ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

CARDIOLOGY JOURNAL

ISSN: 1897-5593

e-ISSN: 1898-018X

STRUGGLE FOR. Italian-Polish-Spanish-Uzbek-Vietnamese Expert Forum Position Paper 2023 for better control of classical modifiable risk factors in clinical practice

Authors: Krzysztof J. Filipiak, Vivencio Barrios, Claudio Ferri, Khurshid Fozilov, Santiago Jesus Freire Castro, Agnieszka Kuzior, Francisco Javier Martinez-Martin, Guzal Mullabaeva, Lan Hieu Nguyen, Ulugbek Nizamov, Anna Tomaszuk-Kazberuk, Raisa Trigulova, Aleksandra Gąsecka

DOI: 10.5603/cj.96912

Article type: Experts' Viewpoint

Submitted: 2023-08-09

Accepted: 2023-09-19

Published online: 2023-11-15

Articles in "Cardiology Journal" are listed in PubMed.

STRUGGLE FOR. Italian-Polish-Spanish-Uzbek-Vietnamese Expert Forum Position Paper 2023 for better control of classical modifiable risk factors in clinical practice

Krzysztof J. Filipiak et al., Italian-Polish-Spanish-Uzbek-Vietnamese Position Paper 2023

Krzysztof J. Filipiak[1, 2], Vivencio Barrios[3], Claudio Ferri[4], Khurshid Fozilov[5], Santiago Jesus Freire Castro[6], Agnieszka Kuzior[7], Francisco Javier Martinez-Martin[7, 8], Guzal Mullabaeva[9], Lan Hieu Nguyen[10], Ulugbek Nizamov[5], Anna Tomaszuk-Kazberuk[11], Raisa Trigulova[12], Aleksandra Gąsecka[13]

[1]Institute of Clinical Science, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland

[2]Department of Hypertensiology, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland

[3]Cardiology Department, University Hospital Ramon y Cajal, Alcalá University, Madrid, Spain

[4]University of L'Aquila – MeSVA Department – UOC Internal Medicine and Nephrology – Hypertension and Cardiovascular Prevention Unit, San Salvatore Hospital, Coppito, AQ, Italy

[5]Republican Specialised Center of Cardiology, Tashkent, Uzbekistan

[6]Servicio de Medicina Interna Complexo, Hospitalario Universitario A Coruña, Spain

[7]Endocrinology and Nutrition Department at Hospitales Universitarios San Roque, Las Palmas de Gran Canaria, Spain

[8]Endocrinology and Nutrition Department at Hospital Universitario de Gran Canaria Doctor Negrin, Las Palmas de Gran Canaria, Spain

[9]Department of Mini-invasive Cardiac Surgery and Rehabilitation, Republican Specialised Center of Cardiology, Tashkent, Uzbekistan

[10]Cardiology Department, Hanoi Medical University Hospital, Hanoi, Vietnam

[11]Department of Cardiology, Lipidology and Internal Medicine with Intensive Cardiac Care Unit, Medical University of Bialystok, Poland

[12]Department of Ischemic Heart Disease and Atherosclerosis, Republican Specialised Center of Cardiology, Tashkent, Uzbekistan

[12]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland

Address for correspondence: Prof. Krzysztof J. Filipiak, FESC, Institute of Clinical Science, Maria Sklodowska-Curie Medical Academy, Pl. Żelaznej Bramy 10, 00–136 Warszawa, Poland, tel: +48 22 703 43 86, e-mail: krzysztof.filipiak@uczelniamedyczna.com.pl

Abstract

The progress in pharmacotherapy that has been made in recent years, including the introduction of very effective and safe lipid-lowering and antihypertensive drugs, has not yet translated into the expected universal control of blood pressure, lipid disorders and diabetes. In the STRUGGLE FOR Italian-Polish-Spanish-Uzbek-Vietnamese Expert Forum Position Paper 2023, experts from five countries recounted several points about the paradigms of cardiological and cardiometabolic care for better control of classical modifiable risk factors in the year 2023. It is believed herein, that the need to intensify treatment, actively search for patients with cardiovascular risk factors, especially with arterial hypertension, hypercholesterolemia and diabetes, should go hand in hand with the implementation of the latest therapy, based on single pill combinations including proven, effective antihypertensive, lipid-lowering and antidiabetic molecules, many of which are listed in the present document. There is a need to use both new technological concepts, completely new drugs, as well as novel treatment concepts such as metabolic treatment in coronary artery disease, try to intensify the fight against smoking in every way, including the available range of drugs and procedures reducing the harm. This approach will provide substantially better control of the underlying cardiovascular risk factors in countries as varied as Italy, Poland, Spain, Uzbekistan and Vietnam.

Keywords: cardiovascular prevention, diabetes, smoking, single-pill combination (SPC)

Introduction

The progress in pharmacotherapy that has been made in recent years — the introduction of very effective and safe lipid-lowering and antihypertensive drugs — has not yet translated into the expected universal control of blood pressure and lipid disorders [1]. We have much to do in terms of non-pharmacological and pharmacological methods to control these risk factors, detect them early and implement effective therapy [2–4]. We still do not deal well with such basic risk factors as obesity and smoking [5]. On the other hand, an increasing number of patients worldwide suffer nowadays from diabetes, and a growing number are being diagnosed with chronic kidney disease [6]. All these factors lead to increased prevalence of atherosclerotic cardiovascular diseases (ASCVD) such as coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease, heart failure and chronic kidney disease [7].

Experts from five countries as varied as Italy, Poland, Spain, Uzbekistan and Vietnam, located on one Eurasian continent, decided to recall in several points the selected paradigms of cardiological and cardiometabolic care from the perspective of the year 2023 and highlight those aspects that might be, in our opinion, successfully implemented in clinical practice. A comparison of the epidemiological, population wealth, social-economic and medical care characteristics in our countries are presented in Table 1 [8, 9].

According to the classification made by the European Society of Cardiology (ESC), four of the countries represented by experts fell into completely separate categories of the population for cardiovascular risk [10]:

— Spain — to low cardiovascular risk countries;

— Italy — to countries of intermediate cardiovascular risk;

— Poland — to high cardiovascular risk countries;

— Uzbekistan — to very high cardiovascular risk countries.

This classification does not include Vietnam, but based on the recently published data, it might be considered as a country of at least highest cardiovascular risk, like Poland [11].

The gathered experts from five countries with fundamentally different populations for cardiovascular risk: Italy, Poland, Spain, Uzbekistan and Vietnam believe that common guidelines for optimizing pharmacotherapy can be formulated for all these countries based on the strategy: STRUGGLE FOR.

