DOI 10.1007/s11094-022-02678-z
Pharmaceutical Chemistry Journal, Vol. 56, No. 5, August, 2022 (Russian Original Vol. 56, No. 5, May, 2022)

MOLECULAR-BIOLOGICAL PROBLEMS OF DRUG DESIGN AND MECHANISM OF DRUG ACTION

POLYPILL CONCEPT IN THE TREATMENT OF ARTERIAL HYPERTENSION (REVIEW)

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 56, No. 5, pp. 3 – 9, May, 2022.

Original article submitted February 28, 2022.

This review discusses relevant issues of antihypertensive therapy with fixed-dose combination pills (polypills). Special features of polypills are considered. Their technology classification is given. Evidence is presented that treatment with polypills affecting several risk factors (e.g., antihypertensive, hypolipidemic, antithrombotic) can improve medication adherence; provide effective cure, particularly blood pressure (BP) lowering; and cause fewer adverse events. It is important to note that polypill-based therapy implements a personalized approach in the treatment of hypertension, provides effective and safe BP control, and decreases the level of cardiovascular risk factors.

Keywords: hypertension, polypills, personalized medicine.

The incidence of arterial hypertension (AH) among the adult population of the Russian Federation is 30 – 45%, reaching >60% among those older than 60 years [1]. According to predictions, the number of hypertension patients in the world will increase by 2025 by 15 – 20%, reaching almost 1.5 billion people [2]. Elevated arterial pressure (AP) is the main cause of premature death because of ischemic heart disease (IHD) and stroke. Also, AH is a leading risk factor for the development of heart failure, atrial fibrillation, chronic kidney disease, peripheral artery disease, and cognitive decline [3, 4]. This makes the search for approaches to effective and safe therapy of AH exceptionally important for modern medicine and pharmacy. The complex of such measures includes a change of (healthier) lifestyle, correction of risk factors, and pharmacotherapy [4]. A preferably fixed combination of antihypertensive drugs that facilitates not only higher efficacy than monotherapy but also increased adherence to treatment as compared to unfixed combinations is recommended for use as starting pharmacotherapy for practically all patients (with few exceptions) [4, 5]. Hence, the design and use of drugs in tablet or capsule form that contain simultaneously several drug substances (polypill) are especially interesting. The goal of the present study was to review modern data on combined AH therapy using the polypill concept to achieve the required clinical outcomes and to ensure patient adherence to the treatment.

Modern groups of antihypertensive drugs and their rational combinations

Five major classes of antihypertensive drugs are currently recommended for use in AH therapy. These are angiotensin-converting enzyme inhibitors (iACE), angiotensin II receptor blockers (ARB), calcium-channel blockers (CCB), thiazide and thiazide-like diuretics, and β-adrenergic blockers (BB) [4].

AH therapy should begin with a combination of two drugs, preferably as a fixed combination. The exception is a small cohort of patients with a low initial AP level close to

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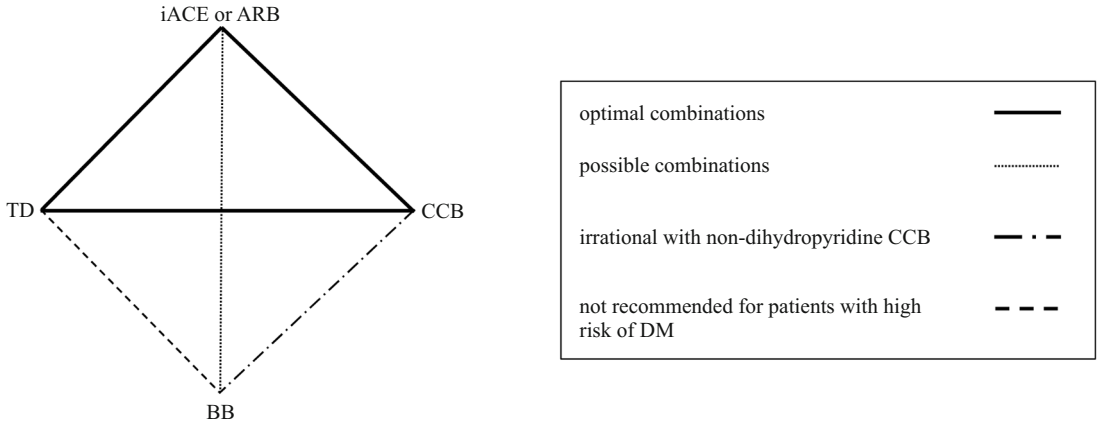

