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Safety Profile of Cardiovascular Pharmacotherapy in Patients with Multiple Comorbidities: A Narrative Review of Polypharmacy, Drug Interactions, and Individualized Treatment

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Abstract

Patients with multiple chronic diseases frequently require complex cardiovascular pharmacotherapy, creating a major challenge for achieving therapeutic benefit while minimizing adverse drug reactions, drug–drug interactions, drug–disease interactions, and treatment-related complications. Cardiovascular diseases commonly coexist with diabetes mellitus, chronic kidney disease, obesity, chronic obstructive pulmonary disease, liver dysfunction, anemia, neurological disorders, and other age-related conditions. The resulting polypharmacy can substantially alter drug pharmacokinetics and pharmacodynamics and may increase the risk of hypotension, electrolyte abnormalities, bleeding, bradycardia, arrhythmias, renal injury, metabolic disturbances, and hospitalization. Older adults are particularly vulnerable because of age-related changes in renal and hepatic function, altered body composition, frailty, and increased sensitivity to several cardiovascular agents. This narrative review examines the safety profile of commonly used cardiovascular drugs in patients with multiple comorbidities, emphasizing antihypertensive agents, diuretics, β-blockers, renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, calcium channel blockers, antiplatelet agents, anticoagulants, lipid-lowering drugs, antiarrhythmic agents, and newer cardiometabolic therapies. Particular attention is given to patients with chronic kidney disease, diabetes, heart failure, atrial fibrillation, obesity, and geriatric multimorbidity. The review also discusses clinically important drug–drug and drug–disease interactions, renal and hepatic dose adjustment, polypharmacy, potentially inappropriate medications, medication reconciliation, therapeutic monitoring, and deprescribing. Contemporary guideline recommendations increasingly support individualized, multidisciplinary treatment rather than a disease-by-disease prescribing approach. A structured medication review integrating comorbidity burden, renal and hepatic function, frailty, life expectancy, treatment goals, and patient preferences is therefore essential. Safe cardiovascular pharmacotherapy should ultimately balance evidence-based cardiovascular risk reduction with the prevention of medication-related harm.

Keywords: cardiovascular drugs, multimorbidity, polypharmacy, drug interactions, medication safety

Graphical Abstract

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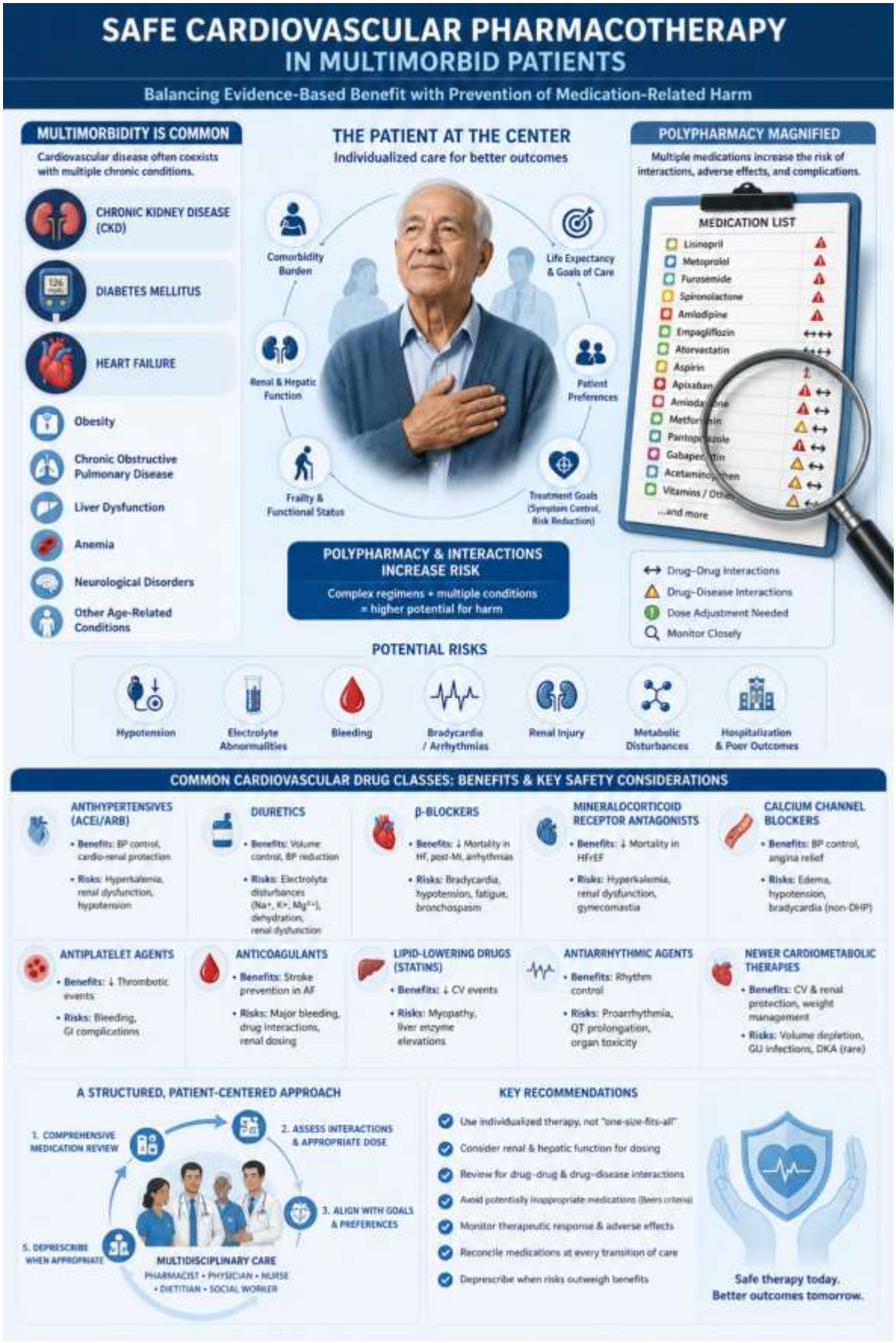

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1. Introduction

Cardiovascular diseases (CVD) is known to be one of the major causes of morbidity and mortality all around the world and necessitates permanent pharmacological management for many people in the adult age span. The effectiveness of modern cardiovascular therapies has drastically changed with the advent of antihypertensive drugs, antiplatelet agents, anticoagulants, lipid-lowering drugs, heart failure medications, antiarrhythmic agents, and new cardiometabolic therapies [1,2]. However, the category of the group to whom these therapeutic drugs are given has recently changed dramatically, and now it is better known as multimorbidity when two or more chronic diseases are diagnosed in the same person. The presence of diverse diseases has significantly impacted the process of treatment since pharmacotherapy that is effective for one disease can negatively affect another disease, interact with other medications taken with the same time, or yield an increased risk of possible adverse drug reactions [3].

Multimorbidity is particularly widespread among old-aged people. Hypertension, coronary artery disease, heart failure, atrial fibrillation, diabetes, chronic kidney disease, dyslipidemia, obesity and chronic pulmonary or musculoskeletal diseases are usually diagnosed at the same time. Therefore, one and the same patient can receive an ACEI or ARB, beta-blocker, diuretic, mineralocorticoid receptor antagonist, statin, antiplatelet agents or anticoagulant, glucose-lowering medicines and non-cardiovascular medicines at the same time. Although the prescribed medicines can be wise, their quantity can provoke interaction between them that can result in some side effects. The situation can worsen, when the number of prescribed medications is increased [4].

Thus, polypharmacy becomes very important issue in terms of safe cardiovascular medication.Proper management of a patient struggling with heart failure, diabetes, CKD, and atherosclerotic cardiovascular disease involves the application of several evidence-based therapies at the same time. The challenge of such treatment is to distinguish correct polypharmacy, where the prescriptions have a therapeutic effect, from bad polypharmacy, where the overall medication burden is more than the benefit obtained from its use or some risks could be avoided. It should be noted that in elderly people, the appropriateness of medications should be constantly evaluated since changes in the state of the patient’s kidneys, energy levels, and nutrition state, cognitive decline, ageing trajectory, and objectives of treatment may make the initially suitable prescriptions no longer suitable or even dangerous.

