Challenging Cases in Hypertension

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CONTINUING EDUCATION COMPANY

1

Disclosure

Consultant: Eli Lilly; Medtronic; Novo Nordisk; ReCor; UpToDate (Hypertension Section)

Research Grant: Ablative Solutions; ReCor

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LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to:

-Care for an African-American Patient with Hypertension.

-Care for a Patient with Possible Secondary Hypertension.

-Care for a Patient with Hypertension and Cancer Whose BP has recently increased.

3

Case 1

- 58 year Old AA male comes for his first office visit.
- History: Hypertension for 20 years that has been poorly controlled. No hx of smoking.
- Family history of hypertension but no family or personal hx of premature ASCVD, heart disease, or kidney disease.
- BP: 154/92 mm Hg (average of 3), BMI 28 kg/m^2, WC = 36 inches.
- BP's at home taken properly have been similar to the BPs taken in the office.
- He states he has not been taking his BP medications for some time and had been on as many as 3 medications in the past but was not taking them "regularly".

4

Case 1 (Cont.)

- Meds: None.
- Exam: discs flat, eyegrounds with a/v crossing changes but no hemorrhages or exudates.

  Chest-clear to auscultation

  Heart-regular rate without murmurs, gallops, or rubs.
- EKG-NSR, LVH, otherwise unremarkable.
- Labs-Na++ 136, K+ 4.2, Creatinine 0.9, eGFR 82, LDL-C 68, Total-C 140, HDL-C 42, TG-150, urine for microalbumin 24 mg/g creatinine, A1C 5.2%

5

One of the More Important Things to Do in This 58-Year-Old Male with Hypertension Is?

A. A Coronary Calcium Score
B. A Hs-CRP
C. An Echocardiogram
D. Calculate his 10-year risk of a first ASCVD event to know what to do about his BP
E. None of the above

6

Use Pooled Cohort Equation (PCE) as the Risk Estimator When Determining Three Things:

- Need for Lipid Medication (Statins) in Primary Prevention [when risk is between 5.0 and 19.9%].-unless known diabetic or LDL-C ≥ 190 mg/dl [when start statin] or < 70 mg/dl (when you can't calculate risk).

Grundy, S. M. et al. *J Am Coll Cardiol* 2019 Vol 139, Issue 25:e1082-e1143.

7

2018 Cholesterol Guidelines

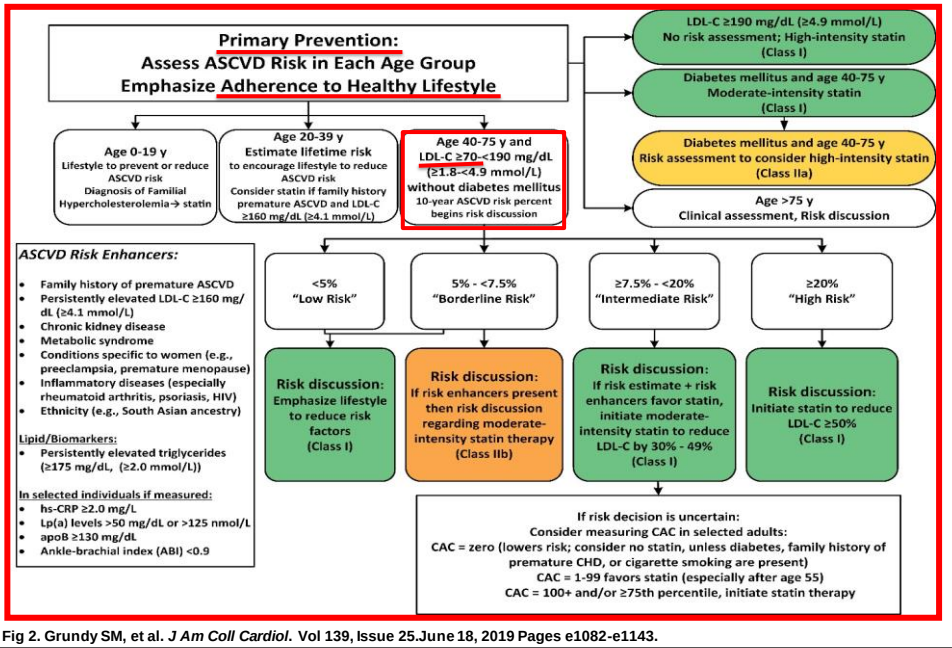
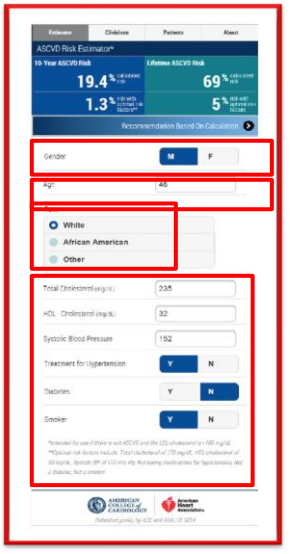


Fig 2. Grundy SM, et al. *J Am Coll Cardiol.* Vol 139, Issue 25.June 18, 2019 Pages e1082-e1143.

8

ACC/AHA ASCVD Risk Estimator

Optimal risk factors
- → Age, sex, race,
- → TC
- → HDL-C
- → LDL-C
- → Systolic BP mmHg
- → Diastolic BP mm Hg
- → Not taking medications for HTN
- → Not a diabetic
- → Not a smoker
- → On a statin, on ASA



10-year risk of non-fatal MI, coronary heart disease death, and fatal and non-fatal stroke

http://tools.acc.org/ASCVD-Risk-Estimator/
Goff DC, et al. *J Am Coll Cardiol* 2014;63:2935-59

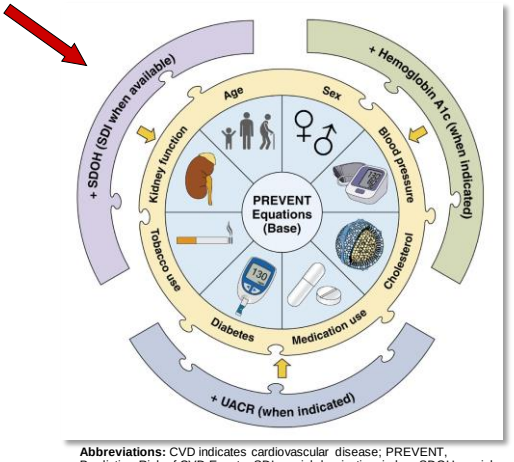
9

Case 1 (Cont.)

- Current 10-year ASCVD Risk: Can't be calculated with LDL-C < 70 mg/dl.
- Lifetime ASCVD Risk: 46%
- Optimal ASCVD Risk: 5.5%

10

NEW PARADIGM FOR CVD RISK: PREVENT™



Abbreviations: CVD indicates cardiovascular disease; PREVENT, Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

Predictors:

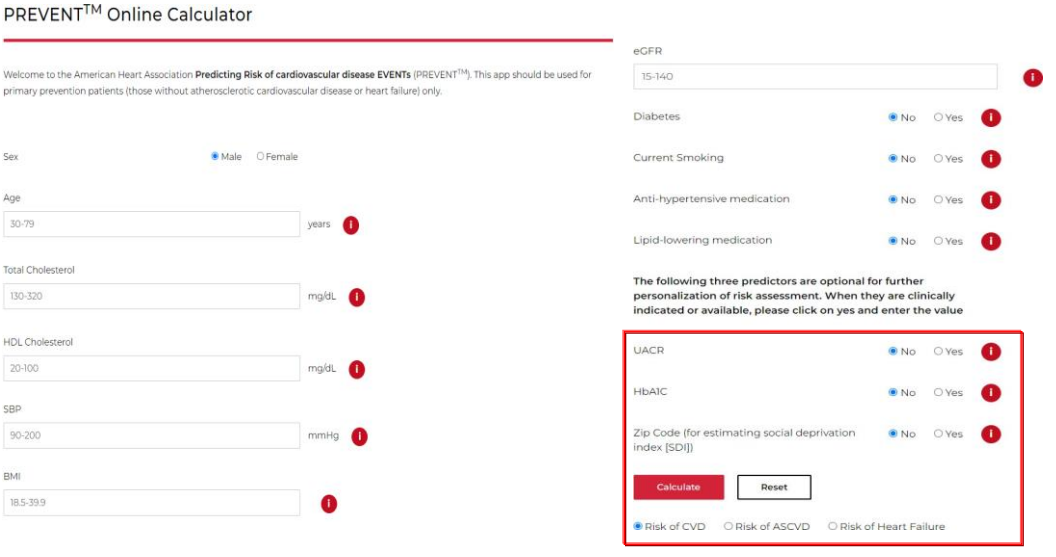
- Base: Traditional risk factors (Gender, Age, SBP, Total and HDL cholesterol, diabetes, use of anti-hypertensive and lipid-lowering medication, smoking, eGFR, and BMI
- Add-on: UACR, HbA1c, SDI

Khan SS et. al. *Circulation* 2023

11

NEW PARADIGM FOR CVD RISK: PREVENT™

https://professional.heart.org/prevent



Khan SS et. al. *Circulation* 2023

12

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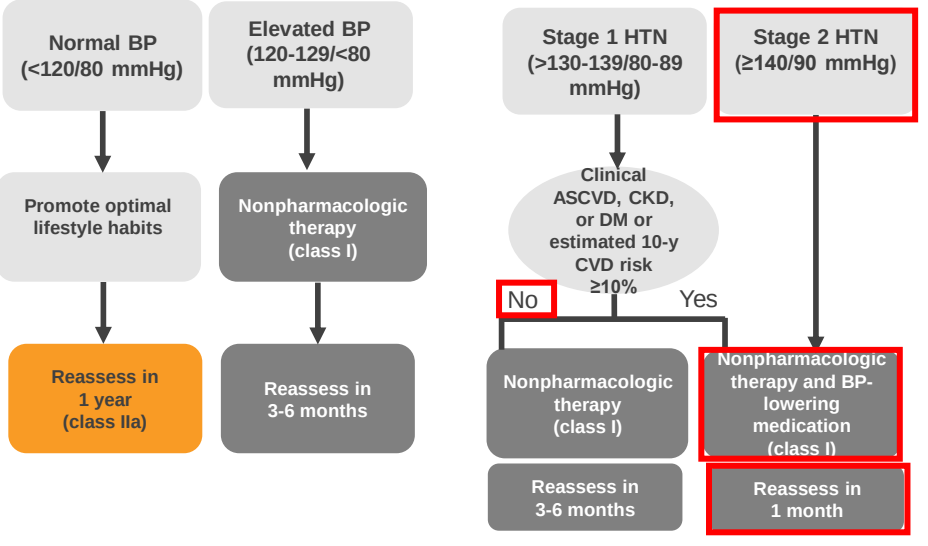
- Need for BP (Antihypertensive) Medication as Primary Prevention [when risk is ≥10%].-unless known ASCVD, diabetic, CKD, or Stage 2 HTN
- Need for Baby Aspirin when risk is ≥10% for Primary Prevention in those 40-59 years of age w/o underlying ASCVD and not at increased risk of bleeding. [Grade C USPSTF- at least moderate certainty of a small benefit.

