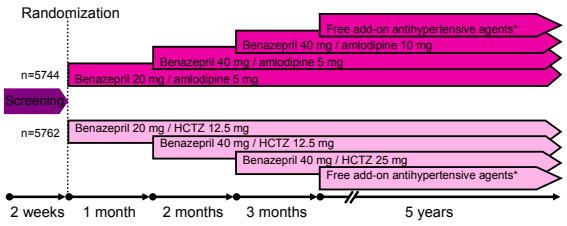
Kenneth Jamerson[1], George L. Bakris[2], Bjorn Dahlof[3], Bertram Pitt1, Eric J. Velazquez[4], Michael A. Weber[5]
for the ACCOMPLISH Investigators

1. University of Michigan Health System, Ann Arbor, MI; 2. University of Chicago-Pritzker School of Medicine, Chicago, IL; 3. Sahlgrenska University Hospital, Gothenburg, Sweden; 4. Duke University School of Medicine, Durham, NC; 5. SUNY Downstate Medical College, Brooklyn, NY

Primary and secondary endpoints

- Primary endpoint:
  - Composite of CV mortality and morbidity
    - (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, coronary revascularization procedure [PCI or CABG], or resuscitated sudden death)
- Secondary endpoints:
  - Composite of CV morbidity
  - Composite of CV mortality, non-fatal stroke, or non-fatal MI
  - Prespecified-CKD progression

ACCOMPLISH study design



Up-titration performed for patients not achieving a BP of <140/90 mmHg (<130/80 mmHg for patients with diabetes or renal insufficiency)

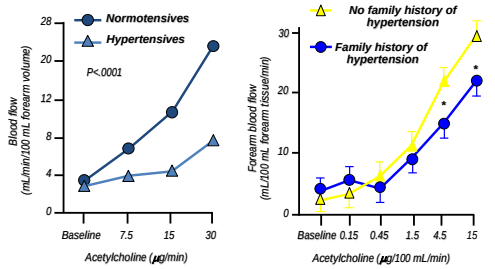
*β-blockers, α-blockers, clonidine, loop diuretics

Jamerson K, et al. Am J Hypertens 2004;17:793–801

Background for ACCOMPLISH

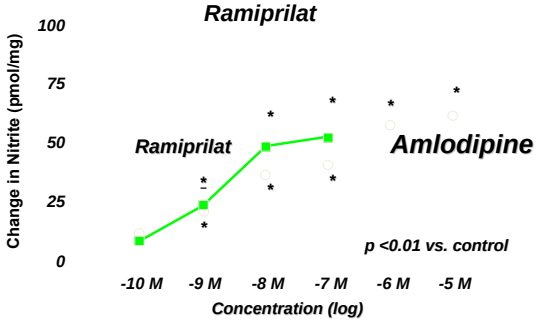
- Experimental work demonstrates that amlodipine, releases nitric oxide from canine coronary *microvessels* *(Zhang X, et.al. Circulation 1998)*.
- Early animal studies also demonstrate that ACE inhibition combined with amlodipine potentiates nitric oxide production compared to either agent alone and blunts atheroma formation in the coronary arteries. (*Raicu M, et.al. J Submicrosc Cytol Pathol 1997; Lüscher TF et.al. Cardiovasc Drugs Ther., 1995*)
- More recently, animal studies note the beneficial effect of the benazepril-amlodipine combination on cardiac nitric oxide, cGMP, and TNF-alpha production after cardiac ischemia (*Siragy H et.al. J Cardiovasc Pharmacol 2006.*)

Correlation Between Endothelial Function and Hypertension



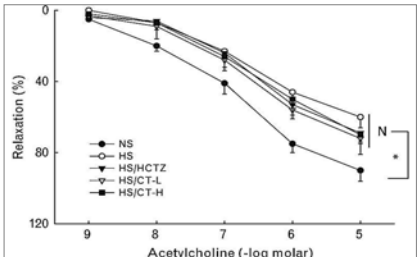
Panza JA, et al. J Am Coll Cardiol. 1993;21:1145-1151.
Taddei S, et al. J Cardiovasc Pharmacol. 1992;20(suppl 12):S193-S195.

