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The Role of Lipoprotein A in Cardiac Risk Stratification and Evaluation of Hypolipemizing Treatment

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ABSTRACT

Introduction and purpose

Cardiovascular diseases are one of the most common causes of death. Due to their popularity and the costs they generate, they are a significant problem. One of the cardiovascular risk factors is the level of lipoprotein(a). Lipoprotein (a) levels are not commonly used to stratify cardiovascular risk, but recommendations suggest that every adult should have them checked. The aim of this study is to discuss current knowledge about the role of lipoprotein (a) in cardiac risk stratification and evaluation of hypolipemizing treatment.

Material and methods

The PubMed database was used to review the literature. An electronic literature search was conducted, publication years were limited to 2018-2024. Three articles that did not meet this criterion due to their earlier publication dates were included because they served as important sources of information for this article. Keywords were used as search terms.

Conclusion

Based on the available data, the benefits of lowering lipoprotein(a) levels in the context of cardiovascular diseases cannot be confirmed. There is a need for further research into the role of lipoprotein (a) in stratifying cardiovascular risk, the benefits of lowering its levels, and specific therapeutic approaches for this disorder.

Keywords: lipoprotein (a); cardiovascular risk; cardiovascular disease

Introduction

Cardiovascular diseases are a significant problem not only because of the number of people affected by them, but also because of the high costs of their treatment [1,2]. According to data published in the European Heart Journal, cardiovascular diseases generate costs of approximately 282 billion euro annually in the European Union. This amount comprises the costs of medical treatment and patient care, as well as losses caused by the inability to work. The largest share of costs, at 27% each, consists of expenditures related to ischemic heart disease and cerebrovascular diseases. Per capita, German citizens incur the highest expenses, around 903 euros per person, while Cypriot citizens have the lowest expenses, approximately 381 euros per person [2]. For years, numerous cardiovascular risk factors have been known.

Cardiovascular risk factors can be divided into modifiable and non-modifiable. Modifiable factors include smoking, obesity, overweight, hypertension and a sedentary lifestyle [3,4]. The main non-modifiable risk factor is age [4]. Nevertheless, understanding numerous risk factors does not negate the need to search for additional ones. Thanks to such activities, cardiovascular risk can be effectively reduced, which, combined with the promotion of check-ups aimed at the early detection of cardiovascular diseases, may contribute to reducing their prevalence in populations around the world [1]. Lately, there has been increasing interest in the role of lipoprotein (a) in cardiovascular risk assessment and in evaluating the effects of lipid-lowering therapy. To deepen our knowledge on this subject, we conducted a review of the latest scientific articles. The collected conclusions are presented in the article.

