Update on the drug treatment of hypertension: perspectives in clinical pharmacology

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Abstract

Drug therapy to achieve the recommended target blood pressure remains the cornerstone of the management of hypertension. Today, there are strong evidences from randomized controlled trials that antihypertensive drugs are more effective than placebo at reducing cardiovascular mortality and morbidity. According to more recent guidelines, there are three main classes of drugs that have been used for initial monotherapy: inhibitors of the renin-angiotensin system, calcium channel antagonists, and diuretics. The use of beta blockers has been restricted for initial monotherapy in the absence of a specific indication associated with adverse effects on some outcomes, particularly in older patients. Many studies have demonstrated that antihypertensive agent classes can be combined effectively and nowadays, it is strongly recommended to use single-pill combinations containing two or three antihypertensive agents. Combination therapy provides greater antihypertensive potential, reduced risks for side effects, lower medical cost, increase compliance, and promotes long-term adherence, this latter being the major challenge of drug therapy for hypertension.

Key words: *hypertension, drug therapy.*

Nowadays, several different classes of antihypertensive drugs are available, and new agents continue to be introduced, thus increasing the choice of drugs for hypertension treatment. Although most antihypertensive drugs are equally effective in the treatment of mild to moderate (stage 1-2) hypertension, specific choices and preferences are individualized based on the cardiology societies and associations. In this section, we summarize the pharmacology of antihypertensive drug classes, update the treatment of hypertension based on hypertension guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) [1], the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) [2], the Vietnamese Society of Hypertension/Vietnam Nation Heart Association (VSH/VNHA) [3], and present evidence from large trials showing the benefits of the drug combination therapy and the single-pill combinations in the treatment of hypertension.

1. OVERVIEW OF THE PHARMACOLOGY OF THE MAJOR CLASSES OF ANTIHYPERTENSIVE DRUGS

Arterial blood pressure depends on cardiac output and peripheral vascular resistance. Drugs lower blood pressure by reducing cardiac output, systemic vascular resistance, or both. Drugs can decrease cardiac output by inhibiting myocardial contractility or by decreasing ventricular filling pressure. Reduced ventricular filling pressure due to a decrease in the venous tone or by a change in blood volume via renal effects. Drugs may reduce peripheral vascular resistance by directly vasodilating blood vessels in the periphery or by counteracting vasoconstrictor mechanisms (e.g., the sympathetic nervous system, the RAS). Antihypertensive agents are classified according to site or mechanism of action.

1.1. Diuretics

1.1.1. Thiazide diuretics

Thiazide diuretics: are the most commonly used diuretic agents in the treatment of hypertension. The initial hypotensive response is mediated by a reduction in cardiac output. However, at steady state, hypotension result from a decrease in systemic vascular. *Dosage forms and strengths of hydrochlorothiazide (HTCZ):* oral capsule (12.5 mg); oral tablet (12.5 mg; 25 mg; 50 mg). *Administration:* Initially, 12.5 to 25 mg PO once daily [4]. Maintenance dose may increase to 50 mg PO once daily or twiced daily. The use of the lowest possible dose would further decrease the risk of adverse effects, while higher doses are not generally more efficacious in lowering blood pressure. Take this drug in the morning, if patients are on a twice daily dosing schedule, the second dose should be given before 6 PM. *Effectiveness:* The maximal effect occurs by 4 - 6 weeks after the start of therapy, so it is necessary to wait enough time to assess the response and

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the doses should not be increased too soon. Their effectiveness is reduced by high dietary sodium intake, in CKD with eGFR < 30 ml/min, and by the coadministration of NSAIDs. *Side effects:* hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia and glucose intolerante, hypelipidemia, and hyponatremia. Hypokalemia should be monitored during the first 2-3 weeks of HTCZ therapy.

Thiazide-like diuretics (indapamide and chlorthalidone): have a longer half-life resulting in better antihypertensive efficacy and neutral effects on metabolism than thiazide diuretics [5]. *Dosage forms and strengths:* indapamide: oral tablet (1.25 mg; 1.5 mg; 2.5 mg); chlorthalidone: oral tablet (15 mg; 25 mg; 50 mg; 100 mg). *Administration:* for indapamide, 1.25 mg once a day initially, taken in the morning; if there is an inadequate response, the dose can be increased to 2.5 mg after four weeks but not more than 10 mg. For chlorthalidone, the starting dose is 15 mg taken once per day with breakfast; this doseage may be gradually increased if needed to 50 mg/day but not to exceed 100 mg/day. *Effectiveness:* the antihypertensive effect increases gradually within 1 - 2 weeks and can be achieved at peak at low doses (12.5 to 25 mg daily) [4].

