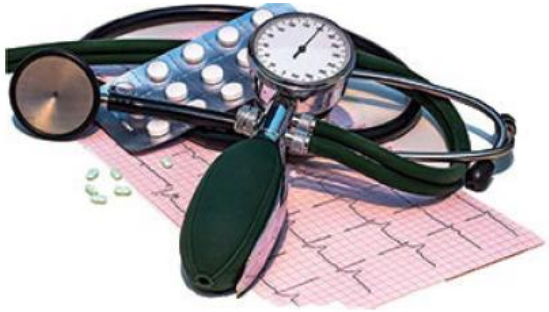
# Blood pressure and CKD: the lower the better?

JM Krzesinski

Nephrology department

CHU Liège



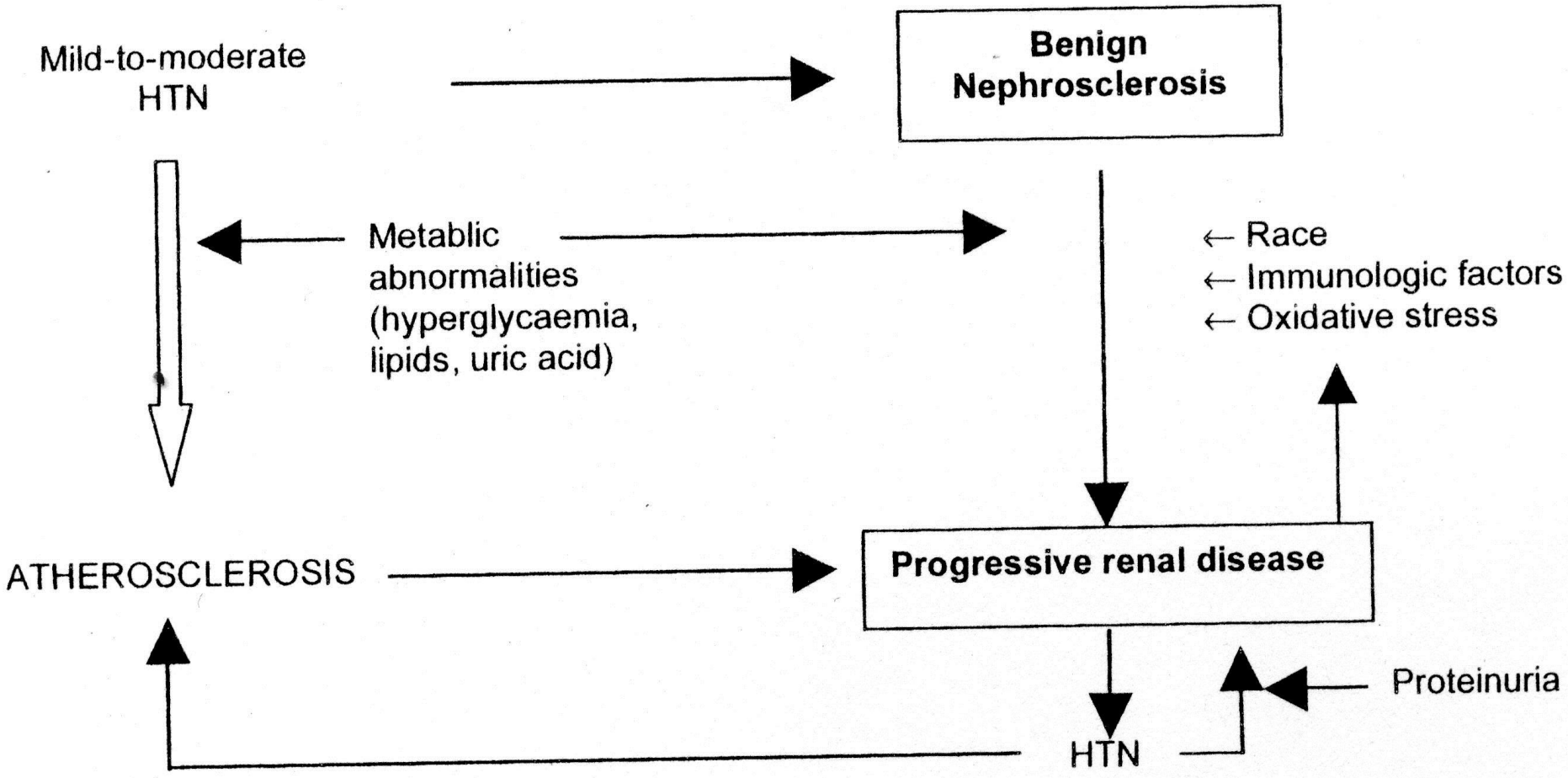
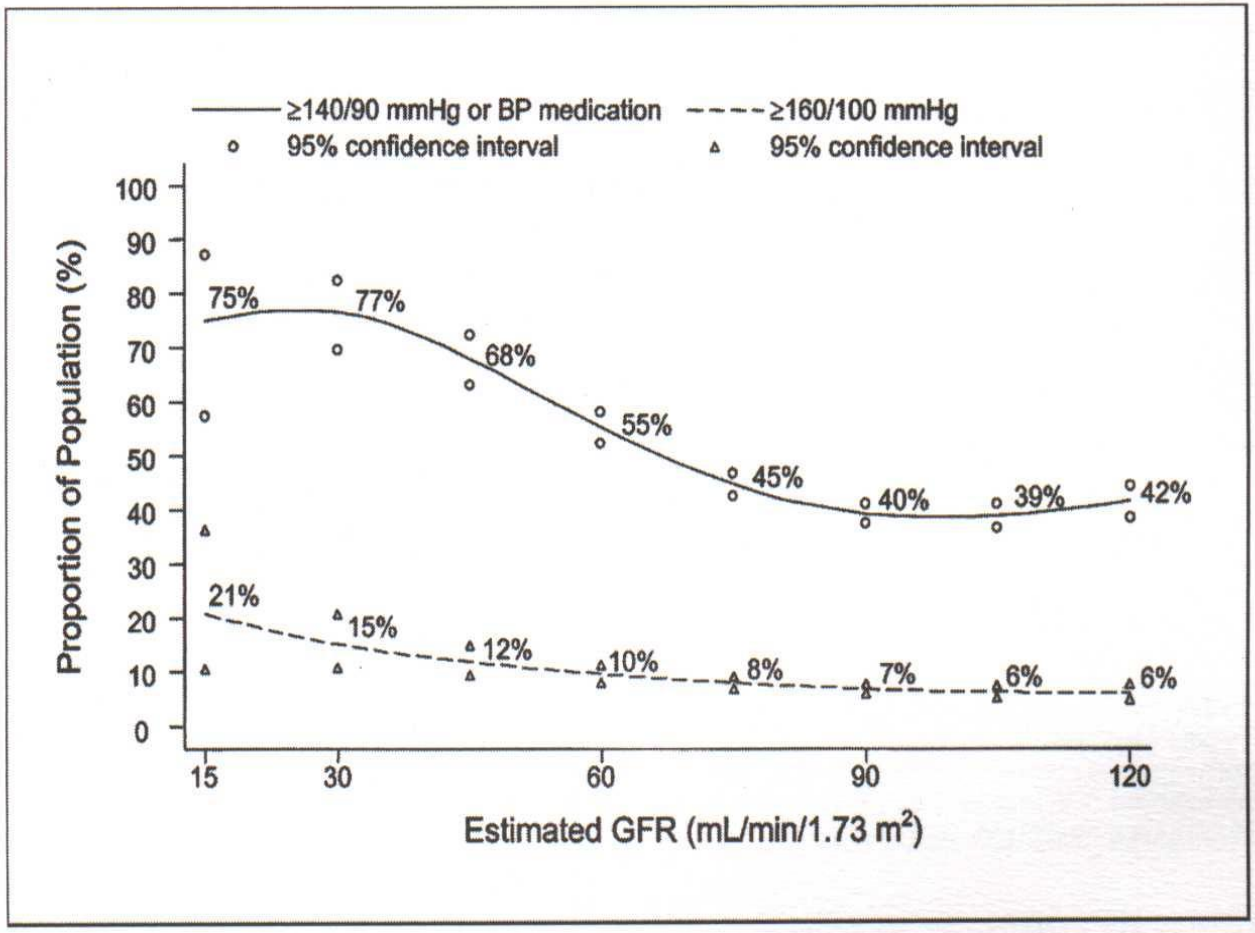



***Figure 1 :*** *Relation between Hypertension and Chronic Kidney Disease*

Krzesinski J-M and Cohen E., *Acta Clinica Belgica* 2007, **62**, 5-14.

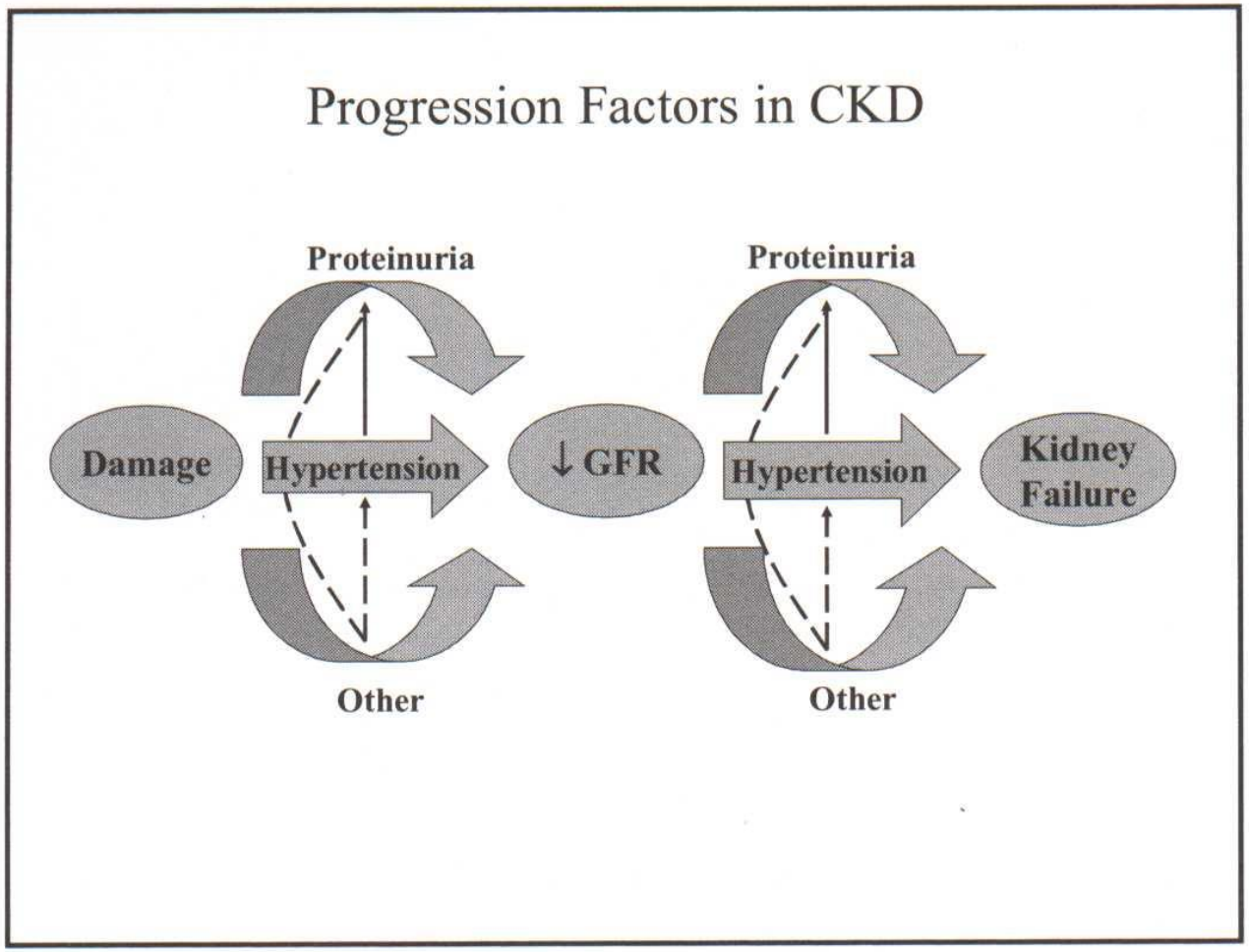
## Figure E.2. Prevalence of High Blood Pressure by Level of GFR, Adjusted to Age 60 Years (NHANES III)




Prevalence of hypertension by level of GFR, adjusted to age 60 years in NHANES III. GFR was estimated using the abbreviated MDRD Study equation. Hypertension was defined as JNC >Stage 1 (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg, or taking medications for hypertension) or JNC >Stage 2 (systolic blood pressure >160 or diastolic blood pressure >100 mm Hg). Values are adjusted to age 60 years using a polynomial regression. 95% confidence interval are shown at selected levels of estimated GFR. Reproduced with permission.

