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CETP INHIBITORS: UPCOMING STRATEGIES TO TREAT ATHEROSCLEROSIS

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Abstract

Atherosclerosis is a chronic vascular disease strongly associated with elevated concentrations of atherogenic apolipoprotein B-containing lipoproteins. Cholesteryl ester transfer protein (CETP) plays an important role in lipid metabolism by transferring cholesteryl esters from high-density lipoprotein to low- and very-low-density lipoproteins. Inhibition of CETP has therefore been investigated as a strategy to increase HDL cholesterol and reduce atherogenic lipoproteins. Early CETP inhibitors produced disappointing results because of off-target toxicity, insufficient cardiovascular benefit, or unfavorable pharmacokinetic properties. However, newer compounds have renewed interest in this therapeutic target. Obicetrapib, a next-generation CETP inhibitor, has demonstrated substantial reductions in LDL cholesterol, apolipoprotein B, non-HDL cholesterol, and lipoprotein(a) when added to existing lipid-lowering therapy [1,2]. The aim of this review is to summarize the mechanisms, previous limitations, and future therapeutic potential of CETP inhibition in atherosclerosis. Current evidence suggests that future CETP-directed therapy will focus less on simply raising HDL cholesterol and more on reducing the overall burden of atherogenic lipoproteins.

Keywords: CETP inhibitors, atherosclerosis, obicetrapib, LDL cholesterol, HDL cholesterol, lipoprotein(a), cardiovascular disease.

Introduction

Atherosclerosis develops through progressive accumulation of cholesterol-containing lipoproteins within the arterial wall, accompanied by inflammation, endothelial dysfunction, and plaque formation.

Low-density lipoprotein cholesterol remains one of the principal modifiable risk factors for atherosclerotic cardiovascular disease.

Statins are considered first-line therapy, while ezetimibe, PCSK9 inhibitors, and other lipid-lowering agents may be added when LDL cholesterol remains above recommended targets.

Nevertheless, many high-risk patients continue to have residual cardiovascular risk.

CETP has therefore remained an important therapeutic target.

CETP is a plasma glycoprotein that facilitates transfer of cholesteryl esters from HDL particles to apoB-containing lipoproteins in exchange for triglycerides.

Inhibition of CETP generally increases HDL cholesterol while reducing LDL cholesterol and other atherogenic lipoproteins [1].

The concept initially appeared highly promising, but development of the first CETP inhibitors encountered major difficulties.

Torcetrapib increased HDL substantially but was associated with increased cardiovascular events and mortality because of adverse off-target effects, including increases in blood pressure and aldosterone activity [3].

Dalcetrapib failed to demonstrate meaningful cardiovascular benefit, while evacetrapib also failed to reduce clinical cardiovascular events despite favorable lipid changes.

Anacetrapib was more successful and demonstrated a modest reduction in major coronary events, providing evidence that CETP inhibition itself was not necessarily an ineffective therapeutic strategy [4].

These findings contributed to development of more selective next-generation agents.

Materials and Methods

This article was prepared as a concise literature-based review.

Recent clinical studies and reviews concerning CETP biology, lipid metabolism, atherosclerosis, earlier CETP inhibitors, and newer agents such as obicetrapib were analyzed.

The main outcomes considered were changes in LDL cholesterol, HDL cholesterol, apolipoprotein B, non-HDL cholesterol, lipoprotein(a), safety, and cardiovascular outcomes.

Results

The history of CETP inhibitors demonstrates that increasing HDL cholesterol alone is not sufficient to guarantee cardiovascular protection.

Torcetrapib markedly increased HDL but caused clinically important off-target toxicity.

Dalcetrapib produced weaker LDL reduction and failed to improve cardiovascular outcomes.

Evacetrapib substantially modified lipid levels but also failed to demonstrate clinical benefit.

Anacetrapib represented an important turning point.

In the REVEAL trial, addition of anacetrapib to statin therapy reduced the incidence of major coronary events, although the compound was not developed commercially because of its prolonged accumulation in adipose tissue and other practical considerations [4].

The newer CETP inhibitor obicetrapib has renewed interest in this drug class.

Recent studies indicate that obicetrapib lowers LDL cholesterol, apolipoprotein B, non-HDL cholesterol, and lipoprotein(a), while increasing HDL cholesterol [1,2].

