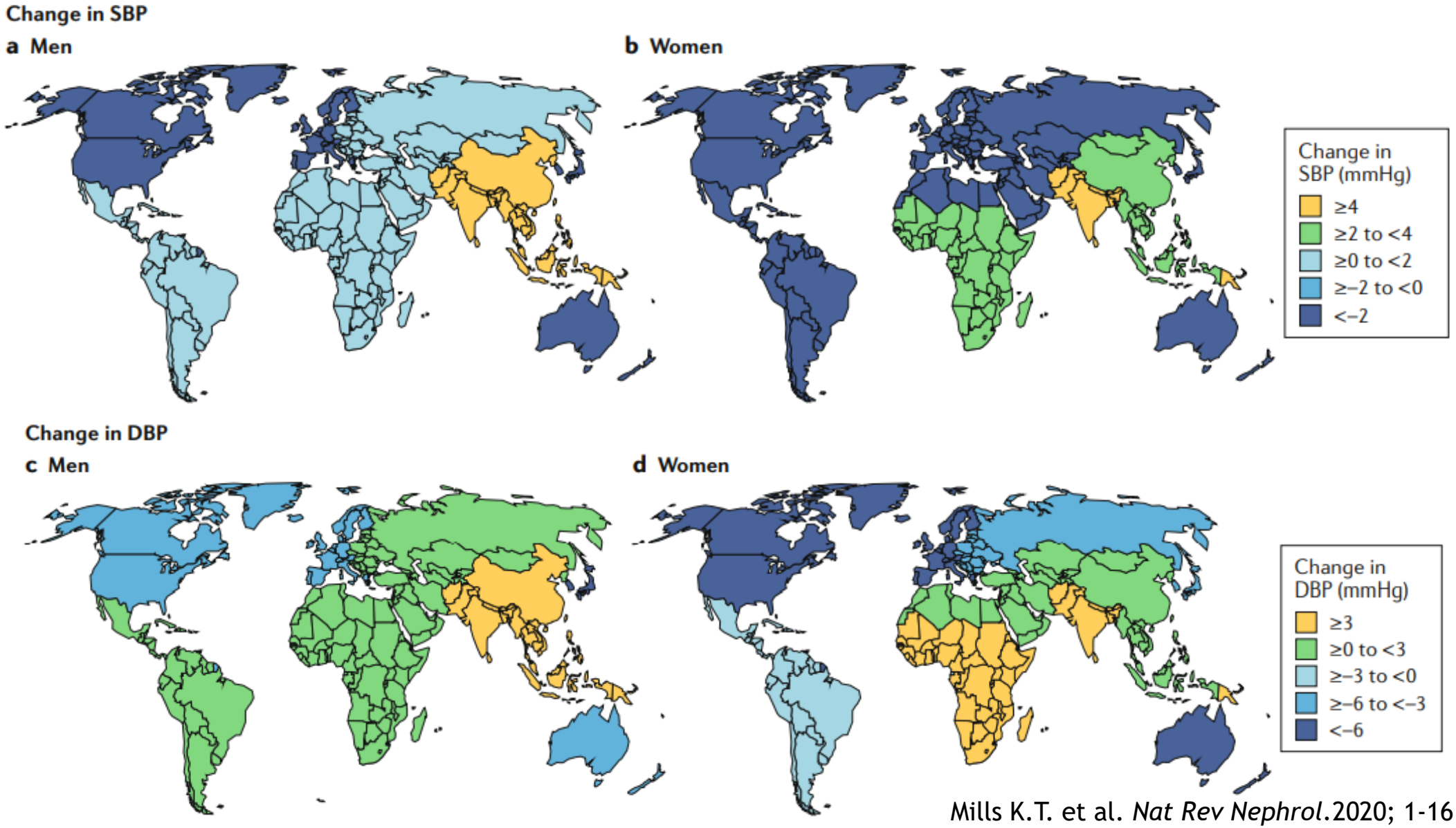
Exacerbators and inducers of hypertension

Introduction

- Hypertension is the leading preventable risk factor for Cardiovascular disease.[1]
- The global burden of hypertension has been growing over time, largely driven by population growth, changes in lifestyle, and aging.[1]
- Alarmingly, hypertension is controlled in less than a fifth of patients worldwide.[1]
- Blood pressure of 120/80 mm Hg or higher is linearly related to risk for fatal and nonfatal stroke, ischemic heart disease, and noncardiac vascular disease. [2]
- Each increase of 20/10 mm Hg doubles the risk for a fatal CVD event. [2]

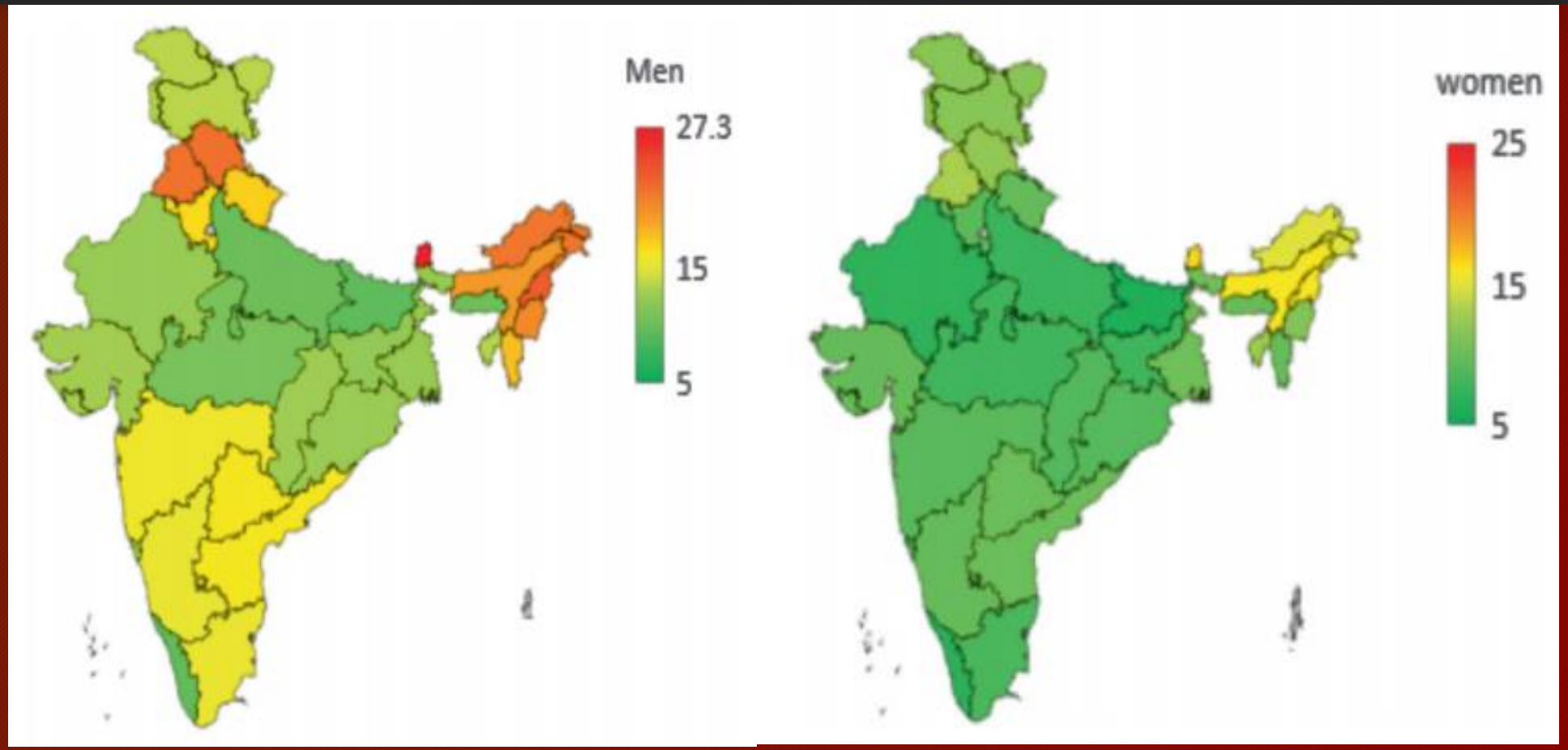
1) Mills K.T. et al. *Nat Rev Nephrol*.2020; 1-16
2) Carey RM et al. Ann Intern Med. 2018;168:351-358.