2017 ACC-AHA Guideline of High Blood Pressure in Adults; *Hypertension; J Am Coll* Cardiol Nov 2017
Arnett, D. K. et al. *J Am Coll Cardiol* 2019 Sep 10;74(10):e177-e232.

13

BP Thresholds and Recommendations for Treatment and Follow-Up



Adapted from Figure 4. Whelton et al. 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension 2018; 71:e13-e115.

14

Treatment Starts with Non-Pharmacologic (Lifestyle) Management Each with a 1A LOE

Goal	Nonpharmacological Interventions	Dose	Systolic BP Impact in Hypertension	Systolic BP Impact in Normotension
Weight loss	Weight/ body fat	• Best goal is ideal body weight • Expect about 1 mm Hg for every 1 kg reduction in body weight	-5 mm Hg	-2/3 mm Hg
Healthy diet	DASH dietary pattern	• Consume a diet rich in fruits, vegetables, whole grains and low-fat dairy products with reduced content of saturated and total fat	-11 mm Hg	-3 mm Hg
Reduced intake of dietary sodium	Dietary sodium	• Optimal goal is <1500 mg/day, most Americans 3400 mg/day • Aim for at least a 1000 mg/day reduction in most adults	-5/6 mm Hg	-2/3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	• Aim for 3500-5000 mg/day, preferably by consumption of a diet rich in potassium	-4/5 mm Hg	-2 mm Hg
Physical activity	Aerobic	• 90-150 min/week • 65%-75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg
Physical activity	Dynamic resistance	• 90-150 min/week; 50%-80% 1 rep maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
Physical activity	Isometric resistance	• 4 x 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/week; 8-10 weeks	-5 mm Hg	-4 mm Hg
Moderation of alcohol intake	Alcohol consumption	• ≤1 drink daily for women Drink= 5 oz of wine, 12 oz of beer • ≤2 drinks daily for men 1 oz 100 proof or 1.5 oz of 70 proof	-4 mm Hg	-3 mm Hg

Adapted from Whelton PK et al. *J Am Coll Cardiol.* 2018;71:e127-e248. LOE-Level Of Evidence

15

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United States Public Service Task Force JAMA 2022; 327(16): 1577-1584.

16

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Aspirin Use to Prevent Cardiovascular Disease
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

Adults aged 40 to 59 years with a 10% or greater 10-year cardiovascular disease (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.	C
Adults 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older.	D

United States Public Service Task Force JAMA 2022; 327(16): 1577-1584.

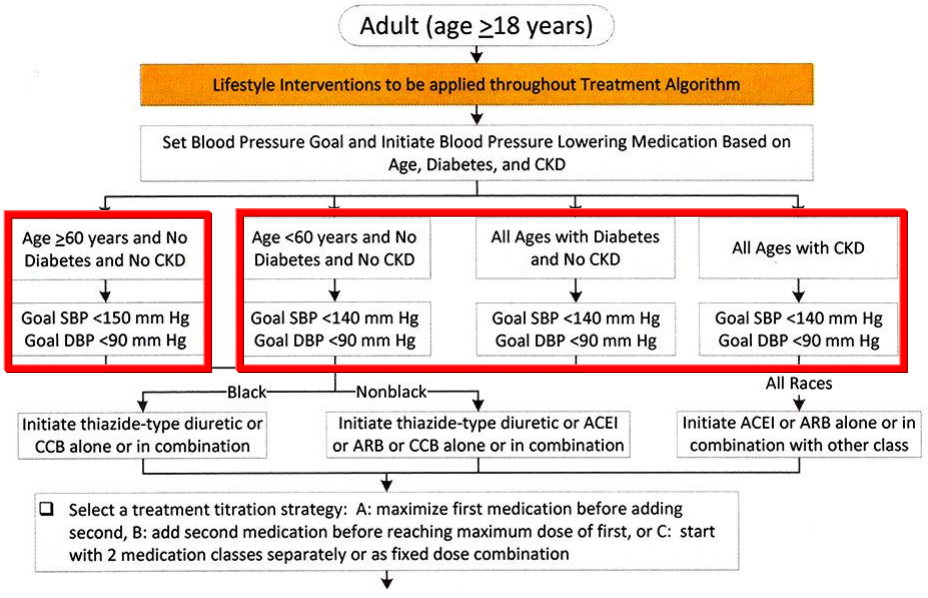
17

What Goal BP Would You Try to Achieve in This 58-Year-Old AA Male with Hypertension?

A. < 120/80 mm Hg
B. < 130/80 mm Hg
C. < 140/90 mm Hg
D. < 150/90 mm Hg
E. Shared patient-provider informed decision as to the best BP goal

18

JNC 8 Hypertension Guideline Management Algorithm-Endorsed by the AAFP and ACP



James PA, Oparil S, Carter BL et al. *JAMA* 2014: 311 (5):507-520, Feb 5, 2014.

19

BONUS DIGITAL CONTENT

Practice Guidelines

Blood Pressure Targets in Adults With Hypertension: A Clinical Practice Guideline From the AAFP

Sarah Coles, MD, FAAFP, Colorado Plateau Family and Community Medicine Residency Program, North County HealthCare, Flagstaff, Arizona; University of Arizona College of Medicine, Phoenix, Arizona
Lynn Fisher, MD, FAAFP, University of Kansas School of Medicine, Wichita, Kansas
Kenneth W. Lin, MD, MPH, Lancaster General Hospital Family Medicine Residency Program, Lancaster, Pennsylvania
Corey Lyon, DO, FAAFP, University of Colorado School of Medicine, Denver, Colorado
Alexis A. Vosooney, MD, Allina Health Group, West Saint Paul, Minnesota
Melanie D. Bird, PhD, MSAM, American Academy of Family Physicians, Leawood, Kansas

Am Fam Physician. 2022;106(6):721-722

20

TABLE 4

Comparison of Recommended Blood Pressure Targets in Recent Guidelines

Guideline	18 to 59 years of age (mm Hg)	60 to 69 years of age (mm Hg)	70 to 79 years of age (mm Hg)	Older than 80 years (mm Hg)
2022 American Academy of Family Physicians*	< 140/90	< 140/90	< 140/90	< 140/90
2022 National Institute for Health and Care Excellence[13]	< 140/90	< 140/90	< 140/90	< 150/90
2021 European Society of Hypertension Council[14]	< 130/80†	< 130/80†	< 140/80	< 140/80
2020 International Society of Hypertension‡[44]	< 130/80	< 140/90§	< 140/90	< 140/90
2020 U.S. Department of Veterans Affairs/U.S. Department of Defense‖[15]	< 130/90¶	< 150/90	< 150/90	< 150/90
2017 American College of Cardiology/American Heart Association*[16]	< 130/80	< 130/80	< 130/80	< 130/80
2017 American College of Physicians and American Academy of Family Physicians[11]	—	< 150/90	< 150/90	< 150/90
2014 Eighth Joint National Committee[10]	< 140/90	< 150/90	< 150/90	< 150/90

*—Lower targets are reasonable based on clinical judgment and patient preferences or values.
†—A target of less than 140/90 mm Hg is recommended for patients with chronic kidney disease.
‡—Recommendation is to treat all patients to less than 140/90 mm Hg but states it is optimal to treat persons younger than 65 years and people with coronary artery disease, chronic kidney disease, heart failure, previous stroke, chronic obstructive pulmonary disease, or diabetes mellitus to less than 130/80 mm Hg (less than 140/80 mm Hg in older patients).
§—Recommendation is to transition from target of 130/80 mm Hg to 140/90 mm Hg at 65 years of age.
‖—A target of less than 140/90 mm Hg is recommended in patients with diabetes.
¶—Recommendation is to treat all patients 18 to 59 years of age (including those with diabetes) to a systolic blood pressure target of less than 130 mm Hg. For patients 30 years and older, a diastolic blood pressure target of less than 90 mm Hg is recommended.

Information from references 10, 11, 13-16, and 44.

Am Fam Physician. 2022;106(6):721-722

21

Changes in BP Categories from JNC 7 (2003) to the New 2017 Guideline

SBP		DBP	2003 JNC7[1]	2017 ACC/AHA[2]
<120	and	<80	Normal BP	Normal BP
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

The categorization of BP should be based on the average of ≥ 2 readings on ≥ 2 occasions following a standardized protocol.

