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Overview of the Impact of Statin Therapy on Cardiac Incident Risk

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Abstract

Statin therapy is a cornerstone in preventing and managing cardiovascular diseases, particularly in reducing the risk of cardiac incidents. This review presents a comprehensive overview of the impact of statin therapy on cardiac incident risk, examining its efficacy in primary and secondary prevention, the underlying mechanisms of action, associated adverse effects, and considerations for patient adherence. Evidence from large-scale randomized controlled trials and meta-analyses consistently demonstrates that statins significantly reduce the incidence of major cardiovascular events by lowering low-density lipoprotein (LDL) cholesterol levels and exerting pleiotropic effects like improving endothelial function and stabilizing atherosclerotic plaques. Although generally well-tolerated, statins may cause side effects, including muscle-related symptoms and a modest increase in the risk of type 2 diabetes. Patient adherence remains a critical factor in maximizing the therapeutic benefits of statin therapy.

Keywords: cardiovascular disease, LDL cholesterol, sclerosis, statins

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with coronary heart disease (CHD) being a predominant contributor. It is estimated that by the year 2030, 23.6 million people will die annually because of CVD [2]. Elevated levels of LDL cholesterol are a well-established risk factor for the development of atherosclerosis and subsequent cardiac events. Statins, or HMG-CoA reductase inhibitors, have been extensively utilized to lower LDL cholesterol levels and reduce the risk of cardiac incidents [1]. This review aims to elucidate the impact of statin therapy on cardiac incident risk, exploring its efficacy, mechanisms of action, associated adverse effects, and factors influencing patient adherence.

Epidemiology of Cardiovascular Disease and Statin Use

The global burden of cardiovascular diseases (CVDs) has prompted widespread use of statin therapy in both primary and secondary prevention settings. In the United Kingdom, for instance, around 5.3 million people were given a NICE-recommended statin or ezetimibe by

their GP to help reduce their cholesterol during 2023/24, marking the largest number on record and almost 900,000 more than in 2022/23 [3]. The accessibility and cost-effectiveness of statins have led to their inclusion in clinical guidelines for individuals with varying degrees of cardiovascular risk.

In Poland, the use of statins remains suboptimal despite the high prevalence of cardiovascular diseases. According to a study published in the Polish Heart Journal, only a fraction of high-risk patients receive appropriate statin therapy [6]. This highlights the need for improved healthcare strategies to ensure better cardiovascular outcomes.

Similarly, the United States has seen a significant increase in statin use over the past decades. As reported in the Journal of the American College of Cardiology, the prevalence of statin use among adults aged 40 and older rose from 17.9% in 1999-2000 to 47.2% in 2011-2012 [7]. This rise is attributed to the expanding clinical guidelines that recommend statin use for a broader range of patients, including those with diabetes and other risk factors.

Furthermore, research published in the European Heart Journal indicates that statin therapy has contributed to a substantial reduction in cardiovascular mortality rates in Europe. Countries like Germany and France have observed significant declines in deaths related to heart disease and stroke, largely due to the widespread adoption of statin therapy and other preventive measures [8].

Mechanisms of Action

Statins primarily function by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. This inhibition results in decreased hepatic cholesterol production and upregulation of LDL receptors, enhancing the clearance of LDL cholesterol from the bloodstream. Beyond lipid-lowering, statins exhibit pleiotropic effects, including anti-inflammatory properties, improvement of endothelial function, and stabilization of atherosclerotic plaques. These effects collectively contribute to their cardiovascular protective benefits [12][16].

Moreover, statins have been shown to reduce oxidative stress and inhibit the proliferation of smooth muscle cells within arterial walls, which further prevents the progression of atherosclerosis. Recent studies have also highlighted the role of statins in promoting

autophagy, a cellular process that removes damaged components, thereby enhancing cellular health and longevity [9][24].

Impact on Glucose Metabolism and Diabetes Risk

Statins have been associated with an increased risk of developing type 2 diabetes (T2D). The mechanisms underlying this diabetogenic effect include impaired insulin sensitivity and secretion by pancreatic β-cells [2]. Statins may reduce the synthesis of mevalonate pathway products, leading to increased cholesterol loading and impaired β-cell function. Additionally, statins can decrease insulin sensitivity and increase insulin resistance in peripheral tissues [2].