Global epidemiology of hypertension



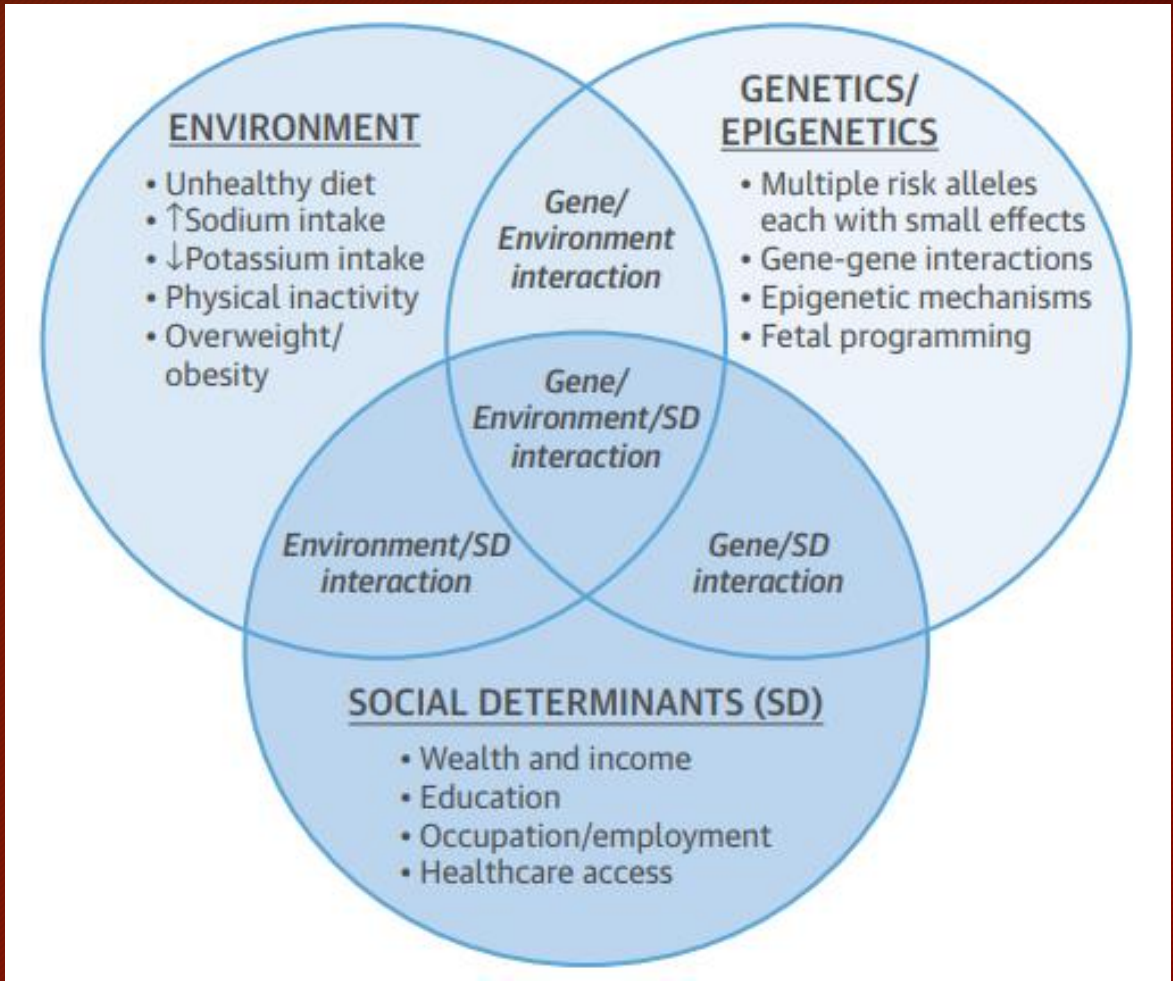
Mills K.T. et al. *Nat Rev Nephrol*.2020; 1-16

The hypertension prevalence in India according to National Family Health Survey-4



Gupta R et al. Journal of Human Hypertension. 2019; 33:575–587

Major determinants of BP in hypertension



Carey R.M. et al. J Am Coll Cardiol. 2018;72(11):1278–93.

Exacerbators and inducers of hypertension

- Different medications and substances may increase BP or antagonize the BP-lowering effects of antihypertensive therapy in individuals.
- It is important to note that the individual effect of these substances on BP can be highly variable
- A greater increase noted in the elderly, those with higher baseline BP, on antihypertensive therapy or with kidney disease.

Unger T et al. *Hypertension*. 2020 ; 75 (6) : 1334 - 1357

Drug/Substance - Exacerbators and Inducers of Hypertension

Drug	Comments
Nonsteroidal anti-inflammatory drugs (NSAIDs)	No difference or an increase of up to 3/1 mmHg with celecoxib 3/1 mmHg increase with nonselective NSAIDs No increase in blood pressure with aspirin NSAIDs can antagonize the effects of RAAS-inhibitors and beta blockers
Combined oral contraceptive pill	6/3 mmHg increase with high doses of estrogen (>50 mcg of estrogen and 1–4 mcg progestin)
Antidepressants	2/1 mmHg increase with SNRI (selective norepinephrine and serotonin reuptake inhibitors) Increased odds ratio of 3.19 of hypertension with tricyclic antidepressant use No increases in blood pressure with SSRI (selective serotonin reuptake inhibitors)

Unger T et al. *Hypertension*. 2020 ; 75 (6) : 1334 - 1357

Drug/Substance Exacerbators and Inducers of Hypertension

Drug	Comments
Acetaminophen	Increased relative risk of 1.34 of hypertension with almost daily acetaminophen use
Other medications	Steroids, Antiretroviral therapy: inconsistent study findings for increased blood pressure Sympathomimetics: pseudoephedrine, cocaine, amphetamines Antimigraine serotonergics ,Recombinant human erythropoietin, Calcineurin inhibitors, Antiangiogenesis and kinase inhibitors, 11 ß-hydroxysteroid dehydrogenase type 2 inhibitors.
Herbal and other substances	Alcohol, ma-huang, ginseng at high doses, liquorice, St. John's wort, yohimbine