Fig. 1. Combinations of antihypertensive drugs. Abbreviations: BB, beta-adrenergic blockers; CCB, calcium-channel blockers; ARB, angiotensin II receptor blockers; iACE, ACE inhibitors; TD, thiazide/thiazide-like diuretics; DM, diabetes mellitus.

the recommended target values for whom monotherapy may be efficacious and impaired elderly patients that require a gradual reduction of AP [4]. The optimal combinations are considered a blocker of the renin-angiotensin system (RAS) (iACE or ARB) with a dihydropyridine CCB or a thiazide/thiazide-like diuretic (TD) (Fig. 1) [6].

Combined therapy, including an iACE or ARB in combination with a CCB or thiazide/thiazide-like diuretic, is based on the complementary action of the drugs because CCBs and diuretics lead to RAS activation, which is compensated by the combined use of an iACE or ARB. These combinations also reduce the probability of developing adverse effects characteristic of CCB or diuretic monotherapy because they help to lower the risk of hypokalemia due to the diuretics and peripheral edemas associated with CCB administration. These combinations also block the RAS, which is an important therapeutic strategy for many patient categories, e.g., those with diagnosed diabetes mellitus, left ventricle hypertrophy, or proteinuria [3].

An understanding of the limitations of a monotypic approach to patient treatment based on the application of unified rules for all patients makes it imperative to develop personalized medical solutions in terms of rationally justified therapy, despite ground-breaking anecdotes on combined antihypertensive therapy being given in clinical recommendations of professional societies [7]. This allows consideration of age and gender specifics of individual patients, features of the pathological evolution of the process, possible comorbidities and risk factors, and the personal response to the pharmacotherapy and a recommendation for an individually selected combination of specific pharmacological agents within recommended drug classes [8, 9].

Polypill concept in therapy of arterial hypertension

A personalized choice of antihypertensive combinations and doses as polypills is one such solution for AH therapy. A polypill is a fixed combination of three and more drugs in a single tablet or capsule [10]. The term was first proposed by the English scientists Wald and Law [11]. The polypill concept arose from the theoretical hypothesis that administration of different drugs as a fixed combination used to monitor various cardiovascular risk factors could reduce the frequency of cardiovascular events by 80% [11].

The first polypill was a fixed, theoretically justified combination of a statin, acetylsalicylic acid, folic acid, and three antihypertensive drugs (iACE, TD, BB). Half doses of the antihypertensive drugs used in the polypill significantly reduced the AP with less frequent manifestation of side effects [11].

The main distinguishing feature of polypill drugs is the simultaneous action on several pathogenetic patterns of disease formation and progression [12]. Greater adherence to the treatment by patients and improved clinical outcomes are promoted by using polypills instead of free combinations [13].

Antihypertensive therapy as a fixed combination or polypill should meet the following criteria [12, 14]:

the existence of an evidence base confirming the efficacy and safety of each polypill component, inclusion of drugs in international recommendations for treatment of cardiovascular diseases (CVD) with a high level of proof;

complementary action of antihypertensive drugs and improvement of the therapeutic outcome if used in combination;

similar pharmacodynamic and pharmacokinetic parameters of the drugs;

use of the polypill drug for base and not temporary therapy;

the ability to prescribe polypills to patients with a different associated pathology.

Polypill as a dosage form

With respect to pharmaceutical technology, polypills can be a solid gelatin capsule with various fillers or a multi-layered tablet.

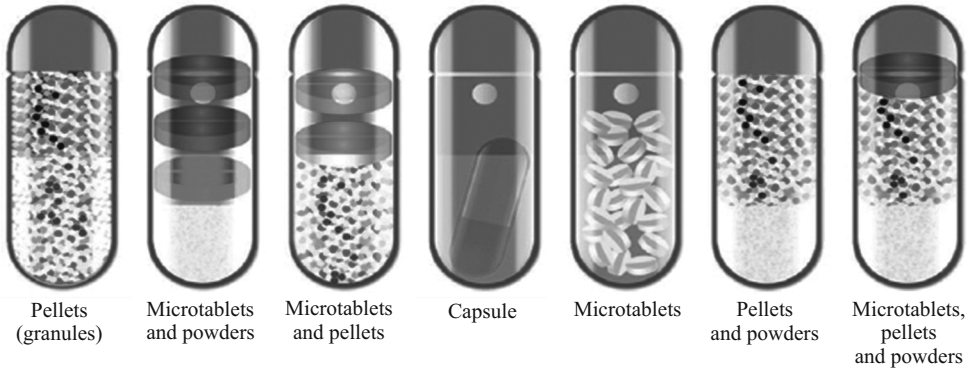

Fig. 2. Filling variations of solid gelatin capsules, i.e., polypills.