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The safety aspect of this problem becomes more complicated when taking into consideration changes that accompany ageing. Poor glomerular filtration, changed liver metabolism, reduced amount of water in the body, changes in the fat mass of the body and changes in pharmacokinetic properties of medicines are among changes that influence the process of taking medicines. These changes matter for medications with narrow therapeutic indices or those that are eliminated by the kidneys. The administration of anticoagulant agents, digoxin, some groups of antiarrhythmics and certain cardiovascular medications requires special consideration of kidney function. At the same time, medicines that lower blood pressure or improve cardiac conduction may lead to strong hypotonia or peripheral and internal negative effect in the case when several medications are applied together[5-7].

The connection between the CV and CKD shows how complicated the pharmacological treatment process may be in the case of multimorbidity. The fact that CKD is a risk factor for heart diseases and that kidney impairment influences the absorption of the medicines shows how complex the relationship between kidneys and heart can be. Lower functioning of kidneys may lead to more serious effect of the medicines that are connected with renal metabolism while some heart medications may also influence the mechanisms happening in kidneys.Renin-angiotensin system antagonists, diuretics, and mineralocorticoid receptor blockers are very helpful in carefully selected patients, but monitoring of kidney function and potassium level is required. Therefore, the goal of therapy is not just to steer clear of medicines that influence the kidneys, but to utilize them properly through personalized dosing and laboratory monitoring.

Diabetes mellitus is another significant comorbidity. Diabetes patients are often diagnosed with hypertension, dyslipidemia, atherosclerotic cardiovascular disease, chronic kidney disease, and heart failure at the same time. Today’s cardiovascular recommendations place great importance on treating cardiovascular and metabolic risks together rather than treating separate diseases alone. As a result, medications that act to reduce glucose concentrations have lately gained popularity in cardiovascular therapy [8].

The 2023 European Society of Cardiology guidelines focus on the comprehensive approach to managing patients who have both diabetes and cardiovascular diseases and emphasizes the necessity of creating individually customized treatment plans for atherosclerosis, heart failure, atrial fibrillation, and chronic kidney disease.

The same tendency of personalized treatment can be observed in hypertension management. 2024 recommendations of the European Society of Cardiology define cardiovascular risk as a constant phenomenon and not merely a phase of normal and high blood pressure. Notably,

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overall cardiovascular risk, treatment response, age, and other parameters must be taken into account by doctors. The guideline brought in the notion of “high blood pressure” and shifted the focus from lowering blood pressure to achieving good cardiovascular outcomes.Modern guidelines for drug therapy allow for the use of several groups of drugs having complementary mechanism action like renin-angiotensin receptor inhibitors or angiotensin receptor-neprilysin inhibitors, β-blockers, mineralocorticoid receptor blockers, and SGLT2 inhibitors. These treatments can provide an excellent clinical outcome; however, they should be used simultaneously with attention to blood pressure, renal function, potassium level, volume status, and tolerance. Several illnesses like diabetes, CKD, hypotension, frailty, and imbalances in electrolytes make treatment sequencing and dose adjustment more complicated [9].

Atrial fibrillation creates another issue of safety as it requires rate/rhythm control and thromboembolic prevention in the same patient. The choice of anticoagulant depends on the age, functioning of kidneys, body weight, bleeding risk, use of antiplatelet drugs, and possibility for drug interactions. Using anticoagulants together with antiplatelet drugs may be necessary in some cases; however, it makes patients more exposed to bleeding if used too long. β-blockers, non-dihydropyridine calcium antagonists, digoxin, and antiarrhythmic medications also have synergistic effects on conduction and heart rate [10-11].

The interaction of cardiovascular drugs with other medications represents another important safety aspect. Most of the patients suffering from several diseases have to deal with other medicines like analgesics, hypoglycemic agents, antidepressants, antibiotics, proton pump inhibitors, corticosteroids, respiratory drugs, etc. Many of these medicines affect blood pressure, kidney function, electrolyte balance, coagulation, cardiac repolarization, and metabolism. For instance, when diuretics, renin-angiotensin inhibitors, and non-steroidal anti-inflammatory drugs are used together, they can negatively influence kidney function in vulnerable patients.It is essential to pay attention to the geriatric population because medication-related injuries can be quite different from regular adverse drug reactions. In case of an adverse drug reaction, the patient usually exhibits pharmacological toxicity. However, the elderly patient may show signs of confusion, functional decline, anorexia, weakness, falls, etc. The 2023 Beers Criteria developed by the American Geriatrics Society offer healthcare professionals evidence-based tools to identify inappropriate medicines for adults aged 65 and over. Besides, the criteria include medicines that must be avoided, drugs that can worsen a certain disease, those that require caution, important drug-drug interactions, and medications

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that must be avoided or dosed depending on the renal function. Nonetheless, the Beers Criteria are aimed at supporting clinical decision making, not replacing individualized prescriptions.

In recent years, the evidence shows the prevalence of inappropriate drug usage among older patients with cardiovascular diseases. A 2026 research on elderly patients hospitalized with heart failure revealed that there are cases of inappropriate use of medicines, including cardiovascular agents; the severity of comorbidities ensured the high risk of medication-related complications. Following this, one more conclusion could be made that medication safety should be regarded as an integral part of managing cardiovascular diseases rather than a subject to be considered after an adverse event takes place [12-13].

To summarize, the safety profile of cardiovascular pharmacotherapy has to be analyzed from different interconnected points of view such as patient characteristics, disease characteristics, pharmacodynamics, pharmacokinetics, and so on.Proving a drug to be completely "safe" or "unsafe" is impossible; the safety of the drug will depend on various aspects of the situation. For active patients such as those suffering from congestion due to the heart failure, diuretics may be important; however, if used by a patient unable to drink orally, diuretics will cause excessive fluid loss. Similarly, ACEIs and ARBs should be very beneficial to the heart and kidneys, but the choice of their use requires consideration of the current kidney function and potassium levels. Anticoagulants may significantly minimize the risk of stroke in patients with atrial fibrillation, but these drugs can lead to more severe consequences of falls or bleeding in some patients [14-16].

The fact that this sphere is so context-dependent results in the necessity of pharmacotherapy to be patient-centered. Therefore, the decisions on treatment have to be based on the patient’s cardiovascular risk, comorbidities, kidney and liver function, age, weakness, burden of drugs taken, bleeding risk, performance, and lifespan and preferences. In this case, inter-professional approach to medication control will help doctors, pharmacists, nurses, and other health professionals check possible interactions and educate patients [17].

What is equally important is the point about drug safety as being a dynamic process rather than a single decision on starting treatment. A drug that was indicated at the beginning of treatment might become unnecessary or harmful after the emergence of chronic kidney disease, serious illness, loss of weight, hypotension, disturbances in electrolytes or development of other comorbidities. The discontinuation of the use of cardioprotective drug based on an episode of abnormality will prevent the patient from receiving the substantial result from the treatment.

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The narrative review aims to investigate the safety of cardiovascular drugs in patients with comorbidities. Special focus will be made on the aspects of polypharmacy, interactions between drugs and diseases, dysfunctions of renal and hepatic systems, older age of the patients and the advantages and disadvantages of cardiovascular treatments [18].

2. Cardiovascular Pharmacotherapy in Patients with Multiple Comorbidities: Major Drug Classes and Safety Considerations

In patients suffering from multiple comorbidities, cardiovascular pharmacotherapy necessitates a fine balance between therapeutic efficacy and medication-related risks. Unlike patients having an isolated cardiovascular condition, patients with multimorbidity may show altered pharmacokinetics, decreased physiological reserve, competing therapeutic indications, and much higher chances of clinically relevant drug-drug and drug-disease interactions. Therefore, the safety of a cardiovascular medication is dependent not only on its inherent side-effect profile but also on the renal and liver function, age, frailty state, concurrent medications taken, electrolyte levels, blood pressure, heart rhythm, and overall burden of diseases. Today's cardiovascular practice guidelines stress the importance of individualized treatment and repeated assessments as opposed to formal disease-oriented prescribing [19-21].

2.1 Renin-Angiotensin System Inhibitors

Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) belong to the significant group of drugs used in cardiovascular therapy – primarily, treatment of hypertension, heart failure, diabetic kidney disease, and patients at high cardiovascular risk. The most relevant therapeutic effects of ACEs include systemic vascular resistance reduction, neurohormonal activation prevention, limitation of cardiac remodeling, and, in some cases, preventing complications related to renal and cardiovascular diseases.

The major safety issues related to ACEIs include hypotension and hyperkalemia and renal function impairments. An associated common cough due to ACEIs also raises the compliance problem in treatment due to the potentially high incidence of treatment discontinuation.A small rise in serum creatinine could be present after the commencement or increase of dosage due to changes in intraglomerular hemodynamics but a large decline must be looked at for volume depletion, renal artery disease, nephrotoxic medications or overdoses.