Unger T et al. *Hypertension*. 2020 ; 75 (6) : 1334 - 1357

Points to consider to determine drug-induced BP effect

- Duration of action of the drug
- PK/PD relationship
- Timing of BP effect in relationship to the timing of administration
- Duration of the PD effect (increase in BP)*
- Whether the BP effect is sustained, episodic, or transient*
- Discontinuation rate during trials because of hypertension*
- Reversibility of the BP effect*
- Other cardiac effects (eg, reflexive heart rate changes or functional changes)

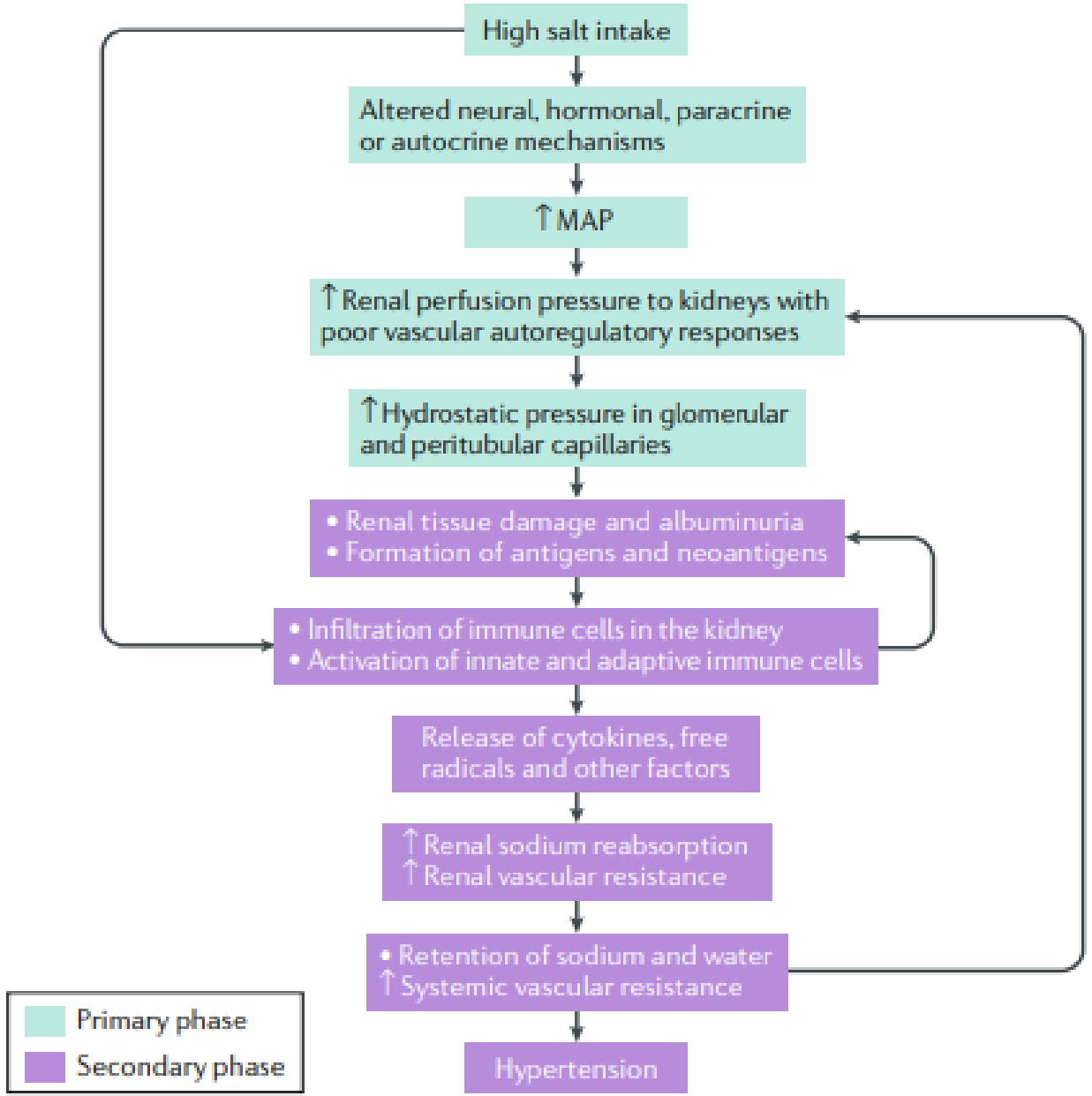
Sager P et al. Am Heart J 2013;165:477-88.

Points to consider to determine drug-induced BP effect

- Postural effects of the drug on BP (particularly if increased when supine)
- Intended use of drug for a short-term illness vs a chronic disease
- Targeted population's age and underlying CV risk
- Determination if BP effects are in the total study population or important subgroups (normortensives, controlled hypertensives, uncontrolled hypertensives)
- Interaction with antihypertensive medications
- Effect in populations like impaired kidney function, concomitant medications known to increase the BP (eg, NSAIDs), older people and hypertensives

