Hypertension and Chronic Kidney Disease… An Unhappy Marriage

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1

Outline

- Epidemiology and the bidirectional pathophysiologic relationships between hypertension and CKD
- Hypertension phenotypes prevalent in CKD
- Key points in evaluation of hypertension in CKD
- Comorbidities associated with hypertension in CKD
- New 2021 KDIGO hypertension guideline for CKD Comparison with the 2017 ACC/AHA hypertension guideline

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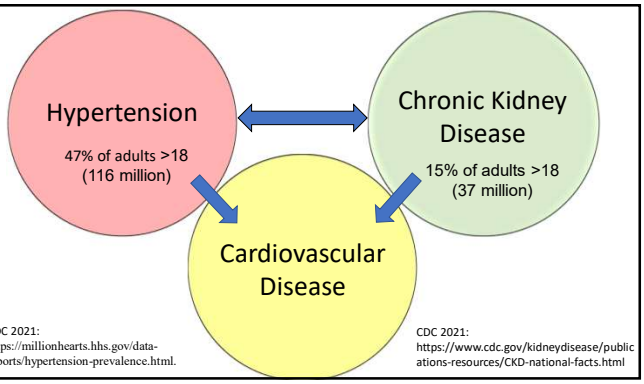

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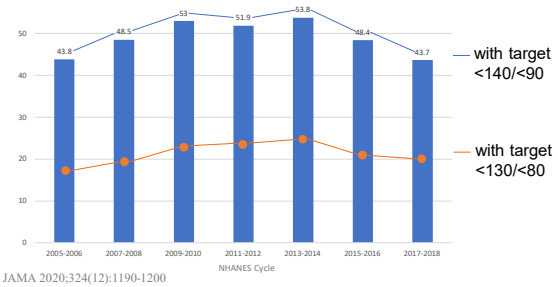
We're doing a poor job at controlling hypertension

Age-Adjusted Estimated Proportion of Adults with Controlled Hypertension



Muntner P et al. JAMA 2020;324(12):1190-1200

4

We're doing a poor job at diagnosing and managing CKD

9 in 10 adults with CKD don't know they have CKD

2 in 5 adults with *severe* CKD don't know they have CKD

CDC 2021: https://www.cdc.gov/kidneydisease/publications-resources/CKD-national-facts.html

Cross-sectional study of patients in 466 *primary care practices* across the U.S.:
Only 12.1% of the 5,036 patients with CKD were diagnosed!

CKD Stage	Percent diagnosed
1 (Kidney damage with GFR >90 mL/min/1.73 m^2)	1.1
2 (Mild reduction in GFR, 60-89 mL/min/1.73 m^2)	4.9
3 (Moderate reduction in GFR, 30-59 mL/min/1.73m^2)	18.0
4 (Severe reduction in GFR, 15-29 mL/min/1.73m^2)	**52.9**
5 End-stage kidney disease, GFR <15 mL/min/1.73m^2)	**58.8**

Szczech LA. PLoS One 2014;9(11):e110535

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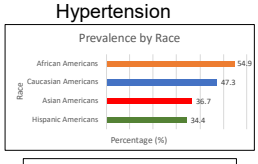
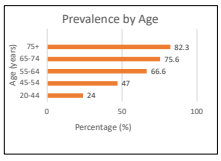
The prevalence of hypertension and CKD is not uniformly distributed

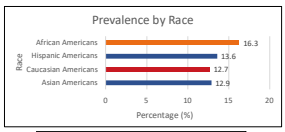
Hypertension

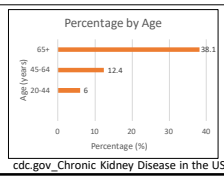




Muntner P et al. Circulation 2018;137:109-118

Chronic Kidney Disease



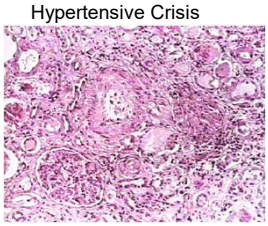


cdc.gov_Chronic Kidney Disease in the US 2021

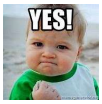
6

Does Hypertension CAUSE Kidney Disease?