1.1.2. Loop diuretics

Available loop diuretics include bumetanide, ethacrynic acid, furosemide, and torsemide.

Furosemide: *Dosage forms and strengths:* injectable solution (10 mg/mL); oral solution (10 mg/mL); tablet 20 mg, 40 mg, 80 mg *Administration:* dose of 20 - 40 mg B.I.D orally, when with renal insufficiency or congestive heart failure, a higher dose can be used, up to a maximum of 480 mg per day (4). May be administered I.M or I.V when a rapid diuretic effect is required or the patient is unable to swallow. When administered I.V, furosemide must be injected slowly over 1 - 2 minutes, or I.V infusion rate not exceeding 4 mg/min. *Effectiveness:* loop diuretics have a rapid onset and a short duration of action. The strong initial diuretic results in compensatory responses, so they may not have useful long-term antihypertensive effect when used alone [4]. *Warnings:* avoid use in patients with severe hepatic impairment. Reduce dose in the elderly to reduce the risk of ototoxicity. When urine volume is low, adequate fluid volume must be replaced before administration.

Bumetanide and torsemide: the bioavailability is more predictable (about 80%), and the half-life is longer than furosemide, so it can be used once a day.

Ethacrynic acid: more ototoxic and should only be used in patients allergic to thiazides and other loop diuretics.

1.1.3. Potassium-sparing diuretics

Spironolactone: *Dosage forms and strengths:* oral tablet (25 mg; 50 mg; 100 mg). *Administration:* initially 25 - 50 mg once daily or twiced daily, for at least 2 weeks; maintenance dose should be individualized [4]. Spironolactone should be taken with food to reduce gastric irritation and increase absorption. *Effectiveness:* It is the most effective fourth medication for combination therapy in the treatment of resistant hypertension [4]. Less effective if used alone. *Side effects:* Spironolactone is a non-selective mineralocorticoid receptor antagonist and also an androgen and progesterone receptor antagonist. Adverse effects due to antiandrogen include gynecomastia, loss of libido, erectile dysfunction in men and menstrual disorders in women.

Eplerenone: more selective with fewer antiandrogen effects, but less effective in lowering blood pressure.

Amiloride and triamterene: less effective when used alone.

The potassium-sparing diuretics should combine with ARBs/ARBs or other potassium supplements with caution to avoid hyperkalemia, especially in those with impaired renal function.

1.2. Calcium Channel Blockers (CCBs)

Calcium channel blockers are classified according to chemical structure and site of interaction within the calcium channel as dihydropyridines (amlodipine, clevidipine, felodipine, isradipine, lercanidipine, nicardipine, nifedipine, nimodipine, and nisoldipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem). Dihydropyridine-class are categorized into four generations based on the difference in the formula and the length of their action. *Dosage forms and strengths* Amlodipine is available in doses of 2.5 mg, 5 mg, and 10 mg; Nifedipine extended-release tablets contain either 30 mg, 60 mg or 90 mg of nifedipine. *Administration:* The usual initial dose of amlodipine is 2.5 to 5 mg once daily which may be increased every 7-14 days to a maximum dose of 10 mg. Initial dose of nifedipine is 30 to 60 mg orally once a day; maximum dosage is 90 mg per day. Swallow it as a whole, do not break, crush, or chew it. *Effectiveness:* the CCBs most used for monotherapy and combination therapy for hypertension are long-acting dihydropyridines (e.g., amlodipine) [6] with sufficient 24-h efficacy at once-daily dosing. Immediate-release nifedipine and other short-acting dihydropyridines have no place in hypertension management due to excessive sympathetic activity can worsen myocardial ischemia. *Side effects:* vasodilation

cause peripheral edema, headache, flushing, and hypotension. The combination CCBs with ACEIs can reduce the incidence of peripheral edema and increase effectiveness. *Warnings:* In older adults or in patients with severe liver disease, doses should be reduced. The concurrent use of β blockers with either verapamil or diltiazem should be avoided because of potentially profound adverse effects on atrioventricular nodal conduction, heart rate, or cardiac contractility.