Amlodipine Stimulates NO Production From Human Coronary Microvessels: Comparison to Ramiprilat



Zhang et al. Am J Cardiol. 1999;84:27L-33L.

Effect of thiazide diuretics on aortic endothelium-dependent relaxation to Ach



Effect of thiazide diuretics on aortic endothelium-dependent relaxation to acetylcholine in Dahl salt-sensitive rats. Compared with normal salt (NS), endothelium-dependent relaxation was significantly impaired by a high salt (HS) diet. Neither treatment with hydrochlorothiazide (HCTZ) nor chlorthalidone improved endothelium-dependent relaxation. CT-H, High-dose chlorthalidone; CT-L, low-dose chlorthalidone; N, non-significant difference. *$P < 0.05$ versus HS; $n = 6$ ≠Journal of Hypertension

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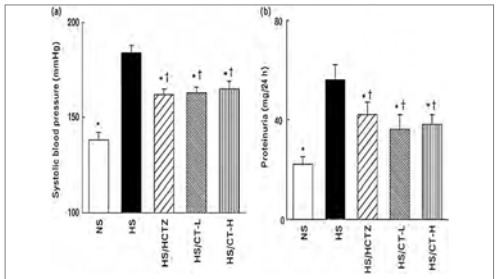
Zhou MS et al. J Hypertens 2008;26:494-500

Effects of Thiazides on BP and Proteinuria in Dahl SS rat model



Effect of thiazide diuretics on systolic blood pressure (a), measured by the tail cuff method, and 24-h urine protein excretion (b) in Dahl salt-sensitive rats. High salt (HS) intake significantly increased systolic blood pressure (SBP) and urine protein excretion. Both hydrochlorothiazide and chlorthalidone significantly reduced SBP and proteinuria. HS: fed a high salt (4% NaCl) diet for 6 weeks; normal salt (NS): fed a normal salt (0.5% NaCl) diet; HS/hydrochlorothiazide: fed a high salt diet plus hydrochlorothiazide 75 mg/l in the drinking water; HS/low-dose chlorthalidone (CT-L): fed high salt diet plus chlorthalidone 37 mg/l in the drinking water; HS/high-dose chlorthalidone (CT-H): fed high salt diet plus chlorthalidone 75 mg/l in the drinking water. The data are expressed as mean ± SEM. *$P < 0.05$ versus HS; †$P < 0.05$ versus NS; $n = 6–8$. Journal of Hypertension

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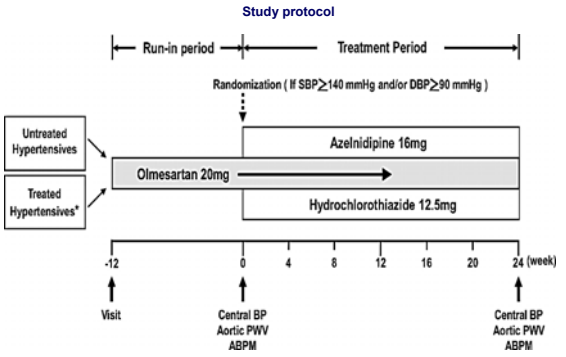
Zhou MS et al. J Hypertens 2008;26:494-500

ARB+CCB vs. HCTZ on Baseline

(Matsui Y et.al. Hypertension. 2009;54:716)

Variable	Olmesartan/Azelnidipine (n=103)	Olmesartan/HCTZ (n=104)	P
Age, y	68.9±8.1	68.0±9.1	0.41
Male, %	40	40	0.93
Body height, cm	153.6±7.9	152.8±9.2	0.38
BMI, kg/m^2	23.4±3.6	23.8±3.0	0.18
Waist circumference, cm	81.8±9.6	83.2±9.1	0.22
Duration of hypertension, y	13.7±11.3	13.3±10.3	0.79
Duration of hypertensive treatment, y	8.9±8.7	9.0±9.5	0.92
Current smoking, %	4	7	0.36
Pack-years	12.7±24.6	11.9±22.4	0.79
Regular alcohol drinkers, %	23	33	0.13
Hyperlipidemia, %	30	29	0.84