Hyperkalemia is particularly significant for multi-morbid patients in light of the fact that in these patients CKD, diabetes, heart failure and potassium-sparing diuretics can be found. The risk of this condition growth increases if more than one potassium-retaining drug is prescribed.

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Therefore, it is necessary to obtain a clear medication list that shows potassium supplements in their medications' names, potassium salts and NSAIDs that are to be used.

ACE inhibitors and ARBs should not be combined for regular use, as employing dual renin–angiotensin therapy leads to an increase in negative effect on kidneys and electrolytes, yet a limited positive effect on the state of health [22-23].

2.2 Angiotensin Receptor–Neprilysin Inhibitors

Sacubitril/valsartan is a breakthrough for heart failure treatment. The drug inhibits neprilysin activity and angiotensin II type-1 receptor, so natriuretic peptide can function because of neprilysin inhibition and renin–angiotensin system does not work inefficiently.

In the case of patients with heart failure with reduction of ejection fraction, the major points that must be considered for safety are hypotension, hyperkalemia and kidney function. One more thing to worry about is angioedema, which can happen in case of neprilysin dysfunction occurring especially in the case of patients who experienced it before.Individuals with multiple health problems may experience hypotension when taking sacubitril/valsartan in combination with β-blockers, diuretics, nitrates, calcium-channel blockers, or any other drugs that lower blood pressure. This is why it is necessary to check how much fluid is in the body before increasing the dose of medication. In patients receiving diuretics, decreased blood volume may worsen low blood pressure and kidney problems [24].

2.3 β-blockers

β-blockers are often prescribed for the treatment of patients with hypertension in certain cases, ischemic heart disease, heart failure, and arrhythmia. The main benefits of these drugs are associated with the decrease in stimulation by the sympathetic nervous system, heart rate, and need for oxygen.

One of the main negative effects of this drug group is low heart rate, hypotension, tiredness, dizziness, problems with exercising, and negative changes in the heart function. If a patient takes several heart-rate-decreasing medications, the chances of experiencing a low heart rate increase significantly. For instance, combining β-blockers with digoxin, diltiazem, and verapamil can lead to a negative effect on heart function.

When using β-blockers for patients with respiratory problems, it is better to choose selective drugs unless doctors see that a patient can have problems taking them.In chronic patients of β-blocker therapy, abrupt termination should, as a rule, be avoided; sudden withdrawal of the drug may lead to rebound sympathetic activation, deterioration of angina, tachycardia, elevated

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blood pressure, or other CVD complications. Therefore, tapering off medication must always be gradual when discontinuation becomes necessary for medical reasons.

Diuretics, as important agents in the treatment of hypertension and fluid overload due to chronic heart failure, are represented by loop diuretics (furosemide, bumetanide, and torsemide) known for assisting in eliminating congestion, and thiazide and thiazide-like diuretics, which are commonly applied for controlling blood pressure.

The main safety issue associated with diuretic therapy is excessive fluid depletion, which can result in hypotension, dizziness, symptoms occurring on standing up, acute renal failure, and electrolyte balance disorders. All of these aspects become of paramount importance in elderly patients, patients with chronic kidney disease, and individuals taking various antihypertensive medications.

Loop diuretics may lead to hypokalemia, hypomagnesemia, hyponatremia, and metabolic alkalosis, while thiazides can cause hyponatremia, hypokalemia, hyperuricemia, and glucose metabolism disorders. Thus, monitoring of electrolyte balance and renal function becomes crucially important when the amount of the prescribed dosage is either increased or decreased.

Possible adverse effects connected with diuretics can be aggravated by the use of other medications. For example, the combination of renin-angiotensin system inhibitors with diuretics may increase the likelihood of hypotension and renal dysfunction associated with excessive volume depletion. The addition of non-steroidal anti-inflammatory drugs may complicate renal perfusion and possibly reduce the efficacy of treatment regarding both antihypertensives and diuretics [25-28].

Patients suffering from multiple diseases should not necessarily aim at achieving maximal diuresis, but rather maintain euvolemia with sufficient medications at the lowest dose possible. It is also required that detailed measurements are made regularly to monitor the body weight, edema, blood pressure, renal function, electrolyte levels, as well as fluid and general condition of the organism.2.5 Mineralocorticoid Receptor Antagonists

Mineralocorticoid receptor antagonists are specific drugs that are used in the treatment of heart failure or hypertension. These drugs, spironolactone and eplerenone, have the positive effects of decreasing the effects of aldosterone, including sodium retention and myocardial fibrosis.

The risk of hyperkalemia is a major side effect of these drugs, especially among patients suffering from chronic kidney disease. In addition, it occurs if MRA is used together with ACE inhibitors.

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Spironolactone can have endocrine side effects which include gynecomastia and breast pain in certain men. Eplerenone is a more selective drug and can be used when spironolactone has adverse side effects.

Using MRA together with other potassium-retaining therapies is discouraged because it increases the risk of hyperkalemia. The risk of having hyperkalemia increases in patients with diabetes [29-32].

2.6 Calcium Channel Blockers

Calcium blockers can be divided into dihydropyridine agents, for example, amlodipine and nifedipine, and non-dihydropyridine agents, such as verapamil and diltiazem. Dihydropyridine calcium blockers mainly act as vasodilators, being widely used for the treatment of hypertension and angina. Non-dihydropyridine blockers can also affect the conduction in the heart and decrease heart rate.

Peripheral edema is a common complication of treatment with dihydropyridine drugs. It can cause problems among patients suffering from heart failure and chronic venous insufficiency since the appearance of edema can be mistaken for the worsening of the condition.When used in patients belonging to groups such as those with bradycardia, conduction disorder, and reduced left ventricular function, the use of verapamil and diltiazem should be done with extra caution. It should be noted that the use of both of these drugs together with beta-blockers can slow down the AV conduction process and cause bradycardia.

It is stated in the ESC 2024 guidelines for atrial fibrillation that beta-blockers and digoxin should be used to reduce the heart rate and in patients with preserved left ventricle systolic function diltiazem or verapamil may be included. An important point is that the drug that is chosen should be based on several features such as ventricular function, comorbidities, and current medications being taken [33].

2.7 Drugs Affecting Platelets

Antiplatelet drugs take an important place in preventing thrombotic events associated with coronary artery disease and acute coronary syndrome. The main drugs that are used in antiplatelet therapy are aspirin and P2Y12 receptor blocker drugs, including clopidogrel, prasugrel, and ticagrelor.

The main adverse event that is related to antiplatelet therapy is bleeding. The incidence of gastrointestinal bleeding is significantly higher in older adults and individuals who have a history of ulcers, use anticoagulants, take anti-inflammatory medications, or corticosteroid therapy.

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The 2023 ESC process for managing patients with acute coronary syndrome states that there should be a balance between preventing ischemic events and balancing the risk of bleeding.

Prasugrel should be used with caution by elderly patients and is contraindicated for people with a history of stroke and transient ischemic attack. It should also be noted that in patients with lower body weight dosing needs to be reconsidered.

All of this suggests that drug safety cannot be assessed without demographic and clinical characteristics being taken into consideration.2.8 Oral Anticoagulants

Anticoagulation treatment is vital for preventing stroke in those patients suffering from atrial fibrillation and for treating/preventing their venous thromboembolism. The emergence of the direct oral anticoagulants (DOACs) made it possible to substitute vitamin K antagonists in multiple therapeutic settings.

The main concern regarding safety issues is bleeding, which is more likely to occur at older age, with renal impairment, use of concomitant antiplatelet therapies, uncontrolled high blood pressure, previous gastrointestinal bleeding episodes, and concurrent medications. It should be noted that renal function plays a great role in determining several DOACs that are substantially eliminated through kidneys [33-35].

Note that the 2024 European Society of Cardiology Atrial Fibrillation Guidelines underlines the importance of controlling modifiable factors that contribute to bleeding risk and discourages the combination of different anticoagulant therapies unless there is a specific need like acute embolism or a requirement for the procedure.

For patients with multiple comorbidities, the choice of anticoagulation and dosage of anticoagulants should take into account renal function, age, weight, simultaneously used medicines, liver function, adherence to treatment and reasons for anticoagulation. It is important that the dosage is reduced according to some justified and verified medicine-specific guidelines instead of arbitrary underdosage choices because this can jeopardize thromboembolic protection [36-39].