1.3. Inhibitors of the Renin-Angiotensin System

1.3.1. Angiotensin-converting enzyme inhibitors (ACEIs)

Captopril is an FDA-approved medication used in the management of hypertension. Since then, the following ACEIs are currently available: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril. Except for captopril and lisinopril, most ACE inhibitors are prodrugs that are metabolized in the liver into active forms. *Administration:*All the ACEIs are prescribed orally, except for enalapril, which can be given intravenously. Although they are typically dosed once daily, some ACEIs may require twice-daily dosing for adequate control of blood pressure (e.g., enalapril, ramipril). *Effectiveness:* the antihypertensive effects of ACEIs due to vasodilation from accumulation of bradykinin and depletion of angiotensin II, as well as a decrease in aldosterone-mediated sodium and water retention. The ACEIs lower blood pressure and slow progression of nephropathy in patients with type 2 diabetes. Long-term treatment reduces post-infarction morbidity and mortality in patients with left ventricular systolic dysfunction or symptomatic heart failure. Thus, ACEIs are indicated for all hypertensive patients with acute MI who have no contraindications. ACEIs counter diuretic-induced increases in serum aldosterone concentration and enhance the antihypertensive efficacy of diuretics. *Side effects:* ACEIs are associated with hyperkalemia ranging from mild and asymptomatic to clinically evident and life-threatening. Cough is one of the common adverse effects. Angioedema is a rare but life-threatening side effect. Captopril has been associated with a higher incidence of dysgeusia, skin rash, proteinuria, neutropenia or granulocytopenia than other ACEIs. *Contraindication:* ACEIs are contraindicated in patients with bilateral renal artery stenosis, pregnancy, known allergy or hypersensitivity, and hyperkalemia. *Warnings:* In patients with renal insufficiency, the dose should be decreased because ACEIs or their active metabolites are excreted predominantly by the kidneys.

1.3.2. AT_1 Receptor Blockers (ARBs)

The FDA has approved candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, which are now widely used in the treatment of hypertension. These agents block the interaction of angiotensin II at the AT_1 receptor, thereby relaxing smooth muscle, increasing renal salt and water excretion, reducing plasma volume, and decreasing cellular hypertrophy. *Administration:* except losartan which has a relatively short half-life should be used twice a day, the effects of ARBs persisted over 24 hours, so they were administered once daily. *Effectiveness:* The full effect of ARBs on blood pressure typically is reached in 4-6 weeks after the initiation of therapy. The ARBs have additive blood pressure lowering effects when combined with diuretics, so many combination products are available containing HTCZ and ARBs. *Side effects:* ARBs has significantly lower risk of angioedema, cough, pancreatitis and gastrointestinal bleeding, and better tolerated than ACEIs. According to a head-to-head analysis of the 2 drug classes, ARBs work as well as ACEIs for treatment of hypertension. These findings support preferentially prescribing ARBs over ACEIs for the treatment of hypertension [7]. *Contraindication:* ACEI with ARB combinations are not recommended for the treatment hypertension associated with more adverse events without an increase in benefit. ARBs are contraindicated during pregnancy and must be discontinued when pregnancy is detected.

1.3.3. Direct Renin Inhibitors

Aliskiren is the first orally effective direct renin inhibitor that is FDA approved to treat hypertension. *Dosage forms and strengths*: Aliskiren is available as 150 mg or 300 mg tablets. *Pharmacokinetics:* It is poorly absorbed from the gastrointestinal tract (with bioavailability of less than 2%). *Administration:* the starting dose is 150 mg PO once daily, may be increased to 300 mg daily if necessary. Doses greater than 300 mg/day did not give an increased blood pressure response but resulted in an increased rate of diarrhea [8]. *Effectiveness:* The antihypertensive effect is substantially attained (85 - 90%) within two weeks after initiating therapy. Aliskiren reduce blood pressure effectively but did not reduce total mortality or cardiovascular death, so that the place of this drug in the treatment of hypertension remains unclear [9]. *Side effects:* The most common adverse effects is diarrhea, fatigue, headache, and dizziness.