1. Chobanian AV et al. *Hypertension*. 2003;42:1206–1252.
2. 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

22

A SBP < 130 mm Hg Is Associated with Reduced CV Outcomes and Death

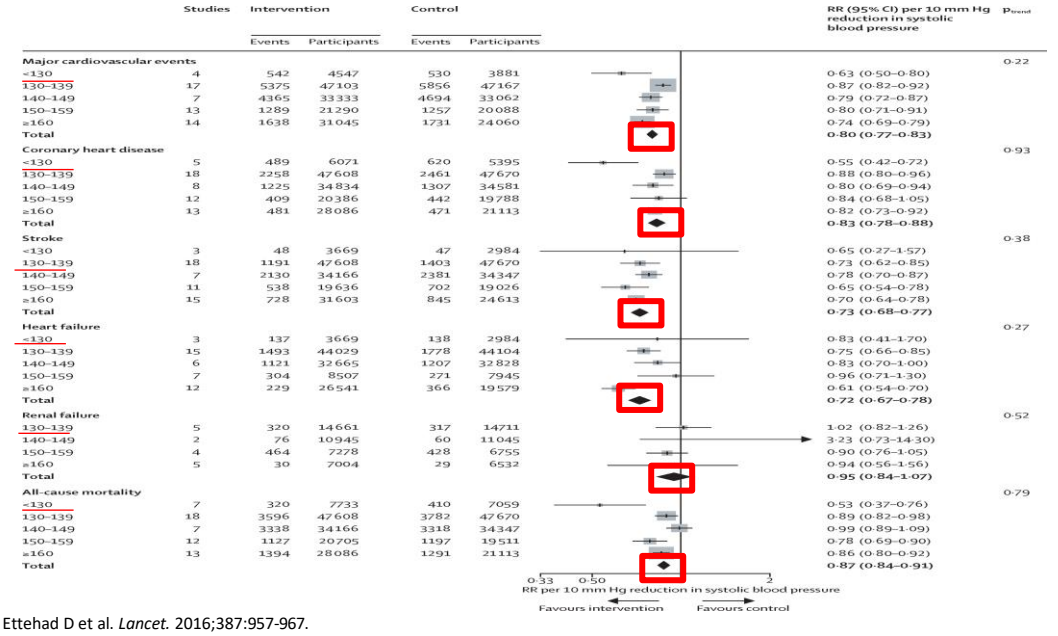


Figure 4. Ettehad D et al. *Lancet.* 2016;387:957-967.

23

2017 ACC/AHA HYPERTENSION GUIDELINE
*ERC SYSTEMATIC REVIEW**

More intensive BP lowering significantly reduced CVD risk

Relative risks comparing SBP goal < 130 mm Hg versus higher goals*

	CV Event	Relative Risk	95% CI
↓	MI	0.86	0.76-0.99
↓	Stroke	0.77	0.65-0.91
↓	Heart failure	0.75	0.56-0.99
↓	CVD composite	0.83	0.75-0.92

*Based on observational, meta-analyses, and clinical trials

Whelton PK, Carey RM et al. 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension 2018; 71:e13-e115.

24

Now 3 Trials Finding <130 mm Hg vs < 140 mm Hg

- 1. SPRINT
  - < 120 vs < 140 mm Hg [ave achieved BP 121.5 mm Hg vs 134.6 mm Hg]
  - No Diabetics (ACCORD), No Stroke Patients
  - Primary Composite End Pt ⬇25%(p < 0.001); HF ⬇38%(p=0.002) and CV Death ⬇43%(p=0.005)
  - Significant Reduction in Total Mortality
- 2. STEP
  -Older Chinese Hypertensives
  -8,511 age 60 to 80 years old; 110 to <130 mm Hg (Final Ave Achieved 126.7 mm Hg) vs < 150 mm Hg (Final Ave Achieved 135.9 mm Hg)
  -median f/up 3.34 years
  -primary composite CV endpoint reduced 26% HR=0.74 (0.60-0.92)
  -33% reduced stroke, 28% reduced CV death, 73% reduced HF
- 3. ESPRIT
  - 11,255 Chinese Adults (ave age 64, 41% women
  - Baseline SBP 130-180 mm Hg (ave baseline 147/83 mm Hg)
  - At 1 year of 3.4 total years of f/up, Intensive BP 120.3 mm Hg vs 135.6 mm Hg in Standard BP
  - CV death (HR 0.61; 95% CI, 0.44-0.84)
  - Total Mortality (HR 0.79; 95% CI, 0.64-0.97)
  - HF, MI, and Stroke all reduced but not SS

1.Lewis CE et al. Final Report SPRINT Trial. *N. Engl. J. Med.* 2021;384(20):1921-1930.
2.Zhang W. et al. STEP Study. *N. Engl. J. Med.* 2021;385(14): 1268-1279.
3.ESPIRIT Trial. Am Heart J. 2023;257:93-102; Presented at 2023 AHA Scientific Sessions Nov 2023

25

In Addition to a High Potassium/Low Sodium DASH Diet, What Antihypertensive Agent(s) Would You Now Start in this Patient with Uncontrolled HTN?

A. Start an ACE inhibitor (ACEi) or ARB.
B. Start a CCB or Thiazide/thiazide-type diuretic
C. Start either an ACEi or ARB + CCB or
   ACEi or ARB + thiazide or thiazide-type diuretic)
D. Start a Beta Blocker
E. Start an Alpha Blocker

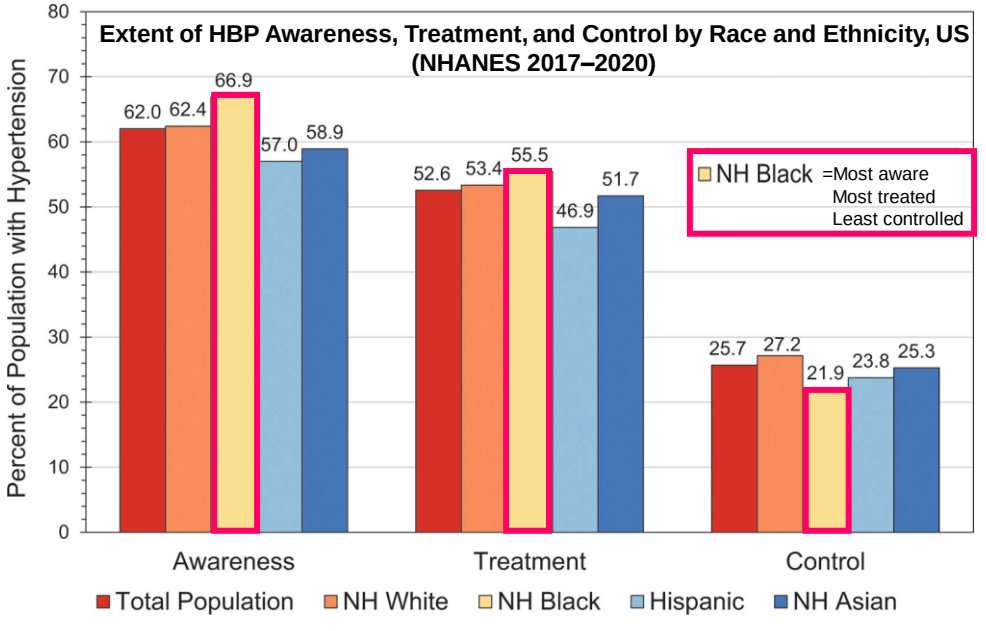
26

Characteristics of Hypertension in African-American Patients Compared to White Americans

- **Premature Onset**
- **Greater Severity**
- **Greater likelihood of target-organ disease**
  - **-LVH**
  - **-ESRD (4.2x)**
  - **-Heart Failure (1.5x)**
  - **-NF Stroke (1.3x) and Fatal Stroke (1.8x)**
- **Greater Risk of Heart Disease and Overall Mortality**

JNC VI. Arch Intern Med. 1997; 157: 2413-2446

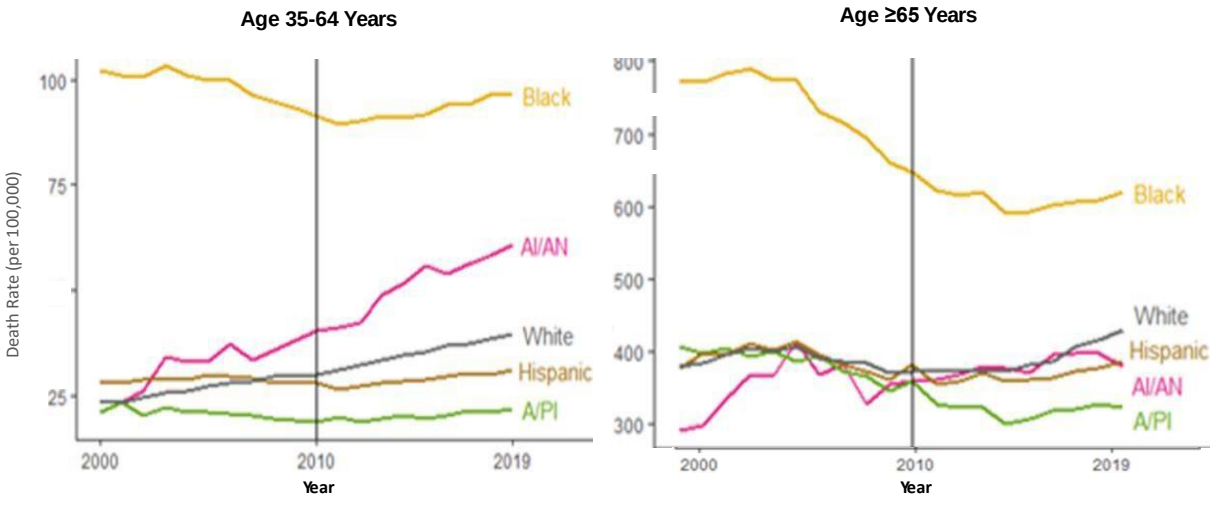
27



Connie W. Tsao. Circulation. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association.

28

US Hypertension-Related CV Disease Mortality-2000-2019



Black-Non-Hispanic
AI/AN-American Indian/Alaska Native, Non-Hispanic
White-Non-Hispanic
A/PI -Asian/Pacific Islander, Non-Hispanic

Vaughan A et al. *JAHA* 2022;11:e024785.

29

Initial Medications for the Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

Diuretics

ACE Inhibitors or ARBs*

Calcium antagonists

Dihydropyridine preferred

*** Recommended for CKD or Clinical Proteinuria**
Combining ACEI + ARB discouraged-Class 3, Harm

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311(5): 507-520. Feb 5, 2014

2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Whelton PK, Carey RM et al. Hypertension 2018; 71:e13-e115.

30

Key Point: Evidence-Based Monotherapy Did Not Improve HTN Control Rates


Hypertension
Volume 79, Issue 2, February 2022; Pages 338-348
https://doi.org/10.1161/HYPERTENSIONAHA.121.17102

American Heart Association.

ORIGINAL ARTICLE

Self-Reported Antihypertensive Medication Class and Temporal Relationship to Treatment Guidelines

See Editorial, pp 349–351

Brent M. Egan, Jianing Yang, Michael K. Rakotz, Susan E. Sutherland, Kenneth A.

