

## EVALUATING THE SAFETY OF EVOLOCUMAB IN CARDIOVASCULAR DISEASE

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### ABSTRACT

Evolocumab is a ground breaking monoclonal antibody that plays a crucial role in managing cardiovascular disease by targeting PCSK9, a protein involved in cholesterol regulation. By inhibiting PCSK9, evolocumab enhances the liver's ability to clear LDL cholesterol, effectively reducing cardiovascular events. This powerful LDL-lowering mechanism is especially advantageous for patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD) who do not respond well to standard treatments. Clinical studies, such as the FOURIER trial, have shown that evolocumab can lower LDL cholesterol by 50-60% and decrease cardiovascular events by 15%. Despite current therapies, residual cardiovascular risk persists, underscoring the need for additional treatments. Evolocumab fills this gap as a valuable complement to statin therapy. Its safety and efficacy, confirmed by extensive clinical trials, make it a reliable option for a wide range of patients. Incorporating evolocumab into clinical practice represents a major advancement in reducing cardiovascular risk, enhancing patient outcomes, and improving the quality of life for high-risk individuals not adequately managed by conventional lipid-lowering therapies.

**KEYWORDS:** Evolocumab, PCSK9, HeFH.

### 1. INTRODUCTION

Evolocumab is a monoclonal antibody that has been ground-breaking in the treatment of cardiovascular disease because of its unique mechanism of action, wide range of therapeutic applications, and significant influence on lipid regulation. Evolocumab is a medication that works as a strong inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9). It works by increasing the removal of low-density lipoprotein (LDL) cholesterol. It specifically binds to PCSK9 to block it from interacting with hepatocyte LDL receptors. As a result of this disturbance, LDL receptors are upregulated, which improves the liver's capacity to eliminate bloodstream-circulating LDL cholesterol. When it comes to treating hypercholesterolemia, evolocumab is a clinically significant treatment that is especially helpful for people who have heterozygous familial hypercholesterolemia (HeFH) or symptomatic atherosclerotic cardiovascular disease

(ASCVD). Its approbation as a supplement to diet and maximally tolerated statin medication highlights how important it is to meet unmet requirements in patient populations at high risk. Evolocumab lowers LDL cholesterol levels dramatically, which lowers the risk of cardiovascular events and provides a new therapeutic option for people who don't respond to traditional lipid-lowering medications. Evolocumab shines as a beacon of innovation as we negotiate the complex terrain of managing cardiovascular illness, ushering in a new era in the search for the best possible patient outcomes.<sup>[1]</sup>

### **1.1 Mechanism of action**

Evolocumab, a monoclonal antibody, targets PCSK9, a protein crucial in cholesterol metabolism. Typically, PCSK9 binds to LDL receptors on liver cells, leading to their degradation and hindering the liver's capacity to remove LDL cholesterol from the blood. Evolocumab binds to PCSK9, preventing this interaction and stopping receptor degradation. This process increases the number of functional LDL receptors on liver cells, which enhances LDL cholesterol clearance. Consequently, evolocumab significantly lowers LDL cholesterol levels and reduces cardiovascular risk, offering a targeted treatment approach for hypercholesterolemia, especially in patients who do not respond well to standard therapies.<sup>[2]</sup>

#### **1.2.1 Reduction of Cardiovascular Risk**

Evolocumab is prescribed to adult patients with established cardiovascular disease to mitigate the risk of myocardial infarction (heart attack), stroke, and the need for coronary revascularization procedures. By significantly lowering LDL-cholesterol levels through its mechanism of action, evolocumab addresses a crucial modifiable risk factor for cardiovascular events, providing additional protection beyond standard therapies. This targeted reduction in cardiovascular risk underscores the importance of LDL-cholesterol management in improving patient outcomes and preventing adverse cardiovascular events.<sup>[3,4]</sup>

#### **1.2.2 Hyperlipidemia Management**

Evolocumab serves as an adjunct to dietary measures, either alone or alongside other hypolipidemic treatments, for adults dealing with primary hyperlipidemia. Moreover, it's approved for pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia, aiming to lower LDL-C levels effectively. This broadens the therapeutic options for individuals with these conditions, addressing unmet needs in managing lipid profiles, especially in cases of genetic predispositions to high cholesterol levels.<sup>[3,4]</sup>

#### **1.2.3 Homozygous Familial Hypercholesterolemia Treatment**

Evolocumab, an injectable medication, is prescribed alongside other lipid-lowering therapies for individuals aged 10 and above diagnosed with homozygous familial hypercholesterolemia. This condition leads to extremely high levels of LDL cholesterol, putting patients at significant risk of cardiovascular complications. By specifically targeting LDL-C levels, evolocumab helps mitigate this risk, offering a crucial adjunctive treatment option in managing this rare, severe form of hypercholesterolemia.<sup>[3,4]</sup>

### **1.3 Importance in managing cardiovascular disease**

Since it significantly decreases the risk of cardiovascular events, the powerful lipid-lowering medication evolocumab is essential in the management of cardiovascular disease. The medication is a valuable supplement to statin therapy for individuals with established cardiovascular disease because of its capacity to reduce low-density lipoprotein cholesterol

(LDL-C) levels by 50–60% and its effectiveness in reducing cardiovascular events by 15% when compared to placebo. Evolocumab was found to reduce the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization by 15% when compared to placebo in the FOURIER trial, which included 27,564 patients with atherosclerotic cardiovascular disease. For individuals who already have cardiovascular disease and are at high risk, this decrease in cardiovascular events is very important.