Matsui, Y. et al. Hypertension 2009;54:716-723

ARB+CCB vs. HCTZ on Ambulatory BP

(Matsui Y et.al. Hypertension. 2009;54:716)

Variable	Olmesartan/Azelnidipine (n=103)	Olmesartan/HCTZ (n=104)	Between-Group Difference*	P*
24-h SBP, mm Hg				
Baseline	142.4±17.1	141.3±16.6		
End of study	130.4±13.9	130.3±15.3		
End of study*	130.2 (128.0 to 132.4)	130.9 (128.8 to 133.1)	0.7 (–2.3 to 3.8)	0.63
24-h DBP, mm Hg				
Baseline	83.2±8.7	82.4±7.9		
End of study	76.0±7.2	77.0±8.2		
End of study*	75.7 (74.5 to 76.9)	77.1 (76.0 to 78.3)	1.4 (–0.2 to 3.1)	0.09
24-h PR, bpm				
Baseline	69.1±7.8	68.8±7.9		
End of study	65.7±7.2	69.5±8.1		
End of study*	65.4 (64.5 to 66.3)	69.4 (68.6 to 70.3)	4.0 (2.8 to 5.2)	<0.001

ARB+CCB vs. HCTZ on Aortic Compliance

(Matsui Y et.al. Hypertension. 2009;54:716)

Variable	Olmesartan/Azelnidipine (n=103)	Olmesartan/HCTZ (n=104)	Between-Group Difference*	P*
Aortic PWV, m/s				
Baseline	10.2±2.0	10.3±2.2		
End of study	8.9±1.9	9.8±2.2		
End of study*	8.9 (8.7 to 9.2)	9.7 (9.5 to 10.0)	0.8 (0.5 to 1.1)	**<0.001**
Aortic AIx, %				
Baseline	34.7±6.3	34.6±8.1		
End of study	31.2±8.5	32.0±9.6		
End of study*	30.7 (29.3 to 32.2)	31.8 (30.4 to 33.2)	1.1 (–1.0 to 3.0)	0.30
Aortic AIx@75, %				
Baseline	31.7±6.3	31.4±6.8		
End of study	26.0±7.5	28.4±7.9		
End of study*	25.4 (24.3 to 26.5)	28.2 (27.2 to 29.3)	2.8 (1.3 to 4.4)	**<0.001**
Augmentation pressure, mm Hg				
Baseline	21.1±8.9	21.9±9.6		
End of study	15.7±8.3	17.0±9.8		
End of study*	15.4 (13.9 to 16.9)	16.8 (15.3 to 18.2)	1.4 (–0.7 to 3.5)	0.18
PP amplification, ratio				
Baseline	1.20±0.09	1.20±0.11		
End of study	1.27±0.12	1.23±0.13		
End of study*	1.28 (1.26 to 1.30)	1.23 (1.21 to 1.25)	–0.04 (–0.07 to –0.02)	0.003
LV ejection duration, ms				
Baseline	301.8±25.7	304.9±26.5		
End of study	304.6±25.3	301.8±26.0		
End of study*	304.3 (300.2 to 308.5)	300.5 (296.3 to 304.6)	–3.9 (–9.7 to 2.0)	0.19

Patient baseline demographics

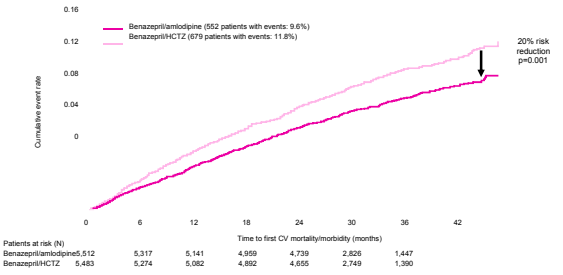
	Benazepril/amlodipine (n = 5744)	Benazepril/HCTZ (n = 5762)
Gender		
Male, n (%)	3448 (60.0)	3515 (61.0)
Female, n (%)	2296 (40.0)	2246 (39.0)
Race		
Caucasian, n (%)	4817 (83.9)	4795 (83.2)
Black, n (%)	697 (12.1)	719 (12.5)
Hispanic, n (%)	300 (5.2)	323 (5.6)
Other, n (%)	230 (4.0)	247 (4.3)
Age		
Mean, years	**68.4**	**68.3**
≥65, n (%)	**3813 (66.4)**	**3827 (66.4)**
≥70, n (%)	**2363 (41.1)**	**2340 (40.6)**
Region		
Nordic countries*, n (%)	1677 (29.3)	1676 (29.2)
United States, n (%)	4042 (70.7)	4059 (70.7)