Hypertensive Crisis



Malignant Nephrosclerosis
Fibrinoid necrosis and thrombosis in renal vessels, inflammation

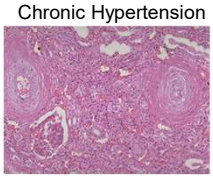


- Clinically…..
  - Acute kidney injury
  - Hematuria
  - Proteinuria
  - Microangiopathic hemolytic anemia (schistocytes)

7

Does Hypertension CAUSE Kidney Disease?

Chronic Hypertension



Benign Nephrosclerosis (hypertensive nephrosclerosis)
Scarring of vessels (onion ringing), glomeruli, and interstitium, and tubular atrophy and dilation

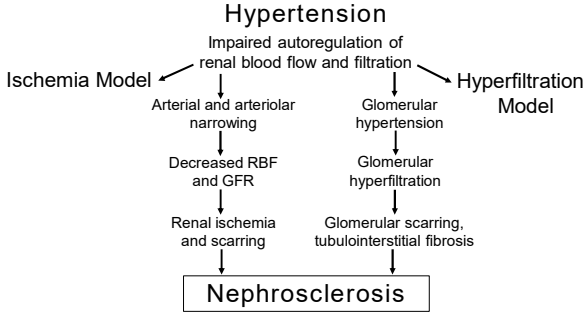
- Clinically…..
  - Slowly rising creatinine (over many years)
  - Little or no proteinuria
  - Accounts for 25% of ESKD

Problems…..

- HTN is so common, a small percentage of patients at risk of ESKD = large number
- Kidney biopsies are rarely done to r/o other dxs
- Pathology and clinical phenotype are nonspecific
- African Americans with ESKD attributed to HTN may have ESKD due to the APOL1 gene variant

8

How does hypertension cause kidney disease?



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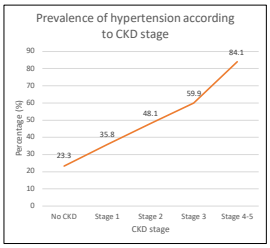
Does Kidney Disease CAUSE Hypertension?



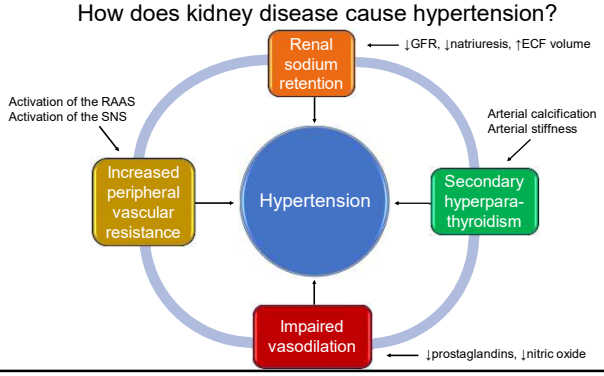
CKD is a leading cause of secondary hypertension

- Prevalence of HTN increases with severity of CKD
- Albuminuria is a strong risk factor for HTN in CKD and correlates with poor BP control
- Etiology of CKD affects prevalence of HTN (patients with ischemic and diabetic kidney disease have the highest rates of HTN)
- Blacks and Hispanics with CKD have the highest severity of HTN and are more likely to progress to ESKD

Tedla FM. Int j Hypertens 20011;132405.
Johansen KL. Am J Kidney Dis 2021;77(4)(suppl 1):S1-S597. Agarwal R. Hypertens 2005;46:514-20.

10

How does kidney disease cause hypertension?



11

Hypertension Phenotypes based on office and home or ambulatory BP

Untreated patients		Treated patients	
Normal office BP and Normal home or ABPM **Sustained normotension**	High office BP but Normal home or ABPM **White coat hypertension**	Normal office BP and Normal home or ABPM **True BP control**	High office BP but Normal home or ABPM **White coat effect (white coat uncontrolled HTN)**
High office BP and High home or ABPM **Sustained hypertension**	Normal office BP but High home or ABPM **Masked hypertension**	High office BP and High home or ABPM **True uncontrolled or resistant HTN**	Normal office BP But High home or ABPM **Masked uncontrolled hypertension or masked resistant HTN**

Patients with white coat hypertension or white coat effect tend to progress to sustained hypertension over time.