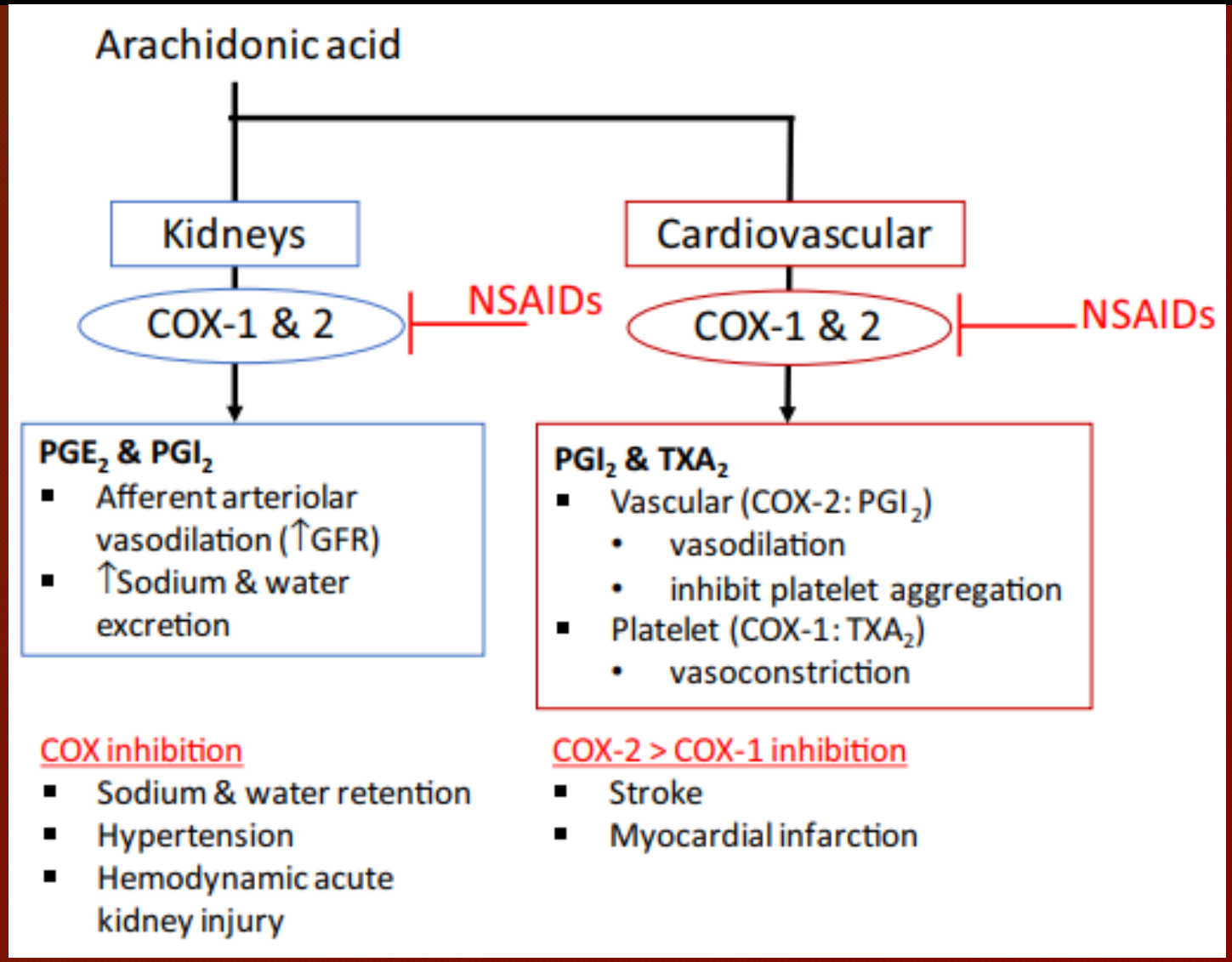
Sager P et al. Am Heart J 2013;165:477-88.

Mechanism of Salt sensitive hypertension



Mattson DL. Nat Rev Nephrol. 2019;15(5):290-300

Mechanism of hypertension with NSAID's



Cooper C et al. Drugs Aging. 2019;36(1):15-24

Difference in SBP with Celecoxib, Ibuprofen and Naproxen

Parameter	Celecoxib 100–200 mg BID *n* = 146	*P*-value	Ibuprofen 600–800 mg TID *n* = 151	Naproxen 375–500 mg BID *n* = 147	*P*-value
Systolic blood pressure					
Baseline	124.18 ± 12.351		125.24 ± 11.775	123.55 ± 11.00	
After 4 months	124.00 ± 13.213		128.65 ± 13.542	125.46 ± 12.487	
Change from Baseline	-0.18 ± 9.400		3.42 ± 12.259	1.91 ± 9.796	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-3.9 (-6.19, -1.61)	0.0009		-2.06 (-4.36, 0.23)	0.08
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.84 (-4.15, 0.47)	0.12			
Diastolic blood pressure					
Baseline	70.88 ± 8.00		70.53 ± 8.457	70.12 ± 7.399	
After 4 months	70.87 ± 8.770		71.26 ± 9.002	70.85 ± 7.922	
Change from baseline	-0.01 ± 5.933		0.74 ± 6.878	0.74 ± 6.294	
Change from BL vs. Ibuprofen (difference in LS Mean (CI))	-0.65 (-2.04, 0.74)	0.36		-0.12 (-1.51, 1.27)	0.87
Change from BL vs. Naproxen (Difference in LS mean (CI))	-0.53 (-1.94, 0.87)	0.46			
Mean blood pressure					
Baseline	89.65 ± 8.454		89.86 ± 8.806	88.87 ± 7.475	
After 4 months	89.69 ± 9.481		91.56 ± 9.295	90.26 ± 8.470	
Change from Baseline	0.04 ± 6.972		1.71 ± 8.742	1.39 ± 7.357	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-1.75 (-3.4, -0.10)	0.04		-0.69 (-2.34, 0.96)	0.41
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.06 (-2.72, 0.61)	0.21			
Pulse pressure					
Baseline	53.31 ± 9.920		54.71 ± 10.087	53.43 ± 9.833	
After 4 months	53.13 ± 9.871		57.39 ± 11.804	54.60 ± 10.334	
Change from baseline	-0.17 ± 4.884		2.68 ± 7.018	1.17 ± 5.348	
Change from BL vs. Ibuprofen (Difference in LS Mean (CI))	-2.99 (-4.3, -1.68)	<0.0001		-1.71 (-3.02, -0.40)	0.01
Change from BL vs. Naproxen (Difference in LS mean (CI))	-1.28 (-2.60, 0.04)	0.06			

Ruschitzka F et al. Eur Heart J. 2017 ; 38 (44) : 3282-3292

Difference in SBP with Celecoxib, Ibuprofen and Naproxen

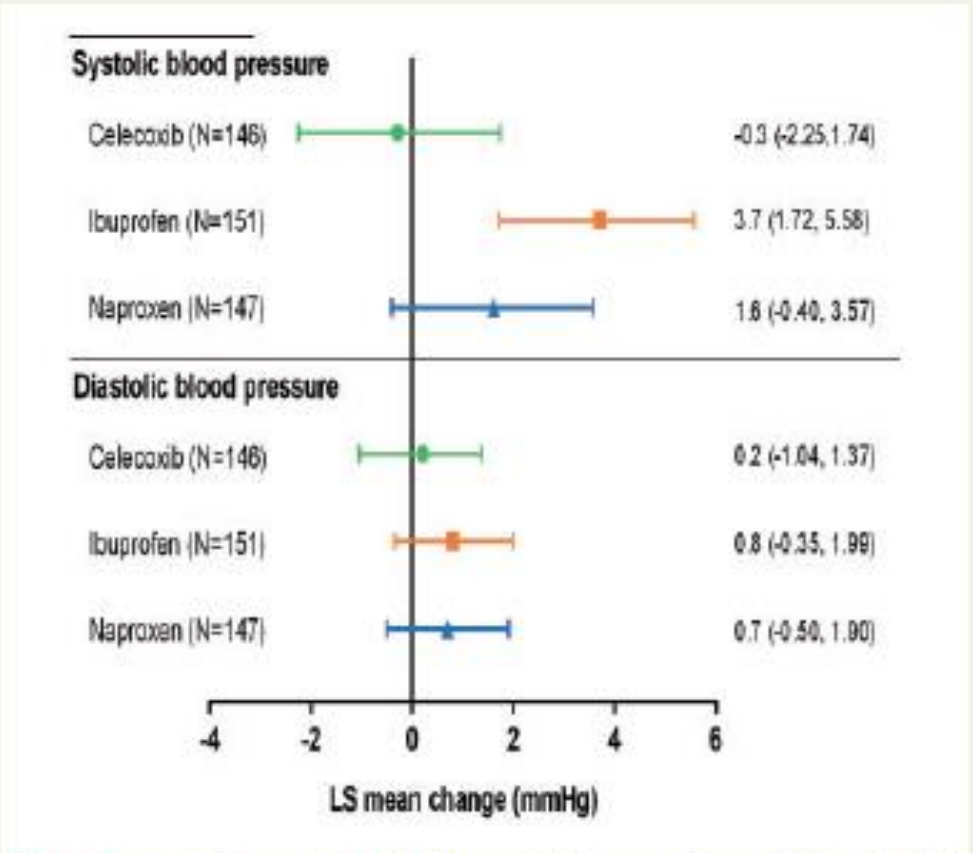


Figure Change in ambulatory 24-h systolic and diastolic BP from baseline at 4 months. These changes resulted in difference of -3.9 mmHg (95% CI, -6.19, -1.61; $P \leq 0.001$) between celecoxib and ibuprofen; differences of -1.8 mmHg (95% CI, -4.15, 0.47; $P = 0.12$) between celecoxib and naproxen, and of -2.1 mm Hg (95% CI, -4.36, 0.23; $P = 0.08$) between naproxen and ibuprofen.