Role of salt retention
Endothelial dysfunction
Sympathetic and RAS systems activation

## Figure E.6. Risk Factors for Kidney Disease Progression Related to Blood Pressure Management

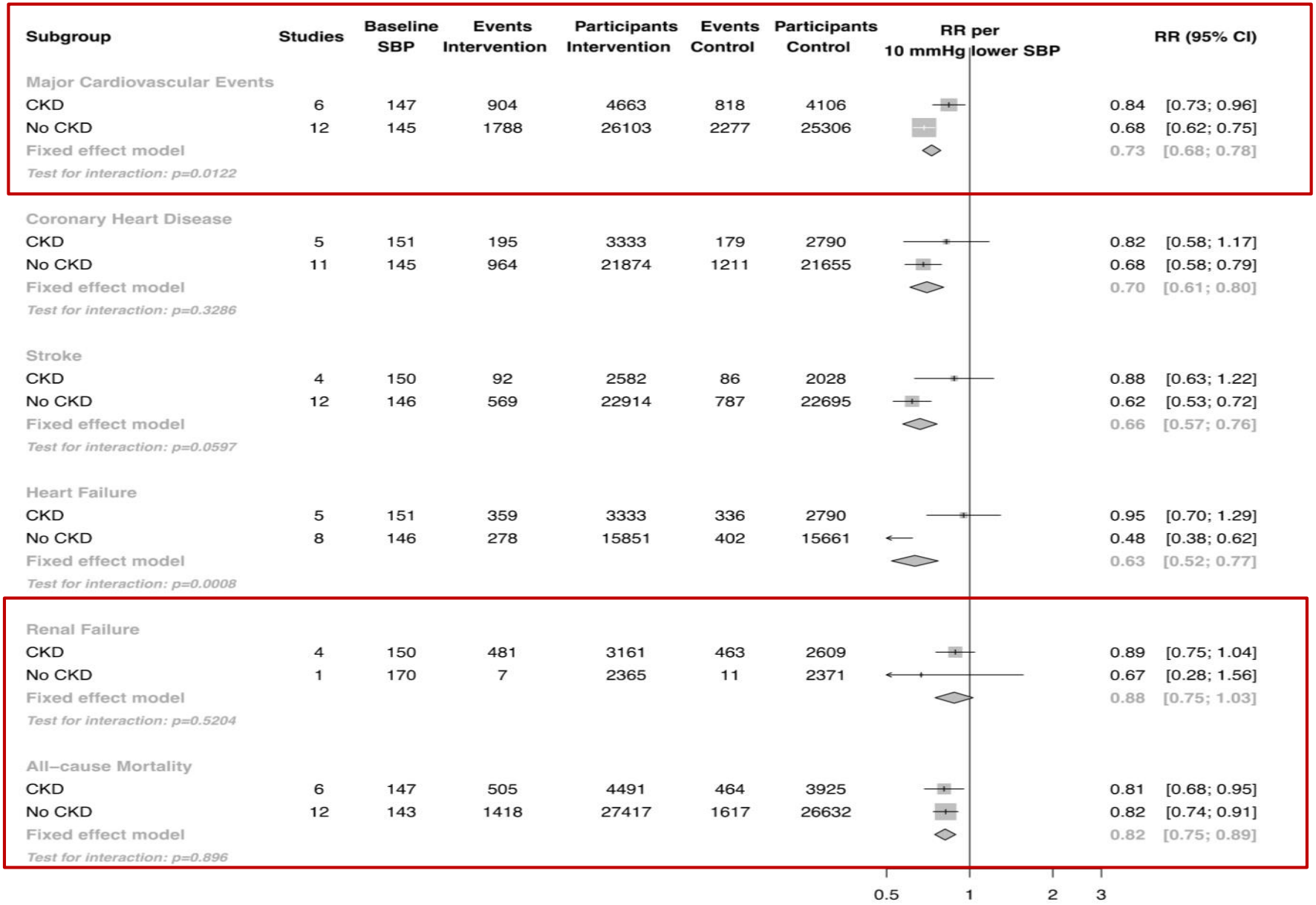



Shaded ellipses represent stages of kidney disease. Thick arrows between ellipses represent "risk factors" associated with progression of disease that can be affected by interventions. Thin arrows represent relationships between risk factors. Dashed lines indicate hypothesized relationships.

K/DOQI Clinical Practice guidelines, Executive Summary, October 2003.

# Meta-analysis 123 studies (>600000 pts) : 10 mmHg lower SBP lower all-cause mortality

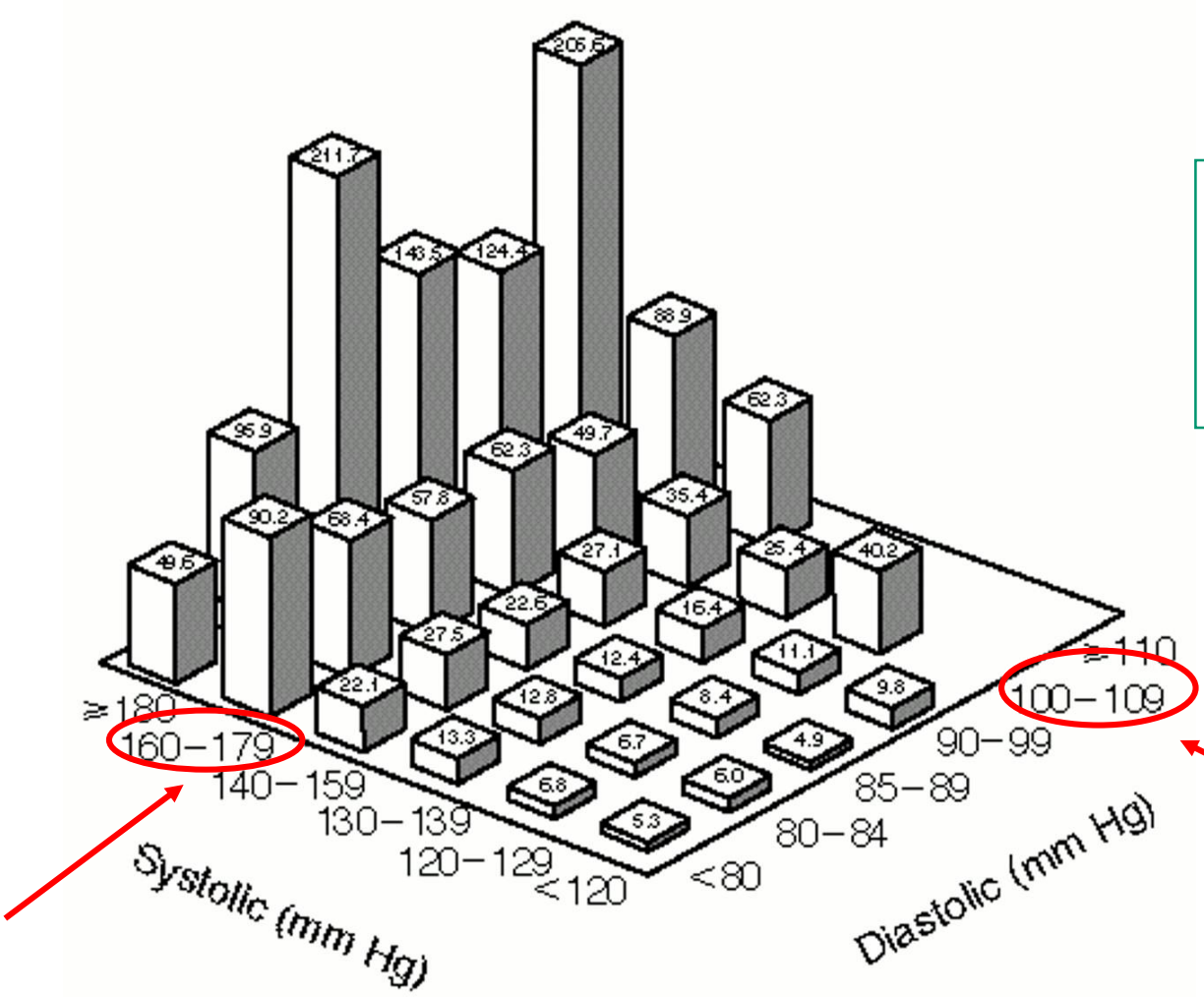
Ettehad et al. Lancet 2016, p957



# Questions

- What is the optimal level of BP in CKD patients for preventing CV events and kidney disease progression?
- Is this BP target influenced by proteinuria or aging?

Age-Adjusted Rate of ESRD Due to Any Cause per 100.000 Person-Years, According to Systolic and Diastolic BP in 332.544 Men Screened for MRFIT




stage 2 HTA
⟶ ESRD

Klag et al, NEJM 1996

# Blood Pressure Components and End-stage Renal Disease in Persons With Chronic Kidney Disease

## *The Kidney Early Evaluation Program (KEEP)*

*Carmen A. Peralta, MD; Keith C. Norris, MD; Suying Li, PhD; Tara I. Chang, MD; Manjula K. Tamura, MD; Stacey E. Jolly, MD; George Bakris, MD; Peter A. McCullough, MD; Michael Shlipak, MD;*

*Arch Intern Med. 2012;172(1):41-*

16129 CKD patients FU 3y

**Table 2. Association of Each Blood Pressure (BP) Component With Incident ESRD Among KEEP Participants With Chronic Kidney Disease**

| BP, mm Hg | Patients, No. | Age- and Sex-Adjusted HR (95% CI) | Adjusted[a] HR (95% CI) |
|---|---|---|---|
| Systolic | | | |
| <130 | 4556 | 1 [Reference] | 1 [Reference] |
| 130-139 | 2932 | 1.08 (0.74-1.59) | 0.71 (0.48-1.05) |
| 140-149 | 2481 | 1.72 (1.21-2.45) | 1.27 (0.88-1.83) |
| ≥150 | 3685 | 3.36 (2.51-4.49) | 1.36 (1.02-1.85) |
| Diastolic | | | |
| <60 | 692 | 1.40 (0.81-2.41) | 1.12 (0.65-1.95) |
| 60-74 | 5207 | 1 [Reference] | 1 [Reference] |
| 75-89 | 5716 | 0.90 (0.69-1.17) | 0.91 (0.69-1.19) |
| ≥90 | 2039 | 1.67 (1.25-2.23) | 1.81 (1.33-2.45) |

[a] Adjusted for age, sex, race/ethnicity, insurance, access to a physician, current smoking, diabetes mellitus, body mass index, baseline estimated glomerular filtration rate, albuminuria, and prevalent cardiovascular disease.

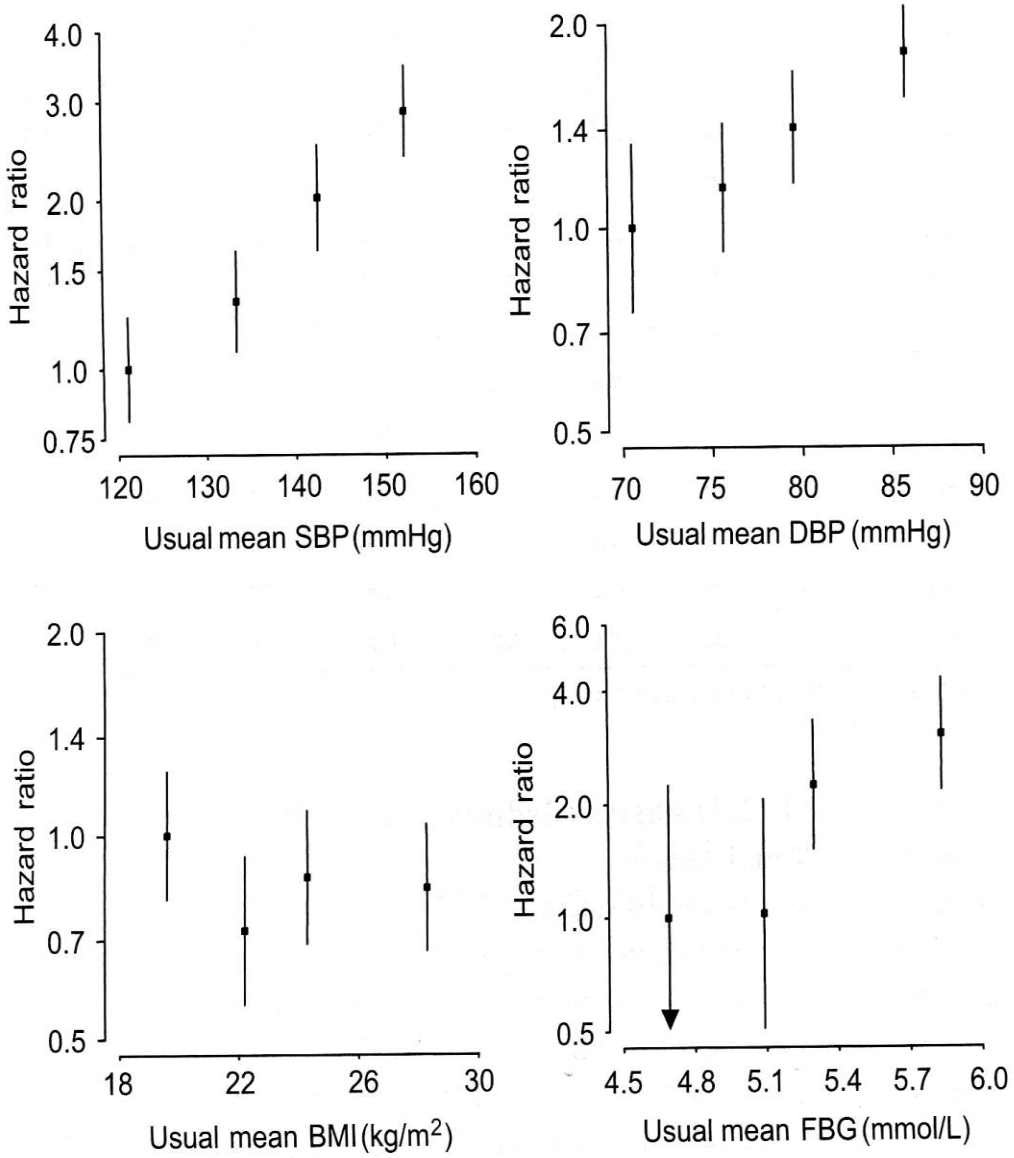



**Figure 1.** HRs, with 95% CIs, for renal death for usual levels of SBP (millimeters of mercury), DBP (millimeters of mercury), FBG (millimoles per liter), and BMI (kilograms per meter squared) by fourths (base: lowest fourth).

