MANAGEMENT OF UNCONTROLLED HYPERTENSION IN POSTMENOPAUSAL WOMAN

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CONFLICT OF INTEREST

I declare no conflict of interest

OUTLINE

- **Why we should focus on hypertension in Postmenopausal woman?**
- EPIDEMIOLOGY
- MECHANISMS RESPONSIBLE FOR BP RISE WITH AGING IN WOMEN
- CASE STUDY
- CONTROL OF HYPERTENSION IN POSTMENOPAUSAL WOMEN
- WOMEN IN CLINICAL TRIALS OF HYPERTENSION
- CARDIAC RISK IN MENOPAUSE AND SAFETY OF HORMONE THERAPY
- CONCLUSION

Why we should focus on hypertension in Postmenopausal women?

WHY WE SHOULD FOCUS ON HYPERTENSION IN POSTMENOPAUSAL WOMEN?

- **According to WHO 2020, up to 40% of Iraqi people who are ≥25 years have HTN and they reported that there was a higher prevalence of HTN in women.**

WHO.Hypertension in Ieaq.2020

IRAQ: HYPERTENSION

Deaths	%	Rate	World Rank
2,451	1.67	16.27	101

According to the latest WHO data published in 2020 Hypertension Deaths in Iraq reached 2,451 or 1.67% of total deaths. The age adjusted Death Rate is 16.27 per 100,000 of population ranks Iraq #101 in the world. Review other causes of death by clicking the links below or choose the full health profile.

WHY WE SHOULD FOCUS ON HYPERTENSION IN POSTMENOPAUSAL WOMEN?

- **HTN control rates appear higher in women than men age >18 years**
- **In those age >60 years, control in women is less than in men .**
- **Elderly women also have more severe HTN and lower BP control rates versus middle-aged and young women**

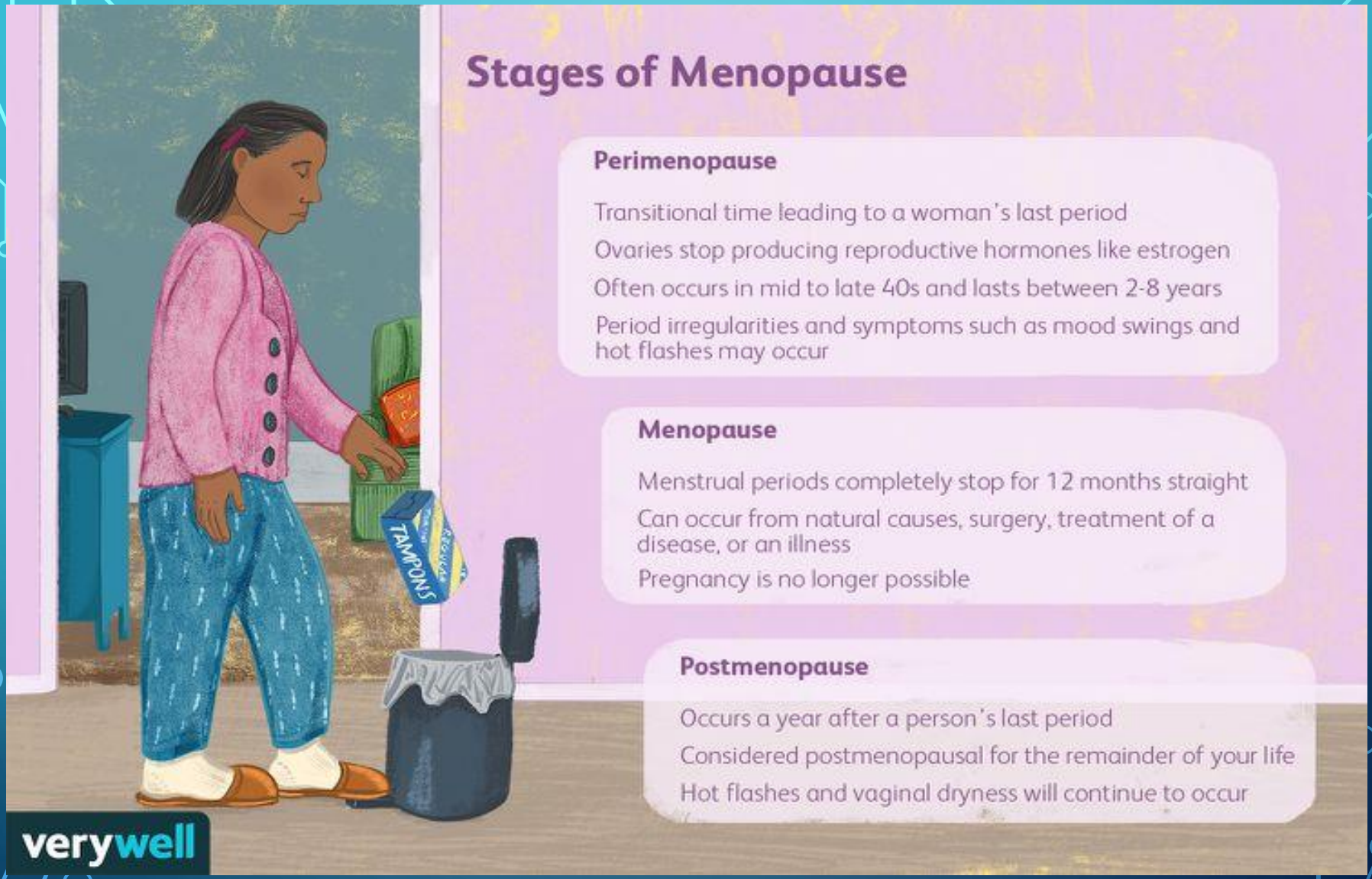
- **Debate remains because optimal (BP) targets have not been established by the highest level of evidence, particularly for older women**

Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Cir- culation 2017;135:e146–603.

The risk hypertension in women

- **Each year, 55,000 more women have a stroke than men. Because, in general, women live longer than men.**
- **Each year, twice as many women die from stroke as from breast cancer , yet HTN is not generally recognized as their major risk factor.**

National Stroke Foundation. Available at: http://www.stroke.org. Accessed February 17, 2017.



World Health Organization. Research on the menopause in the 1990s: report of a WHO scientific group. Geneva: World Health Organization; 1996.