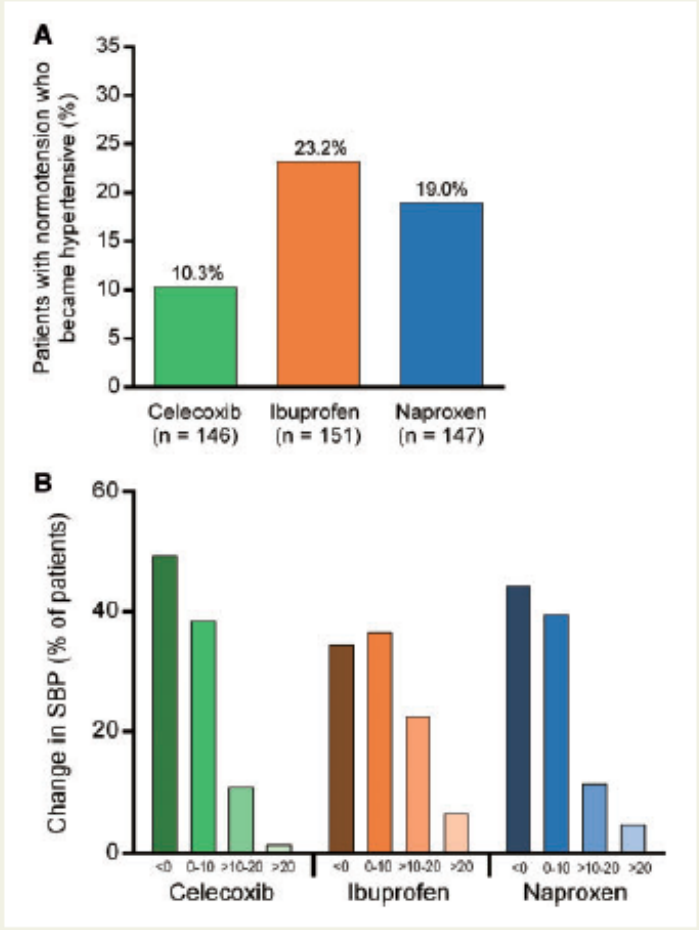


Figure *(A)* The percentage of patients with baseline normotension who developed hypertension was significantly greater for both ibuprofen and naproxen than for celecoxib ($P = 0.004$ and $P = 0.035$, respectively). *(B)* Compared with celecoxib, the ibuprofen treatment groups had larger proportions of patients whose 24-h SBP increased ($P = 0.003$). There was no significant difference between celecoxib and naproxen ($P = 0.07$).

Ruschitzka F et al. Eur Heart J. 2017 ; 38 (44) : 3282-3292

Changes in blood pressure and other cardiovascular effects with NSAIDs

Medication	*Change in systolic blood pressure (mm Hg; 95% CI)*	*Change in diastolic blood pressure (mm Hg; 95% CI)*	*Relative risk of hypertension vs. placebo (95% CI)*	*Rate ratio of myocardial infarction vs. placebo (95% credibility interval*)*	*Rate ratio of stroke vs. placebo (95% credibility interval*)*
Celecoxib (Celebrex)	2.6†	1.0†	1.2 (0.8 to 1.9)	1.4 (0.7 to 2.7)	1.1 (0.6 to 2.1)
Diclofenac	−0.5 (−1.5 to 0.6)	−0.56 (−1.2 to 0.07)	NA	0.8 (0.3 to 2.2)	2.9 (1.1 to 8.4)‡
Ibuprofen	3.5 (2.7 to 4.4)‡	1.2 (0.7 to 1.6)	2.8 (1.4 to 5.7)‡	1.6 (0.5 to 5.8)	3.4 (1.0 to 12)
Indomethacin	2.9 (−0.3 to 6.1)	1.6 (0.3 to 2.9)	NA	NA	NA
Nabumetone	1.7 (−0.02 to 3.4)	−0.1 (−1 to 0.86)	1.5 (0.5 to 4.5)	NA	NA
Naproxen (Naprosyn)	0.73 (−1 to 2.5)	−0.14 (−1.2 to 0.86)	2.1 (0.97 to 4.4)	0.8 (0.4 to 1.7)	1.8 (0.9 to 3.3)
Sulindac (Clinoril)	1.5 (−1.2 to 4.3)	0.17 (−1.3 to 1.7)	NA	NA	NA

CI = confidence interval; NA = not available.