NHANES data comparing self-reported medication use before and after JNC-8/ACC/AHA race-based HTN guidelines

- Black individuals reported increased CCB use and decreased renin-angiotensin system blocker use
- Rates of monotherapy increased in Blacks
- HTN control decreased

Egan B.M. et al. *Hypertension* 2022; 121:26–34

31

Differences in Hypertension Medication Prescribing for Black Americans vs Non-Black Americans on BP Control

Retrospective 2-yr EMR observation of 10,875 patients aged 18-85 with HTN on 1- or 2 BP drugs

Medication	Non-Black/AA	Black/AA
Monotherapy		
Thiazide	27.7%	41.3%
Calcium Chanel Blocker	30.1%	40.1%
ACE-I/ARB	42.3%	↓ 18.6%
2-Drug Regimen		
Thiazide and CCB	19.8%	↑ 35.8%
Thiazide and ACE-I/ARB	49.4%	↓ 44.3%
CCB and ACE-I/ARB	30.8%	↓ 19.8%

Holt H. et al. *J Am Board Fam Med* 2022;35:26–34

32

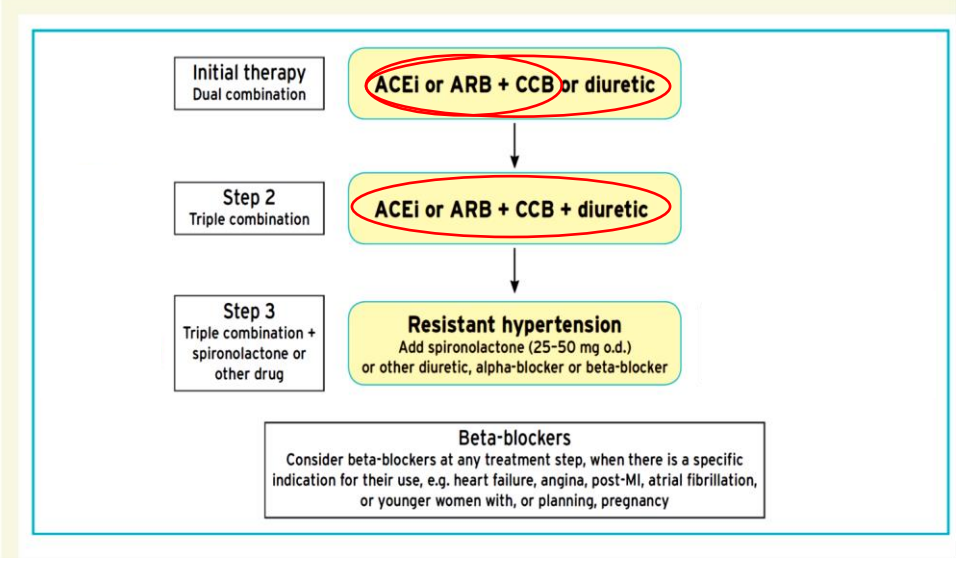
Antihypertensive Drug Treatment of Hypertension

I	C-LD	Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.

Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

33

Ideal Triple Coverage-ESC/ESH 2018



Williams B et.al. European Heart Journal (2018) 39, 3021–3104.

34

Hypertension

ORIGINAL ARTICLE

Improved Persistence to Medication, Decreased Cardiovascular Events and Reduced All-Cause Mortality in Hypertensive Patients With Use of Single-Pill Combinations: Results From the START-Study

Roland E. Schmieder, Sven Wassmann, Hans-Georg Predel, Burkhard Weisser, Jörg Blettenberg, Anton Gillessen, Olaf Randerath, Antje Mevius, Thomas Wilke, Michael Böhm

(Hypertension. 2023;80:1127–1135. DOI: 10.1161/HYPERTENSIONAHA.122.20810.)

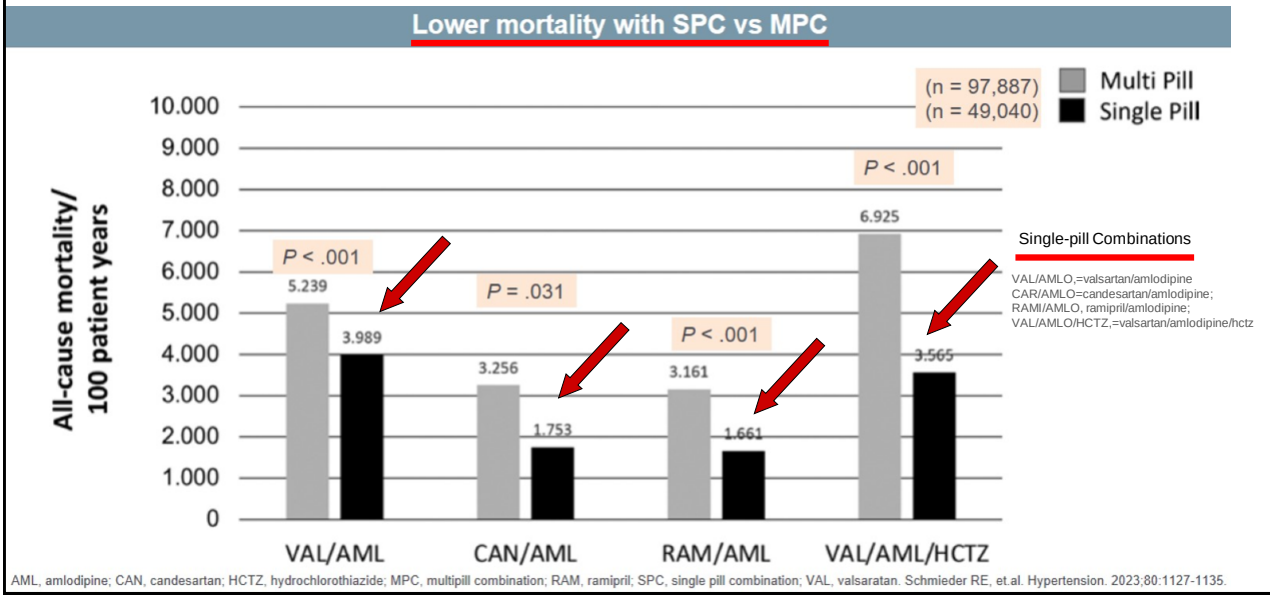
35

Methodology of START-Study

- Retrospective Observational Claims Data Analysis.
- Hypertensive Adults 18 years and older.
- All patients treated with renin-angiotensin system combinations given as single pill or identical multi-pills covering the years 2012 to 2018.
- Patients were not allowed to have any of the fixed-dose combinations evaluated the last year prior to the inclusion in the data set analysis.
- Followed up to at least 1 year.
- 1:1 propensity score matching used.
- Persistence to medication, CV events, and all-cause mortality were compared using non-parametric tests.
- Adherence with the single-pill fixed-dose combination antihypertensive agents was improved 20-50% over the same medications given as multiple single-pill antihypertensive agents.

36

All-Cause Mortality in Single-Pill Combination vs Multi-pill Combination Groups: The START Study

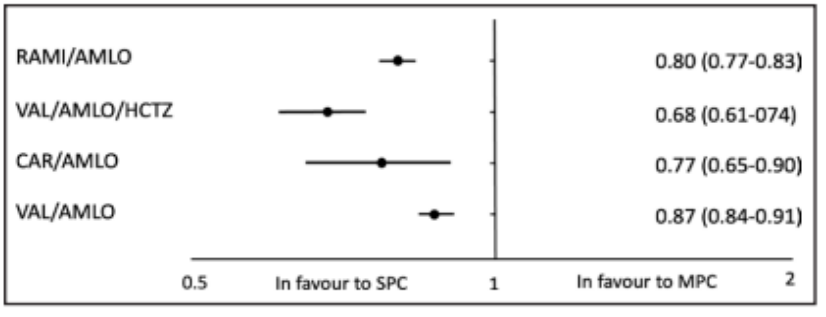


AML, amlodipine; CAN, candesartan; HCTZ, hydrochlorothiazide; MPC, multipill combination; RAM, ramipril; SPC, single pill combination; VAL, valsaratan. Schmieder RE, et.al. Hypertension. 2023;80:1127-1135.

37

Reduced All-Cause Hospitalization and All-Cause Mortality in the SPC vs MPC Groups in Patients w HTN

Results for the composite outcome of All-Cause Hospitalization and All-Cause Death



Comparisons are done between matched SPC (Single-Pill Combinations) versus MPC (Multiple Pill Combinations) cohorts..

RAMI/AMLO, ramipril/amlodipine;
VAL/AMLO/HCTZ,=valsartan/amlodipine/hydrochlorothiazide
CAR/AMLO=candesartan/amlodipine;
VAL/AMLO,=valsartan/amlodipine

Fig 3. Schmieder RE et al. Hypertension May.2023;80:1127–1135.

38

Improved Adherence with SPC's

Study*	Design	SPC, N	FEC, N	†PDC SPC vs. FEC, *p*-value
Ah, *et al*	RetroDB	20,175	20,175	80% vs. 70%, $p < 0.01$
Breitscheidel, *et al*	RertroDB	45,511	26,172	78.1% vs. 71.5%, $p < 0.0001$
Degli Esposti, *et al*	RetroCoh	302	791	79.8% vs. 70.9%, $p < 0.01$
Dickson, *et al*	RetroCoh	2336	3368	63.4% vs. 49%, $p < 0.0001$
Hess, *et al*	RetroCoh	7225	7224	76.9% vs. 54.4%, $p < 0.001$
Ho, *et al*	RetroDB	13,176	4392	58% vs 47%, $p < 0.001$
Hsu, *et al*	RetroDB	5725	1623	42.1% vs 32.4%, $p < 0.001$
Jin-Young, *et al*	RetroOB	757	707	MPR $\geq$ 80%: 91.9% vs. 88.9%, NS
Koval, *et al*	RandPG	39	36	87% vs. 61%, $p < 0.05$
Machniki, *et al*	RetroDB	1884	1884	70.0% vs. 60.6%, $p < 0.0001$
Marazzi, *et al*	RanPro	154	152	94% vs. 85%, $p = 0.034$
Schweizer, *et al*	NRPro	197	138	100% vs. 92%, p=NS
Tung, *et al*	RetroDB	1136	4544	PDC $\geq$ 80%: 65.0% vs. 56.9%, $p < 0.001$
Yang, *et al*	RetroDB	382,476	197,375	72.8% vs. 61.3% (11.6% [11.4–11.7])

* Adapted from Parati. et al.Hypertension 2021;77(2):692-705

†When only medication possess ratio (MPR) provided, MPR multiplied × 100 and expressed as percent to approximate proportion of days covered (PDC).

