

**Φαρμακευτική αγωγή στην
υπέρταση: Είναι όλοι οι
παράγοντες εξίσου
αποτελεσματικοί;**

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Νεφρολόγος**



- ~1 in 3 adults have high BP in USA
- 49,707 deaths in 2002
- contributing cause to 261,000 deaths in 2002
- ~40% African-Americans have high BP
- 30% of people with high BP don't know it
- no symptoms!



2017 Guideline for High Blood Pressure in Adults

Nov 13, 2017

BP should be categorized as normal, elevated, or stages 1 or 2 hypertension to prevent and treat high BP

Normal BP is defined as $<120/<80$ mm Hg; **elevated BP** 120-129/ <80 mm Hg; **hypertension stage 1** is 130-139 or 80-89 mm Hg, and **hypertension stage 2** is ≥ 140 or ≥ 90 mm Hg.

A 20 mm Hg higher SBP and 10 mm Hg higher DBP are each associated with a doubling in the risk of death from stroke, heart disease, or other vascular disease.

It is important to screen for and manage other CVD risk factors in adults with hypertension:

smoking,

diabetes,

dyslipidemia,

excessive weight,

low fitness,

unhealthy diet,

psychosocial stress, and

sleep apnea



Nonpharmacologic interventions to reduce BP include:

weight loss for overweight or obese patients with a heart healthy diet,

sodium restriction, and potassium supplementation within the diet;

and increased physical activity with a structured exercise program.



Men should be limited to no more than 2 and women no more than 1 standard alcohol drink(s) per day.

The usual impact of each lifestyle change is a 4-5 mm Hg decrease in SBP and 2-4 mm Hg decrease in DBP; but diet low in sodium, saturated fat, and total fat and increase in fruits, vegetables, and grains may decrease SBP by approximately 11 mm Hg.



Effectiveness of Drug Therapy in Hypertension: Present Status

A REVIEW

By Edward D. Freis, M.D.

ABSTRACT

Progress in the development of effective antihypertensive agents is briefly reviewed. Evidence that drug treatment reduces the incidence of major complications is presented. The recently completed controlled trial carried out in Veterans Administration hospitals indicates that in men with diastolic blood pressure levels of 90 through 114 mm Hg the risk of developing a morbid event over a five-year period was reduced from 55% to 18% by treatment. The degree of benefit was proportional to the risk, which in turn was related directly to the level of blood pressure.

KEY WORDS essential hypertension antihypertensive drugs
hydrochlorothiazide reserpine hydralazine

■ The interplay of pathogenetic factors that result in hypertension still remains unknown for most patients with this disorder. Nevertheless, it has been suspected for some years that regardless of etiology the cardiovascular complications producing disability or death in hypertension are the direct result of the elevated blood pressure. This has led to the hypothesis that reduction of blood pressure by pharmacological agents, even though nonspecific, will prevent the major complications of the disease. The present review attempts to summarize the available evidence bearing on this hypothesis. Particular emphasis will be given to the results of the Veterans Administration (VA) Cooperative Study, a recently completed controlled trial in patients with essential hypertension.

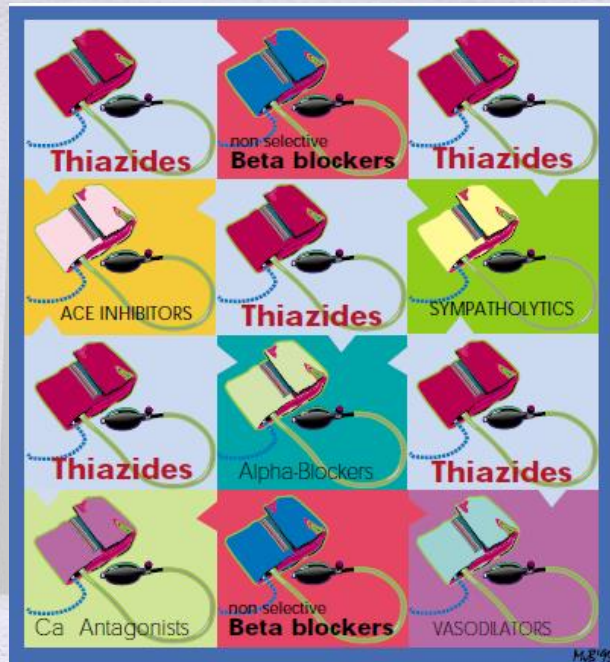
Historical Perspective

Although it was demonstrated even prior to 1950 that in a few isolated patients antihypertensive agents could reverse the malignant phase of hypertension and hypertensive congestive heart failure,^{1,2} it was not until the advent of hexamethonium that a practical (if somewhat troublesome) method was available