2.9 Lipid-Lowering Drugs

Statins are still at the forefront of pharmacological treatment of atherosclerotic cardiovascular risk. Statins can produce adverse effects connected with muscles, enzymatic activity of liver and rarely even serious damage of muscles. The risk of statin-related muscle toxicity is higher in case high doses of medication, a patient made advanced age, renal or liver dysfunction, and using other drugs.

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One should pay special attention to drug interaction issues for statins that are processed with the help of cytochrome P450. Some antibiotics from the group of macrocyclic antibiotics, azole antifungals, calcium-channel blockers and other medicines could increase the doses of some statins.Medication reconciliation is crucial when it comes to patients undergoing long-term cholesterol-lowering treatment getting new medications.

When muscle side effects appear, the physician has to think about other conditions that could be causing the problem, like hypothyroidism, overtraining, vitamin deficiency, inflammatory diseases, or drug-drug interactions and not just blame it on the statin drug. This will lead to understanding what causes the side effect and will prevent the patients from stopping a medication that is helpful to them.

2.10 Antiarrhythmic Drugs

Antiarrhythmics represent one of the most difficult areas of cardiovascular pharmacology in terms of safety since many drugs in this class have narrow therapeutic ranges and are themselves capable of producing proarrhythmic effects.

Amiodarone is very effective in the management of many atrial and ventricular arrhythmias, but it has a complicated toxicity profile, affecting almost every organ including the thyroid, liver, lungs, eyes, skin, nervous system, and heart. Therefore, the long term treatment with amiodarone requires tight clinical and laboratory monitoring. As for its great ability to interact with other drugs, it is especially important for people on multiple medications [40-42].

Digoxin should also be administered with caution, especially in the older patients and those with CKD. Kidney function can decrease the clearance of digoxin from the body leading to its increased levels in the body while hypokalemia may increase the side effects of digoxin. Additionally, the use of other medications thatClinical manifestations of toxicity may encompass gastrointestinal symptoms, confusion, visual disturbances, and arrhythmias. The sophistication of antiarrhythmic pharmacotherapy contributes to the principle that rhythm control strategies must be reassessed regularly. The 2024 ESC guidelines on atrial fibrillation highlight the need to factor in toxicity and interactions with concurrent therapies when choosing antiarrhythmic medications. SGLT2 inhibitors have assumed increasing significance in cardiology and cardiorenal medicine because of their advantages in certain populations suffering from diabetes, heart failure, and chronic kidney disease. The medication has advantage beyond glucose-lowering effects, offering decreased risks of hospitalization due to heart failure and improved kidney health in the right patients. The safety profile of the drug is different from that of standard cardiological drugs, with frequent adverse effects being genital

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mycotic infections, dehydration, and rare occurrence of euglycemic diabetic ketoacidosis. The risk of dehydration becomes important when an SGLT2 inhibitor is combined with aggressive diuretic therapy. Interruption of treatment can be indicated during the periods of prolonged fasting, severe illness, and surgery because of the risk of ketoacidosis. Patients should be counseled appropriately about hydration and acute illness. GLP-1 receptor agonists have broadened the treatment landscape for individuals suffering from diabetes, obesity, and cardiovascular diseases. GLP-1 receptor agonists can produce a range of benefits, most importantly being glycemic control, reduction of weight, and lowering the risk of cardiovascular diseases in patients at risk. However, there can be gastrointestinal side effects, including nausea, vomiting, diarrhea, and appetite suppression, which can limit the treatment tolerability significantly. Moreover, for frail or elderly patients, excessive weight loss or reduction of food intake may be undesirable. As a result, the safety assessment must not only consider cardiovascular advantages but also the state of nutrition and weight, body composition, kidney function, etc. An important feature of multimorbidity is that side effects may be additive and/or synergistic. An example of this is the occurrence of hypotension in a patient who is taking ACEIs/ARBs/ARNI and beta-blockers or diuretics, nitrates or calcium channel blockers. Bradycardia may result from interactions with beta-blockers plus digoxin/diltiazem/verapamil. Hyperkalemia may occur in a patient suffering from CKD when ACEIs + ARBs + MRAs + potassium supplements are used. In addition, bleeding risk may elevate significantly when concurrent anticoagulant and antiplatelet use takes place. Hence, medication safety should be considered with respect to the whole therapy regimen rather than investigated separately [43].

3. Polypharmacy, Drug–Drug Interactions, and Drug–Disease Interactions in Cardiovascular Patients with Multimorbidity

Polypharmacy stands as one of the significant factors causing the medication-related harm among patients with cardiovascular illness and various comorbidities. However, there is no standardized numerical value regarding polypharmacy, although in practice polypharmacy is defined as using five medications or more and excessive polypharmacy as eleven medications and more. However, the quantity of the medications is not the factor, which shall define if the treatment is a good one. For instance, it is possible for a patient suffering from heart failure, diabetes, CKD, atrial fibrillation, and atherosclerotic cardiovascular disease to undergo multiple evidence-based therapies concurrently. However, the great challenge is to ensure that every medication has ongoing rationale and that the overall burden of treatment is not

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excessive. Currently, there is evidence that multimorbidity correlating with polypharmacy is prevalent, especially among elderly patients, and that a number of cardiovascular drugs make an important part of the treatment regimen [44-45].

3.1 Pathways of Medication-Related Harm

Medication-related harm of patients with multimorbidity and cardiovascular diseases may occur through several routes. First of all, the pharmacokinetic interactions take place when one drug influences the mechanisms of absorption, distribution, metabolism, or excretion of another drug. The difference in the activity of cytochrome P450, transport systems and functions of kidneys, liver, and etc. may alter the drug exposure in the body. The interactions under investigation become particularly relevant for drugs with narrow therapeutic index; such as certain anticoagulants, antiarrhythmic medicines, and digoxin.

At the same time, pharmacodynamic interactions refer to the phenomenon when two or more drugs act through the same mechanisms or add to the effect without affectingAs an illustration, using verapamil or diltiazem together with β-blockers can lead to an increase in the incidence of atrioventricular conduction problems and bradycardia. Likewise, the simultaneous application of several drugs designed to treat decreased blood pressure can contribute to the emergence of hypotensive symptoms, especially among older adults who are weak [46].

Drug-disease interaction is a term referring to a situation when the effect of a certain medicine makes a situation worse in a patient suffering from a respective disease. Examples can be seen in cases whereby patients suffering from a renal disease are given NSAIDs, while the use of β-blockers can lead to bronchospasms in susceptible patients, while patients suffering from arrhythmia face an increased risk of it, being treated with the medicines causing QT prolongation.

There is a direct correlation between the number of drugs given to a patient and the chances of the side effects occurring, although it is necessary to note that the number of drugs is not the only factor. The effect the treatment will have on a patient depends on other factors such as the overall complexity of treatment, time that is needed to treat a patient, as well as patients' individual features and presence of drugs that possess a high risk of complications in patients [47].

3.2 Cumulative Drug Treatment and Heart Disease

Obviously, treatment of a heart disease practically always implies the combination of several drugs with respect to their mechanism of action, numbered among antihypertensive agents and various other groups of drugs, such as diuretics and the medicines belonging to SGLT2 class.

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A patient suffering from chronic heart failure may also require anticoagulants and antiplatelet drugs with regard to the fact that he also suffers from coronary artery disease.

Such combinations may be considered justified from the point of view of clinical practice, but systematic combination of many drugs may lead to complications. For example, possible occurrence of bleeding, hypotension, bradycardia, and other diseases may also occur as the result of the treatment which would otherwise provide positive results for a patient.Lowering the total number of medications without taking into account the indications may lead to discontinuation of therapies that could have an important influence on mortality/morbidity. On the other hand, continuing all treatments pursued earlier for a patient for an undefined period of time may lead to increased risk of complications. In their statement, the Working Group of the European Society of Cardiology on Cardiovascular Pharmacotherapy mentioned that aged patients with cardiovascular diseases have high risk of adverse effects due to age-related alterations in organ functioning, body composition, homeostasis, and other comorbidities. It is also emphasized that patients suffering from several diseases and multiple medication therapy remain underrepresented in research and clinical studies [48-49].

3.3 Interactions Between Drugs Affecting Blood Pressure

One of the possible problems caused by polypharmacy is the excessive decrease in the blood pressure due to the combination of ACE inhibitors, ARBs, ARNI, beta-blockers, diuretics, calcium channel blockers, nitrates, vasodilators, and other medications leading to hypotension. This issue is particularly relevant for elderly patients, patients with autonomic dysfunction, dehydration, and poor nutrition and fluid intake. The clinical manifestation of this problem may be faintness, malaise, problems with vision, problems connected with changes in the position of the body, etc.

