

The Role of Central Aortic Pressure in the Management of High Blood Pressure

Objective of Presentation

The presentation will describe data demonstrating the following:

- Clinical evidence supports incorporating non-invasive central aortic blood pressure measurements into blood pressure management.
- The SphygmoCor[®] System can help guide treatment decisions designed to prevent or reduce long-term target organ damage and cardiovascular events resulting from increased aortic pressure and therefore reduce the socioeconomic burden of hypertension.

Agenda

- Background
- Central Aortic Pressure as a Predictor of Cardiovascular (CV) Events
- Central Aortic Pressure Threshold Values for Management Decisions
- White Coat Hypertension: The Role of Central Pressure Measurements
- Implications for Pharmacotherapy
- Summary and Conclusions

Background

Hypertension: Socioeconomic Impact

Epidemiology (USA)

- Prevalence ≈45% of adults¹
- Responsible for ≈500,000 deaths²
- CDC reports that hypertension is under control in only 24% of patients²

Economics

- Average annual medical expenditure attributable to hypertension = \$9,089 per diagnosed patient³
- Relative to non-hypertensives: \$1,920 higher annual adjusted incremental expenditure, 2.5x inpatient cost, 2x outpatient cost, and 3x prescription medication costs³
- Adjusted annual incremental cost = \$131 billion/year higher for adults with hypertension relative to adults without hypertension³

1. CDC. [Hypertension Cascade: Hypertension Prevalence, Treatment and Control Estimates Among US Adults Aged 18 Years and Older Applying the Criteria from the American College of Cardiology and American Heart Association's 2017 Hypertension Guideline—NHANES 2013–2016](#).; 2. CDC. Underlying Cause of Death, 1999–2018. CDC WONDER Online Database. Atlanta, GA: Centers for Disease Control and Prevention; 2018. <http://wonder.cdc.gov/ucd-icd10.html>. Accessed March 12, 2020; 3. Kirkland et al. Trends in Healthcare Expenditures Among US Adults With Hypertension: National Estimates, 2003–2014 J Am Heart Assoc. 2018;7:e008731. DOI: 10.1161/JAHA.118.008731.)

Hypertension Management

Diagnosis and management based on cuff measurement of peripheral (brachial artery) pressures

- Widespread use of brachial BP has led to substantial but incomplete improvement in hypertension control and reduction in end-organ damage

Why are there ongoing problems with hypertension management?

- Various reasons: case finding (early diagnosis), continuity and continued follow-up of care, affordability of care, medication adverse effects and medication compliance, challenges in modifying lifestyle behavior

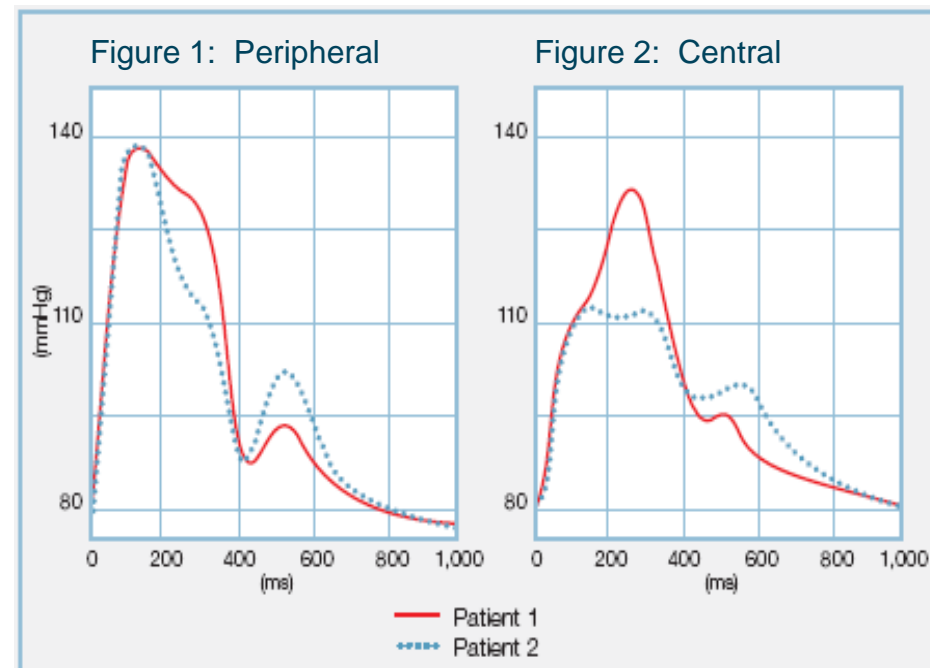
Additional issue: current monitoring based on brachial blood pressure

- Variable precision and reliability of measuring brachial BP (patient and health care provider factors)
- Brachial BP is a surrogate for central (i.e., aortic) blood pressures, which represent the actual pressures that are transmitted to organs effected by hypertension (e.g., heart, brain, kidney)
- Cuff brachial blood pressure measurement “is not so much a surrogate, but a compromised measure that is recorded because of technical limitations.” (Cheng et al)¹

1. Cheng et al. Derivation and validation of diagnostic threshold for central blood pressure measurements based on long-term cardiovascular risks. J Am Coll Cardiol. 2013;62:1780-7.

Non-Invasive Measurement of Central Aortic Pressure

- Non-invasive pulse wave analysis (PWA) is a technique that transforms the data from peripheral arterial pressure waveforms obtained into an evaluation of central aortic pressures
- Calculations are performed through a generalized transfer function that corrects for pressure wave amplification in the upper limb
- Variables produced:
 - Central aortic systolic and diastolic pressures
 - Central aortic pulse pressure (systolic minus diastolic pressure)
 - Augmentation pressure (difference between (a) reflected wave added to incident wave, and (b) incident pressure during systole)
 - Augmentation index (augmentation pressure divided by the pulse pressure)
- Peripheral (brachial) blood pressures are highly correlated to central pressures
 - Brachial systolic pressure is higher than central aortic systolic pressure
 - Diastolic pressures are similar



The SphygmoCor® XCEL System

Dual Arterial Pressure Monitoring System

- Obtains brachial pressures immediately followed by measurement of central aortic pressures
- Performed in the same session
- The only FDA cleared medical device for non-invasive central arterial pressure waveform analysis in adults



Arterial Waveform Capture

- A cuff is applied on the upper arm in the standard position
- The cuff is partially inflated to record the brachial waveforms
- These waveforms are detected by sensing changes in the pressure inside the cuff related to arterial pulsation
- The ascending aortic waveform is subsequently derived using a validated mathematical transfer function*



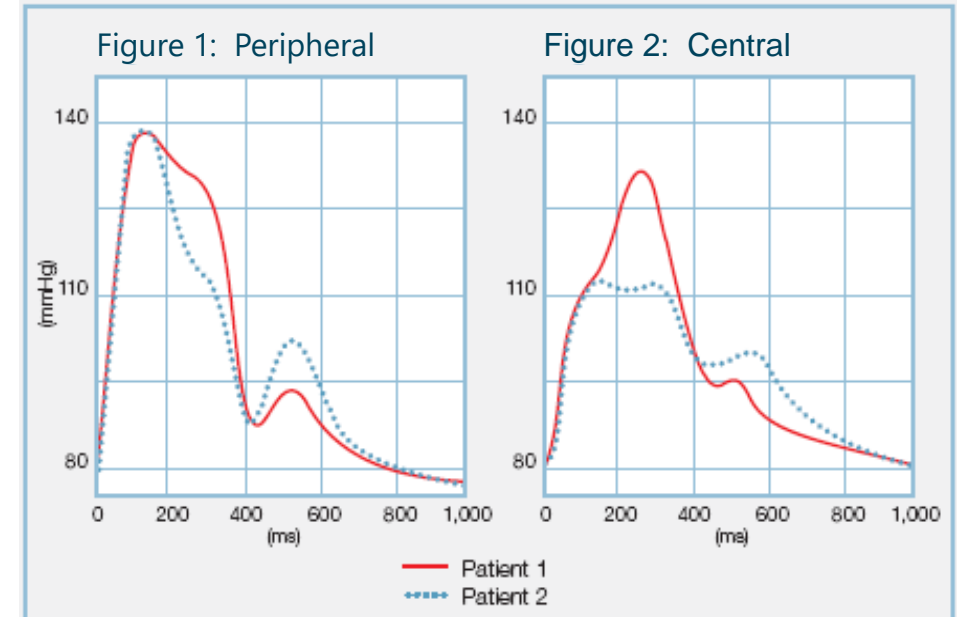
*Generalized transfer function cleared by FDA

Brachial Pressure Differs from Central Pressure

Brachial Cuff Pressure vs. Central Aortic Pressure

Two patients with IDENTICAL BRACHIAL CUFF pressures (Figure 1), but with significantly DIFFERENT CENTRAL/AORTIC arterial pressure waveforms (Figure 2).

- The difference in waveform shapes, due to differences in arterial stiffness and the effects of wave reflections, effects the aortic but not the brachial systolic and pulse pressures



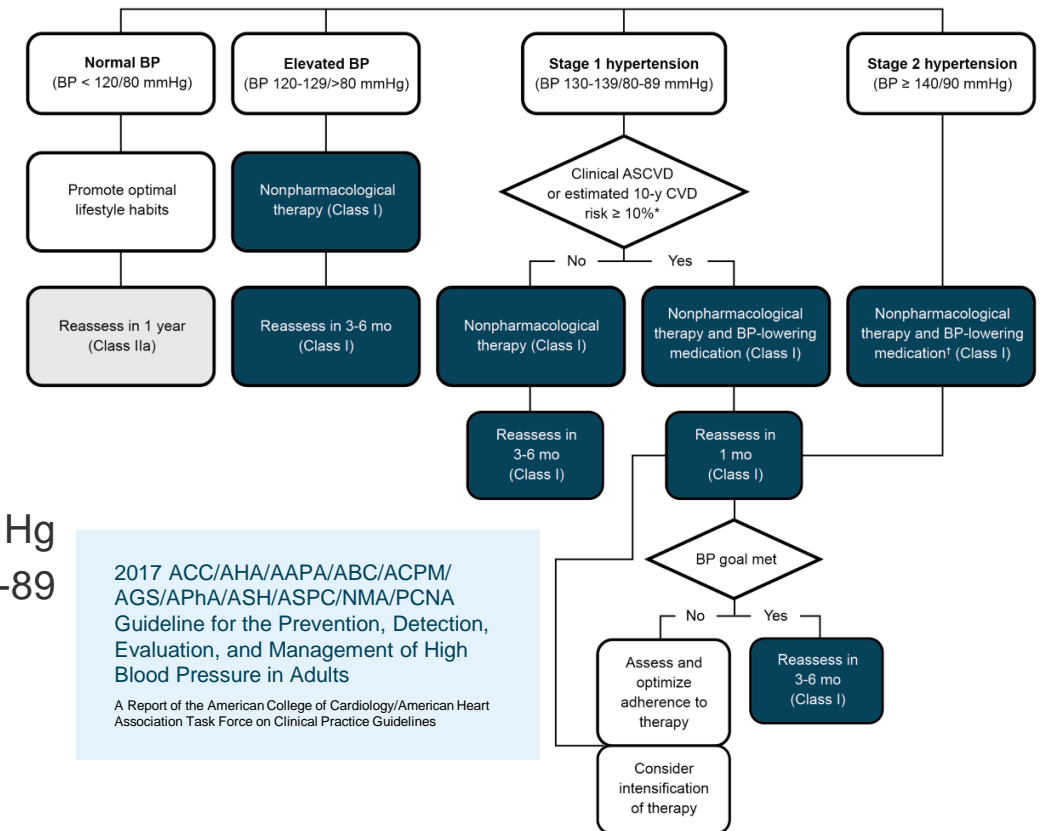
Both Brachial and Central Aortic Pressure Measurements Provide Clinically Relevant and Complimentary Information

Central Aortic Pressure Predicts End-Organ Damage and Cardiovascular Events

Brachial BP Monitoring: A Key Success Factor Responsible for Lowering Cardiovascular Risk

Brachial BP

- Prominent risk factor for vascular-related end-organ damage, morbidity, and mortality
- Reductions proven to reduce vascular end-organ damage, morbidity, and mortality
 - Based on threshold (baseline) blood pressure $\geq 140/90$ mm Hg¹
 - SPRINT study suggests that the thresholds for initiation of pharmacotherapy could be lower²
- ACA/AHA Guidelines (2017) Recommendation¹
 - Follow-up monitoring and lifestyle modifications at 120-139/80 mm Hg
 - Pharmacotherapy with risk factors for CV disease and 130-139/ 80-89 mm Hg
 - Pharmacotherapy with BP $\geq 140/90$ mm Hg



1. Whelton et al. 2017 ACC/AHA/AAPA/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2018;138:e484-e594. 2. Wright et al. A randomized trial of intensive versus standard blood-pressure control. SPRINT Research Group. *N Engl J Med.* 2015;373:2106-16.

Central BP Predicts End-Organ Damage and Cardiovascular Risk

End-organ damage associated with hypertension is directly related to central pressures as these, rather than peripheral pressures, are the pressures that are transmitted to vital organs

Central systolic pressures

- Correlated to peripheral systolic pressures (correlation coefficients 0.6 to 0.97)
- Multiple studies, including meta-analyses, have evaluated cBP variables and suggested that cBP has a higher predictive value for cardiovascular events relative to peripheral BP, with others uniformly demonstrating that cBP is at least as predictive as peripheral BP.