for the treatment of severe hypertension.^{3,4} With the advent of hydralazine,^{5,6} these two drugs with different sites of action were combined to obtain an enhanced antihypertensive effect.⁷ *Rauwolfia serpentina* then became popular as a treatment for less severe forms of hypertension,⁸ although its initial enthusiastic reception was somewhat dampened by the realization that the *Rauwolfia* alkaloids could induce emotional depression.⁹ A great step forward was made when the thiazide diuretics became available¹⁰; these not only had antihypertensive properties of their own, but also enhanced the effectiveness of other antihypertensive drugs.^{11,12} Guanethidine, by producing a selective sympathetic blockade, replaced the formerly used ganglion-blocking drugs in the management of patients with severe forms of hypertension.^{13,14} The therapeutic armamentarium was further broadened by the advent of alpha-methyl-dopa, which has proved useful in all forms of hypertension.¹⁵

By 1960 a choice of effective and fairly well-tolerated antihypertensive agents were available for controlling blood pressure. Controlled comparative drug trials demonstrated that the antihypertensive effects of these agents were additive and that combinations usually provided better control with fewer disturbing

From the Veterans Administration Hospital, Washington, District of Columbia 20422.



Our process is easy

The benefit of pharmacologic treatment for BP reduction is related to atherosclerotic CVD (ASCVD) risk

For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher, a BP target of <130/80 mm Hg is recommended

Follow
-up



Thiazide Diuretics

mechanism of action

lower plasma volume

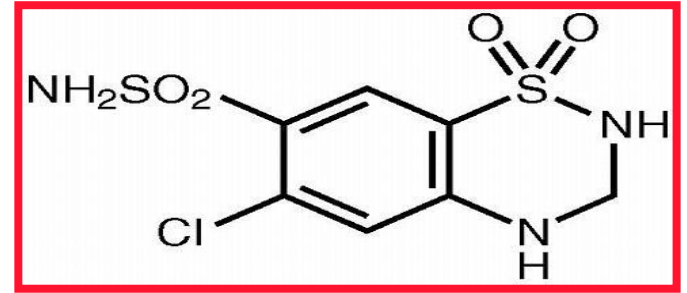
monotherapy for mild to moderate hypertension

ALLHAT: reduction of CVD superior to other agents

adjunct agent

most effective in patients with normal kidney function

Chlorthalidone (12.5-25 mg) is the preferred diuretic because of long half-life and proven reduction of CVD risk



Hydrochlorothiazide

Considerations

long-term hypokalemia: increases mortality

include K⁺ sparing diuretic in therapy

most efficacious in “low-renin” or volume-expanded forms of hypertension

very effective in African-American patients

mostly well tolerated

cheap!

Loop diuretics are preferred in HF and when glomerular filtration rate (GFR) is <30 ml/min.

Amiloride and triamterene can be used with thiazides in adults with low serum K^+ , but should be avoided with GFR <45 ml/min.