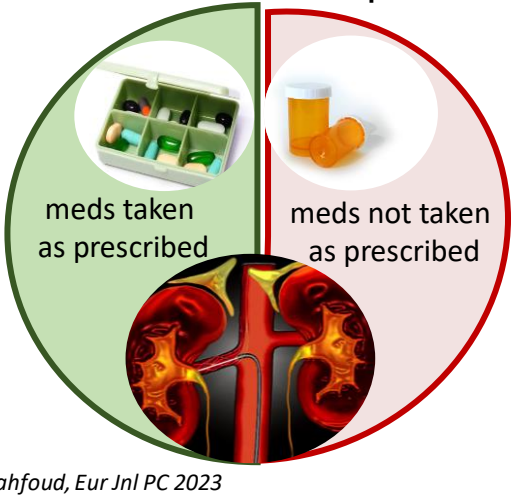
SPC: single-pill combinations; FEC: free equivalent combinations; RetroDB: retrospective database design; RetroCor: retrospective cohort; RetroOb: retrospective observational; RanPro: randomised, prospective; NRPro: non-randomised prospective; P = NS: not significant or not provided.

Table 1. Egan, B.M. Et al. Blood Pressure, 31:1, pg 164-168. 2022

39

TRIO Ultrasound Renal Denervation-ON 3 MEDS

After 1 month on Triple Single-Pill Combination Agent only 43% now qualified for the Study



RDN may be of particular benefit to patients who do not, will not, or cannot take additional medications.

Fisher & Mahfoud, Eur Jnl PC 2023

40

ACCOMPLISH Trial

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 4, 2008 VOL. 359 NO. 23

Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

- Compared Benazapril-Amlodipine with Benazapril-HCTZ
- Combined CV endpoint (CV death, nonfatal MI, nonfatal stroke, hospitalization from angina, resuscitation from sudden cardiac death, coronary revascularization)
- At 3 years, Composite endpoint lower in Benazapril-Amlodipine arm

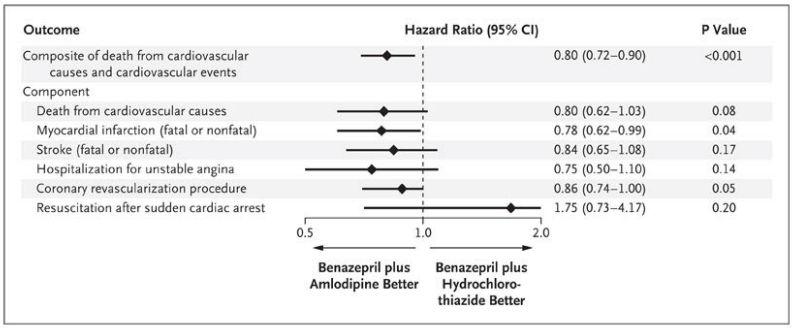
Jamerson K. et al. N Engl J Med Volume 359(23):2417-2428 December 4, 2008

41

Original Article

Benazepril Plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients

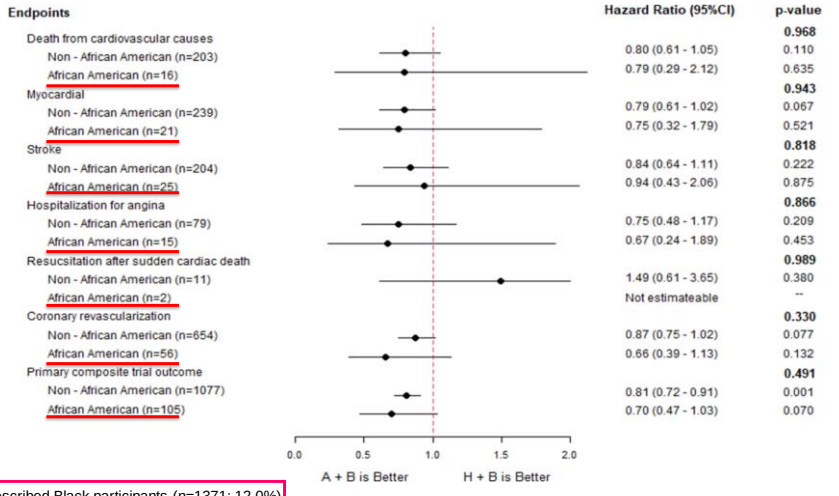
Hazard Ratios for the Primary Outcome and the Individual Components



Jamerson K et al. N Engl J Med 2008;359:2417-2428

42

CV Benefits of Combination ACE Inhibition Plus Calcium Channel Blockade in Black Hypertensive Patients



Self-described Black participants (n=1371; 12.0%)
All others (n=10 083; 88%)

Brook R.D. et al. Hypertension. 2021; Vol: 78, Issue: 4, Pages: 1150-1152.

43

DRUG COMBINATIONS IN HYPERTENSION: RECOMMENDATIONS

Preferred

- ACE inhibitor/diuretic*
- ARB/diuretic*
- ACE inhibitor/CCB*
- ARB/CCB*

*Single Pill Combinations available in the US

Acceptable

- Beta blocker/diuretic*
- CCB (dihydropyridine)/β-blocker
- CCB/diuretic
- Direct Renin inhibitor/diuretic
- Direct Renin inhibitor/ARB
- Thiazide diuretics/K+ sparing diuretics*

Unacceptable

- ACE inhibitor/ARB
- ACE inhibitor/β-blocker
- ARB/β-blocker
- CCB (nondihydropyridine)/β-blocker
- Centrally acting agent/β-blocker

	*Good Rx 90 days 5/15/24
"Ideal" Combinations Available**	
Benazepril 40 mg/Amlodipine 10 mg	$16.75 (30)
+	
Spironolactone 25/HCTZ 25	$15.85 (30)
or	
Atenolol 100 mg/Chlorthalidone 25 mg	$19.07 (30)

Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. *J Am Soc Hypertens.* 2010;4:42-50.
**Basile Personal Communication-Good Rx site 5/15/24, Costco/Publix

44

Triple Fixed Dose Combinations-Good Rx 5/15/24

Tribenzor (olmesartan / amlodipine / HCTZ)	40mg/10mg/25mg (30 tablets)	$ 42.90	View prices
Exforge HCT (amlodipine / valsartan / HCTZ)	10mg/320mg/25mg (30 tablets)	$ 59.83	View prices

45

Back to Case 1

- The patient was started on benazepril/amlodipine 20/5 bid.
- His BMP drawn 2 weeks after he starts benazepril/amlodipine is unremarkable.
- BP: 128/82 mm Hg (average of 3) when next seen in one month.
- BP's at home are even slightly lower and he remains asymptomatic on his current regimen.
- He will continue taking his BPs at home 1 week a month, appropriately taken, twice when he first gets up in the morning and twice when he goes to bed, each measurement separated by 1 minute.
- Unless there is a problem with his BP, he will return in 3 months with his last filled medication bottles. A BMP is drawn 3 days before.

46

SUMMARY of CASE 1:

1. Take a good history on all patients and understand that social determinants of health (SDOH) may strongly influence BP control.
2. Blood Pressure control rates have recently fallen.
3. The basic workup for hypertension after a complete history and physical examination is basic and simple. Don't spend money on the workup if it will not improve patient outcome.
4. We should endorse lifestyle modification in all patients for effective BP control with a special emphasis on dietary potassium supplementation and sodium restriction.
5. Remember the first three classes of drugs to use when pharmacologic therapy is required do not include *B*-blockers unless there is a compelling reason for their use.
6. Patients with Stage 2 Hypertension have increased CV morbidity and mortality. Rule out non-adherence, consider secondary causes when clinically indicated, and be aware of the increasing role of fixed-dose combination agents to improve adherence, BP control, and outcome!

47

Questions/ Discussion

48

Case 2

- 43-year-old white female is referred to you for evaluation of her HTN.
- History: She has been having “spells” over the past 12 months characterized by palpitations, sweating, anxiousness, and headaches. They last 15 to 30 minutes and have no specific trigger or alleviating factors.
- BP is elevated during a spell, as high as 170/100 mm Hg, but is normal in between spells.
- Spells can interfere with her sleep, and they are associated with a sense of impending doom.
- She has visited the ER on many occasions but nothing has been found on exam with normal labs but she has never presented during a spell.

49

Case 2

- Family hx is positive as her grandmother had hypertension but no other + family hx and no personal hx of heart failure, strokes, or MI.
- She is on desipramine 50 mg qhs and a laxative for constipation.
- BP in the office: 128/78 mm Hg (average of 3), BMI 26 kg/m^2, WC = 30 inches.
- BP’s at home have been normal but she is often too anxious to take her BP during a spell.
- Physical exam is normal with no phakomatoses (no café au lait spots, mucosal neuromas, retinal angiomas, or neurofibromas).
- Routine labs are normal, K+ is 4.6, glucose 88, Creat-nl.
- EKG-NSR, no ischemic changes, no evidence of LVH.

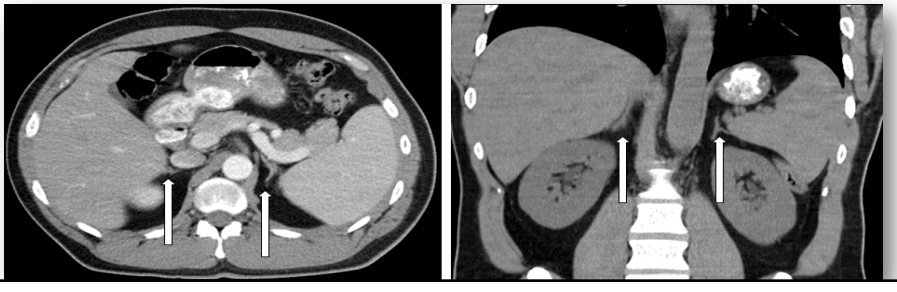
50

One of the Most Important Things to Do in This Patient Is:

A. Take a detailed social hx including hx of traumatic experiences.
B. Do a 24-hour ABPM with diary, if available.
C. Draw plasma catecholamines (NE and Epi).
D. Draw plasma fractionated metanephrines (metanephrine and normetanephrine).
E. A and B
F. A, B, and C
G. A, B, and D
H. A, B, C, and D

Case 2

- Plasma metanephrine level was normal.
- Plasma normetanephrine was 1.2 nmol/L (nl < 0.9 nmol/L).
- 24-hour urine fractionated metanephrines done at her insistence are nl.
- 24-hr ABPM is nl.
- You think you know what the patient has but the patient insists you are missing something, so you do a CT scan.
- Adrenal-CT scan-normal



The Most Likely Diagnosis in This Patient Is:

A. Essential Hypertension with Panic Attacks
B. Hyperaldosteronism
C. Subclinical Pheochromocytoma
D. Pseudopheochromocytoma
E. Unrecognized Hypoglycemia

53

Pseudopheochromocytoma

- A distinct entity with symptoms suggestive of a pheochromocytoma.
- Biochemical findings of a Pheo are absent.
- Up to 40% present similarly to a panic disorder.
- Patients state that their attacks are not related to stress or emotional distress and patients believe “these spells are not in my head”.
- Presenting sxs are usually physical rather than emotional so patients usually present to their primary care physician rather than to mental health clinicians.

