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TIMES TO ACT. Italian-Spanish-Polish-Uzbek Expert Forum Position Paper 2022. Dyslipidemia and arterial hypertension: The two most important and modifiable risk factors in clinical practice

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Abstract

Hypertension and lipid disorders are two of the main cardiovascular risk factors. Both risk factors — if detected early enough — can be controlled and treated with modern, effective drugs, devoid of significant side effects, available in four countries as different as Italy, Spain, Poland, and Uzbekistan. The aim herein, was to develop this ***TIMES TO ACT*** *consensus to raise the awareness of the available options of the modern and intensified dyslipidemia and arterial hypertension treatments. The subsequent paragraphs involves consensus and discussion of the deleterious effects of COVID-19 in the cardiovascular field, the high prevalence of hypertension and lipid disorders in our countries and the most important reasons for poor control of these two factors. Subsequently proposed, are currently the most efficient and safe therapeutic options in treating dyslipidemia and arterial hypertension, focusing on the benefits of single-pill combination (SPCs) in both conditions. An accelerated algorithm is proposed to start the treatment with a PCSK9 inhibitor, if the target low-density-lipoprotein values have not been reached. As most patients with hypertension and lipid disorders present with multiple comorbidities, discussed are the possibilities of using new SPCs, combining modern drugs from different therapeutic groups, which mode of action does not confirm the "class effect". We believe our consensus strongly advocates the need to search for patients with cardiovascular risk factors and intensify their lipid-lowering and antihypertensive treatment based on SPCs will improve the control of these two basic cardiovascular risk factors in Italy, Spain, Poland and Uzbekistan.* (Cardiol J 2022; 29, 5: 730–738)

Key words: cardiovascular prevention, hypertension, hypercholesterolemia, single-pill combination (SPC)

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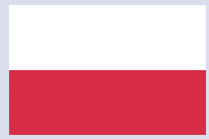
Introduction

Hypertension and lipid disorders, especially hypercholesterolemia (too high plasma low-density lipoprotein [LDL] concentration, which is the most atherogenic lipid fraction) are two of the main cardiovascular risk factors. Both risk factors — if detected early enough — can be controlled and treated with modern, effective drugs, devoid of significant side effects. All these drugs are currently available in the four countries mentioned, which are as different as Italy, Spain, Poland, and Uzbekistan. Table 1 presents a comparison of the epidemiological, population, wealth and medical care characteristics in these countries. Considering the high prevalence of cardiovascular risk factors in these countries and the deleterious effect of coronavirus disease 2019 (COVID-19) on the cardiovascular community, the aim was to develop the **TIMES TO ACT** consensus to raise the awareness of the available options of the modern and intensified dyslipidemia and arterial hypertension treatment. Below, in the subsequent paragraphs of the consensus, the treatment of dyslipidemia and arterial hypertension is discussed, focusing on the benefits of single-pill combination (SPC) approach in both conditions [1, 2].

TIMES TO ACT

The pandemic time has impacted all patients over the last 2 years. The COVID-19 pandemic

Table 1. Comparison of the epidemiological, population, wealth and medical care characteristics in countries of the authors of the presented Position Paper. Regarding the different methods of data collection and management in different countries, the presented data should be interpreted with caution.

Parameters	 Italy	 Spain	 Poland	 Uzbekistan
Population at the time of writing the Position Paper	60 million	47 million	38 million + 2 million immigrants from the Ukraine	33 million
Population density (inhabitants/km^2)	200	96	122	77
GDP per capita — recent data announced before the pandemic in 2019	36,957 USD	40,139 USD	31,939 USD	7665 USD
Elevated LDL cholesterol	20 million (33%)	7 million (15%)	19 million (48%)	17.5 million (53%)
Arterial hypertension	18 million (31%)	19 million (40%)	12 million (30%)	8.6 million (26%)
Active smoking	11 million (18%)	9 million (19%)	8 million (20%)	6.3 million (19%)
Obesity (BMI > 30 kg/m^2)	10 million (17%)	8 million (17%)	7 million (18%)	6.2 million (18%)
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)	4 million (7%)	8 million (17%)	4.5 million (11%)	3.1 million (9%)
Diabetes mellitus	3.5 million (6%)	4 million (9%)	3 million (8%)	5.2 million (16%)
Heart failure with reduced ejection fraction	1.2 million (2%)	1.2 million (2.5%)	1.2 million (3%)	0.9 million (2.7%)
Number of doctors per 10,000 inhabitants	40	53	24	26
Number of cardiologists per million inhabitants	300	50	100	30
Number of internists per million inhabitants	480	228	480	182
Number of family doctors/ /general practitioners per million inhabitants	600	770	580	686