Objective of hypertension management

- Should include lowering central systolic pressures to values (or thresholds) that correspond to the targets set for peripheral systolic pressures for the purpose of reducing vascular risk

Elevated Central BP is Associated with End-Organ Damage

Study Objective: determine relationship of blood pressures to organ damage

Subjects: N= 1,169, ≥ 16 years old, randomly recruited from Johannesburg, South Africa

Brachial BP (mm Hg)	Optimal <120/80	Normal/High Normal ≥120/80 + <140/90		Hypertension ≥140/90 or Treatment
Aortic Systolic BP (mm Hg)	-	<112	≥112	-
Unadjusted Values				
eGFR (ml/min/1.73m ²) (n)	128±32 (244)	126±32 (108)	111±26 (149)	103±28 (443)
LVMI (g/m ²) (n)	35.5±10.2 (181)	38.2±11 (82)	44.0±12.1 (109)	47.5±15.8 (318)
Adjusted Values				
eGFR (ml/min/1.73m ²) (n)	118±29 (244)	115±27 (108)	108±26 (104)	112±30 (443)
LVMI (g/m ²) (n)	40.0±14.3 (181)	40.7±13.2 (82)	44.5±12.6 (109)	44.0±14.6 (318)

Central pressure added relevant data determining risk of end-organ damage

eGFR: estimated glomerular filtration rate; LVMI left ventricle mass index

Multivariate adjustment for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate.

Central BP Relates to Target Organ Damage

1,272 normotensive and untreated hypertensive (SBP \geq 140 or DBP \geq 90 mmHg) participants
 Baseline values correlated to laboratory and clinical outcomes over a period of up to 10 years

	LVM		IMT		GRF	
	r	Partial r	r	Partial r	r	Partial r
SBP-B	0.370	0.231	0.225	0.101	-0.170	-0.041**
SBP-C	0.410	0.270	0.252	0.137	-0.179	-0.058*
PP-B	0.219	0.112	0.204	0.072*	-0.131	0.032**
PP-C	0.286	0.194	0.265	0.127	-0.187	-0.012**

LVM: left ventricular mass
 IMT: intima-medial thickness
 GFR: glomerular filtration rate

*p<0.05
 **not significant
 p<0.001 for all other fields

SPB systolic blood pressure, PP pulse pressure, B brachial, C central

Partial r: adjusted for age, sex, heart rate, body mass index, current smoking, fasting plasma glucose, total cholesterol/high-density lipoprotein cholesterol, and carotid-femoral pulse wave velocity.

Central BP Relates to CV Mortality

Hazard ratios and 95% CI for all-cause and CV mortality by univariate analysis.

	All-Cause Mortality		CV Mortality	
	Women	Men	Women	Men
SBP-B (10 mm Hg)	1.15 (1.04-1.27)	1.11 (1.00-1.22)	1.30 (1.08-1.55)	1.33 (1.11-1.60)
SBP-C (10 mm Hg)	1.23 (1.12-1.36)	1.11 (1.01-1.23)	1.51 (1.27-1.80)	1.35 (1.50-1.59)
PP-B (10 mm Hg)	1.25 (1.10-1.43)	1.36 (1.20-1.53)	1.41 (1.12-1.77)	1.54 (1.24-1.91)
PP-C (10 mm Hg)	1.50 (1.32-1.71)	1.36 (1.21-1.53)	1.77 (1.41-2.21)	1.43 (1.15-1.78)

SPB systolic blood pressure, PP pulse pressure, B brachial, C central

Central BP Relates to CV Mortality

		HR/10 mm Hg (CI)	HR/SD increment (CI)
Model 1	SBP-B	1.049 (0.800–1.374)	1.119 (0.590–2.122)
	PP-B	1.138 (0.802–1.616)	1.238 (0.694–2.209)
Model 2	SBP-B	0.957 (0.787–1.164)	0.902 (0.567–1.434)
	SBP-C	1.336 (1.107–1.612)	2.002 (1.276–3.140)
Model 3	SBP-B	1.076 (0.906–1.278)	1.189 (0.791–1.789)
	PP-C	1.199 (0.941–1.530)	1.330 (0.908–1.947)
Model 4	PP-B	1.042 (0.835–1.299)	1.070 (0.743–1.540)
	SBP-C	1.286 (1.089–1.520)	1.828 (1.226–2.726)
Model 5	PP-B	1.116 (0.895–1.393)	1.199 (0.832–1.728)
	PP-C	1.190 (0.933–1.518)	1.314 (0.898–1.923)
Model 6	SBP-C	1.491 (1.154–1.928)	2.606 (1.408–4.821)
	PP-C	0.786 (0.541–1.141)	0.685 (0.381–1.230)

Multivariate Cox proportional hazards regression models relating incidence of cardiovascular mortality to dual blood pressure components of SBP-B, PP-B, SBP-C, and PP-C (HR = Hazard Ratio)

Numbers in bold letters indicate statistical significance.

All adjusted for age, sex, heart rate, BMI, current smoking, fasting plasma glucose levels, cholesterol/HDL ratio, carotid-femoral pulse wave velocity, LVM, IMT, and eGFR. PP-B = brachial pulse pressure; PP-C = central pulse pressure; SBP-B = brachial systolic blood pressure; SBP-C = central systolic blood pressure.

BP Predicts CV Events: Meta-Analysis

Five studies included both central and brachial pressures

Relative Risk (RR) and 95%CI of clinical events for a 1 SD increase in (A) PP and (B) SP

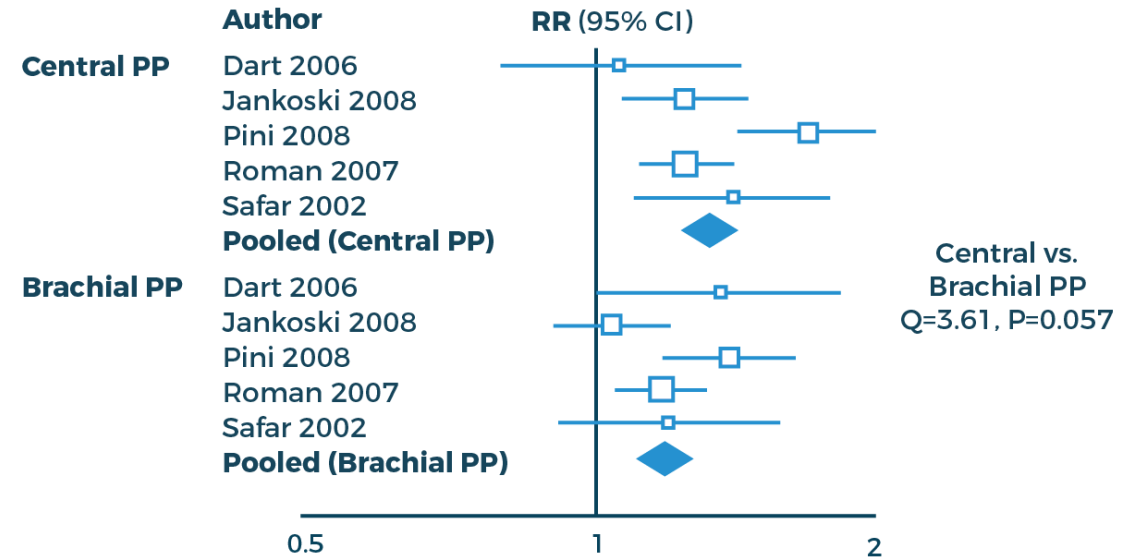
Boxes = RR, **Lines** = 95% CI.

Diamonds = pooled RR, **Diamond width** = 95% CI.

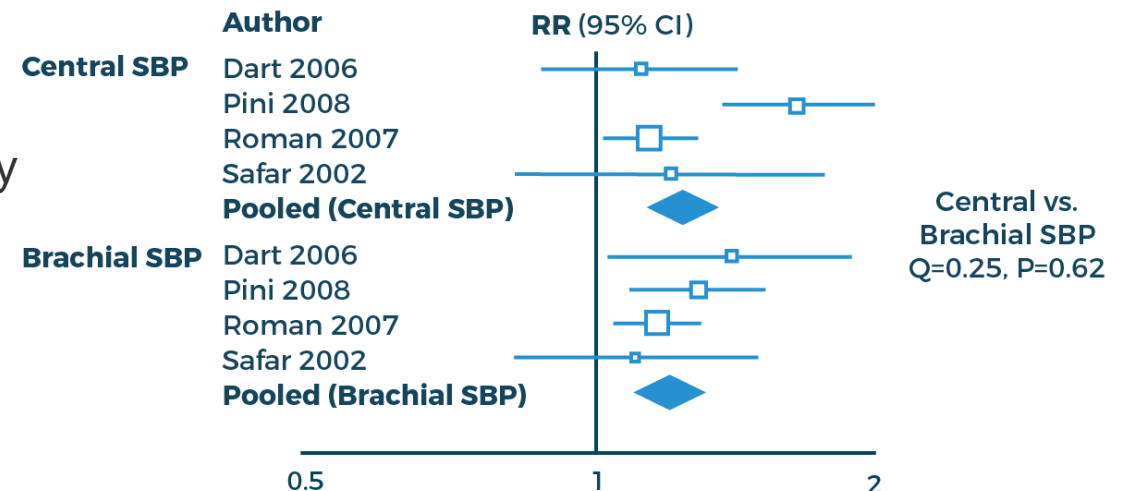
Conclusion

Elevated central and peripheral systolic pressures and pulse pressures increased risk of CV events and all-cause mortality

(A) PP and Clinical Outcome



(B) SBP and Clinical Outcome



Central BP Predicts CV Events

Study

- Design: meta-analysis from International Database of Central Arterial Properties for Risk Stratification.
- Objective: examine thresholds for central aortic systolic BP (cSBP) associated with clinical outcomes and whether cSBP, either alone or in combination with brachial systolic BP (bSBP) improved risk stratification
 - 5,576 subjects (mean age 54.2 years, 54% women)

Results

	Central Systolic Normotension (NT)		Central Systolic Hypertension (HT)	
	Brachial NT	Brachial HT	Brachial NT	Brachial HT
Number at risk	2403	277	209	2687
Systolic BP thresholds, mm Hg				
Central	<120	<120	≥120	≥120
Brachial	<130	≥130	<130	≥130
Primary end-point				
HR (95% CI)	1 (reference)	1.30 (0.58–2.94)	2.28 (1.21–4.30)‡	2.02 (1.41–2.91)†
Secondary end points				
Mortality HR (95% CI)	1 (reference)	1.03 (0.44–2.43)	0.54 (0.20–1.51)	1.05 (0.74–1.48)
Cardiac end-point HR (95% CI)	1 (reference)	1.26 (0.62–2.60)	1.15 (0.56–2.36)	1.37 (0.97–1.91)*
Cerebrovascular end-point HR (95% CI)	1 (reference)	2.21 (0.62–7.97)	3.71 (1.37–10.06)*	2.60 (1.35–5.00)*

*p<0.01
 †p<0.001
 ‡p<0.05
 relative to the reference group

Conclusion

“Irrespective of the brachial blood pressure status, central hypertension increased cardiovascular and cerebrovascular risk indicating the importance of controlling central hypertension.”

Central Pressure Threshold Values for Management Decisions

Hypertension Management Decisions are Based on Brachial BP

	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
NICE (2019)		
Normotension	<120	<80
Stage 1 Hypertension	≥140	≥90
Stage 2 Hypertension	≥160	≥100
Severe hypertension	≥180	or ≥120
ESH/ESC (2018)		
Normotension	<120	<80
Grade 1 Hypertension	140–159	and/or 90–99
Grade 2 Hypertension	160–179	and/or 100–109
Grade 3 hypertension	≥180	and/or ≥110
ACC/AHA (2017)		
Normotension	<120	and <80
Elevated BP	120–129	and <80
Stage 1 Hypertension	130–139	or 80–89
Stage 2 Hypertension	≥140	or ≥ 90

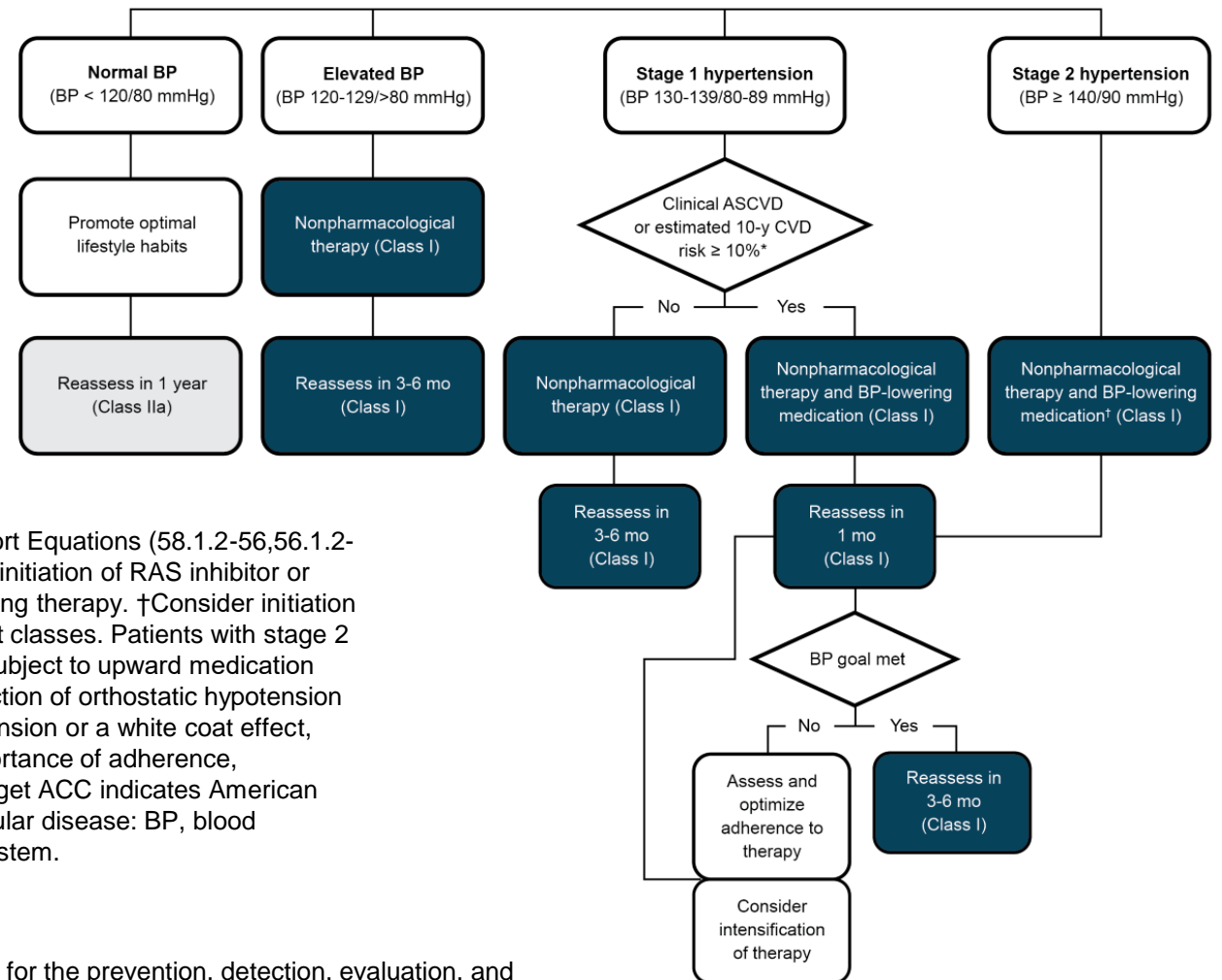
Management decisions for the treatment of hypertension are based on specific threshold values for systolic and diastolic brachial pressures regardless of age and gender.

ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; NICE, National Institute for Health and Care Excellence.

BP Thresholds and Recommendations for Treatment and Follow-Up

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines



Colors correspond to Class of Recommendation in Table 1. *Using the ACC/ANA Pooled Cohort Equations (58.1.2-56,56.1.2-57). Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy. †Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP $\geq 160/100$ mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; and RAS, renin-angiotensin system.

Whelton PK et al. 2017 ACC/AHA/AAPA/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2018;138:e484-e594.

Threshold Values for Central Systolic BP and Organ Damage

Study Objective

- Prevalence of central hypertension and its association with end-organ damage in 1,983 elderly people

Hypertension Definition

- Brachial BP $\geq 140/90$ mmHg or using antihypertensive medications
- Central BP $\geq 130/90$ mmHg or using antihypertensive medications

Population Groups

		Central Hypertension		
		No	Yes	
Brachial Hypertension	No	BCCN, 563 (28.4%)	ICH, 27 (1.4%)	BCCN: brachial & central consistent normotension BCCH: brachial & central consistent hypertension IBH: isolated brachial hypertension (e.g., white coat hypertension) ICH: isolated central hypertension (e.g., masked hypertension)
	Yes	IBH, 46 (2.3%)	BCCH, 1347 (67.9%)	

Threshold Values for Central Systolic BP and Organ Damage

Organ Damage

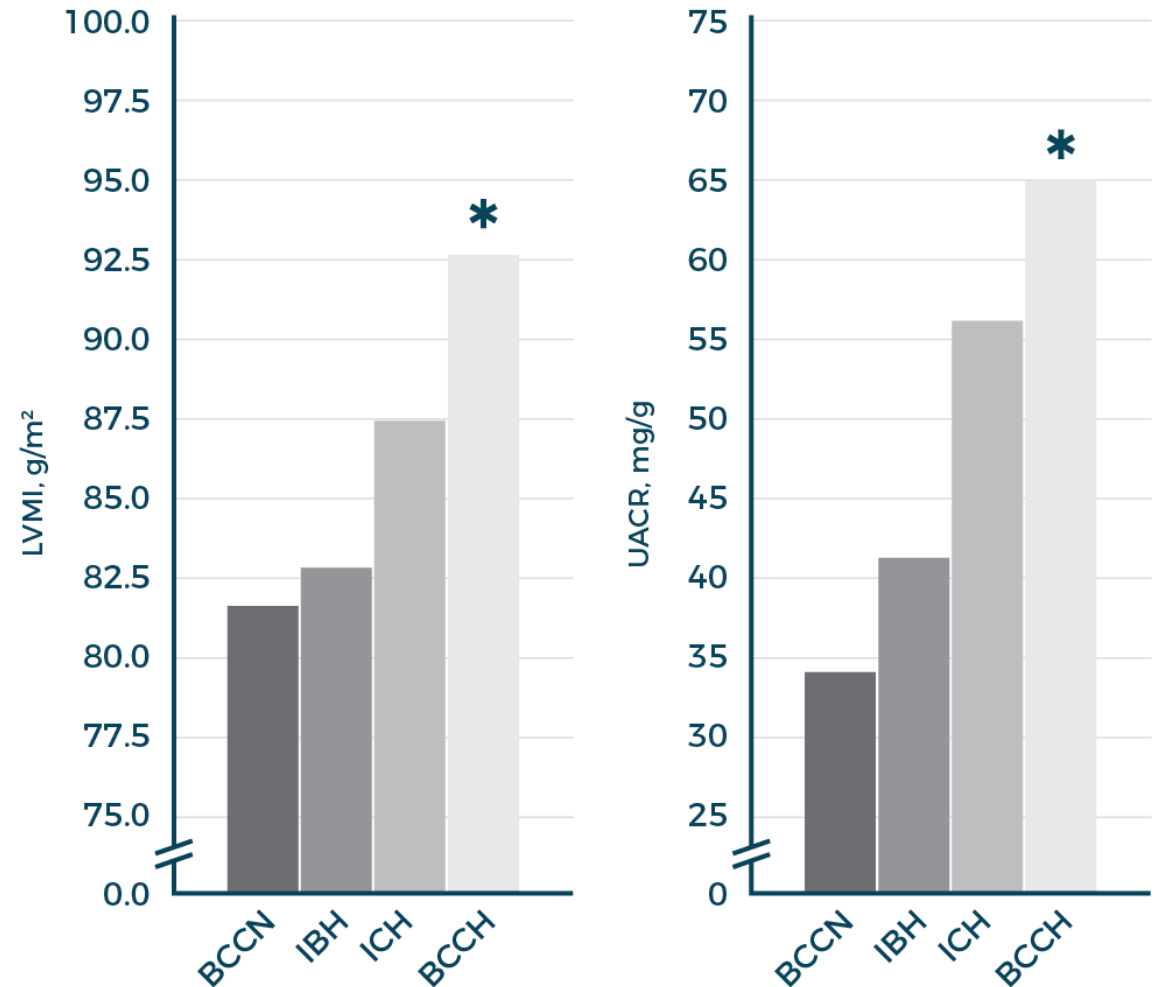
ANCOVA performed to compare the mean levels between subtypes of brachial and central hypertensions. The mean values of LVMI and UACR in different subtypes and the results of comparisons are displayed.

* $p < 0.05$, compared with BCCN

LVMI, left ventricular mass index

UACR, urinary albumin-creatinine ratio.

Central pressure added relevant data determining risk of end-organ damage



Threshold Values for Central Systolic BP and Organ Damage

Results

- Measures of end-organ damage were significantly associated with concordant hypertension group
- Compared to isolated brachial or isolated central hypertension (adjusted odds ratio [95% CI])
 - LVH = 2.03 [1.55, 2.68]
 - LV diastolic dysfunction = 2.29 [1.53, 3.43]
 - Urinary albumin-creatinine ratio >30 mg/g: 1.97 [1.58, 2.44]

Conclusions

- Groups can be distinguished based on concordance and discordance of hypertension based on threshold values of 140/90 mm Hg (brachial pressure) and 130/90 (central aortic pressure) for risk evaluation and treatment decisions.
- Both measurements of central and peripheral pressures should be reviewed given that treatment decisions often constitute a life-commitment to pharmacotherapy.

Elevated Central BP is Associated with Target Organ Damage

Study Objective: determine relationship of blood pressures to target organ damage

Subjects: N= 1,169, ≥ 16 years old, randomly recruited from Johannesburg, South Africa

Brachial BP (mm Hg)	Optimal <120/80	Normal/High Normal ≥120/80 + <140/90		Hypertension ≥140/90 or Treatment
Aortic Systolic BP (mm Hg)	-	<112	≥112	-
Unadjusted Values				
eGFR (ml/min/1.73m ²) (n)	128±32 (244)	126±32 (108)	111±26 (149)	103±28 (443)
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Central pressure added relevant data determining risk of end-organ damage

eGFR: estimated glomerular filtration rate; LVMI left ventricle mass index

Multivariate adjustment for age, sex, BMI, diabetes mellitus and/or an HbA1c>6.1%, regular tobacco use, regular alcohol intake and pulse rate.

Threshold Values for Central Aortic Systolic BP and CV Outcomes

Study

- Objective: determine thresholds for predication of CV outcomes
- Design
 - Derivation cohort (1,272 individuals, median follow-up of 15 years)
 - Determined diagnostic thresholds using guideline-endorsed cut-offs for brachial blood pressure with a bootstrapping method (resampling by drawing randomly with replacement) and an approximation method.
 - Validated with an independent cohort (validation cohort, 2,501 individuals, median follow-up of 10 years)

Results

- Derivation and validation cohort yielded similar threshold values for central aortic pressures.
- Relative to optimal (central BP < 110/80 mmHg), the risk of CV mortality in subjects with hypertension (central BP \geq 130/90 mm Hg) was clinically and statistically elevated (hazard ratio: 3.08, 95% CI 1.05 to 9.05).

Conclusion

- Central BP \geq 130/90 mm Hg was associated with the largest contribution to the prediction of cardiovascular events.

Threshold Values for Central Aortic Systolic BP and CV Outcomes

Proposed Threshold Values for Central Aortic Pressure

Optimal: BP < 110/80 mmHg

Prehypertension: 110-129 / 80-89 mm Hg

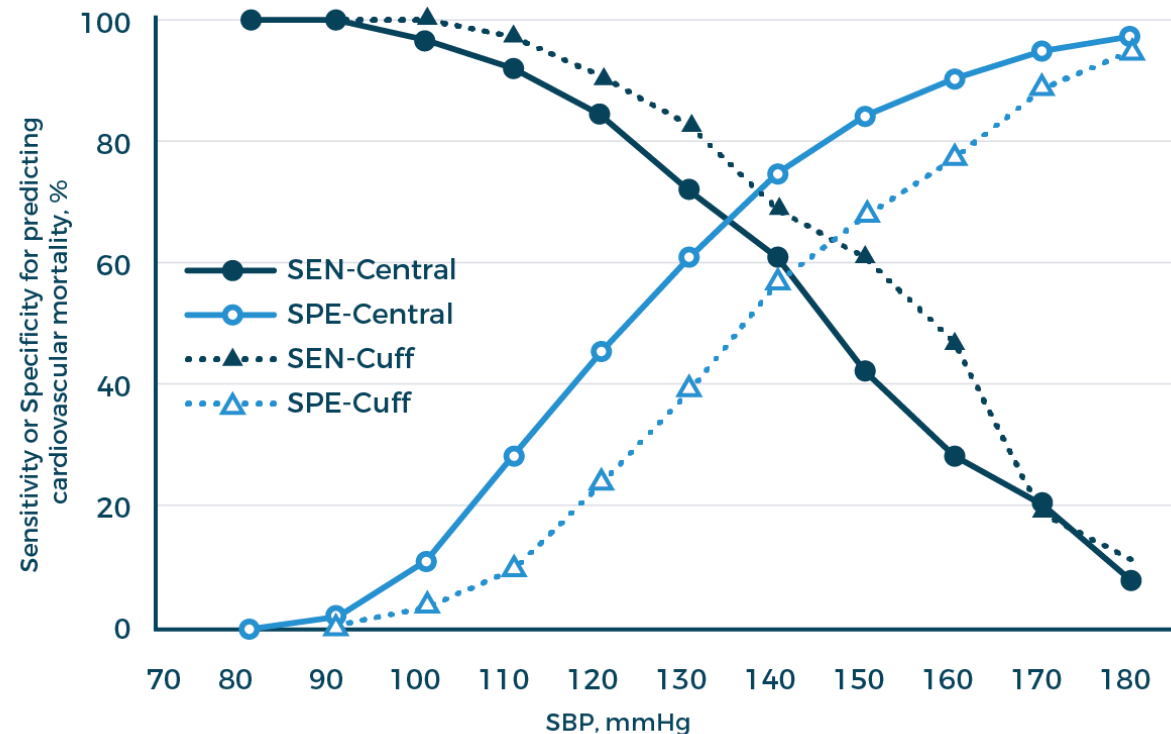
- corresponding to “elevated” and Stage 1 hypertension in the 2017 Guidelines

Hypertension: \geq 130/90 mm Hg

- corresponding to Stage 2 hypertension in the 2017 Guidelines

With increasing systolic BP cutoff values, specificity (SPE) improved at the expense of decreasing sensitivity (SEN). Reasonable cutoff limits for central SBP can be determined by approximating based on the sensitivity or specificity of the guideline-endorsed cuff SBP cutoff points.

