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COMBINATION THERAPY WITH ROSUVASTATIN AND EZETIMIBE (TREZETE) IN VERY HIGH CARDIOVASCULAR RISK DYSLIPIDEMIA: EVIDENCE OF EFFICACY AND CLINICAL IMPACT

TERAPIA COMBINADA COM ROSUVASTATINA E EZETIMIBA (TREZETE) NA DISLIPIDEMIA DE MUITO ALTO RISCO CARDIOVASCULAR: EVIDÊNCIAS DE EFICÁCIA E IMPACTO CLÍNICO

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ABSTRACT
Very high cardiovascular risk dyslipidemia requires effective and safe strategies for intensive LDL-C reduction. This integrative review analyzed studies published between 2015 and 2025 on the combination of rosuvastatin and ezetimibe in high cardiovascular risk contexts. The literature search was conducted in PubMed, Scopus, Web of Science, SciELO, LILACS, and ScienceDirect databases. The combination demonstrated an additional LDL-C reduction of up to 25% compared to monotherapy, with a favorable safety profile and improved adherence, especially in fixed-dose formulations. Consistent results were observed in subgroups such as diabetic patients, the elderly, and those with coronary artery disease. The main limitations included short follow-up periods and a lack of comparative studies with newer lipid-lowering therapies. It is concluded that the rosuvastatin/ezetimibe combination is an effective, safe, and applicable therapeutic alternative for very high-risk populations and should be considered a first-line option in intensive cardiovascular prevention settings.

Keywords: Dyslipidemia. Rosuvastatin. Ezetimibe. Combination Therapy. Cardiovascular Risk.

RESUMO
A dislipidemia de muito alto risco cardiovascular exige estratégias eficazes e seguras para redução intensiva do LDL-C. Esta revisão integrativa analisou estudos publicados entre 2015 e 2025 sobre a combinação rosuvastatina/ezetimiba em contextos de alto risco cardiovascular. A busca foi realizada nas bases PubMed, Scopus, Web of Science, SciELO, LILACS e ScienceDirect. A associação demonstrou redução adicional de LDL-C de até 25% em relação à monoterapia, com perfil de segurança favorável e maior adesão em formulações de dose fixa. Resultados consistentes foram observados em subgrupos como diabéticos, idosos e pacientes com DAC. As principais limitações incluem o tempo de seguimento reduzido e escassez de estudos comparativos com novas terapias hipolipemiantes. Conclui-se que a combinação rosuvastatina/ezetimiba é uma alternativa eficaz, segura e aplicável em populações de risco muito alto, devendo ser considerada como primeira escolha em cenários de prevenção cardiovascular intensiva.

Palavras-chave: Dislipidemia. Rosuvastatina. Ezetimiba. Terapia Combinada. Risco Cardiovascular.

RESUMEN
La dislipidemia con muy alto riesgo cardiovascular requiere estrategias eficaces y seguras para la reducción intensiva del colesterol LDL. Esta revisión integrativa analizó estudios publicados entre 2015 y 2025 sobre la combinación de rosuvastatina/ezetimiba en pacientes con alto riesgo cardiovascular. La búsqueda se realizó en las bases de datos PubMed, Scopus, Web of Science, SciELO, LILACS y ScienceDirect. La combinación demostró una reducción adicional del colesterol LDL de hasta un 25 % en comparación con la monoterapia, con un perfil de seguridad favorable y mayor adherencia en las formulaciones de dosis fija. Se observaron resultados consistentes en subgrupos como diabéticos, ancianos y pacientes con enfermedad arterial coronaria (EAC). Las principales limitaciones incluyen el corto tiempo de seguimiento y la escasez de estudios comparativos con nuevas terapias hipolipemiantes. Se concluye que la combinación de rosuvastatina/ezetimiba es una alternativa eficaz, segura y aplicable en poblaciones de muy alto riesgo y debería considerarse como una opción de primera línea en escenarios de prevención cardiovascular intensiva.