BMI — body mass index; GDP — gross domestic product; eGFR — estimated glomerular filtration rate; LDL — low-density lipoprotein

was associated not only with a significant number of deaths due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and collateral deaths resulting from the failure of the health care system, but has also drawn attention to the need for good control of cardiovascular risk factors, with multiple measures undertaken to improve prognosis, especially in patients at high cardiovascular risk [3–6]. It is people with cardiovascular risk factors who died more often and experienced the severe course of COVID-19 more often [4, 7, 8]. The literature frequently refers to syndemics — diseases accompanying the pandemic, in which the deterioration of care, as well as particularly high mortality in the case of SARS-CoV-2 virus infections were observed [9, 10]. Syndemics includes: arterial hypertension, hypercholesterolemia, diabetes, obesity or heart failure [11, 12]. All of these conditions increased the risk of death due to COVID-19 [13]. At the same time, the pandemic itself was associated with less frequent detection of arterial hypertension, less frequent laboratory tests in the field of lipid disorders, generating the so-called health debt in many countries [14]. Therefore, there is a need to make up for this debt and to intensify the treatment of hypertension and lipid disorders in all our countries [15].

Irrespective of which country was analyzed, in each of the countries, the percentage of patients with hypertension ranges from 26% to 40% and patients with hypercholesterolemia — from 15% to 53%. In total, in four of these countries it was estimated that 17–32% of patients were obese, 18–21% smoked cigarettes, 6–15% had diabetes, 7–17% suffered from chronic kidney disease, and at least 1–3% had heart failure [16–18]. When analyzing medical care that targets the most important cardiovascular risk factors, the biggest problem is the relatively small number of cardiologists per 10,000 inhabitants in Uzbekistan, there were a small number of all medical doctors in Poland and Uzbekistan, a high prevalence of obesity and diabetes in Uzbekistan, a high prevalence of chronic kidney disease in Spain and too many active smokers in all the countries [19–21].

Cardiovascular risk factors closely coexist, but hypertension and hypercholesterolemia are undoubtedly the easiest to control with the use of adequately selected, modern drugs, which are well-tolerated by patients. The most important reasons for poor control of these two factors on a population scale remain unchanged and mainly include:

— Insufficient awareness and diagnostics of these diseases [22–24];
— No treatment, even after setting the diagnosis [25–27];
— Low adherence and persistence to chronic long-term treatment [28–32];
— Lack of properly selected and, if necessary, increasing intensity of pharmacotherapy (therapeutic inertia) — using too low doses of medications [33–35];
— Lack of consciousness that the medications should be administered for the rest of patients' life [36–38];
— Failure to use the most modern pharmacological options which are very effective and safe, and instead — continuation of therapy using medications from older generations, with lower efficacy [39–41];
— The lower target levels of these risk factors recommended in the recent years, especially with regard to LDL-cholesterol, with the target levels < 55 mg/dL (< 1.4 mmol/L), along with a reduction of at least 50% from the initial value in patients at very high cardiovascular risk, and < 70 mg/dL (< 1.8 mmol/L) in patients at high cardiovascular risk [42, 43].

