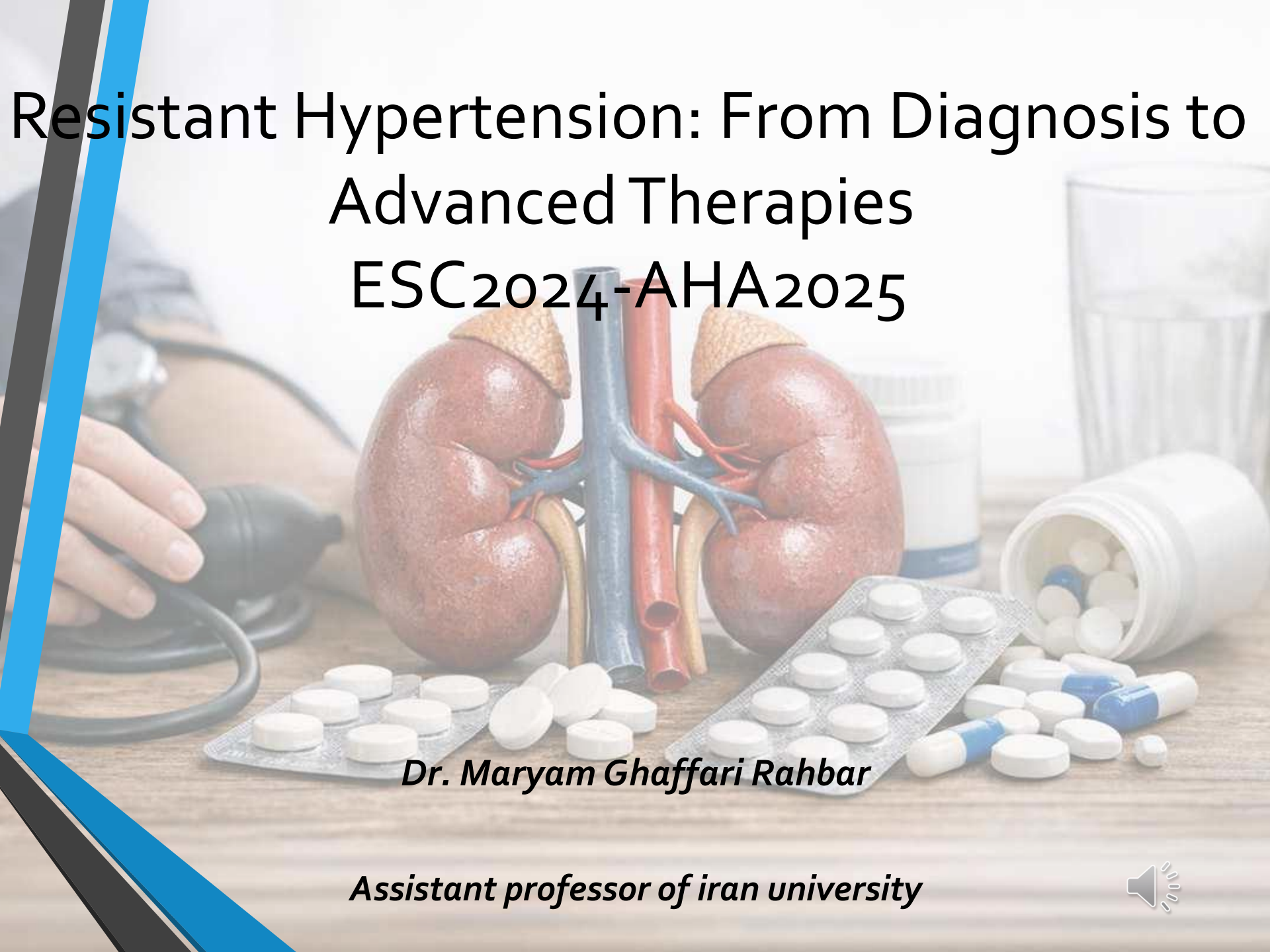
Resistant Hypertension: From Diagnosis to Advanced Therapies ESC2024-AHA2025



Dr. Maryam Ghaffari Rahbar

Assistant professor of iran university

Clinical Case

58-year-old male,

PMH :CKD, DM, HTN

BP 165/95 despite triple therapy

Valsartan 160 BID

Amlodipin 10 daily

Chlorthalidone 25 mg/day

Question:

Is this resistant hypertension?

Definition of Resistant Hypertension

BP above goal despite(<130/80)

ACEi/ARB + CCB + thiazide or thiazid-like diuretic (Indapamide or chlorthalidne)

all at maximally tolerated doses

OR

BP controlled with ≥4 medication

Definition of Refractory hypertension

uncontrolled blood pressure despite use of ≥5 antihypertensive agents of different classes, including a long-acting thiazide-like diuretic and an MR (mineralocorticoid receptor) antagonist at maximal or maximally tolerated doses

Epidemiology

Epidemiology

Prevalence: 8.5–20%

More common in:

- CKD
- Diabetes
- Obesity
- Older age
- OSA

Why dose RH matter?

Compared with controlled hypertension:

Stroke ↑ 14%

Heart failure ↑ 46%

ESRD ↑ 32%

Myocardial infarction ↑

Cardiovascular mortality ↑

47%

Mechanisms of Resistant Hypertension

Sodium retention

Volume overload

RAAS activation

Sympathetic activation

Aldosterone excess

Arterial stiffness

Pseudo vs True Resistant HTN

True Resistant HTN

Persistent uncontrolled BP after exclusion of:

Measurement errors

White coat effect

Poor adherence

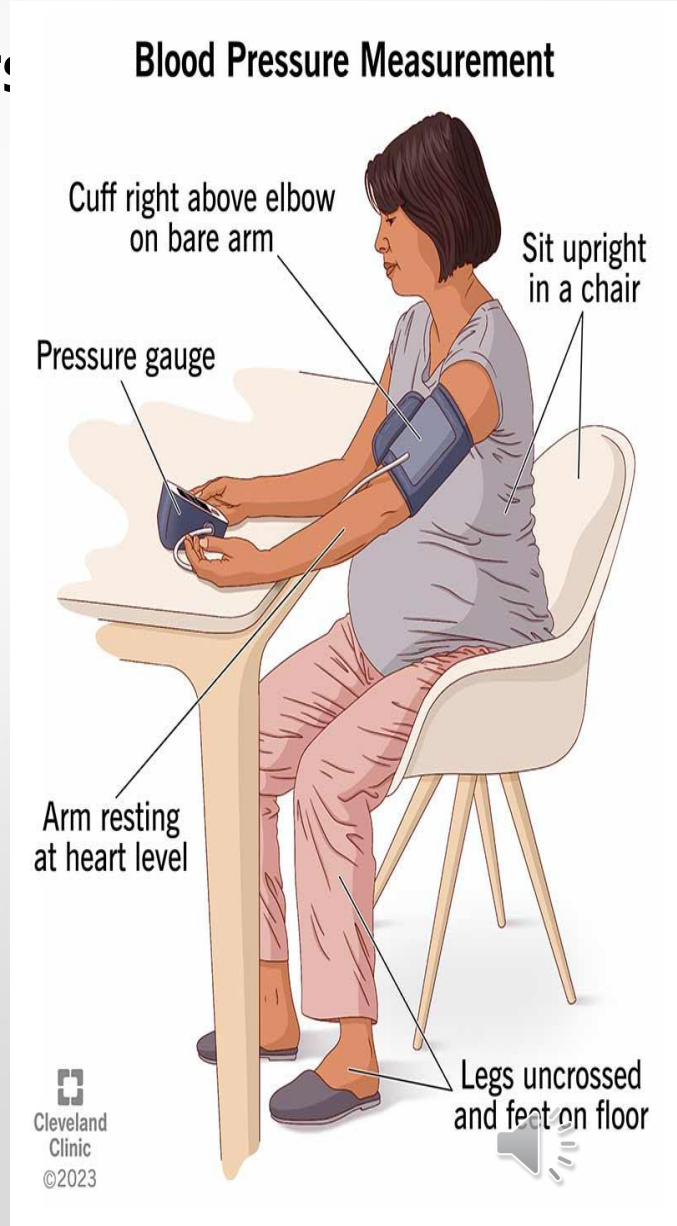
Drug interference

Osler phenomenon

BP Measurement Errors

Common BP Measurement Errors

- Inadequate rest
- Incorrect cuff size
- Talking during measurement
- Full bladder
- Unsupported back
- Crossed legs



White Coat Effect

Office BP elevated

but

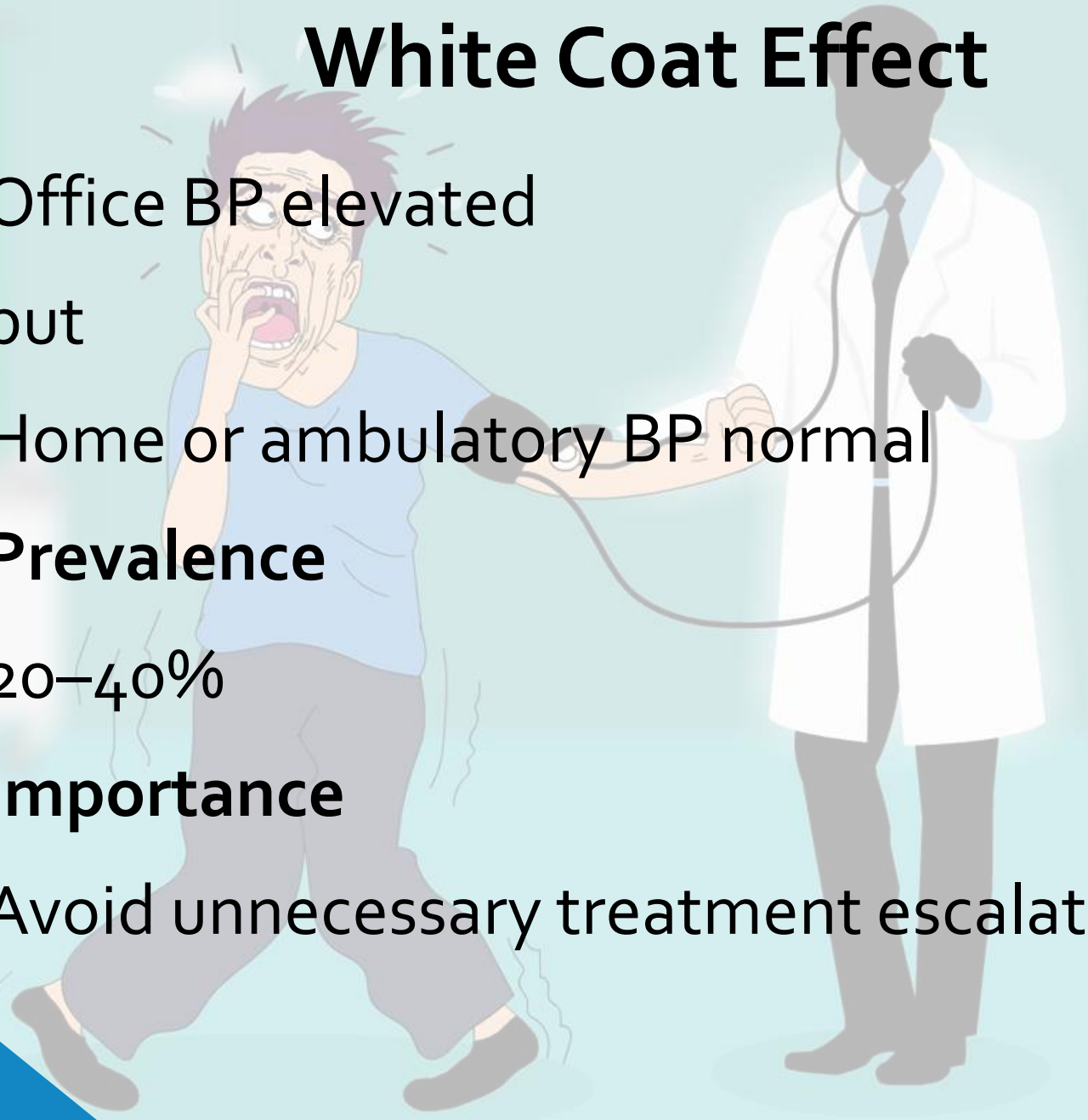
Home or ambulatory BP normal

Prevalence

20–40%

Importance

Avoid unnecessary treatment escalation



HBPM

Home Blood Pressure Monitoring (HBPM)

Protocol:

Morning and evening

2 measurements each time

7 consecutive days

Average excluding day 1

ABPM

Gold standard

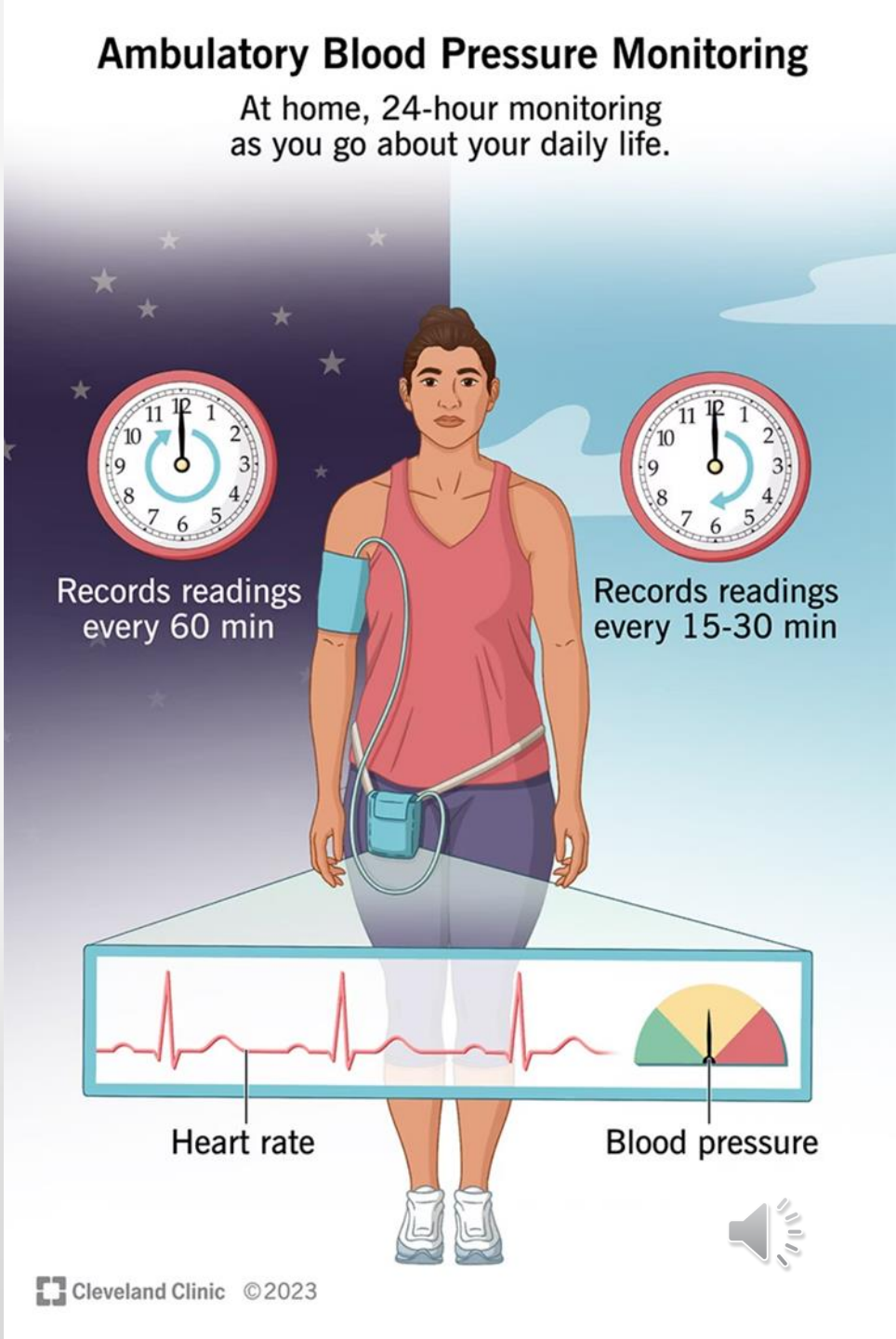
Provides:

24-hour BP

Daytime BP

Nighttime BP

Dipping status



Medication Nonadherence

Reasons:

- Pill burden
- Cost
- Side effects
- Complex regimens

Assessment:

- Patient interview
- Pharmacy refill records
- Pill counts
- Drug level testing

Drug-Induced HTN

Medications That Raise BP

NSAIDs

Corticosteroids

Oral contraceptives

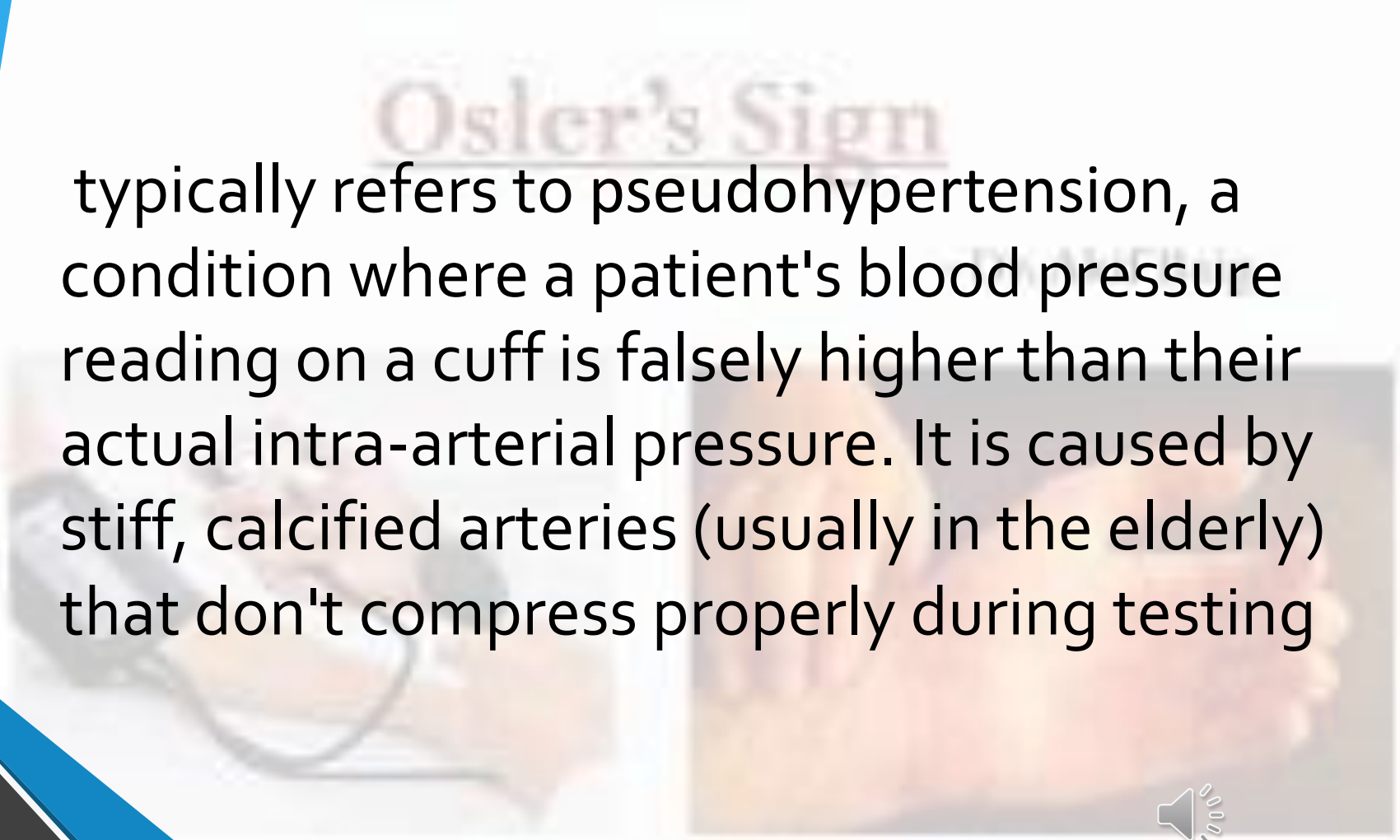
Calcineurin inhibitors

Erythropoietin

VEGF inhibitors

Decongestants

Osler phenomenon



typically refers to pseudohypertension, a condition where a patient's blood pressure reading on a cuff is falsely higher than their actual intra-arterial pressure. It is caused by stiff, calcified arteries (usually in the elderly) that don't compress properly during testing

Secondary Causes

Secondary Causes of Hypertension

Most common:

Primary aldosteronism

Obstructive sleep apnea

CKD

Renal artery stenosis

Pheochromocytoma

Primary Aldosteronism

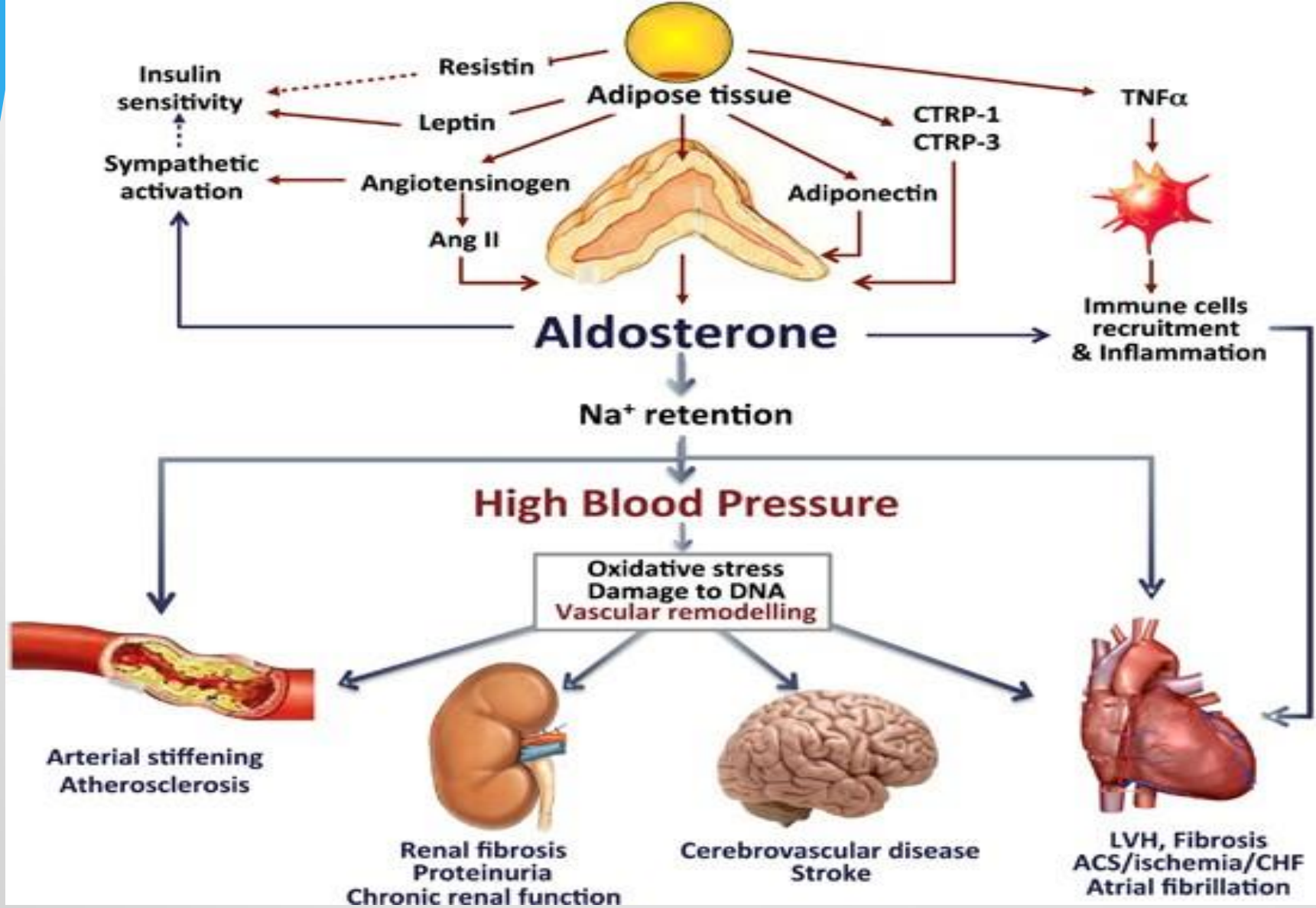
The Most Important Secondary Cause

Present in:

5–10% of all hypertensive patients

20 -35% of resistant hypertension

Should be considered in all patients with HTN and especially in RH (ESC2024&AHA2025)



Effects of Aldosterone

Why We Miss PA

Classically taught:

Hypertension

Hypokalemia

Reality:

Most patients have:

Normal potassium

When to Suspect Primary Aldosteronism?