EPIDEMIOLOGY OF HYPERTENSION IN POSTMENOPAUSAL WOMEN

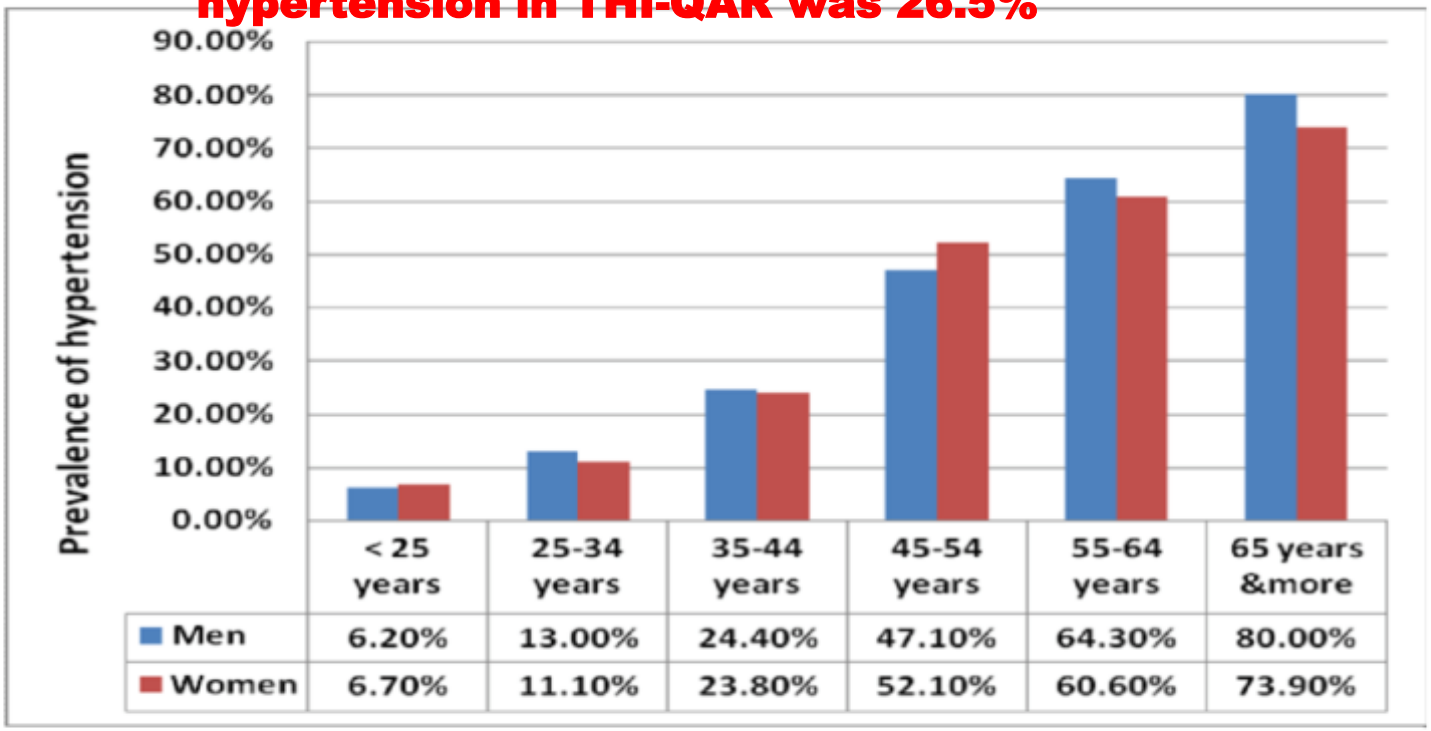
GENDER DIFFERENCE IN THE PREVALENCE OF HTN IN IRAQ

- In 2006, a survey conducted in Iraq on chronic noncommunicable disease risk factors (Iraq STEPS Report) revealed that the prevalence of hypertension was 40.4%.
- The WHO Eastern Mediterranean Region health statistics published in 2008 revealed that the prevalence of hypertension in Iraq for both sexes was 29.4% (20.4–38.9%)

Ministry of Health, Directorate of public health and primary health care and Ministry of Planning and Development in collaboration with World Health Organization. Chronic non communicable diseases risk factors survey in Iraq. 2006 (www.who.int/chp/steps/IraqSTEPSReport2006.pdf ?ua=1, accessed 23 July 2017).
World Health Organization: World Health Statistics 2012. Part II, Highlighted Topics. In Geneva: WHO Press; 2012.

AGE & SEX DISTRIBUTION OF THE PREVALENCE OF HTN IN THI-QAR GOVERNORATE-IRAQ

The overall prevalence of hypertension in THI-QAR was 26.5%



	< 25 years	25-34 years	35-44 years	45-54 years	55-64 years	65 years &more
Men	6.20%	13.00%	24.40%	47.10%	64.30%	80.00%
Women	6.70%	11.10%	23.80%	52.10%	60.60%	73.90%

Figure 3. Age and sex distribution of the prevalence of hypertension

Al-Ghuzi Ali A.Saadon, Al-Asadi Jasim N.Prevalence and Socio-Demographic Determinants of Hypertension in Thi-Qar Governorate: A Household Survey. American Journal of Advanced Drug Delivery. 2014,www.ajadd.co.uk