Therefore, the targets of the treatment should be individual rather than based on the indicator of blood pressure. A patient who tolerates aggressive treatment without unwanted consequences will get a lot of advantages compared to a similar patient suffering from repeated episodes of orthostatic hypotension.

Sometimes, medications can be given in a way that leads to minimal adverse effects. For instance, to avoid maximum effects of medications at a definite moment of time throughout taking medications.3.4 Interactions between Drugs Affecting Heart Rate and Heart Function

Bradycardia and disorders of conduction can occur due to the combination of several drugs that lower heart rate. These include β-blockers, digoxin, diltiazem, and verapamil. Since the medicines are used Greece, they can have an additive effect.

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This is important in the elderly, patients with existing conduction disorders, and those with impaired elimination of drugs. For instance, a patient treated for heart failure with β-blockers and another medicine for atrial fibrillation might need to monitor the resting heart rate, evaluate the symptoms, perform ECG, and decide whether the treatment is still needed.

In the case of digoxin, extra caution should be applied since its therapeutic range is narrow. Renal impairment can increase exposure to this medicine, while electrolyte imbalance, especially low potassium level, may increase the chance of toxicity. Therefore, it is necessary to evaluate a patient receiving digoxin for the function of the kidneys, electrolytes, medications that interact with digoxin, and symptoms rather than merely relying on the serum concentration of digoxin [50].

3.5 Presence of Hyperkalemia and Interaction of Drugs on the Kidney

Everyone suffering from cardiovascular diseases and chronic kidney disease needs to be aware of hyperkalemia, as it is an important safety issue. Some cardiovascular medicines can lead to hyperkalemia; this includes ACEIs, ARBs, mineral corticoid receptor antagonists, and certain potassium-sparing diuretics. Other drugs contributing to hyperkalemia include NSAIDs, certain β-blockers, heparin, and potassium supplements.

The KDIGO 2024 CKD guideline includes a list of drugs responsible for hyperkalemia and states that it is important to manage factors that can be modified regarding hyperkalemia. It is important to note that hyperkalemia does not always indicate that it is necessary to stop any treatment related to renin-angiotensin system.Because the fear of hyperkalemia may contribute to the avoidance and too early abandonment of cardiovascular therapies, it is a relevant issue. On the other side, not recognizing the effects of potassium accumulation may lead to arrhythmias [12].

3.6 The “Triple Whammy” and Acute Kidney Injury

A clinically relevant combination of drugs in cardiology is the usage of a renin–angiotensin system blocker, a diuretic, and an NSAID. This combination is called the "triple whammy" because of the three actions leading to a decrease in renal blood flow and elevation of the acute kidney injury risk.

Patients suffering from heart failure, high blood pressure, chronic kidney disease, and diseases of the second range are particularly at risk as NSAID therapy may be added for chronic pain treatment, whereas other drugs will continue to be taken chronically.

NSAID therapy can cause sodium and water retention, thereby counteracting the diuretic action and making hypertension and heart failures worse. Thus, it is crucial to correctly investigate

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the use of analgesics during medication reconciliation, rather than believing the information in the medicine profiles.3.7 Combinations of Anticoagulants with Antiplatelet Agents

Combination therapy with anticoagulants with that of antiplatelet agents should be utilized cautiously in selected situations, particularly when the patient suffers from acute coronary syndromes or undergoes coronary interventions. However, a prolonged duration of combination therapy could cause an increase in the bleeding risk.

Patients with atrial fibrillation who require coronary intervention are quite difficult to manage since both the prevention of thromboembolic events and the protection from coronary ischemia should be provided. The treatment approach should be reevaluated regularly to avoid using combination therapy unnecessarily long.

Moreover, the additional medications which may contribute to bleeding need to be identified such as NSAIDs, corticosteroids, and some antidepressants because the risk of bleeding increases together with the use of antithrombotic agents. Some other risk factors such as history of gastrointestinal bleeding, age, renal failure, anemia, and uncontrolled hypertension make the risk even more significant.

Thus, the rule of minimum effective exposure to antithrombotic agents is of great importance in this case; the severity and length of treatment should reflect patient's current bleeding and ischemic risks [30].

3.8 Drug Interactions with Statins

The statin safety issues related to the use of several drugs are quite common. Several statins are metabolized in the liver thanks to cytochrome P450 pathways and thus drug-drug interactions may increase the levels of statins in the blood increasing the risk of muscle toxicity. Statin side effects manifest in different severity from mild myalgia to rhabdomyolysis.

The risks increase with the use of high doses, age, renal impairment and thyroid disease.

When the muscle symptoms occur, the physician should perform a thorough medication review since several factors may be responsible for the development of muscle side effects.The use of alternative statins or alternate dosing methods may enable patients to continue treatment for lowering cholesterol despite having treatment side effects [36].

3.9 Drug-Disease Interactions in Patients with Chronic Kidney Disease

CKD completely alters drugs used for treatment of heart diseases as renal function limits drugs elimination and heart physiology. Patients with CKD experience increased risk of solvable problems, as they are exposed to the adverse effects of medication.

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Reduced renal clearance implies that blood concentration of drugs is high. However, change in volume status will affect volume distribution.

KDIGO guidelines of 2024 stress that drug management should be a part of CKD treatment. Medicines used in cardiovascular therapy require special attention:

- anticoagulants cleared by the kidneys;
- digoxin;
- certain beta-blockers;
- various antiarrhythmic agents;
- diuretics;
- antagonists of mineralocorticoid receptors;
- ACEIs and ARBs;
- SGLT2 inhibitors (indications are given based on kidney status).

It is important to monitor kidney condition not only at the beginning of treatment. In case of any acute condition, dehydration and infections, kidney function may alter very quickly.

3.10 Drug-Disease Interaction in Diabetes Mellitus

Diabetes presents various challenges in cardiovascular therapy. For example, beta-blockers are not recommended due to the possible suppression of adrenergic symptoms of hypoglycemia; however, they may be used in case they are necessary for therapy.

Diabetes also causes additional risks for getting hyperkalemia and medicine accumulation. Patients often take drugs that cause reduction of cardiovascular risks like antihypertensives, statins, antiplatelet drugs, and medications that lower sugar levels.In order to gluclose lowering treatment we see that SGLT2 inhibitors and GLP-1 receptor agonists have touched upon a new less aggressive choice that accounts for cardiovascular and renal activity. However, we still need to provide personalized treatment based on the kidney condition, nutrition, body weight, side effects of the medication and other treatments used [20].

3.11 Drug-Disease Interactions in Heart Failure

Heart failure is among the diseases with which patients suffer from side effects of the treatment prescribed in connection to other diseases. For instance, NSAIDs promote sodium retention, reduce kidney circulation, thus contributing to pulmonary congestion. The use of some calcium channel blockers is inadvisable in patients with reduced left ventricular function depending on the drug and the situation. Some antiarrhythmic drugs have an ability to worsen the heart failure or facilitate the emergence of hyperarrhythmia.

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In turn, some medications used in heart failure can have side effects that are similar to the progression of the disease itself. For instance, dehydration caused by diuretics can lead to weakness and kidney dysfunction, whereas excessive vasodilation can provoke vertigo and hypo-tension.

It is therefore essential to interpret any newly appeared sign as either a sign of the disease progression or the effect of the prescribed treatment [3].

3.12 Drug-disease interactions in COPD

Cardiovascular and lung diseases often occur together. In this sense, it is important to choose appropriate β-blockers. When β-blockers are used in patients suffering from respiratory disease, cardioselective β-blockers are always preferred as opposed to non-selective β-blockers that may result in more pronounced bronchoconstriction.

At the same time, bronchial drugs can also influence the cardiovascular system. Specifically, β2-agonists can lead to increased heart rate and reduced level of potassium, while systemic corticosteroids increase sodium retention and blood sugar levels together with hypertension and fluid retention.

As a result, it is necessary to analyze the cardiovascular treatment along with the respiratory one [10].

3.13 Polypharmacy and Frailty

Frailty increases the likelihood of harm caused by medications. People who are frail may have limited physiological reserve and react overly to small changes in BP, renal function, electrolyte levels, or drug use.

The effects of too much cardiovascular treatment on frail patients are as follows:

- orthostatic hypotension;
- fall;
- syncope;
- acute kidney injury;
- electrolyte disorders;
- anorexia;
- weakness;
- confusion; and
- functional decline.

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The issue is very important, as frailty is not synonymous with old age. While some older people cope with intensive cardiovascular treatment well, some younger patients with significant multimorbidity may be in danger.