560352 pts, FU 6.8y
420 renal deaths
HR 1.84 for each
19 mmHg increase of SBP

O'Seaghdha C. et al., *Hypertension*, 2009, **54**, 509-515.

For CKD not on dialysis, until 2015, the guidelines were:

**Table 1** | Blood pressure targets and treatment recommendations in CKD

| Guideline | Blood pressure target in CKD without proteinuria* | Blood pressure target in CKD with proteinuria | Recommended first line medication |
|---|---|---|---|
| USA JNC8[91] | <140/<90 mmHg | <140/<90 mmHg | ACEI or ARB |
| KDIGO[76] | <140/<90 mmHg | <130/<80 mmHg | ACEI or ARB |
| NICE[80] | <140/<90 mmHg | <130/<80 mmHg | ACEI or ARB‡ |
| CHEP[78] | <140/<90 mmHg | <140/<90 mmHg | ACEI; ARB if ACEI intolerant |
| ESC/ESH[79] | <140 mmHg | <130 mmHg | ACEI or ARB |
| ASH/ISH[123] | <140/<90 mmHg | <140/<90 mmHg§ | ARB or ACEI |
| ISHIB[124] | <130/<80 mmHg | <130/<80 mmHg | Diuretic or CCB |

*Nat. Rev. Nephrol.* advance online publication 28 July 2015;

# CKD-BP lowering

- African American Study of Kidney Disease and Hypertension (J. Wright et al JAMA 2002)
  - Overall showed no benefit in BP< 140/90 for adults with hypertensive kidney disease
  - Suggested benefits in those with proteinuria
- Modification of Diet in Renal Disease (J Am Soc Nephrol 1997)
  - 585 participants without diabetes
  - 24% had polycystic kidney disease
  - Beneficial effect noted in those with proteinuria

**Effect of Blood Pressure Lowering and Antihypertensive Drug Class on Progression of Hypertensive Kidney Disease**
Results From the AASK Trial

JAMA, November 20, 2002-

The AASK is the first published large-scale trial to our knowledge that examines both the effect of 3 different antihypertensive regimens as well as the effect of 2 BP goals on decline in kidney function in a population with chronic kidney disease attributed to hypertensive nephrosclerosis.[38]

# BP Control and Long-Term Risk of ESRD and Mortality

AASK

**Table 1.** Characteristics of participants in AASK with long–term follow-up by BP arm assignment at time of randomization

| Characteristics at Time of Randomization | Strict BP, *n*=522 | Usual BP, *n*=545 | *P* Value |
|---|---|---|---|
| Mean age ± SD, yr | 54.3±10.8 | 54.2±10.4 | 0.78 |
| Men | 321 (61.5) | 332 (60.9) | 0.85 |
| Systolic BP ± SD, mmHg | 151.6±24.9 | 149.1±22.6 | 0.09 |
| Diastolic BP ± SD, mmHg | 96.2±14.8 | 94.9±13.7 | 0.14 |
| Mean GFR ± SD, ml/min per 1.73 $m^2$ | 46.8±13.3 | 46.1±14.0 | 0.40 |
| Median proteinuria [interquartile range], g/d | 0.12 [0.04, 0.53] | 0.11 [0.04,0.59] | 0.75 |
| Current smoker | 176 (33.7) | 135 (24.8) | 0.004 |
| Heart disease[a] | 282 (54.0) | 264 (48.4) | 0.07 |
| Drug arm assignment | | | 0.91 |
| Angiotensin–converting enzyme inhibitor | 207 (39.7) | 218 (40.0) | |
| β-Blocker | 209 (40.0) | 222 (40.7) | |
| Calcium channel blocker | 106 (20.3) | 105 (19.3) | |

*J Am Soc Nephrol* 28: 671–677, 2017.

J Am Soc Nephrol 28: 671–677, 2017

# BP Control and Long-Term Risk of ESRD and Mortality

AASK

Usual BP 141/85
Strict BP 128/78

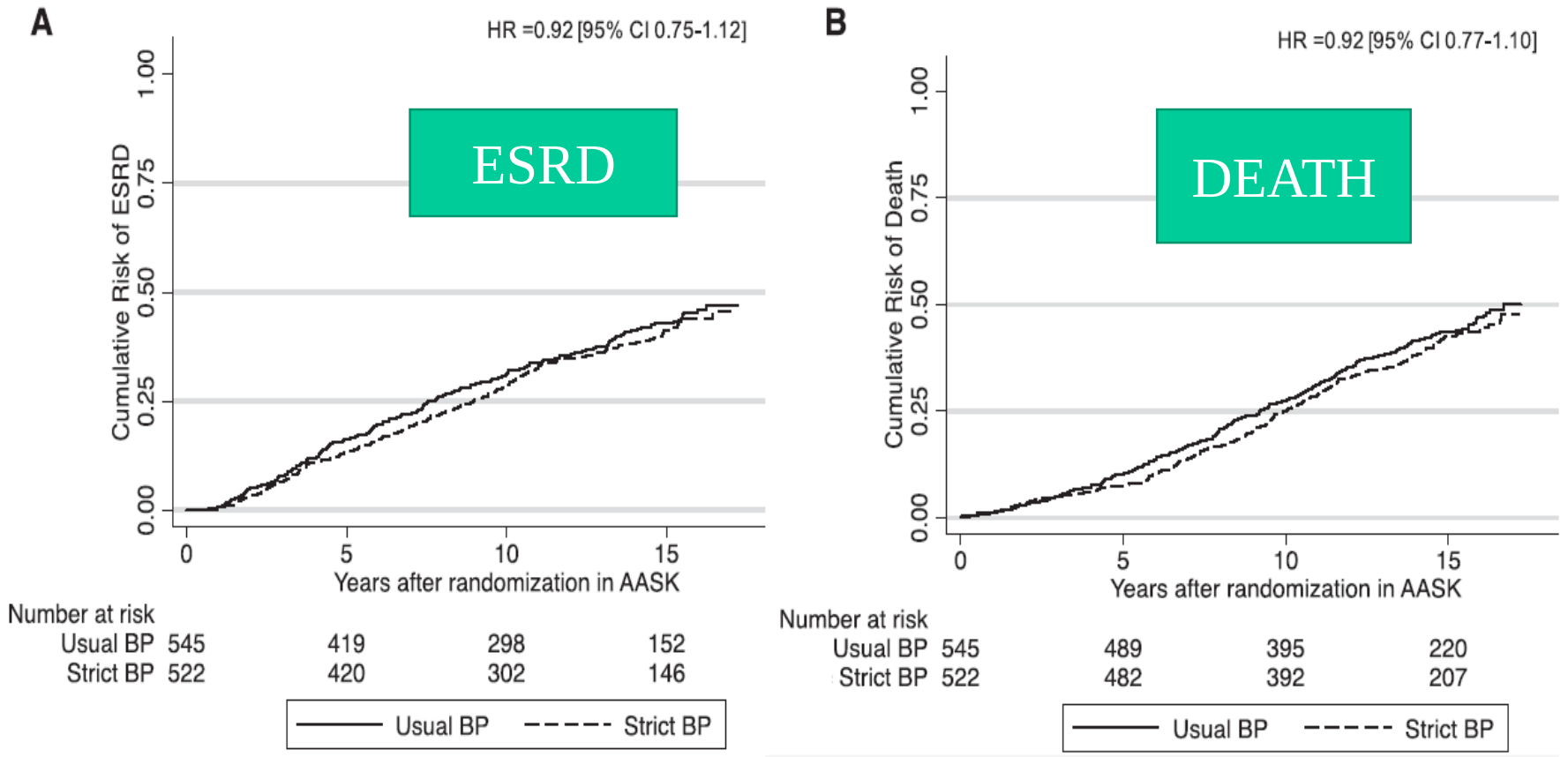
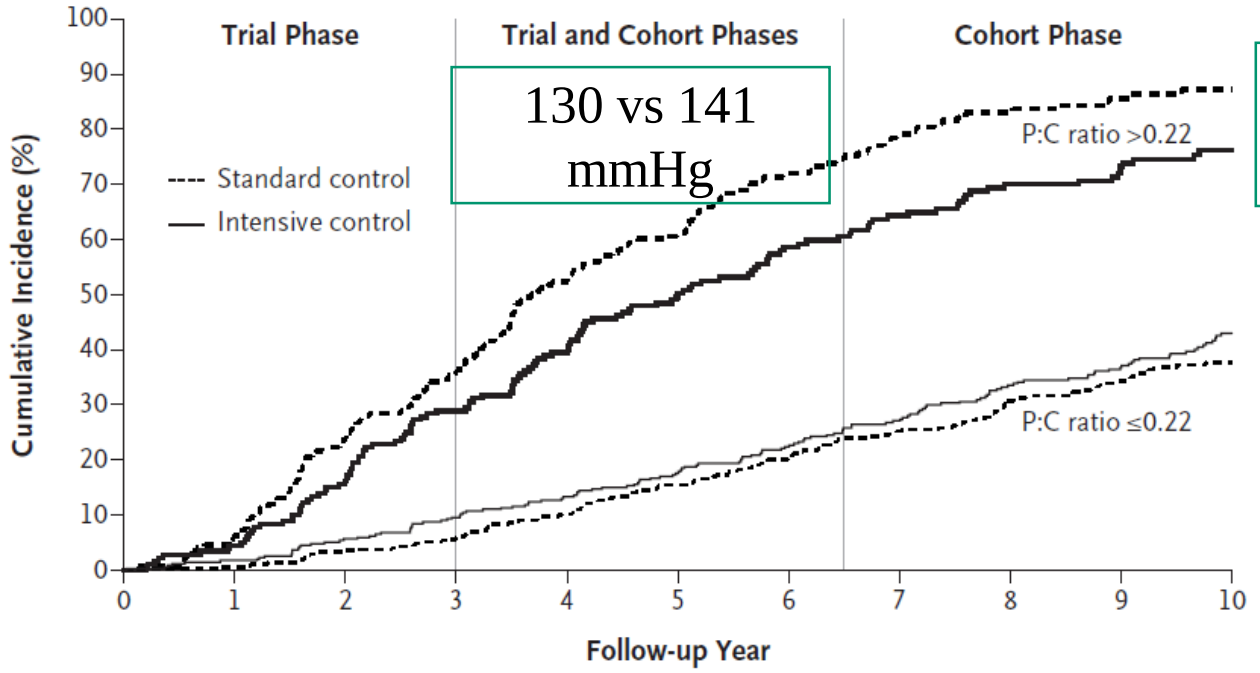



**Figure 2.** Long-term risk of adverse outcomes in AASK. Risk of (A) ESRD and (B) death during long–term extended follow-up of participants in the AASK.