The potential of evolocumab to consistently improve a range of patient subgroups, including as those with varying baseline LDL-C levels, age, gender, and vascular disease types, highlights the drug's significance in the management of cardiovascular disease. Furthermore, the medication has a good safety profile, with the most frequent side effect being mild injection site responses.

All things considered, evolocumab is a valuable treatment choice for cardiovascular disease, especially for individuals who are already at high risk from their underlying condition. It can lower cardiovascular events and consistently improve different patient subgroups, making it a useful supplement to statin therapy for these patients.<sup>[5]</sup>

## 2. Cardiovascular Disease

Cardiovascular diseases (CVDs) stand as the primary cause of death globally, constituting approximately 32% of all fatalities in 2019, totaling around 17.9 million lives lost. Among CVDs, heart attacks and strokes contribute to a staggering 85% of the overall burden. This prevalence underscores their immense impact on public health. CVDs fall within the spectrum of non-communicable diseases (NCDs), a broad category responsible for over three-quarters of all deaths worldwide. NCDs, including CVDs, cancer, chronic respiratory diseases, and diabetes, pose a substantial challenge to healthcare systems globally due to their chronic nature and long-term management requirements. The rise in CVDs is closely linked to lifestyle factors such as poor diet, physical inactivity, tobacco use, and excessive alcohol consumption. Addressing these modifiable risk factors through comprehensive public health initiatives and individual behavior changes is critical to reducing the burden of CVDs and improving global health outcomes. Additionally, access to quality healthcare services, early detection, and effective management of CVDs are essential components of strategies aimed at combating this leading cause of mortality worldwide. The economic burden of CVDs extends beyond healthcare costs, encompassing lost productivity and diminished quality of life for affected individuals and their families. Efforts to prevent and control CVDs require a multi-sectoral approach involving governments, healthcare providers, civil society organizations, and individuals to mitigate this significant public health challenge and save lives on a global scale.<sup>[5]</sup>

## 3. The Need for Additional Therapies

### 3.1 Persistence of residual risk despite standard treatments

The necessity for additional therapies to effectively manage cardiovascular diseases (CVDs) arises due to the persistence of residual risk despite standard treatments. These standard therapies primarily involve lifestyle modifications and medication use. Lifestyle changes include smoking cessation, adopting a heart-healthy diet, regular exercise, and stress management. Additionally, medications such as statins, beta blockers, nitrates, ACE inhibitors, and ARBs are commonly prescribed to address various aspects of CVDs.

Statins work by reducing levels of LDL cholesterol, often referred to as "bad" cholesterol, thereby preventing the buildup of plaque in the arteries and reducing the risk of heart attacks and strokes. Beta blockers lower blood pressure

by inhibiting the heart's response to adrenaline, thereby reducing heart rate and workload. Nitrates dilate blood vessels to improve blood flow to the heart, reducing workload and alleviating symptoms of angina. ACE inhibitors block the action of angiotensin-converting enzyme (ACE), lowering blood pressure and protecting the heart and kidneys. ARBs, on the other hand, block the effects of angiotensin II directly, leading to vasodilation and decreased blood pressure.

Despite the effectiveness of these standard treatments, residual risk remains, highlighting the need for additional therapies to further manage CVDs.<sup>[6]</sup>

### **Residual Risk**

Even with these conventional interventions, residual risk persists for a number of reasons:

#### **Uncontrolled risk factors**

Cardiovascular events are much more likely when uncontrolled risk factors like high blood pressure and excessive cholesterol levels are present. Heart attacks and strokes are more likely to occur when blood pressure is high because it strains the heart and arteries. Likewise, a buildup of plaque in the arteries can cause them to constrict and restrict blood flow due to elevated cholesterol. These variables can worsen and endanger cardiovascular health if they are not properly managed with medication and lifestyle modifications. Mitigating these risks and promoting heart health require proactive actions and routine monitoring.<sup>[6-8]</sup>

#### **Lack of adherence**

Patients who don't follow their treatment regimens may not be able to control risk factors including high blood pressure and cholesterol. Efforts to properly manage these risk factors may be hampered by inconsistent drug use, dietary recommendations, or suggested lifestyle modifications. Patients may suffer from worsening symptoms and a higher risk of cardiovascular events if appropriate adherence is not followed. When it comes to removing obstacles to adherence and enabling patients to stick to treatment plans for the best possible heart health, healthcare practitioners are essential.<sup>[6,9]</sup>