A 2025 review summarized Phase III studies showing LDL cholesterol reductions of approximately 30–51%, apoB reductions of around 20–33%, and substantial decreases in lipoprotein(a), with a safety profile broadly similar to placebo [2].

These effects are especially relevant because contemporary cardiovascular prevention focuses strongly on reducing apoB-containing particles rather than merely increasing HDL concentration.

Mechanism of Action

CETP transfers cholesteryl esters from HDL to LDL and VLDL particles.

When CETP is inhibited, more cholesterol remains within HDL particles and less is transferred into atherogenic apoB-containing lipoproteins.

This produces several lipid changes:

- increased HDL cholesterol;
- decreased LDL cholesterol;
- decreased non-HDL cholesterol;
- reduced apolipoprotein B;
- potential reduction in lipoprotein(a).

The reduction in apoB-containing particles is likely to be particularly important for atherosclerosis prevention.

Modern understanding increasingly suggests that the cardiovascular benefit of CETP inhibition depends more on lowering atherogenic particles than on simply increasing HDL cholesterol.

Obicetrapib as a New Strategy

Obicetrapib is an oral, highly selective next-generation CETP inhibitor.

Phase II and Phase III studies have demonstrated meaningful additional lipid lowering when obicetrapib is given on top of intensive background therapy [1,2].

The BROOKLYN and BROADWAY programs evaluated patients with significant hypercholesterolemia despite maximally tolerated lipid-lowering therapy.

TANDEM has examined fixed-dose combination therapy with ezetimibe, while PREVAIL is evaluating cardiovascular outcomes.

As of 2026, the major unanswered question is whether the strong lipid changes produced by obicetrapib will translate into definitive reductions in cardiovascular events in the ongoing outcomes program.

Potential Role of Lipoprotein(a)

Another important future application of CETP inhibition concerns lipoprotein(a).

Elevated lipoprotein(a) is an independent genetic risk factor for atherosclerotic cardiovascular disease.

Traditional statins have little ability to reduce Lp(a), and highly effective targeted Lp(a)-lowering therapies are still an evolving therapeutic area.

Obicetrapib has shown notable reductions in Lp(a), potentially providing an additional advantage in high-risk patients [2].

This makes CETP inhibition particularly interesting as a multidimensional lipid-lowering strategy.

Discussion

The development of CETP inhibitors provides an important example of how therapeutic concepts can change after initial clinical failures.

Early CETP inhibitors were largely developed with the assumption that increasing HDL cholesterol would automatically reduce cardiovascular risk.

Current evidence suggests that this concept was overly simplistic.

HDL concentration alone does not necessarily reflect HDL function, and pharmacologically increasing HDL does not automatically prevent atherosclerosis.

The newer strategy therefore focuses more strongly on reducing LDL cholesterol, apoB, non-HDL cholesterol, and Lp(a).

Obicetrapib appears promising because it combines CETP inhibition with clinically relevant reductions in several atherogenic lipid markers.

It may eventually become useful for patients who do not achieve adequate lipid control with statins and ezetimibe or who prefer an oral option rather than injectable therapy.

However, cardiovascular outcome evidence remains essential.

Large reductions in lipid biomarkers do not automatically guarantee reductions in myocardial infarction, stroke, or cardiovascular mortality.

Long-term safety will also need continued evaluation.

Another emerging strategy is CETP-directed immunotherapy.

Research has investigated vaccines designed to stimulate antibody formation against CETP, potentially producing longer-lasting inhibition of CETP activity [5].

These approaches remain experimental but illustrate the broader future potential of CETP targeting.

Conclusion

CETP inhibition remains a promising strategy for the treatment and prevention of atherosclerosis.

The failure of early agents demonstrated that simply raising HDL cholesterol is insufficient and that drug-specific safety and the reduction of atherogenic lipoproteins are more important.

Next-generation CETP inhibitors, particularly obicetrapib, have shown strong reductions in LDL cholesterol, apolipoprotein B, non-HDL cholesterol, and lipoprotein(a).

The future role of this class will depend largely on cardiovascular outcome data, long-term safety, and its ability to complement established therapies such as statins, ezetimibe, and PCSK9 inhibitors.

CETP inhibition may therefore re-emerge not as an HDL-raising strategy, but as a broader oral approach for reducing residual atherosclerotic cardiovascular risk.

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