PREVALENCE OF HTN IN WOMEN ERBIL,KURDISTAN,IRAQ

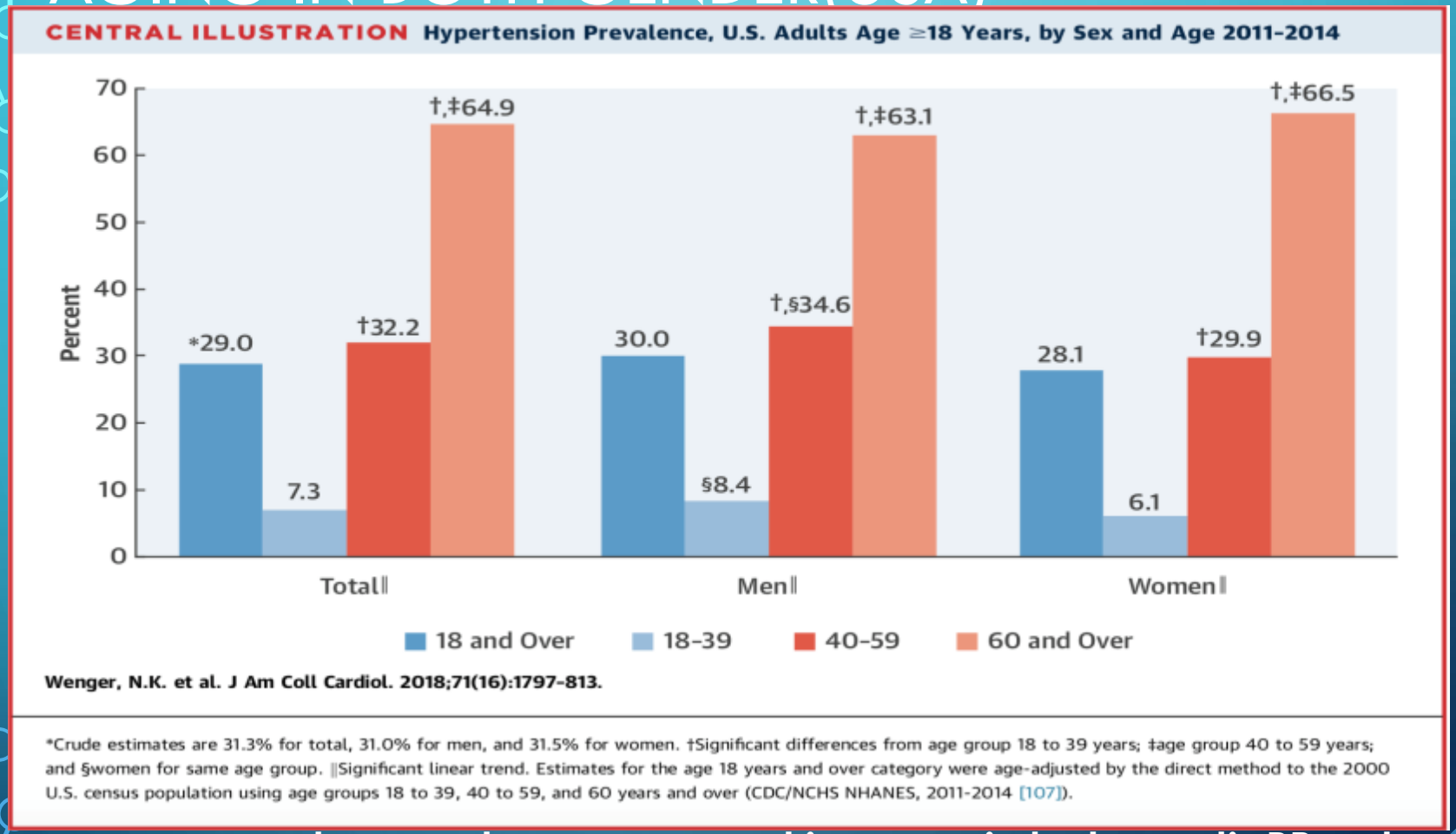
HTN Prevalence in Erbil: 54.7%

Table 3. Association between hypertension prevalence and other variables

Variables	Hypertension			*P* value
	Yes No. (%)	No No. (%)	Total No. (%)	
Age groups				
20-29	44 (17.5)	207 (82.5)	251(100)	
30-39	96 (28.6)	240 (71.4)	336 (100)	
40-49	172 (56.0)	135 (44.0)	307 (100)	<0.001
50-59	164 (77.7)	47 (22.3)	211 (100)	
60+	333 (88.8)	42 (11.2)	375 (100)	
Sex				
Male	230 (63.4)	133 (36.6)	363 (100)	<0.001
Female	579 (51.8)	538 (48.2)	1117 (100)	
Marital status				

Saka M.H,Shabu S.A,Shabila N.P.Prevalence of hypertension and associated risk factors in a population sample of older adults in Kurdistan, Iraq . East Mediterr Health J.2020 Mar 24;26(3):268-275

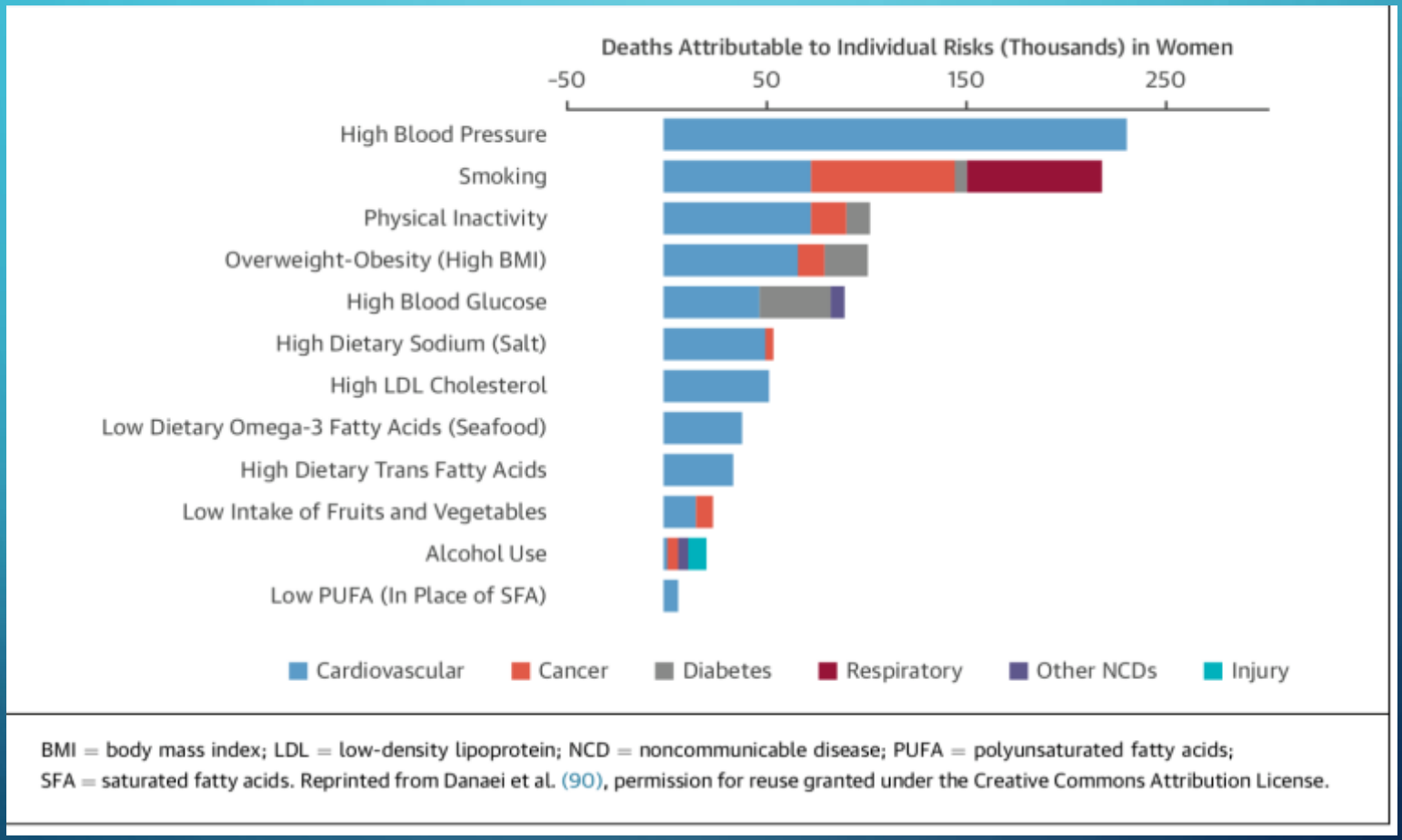
PREVALENCE OF HYPERTENSION WITH AGING IN BOTH GENDER(USA)