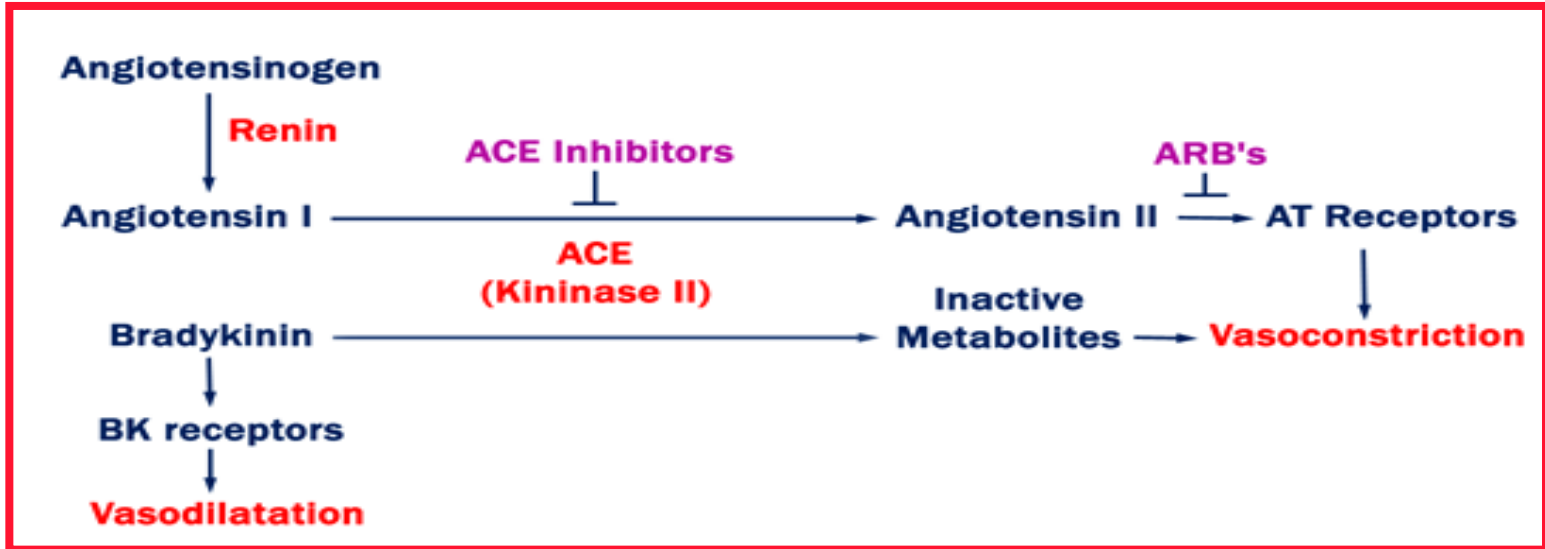
Spironolactone or eplerenone is preferred for the treatment of primary aldosteronism and in resistant hypertension



Drugs interacting with Renin-Angiotensin system

Angiotensin-converting enzyme inhibitors (ACE): inhibit Angiotensin II formation

Angiotensin-receptor blockers (ARBs) : block Angiotensin receptor activation



Systemic Effects of ACE inhibitors

Reduction in

total peripheral resistance

systolic and diastolic pressure

mean arterial pressure

aldosterone secretion

cardiac remodeling

Increase in

regional blood flow in vascular beds

large artery compliance

Therapeutic Uses

initial choice for mild to moderate hypertension

drug of choice for hypertension due to diabetes mellitus

most effective in high renin patients

more effective in caucasian patients

excellent for patients with hypertension secondary to CHF, arrhythmias, kidney disease

efficacy enhanced by diuretics

Side Effects

hypotension

cough

hyperkalemia

angioedema

renal insufficiency

teratogenic

skin rash

neutropenia

proteinuria (protein in urine)

ageusia (loss of taste)



Therapeutic Uses ARBs

same uses as ACE inhibitors

excellent for inhibiting cell growth

no bradykinin effects

no cough

useful for hypertension secondary to CHF

used for prevention of re-stenosis after angioplasty

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and direct renin inhibitors should not be used in combination.

ACE inhibitors and ARBs increase the risk of hyperkalemia in CKD and with supplemental K^+ or K^+ -sparing drugs.

ACE inhibitors and ARBs should be discontinued during pregnancy.



Adrenergic receptor antagonists

β -adrenergic receptor antagonists

“ β -blockers”

Non-selective: Propranolol, Nadolol, Timolol, Pindolol, Labetolol

Cardioselective: Metoprolol, Atenolol, Esmolol, Betaxolol

α 1-adrenergic receptor antagonists

“ α -blockers”

Non-selective: Phentolamine, Phenoxybenzamine, Dibenamine

Selective: Prazosin, Doxazosin, Terazosin

β -blockers: Therapeutic Uses

Used as monotherapy

reduce cardiac output

reduce renin release

CNS effects: reduce SNS outflow

Most effective in high-renin hypertension

Used in hypertensive patients with coronary insufficiency

Non-selective and cardioselective drugs are equally effective for lowering BP

Cheap!