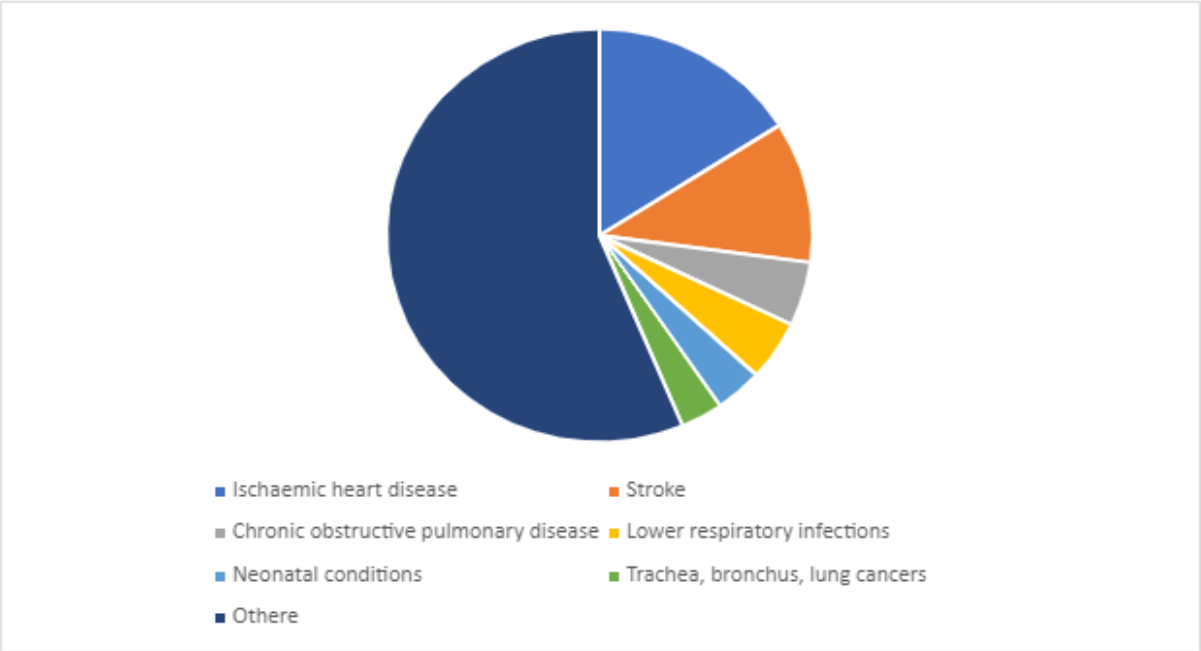
Cardiovascular diseases

According to the definition of the World Health Organization (WHO), cardiovascular diseases are diseases of the heart or blood vessels. They include coronary artery disease, including its most severe manifestation, myocardial infarction, cerebrovascular diseases including stroke, congenital heart defects, acquired heart defects such as those resulting from rheumatic fever, heart failure, deep vein thrombosis, pulmonary embolism, and peripheral arterial diseases. [1,5].

Epidemiology of cardiovascular diseases

According to data, cardiovascular diseases are one of the main causes of death in the world [1]. They are responsible for approximately 18 million deaths per year [6]. The predominant cause of death is myocardial infarction. [7]. There has been a significant increase of deaths caused by myocardial infarction over the past few years [7]. From 2000 to 2019, their number increased by more than two million, reaching approximately 8.9 million [7]. The second most common cause of death in 2019 was stroke, accounting for 11% of deaths [7]. The main causes of death worldwide in 2019 are presented in the chart below [Fig.1]. In 2019, 38% of premature deaths were caused by cardiovascular diseases, excluding infectious diseases [1]. It is also worth mentioning the variable percentage share of the main causes of death in the overall statistics depending on the economic status of the country [7]. Countries' economies have been classified into four groups based on gross national income [7]. The classification with examples of countries belonging to each category has been provided below [7,8], [Tab.1]. It is estimated that approximately 75% of deaths caused by cardiovascular diseases occur in middle- or low-income countries [1]. This is a result of limited access to healthcare services. This results in too late detection of cardiovascular diseases. Moreover, medical services in these countries are

provided at a much lower level than in higher-income countries. As a consequence, deaths from cardiovascular causes are more common in these countries and occur at lower ages than in high-income countries [1]. The total number of deaths caused by myocardial infarction or stroke decreased only in high-income countries. In these countries, 327,000 fewer deaths due to ischemic heart disease were recorded in 2019 than in 2000, and 205,000 fewer deaths due to stroke. Despite this, the main causes of death in these countries are still stroke and ischemic heart disease [7].



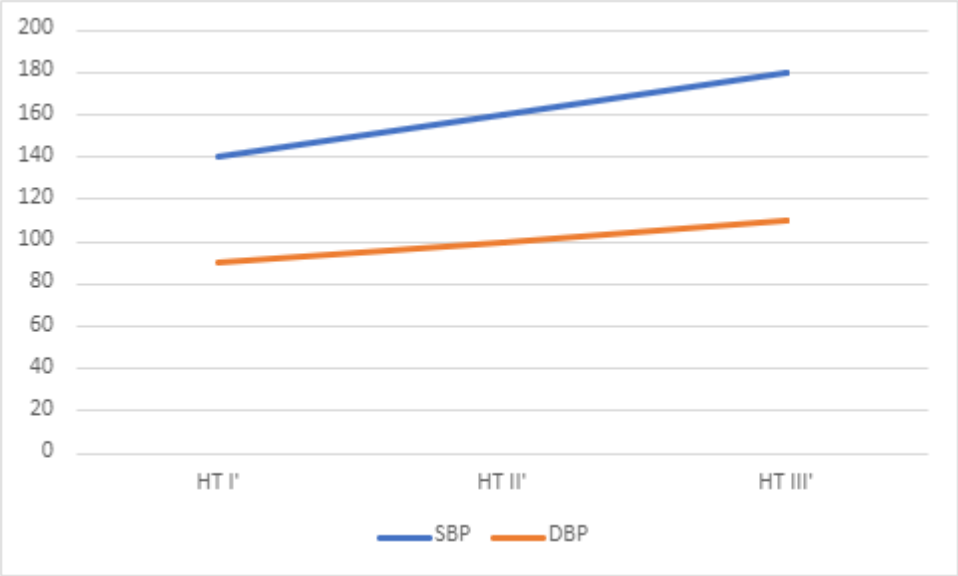
[Fig.1] Main causes of death in the world in 2019.