postmenopausal women have pronounced increases in both systolic BP and pulse pressure versus age-matched men

Martins D, Nelson K, Pan D, Tareen N, Norris K. The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. J Gend Specif Med. 2001; 4:10–3. 20. [PubMed: 11605350]

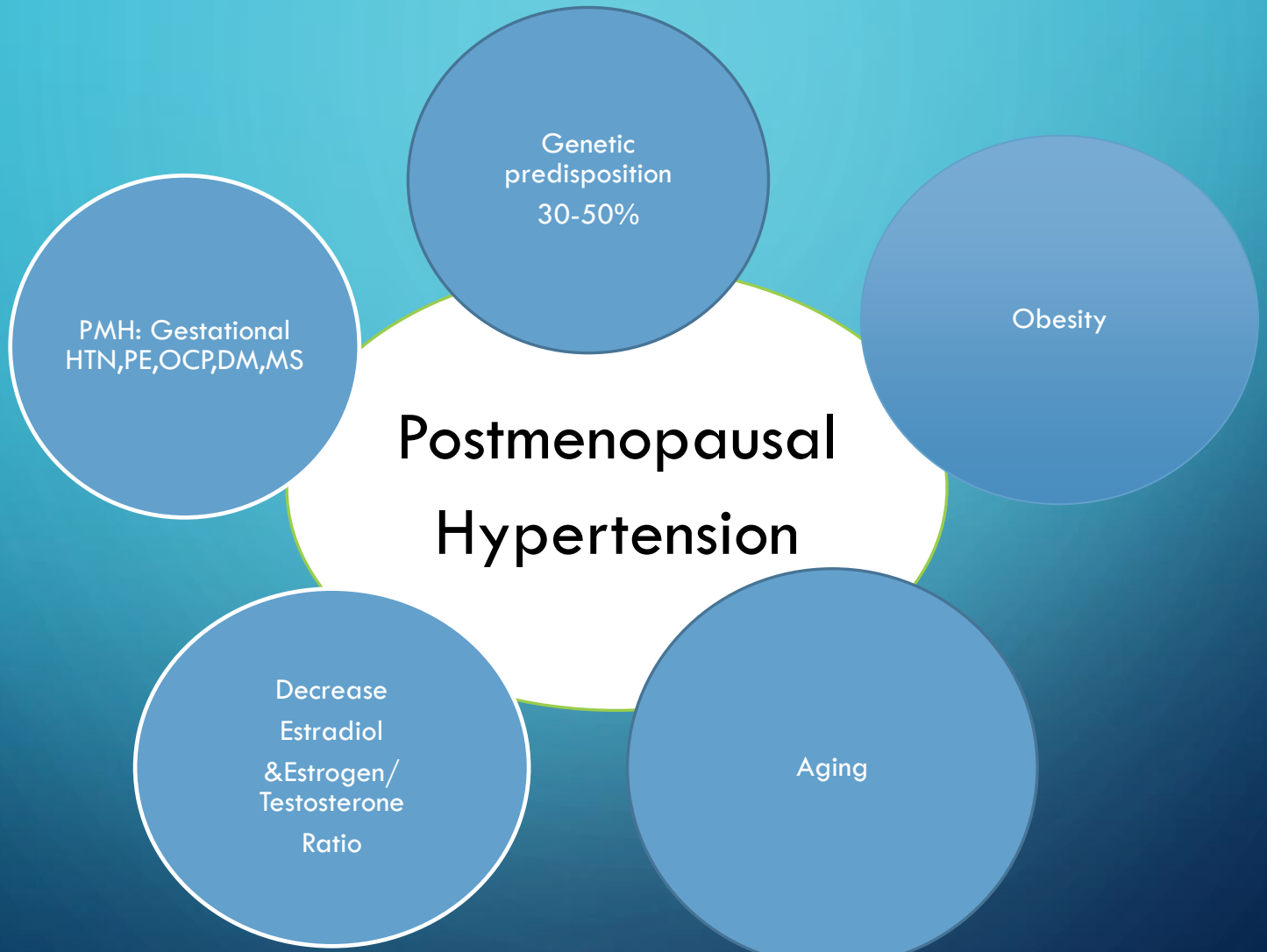
DEATH ATTRIBUTABLE TO INDIVIDUAL RISKS IN WOMEN IN THE US.



BMI = body mass index; LDL = low-density lipoprotein; NCD = noncommunicable disease; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acids. Reprinted from Danaei et al. (90), permission for reuse granted under the Creative Commons Attribution License.