β -blockers: Considerations

Intrinsic sympathomimetic activity

Pindolol, Acebutolol, Penbutolol: partial β_2 -AR agonism

Mixed antagonism

Labetolol, Carvedilol: β - and α -adrenergic receptor antagonists

Differences in ability to penetrate CNS

Propranolol readily enters CNS

Sotalol unable enter CNS

β -blockers: Side Effects

Bradycardia

Bronchospasm

Coldness of extremities

Heart failure

Contraindicated in insulin-dependent diabetes

CNS effects

Increased plasma triglyceride concentration

Decreased plasma HDL concentration

Do not use in conjunction with Ca^{2+} channel blockers, conduction effects in heart

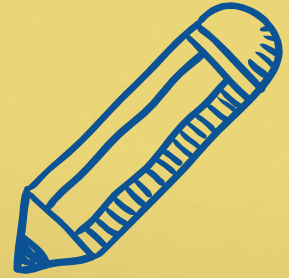
NSAID's blunt β -blocker effects

▪Beta-blockers are not first-line therapy except in CAD and HFrEF.

▪Abrupt cessation of beta-blockers should be avoided.

▪Bisoprolol and metoprolol succinate are preferred in hypertension with HFrEF and bisoprolol when needed for hypertension in the setting of bronchospastic airway disease.

▪Beta-blockers with both alpha- and beta-receptor activity such as carvedilol are preferred in HFrEF.



α -blockers: Therapeutic Uses

Mechanism of action: block vascular receptors

α 1-adrenergic

inhibit vasoconstriction

decrease total peripheral resistance

Non-selective blockers used for treatment of hypertensive crisis in pheochromocytoma

Selective α -blockers used as monotherapy or adjunct therapy in resistant patients

α -blockers: Side Effects

First dose phenomenon

hypotension

tachycardia

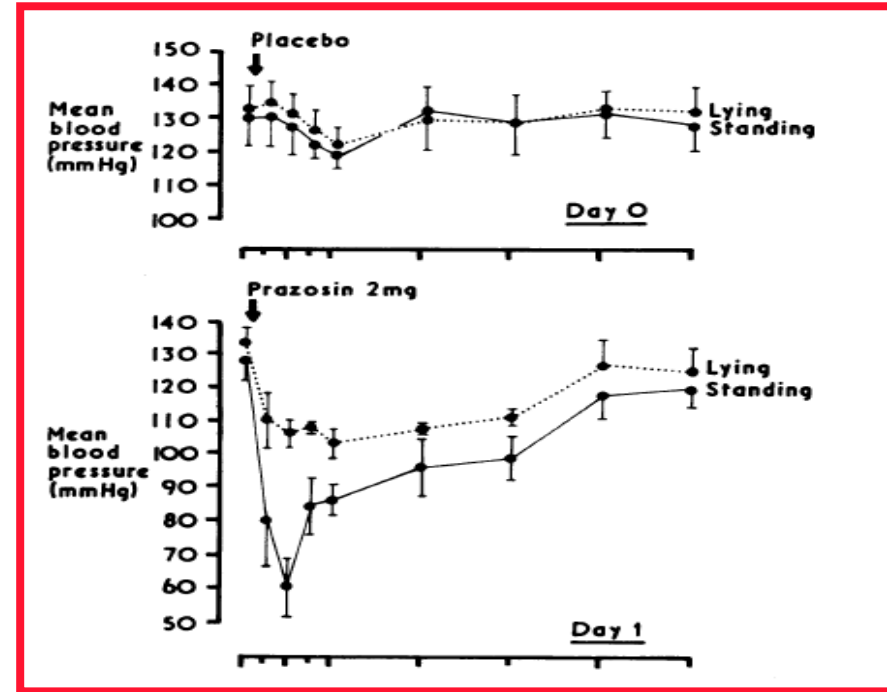
baroreceptor reflex

GI effects

Fluid retention

use with diuretic

ALLHAT study



Graham et al, BMJ, 1976

Centrally acting sympatholytics

Sympatholytics

Clonidine

α -methyldopa

Guanfacine

Guanabenz

Peripherally acting sympatholytics

Metyrosine

Guanethidine, Bretylium

Reserpine

CNS Sympatholytics

α 2-AR receptor agonists

act in CNS to reduce sympathetic neuron firing rate

nucleus of solitary tract

C1 neurons of rostral ventrolateral medulla

act on prejunctional sympathetic neurons in vascular tissue

autoreceptor on sympathetic neurons

prevent NE release

stimulate post-junctional α 2-ARs on vascular smooth muscle (I.V. only)