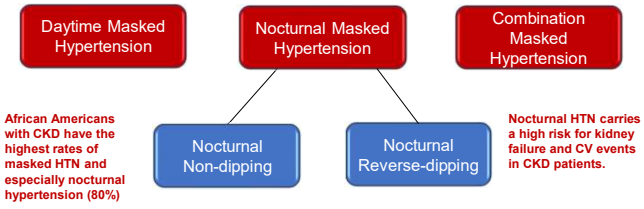
12

Hypertension Phenotypes
more common in CKD than in the general population

Untreated patients		Treated patients	
Normal office BP and Normal home or ABPM **Sustained normotension**	High office BP but Normal home or ABPM **White coat hypertension**	Normal office BP and Normal home or ABPM **True BP control**	High office BP but Normal home or ABPM **White coat effect (white coat uncontrolled HTN)**
High office BP and High home or ABPM **Sustained hypertension**	Normal office BP but High home or ABPM **Masked hypertension**	High office BP and High home or ABPM **True uncontrolled or resistant HTN**	Normal office BP But High home or ABPM **Masked uncontrolled hypertension or masked resistant HTN**

13

Masked hypertension subtypes



African Americans with CKD have the highest rates of masked HTN and especially nocturnal hypertension (80%)

Nocturnal HTN carries a high risk for kidney failure and CV events in CKD patients.

Nocturnal HTN: Nighttime BP above hypertensive threshold by ABPM (110/65 per ACC/AHA 2017 Guideline)

Non-dipping: Failure of nocturnal BP to fall by at least 10% with or without medication (night:day ratio 0.9-1.0)

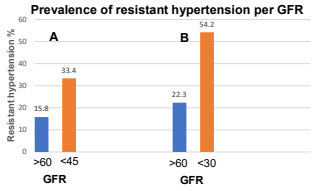
Reverse-dipping: Paradoxical rise in nocturnal BP with or without medication (night:day ratio >1.0)

Draws PE et al. Clin J Am Soc Nephrol 2016; 11: 642–652

14

Resistant Hypertension

- Definition: BP above goal on optimal doses of three or more medications of different classes including a diuretic if tolerated, or that is controlled with four or more medications.
- Resistant hypertension is common in CKD and its prevalence is inversely related to GFR

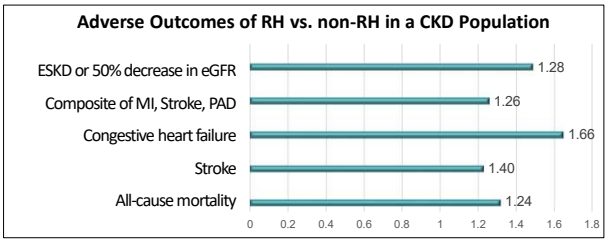


A: Tanner RM et al. Clin J Am Soc Nephrol 2013;8:1583-90

B: Thomas G et al. Hypertension 2016;67:387-396.

15

Resistant hypertension is associated with increased morbidity and mortality in CKD

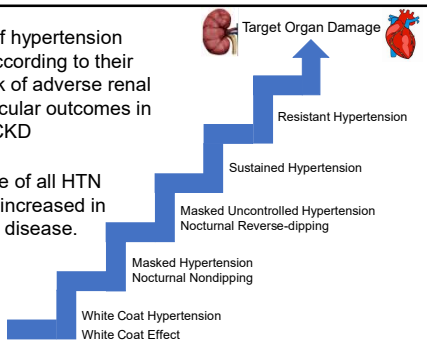


Thomas G et al. Hypertension 2016;67:387-396

16

Stratification of hypertension phenotypes according to their associated risk of adverse renal and cardiovascular outcomes in patients with CKD

The prevalence of all HTN phenotypes is increased in chronic kidney disease.