STRUGGLE FOR

Struggle for better control of the cardiovascular risk factors remains the cornerstone of medical activity. Daily therapeutic efforts should be aimed at combating cardiovascular risk factors, implementing healthy lifestyle, appropriate diet — optimally in the DASH model or the Mediterranean diet, maintaining optimal body weight, increasing physical activity and combating smoking [12].

TIMES TO ACT — the first Expert Position Paper of the present group, published in the year 2022, mainly focused on combating hypertension and hypercholesterolemia, which are still important epidemiological problems, since the percentage of patients with hypertension ranges from 25% to 40% and patients with hypercholesterolemia ranges from 15% to 53% in all these five countries [13–16]. We should not forget, however, that in total, in these five countries, it is estimated that over 34 million patients are obese, over 53 million smoke cigarettes, over 21 million suffer from diabetes, more than 28 million have chronic kidney disease, and at least 5 million suffer from heart failure with reduced left ventricular ejection

fraction (HFrEF). Millions of these patients suffer from ASCVD and should be chronically treated with three basic drugs: acetylsalicylic acid (ASA), statins, angiotensin-converting enzyme (ACE) inhibitors in many cases; often also beta-blockers, cardioprotective and metabolic drugs [17]. Cardiovascular risk factors closely coexist, but arterial hypertension and hypercholesterolemia are undoubtedly among the most feasible to control with the use of adequately selected, modern drugs, well-tolerated by patients [18, 19]. The most important reasons for poor control of these two factors on a population scale remain unchanged and can be mainly considered as:

— insufficient diagnosis of these diseases [20];

— no treatment initiation, even after diagnosis [21];

— inappropriate drug selection and too low intensity of therapy (therapeutic inertia) — too low treatment intensity [22];

— lack of awareness of doctors and patients that is needed to continue the therapy mostly for the rest of a patients' lifetime [23];

— no implementation of latest available pharmacological options and instead continuation of therapy with older, less effective drugs [24];

— changing target values of proper control of these risk factors in the recent years, especially in terms of low-density lipoprotein (LDL)-cholesterol, with target concentrations reaching < 55 mg/dL (< 1.4 mmol/L) in patients at very high and < 70 mg/dL (< 1.8 mmol/L) in patients at high cardiovascular risk;

— increasing amount of data supporting the benefits of lowering blood pressure to 120–129/70–79 mmHg, not only in patients under 65 years of age, which will probably be discussed in the new treatment guidelines for the management of arterial hypertension of the European Society of Hypertension (2023) and the European Society of Cardiology (2024).

Roughly speaking, 80-90% of cardiovascular risk reduction could be obtained by controlling only four major cardiovascular modifiable factors [25, 26]:

— arterial hypertension;
— hypercholesterolemia;
— smoking;
— diabetes.

Since our first document TIMES TO ACT was mainly dedicated to arterial hypertension and hypercholesterolemia, in the document STRUGGLE FOR we will focus more on diabetes and smoking, among other risk factors [27, 28].

Urgent actions in many of our countries are required to implement easier, more convenient forms of drugs essential for the optimal control of the above risk factors and diseases, mainly:

arterial hypertension, hypercholesterolemia, diabetes. Many different forms of single pill combinations (SPCs) were introduced to the pharmaceutical market, and it is our duty to promote this form of therapy in the guidelines of national scientific societies and in the reimbursement regulations of individual countries [29, 30]. For example, in an Italian Awareness-raising Campaign on Hypertension, among 13,196 treated hypertensive elderly patients, only 25% were on a fixed combination therapy of two and only 1.3% of three drugs. What is crucial, patients on a fixed combination therapy were more adherent to treatment than their counterparts ($p < 0.001$) and full adherence increased with the number of pills used [14].

These SPCs may include:

— combinations of antihypertensive drugs such as ACE inhibitors/angiotensin receptor blockers (ARBs) with diuretics and/or calcium antagonists, both in two-component and three-component SPCs. Such combinations remain the first, most often recommended step in the treatment of hypertension (two-component SPC) or the second step in the therapeutic algorithm (three-component SPC) to treat hypertension as long as possible with one tablet;

— combinations of one of the most popular ACE inhibitors (ramipril) and beta-blockers (bisoprolol), which can be used in a wide range of patients, including patients with arterial hypertension, CAD and HFrEF. In all these indications, a combination of ACE inhibitor and beta-blocker reduces the number of administered tablets and promotes compliance;

— combinations of statins — the most important lipid-lowering drugs, including the most potent statin — rosuvastatin — both with ezetimibe (increasingly recommended as first-line SPC in patients at high and very high cardiovascular risk) [31, 32] and with ASA for patients with ASCVD [33].

— combinations of basic oral antihyperglycemic drugs in one tablet, such as metformin extended release (XR) and dipeptidyl peptidase 4 (DDP-4) inhibitors (metformin XR/sitagliptin), metformin with sodium-glucose cotransporter-2 (SGLT-2) inhibitors or DDP-4 inhibitors with SGLT2 inhibitors and metformin could be very helpful for metabolic control and cardio-nephro-vascular protection.

Goals of treatment are more easily achievable when the means leading to their accomplishment are more straightforward, easier to apply and more accepted by patients. Common cardiovascular risk factors (especially hypertension, dyslipidemia, diabetes, smoking) accelerate atherosclerosis, thus leading to ASCVD. In many patients, the first manifestation of CAD is an acute coronary syndrome, the latter resulting sometimes in left ventricular damage and the pandemic of HFrEF. Heart failure is also a consequence of

hypertension and diabetes, where it manifests mainly as heart failure with preserved left ventricular ejection fraction (HFpEF) and less commonly as HFrEF.

Patients from these three large epidemiological groups:

— arterial hypertension;

— CAD;

— heart failure;

— can also be offered, among the basic drugs used in these diseases, various forms of SPC, the use of which is still too rare. The chart below illustrates well how some patient groups can be treated according to the current guidelines with the use of only a few tablets, for example patients with heart failure — with only three tablets, CAD — only two tablets, and arterial hypertension — with only one two- or three-compound tablet (Central illustration).