Warnings and contraindication: Aliskiren can cause fetal harm if administered to a pregnant woman. The combination of aliskiren with other RAS inhibitors is should not be used.

1.4. *β-Adrenergic receptor antagonists (β-blockers)*

β-blocker agents differ in their β_1-receptor selectivity, intrinsic sympathomimetic activity, and vasodilator capacity. In addition to β-receptor blockers, labetalol and carvedilol also inhibit α_1-receptors with α_1:β blocking ratios of 1:10 and 1:4, respectively [4], and nebivolol causes NO-mediated vasodilation. *Administration:* many β blockers have relatively short plasma half-life (e.g., metoprolol, propranolol, carvedilol) and should generally be given in sustained-release forms. Bisoprolol and nebivolol have half-life values of 10 - 12 h that can be used once daily. *Effectiveness:* the ideal β-blocker for hypertension is long acting, cardioselective, and usually effective in a standard dose. β-blockers also effective in post-MI patients, heart failure, and can be considered in young patients with hypersympathetic activity. The β-blockers should not prioritizing as an early selection for other circumstances of hypertension, especially elderly patients at high risk of stroke [4]. Warnings and contraindication: β-blockers should be avoided in patients with asthma or with SA or AV node dysfunction. The drug may attenuate hypoglycemic symptoms or lead to worsening of hypoglycemia in patients with insulin-dependent diabetes, and increase blood glucose in non-insulin-dependent diabetes. Avoid stopping the β-blockers suddenly, the dosage should be reduced gradually 10 - 14 days before discontinuing the drug to avoid the rebound effects.

2. HYPERTENSION PHARMACOLOGICAL TREATMENT

Non-pharmacological interventions, or lifestyle modifications is an important part for hypertensive patients. In some patients with stage 1 hypertension, blood pressure can be controlled by a combination of weight loss (in overweight patients), salt restriction (< 5 g per day), regular physical activity (at least 30 minutes a day), moderation of alcohol consumption (ethanol intake ≤ 20 g/day in women and ≤ 30 g/day in men), smoking cessation, and high consumption of vegetables, fruit and low-fat dairy products. Most patients will require drug therapy to achieve optimal BP control. The optimal blood-pressure goals remain controversial and vary slightly among cardiovascular organizations.

Ideal characteristics of drug treatment: [6]

1. Evidence on morbidity/mortality prevention.
2. Use a once-daily regimen which provides 24-hour blood pressure control.
3. Affordable and/or cost-effective relative to other agents.
4. Well tolerated.
5. Evidence of benefits of use of the medication in populations to which it is to be applied.

Table 1. Drug treatment strategies for hypertension [2]

Recommendations	Class	Level
Among all antihypertensive drugs, ACE inhibitors, ARBs, β-blockers, CCBs, and diuretics (thiazides and thiazide-like drugs such as chlorthalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used.	I	A
It is recommended that β-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.	I	A
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in an SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is < 150 mmHg).	I	B
It is recommended that if BP is not controlled with a two-drug combination, treatment should be increased to a three-drug combination, usually a RAS blocker with a CCB and a thiazide/thiazide-like diuretic, preferably as an SPC.	I	A

It is recommended that if BP is not controlled with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a β-blocker, or an alpha-blocker.	I	A
The combination of two RAS blockers is not recommended.	III	A

CV = cardiovascular; RAS = renin-angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SPC = single-pill combination.

3. INITIAL MONOTHERAPY

Drug therapy for grade 1 hypertension (SBP from 140 mmHg to 159 mmHg and/or DBP from 90 mmHg to 99 mmHg) provided level A evidence in reducing cardiovascular disease risk [10]. However, younger individuals often have low estimated 10-year CVD risk, therefore lifetime benefit of treatment should be considered and discussed with the patient before initiating treatment. The presence of hypertension-mediated organ (HMOD) damage mandates treatment in most cases of grade 1 hypertension. For grade 2 hypertension or higher (SBP > 160 mmHg), drug treatment is recommended because of the high lifetime benefit of reducing BP in such patients and reducing the risk of HMOD [5, 6].

