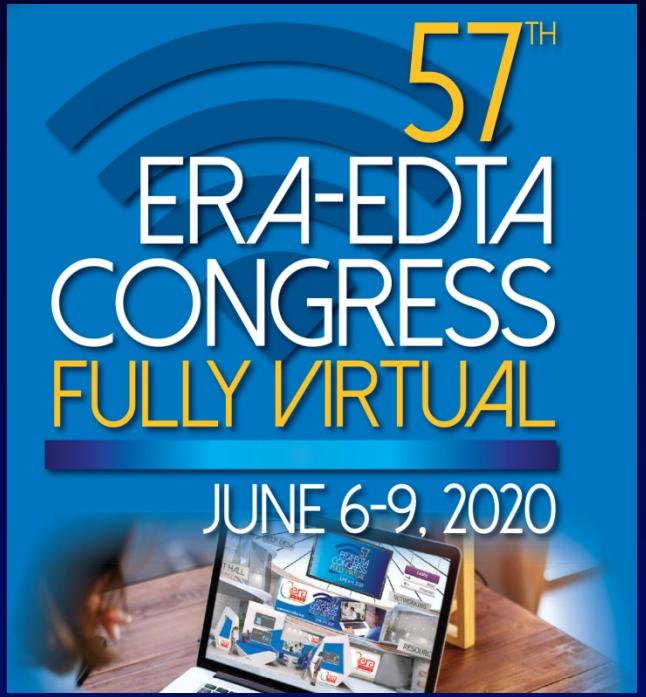
Blood pressure in CKD.
The KDIGO 2019 standpoint



Pantelis Sarafidis, MD, MSc, PhD

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Department of Nephrology, Hippokration Hospital,
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DOI statement

Professor Sarafidis has served as an Advisor for Elpen, Genesis Pharma, Astra-Zeneca, Menarini, Innovis Pharma, Winmedica and as a Speaker for Amgen, Boehringer Ingelheim, Mediquest India, Menarini, Winmedica, Bayer.

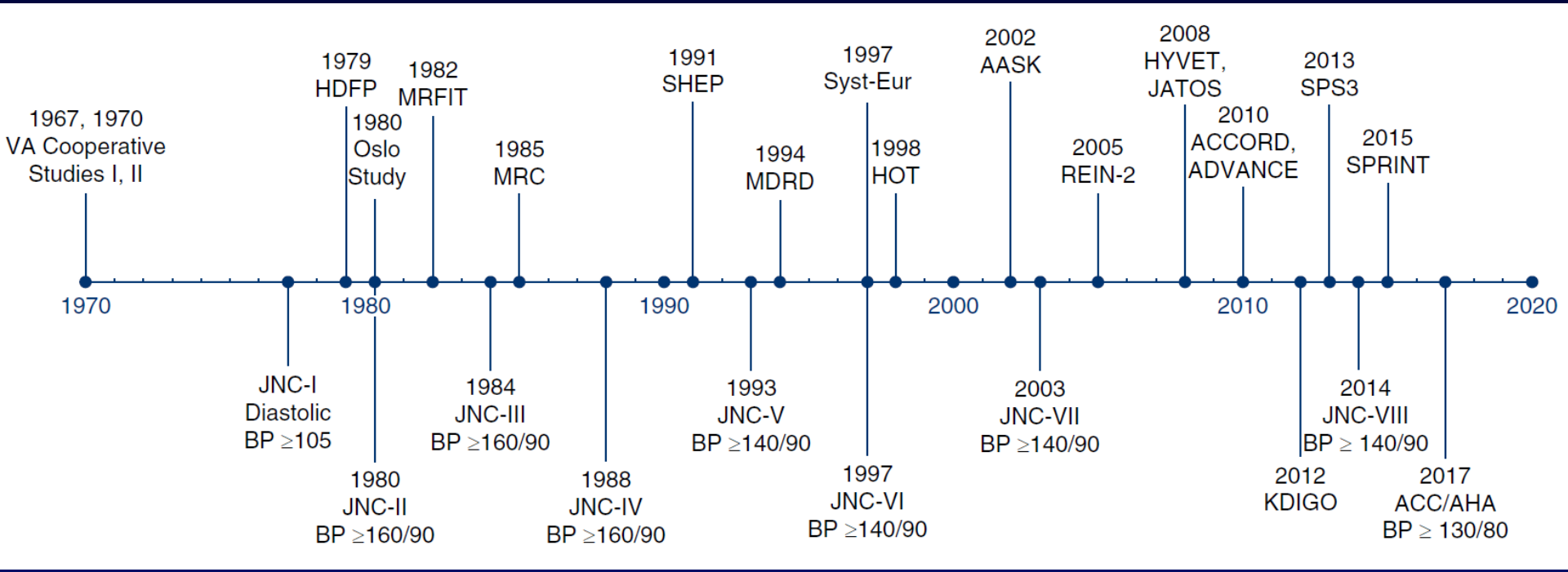
He has received grant support for an Investigator-Initiated Study from Astra-Zeneca and serves as a Member of Steering Committee and of Endpoint Adjudication Committee for FIGARO and FIDELIO Studies of Bayer.

He is an Associate Editor for the Journal of Human Hypertension and a Theme Editor for Nephrology Dialysis and Transplantation.

BP Targets in CKD

Previous Evidence

BP targets: Changes in Guidelines following major studies



Chang et al. Clin J Am Soc Nephrol 2018

To identify the optimal BP Target in CKD we need an RCT:

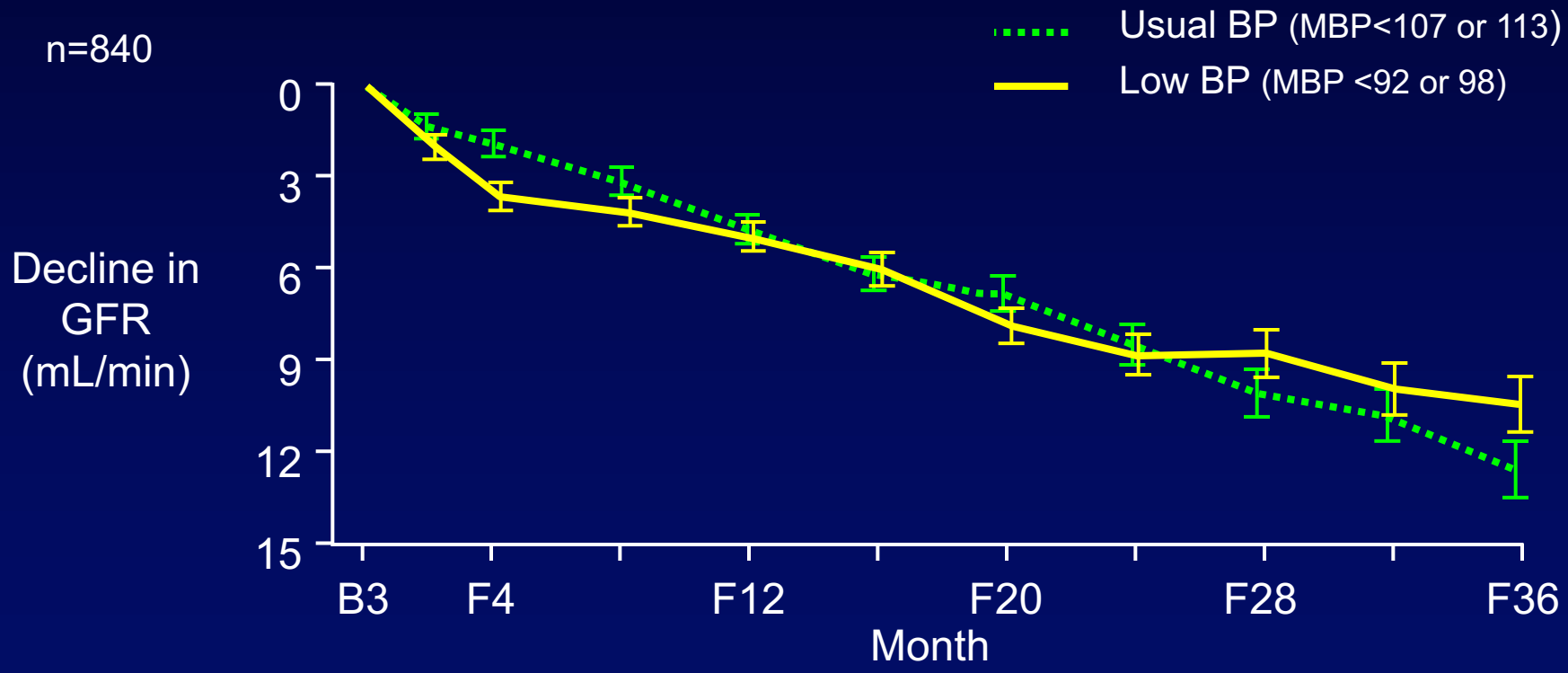
- including solely CKD patients

- having an appropriate mix of CKD etiology and Stage

- achieving the targets under study (i.e. <140? <130? <120?) during follow-up

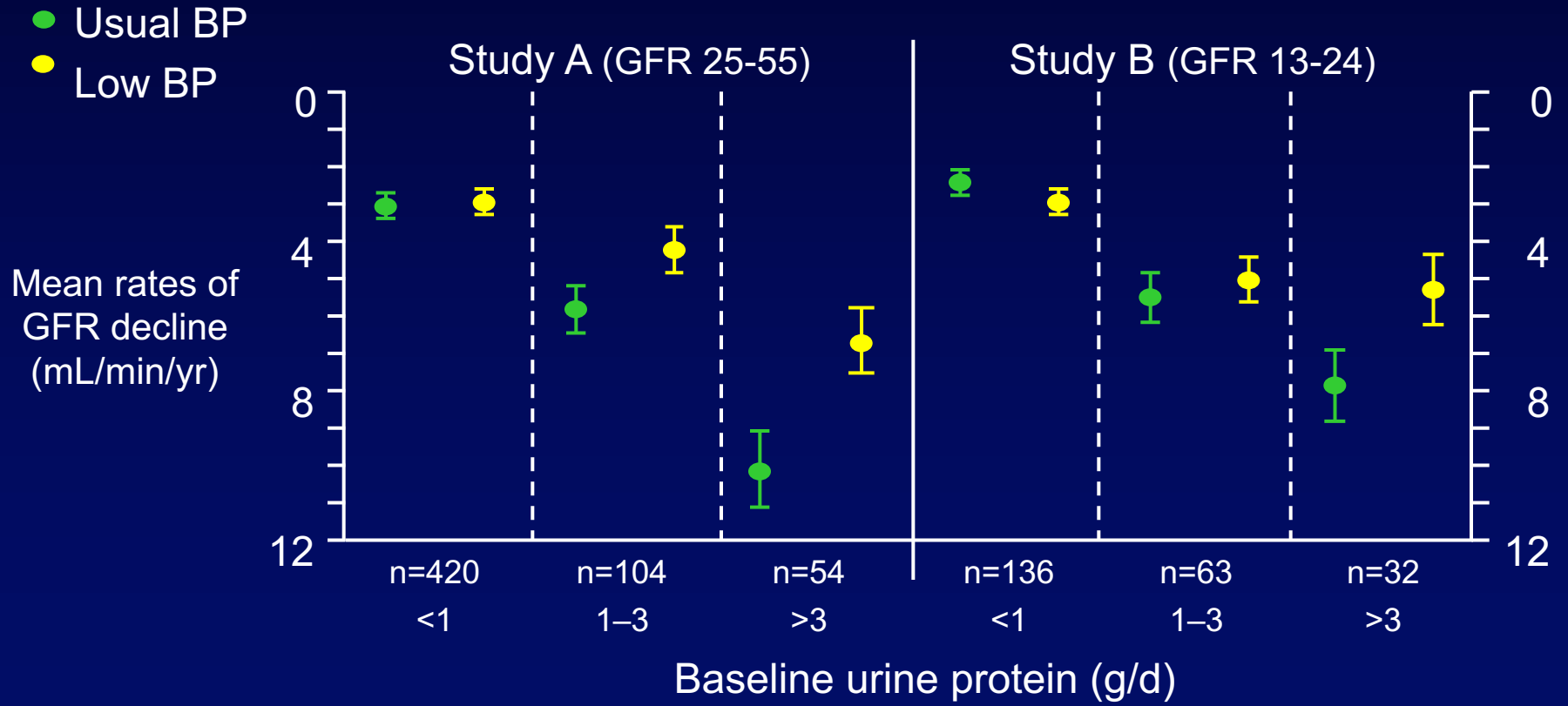
- powered for CV outcomes, hard renal outcomes and mortality

MDRD: Impact of Usual and Low BP on GFR



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

MDRD: Impact of BP Goal on GFR decline as a Function of Proteinuria



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

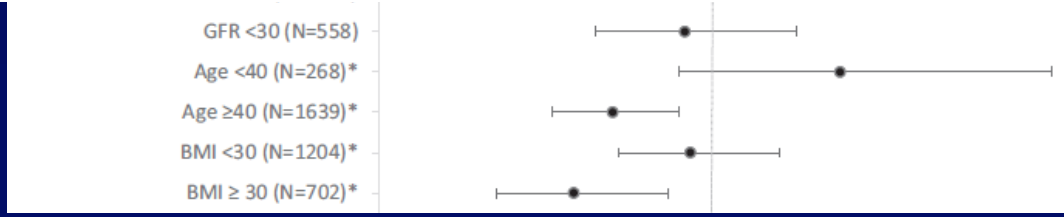
MDRD & AASK Combined: Long-term follow-up

ORIGINAL RESEARCH

American Heart Association.