Consequently, the choice of cardiovascular treatment should consider patient functionality, mobility, cognition, nutrition, frailty, and preferences in addition to traditional cardiovascular risk factors [12].

3.14 Prescribing Cascades

Prescribing cascade happens when the side effect of one medical product is perceived as a new health issue and treated with the help of another medication, which is a wrong approach.

For instance, a calcium-channel blocker can result in peripheral edema, which may be regarded as an aggravation of heart failure and result in increasing diuretic therapy. The new diuretic can provoke dehydration or electrolyte imbalance.

As a result, excess use of antihypertensive medicine can result in dizziness, which becomes the basis for prescribing other medications.

Thus, it is crucial to identify prescribing cascades. When new symptoms appear, doctors need to determine whether they are caused by the effects of medicine rather than prescribe additional medications.3.15 Medication Reconciliation

Medication reconciliation is a key element of effective cardiovascular medication therapy. The three elements included in this step are the collection of accurate medication information and comparison of this with current medications taken.

Medication reconciliation includes:

• prescription medications;
• over-the-counter medications;
• herbal medications;
• nutritional supplements;
• specialist-prescribed medications;
• recently reduced medications;
• temporary pain relief medications; and
• medications obtained outside the doctor's prescription.

Medication reconciliation should be practiced during transitions of treatment, including admission to the clinic, leaving hospital, referral to a specialist, or passing from one institution to another.

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A systematic review of interventions for polypharmacy among elderly patients with multiple diseases showed that interventions based on medication can help decrease the rate of possibly inappropriate medication and improve results for patients, but the impact on the overall efficacy may not be as significant [46].

3.16 The Role of Pharmacists

Cardiovascular polypharmacy is characterized by extremely high complexity of treatment, thus teamwork is extremely crucial. Pharmacists can take part in medication reconciliation, finding interactions, adjusting dosage, calculating the renal dosage, teaching patients, checking compliance and spotting possible unsuitable medications.

Physicians provide diagnosis and therapeutic prioritization while nurses recognize symptoms and problems with adherence and continuously monitor, comparing something with their functional status. Moreover, communication between professionals minimizes duplication and makes sure that changes made by one doctor will be accepted by the rest.3.16 Lack of Communication among Clinicians

Without an effective coordination mechanism, individual practitioners may find ways to improve their own medical practice in a particular disease area, but unintentionally contribute to an increase in the medication burden for the patient in total [50].

3.17 Deprescribing as a Component of Cardiovascular Safety

Deprescribing means supervised reduction of the dose or cessation of using drugs that create negative outcomes that exceed the expected benefits resulting from the medication. This cannot be regarded as a form of undertreatment.

In the sphere of cardiovascular medicine, deprescribing may become meaningful when:

- indications for use disappear;
- treatment goals change;
- negative effects become pronounced;
- renal or liver functions change drastically;
- changes of life expectancy or presence of frailty alter the treatment.

With that said, drugs in cardiovascular medicine usually have to be withdrawn gradually after proper clinical assessment. The use of β-blockers, clonidine, some drugs for alleviating angina symptoms, and some other drugs may provoke withdrawal symptoms if not done gradually.

For this reason, the process should consist of the following stages: determination of treatment goals, assessment of benefits and risks produced by the prescription, shared decision making, gradual withdrawal when possible, and follow-up [40].

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3.18 Patient-Centered Medication Optimization

To make the cardiovascular medication safe from the standpoint of clinical practice, it is necessary not only to minimize the number of drugs but to maximize the clinical benefit.

The effective medication optimization model can be depicted as follows:

Indication → Benefit → Risk → Interaction → Dose → Monitoring → Patient preference → Reevaluation

Every medication used must have clear indications as well as the expected benefit from its use, possible negative effects, and interactions. The prescribed dose should be suitable for the patient's age, kidney and liver functions, and other characteristics of the patient. There should be a monitoring system designed for assessing the effectiveness of the treatment.

This issue is very important because the baseline evidence on the treatment of older individuals with different diseases is not as extensive as the one concerning patients with only one specific ailment. Cardiovascular medicine has numerous guidelines that are consistent with a certain disease, while real patients have many synchronized health problems. The ESC study aimed at the analysis of cardiovascular polypharmacy especially emphasizes the emergence of that contradiction.

On the whole, polypharmacy has to be perceived as an issue of clinical quality and safety, not just a number of prescribed medications. The appropriate polypharmacy may increase the chances of survival for the patient while inappropriate polypharmacy may result in negative drug interactions, use of too many drugs, and further decline of health status [11].

4. Safety Considerations in Specific Comorbid Conditions

Cardiovascular pharmacotherapy is significantly dependent on the clinical traits of a patient. Due to the fact that cardiovascular disease is seldom found on its own, comorbidity alters the risk–benefit ratio of medicines. Renal insufficiency, diabetes, heart problems, atrial fibrillation, COPD, liver insufficiency, obesity, ageing and frailty have the potential to change drug exposure, efficacy and vulnerability to side effects. This means that the safety of cardiovascular treatments should be evaluated in relation to the whole medical history of the patient and not only the side effects of one particular drug.

The coexistence of chronic diseases is common and comorbidity leads to polypharmacy in most cases. A review showed that there is commonality between comorbidity and polypharmacy, especially in the older generation. This leads to an interesting paradox: patients with a higher risk of cardiovascular diseases tend to receive stronger drugs but they are also more prone to suffer from the adverse effects of medication[13].

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4.1 Chronic Kidney Disease

Chronic kidney disease is one of the most important comorbidities influencing the safety of cardiovascular drugs. Patients with chronic kidney disease suffer from cardiovascular disease much more often than people without kidney problems and at the same time, kidney disease alters the elimination of drugs in the body. Thus chronic kidney disease raises the need for cardiovascular treatment and raises the dangers of this treatment at the same time.

It is crucial to take the impairment of kidney function into consideration for drugs that are eliminated from the body with the help of the kidneys. In case there is no adjustment in terms of the dosage of the drug, it may cause an accumulation process and toxicity.Before commencing therapy, kidney function must be assessed and then frequently evaluated afterwards especially in elderly and patients with rapidly changing medical condition.

The usage of inhibitors of renin–angiotensin system illustrates the complexity of treatment in the case of chronic kidney diseases. ACE inhibitors and ARBs provide important benefits in both heart and kidney function particularly in individuals suffering from hypertension, albuminuria, diabetes, and heart failure. However, medication initiation and dosage increase can lead to the increase of creatinine and potassium levels which should be interpreted taking into account renal function status, volume status, and the medicines taken at the same time.

Hyperkalemia plays a very important role when ACEIs or ARBs are used with mineralocorticoid receptor antagonists. The risk goes higher when one has chronic kidney disease, diabetes, takes potassium supplementation, uses potassium-containing salt substitutes, and takes some non-cardiovascular medicines. Thus, it is necessary to analyze both prescribed drugs and over-the-counter medication.

Diuretics should be individually managed when it comes to treating chronic kidney diseases. Loop diuretics are of great importance for dealing with volume overload especially for people with late-stage chronic kidney disease or heart failure. However, excessive diuretics can lead to intravascular volume depletion, hypotension, electrolyte disturbances, and acute kidney injury. Conversely, insufficient treatment with diuretics can lead to persistency of congestion and worsening of heart failure.

That is why, kidney function should be seen dynamically. For instance, creatinine measurement obtained months earlier may not actually show the situation in a patient who has recently been hospitalized, suffered from dehydration, infection, or gastrointestinal loss.4.2 Diabetes Mellitus

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Diabetes mellitus normally exists alongside hypertension, dyslipidemia, coronary vascular disease, chronic kidney disease, heart failure, and obesity. Thus, multiple treatments for cardiovascular illness and metabolic conditions are often given to patients suffering from diabetes mellitus.

The management of hypertension in patients with diabetes mellitus entails consideration of specific aspects such as protection of the kidneys, management of blood pressure, ensuring balance of electrolytes, and assessing the risk of cardiovascular disease. ACE inhibitors and ARBs play an important role in treatment for people with diabetes who present with symptoms related to various conditions.

Management of hypertension in patients suffering from diabetes mellitus requires consideration of the following aspects – renal health, blood pressure management, electrolyte balance, and cardiovascular disease risk. Use of beta-blockers in cases of hypertension associated with diabetes is particularly important in patients at risk of endothelial dysfunction. Children suffering from diabetes mellitus are at a higher risk of CKD through renal failure due to using numerous drugs. Assessment of cardiovascular function in these children must take into account such factors as level of glycemic control, kidney function, blood pressure levels, and presence of coronary disease.