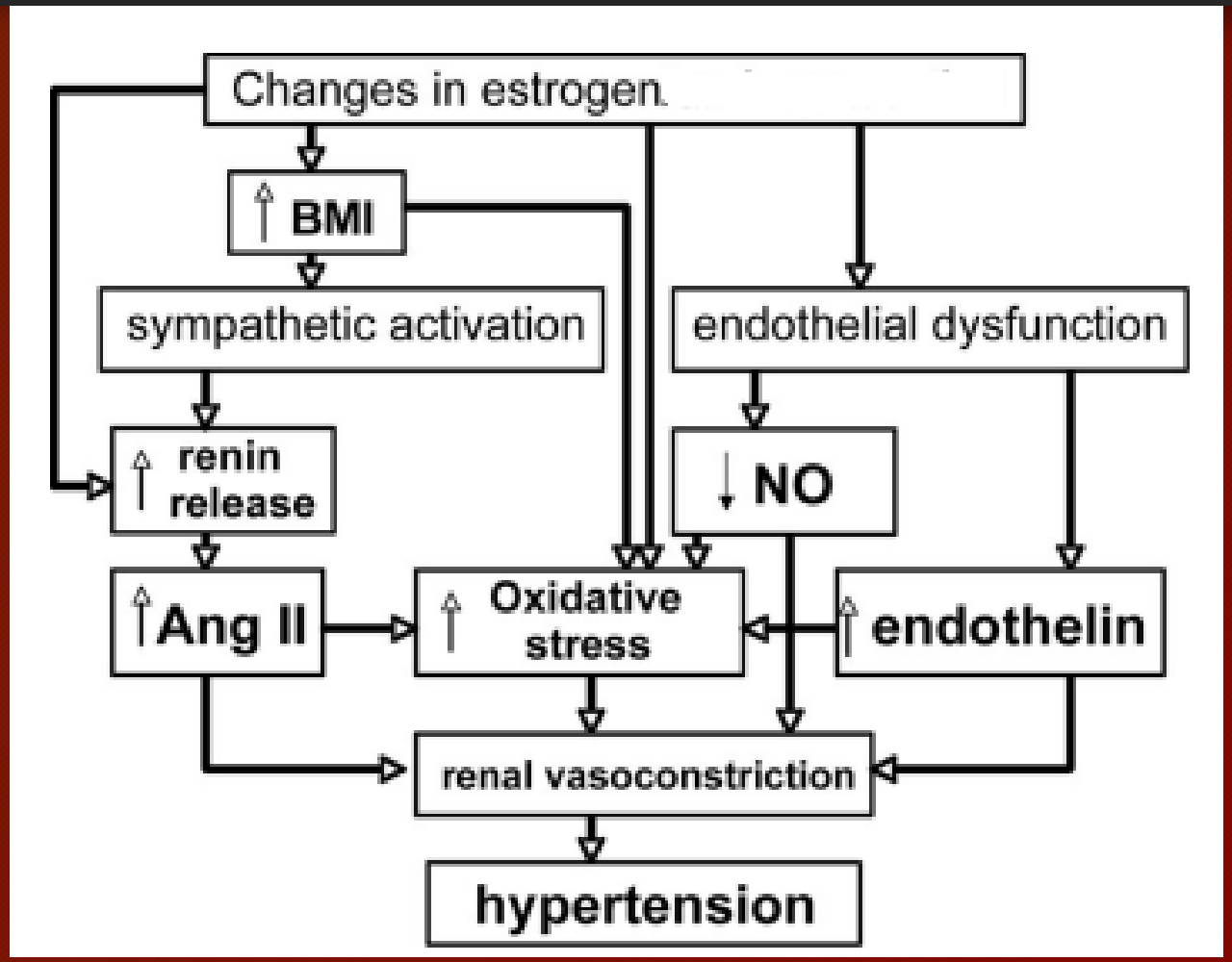
**—Bayesian credibility intervals may be interpreted as conventional CIs because the study authors assumed minimally informative prior distributions.*

†—*The meta-analysis did not give statistics for mean blood pressure changes resulting from treatment with celecoxib compared with baseline.*

‡—*Statistically significant.*

Sherve K et al.Am fam physician. 2014 Aug 15;90(4): 256A- 256B.

Mechanism of hypertension with oral contraceptive pills



Coylewright M et al. Hypertension. 2008;51(4):952-959

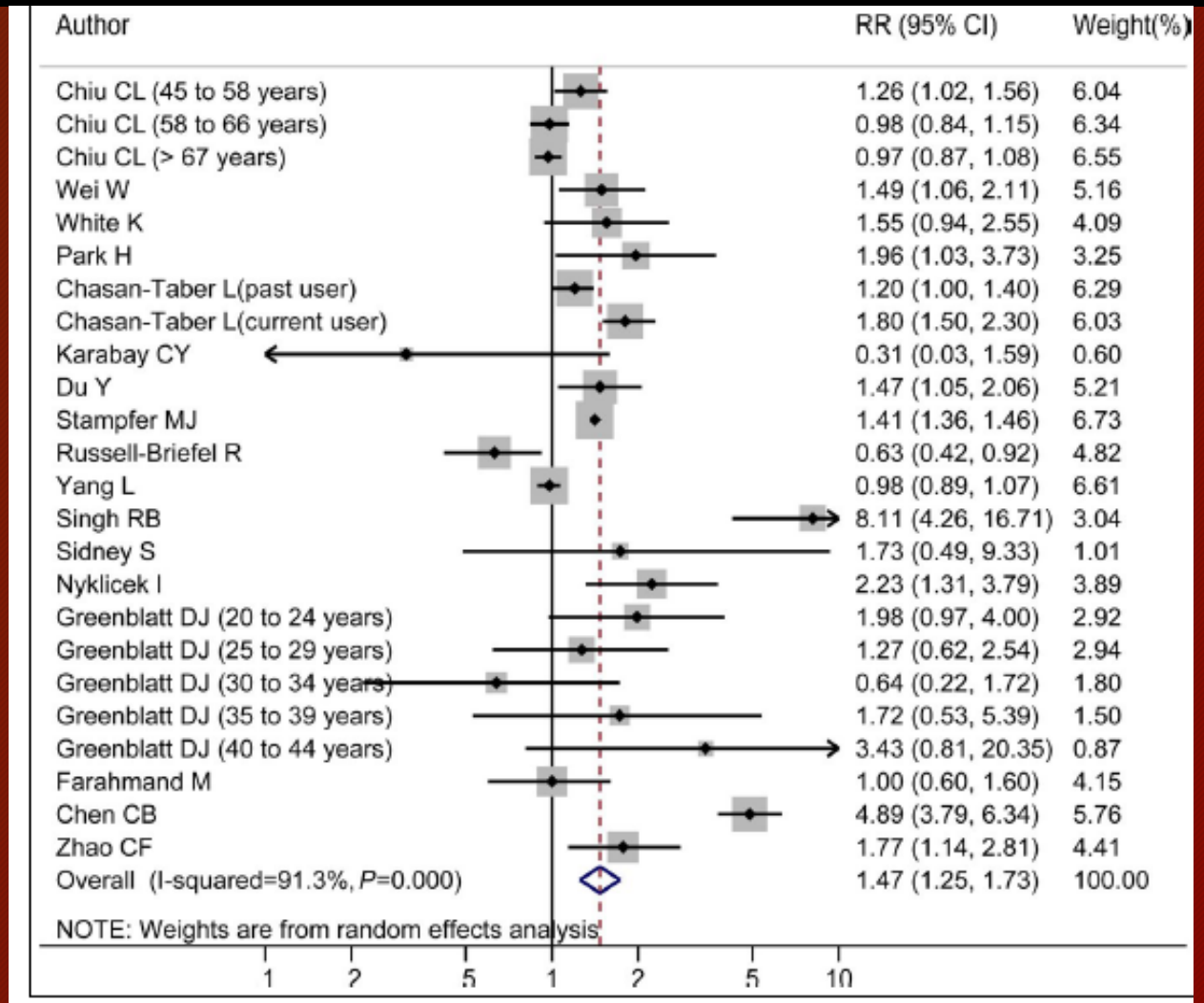
Clinical trials on hypertension with oral contraceptive pills

Modification of 24-h ambulatory blood pressure and heart rate during contraception with the vaginal ring: a prospective study	2013 English	Cross-sectional Healthy women (N = 18).	Blood pressure was monitored every 30 minutes for 41 hours, with an oscillometric device. Each participant used vaginal rings for six cycles, and pressure measurements were taken in the last days of the sixth cycle.	The results showed increased values in the 24h monitoring for diastolic pressure and average pressure. Even the smaller dose of estrogen, as contained in the vaginal ring, can stimulate the synthesis of angiotensinogen.
Associations between oral contraceptive use and risks of hypertension and prehypertension in a cross-sectional study of Korean women	2013 English	Retrospective and observational Women, selected from a database (N = 3,356).	Information on sociodemographic characteristics and use of oral contraceptive were collected, including time of use. Blood pressure was measured while the women were in a sitting position with their back supported, after 5 minutes of rest. A mercury gauge was used in the right arm, and three measurements were carried out. The final value was the average of the last two measurements.	The average of systolic and diastolic pressures was higher in participants who have been using oral contraceptive for longer periods. In addition, there was a significant relationship between time of use of contraceptives and prevalence of hypertension: 34.8% in the group of users for more than 24 months, against 18.1% in the group of non-users. The same relationship was observed for the prevalence of prehypertension.