Monotherapy seems to still be a very important step in hypercholesteremia treatment. Therefore, it is so crucial to choose the right statin to start the LDL-cholesterol lowering therapy. Statins reduce cholesterol synthesis in the liver by competitively inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA, hydroxy-methylglutaryl coenzyme A) reductase. They belong to the most extensively-studied drugs in the prevention of cardiovascular diseases, and their effect on the reduction of cardiovascular deaths has been demonstrated in many clinical studies. The most effective statin to reduce the LDL-cholesterol level available today is rosuvastatin [44]. Even in the apparently statin-intolerant patients, re-starting lipid-lowering treatment with low-dose rosuvastatin is a reasonable option [45].

Regarding the lipid-lowering potency, the lowest recommended dose of rosuvastatin, 5–10 mg, is equivalent to 20–30 mg atorvastatin. This means that the conversion of the lipid-lowering effectiveness of rosuvastatin to atorvastatin corresponds more to a ratio of 1:3 rather than 1:2. Therefore, the availability of the 15 mg and 30 mg doses of rosuvastatin in some countries increases the applicability of rosuvastatin to patients who are already taking 40 mg and 80 mg of atorvastatin, respectively. Atorvastatin undergoes biotransformation in the liver via the CYP450 3A4 system, while rosuvastatin is metabolized by the liver only to a minor

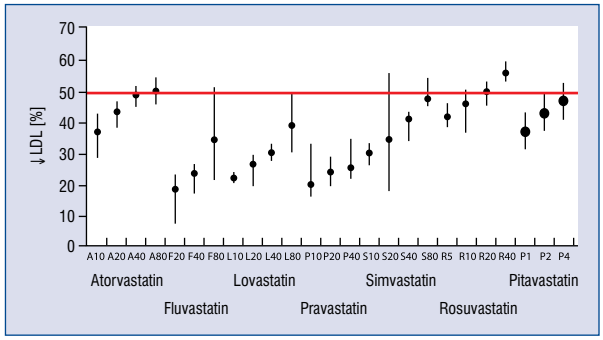


Figure 1. Comparison of lipid-lowering efficacy of the currently available statins in different doses. The horizontal line shows the 50% low-density lipoprotein (LDL) reduction, required by the latest European guidelines for the treatment of hypercholesterolemia in all patients at high and very high cardiovascular risk (adapted from: [45, 47]).

extent, interacting with the CYP2C9 isoenzyme and to a much lesser extent with CYP3A4. These differences are important because of the potential for drug interactions, which are very rare with rosuvastatin. Rosuvastatin doses of 40 mg/24 h provide the greatest confidence in reducing the baseline LDL-cholesterol by at least 50%, which is required by the latest European guidelines for the treatment of hypercholesterolemia in all patients at high and very high cardiovascular risk (Fig. 1) [46, 47].

Ezetimibe is an essential companion for statin, preferably rosuvastatin to maximize the lipid-lowering effect nowadays [48]. It is estimated that only few percent of patients in the studied countries achieve the currently recommended target levels of LDL-cholesterol, and the reasons for this therapeutic failure are mainly:

— Lack of determination of doctors to use the strongest statins in the maximum tolerated doses (therapeutic inertia);
— Patients' reluctance and fear of using statins and disinformation by the so-called anti-statin movements, especially active in social media ("nocebo" phenomenon);
— A real intolerance of high doses of statins in some patients, mainly in the form of myalgia;
— Too infrequent use of combination therapy, based on the use of several lipid-lowering drugs with different mechanisms of action, which allow using the maximal tolerated doses of statins, while maintaining the therapeutic efficacy.

The above-mentioned reasons make it reasonable to recommend SPC, a single pill containing at least two substances, as the next step in pharmacotherapy — combinations containing statin and ezetimibe — a drug that reduces the absorption of cholesterol from the intestine.

The current European recommendations are based on models suggesting starting the therapy with a statin, adding ezetimibe after a few weeks (another oral drug with a different mechanism of action), and if it does not work — introducing additional injections of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (Fig. 2) or inclisiran, introduced recently in some countries [49, 50].