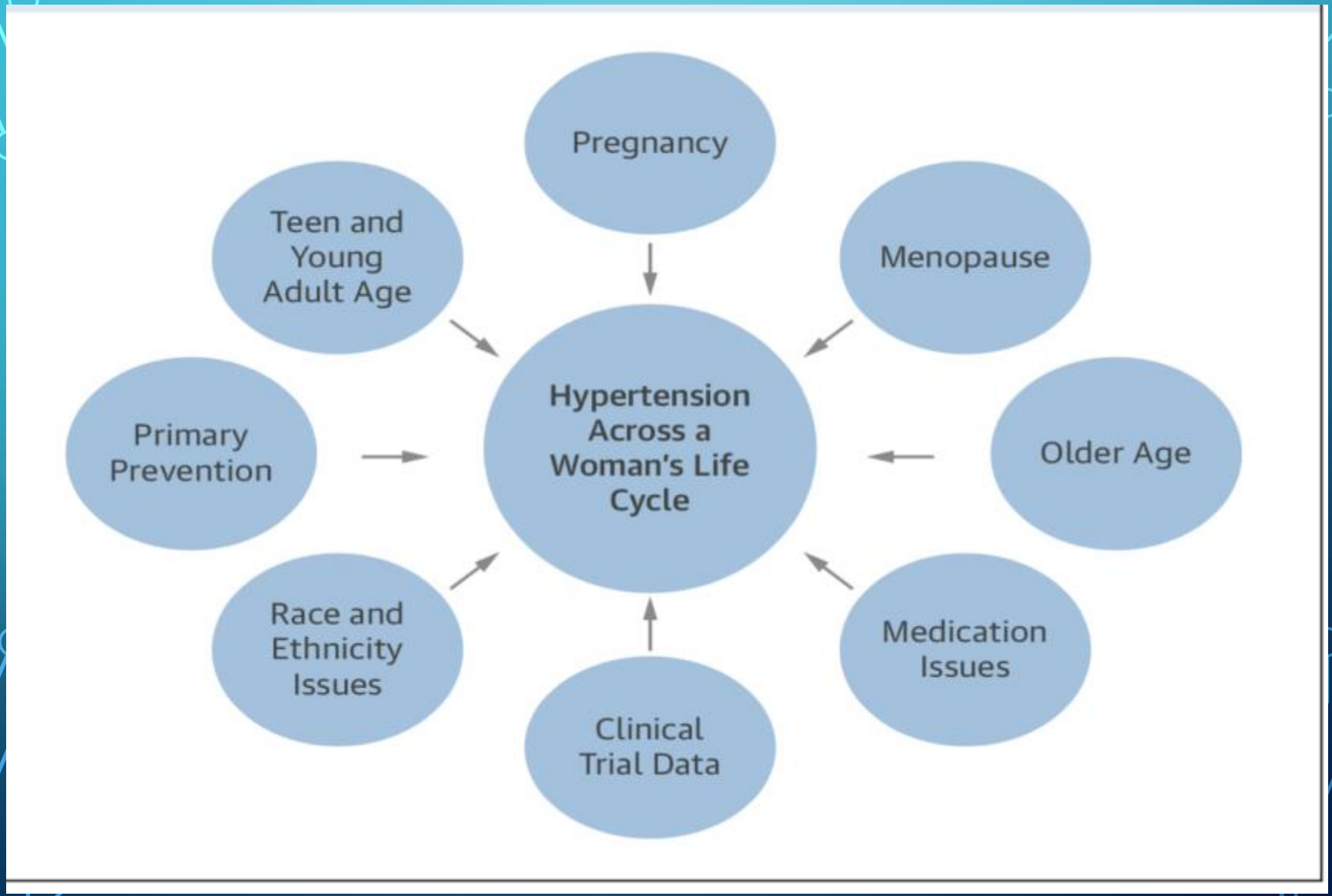
Danaei G, Ding EL, Mozaffarian D, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 2009;6: e1000058.

MECHANISMS RESPONSIBLE FOR BP RISE WITH AGING IN WOMEN



Meyer MR, Haas E, Barton M. Gender differences of cardiovascular disease: new perspectives for estrogen receptor signaling. Hypertension. 2006; 47:1019–26. [PubMed: 16651458]

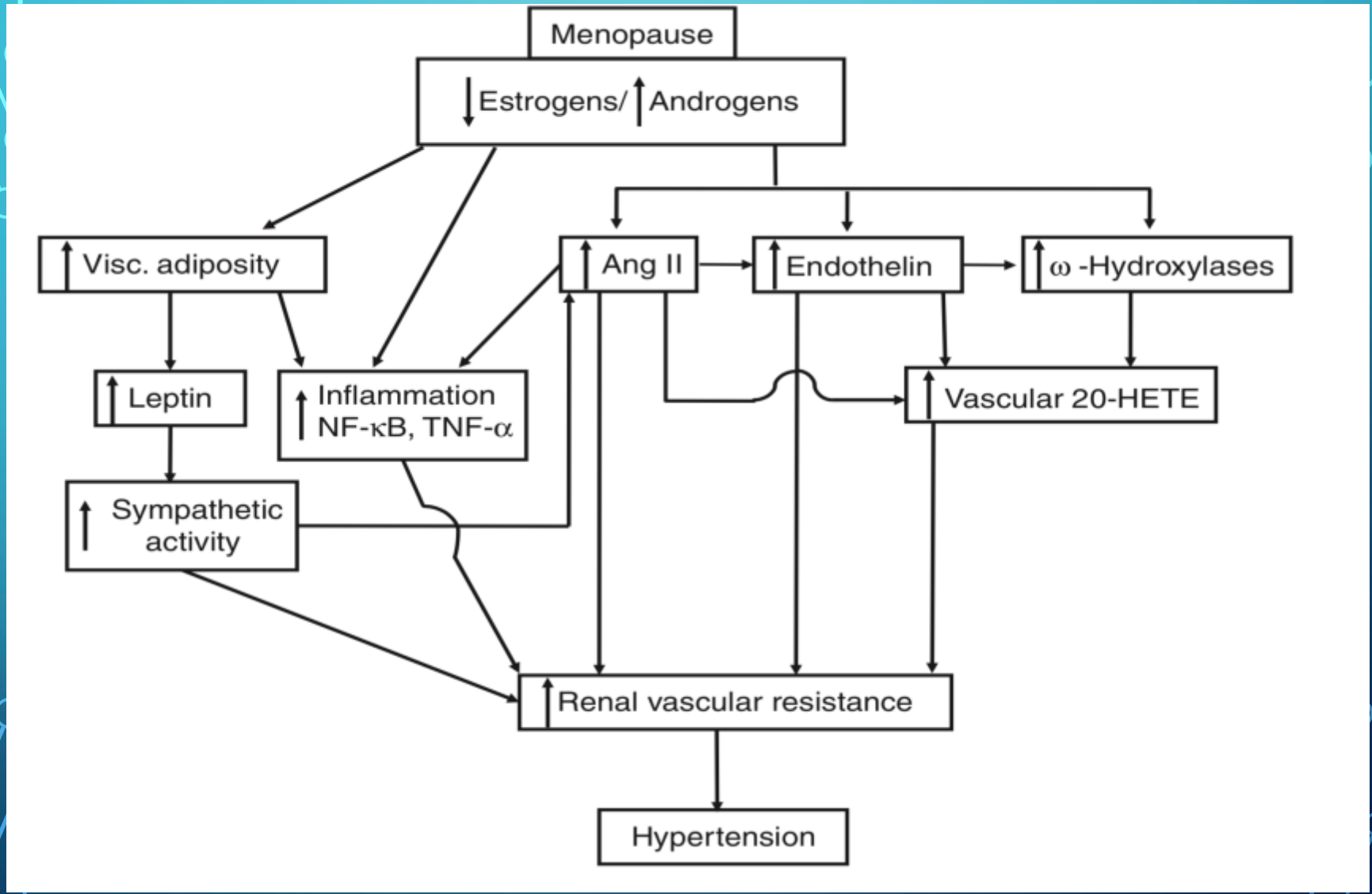
Hypertension across the women's life cycle