Sensitivity and Specificity of Cuff SBP and Central SBP for Predicting CV Mortality in the Derivation Cohort



Threshold Values for Central BP (CBP) and CV Outcomes

CBP Levels and CV Mortalities With Different Cuff SBP and DBP Cutoffs Based on Conventional Criteria in the Derivation Cohort

Hypertension Staging	Category	Diagnostic Thresholds for Cuff BP, mm Hg	Cardiovascular Mortalities, %	Corresponding CBP Levels, mm Hg (95% CI)
Optimal–pre-hypertension	SBP	120	2.7	112.80 (111.15–113.61)
	DBP	80	4	80.92 (79.60–82.22)
Prehypertension–hypertension	SBP	140	4.3	132.43 (130.89–133.88)
	DBP	90	5	90.98 (89.93–91.96)

The cutoff criteria are based on international standards. Point estimates and 95% CIs were obtained from the bootstrap distribution of 1,000 random samples with replacement of CBP levels for participants in the derivation cohort.

Hazard Ratios for Total, Cardiovascular, and Stroke Mortality in Relation to CBP at Entry in the Validation Cohort (n=2,501)

	Total Death	Cardiovascular Death	Stroke Death
Endpoints	185 (7.4%)	34 (1.36%)	18 (0.72%)
Pre-hypertension vs. optimal BP	1.31 (0.87–3.35)	1.59 (0.57–4.43)	1.93 (0.45–8.31)
Hypertension vs. optimal BP	2.14 (1.36–3.35)	3.08 (1.05–9.05)	6.12 (1.43–26.21)

Values are n (%) or hazard ratio (95% CI). Hazard ratios were adjusted for sex, age, body mass index, smoking, and serum total cholesterol level.

Threshold Values for Central Aortic Systolic BP

Discussion

“...in current international guidelines, the classification of cuff BP values disregards age, sex, and other cardiovascular risk factors. In our multivariate model, the results were consistent after accounting for these factors. In line with current clinical practice and considering the higher clinical events in the aged population, we now propose diagnostic thresholds of central BP without age and sex specification.”

Regarding “spurious systolic hypertension” and “white coat hypertension”, the authors recognized the clinical utility of measuring central aortic BP in that the diagnosis can be inferred based on a high cuff (brachial) BP and low/normal central BP.

Threshold Values: Associations of Systolic Pressures with MACE*

Prospective study

- 13,461 patients using available central blood pressure measurements and follow-up data from administrative databases
- 1,327 MACE, median follow-up ≈9 years)

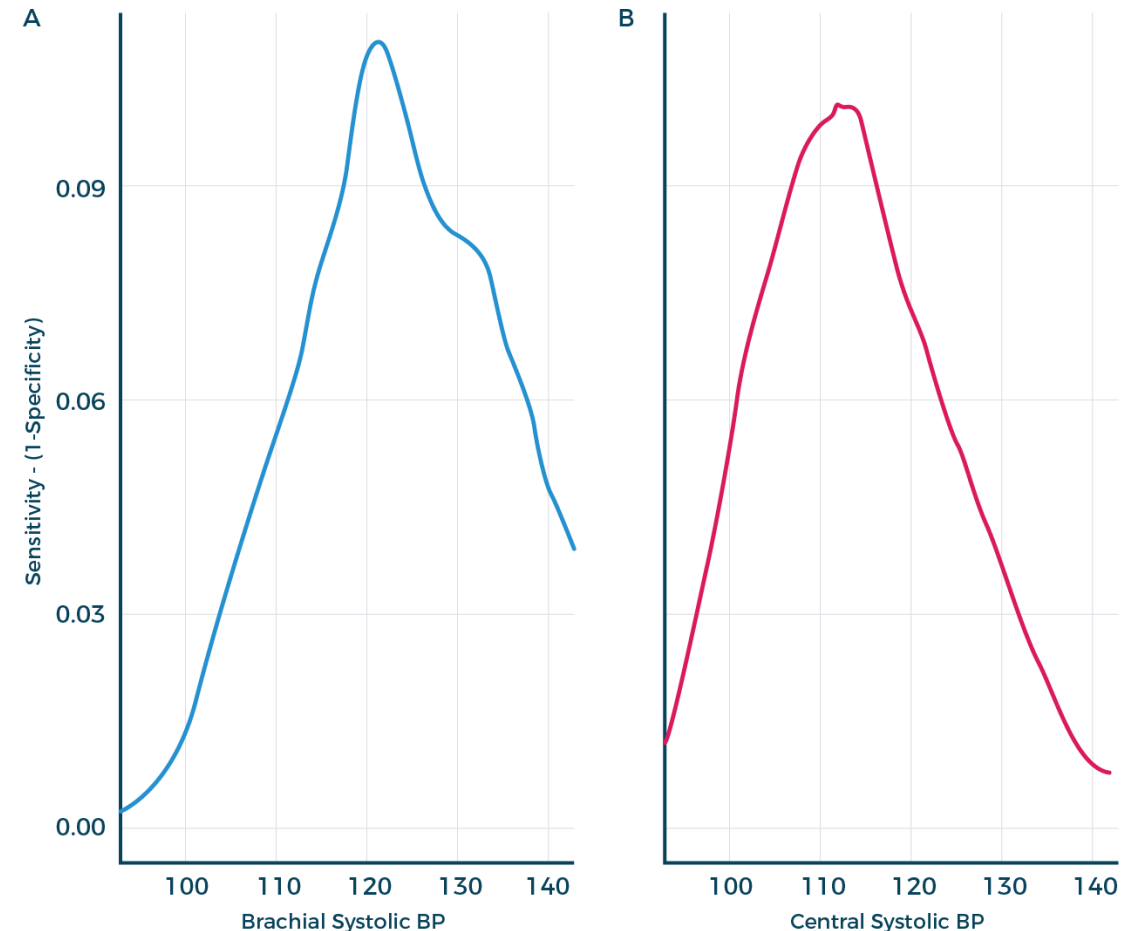
Hazard ratio for risk of MACE* (for 1 SD increase)

- Central SBP 1.16 (95% CI 1.09-1.22)
- Brachial SBP 1.15 (95%CI 1.09-1.22)
- Modeling data (AUC) for risk indicated a slightly higher risk using cSBP vs. brachial SBP that was statistically significant

Conclusion

- Central and brachial SBPs of 112 mm Hg (95% CI, 111.2–114.1) and 121 mm Hg (95% CI, 120.2–121.9) were identified as optimal BP thresholds.

*MACE: Major Adverse Cardiovascular Events



Optimal brachial and central systolic blood pressure thresholds.

Youden index according to (A) brachial systolic blood pressure (BP) and (B) central systolic BP. Youden index is the maximal value obtained, a brachial systolic BP threshold of 121mmHG (95%CI, 120.1-121.9 mmHG) and a central systolic BP threshold of 112 mmHG (95% CI, 111.2-114.1 mmHG).

White Coat Hypertension: The Role of Central Pressure Measurements

White Coat Hypertension

Definition

- An elevated BP in an office setting with normal values for home-assessed blood pressure values (ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM))

Prevalence

- Somewhat variable among published research
- Meta-analysis (7 studies, 11,502 participants): 13%¹
- National registry study: 35%²
- National and international registries: 10% and 50%³

Diagnosis

- Requires confirmation with repeated office and out-of-office BP measurements, including ABPM

Payer Response

- CMS has provided reimbursement for ABPM for suspected white coat hypertension since 2001
- In 2019, CMS expanded ABPM coverage to include masked hypertension

Reality

- Use of ambulatory blood pressure monitoring is low given the documented prevalence of white coat hypertension

1. Fagard et al. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *J Hypertens* 2007;25:2193-8; 2. de la Sierra et al. Prevalence and clinical characteristics of white-coat hypertension based on different definition criteria in untreated and treated patients. *J Hypertens* 2017; 35: 2388–2394; 3. Gorostidi et al. Prevalence of white-coat and masked hypertension in national and international registries. *Hypertens Res* 2015; 38: 1–7.

White Coat Hypertension: Summary

Definition

- ESH: clinic BP \geq 140/90 mm Hg + mean 24-hour BP $<$ 130/80 mm Hg
- ACC/AHA: clinic BP \geq 130/80 + daytime ambulatory or home BP $<$ 103/80 mm Hg
- NICE: clinic BP \geq 140/90 mm Hg + daytime ambulatory or home BP $<$ 103/80 mm Hg

Etiology

- Psychological factors (stress, anxiety)

Physiology

- Poorly understood, sympathetic and endocrine factors implicated, possible poor BP technique

Relevance*

- Increased risk of sustained hypertension
- Worse target organ damage
- Some studies – higher rates of CVD

*Cardiovascular (CV) clinical relevance compared to people with normal blood pressure

ACC: American College of Cardiology, AHA: American Heart Association, ESH: European Society of Hypertension, NICE: National Institute for Health and Care Excellence, WCH: White Coat Hypertension

Threshold Values for Central Systolic BP and Organ Damage

Study Objective

- Prevalence of central hypertension and its association with end-organ damage in 1,983 elderly people

Hypertension Definition

- Brachial BP $\geq 140/90$ mmHg or using antihypertensive medications
- Central BP $\geq 130/90$ mmHg or using antihypertensive medications

Population Groups

		Central Hypertension		
		No	Yes	
Brachial Hypertension	No	BCCN, 563 (28.4%)	ICH, 27 (1.4%)	BCCN: brachial & central consistent normotension BCCH: brachial & central consistent hypertension IBH: isolated brachial hypertension (e.g., white coat hypertension) ICH: isolated central hypertension (e.g., masked hypertension)
	Yes	IBH, 46 (2.3%)	BCCH, 1347 (67.9%)	

Threshold Values for Central Systolic BP and Organ Damage

Organ Damage

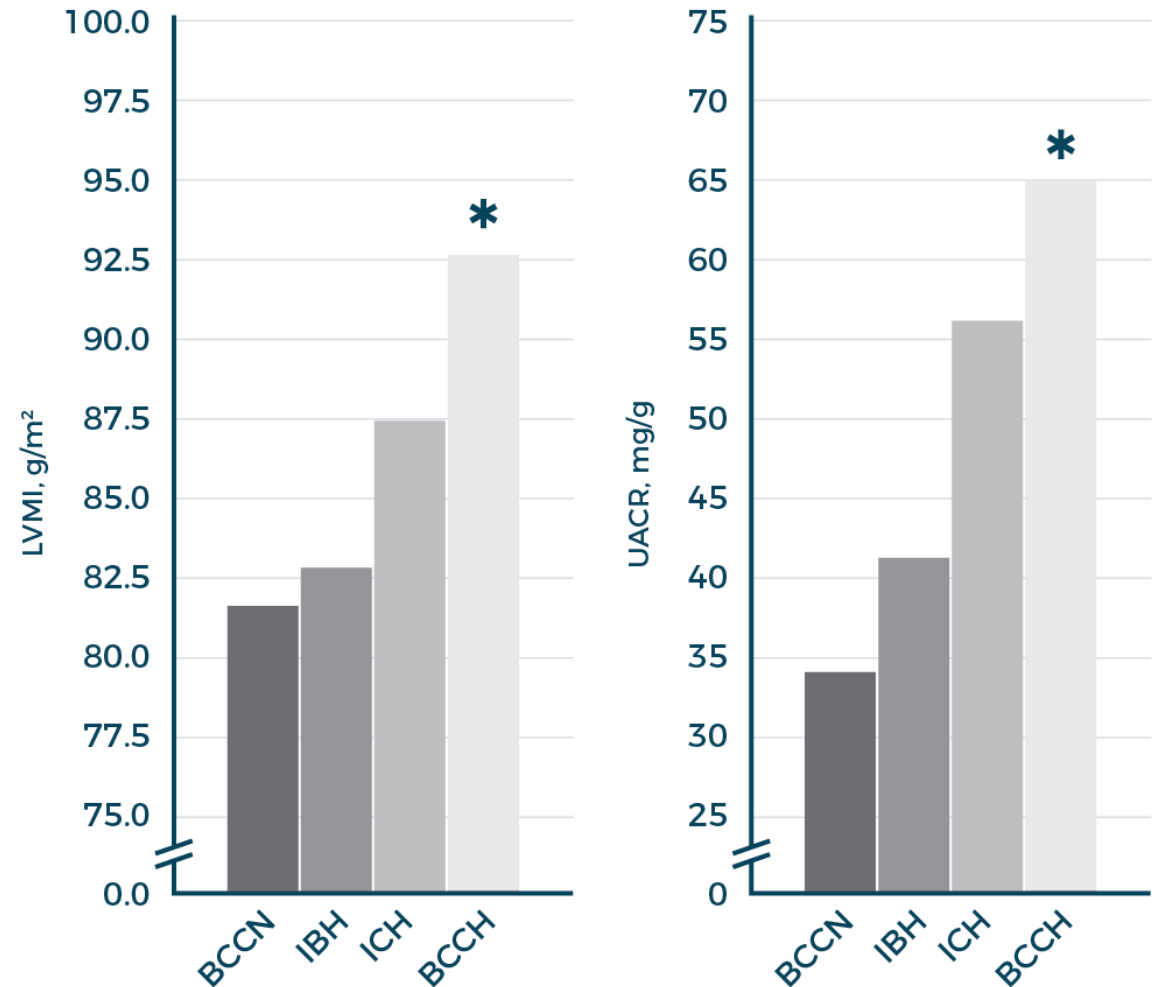
ANCOVA performed to compare the mean levels between subtypes of brachial and central hypertensions. The mean values of LVMI and UACR in different subtypes and the results of comparisons are displayed.

* $p < 0.05$, compared with BCCN

LVMI, left ventricular mass index

UACR, urinary albumin-creatinine ratio.