All of the antihypertensive agents is roughly equally effective in lowering the blood pressure, producing a good antihypertensive response in 30 to 50 percent of cases. However, there is a wide interpatient variation as some patients may respond well to one medicine but not to another, such as older patients generally responding better to monotherapy with a thiazide diuretic or CCB and relatively poorly to an ACEI or β blocker.

After the initial dose, going to higher doses produce more side effects often with little further reduction in blood pressure. Therefore, we generally limit dose titration to one step with a given antihypertensive drug (eg, 12.5 to 25 mg of chlorthalidone and 5 to 10 mg of amlodipine). According to the recent observations, a combination of two or three drugs at half-standard doses might have greater antihypertensive efficacy, less toxicity and better patient outcomes than one drug at standard or twice-standard doses.

4. COMBINATION THERAPY

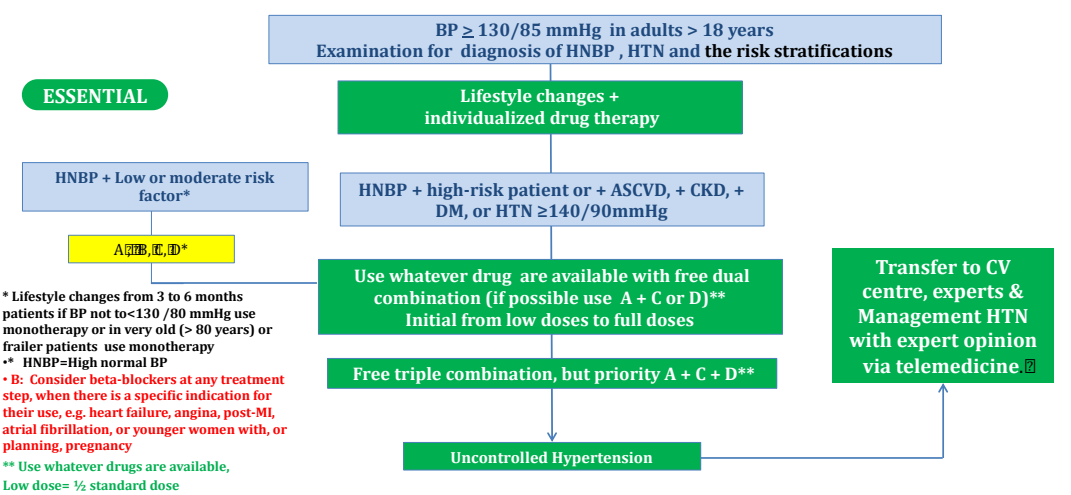

Figure 1. Essential standards with an evidence-based simplified treatment algorithm [3]

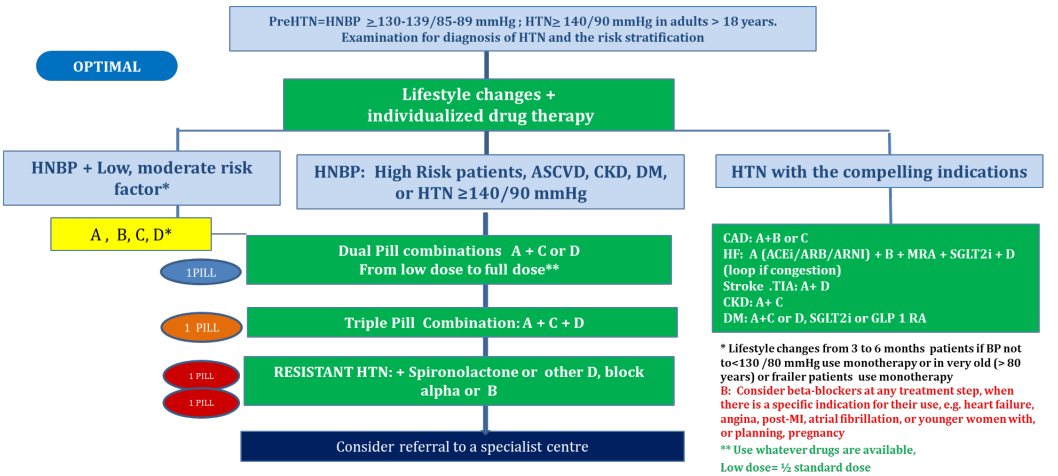

Figure 2. Optimal standards with an evidence-based simplified treatment algorithm (3)
A: ACEi/ ARB; ARNI: Angiotensin receptor-neprilysin inhibition; B: B-blocker; C: CCB; D: Diuretic; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose cotransporter inhibitor; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; HNBP: High-normal blood pressure; ASCVD: Atherosclerotic Cardiovascular Disease; CKD: Chronic kidney disease; DM: Diabetes mellitus; CAD: Coronary artery disease; HF: Heart failure; TIA: Transient ischemic attack