*Denmark, Finland, Norway or Sweden

Jamerson K, et al. N Engl J Med 2008;359:2417–28

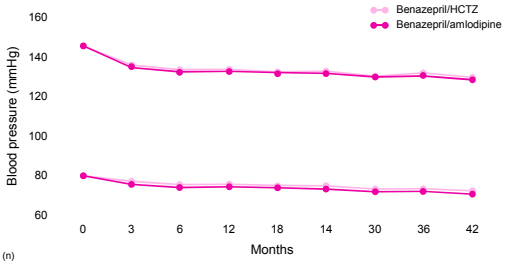
Kaplan-Meier curve for time to primary endpoint

(based on 1231 patients with primary events)



*Hazard ratio (95% confidence interval): 0.80 (0.72, 0.90)
CV = cardiovascular; HCTZ = hydrochlorothiazide
Jamerson K, et al. N Engl J Med 2008;359:2417–28

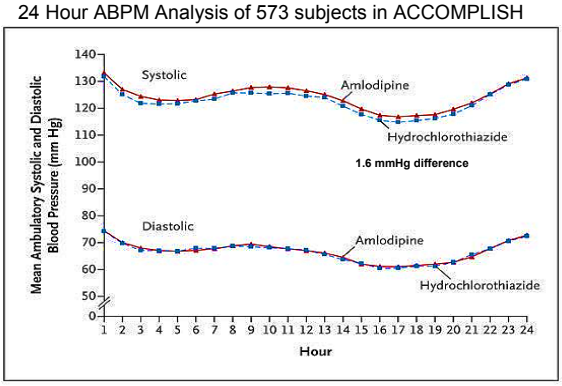
SBP/DBP over time



Patients (n)									
Benazepril/amlodipine	5740	5517	5404	5178	5010	4866	4298	2804	1074
Benazepril/HCTZ	5757	5537	5408	5222	5033	4825	4299	2529	1042

SBP = systolic blood pressure; DBP = diastolic blood pressure
HCTZ = hydrochlorothiazide
Jamerson K, et al. N Engl J Med 2008;359:2417–28

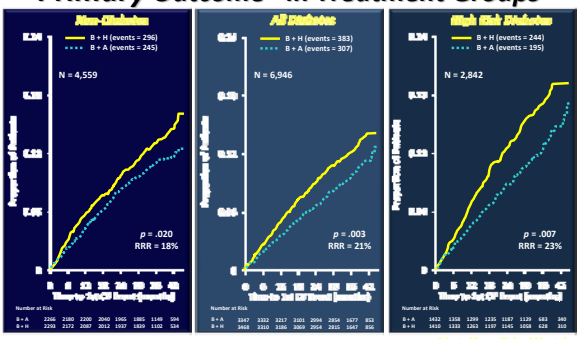
24 Hour ABPM Analysis of 573 subjects in ACCOMPLISH



Jamerson K et al. N Engl J Med 2010;363:98

ACCOMPLISH Study

Primary Outcome in Treatment Groups*



* Time to first event, defined as a composite of CV events or death from CV causes

Adapted from: Weber MA, et al. *J Am Coll Cardiol.* 2010;56:77-85.