The introduction of SGLT2 inhibitors and GLP-1 receptor agonists has also changed the approaches to treatments of patients with diabetes and cardiovascular disease. Thus, the concept of integrated cardiorenal management emerges. However, some adverse effects such as volume depletion and pathway blockage need to be properly overseen [23].

4.3 Heart Failure

Heart failure serves as one of the most difficult situations in terms of polypharmacy of the heart.Patients may need to undergo treatment with several evidence-based therapies concurrently, which may include inhibitors of the renin-angiotensin system or angiotensin receptor-neprilysin inhibitors along with β-blockers, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and diuretics.

The use of multiple therapies may lead to the acquisition of many benefits for patients; however, it may result in overlapping action on blood pressure, kidney, and potassium levels in addition to a patient’s volume status. For instance, a patient taking a diuretic, sacubitril/valsartan, an MRA, and SGLT2 inhibitor may develop hypotension or suffer from kidney damages due to aggressive volume depletion.

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Importantly, changes provoked by treatment must not be treated as a disease progression per se. For instance, a rise in creatinine levels indicates a change in renal hemodynamics or volume status but not irreversible renal damage. The same is true about weakness or dizziness, which may be associated with excessive reduction of blood pressure rather than worsening of heart failure.

Non-steroidal anti-inflammatory drugs should be paid much attention to in patients with heart conditions because they can cause sodium and water retention as well as harm to renal function. Thus, their long-term use in patients with heart failure should be appropriately considered.

Reconsider whether diuretics have been prescribed in correlation with patients' congestion and volume status instead of obtaining a certain fixed dose regardless of patients' current condition.In older adults, patients with chronic kidney disease, patients receiving antiplatelet treatment, and those who experienced previous gastrointestinal or intracranial bleeding disorders, such balance is especially crucial. Renal function is critical for DOAC therapy due to the differences in the renal clearance of certain drugs in certain individuals. When deciding on the optimum dose, experts must follow precise recommendation and guidelines for the corresponding drug but not depend on arbitrary reduction caused by age and lost health status. Excellent rate-control is needed as well. Though β-blockers, digoxin, diltiazem, and verapamil can be administered in appropriate situations, combinations can bestow its users with bradycardia or atrioventricular conduction blockade. Thus, if patients take different doses of drugs affecting heart rate, their heart rate, symptoms, electrocardiogram changes, and the necessity of taking drugs should be regularly monitored.

Antiarrhythmics may endanger the patient's life organism-specific toxicity. Amiodarone is one of the many medications that should not be disregarded due to the adverse side effects of prolonged use on the functions of the thyroid gland, liver, lungs, eyes, skin, and nervous system of patients. Furthermore, the drug can be interacted with other medications of various uses [21].

4.5 Coronary Artery Disease

Coronary artery disease causes the need of taking various preventive and precautionary drugs at the same time, which may include statins, antiplatelet medications, β-blockers, ACEIs/ARBs and antianginals as well as possibly anticoagulants.

A major problem involving antithrombotic therapy is of course bleeding as it is multiplied by the risks that accompany the treatment involving anticoagulants as well as antiplatelet medications. Some combinations are even absolutely necessary in some situations such as during the rehabilitation period after coronary intervention, but there must be adjustment of

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combined treatment over the whole course of the disease.Statins provide considerable cardiovascular advantage, especially in those with established atherosclerosis. However, high-intensity therapy may cause muscle problems as well as clinically important drug interactions. Nitrates and other vasodilators can result in hypotension, dizziness, headaches, and their effects may become stronger when combined with various anti-hypertensive drugs. Thus, medication reconciliation should concern a full vasodilator burden.

Chronic Obstructive Pulmonary Disease

COPD and cardiovascular diseases are often present together, in particular in older people. It becomes difficult to choose β-adrenergic therapy.

When a strong cardiovascular indication for the use of β-blocker exists, it may be rational to use cardioselective β-blockers in diagnosed obstructive airway disease patients since they demonstrate higher β1 selectivity during usual dosages. However, it is also crucial to know about a patient's lung health, seriousness of airway blockage, and his/her response to treatment. The effect of respiratory medications on cardiovascular background should be remembered as well. β2-agonists may trigger tachycardia and change electrolytes, while systemic corticosteroids can affect water retention, hypertension, and hyperglycemia.

The presence of COPD should not automatically prevent one from obtaining profitable cardiovascular treatment. It is essential to develop personalized therapy with taking into consideration: bronchospasm monitoring, heart rate, and blood pressure.

Hepatic dysfunction affects the liver's function of drug metabolism and excretion. Statins, antiarrhythmic medications, anticoagulants, and several calcium-channel blockers should be prescribed carefully in patients with developed liver diseases.Based on the severity of liver dysfunction, the drug's pharmacological disposition and possible dysfunction of other organs, treatment will be chosen accordingly.

To clarify, amiodarone is a valuable example of a medication that can lead to liver toxicity after a lengthy use. The patients on long-term medication, thus, need to be monitored appropriately. Liver dysfunction may alter protein production as well as the binding of blood proteins. If the liver disease is severe, the changes in proteins level and blood coagulation can problematize interpretation of conventional laboratory tests, complicating anti-thrombotic therapy.

4.8 Obesity

Obesity is linked to development of hypertension, diabetes, dyslipidemia, coronary heart disease, heart failure, and atrial fibrillation. Therefore, obesity would add to the risk associated with cardiovascular diseases as well as make treatment more challenging.

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However, obesity does not mean that the patients need medication dosing according to their weight without exceptions. Weight to be used in the calculation depends on the characteristics of the drug in question and the condition treated.

It is important to note that obesity may change the effectiveness of treatment due to variations in distribution volume and metabolic activity. On the other hand, losing too much weight will also suggest reduction in the doses of drugs used for treating conditions such as hypertension and diabetes.

Patients receiving cardiometabolic medications should be reassessed once they lose considerable amounts of weight. Too much weight loss should be distinguished from planned therapeutical loss of weight and in some cases may bring additional issues, especially to older and weak patients [32].

4.9 Geriatric people

Older people are one group that is highly likely to suffer from the effects of medicines. One of the reasons for this is that aging is accompanied by various changes in the body that can affect the pharmacokinetics and pharmacodynamies of drugs used.There can be a progressive decrease in renal function, changes in hepatic metabolism, and even greater susceptibility to effects of drugs affecting blood pressure and central nervous system in older patients. Seniors also have higher chances of having comorbid illnesses, and, consequently, they receive multiple medications. The AGS Beers Criteria published in 2023 identify medications that can be especially inappropriate for older adults in certain situations, and they clarify that these criteria are meant to guide clinical decisions and not to replace individualized treatment decisions.

Cardiovascular medicines are of special concern due to the following side effects:

- orthostatic hypotension
- bradycardia
- electrolyte abnormalities
- renal failure
- hemorrhage
- sedation or dizziness
- clinically significant interactions with drugs

Falls are especially critical since they could be a consequence of polypharmacy in the cardiovascular domain. A patient who takes several medications for hypertension can get orthostatic hypotension and then fall due to dizziness. Besides, if anticoagulants are used, the consequences of falling can be worse than otherwise.

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However, while age may be one of the factors, there should not be an automatic assumption of applying a conservative approach in managing older adults. Older patients can benefit from treatment in accordance with guidelines. Treatment decisions should rather be based on biological age, frailty, functional status, cognitive status, comorbidity, life expectancy, treatment objectives, and patient preference [46].

4.10. Frailty and Functional Decline

Frailty has been increasingly acknowledged as an important factor in achieving success in cardiovascular therapies. Frail individuals are less capable of dealing with physiological stress and they respond less positively to aggressive efforts for reducing blood pressure, intensive diuretic therapy, and rapid increase in the dosage of medications as compared with healthy patients. The effects of medications (dizziness, weakness, loss of appetite, and orthostatic hypotension) may contribute to functional decline.The goal in such cases should be to produce meaningful cardiovascular results while ensuring patients retain their mobility, independence, and quality of life. This implies that frailty should work in parallel with traditional cardiovascular risk assessment methods to enable health professionals to define cases where treatment goals should be personalized, and monitoring intensified.

4.11 Dementia and Medication Intake

Dementia may reduce adherence to medications and contribute to errors in their intake. Complex medication regimens where medications should be taken at different times may worsen the problem.