Great progress has been made recently in the pharmacotherapy of diabetes. Oral antidiabetic drugs that prolong life, reduce the risk of cardiovascular death, decrease the risk of heart failure or kidney damage have emerged in front of our eyes [34]. Today, we attribute the above-mentioned features to flozins (SGLT-2 inhibitors) [35, 36]. The second extremely important group of drugs — GLP-1 receptor agonists — seem to be even more beneficial than SGLT-2 inhibitors in two aspects: weight loss and stroke prevention [37]. Unfortunately, in some of our countries, the economic availability of SGLT-2 inhibitors and GLP-1 receptor agonists is low, as these drugs are not reimbursed at all or not in the first line of treatment, which means that antidiabetic therapy is still initiated with other oral drugs. While metformin is still the first-line drug in this situation, including its more favourable and more convenient forms of extended release for the patient (metformin XR), which have much improved gastrointestinal tolerance [38] and are recommended in the current NICE (UK) guidelines for type 2 diabetes as first-line treatment when conventional (immediate release) metformin is not well tolerated [39]. In addition, the wide use of sulfonylureas in many countries (including Poland and Uzbekistan) raises serious concerns. Therefore, it seems necessary to introduce more modern oral drugs, which are not associated with weight gain and risk of hypoglycemia, and have proven cardiovascular and renal safety such as DPP-4 inhibitors [40] instead of sulfonylureas, as well as SPCs combining DPP-4 inhibitors with modern forms of metformin (for example sitagliptin/metformin XR). The early use of metformin and DPP-4 inhibitors as first-line therapy is recommended in the present American Diabetes Association type 2 diabetes guidelines [41] when there are no compelling indications for SGLT-2 inhibitor or GLP-1 receptor agonists, and is associated with greater and more long-term benefits than the conventional first-line monotherapy with metformin [42].

In some countries, there is plenty of action to be taken to switch the therapy from drugs with no cardiovascular benefit and safety concerns (sulfonylureas) to newer classes of drugs with well-established safety profile in terms of hypoglycaemia and cardiovascular risk such as DPP-4 inhibitor/metformin XR combinations, SGLT-2 inhibitors and GLP-1 receptor agonists. The latter two also have well-established cardioprotective effects. The difference in the use of particular groups of drugs in some of our countries is striking, for example in Spain approximately 50% of oral antidiabetics prescribed are DPP-4 inhibitors and only 10% are sulfonylureas. In contrast, in Poland and Uzbekistan over 50% are sulfonylureas and only below 10% are DPP-4 inhibitors, according to pharmaceutical data reports from the beginning of 2023.

The availability of metformin XR varies per country as well. For example, in Italy and Poland it is present and reimbursed, in Uzbekistan it is present, but not reimbursed, while in Spain it was not available until last year.

Surprisingly, the current targets for blood pressure, LDL-cholesterol, HbA1c and the use of flozins/GLP-1 receptor agonists are met in only a small minority of our patients with type 2 diabetes. New drugs and SPCs might help our patients in many aspects. The introduction of an SPC consisting of metformin XR and sitagliptin to the Spanish market, where extended-release metformin was never available before, in spite of its greatly improved tolerability, has created the opportunity to rechallenge patients previously labelled as metformin-intolerant [43]. The recent observational trial has been highly successful, with 86% of patients tolerating half the target dose and 72% tolerating the full target dose; while the metabolic control of the patients was significantly improved, both for fasting glucose and HbA1c [43]. Many of those patients with diabetes also have CAD or heart failure. Here, too, substantial use of the newer SPCs can be made, as we have proposed in the Central illustration.

Last but not least, some CAD patients still need better control of ischemic syndromes irrespectively of cardiac invasive procedures, statins, beta-blockers, ACE-inhibitors, anti-platelets. In those patients, European Guidelines for the diagnosis and management of CAD offer optimization of treatment based on metabolic drugs [44], among which they mention four substances in the following order:

— ranolazine;

— ivabradine;

— nicorandil;

— trimetazidine.

The current place of these drugs as an adjunctive to the classical therapy of CAD is shown in Table 2. While nicorandil is not available in many countries, the use of ranolazine, ivabradine, trimetazidine differs between our countries.

Ranolazine mechanism of action is summarized in Figure 4. Ranolazine is becoming more and more popular in some countries, as a unique inhibitor of the fast Na^+ current (I_{NaF}) and the late Na^+ current (I_{NaL}), which is responsible for depolarization of the myocardial cell. The effects of ranolazine are mainly related to the influence on the late I_{NaL} current. I_{NaL} current activation is induced by "acquired" pathological conditions such as ischemia and myocardial infarction, where its benefits are supported by large-scale clinical data. Moreover, some benefits in terms of left ventricular hypertrophy, HFpEF and HFrEF, as well as atrial fibrillation and genetically determined diseases: long QT syndrome (types 3, 9, 10) and Brugada syndrome have been suggested. However, these data are mostly experimental and currently do not support the clinical use of ranolazine in these conditions [45].

Ranolazine was first used as an antianginal drug. Information regarding its antiarrhythmic properties emerged from the MERLIN-TIMI 36 study. In a group of 6,560 patients with acute coronary syndrome without ST segment elevation in whom ranolazine was started and the ambulatory electrocardiogram was monitored to assess ischemic changes, a significant reduction in arrhythmias including atrial fibrillation and ventricular tachycardia was observed. Thus, ranolazine has a satisfactory safety profile and seems to have additional anti-arrhythmic activity.

Eventually, our attention goes back to nonpharmacological optimalization and control of traditional risk factors. Smoking is such a risk factor. Among the nicotine addiction treatment, short-term administration of nicotine is considered to be an adjunctive to behavioural therapy for patients planning to quit smoking. Various forms of nicotine replacement therapy are available in the world in the form of gums (may cause: dry mouth, dyspepsia, hiccups, heartburn, nausea), patches (may cause: local skin reactions in a very large percentage of people, the need to stick them on depilated skin or in anatomical areas with little hair, sleep disorders, heart rhythm disturbances, strong morning craving for nicotine when using the patches at night), oral inhalers, pulmonary inhalers, nasal sprays, nicotine tablets (may cause: local reactions in the administration routes). Due to the above-mentioned heart rhythm disorders, relative contraindications to such therapy include tachycardia, arrhythmias, CAD, acute coronary syndromes or other conditions corresponding to high cardiovascular risk. The use of the described forms of nicotine replacement therapy is assessed as burdensome, potentially harmful for patients with a cardiovascular history and not very effective.

Therefore, it is difficult to qualify nicotine replacement therapy as a form of the real treatment of nicotine addiction.

Varenicline, bupropion or cytisine may be administered as an aid in the treatment of nicotine addiction. Varenicline, invented as anti-depressant, may be associated with the risk of suicidal thoughts, aggravation of depression, and sleep disorders. Bupropion, a dopamine and norepinephrine reuptake inhibitor, may be effective, but it lowers the seizure threshold and is contraindicated in patients with risk factors for seizures. The drug can also cause headaches, dry mouth, agitation, and insomnia. It has been used traditionally for anxiety-related depression in the United States since 1985 (withdrawn from use in 1986–1989 due to the aforementioned risk of seizures), but since 1997 it also has registration in helping to quit smoking. Caution is also required when using bupropion in patients with hypertension and/or tachycardia. Cases of smoking cessation in people using a combined preparation of bupropion and naltrexone are described, but this form is registered only in the treatment of obesity in some countries and in some cases of overweight associated with chronic diseases. Altogether, the clinical use of varenicline and bupropion in our countries is scarce.