LOW INCOME	LOWER MIDDLE INCOME	UPPER LOWER INCOME	HIGH INCOME
MALI	MAROCCO	RUSSIA	USA
NIGER	ALGIERIA	MEXICO	CANADA
AFGHANISTAN	BOLIVIA	ARGENTINA	JAPAN
YEMEN	INDIA	BRAZIL	POLAND
SUDAN	UKRAINE	BELARUS	GERMANY
MADAGASCAR	MONGOLIA	LIBYA	FRANCE
UGANDA	IRAN	SOUTH AFRICA	AUSTRALIA

[Tab.1] Division of countries according to national income

Risk factors of cardiovascular diseases

The division of cardiovascular risk factors into modifiable and non-modifiable factors was indicated earlier in the article. Modifiable factors include hyperglycemia, lipid disorders, inappropriate diet, overweight, obesity, lack of physical activity, sedentary lifestyle, excessive alcohol consumption and smoking [1,4,6,9]. Non-modifiable factors include, age (at least 55 years in the female population and at least 45 years in the male population), gender (higher risk among men and postmenopausal women) and early occurrence of cardiovascular diseases in the family [4,9]. Based on the study, which included more than 1,500,000 participants from 34 countries, researchers identified five modifiable risk factors that were responsible for 57.2% of cardiovascular events in men and 52.6% of cardiovascular events in women. These factors include body weight, systolic blood pressure, smoking, LDL cholesterol levels and diabetes [10]. Arterial hypertension is recognized as one of the primary risk factors for cardiovascular diseases [4,11]. According to the WHO definition, arterial hypertension is identified by systolic blood pressure measurements equal to or greater than 140 mmHg and diastolic blood pressure measurements equal to or greater than 90 mmHg [12]. Due to the blood pressure values, three degrees of hypertension were distinguished. It is shown in the chart below [12], [Fig.2].



[Fig.2] Correlation between the degree and value of blood pressure.

The World Health Organization presents very concerning data regarding arterial hypertension. According to them, over one billion people aged 30-79 suffer from hypertension, which makes it one of the most common cardiovascular diseases in the world [12,13]. Almost half of these people are unaware of their elevated blood pressure, which is why regular monitoring is so

important. Equally alarming is the fact that only 1 of 5 people diagnosed with hypertension achieve their blood pressure goals and treat them appropriately [12]. The lipid profile measured in clinical practice includes the level of total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides. So far, LDL cholesterol level has been considered the most significant risk factor for cardiovascular diseases and the primary determinant of the effectiveness of lipid-lowering treatment. According to the latest research, non-HDL cholesterol levels and apolipoprotein B levels may better correlate with the risk of coronary heart disease [14]. These findings have resulted in the incorporation of non-HDL cholesterol levels into the SCORE2 and SCORE2-OP algorithms, which are used for cardiovascular risk estimation [15]. Smoking tobacco is a highly significant risk factor for cardiovascular diseases [14]. It is associated with more than half of premature myocardial infarctions [16]. Smoking increases the risk of thrombosis and causes vasoconstriction. These adverse effects are caused by oxidative stress, endothelial dysfunction, reduced nitric oxide levels, as well as inflammation [17]. Stopping smoking reduces the risk of cardiovascular disease. Therefore, it is an important element of primary and secondary prevention [16]. Over one billion people are obese [18]. Obesity has a negative impact on the cardiovascular system through many mechanisms [18,19]. To stop the obesity pandemic, it is crucial to promote regular physical activity and a healthy, balanced diet. People with diabetes have a much higher risk of developing cardiovascular diseases and dying from them [20]. Medications used to normalize blood glucose levels, which belong to the group of SGLT2 receptor inhibitors and GLP-1 receptor agonists, reduce cardiovascular risk [21]. In the course of diabetes, it is also essential to control other disorders such as hyperlipidemia and arterial hypertension [21].