17

Standardized Blood Pressure Measurement is ESSENTIAL

ACC/AHA 2017 Hypertension Guideline

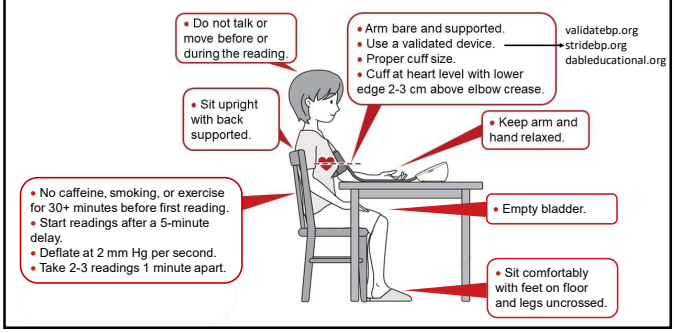
4.1. Accurate Measurement of BP in the Office

Recommendation for Accurate Measurement of BP in the Office

COR	LOE	Recommendation
I	C-EO	1. For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP (Table 8).

18

Standardized Blood Pressure Measurement is ESSENTIAL



19

Automated Office Blood Pressure Device

- Observer-free; starts automatically after 5-minute delay
- Takes 3 readings 1-minute apart
- Averages the 3 readings

20

Improper technique can raise BP levels

Cuff size too small	2-10 mm Hg
Cuff over clothing	5-50 mm Hg
Arm unsupported or dependent	10-15 mm Hg
Unsupported back and feet	6 mm Hg
Legs crossed	2-8 mm Hg
Talking or active listening	10 mm Hg
Full bladder	10 mm Hg

Data from AHA/AMA TARGET:BP (targetbp.org)

21

Adherence to proper technique is uncommon in primary care practice

26 primary care practices in Geneva, Switzerland
Mean difference in BP between PCP and research assistant after PCP training: 23 mm Hg SBP and 14 mm Hg DBP

- Common errors

Back unsupported	50%
Arm unsupported	64%
Center of cuff not over brachial artery	52%
Single blood pressure reading	83%

Sebo P et al. J Hypertension 2014;509-517

22

Why is standardized measurement essential?

- All clinical trials on which current guideline BP targets are based used standardized office BP measurements.

Clinical Trial	Method	Rest (minutes)	# of readings
SPRINT	AOBP	5	3
SPS3	AOBP	15	3
ADVANCE	AOBP	5	2
ACCORD	AOBP	5	3
ONTARGET	AOBP	3	2
AASK	Manual	5	3
MDRD	Manual	5	3

AOBP = **A**utomated **O**ffice **B**lood **P**ressure measurements

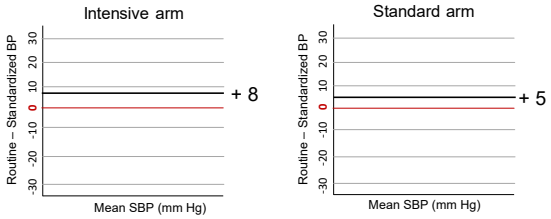
23

SPRINT
Systolic **Pr**essure **In**tervention **T**rial

- Randomized 9361 non-diabetic participants at high risk for CVD to a target SBP <120 mm Hg vs. SBP <140 mm Hg
- Inclusion criteria
  - Age ≥50 - ≥75 if not institutionalized
  - SBP 130-180 mm Hg
  - Clinical or subclinical CVD, excluding stroke
  - CKD (eGFR 20-59 ml/min), excluding PKD
  - Framingham 10-year risk score for CVD ≥15%
- Outcomes
  - Primary (composite of AMI, ACS, stroke, acute HF, CV death): -25%
  - Main secondary outcome (mortality): -27%

24

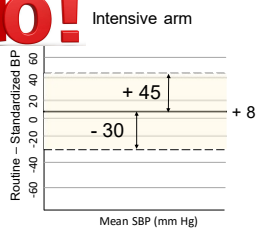
Comparison of routine office BPs and standardized BPs in SPRINT



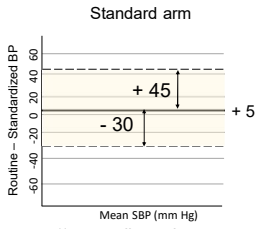
Drawz PE et al. JAMA Intern Med. 2020;180(12):1655-1663

25

So, can subtracting 5-10 mm Hg from routine BP approximate standardized BP?