Central pressure added relevant data determining risk of end-organ damage



Role of Central BP in White Coat Hypertension

Study Objective

- Investigate whether prognosis of ISH in young-to-middle-age individuals differs according to central BP

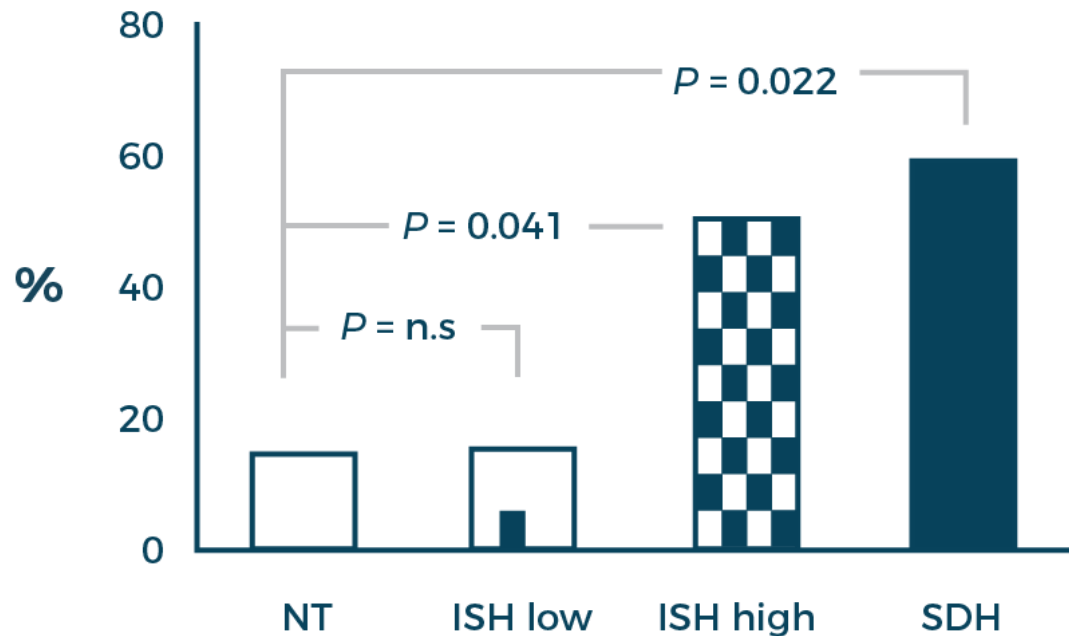
Study Population

- Isolated systolic hypertension: 354 participants (18 to 45 years), Stage 1 hypertension, untreated
- Control group of 34 participants with normal blood pressure
- Divided into groups based on the group median central systolic pressure (120.5 mm Hg)
 - Low (ISH-low) <120.5 mm Hg
 - High (ISH-high) \geq 120.5 mm Hg
- Duration of follow-up = 9.5 years

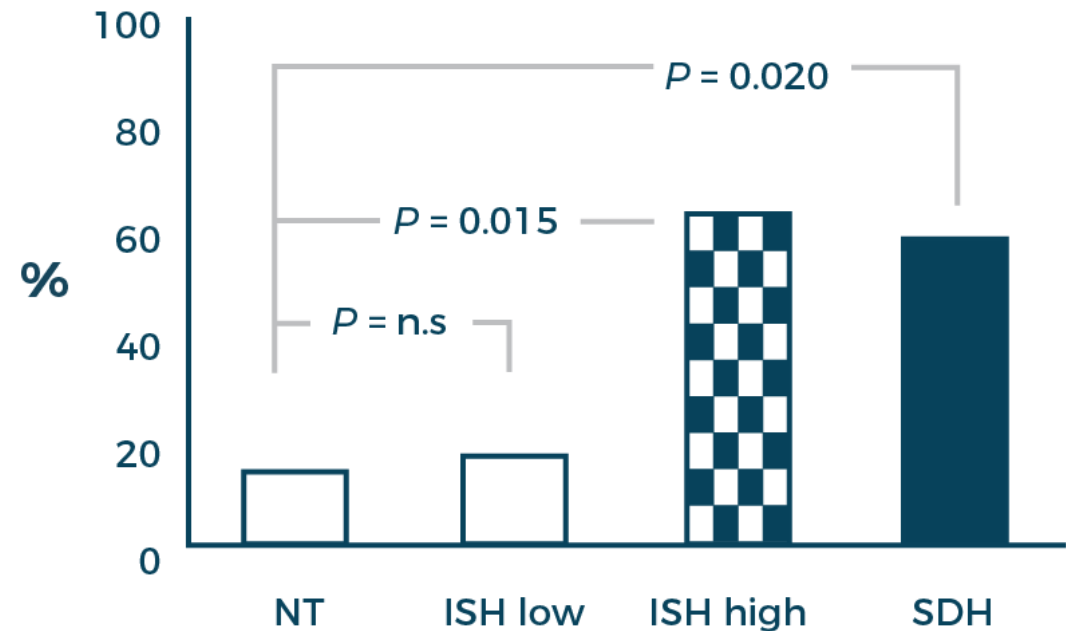
Role of Central BP in White Coat Hypertension

Incidence of Sustained Hypertension Needing Antihypertensive Treatment

(A) Median Central Pressure = 120.5 mm Hg



(B) Median Central Pressure = 125 mm Hg



NT: BP < 140/90 mmHg; ISH-low: isolated systolic hypertension + central SBP < 120.5 mmHg (figure a) [125 mm Hg for figure b]
ISH-high: isolated systolic hypertension + central SBP > 120.5 mmHg; SDH: BP > 140/90 mmHg (systolic/diastolic hypertension)
P-values adjusted for age, sex, baseline BMI and change during the follow-up, lifestyle factors, parental hypertension, follow-up duration, 24-h SBP and DBP, and 24-h heart rate.

Role of Central BP in White Coat Hypertension

Results

Odds ratio for developing sustained hypertension:

- ISH-high vs. control = 6.0 (95% CI 1.5 – 24.0, p=0.01)
- ISH-low vs. control group = 1.1 (95% CI 0.2 – 5.3, p=0.90)
- Associations remained statistically significant when a threshold central systolic pressure of 125 mm Hg was used and when the model included ambulatory blood pressure

Conclusion

Including central pressure measurement in the assessment and management of hypertension is clinically relevant.

Implications for Pharmacotherapy

Optimizing Hypertension Pharmacotherapy

Pharmacotherapy Concerns

- Undertreatment, overtreatment, compliance, drug cost, adverse events, drug interactions
- Generally, lifetime treatment
- All above impact a patient's adherence behavior to prescribed treatment and the burden of hypertension

Prescription Optimization

- Optimizing prescription medication including self-administration of therapy is critical to controlling hypertension

Optimizing Hypertension Pharmacotherapy

Incorporation of PWA into the treatment paradigm for hypertension (i.e., in addition to brachial pressure monitoring) can provide clinically relevant value to patient care:

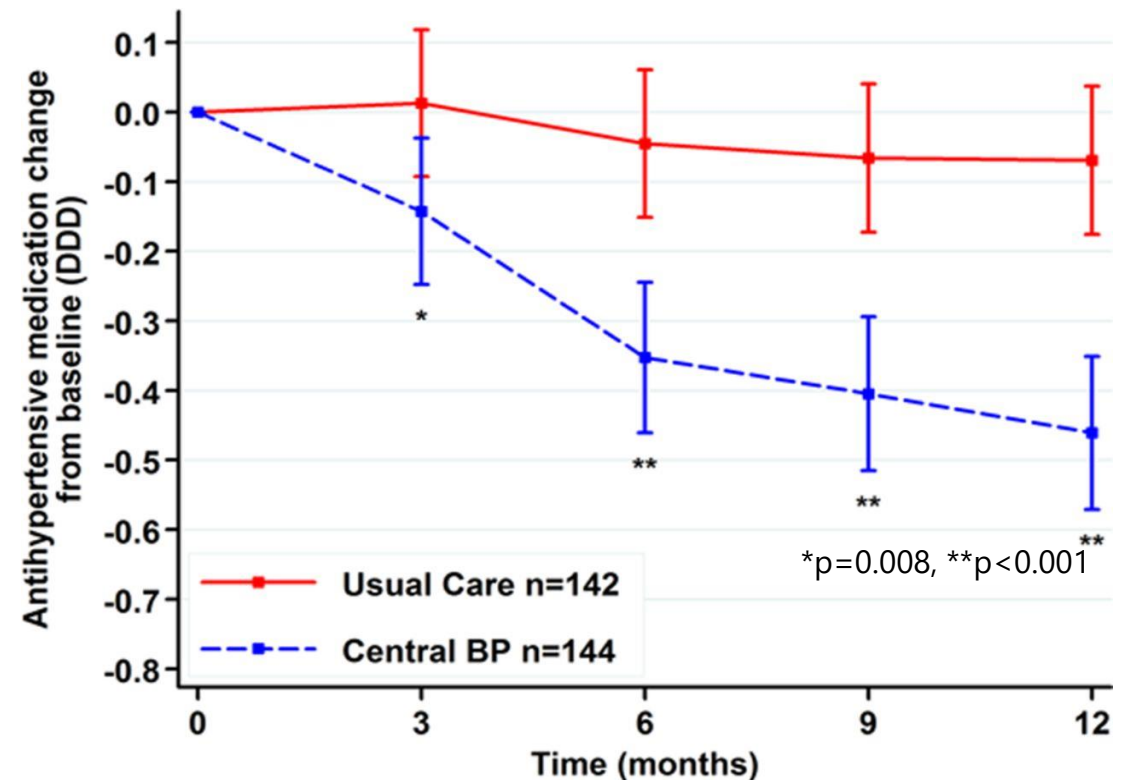
1. Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for an individual patient
Scenario: Concurrent elevation in brachial and central pressures
2. Avoiding initiation of medication when white coat hypertension is suspected
Scenario: Elevated brachial pressure and normal central pressures
3. Confirmation that increased treatment may not be needed
Scenario: Borderline high peripheral pressures and normal central pressures
4. Targeting when to consider reduction of medication
Scenario: Normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures (particularly in the setting of medication tolerance issues)

Using Central Arterial Pressure to Guide Hypertension Management

BP Guide Study

- 286 hypertensive patients randomized to best-practice brachial BP management* +/- PWA
- Hypertension management guided by PWA resulted in significantly less medication needed to maintain brachial BP control
- 16% of PWA guided patients had complete cessation of medication vs. only 2% of usual care
- No adverse effects on LV mass, aortic stiffness, or quality of life in the PWA guided treatment cohort

Between-group change in daily defined dose (DDD) of antihypertensive medications.



*Best-practice usual care included office, home, and 24-hour ambulatory blood pressure

Sharman et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care. Principal findings of the BP Guide Study. Hypertension 2013;62:1138-45.

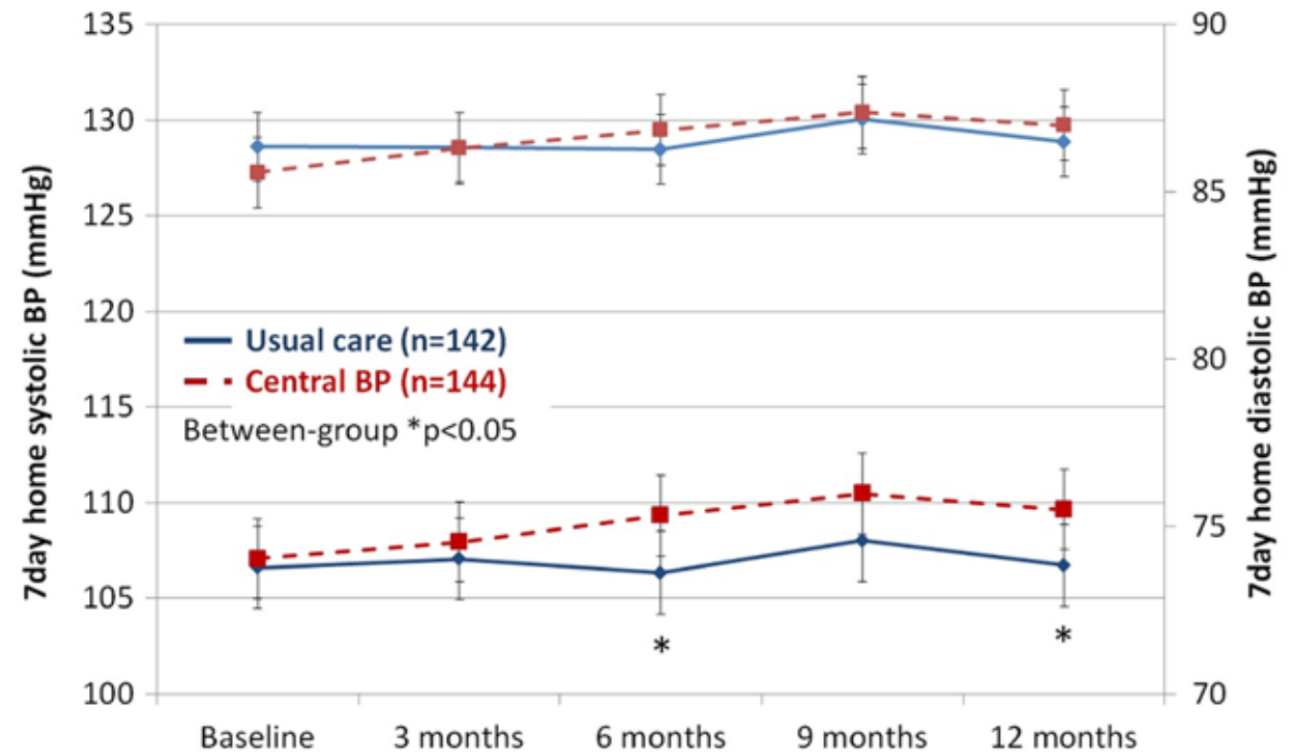
Using Central Arterial Pressure to Guide Hypertension Management

BP Guide Study: BP Results

No differences in between-group changes in 7-day home systolic BP. (Figure)

- Diastolic BP was higher in the intervention group at 6 and 12 months but was still below the threshold of raised home diastolic BP

No relevant changes office brachial BP, central BP or 24-hour ambulatory BP.