ACCORD BP Study: Primary and Secondary Outcomes

- Patients with T2D and hypertension (N = 4733)
- Random assignment
  - Intensive therapy: target SBP < 120 mm Hg
  - Standard therapy: target SBP < 140 mm Hg
- 1° outcome: nonfatal MI, nonfatal stroke, death from CV causes
- Mean follow-up = 4.7 y

Outcome	Intensive	Standard	HR	*P*-value
SBP after 1 year (mmHg)	119.3	133.5	NR	NR
1° outcome (annual rate)	1.87	2.09	0.88	.20
Death from any cause (annual rate)	1.28	1.19	1.07	.55
Stroke (annual rate)	0.32	0.53	0.59	.01
AEs (rate)	3.3	1.3	NR	<.001

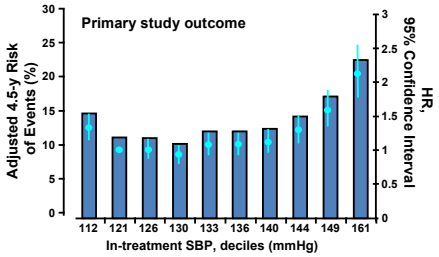
The ACCORD Study Group. *N Engl J Med* 2010 March 14. [Epub ahead of print]

Recent INVEST Outcomes

- Patients with diabetes and CAD (N = 6400)
  - **Random assignment to CCB or BB + ACEI and/or thiazide diuretic**
  - **BP target: 130/85 mm Hg**
  - **Level of control determined by achieved BP**
    - **"Tight": SBP < 130 mm Hg**
    - **"Usual": SBP 130-140 mm Hg**
    - **"Not controlled": SBP > 140 mm Hg (≈ 1/3 of patients)**
- Outcomes: MI, stroke, all-cause mortality
- "Not controlled" had worst outcomes
- CV outcomes not improved for "tight" vs "usual"
  - Increased mortality risk in "tight" group
  - Particularly SBP < 115 mm Hg

Cooper-DeHoff, R et.al. JAMA 2010;304:61-68

ONTARGET: Relationships Between Outcome Risks and In-Trial BP



- **J-shaped curve (nadir ≈ 130 mm Hg) for primary outcome[a], MI, CV mortality (not stroke)**
- **Continual risk increase (no J-shaped curve) for stroke**
- **Suggests increased risk of events in patients with extensive vascular disease when BP is decreased below a critical level**

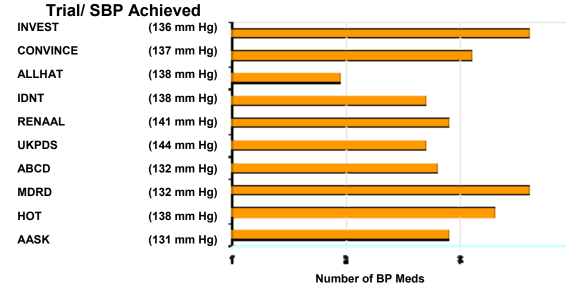
[a]Composite of cardiovascular death, MI, stroke, or hospitalization for congestive heart failure (CHF).

Sleight P, et al. *J Hypertens.* 2009;27:1360-1369.

Considering Comorbidities and Individual Needs

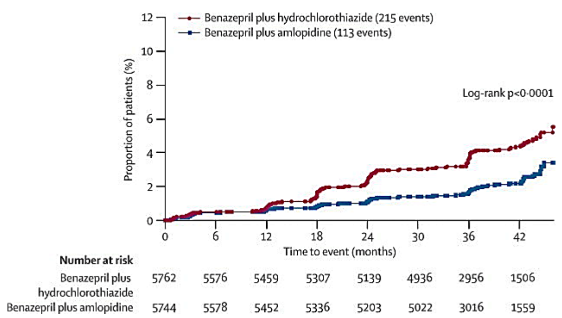
- CVD status
  - Family history
  - Personal history of CV event
  - Hypertension severity
  - Microalbuminuria
- **Renal function status**
  - Macroalbuminuria (> 300 mg/d)
  - eGFR (< 45 mL/min/1.73m^2)

Average Number of Antihypertensive Agents Needed per Patient to Achieve Target BP Goals



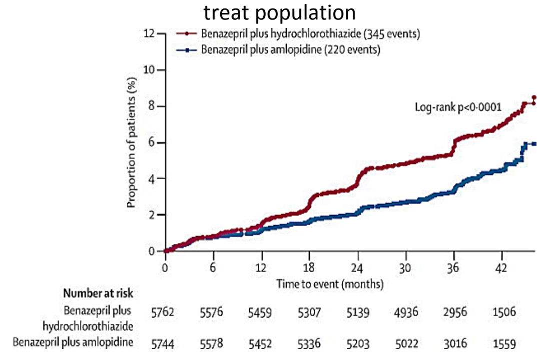
Updated from Bakris GL, et al. Am J Kidney Dis. 2000;36(3):646-661.