4.1. Initial therapy with a combination of two drugs

Initial therapy with a combination of two drugs should be considered usual care when the blood pressure is more than 20/10 mmHg above goal, except very old patients (> 80 years), and frail patients who may better tolerate a more gentle reduction of BP. Rationale for combination of 2 drugs as initial treatment strategy is that it can lead to more effective BP lowering by acting on a variety of pathophysiological mechanisms, more rapid blood pressure control than monotherapy, better 24-h BP control and reduce heterogeneity in response [11, 12]. Moreover, low-dose combination therapies provide fewer adverse events than the higher doses monotherapies that would be required to achieve the same level of BP control

4.2. Single-pill strategy to treat hypertension

Among various factors, poor adherence to antihypertensive medications is a major cause of failure to control hypertension, and is directly related to the number of pills. Single-pill combination therapy can combine different classes of drugs to increase efficacy while mitigating the risks of treatment-related adverse events, reduce pill burden, lower medical cost, and improve patient adherence. Today, many efficient two- and three-drug fixed combinations are currently available and approved by the FDA for the treatment of hypertension.

Currently available two-drug FPCs for the management of hypertension are:

- ACEI + thiazide diuretic
- ACEI + thiazide-like diuretic
- ACEI + loop diuretic
- ARB + thiazide diuretic
- Direct renin inhibitor + thiazide diuretic
- ACEI + CCB
- ARB + CCB
- Potassium-sparing diuretic + thiazide diuretic
- Potassium-sparing diuretic + loop diuretic
- β-blocker + thiazide diuretic
- β-blocker + thiazide-like diuretic
- β-blocker + ACEI

Besides the several two-drug FPCs, there are also triple FPC formulations available for the treatment of hypertension including the combination of perindopril/indapamide/amlodipine and olmesartan/amlodipine/hydrochlorothiazide. Furthermore, the dual FPC of ARB/statin, CCB/statin, or the triple combination of atorvastatin/perindopril/amlodipine are also available for the management of both hypertension and dyslipidemia [13].

4.3. Choice of drug

The choice of the best antihypertensive therapeutic strategy should be based on global CV risk profile, primary or secondary prevention setting, comorbidities, and medication adherence

of individual patient. In any case, this choice must rely on evidence-based medicine and randomized controlled trials that evaluated the efficacy, safety, and tolerability of each available FPC.

4.3.1. The drug of choice for two-drug fixed-dose combination

The preferred dual combination of initial therapy for most hypertensive patients is comprise an ACEI/ ARB with a CCB or diuretic [5], so there are four basic two-drug combinations: ACEI + CCB; ACEI + thiazide or thiazide-like diuretic; ARB + thiazide diuretic and ARB + CCB. These agents are well tolerated, effectively lower blood pressure, reduce cardiovascular risk, and are available worldwide in the form of combination preparations in a wide range of doses [14].

In the ASCOT-BPLA trial in 19,257 hypertensive patients aged 40 - 79 years with at least three cardiovascular risk factors, treatment with amlodipine ± perindopril resulted in major CV prevention, mortality, and metabolic safety better than the combination of β-blocker ± thiazide diuretic. The single-pill FPC perindopril/amlodipine (ACEI and CCB) has been shown to effectively reduce BP, target organ damage, and cardiovascular risk in hypertensive patients. In the PEARL ABPM study, 262 patients were evaluated with ambulatory BP monitoring, the dual-drug FPC perindopril/ amlodipine provided an effective, safe, and sustained 24-h BP control in patients whose hypertension was not controlled by ACEI or CCB alone or a free combination of them [13].