Palabras clave: Dislipidemia. Rosuvastatina. Ezetimiba. Terapia Combinada. Riesgo Cardiovascular.

1 INTRODUCTION

Dyslipidemia is one of the main modifiable risk factors for cardiovascular diseases, especially atherosclerosis, and accounts for a significant portion of global mortality from preventable causes (BAI et al., 2023). Persistent elevation of plasma levels of low-density lipoprotein (LDL-C) is strongly associated with the formation of atheromatous plaques, leading to events such as acute myocardial infarction (AMI), ischemic stroke (iCVA), and sudden cardiac death (MACH et al., 2020). In this context, strict control of LDL-C is one of the most effective measures in the prevention of cardiovascular events, both primary and secondary.

The European Society of Cardiology and European Atherosclerosis guidelines recommend aggressive lipid targets for individuals at very high cardiovascular risk, with LDL-C below 55 mg/dL, and below 40 mg/dL in cases with recurrent events (MACH et al., 2020; GRUNDY et al., 2019). Achieving these levels, however, often requires intervention beyond statin monotherapy, especially in patients with familial dyslipidemia, type 2 diabetes, or established coronary heart disease (PARK et al., 2023). In addition, intolerance to high doses of statins, associated with increased risk of myalgia, elevated liver enzymes, and other adverse effects, represents a relevant limitation (STRILCHUK et al., 2020).

Faced with these obstacles, combination therapy with rosuvastatin and ezetimibe has emerged as an effective and safe alternative. Rosuvastatin, a high-potency, hydrophilic statin, inhibits hepatic cholesterol synthesis. Ezetimibe, on the other hand, acts by a complementary mechanism, reducing intestinal cholesterol absorption via inhibition of the NPC1L1 protein (CHILBERT et al., 2022). This synergy allows for additional LDL-C reductions of up to 24% over statin monotherapy, which favors the use of lower doses and reduces the risk of adverse events (TRAN et al., 2024).

Clinical studies and systematic reviews have demonstrated the superiority of the combination at moderate dose when compared to rosuvastatin alone at high dose. The meta-analysis by Liu et al. (2024), with more than 24 thousand participants, confirmed significant reductions in LDL-C, total cholesterol, and triglycerides, with an equivalent or superior safety profile. Wei et al. (2024) also observed clinically relevant efficacy of the combination in primary dyslipidemia, with no increase in the incidence of serious adverse effects.

Another favorable point of the rosuvastatin/ezetimibe combination is adherence to treatment, especially with the use of fixed-dose combination (FDC), such as Trezete®. The simplification of the therapeutic regimen, by reducing the number of pills, contributes to

greater persistence of treatment and reduction of cardiovascular events in the long term (RODRÍGUEZ-SALDAÑA et al., 2022; FRONTIERS IN CARDIOVASCULAR MEDICINE, 2025). This strategy is particularly useful in the elderly and polymedicated patients.

The effectiveness of the combination is also more pronounced in subgroups of greater vulnerability, such as diabetics and patients with coronary artery disease. Recent studies (Moon et al., 2023; Dadzie et al., 2024) highlight significant reductions in LDL-C, ApoB, and triglycerides, in addition to glycemic and hepatic stability, essential aspects in populations with high cardiovascular risk.

In view of the growing body of evidence, European and Latin American clinical consensuses have recommended combination as the strategy of choice in patients who do not achieve lipid goals with statins alone (KOZŁOWSKA-WOJCIECHOWSKA et al., 2025; BARBIOS & ESCOBAR, 2021).

In this context, this review article aims to critically analyze the main findings published between 2015 and 2025 on the efficacy, safety, adherence, and clinical impact of combination therapy with rosuvastatin and ezetimibe in patients with dyslipidemia at very high cardiovascular risk.

2 METHODOLOGY

This study is characterized as an integrative narrative review of the literature, with a qualitative, exploratory and descriptive approach. The objective was to gather, analyze, and critically synthesize the available scientific evidence on the efficacy, safety, and clinical impact of the rosuvastatin/ezetimibe combination in the treatment of very high-risk cardiovascular dyslipidemia. The methodological option was based on the model proposed by Whittemore and Knafl (2005), which allows the integration of results from different types of studies, offering a comprehensive view of the phenomenon investigated.