Effect of Blood Pressure Control on Long-Term Risk of End-Stage Renal Disease and Death Among Subgroups of Patients With Chronic Kidney Disease

Elaine Ku, MD, MAS; Mark J. Sarnak, MD; Robert Toto, MD; Charles E. McCulloch, PhD; Feng Lin, MS; Miroslaw Smogorzewski, MD; Chi-yuan Hsu, MD, MSc



Ku et al, J Am Heart Assoc 2019

BP Target in Diabetes: Important facts

- There is no study in DM studying BP target effects on renal outcomes

- There is no study in DKD studying BP target effects on CV outcomes

- Early studies randomized patients based on DBP levels

ACCORD study:
Three Medical Strategy Questions for type 2 DM

- Glycaemia:
  Intensive control (HbA1c<6.0%) vs Standard control (HbA1c 7.0%-7.9%)

- Blood Pressure:
  In
  m

Excluded: SCr >1.5 mg/dL (132.6 µmol/L)

- Lipids:
  Fibrates to increase HDL-C and lower TG + statins to lower LDL-C vs Statins to lower LDL-C alone

BP Targets in patients with diabetes or CKD

Organization	Year	Systolic BP	Diastolic BP
NICE	2008	**<130**	**<80**
ESH/ESC	2007	**<130**	**<80**
British Hypertension Society	2004	**<130**	**<80**
JNC VII	2003	**<130**	**<80**
ESH/ESC	2003	**<130**	**<80**
American Diabetes Association	2001	**<130**	**<80**
National Kidney Foundation	2000	**<130**	**<80**
Canadian Hypertension Society	1999	**<130**	**<80**
British Hypertension Society	1999	**<140**	**<80**
WHO/ISH	1999	**<130**	**<85**
JNC VI	1997	**<130**	**<85**

BP Targets in patients with diabetes or CKD

Organization	Year	Diabetes	CKD
JNC 8	2014	<140/90	<140/90
ESH/ESC	2013	<140/85	<140 <130 in proteinuria
ADA	2013	<140/80	
K-DIGO	2012	≤140/90 ≤130/80 in micro/macro albuminuria	

BP in CKD

Upcoming KDIGO 2020 Guidelines

CONFIDENTIAL: DO NOT DISTRIBUTE

PUBLIC REVIEW DRAFT

JANUARY 2020

FULL GUIDELINE

Expected Publication: Q4 2020

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

KDIGO BP Public Review Document 2019

Updates to the KDIGO guideline format

Practice Points are used when	Recommendations will be provided when
• No systematic review was conducted	• Systematic review was conducted
• There is insufficient evidence	• Ample evidence is available
• Evidence was inconclusive (less evidence than required)	• Evidence shows a clear preference for one action over the alternatives
• The alternative option is illogical	• Consensus statements are supported with evidence and explicit discussion of the balance of benefits and harms, values and preferences will be necessary
• The guidance does not imply action for the physician	• Application of guidance requires explicit discussion of values and preferences or on resource
• Consensus statements providing guidance and guidance in the absence of evidence may consider benefits and harms but will not be explicitly discussed	• Guidance is always actionable
• Guidance does not require an explicit discussion of values and preferences or of resource considerations, although is implied that these were considered	• The guidance is more useful displayed as or requires additional explanation in text
• The guidance may be more useful as a table/figure/algorithm	

KDIGO BP Public Review Document 2019

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Chapters

Chapter 1. Blood Pressure Measurement

Chapter 2. Lifestyle Treatment for Lowering Blood Pressure in Non-dialysis CKD Patients

Chapter 3. Blood Pressure Management in Non-dialysis CKD Patients with and without Diabetes

Chapter 4. Blood Pressure Management in Kidney Transplant Recipients

Chapter 5. Blood Pressure Management in Children with CKD

Chapter 1. Blood Pressure Measurement

Recommendation 1.1. We recommend standardized office BP in preference to routine office BP for the diagnosis and management of high BP in adults (1B).

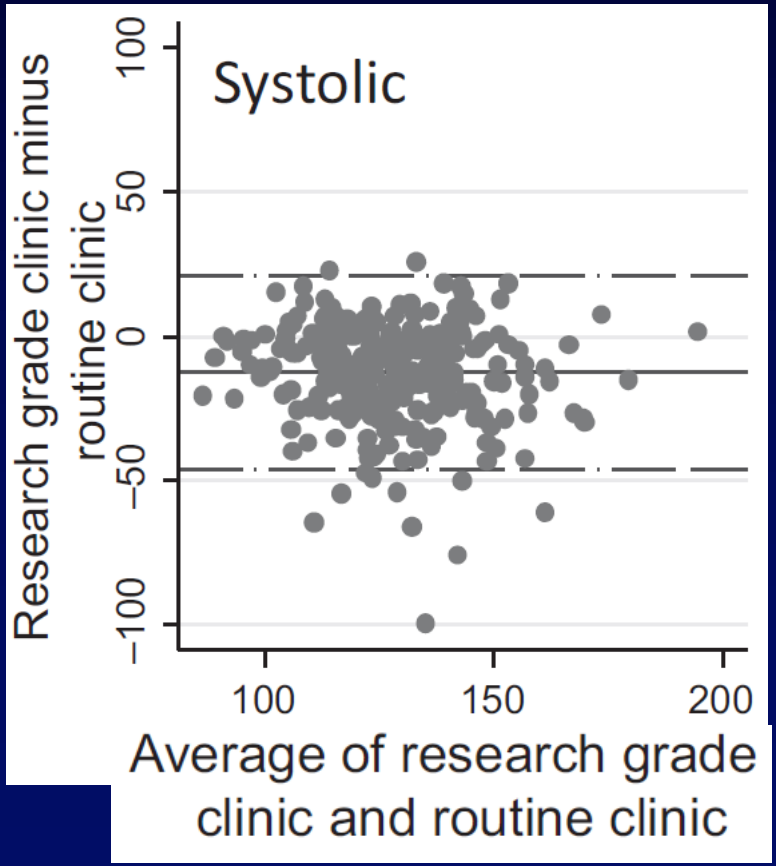
Practice Point 1.1. An oscillometric BP device may be preferable to a manual BP device for standardized office BP measurement.

Practice Point 1.2. Automated office BP (AOBP) may be the preferred method of standardized office BP measurement.

Practice Point 1.3. Oscillometric devices can be used to measure BP among patients with atrial fibrillation.

Recommendation 1.2. We suggest that out-of-office BP measurements be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the diagnosis and management of high BP (2B).

Correlation between routine and standardized BP

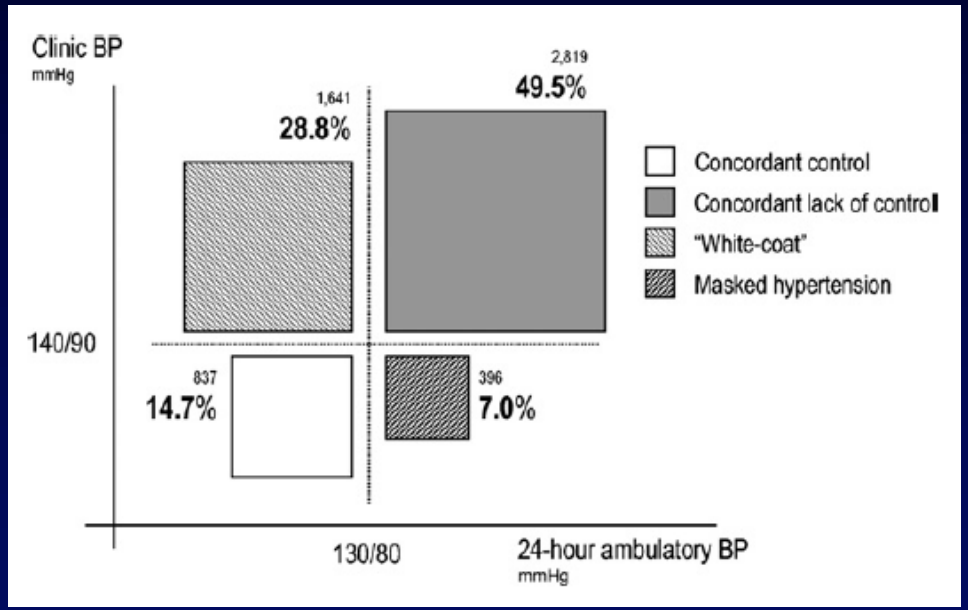


n=275
eGFR 29+/-10 ml/min/1.73m^2

-12.7 mmHg

Agarwal R. J Am Heart Assoc 2017

White Coat and Masked Hypertension in CKD



N=5693 CKD patients

Table 5. Predictors of Underestimation and Overestimation of BP Control From Multivariate Logistic Analysis