# Intensive Blood-Pressure Control in Hypertensive Chronic Kidney Disease

AASK Collaborative Research Group




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 |

**Figure 2. Cumulative Incidence of the Composite Primary Outcome, According to Baseline Proteinuria Status.**

# Association between strict blood pressure control during chronic kidney disease and lower mortality after onset of end-stage renal disease

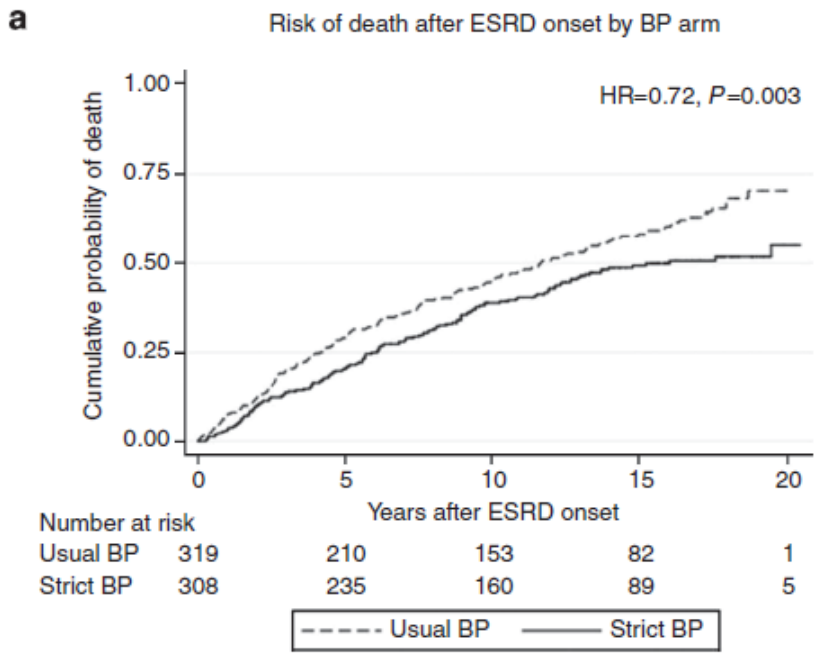
*Kidney International* (2015) **87,** 1055–106

median follow-up of 19.3 years. (MDRD)

randomized 840 patients with CKD to strict (mean arterial pressure under 92 mm Hg) versus usual (mean arterial pressure under 107 mm Hg) blood pressure control between

140/90 vs 125/75





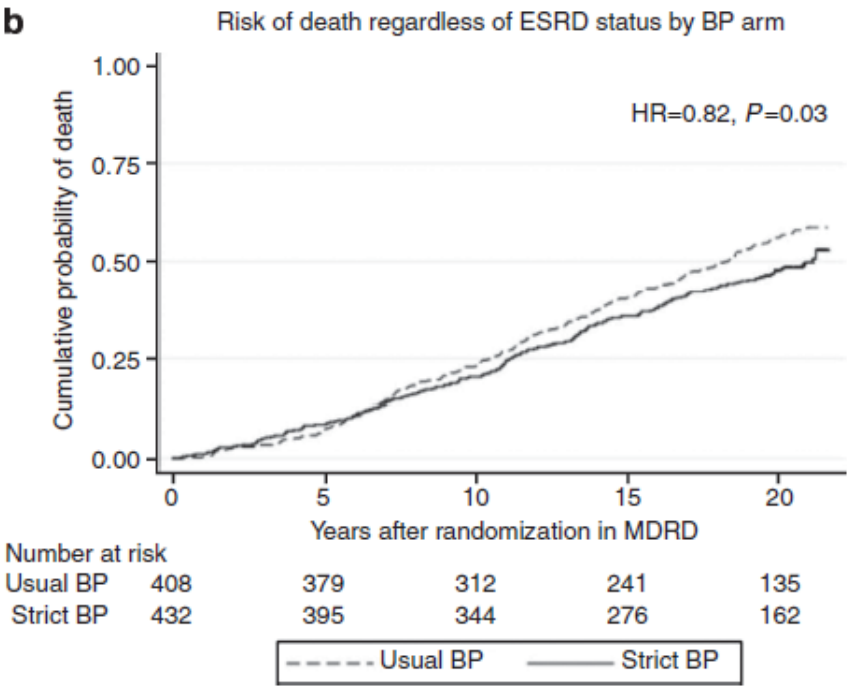
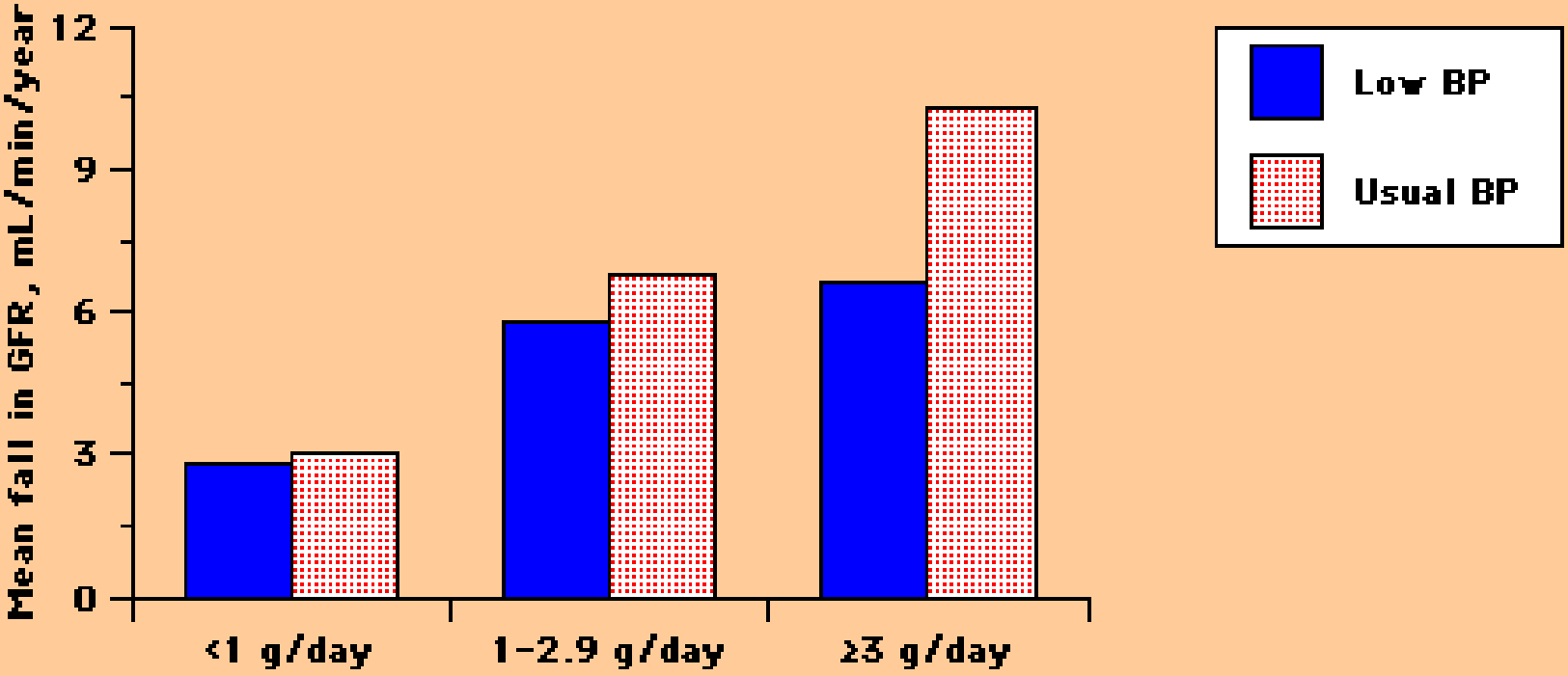




**Figure 2 | Risk of death during long-term extended follow-up of MDRD trial participants.** (**a**) Risk of death after ESRD onset by BP arm. (**b**) Risk of death regardless of ESRD status by BP arm.

Thus, although strict blood pressure control did not delay progression of CKD to ESRD, this strategy was associated with a lower risk of death after ESRD




**Aggressive BP control preserves renal function in proteinuric patients**

Mean fall in glomerular filtration rate (GFR) according to the degree of proteiuria in patients treated with usual blood pressure control (mean BP about 130/80) or with more aggressive antihypertensive therapy in which the mean BP was 4.7 mmHg lower over a three year period. The rate of fall in GFR varied directly with protein excretion and the benefit of aggressive BP control was absent in the 420 patients excreting less tean 1 g/day, modest in the 104 patients excreting between1 and 3 g/day, and substantial (3.5 mL/min per year slower) and statistically significant in the 54 patients excreting at least 3 g/day. (Data from Klahr, S, Levey, AS, Beck, GJ, et al, N Engl J Med 1994; 330:877.)

JAMA Internal Medicine | Original Investigation

# Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5

## A Systematic Review and Meta-analysis

*JAMA Intern Med.* doi:10.1001/jamainternmed.2017.4377
Published online September 5, 2017.

Rakesh Malhotra, M

**132 vs 140 mmHg**

**RESULTS** This study identified 30 RCTs that potentially met the inclusion criteria. The CKD subset mortality data were extracted in 18 trials, among which there were 1293 deaths in 15 924 participants with CKD. The mean (SD) baseline systolic BP (SBP) was 148 (16) mm Hg in both the more intensive and less intensive arms. The mean SBP dropped by 16 mm Hg to 132 mm Hg in the more intensive arm and by 8 mm Hg to 140 mm Hg in the less intensive arm. More intensive vs less intensive BP control resulted in 14.0% lower risk of all-cause mortality (odds ratio, 0.86; 95% CI, 0.76-0.97; *P* = .01), a finding that was without significant heterogeneity and appeared consistent across multiple subgroups.

**CONCLUSIONS AND RELEVANCE** Randomization to more intensive BP control is associated with lower mortality risk among trial participants with hypertension and CKD. Further studies are required to define absolute BP targets for maximal benefit and minimal harm.

JAMA Internal Medicine | Original Investigation

# Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease

## A Systematic Review and Meta-analysis

Wan-Chuan Tsai, M

JAMA Intern Med. 2017;177(6):792-799.

**OBJECTIVE** To compare intensive BP control (<130/80 mm Hg) with standard BP control (<140/90 mm Hg) on major renal outcomes in patients with CKD without diabetes.

**MAIN OUTCOMES AND MEASURES** Differences in annual rate of change in GFR were expressed as mean differences with 95% CIs. Differences in doubling of serum creatinine or 50% reduction in GFR, ESRD, composite renal outcome, and all-cause mortality were expressed as risk ratios (RRs) with 95% CIs.

**RESULTS** We identified 9 trials with 8127 patients and a median follow-up of 3.3 years. Compared with standard BP control, intensive BP control did not show a significant difference on the annual rate of change in GFR (mean difference, 0.07; 95% CI, −0.16 to 0.29 mL/min/1.73 $m^2$/y), doubling of serum creatinine level or 50% reduction in GFR (RR, 0.99; 95% CI, 0.76-1.29), ESRD (RR, 0.96; 95% CI, 0.78-1.18), composite renal outcome (RR, 0.99; 95% CI, 0.81-1.21), or all-cause mortality (RR, 0.95; 95% CI, 0.66-1.37). Nonblacks and patients with higher levels of proteinuria showed a trend of lower risk of kidney disease progression with intensive BP control.

JAMA Internal Medicine | Original Investigation

# Association of Intensive Blood Pressure Control and Kidney Disease Progression in Nondiabetic Patients With Chronic Kidney Disease
## A Systematic Review and Meta-analysis

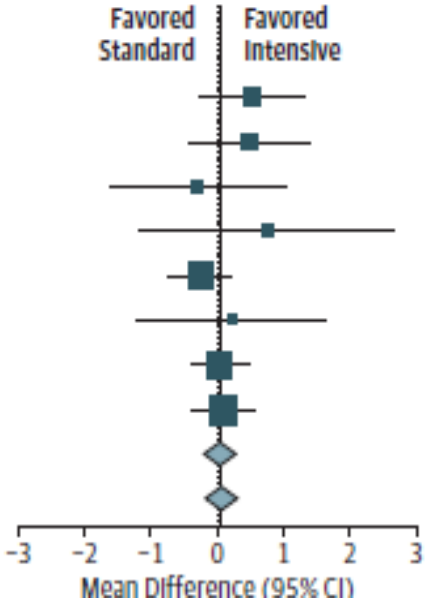
Wan-Chuan Tsai, M

JAMA Intern Med. 2017;177(6):792-799. doi:10.1001/jamainternmed.2017.0197
Published online March 13, 2017.

**Figure. Pooled Estimates Comparing Intensive Blood Pressure Control With Standard Blood Pressure Control on the Study Outcomes**

A Annual rate of change in GFR (mL/min/1.73 $m^2$/y)

| Study | Intensive Total | Intensive Mean (SD) | Standard Total | Standard Mean (SD) | Mean Difference 95% CI | W (Fixed), % | W (Random), % |
|---|---|---|---|---|---|---|---|
| Klahr et al (Study A),[15] 1994 | 300 | −3.57 (4.86) | 285 | −4.10 (4.88) | 0.53 (−0.26 to 1.32) | 8.4 | 8.4 |
| Klahr et al (Study B),[15] 1994 | 132 | −3.70 (3.52) | 123 | −4.20 (3.68) | 0.50 (−0.39 to 1.39) | 6.7 | 6.7 |
| Toto et al,[28] 1995 | 42 | −0.31 (2.92) | 35 | −0.05 (2.96) | −0.26 (−1.58 to 1.06) | 3.0 | 3.0 |
| Schrier et al,[29] 2002 | 41 | −2.75 (4.20) | 34 | −3.51 (4.20) | 0.76 (−1.15 to 2.67) | 1.4 | 1.4 |
| Wright et al,[16] 2002 | 540 | −2.21 (3.95) | 554 | −1.95 (4.00) | −0.26 (−0.73 to 0.21) | 23.6 | 23.6 |
| Ruggenenti et al,[17] 2005 | 93 | −2.64 (4.36) | 80 | −2.88 (4.98) | 0.24 (−1.17 to 1.65) | 2.6 | 2.6 |
| Hayashi et al,[30] 2010 | 1230 | 3.10 (5.47) | 1269 | 3.05 (5.47) | 0.05 (−0.38 to 0.48) | 28.4 | 28.4 |
| Schrier et al,[31] 2014 | 274 | −2.90 (2.71) | 284 | −3.00 (2.71) | 0.10 (−0.35 to 0.55) | 25.9 | 25.9 |
| Fixed-effect model | 2652 | | 2664 | | 0.07 (-0.16 to 0.29) | 100 | NA |
| Random-effects model | | | | | 0.07 (-0.16 to 0.29) | NA | 100 |




**CONCLUSIONS AND RELEVANCE** Targeting BP below the current standard did not provide additional benefit for renal outcomes compared with standard treatment during a follow-up of 3.3 years in patients with CKD without diabetes. However, nonblack patients or those with higher levels of proteinuria might benefit from the intensive BP-lowering treatments.