Cytisine has been used for years in Eastern European countries in the treatment of nicotine addiction, available as an over-the-counter drug (Italy, Poland), and recently as a prescribed drug in other countries (Spain, Vietnam) [46]. Cytisine is a natural alkaloid that occurs naturally in several plant genera, such as Laburnum and Cytisus of the family Fabaceae and is generally obtained from the seeds of golden rain Acacia (*Cytisus laborinum*). The drug has a growing scientific literature on its use [47]. Cytisine is a partial agonist of nicotinic receptors, and its mechanism of action is not fundamentally different from varenicline, which is, after all, its derivative. The above drug approaches can be used sequentially, but subsequent therapeutic failures do not predict success in terms of undertaking the next attempt of pharmacological treatment. Some experts are also inclined to postulate earlier inclusion of heat-not-burn products or electronic cigarettes in schemes facilitating quitting cigarettes in a shared-decision making process with a patient [48].

STRUGGLE FOR better control of the cardiovascular risk factors remains the cornerstone of our medical activity **and "STRUGGLE for"** is 2023-year title of our position paper. We believe that the need to intensify treatment, actively search for patients with cardiovascular risk factors, especially with arterial hypertension, hypercholesterolemia and diabetes, should go hand in hand with the implementation of the latest therapy, based on SPCs including proven, effective antihypertensive, lipid-lowering and antidiabetic molecules, many of which we have listed in our document and in the recent European Society of Hypertension

Guidelines for the management of arterial hypertension and 2023 European Society of Cardiology Guidelines for the management of cardiovascular disease in patients with diabetes [49, 50]. We need to use new technological concepts (SPC preparations), completely new drugs and treatment concepts (metabolic treatment in CAD), try to intensify the fight against smoking in every way, including the available range of drugs and procedures in reducing harm. Given that over 55% of cases of incident cardiovascular may be attributable to five modifiable risk factors [51], this approach will give us substantially better control of the underlying cardiovascular risk factors in Italy, Poland, Spain, Uzbekistan and Vietnam. Since many of the risk factors might be attributed to impaired microcirculation function in different vascular beds, therapies to improve microcirculatory function might also prevent cardiovascular complications and subsequently improve prognosis [52].

Acknowledgments

The material was prepared by the International Council of Experts in cooperation with Adamed Pharma S.A.

Conflict of interest: Krzysztof J. Filipiak — Adamed, Alfasigma, AstraZeneca, Bausch Health, Boehringer Ingelheim, Krka, Mundipharma, Mylan, Novartis, Pro.Med.Pl, Servier; Vivencio Barrios — Adamed, Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Ferrer International, Menarini, MSD, Novartis, NovoNordisk, Organon, Pfizer, Recordati, Sanofi-Aventis, Servier, Viatris; Claudio Ferri — Adamed; Khurshid Fozilov — Adamed; Santiago Jesus Freire Castro — Adamed; Ravshanbek Kurbanov — Adamed; Agnieszka Kuzior — NovoNordisk (scientific and teaching activities); Francisco Javier Martinez-Martin — Adamed, Amgen, Boehringer-Ingelheim, Eli Lilly, Menarini, Novo-Nordisk (honoraria for advisories, scientific and teaching activities); Guzal Mullabaeva — NovoNordisk, Pfizer, Servier; Lan Hieu Nguyen — Adamed; Ulugbek Nizamov — Adamed; Anna Tomaszuk-Kazberuk — Adamed, Boehringer Ingelheim, Krka, Novartis, NovoNordisk, Pfizer, Sanofi, Servier, Takeda; Raisa Trigulova — Adamed; Aleksandra Gąsecka — Abiomed, Adamed, AstraZeneca, Krka, Philips.

References

1. Barrios V, Soronen J, Carter AM, et al. Lipid management across Europe in the real-world setting: a rapid evidence review. Curr Med Res Opin. 2021; 37(12): 2049–2059, doi: 10.1080/03007995.2021.1973396, indexed in Pubmed: 34517739.

2. Koutentakis M, Surma S, Rogula S, et al. The effect of a vegan diet on the cardiovascular system. J Cardiovasc Dev Dis. 2023; 10(3), doi: 10.3390/jcdd10030094, indexed in Pubmed: 36975858.

3. Konwerski M, Gromadka A, Arendarczyk A, et al. Atherosclerosis pathways are activated in pericoronary adipose tissue of patients with coronary artery disease. J Inflamm Res. 2021; 14: 5419–5431, doi: 10.2147/JIR.S326769, indexed in Pubmed: 34707383.

4. Gasecka A, Siwik D, Gajewska M, et al. Early biomarkers of neurodegenerative and neurovascular disorders in diabetes. J Clin Med. 2020; 9(9), doi: 10.3390/jcm9092807, indexed in Pubmed: 32872672.

5. Barrios V, Escobar C. Obesity, blood pressure, and cardiovascular outcomes. Lancet. 2013; 381(9882): 1981, doi: 10.1016/S0140-6736(13)61193-9, indexed in Pubmed: 23746891.

6. Liyanage T, Toyama T, Hockham C, et al. Prevalence of chronic kidney disease in Asia: a systematic review and analysis. BMJ Glob Health. 2022; 7(1), doi: 10.1136/bmjgh-2021-007525, indexed in Pubmed: 35078812.

7. Gąsecka A, Rogula S, Szarpak Ł, et al. LDL-Cholesterol and platelets: insights into their interactions in atherosclerosis. Life (Basel). 2021; 11(1), doi: 10.3390/life11010039, indexed in Pubmed: 33440673.

8. De Feo M, Del Pinto R, Pagliacci S, et al. Real-World hypertension prevalence, awareness, treatment, and control in adult diabetic individuals: an italian nationwide epidemiological survey. High Blood Press Cardiovasc Prev. 2021; 28(3): 301–307, doi: 10.1007/s40292-021-00449-7, indexed in Pubmed: 33835433.

9. Del Pinto R, Grassi G, Muiesan M, et al. World hypertension day 2021 in Italy: results of a nationwide survey. High Blood Pressure Cardiovascular Prevention. 2022; 29(4): 353–359, doi: 10.1007/s40292-022-00519-4.

10. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol. 2022; 29(1): 5–115, doi: 10.1093/eurjpc/zwab154, indexed in Pubmed: 34558602.