Predictor	OR (95% CI)	*P*
Underestimation ("white-coat" hypertension)		
Sex (female vs male)	1.217 (1.040-1.424)	0.02
Age (per 1-y older)	1.009 (1.003-1.015)	0.004
BMI (per 1-kg/m^2 higher)	1.022 (1.005-1.040)	0.01
Albuminuria (per 1-mg/g greater ACR)	1.001 (1.001-1.002)	<0.001
Target-organ damage (yes vs no)	1.201 (1.065-1.339)	0.02
Overestimation (masked hypertension)		
Age (per 1-y older)	1.017 (1.009-1.025)	<0.001
BMI (per 1-kg/m^2 higher)	1.032 (1.009-1.057)	0.008

Gorostidi, Sarafidis, de la Sierra, et al. Am J Kidney Dis 2013

Chapter 2. Lifestyle Treatment for Lowering Blood Pressure in Non-dialysis CKD Patients

2.1. Sodium Intake

Recommendation 2.1.1. We suggest targeting salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) among CKD patients with high BP (2C).

Practice Point 2.1.1. Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.

Practice Point 2.1.2. The DASH-type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism because of the potential for hyperkalemia.

Chapter 2. Lifestyle Treatment for Lowering Blood Pressure in Non-dialysis CKD Patients

2.2. Physical Activity

Recommendation 2.2.1. We suggest that patients with high BP and CKD undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).

Practice Point 2.2.1. Consider the cardiorespiratory fitness status, physical limitations,cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.

Practice Point 2.2.2. The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.

Chapter 3. Blood Pressure Management in Non-dialysis CKD Patients with and without Diabetes

3.1. Blood Pressure Targets

Recommendation 3.1.1. We suggest that adults with CKD and high BP be treated with a target systolic blood pressure (SBP) of less than 120 mm Hg using standardized office BP measurement (2B).

Practice Point 3.1.1. It is potentially hazardous to apply the recommended SBP target of <120 mm Hg to BP measurements obtained in a non-standardized manner.

Practice Point 3.1.2. Clinicians can reasonably offer less intensive BP-lowering therapy in patients with very limited life expectancy, or symptomatic postural hypotension due to autonomic neuropathy.

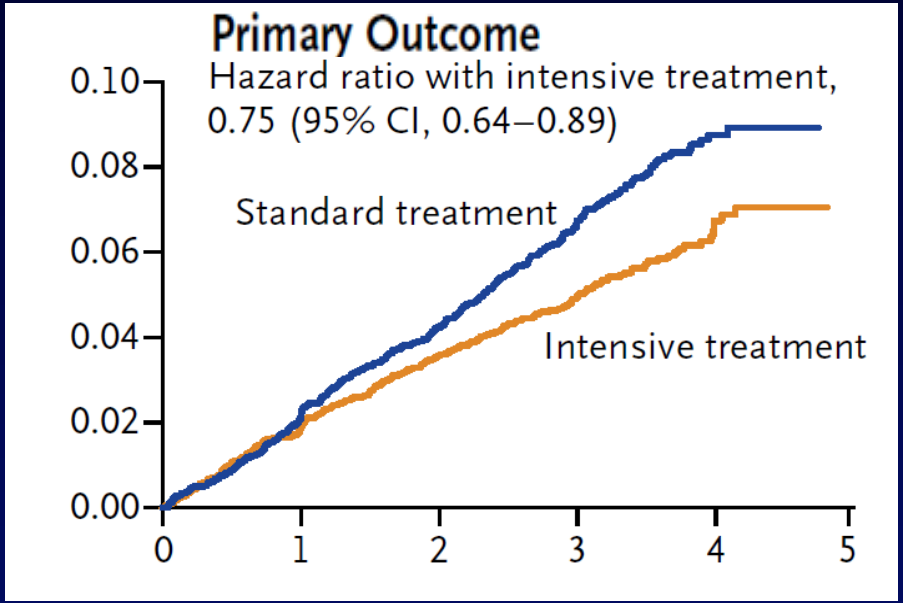
Table 1. Baseline Characteristics of the Study Participants.*

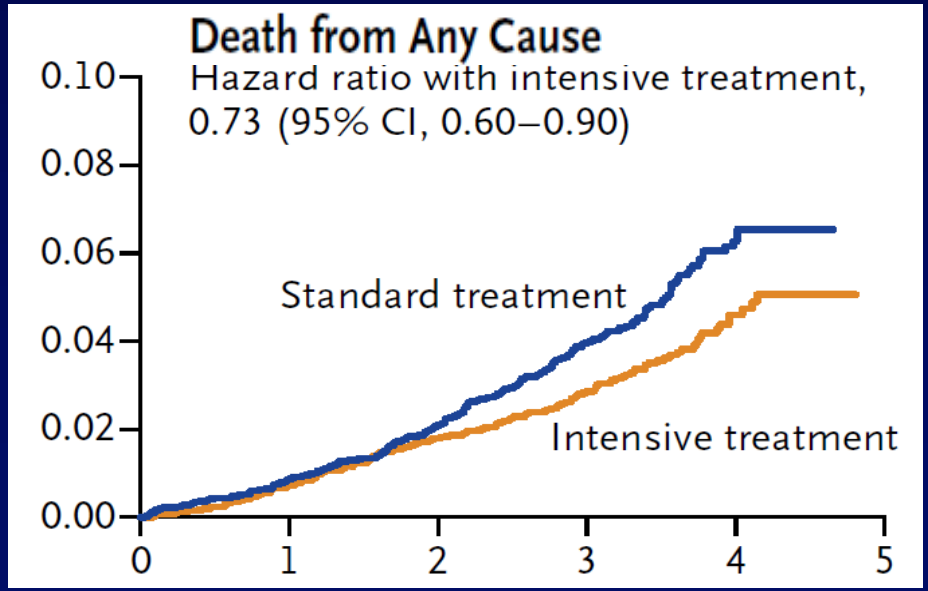
Characteristic	Intensive Treatment (N = 4678)	Standard Treatment (N = 4683)
Criterion for increased cardiovascular risk — no. (%)†		
Age ≥75 yr	1317 (28.3)	1319 (28.2)
Chronic kidney disease‡	1330 (28.4)	1316 (28.1)
Cardiovascular disease	940 (20.1)	937 (20.0)
Clinical	779 (16.7)	783 (16.7)
Subclinical	247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%	2870 (61.4)	2867 (61.2)
Female sex — no. (%)	1684 (36.0)	1648 (35.2)
Age — yr		
Overall	67.9±9.4	67.9±9.5
Among those ≥75 yr of age	79.8±3.9	79.9±4.1
Race or ethnic group — no. (%)§		
Non-Hispanic black	1379 (29.5)	1423 (30.4)
Hispanic	503 (10.8)	481 (10.3)
Non-Hispanic white	2698 (57.7)	2701 (57.7)
Other	98 (2.1)	78 (1.7)
Black race§¶	1454 (31.1)	1493 (31.9)
Baseline blood pressure — mm Hg		
Systolic	139.7±15.8	139.7±15.4
Diastolic	78.2±11.9	78.0±12.0
Distribution of systolic blood pressure — no. (%)		
≤132 mm Hg	1583 (33.8)	1553 (33.2)
>132 mm Hg to <145 mm Hg	1489 (31.8)	1549 (33.1)
≥145 mm Hg	1606 (34.3)	1581 (33.8)
Serum creatinine — mg/dl	1.07±0.34	1.08±0.34
Estimated GFR — ml/min/1.73 m^2		
Among all participants	71.8±20.7	71.7±20.5
Among those with estimated GFR ≥60 ml/min/1.73 m^2	81.3±15.5	81.1±15.5
Among those with estimated GFR <60 ml/min/1.73 m^2	47.8±9.5	47.9±9.5
Ratio of urinary albumin (mg) to creatinine (g)	44.1±178.7	41.1±152.9
Fasting total cholesterol — mg/dl	190.2±41.4	190.0±40.9
Fasting HDL cholesterol — mg/dl	52.9±14.3	52.8±14.6
Fasting total triglycerides — mg/dl	124.8±85.8	127.1±95.0
Fasting plasma glucose — mg/dl	98.8±13.7	98.8±13.4
Statin use — no./total no. (%)	1978/4645 (42.6)	2076/4640 (44.7)
Aspirin use — no./total no. (%)	2406/4661 (51.6)	2350/4666 (50.4)
Smoking status — no. (%)		
Never smoked	2050 (43.8)	2072 (44.2)
Former smoker	1977 (42.3)	1996 (42.6)
Current smoker	639 (13.7)	601 (12.8)
Missing data	12 (0.3)	14 (0.3)
Framingham 10-yr cardiovascular disease risk score — %	20.1±10.9	20.1±10.8