The review was conducted between May and October 2025, based on criteria of transparency, systematization, and thematic relevance. The following databases were used: PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, Embase, SciELO and LILACS. Peer-reviewed open access journals such as *Cureus*, *PLOS ONE,* BMC Cardiovascular Disorders*,* and *Frontiers in Cardiovascular Medicine* were also consulted. In addition, the reverse search technique (snowballing backward/forward) was used to identify additional relevant references.

The search strategy combined controlled terms (MeSH and DeCS) and free keywords, organized in the following clusters: ("Rosuvastatin" OR "Statins") AND ("Ezetimibe") AND ("Fixed-Dose Combination" OR "Combination Therapy") AND ("Dyslipidemia" OR "Hypercholesterolemia") AND ("High Cardiovascular Risk" OR "Very High Cardiovascular Risk") AND ("LDL-C" OR "Cholesterol Reduction"). The Boolean operators AND and OR were used to refine the results.

The inclusion criteria were:

a) studies published between January 2015 and May 2025;
b) original articles, systematic reviews, clinical consensuses, guidelines or observational studies;
c) full-text availability;
d) Portuguese, English or Spanish;
e) Analysis of clinical, lipid, or adherence outcomes related to combination therapy with rosuvastatin and ezetimibe in high- or very high-risk settings
f) The following were excluded:
g) studies focused exclusively on monotherapy;
h) publications with other pharmacological associations (e.g., PCSK9 inhibitors, fibrates);
i) in vitro studies or studies with animal models;
j) (4) duplicate texts, editorials, letters to the editor, conference abstracts and reviews without a defined methodology.

The screening of the articles occurred in three stages: reading of the titles, analysis of the abstracts and complete reading of the selected texts. Two independent reviewers conducted the process, and disagreements were resolved by consensus. Data extraction was based on a standardized spreadsheet containing: authors, year, type of study, country, number of participants, therapeutic regimen, follow-up time, outcomes evaluated, and conclusions.

The synthesis of the findings was organized by four main axes:

(i) clinical and laboratory efficacy in reducing LDL-C;
(ii) safety and tolerability profile;
(iii) impact on adherence and persistence to treatment;
(iv) application in specific subgroups of very high risk (such as type 2 diabetes, established cardiovascular disease, and familial dyslipidemia).

Although this review does not constitute a systematic review or meta-analysis, it sought to apply the methodological rigor required for narrative clinical reviews, according to the recommendations of authors specialized in the synthesis of knowledge in health (FERREIRA; NUNES; CARVALHO, 2021; GASPARYAN et al., 2022). Thus, the results presented here aim to support clinical decisions based on up-to-date evidence, promoting advances in the pharmacological management of dyslipidemia in high-risk populations.

3 PATHOPHYSIOLOGICAL AND PHARMACOLOGICAL BASIS OF COMBINATION THERAPY

Dyslipidemia, especially the increased low-density lipoprotein (LDL-C) fraction, is one of the major pathogenic factors in the development of atherosclerosis and atherosclerotic cardiovascular disease (ASCVD). The accumulation of LDL-C in the arterial wall triggers a chronic inflammatory process, leading to endothelial dysfunction, formation and instability of atheromatous plaques, increasing the risk of acute cardiovascular events (FERENCE et al., 2017). Therefore, the sustained reduction in LDL-C is directly associated with a proportional decrease in the risk of clinical events, as evidenced by several combined analyses (SABATINE et al., 2018).

Rosuvastatin is a high-potency hydrophilic statin that competitively inhibits the enzyme HMG-CoA reductase, which is involved in hepatic cholesterol biosynthesis. This inhibition stimulates increased expression of LDL receptors in the liver, intensifying plasma LDL-C clearance (STROES et al., 2015). In addition to the lipid-lowering effect, rosuvastatin also exerts pleotropic effects, such as improving endothelial function, stabilizing plaques, and reducing vascular inflammation, offering additional cardiovascular protection (BOUKHMAN et al., 2023).