A solid gelatin capsule is filled with a mixture of powders, pellets (granules), microtablets, or smaller capsules. Also, various combinations of fillers, e.g., powder and microtablets, pellets and microtablets, powder, pellets, and microtablets can be used (Fig. 2) [15 – 17].

Polypills as multi-layered tablets can be divided by technology class into tablets produced by a multi-layered method (multi-layered matrix tablets) [18] (Fig. 3) and tablets produced by deposition of a film shell on a tablet core (tablet in tablet) [19]. The active ingredients and excipients can be added in the shell or core composition [20].

The popularity of multi-layered tablets grew as the equipment improved and experience with their fabrication and use accumulated. A single-die tablet press and rotary tableting machines with multiple loading of the matrix are used to manufacture multi-layered tablets by layered tableting. The latter can be used for multiple supply of various granulates [18].

Also, 3D printing is used to manufacture multi-layered tablets. An example is the development by English researchers of a 3D polypill with antihypertensive and hypolipidemic action [21]. This dosage form contains three antihypertensive drugs (lisinopril dihydrate, indapamide, and amlodipine besylate) and a hypolipidemic agent (rosuvastatin calcium). The 3D polypill was produced as follows. A 3D printer operating by fused deposition modeling (FDM) technology (layered fusion) melted filaments (threads, each of which contained one drug in a certain concentration) and deposited them by layers, forming a model of a four-layered tablet set by a program. The release profile of the drugs with various physicochemical properties could be controlled by varying the sequence of layers of the multi-layered tablet [21]. Therefore, the proposed systems provided flexibility for including several active ingredients in a single polypill with an optimized release profile of each active ingredient and individual doses. This was important for developing approaches to personalized therapy of cardiovascular diseases.

Figure 4 shows an example of a multi-layered tablet in which the tablet core contains the active ingredient clopidogrel bisulfate. The core is coated with an impermeable hydrophobic shell. The outer layer contains rosuvastatin calcium. The impermeable hydrophobic layer prevents degenerative processes caused by direct mixing of clopidogrel and rosuvastatin [22].

A polypill as a solid gelatin capsule or multi-layered tablet solves important problems of combined drugs such as [16, 18]:

physicochemical or pharmacological incompatibility of combined components;

monitoring release of active ingredients, e.g., prolonged action of several active ingredients, regulation of their absorption sequence;

adherence of patients to therapy by combining several drugs into one dosage form.

Advantages of using polypills in therapy of AH

The use of polypill drugs for AH therapy has several advantages:

1. Enhancement of the antihypertensive effect by the multi-directional action of the drugs on pathogenic mechanisms of AH development. This increases the number of patients with stable AP lowering [14, 23]. According to current

Fig. 3. Bilayer tablet (layered tableting method).