Cardiovascular risk stratification

The SCORE2 (Systemic Coronary Risk Estimation 2) scale is used to assess the 10-year risk of developing fatal or non-fatal cardiovascular disease in clinical practice. In the population of people over the age of 70., the SCORE2-OP (Systemic Coronary Risk Estimation 2 - Older Persons) scale is used. The algorithms are based on risk factors such as age, gender, smoking, non-HDL cholesterol level and systolic blood pressure. However, there are limitations to their use. They cannot be used to assess the risk among people with diabetes, moderate and severe chronic kidney disease, familial hypercholesterolemia and diagnosed atherosclerotic cardiovascular disease. Another problem is the correct risk stratification among individuals reaching borderline percentage values using the SCORE algorithm. In this case, it is helpful to

analyze the presence of risk factors not included in the SCORE algorithm, such as the level of lipoprotein(a) [15].

Lipoprotein a - basic information

Lipoprotein (a) structurally resembles low-density lipoprotein (LDL), containing apolipoprotein B, which is covalently linked to apolipoprotein(a) [22]. Its structure results in its pro-inflammatory, atherogenic and prothrombotic properties [23,24]. The atherogenicity of lipoprotein (a) results from its effect on the formation of foam cells, activation of inflammatory processes, destabilization of atherosclerotic plaques and proliferation of muscle cells [22]. The adverse effect of lipoprotein (a) on the cardiovascular system may be related to its function of transporting oxidized phospholipids [25]. The level of lipoprotein(a) is genetically determined through the LPA gene [22,26]. It is characterized by high individual and ethnic variability [22]. Its values are higher among people living in African countries and lower among people living in Asian or European countries [22].

The role of lipoprotein a in cardiac risk stratification

The level of lipoprotein(a) is considered as an independent cardiovascular risk factor [24]. Its negative impact on the cardiovascular system is associated with pro-inflammatory, atherogenic and prothrombotic properties [24]. Scientific research shows a relationship between increased levels of lipoprotein (a) and diseases such as aortic valve calcification, ischemic heart disease, peripheral arterial diseases, heart failure or ischemic stroke [22,23]. A high level of lipoprotein(a) has also been associated with an increased risk of developing cardiac rhythm disorders, such as atrial fibrillation [27]. A lipoprotein(a) level below 30 mg/dL (75 nmol/L) is considered normal. Levels between 30-50 mg/dL (75-125 nmol/L) suggest moderate cardiovascular risk, while levels exceeding 50 mg/dL (125 nmol/L) indicate high risk [28]. Lipoprotein(a) levels surpassing 50 mg/dL are estimated to be present in approximately 20-25% of the global population [23]. High lipoprotein(a) values are associated with increased cardiovascular risk despite normal values of other lipid fractions, including LDL [27]. According to the European Society of Cardiology guidelines, it is recommended to test the lipoprotein(a) level at least once in all adults due to its limited variability throughout life. Determining its level may result in restratification of cardiovascular risk [29]. Special advantages may result from assessing its level among patiensts categorized using the SCORE2/SCORE2-OP scale into the high or very high-risk group, in cases of borderline cardiovascular risk, premature or recurrent cardiovascular diseases despite treatment, in

individuals with a family history of early-onset cardiovascular disease or high levels of lipoprotein(a) [29]. Despite recommendations, measurements of lipoprotein(a) levels are rarely performed and are not included in available cardiovascular risk stratification algorithms [30].

