Title: Combination Therapy in Hypertension – Concepts, Strategies & Clinical Considerations

1. Introduction

- Hypertension (HTN) is a major modifiable risk factor for cardiovascular disease, stroke, and kidney failure.
- Monotherapy (single-drug treatment) often fails to achieve target BP levels in most patients.
- Therefore, combination therapy (using two or more antihypertensives) is essential, especially in:
- Stage 2 hypertension (≥140/90 mmHg)
- Patients with high cardiovascular risk
- Special populations (elderly, diabetics, CKD patients, South Asians)

2. Why Use Combination Therapy?

- Synergistic Effects: Combines drugs that act via different mechanisms to lower BP more effectively.
- Lower doses = fewer side effects: Using low-dose combinations reduces individual drug toxicity.
- Faster BP control: Reduces the risk of complications (stroke, MI, kidney damage).
- Prevents treatment resistance: Effective even in populations with resistant or poorly responsive hypertension.

3. First-Line Drug Classes for Combination Therapy

Drug Class	Mechanism	Common Combinations
ACE Inhibitors (e.g., Ramipril)	RAAS blockade	ACEI + CCB / ACEI + Thiazide
ARBs (e.g., Valsartan)	RAAS blockade	ARB + CCB / ARB + Thiazide
CCBs (e.g., Amlodipine)	Vasodilation	CCB + Thiazide / CCB + ACEI
Thiazide Diuretics (e.g., Chlorthalidone)	Diuresis & sodium loss	Thiazide + ACEI / CCB

4. Preferred Drug Combinations

1. ACEI or ARB + CCB

- Complementary mechanism: Vasodilation + RAAS inhibition
- Evidence-based: Shown in ACCOMPLISH trial to reduce cardiovascular events
- Good tolerability and efficacy

2. ACEI or ARB + Thiazide Diuretic

- Reduces volume and addresses salt retention
- Effective in obese and salt-sensitive patients

3. CCB + Thiazide Diuretic

- Used when ACEI/ARB not tolerated
- Effective in elderly, African-origin, or South Asian patients

5. Fixed Dose Combinations (FDCs)

Definition: Single pill containing two antihypertensive agents

Advantages:

- Improves patient adherence

- Simplifies regimen
- Reduces pill burden
- Predictable pharmacokinetics

Examples:

1. Amlodipine + Valsartan
2. Perindopril + Indapamide
3. Telmisartan + Hydrochlorothiazide

6. Triple Drug Combination Therapy

Used when BP is not controlled on two drugs

Typical triple combinations:

1. RAAS blocker + CCB + Thiazide

Available as single-pill triple combinations

e.g., Olmesartan + Amlodipine + Hydrochlorothiazide

Goals:

- Intensify therapy
- Improve compliance
- Minimize side effects

7. Special Populations

1. Diabetics & CKD

- Prefer ACEI or ARB to reduce proteinuria and protect kidneys
- Add CCB for vasodilation and diuretics for volume control
- Avoid ACEI + ARB combination → ↑ risk of hyperkalemia & renal dysfunction

2. Elderly

- Commonly need multiple agents due to:
- Vascular stiffness
- Comorbid conditions

Preferred drugs:

i. Thiazides and CCBs
ii. Start at low doses to prevent hypotension

3. South Asians

More prone to:

- Salt sensitivity
- Central obesity
- Early stroke risk

First-line drugs:

CCBs, thiazides, ACEIs/ARBs if diabetes or CKD present

8. Combinations to Avoid

Combination	Risk
ACEI + ARB	No added benefit; ↑ hyperkalemia, hypotension, kidney injury
Beta-blocker + non-DHP CCB (e.g., Verapamil)	Risk of bradycardia or AV block
Alpha-blocker + central alpha agonist	Severe hypotension, dizziness

9. Benefits of Combination Therapy

- Better BP control and faster achievement of targets
- Reduces need for high doses of single drugs
- Minimizes individual side effects
- Proven to lower the risk of cardiovascular events (MI, stroke)
- Improves kidney function in CKD

10. Challenges & Considerations

- Higher cost of some fixed-dose combinations
- Risk of side effects: hypotension, electrolyte imbalance
- Requires close monitoring and patient education
- Must be tailored to comorbidities, age, and ethnicity