# New US guidelines November 2017

**BP goal <130/80 mmHg**

**Whelton PK, et al.**

**2017 High Blood Pressure Clinical Practice Guideline: Executive Summary**

## 9.3. Chronic Kidney Disease

| **Recommendations for Treatment of Hypertension in Patients With CKD**<br>References that support recommendations are summarized in Online Data Supplements 37 and 38 and Systematic Review Report. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| I | SBP: B-R[SR]<br>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). |

# SPRINT (NEJM Nov 2015)

## Who can participate?

Men and women age 50 years or older

- With systolic blood pressure of 130 mm Hg or higher
- And at least one of the following
  - A history of CVD, or
  - Stage 3-4 CKD without overt proteinuria
  - At intermediate to high risk for CVD
- Patients with a history of stroke, diabetes, polycystic kidney disease or proteinuric kidney disease are not eligible for SPRINT because of recently completed or ongoing other studies

# A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

This article was published on November 9, 2015, and updated on September 1, 2017, at NEJM.org.

**BACKGROUND**

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

**METHODS**

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

SPRINT: 2 BP goals: <120/80 and <140/90 mmHg
No placebo
BP at the beginning 140/78 mmHg
Difference in BP at the end 15/8 mmHg

# A Randomized Trial of Intensive versus Standard Blood-Pressure Control

Nov 2015

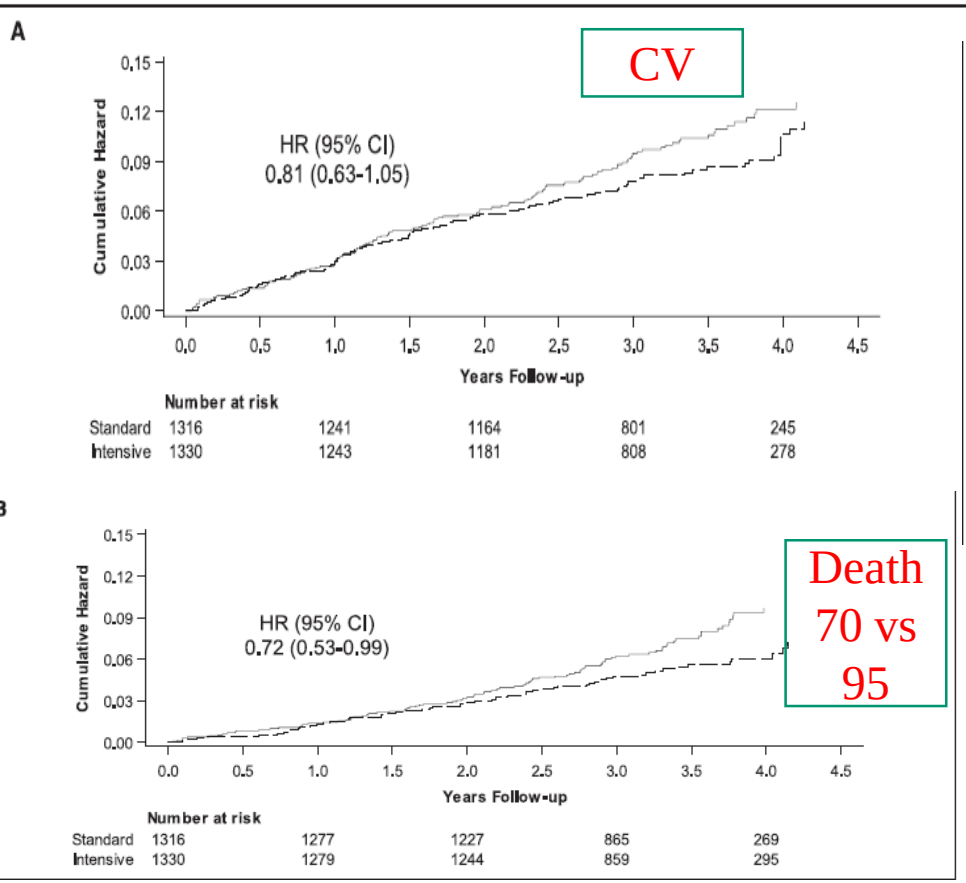
**Table 1.** Baseline characteristics of the SPRINT participants with CKD

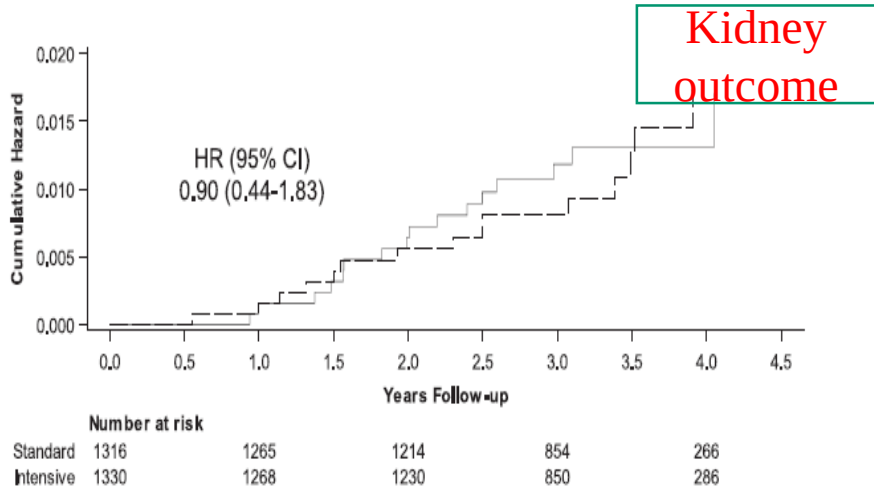
| Characteristics | Intensive Treatment, *n*=1330 | Standard Treatment, *n*=1316 | Total, *n*=2646 |
|---|---|---|---|
| Age, mean±SD, yr | 72.0±9.0 | 71.9±9.5 | 71.9±9.3 |
| Age ≥75 yr, no. (%) | 584 (43.9) | 577 (43.8) | 1161 (43.9) |
| Women, no. (%) | 537 (40.4) | 521 (39.6) | 1058 (40.0) |
| Race or ethnicity, no. (%) | | | |
| Non-Hispanic black | 325 (24.4) | 312 (23.7) | 637 (24.1) |
| Hispanic | 94 (7.1) | 96 (7.3) | 190 (7.2) |
| Non-Hispanic white | 885 (66.5) | 893 (67.9) | 1778 (67.2) |
| Other | 26 (2.0) | 15 (1.1) | 41 (1.6) |
| Serum creatinine, mg/dl | | | |
| All | 1.43 (0.39) | 1.43 (0.38) | 1.43 (0.39) |
| Age ≥75 yr | 1.41 (0.38) | 1.39 (0.31) | 1.40 (0.34) |
| Age <75 yr | 1.46 (0.41) | 1.47 (0.42) | 1.46 (0.41) |
| eGFR, mean (SD), ml/min per 1.73 $m^{2a}$ | | | |
| All | 47.9 (9.5) | 47.9 (9.5) | 47.9 (9.5) |
| Age ≥75 yr | 47.4 (9.5) | 47.3 (9.0) | 47.4 (9.2) |
| Age <75 yr | 48.2 (9.4) | 48.3 (9.9) | 48.2 (9.7) |
| Urinary ACR | | | |
| Mean (SD), mg/g[b] | 80.9 (236.2) | 80.3 (250.5) | 80.6 (243.4) |
| Median (interquartile range) | 12.8 (6.5–42.6) | 13.8 (6.1–43.5) | 13.3 (6.4–43.1) |
| BP, mean±SD, mm Hg | | | |
| SBP | 139.1±16.1 | 139.2±16.0 | 139.2±16.1 |
| DBP | 75.1±12.2 | 74.8±12.2 | 74.9±12.2 |

J Am Soc Nephrol **28:** 2812–2823, 2017

# Effects of Intensive BP Control in CKD

SPRINT Research Group




121 vs 136 mmHg

*J Am Soc Nephrol* 28: 2812–2823, 2017.

**Figure 2.** Kaplan-Meier curves for pre-specified outcomes in SPRINT participants with CKD. Panel A shows the primary cardiovascular outcome, defined as the composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular causes. Panel B shows the all-cause death outcome. Panel C shows the main kidney outcome, defined as the composite of a decrease in eGFR of ≥50% from baseline (confirmed by repeat testing ≥90 days later) or the development of ESRD. The broken lines depict the intensive group; the solid lines depict the standard group.

# Harm of anti-hypertensive treatment

**Hyperkalemia**

**Hyponatremia**

**Hypotension**

**Acute Kidney Injury**
**(but complete reversal in 90%!)***

**Syncope/falls**

Rocco et al. AJKD 2018, p352

# Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT)

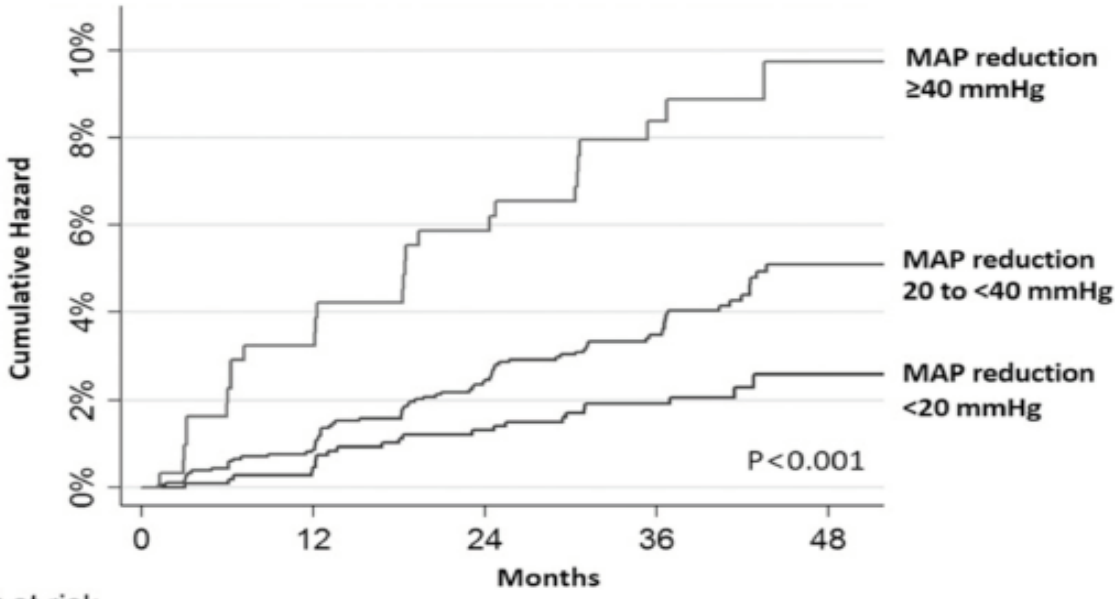
*Am J Kidney Dis. 71(3): 352-361. Published online November 20, 2017.*

**Table 4.** Multivariable Predictors of Time to Development of AKI

| Baseline Variables | HR (95% CI) | *P* |
|---|---|---|
| Male sex | 1.86 (1.43-2.44) | <0.001 |
| Black race | 2.08 (1.62-2.66) | <0.001 |
| eGFR (per 10 mL/min/ 1.73 $m^2$ greater) | 0.71 (0.66-0.75) | <0.001 |
| CVD subgroup | 1.48 (1.14-1.90) | 0.003 |
| Senior subgroup | 1.52 (1.18-1.95) | 0.001 |
| ACE-inhibitor use | 1.20 (0.95-1.51) | 0.1 |
| ARB use | 1.30 (0.62-2.39) | 0.4 |
| Diuretic use | 0.98 (0.77-1.24) | 0.9 |
| Randomly assigned to intensive arm | 1.64 (1.30-2.09) | <0.001 |