EFFECTS OF THE DECLINE IN OESTROGEN LEVELS ON BLOOD PRESSURE

- **Relative increase in androgen levels - Activation RAS, higher renin levels**
- **Increase plasma-endothelin levels**
- **Higher salt sensitivity**
- **Increase in insulin resistance - Higher sympathetic activity**
- **Increase in weight**

Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hyper- tension. An age-old debate. Hypertension 2008;51:952-9.


Menopause
↓Estrogens/ ↑Androgens
↑Visc. adiposity
↑Ang II
↑Endothelin
↑ω -Hydroxylases
↑Leptin
↑Inflammation
NF-κB, TNF-α
↑Vascular 20-HETE
↑Sympathetic activity
↑Renal vascular resistance
Hypertension

CASE STUDY

- 64 year old housewife
- HTN for 10 years on amlodipine 5mg tablet, not diabetic
- Presented with uncontrolled HTN for the last month,no chest pain, no dyspnea
- BMI 28, BP 180/90,PR 85bpm regular,JVP: 9cm water
- Normal S1,Loud P2,Chest : NVB,No leg edema

ECG: Sinus rhythm,No resting ischemic changes.

FBS:125mg/dl,HBa1c:5.9%,B urea 37mg/dl,S creatinine 0.8mg/dl,S K4.4meq/l,

T chol 225mg/dl, LDL 120mg/dl,HDL 31mg/dl,TG95mg/dl,

TTE: Mildly dilated LA,Mild LVH,Mild LVDD,EF

72%,FS41%

What is the expected 10 years CV risk?

Mild

Moderate

Severe

In addition to life style modification:

Which antihypertensive medication should be added to control her BP?

- What is the target of BP that should be achieved to lower rates of fatal and nonfatal major cardiovascular events and death ?

TREATMENT OF POSTMENOPAUSAL HYPERTENSION

FEMALE SPECIFIC RISK FACTORS & STRATIGIES FOR PREVENTION

Excess CV Risk

Menopause

- Central adiposity ↑
- Insulin resistance ↑
- Pro-atherogenic lipid profile
- Autonomic dysfunction→ heart rate variability ↑↑

Strategies to address excess CV risk

- Assess glucose, lipid levels and BP during menopause transition
- Menopause may interfere with working ability → increased employer awareness

- Healthy lifestyle and diet with regular exercise

- MHT is indicated to alleviate menopausal symptoms.
- In young women around the menopause MHT may offer cardioprotection

- MHT is not recommended in women at high CV risk and after a previous CVD event

Other endocrine and gynaecological conditions

- Polycystic ovarian syndrome (PCOS)
- hypogonadotrophic hypogonadism
- Premature ovarian insufficiency (POI)
- Endometriosis

Women with PCOS should have CV risk assessment:

- Measurement of BP
- OGTT
- Fasting lipid profiles
- Screening for GDM in pregnancy.

- Dietary and lifestyle modifications should be discussed in women with PCOS

- All women with POI below the age of 50 should be offered HRT

LIFESTYLE MODIFICATION IN WOMEN VS MEN

- DASH trial, which showed a pronounced antihypertensive effect in women with dietary sodium restriction

Vollmer WM, Sacks FM, Ard J, et al. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med. 2001; 135:1019–28. [PubMed: 11747380]

Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001; 344:3–10. [PubMed: 11136953]

BP TREATMENT THRESHOLDS,BP TARGET & TYPES OF ANTIHYPERTENSIVE MEDICATION

- **The BP threshold for initiating drug treatment, BP goal, which drugs and drug combinations are most effective for reducing CV events are not conclusive.**
-
- **The ACC/AHA 2017 Hypertension Guideline notes that there is no evidence that these issues differ for women versus men.**

Whelton PK, Carey RM, Aronow WS, et al. 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. J Am Coll Cardiol. 2017 Nov 7. pii: S0735-1097(17)41519-1 doi: 101016/jjacc201711006.

Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. JAMA. 2016; 315:2673–82. [PubMed: 27195814]

THE BENEFIT OF EARLIER REDUCTION OF BP

- It is reasonable to assume that earlier BP reduction (e.g. at ~120–139 mmHg) would reduce risks across multiple conditions (e.g. death, stroke, heart failure, diabetes, cognitive impairment, etc.).
- Cognitive impairment is particularly prevalent among older women, and HTN carries the highest population attributable risk for dementia

de Bruijn RF, Bos MJ, Portegies ML, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Med. 2015; 13:132. [PubMed: 26195085]

WHICH ANTI HTN GROUP IS BETTER FOR OLDER WOMEN

- Among multiple agents and strategies, none has proven clearly more beneficial for older women, except perhaps thiazide diuretics since they reduce calcium excretion and prevent osteoporosis to prevent fractures.
- BP control rates declined in older women with increasing age.

Puttnam R, Davis BR, Pressel SL, et al. Association of 3 different antihypertensive medications with hip and pelvic fracture risk in older adults: secondary analysis of a randomized clinical trial. JAMA Intern Med. 2017; 177:67–76. [PubMed: 27893045]

SIDE EFFECTS OF ANTIHYPERTENSIVE MEDICATION (WOMEN VS MEN)

- Women more frequently experience edema with calcium antagonists and cough with ACE inhibitors versus men.
- Hyponatremia and hypokalemia are more frequently associated with diuretic therapy among women.

Turner ST, Schwartz GL, Chapman AB, et al. Plasma renin activity predicts blood pressure re- sponses to beta-blocker and thiazide diuretic as monotherapy and add-on therapy for hyperten- sion. Am J Hypertens 2010;23:1014–22.