High-Risk Groups

- Resistant hypertension
- Hypertension + hypokalemia
- Severe hypertension
- Adrenal incidentaloma
- Early-onset hypertension
- Family history of PA
- Hypertension with OSA
- CKD with difficult BP control

Medication Management Before ARR

2025 Guideline Update

Most antihypertensive drugs can be continued

Preferably stop:

Spironolactone

Eplerenone

Finerenone

for approximately 4–6 weeks before testing

ARR Screening

Aldosterone-Renin Ratio (ARR)

Screening test

ARR = PAC / PRA

Positive screen:

ARR >20–30

PAC >10–15 ng/dL

Treatment of PA

Unilateral Disease

Laparoscopic adrenalectomy

Bilateral Disease

Mineralocorticoid receptor antagonists

Spironolactone

Eplerenone

Goals

BP control

Potassium normalization

Reduction of CV risk

Approach to Resistant Hypertension

Exclude pseudoresistance with special focus on adherence and use out of office BP to detect white coat hypertension

Identify lifestyle factors such as diet, salt intake and physical activity

Discontinue and/or minimize interfering substance

Screen for secondary causes of hypertension, especially primary aldosteronism

Optimize medical treatment including the use of long acting CCBs, RAS inhibitors and thiazide type and thiazide like diuretics

Consider the use of fixed dose combination to improve adherence, spironolactone, beta blockers, alpha-blockers and vasodilators

Why Thiazide-like diuretic ?

Compared with HCTZ:

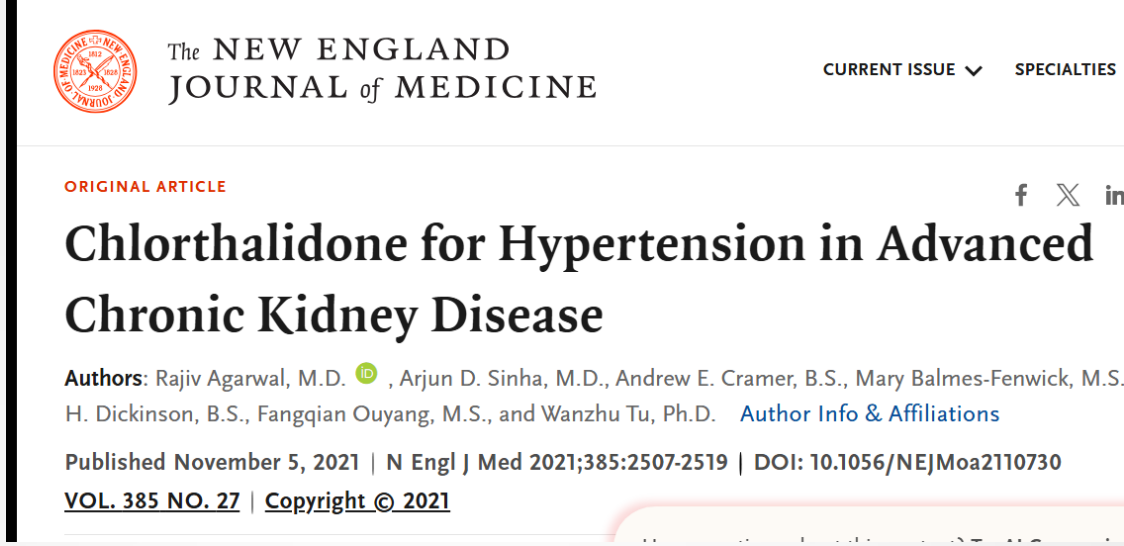
Longer half-life

Greater BP reduction

Better nocturnal BP control

Preferred thiazide-like diuretic

CLICK Trial



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES

ORIGINAL ARTICLE

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Authors: Rajiv Agarwal, M.D. , Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S. H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D. Author Info & Affiliations

Published November 5, 2021 | N Engl J Med 2021;385:2507-2519 | DOI: 10.1056/NEJMoa2110730

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Population

Stage 4 CKD

Mean eGFR ≈23

Findings

Chlorthalidone significantly reduced:

24-hour SBP

Albuminuria

Clinical Message

Chlorthalidone remains effective even in advanced CKD

fourth-line therapy

eGFR≥ 45

K< 4.5-5 mEq/L

MRA (Spironolactone 25-50 mg/day)

Why Spironolactone Works

Because many patients have:

Aldosterone Excess

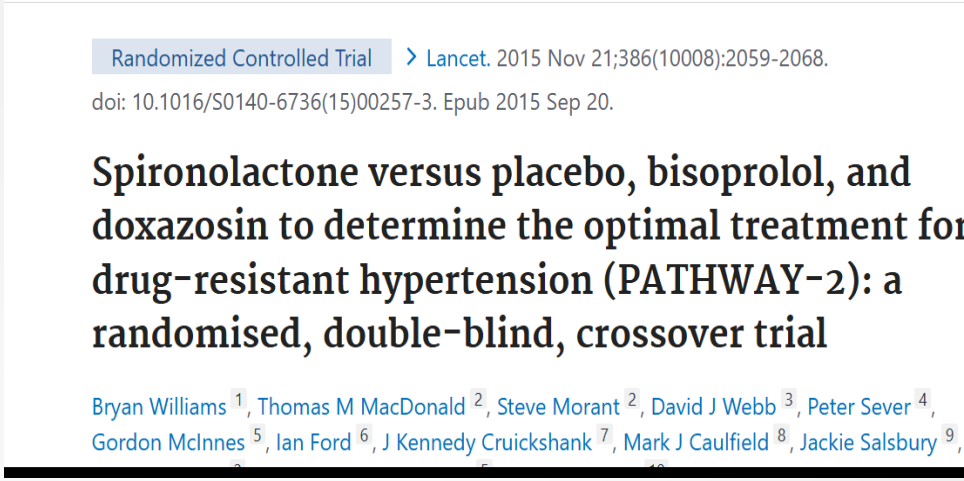
even without overt primary aldosteronism

Spironolactone targets:

Sodium retention

Volume expansion

PATHWAY-2 Trial



Randomized Controlled Trial › Lancet. 2015 Nov 21;386(10008):2059-2068.

doi: 10.1016/S0140-6736(15)00257-3. Epub 2015 Sep 20.

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Bryan Williams [1], Thomas M MacDonald [2], Steve Morant [2], David J Webb [3], Peter Sever [4], Gordon McInnes [5], Ian Ford [6], J Kennedy Cruickshank [7], Mark J Caulfield [8], Jackie Salsbury [9],

Landmark Study

Compared:

Spironolactone

Bisoprolol

Doxazosin

Placebo

Result

Spironolactone was superior

Spironolactone

Advantages

✓ Powerful BP reduction

✓ Inexpensive

✓ Evidence-based

Limitations

Hyperkalemia

Gynecomastia

Menstrual abnormalities

Eplerenone

Eplerenone

Advantages

More selective

Less gynecomastia

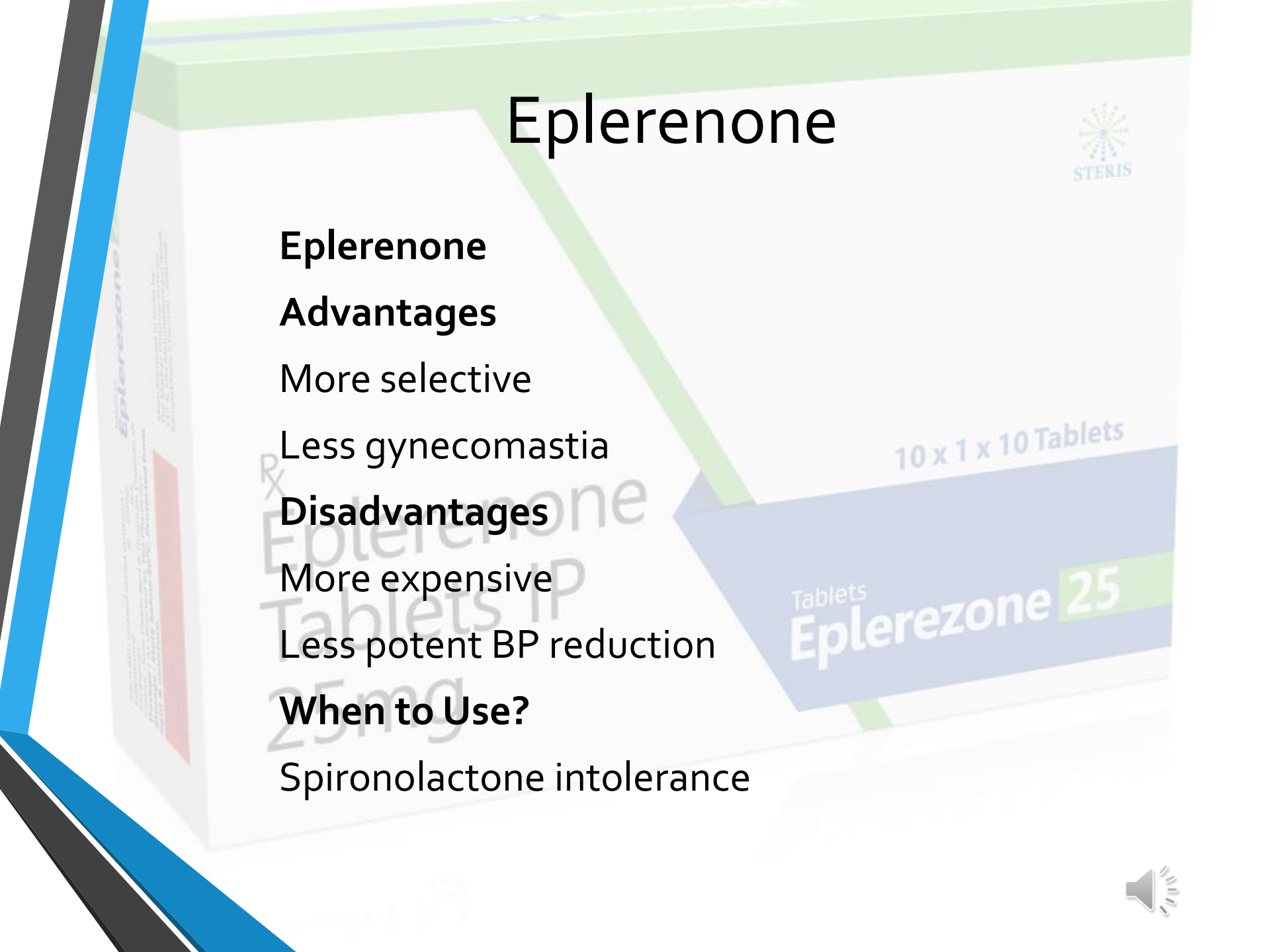
Disadvantages

More expensive

Less potent BP reduction

When to Use?

Spironolactone intolerance



In patients who are unable to tolerate or contraindications to MRA

Amiloride

Beta blocker

Alpha blocker

Central sympatholytic (Clonidine)

Direct vasodilator(hydralazine)

Resistant HTN in CKD

Mechanisms:

Sodium retention

Volume overload

RAAS activation

Sympathetic overactivity

Vascular calcification

Managing Resistant HTN in CKD

Core Principles

Salt restriction

Volume assessment

Chlorthalidone

MRA when appropriate

Hyperkalemia monitoring

ADVANCED THERAPIES

Renal Denervation

May be considered in patients who have (AHA2025):

SBP=140-180

DBP≥90

eGFR≥40

Resistant HTN despite optimized medical therapy or

Patients who are unable to tolerate further antihypertensive drugs because of adverse effects

Reduction of approximately 4-6 mmHg

Renal Denervation

Mechanism

Catheter-based ablation of renal sympathetic nerves

Results:

↓ Sympathetic activity

↓

↓ Blood pressure

HTN Trial SPYRAL

Findings

Significant reduction in:

Office BP

Ambulatory BP

Important Message

Proof of concept for RDN

Randomized Controlled Trial › Circ Cardiovasc Interv. 2025 Jul;18(7):e015194.
doi: 10.1161/CIRCINTERVENTIONS.125.015194. Epub 2025 May 20.

Long-Term Safety and Efficacy of Renal Denervation: 24-Month Results From the SPYRAL HTN-ON MED Trial

David E Kandzari [1], Felix Mahfoud [2 3], Raymond R Townsend [4], Kazuomi Kario [5], Michael A Weber [6], Roland E Schmieder [7], Konstantinos Tsioufis [8], Stuart Pocock [9], Minglei Liu [10], Vanessa DeBruin [10], Sandeep Brar [10], Michael Böhm [11]

New drugs

Therapeutics

New drug therapies for hypertension

Michel Azizi, Katherine R Tuttle, Jenifer M Brown, Daniel L Piskorz, Kazuomi Kario, Bryan Williams

Despite the availability of effective antihypertensive therapies, global blood pressure control rates remain unacceptably low. Contributing factors, such as low treatment adherence, therapeutic inertia, and rising multimorbidity, underscore the need for innovative approaches to improve hypertension care. New antihypertensive drug therapies that act on physiological pathways beyond those targeted by conventional drug classes are emerging. These therapies include small interfering RNA agents that inhibit angiotensinogen synthesis as a novel approach to inhibit the renin–angiotensin system, and new strategies to more selectively modulate aldosterone, such as aldosterone synthase inhibitors and non-steroidal mineralocorticoid receptor antagonists. There is also growing interest in therapies to enhance the action of the natriuretic peptide system. Although these innovations present valuable therapeutic opportunities, their benefits must be carefully balanced against considerations of safety, cost, clinical outcomes, and equitable access—all of which are crucial to reducing the residual burden of cardiovascular and chronic kidney disease.