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

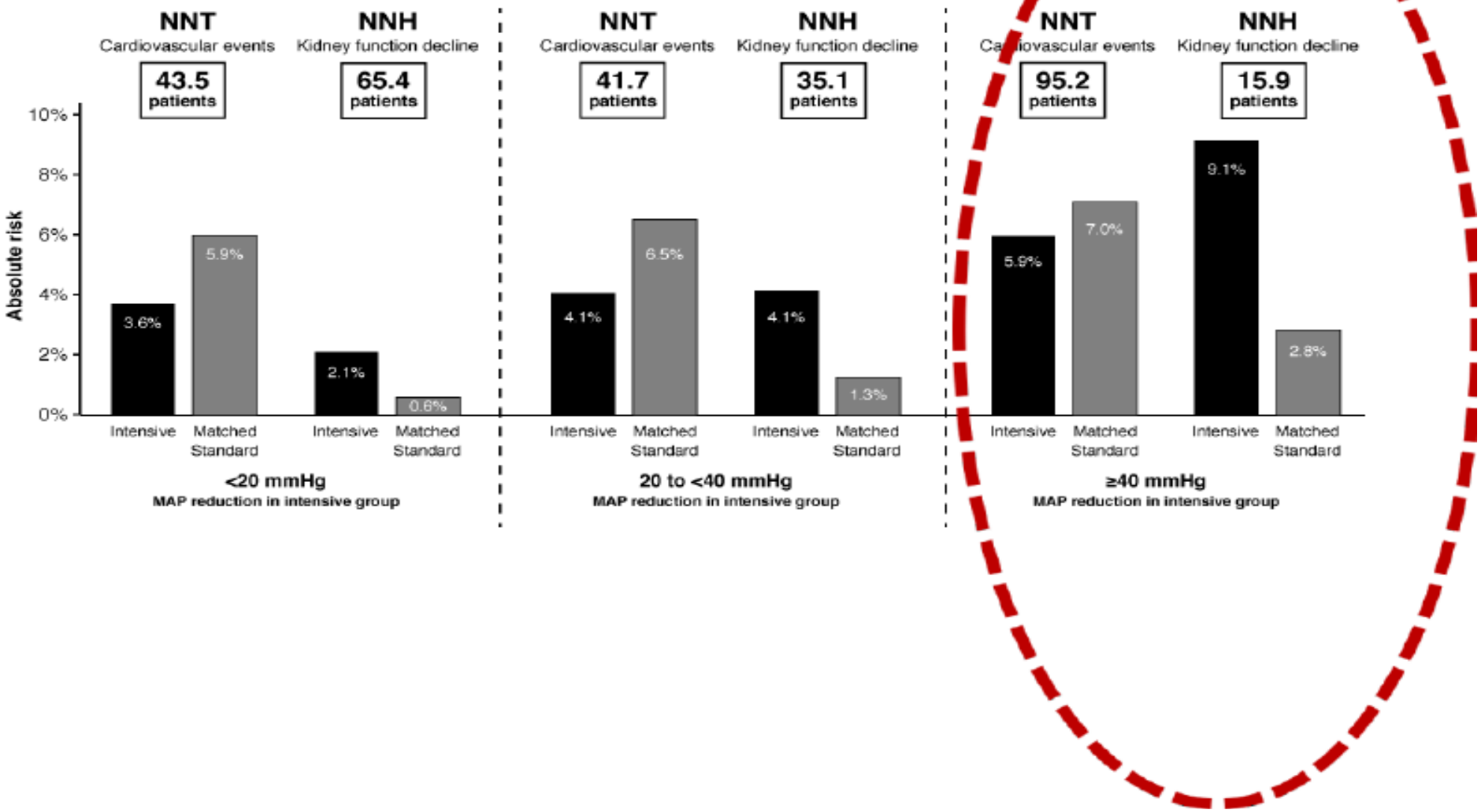
# SPRINT AKI




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Less than 20 mmHg | 1126 | 1068 | 1022 | 712 | 170 |
| 20 to <40 mmHg | 1854 | 1816 | 1750 | 1266 | 368 |
| 40 mmHg or more | 309 | 297 | 281 | 204 | 59 |

*Magriço et al CJASN 2018*

# SPRINT




*Magriço et al CJASN 2018*

# ESH 2018
# HTA management

**Table 19** Summary of office blood pressure thresholds for treatment

| Age group | Office SBP treatment threshold (mmHg) | | | | | Office DBP treatment threshold (mmHg) |
|---|---|---|---|---|---|---|
| | Hypertension | + Diabetes | + CKD | + CAD | + Stroke/TIA | |
| 18 - 65 years | ≥140 | ≥140 | ≥140 | ≥140[a] | ≥140[a] | ≥90 |
| 65 - 79 years | ≥140 | ≥140 | ≥140 | ≥140[a] | ≥140[a] | ≥90 |
| ≥80 years | ≥160 | ≥160 | ≥160 | ≥160 | ≥160 | ≥90 |
| **Office DBP treatment threshold (mmHg)** | ≥90 | ≥90 | ≥90 | ≥90 | ≥90 | |

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## Therapeutic strategies for treatment of hypertension in CKD

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.[9,203,485] | I | A |
| In patients with diabetic or non-diabetic CKD:<br>• It is recommended to lower SBP to a range of 130–139 mmHg.[9,487,489] | I | A |
| • Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes. | IIa | C |

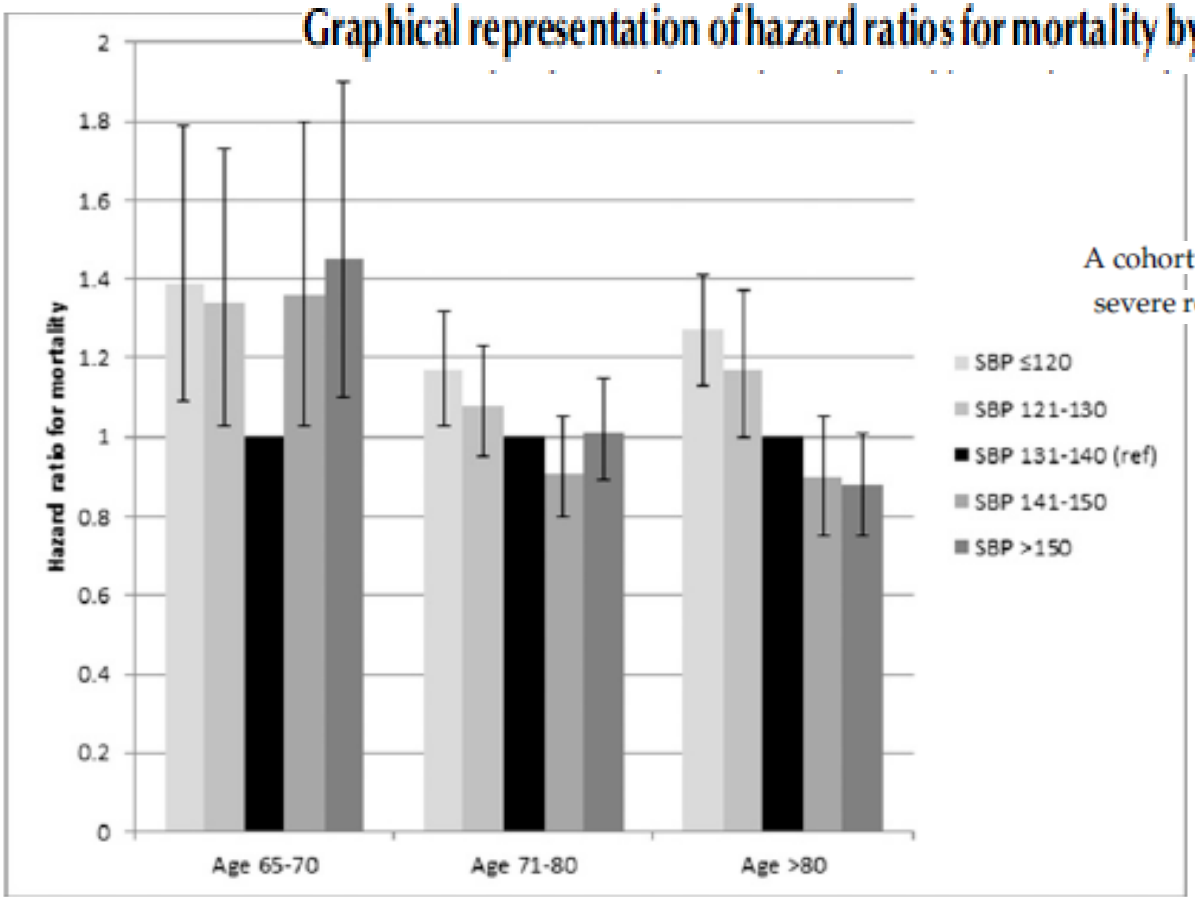
ESH 2018

# Systolic BP and Mortality in Older Adults with CKD

*Jessica W. Weiss,* Dawn Peters,† Xiuhai Yang,‡ Amanda Petrik,‡ David H. Smith,‡ Eric S. Johnson,‡ Micah L. Thorp,‡ Cynthia Morris,§ and Ann M. O'Hare‖*

*Clin J Am Soc Nephrol* 10: 1553–1559, 2015.

## Graphical representation of hazard ratios for mortality by age and systolic blood pressure




A cohort of 21,015 adults age 65–105 years with a moderate or severe reduction in eGFR (<60 ml/min per 1.73 $m^2$)

followed for up to 11 years

**Conclusions** In a cohort of older adults, the relationship between SBP and mortality varied systematically with age. A relationship between higher SBP and mortality was present only for younger members of this cohort and not for those older than 70. These results raise the question of whether the relative benefits and harms of lowering BP to recommended targets for older adults with CKD may vary as a function of age.

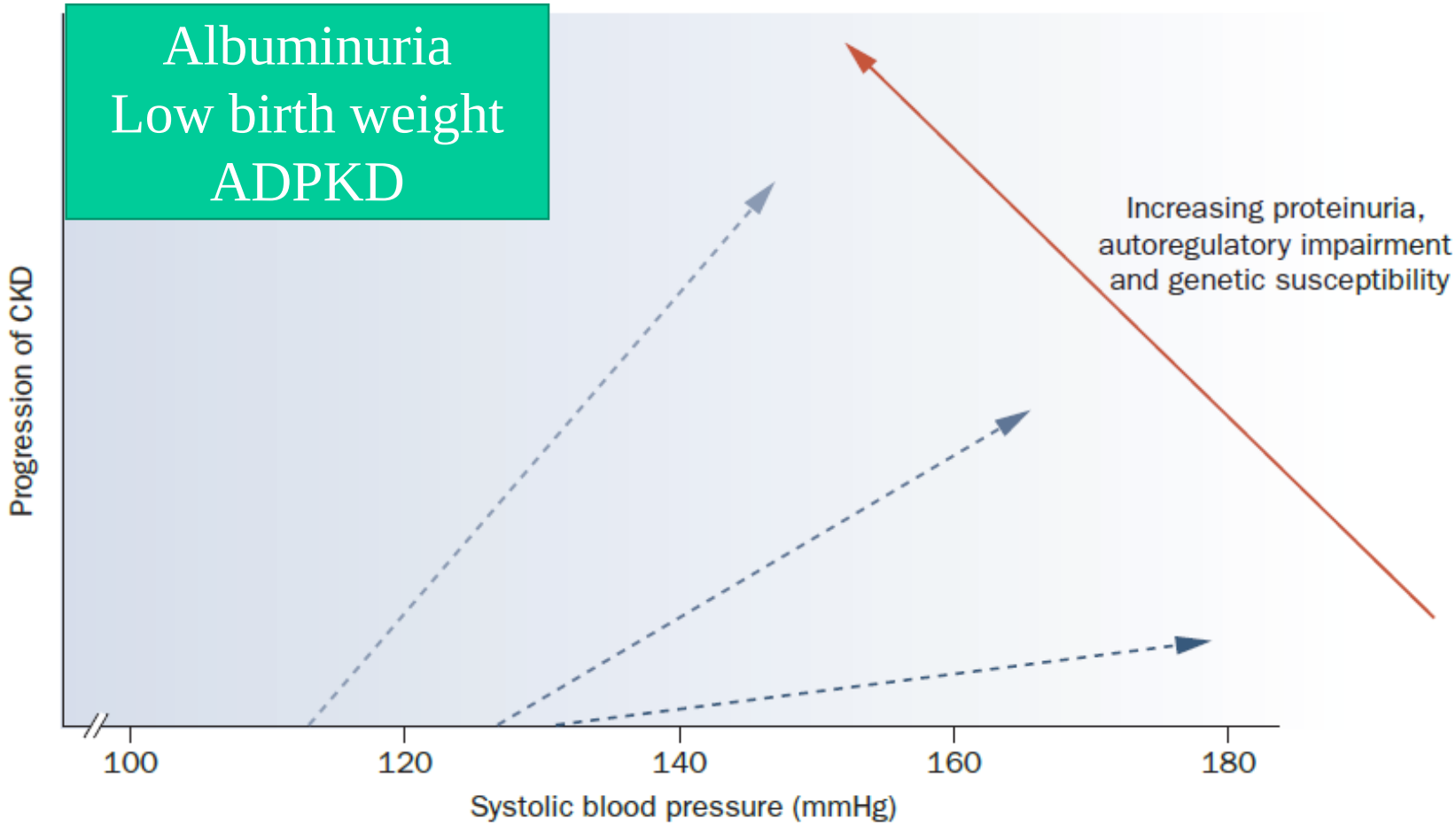



**Figure 1** | Differences in underlying pathology alter the threshold level of blood pressure that affects CKD progression. The progression of CKD (doubling of serum creatinine level, development of end-stage renal disease and reduction in glomerular filtration rate) is influenced by blood-pressure levels. Moreover, the underlying pathology of patients with CKD (such as genetic susceptibility to kidney disease, severity of proteinuria and autoregulatory impairment) alters the relationship between blood-pressure level and renal damage. Abbreviation: CKD, chronic kidney disease. Permission obtained from the American Society of Nephrology © Griffin, K. A. & Bidani, A. K. *Clin. J. Am. Soc. Nephrol.* **1**, 1054–1065 (2006).

# Prognostic Role of Ambulatory Blood Pressure Measurement in Patients With Nondialysis Chronic Kidney Disease

*Roberto Minutolo, MD, PhD; Rajiv Agarwal, MD; Silvio Borrelli, MD; Paolo Chiodini, MSc; Vincenzo Bellizzi, MD, PhD; Felice Nappi, MD; Bruno Cianciaruso, MD; Pasquale Zamboli, MD; Giuseppe Conte, MD; Francis B. Gabbai, MD; Luca De Nicola, MD, PhD*

*Arch Intern Med. 2011;171(12):1090-1098*

**Conclusion:** In chronic kidney disease, ambulatory BP measurement and, in particular, nighttime BP measurement, allows more accurate prediction of renal and cardiovascular risk; office measurement of BP does not predict any outcome.