Kaplan-Meier curves for progression of chronic kidney disease for the intention-to-treat population



Bakris GL et.al.. Lancet. 2010; 375: 1173–81.

Kaplan-Meier curves for progression of chronic kidney disease plus cardiovascular death for the intention-to-treat population



Bakris GL et.al.. Lancet. 2010; 375: 1173–81.

Outcomes in the intention-to-treat population and in patients aged 65 years or older

	Benazepril plus amlodipine	Benazepril plus hydrochlorothiazide	Hazard ratio (95% CI)	p value
Intention-to-treat population (N=11 506)*				
Main endpoint of progression of chronic kidney disease	113 (1·97%)	215 (3·73%)	0·52 (0·41–0·65)	<0·0001
Doubling of serum creatinine concentration	105 (1·83%)	208 (3·61%)	0·51 (0·39–0·63)	<0·0001
Dialysis	7 (0·12%)	13 (0·23%)	0·53 (0·21–1·35)	0·180
eGFR <15 mL/min/1·73 m²	18 (0·31%)	17 (0·30%)	1·06 (0·54–2·05)	0·868
Progression of chronic kidney disease and cardiovascular death	220 (3·83%)	346 (5·99%)	0·63 (0·53–0·74)	<0·0001
Progression of chronic kidney disease and all-cause mortality	346 (6·02%)	465 (8·07%)	0·73 (0·64–0·84)	<0·0001
Patients aged ≥65 years (n=7640)†				
Main endpoint of progression of chronic kidney disease	70 (1·83%)	138 (3·62%)	0·50 (0·37–0·67)	<0·0001
Doubling of serum creatinine concentration	66 (1·73%)	132 (3·46%)	0·49 (0·37–0·67)	<0·0001
Dialysis	3 (0·08%)	10 (0·26%)	0·30 (0·08–1·09)	0·053
eGFR <15 mL/min/1·73 m²	11 (0·29%)	11 (0·29%)	1·00 (0·43–2·31)	0·99
Progression of chronic kidney disease and cardiovascular death	160 (4·19%)	234 (6·13%)	0·68 (0·55–0·83)	0·0002
Progression of chronic kidney disease and all-cause mortality	266 (6·96%)	327 (8·57%)	0·81 (0·68–0·95)	0·010

Bakris GL et.al.. Lancet. 2010; 375: 1173–81.

Importance of Albuminuria over GFR on Risk of Cardio-Renal Endpoints in Type 2 Diabetes

	eGFR (ml/min per 1.73 m^2)			
	≥90	60–89	30–59	15–29
Cardiovascular end points				
No albuminuria [HR (95% CI), P value]	1.00 (referent)	1.00 (0.59–1.72), P = 0.991	[redacted]	Not enough subjects
Albuminuria [HR (95% CI), P value]	[redacted]	1.89 (1.13–3.16), P = 0.016	1.35 (0.74–2.49), P = 0.33	5.46 (2.78–10.7), P < 0.001
Renal end points				
No albuminuria [HR (95% CI), P value]	1.00 (referent)	0.83 (0.35–1.96), P = 0.67	0.82 (0.12–6.22), P = 0.85	Not enough subjects
Albuminuria [HR (95% CI), P value]	[redacted]	4.13 (2.19–7.78), P < 0.001	[redacted]	90.29 (45.80–178.03), P < 0.001
Composite end points*				
No albuminuria [HR (95% CI), P value]	1.00 (referent)	1.21 (0.80–1.84), P = 0.36	2.98 (1.57–5.64), P = 0.001	Not enough subjects
Albuminuria [HR (95% CI), P value]	2.34 (1.58–3.50), P < 0.001	2.43 (1.64–3.59), P < 0.001	3.15 (2.06–4.82), P < 0.001	16.2 (10.0–26.0), P < 0.001