The SPRINT Study:
SBP 140 mmHg vs 120 mmHg

Wright JT et al. N Engl J Med 2015

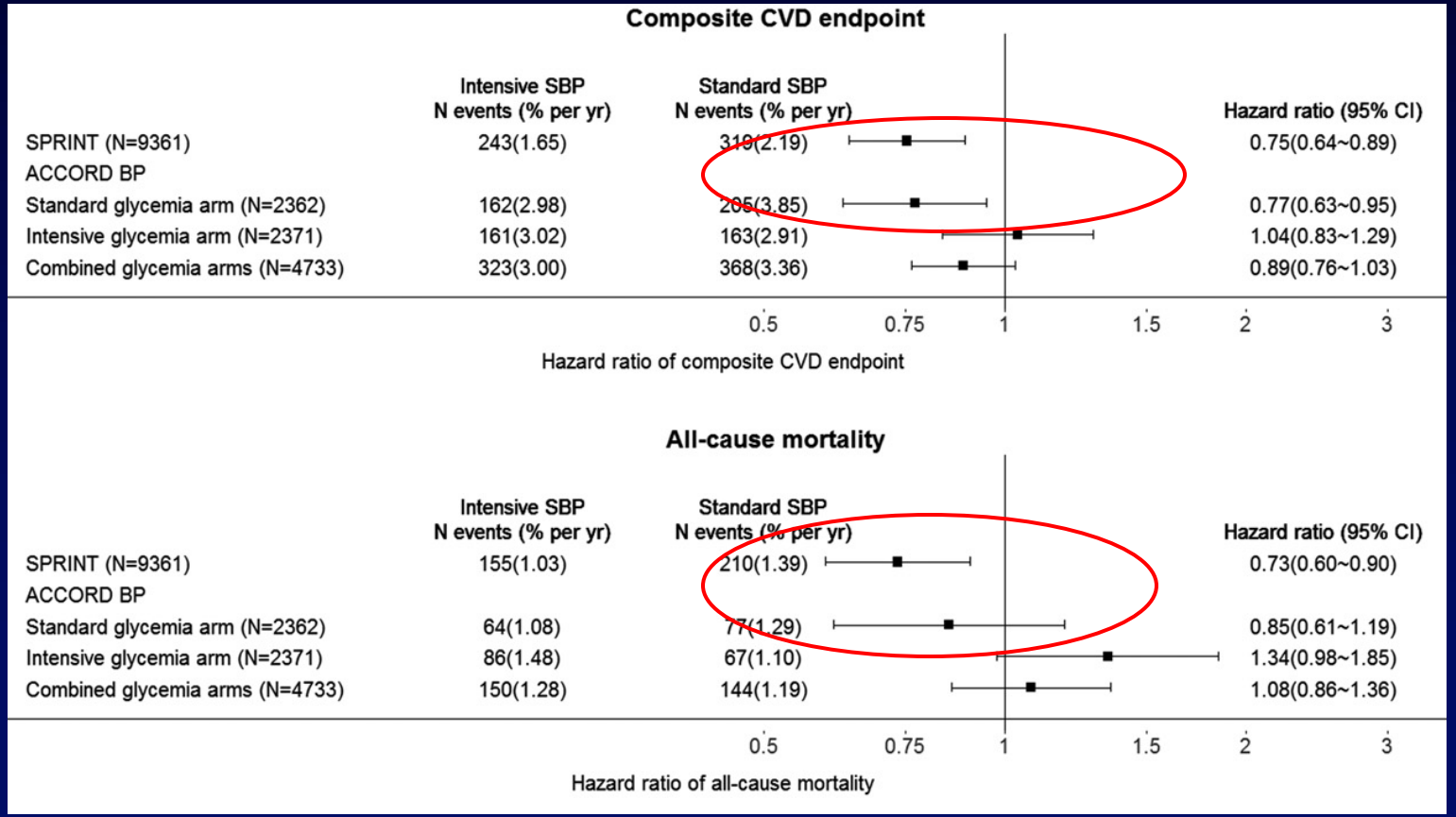
The SPRINT Study: SBP 140 mmHg vs 120 mmHg