WOMEN IN CLINICAL TRIALS OF HYPERTENSION

- Trialists' collaboration compared drug treatment outcomes by sex and found no major differences
- In contrast, randomized controlled trials have reported that some antihypertensive drugs have sex-specific adverse profiles

TABLE 2 Representation of Women in Hypertension Clinical Trials

Paper	Trial Name (Ref. #)	N (Total)	Women, n (%)	% Women	Results Stratified by Sex
Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet	DASH diet, sodium intake and blood pressure trial (DASH-sodium) (24)	DASH Diet (n = 208) Control Diet (n = 204)	233 (56.5)	DASH Diet = 59; Control Diet = 54	In all subgroups, including sex, DASH diet and reduced sodium intake were each associated with decreases in blood pressure (p = 0.07) (124)
Effects of losartan in women with hypertension and left ventricular hypertrophy: results from the Losartan Intervention for Endpoint Reduction in Hypertension Study	LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) Study (120)	9,193	4,963	54	Treatment effect consistent in women and men, but more women in losartan group required hospitalization for angina (120)
A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly	Second Australian National Blood Pressure Study Group (121)	6,083	3,102	51	ACE inhibitor-based regimen benefit was restricted to men (121)
Influence of age, sex and blood pressure on the Principal Endpoints of the Nordic Diltiazem (NORDIL) Study	NORDIL Study (116)	10,876	5,587	51.3	Consistency of benefit was present across subgroups including sex (116)

- The LIFE study suggested that angiotensin receptor blockade (ARB, losartan) with a thiazide diuretic was superior to β-blockade (atenolol) plus thiazide diuretic in preventing CVD outcomes in hypertensive women with LVH.

Dahlof B et al.Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol.Lancet 2002 Mar 23;359(9311):995-1003.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

TABLE 2 Representation of Women in Hypertension Clinical Trials

Paper	Trial Name (Ref. #)	N (Total)	Women, n (%)	% Women	Results Stratified by Sex
A randomized trial of intensive versus standard blood-pressure control	SPRINT (Systolic Blood Pressure Intervention Trial) (122)	Intensive treatment (n = 4,678); Standard treatment (n = 4,683)	Intensive treatment (n = 1,684); Standard treatment (n = 1,648)	Intensive treatment = 36; Standard treatment = 35.2	No

ACE = angiotensin-converting enzyme; BP = blood pressure.

Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.

CARDIAC RISK IN MENOPAUSE AND SAFETY OF HORMONE THERAPY (HT)

- **High-risk HT**
- - Documented atherosclerosis
  - Previous CHD event, stroke, PVD - Current smokers
  - Diabetes mellitus
  - Metabolic syndrome
  - Age >60 years
- **Intermediate-risk HT**
  - ≥2 CHD risk factors
- **Low-risk HT**
  - 1 risk factor (no smoking or DM) - Age 45-55 years

Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al. Evidence- based guidelines for cardiovascular disease pre- vention in women: 2007 update. J Am Coll Cardiol 2007;49: 1230-50.

ISSUES AFFECTING MEDICATION ADHERENCE

- Reduction in medication cost,
- Depressive symptoms
- Women are more likely to develop hyponatremia, hypokalemia, or arrhythmia with diuretics versus men,

10 YEARS PREDICTED RISK OF OUR PATIETN

31.5%

TARGET BP

<120/80

WHICH MEDICATIONS SHOULD BE ADDED?

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up

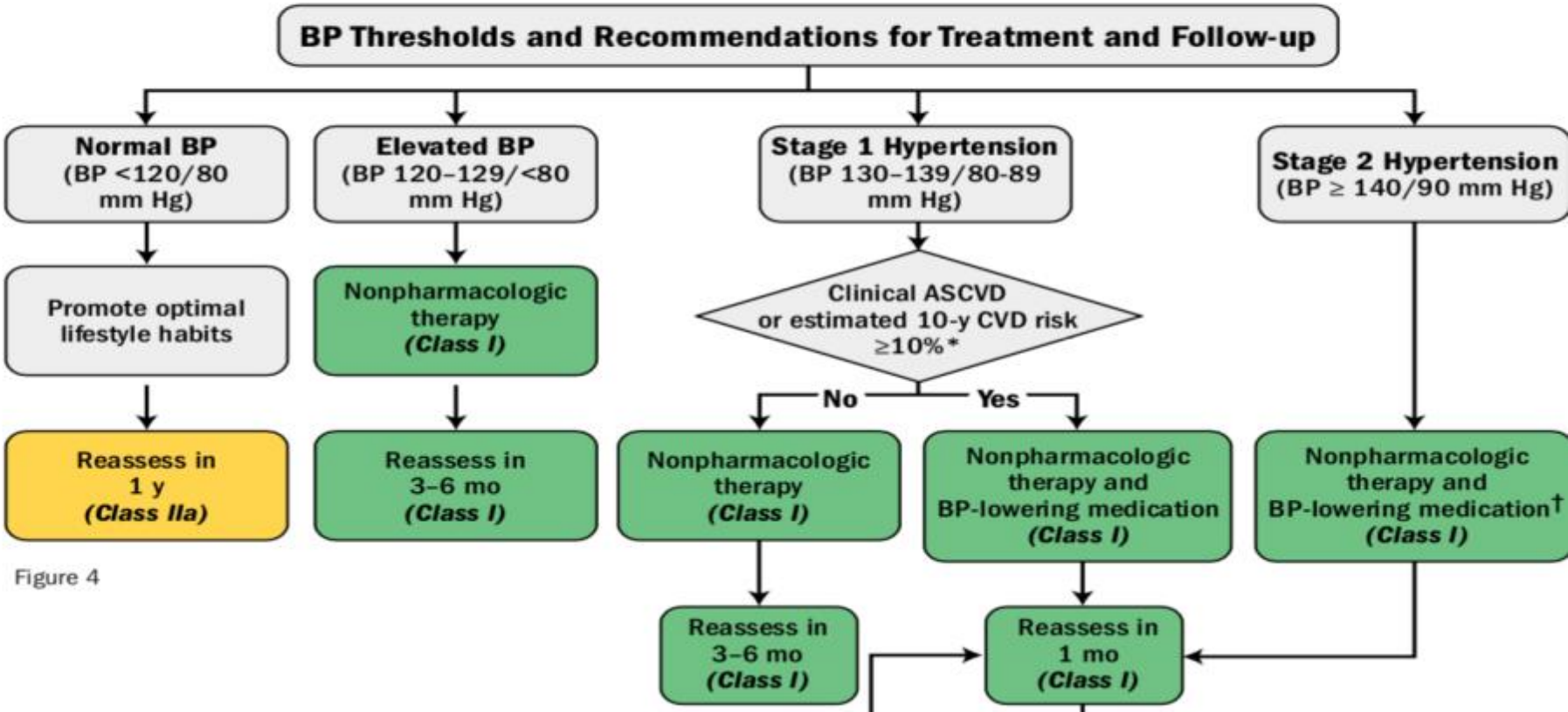


Figure 4

* Using the ACC/AHA Pooled Cohort Equations. 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 ≥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