# Prognostic Role of Ambulatory Blood Pressure Measurement in Patients With Nondialysis Chronic Kidney Disease

*Arch Intern Med. 2011;171(12):1090-1098*

*Roberto Minutolo, MD, PhD; Rajiv Agarwal, MD; Silvio Borrelli, MD; Paolo Chiodini, MSc; Vincenzo Bellizzi, MD, PhD; Felice Nappi, MD; Bruno Cianciaruso, MD; Pasquale Zamboli, MD; Giuseppe Conte, MD; Francis B. Gabbai, MD; Luca De Nicola, MD, PhD*

CV

Kidney

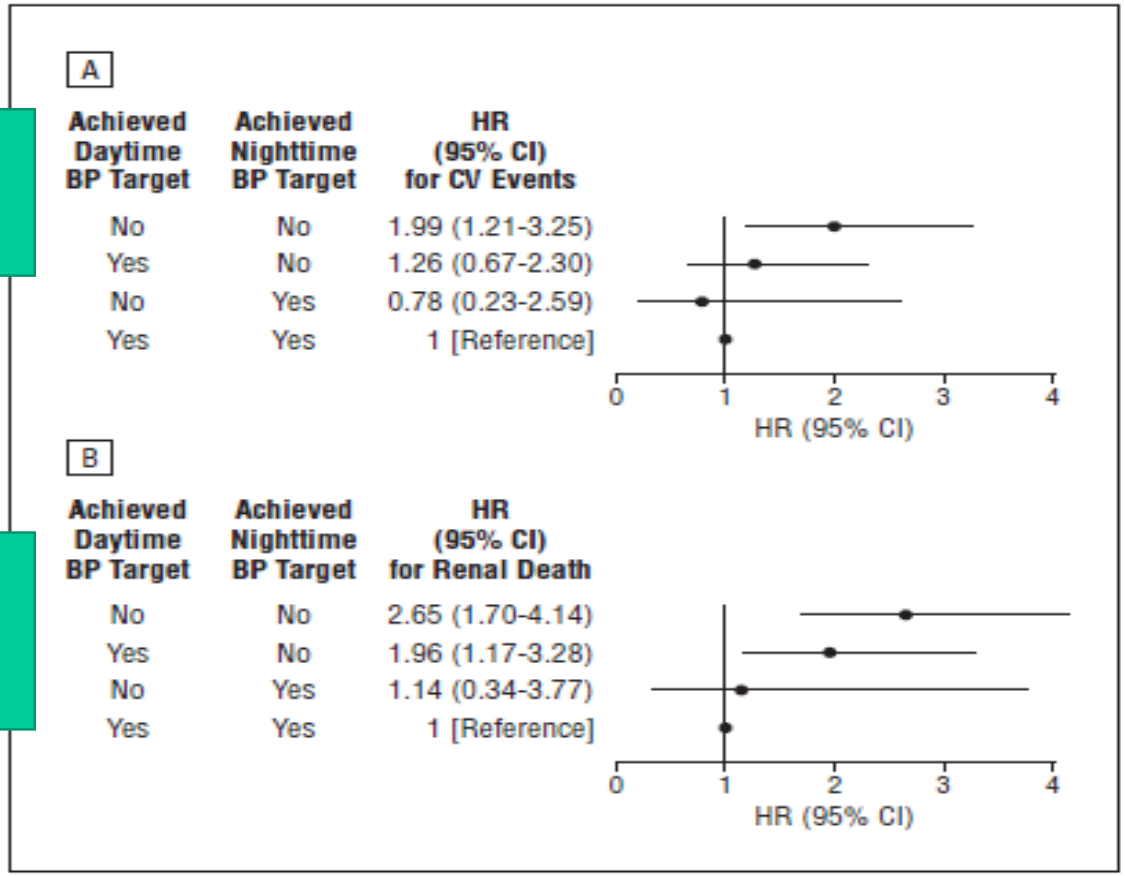
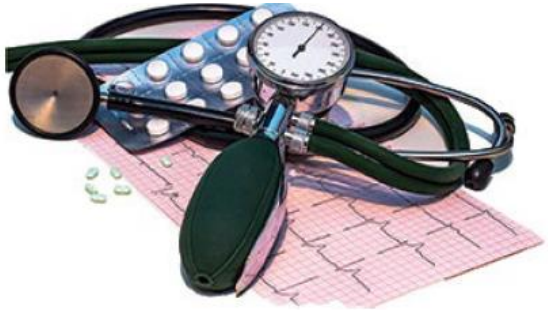



**Figure 3.** Risk of fatal and nonfatal cardiovascular (CV) events (A) and renal death (B) in patients stratified according to achievement of daytime blood pressure (BP) target (<135/85 mm Hg) and nighttime BP target (<120/70 mm Hg). CI indicates confidence interval; HR, hazard ratio.

# CONCLUSIONS in HTA with CKD : individualization of the BP target!

- BP lowering is a critical component of preventing mortality, CKD progression and CV complications among those with CKD
- Evidence supports  at least a goal BP <140/90 mmHg (Level I A/B)
- The exception to this statement is if albuminuria is present, <130/80 mmHg can then be supported for CKD slower (Level II B)
- In oldest patients (>75) a BP target not lower than 140 mmHg must be proposed.
- ABPM should be used to test the 24h BP control

# Thank you
# Questions?



| Subgroup | Intensive Treatment | Standard Treatment | Hazard Ratio (95% CI) | P Value for Interaction |
|---|---|---|---|---|
| | *no. of patients with primary outcome/total no. (%)* | | | |
| Overall | 243/4678 (5.2) | 319/4683 (6.8) | 0.75 (0.64–0.89) | |
| Previous CKD | | | | 0.36 |
| No | 135/3348 (4.0) | 193/3367 (5.7) | 0.70 (0.56–0.87) | |
| Yes | 108/1330 (8.1) | 126/1316 (9.6) | 0.82 (0.63–1.07) | |
| Age | | | | 0.32 |
| <75 yr | 142/3361 (4.2) | 175/3364 (5.2) | 0.80 (0.64–1.00) | |
| ≥75 yr | 101/1317 (7.7) | 144/1319 (10.9) | 0.67 (0.51–0.86) | |
| Sex | | | | 0.45 |
| Female | 77/1684 (4.6) | 89/1648 (5.4) | 0.84 (0.62–1.14) | |
| Male | 166/2994 (5.5) | 230/3035 (7.6) | 0.72 (0.59–0.88) | |
| Race | | | | 0.83 |
| Black | 62/1454 (4.3) | 85/1493 (5.7) | 0.77 (0.55–1.06) | |
| Nonblack | 181/3224 (5.6) | 234/3190 (7.3) | 0.74 (0.61–0.90) | |
| Previous cardiovascular disease | | | | 0.39 |
| No | 149/3738 (4.0) | 208/3746 (5.6) | 0.71 (0.57–0.88) | |
| Yes | 94/940 (10.0) | 111/937 (11.8) | 0.83 (0.62–1.09) | |
| Systolic blood pressure | | | | 0.77 |
| ≤132 mm Hg | 71/1583 (4.5) | 98/1553 (6.3) | 0.70 (0.51–0.95) | |
| >132 to <145 mm Hg | 77/1489 (5.2) | 106/1549 (6.8) | 0.77 (0.57–1.03) | |
| ≥145 mm Hg | 95/1606 (5.9) | 115/1581 (7.3) | 0.83 (0.63–1.09) | |

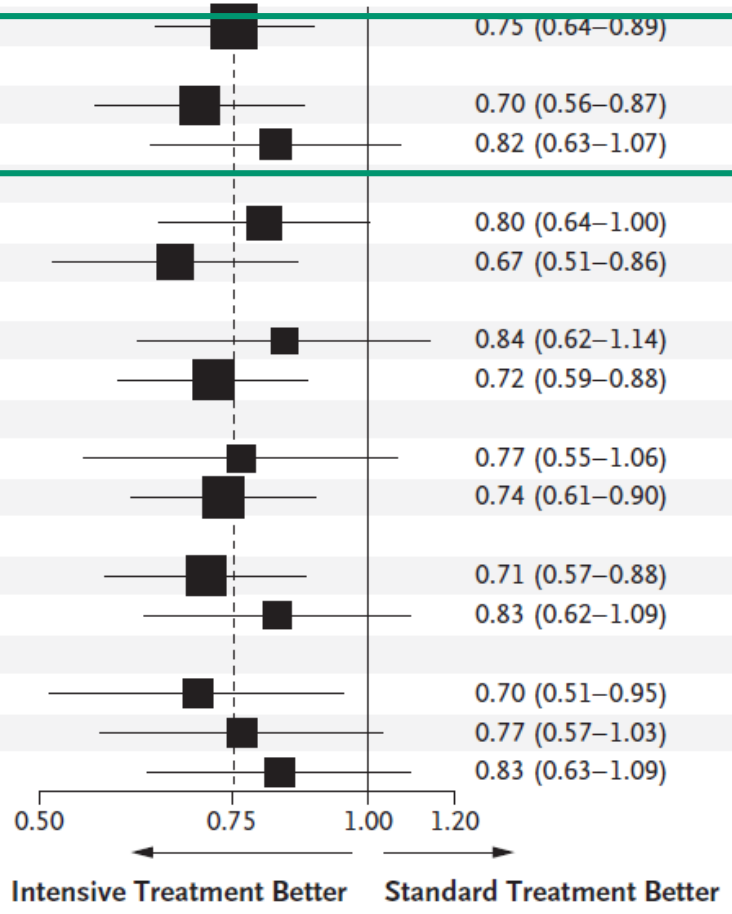



**Figure 4. Forest Plot of Primary Outcome According to Subgroups.**

# Effects of Intensive BP Control in CKD

Alfred K. Cheung,* for the SPRINT Research Group

*J Am Soc Nephrol* 28: 2812–2823, 2017.


## ABSTRACT

The appropriate target for BP in patients with CKD and hypertension remains uncertain. We report prespecified subgroup analyses of outcomes in participants with baseline CKD in the Systolic Blood Pressure Intervention Trial. We randomly assigned participants to a systolic BP target of <120 mm Hg (intensive group; *n*=1330) or <140 mm Hg (standard group; *n*=1316). After a median follow-up of 3.3 years, the primary composite cardiovascular outcome occurred in 112 intensive group and 131 standard group CKD participants (hazard ratio [HR], 0.81; 95% confidence interval [95% CI], 0.63 to 1.05). The intensive group also had a lower rate of all-cause death (HR, 0.72; 95% CI, 0.53 to 0.99). Treatment effects did not differ between participants with and without CKD (*P* values for interactions ≥0.30). The prespecified main kidney outcome, defined as the composite of ≥50% decrease in eGFR from baseline or ESRD, occurred in 15 intensive group and 16 standard group participants (HR, 0.90; 95% CI, 0.44 to 1.83). After the initial 6 months, the intensive group had a slightly higher rate of change in eGFR (−0.47 versus −0.32 ml/min per 1.73 $m^2$ per year; $P<0.03$). The overall rate of serious adverse events did not differ between treatment groups, although some specific adverse events occurred more often in the intensive group. Thus, among patients with CKD and hypertension without diabetes, targeting an SBP<120 mm Hg compared with <140 mm Hg reduced rates of major cardiovascular events and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.

# A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

*J Am Soc Nephrol* 28: 2812–2823, 2017.

**Table 3.** Cardiovascular and mortality events in the SPRINT participants with CKD

| Outcome | Intensive Treatment, *n*=1330 | | Standard Treatment, *n*=1316 | | Intensive Treatment Versus Standard Treatment | |
|---|---|---|---|---|---|---|
| | No. of events | Percent per 1 yr | No. of events | Percent per 1 yr | HR (95% CI) | *P* Value |
| Primary[a] outcome | 112 | 2.68 | 131 | 3.19 | 0.81 (0.63 to 1.05) | 0.12 |
| Myocardial infarction | 44 | 1.03 | 45 | 1.07 | 0.94 (0.62 to 1.44) | 0.79 |
| Acute coronary syndrome | 15 | 0.35 | 11 | 0.26 | 1.35 (0.60 to 3.08) | 0.47 |
| Stroke | 27 | 0.63 | 27 | 0.64 | 0.99 (0.57 to 1.70) | 0.96 |
| Heart failure | 41 | 0.96 | 52 | 1.24 | 0.72 (0.47 to 1.10) | 0.13 |
| CVD death | 18 | 0.41 | 30 | 0.70 | 0.57 (0.31 to 1.02) | 0.06 |
| All-cause death | 70 | 1.61 | 95 | 2.21 | 0.72 (0.53 to 0.99) | 0.04 |
| Primary outcome or all-cause death | 152 | 3.62 | 179 | 4.35 | 0.82 (0.66 to 1.02) | 0.08 |
| Primary outcome or cardiovascular procedure | 127 | 3.06 | 161 | 3.98 | 0.81 (0.63 to 1.05) | 0.12 |

# Who benefits from more stringent BP control?

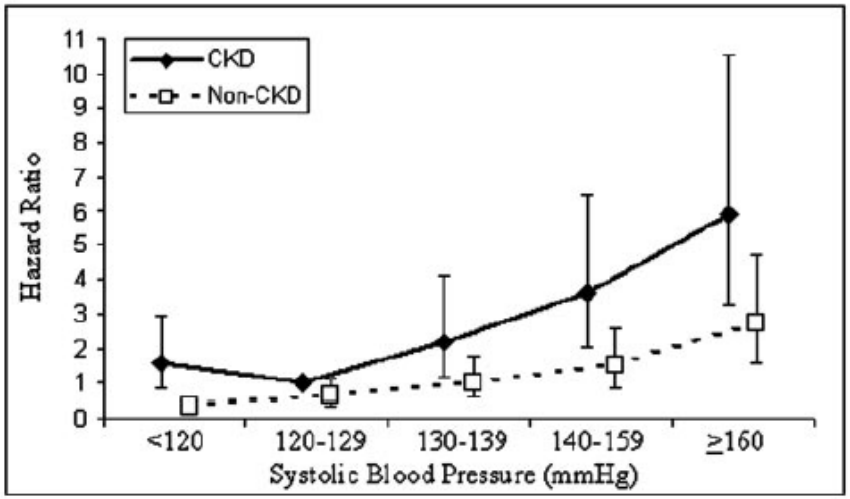
- Proteinuria
- Young age
- When achieved with low treatment burden
- Stroke prevention
- High CV risk (but what about atherosclerotic coronary heart disease?)