Between-group changes in average 7-day home systolic and diastolic BP. Data adjusted for age, sex, and body mass index. No significant differences in systolic BP; however, there was a significant group x time interaction for diastolic BP ($p=0.025$). Error bars indicate 95% CI.

Morbidity from Hypertension Medications

- Overtreatment may occur if office-based cuff measurements are misleadingly high
- Potential consequences of over-treatment
 - Adverse effects specific to the medication class (e.g., cough with ACE inhibitors)
 - Adverse effects common to all anti-hypertensive medications (i.e., hypotension)
- Elderly patients are likely more susceptible to hypotension and associated adverse consequences
- Association of BP with CV events appears to be bimodal with higher rates at both low and high blood pressures.¹
- Several studies have noted an increased mortality in elderly patients related to lower treated blood pressure.^{2,3}
- Reduced kidney function was associated with lower BP in a study in older subjects.⁴
- Older hypertensive patient have an increased risk of postural hypotension, balance and gait impairment, confusion, and dizziness.⁵
- Increased risk for injuries related to falls may result from overly aggressive treatment of hypertension.⁵

1. Bangalore et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *Eur Heart J.* 2010; 31(23): 2897–2908. 2. Kovesdy et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease. A cohort study. *Annals Intern Med.* 2013; 159(4):233–242. 3. Sim et al. Impact of achieved blood pressures on mortality risk and end-stage renal disease among a large, diverse hypertension population. *JACC.* 2014; 64(6):588–597. 4. Cushman et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010; 362(17):1575–1585. 5. Aronow et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Curr Hypertens Rep. *Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. JACC.* 2011; 57(20):2037–2114.

Low BP and Increased Mortality in Patients with CAD

Study Group

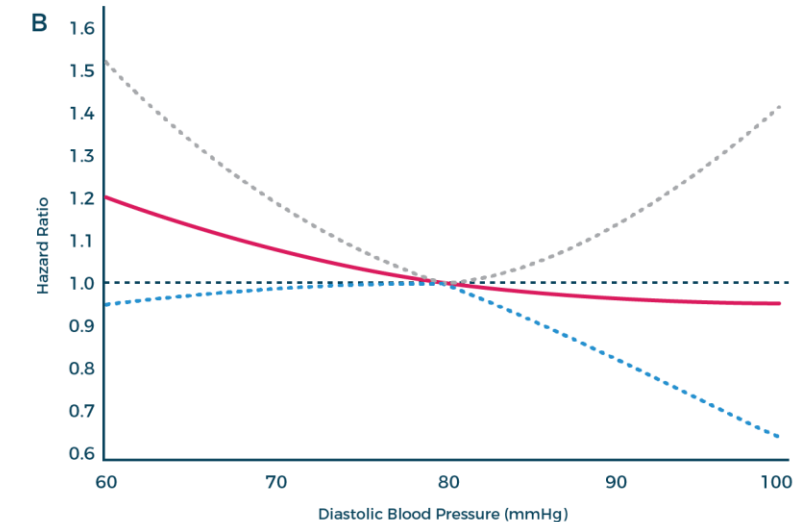
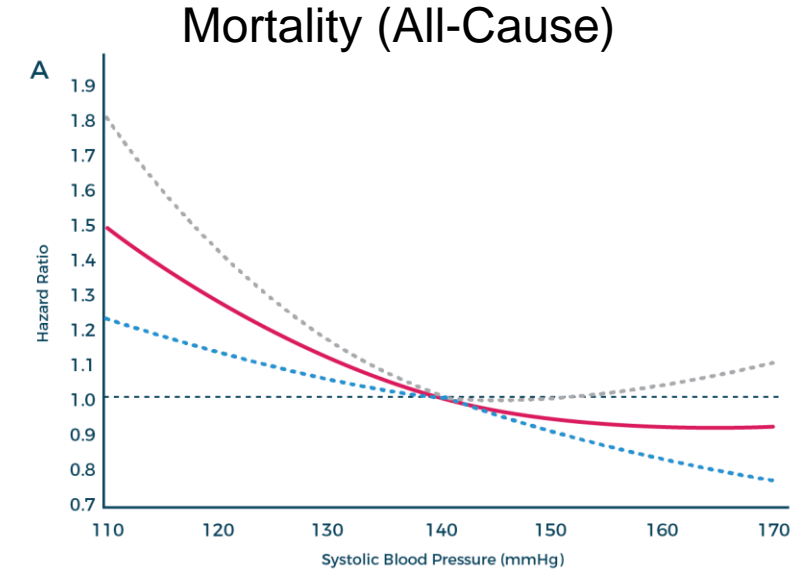
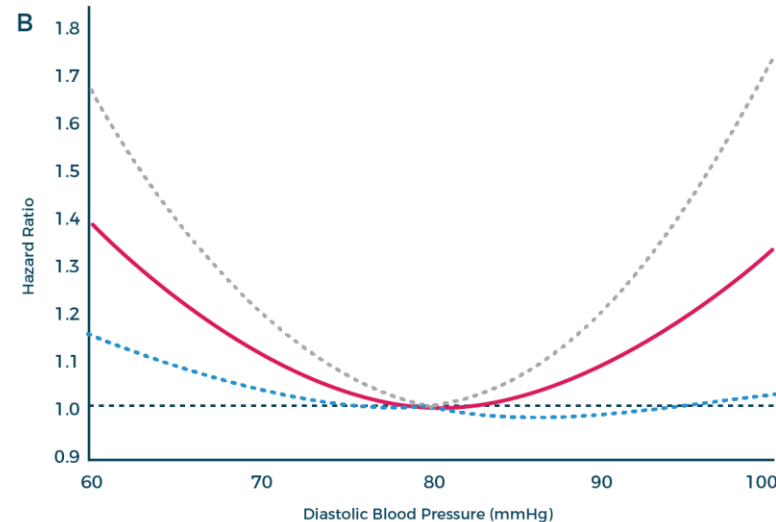
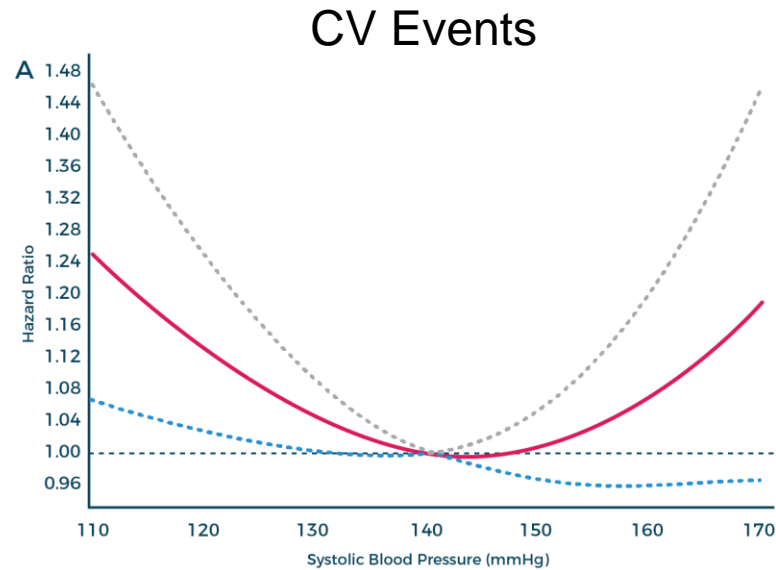
10,001 patients with CAD followed \approx 5 years

Results

Patients with pre-existing CAD + low BP (110–120/60–70 mmHg) had an increased risk of CV events other than stroke and mortality

Solid line: HR

Dotted lines: 95% CI



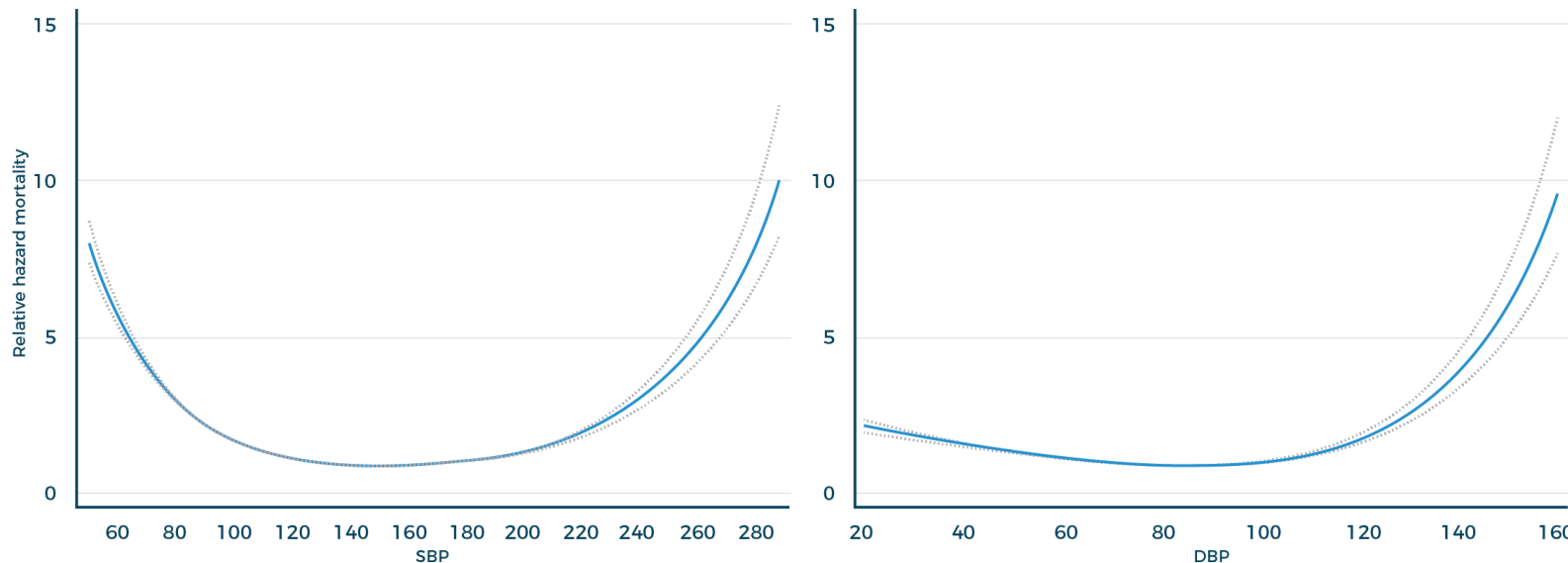
Mortality in Chronic Kidney Disease (CKD) and Low BP

Study Design: Historical cohort during 2005–2012 (Veterans Affairs Health Care Facilities)

Patients: 651,749 US veterans with CKD

Results:

- Lowest mortality: BP 130–159/70–89 mmHg
- Highest mortality: SBP and DBP concomitantly very high or very low
- Results were consistent in subgroups of patients with normal and elevated levels of urine microalbumin-creatinine ratio.



Multivariable adjusted HR (95%CI) of all-cause mortality associated with systolic and diastolic BP in time-dependent Cox models using restricted cubic splines, adjusted for age, gender, race, diabetes mellitus, CV and cerebrovascular disease, heart failure, the Charlson comorbidity index, medications (angiotensin converting enzyme inhibitors/angiotensin receptor blockers, alpha-, beta- and calcium channel blockers, loop and thiazide diuretics, and cholesterol lowering agents), eGFR and blood cholesterol. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Increased Mortality in Chronic Kidney Disease (CKD) and Low BP

Study Design: Historical cohort during 2005–2012 (Veterans Affairs Health Care Facilities)

Patients: 651,749 US veterans with CKD

HR (95%) CI for Mortality Across Hypertension Categories

	SBP <120 mm Hg and DBP <80 mm Hg	SBP 120–139 mm Hg or DBP 80–89 mm Hg	SBP 140–159 mm Hg or DBP 90–99 mm Hg	SBP ≥160 mm Hg or DBP ≥100 mm Hg
1	1.62 (1.61–1.64)	1.00 (reference)	0.94 (0.93–0.95)	1.08 (1.06–1.10)
2	1.59 (1.58–1.61)	1.00 (reference)	0.93 (0.92–0.95)	1.04 (1.02–1.06)
3	1.48 (1.46–1.49)	1.00 (reference)	0.94 (0.93–0.95)	1.06 (1.04–1.07)
4	1.44 (1.42–1.45)	1.00 (reference)	0.95 (0.94–0.96)	1.05 (1.03–1.07)
5	1.42 (1.41–1.43)	1.00 (reference)	0.95 (0.94–0.96)	1.05 (1.03–1.07)

†Models represent unadjusted association (model 1) and associations after adjustment for age, sex, and race (model 2); model 2 variables plus diabetes mellitus, CV and cerebrovascular disease, chronic heart failure, Charlson Comorbidity Index scores (model 3); model 3 variables plus medication use (angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers; α -blockers, β -blockers, and calcium channel blockers; loop and thiazide diuretics; and cholesterol-lowering agents) (model 4); and model 4 variables plus eGFR rates and blood cholesterol levels (model 5).