In the current situation, in the post-COVID-19 era, it is often not possible to wait a few weeks to reach the target LDL level due to the difficulties in contacting the treating physician or a generated "health debt" in the system. It is also not reasonable to start the treatment with even the highest dose of a statin, if it is clear that it will not achieve the LDL target level anyway. In such cases, particularly in patients who require more than 50% LDL-cholesterol reduction, we propose the second model (Fig. 3) — to accelerate the algorithm — administer a statin with ezetimibe immediately and control the LDL cholesterol level a few weeks later to assess whether the addition of PCSK9 inhibitor is required [51, 52].

Statin choice with specific rosuvastatin increasing rapidly in many countries has also some pharmacological background reasons. As rosuvastatin has a lower risk of drug interactions, it has recently become a combination substance in SPC formulas, not only with ezetimibe [45]. An SPC combining rosuvastatin and an antiplatelet drug in one tablet (acetylsalicylic acid), recommended especially in the secondary prevention, may substantially simplify the therapy of many patients who have indications for both acetylsalicylic acid and a statin therapy [53]. On the other hand, the combination of rosuvastatin with the most popular and most extensively studied calcium antagonist (rosuvastatin/amlodipine) is an example of a hybrid, two-component SPC that simultaneously treats hypertension and hypercholesterolemia [54].

Treatment of arterial hypertension differs among many countries, but the principles and groups of antihypertensive drugs are common and widely recognized by International, American, European and national hypertension societies guidelines [55]. It has been proven many times that countries where an exceptionally high percentage of SPC preparations are used — such as Portugal or Spain — achieve better population

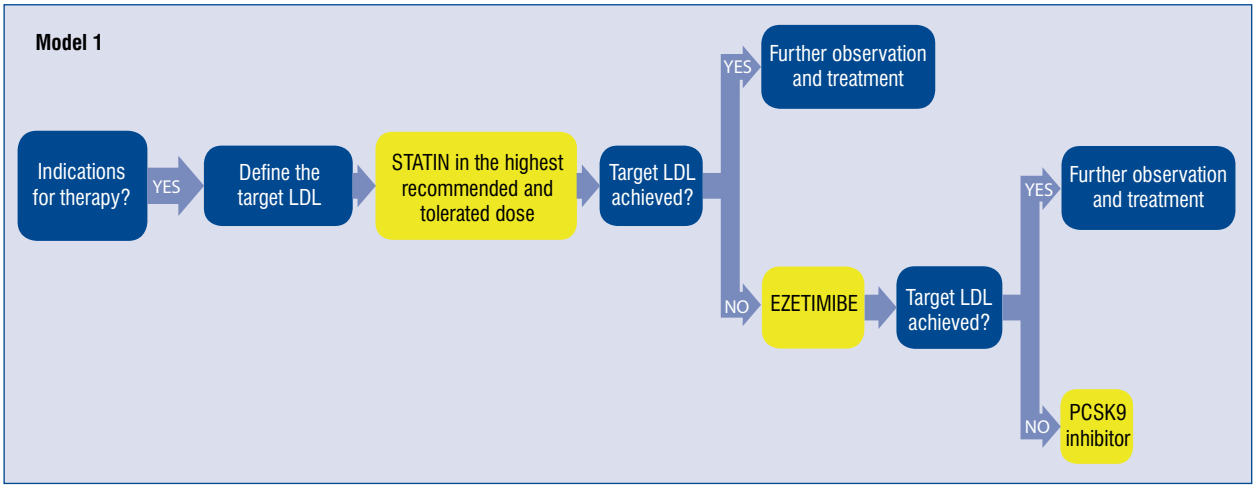


Figure 2. First model: the three-step algorithm for the treatment of hypercholesterolemia promoted in Europe from 2019; mandatory from 2020 (date of guidelines publication), developed by the European Society of Cardiology (adapted from: [48], modified); Y (yes) — goal achieved; N (no) — goal not achieved; LDL — low-density lipoprotein; PCSK9 — proprotein convertase subtilisin/kexin type 9.