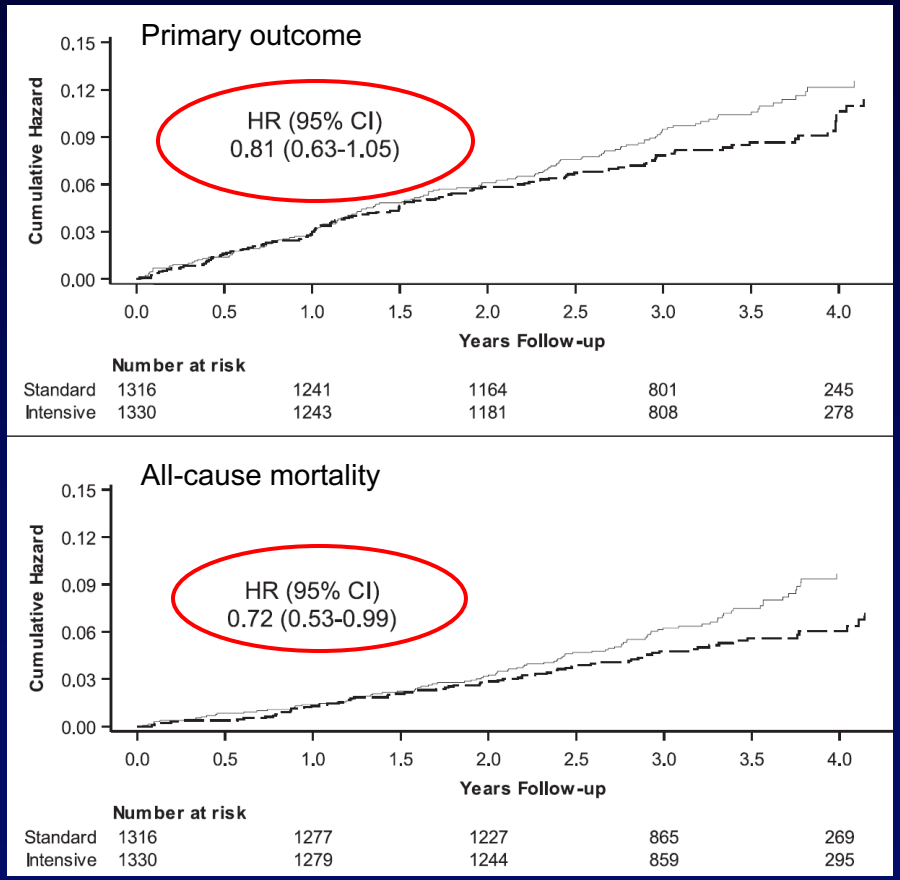
Wright JT et al, N Engl J Med 2015

The SPRINT and ACCORD together

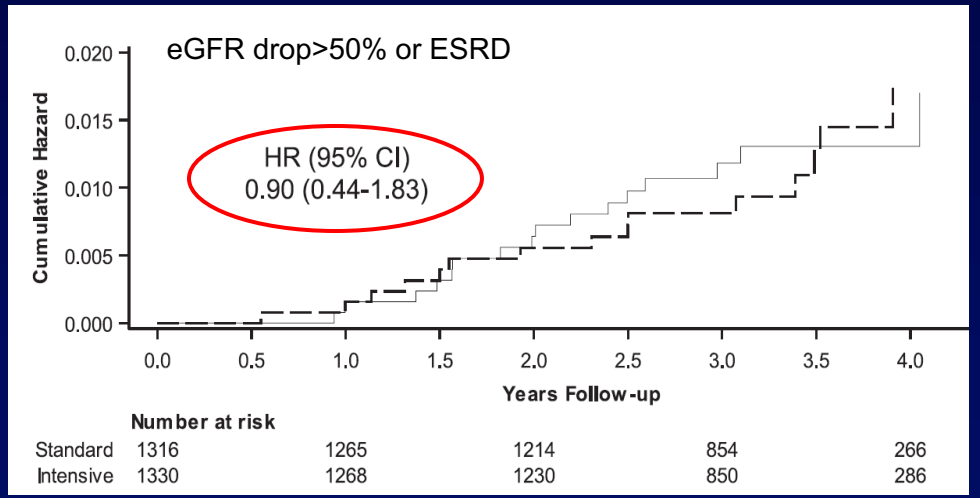


Beddu et al. J Am Heart Assoc 2018

The SPRINT Study: Outcomes in CKD Patients



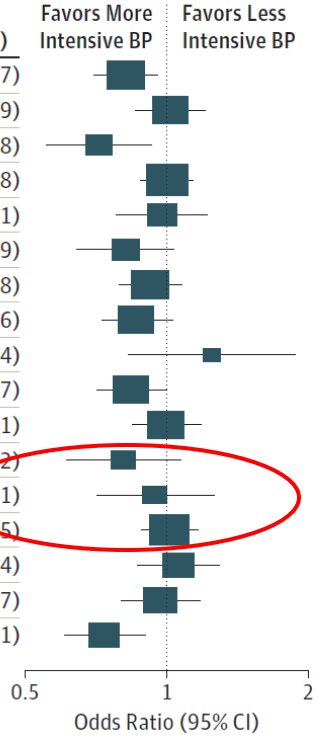
n=2446
age 72 years
eGFR 47.9 ml/min
UACR 81 mg/g



Cheung et al, J Am Soc Nephrol 2017

Mortality with different BP Targets in CKD Stage 3-5

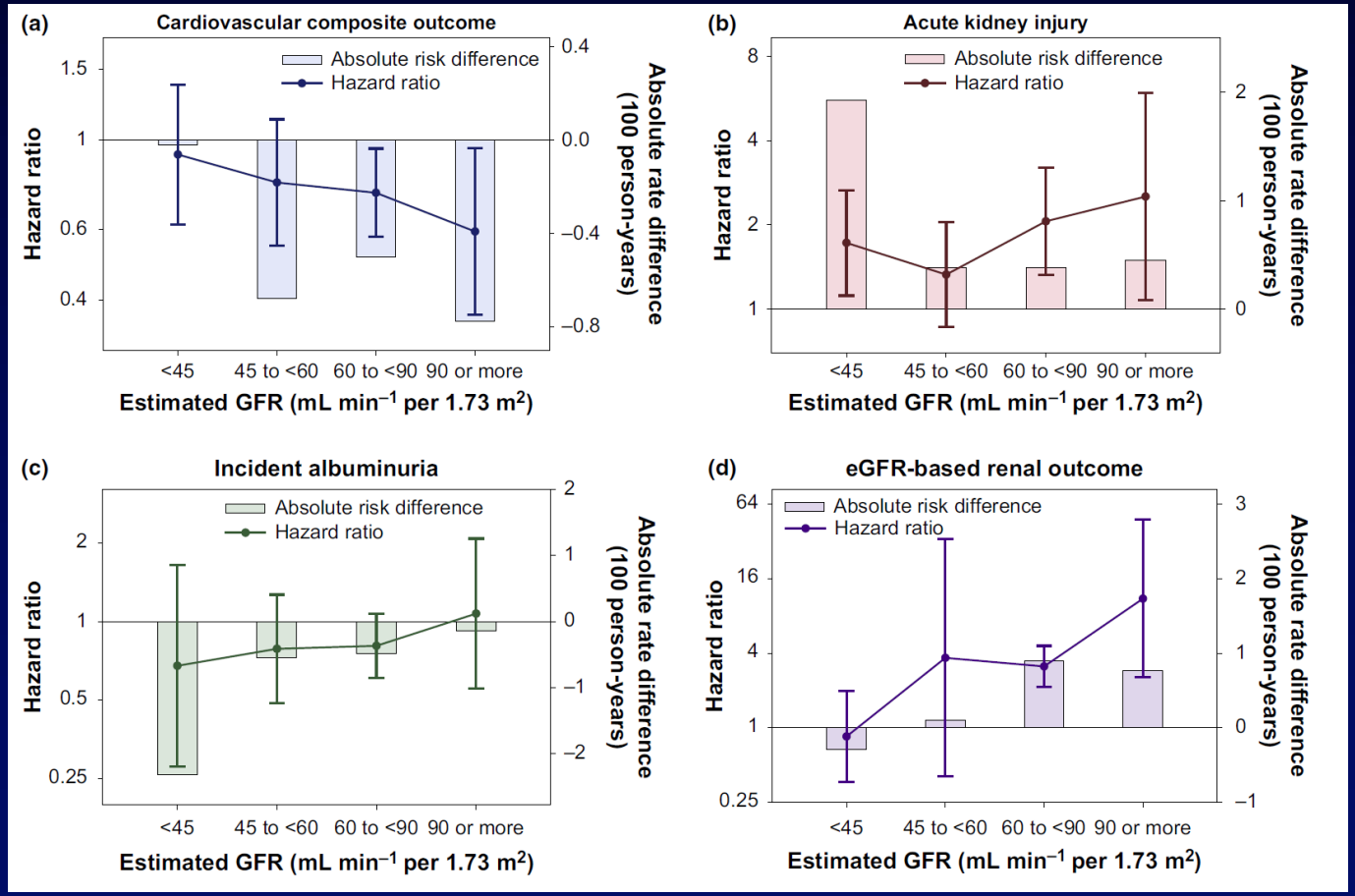
Subgroup		No. of Trials	No. of Deaths/Total No. More Intensive BP	No. of Deaths/Total No. Less Intensive BP	Odds Ratio (95% CI)	*P* Value for Heterogeneity
Drug vs placebo		5	328/2976	395/3006	0.819 (0.700-0.957)	.06
Defined BP arms		13	256/4375	314/5467	1.020 (0.860-1.209)	
Follow-up	<3 y	4	112/1223	153/1242	0.718 (0.555-0.928)	.38
	≥3 y	14	472/6128	556/7231	1.002 (0.882-1.138)	
Diabetes	Yes	6	174/1428	178/1431	0.977 (0.781-1.221)	.29
	No	6	131/2552	156/2515	0.818 (0.644-1.039)	
Severe renal dysfunction	Yes	10	307/4960	403/6051	0.925 (0.793-1.078)	.56
	No	8	277/2468	306/2395	0.863 (0.726-1.026)	
Baseline SBP	<140 mm Hg	6	55/929	44/916	1.247 (0.830-1.874)	.14
	140-160 mm Hg	8	275/3293	315/3225	0.842 (0.710-0.997)	
	>160 mm Hg	4	254/3129	350/4302	0.998 (0.843-1.181)	
Achieved SBP	<125 mm Hg	4	97/1602	116/1575	0.811 (0.613-1.072)	.37
	125-135 mm Hg	8	96/1542	101/1538	0.945 (0.708-1.261)	
	>135 mm Hg	6	391/4207	492/5360	1.014 (0.882-1.165)	
SBP difference	≤6 mm Hg	7	175/2550	244/3750	1.059 (0.866-1.294)	.06
	>6 to <12 mm Hg	7	229/2434	228/2359	0.971 (0.800-1.177)	
	≥12 mm Hg	4	180/2367	237/2364	0.761 (0.621-0.931)	