Effects of Intensive BP Control in Type 2 Diabetes Mellitus

Study Population

- 4,733 participants with type 2 diabetes, follow-up 4.7 years (mean)

Study Arms

- Intensive therapy (IT) (systolic < 120 mm Hg) vs. standard therapy (ST) (systolic < 140 mm Hg)

Primary Outcome

- Composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

Results

	Therapy		p-value
	Intensive	Standard	
Primary	1.9%	2.1%	0.2
Death ¹	1.3%	1.2%	0.55
Serious Adverse Event ²	3.3%	1.3%	<0.001
Elevated creatinine	23.8%	15.5%	<0.001
eGFR ³	4.2%	2.2%	<0.001
Renal Failure ⁴	0.2%	0.04%	0.12

1. Annual rates

2. Attributed to antihypertensive medications

3. eGFR: estimated glomerular filtration rate (<30 ml/min/1.73m²)

4. Represents 5 vs. 1 patient

Effects of Intensive BP Control in Type 2 Diabetes Mellitus

Increased Serious Adverse Events Attributed to Blood-Pressure Medications In the Intensive Therapy Group

Serious Adverse Events n(%)	Intensive Therapy	Standard Therapy	p-value
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12

Summary

New Paradigm of Incorporating Central Pressures: Not a New Concept

Analogies to Advancement in Medical Evaluation

- Fasting blood glucose followed by introduction of HbA1C
- Electrocardiograms followed by introduction of echocardiogram
- COPD Guidelines: FEV₁ only, followed by incorporation of COPD exacerbations

Every-Day Analogies

- 2-factor identification
- Dead-bolt lock in addition to regular latch and lock

Common Sense Practice of Medicine

- BP measurement needs to be correct and confirmed
- Brachial pressures and central aortic pressures should be considered as part of management of all patients requiring blood pressure management, but particularly those with renal and/or cardiac disease

Economic Implications

- Reduced additional costs for confirmation of white coat hypertension (reduced ABPM, repeated office visits)
- Avoidance of medication costs for treatment when elevation in brachial blood pressure (untreated and treated hypertension) is not reflective of the usual physiologic state
- Reduced costs due to avoidance of medication adverse effects (medication specific, hypotension)
- Earlier treatment when there is confirmation of hypertension with associated reduction in socioeconomic costs due to subsequent reduced morbidity
- Guidance to attempting trials of medication reduction in treated patients who may have low or low-normal central pressures and normal brachial pressures

Summary and Conclusions (1)

Hypertension

- Responsible for continued morbidity and high socioeconomic costs despite the widespread availability and use of cuff brachial artery measurements for diagnosis and monitoring.

Brachial blood pressure monitoring

- Elevated pressure predicts CV events, mortality, and organ damage (e.g., LVH, intima-medial thickness and reduced GFR).
- Lowering elevated brachial BP reduces the risk of CV events and improves survival.

Central aortic systolic pressure monitoring

- Elevated pressure predicts CV events, mortality, and organ damage (e.g., LVH, intima-medial thickness and reduced GFR).
- Correlated to brachial systolic pressures.
- Risk of adverse outcomes with elevated central pressure is higher than brachial pressure in multiple studies and uniformly at least as high as brachial pressure in others.
- Central systolic pressure is independently predictive of CV events and therefore provides additional risk information.

Conclusion

- Lowering elevated central systolic pressures will reduce the risk of CV events.

Summary and Conclusions (2)

Central Pressures

- Threshold values for the diagnosis and treatment of elevated central pressures have been defined.

Incorporation of central pressures into hypertension management has the following advantages:

- Confirmation of hypertension so that initiation of medication is more likely to be the correct decision for an individual patient (*concurrent elevation in brachial and central pressures*).
- Avoiding initiation of medication when white coat hypertension is suspected (*elevated brachial pressure and normal central pressures*).
- Confirmation that increased treatment may not be needed (*borderline high peripheral pressures and normal central pressures*).
- Targeting when to consider reduction of medication (*normal peripheral and low central pressures, or extended period of normal peripheral and normal central pressures particularly in the setting of medication tolerance issues*).

Conclusions

- Incorporation of central aortic pressure monitoring, which is complementary to continued reliance on brachial pressure monitoring, should be a part of the care of all patients with hypertension.
- The Dual Arterial Pressure SphygmoCor XCEL system provides both peripheral and central pressures in the same office-based setting and therefore represents a cost-effective addition to BP management.

APPENDIX

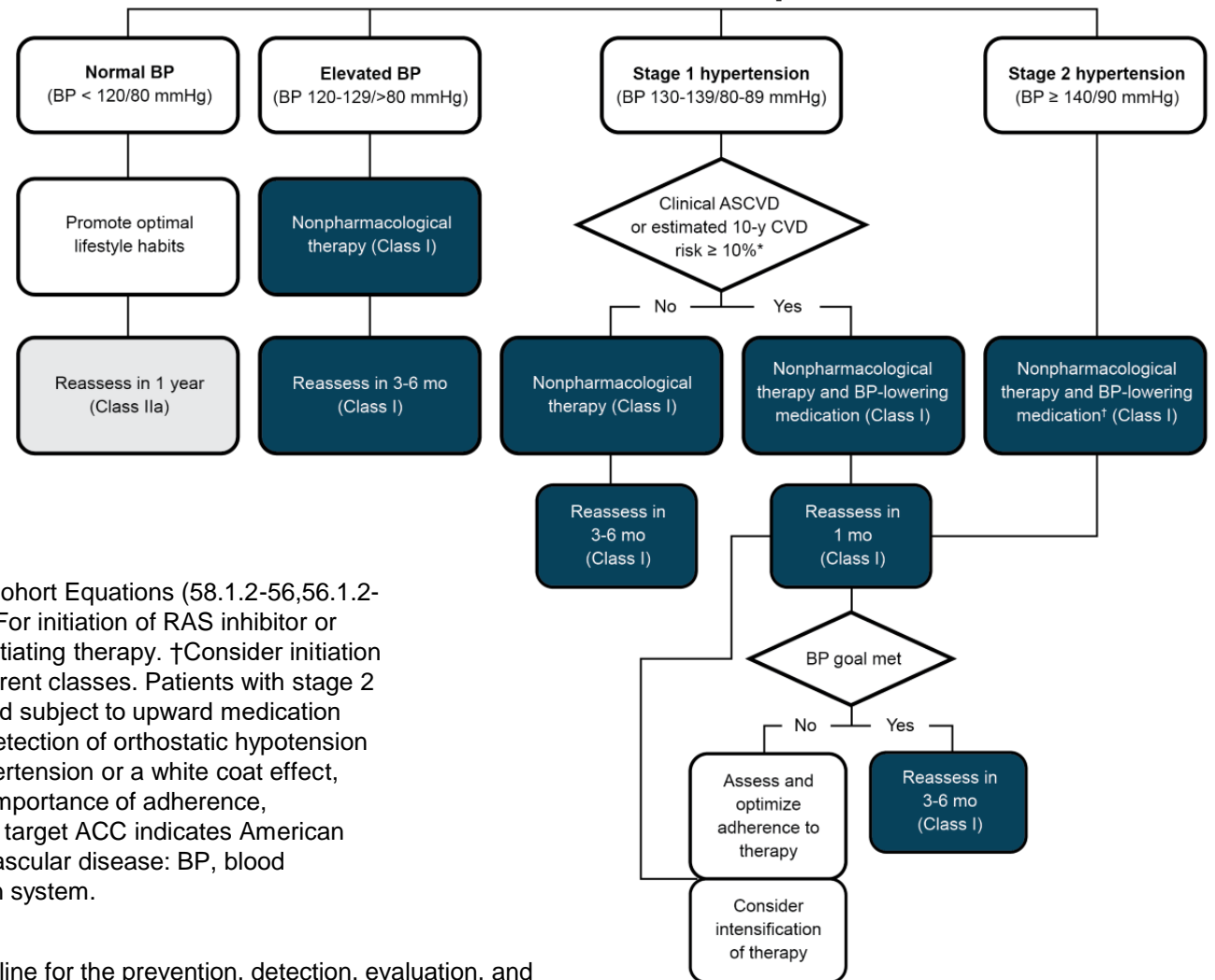
How to Use Central Blood Aortic Blood Pressure

Guidelines for Hypertension (2017)

BP Thresholds and Recommendations for Treatment and Follow-Up

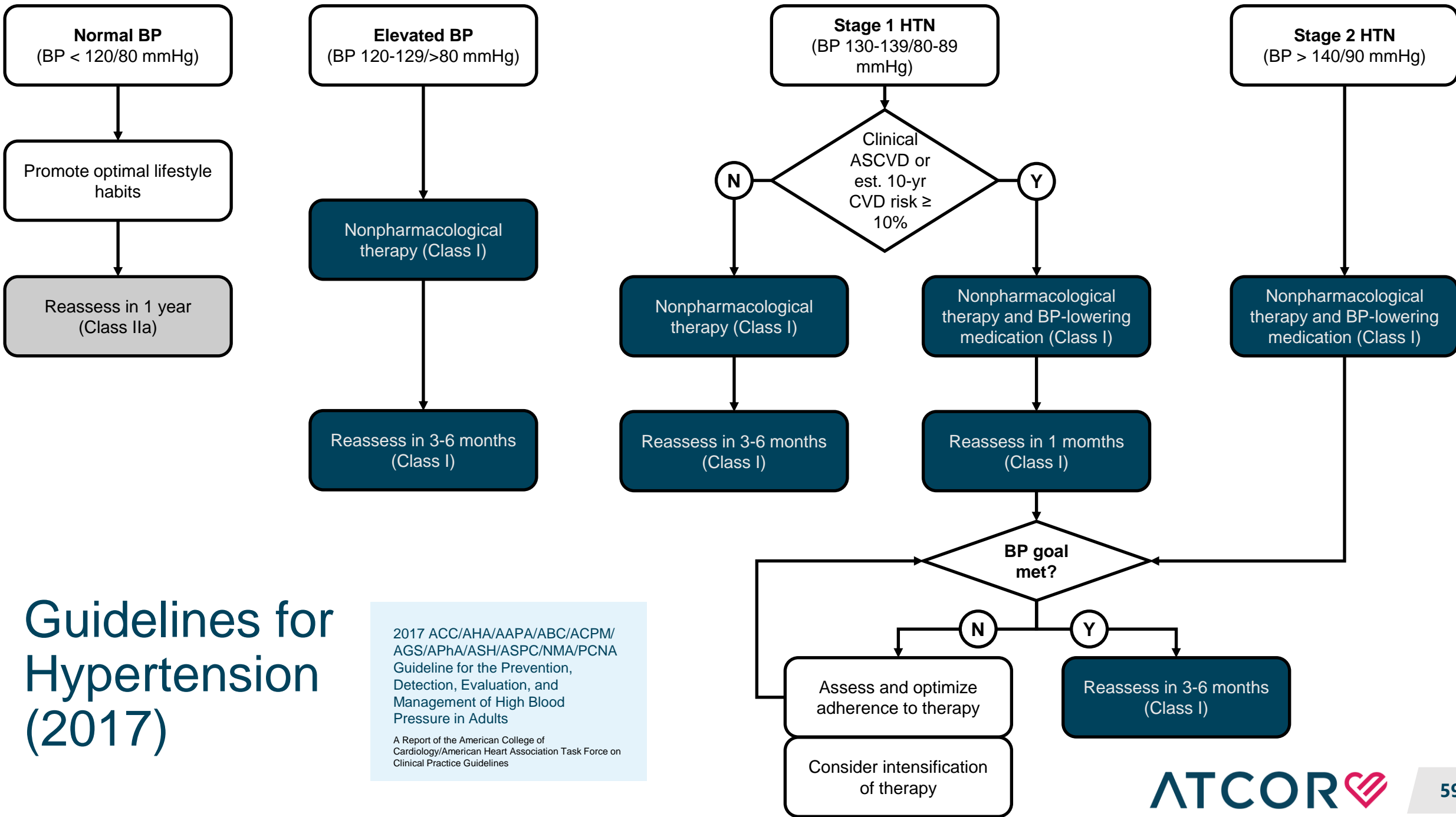
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines



Colors correspond to Class of Recommendation in Table 1. *Using the ACC/ANA Pooled Cohort Equations (58.1.2-56,56.1.2-57). Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy. †Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP $\geq 160/100$ mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; and RAS, renin-angiotensin system.

Whelton PK et al. 2017 ACC/AHA/AAPA/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2018;138:e484-e594.



Guidelines for Hypertension (2017)

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Selection of Central Pressure Variable for Incorporation into Guidelines

Overall

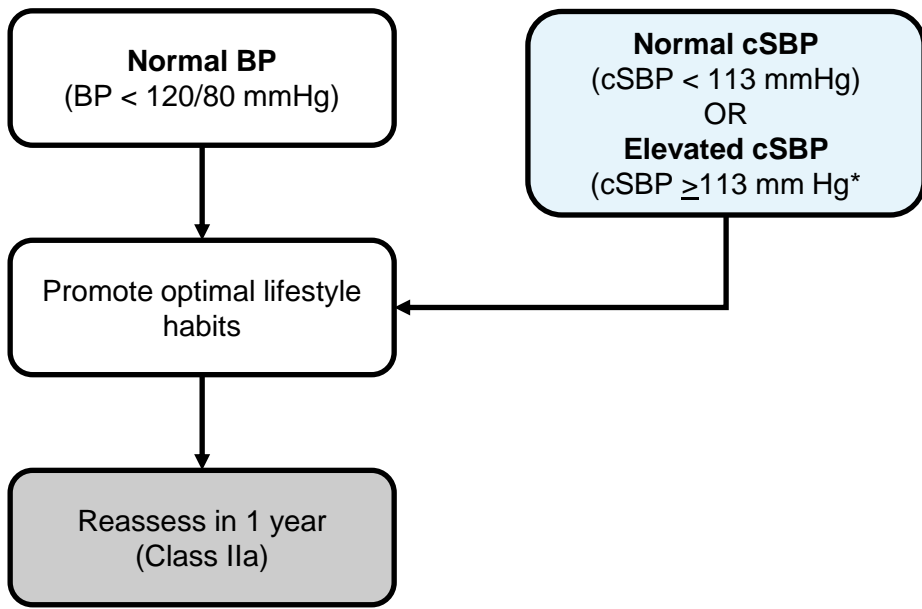
- All variables add value to the understanding of the physiology and impact of high blood pressure; however, for practical purposes, focus is one variable as the key to management decisions.