Therapeutic Uses

Reduce BP by lowering TPR and CO

Peripheral sympatholytics produce marked fluid retention and impairment of baroreceptor reflexes

use with diuretic

α 2-agonists effective in ALL patients

**clonidine used in diagnosis of pheochromocytoma:
reduces plasma NE < 500 pg/mL in tumor-free patients**

Adverse Effects

Hypotension

Sedation: ~ 50% of all patients

Dry mouth

Vivid dreams

Depression

Withdrawal

hypertension

tachycardia

nervousness, excitement

α -methyldopa specific effects

heart block

autoimmune: Lupus, leukopenia

hyperthermia

reduced mental acuity

Peripheral Sympatholytics

rarely used

Metyrosine (or α -methyl-tyrosine):

inhibits tyrosine hydroxylase

rate-limiting enzyme for NE synthesis

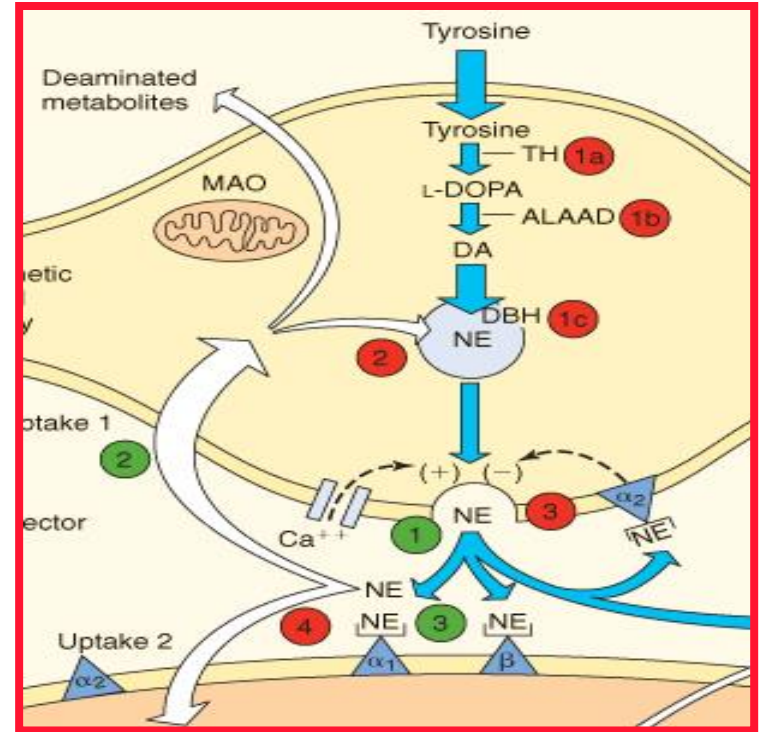
Bretylium, Guanethidine

uptaken into NE vesicle

prevent NE release from vesicle

Reserpine

inhibits accumulation of NE into vesicle



Ca²⁺ channel blockers (CCBs)

an initial choice for monotherapy of mild to moderate hypertension

all antagonists are equally effective for Stage 1 hypertension

Verapamil and Diltiazem do not cause reflex tachycardia

directly inhibit cardiac chronotropy

Effective in low-renin hypertension

African-americans

Elderly

Non-dihydropyridine CCBs are associated with bradycardia and heart block and should be avoided in HF with reserved EF HFrEF

Direct acting vasodilators

Hydralazine

liberates NO from vascular endothelium

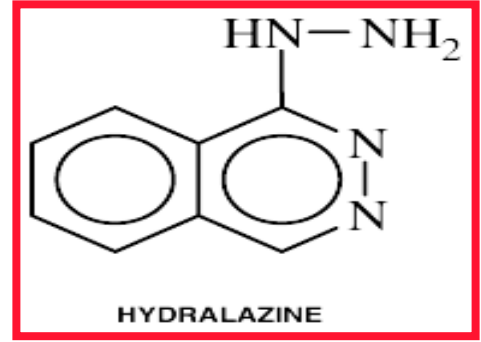
decreases TPR

not used as monotherapy

bioavailability dependent on genetic factors

adverse effects: tachycardia, hypotension, fluid retention, lupus-like syndrome

**only used in severe or refractory hypertension
are associated with sodium and water retention
and must be used with a diuretic and beta-blocker**