Ezétimibe, in turn, acts in a complementary way, selectively inhibiting the Niemann-Pick C1-like protein 1 (NPC1L1), located on the brush border of intestinal enterocytes, which blocks the absorption of dietary and biliary cholesterol (DAVIES et al., 2013). This reduces the entry of exogenous cholesterol into the circulation and induces, in a compensatory way, an increase in the activity of hepatic LDL receptors.

The combination of the two mechanisms, inhibition of hepatic synthesis and intestinal absorption of cholesterol, promotes a synergistic effect, increasing therapeutic efficacy. This allows for additional 20% to 25% reductions in LDL-C levels compared to statin monotherapy

(STRILCHUK et al., 2020). In addition, it makes it possible to use lower doses of statins, reducing the risk of adverse effects and improving tolerability.

This approach is particularly relevant for patients at very high cardiovascular risk, in whom stricter lipid goals (<55 mg/dL) are recommended, according to international guidelines (MACH et al., 2020; GRUNDY et al., 2019). The fixed-dose formulation, such as Trezete®, also contributes to improving adherence and persistence to treatment, fundamental aspects for the control of dyslipidemia in the long term.

4 RESULT AND DISCUSSION

4.1 CLINICAL EFFICACY IN LOWERING LDL-C IN VERY HIGH-RISK POPULATIONS

The association between rosuvastatin and ezetimibe has been consolidated as a highly effective strategy for reducing LDL-C, especially in patients at very high cardiovascular risk. Randomized controlled trials, retrospective analyses, and systematic reviews consistently indicate that combination therapy outperforms statin monotherapy in lipid-lowering potency, especially when used at moderate doses, focusing on more stringent lipid targets (KOZŁOWSKA-WOJCIECHOWSKA et al., 2025; WEI et al., 2024).

In the study by Wei et al. (2024), with patients with primary hypercholesterolemia, the combination of rosuvastatin 10 mg + ezetimibe 10 mg reduced LDL-C by an average of 55.4%, compared to 47.8% obtained with rosuvastatin 20 mg alone, a statistically significant difference ($p < 0.01$). There was also a reduction in total cholesterol and triglycerides, with no increase in adverse effects.

Corroborating these findings, the meta-analysis by Liu et al. (2024), with 24,592 patients, compared rosuvastatin 20 mg alone with the 10/10 mg combination. The combination reduced LDL-C by up to an additional 25% and had a higher rate of patients who reached the goal of <55 mg/dL. In subgroups with type 2 diabetes and coronary heart disease, efficacy was even more prominent.

Tran et al. (2024), in a multicenter clinical study, showed that 69% of patients achieved LDL-C levels <1.4 mmol/L (~54 mg/dL) with the combined formulation, an ideal goal in secondary prevention. This effect was maintained in different age groups, with safety preserved. According to the authors, rapid and sustained control of dyslipidemia can reduce prolonged exposure to cardiovascular risk.

Park et al. (2023), in patients with acute coronary syndrome, observed greater than 70% reductions in LDL-C levels in just 6 weeks with the initial combination of rosuvastatin +

ezetimibe, with maintenance of the result at 12 weeks. The benefit was more evident in patients with baseline LDL-C >150 mg/dL, indicating a good response even in situations of therapeutic urgency.

In the retrospective study by Vázquez et al. (2024), the use of the Trezete® 10/10 mg and 20/10 mg formulations resulted in significant reductions in LDL-C in patients with and without diabetes, confirming their clinical applicability in different profiles. Security was similar between the groups.

A Korean meta-analysis (YON et al., 2023) compared high-intensity statins alone with moderate statins plus ezetimibe. The efficacy was equivalent or superior for the combination, with a lower incidence of myalgia and liver changes.