Variables considered

- Pulse Pressure – Ease of calculation, may be relevant, but not currently in any hypertension guidelines.
- Central diastolic pressure – expected to be similar to peripheral diastolic pressure with minimal if any additional value.
- Augmentation Index (or Pressure) – Although relevant, significant education would be required. Not in any current guidelines and threshold values not well-defined.
- Central systolic pressure – Peripheral systolic pressure is in guidelines (i.e., analogous variable), thresholds have been proposed, minimal increase in education.

Proposed Guideline

- Central systolic pressure (cSBP) is most practical variable for initial focus. Possible inclusion of augmentation index (or pressure) for specialized practices.
- Threshold cSBP values : normal < 113 mm Hg, elevated/stage 1 hypertension: 113 – 129 mm Hg, stage 2 hypertension: ≥ 130 mm Hg

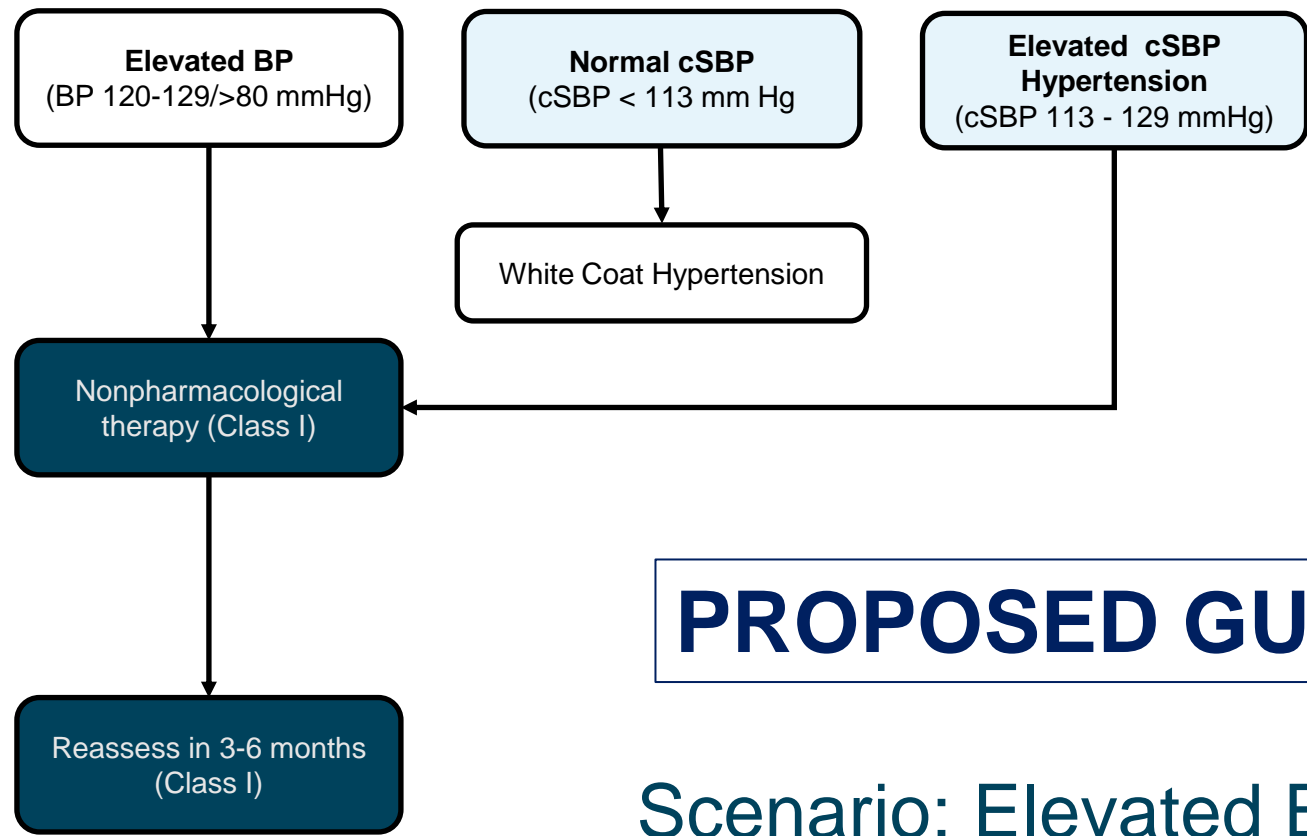


PROPOSED GUIDELINE

Scenario: Normal Brachial BP

- No change in guideline

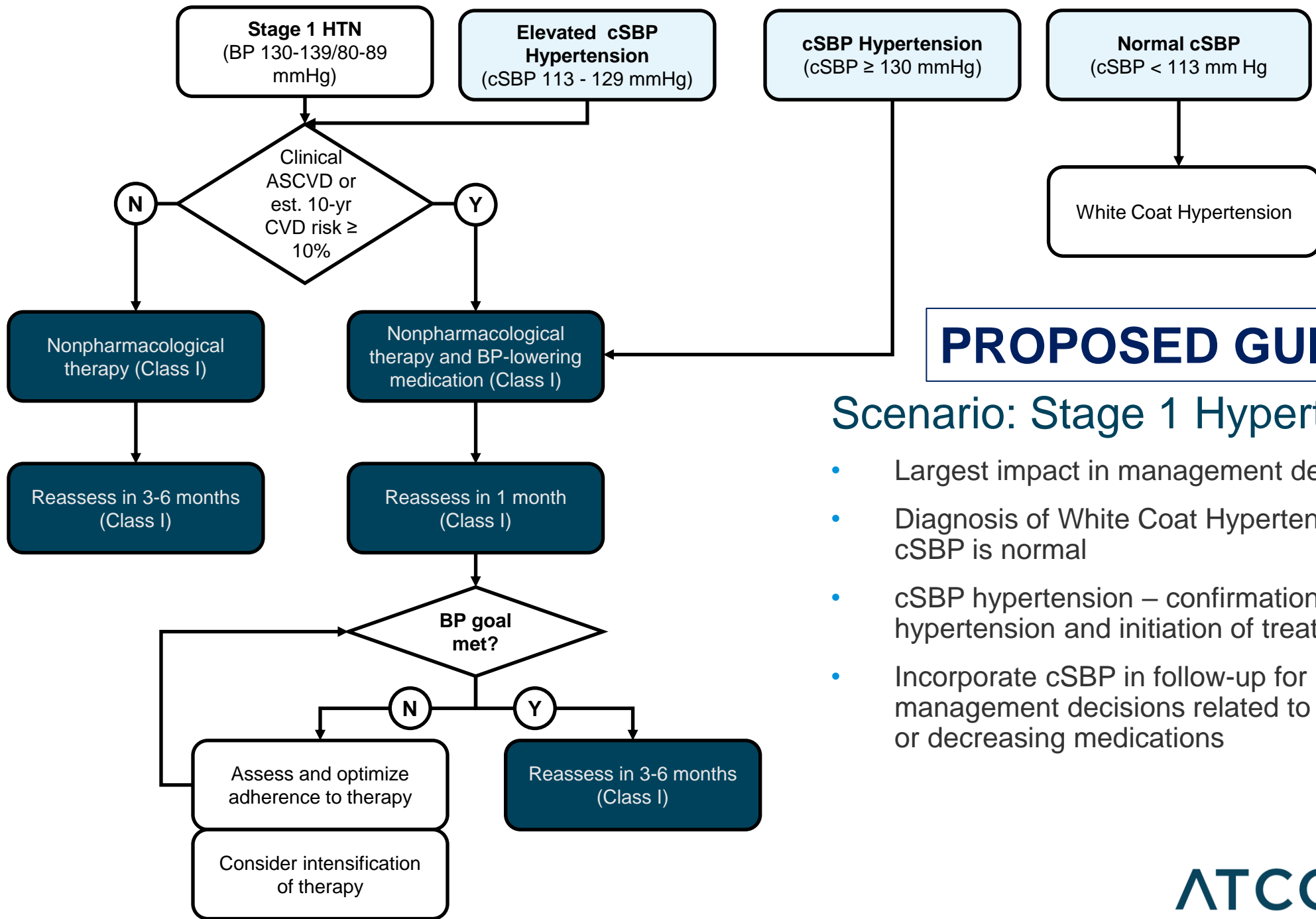
*cSBP cannot exceed brachial systolic BP (i.e., will always be < 120 mm Hg)



PROPOSED GUIDELINE

Scenario: Elevated Brachial BP

- Diagnosis of White Coat Hypertension when cSBP is normal
- Schedule routine follow-up



PROPOSED GUIDELINE

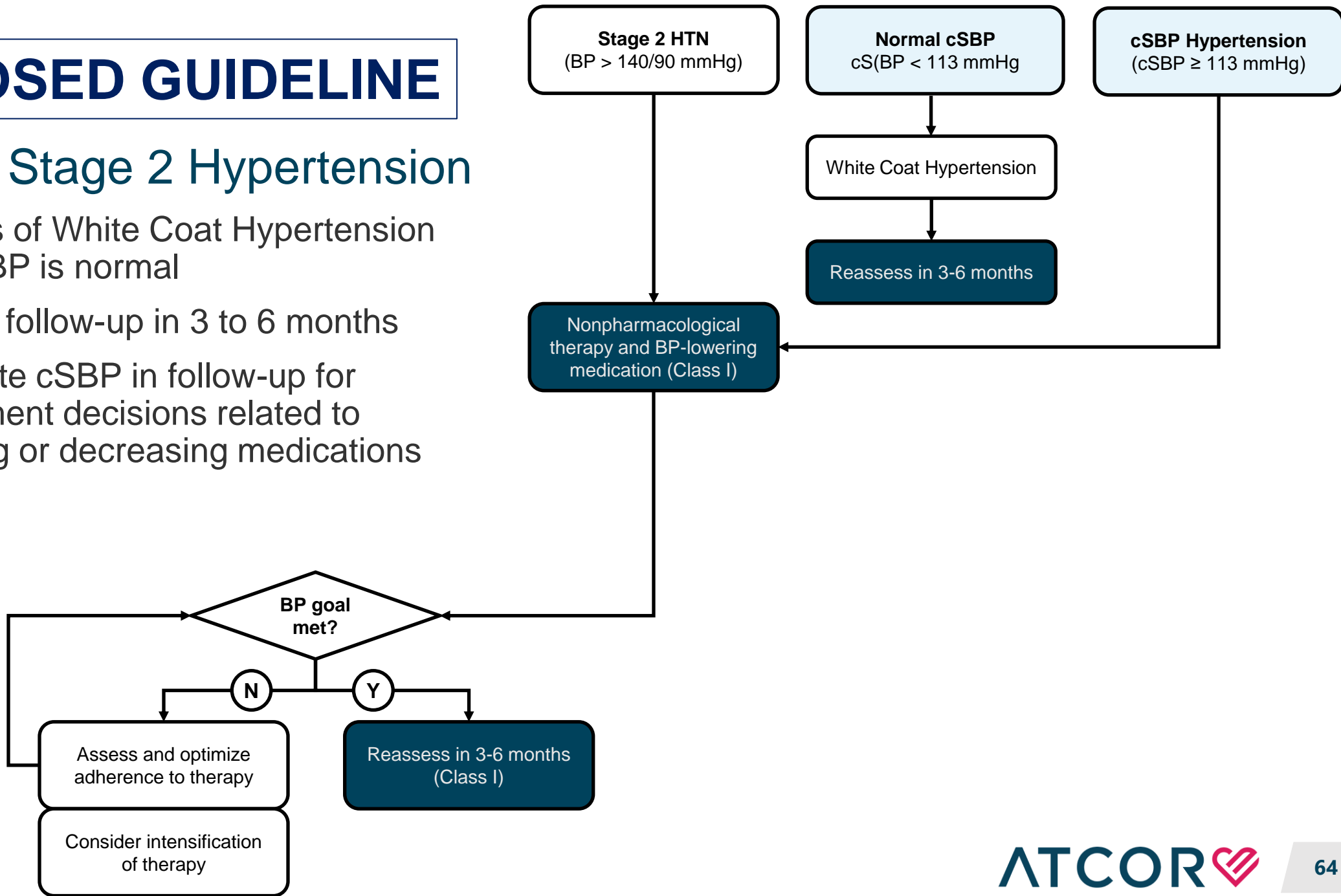
Scenario: Stage 1 Hypertension

- Largest impact in management decisions
- Diagnosis of White Coat Hypertension when cSBP is normal
- cSBP hypertension – confirmation of hypertension and initiation of treatment
- Incorporate cSBP in follow-up for management decisions related to increasing or decreasing medications

PROPOSED GUIDELINE

Scenario: Stage 2 Hypertension

- Diagnosis of White Coat Hypertension when cSBP is normal
- Schedule follow-up in 3 to 6 months
- Incorporate cSBP in follow-up for management decisions related to increasing or decreasing medications



CPT® Category I Code 93050: Arterial Pressure Waveform Analysis

- Coding request sponsored by Renal Physicians Association (RPA)
- CPT Category I code 93050 assigned, effective **January 1, 2016**

Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive

(Do not report 93050 in conjunction with diagnostic or interventional intra-arterial procedures)