11. Anh Hien Ho, Tam NM, Tam Vo, et al. Estimation of the cardiovascular risk using world health organization/international society of hypertension risk prediction charts in Central Vietnam. PLoS One. 2020; 15(11): e0242666, doi: 10.1371/journal.pone.0242666, indexed in Pubmed: 33227012.

12. Agabiti Rosei C, Del Pinto R, Grassi G, et al. Prevalence of cardiovascular risk factors and related medical and lifestyle interventions among italian cardiovascular specialists: a proof-of-concept study. High Blood Press Cardiovasc Prev. 2023; 30(3): 255–264, doi: 10.1007/s40292-023-00578-1, indexed in Pubmed: 37155127.

13. Filipiak KJ, Babkowski MC, Cameli M, et al. 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. Cardiol J. 2022; 29(5): 730–738, doi: 10.5603/CJ.a2022.0087, indexed in Pubmed: 36117294.

14. Cardiovascular Prevention Springer. 2021; 28: 457–66.

15. Del Pinto R, Pagliacci S, De Feo M, et al. Italian Society of Hypertension and Federfarma. Prevalence of hypertension and associated cardiovascular risk factors among pharmacies customers: an Italian nationwide epidemiological survey. Eur J Prev Cardiol. 2020; 27(11): 1228–1230, doi: 10.1177/2047487319851301, indexed in Pubmed: 31116573.

16. Van Minh H, Van Huy T, Long DP, et al. Highlights of the 2022 Vietnamese Society of Hypertension guidelines for the diagnosis and treatment of arterial hypertension: The collaboration of the Vietnamese Society of Hypertension (VSH) task force with the contribution of the Vietnam National Heart Association (VNHA): The collaboration of the Vietnamese Society of Hypertension (VSH) task force with the contribution of the Vietnam National Heart Association (VNHA). J Clin Hypertens (Greenwich). 2022; 24(9): 1121–1138, doi: 10.1111/jch.14580, indexed in Pubmed: 36196473.

17. Del Pinto R, Pietropaoli D, Desideri G, et al. Analysis of aspirin use and cardiovascular events and mortality among adults with hypertension and controlled systolic blood pressure. JAMA Netw Open. 2022; 5(4): e226952, doi: 10.1001/jamanetworkopen.2022.6952, indexed in Pubmed: 35412629.

18. Barrios V, Escobar C, Echarri R, et al. Antihypertensive drugs in daily clinical practice: are there differences between genders? Eur Heart J. 2009; 30(5): 624, doi: 10.1093/eurheartj/ehn583, indexed in Pubmed: 19147607.

19. Barrios V, Pintó X, Escobar C, et al. Real-World attainment of low-density lipoprotein cholesterol goals in patients at high risk of cardiovascular disease treated with high-intensity statins: the TERESA study. J Clin Med. 2023; 12(9), doi: 10.3390/jcm12093187, indexed in Pubmed: 37176627.

20. Del Pinto R, Grassi G, Ferri C, et al. Diagnostic and therapeutic approach to sleep disorders, high blood pressure and cardiovascular diseases: a consensus document by the italian society of hypertension (SIIA). High Blood Press Cardiovasc Prev. 2021; 28(2): 85–102, doi: 10.1007/s40292-021-00436-y, indexed in Pubmed: 33630269.

21. Del Pinto R, Grassi D, Bocale R, et al. Blood pressure profiles and cognitive function from adulthood to old age: chasing a golden middle way? J Clin Med. 2021; 10(15), doi: 10.3390/jcm10153243, indexed in Pubmed: 34362026.

22. Del Pinto R, Ferri C. Hypertension management at older age: an update. High Blood Press Cardiovasc Prev. 2019; 26(1): 27–36, doi: 10.1007/s40292-018-0290-z, indexed in Pubmed: 30467638.

23. Del Pinto R, Pietropaoli D, Dobre M, et al. Prognostic importance of long-term SBP variability in high-risk hypertension. J Hypertens. 2020; 38(11): 2237–2244, doi: 10.1097/HJH.0000000000002552, indexed in Pubmed: 32649637.

24. Del Pinto R, Giua C, Keber E, et al. Impact of 2021 ESC guidelines for cardiovascular disease prevention on hypertensive patients risk: secondary analysis of save your heart study. High

Blood Press Cardiovasc Prev. 2023; 30(2): 167–173, doi: 10.1007/s40292-023-00568-3, indexed in Pubmed: 36906668.

25. Rosengren A, Hawken S, Ounpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364(9438): 953–962, doi: 10.1016/S0140-6736(04)17019-0, indexed in Pubmed: 15364186.

26. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364(9438): 937–952, doi: 10.1016/S0140-6736(04)17018-9, indexed in Pubmed: 15364185.

27. Alunno A, Carubbi F, Mariani FM, et al. The interplay between cardiovascular risk, cardiovascular events, and disease activity in primary Sjögren's syndrome: is uric acid the missing link? Nutrients. 2023; 15(7), doi: 10.3390/nu15071563, indexed in Pubmed: 37049403.

28. Casiglia E, Tikhonoff V, Virdis A, et al. Serum uric acid/serum creatinine ratio as a predictor of cardiovascular events. Detection of prognostic cardiovascular cut-off values. J Hypertens. 2023; 41(1): 180–186, doi: 10.1097/HJH.0000000000003319, indexed in Pubmed: 36453660.

29. Szymański FM, Mickiewicz A, Dzida G, et al. Management of dyslipidemia in Poland: interdisciplinary expert position statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. The fourth declaration of Sopot. Cardiol J. 2022; 29(1): 1–26, doi: 10.5603/CJ.a2021.0147, indexed in Pubmed: 34811718.

30. Czech M, Boguslawski S, Smaga A, et al. Use of single pill combinations in the treatment of arterial hypertension in Poland: The current practice and guidelines, the impact on reimbursement spending and patient co-payment. Cardiol J. 2022; 29(3): 405–412, doi: 10.5603/CJ.a2022.0031, indexed in Pubmed: 35578761.

31. Barrios V, Escobar C. Fixed-dose combination of rosuvastatin and ezetimibe: treating hypercholesteremia according to cardiovascular risk. Expert Rev Clin Pharmacol. 2021; 14(7): 793–806, doi: 10.1080/17512433.2021.1925539, indexed in Pubmed: 33970743.

32. Grassi G, Del Pinto R, Agabiti Rosei C, et al. Reduction of high cholesterol levels by a preferably fixed-combination strategy as the first step in the treatment of hypertensive patients with hypercholesterolemia and high/very high cardiovascular risk: a consensus document by the italian society of hypertension. High Blood Press Cardiovasc Prev. 2022; 29(2): 105–113, doi: 10.1007/s40292-021-00501-6, indexed in Pubmed: 34978703.