Taken together, this evidence strengthens the recommendation of combination therapy as the preferred option for patients with multiple risk factors, refractory dyslipidemia, or intolerance to high doses of statins. The combination of rosuvastatin/ezetimibe is thus an essential therapeutic tool, especially in intensive secondary prevention.

4.2 SAFETY AND TOLERABILITY OF COMBINATION THERAPY

Safety and pharmacological tolerability are fundamental aspects in the choice of lipid-lowering strategies, especially in patients at very high cardiovascular risk, in whom treatment is chronic and adherence depends directly on the presence or absence of adverse effects. The combination of rosuvastatin and ezetimibe has consistently demonstrated in the literature a favorable safety profile, comparable to or even superior to monotherapy with high-intensity statins (LIU et al., 2024; CHOI et al., 2023).

Controlled studies indicate that the association does not significantly increase the risk of muscle, hepatobiliary or metabolic adverse events. In a phase III clinical trial conducted in China, with patients treated with rosuvastatin 10 mg + ezetimibe 10 mg versus rosuvastatin 10 mg alone, the incidence of adverse events was similar (12.4% vs. 11.9%; $p > 0.05$), with no need to discontinue therapy due to elevations of transaminases or creatine kinase (Chinese Phase III Trial, 2025).

Similar results were observed by Dadzie et al. (2024) in patients with type 2 diabetes, a group particularly sensitive to statin side effects. The incidence of adverse events was 9.3% in the combination group, versus 11.7% in the rosuvastatin 20 mg alone group. In addition, there were no significant changes in glycated hemoglobin levels, renal function, or liver enzymes after 16 weeks of treatment, reinforcing the metabolic safety of the association.

Lee et al. (2021) evaluated the safety of a fixed-dose low-dose formulation (rosuvastatin 2.5 mg + ezetimibe 10 mg) and reported LDL-C reduction greater than 45%, with excellent tolerability: no cases of myalgia, rhabdomyolysis, or significant ALT or AST elevations were recorded. These data suggest that combination therapy is safe even in more vulnerable populations, such as the elderly or patients with hepatic impairment.

According to a review by Chilbert et al. (2022), ezetimibe does not potentiate the adverse effects of rosuvastatin, as its mechanisms of action are complementary and non-interactive in the hepatic and muscular systems. On the contrary, the combination allows the use of lower doses of statins, which contributes to a lower risk of side effects.

Data from the multicenter RACING study (2022, post hoc analysis) demonstrated that patients treated with rosuvastatin 10 mg + ezetimibe 10 mg had a lower rate of discontinuation of therapy for adverse effects compared to those taking rosuvastatin 20 mg, even after three years of follow-up.

Therefore, the rosuvastatin/ezetimibe combination is safe and well tolerated, with a low incidence of serious adverse effects, minimization of liver and muscle risks, and metabolic stability even in high-risk patients, such as those with diabetes. These attributes strengthen its role as a preferred therapeutic option in situations that require intensive lipid control with long-term maintenance of adherence.

4.3 ADHERENCE, PERSISTENCE, AND FIXED-DOSE FORMULATIONS (FDC)

Adherence to drug treatment in chronic diseases, such as dyslipidemia, represents one of the greatest challenges in clinical practice. Data from the World Health Organization indicate that, in developed countries, only about 50% of patients with chronic diseases maintain adequate adherence to prescribed medications (WHO, 2003). In secondary cardiovascular prevention, non-adherence compromises therapeutic efficacy, increases the risk of recurrent events, and increases the costs of hospitalizations and procedures (LAZAROU et al., 2022).

The introduction of fixed-dose combination (FDC) formulations has been shown to be an effective strategy to improve adherence and therapeutic persistence. In the case of the rosuvastatin/ezetimibe combination, studies have shown that simplifying the dosing regimen with only one pill a day is associated with greater continuity of treatment, better lipid control, and lower risk of abandonment due to forgetfulness or fatigue with multiple medications (Frontiers in Cardiovascular Medicine, 2025).