Mann S. *Arch Intern Med*. 1999 Apr 12;159(7):670-4.
Mann S. Up to Date Accessed Sept 2022.

54

Pseudopheochromocytoma

- Patients are often told there is nothing wrong with them.
- With careful psychosocial interviewing, the disorder is attributed to emotions the patient is not aware of, or has repressed, and is thus not able to report the reasons for emotional distress.
- Psychotherapy, w or w/o anxiolytics or antidepressants can help patients who are relieved when they are told they have a disorder.
- Chronic disability can occur in these patients.
- The disorder most likely involves activation of the Sympathetic Nervous System from underlying emotional stress.
- BP can be significantly elevated during an “attack” but is not associated with any target organ disease.

Mann S. *Arch Intern Med*. 1999 Apr 12;159(7):670-4.
Mann S. Up to Date Accessed Sept 2022.

55

Case 2-(Con’t)

- Our patient went to a psychotherapist and additional history uncovered that she was abused as a child.
- She was relieved when she realized what could have caused her attacks and there was a “real reason” for the attacks.
- She was treated with an anxiolytic for a couple of months but with further counseling, her attacks became infrequent.
- She was able to stop the desipramine.

56

Pheochromocytoma

- A Catecholamine-secreting tumor that is usually localized to the adrenal gland.
- When outside the adrenal, it is called a paraganglioma.
- It is frequently sought but rarely found.
- When correctly diagnosed and properly treated, it is curable.
- When undiagnosed or improperly treated, it can be fatal.

57

Pheo: Clinical Presentation

- **Prevalence** -- 0.01% to 0.2% of patients with HTN
- **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades.
- **Symptoms** – in 2024 symptoms are present <50% of patients; when present, typically paroxysmal.
- **Mode of Diagnosis** – has changed dramatically over the past 100 yrs—60% are currently discovered as adrenal incidentalomas*****

*****Gruber LM, et al. Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery. *J Clin Endocrinol Metab*. 2019; 104(5):1386-1393.

58

Pheochromocytoma: How They Present

- Hyperadrenergic spells-when sxs occur they have episodes of forceful palpitations, diaphoresis, headache, tremor, pallor). However, most patients with spells do NOT have a pheo!
- Resistant hypertension
- Most today present as an adrenal incidentaloma (≥ 1 cm incidental mass on CT)-60% present this way, but only 2% of all adrenal incidentalomas are pheo's!
- A family history of pheochromocytoma-10% present through genetic testing.
- A familial syndrome that predisposes to pheo/paraganglioma (eg, MEN 2, NF-1, VHL, SDSG Hx)
- May be noted when there is a pressor response to anesthesia, surgery, angiography, high-dose corticosteroid (eg, 8-mg overnight DST), β-blocker, or metoclopramide
- Onset of hypertension at a young age (eg, <30 yrs)

Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. *N Engl J Med*. 2019: 8;381:552-565.

59

Pheo: Case Detection

- It would be ideal if patients are not receiving any meds during lab testing but this is unrealistic.
- So most meds may be continued including all BP agents.
- Tricyclic antidepressants (TCAs) interfere most frequently with the interpretation of 24-hr urinary fractionated metanephrines-(metanephrine and normetanephrine).
- Rx with TCAs & antipsychotic agents should be tapered & D/C at least 4 wks before testing—frequently this is not possible → so go ahead and test-if labs normal, you are done!
- Don't measure catecholamines, they are secreted in spurts and catecholamine secretion may be appropriately ↑ed in situations of physical stress or illness (eg, stroke, MI, etc.)*

*Kline GA, et al. Inpatient Measurements of Urine Metanephrines are Indistinguishable from Pheochromocytoma: Retrospective Cohort Study. *Am J Med*. 2021;134(8):1039-1046.e3.

60

Medications That May ↑ Measured Levels of NE & Normetanephrine

- Tricyclic antidepressants (including cyclobenzaprine [Flexeril®])
- Levodopa-DA (↑ 10-20 X) & NE & Normetanephrine—↑2-4 X
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines-variable effect
- Buspirone and Antipsychotic agents—↑3-10 X
- SNRIs may cause < 2-4 fold increase above upper limit of the reference range
- SSRIs do not interfere with the assay
- Prochlorperazine —variable
- Reserpine —↑3-10X
- Withdrawal from clonidine, benzodiazepines, and other drugs (eg, illicit drugs) —variable effect
- Ethanol and ethanol withdrawal — variable effect

Eisenhofer, G. *J Clinc Endocrinol Metab. 2003; 88:2656-2666.*

61

Screening Tests for Common Causes of 2^{O} HTN

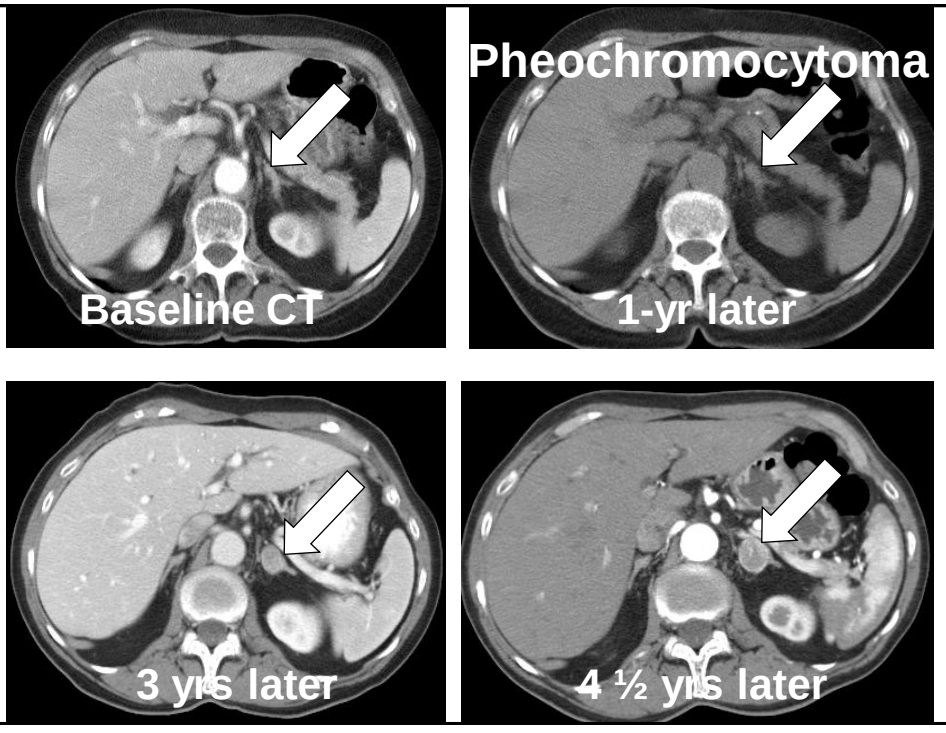
Condition	Screening Test	Routinely
• ↓, ↑ thyroid	TSH, (free T4)	*
• Pheochromocytoma	plasma free or 24-hr urinary fractionated metanephrines	*
• 1^{O} aldosteronism	↓ or nl K^{+}, ↑ plasma aldo with suppressed plasma renin	*
• Cushing's syndrome	24 hr urinary free cortisol, Overnight dex supp	Hx PE
• Hyperparathyroid	Ca^{++}, alb, Cl/P, iPTH	Ca++
• Renal artery stenosis	Duplex Ultrasound, Selective renal arteriogram	↑ Creat FPE*
• Sleep apnea	Hx*, polysomnography, overnight oximetry	Hx**

**Flash Pulmonary Edema*
***Positive Epworth Sleepiness Score*

Carey R M et.al. Hypertension 2018; 72:e53-e90. November 2018*

62

Pheo's Don't Just "Suddenly Appear"— they Grow Slowly: 0.5 to 1 cm in Diameter/

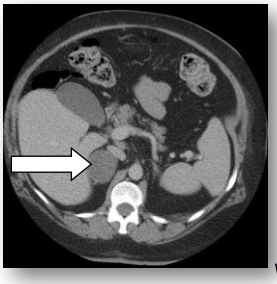


63

"Imaging Phenotype"

Radiodensity Measured in Hounsfield Units (HU)

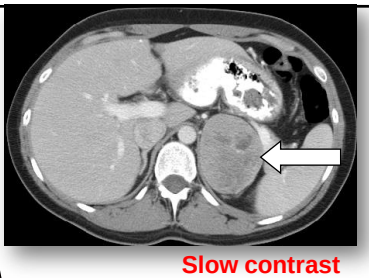
Fast contrast washout >50% at 10 min



Lipid-rich
Benign

+60 HU

-20 HU



Slow contrast washout <50% at 10 min

Lipid-poor
1)ACCarcinoma
2)Mets to adrenal
3)Pheo
4)Lipid-poor adenoma

64

Pheo: Summary Points

- Screening with early morning plasma free metanephrines is recommended. Typically, when a pheo is present, they are 2-3 times above the normal level.
- "All" false + testing for pheo is normetanephrine (NE). When metanephrine (EPI) is increased—pay attention!
- However, these biochemical tests may be normal in an asymptomatic pt presenting as an adrenal incidentaloma discovered in the "pre-biochemical phase"of the pheo—but the imaging phenotype will guide your management (Hounsefield Units)!