33. Barrios V, Escobar C, Suarez C, et al. Clinical profile and management of patient patients with ischemic heart disease and/or peripheral artery disease in clinical practice: the APALUSA study. J Clin Med. 2022; 11(12), doi: 10.3390/jcm11123554, indexed in Pubmed: 35743622.

34. Kasprzak JD, Gorczyca-Głowacka I, Sobczak-Kaleta M, et al. Pharmacotherapy of heart failure A.D. 2023. Expert opinion of Working Group on Cardiovascular Pharmacotherapy, Polish Cardiac Society. Kardiol Pol. 2023; 81(5): 537–556, doi: 10.33963/KP.a2023.0110, indexed in Pubmed: 37179465.

35. Gager G, Lewinski Dv, Sourij H, et al. Effects of SGLT2 inhibitors on ion homeostasis and oxidative stress associated mechanisms in heart failure. Biomedicine Pharmacotherapy. 2021; 143: 112169, doi: 10.1016/j.biopha.2021.112169.

36. Gager GM, Gelbenegger G, Jilma B, et al. Cardiovascular outcome in patients treated with SGLT2 inhibitors for heart failure: a meta-analysis. Front Cardiovasc Med. 2021; 8: 691907, doi: 10.3389/fcvm.2021.691907, indexed in Pubmed: 34336954.

37. Wełnicki M, Gorczyca-Głowacka I, Mamcarz A, et al. The use of GLP-1 analogues in the treatment of diabetes in patients with cardiovascular diseases. The expert opinion of the Working Group of Cardiovascular Pharmacotherapy of the Polish Cardiac Society. Kardiol Pol. 2022; 80(12): 1286–1289, doi: 10.33963/KP.a2022.0282, indexed in Pubmed: 36601885.

38. Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. Postgrad Med. 2011; 123(1): 15–23, doi: 10.3810/pgm.2011.01.2241, indexed in Pubmed: 21293080.

39. Guideline N. Type 2 diabetes in adults: Management (update). United Kingdom: National Institute for Health and Care Excellence; 2022.

40. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373(3): 232–242, doi: 10.1056/NEJMoa1501352, indexed in Pubmed: 26052984.

41. Elsayed N. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2017; 40(Suppl 1): S64–S74, doi: 10.2337/dc17-S011 , indexed in Pubmed: 27979895.

42. Matthews DR, Paldánius PM, Proot P, et al. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet. 2019; 394(10208): 1519–1529, doi: 10.1016/S0140-6736(19)32131-2, indexed in Pubmed: 31542292.

43. Martinez Martin JF, Rios-Gomez C, Santana-Ojeda B, et al. Rechallenge with a single-pill combination of sitagliptin plus extended-release metformin in patients labelled as metformin-intolerant: Mostly successful. Endocrine Abstracts. 2023, doi: 10.1530/endoabs.90.ep1105.

44. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425.

45. Gilbert BW, Sherard M, Little L, et al. Antihyperglycemic and metabolic effects of ranolazine in patients with diabetes mellitus. Am J Cardiol. 2018; 121(4): 509–512, doi: 10.1016/j.amjcard.2017.11.021, indexed in Pubmed: 29274809.

46. Walker N, Howe C, Glover M, et al. Cytisine versus nicotine for smoking cessation. N Engl J Med. 2014; 371(25): 2353–2362, doi: 10.1056/NEJMoa1407764, indexed in Pubmed: 25517706.

47. Giorgini P, Di Giosia P, Ferri L, et al. Cardiovascular events in patients with chronic obstructive bronchopulmonary disease. J Cardiovasc Med (Hagerstown). 2017; 18 Suppl 1: e23–e29, doi: 10.2459/JCM.0000000000000437, indexed in Pubmed: 27755224.

48. Gorini G, Ferrante G, Quarchioni E, et al. Electronic cigarette use as an aid to quit smoking in the representative Italian population PASSI survey. Prev Med. 2017; 102: 1–5, doi: 10.1016/j.ypmed.2017.06.029, indexed in Pubmed: 28652088.

49. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023 [Epub ahead of print], doi: 10.1097/HJH.0000000000003480, indexed in Pubmed: 37345492.

50. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J. 2023; 44(39): 4043–4140, doi: 10.1093/eurheartj/ehad192, indexed in Pubmed: 37622663.

51. Magnussen Ch, Ojeda FM, Leong DP, et al. Global Cardiovascular Risk Consortium. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. N Engl J Med. 2023; 389(14): 1273–1285, doi: 10.1056/NEJMoa2206916, indexed in Pubmed: 37632466.

52. Gąsecka A, Filipiak KJ, Jaguszewski MJ. Impaired microcirculation function in COVID-19 and implications for potential therapies. Cardiol J. 2020; 27(5): 485–488, doi: 10.5603/CJ.2020.0154, indexed in Pubmed: 33165898.

Figure 1. Classification of cardiovascular risk in individual countries according to the 2021 European Society of Cardiology Guidelines on cardiovascular disease prevention in clinical practice.