Published Online
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https://doi.org/10.1016/
S0140-6736(25)02064-1

Hypertension Department, INSERM CIC1418, Hôpital Européen Georges Pompidou APHP, Université Paris Cité, Paris, France (Prof M Azizi MD); **Division of Nephrology and Kidney Research Institute, University of Washington School of Medicine, Seattle, WA, USA** (Prof K Tuttle MD);

Why do we need NEW DRUGS

Global BP control rates remain poor despite available therapies
Resistant hypertension remains common
Poor adherence and therapeutic inertia are major barriers
Novel therapies target pathways beyond conventional drugs

New drug classes

RNA-based therapies (Zilebesiran)

Aldosterone Synthase Inhibitors

Non-steroidal MRA

Endothelin Receptor Antagonists

Zilbesiran -The first long-acting RNA Therapy

Mechanism

Small interfering RNA (siRNA (

Targets hepatic angiotensinogen mRNA

Suppresses RAAS at its origin

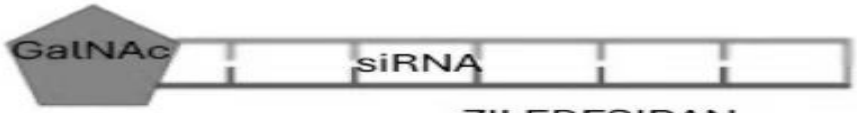
Key Features

Subcutaneous injection

Effect lasts ≥6 months

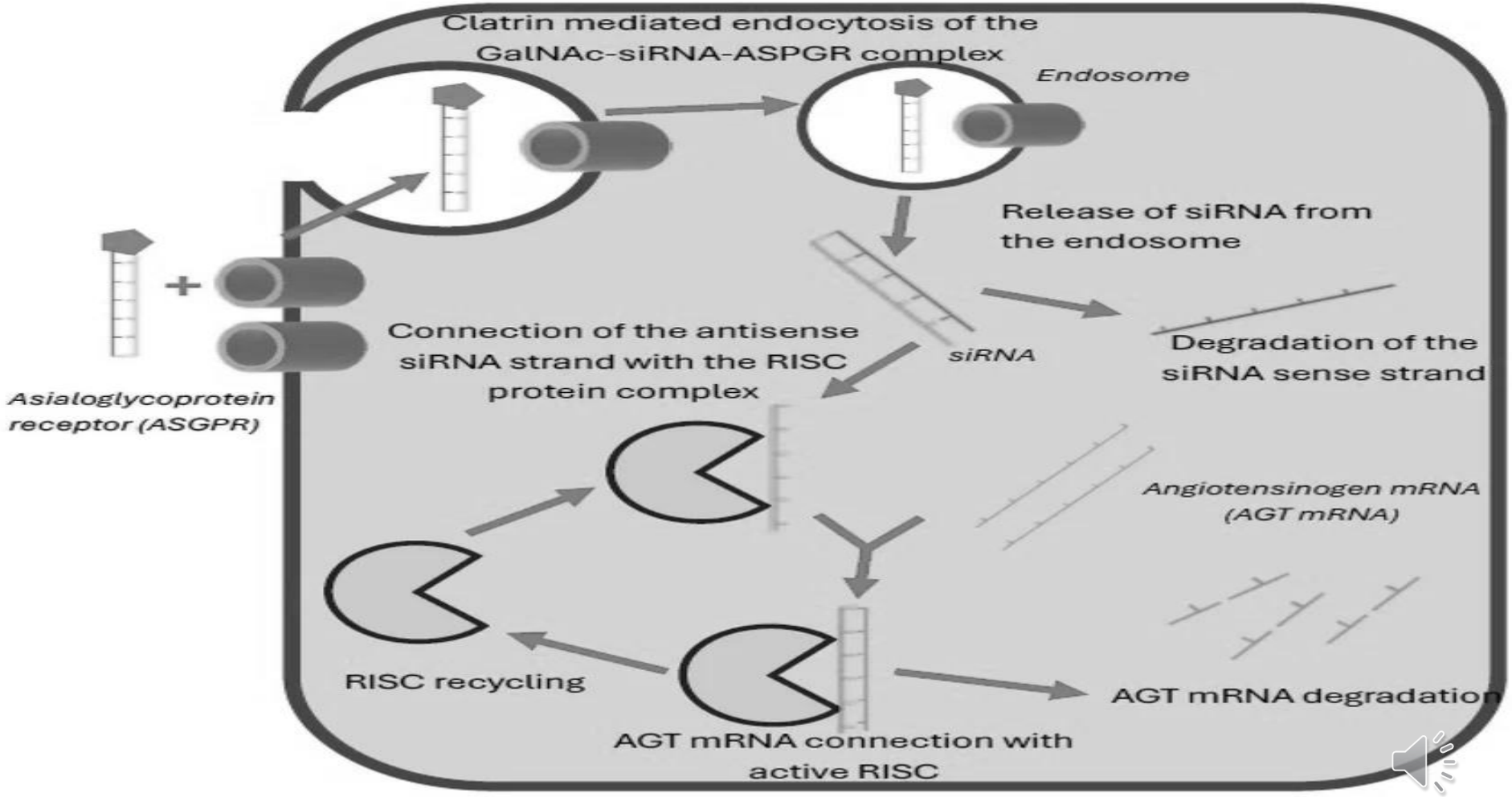
May improve medication adherence

%90 reduction in circulating angiotensinogen



ZILEBESIRAN

N-acetylgalactosamine (GalNAc) linked to double-stranded small interfering RNA (siRNA)



KARDIA-1

Ambulatory SBP reduction:

- 150 mg → ~14 mmHg vs placebo
- 300 mg → ~17 mmHg vs placebo
- 600 mg → ~16 mmHg vs placebo

KARDIA-2

Additional BP reduction when combined with:

- Indapamide
- Amlodipine

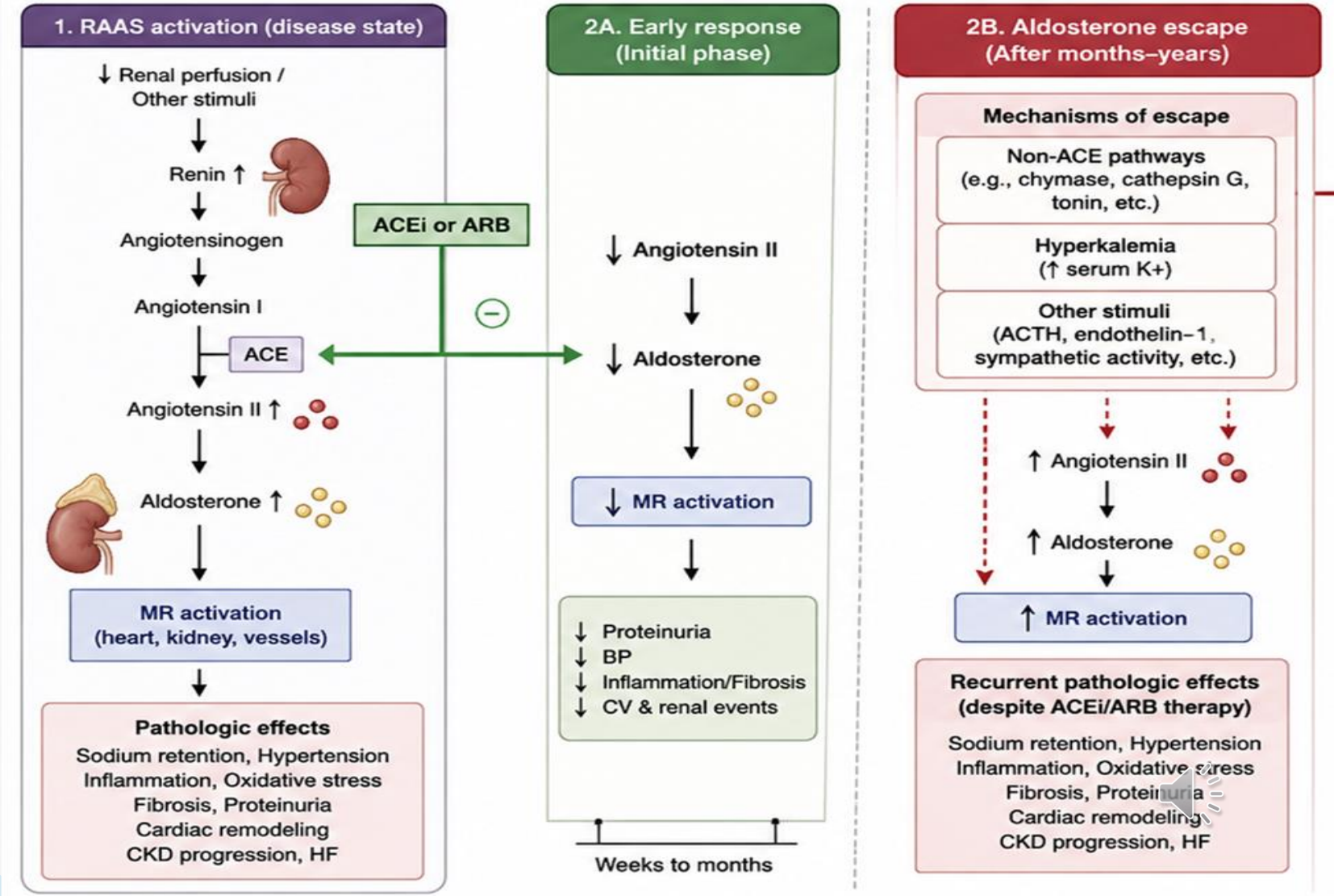
Main adverse effects

Mild hyperkalemia

Small eGFR decline

Injection-site reactions

Aldosterone Synthase Inhibitors



Aldosterone Synthase Inhibitors

Baxdrostat

Lorundrostat

Advantages

Overcome aldosterone escape

Effective in resistant hypertension

Finerenone

Non-Steroidal MRA

Unique properties:

Less endocrine side effects

Strong anti-inflammatory effects

Strong anti-fibrotic effects

Endothelin Receptor Antagonists (ERAs)

Endothelin-1 is one of the most potent endogenous vasoconstrictors. Effects:

Vasoconstriction

Sodium retention

Vascular remodeling

Increased arterial stiffness

↑ Endothelin activity is common in:

Resistant hypertension

CKD

Obesity

Diabetes

Aprocitentan – First ERA Approved for Resistant Hypertension

Dual Endothelin Receptor Blockade:

ETA receptor blockade

ETB receptor blockade

Results:

Sustained BP reduction

Effective as add-on therapy in resistant hypertension

Useful when:

BP remains uncontrolled despite standard therapy

MRA is contraindicated

MRA is not tolerate

Advantages & Limitations of Aprocitentan

Advantages

✓ Novel mechanism
✓ Works independently of RAAS
✓ Useful in resistant HTN
✓ Can be combined with existing therapies

Limitations

⚠ Fluid retention
⚠ Peripheral edema
⚠ Caution in heart failure
⚠ Contraindicated in pregnancy

Recommendation for the Management of RH

Step 1

Lifestyle Intervention

- Sodium restriction
- Weight control
- Exercise
- Healthy sleep

BP not at target (≥140/90 mmHg)

Step 2

Maximize Evidence-based Antihypertensive Medications

- Ensure the use of the maximum recommended or best tolerated doses for a 3-drug combination
- Substitute thiazide with long-acting thiazide-like diuretics - chlorthalidone or indapamide or loop diuretic in patients with eGFR <30-45 ml/min/1.73 m^2
- Add spironolactone or eplerenone in patients with eGFR ≥30 ml/min/1.73 m^2
- Add chlorthalidonein patients with eGFR 15-30 ml/min/1.73 m^2 if not previously used

BP not at target (≥140/90 mmHg)

Step 3

Suggested Additional Antihypertensive Medications

- Carefully substitute ARNI for the prior RAS blockers (either an ACEi or an ARB)
- Add BB if heart rate ≥70 beat/min or add alpha-1 blocker or centrally acting agent
- Add direct acting vasodilators (hydralazine or minoxidil)

BP not at target (≥140/90 mmHg)

Step 4

- Consider renal denervation if eGFR ≥30 ml/min/1.73 m^2 in patients with refractory hypertension or patients with RH who has clinical ASCVD or progressive HMOD

Case Revisited

58-year-old man

CKD

Diabetes

Triple therapy

BP 165/95

Next Steps?

✓ HBPM/ABPM

✓ Check adherence

✓ Screen for PA

✓ Add spironolactone if appropriate

Take Home Messages

1. Resistant HTN is common and high-risk
2. Always exclude pseudoresistance
3. Screen every resistant HTN patient for primary aldosteronism
4. Spironolactone remains the preferred fourth-line therapy
5. Chlorthalidone works even in advanced CKD
6. Finerenone provides cardiorenal protection
7. Renal denervation is becoming a legitimate adjunctive therapy
8. Future therapies include Baxdrostat and Zilebesiran


Thank You