Minoxidil

Direct acting vasodilators

prodrug of N-O sulfate

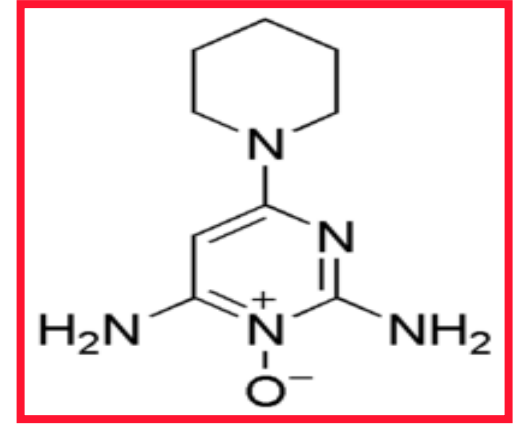
K⁺ channel opener, reduces smooth muscle contractility

not used as monotherapy

long duration of action (~24 hours)

adverse effects: tachycardia, fluid retention, hypertrichosis

only used in severe or refractory hypertension



Minoxidil

Instructions for use

Initial first-line therapy for stage 1 hypertension includes thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

Two first-line drugs of different classes are recommended with stage 2 hypertension and average BP of 20/10 mm Hg above the BP target.

Improved adherence can be achieved with once-daily drug dosing, rather than multiple dosing, and with combination therapy rather than administration of the free individual components

For adults with confirmed hypertension and known stable CVD or $\geq 10\%$ 10-year ASCVD risk, a BP target of $< 130/80$ mm Hg is recommended.

The strategy is to first follow standard treatment guidelines for CAD, HFrEF, previous MI, and stable angina, with the addition of other drugs as needed to further control BP.

In HFpEF with symptoms of volume overload, diuretics should be used to control hypertension, following which ACE inhibitors or ARBs and beta-blockers should be titrated to SBP < 130 mm Hg. Treatment of hypertension with an ARB can be useful for prevention of recurrence of atrial fibrillation



Instructions for use CKD

CKD: BP goal should be <130/80 mm Hg. In those with stage 3 or higher CKD or stage 1 or 2 CKD with albuminuria (>300 mg/day),

treatment with an ACE inhibitor is reasonable to slow progression of kidney disease.
An ARB is reasonable if an ACE inhibitor is not tolerated.



Pharmacotherapy for Hypertension in Patients with Diabetes

X For persons with cardiovascular or kidney disease, including microalbuminuria or with cardiovascular risk factors in addition to diabetes & hypertension, initial recommended therapy is an:

X Angiotensin converting enzyme (ACE) inhibitor or an Angiotensin receptor blocker (ARB)

X For persons with diabetes & hypertension not included in the above recommendation, appropriate choices include (in alphabetical order):

X ACE inhibitors

X Angiotensin Receptor Blockers (ARBs)

X Dihydropyridine calcium channel blockers (CCBs)

X Thiazide/thiazide-like diuretic

Hypertension & Diabetes: Key Messages

Up to 80% of people with diabetes will die of cardiovascular disease, especially stroke.

1. Ensure people with diabetes are screened for hypertension (blood pressure $\geq 130/80$ mmHg)
2. Assess blood pressure at all healthcare visits
3. Encourage home blood pressure monitoring with approved devices
4. Pharmacotherapy and lifestyle should be initiated **concurrently**
5. Assess and manage all other vascular risk factors
6. Enable sustained lifestyle modification and medication adherence

Conclusion is that some older patients are helped by antihypertensive medications while others are harmed. The questions for the clinician are as follows:

1. Which older patients should I treat?
2. How should I treat hypertension in the elderly?
3. What should I monitor?

A MATTER OF BALANCE



HOW SHOULD I TREAT HYPERTENSION IN THE ELDERLY?