Recent studies have shown that statins can affect glucose metabolism, potentially leading to higher blood glucose levels. A study published in the Journal of Clinical Lipidology underscores the impact of statins on reducing the risk of major adverse cardiovascular events, such as heart attacks and strokes, particularly in high-risk populations [9]. However, it is important to monitor blood glucose levels in patients receiving statin therapy to ensure early detection and management of potential hyperglycemia [11].

Efficacy in Primary Prevention

In individuals without established cardiovascular disease, the use of statin therapy is significantly effective in lowering the risk of major cardiovascular events. Notably, the JUPITER trial illustrated that rosuvastatin decreased the incidence of major cardiovascular events in patients who had elevated high-sensitivity C-reactive protein levels but normal LDL cholesterol levels. This study concluded that rosuvastatin not only reduced LDL cholesterol but also lessened inflammation, as indicated by lower CRP levels, thereby leading to a reduction in heart attacks, strokes, and the necessity for revascularization procedures [12].

Additionally, the HOPE-3 trial corroborated the advantages of statin therapy in a wider range of patients, including those with intermediate cardiovascular risk. This research discovered that rosuvastatin substantially lowered the risk of cardiovascular events even in individuals without conventional risk factors such as high LDL cholesterol, emphasizing the significance of statins in primary prevention [13].

Further investigations, such as the WOSCOPS trial, have showcased the long-term advantages of statin utilization in primary prevention. The WOSCOPS trial demonstrated that

pravastatin markedly reduced the risk of coronary heart disease events and enhanced overall survival in men with hypercholesterolemia. This trial provided compelling evidence supporting the use of statins to prevent first-time cardiovascular events and highlighted their role in improving long-term health outcomes [16].

Moreover, meta-analyses of multiple primary prevention trials have consistently indicated that statins are effective in lowering the risk of major cardiovascular events, irrespective of baseline cholesterol levels, underscoring the broad applicability of statin therapy in diverse patient populations.

Efficacy in Secondary Prevention

For patients with a history of cardiovascular events, statins are a cornerstone in reducing the risk of recurrent incidents. Research has shown that statin therapy effectively decreases the risk of major atherosclerotic cardiovascular disease events, including coronary death, myocardial infarction, stroke, and coronary revascularization, by about 25% for each 1 mmol/L reduction in LDL cholesterol during each year of continued therapy. The 4S (Scandinavian Simvastatin Survival Study) trial highlighted that simvastatin significantly reduced overall mortality by 30%, coronary mortality by 42%, and the incidence of major coronary events by 34% in patients with established coronary heart disease [14]. This pivotal study was crucial in establishing the role of statins in secondary prevention. The Heart Protection Study (HPS) further reinforced the effectiveness of statins in secondary prevention by demonstrating that simvastatin significantly reduced the risk of major vascular events, including heart attack, stroke, and revascularization, in a wide range of high-risk patients [18]. The study concluded that the benefits of statin therapy extend to patients with diabetes, peripheral arterial disease, and a history of cerebrovascular events, underscoring the extensive applicability of statins in reducing cardiovascular risk.

Furthermore, the PROVE-IT TIMI 22 trial showed that high-intensity statin therapy with atorvastatin significantly reduced the incidence of major cardiovascular events compared to standard therapy with pravastatin in patients who had recently experienced an acute coronary syndrome. This trial underscored the importance of intensive lipid-lowering therapy in achieving better outcomes in secondary prevention [19]. Meta-analyses of secondary

prevention trials have consistently demonstrated that statins reduce all-cause mortality, cardiovascular mortality, and the incidence of major cardiovascular events across diverse patient populations, confirming their central role in the management of patients with established cardiovascular disease.

Adverse Effects

While statins are generally well-tolerated, they are associated with certain adverse effects. Muscle-related symptoms, such as myalgia, occur in a small percentage of patients. Additionally, statin therapy has been linked to a modest increase in the risk of developing type 2 diabetes, particularly in individuals with predisposing risk factors. However, the cardiovascular benefits of statins typically outweigh these risks [2][11].