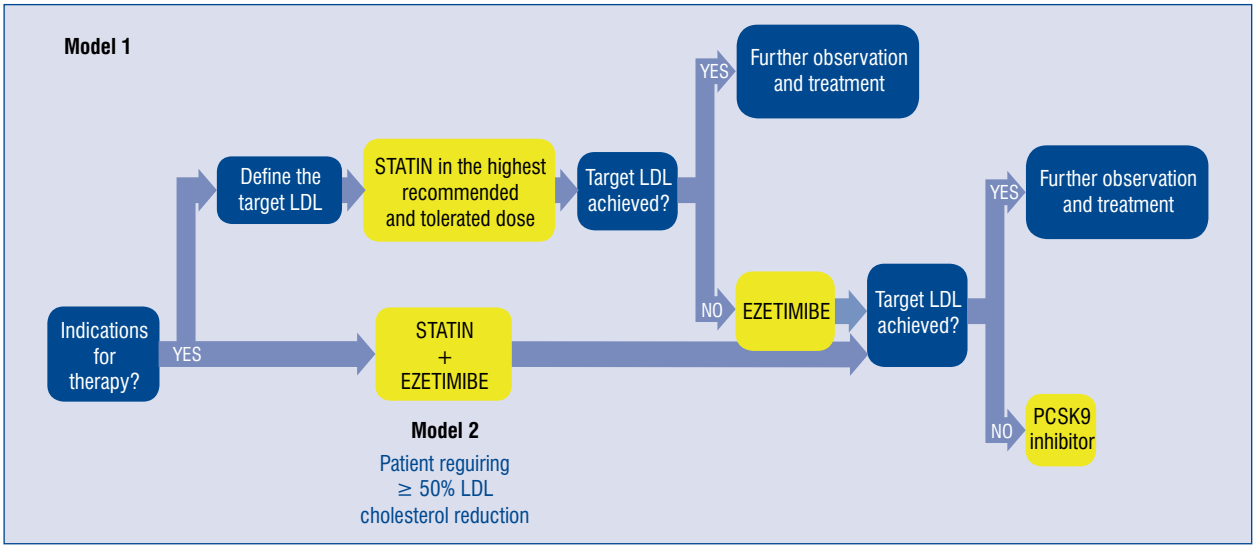


Figure 3. Second model. Accelerated algorithm to start the potential treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (adapted from: [48], modified); LDL — low-density lipoprotein.

blood pressure control. The European guidelines from 2018 recommend the use of SPC as the first step of antihypertensive treatment [56]. An SPC should consist of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist (ARB), in combination with a calcium channel blocker or a diuretic. Already in the second step of treatment, the combination of a drug that inhibits the renin–angiotensin system with a calcium antagonist and a diuretic in SPC can be used. A summary of this algorithm is shown in Figure 4. Hence, it is so important to be able to use the combined SPC of the most popular ACE inhibitors or ARB with a calcium channel blocker and/or a diuretic [57, 58].

One pill to treat arterial hypertension in SPC formula is becoming more and more popular [59, 60]. As a rule, SPC are available in several potencies, so the doses of drugs within a single SPC can be tailored to the individual needs of a patient [61–63].

For example, ramipril is one of the most commonly used ACE inhibitors in Europe and in the

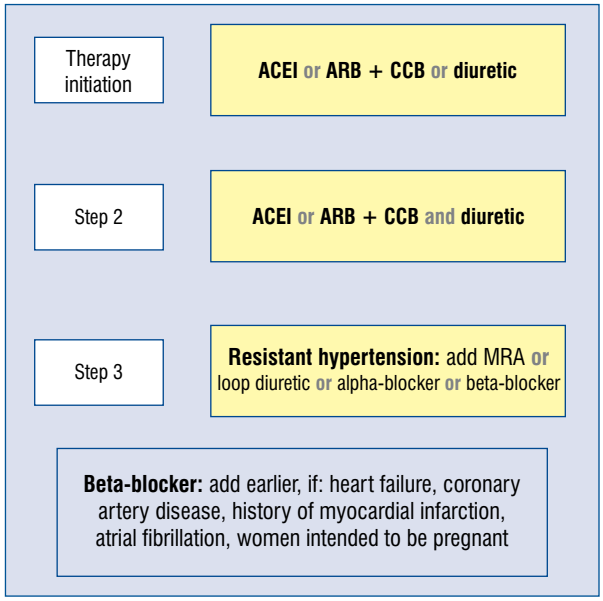


Figure 4. Algorithm to initiate antihypertensive therapy in most patients with arterial hypertension, as recommended in the 2018 guidelines of the European Society of Cardiology (adapted from: [56], modified); ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor antagonist; CCB — calcium channel blocker; MRA — mineralcorticoid receptor antagonist.