Clinical studies on the use of single-pill FPC of telmisartan/amlodipine and telmisartan/HCTZ have shown these therapies resulted in more significant PB reduction, BP goal rates, and response rates at all stages of hypertension than with either drug alone. In mild-moderate hypertension, the combination of telmisartan/amlodipine had a superior 24-hour BP-lowering efficacy compared with either treatment administered as monotherapy. Telmisartan/HCTZ dual FPC provides superior 24 h BP lowering, particularly in the last 6 h, compared with other RAS inhibitor combinations such as losartan/HCTZ. With a long half-life, once-a-day olmesartan/amlodipine FPC greatly reduced BP consistent across the 24-h dosing interval, and controlled nighttime BP well. In the COACH trial, a reduction in BP (-30.1 mmHg in office SBP at maximum dose) was achieved in the first 2 weeks of treatment with olmesartan/ amlodipine FPC. Both the FPC of olmesartan/ amlodipine and perindopril/amlodipine have been shown to maintain their similar antihypertensive effect after 48 hours from the last dose. The FPC valsartan/amlodipine is more effective and better tolerated than nifedipine GITS in patients with hypertension inadequately controlled by monotherapy. Furthermore, the availability of FPC with valsartan/thiazide diuretics and valsartan/CCB allows the use of first FPC in the morning and of the second FPC in the evening, with valsartan taken twice a day to obtain an adequate 24-h coverage [13].

Moreover, there are four dual FPCs used in special situations of hypertension or in the case of multi-drug therapy are: CCB + β-blocker; thiazide-like diuretic + CCB; β blocker + ACEI; thiazide diuretic + vasodilator β-blocker [14].

4.3.2 The drug of choice for triple-drug fixed-dose combination

The most frequently triple-drug FPC were ACEI/ ARB + CCB + thiazide/thiazide-like diuretic. Two triple FPCs perindopril/indapamide/amlodipine and olmesartan/amlodipine/HTC are available for patients who fail to meet blood pressure goals with the combination of two drugs. They contain the direct vasodilator amlodipine, indapamide that increases natriuresis, while the consequent RAS stimulation is efficaciously counteracted by the ACEI perindopril.

The PIANIST trial included 4731 uncontrolled hypertensive patients at high or very high CVD risk treated with perindopril/indapamide/amlodipine. BP targets were reached by 72.0% of patients treated with triple therapy and by 81% and 91% of patients previously treated with an ACEI/HCTZ or an ARB/HCTZ combination, respectively. To confirm, the PAINT trial also showed that perindopril/ indapamide/amlodipine provided an adequate 24-h BP control in patients who did not achieve PB target with 2 antihypertensive agents. The TRINITY trial performed on 2492 patients with BP ≥ 140/100 or ≥ 160/90 mmHg showed a significantly higher proportion (69.9%) in achieving BP target at the end of the study compared with treatment with two drugs olmesartan/amlodipine (52.9%), olmesartan/ HCTZ (53.4%) and amlodipine/HCTZ (41.1%) [13].

4.3.3. Dual and triple fixed-dose combination of other classes of antihypertensive drugs

Available drug combinations of potassium-sparing diuretics or β-blockers are possible further therapeutic options in patients with hypertension resistance or in patients with specific indications for these agents. The salt-retaining state often present

in patients with resistance hypertension most likely due to inappropriate aldosterone secretion, so spironolactone may be more beneficial than other classes of drugs. β-blockers are in certain clinical settings such a. angina, post-MI, heart failure, or ventricular rate control).

4.3.4. The quarter-dose quadruple combination

One small trial reported in 2007 studied the effect of the quadpill, a single capsule containing 4 BP-lowering drugs, and showed a substantially greater blood pressure reduction in the quarter-dose group of -13.1 (-20.1 to -6.1)/-7.9 (-12.1 to -3.7) mm Hg compared with monotherapy [15]. A randomised, placebo-controlled, double-blind, crossover trial of a quadpill-a single capsule with 55 patients in 2017 has demonstrated the efficacy and safety of a single pill combination containing four blood pressure-lowering drugs each at quarter-dose (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg, and atenolol 12.5 mg) [16]. Recently, the multi-centre trial termed Quadruple UltrA-low-dose tReatment for hypErTension (QUARTET), has demonstrated the efficacy, tolerability, and simplicity of a quadpill-based strategy and showed a fixed-dose quadruple quarter-dose combination achieved and maintained greater blood pressure lowering compared with the traditional approach of starting monotherapy [17].

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