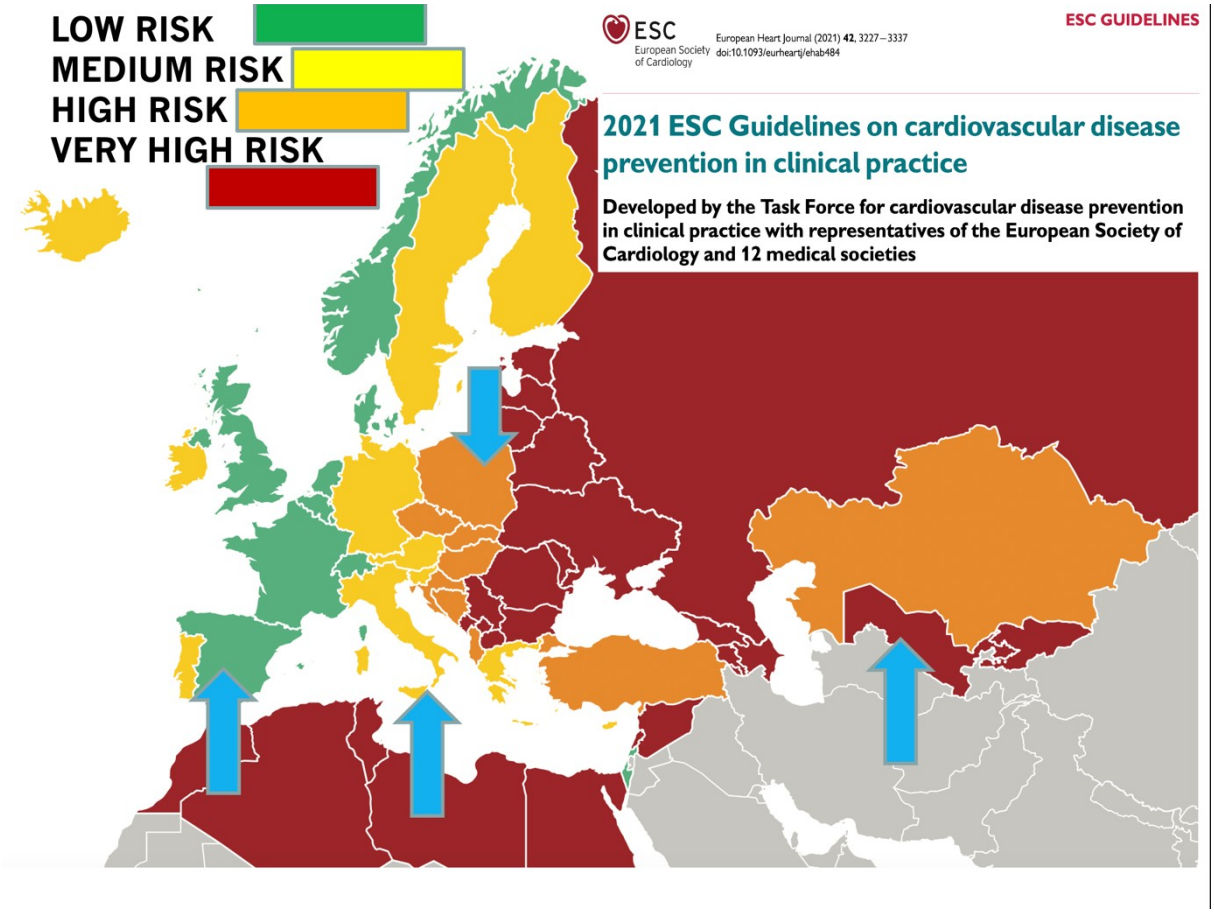
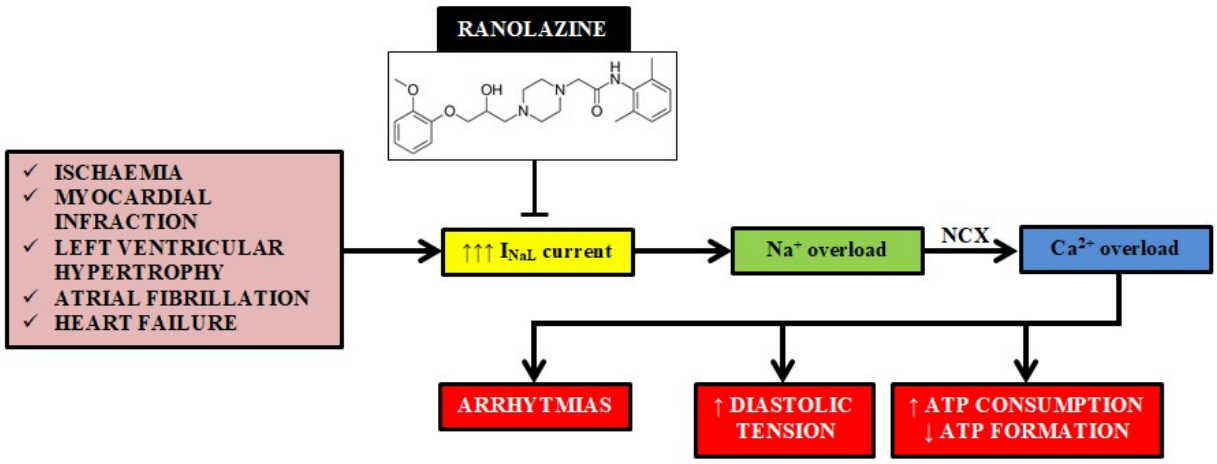


Figure 2. The mechanism of action of ranolazine. The effect of INaL activation is the accumulation of Na^+ ions inside the cell, which leads to increased activity of the sodium-calcium exchanger (NCX) and Ca^{2+} overload. Intracellular excess of Ca^{2+} leads to contractile dysfunction of the heart muscle and its electrical instability. Ranolazine therefore counteracts this phenomenon. Reducing the concentration of Na^+ ions decreases the intracellular concentration of Ca^{2+} ions, which improves the intracellular ion balance [33]; ATP — adenosine triphosphate.



Central illustration. Coexistence of diseases and available single pill combinations; **A.** Coexistence of three cardiovascular diseases: arterial hypertension, heart failure and coronary artery disease with indication for pharmacotherapy recommended by the current guidelines in these diseases, as well as a list of available drug combinations (rectangular frames) that can be used to reduce the number of tablets taken and improve compliance. To simplify the chart, the widely available single pill combinations (SPCs) of angiotensin-converting enzyme (ACE) inhibitors with diuretics and ACE inhibitors with calcium antagonists were omitted, which was extensively discussed in the first document of our group — TIMES TO ACT [13]; **B.** Coexistence of three diseases: diabetes, heart failure and coronary artery disease with indications for pharmacotherapy recommended by the current guidelines in these diseases, as well as a list of available drug combinations (rectangular frames) that can be used to reduce the number of tablets taken and improve compliance; ASA — acetylsalicylic acid.