Lenders JW, et al. *J Clin Endocrinol Metab* 2014;99(6):1915-42
Carey RM, et al. *Hypertension* 2018; 72:e53-e90
Young WF Jr. N. Engl. J. Med 2007;356(6):601-610.

65

Pheo: Summary Points

- Surgery is the recommended treatment with pre-operative alpha blockade used to prevent peri-operative labile BPs. *B*-Blockers are only used for symptomatic tachycardia and never in isolation.
- Patients are followed yearly with fractionated metanephrines to check for recurrence after surgery or if in the pre-biochemical phase.
- ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is used to evaluate for metastases when additional tumors are detected on CT or in those with recurrent disease.
- Finally, genetic testing is recommended in all pheo patients as germline mutations are found in 20-30% of patients.

Lenders JW, et al. *J Clin Endocrinol Metab* 2014;99(6):1915-42.
Schwartz G.L. *Endocrinol Metab Clin North America* 2011;40(2):279-294.

66

Questions/ Discussion

67

Case # 3 - HTN

- **A 56 yo man with a hx of well-controlled Htn treated with metoprolol 50 mg and hctz 12.5 mg both given in the am presented for evaluation.**
- **He has a history of alcohol and tobacco use.**
- **He is on no other medications.**
- **He was concerned about a 20 pound weight loss over the last 6 months with a decreased appetite.**
- **Afebrile, his physical examination was normal with no organomegaly or adenopathy but left flank fullness was noticed on palpation.**
- **His BP was 126/86 without orthostasis.**

68

At This Stage, You Would Order:

A. SPEP and UPEP
B. Renal ultrasound
C. CT scan of the abdomen
D. PET scan
E. None of the Above

69

Case # 3 - HTN (Con't)

- **A CT scan was done for the left flank fullness and abnormal urine and confirmed a left renal mass suggestive of a hypernephroma localized to the kidney.**
- **After discussion with his primary care physician, oncologist, and urologist, he underwent a radical nephrectomy with the pathology revealing a Fuhrman Grade 3 clear cell cancer.**
- **After nephrectomy, his serum creatinine was 1.2 mg/dl and a 24-hour protein excretion was 170 mg/24 hours.**
- **At discharge, he was started on single-agent sunitinib therapy administered in a 4-week-on, 2-week-off regimen.**

70

Case # 3 - HTN (Con't)

- He is told to check his BPs at home which start to rise with values of 140-150/86-96 mm Hg.
- Two weeks after starting sunitinib, he returns to his primary care clinician.
- His office BP today is 160/100 mm Hg which he says is a little higher than his home values.
- He feels well and is asymptomatic.
- His physical examination was unremarkable, and his weight was unchanged from discharge.
- His serum electrolytes and creatinine were also unchanged.
- He asks could this be a white coat effect?

71

What Do You Think Is the Most Likely Cause of His Recently Elevated BPs?

A. Non-adherence to his metoprolol and hctz
B. White coat-effect
C. Salt and alcohol indiscretion
D. Initiating sunitinib therapy
E. None of the above

CONTINUING EDUCATION COMPANY

72

His Oncologist Tells You That He Needs to Continue His Sunitinib. The Best Strategy to Control His BP Is:

A. Double the dose of atenolol and hctz.
B. Switch to tenoretic (atenolol/chlorthalidone 100/25 mg) giving ½ tablet bid
C. Add Lisinopril 10 mg qam
D. Add Diltiazem 240 mg qam
E. Continue to observe his BP elevation

73

Case # 3- HTN (Con't)

- **After 2 weeks, his lisinopril is advanced to 20 mg and his BP is back to his baseline (well controlled). Metoprolol and Hctz are continued.**
- **Four weeks later, he develops a severe hand-foot skin reaction felt to be secondary to the sunitinib which is held.**
- **While off the sunitinib for 2 days he reports episodes of lightheadedness on standing.**
- **On evaluation, his seated office BP is 102/64 mm Hg and 94/58 mm Hg upon standing.**

74

Case # 3 - HTN (Con't)

- **His lisinopril dose is reduced to 10 mg while he continues his metoprolol and hctz.**
- **His home BPs become well controlled at 110-120/80-86 mm Hg and he no longer has lightheadedness.**
- **After sunitinib is re-started at a lower dose, his BP goes up and his lisinopril dose is increased back to 20 mg.**
- **His BP remains stable in the 120 to 130s/80s mm Hg on the 3 antihypertensive agents.**

75

Drug-Induced (Medications) That Can Interfere with BP Control[1, 2]

- NSAIDs/COX-2 inhibitors
- Sodium-containing Antacids[2]
- Oral contraceptives (estrogen predominant)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (amphetamines, methylphenidate)
- Alcohol
- Anti-depressants (TCAs and SNRIs)
- Cyclosporine[1] or tacrolimus[2]
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra or ma huang)
- Tyrosine Kinase Inhibitors (VEGF inhibitors)—Cardio-Oncology

[1] *Calhoun et al. AHA Scientific Statement: Hypertension 2008;51:1403-1419*

[2] 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; *Hypertension; JACC* Nov 2017

76

Screening for Secondary Hypertension

New onset or uncontrolled hypertension in adults

CONDITIONS:

- **Treatment resistant hypertension; drug-induced htn**
- **Abrupt onset of hypertension;**
- **Onset of hypertension at <30 years of age;**
- **Unprovoked or excessive hypokalemia**
- **Exacerbation of previously controlled hypertension;**
- **Disproportionate TOD for degree of hypertension;**
- **Accelerated/malignant hypertension**

Yes / No

Screen for secondary HTN (Class I)

Screening not indicated

Positive screening test

Yes / No

Refer to clinician with specific expertise (Class IIb)

Referral not necessary

Whelton P et.al. Hypertension 2017

77

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 31, 2003 VOL. 349 NO. 5

A Randomized Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D., Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D., and Steven A. Rosenberg, M.D., Ph.D.

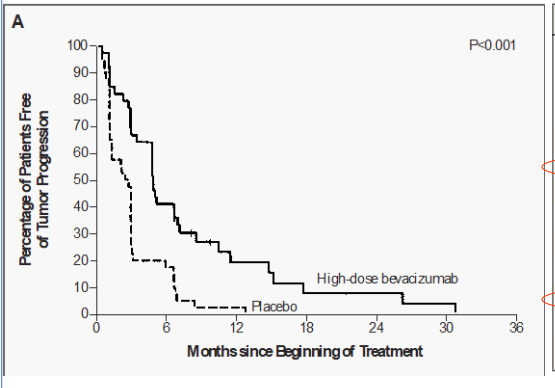


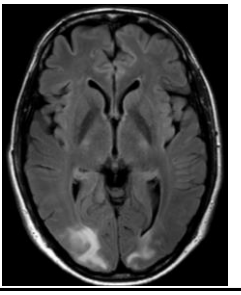
Table 2. Toxic Effects of Treatment.*

Effect	High-Dose Bevacizumab (N=39)	Low-Dose Bevacizumab (N=37)	Placebo (N=40)
	number		
Epistaxis	8†	5	1
Hypertension	14† (8†)	1	2
Fever without infection	4	1	0
Malaise	13	6	6
Hematuria	5†	1	0
Hyponatremia	3	4†	0
Proteinuria (≥1+ or ≥150 mg/24 hr)	25† (3)	15 (2)	15
Elevated alanine aminotransferase	4	2	0
Chest pain	2 (2)	0	0

78

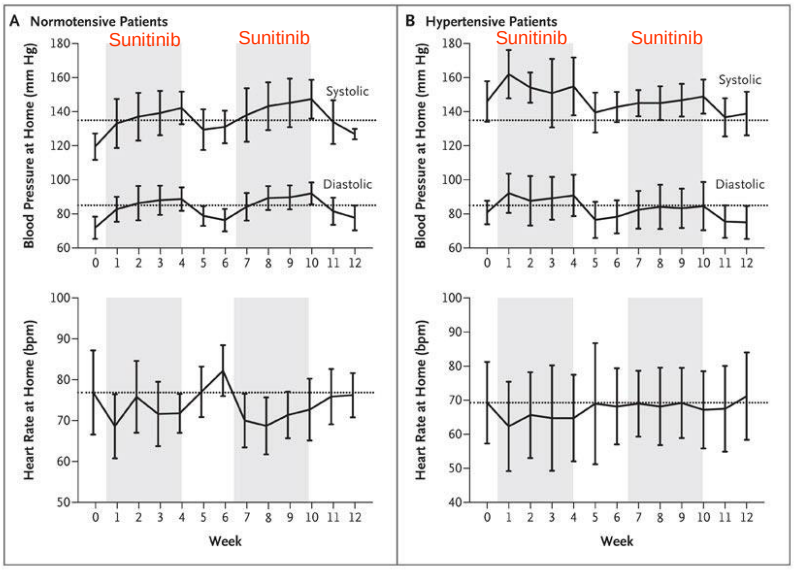
Characteristics of VEGFI-induced Hypertension

- BP increase following VEGFI treatment is rapid and directly linked to treatment.
- BP increase is dose-dependent and may be a marker of treatment efficacy (on-target effect).
- VEGFIs increase BP in 80-90% of patients and cause HT in 30-60% of patients. Combination VEGFIs cause HT in ≈ 100% of patients.
- Hypertension is usually severe and may be treatment-resistant.
- Hypertension may be associated with reversible posterior leukoencephalopathy