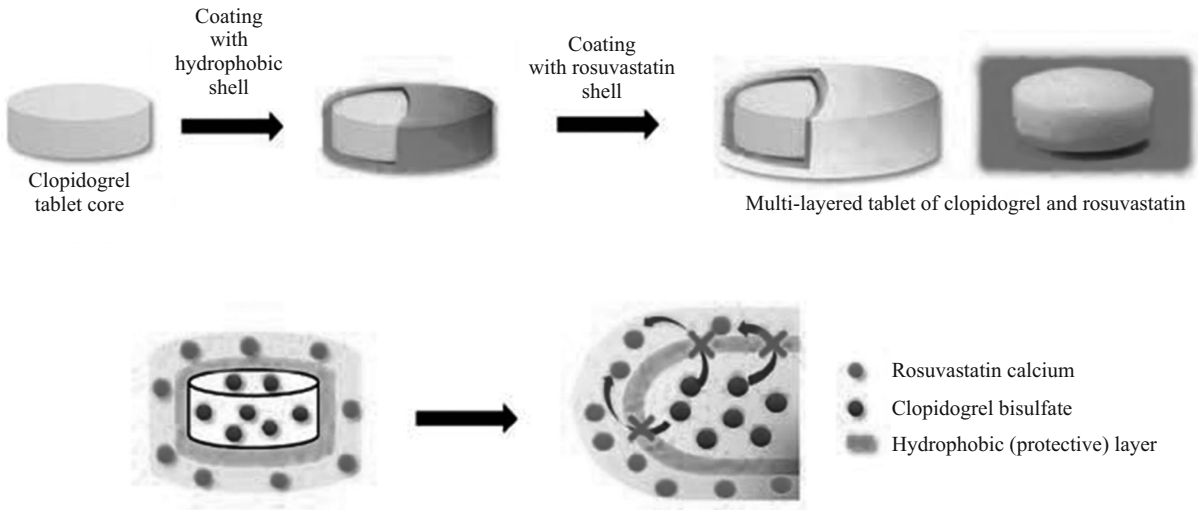

Fig. 4. Diagram of production of multi-layered tablet of clopidogrel and rosuvastatin.

thinking, AP is raised by various mechanisms and systems (renin-angiotensin-aldosterone, sympathoadrenal, etc.) closely interacting with each other. The effect on the AP of antihypertensive drugs is often disrupted because counter-regulatory mechanisms are activated. The combination of several drugs actually interacting with compensatory responses of each of them significantly increases the monitoring frequency of the AP level [14].

2. The known rationality of the proposed combination of antihypertensive drugs, which allows the treating physician to avoid mistakes possible with prescription of arbitrary (unfixed) combinations of antihypertensive drugs [13].

3. The decreased incidence of side effects because smaller doses of combined drugs are used. The reduced doses in fixed combinations allows the incidence of side effects to be reduced upon reaching the target AP level. Also, the incidence of side effects can be reduced because of the mutual neutralization of them [14, 23, 24].

4. Increased adherence of patients to the treatment. A decrease in the number of administered tablets is a significant factor increasing adherence of patients to treatment and improving clinical effects [13]. The probability that patients will stop treatment in those situations where they stop administration upon prescription of drugs in free combinations, e.g., without disease symptoms felt by the patients, inability to reach the desired levels, complicated prescription protocols and many prescribed drugs, wishes to lower costs by refusing to purchase the most expensive drugs, is reduced [25].

5. Provision of the most effective organic protection and decreased risk and number of cardiovascular complications [26]. Modern research comparing antihypertensive therapy by polypills and unfixed combinations demonstrates 20 – 25% increased adherence to treatment, good tolerability, and more pronounced correction of risk factors in groups of patients receiving polypills and not drugs in free combinations [25].

6. The ability to affect additional risk factors of cardiovascular disease progression (dyslipidemia, hypercoagulation) [11].

Results of international research ASCOT-BPLA, HOT, ALLHAT, IDNT, MDRD demonstrate that the AP target level in most cases can be achieved and maintained using combined low-dose therapy [26].

An analysis of results from 354 clinical trials showed that a single administration of half a standard dose provides ~80% efficacy of a standard dose with fewer side effects for TD, BB, and CCB and comparable efficacy upon use of a standard and half dose of iACE and ARB. Also, it is noteworthy that an additive effect upon combination of antihypertensive drugs from various classes reduces AP better than a double dose [27]. This is highly significant not only with respect to the efficacy of AH pharmacotherapy but also for improvement of the treatment tolerability because the incidence of developing side effects after administration of antihypertensive drugs is distinctly dose-dependent [14].

Various clinical trials confirmed the effectiveness of the polypill concept with respect to reduction of the low-density lipoprotein cholesterol (LDL CS) level and AP in terms of both primary and secondary prevention [28].

The randomized clinical trial TIPS-3, in which the efficacy and safety of a polypill containing a combination of simvastatin, three drugs for reducing AP, and aspirin in comparison to a placebo for reducing systolic arterial pressure (SAP), the LDL CS level, and fatal or nonfatal cardiovascular events in patients of moderate risk without CVD in anamnesia, yielded rather interesting data [29]. Use of this fixed combination led to a reduction of the relative risk of adverse outcomes by 31% and by 1.7% on an absolute scale. The dynamics of clinical outcomes were like those in the HOPE-3 trial, where administration of a combination polypill comprising rosuvastatin and two drugs reducing AP (candesartan and hydrochlorothiazide) led to a reduction of

the relative risk by 29% during the middle observation period of 5.6 years [30]. Similar results were obtained during the PolyIran trial, which showed that a combination of atorvastatin, two antihypertensive drugs (hydrochlorothiazide and enalapril or valsartan), and aspirin led to a relative risk reduction by 34% during observation for five years [31].