- 18 trials
- n=15,294
- mortality

Malhotra et al, JAMA Int Med 2018

The SPRINT Study: outcomes by baseline eGFR



Obi et al, J Int Med 2017

Chapter 3. Blood Pressure Management in Non-dialysis CKD Patients with and without Diabetes

3.2. Treatment with RAAS inhibitors (RAASi) and other antihypertensives

Recommendation 3.2.1. We suggest starting RAASi (ACEi or ARB) for people with concomitant CKD without diabetes, albuminuria (≥3 mg/mmol, G1-G4, A2, A3), and high BP (2C).

Recommendation 3.2.2. We recommend RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, albuminuria (≥3 mg/mmol), normal or low GFR (G1-G4, A2, A3), and high BP (1B).

Recommendation 3.2.3. We suggest RAASi (ACEi or ARB) for people with concomitant CKD and diabetes, eGFR <60 ml/min/1.73 m2, normal albuminuria, and high BP (2C).

Chapter 3. Blood Pressure Management in Non-dialysis CKD Patients with and without Diabetes

3.2. Treatment with RAAS inhibitors (RAASi) and other antihypertensives

Practice Point 3.2.1. RAASi (ACEi or ARB) should be administered using maximally recommended doses to achieve the benefits described because the proven benefits were achieved in trials using this dose.

Practice Point 3.2.2. Monitor for changes in blood pressure, serum creatinine, and serum potassium within two to four weeks of initiation or increase in the dose of an ACEi or ARB.

Practice Point 3.2.3. Reduce the dose or discontinue ACEi or ARB in the setting of symptomatic hypotension, uncontrolled hyperkalemia despite medical treatment, or while preparing for imminent kidney replacement therapy.

Practice Point 3.2.4. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR.

3.3. Role of dual therapy with RAAS inhibition

Recommendation 3.3.1. We recommend not treating with any combination of ACEi, ARB, and direct renin inhibitor therapy in patients with CKD with or without diabetes (1B).

KDIGO BP Public Review Document 2019

CREDENCE study

Nephrol Dial Trans

A Primary Composite Outcome

RESEARCH RECOMMENDATIONS

- SGLT2 inhibitors have major CV, kidney. and survival benefits among patients with CKD and concomitant T2D. In addition to reducing BP, they cause an early, acute fall in GFR, a pattern that is also observed in intensive SBP-lowering. The effects of these drugs in combination with intensive BP-lowering therapy on CV outcomes, all-cause mortality, as well as acute and chronic changes in kidney function require further examination.
- Conduct studies examining the combination of RAAS blockade with endothelin blockade, SGLT-2 inhibition, or GLP-1 receptor activation and other therapies for potential kidney benefits.

Pantelis Sara
Radovan Ho
Ziad Massy[11]
Francesca Mallamaci[15] and Mads Hornum[16]
...don[10],

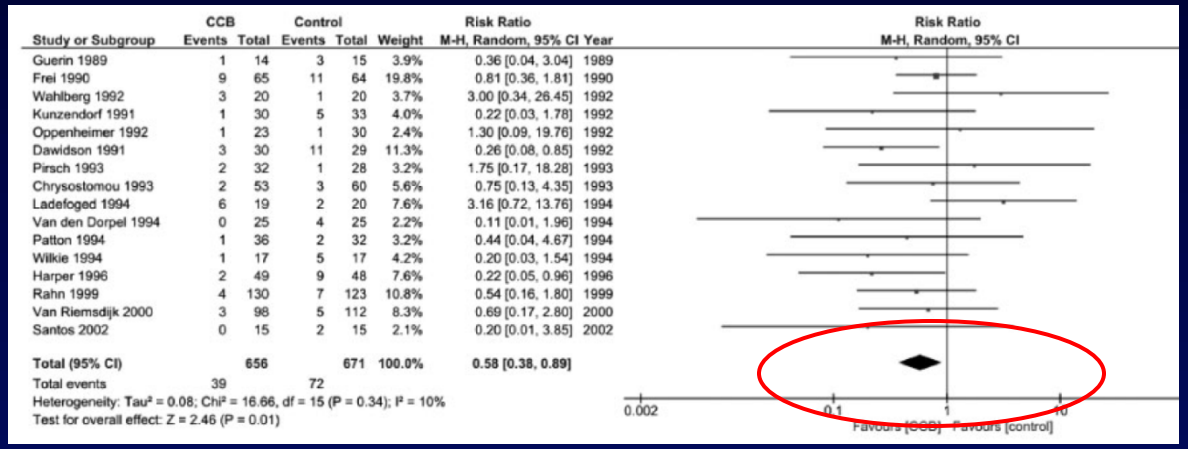
Perkovic et al. *N Engl J Med* 2019

Chapter 4. Blood Pressure Management in Kidney Transplant Recipients

Recommendation 4.1. We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).

Practice Point 4.1. Treat adult kidney transplant recipients with high BP to a target BP that is <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1.).