CVA – Cerebrovascular Accident, CHC – Combined Hormonal Contraceptives, COC – Combined Oral Contraceptives, SAH – Systemic Arterial Hypertension; RAAS – Renin-Angiotensin-Aldosterone System.

Ribeiro CC et al. Rev Bras Enferm. 2018;71(3) : 1453-9.

Clinical trials on hypertension with oral contraceptive pills



Forest plot of oral contraceptive use and risk of hypertension. White diamond denotes the pooled RR. The size of gray box is positively proportional to the weight assigned to each study. Black point indicates the RR in each study, and the horizontal lines represent the 95% confidence intervals (CIs).

Liu H et al. J Clin Hypertens (Greenwich). 2017 ; 19 (10) : 1032-1041

Mechanism of hypertension with antidepressants

- Tricyclic antidepressants (TCAs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are associated with elevations in blood pressure.
- Hypertension occurs through an increase in norepinephrine and sympathetic activity.
- Venlafaxine is associated with dose-related increase in blood pressure.
- Bupropion is another common antidepressant that increases blood pressure through dopaminergic pathways.

Lovell AR et al. Curr Hypertens Rep (2017) 19:39.

Blood pressure effects of antidepressant drugs.

Class	Examples	Blood pressure effect
SSRIs	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	No change
Tricyclics	Amitriptyline, desipramine, imipramine, nortriptyline	Increase
SNRIs	Venlafaxine, duloxetine	Greater increase
NDRIs	Bupropion	No change
CRIRBs	Trazodone, nefazodone, maprotiline, mirtazapine	Increase, no change
MAO	Phenelzine, tranylcypromine	Increase

Association of hypertension with depression makes these data very difficult to quantitate. CRIRB: Combined reuptake inhibitors and receptor blocker; MAO: Monoamine oxidase inhibitor; NDRI: Norepinephrine–dopamine reuptake inhibitor; SNRI: Serotonin–norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

Sander GE. Therapy. 2011; 8(3) : 275-282

Antidepressant medication and effect on BP

Variable	Total (n = 6244)	No ADM (n = 4182)	ADM-BP− (n = 1008)	ADM-BP+ (n = 1054)	P Value
Hypertension, cumulative incidence	774 (12.4)	507 (12.1)	125 (12.4)	142 (13.5)	.494
Age (years), mean (SD)	46.4 (15.6)	46.0 (16.0)	47.2 (15.7)	47.2 (13.8)	.012
White race	4297 (68.8)	2713 (64.9)	772 (76.6)	812 (77.0)	<.0001
Female sex	3949 (63.2)	2449 (58.6)	706 (70.0)	794 (75.3)	<.0001
Married	2968 (47.5)	2058 (49.2)	426 (42.3)	484 (45.9)	<.001
High neighborhood SES	3649 (58.4)	2378 (56.9)	618 (61.3)	653 (62.0)	.001
High clinic utilization	1380 (22.1)	628 (15.0)	297 (29.5)	455 (43.2)	<.0001
Current smoker	1164 (18.6)	620 (14.8)	214 (21.2)	330 (31.3)	<.0001
Substance use disorder	190 (3.0)	65 (1.6)	51 (5.1)	74 (7.0)	<.0001
Depression	771 (12.4)	24 (0.6)	337 (33.4)	410 (38.9)	<.0001
Any anxiety disorder	665 (10.7)	92 (2.2)	289 (28.7)	284 (26.9)	<.0001
Obese	2365 (37.9)	1480 (35.4)	413 (41.0)	472 (44.8)	<.0001
Hyperlipidemia	1429 (22.9)	898 (21.5)	261 (25.9)	270 (25.6)	.001
Type 2 diabetes	391 (6.3)	228 (5.4)	79 (7.8)	84 (8.0)	.001
Vascular disease	605 (9.7)	356 (8.5)	110 (10.9)	139 (13.2)	<.0001

Data are n (%) unless otherwise indicated.
ADM, antidepressant medication; BP−, no effect on blood pressure; BP+, increases blood pressure; SD, standard deviation; SES, socioeconomic status.

Breeden M et al. J Am Board Fam Med 2018;31:22-28

Mechanism of Other drugs causing hypertension

- Corticosteroids: Act on mineralocorticoid receptors increasing sodium resorption and fluid retention.
- Decongestants: Stimulate the alpha-1 adrenergic receptors on vascular smooth muscle and causing vasoconstriction .
- Caffeine :Increases catecholamine release, and antagonizes endogenous adenosine which is responsible for vasodilation of coronary vessels
- Cocaine: Prevents the peripheral re-uptake of norepinephrine, leaving the neurotransmitter in the synapse to excessively stimulate adrenergic receptors causing potent vasoconstriction
- Psychostimulants: Increase the amount of norepinephrine in presynaptic nerve terminals causing adrenergic activation and vasoconstriction

Lovell AR et al. Curr Hypertens Rep. 2017; 19:39

Mechanism of Other drugs causing hypertension

- Calcineurin Inhibitors: Reduce the amount of nitric oxide production, inhibiting vasodilation and causing systemic and renal vasoconstriction as well as sodium retention in the kidneys
- VEGF Inhibitors : Decreases nitric oxide production and stimulating endothelin-1 receptors promoting vasoconstriction
- Erythropoietin : Raise the cytosolic calcium content in vascular smooth muscle cells, activate the local RAAS system, increase ET-1 production, decrease nitric oxide synthesis, and increase vasoconstriction
- Alcohol: Stimulates the sympathetic nervous system, activating RAAS, or abnormal calcium mediated vasoconstriction

Lovell AR et al. Curr Hypertens Rep. 2017; 19:39

Herbal Products Contributing to Hypertension

Common Name	Latin Name	Common Uses	Mechanism
Arnica	*Arnica montana*	Antiinflammatory, analgesic, antiseptic	Unclear
Bitter orange	*Citrus auranti um*	Sedative, sore throat, gastritis, gout	α_1-adrenergic receptor
Blue cohosh	*Caulophyllum thalictroides*	Amenorrhea, dysmenorrhea	Alkaloid effect
Ephedra	*Ephedra sinica*	Energy, weight loss, decongestant	Stimulating adrenergic receptor
Ginkgo	*Ginkgo biloba*	Vertigo, tinnitus, symptomatic relief of organic brain dysfunction	Unclear
Ginseng	*Panax* species	Cachexia, anxiety, impotence, neuralgia, insomnia	Unclear
Guarana	*Paullinia cupana*	Headache, dysmenorrhea, energy	Caffeine (purinergic stimulant)
Licorice	*Glycyrrhiza glabra*	Gastritis, cough, bronchitis, constipation	Inhibiting 11-β-HSD*
Pennyroyal oil	*Mentha pulegium*	Amenorrhea, gout, colds	Unclear
Scotch broom	*Cytisus scoparius*	Cardiac arrhythmia, pathologic edema	Sparteine alkaloid effect
Senna	*Cassia senna*	Constipation	Hyperaldosteronism
Southern bayberry	*Myrica cerifera*	Antipyretic, circulatory stimulant, astringent	Mineralocorticoid side effect
St. John's wort	*Hypericum perforatum*	Anxiety, depression, insomnia, infection, pain	MAOI* activity
Yohimbine	*Pausinystalia yohimbe*	Impotence, aphrodisiac, fat loss	α_2-adrenoreceptor block