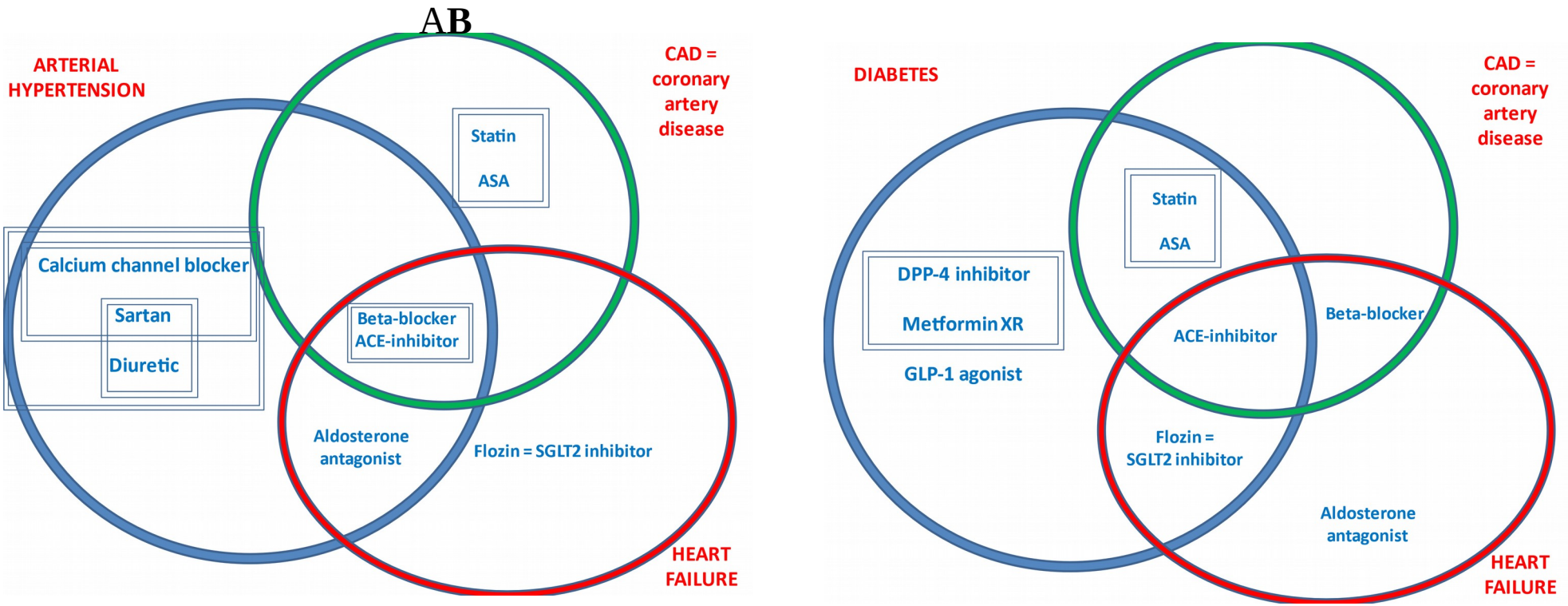
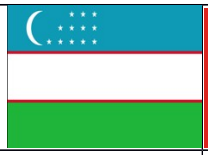


Table 1. Comparison of the epidemiological, population, wealth and medical care characteristics in countries of the authors of the presented Position Paper. Regarding the different methods of data collection and management in different countries, the presented data should be interpreted with caution.

					
	Italy	**Poland**	**Spain**	**Uzbekistan**	**Vietnam**
Population at the time of writing the Position Paper	60 million	38 million + 2 million immigrants from the Ukraine	47 million	33 million	100 million
Population density (inhabitants/km^2)	200	122	96	77	314
GDP per capita — recent data announced before the pandemic in 2019	36 957 USD	31 939 USD	40 139 USD	7 665 USD	3 439 USD
Elevated LDL-C*	20 million (33%)	19 million (48%)	7 million (15%)	17.5 million (53%)	19 million (24.7% among adults)
Arterial hypertension*	18 million (31%)	12 million (30%)	19 million (40%)	8.6 million (26%)	17 million (26% aged 18–69)
Active smoking	11 million (18%)	8 million (20%)	9 million (19%)	6.3 (19%)	19 million (24.8% ages ≥ 15)
Obesity (BMI > 30 kg/m^2)	10 million (17%)	7 million (18%)	8 million (17%)	6.2 (18%)	3.24 million (3.6%)
Chronic kidney disease (eGFR < 60 mL/min)	4 million (7%)	4.5 million (11%)	8 million (17%)	3.1 (9%)	8.74 million (12.8% ages ≥ 20)
Diabetes mellitus	3.5 million (6%)	3 million (8%)	5 million (10%)	5.2 (16%)	4.6 million (7.06% ages 18–69)
Heart failure with reduced ejection fraction	1.2 million (2%)	1.2 million (3%)	1.2 million (2.5%)	0.9 (2.7%)	0.5–1.5 million
Number of doctors per 10,000 inhabitants	40	31	53	26	10
Number of cardiologists per million inhabitants	300	100	50	30	110
Number of	480	480	228	182	64

internists per million inhabitants					
Number of family doctors/general practitioners per million inhabitants	600	580	770	686	92

*Different methodologies for assessing the frequency of elevated LDL-C and arterial hypertension in individual countries have been adopted, but the members of the Expert Panel have chosen the values that are based on the most frequently cited studies in a specific country; BMI — body mass index; GDP — gross domestic product; eGFR — estimated glomerular filtration rate; LDL-C — low density lipoprotein cholesterol

Table 2. Comparison of four main metabolic drugs proposed by 2019 European Society of Cardiology Guidelines for the diagnosis and management of coronary artery disease.

	ranolazine	**ivabradine**	**nicorandil**	**trimetazidine**
Mechanism of action	Selective inhibitor of the late inward sodium current	Inhibitor of the If current in the sinus node	Potassium channel opener	Metabolic activity at the energy level of a single cardiomyocyte
Main use — current position in the guidelines	Chronic coronary syndromes (especially in patients with supraventricular arrhythmias and/or diabetes)	Heart failure as an adjunctive to beta-blocker in patients with sinus tachycardia to lower heart rate; less often — chronic coronary syndromes	Chronic coronary syndromes	Chronic coronary syndromes
Particular benefits of combination with other coronary drugs: beta-blockers or calcium antagonists	+	(+)	–	+
Particular benefit in patients with heart failure and left ventricle systolic dysfunction	–	+	–	–
Particular benefit in patients with tachycardia	–	+	–	–
Particular benefits in patients with diabetes	+	–	–	–

Particular benefits in patients with atrial fibrillation	+	–	–	–
Precautions	Prolongs the QTc interval — requires caution in patients with QT prolongation or in combination with drugs that prolong QT; on the other hand, in some congenital long QT syndromes, ranolazine may be the drug of choice	Only used in patients with sinus rhythm, increased risk of bradycardia	May cause nausea, vomiting, potentially severe ulceration of the mouth, intestines and mucous membranes	Contraindicated in Parkinson's disease, tremors, muscle stiffness, gait and restless legs syndrome; caution required in elderly patients with chronic kidney disease
Evidence-based medicine	Study in > 6,500 patients with acute and chronic coronary syndromes — reduction of recurrent ischemia in subgroups	BEAUTIFUL studies — 10,917 patients with chronic coronary syndrome and LVSD — no significant benefit, SIGNIFY study — 19,102 patients with coronary syndrome and without LVSD — no benefit; SHIFT study — very favourable results in patients with HFrEF	Randomized controlled trial IONA in 5,126 patients — reduced risk of major adverse cardiovascular events (composite endpoint), with no effect on mortality and the risk of myocardial infarction	Available meta-analyses of smaller studies — anti-ischemic effect

LVSD — left ventricle systolic dysfunction; HFrEF — heart failure with reduced ejection fraction