- Evidence suggests that physical activity and weight control are also effective in the elderly
- Pharmacological management:
 - Beta blockers – OUT since British-MRC trial
 - Alpha blockers- OUT since ALLHAT
 - Diuretics, ACE-I's, CCB's – IN
 - ARB's – possibly only if ACE-I not tolerated

Conclusion

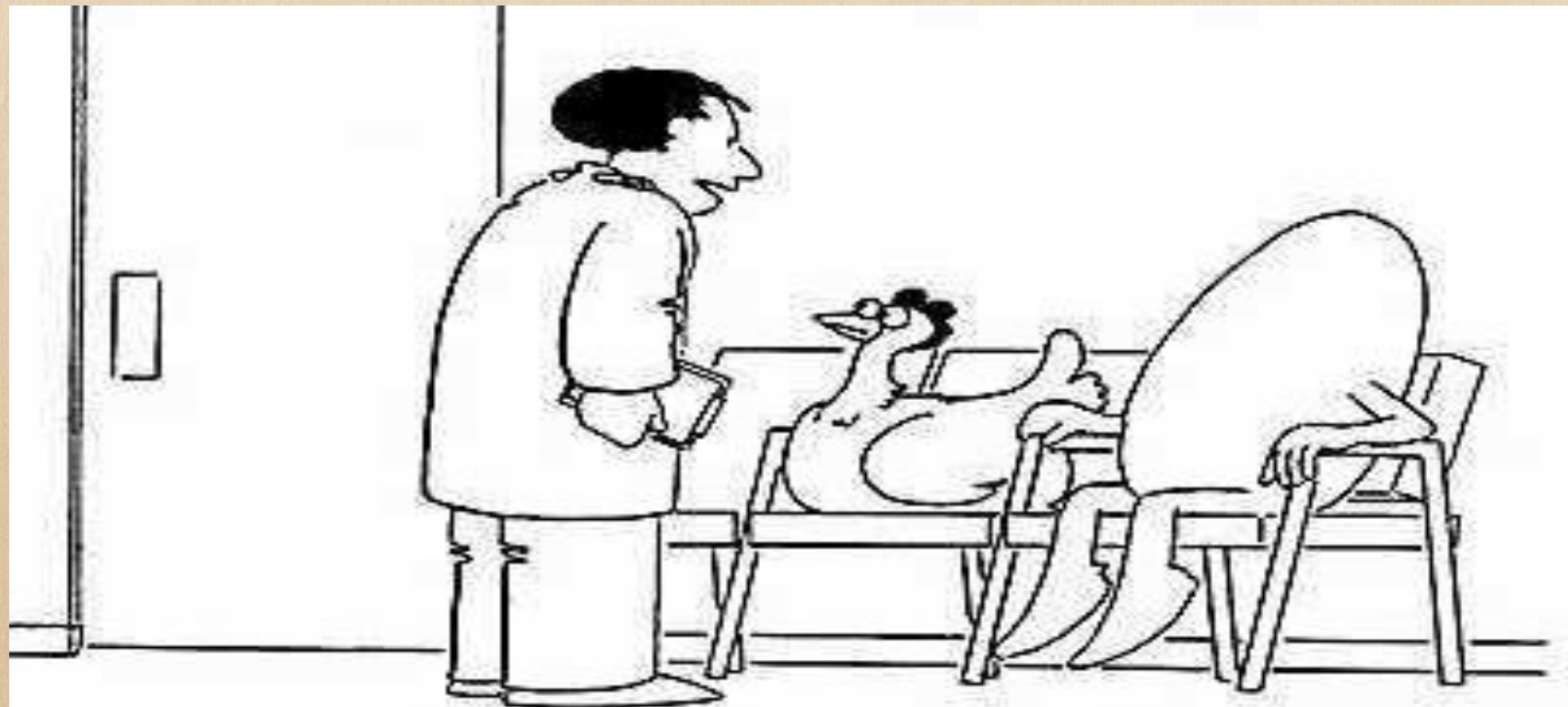
- X Every adult with hypertension should have a clear, detailed, and current evidence-based plan of care that ensures the achievement of treatment and self-management goals;
- X effective management of comorbid conditions;
- X timely follow-up with the healthcare team; and
- X adheres to CVD evidence-based guidelines.
- X Effective behavioral and motivational strategies are recommended to promote lifestyle modification.



Conclusion

- X A structured team-based approach including a physician, nurse, and pharmacist collaborative model is recommended, along with integrating home-based monitoring and telehealth interventions.
- X Outcome may be improved with quality improvement strategies at the health system, provider, and patient level.





"Who was first?"

Thanks!

Any questions?