Lack of compliance should not always be interpreted as a patient’s unwillingness to follow treatment. There are many factors affecting compliance such as cognitive problems or visual impairment, financial problems, and so on.

Compliance can and should be improved by simplifying medication regimens, using pillboxes, giving patients written instructions, involving caregivers into the treatment process, and avoiding unnecessary medications.

4.12 Gastrointestinal Disorders and Bleeding Risk

Gastrointestinal disorders might have an impact on the safety of antiplatelet and anticoagulant therapy. Past history of peptic ulcer disease, gastrointestinal bleeding, anemia, and NSAID or corticosteroid usage can lead to increased bleeding risk.

Patients on antithrombotic therapy shall be assessed in terms of modifiable gastrointestinal risk factors. If appropriate in the clinical setting, gastroprotective strategies might be applied.

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Anemia occurring in a patient treated with anticoagulants should not be thought of as chronic disease.The existence of occult gastrointestinal bleeding should always be considered in differential diagnosis when clinically necessary.

4.13 Electrolyte disorders

Electrolyte disturbances are a frequent side effect of some cardiovascular drug treatments and can, in their own turn, increase cardiovascular risk.

The presence of hypokalemia increases the risk of the development of ventricular arrhythmias and may make a person more sensitive to digoxin. Hyperkalemia can cause conduction problems and deadly cardiac arrhythmias. Hyponatremia may lead to disorientation, weakness, and falls, especially in older patients.

It should be noted that diuretics, different drugs affecting the renin-angiotensin system, MRAs, and many other cardiotropic preparations can change the electrolyte status of the patient. Thus, tests for electrolytes should be conducted depending on the treatment regimen of the patient as well as his/her risk factors, and not only when some symptoms appear [33].

4.14 Multimorbidity and PIM use

The issue of potentially inappropriate medication use is associated with unsafe treatment in older patients. The 2023 AGS Beers Criteria recommend using distinct criteria to identify the drugs that need to be avoided in various older patient populations.

Nevertheless, substances belonging to the potentially inappropriate medication list are not necessarily inappropriate.

The high frequency of cases when it is justified to use drugs despite the fact that they belong to the potentially inappropriate medicine list is another reason for utilizing PIM screening tools only as aides in decision-making.

Other tools like STOPP/START and FORTA can supplement the Beers Criteria, as they can assess both potentially inappropriate medications and the potential absence of necessary prescribing [16].

4.15 The importance of risk–benefit assessment

The focus of the good cardiovascular treatment in cases of multimorbidity is the importance of the individualized risk–benefit assessment. One should prescribe drugs only if the expected benefits outweigh the inherent risks, while unnecessary and harmful treatment should be reconsidered.

An excellent way to assess a drug validity is through the process that includes consideration of the following components:

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Indication → Expected benefit > Potential harm > Interaction > Organ function > Monitoring > Patient's aims > Reassessment [15].

4.16 Clinical implications

It is time to change the methods of treatment of cardiovascular diseases in patients with a lot of comorbidities, moving from a pure meaning of treating one illness to a careful approach of treating patients as a whole [19].

5. Conclusion

Medication treatment for cardiovascular diseases among patients with various medical disorders entails a careful assessment of how to guarantee maximum protection as well as keeping medications at a minimum. The existence of medical illnesses like chronic renal failure, diabetes, heart failure, atrial fibrillation, obesity, chronic pulmonary diseases, liver disorders, and frailty significantly influences the safety of medication for treating cardiovascular diseases. Multidrug treatment is effective in decreasing cardiovascular disorders and death, but polypharmacy raises risks of ADR, DDI, DDI, therapeutic duplication, and medication errors.

Cardiovascular medication must be evaluated on the basis of the complete medication scheme and specific medical characteristics of the patient rather than on the basis of the safety profile of the medicines. Renin angiotensin system blockers, beta-blockers, diuretics, mineralocorticoid antagonists, antiplatelet drugs, anticoagulants, statins, antiarrhythmic medicines, SGLT2 medications, and other drugs can offer considerable advantages in treatment of patients via their proper application and monitoring. Renal and electrolyte impairment, hypotension, bradycardia, bleeding, liver impairment, and age factors need to be taken into account when estimating how medications will work.

Polypharmacy does not mean inappropriate prescribing. As for proper polypharmacy, it may be even necessary for patients with vascular diseases, while inappropriate polypharmacy takes place when medicines are overprescribed thus making the treatment more dangerous than it actually is. Therefore, medication reconciliation is essential especially when going to the hospital, getting discharged from the hospital, going for specialists' consultations, and making transitions between medical facilities.Medication review consists of prescription agents, over-the-counter medicines, herbal preparations, dietary ones, including some last-used or short-term used medicines.

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It is important to underline the necessity to consider elderly and weak patients who can experience more side effects from the medicines, moreover, they are more prone to orthostatic hypotension, falls, renal disturbances, impairment of electrolytes balance, cognitive impairment, and availability of bleeding. Thus the doctors should take into consideration not only the cardiovascular risk but also frailty of the patients, their functional status, life expectancy, goals of treatment, adherence to the treatment, quality of life, and preferences of the patient. Using screening programs such as the Beers criteria, STOPP/START, etc. could help to make a decision in the treatment, but it should be remembered that such programs do not replace personal evaluations.

A lot is dependent on continuous control and timely adjustment of treatment. The monitoring should include renal activity, serum electrolytes, blood pressure, heart rate, liver function, bleeding signs, body weight and clinical signs depending on the pharmacological risks of the treatment. Special vigilance is required at the beginning of each therapy period, its dosage increase, during acute disorders and changes in renal activity.

Deprescribing can be also considered as an important part of safety in the area of cardiovascular medications when the anticipated risks of a medicine are higher than its current effects. But it is necessary to understand that deprescribing is a part of the system, clinical supervision as well as common-making process instead of only decreasing the number of medications used. One should remember that undertreatment should be avoided, because multimorbidity and older age do not mean lack of beneficial effects of evidenced-based medications.

Summarizing everything above, the best approach in the patients with multiple comorbidities in the field of pharmacotherapy of cardiovascular diseases is a patient-oriented, multidisciplinary, continuously studied strategy. The principle of the correct treatment is to choose the right medicine of the right dose for the right patient. In the future, research should focus on patients with multiple comorbidities to develop new methods of predicting the risk of the drug action and find methods of optimal depressant rehabilitation.

6. Ethical Statements

Ethics Approval and Consent to Participate

Not applicable. This article is a narrative review based exclusively on previously published literature and does not involve human participants, human biological samples, or animal experimentation.

Consent for Publication

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Not applicable. No individual-level personal data, identifiable patient information, or clinical photographs are included in this review.

Availability of Data and Materials

Not applicable. This narrative review is based on information available in previously published scientific literature.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

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7. Abbreviations

ACEI – Angiotensin-Converting Enzyme Inhibitor

AF – Atrial Fibrillation

ARB – Angiotensin II Receptor Blocker

ACS – Acute Coronary Syndrome

CCB – Calcium-Channel Blocker

CKD – Chronic Kidney Disease

COPD – Chronic Obstructive Pulmonary Disease

CVD – Cardiovascular Disease

DOAC – Direct Oral Anticoagulant

ESC – European Society of Cardiology

GLP-1 – Glucagon-Like Peptide-1

HF – Heart Failure

HFrEF – Heart Failure with Reduced Ejection Fraction

MRA – Mineralocorticoid Receptor Antagonist

NSAID – Nonsteroidal Anti-Inflammatory Drug

PIM – Potentially Inappropriate Medication

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SGLT2 – Sodium–Glucose Cotransporter-2

STOPP – Screening Tool of Older Persons' Prescriptions

START – Screening Tool to Alert to Right Treatment

P450 – Cytochrome P450

RAAS – Renin–Angiotensin–Aldosterone System

ARNI – Angiotensin Receptor–Neprilysin Inhibitor

MACE – Major Adverse Cardiovascular Events

ADR – Adverse Drug Reaction

ADE – Adverse Drug Event

QT – QT Interval

ECG – Electrocardiogram

eGFR – Estimated Glomerular Filtration Rate

GI – Gastrointestinal

AKI – Acute Kidney Injury

BP – Blood Pressure

HR – Heart Rate

PPI – Proton Pump Inhibitor

ASCVD – Atherosclerotic Cardiovascular Disease

TIA – Transient Ischemic Attack

VTE – Venous Thromboembolism

ICH – Intracranial Hemorrhage

AGS – American Geriatrics Society

KDIGO – Kidney Disease: Improving Global Outcomes

EuGMS – European Geriatric Medicine Society

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