The role of lipoprotein (a) in evaluating the effectiveness of hypolipemizing treatment

Lifestyle modifications such as healthy diet or increasing physical activity do not have a significant impact on the level of lipoprotein (a) due to its genetic determination [25,29]. Conventional pharmacological treatment of lipid disorders does not have a significant effect on the level of lipoprotein(a) [25]. Statins are the most commonly used drugs in the treatment of lipid disorders. However, their effect on lipoprotein(a) level is not definitively determined. A study conducted on over 29,000 patients did not show a significant change in the level of Lp(a) during statin therapy [31]. According to a meta-analysis involving over 5,000 patients, statin use was associated with an elevation in lipoprotein(a) levels [32]. The conclusions of this study were confirmed in a retrospective cohort study that included over 42,000 people [33]. Due to the uncertain risk of lipoprotein(a) level elevation during statin use and their favorable effect on LDL concentration, discontinuation of statin therapy is not recommended [29]. The effect of ezetimibe on lipoprotein(a) levels is also uncertain. Conclusions from individual articles contradict each other. According to them, ezetimibe does not affect lipoprotein(a) levels or causes its slight decrease [25,29]. Fibrates used in clinical practice to lower triglyceride levels do not reduce lipoprotein(a) levels [34]. Nicotinic acid demonstrates a positive impact on lipid profile. It reduces LDL and triglyceride levels while increasing HDL cholesterol levels. Additionally, nicotinic acid has been shown to lower lipoprotein(a) levels by approximately 25% [35]. However, according to the European Medicines Agency (EMA) prohibition, nicotinic acid is not used in treatment [36]. Therefore, lipoprotein(a) cannot be used to evaluate the efficacy of lipid-lowering treatment because most commonly used preparations do not impact its levels or their effect remains incompletely understood [37]. PCSK9 inhibitors (proprotein convertase subtilisin/kexin 9 inhibitors) are the only drugs used in clinical practice that reduce the level of lipoprotein(a) by 20-30% [25,38].

Lipoprotein (a) lowering therapy

According to the earlier part of the article, the only drug currently used in the treatment of lipid disorders that significantly reduces lipoprotein(a) levels is PCSK9 inhibitors. Apheresis is a recognized treatment method, but it is not approved in all countries [39]. Encouraging results come from studies on drugs aiming to influence the expression of the LPA gene, which encodes

lipoprotein(a). There are two classes of these drugs: single-stranded antisense oligonucleotides (ASO) and small interfering RNA (siRNA) [34]. According to research results, pelacarsen (ASO) reduces the level of lipoprotein(a) by 72-80%, depending on the dose. During the use of olpasiran (siRNA), the level of lipoprotein (a) decreased by 71-97% [40]. The available results indicate a favorable safety profile of the above drugs and the durability of the obtained effect [41].

Conclusion

Cardiovascular diseases represent a significant social and economic issue. To prevent their occurrence, it is crucial to promote a healthy lifestyle, a diet rich in vegetables and fruits, regular physical activity, reduction of alcohol consumption, and cessation of smoking. Another important aspect is the increased detection of lipid and carbohydrate disorders and hypertension, the treatment of which significantly reduces the cardiovascular risk. A key aspect of combating cardiovascular diseases is striving for a better understanding of their pathophysiology. This allows for the identification of further risk factors such as high levels of lipoprotein (a). Despite numerous studies and scientific articles on lipoprotein (a), many questions remain unanswered or uncertain. Lowering the level of lipoprotein (a) remains a challenge due to the lack of specific treatment for this disorder. Based on the available data, the benefits of lowering lipoprotein(a) levels in the context of cardiovascular diseases cannot be confirmed. However, there are reports of a negative impact of low lipoprotein(a) levels on the risk of developing type 2 diabetes [26,42]. There is a need for further research into the role of lipoprotein (a) in stratifying cardiovascular risk, the benefits of lowering its levels, and specific therapeutic approaches for this disorder.

Author's contribution

Conceptualization: Maria Maciąg, Karolina Garbacz, Aleksandra Marczak; methodology: Maria Maciąg, Małgorzata Pasztelan, Jarosław Pulikowski, Maciej Sobczyk; investigation: Maria Maciąg, Małgorzata Słaboń; software: Julia Krawczuk vel Walczuk; formal analysis: Aleksandra Muca, Joanna Baran; writing – review and editing: Maria Maciąg, Karolina Garbacz, Maciej Sobczyk, Małgorzata Pasztelan, Jarosław Pulikowski; resources: Małgorzata Słaboń, Aleksandra Marczak, Aleksandra Muca; supervision: Julia Krawczuk vel Walczuk, Joanna Baran;

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