world, and the availability of its combinations with a diuretic, a calcium channel blocker (amlodipine), and as a triple combination (ramipril/amlodipine/ /hydrochlorothiazide) allows the continuation of antihypertensive treatment at various stages, intensification of treatment, if necessary, and enables the therapy with substances belonging to the most--extensively studied cardiological drugs [64, 65].

Regarding the ARB group, the most frequently selected drugs are those which ensure the 24-h blood pressure control, and which were showed to have the highest treatment efficacy in head-to--head studies against other drugs. According to the Experts of this Position Paper, the long-acting ARB like candesartan, olmesartan and telmisartan might be considered in the first place. In the case of their use, clinicians should be able to use SPC combining them with a calcium antagonist or a diuretic.

In the next stage of treatment, the availability of the three-component SPCs, such as candesartan/ /amlodipine/hydrochlorothiazide, olmesartan/amlodipine/hydrochlorothiazide, telmisartan/amlodipine/hydrochlorothiazide might further facilitate the control of the difficult to manage hypertension.

Additional SPC combinations are needed for some subsets of patients. For some patients, SPCs combinations other than those listed in the general arterial hypertension algorithm are particularly useful in clinical practice. A large group of patients in the secondary prevention of cardiovascular events requires the simultaneous administration of an ACE inhibitor and highly cardioselective beta--blocker. In this subgroup, SPC combining the most commonly used drugs in this group — bisoprolol and ramipril in one pill is of particular importance. Large groups of patients with chronic coronary syndromes, acute coronary syndromes, heart failure or atrial fibrillation are also typical patients who might benefit from such SPC. In some patients, an SPCs combining a beta-blocker and a calcium antagonist and a calcium antagonist with a diuretic may also be considered in some patients.

Comorbidities will be the essential factor for optimal treatment of arterial hypertension and hypercholesterolemia, as they contribute to the whole-panel risk factors of the patient. Therefore, it is so important for the patients who are the target population of this Position Paper to take care of weight reduction, smoking, adequate diabetes control, physical activity, salt restriction, healthy diet, inhibition of the chronic kidney disease and prevention of heart failure. To achieve this goal, regulation follow-up visits where compliance will be assessed are crucial. New therapies recently introduced in Europe (sodium-glucose co-transporter-2 [SGLT2] inhibitors — flozins or glucagon-like peptide 1 agonists) may help to tackle many of the above-mentioned health challenges and can be compared with statins regarding their wide-range action. New SPCs based on SGLT2 inhibitors are also expected to be introduced to the market in the future. Before our eyes, an epochal change in the treatment of diabetes is taking place, with the shift from sulfonylurea derivatives to the newest drugs: SGLT2 inhibitors, glucagon-like peptide 1 analogues.

Furthermore, there are many implications of wider possibilities of using new, modern drugs within the individual therapeutic groups, which mode of action does not confirm the "class effect". In this context, the following molecules might be particularly preferable as SPC combinations in the future:

- Eplerenone, and in the future finerenone over spironolactone [66];
- Torasemide over furosemide [67];
- Ranolazine over trimetazidine [68];
- Nebivolol over older beta-blockers [69].

Times to act is the title of our Position Paper. We believe that in post-COVID times, the need to

intensify treatment, to actively search for patients with cardiovascular risk factors, especially with hypercholesterolemia and arterial hypertension, should go hand in hand with the implementation of the latest therapy based on SPC with well-established, effective lipid-lowering and antihypertensive molecules, many of which are mentioned in our document [70]. This approach will enable even better control of these two basic cardiovascular risk factors in Italy, Spain, Poland and Uzbekistan.

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