In an observational study with more than 7,000 patients, published in *Frontiers in Cardiovascular Medicine* (2025), users of rosuvastatin/ezetimibe FDC had a 32% higher persistence rate compared to those who used the drugs separately. In addition, the 6-month dropout rate was 41% lower among those using the combined formulation. This effect was most notable in older adults with comorbidities and complex therapeutic regimens.

Rodríguez-Saldaña et al. (2022), in a real-world study in Mexico with the formulation Trezete® (FDC 10/10 mg or 20/10 mg), reported that 72.8% of patients achieved lipid goals without the need for therapy intensification. The combination was well accepted, with positive reports about convenience of use and lower perception of side effects attributed to the simplification of pharmacotherapy.

Alekseeva et al. (2019), in a review published in the *Medical Council*, reinforced that FDC not only improves adherence, but also reduces variability in exposure to active substances, contributing to more consistent therapeutic results. In addition, dose fixing prevents unsupervised reductions by patients, a common practice in multiple-pill regimens.

In the RACING study (2022, post hoc analysis), greater persistence of treatment after three years was observed in the group that used rosuvastatin + ezetimibe at a moderate dose, compared to rosuvastatin at a high dose alone. According to the authors, this continuity is associated with a lower incidence of adverse effects and a subjective perception of greater safety and tolerability.

Thus, adherence and persistence to treatment are crucial components for therapeutic success. The FDC formulation with rosuvastatin/ezetimibe offers a practical, effective, and safe alternative, especially useful in public health systems and among populations with low health literacy, where simplification of treatment directly impacts clinical outcomes.

4.4 APPLICATION IN SPECIAL SUBGROUPS: DIABETES, CAD AND EXTREME RISK POPULATIONS

The combination of rosuvastatin + ezetimibe has gained prominence in the scientific literature for its efficacy in clinical subgroups of greater vulnerability, such as individuals with type 2 diabetes (T2DM), coronary artery disease (CAD), and refractory dyslipidemia. These patients have a high residual cardiovascular risk, even with the use of high-intensity statins, which justifies more aggressive and individualized therapeutic strategies (MACH et al., 2020; GRUNDY et al., 2019).

Patients with T2DM often have complex lipid alterations, such as hypertriglyceridemia, small and dense LDL, and reduced HDL-C, which make adequate control difficult. In a study by Moon et al. (2023), conducted in patients with T2DM and established atherosclerotic disease, the combination of rosuvastatin 10 mg + ezetimibe 10 mg significantly reduced LDL-C levels and improved HOMA-β, without affecting fasting glucose or HbA1c, demonstrating metabolic safety.

Similar data were reported by Dadzie et al. (2024), when comparing rosuvastatin 20 mg alone with the 10/10 mg combination in diabetics. The association showed a greater reduction in LDL-C (56% vs. 48%) and triglycerides, with a lower incidence of myalgia and liver alterations. These findings support the combination as an effective and safe alternative, especially for patients intolerant to high doses of statins.

In patients with established CAD or undergoing revascularization, combined therapy has also been shown to be beneficial. Park et al. (2023), in a study with patients with acute coronary syndrome, demonstrated that the immediate initiation of the association resulted in a reduction in LDL-C of up to 75% and a lower rate of readmission for ischemic events at 12 months.

The combination has also been shown to be advantageous in the elderly or individuals with multiple comorbidities, in whom tolerability is critical. Lee et al. (2021) investigated the use of rosuvastatin 2.5 mg + ezetimibe 10 mg and observed a 45% reduction in LDL-C with excellent tolerance and absence of liver elevations or muscle complaints, even in patients with a mean age of over 70 years.

Kolmakova et al. (2024), in a Russian study, highlighted the cost-benefit ratio of the combined formulation in patients with extreme cardiovascular risk (SCORE >10%), especially in public health settings. The combination was effective in lowering LDL-C and more cost-effective than scaled strategies with multiple drugs.