# Lowest Systolic Blood Pressure Is Associated with Stroke in Stages 3 to 4 Chronic Kidney Disease

Daniel E. Weiner,* Hocine Tighiouart,† Andrew S. Levey,* Essam Elsayed,*
John L. Griffith,† Deeb N. Salem,‡ and Mark J. Sarnak*

*J Am Soc Nephrol* 18: 960–966, 2007.

a.




b.

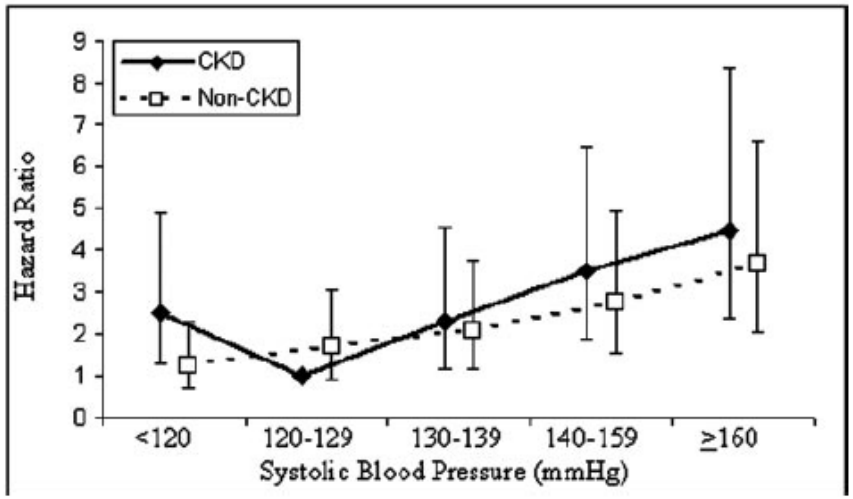



*Figure 1.* The hazard of incident stroke associated with systolic BP (SBP) and chronic kidney disease (CKD) using an unadjusted model that contained dummy variables for CKD and BP groups (A) and a fully adjusted model that contained dummy variables for CKD and BP groups (B; model adjusted for age, race, gender, history of diabetes, history of coronary disease, left ventricular hypertrophy, use of antihypertensive medication, education status, smoking status, serum albumin, non-HDL cholesterol, hemoglobin, and study of origin). Reference group is individuals with CKD and SBP 120 to 129 mmHg.

# Acute Declines in Renal Function during Intensive BP Lowering: Implications for Future ESRD Risk

Elaine Ku,*† George Bakris,‡ Kirsten L. Johansen,* Feng Lin,§ Mark J. Sarnak,‖ Vito M. Campese,¶ Kenneth Jamerson,** Jennifer J. Gassman,†† Miroslaw Smogorzewski,¶ and Chi-yuan Hsu*

## ABSTRACT

The magnitude of decline in renal function that should be tolerated during intensive BP lowering and its association with risk of ESRD are unclear. To determine whether the acute declines in kidney function in the intensive BP lowering arm of two trials in CKD associated with higher risk of ESRD, we performed a retrospective study of 899 African American Study of Kidney Disease and Hypertension (AASK) and 761 Modification of Diet in Renal Disease (MDRD) Trial participants previously randomized to strict versus usual BP control. The predictor was the percentage decline in eGFR (<5%, 5% to <20%, or ≥20%) between randomization and months 3 and 4 of the trial (time to achieve BP goals). ESRD was the outcome of interest. Compared with a <5% eGFR decline in the usual BP arm, a 5% to <20% eGFR decline during intensive BP lowering did not associate with a higher risk of ESRD in the AASK (adjusted hazard ratio [aHR], 1.19; 95% confidence interval [95% CI], 0.84 to 1.68) or the MDRD Trial (aHR, 1.08; 95% CI, 0.84 to 1.40). However, a 5% to <20% eGFR decline in the usual BP arm associated with higher risk of ESRD in AASK (aHR, 1.83; 95% CI, 1.30 to 2.57) and MDRD Trial (aHR, 1.62; 95% CI, 1.25 to 2.11). A ≥20% eGFR decline associated with higher risk of ESRD in both strict and usual BP arms. Thus, acute eGFR declines ≥20% during intensive BP lowering identified a subset of patients at higher risk for adverse outcomes.

*J Am Soc Nephrol* 28: 2794–2801, 2017. doi: https://doi.org/10.1681/ASN.2017010040

## Acute Declines in Renal Function during Intensive BP Lowering: Implications for Future ESRD Risk

*J Am Soc Nephrol* 28: 2794–2801, 2017.

**Table 2.** Association between percentage decline in renal function in the AASK participants (*n*=899) from time of randomization until month 3 and risk of ESRD

| Renal Function Decline, % | Strict BP Arm | | | | Usual BP Arm | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | ESRD Incidence[a] (95% CI) | Unadjusted HR (95% CI) | Adjusted HR[b] (95% CI) | *N* | ESRD Incidence[a] (95% CI) | Unadjusted HR (95% CI) | Adjusted HR[b] (95% CI) |
| AASK | 448 | | | | 451 | | | |
| <5 | 271 | 2.9 (2.4 to 3.6) | 1.00 (0.75 to 1.34) | 0.94 (0.70 to 1.25) | 319 | 2.9 (2.4 to 3.5) | 1.0 (Reference) | 1.0 (Reference) |
| 5 to <20 | 139 | 3.6 (2.7 to 4.7) | 1.26[c] (0.90 to 1.76) | 1.19[c] (0.84 to 1.68) | 98 | 6.3 (4.8 to 8.1) | 2.22[c] (1.60 to 3.09) | 1.83[c] (1.30 to 2.57) |
| ≥20 | 38 | 9.8 (6.7 to 14.4) | 3.58 (2.32 to 5.52) | 3.04 (1.95 to 4.77) | 34 | 10.4 (6.9 to 15.7) | 3.83 (2.43 to 6.04) | 2.56 (1.60 to 4.11) |
| MDRD | 388 | | | | 373 | | | |
| <5 | 190 | 7.1 (6.0 to 8.5) | 0.93 (0.73 to 1.19) | 0.88 (0.68 to 1.13) | 182 | 7.6 (6.4 to 9.0) | 1.0 (Reference) | 1.0 (Reference) |
| 5 to <20 | 150 | 9.7 (8.1 to 11.7) | 1.28[c] (0.99 to 1.64) | 1.08[c] (0.84 to 1.40) | 136 | 12.6 (10.5 to 15.1) | 1.66[c] (1.29 to 2.13) | 1.62[c] (1.25 to 2.11) |
| ≥20 | 48 | 15.5 (11.5 to 20.9) | 2.03 (1.44 to 2.87) | 1.57 (1.09 to 2.24) | 55 | 17.3 (13.0 to 23.7) | 2.39 (1.71 to 3.35) | 1.48 (1.04 to 2.1) |

# Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease?

David C. Wheeler[1] and Gavin J. Becker[2]

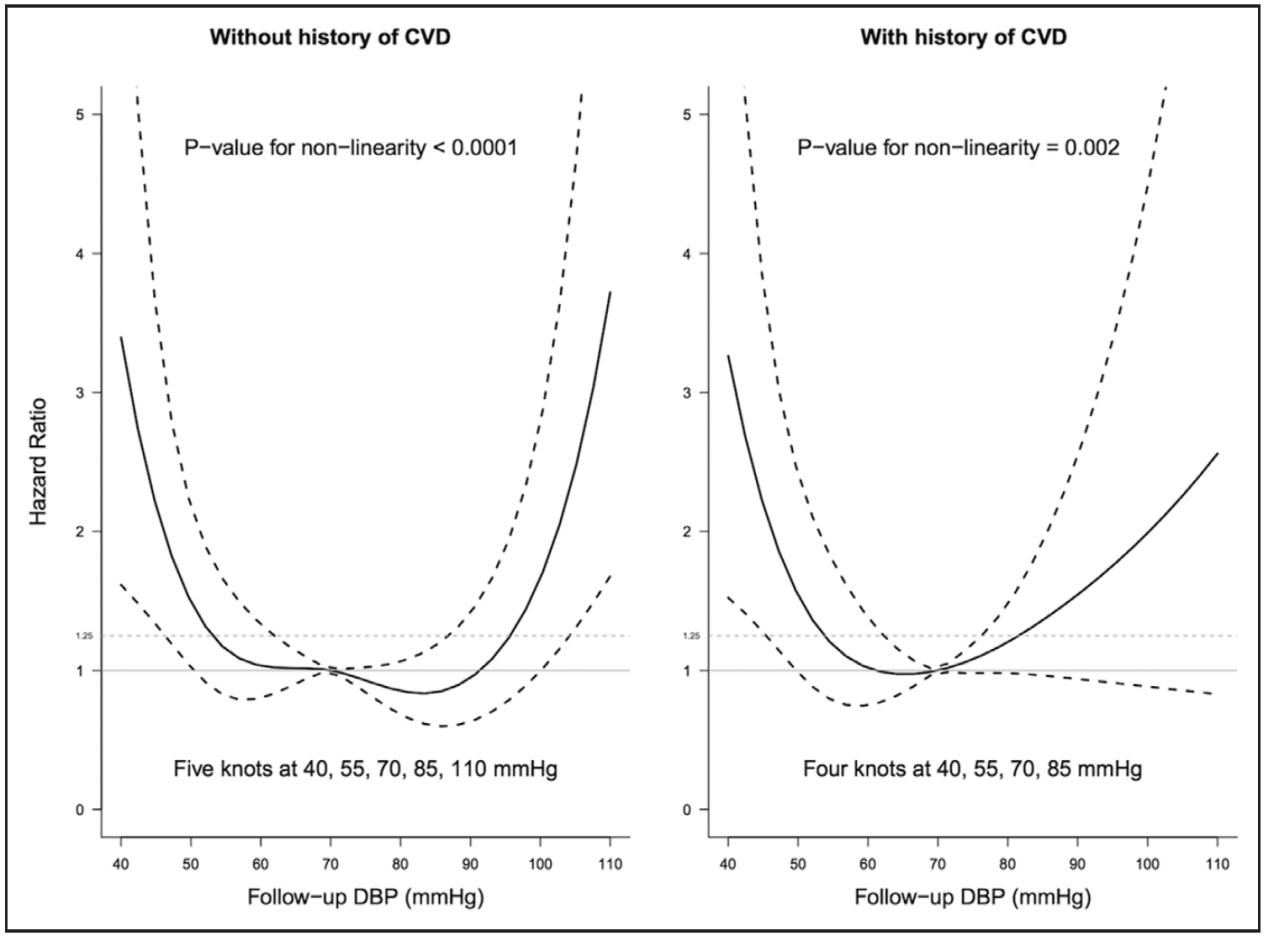
*[1]Centre for Nephrology, University College London Medical School, London, UK and [2]Department of Nephrology, Royal Melbourne Hospital, Parkville, Victoria, Australia*

**Table 2 | Summary of recommendations for management of blood pressure in adult CKD patients with and without diabetes**

| Albuminuria (mg/day)[a] | BP Target mm Hg | Preferred agent |
|---|---|---|
| <30 | ≤140/90 mm Hg | None |
| 30–300 | ≤130/80 mm Hg | ACE-I or ARB |
| >300 | ≤130/80 mm Hg | ACE-I or ARB |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease.

# Caution on Diastolic BP <55 mmHg (SPRINT)




←25% higher hazard

**Figure 2.** Association between diastolic blood pressure (DBP) and the composite cardiovascular outcome according to history of cardiovascular disease (CVD). Hazard ratios and 95% confidence intervals of the composite cardiovascular outcome for a range of follow-up diastolic pressure (**left**, for subjects without history of CVD and [**right**] for patients with CVD). Model was adjusted for treatment arm, baseline systolic blood pressure (SBP), follow-up SBP, age, sex, body mass index, Framingham 10-year risk score, estimated glomerular filtration rate.

Kahn et al. Hypertension 2018, p840