CCB vs control in kidney transplant recipients

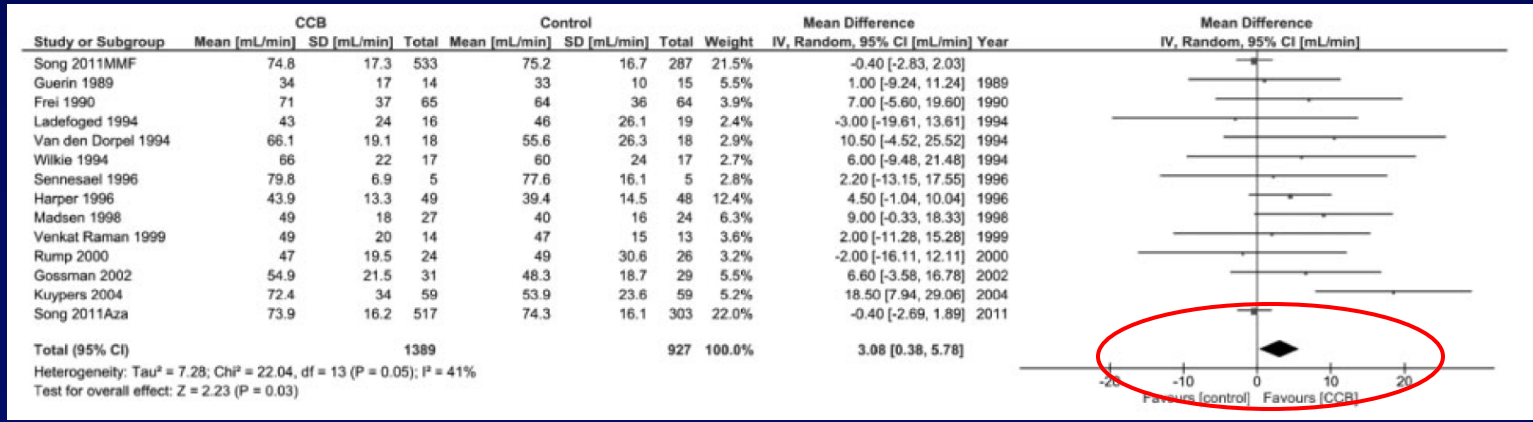


Study or Subgroup	CCB Events	CCB Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Guerin 1989	1	14	3	15	3.9%	0.36 [0.04, 3.04]	1989
Frei 1990	9	65	11	64	19.8%	0.81 [0.36, 1.81]	1990
Wahlberg 1992	3	20	1	20	3.7%	3.00 [0.34, 26.45]	1992
Kunzendorf 1991	1	30	5	33	4.0%	0.22 [0.03, 1.78]	1992
Oppenheimer 1992	1	23	1	30	2.4%	1.30 [0.09, 19.76]	1992
Dawidson 1991	3	30	11	29	11.3%	0.26 [0.08, 0.85]	1992
Pirsch 1993	2	32	1	28	3.2%	1.75 [0.17, 18.28]	1993
Chrysostomou 1993	2	53	3	60	5.6%	0.75 [0.13, 4.35]	1993
Ladefoged 1994	6	19	2	20	7.6%	3.16 [0.72, 13.76]	1994
Van den Dorpel 1994	0	25	4	25	2.2%	0.11 [0.01, 1.96]	1994
Patton 1994	1	36	2	32	3.2%	0.44 [0.04, 4.67]	1994
Wilkie 1994	1	17	5	17	4.2%	0.20 [0.03, 1.54]	1994
Harper 1996	2	49	9	48	7.6%	0.22 [0.05, 0.96]	1996
Rahn 1999	4	130	7	123	10.8%	0.54 [0.16, 1.80]	1999
Van Riemsdijk 2000	3	98	5	112	8.3%	0.69 [0.17, 2.80]	2000
Santos 2002	0	15	2	15	2.1%	0.20 [0.01, 3.85]	2002
Total (95% CI)		**656**		**671**	**100.0%**	**0.58 [0.38, 0.89]**	
Total events	39		72				

Heterogeneity: Tau² = 0.08; Chi² = 16.66, df = 15 (P = 0.34); I² = 10%
Test for overall effect: Z = 2.46 (P = 0.01)

Graft loss

eGFR/CrCl



Study or Subgroup	CCB Mean [mL/min]	CCB SD [mL/min]	CCB Total	Control Mean [mL/min]	Control SD [mL/min]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mL/min]	Year
Song 2011MMF	74.8	17.3	533	75.2	16.7	287	21.5%	-0.40 [-2.83, 2.03]	
Guerin 1989	34	17	14	33	10	15	5.5%	1.00 [-9.24, 11.24]	1989
Frei 1990	71	37	65	64	36	64	3.9%	7.00 [-5.60, 19.60]	1990
Ladefoged 1994	43	24	16	46	26.1	19	2.4%	-3.00 [-19.61, 13.61]	1994
Van den Dorpel 1994	66.1	19.1	18	55.6	26.3	18	2.9%	10.50 [-4.52, 25.52]	1994
Wilkie 1994	66	22	17	60	24	17	2.7%	6.00 [-9.48, 21.48]	1994
Sennesael 1996	79.8	6.9	5	77.6	16.1	5	2.8%	2.20 [-13.15, 17.55]	1996
Harper 1996	43.9	13.3	49	39.4	14.5	48	12.4%	4.50 [-1.04, 10.04]	1996
Madsen 1998	49	18	27	40	16	24	6.3%	9.00 [-0.33, 18.33]	1998
Venkat Raman 1999	49	20	14	47	15	13	3.6%	2.00 [-11.28, 15.28]	1999
Rump 2000	47	19.5	24	49	30.6	26	3.2%	-2.00 [-16.11, 12.11]	2000
Gossman 2002	54.9	21.5	31	48.3	18.7	29	5.5%	6.60 [-3.58, 16.78]	2002
Kuypers 2004	72.4	34	59	53.9	23.6	59	5.2%	18.50 [7.94, 29.06]	2004
Song 2011Aza	73.9	16.2	517	74.3	16.1	303	22.0%	-0.40 [-2.69, 1.89]	2011
Total (95% CI)			**1389**			**927**	**100.0%**	**3.08 [0.38, 5.78]**	

Heterogeneity: Tau² = 7.28; Chi² = 22.04, df = 13 (P = 0.05); I² = 41%
Test for overall effect: Z = 2.23 (P = 0.03)

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Chapter 5. Blood Pressure Management in Children with CKD

Recommendation 5.1. We suggest that in children with CKD, BP should be treated to lower 24-hour mean arterial pressure (MAP) by ABPM to less than or equal to the 50th percentile for age, sex, and height (2C).

Practice Point 5.1. We suggest monitoring BP once a year with ABPM, and monitoring every three to six months with standardized auscultatory office BP.

Practice Point 5.2. Use ACEi or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated but they carry risk of hyperkalemia and have adverse fetal risks for pregnant women.

KDIGO BP Standpoint: Key Point Summary

• Recommendation for standardized office BP measurements (because they were used in ACCORD and SPRINT) (1B)

BUT: No RCT comparing standardized vs routine BP measurement in CKD

• Suggestion for target SBP <120 mmHg using standardized office BP (2B)

BUT: Evidence only from SPRINT sub-analysis with negative primary outcome

Little evidence for patients with advanced CKD, DM, low DBP, very old

What if standardized BP measurement is not feasible?

• Suggestion to lower salt and use CCB in transplant patients; no change in RAS use, children

BUT: no info on SGLT2-inhibitors despite hard evidence

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Thank you !