79

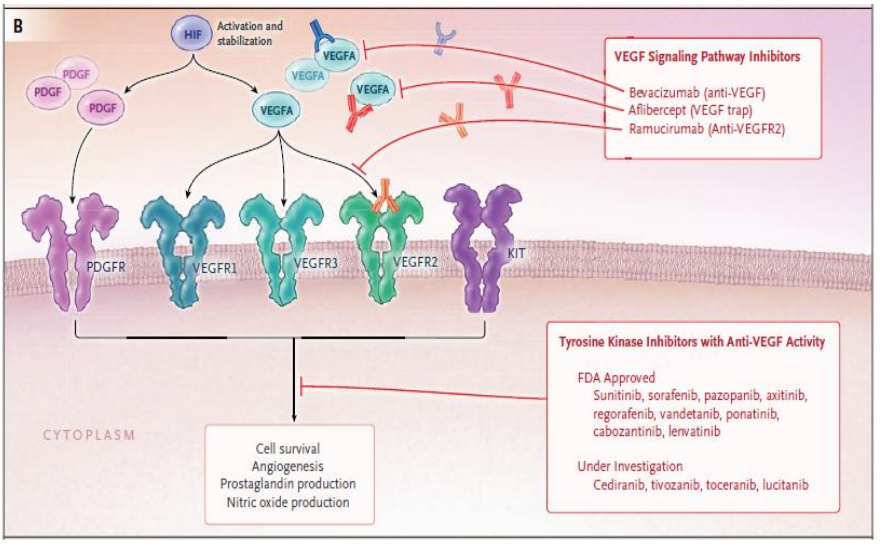
BP and HR in Normotensive and Hypertensive Patients Treated with Sunitinib for Renal Cancer



Azizi M. New Engl J Med 2008

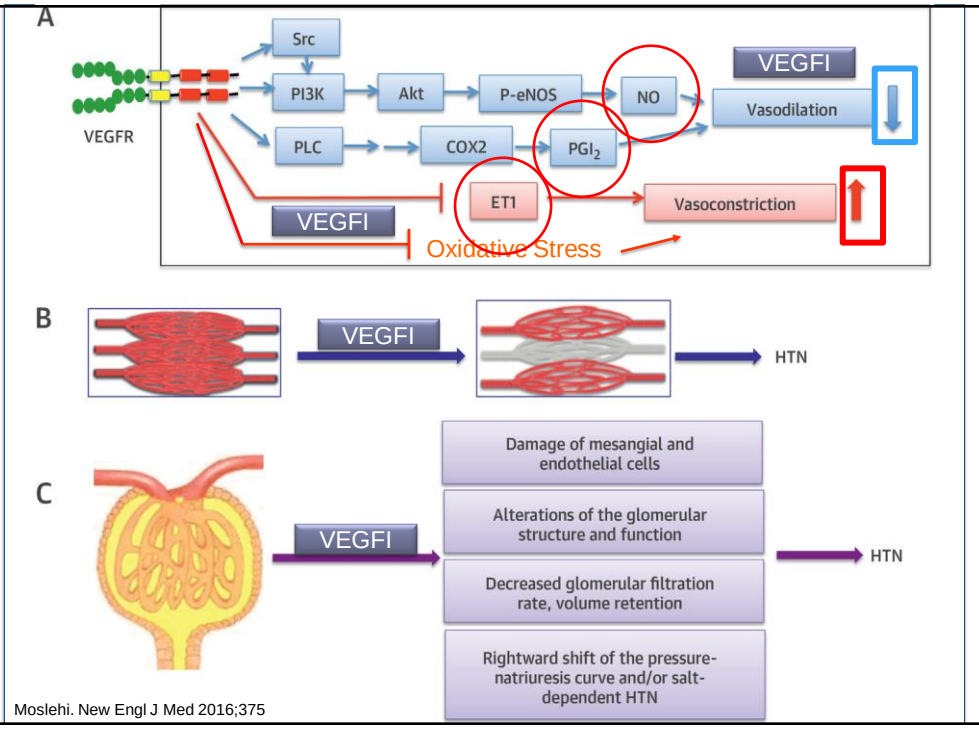
80

Targeting of VEGF Signaling Pathways for Cancer Therapies



Moslehi et al. *N Engl J Med* 2016;375:1457-67

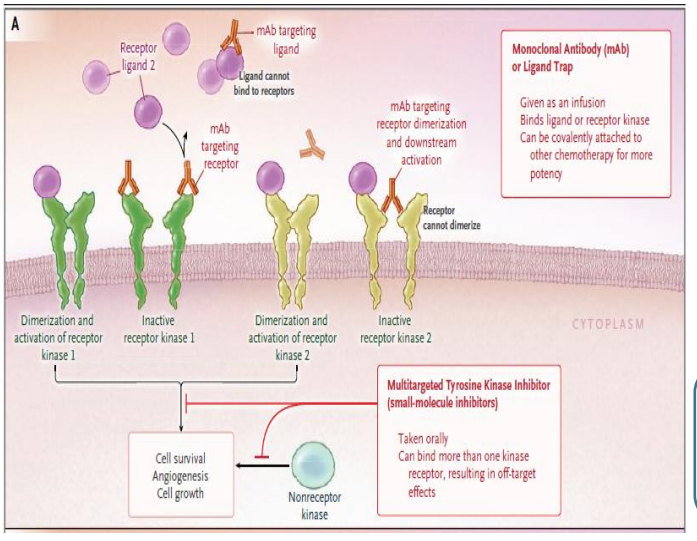
81



Moslehi. New Engl J Med 2016;375

82

Targeting of Kinases for Cancer Therapies



Off-Target Effects

- Hypertension
- Thromboembolic events
- Proteinuria
- Cardiomyopathy

Moslehi et al. N Engl J Med 2016;375:1457-67

83

VEGF Inhibitor Induced Hypertension: Risk Factors

- Prior history of hypertension
- Combination therapy with > 1 VEGF inhibitor
- Age >65 years
- History of CV disease
- History of renal disease
- Tobacco use
- Dyslipidemia
- Abdominal obesity

84

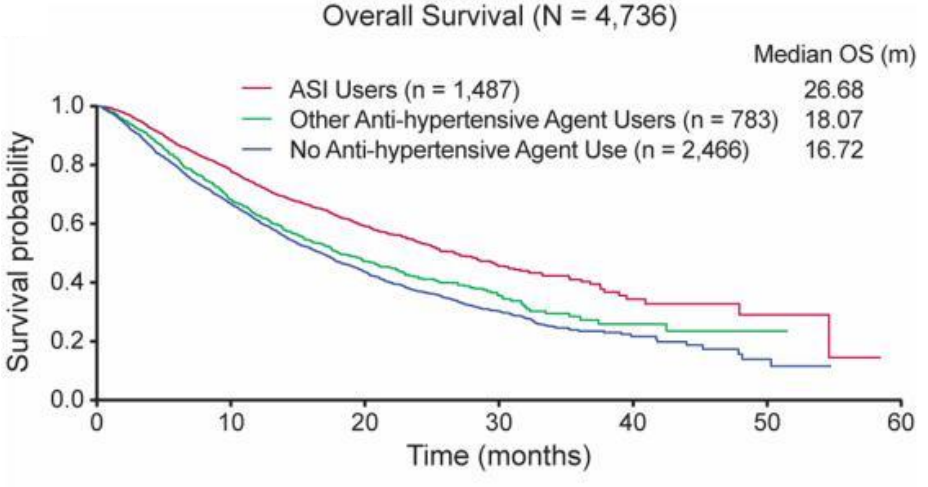
VEGFI-induced Hypertension: Treatment Options

- **First Line Therapies**
  - ACE Inhibitors/Angiotensin Receptor Blockers
  - Dihydropyridine Calcium Channel Blockers (CCBs)
- **Second Line Therapies**
  - Beta blockers and Diuretics
- **Novel/Investigational Therapies**
  - Nitric Oxide Donors
  - Endothelin-1 Receptor Antagonists

85

ACEi and ARBs

Angiotensin System Inhibitors (ASI) vs Other Antihypertensive Drugs Improve Overall Survival in VEGFI-treated Cancer Patients



McKay. Clin Cancer Res 2015:21

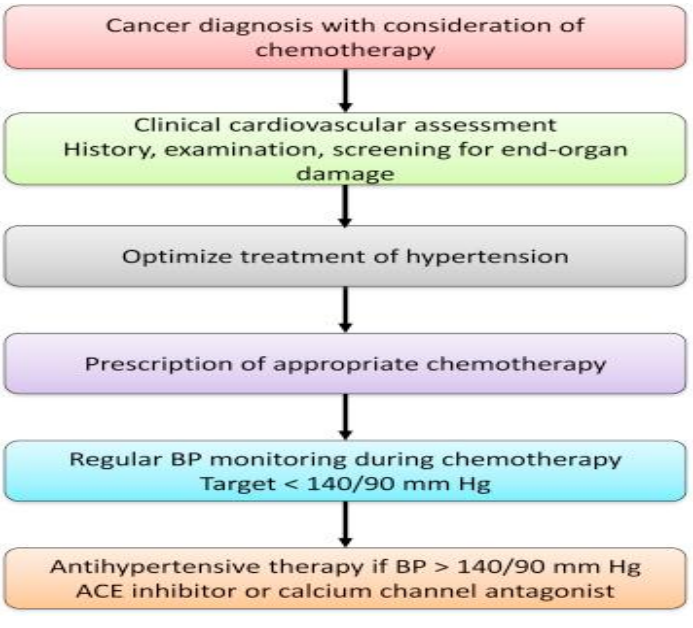
86

Managing VEGFI-induced Hypertension

1. Discontinuation of VEGFI due to hypertension is controversial since hypertension is associated with better oncologic response to VEGFI.
2. Maintenance of chemotherapy and effective BP control is therefore recommended to BP targets currently recommended.
3. ACE inhibitors may be beneficial as first-line treatment, since they reduce proteinuria and control BP.
4. While DHP-CCB's are recommended, non-dihydropyridine calcium channel blockers (verapamil, diltiazem) inhibit the cytochrome P450 system and should not be administered with VEGFI since they are metabolized by cytochrome P450 and may increase any toxic effects of VEGFI therapy.

87

Clinical Approach in Managing VEGFI-induced Hypertension



Cameron. Can J Cardiol 2016

88

Summary

- VEGF regulates vascular function, by stimulating extracellular growth and vasodilation.
- VEGF inhibition limits tumor growth but also increases BP (90% of patients) and causes hypertension (30-60% of patients).
- VEGFI-induced hypertension may be a biomarker of effective anti-cancer treatment.
- Mechanisms of VEGFI-induced hypertension are unknown.
- Factors implicated in VEGFI-induced hypertension include:
  - ↓NOS activity
  - ↑oxidative stress and decreased antioxidant status
  - ↓vasodilation and rarefaction
  - ↑vasoconstriction, ET-1
- **Challenges:** Increased cancer survival + increased CVD risk
  Increased number of FDA-approved VEGFi
- New (bio)medical discipline- cardiovascular oncology

89