Some patients may also experience gastrointestinal symptoms, such as nausea or constipation, and in rare cases, liver enzyme abnormalities may occur. It is essential to monitor liver function during statin therapy to detect any potential hepatotoxicity early [16]. Furthermore, recent studies have indicated that high doses of statins may increase the risk of hemorrhagic stroke, although this risk remains relatively low compared to the overall cardiovascular benefits [25].

Despite these potential adverse effects, extensive clinical trials have consistently demonstrated that the benefits of statin therapy in reducing cardiovascular events significantly outweigh the risks. For instance, the PROVE-IT TIMI 22 trial highlighted the overall safety profile of statins, showing that intensive statin therapy led to a substantial reduction in recurrent cardiovascular events without a significant increase in adverse effects [17][19].

Patient Adherence

Adherence to statin therapy is crucial for achieving optimal cardiovascular outcomes. Discontinuation of statins has been associated with an increased risk of adverse cardiovascular events. Factors influencing adherence include side effects, patient perceptions, and understanding of the therapy’s benefits. Effective patient-provider communication and addressing concerns about side effects are essential in promoting adherence [20].

Furthermore, studies have shown that simplified dosing regimens and the use of fixed-dose combination pills can improve adherence rates. Financial constraints also play a significant role; ensuring affordability and access to medication can enhance adherence [1]. Additionally, educational interventions that provide patients with a clear understanding of the importance and benefits of statin therapy have been shown to significantly improve adherence and persistence with treatment [4].

Patient adherence can be further supported through regular follow-up appointments and the use of digital health tools, such as mobile apps that remind patients to take their medication. Personalized care plans that consider individual patient needs and preferences are also effective in promoting long-term adherence to statin therapy [5].

Recent research has highlighted the importance of patient education and support in improving adherence. A study published in the European Journal of Preventive Cardiology found that patients who received comprehensive education about the benefits and potential side effects of statins were more likely to adhere to their medication regimen [21]. Additionally, real-world data have shown that adherence to statin therapy is associated with a significant reduction in cardiovascular events and mortality [22].

Conclusions

Statin therapy has proven to be a cornerstone in the prevention and management of cardiovascular diseases (CVDs). Through primary prevention, statins significantly reduce the risk of major cardiovascular events, even in individuals with elevated high-sensitivity C-reactive protein levels but normal LDL cholesterol levels, as demonstrated by the JUPITER and HOPE-3 trials. In secondary prevention, statins have shown remarkable efficacy in reducing the recurrence of cardiovascular incidents, with studies like the 4S and Heart Protection Study underscoring their role in lowering mortality and morbidity rates.

While generally well-tolerated, statins are associated with certain adverse effects, including muscle-related symptoms and a modest increase in the risk of developing type 2 diabetes. Despite these risks, the cardiovascular benefits of statin therapy far outweigh the potential side effects, as highlighted in clinical trials.

Patient adherence to statin therapy is crucial for achieving optimal outcomes. Factors influencing adherence include side effects, patient perceptions, and understanding of the

therapy's benefits. Effective communication between healthcare providers and patients, along with educational interventions and support tools, can significantly enhance adherence and persistence with treatment. Ensuring patient adherence through education and management of side effects is essential to maximize the therapeutic benefits of statin therapy.

In summary, statins play a vital role in reducing the global burden of cardiovascular diseases. Continued efforts to improve patient adherence and address potential adverse effects will ensure that statin therapy remains a key strategy in cardiovascular disease prevention and management.

Disclosure

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Author's contribution

Author's contribution:
Conceptualization: U.Ś, K.K; Methodology: A.K., J.K.; Formal analysis: U.Ś, J.O.; Investigation: M.G., M.O.; Writing - rough preparation: A.P., K.K..; Writing - review and editing: U.Ś, W.B.; Supervision: U.Ś, P.F. All authors have read and agreed with the published version of the manuscript. Funding Statement: This Research received no external funding. Institutional Review Board Statement: Not applicable. Informed Consent Statement: Not applicable. Data Availability Statement: Not applicable. Conflicts of Interests: The authors declare no conflict of interest.

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