In only 44% did the difference fall within 5-15 mm Hg



In only 34% did the difference fall within 5-15 mm Hg

26

Why is standardized measurement essential?
The hazards of routine BP measurements

- Hazards of over-treatment of hypertension
  - Postural hypotension → debilitating symptoms
  - Recurrent falls and fractures
  - Stroke in patients with carotid obstructive disease
  - Acute kidney injury, esp. in those with renovascular disease
- Hazards of under-treatment of hypertension
  - Uncontrolled hypertension
  - Ischemic heart disease
  - Heart failure
  - Chronic kidney disease

Remember: CKD patients are at the **highest risk** for adverse CV outcomes.

∴ They stand to **benefit the most** from accurate BP measurements.

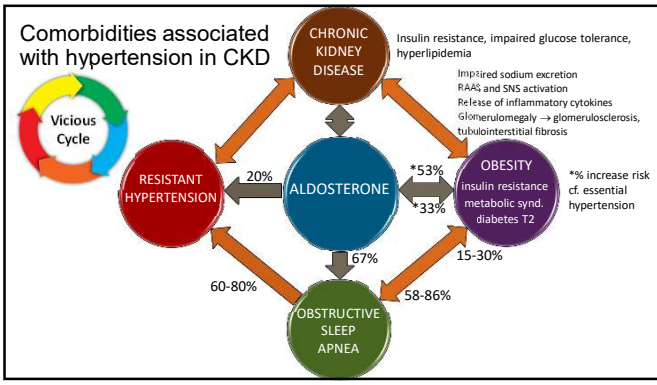
27

But ….Are standardized BP measurements feasible in a primary care practice?

- Equipment
  - AOBP devices can free up staff and provider time
  - Proper cuff sizes available (>40% of patients need a large cuff)
  - Upfront costs may pay off in the long-term
- Staff education
  - Train and re-train in proper BP technique
  - Stress importance of accurate BP measurements
- Workflow
  - Bring patients in 15 minutes before visit
  - Have patients fill out medical information ahead of visit
- Patient education
  - Wear clothing that allows arm to be exposed
  - Don't smoke, exercise, drink caffeine 30 minutes before visit.
  - Empty bladder before entering exam room

28

Comorbidities associated with hypertension in CKD



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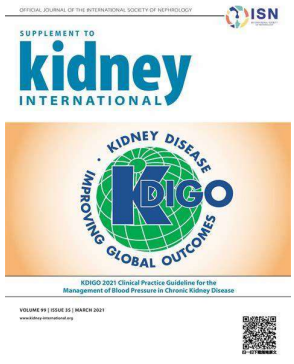

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SPRINT
Systolic **Pr**essure **In**tervention **T**rial

- Randomized 9361 non-diabetic participants at high risk for CVD to a target SBP <120 mm Hg vs. SBP <140 mm Hg
- Entry criteria included: CKD (eGFR 20-59 ml/min)
- Outcomes
  - CVD composite: -25%
  - Mortality: -27%
  - **No heterogeneity based on baseline kidney status**
    - **2646 CKD participants (intended 4600)**

CVD Outcome		Mortality	
Overall	CKD participants	Overall	CKD participants
0.75 (0.64-0.89)	0.81 (0.63-1.05)	0.73 (0.60-0.90)	0.72 (0.83-0.99)

31

KDIGO Recommendation for Blood Pressure Target

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)."

32

KDIGO Recommendation for Blood Pressure Target

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)."

2 = weak recommendation
B = moderate quality of evidence

Based on a subset of participants in a single RCT (SPRINT)
Uncertain benefit in CKD patients excluded from SPRINT:
Diabetes, GFR <30 ml/min, SBP 120-129 mm Hg or >180 mm Hg, very low DBP, age ≥85, very frail or institutionalized, proteinuria >1g/day

33

KDIGO vs. ACC/AHA

ACC/AHA: "Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg (1B)."