So W, et.al. Diabetes Care 29 :2046–2052, 2006

Clinical Trials and Renal Outcomes Based on Proteinuria Reduction

Increased Time to Dialysis
(30-35% proteinuria reduction)

- Captopril Trial-N Engl J Med, 1993
- AASK Trial-JAMA, 2001
- RENAAL-N Engl J Med, 2001
- IDNT-N Engl J Med, 2001

No Change in Time to Dialysis
(NO proteinuria reduction)

- DHPCCB arm-IDNT
- DHPCCB arm-AASK

Hart P & Bakris GL Managing Hypertension in the Diabetic Patient.
IN: Egan BM, Basile JN, and Lackland DT (eds.) **Hot Topics in Hypertension**
Hanley and Belfus, Philadelphia, 2004, pp.249-252.

Ratio of means (95% CI)* for change in proteinuria, by randomized therapy, over two follow-up intervals-Meta-analysis of trials

Randomized Therapy	1-4 Months	5-12 Months
ARBs vs placebo	0.57 (0.47–0.68)	0.66 (0.63–0.69)
ARBs vs ACE-I	0.99 (0.92–1.05)	1.08 (0.96–1.22)
ARBs vs CCBs	0.69 (0.62–0.77)	0.62 (0.55–0.70)
ARB+ACE-I vs ARBs	0.76 (0.68–0.85)	0.75 (0.61–0.92)
ARB+ACE-I vs ACE-I	0.78 (0.72–0.84)	0.82 (0.67–1.01)

Bold=significant P<0.01 at 5-12 Months

Kunz R et al. ***Ann Intern Med*** 2008; 148:30-48

Dual RAAS Blockade

- RAAS inhibitors do not completely inhibit RAAS activity
- Inhibition at 2 points in the cascade may provide greater benefits
- Studies have been initiated to test this theory
  - **ACEI + ARB**
    - **Further BP reduction in some**
    - **Further reduction of proteinuria[a]**
    - **No consistent additional CV benefit**
      - **VALIANT**
      - **CHARM-Added**
      - **ONTARGET**
  - **Renin inhibitor + ARB**
    - **Further BP reduction in some**
    - **Further reduction of proteinuria[a]**
    - **Trials planned to assess CV outcomes**
      - **ALTITUDE**
      - **ATMOSPHERE**

[a]Thought to be related to better outcomes, particularly in advanced proteinuric kidney disease.

Arici M, Erdem Y. *Am J Kidney* Dis. 2009;332-345; ONTARGET Investigators. *N Engl J Med.* 2008;358:1547-1549; CHARM Investigators. *Lancet.* 2003;362:767-771; VALIANT Investigators; *N Engl J Med.* 2003;349:1893-1906; AVOID Study Investigators.*N Engl J Med.* 2008;358:2433-2446; Oparil S, et al. *Lancet.* 2007;370:221-229; Parving HH, et al. *Nephrol Dial Transplant.* 2009;24:1663-1671; ATMOSPHERE. http://clinicaltrials.gov/ct2/show/NCT00853658.

VA NEPHRON-D Study Design

- Primary endpoints
  - eGFR reduction
    - **> 50% if baseline < 60 mL/min/1.73m²**
    - **= 30 mL/min/1.73m² if baseline ≥ 60 mL/min/1.73m²**
  - End-stage renal disease (ESRD)
    - **eGFR < 15 m>/min/1.73m²**
    - **Need for dialysis**
  - Death
- Secondary endpoints: time to eGFR change or ESRD
- Tertiary endpoints: CV events, slope of eGFR change, change in albuminuria at 1 year
- Safety endpoints
  - Serious hyperkalemia (potassium > 5 mEq/L, requiring admission, ER visit, or dialysis)
  - All-cause mortality
  - Other serious events

Fried LF, et al. *Clin J Am Soc Nephrol.* 2009;4:361-368.