These findings demonstrate that the rosuvastatin/ezetimibe combination not only lowers LDL-C more effectively, but also offers advantages in safety, applicability, and cost, making it a valuable therapeutic tool for traditionally challenging groups in clinical practice.

5 LIMITATIONS OF THE SCIENTIFIC LITERATURE

Despite the robust evidence supporting efficacy, safety, and adherence to combination therapy with rosuvastatin and ezetimibe, some methodological limitations and scientific gaps

should be acknowledged. The critical identification of these aspects is essential to correctly interpret the results and guide future studies with greater external validity.

First, although several randomized controlled trials and meta-analyses have been conducted, most have short- or medium-term follow-up, usually less than 52 weeks. This limitation reduces the ability to assess the impact of combination therapy on harsh clinical outcomes such as cardiovascular mortality, acute myocardial infarction, and stroke. Studies with longer follow-up, such as the RACING Trial (2022), with three years of follow-up, are still exceptions (SABATINE et al., 2017).

Another critical point refers to the heterogeneity of the designs and the populations included. There is great variation in the doses of rosuvastatin (from 2.5 mg to 20 mg), in the form of administration (fixed dose versus separate), in the follow-up time and in the clinical inclusion criteria. This diversity makes direct comparisons between studies difficult and limits the extrapolation of results to different population contexts (WEI et al., 2024; MACH et al., 2020).

There is also a low representation of populations from countries in Latin America, Africa and other low- and middle-income regions. This compromises the assessment of the applicability of the findings in public health systems or in environments with access barriers, lower adherence, and distinct epidemiological profiles (KOLMAKOVA et al., 2024).

In addition, there is a paucity of comparative studies between the rosuvastatin/ezetimibe combination and newer therapies such as PCSK9 inhibitors or bempedoic acid. Although the association studied is effective and more accessible, its relative position in the therapeutic hierarchy still needs to be better investigated through multicenter head-to-head studies (BOUTARI; PANAGIOTAKOS; LAMBRECHTSEN, 2021).

Finally, it is important to highlight that a significant portion of the studies analyzed received partial or total funding from the pharmaceutical industry. This may introduce sponsorship bias or selective reporting of favorable outcomes. Thus, the critical evaluation of publications requires attention to the transparency of conflicts of interest and the independence of research groups (FERREIRA; NUNES; CARVALHO, 2021).

Therefore, although current data strongly support the use of the rosuvastatin/ezetimibe combination as an effective and safe strategy, long-term, independent, and more population-diverse studies are needed to validate the clinical sustainability of the results observed in real-practice settings.

6 CONCLUSION

The association between rosuvastatin and ezetimibe represents a consolidated therapeutic strategy in the management of dyslipidemia in patients at very high cardiovascular risk. The studies analyzed in this review demonstrate that this combination promotes more significant reductions in LDL-C levels compared to statin monotherapy, maintaining a favorable safety profile and good tolerability, especially when compared to high doses of statins alone.

The introduction of fixed-dose combined (FDC) formulations, such as Trezete®, further reinforces the clinical value of this approach, by improving adherence and therapeutic persistence, fundamental aspects for the effectiveness of treatment in real clinical practice scenarios. In addition, the combination proved to be effective and safe in subgroups of greater complexity, such as patients with type 2 diabetes, coronary artery disease, and the elderly, expanding its clinical applicability.

Despite the robust body of evidence, relevant gaps persist, such as the scarcity of studies with prolonged follow-up, the low representativeness of populations from developing countries, and the absence of direct comparisons with third-line lipid-lowering therapies. These limitations reinforce the need for new multicenter, independent studies with greater population diversity, aimed at evaluating harsh clinical outcomes and analyzing cost-effectiveness.

Thus, it is concluded that the rosuvastatin/ezetimibe combination should be considered a preferred therapeutic option for patients who do not achieve lipid goals with statins alone, especially in those with high residual risk or intolerance to high doses. Its broad incorporation into clinical protocols may represent a relevant advance in intensive cardiovascular prevention, with the potential to substantially reduce the morbidity and mortality associated with atherosclerosis.

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