- Entry criteria in RCTs limit extrapolation to a more general population.
- BP measurements in RCTs adhere to guideline recommendations that are lower than in clinical practice.
- For these reasons, the recommended SBP target (<130 mm Hg) is higher than in SPRINT.

KDIGO: "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)."

- There are no outcomes trials supporting a target of <130 mm Hg.
- Patients should not be penalized for suboptimal clinical practice.

34

KDIGO Recommendation for Blood Pressure Target

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 less than 120 mm Hg to BP measurements obtained in a non-standardized manner."

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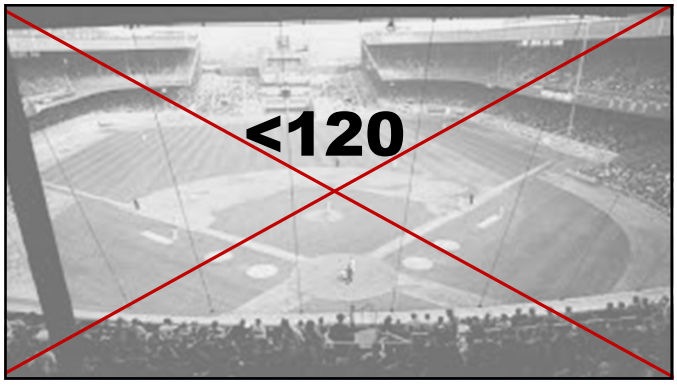

36

Two additional points regarding BP targets

- Incident CKD and acute kidney injury were more frequent with the intensive BP target in SPRINT
  - Biomarkers did not show evidence of structural damage
  - Most likely, this is a hemodynamic effect
  - It is uncertain if lower BP will benefit the kidney in the long-term
- KDIGO suggests out-of-office BPs (home or ABPM) only to "complement" office BPs; only the latter should be used to determine BP targets
  - There are no trials that have established optimal BP targets based on home or ambulatory BP measurements

37

Differences between ACC/AHA and KDIGO Guidelines for Patients with CKD

	ACC/AHA 2017	KDIGO 2021
Definition of hypertension	≥130/≥80	"High BP" is defined as a BP above target.
BP threshold for drug intervention	130/80 (with lifestyle modifications)	BP above target (with lifestyle modifications)
BP target	<130/<80 Deviates from SPRINT SBP <120 to prevent hypotension if casual BP measurements are used	SBP <120 (no DBP target) Adheres strictly to SPRINT based on obligatory use of standardized BP measurements
Out of office BP (HBPM or ABPM)	Strong recommendation to confirm the diagnosis of hypertension and for titration of BP lowering medication	Weaker recommendation: use HBPM or ABPM to "complement standardized office BP readings for the management of high BP"
Initial drug therapy	Monotherapy for <140/90; SPCT for ≥140/90 Algorithm for add-on therapy	RAS inhibitor No formal recommendations given for add-on therapy

38

KDIGO Recommendations for RAS inhibitors

Diabetes status	Urine Albumin-Creatinine Ratio	Recommendation
With diabetes	>30	Strong
Without diabetes	>300 30-300	Strong Weak
With or without diabetes	<30	Reasonable, but other agents acceptable

DO NOT combine an ACEi with an ARB!

39

Take-home Points

- Hypertension and chronic kidney disease share a pathogenetic bidirectional relationship that leads to cardiovascular morbidity and mortality.
- Chronic kidney disease is associated with high-risk hypertension phenotypes, including masked, nocturnal, and sustained hypertension.
- Blood pressure is a vital sign. It must be measured accurately using a standardized protocol. To do otherwise is hazardous.
- Hypertension and chronic kidney disease are closely linked to other cardiovascular risk factors, including aldosterone, obstructive sleep apnea, and obesity-related metabolic disorders.
- The ACC/AHA and KDIGO guidelines both stress the importance of standardized blood pressure measurements but depart in the target blood pressure for chronic kidney disease patients: ACC/AHA <130/<80; KDIGO <120 systolic.

40