Aldosterone Blockers Added to ACEIs or ARBs in CKD

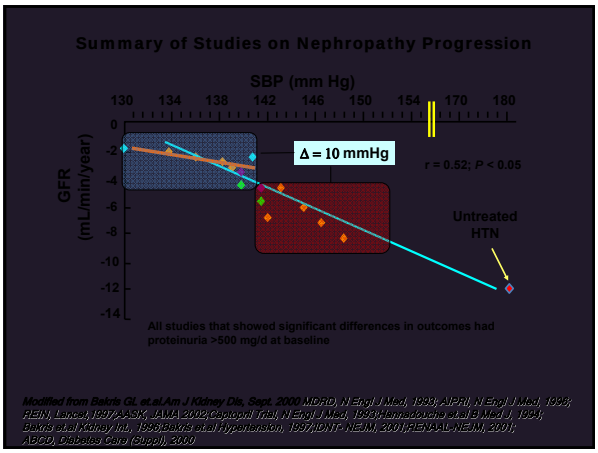
- Systematic review
  - Studies in patients with proteinuric kidney disease
  - Primary outcome: changes in proteinuria
  - Secondary outcomes: changes in BP and glomerular filtration
  - 15 studies included
- Outcomes following addition of aldosterone blockers
  - 15-54% decrease in proteinuria from baseline
  - Significant BP decrease (≈40%)
  - Significant decrease in glomerular filtration rate (≈ 25%)
  - Hyperkalemic events significant in 1 of 8 RCTs

Bomback AS, et al. *Am J Kidney Dis.* 2008;51:199-211.

Predictors of Hyperkalemia Risk With Aldosterone Blockade in Diabetic Nephropathy

- Assess safety/efficacy of aldosterone blocker + existing BP regimen
- Patients (N = 46) with resistant hypertension and stage 2 or 3 CKD
- Endpoints
  - Primary: change in SBP
  - Secondary: change in serum potassium, creatinine, eGFR, DBP and tolerability
- Results
  - SBP reduction = 14.7 ± 5.1 mm Hg (P = .001)
  - 39% of patients had > 30% decrease in eGFR
  - Mean increase in serum potassium = 0.4 mEq/L (P = .001)
  - 17.3% with serum potassium > 5.5 mEq/L
  - **Predictors of hyperkalemia**
    - **Baseline eGFR ≤ 45 mL/min/1.73m² and serum potassium 4.5 mEq/L with diuretics**

Khosla N, et al. *Am J Nephrol.* 2009;30:418-424.



Summary

- The recommendation for BP in diabetes and CKD without proteinuria should be " substantially <140/90 mmHg approaching 130/80 mmHg.
- ACEIs and ARBs are recognized as agents that improve CV outcomes, and renal outcomes in patients with proteinuric nephropathy
- Benefits on renal outcomes in advanced proteinuric kidney disease using ACEI + ARB combination in patients with diabetes will be clear in 2013 with results of NEPHRON-D
- Use of Combined RAAS inhibitor with CCB appears to be better tolerated and results in fewer CV/renal events especially in older people at high CV risk without proteinuric nephropathy
- No CV or renal outcome data, as of yet, on renin inhibition + ACEI or ARB

If Blood Pressure >130/80 mm Hg in Diabetes (*eGFR ≥ 50 ml/min^*)

(*if systolic BP< 20 mmHg above goal*)
Start ARB or ACE Inhibitor titrate upwards

(*if systolic BP ≥20 mmHg above goal*)
START with ACEI or ARB + thiazide diuretic* or CCB

Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)

Add Long Acting Thiazide Diuretic* or CCB

Add CCB or β blocker**

Recheck within 2-3 weeks

If BP Still Not at Goal (130/80 mm Hg)

Consider and Aldosterone Receptor Blocker
If CCB used, Add Other Subgroup of CCB
(ie, amlodipine-like agent if verapamil or diltiazem already being used and the converse)
OR could add alpha blocker is not using vasodilating β blocker with alpha effects

Recheck within 4 weeks

If BP Still Not at Goal (130/80 mm Hg)

Refer to a Clinical Hypertension Specialist#

Bakris GL and Sowers JR, J Am Soc Hypertens 2010;4:62-67