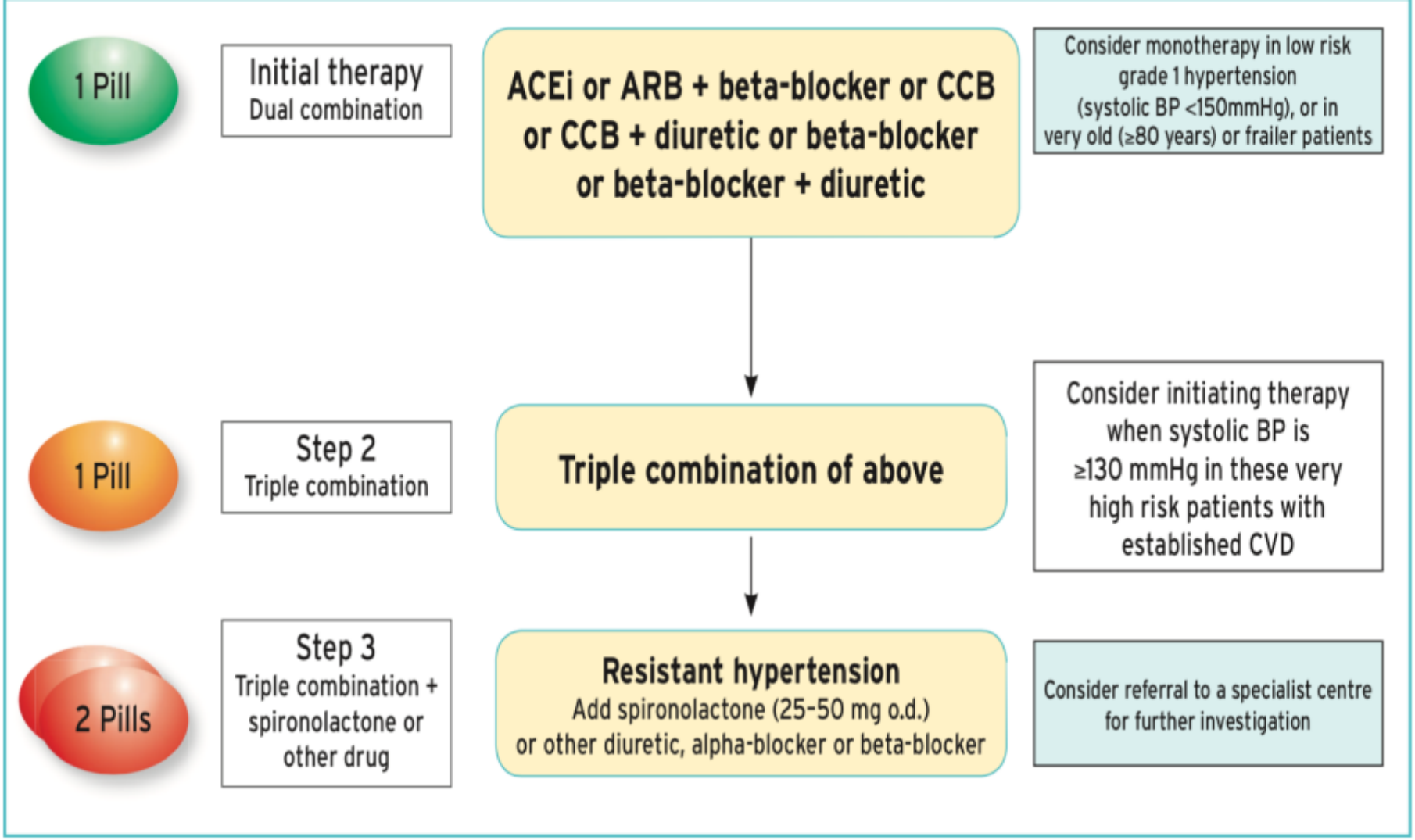


Figure 5 Drug treatment strategy for hypertension and coronary artery disease. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; o.d. = omni die (every day).

TAKE AWAY

- More large scale studies on the prevalence & the control rate of postmenopausal HTN in Iraq is recommended.
- (BP) targets have not been established by the highest level of evidence, particularly for older women
- Many knowledge gaps persist, for example the contribution of hypertensive disorders of pregnancy to future CVD in women, & optimal BP targets for elderly women.

Hormone Therapy in Postmenopausal Women

Effects of a New Hormone Therapy, Drospirenone and 17-β-Estradiol, in Postmenopausal Women With Hypertension

William B. White, Vladimir Hanes, Vijay Chauhan, Bertram Pitt

Abstract—Drospirenone (DRSP), a progestin with antialdosterone activity, has been developed for hormone therapy in combination with 17-β-estradiol (E2) in postmenopausal women. We evaluated the antihypertensive efficacy and safety of various doses of DRSP and E2 and estradiol alone in postmenopausal women with hypertension using ambulatory and clinic blood pressure (BP) monitoring. This was a randomized, double-blind clinical trial of 3 doses of DRSP combined with estradiol, estradiol alone, and placebo in 750 postmenopausal women with stage 1 to 2 hypertension

- **17β-oestradiol as a novel progestin.**
- **Drospirenone is related to spirinolactone and has aldosterone- antagonistic properties.**

- **It lowers ambulatory blood pressure by a mean of 7 mmHg compared with placebo and can easily be combined with other antihypertensive drugs**

Preston RA, Norris PM, Alonso AB, Ni P, Hanes V, Larara AH. Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance

17B-OESTRADIOL (1 MG) IN COMBINATION WITH DROSPIRENONE

- 17β-oestradiol as a novel progestin. Drospirenone is related to spirinolactone and has aldosterone-antagonistic properties.
- It lowers ambulatory blood pressure by a mean of 7 mmHg compared with placebo and can easily be combined with other antihypertensive drugs

Preston RA, Norris PM, Alonso AB, Ni P, Hanes V, Larara AH. Randomized, placebo-controlled trial of the effects of drospirenone-estradiol on blood pressure and potassium balance in hypertensive postmenopausal women receiving hydrochloro-Hthiazide.

Menopause 2007;14:408-14.