#### **Multiple risk factors**

When a person has several risk factors for cardiovascular diseases (CVDs), managing those conditions effectively becomes more difficult. The co-occurrence of conditions such as high blood pressure, high cholesterol, obesity, and diabetes increases the likelihood of issues related to the heart. A comprehensive strategy that includes medication treatment, lifestyle adjustments, and routine monitoring is needed to address these connected variables. Healthcare professionals must customize treatment regimens to address the particular risk factors that each patient possesses, highlighting the significance of comprehensive care to lessen the combined effects of various illnesses on cardiovascular health.<sup>[6,9]</sup>

#### **Long-Term Efficacy**

The long-term efficacy of evolocumab in treating cardiovascular risk factors has been demonstrated by a higher reduction in cardiovascular events when compared to delayed treatment commencement.<sup>[9,10]</sup>

#### **Safety Profile**

The safety profile of the PCSK9 inhibitor evolocumab has been thoroughly examined in a number of clinical trials. Its safety profile has been repeatedly shown in these trials when compared to both placebo and control regimens. This

assurance is given to a wide range of patient populations, demonstrating the drug's dependability for people with different backgrounds in medicine and demographics. More than 6000 patients from various trials are included in the pooled safety study, which offers strong proof of its reliable safety performance. Adverse events associated with evolocumab have been thoroughly assessed, highlighting its tolerability and low risk of serious complications. This collective analysis not only reinforces the drug's safety but also enhances confidence in its clinical utility. Such comprehensive safety evaluations are crucial for informing healthcare decisions and ensuring patient well-being. Therefore, the consistent safety profile of evolocumab underscores its potential as a therapeutic option for managing lipid disorders effectively and safely.<sup>[11,12]</sup>

#### **4. Risk-Benefit Assessment**

##### **4.1 Balancing the benefits of LDL reduction with potential risks**

Weighing the advantages of decreasing LDL cholesterol levels against the potential drawbacks is one way to balance the benefits of LDL reduction with potential hazards. Reducing low-density lipoprotein (LDL) cholesterol has been demonstrated to substantially lower the risk of major cardiovascular events and mortality. A drop of 1 mmol/L is linked to a corresponding decrease in major vascular events. Research has indicated that lowering low-density lipoprotein (LDL) cholesterol levels can significantly lower cardiovascular morbidity and death.<sup>[13,14]</sup>

But as some studies have shown, it is important to take into account possible hazards, like adverse outcomes linked to abnormally low LDL levels. In addition to addressing the residual cardiovascular risk even after reaching suggested LDL levels, the ongoing research seeks to elucidate the long-term consequences of lowering LDL cholesterol levels below current guidelines. Furthermore, the availability of novel medications like as PCSK9 inhibitors has made it possible to reduce LDL levels even more; nonetheless, concerns about the ideal degree of LDL reduction and its effects on outcomes, particularly in patients with varying baseline LDL levels, persist. The evaluation of risks and benefits is crucial for identifying the optimal and safest strategy in managing LDL cholesterol levels. This involves weighing the advantages of reducing cardiovascular risk against the potential drawbacks linked to excessively low LDL levels.<sup>[14,15]</sup>

##### **4.2 Implications for clinical practice and guidelines**

Evolocumab, a PCSK9 inhibitor, demonstrates significant benefits in reducing major cardiovascular events in individuals with atherosclerotic cardiovascular disease (ASCVD), irrespective of metabolic syndrome (MetS) status. Clinical data indicates a 15% risk reduction in the composite endpoint, including cardiovascular death, myocardial infarction, stroke, and more, highlighting its therapeutic potential.<sup>[16]</sup> Specifically in MetS patients, evolocumab showcases a 17% risk reduction in primary endpoints and a 24% decrease in stroke, myocardial infarction, and cardiovascular death.<sup>[17]</sup> Consistent LDL-cholesterol reductions of 63.8% to 69.5% underscore its efficacy in lowering cardiovascular risk.<sup>[17]</sup> Notably, one major adverse cardiovascular event may be prevented for every 36 ASCVD patients treated, suggesting its clinical utility.<sup>[18]</sup> In terms of safety, evolocumab exhibits excellent tolerability in MetS patients, with no significant concerns regarding diabetes mellitus or glycemic control, highlighting its safety profile.<sup>[19]</sup> These findings underscore evolocumab's potential as a therapeutic option in managing ASCVD, especially in MetS patients, where it offers cardiovascular benefits without compromising metabolic parameters.

#### **CONCLUSION**

Evolocumab is a groundbreaking treatment for cardiovascular disease due to its unique mechanism of action and ability to significantly lower LDL cholesterol levels. By inhibiting PCSK9, it enhances the liver's ability to clear LDL

cholesterol, reducing cardiovascular events by 15% in high-risk patients. Despite standard treatments, residual cardiovascular risk persists, necessitating additional therapies like evolocumab. Its proven safety profile and efficacy in clinical trials make it a promising option, especially for those unresponsive to traditional medications. Integrating evolocumab into clinical practice offers hope for better patient outcomes and improved quality of life globally.

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