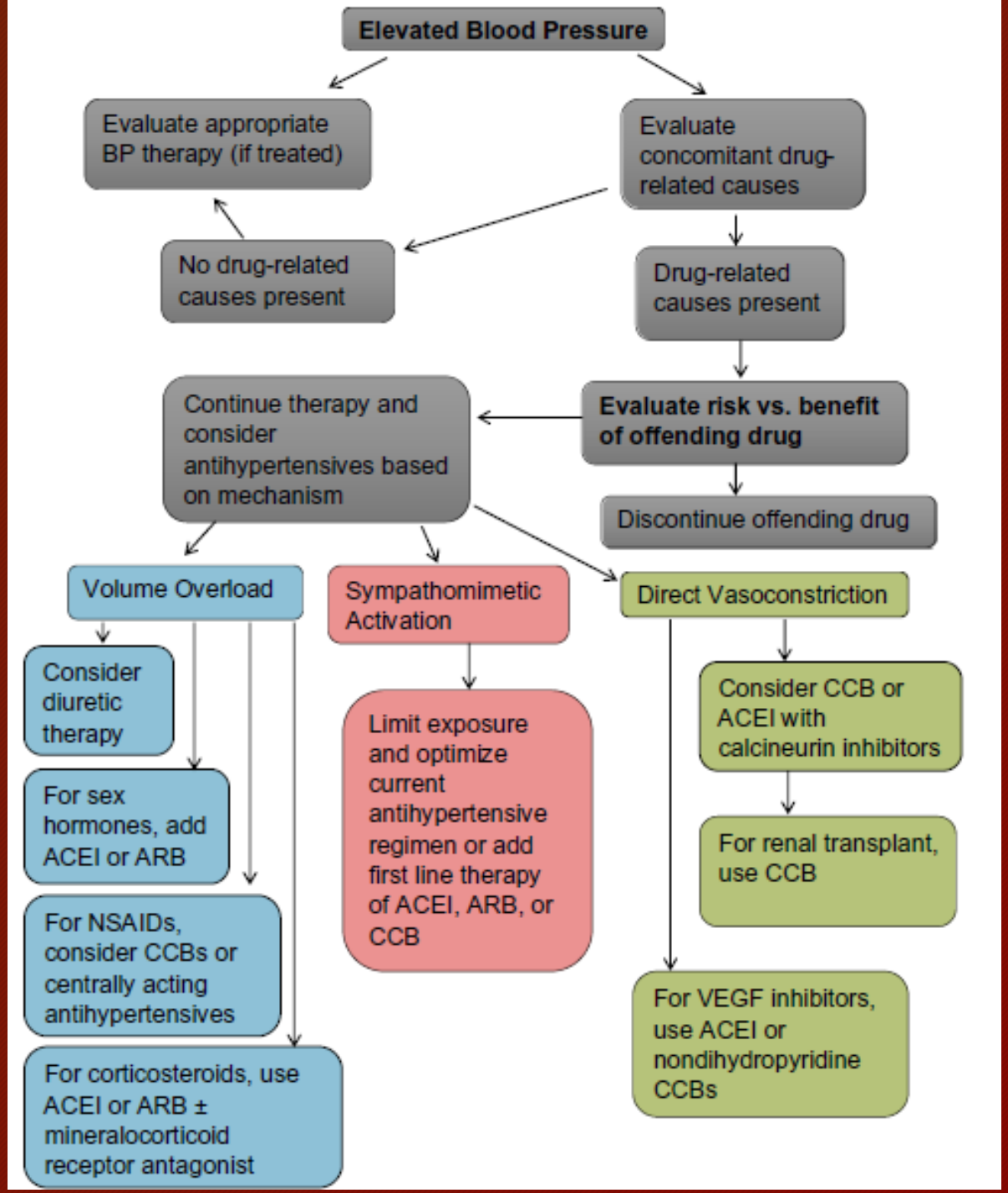
Jalili J et al. Plast Reconstr Surg. 2013;131(1):168-173

Herbal Products Contributing to Hypertension

Common Name	Latin Name	Common Uses	Mechanism
Areca nut	*Areca catechu*	Cystitis, dysuria, diuretic effect	Agonist of muscarinic acetylcholine receptors
Belladonna	*Atropa belladonna*	Hyperkinesis, hyperhidrosis	Anticholinergic and increases dopamine activity
Calamus	*Acorus calamus*	Spasmolytic, carminative, sedative effects	Alkaloid effect
Chilli pepper	*Capsicum* species	Muscular tensions, rheumatism	Increased catecholamine secretion
Coltsfoot	*Tussilago farfara*	Asthma, bronchitis, laryngitis	Pressor activity and pyrrolizidine alkaloid effect
Goldenseal	*Hydrastis canadensis*	Gastritis, peptic ulceration, menorrhagia	Hydrastine alkaloid effect
Henbane	*Hyoscyamus niger*	Dyspeptic complaints, asthma	Anticholinergic and increases dopamine activity
Jimson weed	*Datura stramonium*	Asthma, convulsive cough	Anticholinergic and increases dopamine activity
Khat	*Catha edulis*	Depression, headache, gonorrhea, gastric	Release of monoamines
Lobelia	*Lobelia inflata*	Bronchitic asthma, bronchitis	Agonist of nicotinic acetylcholine receptors
Mandrake	*Mandragora officinarum*	Colic, asthma, homeopathy	Anticholinergic and increase dopamine activity
Mate	*Ilex paraguariensis*	Depression, rheumatic pains, fatigue	Caffeine (purinergic stimulant)
Scopolia	*Scopolia* species	Liver and gallbladder complaints	Anticholinergic and increases dopamine activity
Vervain	*Verbena officinalis*	Depression, antispasmodic, antitussive	Unclear

Jalili J et al. Plast Reconstr Surg. 2013;131(1):168-173

Management of drug induced hypertension



Lovell AR et al. Curr Hypertens Rep. 2017; 19:39

Summary

- Exacerbators and inducers of hypertension interfere with antihypertensive medications.
- All patients are screened (with hypertension and those at risk for hypertension) for substances
- Appropriate reduction or eliminating substances that raise BP is important to regulate hypertension.
- Substances or drugs if really required then BP is controlled with alteration in the dosage or addition of another drug to achieve target BP.