A definite advantage of polypills in the era of compulsory justified polypharmacy is the decreased number of administered tablets, which is recognized as a significant factor increasing the adherence of patients to the treatment and can also to a certain extent increase its efficacy and safety and reduce the cost of antihypertensive therapy [13]. A meta-analysis of 15 trials including a total of 32 thousand patients in which the administration of a fixed combination was compared to a combination of the same components as separate drugs found greater adherence of patients to antihypertensive therapy if polypills were used. Significant differences in the attainment of the target AP level and the incidence of developing side effects were not noted [32].

Adherence of patients to treatment with administration of polypills

The search for ways to overcome the serious burden of comorbidity and the polypharmacy dictated by this in most AH patients is extremely critical. Broader use of fixed combinations of antihypertensive drugs with multi-targeted effects that increase the adherence to therapy and its efficacy and safety is a key to solving these problems [13].

Canadian researchers conducted a trial in which clinical databases of two patient groups aged 65 years and older taking polypill AH therapy and free combinations were compared. It was observed in this trial that the hospitalization level and lethal outcomes related to heart failure, infarct, or stroke were significantly lower in patients receiving therapy as fixed combinations than in the patient group taking free antihypertensive combinations. The researchers drew the conclusion that administration of polypills increased the adherence to treatment, improved clinical outcomes, and reduced the risk of cardiovascular complications [33].

High adherence to treatment could reduce lethality by 46% [34]; development of myocardial infarct, by 24%; stroke, by 23%; chronic heart failure, by 34% [35]. The adherence to treatment with drugs affecting the cardiovascular risk level (antihypertensive drugs, hypolipidemics, hypoglycemics) remained low in actual practice and was inversely correlated to the number of administered tablets [25, 36].

Literature data suggest that the adherence of patients to therapy is inversely related to the complexity of the prescribed treatment regimen and number of administered drugs. For example, low adherence was observed in % of cases with prescription of one tablet. The incidence increased to ~20% if two tablets were prescribed and to 40%, for three tablets. The incidence of nonobservance of recommendations was very high, up to total refusal of treatment, if five or more tablets were prescribed [37].

Therefore, a definite advantage of the administration of polypills is a reduction in the number of tablets taken by patients and a corresponding increase in the adherence of patients to treatment [23].

Limitations on the use of polypills

Several limitations for prescribing polypills exist despite the many advantages of AH therapy as fixed combinations.

1. The probability of prescribing an unneeded component at the start of therapy if polypills are used [23].

2. The presence of contraindications to the prescription of one of the antihypertensive drugs included in the polypill [25].

3. The fixed doses of polypill components limits the ability of the treating physician to select the optimal dose of each antihypertensive agent for the patient. Titration of the dose is objectively difficult and can be accomplished only by increasing the dose of the whole combination or by adding a new antihypertensive drug as an additional tablet [24, 25, 33].

However, the lack of correctly selected doses is not always associated with a fixed combination. The European Society of Cardiology and European Society of Hypertension in guidelines of 2018 reported a problem with treatment inertia, i.e., inadequate dose titration of drugs. Existing evidence suggests that inertia contributes to suboptimal control of AP and leads to many patients remaining on monotherapy and/or receiving suboptimal doses of drugs, despite inadequate AP control [3].

4. The patient remains without immediate protection of all factors before prescription of therapy in free combinations if one component of the treatment must be withdrawn (appearance of a serious side effect) [25].

5. The cost of a polypill in the ideal situation should be less than the cost of each component separately. However, the cost of fixed combinations, in contrast to single drugs, is not regulated by the *State Registry of Limiting Allowed Prices of Manufacturers for Drugs Included in the List of Essential Medicines* [38]. Therefore, the cost of fixed combinations on the Russian pharmaceutical market is often higher than that of the single drugs [23].

Thus, the polypill concept remains an attractive strategy for prevention and treatment of CVD because it combines the major drug classes with a proven effect on the prognosis (antihypertensive, hypolipidemic, antithrombotic) in a single tablet. Such action is characterized not only by the simultaneous effect on several risk factors but also the improvement of adherence to treatment. It probably reduces the treatment costs. This personalized approach to selecting antihypertensive therapy can increase the efficacy and safety of the treatment and reduce the cardiovascular risk level.

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